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Felodipine Solubility Enhancement via Polymeric-Lipid Extrusion 3D Printing, and Public Acceptance Toward 3D Printed Medicines

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Abstract

Poor aqueous solubility of many prospective low molecular weight drug compounds is a barrier to bioavailability and hence therapeutic effectiveness and commercial potential. Multiple formulation-based approaches have been studied to enhance effective solubility, one of which is the formation of the drug in a solid dispersion, whereby the drug is dispersed in a soluble matrix. 3D printing has capabilities to produce personalised medicines and is a manufacturing technique for pharmaceuticals well suited to the creation of solid dispersions. Multiple 3D printing technologies are available, with material extrusion approaches most often used in pharmaceutical research to date. With such advances in 3D printing, there is also the opportunity for studies of patient-perceptions of printed tablets in the context of tablet properties such as size, shape, and colour.

As a new manufacturing technology, understanding patient acceptability of 3D printing of medicines is required to understand the public perception toward future market along with policy shaping. As part of this study a public study is carried out on the acceptance of 3D printed tablets.

The aligned main aim of this study was to study the potential of polymeric-lipid formulations to enhance drug water solubility in extrusion 3D printed solid dosage forms, designed according to the most acceptable geometries of the public. Such formulations have rarely been studied in 3D printing of tablets. Specifically, I investigated the poorly water soluble drug felodipine and its inclusion in a polymeric-lipid formulation. An immediate-release formulation was developed and tested for printability and compatibility. The developed formulation exhibited enhanced solubility, excellent printability, and compatibility. Subsequently I describe the study of sustained-release formulations with altered ratios of drug and excipients. A significant difference was present between formulations with variable drug content. As most lipids

undergo physicochemical changes over time, stability determination is considered. The samples were tested under various storage conditions. Several analytical techniques were used to verify any changes that occur during the stability analysis. Samples stored at room temperature and 0% RH showed rapid crystallisation of felodipine, whereas those stored at 37 ± 1°C and 75% RH maintained their amorphous and dispersed state. Augmentation of the drug release rate was observed in all aged samples compared to the freshly printed samples.

Multiple complementary methods were used to study formulation behaviour and structure. Employment of social study results in the design of future medicines can enhance their effectiveness. Additionally, lipids with their versatility as drug carrier are ideal for extrusion 3D printing for the use in pharmaceutical manufacturing, particularly clinical trials.

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- AAPS PharmSci 360, October 2023, Orlando, United States – “Felodipine solubility enhancement via polymeric-lipid extrusion 3D printing; development and stability”

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Abbreviations

3D	Three Dimensional
3DP	Three Dimensional Printing
3DSP	3D screen printing
AJ-P	Aerosol jet printing
AM	Additive Manufacturing
API	Active pharmaceutical ingredient
ATO	Atomised
ATP	Adenosine triphosphate
ATR-FTIR	Attenuated Fourier transform infra-red spectroscopy
BSC	Biopharmaceutics Classification System
CAD	Computer aided design programs
CLIP	Continuous liquid interface production
CM	Continuous manufacturing
CMC-NA	Sodium carboxymethyl cellulose
COREQ	Criteria for Reporting Qualitative Research
CT	Computed Tomography
DLP	Digital projection lithography

DSA	Drop Shape Analyser
DSC	Differential scanning calorimetry
EC	Ethyl Cellulose
EDS	Energy Dispersive Spectroscopy
EDTA	Ethylenediamine tetraacetic acid
EDX	Energy dispersive X-ray
EMA	European Medicines Agency
ETT	Emerging Technology Team
EVA	Ethylene-vinyl acetate
FaSSGF	Fasted State Simulated Gastric Fluid
FaSSIF	Fasted State Simulated Intestinal Fluid
FeSSIF	Fed State Simulated Intestinal Fluid
FDA	Food and Drug Administration
FDM	Fused deposition modelling
FFF	Fused filament fabrication
FIH	first-in-human
GI	Gastrointestinal
GMP	General manufacturing practice

GP	General practitioner
GRAS	Generally recognised as safe
HLB	Hydrophilic-lipophilic balance
HME	Hot melt extrusion
HPC	Hydroxypropyl cellulose
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl Methylcellulose
HPMCAS	Hydroxypropylmethylcellulose Acetate Succinate
IND	Investigational New Drug
IP	Intellectual Property
IR	Infra-red
IRT	Infrared thermography
ITF	Innovation Task Force
IV	Intravenous
LOM	Laminated object manufacturing
MED	Melt Extrusion Deposition
MHRA	Medicines and Healthcare products Regulatory Agency
MW	Molecular weight
NLC	Nanostructured lipid carriers
OPM	Oxford Performance Material

PAM	Pressure-assisted microsyringes
PAT	Process analytical technology
PCL	Poly carbolactone
PEG	Polyethylene glycol
PEN	Polyethylene naphthalate
PET	Polyethylene terephthalate
PGSS	Particles from Gas Saturated Solution
PHPMA	poly(N-(2-hydroxypropyl)methacrylamide)
PLA	Polylactic acid
PM	Physical mixture
PVA	Polyvinyl alcohol
PVP	Polyvinyl pyridine
pXRD	Powder x-ray diffraction
QbD	Quality by Design
QR	Quick response
RESS	Rapid Expansion of supercritical solutions
RH	Relative humidity
rpm	Round per minute
RS	Raman Spectroscopy
RSD	Relative standard deviation
RT	Room Temperature

SAS	Supercritical anti-solvent	TV	Television
SEDDS	Self-emulsifying drug delivery system	UHMW	Ultra High Molecular Weight
SEM	Scanning Electron Microscopy	UK	United Kingdom
		USA	United States of America
SLA	Stereolithography		
		USP	United States Pharmacopeia
SLN	Solid lipid nanoparticles		
SLS	Selective laser sintering	UV	Ultraviolet
SSE	Semi-solid extrusion	XL	Extended release
TGA	Thermographic analysis	XRPD	X-ray powder diffraction

1 Introduction

1.1 Oral drug delivery

The oral route for drug delivery is the preferred route of medicines administration for most patients. Approximately 90% of marketed drug products are for the oral route [1], despite the availability of various formulation types to be delivered via other routes such as pulmonary, topical, rectal and parenteral (intravenous, intramuscular, transdermal). This preference results from convenience, being non-invasive, generally excellent patient compliance, cost-effectiveness, and limited sterility requirements [2-4]. The main barriers for success of oral delivery are drug solubility, permeability and stability within the gastrointestinal (GI) tract [5].

Many drugs can be delivered via the oral route in either liquid or a solid form. The preference of dosage form varies by age and individual predilection. For better adherence in paediatric patients, liquid dosage forms are usually prescribed due to swallowability concerns [6]. Geriatric patients might have swallowability concerns, however, highly sweetened liquids would not be suitable either to palatability or medical condition [7], so oral dispersible tablets can be used, for example.

For the active ingredient to be pharmaceutically available, tablet based solid dosage forms generally need to disintegrate, allowing the drug to dissolve in GI fluids and permeate through intestinal mucosa and epithelium, and then be available in blood circulation. Disintegration time is dependent on the developed solid formulation [8]. Oral liquid dosage forms omit this step. Dissolution, the release of drug from the solid material, is mainly the rate limiting step of bioavailability of poorly water soluble drugs [9]. Permeability through the wall of the GI primarily take place in the intestine, this can be by passive diffusion or by a carrier [10]. Solubility and permeability are drug

specific characters that have been used by the Food and Drug Administration (FDA) to create the Biopharmaceutics Classification System (BSC) [11] (Table 1.1).

Table 1.1 Biopharmaceutics Classification System (BSC) [12]

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	low
IV	low	low

Additionally, bioavailability of many drugs taken via the oral route can also be affected by first-pass metabolism, where the active drug undergoes metabolism in the liver before reaching the systemic circulation [13].

1.2 Drug solubility

Drug solubility is one of the most critical aspects considered in drug development to avoid later failure. Solubility issues can be resolved by using an appropriate salt of a drug or by formulation approaches. A drug is classified as poorly soluble (Table 1.2) if 250 ml of solvate at pH range of 1-7 cannot dissolve the highest dose strength [14].

Table 1.2 Range of solubility for each solubility detention (USP) [15]

Solubility	Solubility range (mg/ml)
Very soluble	>1000
Freely soluble	100-1000
Soluble	33-100
Sparingly soluble	10-33
Slightly soluble	1-10
Very slightly soluble	0.1-1
Practically insoluble	<0.1

1.3 Solubility enhancement methods

Solubility enhancement can be achieved by various means: chemically, physically or by mixed methods.

Salt formation is one of the widely used methods to enhance the solubility of weak acids and bases in the form of acetate, hydrochloride, fumarate, calcium, sodium, potassium and others. Proper selection of the counterion is necessary to maintain a drugs properties such as hygroscopicity, particle size and flow properties [16]. Counterion properties will directly affect drug-ion (salt) physical properties.

Prodrug also known as molecular modification where a physiochemical modification of drug product is made to improve the solubility and decrease the toxicity. Prodrug is an option when the parent drug has toxicity issues. A prodrug is generally inactive or of limited activity when administered and undergoes chemical modification *in vivo* to produce the active drug [17].

pH modification, many drugs have pH dependent solubility, where it solubilised in certain pH while not in other. Incorporation of a pH modifying agent e.g. sodium carbonate, together with poorly soluble active can create a pH suitable microenvironment that facilitate drug solubility [18].

Complex formation with drug molecules to improve their physicochemical features without molecular alteration can be an attractive approach. Cyclodextrin is an example of a material that is used in complex formation. Combining the use of other pharmaceutical excipients such as surfactants and water soluble polymers with drug complexes could synergise the solubility of the formulation [19].

Particle size reduction can improve dissolution rate and effective bioavailability via increase in surface to mass ratio [20].

Nanocrystals (NCs) are generally obtained by high-speed homogenisation or precipitation. Due to their high surface to volume ratio, NCs improve saturation solubility together with rate and extent of dissolution. NCs present in uniform size particles of nano range size, those bespoke particles control crystal growth, shape, size, anisotropy and crystallinity. With no need for excipients NCs compose the active compound alone, and hence a high drug loading capabilities [21].

Co-crystal is a solid multicomponent system that presents a single homogenous crystalline phase. Typically these rely on hydrogen bonding between the drug and the coformer compound [22].

The combination of nanocrystals and co-crystals has been shown to have a synergistic effect on drug solubility [23].

Supercritical fluid preparation including Rapid Expansion of supercritical solutions (RESS), Supercritical anti-solvent (SAS) and Particles from Gas Saturated Solution (PGSS) is acknowledged as an environmentally friendly

technology that can improve physicochemical properties of drug particles in the form of shape, size, density and hence effective solubility [24].

Solid dispersion is one of the utmost promising technology in solubilisation techniques. Variety of hydrophilic, lipophilic or mixture of both can be used as a carrier to enhance the aqueous solubility e.g. sugars, PVP, PEG, and Gelucires [25].

Solid solution is formed from a drug uniformly distributed in a molecular and amorphous form within a solid matrix. It differs from a solid dispersion in that the later present in two phases. Enhancement of dissolution in solid solution is gained by the high energy of an amorphous form. Due to their high energy such formulations can be physically unstable and hence difficult to use [26].

Polymorphism is the capability of solid compound to differentiate in shape into multiple crystal forms. Molecular arrangement varies between polymorphs, which results in variable physical and chemical properties. Polymorph screening can lead to discovery of new crystal form that have better solubility [27].

Amorphous solid state provides enhanced apparent solubility and dissolution rate due to the low energy requisite to dissolve particles. This method is widely used for solubility enhancement [28].

Surfactants are hydrophobic substances that can form a micelle to incorporate insoluble hydrophobic drugs and hence enhance its solubility. Many factors can affect solubilisation efficacy of the surfactant, of which; solubilised material, hydrophilic-lipophilic balance (HLB), pH of the media, morphology of aggregates and presence of other additives [29]. HLB is the balance between hydrophilic and lipophilic parts of the surfactant in reference to size and strength. The value of HLB represent the type of emulsion can be created (W/O or O/W) [30].

Lipid-based drug delivery system**,** where hydrophilic, lipophilic and amphiphilic excipients could be used to solubilise a hydrophobic compound e.g. lipids, surfactant, cosurfactant and cosolvents. This has the advantage of reducing the effect of food that specially affect class II and IV BSC, due to stimulation of GI secretions similarly to physiological effects of food consumption, along with lymphatic drug absorption [31-33]. It is categorised as liquid and solid lipids according to their physical state. Liquid lipids include; lipid solution, emulsions of variable sizes (fine, micro, nano) and self-emulsifying drug delivery system. While solid lipids are represented in solid lipid nanoparticles of glycerides, glyceride mixtures, and waxes [34].

Lipid-based drug delivery system could also be classified according to their composition and further its properties into four types described in Table 1.3.

Table 1.3 Types of lipid-based formulations (composition and properties) [35]

	Excipients	**Properties**
Type I	Oils only	Non-dispersing
Type II	Oils + water insoluble surfactants	SEDDS
Type III	Oils + surfactants+ cosolvents	Clear dispersion
Type IV	Water soluble surfactants + cosolvents (without oils)	High solubilisation efficiency

Further classification according to composition and properties describes as follow:

Nanoemulsion where two immiscible liquids are dispersed as a biphasic system with the aid of an amphiphilic surfactant in the form of either water in oil or oil in water droplet. Nanoemulsions can be manufactured by a high-energy method; sonication, or a low-energy one; spontaneous emulsification which gives more stable system. Nanoemulsions have proved their ability to

improve the solubility by encapsulating lipophilic drug via decreasing droplet size [36].

Solid lipid nanoparticles (SLN), are a substitute to ordinary polymeric nanoparticles that combine the benefits of liposomes, lipid-emulsion and polymeric nanoparticles. Nanoparticles are particles of lipid origin that present in solid state at ambient temperature. They have a size range of 50- 1000 nm, generally produced by high-pressure homogenisation [37].

Nanostructured lipid carriers (NLC), a combination of the two previously mentioned lipid based drug delivery systems; liquid emulsion and solid lipid nanoparticles forms a synergistic hybrid of solid-liquid lipid hybrid [34].

Self-emulsifying drug delivery system (SEDDS), an isotropic mixture of lipid, surfactant, cosurfactant or cosolvent along with the active compound. Such system is simultaneously able to form a fine emulsion upon mild agitation and contact with GI fluids [38].

Table 1.4 displays many marketed pharmaceutical products that been developed by previously mentioned techniques to enhance their water solubility.

Table 1.4 Some marketed products of poorly water soluble medicines using variable solubility enhancing techniques

Solubility mechanism	Dosage form	Brand name	Active compound	Reference
Salt formation	Topical gel	Voltaren®	Diclofenac (sodium)	[16]
Prodrug	IV injection	Arranon®	Nelarabine (prodrug) arabinofuranosylguanine (ara-G) (active)	[39]
pH modification	Tablet	Prandin®	Repaglinide (meglumine)	[40]
Complex formation	Chewable tablet	Cetrizin®	Cetirzine	[41]
Solid dispersion	Spray-dried tablet	Crestor®	Rosuvastatin	[42]
Amorphous	Oral solution of HME	Kaletra®	Lopinavir/Ritonavir	[42]
Nanocrystal	Tablet	TriCor®	Fenofibrate	[43]
Nanoemulsion	Tablet	Aemcolo®	Rifamycin	[44]
SEDDS	Soft-gelatine capsule	Neoral®	Cyclosporine	[45]

1.4 Pharmaceutical lipids

Lipids are organic materials with a hydrocarbon backbone, often sourced by extraction of a natural material using solvents of low polarity. Oils, waxes, mono/di/tri-glycerides, cholesterol and phospholipids are examples of lipids [46]. Lipidic materials are generally highly flexible and biocompatible, and this allows versatility in dosage forms and routes of administration including oral, topical and parenteral. Relying on their chemical composition lipids can be classified as; homolipids (e.g. cerides, glycerides), hetrolipids (phospholipids), and complex lipids (lipoproteins) [47].

1.4.1 Advantages of lipidic materials in pharmaceuticals

The range of commercially available pharmaceutical lipid excipients empowers versatile formulation design of various drug delivery systems to enhance drug bioavailability of which; emulsion (micro-, nano-), liposomes, micelles and SEDDS [48]. A large variety of marketed lipid excipients are classified as GRAS (Generally recognised as safe), and hence suitable for human use in formulations. Lipid-based drug delivery systems have proven their superiority over other delivery systems in reducing certain drugs toxicity [49, 50]. For example, incorporation of drugs in a lipidic formulation can enhance drug bioavailability over other solubilising techniques [51]. Moreover, dose variation in such systems appears to be minimal [52]. Lipid-based topical delivery systems can show remarkable permeation enhancement due to multiple mechanisms of skin penetration which include: polarity alteration, fluidisation, and lipid exchange [53]. Solid lipidic excipients with high melting points can be used as a matrix to control drug release where water diffusion and tablet porosity mainly control the drug release [54]. Solid lipid matrices can incorporate labile drug substances to protect them from specific environmental challenges and can facilitate drug targeting [55]. Pharmaceutical lipid drug delivery systems have the potential to deliver both lipophilic and hydrophilic moieties. Lipophilic drugs follow the concept of solubilising similar materials, while hydrophilic substances are usually present

in a double emulsion [56]. Lipid excipients are considered non-immunogenic, physiologically biodegradable and highly tolerable, that minimise the adverse effects accompanied with similar polymeric delivery systems and prevent invasive removal [57]. Production of lipidic formulation also has a straightforward scaling ability along with possible sterilisation by various techniques [50, 58] and hence is an attractive route for practical manufacturing reasons.

1.4.2 Mechanism of possible drug transport of lipid-based drug delivery system

In ***paracellular absorption*****,** molecules transfer passively through neighbouring epithelial cells controlled by tight junction between cells and drug concentration gradients [59, 60]. lipid-based materials interact with membrane protein and lipid which result in membrane perturbation and further permeation enhancement [60]. The mechanism behind lipid-membrane interaction was suggested that phospholipase C stimulate the release of Ca^{2+} followed by protein kinase C activation [61]. Additionally, presence of medium chain fatty acids results in reduction in ATP (Adenosine triphosphate) levels together with cellular dehydrogenase activity in a concentration dependent manner [62].

M cell mediated transport (Microfold cells) is responsible for macromolecules transport by the mechanism of transcytosis [63]. Particles of up to 500 nm in diameter can be transferred by M cell transport [64].

Fluid phase macropinocytosis, an extended plasma membrane connected to a non-extended plasma membrane results in droplet engulfment of extracellular fluid in the form of large vacuoles. Dietary lipids of variable states are absorbed through pinocytosis, and lipid-based drug delivery can utilise the same pathway [47, 65].

Endocytosis (protein-mediated) the process of material passage via membrane vesicle through plasma membrane invagination [66]. Particles of 200 nm diameter or less can be transported via endocytosis [67].

Ligand mediated transport is considered a type of endocytosis and represented by interaction between a ligand complex and a cell membrane that leads to internalisation of a foreign substance. Vitamins, proteins, and fatty acids are examples of nutritional ligands. A number of lipid-based systems have exploited transport by this mechanism (Figure 1.1) [68].

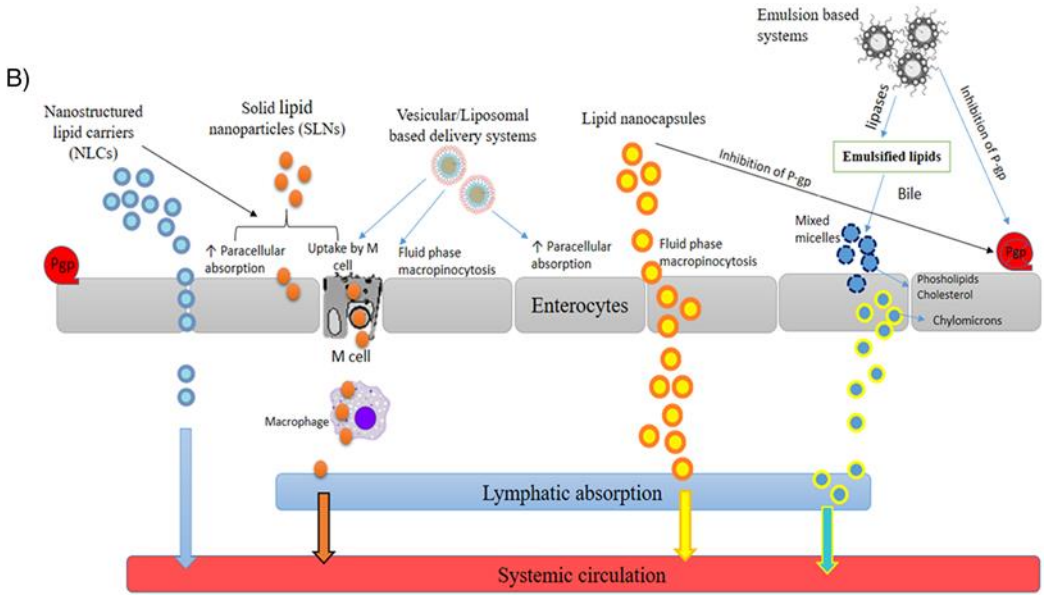


Figure 1.1 Mechanism of drug transport to the systemic circulation via lipidic materials [47]

1.4.3 Challenges with lipidic materials

Dealing with lipid-based materials is challenging as a dosage form and within the body as they are considered unstable and prone to oxidation [69]. However, oxidation can be minimised or prevented by different measures, such as flushing lipid containers with nitrogen after use to avoid the interaction

with the atmospheric environment [70], and the addition of an anti-oxidant (e.g. ascorbyl palmitate) [71]. Moreover, inclusion of chelating agent such as ethylenediaminetetraacetic acid (EDTA) is also recommended to maintain stability [72]. Chelating agents as a secondary antioxidants inhibit oxidative reactions by oxygen scavenging, transition metals sequestering along with providing the hydrogen atoms lost from primary antioxidants to prevent its depletion [70].

1.4.4 Solidification of lipid

As described, lipid-based formulation can be in the form of a liquid or a solid. Liquid and semi-solid forms are prone to physical, chemical and microbial instability. Solidification can solve these problems [48]. Filling a capsule (hard/ soft gelatine) was one of the first methods used to form a solid oral dosage form with liquid lipid formulations [73]. Newer techniques have been investigated in order to solidify liquid lipid formulations including; adsorption to solid carriers, spray drying, lyophilisation, rotatory evaporation, melt granulation and melt extrusion [48].

1.5 Problems with conventional solid dosage form manufacturing

Conventional solid-dosage form medicines manufacturing generally uses complex and multiple step processes to produce a product suitable for the market, including for example, powder feeding, mixing, granulation, drying, dosage manufacture and packaging. Characterisation of each step in this batch manufacturing process for the purposes of quality control and patient safety is a time consuming and expensive process [74]. The dosage forms produced align with the phrase “One dose fits all” as generally seen as not applicable to meeting the needs of personalised medicines via genetic driven variation through the population.

Using conventional tablets, dose adjustment is usually carried out by dispensing numerous small doses to achieve a larger dose, or

clinicians/patients dividing a larger dose tablet either by hand, knife or by tablet splitter. These approaches can lead to unequal dosages and hence different pharmacological effects. In addition, the splitting of tablets cannot be applied to all kinds of tablets, for example, controlled and extended release tablets can lose their functionality on splitting [75].

The use of liquid dosage forms has been used as a way to achieve personalisation. Despite the ease of dose adjustment by alteration in volume, liquid dosage forms cannot be offered on large quantities, as well as the increased possibility of physiochemical instability and microbial contamination of the liquid form versus equivalent solid dosage forms [75].

Although conventional large-scale manufacturing is cost effective, they are time consuming and resource intensive, additionally, large batch sizes lead to dose inflexibility [76], a potential area where three-dimensional (3D) printing could provide a better solution.

3D printing is one of the most rapidly growing manufacturing technologies in many fields [77] due to its ability to manufacture bespoke multi-material items with complex geometries. 3D printing is found to be promising in pharmaceutical industry, with some products having received regulatory approval [78].

1.6 3D printing

1.6.1 Definition of 3D printing

3D printing, or additive manufacturing (AM) can be defined as the production of an object by addition of consecutive layers of the printed material over each other guided by a computer system (Figure 1.2) [79]. 3D printing is also named as rapid prototyping due to its use for many years as a tool for the manufacture of early bespoke prototypes before using more rapid conventional mass manufacture [80]. According to the American Society of Mechanical Engineers, the term additive manufacturing is preferred rather

than 3D printing, however, from a pharmaceutical point of view this could be confused with the process of adding different coating layers [81].

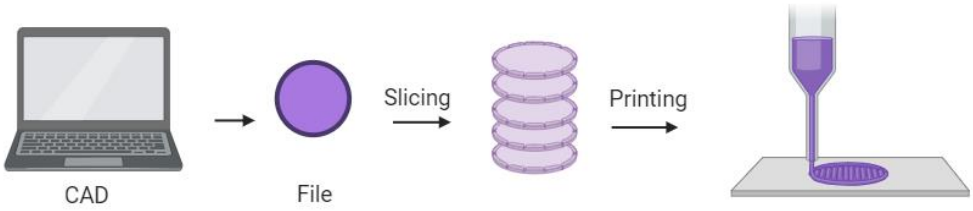


Figure 1.2 Generic 3D printing approach (BioRender.com)

1.6.2 3D printing original principle

Hideo Kodama presented a new approach for the automatic development of solid 3D printing. Kodama used a photo-hardening polymer then applied either a mercury or a xenon lamp as a source of UV radiation [82].

The main idea of this method is construction of a solid object by stacking layers over each other. The desired accuracy and complexity of the final shape is determined by number of layers constructed. In addition, thickness of each layer is a result of UV intensity and time of exposure [82].

1.6.3 History of 3D printing

Standard manufacturing practice in industry is termed subtractive fabrication, in which the process is the removing of material from a solid object to reach the required shape. In contradiction, adding material layer by layer to form the prescribed shape is called additive fabrication or 3D printing [83].

The birth of 3D printing was at the end of 1970s. Ross Housholder illustrated the concept by binding layers of sand by a variety of materials, while Carl Deckard established an approach of powder solidification using a laser, called selective laser sintering [77]. Moreover, the first commercial object fabricated

by 3D printing was in 1984 by Charles Hull; a 5cm tall plastic cup built using stereolithography technique that took months to finish [84].

Two-dimensional (2D) printing is the printing of a huge number of dots on a flat surface. Using 2D printing could be helpful for screening the optimised parameters to develop a 3D object. While the addition of a fourth dimension (4D) is described as self-change of printlet architecture after manufacturing consequently to alteration of pressure, temperature, water or enzymes [85].

1.6.4 The 3D printing process

1.6.4.1 Computer aided design programs (CAD)

AutoDesk, AutoCAD, SolidWorks, or Creo Parametric are examples of CAD software which is used to define the object to be printed. Colour, texture and transparency are the main dissimilarity features between each program [86].

1.6.4.2 Ink Material

Each 3D printing technique relies on distinctive printing materials, or inks, such as polymers, thermoplastics and metals [85]. The most used materials in 3D printing of pharmaceuticals are polymers, such as polylactic acid (PLA), polyvinyl alcohol (PVA), cellulose derivatives, polyethylene glycol (PEG) and others [77]. In pharmaceutical applications, the printing material should be non-toxic, biocompatible and biodegradable [87]. 3D printability of powders usually relates to two properties: (1) powder geometrical characteristics which includes particle size, particle size distribution, surface area and morphology; (2) reactivity between the printed material and the binder [87].

1.6.4.3 3D printing tools

Generically, 3D printers consist of a printing head on a dual horizontal x-y axes and a vertical z axes yielding a three-dimensional motion [88]. 3D

printers range in size and cost. For each printing technique a specific printer is used.

1.6.5 Types of 3D printing

3D printing technologies can be categorised by the state of starting material as either liquid, powder, solid or paper-based. Solidification of liquid is a requirement of liquid-based processes. While powder processes require the unification of loose powder to form a freestanding object. Solid-based processes usually use high temperature to melt or soften solid material and re-join it in desired geometries. Paper-based printing is limited to arrangement of sheets over each other with lamination of external structure [89]

The main 3D printing technologies are discussed in the following section.

1.6.6 3D printing techniques

1.6.6.1 Stereolithography (SLA) or Photopolymerisation

SLA was the first marketed additive manufacturing technique. An ultraviolet beam from a laser or lamp is applied to a photosensitive material to locally polymerise the printed material (Figure 1.3). Excellent spatial resolution and little treatment of the printing materials (incorporation of active/non-active ingredients into the resin whereas they are miscible together) are the main advantages of this technique [90]. Single point solidification at a time contributes to a long time for printing is considered a drawback. To overcome this problem, digital projection lithography (DLP) has been developed, in which a digital mirror device slices and rapidly directs the light source allowing surface rather than one-point curing [91]. SLA currently has limited use in medical field as the resins typically used are potential carcinogens [75].

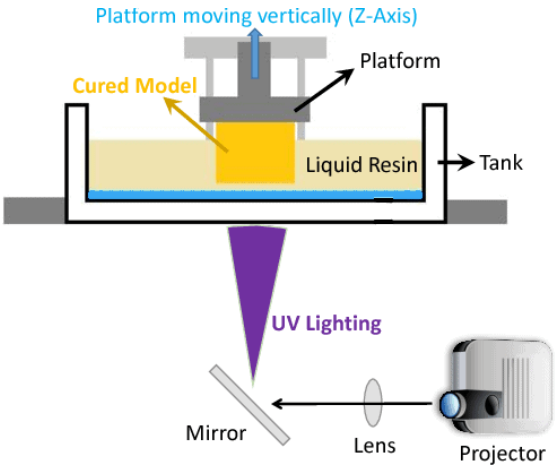


Figure 1.3 Schematic drawing of Stereolithography (SLA) [92]

Combining the advantages of material engineering to develop biocompatible photocurable materials and implement SLA printing can enhance the development of personalised pharmaceutical products with versatile drug release.

1.6.6.2 Continuous liquid interface production (CLIP)

CLIP is an improvement of SLA. Inhibition of oxidation during photopolymerisation avoids partial curing. CLIP provide an oxygen permeable membrane which creates a dead zone allowing a persistent liquid interface leading to faster printing and better resolution (Figure 1.4**)** [93].

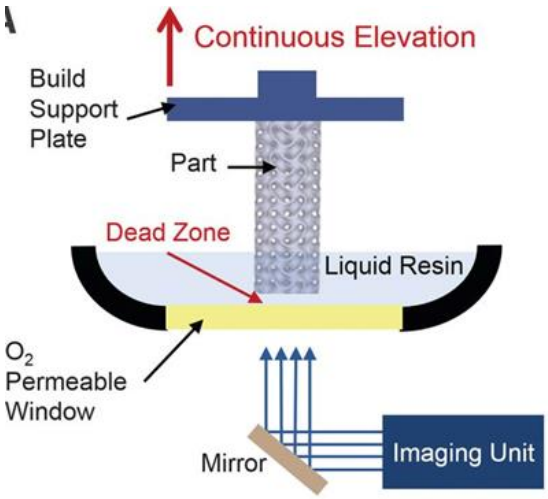


Figure 1.4 Continuous liquid interface production (CLIP) schematic drawing [93]

1.6.6.3 Binder deposition or binder jetting

This process is parallel to conventional pharmaceutical granulation [81]. In binder jetting, layers of solid particles are stacked together upon ink-jet of liquid binder substance to build up 3D object (Figure 1.5). Inkjeting of liquid binder to fuse the particles can be continuous or drop-on-demand printing. The main difference between the two categories is that the size and spacing of the droplet is defined by the pressure wave pattern used to create droplets in the initial category. While in the second method, a voltage induced pressure via a piezo-based doser is used to create separate droplets on demand.

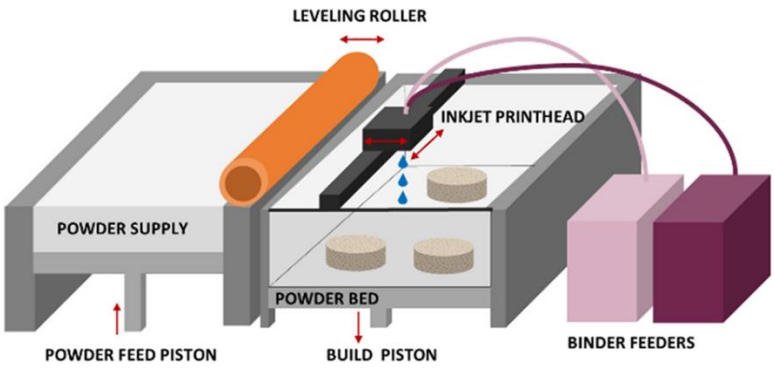


Figure 1.5 Schematic drawing of binder deposition 3D printing [94]

In the pharmaceutical field, binder jetting can yield good reproducibility and rapid output [91] as used by Aprecia, the developer of the only US Food and Drug Administration (FDA) validated 3D printed medicine to date, Spritam® [95].

1.6.6.4 Material jetting

In material jetting, the whole formulation is prepared and jetted together (Figure 1.6). UV-curable resins, suspensions, solutions and molten polymers are commonly used in material jetting [81]. Material jetting is able to formulate micro-particles with a low layer thickness [85].

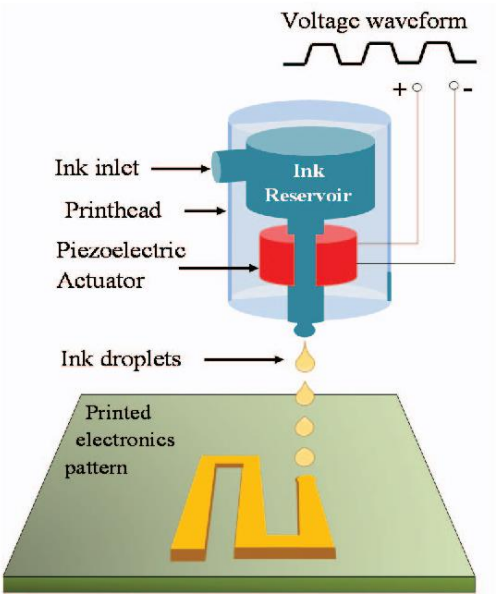


Figure 1.6 Schematic drawing of material jetting [96]

1.6.6.5 Aerosol jet printing (AJ-P)

AJ-P also named maskless mesoscale materials deposition (M^3D), uses ultrasonic vibration or pneumatic atomisation to atomise the printing substance before spraying in layers onto a substrate (Figure 1.7). Aerosol jetting can be scaled up by addition of more nozzles in addition to expansion of the printing platform [80].

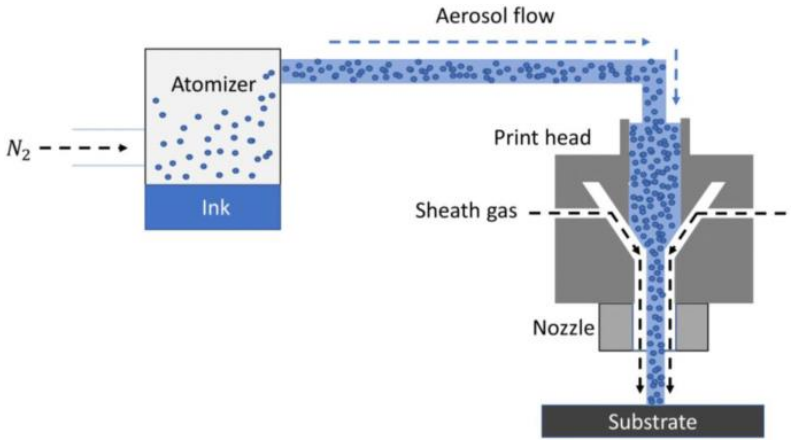


Figure 1.7 Schematic drawing of aerosol jet printing [97]

1.6.6.6 Powder bed fusion

Powder bed fusion is faster and complex substitution of extrusion of thermostable materials where multiple printing elements (part bed temperature, laser power, scanning speed) can be adjusted to produce the required features of the building structure. The process comes through laser heating of a mixture of high melting point substance and a low melting point binder which are then printed (Figure 1.8) [81, 98].

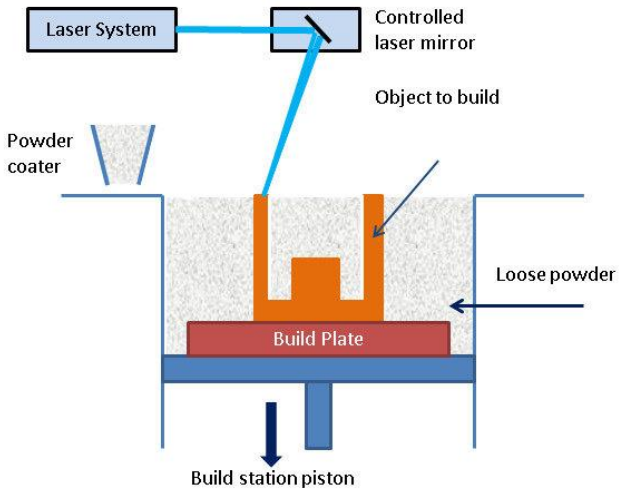


Figure 1.8 Schematic drawing of powder bed fusion [99]

1.6.6.7 Selective laser sintering (SLS)

SLS is a powder-based method resembles binder jetting, however, it differs in that inkjet printing using liquid to bind the solid particles while the SLS uses laser to bring powder particles together (Figure 1.9**)** [84].

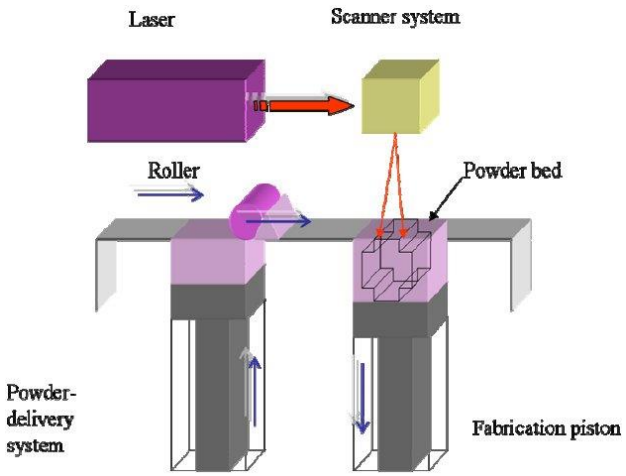


Figure 1.9 Schematic drawing of selective laser sintering (SLS) [100]

SLS system is affected by two crucial factors, laser beam optics and steering which permits the beam to be applied over each layer, along with powder spreading that allows the powder to be spread evenly before the laser is used to heat and sinter the particles [91].

1.6.6.8 Extrusion

Extrusion based approaches includes the most abundant 3D printing methods used in pharmaceutical research, fused deposition modelling and semi-solid extrusion. Extrusion 3D printing resembles ordinary pharmaceutical extrusion somehow in heat application to join drug and excipients, however, pharmaceutical extruded filament needs further treatment to develop a dosage form, while extrusion 3D printing ends with the final drug product. Indeed, not all 3D extrusion needs heat application. Due to the absence of powder bed there is a need for support material “rafts” to hold the printlet in

position while printing, so each layer must ideally solidify before the next is printed [81].

Fused filament fabrication (FFF)

FFF is one of the most commonly used techniques in 3D printing. The 3D object is built up by fusion of layer over layer of extruded semi molten thermoplastic substance printed from a nozzle (Figure 1.10). This process has the ability to use many different materials to print one object either via multiple nozzles or exchange of ink cartridge, beside that it operates with low cost. Moreover, no need of organic solvents in this technique [79]. Fused deposition modelling (FDM^{TM}) is the trademark name for FFF [81].

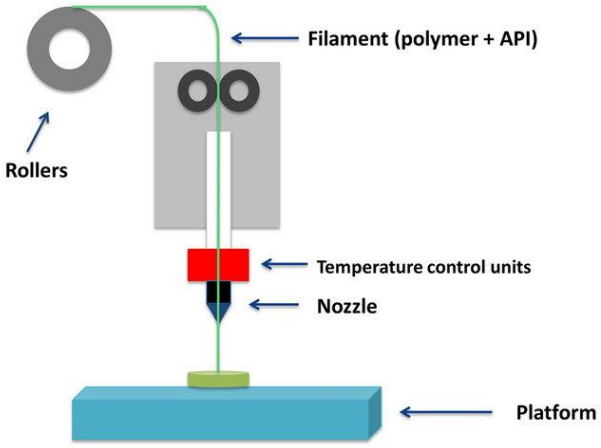


Figure 1.10 Schematic drawing of fused filament fabrication [101]

Semi-solid extrusion (SSE)/ Pressure-assisted microsyringes (PAM)

PAM printing of gels or pastes by blending optimal percentages of polymers with selected solvent/s to achieve a desirable printing viscosity (Figure 1.11). Applying heat to the ink is possible via SSE to get an extrudable ink. The most important aspect of this method is the rheological (printing) properties of the used materials. While the challenge with PAM is the use of toxic organic solvents needed for stability of some printed object. Those solvents are

required to be removed from the final product for patient safety. However, the Roberts group have successfully printed tablets using water as a solvent for SSE. This technique commonly gives a relatively low resolution print as a result of the nozzle orifice size which usually 0.4-0.8 mm [75, 79, 102, 103].

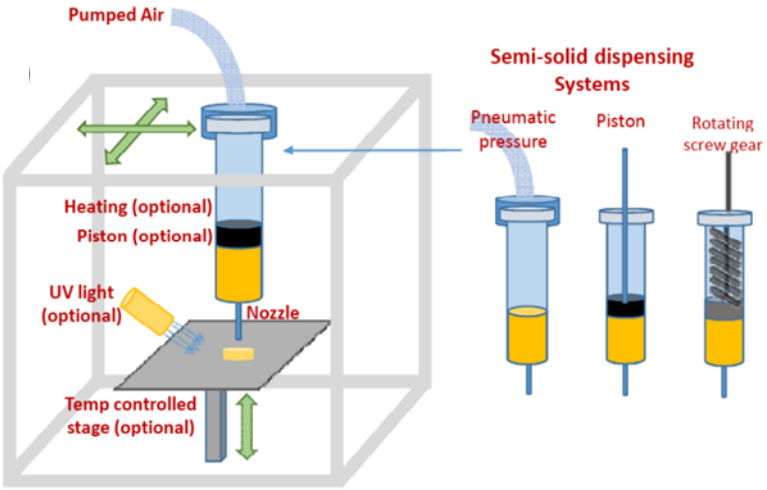


Figure 1.11 Schematic drawing of pressure-assisted microsyringes (PAM) [104]

1.6.6.9 Laminated object manufacturing (LOM)

In LOM, (Figure 1.12) a sheet of material is cut by laser or razor and fused to the next layer by thermal adhesion [105].

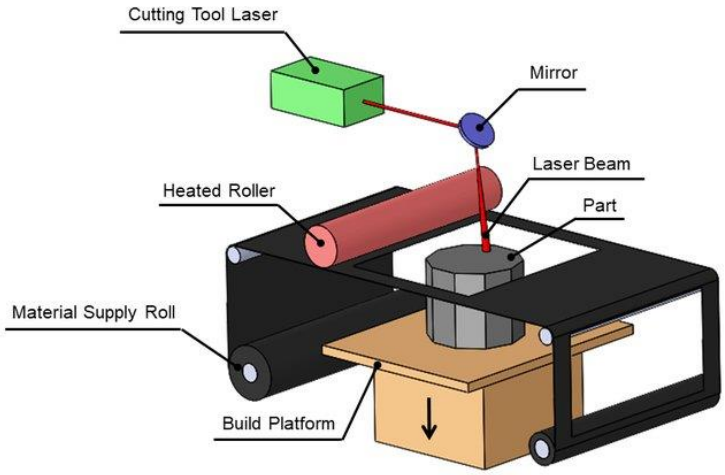


Figure 1.12 Schematic drawing of laminated object manufacturing (LOM) [106]

Recent advancement of pharmaceutical 3D printing will be discussed later in this Chapter (1.6.13).

1.6.7 Applications of 3D printing

The applications of additive manufacturing are broad and rapidly expanding including; medicine [107], moulds [108], toys [109], art [110], food [111], furniture [112], clothes [113], education [114] along with the fabrication of 3D printing printers themselves [115] and much more.

1.6.8 Types of 3D printed dosage forms and therapeutics

Substantial innovations in drug delivery systems have been succeeded employing various formulation approaches that mostly relies on excipients and their properties [116, 117]. Commercial availability remains low despite of scientists efforts, due to manufacturing and scaling-up challenges. 3D printing with its advances offers alternative approaches that resolve current challenges [118]. Table 1.5 presents some applications of 3D printing of pharmaceuticals.

Table 1.5 Examples of 3D printing applications (dosage forms and therapeutics)

Application	Description	Reference
Immediate release tablet	Variable hydrophilic polymers and infill density were printed by FDM to control dissolution	[119]
Bi-layer (immediate and sustained release)	- Each layer is fabricated from a different material composition that produces the desired release profile - A sandwich like scaffold of medicated and drug-free layers are 3D printed to avoid burst drug release - Scaffold printed pattern is selectively designed to disintegrate at certain intervals	[120, 121]
Capsule (caplet)	Prototyping a body that hold liquid or solid formulation in a controlled release system	[122]
Polypill	- A combination of more than one drug in one tablet which can improve patient adherence for those taking multi-drugs for chronic diseases - Five medicines of variable release profile were successfully printed with acceptable tablet size	[123, 124]

Wound Dressing	- Building an individualised dressing with a biocompatible polymer with the appropriate anti-microbial agent - 3D printing allow usage of various polymers (natural, synthetic) together with possible addition of viable cells to promote healing - A thermoresponsive hydrogel with novel polymers incorporated compatible antimicrobial agent. Upon application at body temperature this bioink showed the ability to swell and reform its structure	[125, 126]
Implants	- Customised drug loading and with site-specific physical and mechanical features - Sustained release implants in the form of polymer eluting or core-shell was developed to reduce the burden of frequent administration of medicines	[77, 107]
Microneedles	- Development of biocompatible microneedles in the form of patch that deliver a constant dose in a non-invasive manner - Photopolymerisation was used to print the structure of the patch in a cone or pyramid design, then insulin containing ink was ink-jetted over the patch to allow fast release	[127]
Floating device	- A tablet shape with modifiable floating time - Adjustment of polymers and internal architecture plays a role in water diffusion and floating time	[128]

	- High accuracy printing is essential to unify the floating time of all printed tablets	
Ocular device	Fabricated as biodegradable contact lenses, due to eye limited dose capacity and the need of frequent administration	[129, 130]
Mucoadhesive	- Drug delivery systems have been developed for buccal and vaginal delivery - Suitable for local drug delivery and for drugs undergo first pass metabolism	[131, 132]

1.6.9 Advantages of 3D printing

3D printing offers many potential advantages for pharmaceuticals. High drug loading can be achieved due to the flexibility in printer type and wide ranges of properties that can be achieved to accommodate high loading [78, 133-136]. Khaled *et al.* showed using common pharmaceutical excipients in extrusion 3D printing of paste formulation can achieve drug loading of tablets up to 80% w/w [78].

Dose flexibility in which the dose can be modified by adjustment in printlet geometry. Since the dose is reflected by the size of the printlet, modification of the software design can be used to alter the dose [137].

3D printing is considered a cost-effective manufacturing technique in the right circumstances, since it applies product flexibility, operational flexibility, and capacity flexibility. The capability to produce many products using the same machinery is referred to product flexibility (subject to compliance with GMP standards). Moreover, operational flexibility is the qualification to synthesis a product while utilising variety of equipment, materials, and techniques. The capacity flexibility includes the ability to control the volume of production [138].

3D printed formulations developed with dimensions that promote ease of administration can increase patient compliance. The required shape, size, and colour could be determined by software design. According to Goyanes *et al.*, participants of their study prefer to take ordinary shapes, capsule and disc rather than diamond shape medicine, along with choosing the smallest size printlet [139].

As the simplicity of dose alteration and feasibility for in-process adjustment, 3D printed formulations are particularly attractive for potential use in first-in-human (FIH) trials and in frontline medical care [76].

Rapid manufacturing enabled by 3D printing promotes on demand production of a desired medication. For example, as in the case of nitroglycerine, a drug intended for the treatment of angina pectoris, is one of the most known drugs that undergoes degradation while on storage. However, if it is produced just prior to use, this problem can be reduced significantly [103].

Customisation allows the transfer of the dosage from human to animal size regarding their pharmacokinetics and pharmacodynamics. Testing ordinary medicine in animals has difficulty in delivering the intact dose to the animal. Researchers tend to crush the tablet or dissolve it in order to give it to the animal, which would alter product pharmacokinetics. 3D printing design adaptation could assist delivering the intact dosage form to the tested animal without affecting the integrity of the dosage form [140].

Rapidly changed drug dosing such as for patients on corticosteroids (e.g., prednisolone and budesonide), could be accommodated more simply through 3D printing [76], since each desired dose will be printed regarding to a patient's needs. There are many treatment regimens of corticosteroids that need a variety of dosing during the course starting with high dose and decreasing with time.

Due to capability of 3D printing to control dosing accurately and to very low levels, dosing of high potent and/or narrow therapeutic index drugs could be attractive. Medicines that have narrow window between therapeutic and toxic effect usually have small doses and need to be delivered in accurate, precise, and reproducible doses, such as can be achieved by ink-jet printing [141].

Additive manufacturing gives the ability to build up an easily swallowable multi-drug formulation. Khaled and co-workers have prepared a cardioprotective dosage form using paste extrusion 3D printing consisting of five un-identical APIs with different release mechanisms, separating one from another with a shell to prevent drug interactions. This polypill was designed with dimensions of 5.85 mm x 6 mm [123].

Powder-based 3D printing can produce a highly porous product that contribute to faster disintegration than conventional tableting. As in binder jetting, the binder act like a glue that applied over a bed of loose powder to produce the structure of the printlet rather than compression force. The resulting formulation contains high degree of porosity allowing water to easily penetrate and further disintegrate in a matter of seconds, as is the basis for the medicine Spritam® [142].

1.6.10 Disadvantages of 3D printing

Like any technique, 3D printing has some disadvantages. Thermolabile substances might degrade under printing if heat is required for a specific printing technique. Moreover, 3D printing is currently considered time consuming when applied to large-scale production. Additionally, shortage of formal regulations for 3D printing inhibit uptake by the pharmaceutical market [76].

Similar to other powder-based industries, powder-based 3D printing needs specific handling in removal of excess powder as it is considered as a health hazard. Together with nozzle obstruction, migration and bleeding of the binder, all are problems that require interventions. Stacking layer over layer could affect the morphology of the final product in the form of surface defects leading to consumer un-satisfaction [75].

1.6.11 Consideration about printing materials

Material properties, such as crystallinity state, melting point, density, flowability, and ability to segregate directly influence the mechanical properties and anisotropy of the printed object. This is reflected in the strength, hardness and visual appearance of the end product [143].

High resolution control of printlet printing is important for its physical appearance. Different printing technologies have a range of resolutions, which might be affected by printing orifice, layer thickness, and material properties

[75].In binder jetting for example, the resolution is dependent on the droplet size and the degree of adhesiveness of that droplet [144]. Indeed, in material jetting the precision of printhead rotation plays a role in the resolution along with number of nozzles and their diameter [145]. While extrusion mainly affected by nozzle size and printing speed. Table 1.6 shows resolution and printing speed of variable printing techniques.

Table 1.6 3D printing techniques speed and resolution [144]

3D printing technique	Printing speed (cm/h)	Resolution (element/mm^3)
Binder jetting	1.58	1900
Extrusion	0.05	46
Ink-jet printing	0.4	15200
Powder bed fusion	2.5	211
Stereolithography	1.5	3152
Lamination	0.45	1907

From a safety perspective, materials used in 3D printing of medicines have to be biocompatible. However, until this time, the approved biocompatible polymers useful for 3D printing are few [146]. For internal delivery, the printed object must degrade or eliminated from the body to avoid accumulation and toxicity. Meanwhile, other routes of delivery such as patches and ocular devices should be non-toxic as it absorbed to the systemic circulation.

1.6.12 3D printing from an economics point of view

Direct manufacturing generated using digital models from scratch without the use of moulds or casts has significantly increased. The main limitation is slow outcome, meanwhile, the time takes to build up a certain mould together with

its cost could be greater than 3D printing. From economical provision, 3D printing is at its infancy, and likely with original computers which was very expensive at early times but gradually with time the price reduced. 3D manufacturing will expand due to two exclusive properties; large-scale personalisation and minor adjustment is permitted during manufacturing [147].

Furthermore, while in early phase of drug development toward regulatory approval the failure rate is high [148], additive manufacturing could play an important role in reduction of time and cost loss resulting from later stage fail of development of a new drug [79].

1.6.13 Advancement of 3D printing

Up to date, multiple polymers showed successfulness in 3D printing being printed solely or with addition of low percentages of other excipients of which PLA, PCL, PVA, EVA, PVP, Soluplus®, HPC, HPMC, HPMCAS and different grades of Eudragit® [149]. Tian *et al.* demonstrated the printability of various pharmaceutical fillers (lactose, mannitol, sorbitol), binders (EC, CMC-NA, PEG 4000) and moisturisers (ethanol) of variable ratios and gave an insight about appearance, hardness, friability and disintegration time. They discussed the versatility in adjusting the printed material composition to compensate printed object intended needs [150]. A personalised multivitamins developed by extrusion 3D printing is available in the market with the name Nourished [151].

Continuous manufacturing (CM) is highly encouraged in pharmaceutical manufacturing (Figure 1.13). It denotes to single step manufacturing without any intermediate steps while quality control maintained along the process. CM reduces materials and energy consumption and therefore costs, along with increase the consistency of the process and product quality. Quality by Design (QbD) where “quality should be designed into a product” and Process analytical technology (PAT) which founded by FDA, mainly focuses on in-process monitoring that would boosts continuous manufacturing while the

quality of the product is insured. Hot melt extrusion (HME) is a pharmaceutical process easily accompanied CM theory, it has the benefit of enhancing the solubility of poorly water soluble compounds, besides it have decent process control and easily scalable [152-154]. Extrusion 3D printing is highly comparable to CM HME, where manufacturing occurs in a single step, along with feasibility of printer built-in product quality measuring tools.

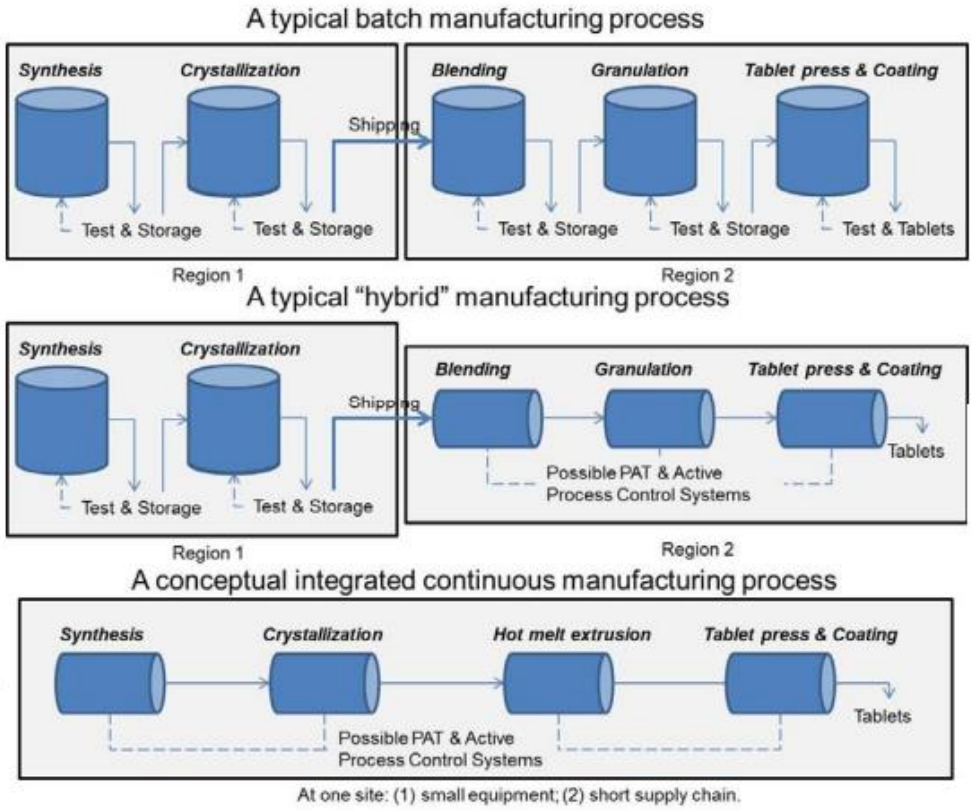


Figure 1.13 Comparison between typical pharmaceutical batch manufacturing and continuous manufacturing illustration [155]

Many companies are working on developing new 3D printing technologies in the pharmaceutical field. With approval of numerous of product serving patient global wise [156], the encouragement of further research is approached. Oxford Performance Material, Inc. (OPM) have synthesised a 3D printed bone scaffold OsteoFab® from multiple grades of OXPEKK polymer. Those scaffolds have highly comparable mechanical and functional features to

human bones with biocompatibility and microbial resistance properties. Selective laser sintering was used to build up a personalised bone structure. The stl. file is generated from Computed Tomography (CT) scan images of a specific patient [157].

Triastek have received Investigational New Drug (IND) approval by US FDA for several 3D printed pharmaceutical products together with others in the approval pathway. They are working in various clinical directions, of which; chronotherapy, single daily use formulation of poor solubility drug, site-specific gastrointestinal delivery and adherence enhancement. Triastek developed Melt Extrusion Deposition (MED) as new technique of 3D printing. This technique relies on mixing API with excipient, melting them together, and then depositing multiple layers by extrusion [158].

Aprecia, the manufacturer of the only approved 3D printed medicine, is now developing more formulations using its ZipDose^{TM} technology platform in 3D printing sector by printing directly within the packaging strip rather than stand alone. At this time point, this system is being tested for GMP suitability. In Z-fill a cup-shaped structure is printed directly in packaging strip (Figure 1.14). Loose powder of API then fills the cup. A lid is printed over to close the tablet. The tablet shell could be either medicated or API free. This Z-fill approach is recommended for heat and moisture sensitive actives [159].

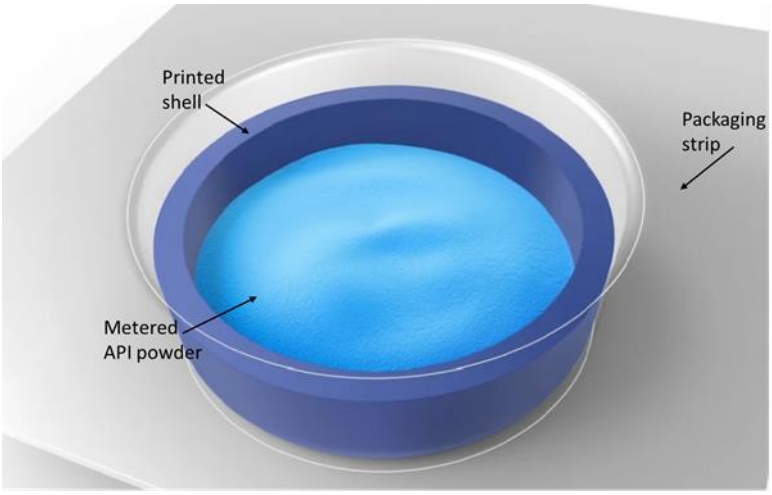


Figure 1.14 Schematic representation of Z-fill technology. Capsule-like structure directly printed in packaging strip and filled with metered dose of powder API [159]

Laxxon Medical has developed a new 3D printing technology, similar to that used for the manufacture of flat screen displays. 3D screen printing (3DSP) is considered as extrusion printing where a medicated semi-solid paste extruded through screen mesh into a substrate. The first layer has to dry before applying the next. The mechanism by how the selected geometries been printed is by blocking the area where no materials needed using a stencil. Small batches along with mass production are achievable using 3DSP, as it is capable of building-up thousands of printlets per screen. The number of products is dependent on the ratio of screen size to unit size. The building-up time could be increased if more than one paste is used in the printing. This includes the cleaning up of the mesh and the squeegees. This technology is dependent on the rheology of the paste. Additionally, Laxxon Medical Corp. have added QR codes to printlets as small as 5 mm radius for easy identification of the printlet content [160, 161].

A recent study summarised the clinical trials of 3D printed devices, finding that around half of the ninety-two of the trials were run in China, 10 multicentre, 2 international (collaboration of scientist in multiple countries) while others were

distributed around the world with majority in USA and Egypt. Just above quarter of the studies were related to orthopaedic surgery. Dentistry and maxillofacial surgery come second in number of clinical trials. Most of the trials were in the last three years from the study. Six thousand patient were enrolled in the studies that demonstrate the popularity and trust of 3D printing [162]. Another study was conducted in the same year; however, this studied the efficacy of 3D printed devices. In contrary to the previous study, here the maxillofacial devices were the majority of the studies. The systematic review concluded that the efficacy and effectiveness of the 3D printed devices was not proven for most of the examined devices and requires further assessments [163]. A difference of this study in relation to ours, that it is mostly associated to surgical devices rather than pharmaceutical dosage forms.

Several patents were gained recently for 3D printed devices including drug delivery systems [164]. Nevertheless, it has been reported that lack of scientific evidence is main barrier for 3D printing in clinical trials rather than the cost, which commonly described as the bottleneck of the practise. Most of the reported studies are case reports or series that do not consider scientific evidence; however, it is essential for hypothesis generation for a new subject. Moreover, additional information of the 3D printing technique, parameters and materials used should be reported [165].

1.6.14 Sustainability of 3D printing

Sustainability is broader than environment considerations alone; it also covers other areas such as social, legal and economic views. A major challenge is to reduce the consumption of energy and materials. It has been proved that certain 3D printing technology are capable to perform at lower energy levels and less materials than conventional manufacturing [166].

Cost, waste of materials and labour effort could be reduced by implementing 3D printing in first-in-human and early phases clinical trials. As the number of

doses at early stages of clinical trials are minimal and the ordinary tableting machines require materials of hundreds of tablets to operate. Whereas, 3D printing could work with only the required materials, with no extra materials to waste. It also capable to produce thousands of tablet per day if needed, which make it practically when scaling up through clinical trials stages [167]. It has been reported that applying 3D printing in early stages of clinical trials could reduce the cost of tableting processes up to 70%, where 50% of API would be saved, and 60% in time [168].

Drug delivery in clinical trials is mostly in liquid form, as no development techniques needed. However, if a controlled release delivery is required here comes the challenge. Liquid drug formulations are easy to develop along with possible small scale production contrary to solid forms that needs excipients of specific characters and relatively developed in larger batches. Certain medications necessitate modification of its release which is not possible in liquid forms as the drug is needed to be available in solidified state and a release retardant can modify its release. Smith *et al.* suggested printing a capsule-like structure that could be filled with liquid or powdered API, the printed capsule shell could be modified in accordance to the delay needed [169].

1.6.15 Reasons for the dearth of 3D printed pharmaceuticals in the market

The limitation of 3D printed materials flexibility, biocompatibility and FDA approval are the main barriers facing the expansion of 3D printing in pharmacy. Most of printable objects cannot tolerate high temperatures used in post-manufacturing sterilisation protocols (121º C- 132º C). In addition, the regulations of personalised 3D printed objects are not clear [170].

1.6.15.1 Regulatory considerations

The release of guidance around the additive manufacturing of medical devices and implants in 2017 is evidence of the progress done by the FDA

after the establishment of the Emerging Technology Team (EET). It has been stated that the evolution of complex dosage form and manufacturing techniques adopting science and risk-based approaches is highly encouraged by the FDA, which make the approval of 3D printing of pharmaceuticals on its way [171]. Similarly, an organisation has been established by the European Medicines Agency (EMA), called Innovation Task Force (ITF), which aid the development of new technologies at early stages [167].

Macromolecules actives are becoming new generation therapeutics. Such compounds fail to reach the market due to their instability. However, on-demand drug production would omit the need for long time stability, as the medicine would be received by the patient immediately after manufacturing [172].

FDA has released a discussion paper on point of care manufacturing at late 2022. It did not include additive manufacturing in words, however, it discussed possible use of different drug concentration and multi-active formulations [173].

In early 2023, UK government have released consultation on point of care manufacturing gathered from the Medicines and Healthcare products Regulatory Agency (MHRA) which include 3D printing in discussion. They proposed establishment of regulatory framework for point of care manufacturing with assurance of products safety, quality and efficacy. In this consultation patients and public were involved. This framework was formed to complement existing regulations but bypass unnecessary regulatory barriers [174].

1.7 An introduction to materials used in this study

Some methods of solubility enhancement of the used API along with implementation of API and excipients in 3D printing are discussed here. Further details about the materials is available in Chapter 2.

1.7.1 Felodipine

Various techniques have been used to enhance the effective solubility of felodipine. Sahu and Das discussed felodipine solubility enhancement through preparation of nanosuspension, which is further increased by ultrasonication [175]. Additionally, solubility of felodipine was increased when developed as an amorphous solid dispersion via hot melt extrusion. As reported, 10% w/w loading yielded complete amorphisation (and hence solubility enhancement), while higher drug loading resulted in partial crystallisation of felodipine when dispersed in an amphiphilic polymer [176]. A solidified self-microemulsifying formulation developed by Jing *et al.* has proven the potential to increase felodipine solubility [177]. Spherical agglomeration was also shown to enhance felodipine solubility due to conversion into amorphous form [178]. Spray drying has also been used to enhance felodipine solubility via amorphisation [179].

Drais and Hussein have developed hybrid lipid-polymer nanocarriers to be administered in the form of nanovesicles prepared by two distinct methods; single emulsification solvent evaporation technique and a microwave-based method. They demonstrated the microwave based method appeared to be significantly superior compared to traditional methods in dissolution rate and permeability enhancement of felodipine [180]. A pharmacokinetic study done by He *et al*., revealed an increase in the area under the drug release curve over free felodipine by more than three folds of lipid nanoparticles developed by effervescent dispersion technique [181]. Sastri and Radha stated that the improvement of oral bioavailability of felodipine incorporated in self nano-emulsifying system in rats [182].

3D printing via FDM was used to develop a felodipine formulation of felodipine/PVA core and PLA shell of different geometries. Cumulative release ranges from 80 -100% were achieved. Various release profiles were seen due to geometrical alteration (and hence surface area) as release is relative to specific surface area to volume ratio [183]. Another study combined hot melt

extrusion and FDM for the development of 3D printed felodipine controlled release tablet. Using different felodipine loadings and printing with variable infill density, Iovanov *et al.* demonstrated sustained felodipine release with increasing drug loading and infill percentage [184]. Another study also used FDM to print felodipine dispersed in multiple polymers. They demonstrated that the release is highly dependent on polymer composition [185]. Additionally, a proof of concept work, demonstrated potential control of felodipine release molecularly dispersed in PVP using inkjet printing [186].

1.7.2 Gelucires

Many grades of gelucire have been used in 3D printing. Either Gelucire® 44/14 or 48/16 in combination with coconut oil was used to formulate suppositories for local action by extrusion 3D printing [23]. The study exposed variable disintegration and release profile, however, it demonstrated that both grades resulted in 80% drug release within 120 min [187]. A melt solidification printing technique was implemented to create an optimum model for a sustained release floating system of ricobendazole using variable ratios of Gelucire® 43/01 and 50/13 [188]. Moreover, Gelucire® 48/16 was printed with other excipients as a chewable tablet for paediatric use using FDM technique [189]. As a proof of concept, the Basit group proved the suitability of lipid-based formulations such as solid self-microemulsifying drug delivery system containing variable gelucires together with Kolliphor® P 188, to be 3D printed in different geometries [190].

1.7.3 Polyethylene glycols (PEGs)

PEGs of different grades have been widely used in 3D printing of pharmaceuticals. PEG 4000 with other polymers was successfully printed by FDM, with drug release associated with the disintegration behaviour of the polymers [185]. A medicated candy-like formulation (Starmix®) was printed with taste masking properties, using PEG 6000 via FDM printing [191]. Zero-order sustained release delivery of antiviral medications was effectively

achieved using FDM printing of a dispersion containing PEG [192]. Another PEG grade (PEG 400) was used to print a topical delivery film by SLA printing technique. Along with its non-irritant properties, PEG enhances *ex-vivo* flux and skin diffusion for topical applications [193]. PEG can also be used as an additive in 3D printing to facilitate filament printability [194].

1.7.3.1 Kollisolv® 8000 (PEG 8000)

Biswal *et al.* demonstrated the enhancement of dissolution of gliclazide when dispersed or physically mixed with PEG 8000, the observed increase in the dissolution is directly proportional to PEG amount [195]. Likewise, Newa *et al.* preliminary study shows promising data in improving solubility, dissolution and bioavailability of ibuprofen [196].

1.7.3.2 Kollisolv® 1450 (PEG 1450)

Krasnyuk *et al.* discussed the advantage of PEG 1500 over other excipients in dissolution enhancement of ampicillin [197]. The same scientific group have confirmed the improvement of solubility and dissolution of indomethacin when incorporated with PEG 1500 [198].

1.7.4 Precirol® ATO5

Das *et al.* demonstrated solubility enhancement and prolongation of drug release when precirol was used in oral preparation of solid lipid nanoparticles [199]. It also has a similar effect when included in transdermal drug delivery systems [200].

In order to support the future of 3D printing of pharmaceuticals, a social study of public perception toward the new technology is needed.

1.8 Public perception toward a new technology

As discussed before regulations of 3D printed medicines are currently developing and, in some areas, remain poorly defined. Public perception towards 3D printed medicines could play a major role in forming policies and this is a reason why it was included in the MHRA recent policy work [174]. Exploring future patients thoughts would help researchers in meeting patients expectations. Multiple guidelines from different international authority have been released recently [173, 174]. Acceptability of a certain technology or product is related to many drivers. Understanding these drivers would facilitate the development of needed products.

1.8.1 General patient perception

The EMA has described acceptability as a patients' overall ability and willingness to use and administer a medicine as intended [201]. The acceptability of medicines is highly related to patient characteristics and drug product features (Figure 1.15) [202]. Failure to achieve patient acceptability can result in poor compliance and further treatment failure [203]. Ternik *et al.* discussed the importance of combining the expertise of academics, manufacturers and regulators to develop acceptable dosage forms [204].

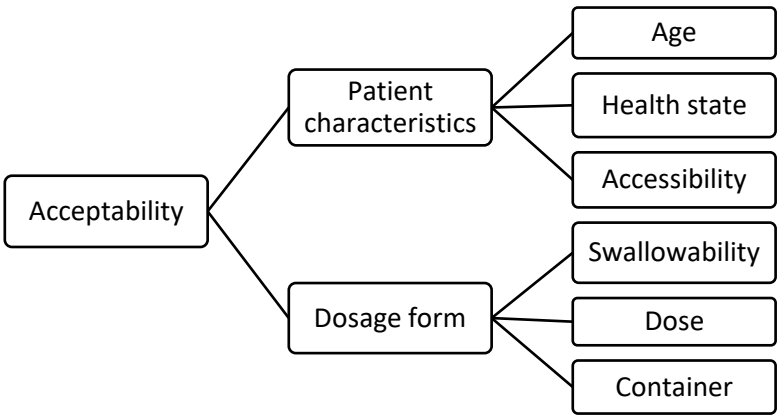


Figure 1.15 Drivers of acceptability of an oral medicine [205]

1.8.2 Patient perception toward 3D printed medicines

Many studies have been performed to understand public perception toward 3D printed medicines in the form of questioners, interviews and focus groups. From a healthcare view, Rautamo *et al.* revealed the possible advantages of 3D printed medicines for paediatric populations of which are possible personalisation of drug dose and dosage form, in addition to precise dose production [206]. Furthermore, participants of multiple acceptability studies preferred printed tablets to be in a disc-shape similar to standard tablets, in an easy swallowable size and of a light colour [139, 207]. Table 1.7 gives examples of acceptability studies performed in variable settings and their results.

Table 1.7 Acceptability studies of pharmaceuticals in general and 3D printed medicines

	Aim of the study	Participants	Study design	Results	Reference
General	To determine the acceptability of solid oral medicines in elderly patients with dysphagia and without	156 participants Age 74±5.7 years 80 female /76 male In community pharmacy	15 questions questionnaire divided in 3 topics (first topic; general health, number of currently used oral medicines, and difficulty in swallowing those medicines if any. Second topic; perception toward different sizes and shapes of tablets and capsules. Third topic; acceptability of other easy to swallow formulations) Open-ended questions regarding participant's impressions toward each given formulation.	The results show that patients with dysphagia symptoms accompanied high acceptability scores in easy to swallow dosage form rather than non-dysphagic patients.	[208]
	Assessment of acceptability (swallowability and palatability) of solid oral medicines	Children Age (0-18)	Five analogous discussions with promoted breakout. A presentation was delivered by a representative from industrial, academic, and regulatory agencies during breakouts.	The need for collaboration between industry, academia, and regulators to assess and develop swallowability and palatability methodologies.	[204]

	To find out the age-appropriate and acceptable solid oral dosage form in paediatrics	132 child/adolescent 6-18 years 8 caregivers In hospital and other community facility	A scaled questionnaire is provided to participants to fill independently. Followed by assessing the willingness to administer various sizes of tablets and capsules without being administered.	Children across ages prefer chewable and orodispersible formulations. On the other hand, multiparticulates appear barely favourable. More than half of children and one third of caregivers expressed that 10 mm diameter tablet is convenient to take.	[209]
3D-printed medicines	To explore the effect of size, shape, and colour of various 3D printed tablets developed via fused deposition modelling on final consumer concerning choosing and swallowing	50 adults 18-45 years	Three concise sessions to examine the willingness of participants to take the printlets, their picking and swallowing ability, and their thoughts about alteration of the size and colour of the printlet. This was documented by facial hedonic scale on a computerised questionnaire. Followed by a semi-structured interview.	Torus printlets beside printlets that resembles ordinary tablet and capsules shape recorded to be easy to pick and swallow. Smaller size printlets seen to be preferred. Additionally, the colour of the prinlet had an effect on participant's perception.	[139]
	To seek the perception and preferences of polypharmacy patients	8 polypharmacy patients	Two semi-structured interviews regarding shapes, colours, polypills, and patient self-designed printlets	Participants preferred printlets that were similar to conventional medicine in shape. The idea of polypill	[207]

	with regard to 3D printed medicines			were felt to be nice because the number of medicines to be taken will be less.	
	To inspect healthcare providers' perception toward 3D printed medicines in paediatrics	19 participants; 8 physicians 6 pharmacists 5 nurses	A presentation about 3D printing followed by focus group discussions	Healthcare providers find many benefits in pharmaceutical manufacturing utilising 3D printing for paediatric patients	[206]

1.9 Conclusion

3D printing is (generally) building a bespoke object layer by layer guided by a computer system. Through the years since its invention in the 1980's, various 3D printing processes have been developed. Stereolithography, material jetting, selective laser sintering, powder-bed fusion, and extrusion are examples of 3D printing techniques. In-order to produce a 3D object, a printable material (ink) is needed to feed a printer. Additive manufacturing has been used in many fields including education, medicine, food, clothes, and so many. In the pharmaceutical field it is been used to manufacture at a small scale diverse delivery systems such as tablets, capsules, implants and polypills. At the time of writing this thesis, Spritam® from Aprecia is the only 3D printed medicine that has been approved by the FDA, in this case for the treatment of epilepsy. 3D printing of medicines can encompass many benefits like low cost, high drug loading and personalisation. In contrast, it possesses some disadvantages such as long printing time and lack of scalability. Other challenges include limited range of printable biocompatible polymers along with absence of a regulatory framework. However, 3D printing of medicine shows superiority over conventional drug manufacturing in formulation complexity, personalisation, and on-demand manufacturing. From an economic prospective, 3D printing can reduce the time and cost resulting from late-stage failure through new drug development.

3D printing of pharmaceutical is promising, considering the advantages over conventional dosage form manufacturing. Development of regulations will promote 3D manufacturing of pharmaceuticals. Along with the adaptation of low cost non-invasive in-process quality control.

1.10 Aims and objectives of this thesis

The aim of the research presented in this thesis is to explore public acceptability of 3D printed medicine as a new technology and to investigate

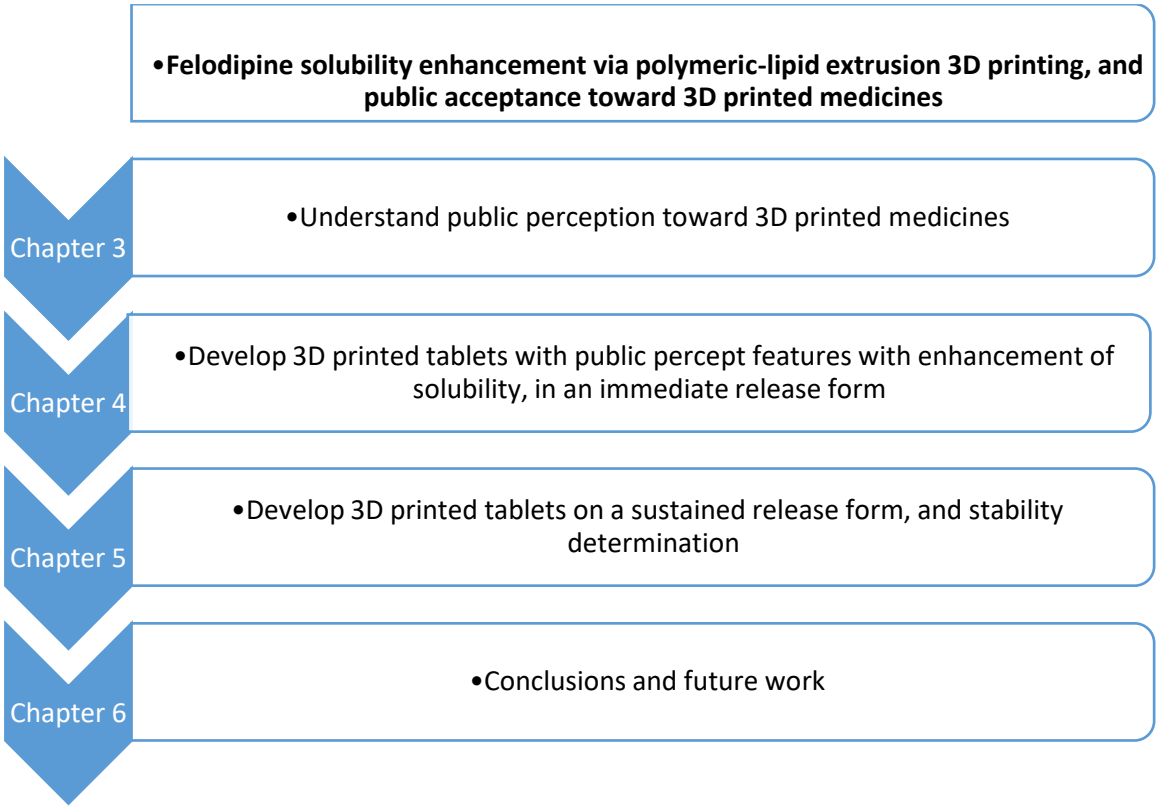
the effect of excipients in the printability and delivery of poorly water soluble drug, felodipine in a lipidic based formulation.

This thesis demonstrates the following objectives:

- Study public perception toward 3D printed medicines
- Develop 3D printed tablets using a lipidic based solid dispersion approach for
    - Immediate release delivery
    - Sustained release delivery
- Analytical testing to confirm the suitability and compatibility of developed formulations
- Evaluate solubility enhancement of felodipine by dissolution testing
- Stability determination of developed formula

1.11 Thesis organisation

The following illustration demonstrates the organisation of this thesis:


•Felodipine solubility enhancement via polymeric-lipid extrusion 3D printing, and public acceptance toward 3D printed medicines
Chapter 3
•Understand public perception toward 3D printed medicines
Chapter 4
•Develop 3D printed tablets with public percept features with enhancement of solubility, in an immediate release form
Chapter 5
•Develop 3D printed tablets on a sustained release form, and stability determination
Chapter 6
•Conclusions and future work

2 Materials and Methods

This chapter combines the methodologies of the social study (acceptability) and laboratory work conducted.

2.1 Materials

2.1.1 Felodipine

Felodipine (Figure 2.1) is a dihydropyridine calcium channel blocker used to treat hypertension through arterial dilatation followed by smooth muscle relaxation [210]. Calcium channel blockers act by inhibiting voltage dependent l-type calcium channels in heart and vascular smooth muscles [211]. Felodipine is lipophilic, crystalline in nature, and classified as class IIB BCS i.e. poor aqueous solubility (Log P 3.8) and high permeability (-4.64) [212-214]. Felodipine *in vivo* also encounters extensive first-pass metabolism, adding to the observed poor bioavailability following oral administration (15-20%) [215]. It has been recorded that felodipine water solubility is 7.2 mg/L (Human Metabolome Database) and 19.7 mg/L (DrugBank) [214], however, a technical report issued by AstraZeneca indicates that felodipine solubility is 0.5 mg/L at 22- 25 °C [216]. Despite the variability in reported values all literature agrees that felodipine has poor aqueous solubility.

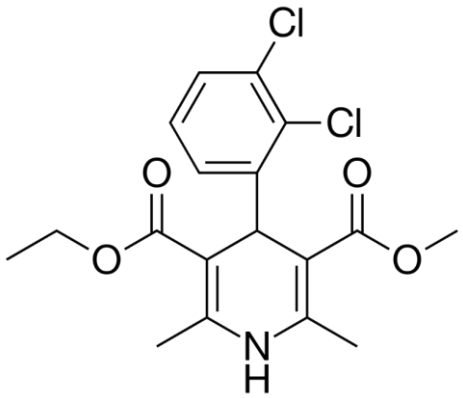


Figure 2.1 Felodipine chemical structure

2.1.2 Gelucires

Gelucires are a group of surface active agents mainly synthesised by esterification of polyethylene glycol and fatty acid. They have a wide range of HLB values and melting points depending on the molecular weight of PEG and fatty acids used which facilitates the selection of an optimised formulation depending on intended use [217]. The type of drug release from gelucire matrices is mainly dependent of gelucire composition; for rapid release, gelucires having PEG esters only are used [218], whilst for prolonged release, gelucires of glycerides only or mixture of glycerides and PEG esters are used [219].

2.1.2.1 Gelucire® 44/14

Gelucire 44/14, also known as Lauroyl Polyoxyl-32 glycerides and Lauroyl Macrogol-32 glycerides, mainly consists of PEG-32 (MW 1500) mono- and diesters of lauric acid and a small fraction of mono, di- and triglycerides. Gelucire® 44/14 is a yellowish-white waxy solid with a melting range 42.5 – 47.5 °C, and HLB of 11. Gelucire® 44/14 is a non-ionic water-dispersible surfactant that primarily used to solubilise poorly water soluble actives and further enhance the bioavailability. When used as a single excipient, it self-emulsifies producing a microemulsion (fine dispersion). It also has wetting properties and works as a binder in melt processes. Gelucires are approved to

be used in pharmaceutical products [220]. Many studies have demonstrated the beneficial effects of implementing Gelucire® 44/14 in various pharmaceutical formulations [221-224].

2.1.2.2 Gelucire® 50/13

Stearoyl polyoxyl-32 glycerides, FDA names it PEG-32 hydrogenated palm glycerides. It comprises mono, di- and triglycerides and PEG-32 (MW 1500) mono- and diesters of palmitic (C_{16}) and stearic (C_{18}) acids with the following molecular formula;

Glyceryl esters: $C_3H_5O_3 . [– CO – (CH_2)_n – CH_3]_{1,2 \text{ or } 3}$

PEG-32 esters: $C_nH_{2n+1}O_2 . (OC_2H_4)_{32} H$

with n = 10 to 16 (personal communication, Gattefossé)

It is supplied as white pellets with a melting range of 46 - 51 °C, and an HLB of 11. Similar to Gelucire® 44/14, it is a non-ionic water dispersible surfactant that can form a fine dispersion (microemulsion) upon exposure to aqueous media. It also shares the same characteristics of Gelucire® 44/14 of enhancing the solubility of poorly water soluble APIs and lipid binding activity. Additionally, Gelucire® 50/13 act as drug release modulator (personal communication, Gattefossé). It has been established that Gelucire® 50/13 increases the dissolution rate via inclusion in various formulations of variable APIs [225-229].

2.1.3 Polyethylene glycols (PEGs)

Polyethylene glycols (Figure 2.2) are partially crystalline, highly water soluble, non-toxic polymers. Due to their good solubilising efficiency, wetting and surface active properties, they have been widely used in solid dispersion formulations [230]. It has been reported that PEGs enhance the solubility of poorly water soluble APIs [231], as well as dissolution, wettability and reduces

drug crystallisation [232]. PEG is hence an efficacy enhancers [233] and stabilising agent [234]. PEG absorption is dependent on molecular weight, the smaller the molecular weight the higher the absorption. Low melting point properties is advantageous in melting manufacturing methods, such as HME [235]. Both PEGs used here Kollisolv® 8000 (PEG 8000) and Kollisolv® 1450 (PEG 1450), are white waxy solids and have an average molecular weight of 7000-9000 or 1305-1595 g/mol respectively [236].

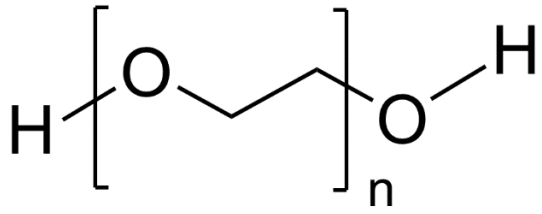


Figure 2.2 Chemical structure of polyethylene glycol (ChemDraw)

2.1.4 Precirol® ATO 5

Precirol® ATO 5 is a glyceryl distearate, which consists of a combination of palmitic and stearic acids esters, where the diester portion predominate. Precirol is a white powder, with melting range 50 – 60 °C and HLB of 2. Precirol categorised as GRAS (Generally Recognised As Safe) and has been used in pharmaceuticals. It is used for its features such as; a modified release matrix, a taste masking agent, and as a lubricant [237].

2.2 Methods

2.2.1 Social study

Social science is framed by epistemology; the way and degree of knowledge and ontology; reality [238]. Social studies rely on appropriate choice of methodologies which is key to generation of knowledge. Methodology defined as the way to explain rationale of selecting a specific research method. Practical considerations such as time, money and logistics have role in selecting research methods in addition to purist methodological ideologies.

Qualitative research can be relatively costly and time consuming compared to quantitative research despite of the smaller sample size [239].

2.2.1.1 Qualitative research

Qualitative research, often described as interpretivist, seeks to demonstrate the understanding of interpretations of people, and constructionist as its believed that the created understanding is a result of interaction between situation actors rather than absolute structure [240]. Qualitative studies often use interviews and/or focus group methodologies but can also include observational approaches [239].

Qualitative interviews

Qualitative interviews are either structured, semi-structured or unstructured. Researchers seek to ask open-ended questions in a flexible way to understand people experiences [239, 241].

Unstructured interviews

Resembles a conversation where the interviewer uses memory or a number of self-prompts to ask questions, giving the interviewee space to answer openly, with further questions developing based on interviewee responses [239, 242].

Semi-structured interview

A more guided interview of a specific topic and questions that does not have to be in order. Nonetheless, the interviewee can give their feedback freely in the direction they want [239, 243].

Structured interview

A very strict interview technique that does not usually allow for deviation from the proposed questions and is often used where individual's expression of choice is required that cannot be pre-categorised for assessment by methods such as surveys [239, 244].

Focus groups

A form of interviews where more than one person (usually more than three) are interviewed together at the same time, usually in a semi-structured format. Focus groups combine the opportunity to ask questions to a number of participants at once, also to enrich this with shared and discussed experiences within the group [239, 245].

Focus groups can be cheaper and less time consuming than individual interviews, however analysis can be considerably more difficult. They also have an advantage over interviews in that participants can add on each other's ideas, which enriches the discussion [246].

2.2.1.2 Quantitative research

Quantitative research expresses objectivism as the existence of social reality in a form of object that does not affected by people's perceptions, where the reality can be measured systematically. In quantitative studies, researchers tend to test hypotheses to determine causality that refers to difficulty in connecting causes to variable factors [247]. The most abundant data gathering method in social sciences is survey research including questionnaires and structured interviews [239].

Questionnaires

A relatively quick and cost effective method to examine multiple questions standardised with minimum intervention from the researcher during data collection time [239].

Structured interviews

Also known as standardised interview where a scheduled interview of specific words and uniform delivery of questions is required. Following the same structure in each interview within the study is crucial to get reliable results [239, 248].

2.2.1.3 Qualitative vs. quantitative research methodologies

The main difference between these methods is that qualitative research tends to use words and their explanations while quantitative methods is based on numbers that are accurately collected and statistically analysed. Another difference is that qualitative studies represent participant's perspective, in contrast quantitative methods require the researcher to lead and represent their views. Additionally, in qualitative methods researchers develop theories from gathered data in an inductive way, in contrary, in quantitative research a deductive manner is used by researchers with a hypothesis in mind and test its validity. Further, qualitative research concentrates on deep understanding of meaning with detailed explanation, whilst, quantitative research tends to describe the behaviour pattern from a large-scale sample in an unambiguous way. Qualitative methods are usually not intended to be generalisable while quantitative research seeks to produce generalisable understanding [247].

Qualitative and quantitative methodologies can be used together in-parallel or sequentially. Where the multiple methods are utilised to explore the same question, this is known as mixed methods research. Where questions are linked but not exactly the same this is referred to as multiple methods [239].

2.2.1.4 Sampling

Sampling in social research is classified as probability and non-probability sampling. Probability sampling describes the process of sample selection with each member of a population having an equal chance to be selected with a view to ensuring representation of the population. Simple random sampling, systematic sampling and stratified random sampling are examples of probability sampling. Non-probability sampling accounts for a systematic non-random sampling where members of population have higher chances than others to be selected. Non-probability sampling can be subdivided into purposive, quota, and convenience sampling. Convenience sampling is a non-probability sampling where participants are proximate, available and willing to participate. Generalisation is generally not possible using this sampling method and mostly used in qualitative studies and pilot testing of quantitative studies. Snowball sampling is a type of convenience sampling, where initial sample is selected conveniently, and participants invite others then after [239, 249].

2.2.1.5 Choice of methodology

The aim of the study is to explore the public thoughts of this emerging area of pharmaceutical science. As this is exploratory in nature and non-hypothesis testing, I chose to use a qualitative methodology. Non-probability convenience sampling was used to maximise data acquisition.

Detailed study methodology is further discussed in the next chapter (Chapter 3).

2.2.2 Laboratory work

2.2.2.1 Extrusion 3D printing

As previously mentioned, extrusion 3D printing can be in different forms. Depending on the final product requirement together with the material used,

selection of the extrusion technique is important. A BIO X (Cellink) printer (Figure 2.3) was chosen in this study. This has a variable compatible printhead to facilitate a range of applications such photocuring, high resolution, thermoplastic, drop-on-demand and in-process control [250].

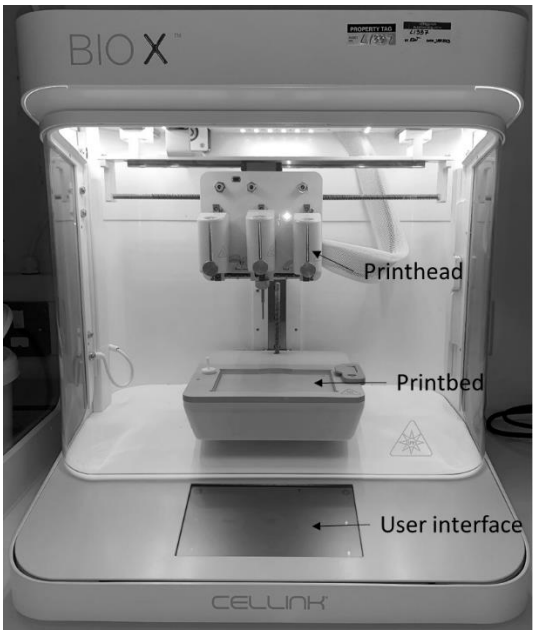


Figure 2.3 BIO X 3D printer

3D printers necessitate the availability of a 3D model to print. A software such as TincerCAD® was used here to create an .stl file. Such models need to be sliced to many layers in the form of G-code in order to be printed. BIO X has a user-friendly built-in software for slicing. Moreover, printhead and printbed temperature, pressure, infill pattern and density are easily selected via the user interface (Figure 2.4).

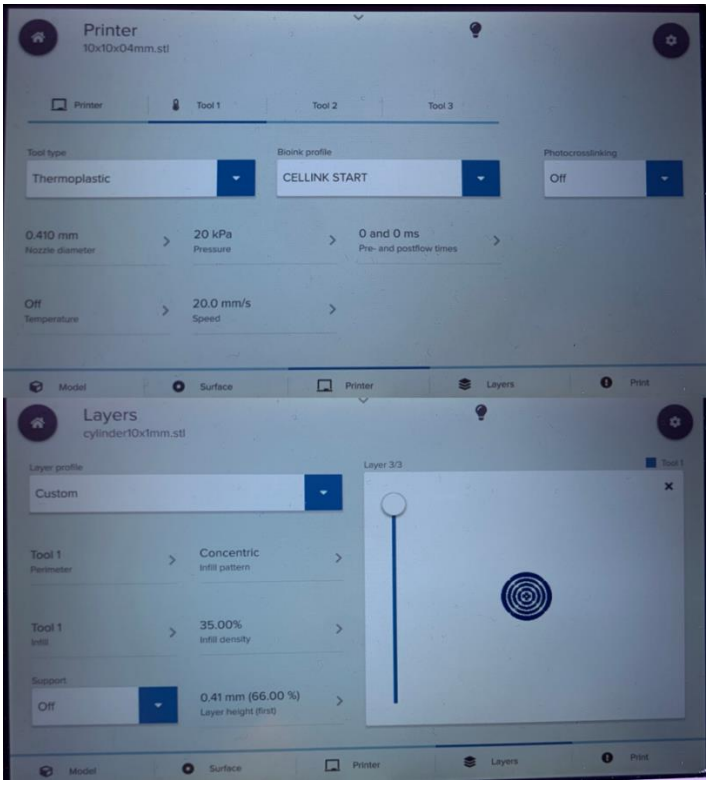


Figure 2.4 Image showing the BIO X user interface

2.2.2.2 Drop Shape Analyser (DSA)

DSA is a technique to measure drop shape by the concept of interfacial tension. The drop shape is created by the balance of two forces; surface tension and external forces such as gravity [251]. DSA is reflecting of contact angle, which is the angle created in the margin between material interface and surface [252]. Printing of semisolid ink would be affected by the force created by the surface where it prints; hence, DSA was applied in this study to understand and select materials to print over.

2.2.2.3 Thermographic analysis (TGA)

Thermographic analysis is considered a rapid and straightforward analysis technique. It is generally destructive, as it heats the tested material [253]. It measures thermal chemical and physical stability of materials by studying the weight changes (e.g. due to water loss or degradation) in relation to

temperature increase. The instrument has a highly sensitive thermostatically isolated balance located above a programmable platinum furnace to thermally control the sample. An additional infrared spectrometer could be equipped with TGA to analyse any generated gases from sample degradation [254-256]. Infrared thermography (IRT) applies the addition of infrared camera to detect emitted infrared energy from an object. An image then created based on the detector optically or thermally to give an indication of arise substances [257]. Since temperature is used to 3D print in this study, determination of possible material changes or degradation was relevant.

2.2.2.4 Differential scanning calorimetry (DSC)

The fundamental principal of DSC is measuring thermal energy changes of a sample in reference to an inert material in accordance to temperature changes [258]. DSC is commonly used in exploration, comparison, and analysis of materials and products. Glass transition, crystallisation, phase changes, melting behaviour and stability could be gathered from DSC data [259]. Heat-flux DSC where sample and empty reference pans are expose to thermal energy of the same source. The difference of heat flow between sample and reference then recorded [260]. DSC is used in this study to determine the thermal changes on excipients upon mixing and printing, along with assessing felodipine inclusion in the matrices and possible amorphisation.

2.2.2.5 Attenuated Fourier transform infra-red spectroscopy (ATR-FTIR)

Attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy is a non-destructive, rapid, easy, cost-effective technique [261]. It relies on functional group identification within molecules. Upon exposure to certain light wavelength, vibration of chemical groups occur in the form of bond stretching or bending. Furthermore, the vibration with its intensity then plotted against the frequency of light that it had an exposure to in the form of absorption or transmission. Fingerprint regions are part of FTIR spectrum that is unique to

specific compound [262, 263]. FTIR also used quantitatively to determine mechanism of bonding between compounds [264]. FTIR was used in this study due its capability to recognise molecular degradation and chemical bonding.

2.2.2.6 X-ray powder diffraction (XRPD)

X-ray powder diffraction is a non-destructive, quantitative measure and one of the techniques that prominently used to characterise ordered (crystalline) solids of variable origins including pharmaceuticals. Bragg's peaks represent diffraction of multiple peaks from a crystalline compound. An internally disordered amorphous material which has no long-range molecular order will lack characteristic diffraction peaks [265, 266]. XRPD has the ability to determine polymorphism [267]. The amount of data gathered from x-ray diffraction is dependent on the sample (degree of crystallinity, structure imperfection, complexity) and quality of instrument [268]. pXRD was useful in this study, as amorphisation and degree of crystallinity would affect felodipine solubility and further drug release.

2.2.2.7 Scanning Electron Microscopy (SEM)/ Energy Dispersive Spectroscopy (EDS)

Scanning electron microscope is commonly used as a high-resolution imaging technique of materials morphology and microstructure [269, 270]. It is widely used in research and development along with industrial labs [271]. In SEM, samples are exposed to a low energy electron beam where various interaction occur with the sample surface and near surface regions. As a result of such interactions, photons and electrons emission arise at sample surface or nearby, represented as signals which can be collected by a detector (x-ray, backscattered electron imaging, and others) [272]. For a non-conductive sample, the radiated electrons would stay within the sample and create charges that could distort the image; hence, a thin conductive material such

as gold is usually applied on non-conductive sample surfaces [273]. Alternatively a variable pressure SEM can be employed [274].

Energy dispersive spectroscopy also known as energy dispersive X-ray (EDX) spectroscopy, is an elementally sensitive mode of SEM. It uses an electron beam that creates an x-ray signal to identify and quantify chemical elements in a detectable limit of approximately 1% per weight. It can be used for both surface and near bulk measurement, however, the electrons have a limited capacity of penetration to the bulk (up to 1 μm). Element distribution and area enrichment within the sample can be mapped. [275-277]. Carbon is usually implemented to coat non-conductive samples for EDS analysis due to its low atomic number [278] and hence very weak x-ray emission [279].

2.2.2.8 Raman spectroscopy

Raman spectroscopy (RS) is based on detection of vibrational mode of molecules linked to polarisability rather than dipole moment (as in FTIR) [280, 281]. Each chemical component has a characteristics reflection wavelength that gives chemical fingerprints to specific materials [282, 283]. To map a sample hyperspectral chemical images can be built by collecting up to thousands Raman spectra from different points of a sample to create a chemical map that represent site and amount of variable sample compositions. Raman is considered a non-destructive technique [283].

2.2.2.9 Tablet Friability

Friability testing is included in the United States (US) Pharmacopeia together with the European and Japanese Pharmacopoeias and must be passed for most marketed tablets. Variable dosage forms such as effervescent and chewable tablets have other specifications [284]. The test aims to simulate the external environment of packaging and shipping that could affect tablet integrity and appearance. The acceptance criteria of friability according to US Pharmacopeia is no more of 1% of tablet weight following a set amount of

physical challenges [285]. Cracking and loss of tablet weight would affect the total delivered dose, which can reduce therapeutic outcomes.

2.2.2.10 Dissolution testing: In-vitro drug release

In-vitro drug release which also known as dissolution testing, is an analytical technique used to test and provide quality control on a final drug product to measure the rate and extent of drug release in a defined media. It is applicable to many dosage forms including tablets, capsules, ointments and other pharmaceutical formulations. Dissolution testing is required during medicines development to generate a defined drug release profile, additional to be an essential test for quality control of developed formulation to insure consistency between batches [286]. Continuous revision of products monographs of different dosage forms are made periodically to meet their requirements [287]. Drug monographs which provide detailed information about crucial quality elements of a medicine are usually generated by legal authorities. A monograph of other than injectables must contain the following; documentation of procedure, an assay method to determine the content of active ingredient, impurities detection assay and dissolution method to measure the release rate of a drug from a dosage form [288]. The felodipine extended release tablet monograph was used later in this research with minor alteration [289]. To my knowledge, all oral felodipine drug products are developed in sustained release form (Table 2.1).

Table 2.1 Felodipine marketed products (UK), (all are available in 2.5, 5, and 10 mg strength)

Product name	UK Supplier
Folpik XL Prolonged Release Tablets	Teva UK Ltd
PLENDIL modified-release tablets	AstraZeneca UK Ltd
Neofel XL	Kent Pharma UK Ltd
Vascalpha modified-release tablets	Accord UK Ltd
Cardioplen XL Prolonged Release Tablets	Chiesi Limited
Delofine XL Prolonged-Release Tablets	Morningside Healthcare Ltd
Felotens XL Prolonged Release Tablets	Genus Pharmaceuticals
Parmid XL Prolonged-release Tablets	Sandoz Limited
Pinefeld XL (felodipine) Tablets	Tillomed Laboratories Ltd

High performance liquid chromatography (HPLC)

High performance liquid chromatography is widely used as a composition analysis tool in pharmaceutical research and development due to its high sensitivity, versatility and relatively low cost [290-292]. HPLC is based on passing a liquid through stationary phase. The liquid mobile phase is typically composed of organic solvents and water with the analyte in question. While the stationary phase is a stainless-steel tube packed with appropriately chemically treated silica able to selectively interact with components of the analyte. The composition resolution is dependent on the particle size of silica and its chemical functionality. Versatile column length and silica specification are available. Relying on hydrophobicity/charge of the material filling the column four different types of HPLC are used; reverse phase, normal phase,

hydrophilic interaction and ion chromatography [293]. Sample is injected into the column with the aid of mobile phase. After sample separation by a differential migration process, a suitable detector is used to collect the gathered data with temporal resolution [294]. For example, if UV absorbance is used each material can be identified by its specific absorbance wavelength at a time in which it elutes from the column. As reported in literature, felodipine has multiple possible measuring wavelengths (238 nm, 275 nm, 364 nm, 381 nm) which was, for example, demonstrated by Pandey and co-workers, which also showed that pH would affect the maximum absorbance wavelength [295-297]. In this research after testing different wavelengths, 362 nm was used as this gave the sharpest peaks.

The following chapters will discuss the instrument specifications and procedures used for each of the methods described above.

3 Public acceptance of 3D printed medicines

Social pharmacy study is discussed in this Chapter.

3.1 Introduction

3.1.1 Aim

To explore patient public perceptions and acceptability of 3D printed medicines to aid future policy decisions using a qualitative approach.

3.1.2 Background

3D printing as a new pharmaceutical manufacturing technology, the acceptability of 3D printed medicines has not yet been assessed. Understanding patient acceptability would enable 3D printed medicines to be evaluated from a consumer perspective. Determining whether future patients are receptive to medicines developed through significantly different manufacturing practices play an important role in shaping future policy. These perspectives may inform the implementation of 3D printing technology on a wider scale than currently incorporated and may support future decisions in the UK by the MHRA when the evidence base is set.

Acceptability as defined by the European Medicines Agency (EMA) guidelines is ‘the overall ability and willingness of the patient to use and its caregiver to administer the medicine as intended’ [201]. Specific characteristics of patient (age, accessibility, health state) together with pharmaceutical product aspects (swallowability, dose, container) deliberated to drive the acceptability [202].

3.2 Methodology

3.2.1 Study design

In this project, in-person semi-structured focus groups (n=5) were conducted on members of the public. Those focus groups were conducted at the University of Nottingham, UK. The focus groups each contained between 2 and 5 participants. All focus groups were audio recorded and transcribed verbatim. Ethical approval was attained from the School of Pharmacy research ethics committee (Ref-009/2022).

3.2.2 Sample and recruitment

The methods in this study was guided by the Consolidation Criteria for Reporting Qualitative Research (COREQ) [298]. Convenience and snowball sampling were used to recruit participants.

3.2.3 Procedure

Recruitment was via professional networks, public adverts, personal contacts and convenience sampling. Participants who showed a willingness to participate in the study was given a participant information sheet and consent form (Chapter appendix: supplementary information). Following consent, a member of the research team communicated with participants to arrange the focus group. The focus group topic guide was created with reference to the literature on 3D printed medicines designs for scope. Given the novelty of the technology, a background presentation and indicative samples were prepared and utilised mid-way through the focus groups to support understanding as required (Figure 3.1).

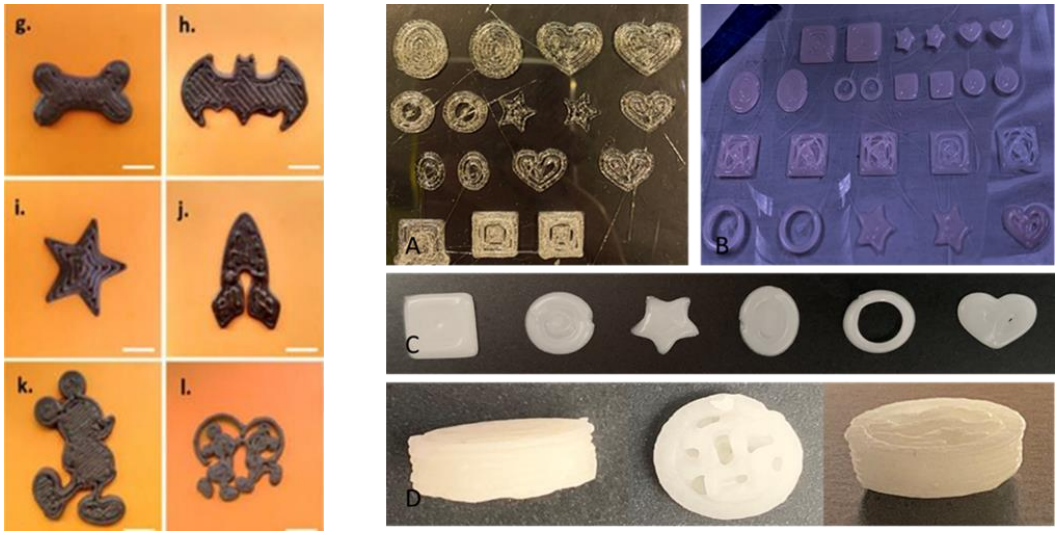


Figure 3.1 3D printed samples presented at the focus groups (left side; from literature (letters represents different shapes) [299], right side; in-home printed and presented physically; A) Eudragit® RL PO, B) coloured Polycaprolactone, C) Polycaprolactone, D))

Participants were informed of the goal of the research was to seek their thoughts about 3D printed medicines. The focus group agenda included an introductory statement to give a brief knowledge about the session. Followed by questioning the participants about their previous knowledge on 3D printing in general. Focus groups were concluded by showing and discussing samples of pre-printed medicine-free sample tablets.

Detailed notes were collected throughout the focus group to augment the recorded transcripts. Audio recordings were transcribed verbatim using University of Nottingham Automated transcription service. The transcripts were checked and amended as necessary for accuracy.

3.2.4 Data analysis

Braun and Clarke's six-step process was applied to the verbatim transcripts for thematic analysis [300]. Those steps included: data familiarity, codes initiation, themes creation, themes reviewing, themes definition, and then writing-up. The themes of this study were generated from an inductive preliminary data-driven approach, not from a pre-defined framework. An

inductive thematic analysis was selected as limited data is available on this research topic.

NVivo 12 (QSR International) was used to organise and analyse the gathered data.

3.3 Materials

Printed samples were designed by Tinckercad® (online 3D modeling program, Autodesk) and printed using extrusion based BioX printer (Cellink, Sweden). Polycaprolactone (PCL), Eudragit® RL PO and Gelucire® 50/13 were selected as ink for their printability and visual appearance. A red food colorant was added to some of the PCL tablets to develop different coloured printlets. Various shapes including star, heart, torus, oval, cube, and cylindrical shaped tablets were printed with dimensions in the range 5-12 mm.

3.4 Results

3.4.1 Demographics

The final sample formed a range of participant characteristics (Table 3.1), forming a diverse selection of perspectives during focus group sessions.

Table 3.1 Participants Characteristics

Focus group	Gender	Characteristic
1	Male (PA)	Member of the Public
	Female (PB)	Member of the Public
	Female (PC)	Member of the Public
2	Male (PD)	Postgraduate Physiotherapy Student
	Male (PE)	Undergraduate Nutrition Student
	Female (PF)	Undergraduate Pharmacy Student
3	Male (PG)	Postgraduate Physics Student
	Male (PH)	Undergraduate Engineering Student
	Male (PI)	Undergraduate Medicine Student
4	Male (PJ)	Undergraduate Management Student
	Female (PK)	Undergraduate Nursing Student
5	Female (PL)	Undergraduate Veterinary Medicine Student
	Female (PM)	Postgraduate Nutrition and Dietetics Student
	Male (PN)	Member of the Public
	Female (PO)	Member of the Public
	Male (PP)	Postgraduate Nutritional Sciences Student

3.4.2 Thematic analysis

Thematic analysis yielded four overarching themes, all reflective of perspectives from members of the public on the 3D printing of medicines (Table 3.2). Pseudonym initials were used to identify participants relative to their characteristics to aid the interpretation of quotes.

Table 3.2 Themes and sub-themes generated

Themes	Sub-themes
Safety of 3D printing and 3D printed medicines	Novel tablets produced
	Concerns about misuse of 3D printing technology
	Drug profile impact
Personalisation and adjustment of medicines	Personalisation of physical tablet features
	Public acceptance of 3D-printed medicines
	Tailoring drug profile to patients
Economic and societal impact of 3D printed medicines	Environmental considerations for 3D printing and 3D printed medicines
	Cost related to production of 3D printed medicines
Governance of 3D-printed medicines	General manufacturing, maintenance, training and use of 3D printers
	Policy, regulation and privacy considerations

3.4.2.1 Safety of 3D printing and 3D printed medicines

Both prior to and during the provision of 3D printed placebo tablets, participants discussed the safety implications of 3D printed medicines compared with traditionally manufactured pharmaceuticals. The primary discussions reflected safety implications in reference to new tablet manufacturing opportunities, drug release profile considerations, and the potential for misuse of printed medications.

Novelty of tablets produced

The majority of participants noted dysphagia concerns regarding novel tablet shapes.

"It's got to be a choking hazard I would say [PF: yeah], yeah looking at that." F2 PE.

When queried about example shapes of concern, the most notable concern was star-shaped tablets, though cartoon character-shaped tablets were also highlighted as potentially problematic particularly with respect to swallowing issues.

"I think, like, if this looked like a star that would maybe stick somewhere" F2 PD.

"Mickey Mouse looks like a bit of a challenge" F2 PE.

The novel tablet shapes were also viewed by participants to potentially trivialise medications overall. Of particular concern was medicated chocolate developed through 3D printing techniques, where potential misinterpretation of medication as sweets was highlighted as a safety concern.

"Yeah, I don't like the idea of it for children, for it to be perceived as a chocolate as a sweet when it's medicine. I can understand that you might need to tempt children, and it may be that it is chocolate-coated in that smell or whatever, but to have it like Batman or Mickey Mouse or whatever else you know, I think there is a great risk involved in them in thinking that they are sweets or others thinking that they are when they're medicine" F5 PO.

Other participants, however, were receptive of 3D printed medicines using chocolate presuming appropriate safety precautions were put in place,

including storage, packaging and supervision in the event of the medication being intended for children.

"… but if it was kept in like a safe place and like good like, packaging, good like packaging, then I think it could be a good idea." F2 PF.

Drug profile impact

Participants also elaborated on public safety in reference to the drugs being printed and held a number of concerns around the dosage accuracy of 3D printed medicines.

"and also you get, well, you know sometimes you might say if the dose changes as they age or something, how do you then work out, you know, is it a Mickey Mouse minus a foot" F5 PM.

In reference to 3D printed medicines, one participant suggested that crumbling or melting of medicines may lead to inaccuracies in dosages provided to patients.

"You know, if, if the tablets or the medical, the chocolate even sort of crumbles or melts, it's going to be difficult to sort of ensure that the entire dosage of the tablet is fully, fully consumed, which could lead to you know lack of well, like a dosage which could lead to you know increased symptoms" F3 PG.

Several participants were also concerned about whether 3D printed medicines were safe from a medical perspective, including the risks associated with allergens and side effects of 3D printed medicines.

"Can it cause allergies? Can it cause any reactions? I guess maybe" F4 PK.

"Have these side effects? Because … if it's a licenced drug, it's very clear what the side effects are because it's standardised." F3 PI.

Other queries regarding the safety of 3D printed medicines revolved around expiration dates, with some focus group discussions queried about shelf-life differences with traditional versus 3D printed medicines.

"Do they have the like the same shelf-life or like an extended shelf-life" F5 PP.

These queries may reflect participant concerns regarding the degradation of medicine produced by 3D printed techniques, as discussions took place regarding the impact of heat from the printers.

"So with regards to sort of thyroid hormone medicine obviously, is, is that more of a sort of organic thing … it's in a hospital. You've got a smaller 3D printer, that's possibly fluctuations and heat. Could say the, the hormone … the protein be denatured by the heat of the, the 3D printer …" F3 PI.

Less considered, but still discussed, was safety in reference to the physical characteristics of tablets, and when provided with placebo examples of 3D printed medicines one participant noted the imperfect manufacturing process observed across medicine printed through the same design and technique.

"I'm looking at it and it looks like very amateur compared to like a pill looks like a professional thing so I would be worried looking at it definitely" F3 PG.

Having been provided an opportunity to touch the placebo tablet designs, one participant further elaborated on the safety of materials used to 3D print medicines, implicating the adhesive nature of the placebo prompts as increasing the potential for overdosing.

"You know an issue with these, perhaps you know I maybe feel that the hearts and they get sort of like stuck in each other. You may have two by accident or something like that" F2 PE.

Misuse of 3D printing technology for medicines

Though less frequently implicated, multiple focus group discussions mentioned the risk of making medication manufacturing equipment readily available to the public. Of particular concern was enabling people to print prescription medication from their home.

"Yeah, I think that's, that's like the main concern. If it's replacing the over the counter medicine then it makes sense because it's easily accessible, the over the counter medicine, and then you can have it 3D printed which make it easier. But if it's not replacing that, if it's replacing the medicine that needs prescription, then making it easy accessible is, is a little bit concerning here, especially if you have kids in the home, especially if you have someone who was, I don't know, some types of medicine makes person addicted to it, so we don't want him to have too many of them." F2 PD.

More negatively, one participant mentioned the divergence of intended medication supplies as concerning from a safety perspective.

"You'd be selling them on street corners, that's the problem." F1 PB.

Another participant viewed having 3D printers situated in hospitals or pharmacies may improve safety associated with the dosage a patient is able to receive.

"Yeah, of course, if it's for example at home or in the street A person can have too many of the medicine could affect them, so the, for dosage control, it could be better in, in like hospitals or pharmacies." F2 PD.

In some, several concerns elaborated on the potential for misuse because of a deviation in expected medication use, with one view even reflecting animal welfare concerns from 3D printed medicines being produced.

"Yeah, and they [children] might share them out. Take them out to share with the friends …..: [even] feed them to the dog." F1 PB.

3.4.2.2 Personalisation and adjustment of medicines

The ability to personalise physical characteristics of tablets proved a key discussion point and tailoring of drug profiles to patients was also a frequent talking point.

Personalisation of physical tablet features

A focal topic when discussing the potential for 3D printing was personalising the physical properties of medication. Participants favoured printed tablets to be similar to conventional tablet forms, preferring round and cylindrical shapes.

*"Psychologically tablets to me have to be a certain shape, otherwise I don't think they are a tablet, but that's because they've always been a certain shape *laughs*" F1 PA.*

When discussing the physical appearance of 3D printed tablets, participants preferred opaque tablets rather than transparent ones.

"Well, I like what we were talking about before, like, I think we agreed that it was kind of like we wanted it more opaque" F2 PF.

On the other hand, some found it more useful to have a variety of medicines shapes and colours especially for elderly people, as the only way to differentiate a medicine from another is their physical appearance.

"I mean, it's good again for older people to actually differentiate what kind of tablets it is, because most of them don't really know what the name is, but

they know what the shape of colour is. So if it's a different shape then that's great that would be able to make sure that it's the right tablet to take" F4 PK.

From size prospective, participants described that printed tablets should be acceptable in size, not too big to be difficult to swallow, nor too small where it could easily be lost.

"I mean, I think they're about a centimetre big credit to the thinking, but that I mean, the bigger the tablets is, the harder it is to swallow. So maybe just keep in mind instead of letting us space be into between, they just make it smaller" F4PK.

"We didn't want it like too small and too fiddly" F2PF.

Tailoring drug profile to patients

Individualising drug release profiles according to patient's need was mentioned from different perspective. Such tailoring comes from the advantages of 3D printing to easily modify the size and shape with a button click, together with minor ink alteration to modify the release pattern. Participants noted the possibility of having multiple medicines in one tablet.

"you can do stuff with three different things that you couldn't do with traditional manufacturing methods, so it's interesting and it's very good and exciting" F2 PD.

Having the opportunity to change the dose without changing the size was similarly labelled.

"It could be quite an effective way to change the dosage of the individual tablets whilst keeping the size the same" F2 PE.

Control of the release profile was noted via utilisation of the unique abilities of 3D printing through material engineering and complex geometrical designs.

“Could, could this be used, perhaps, to, err, sort of you have one drug in the middle, and then you've got others sort of around that. So that then as it's digested, they release at different intervals” F2 PE.

Modifying the medicine excipients to meet patient’s need in case of allergy and intolerance was described at focus groups.

“in principle, you know it sounds great. If someone's allergic to something, you know you can find the specific ingredient components that that person is not allergic to, you know, and therefore prescribing the medication that you know would best suit that individual” F5 PN.

3.4.2.3 Public acceptance of 3D printed medicines

Most of the participants expressed acceptance of 3D printed medicines if they were from licensed source. Even the novel shapes amazed them. Participants compared them to some marketed products like food supplements. Others accepted them since they are easily administered.

“It seems ok, I don't think it's a problem. There's already some stuff like this like the multi vitamins for kids, they sell it in supermarkets, it's almost similar, it's like, looks the same” F2 PD.

“If it was licenced I don't think I would have any issue. It was whoever could give me a normal one or 3D printer one with which every easiest for them. I'd be pretty indifferent if it was unlicensed” F3 PH.

“I like them. They look amazing” F4 PK.

It was noted that through the course of the focus groups, participant acceptability of 3D printed medicines increased. When considering wider public acceptability, participants suggested brief knowledge and general education to make the public aware of such technology before it's been available in the market. Some were with for TV advertisements and some against.

"Think just raising awareness that it kind of exists. It's in it's in the works and it should be targeted to come out in the next few years just to make everyone feel normal about it. Because if we released it right now with no previous knowledge on it, people would be very, very sceptical of it" F4 PK.

[PK] "Scenario, it could be integrated if it's like if it's children specific, it could be integrated into like their TV shows that they most commonly watch like they'll see administration, but like in a fun way it shouldn't be portrayed enough in a very professional kind of way just to get people to understand that. [PJ] it's more common, I think, but that's on the advertisement". [PK] "I don't I. I would disagree with that like I did not want to like advertise children having pills on TV. No like it's just kind of not the thing I would like to show children" F4 PJ.

Novel 3D printed medicines were stated as potentially enticing to young people who do not wish to take a medicine.

"Um, but I think it's very creative. The way, like they're making lots of different shapes that could be as you said appealing for children, which is good" F2 PD.

3.4.2.4 Economic and societal impact of 3D printed medicines

Environmental issues took the majority of the conversation within this theme, socioeconomic consequences of 3D printed medicine and cost of 3D printing of medicines also had a significant part of the talk in distinct directions.

Environmental considerations for 3D printing and 3D printed medicines

Participants mentioned the sort of waste in materials and packaging of conventional medicines that could be reduced with 3D printing, moreover, reducing the overall cost related to both materials and packaging.

"They've only got to look at the money they save on the wastage" F1 PB.

From a logistics perspective, 3D printed medicine was identified as advantageous for people living in rural areas where supply is limited, along with medicines that have a short shelf life or are rarely used medicines.

"You can easily perhaps tailor some drugs that normally you would need to. If it's something really specific for like a specific illness or something you know you'd have to order a certain drug in or something from somewhere. This could be a quick way to against it, like you say. Any transport costs, manufacturing costs there and make it all on site in the small dose that you need for a specific patient" F3 PH.

Cost related to production of 3D printed medicines

Across all focus groups, the cost of 3D printed medicines was mentioned as a concern. Discussions around cost concerns primarily related to 3D printing being a new technology, the high operational energy requirements, the materials used, time-related costs, and the cost of the printers themselves.

"I think that would be my sort of initial reaction is if I think of 3D printing, I think of like bespoke, and then obviously always with bespoke comes like a high price. Yeah" F2 PE.

"printers generally use quite a lot of power, so they have a lot of heat as well, so a lot of waste energy coming out of the actual" F2 PH.

“so it's not faster and it cost more” F4 PK.

“Whether you can actually purchase the printer, like if you can afford the printer, but like most stuff like most institutions, probably can” F4 PJ.

The cost related to infrastructure of 3D printed medicines in society was also part of the discussion. If the price limits the availability everywhere, or the maintenance cost would do so.

3.4.2.5 Governance of 3D medicines

Various interventions related to physical location of the 3D printer for example whether in the home or the point of care. Further policy and regulation considerations were discussed within the focus groups.

General manufacturing, maintenance, training and use of 3D printers

Dealing with potentially complex equipment raised many concerns. Participants discussed technical concerns ranging from unintended overprinting to the printing of incorrect doses.

“Because we get this with all types of machines like normal printers and everything, at some point it can do something wrong, and in this case you're taking medicine, which is something very sensitive and if it's not in a good condition then it could cause harm to the body” F2 PD.

Training on how to use the printer was viewed as important to consider.

“First of all, awareness about the medication they using, what type of ingredients they're using, and what are the potential side effects of this medication and then the actual machine itself, how to use it and all the safety instructions not to make a mistake that makes the medicine go wrong. Also, the safety issues with the handling and how to touch the materials and the

how to clean it and make it sterile, and then how to store the medication after you make it, how to deliver it to the right person" F2 PD.

Maintenance of the printer was also seen critical to assure quality of the printed medicine.

"It would have to depend on the sort of level of the tech [complexity of the 3D printer]. The technology because I just I just assumed that having this you would need certain staff members for maintenance and things of that as well. And I don't know if you could have that" F3 PH.

Policy, regulation and privacy considerations

Policy for the 3D printing of medicines was discussed in reference to both global and national perspectives. Even though participants have limited knowledge about how medicines are regulated, they perceived existing UK and international regulations as difficult to bypass for 3D-printed medicines.

"I don't know much about regulation, but I can imagine that's quite hard to get around" F2 PF.

However, from understanding the process of regulation of conventional drug manufacturing, another participant questioned if each single dose or combination of medicines would need a clinical trial to be approved.

"Yeah, yeah, yeah. If I wanted to create it [a personalised medicine] through this process, yeah, I mean, does that really become viable then for individual medications using this process because you know you're going to have what? potentially 66 million odd people in England? So you've got a problem". F5 PN.

Furthermore, participants had concerns about accountability and the process of escalation that patient could refer to if any issue were to arise.

“I think issues could arise if there, if there were problems with, with the dosage, like who's responsible? Because obviously it would be not approved. Em, so it's like, you know is that, is that the person taking the tablet, is that their risk or, or would it, would it come back to like the regulatory bodies for not having approved it or does it to go to the GP or whoever prescribed it?”. F2 PE.

Patient privacy was also discussed frequently. Participant expressed concern around electronic information relating to 3D-printed medicines being susceptible to data security breaches.

“Potentially, potentially because you know where would it be manufactured for a start? You know you're talking about bespoke equipment processes. Pharmaceuticals have got the IP (Intellectual Property) rights on existing. How would they, you know, subcontract that? With it being electronic, you know what about cyber-attacks, hackers etcetera? You know there's a whole raft of issues I think that you know could manifest themselves potentially in those scenarios” F5 PN.

3.5 Discussion

An initial overview of the acceptability of 3D printed medicines from members of the general public was found with four themes identified: Safety of 3D printing and 3D printed medicines, personalisation and adjustment of medicines, economic and societal impact of 3D printed medicines, and governance of 3D-printed medicines. These themes provide an initial overview of how members of the public perceive 3D printed medicines, outlining excitement at the prospect of 3D printed medicines and the potential for personalisation, but concern around the safety and general regulation of both the manufactured medicines and their associated technology.

3.5.1 Safety concerns

Safety concerns was described the most within the study. Shapes, sizes and materials used were the main discussion points.

The shape of the tablet has been discussed from wide approaching, including the choking hazards and preference for easy swallowability. The FDA has recommended to manufacture flat surface oval or capsule shaped tablets with minimal cross sectional area to be easily swallowed [301]. A shaped printlet that would bring the interest of children or animals had a safety concern. It was described that even though the medicine needs to get the attention of a child to take it; it is very dangerous if it looks such as to attract the child to consume it unnecessarily or inappropriately. The European Medicines Agency (EMA) describes in the guidelines on pharmaceutical development of medicines for paediatric use, the importance of creating a balance between acceptability of the dosage form from all aspects and the risk of accidental misuse if prepared in a candy-like shape [302]. Special shapes such as cartoons and figures created much interest with participants; however, the concern of mislaying weak parts from the shape that would affect the dosing was cited as a concern. Additionally, the likelihood for printed dosage forms to adhere to each other, as some sweets do was further added. Appropriate measures would be needed to ensure stability testing and suitability of packaging to meet all quality assurance requirements.

The risk of allergens in 3D printed medicine was raised as these are new medicines with potentially differing ingredients. As the number and amount of excipients are less in 3D printing, along with potential tailoring agreeing to patient history and allergy, risk could potentially be lower [303].

There was a concern regarding possible reduced shelf life of the printed medicine. Current thinking would suggest that 3D printed medicines would be printed on-demand for short period use e.g. one month and the expiration

would be labelled in the packaging. Participants queried the potential for medicine degradation from heat during printing.

Misusing the technology had a great concern from safety prospective. Either to print more of the dose or to print controlled medicines for personal or commercial use. Beer *et al.* described the scenarios of 3D printing of medicine misuse. They advise that such operations must be controlled by a health care professional [304]. From the perspective of manufacture there is not an issue, as the printer will be controlled in the accurate dispensing of the medical ink, a desired dose for a specific duration would be dispensed for regular prescribed medicines. These checks and balances would be in place irrespective of the ingredients and could also be used for substances subject to tighter controls such as opiate drugs.

3.5.2 Personalisation of 3D printed medicines

All participants agreed for the size of printlet to be in balance, not too large to be difficult to swallow neither excessively small which could be lost. This opinion is common across studies investigating the size of oral dosages regardless the age of the participants [207, 305]. 3D printing would give the patient the opportunity to choose the desirable size while getting the correct dosage. As 3D printing is a single step manufacturing process, minimizing the need for conventional manufacturing excipients within the formulation such as glidants to enhance flow through machinery. For potent drugs, addition of more inactive materials is necessary to increase the size of the tablet, which could be controlled according to patients' preferences without altering the prescribed dosage.

The ability to combine multiple medicines in one tablet was viewed as interesting to participants. Combining different drugs can create issues with compatibility and consequently medicines with more than two drugs are rare. Limited conventional polypills are available in the market, Polycap™ is an example, that comes in the form of capsule which combines five medicines as

these are physically separated by combining pre-developed pellets, granules, and coated particles [306, 307]. Standard direct compression tablets can only be made using compatible medicines, as the drugs are not physically separated in this form. Khaled *et al*. have successfully created a five-in-one tablet with all active ingredients fully separated with differing release profiles using 3D printing technology [123]. Such option could enhance the adherence to medication, when patient take a single tablet despite having many drugs prescribed [308]. When medication is conventionally combined together into one tablet form, the size of the tablet increases. In contrast, 3D printing allows the combination of multiple medicines in single tablet without the same need to increase dosage size.

Participants viewed multi-compartment tablet options in a positive manner, however, there were concerns around the shape of 3D printed tablets in general. More specifically, a notable preference towards traditional tablet shapes was observed, with a predilection noted towards disc and capsule shapes in particular. This preference is likely a result of familiarity with traditional dosage form appearance [207]. Participants found that shapes with sharp edges such as star or square-shapes could present choking hazards. Some suggested that a “Polo™-shaped” tablet (discoid with an inner hole) would be advantageous, as even if it became lodged in the air passage it would not block the air flow as it have a hollow in the middle. Heart shape was somewhat acceptable as there are marketed medicines share the same shape. Bogdahn *et al.* reported that a 3D printed oblong-shaped tablet has a superiority over the same size compressed one. 3D printed pyramid and cuboctahedron shaped tablets resulted in pain during swallowing and failed to be swallowed in multiple occasions during the study despite the blinding at the point of administration [309].

The bulk material that makes the major tablet matrix was also discussed. White or light colours were preferred, so that it was easy to distinguish different medicines, whereas dark colours were avoided. Overgaard *et al.* demonstrated the ideal oral dosage form have a white colour if used solely,

however, coloured tablets were preferred if polypharmacy is present [310]. Transparent ones were not acceptable, together with the ones with plastic appearance. Goyanes *et al.* demonstrated that black and green colour tablets would decrease the acceptability of the medicine [139]. The texture of the material affected perceived palatability with rough surface or overly plastic appearance of the 3D printed tablet accounting for these preferences [311].

The tailoring of the shape and geometry according to patients needs is desirable; however, these adaptations could affect the release profile [312, 313]. Care would need to be exercised to ensure appropriate therapeutic success. Such a property could be used in a positive way to modify the release profile and be more straightforward compared to changing the materials with the additional research burden associated with new chemical entities.

Goyanes *et al.* described the possibility and effectiveness of 3D printed medicines in the treatment of rare disease where only a non-licenced drug is available for treatment [314]. Discussions around the use of 3D printing of medicines, sparked debate between acceptance and rejection of the idea of 3D printed medicines for this purpose. Most of the participants were concerned about the quality and safety of the new technology in this situation. However, the consensus focussed on the trust in the prescribing physician to make informed judgments and promote their acceptability to patients given the unique nature of the circumstance. Additionally, the knowledge exchange between scientists and public were highly encouraged to enhance the acceptability of such new technology.

3.5.3 Socioeconomic impact of 3D printed medicines

From environmental perspective, the waste of materials from unused medicines is estimated to cost around 300 million pounds annually in the UK [315]. Packaging of each medicine could also be reduced through manufacturing medicines with 3D printing technologies. Along with potential

cost reductions of associated costs such as logistics as the finished product would not need larger storage space [316].

For successful adoption, technology needs to confer advantage, this can be in improved effectiveness, cost-effectiveness or both. The price of 3D printer ranges from $180 to hundreds of thousands depending on the printing technique and the resolution needed. Additionally required are the controlling computer and its software, a trained pharmacist, and the cost of the materials to be printed [303]. The potentially higher cost of new technology could be offset by gains in greater effectiveness through personalisation, reducing the overall care cost. As technology becomes more widely available prices generally decrease [317].

The energy consumption and time were noted during the conversations from environmental and economic view. Participants were concerned about the environment impact from potential energy over consumption in relation to 3D printing. Participants showed no prior knowledge about amount of energy consumed in either conventional manufacturing or 3D printing. It has been previously reported by Elbadawi *et al*. that energy consumption of both traditional manufacturing and 3D printing were comparable [318].

3.5.4 Governance of 3D medicines

Medicines are one of the most regulated entities, a burden that has escalated over recent decades to ensure the safety of end users. 3D printed medicines are highly novel and do not have the appropriate regulatory frameworks to expedite development and production of new medicinal forms. Once regulatory authorities publish guidance for 3D printed medicines, researchers and pharmaceutical companies could be led toward a new 3D printed medicines era. FDA have recently released guidance around additive manufacturing of medical devices and implants which considered a milestone guidance for 3D printed medicines [171]. Correspondingly, the EMA has established an organisation named the Innovative Task Force (ITF) to support

new technologies in early stages of development [167]. Many companies are working on new 3D printed medicines technology, however, these novel products take long time to approval, with only one currently approved for human use [319].

3.5.5 Acceptability of 3D printed medicine from health care provider prospective

Many studies have been conducted on the acceptability of 3D printed medicines of health care providers worldwide. A study in Finland cited numerous positive aspects regarding 3D printed medicines, including personalisation of dose, size, flavour and opportunity to combine multiple medicines in a single tablet for patients who have polypharmacy. Conversely, there were many concerns regarding safety, drug administration and costs. Participants of this study gave many suggestions from their experience that 3D printing would help in toward better patients outcomes [206]. There was similarity between this study and views of my participants.

A study in Saudi Arabia investigating the perception of pharmacists toward 3D printed medicine showed positive results. More than 50% of the participants suggested that 3D printed medicines would improve the safety and efficacy of the medication via personalisation. Cost, regulatory consideration and fear of new technology were considered the main barriers by Algahtani, M.S for 3D printed medicines to be available daily life [320]. My findings aligned with many elements of the previously mentioned study, as several participants highlighted cost and regulatory concerns for 3D printing technology as a barrier to the availability of 3D printed medicines. Participants in my study however, generally viewed 3D printed medicines as less safe than traditional manufactured medicines.

A study in Singapore suggested that healthcare professionals would be willing to prescribe 3D printed medicines for their patients but that it would depend on the circumstances of the situations. They still had concerns regarding

formulation stability, compatibility, safety and efficacy. In addition, they describe potential challenges with medication reconciliation and patients reduced health literacy. Regulatory concerns took a part as for narrow therapeutic index medicines along with possible cross contamination [321]. Similar results have been seen in this study, demonstrating the connection between being a health care professional or highly educated persons represents small part of the population would experience the same perspectives for a new technology.

3.6 Limitations

Although this study provides an initial overview of public perceptions towards 3D printed medicines, some limitations are present. The limited number of participants and focus groups conducted. Predetermined number of shapes, sizes, colours and materials used in the printed samples. The inapplicability to swallow the dosage form even though it contains no medicine. Many participants have no prior knowledge about 3D printing of medicines. However, this bias deducted by pre-presenting a short video about the technology and participants were welcome to ask within the discussion.

This study is amongst the first to my knowledge that had deep discussion on the safety of 3D printing in medicine from a patient prospective.

3.7 Conclusion

Hot-melt extrusion 3D printing is applicable to produce tablets with different sizes, colours and geometries. Study participants were asked to comment on the use 3D printed medicines. There were safety concerns about misusing the technology, dosage inaccuracy and being possible choking hazard. After assuring the safety of the technology, participants demonstrated a preference towards capsule and disc tablet shapes with white or bright colours. Socioeconomical and sustainability elements of 3D printed medicines were well-regarded by participants and contributed to their conclusion on the

acceptability of the technology for manufacturing medicines. The adaptation of 3D printing technology may lead to further exposure to the technology from members of the public. In-turn, this may increase public awareness and knowledge of the technology, and its applicability for personalised medicines. This study provides an initial overview of how members of the public perceive 3D printing technologies for the development of medicines, and forms part of the preliminary phase for future policy innovations in the field and acceptance of the use of 3D printing for medicines manufacture.

3.8 Chapter appendix: supplementary information

Participant Information Sheet
(Draft Version 0.1 / Final version 1.0: 07/03/2022)

Title of Study: A Qualitative Exploration of Public Perspectives on the 3D Printing of Pharmaceuticals

Name of Chief Investigator: Clive Roberts
Local Researcher(s): Matthew Boyd, Luke Sawyers, Doa'a Ismail, Martin Baumers, Ricky Wildman.

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?
The purpose of our study is to explore your perspectives on the 3D printing of medicines and to consider any concerns and benefits of this approach.

Why have I been invited?
You are being invited to take part because you are a member of the general public in the UK. You may be a future user of 3D-printed medicines and your perspective is important to consider as 3D printing technology grows in popularity.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

What will happen to me if I take part?
Once you decide to take part, a member of the research team will arrange with you when the focus group will take place and also provide the focus group location (either online or in-person). You will be asked to read and understand this participant information sheet and sign and send back a consent form.

When you arrive at the focus group you will be asked to complete a consent form if you have not yet already done so. You will also have an opportunity to ask any questions you may have about the study.

Two researchers will be co-facilitating the focus group, with one leading the focus group and the other making notes to help with the gathering and analysis of participant discussions. The lead facilitator will provide an introduction and give an opportunity for participants to become acquainted with one another. After this, the researchers will begin to record the session for transcription and documentation purposes, and begin working through questions about the 3D printing of medicines with the group.

You will be asked to attend one focus group, which is estimated to last between 1-2 hours.

Expenses and payments
If you agree to be part of the study and attend the focus group, you will be given a gift voucher (£25) for the retailer Amazon as a thank you for taking part in the study. No other payments will be made.

What are the possible disadvantages and risks of taking part?
There are no risks of taking part in this study. The main disadvantage is the time you will be asked to contribute, which will be approximately 1-2 hours, plus a small amount of time beforehand to speak with one of the researchers whilst they schedule in the focus group.

What are the possible benefits of taking part?
We cannot promise the study will help you directly, but the information we obtain will be used to inform a future roadmap for guiding important policy decisions with regards to 3D-printed medicines in the UK. As a potential future user of 3D-printed medicines, your perspective is vital for better understanding the acceptability of this new manufacturing technology. By understanding what you believe are the concerns and benefits of 3D printing pharmaceuticals, we can use this information to guide future considerations when 3D-printed medicines are implemented more widely in society. Your perspective towards the 3D printing of medicines is consequently of huge importance, particularly for shaping the policy around medicines created through 3D printing.

What happens when the research study stops?
Once the focus groups have concluded, participants will be thanked for their time. After the data collection process, the researchers can begin transcribing the focus group recordings and analysing the discussions to better understand the public's acceptability of 3D-printed medicines. These findings will then be used to support the development of a policy roadmap to guide the implementation of 3D-printed technologies with regards to pharmaceuticals manufacturing. In order to utilise these findings, they will be drafted for publication into a relevant scientific journal and treated confidentially.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers' contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting Dr Jing Yang, Chair of the Research Ethics Committee jing.yang@nottingham.ac.uk

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Nottingham but you may have to pay your legal costs.

Will my taking part in the study be kept confidential?
We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, we will use information collected from you during the course of the research. This information will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database (University of Nottingham OneDrive, Teams and SharePoint) at the University of Nottingham. Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security) and the Chief Investigator of this study (Prof Clive Roberts) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights we will use the minimum

personally – identifiable information possible.

You can find out more about how we use your information and to read our privacy notice at:

https://www.nottingham.ac.uk/utilities/privacy.aspx.

The data collected for the study will be looked at and stored by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people from regulatory organisations to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

Where possible information about you which leaves the University of Nottingham will have your name and address removed and a unique code will be used so that you cannot be recognised from it.

Your contact information will be kept by the University of Nottingham for 6 months after the end of the study so that we are able to contact you about the findings of the study. This information will be kept separately from the research data collected and only those who need to will have access to it. All other research data will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team given permission by the data custodian will have access to your personal data.

In accordance with the University of Nottingham's, the Government's and our funders' policies we may share our research data with researchers in other Universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is usually anonymised (so that you could not be identified) but if we need to share identifiable information we will seek your consent for this and ensure it is secure. You will be made aware then if the data is to be shared with countries whose data protection laws differ to those of the UK and how we will protect your confidentiality.

Although what you say to us is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

What will happen if I don't want to carry on with the study?
Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw we will no longer collect any information about you or from you but we will keep the information about you that we have already obtained as we are not allowed to tamper with study records and this information may have already been used in some analyses and may still be used in the final study analyses. To safeguard your rights, we will use the minimum personally-identifiable information possible.

What will happen to the results of the research study?
The findings from this study may be submitted for publication to a relevant scientific journal and wider university publications. If you are interested in receiving a copy of the published results, please notify one of the researchers either by email or when you attend the focus group. Your identity will be kept confidential in any reports or publications produced from this research.

Who is organising and funding the research?
This research is being organised by the University of Nottingham and is funded by the QR Policy Support Fund (University of Nottingham, Institute for Policy and Engagement).

Who has reviewed the study?
All research in healthcare is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by School of Pharmacy Research Ethics Committee.

Further information and contact details

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University of Nottingham
UK | CHINA | MALAYSIA

CONSENT FORM
(Draft Version 0.1 / Final version 1.0: 07/03/2022)

Title of Study: A Qualitative Exploration of Public Perspectives on the 3D Printing of Pharmaceuticals

Name of Researchers: Clive Roberts, Matthew Boyd, Luke Sawyers, Doa'a Ismail, Martin Baumers, Ricky Wildman.

Name of Participant:

Please initial box

1. I confirm that I have read and understand the information sheet version number 0.1 dated 07/03/2022 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to access this information and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I understand that the focus group will be recorded and that anonymous direct quotes from the focus group may be used in the study reports. ☐

5. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐

6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

2 copies: 1 for participant and 1 for the project notes.

4 Extrusion 3D Printing of Immediate Release Formulation

Upon understanding patient preferences concerning 3D printed medicine, this was applied to the developed formulation. In this chapter, I will discuss the development of lipid-based immediate release 3D printed tablets that enhance the solubility of a poorly water soluble drug.

4.1 Introduction

4.1.1 Aim and objectives

The aim of this chapter is to enhance the solubility of felodipine through inclusion in a polymeric-lipid solid dispersion.

Chapter objectives are:

- To implement extrusion 3D printing to produce a viable pharmaceutical solid oral dosage form.

- Analytical analysis of the printed tablets.

4.1.2 Background

Lipophilicity and solubility are important features of a therapeutic compound that gives an estimation of a drug's journey within the body including absorption and distribution [322]. Lipophilicity is associated with the partition coefficient and usually expressed as log P [323]. Many newly developed small molecules from drug discovery have poor aqueous solubility which affects the final bioavailability and can require formulation enhanced approaches to develop a viable medicine [324].

As reviewed in Chapter 1, improving effective drug solubility is a major pharmaceutical research topic. Solid dispersions and lipid carriers are widely used to facilitate water solubility. Lipid-based formulation are usually developed in a liquid or capsule-filled liquid form, which has many drawbacks [325]. Implementation of new technology such as 3D printing as a solidification technique for lipid-based formulation is hence attractive. Combining the advantages that lipid solid dispersion brings with 3D printing could move lipid-based formulations forward in their wider application in pharmaceuticals.

Felodipine was selected as a model drug of poor aqueous solubility [326]. Gelucires and polyethylene glycols were used for enhancing solubility properties [217, 232, 327]. Implementation of felodipine and selected excipients in 3D printing has been discussed in section 1.7. Felodipine and these materials have a low melting point and hence offer extrusion 3D printing without the need for high temperatures that can degrade a drug. The combination of different grades of gelucires and PEGs is widely investigated in literature [225, 328-330].

Additionally, lipid carriers facilitate the absorption of poorly water soluble drugs through selective lymphatic uptake [331], that was confirmed by Iwanaga *et al.* [332]. They also added that longer alkyl chains of fatty acids have a greater transfer of lipophilic compound to lymph than shorter alkyl groups.

4.2 Materials

Felodipine was kindly provided by AstraZeneca. Gelucire® 44/14 (Lauroyl Polyoxyl-32 glycerides) and Gelucire® 50/13 (Stearoyl polyoxyl-32 glycerides) were generously supplied by Gattefossé (GATTEFOSSÉ UK). Kollisolv® 8000 (Polyethylene glycol 8000) and Kollisolv® 1450 (Polyethylene glycol 1450) were gifted from BASF (BTC, Germany). Biorelevant dissolution media was

purchased from Biorelevant.com Ltd. All other used chemicals were of high chemical grade.

4.3 Methods

4.3.1 API solubility in excipients

The solubility of felodipine in excipients was tested by adding known amounts of felodipine gradually to fixed amounts of each excipient under continuous stirring and a suitable temperature. The potential of exceeding the solubility limit was then determined visually.

Five milligrams of felodipine was added to 2 g of melted excipient (10°C above melting point). After complete dissolving and reaching an equilibrium, an equal amount of felodipine was added. This step was repeated until precipitation occurred. The point immediately before precipitation was recorded as the maximum or saturated solubility.

4.3.2 Ink preparation

To prepare the immediate release formulation all the excipients were weighed and mixed in a glass vial and then melted together, apart from Gelucire® 44/14, which needed melting beforehand as recommended from the manufacturer. The melting process was carried out in an oven at 75°C, 10°C above the melting point of PEG 8000, the highest melting point of the examined materials. After complete melting and addition of Gelucire® 44/14 (if needed), the required amount of felodipine was added and stirred over hotplate at the same temperature for 20-30 min to ensure equilibration of the system. A temperature-controlled printhead was used for preliminary studies and then switched to a thermoplastic one to better fit the experimental purpose (consistent printing) (Figure 4.1). Ranges of temperature, nozzle and cartridge materials and location of heating element within the printhead are the main difference between the printheads. The temperature-controlled printhead has a temperature range between 4- 65°C and uses a plastic nozzle

and cartridge. While the thermoplastic printhead can heat from 50 °C to 250 °C with a stainless-steel nozzle and cartridge. The main problem using the temperature controlled printhead is there is no temperature control of the nozzle which hence persistently clogged, and a consistent filament was difficult to achieve. This required increasing the temperature to maintain consistent filament within the narrow nozzle. The prepared ink was transferred to a plastic cartridge in a melted state when temperature-controlled printhead was used, while in the case of thermoplastic printhead, the ink was allowed to solidify at room temperature and then transferred to stainless steel cartridge.

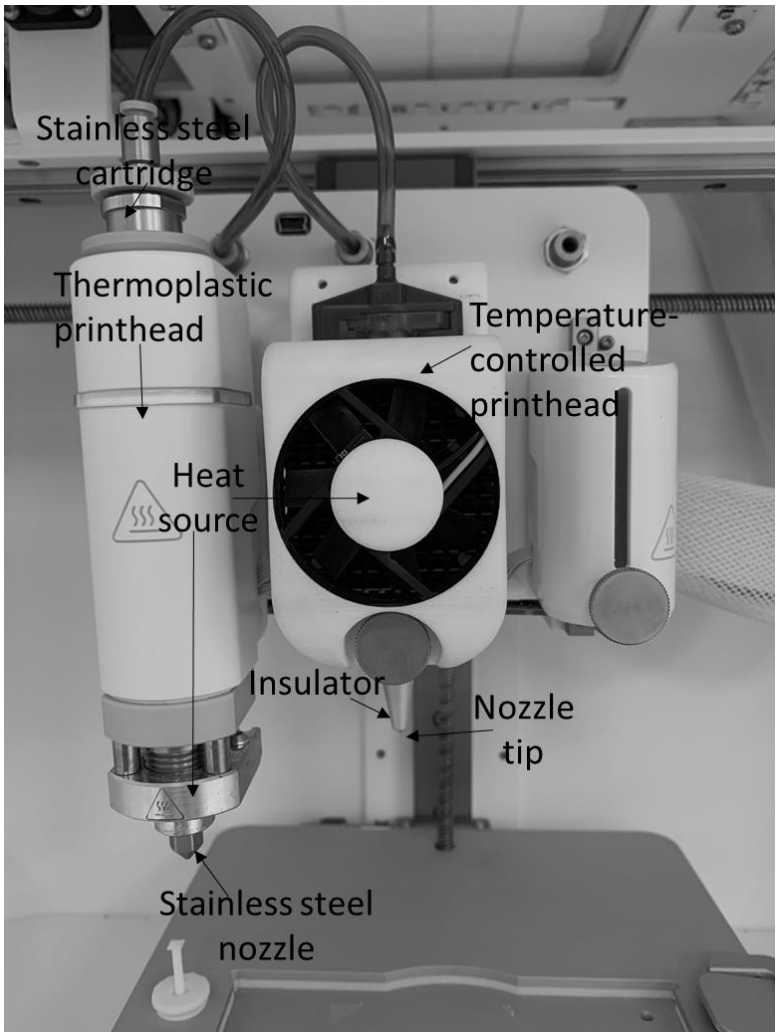


Figure 4.1 Image of thermoplastic and temperature-controlled printheads

4.3.3 Substrate optimization

For partially liquid ink deposition (i.e. the applied temperature does not melt the ink fully), substrate optimization was essential to prevent spreading of the ink over the substrate. A Drop Shape Analyzer DSA 100 (Kruss, Germany) was used to determine the contact angles of the solidified printed formulation droplet on selected substrates. A drop of prepared ink with 1 mm/sec print speed was deposited on stainless steel, ceramic, glass, aluminium foil, polyethylene terephthalate (PET), and polyethylene naphthalate (PEN). The contact angle was then measured to identify the most suitable substrate to print on, the criteria being to maintain printlet shape and avoid over spreading.

4.3.4 Printlet design

The software TinkerCAD® was used to create the required .stl file that represents the printlet shape and external geometries (6 mm × 6 mm × 1.2 mm). I chose to print cylindrical shaped tablets, which are more preferred by public as discussed previously in this thesis. A concentric, 35% infill pattern was selected.

4.3.5 Extrusion 3D printing

A BIO X extrusion 3D printer (Cellink, Gothenburg, Sweden) was used. A temperature controlled printhead was used in preliminary studies, and then switched to a thermoplastic printhead to help ensure consistent filament flowing without nozzle blockage. All formulations were printed at 50°C, modification of the printbed temperature was applied, as specified, in some experiments.

4.3.6 Printlet weight uniformity

Twenty printlets of the selected formulation were chosen, individually weighed, and the average weight calculated along with relative standard deviation (RSD%).

4.3.7 Analytical Characterization

4.3.7.1 Thermogravimetric analysis (TGA)

TGA was conducted to determine whether the processing temperature (3D printing) would result in the decomposition of API or other excipients. A TGA 4000 (PerkinElmer, Waltham, USA) was used. Samples of 5-15 mg of each sample were weighed in the sample holder and placed in the instrument. Samples were heated at 20 ºC/min over a temperature range of 25 to 400 ºC under a nitrogen atmosphere at a 19 ml/min flow rate. The percentage of weight loss was plotted against temperature.

4.3.7.2 Differential scanning calorimetry (DSC)

DSC was carried out to investigate if the 3D printing process and materials combination has an effect on the thermal behaviour of felodipine and the implemented excipients. A DSC Q2000 (TA instruments, USA) was used in this study.

Five to ten mg samples of API, each excipient, and medicated formulation were weighed in aluminium pans then covered with sealed lids.

Single ramp cycles were carried out for all samples. Samples were heated at 10 ºC/min from 0° to 250 ºC under a nitrogen environment at a 19 ml/min flow rate.

4.3.7.3 Attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR)

ATR-FTIR analysis was used to explore possible interactions between the formulation components or process related modification. A Carry 630 FTIR (Agilent Technology, USA) was used to characterise the starting materials and final products.

The samples were either a free flowing powder of the starting materials or a part of printed tablet. A small amount of sample that covered the instrument ATR crystal was pressed into conformal contact. The test was carried out at room temperature with spectrum wavenumber range of 4000-700 cm^{-1} with a resolution of 2 cm^{-1} using 64 scans.

4.3.7.4 X-ray powder diffraction (XRPD)

To differentiate the amorphous and crystalline state along with the degree of crystallinity pXRD analysis was carried out using a Malvern PANlytical Xpert MPD diffractometer (Malvern Panalytical, Malvern, UK).

Around 80 mg amount of each sample was placed in a Teflon sample holder for testing. A CuKα source was used to scan at a voltage of 40 kV and current of 40 mA. Automatic mode of Programmable Divergence Slits and Programmable Anti-Scatter Slits were employed to complement the sample length. A fixed mask coordinating the sample width and fixed 1° anti-scatter slit were applied in the incident beam path.

Optical microscope with polarized light filter was used to identify the crystallinity of pure API.

4.3.8 Drug release

4.3.8.1 Dissolution medium preparation

Biorelevant dissolution media was used to study the release profile of immediate-release formulations containing felodipine. Biorelevant powder contains a mixture of physiological surfactants such as bile salts and lecithin that precisely simulate human GI tract better than ordinary dissolution media. Variable GI conditions media could be prepared from the same powder through mixing with specified excipients [333]. FaSSGF which represents the fasted state of stomach and FaSSIF represents intestinal fasted state were used as dissolution media.

To prepare FaSSGF, I needed to separately prepare buffer by adding 2 g of sodium chloride to 0.9 L of purified water. Adjust the pH to 1.6 using 1M hydrochloric acid. Then complete to 1L with purified water at room temperature. Mix 0.06 g of FaSSIF/FeSSIF/FaSSGF powder with 0.5 L of the previously prepared buffer and stir until completely dissolved. Then make up volume to 1 L with the same buffer at room temperature. Once the simulated gastric media is prepared, it is ready to use and could be stored at room temperature up to 48 hours.

For the first 30 minutes of dissolution, 450 ml of FaSSGF was used to simulate gastric transient time. After 30 min, double strength of FaSSIF was introduced to the media to get a total of 900 ml (Figure 4.2).

Since we are doing the dissolution on two stages, gastric and intestinal on the same run, we need to prepare the FaSSIF as double strength to compensate the effect of gastric to intestinal environment. Mixing up FaSSGF and double strength FaSSIF would simulate the intestinal environment.

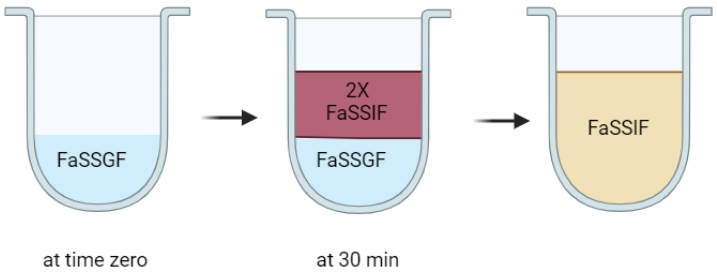


Figure 4.2 Biorelevant dissolution media (2-stage dissolution). Dissolution starts with FaSSGF for 30 minutes then double strength FaSSIF introduced to get FaSSIF (BioRender)

FaSSIF preparation also request make-split buffer. To form this buffer, 0.84 g of sodium hydroxide pellets, 7.9 g of monobasic sodium phosphate monohydrate, and 10.38 g of sodium chloride were mixed with 0.9 L of purified water. pH adjustment to 6.5 whenever needed with 1M sodium

hydroxide or hydrochloric acid. Volume completed to 1 L with buffer at room temperature.

It is obligatory from the manufacturer to let FaSSIF stand for two hours before use. Moreover, it is stable at room temperature for 48 hours from preparation.

4.3.8.2 Dissolution studies

A USP dissolution apparatus (Distek Evolution 6100, North Brunswick,NJ) was used. Type I was used for formulations and type II for Pure API (personal communication, Quotient Sciences). The apparatus set to rotate 75 rpm at 37.0 ± 0.5 °C. Powder samples were mixed with 20 ml of dissolution media (withdrawn form dissolution vessel) just before starting the experiment. Aliquot samples of 5 ml were manually withdrawn, filtered and quenched with an equal volume of acetonitrile (due to the low concentration). Samples were taken at 10, 20, and 30 min of FaSSGF (stage 1). And 5,15,30,45, and 60 min of FaSSIF (stage 2).

Ultraviolet (UV) spectrophotometry was tested and gave a good linearity (50:50 Acetonitrile: FaSSIF), however, solubility determination of API in dissolution media showed variable results. Further investigations demonstrated interference of FaSSGF which makes UV method inappropriate.

4.3.8.3 High performance liquid chromatography (HPLC)

A validated method of felodipine biorelevant dissolution was adopted (personal communication, Quotient Sciences). An Agillent 1100 (Agilent Technologies, Germany). Ascentis C18 column, 150 X 4.6 mm, 5 µm ID. And a column guard KrudKatcher ULTRA HPLC In-line Filter, 0.5 µm Depth Filter x 0.004 in ID were used. The column was heated to 40° C. Isocratic mobile phase consist of 2.5 : 2 : 1 Acetonitrile : Phosphate Buffer, pH 3.0 : Methanol with a flow rate of 1.5 ml/min was introduce. The phosphate buffer was

prepared by combining 6.9 g of sodium phosphate monobasic monohydrate with 0.8 L of water. pH adjusted to pH 3 with phosphoric acid then volume completed with water to 1 L. The injection volume was 100 µL for all samples and each sample run for 10 min. Felodipine absorbance was measured at a λ max of 362 nm, bandwidth of 8 nm, slit ≤ 4 nm, and sampling rate of 2.5 Hz. A stock solution of felodipine at a strength of 0.01 mg/ml was prepared.

4.4 Results and discussion

4.4.1 Solubility of felodipine in excipients

The solubility study revealed that up to 300, 230, 150 and 165 mg/g of felodipine is soluble in Gelucire® 50/13, Gelucire® 44/14, PEG 8000 and PEG 1450 respectively (Table 4.1). Different drugs have variable solubilizing efficiency in various materials. It was consistent that gelucires would solubilize more drug than PEG, due to lipid constituent that lipophilic drugs are attracted to. Lipids accounts the majority of gelucires composition, this can describe the relatively high percent of a lipophilic drug; felodipine being more soluble in excipients that have much lipophilic compounds. Gelucires gain their amphiphilic characteristic from the PEG part, otherwise it would be described as lipophilic. PEG, of polar and non-polar side chain, capacity of solubilizing a lipophilic drug expected to be less.

Table 4.1 Felodipine maximum solubility in variable excipients of the immediate release formulation

Excipient	Temperature (°C)	Solubility (mg/g)
Gelucire® 44/14	53	230
Gelucire® 50/13	60	300
PEG 8000	70	150
PEG 1450	60	165

4.4.2 Printability of excipients

Different ratios of excipients were tested for printability (Table 4.2), (Figure 4.3). Printed mixtures of PEG 8000 and Gelucire® 44/14 were observed to visually separate upon cooling into two components, proposed to be the different materials (Figure 4.4A). This is thought to be in part due to the different melting points of 60 ºC and 44 ºC for PEG 8000 and Gelucire® 44/14 respectively as well as their respective hydrophilic and hydrophobic properties. The solidification of PEG 8000 alone is shown in Figure 4.4B. As described by Dordunoo *et al.*, the rate of cooling, drug content together with the PEG molecular weight affects the developed morphological form of PEG melt solidification. The higher the molecular weight the more effect is seen, along with increasing cooling rate can decrease the degree of crystallinity [329]. As shown in Figure 4.4C, when a single layer was printed no sign of separation occurred as the rate of cooling of a larger surface area was faster. On an attempt to understand PEG solidification behaviour, different ratios of PEG 8000 and Gelucire® 44/14 were melted together and then dropped over a glass slide in the form of a large single drop (150 µl) or consequence dripping of tiny drops (10 µl) using volumetric pipet (not printing). Application of large droplet result in separation of the mixture, while smaller droplets and solidify printed filament appear to be unified (Figure 4.5). That can be related to surface area of contact with external environment of small droplets is much higher than large one which allows very rapid cooling, and uneven cooling rate between the core and shell in the large droplet. Movement of printlet while printing was another issue presented when high PEG 8000 ratio was used. At printing the third layer, the nozzle starts to dig the rough solid surface of the printlet which result in movement of the printlet from its original printing location, while printing continues from another origin (Figure 4.6).

Table 4.2 Excipients ratios for different tested immediate release formulation

	PEG 8000	Gelucire® 44/14	Gelucire® 50/13	PEG 1450	Comments
F1	1	1	-	-	Separation
F2	1	2	-	-	Over extruding (due to low melting point of Gelucire® 44/14)
F3	2	1	-	-	Printlet moves from origin after 2nd layer
F4	1	1	1	-	High weight variability
F5	2	1	1	-	Very fast solidification result in nozzle digging the printlet
F6	1	1	2	-	Smooth printing/ high weight variability
F7	1	2	1	-	Smooth printing/ high weight variability
F8	1	-	1	1	Partial nozzle obstruction lead to weight variation
F9	1	1	-	1	Separation
F10	1	1	1	1	Smooth printing/ high weight uniformity

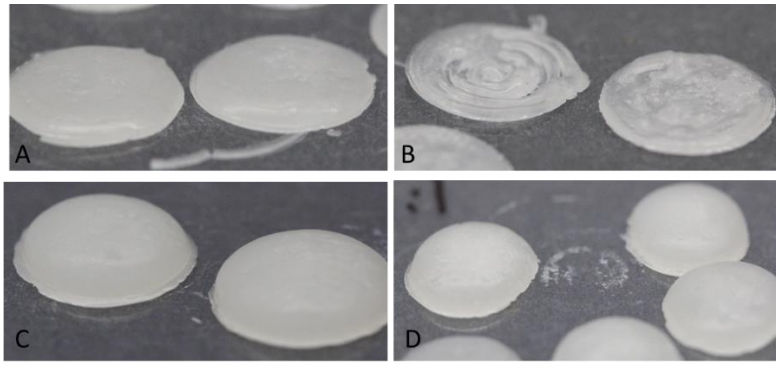


Figure 4.3 Images of Immediate-release formulations, A) F4 , B) F5 , C) F6 , D) F7

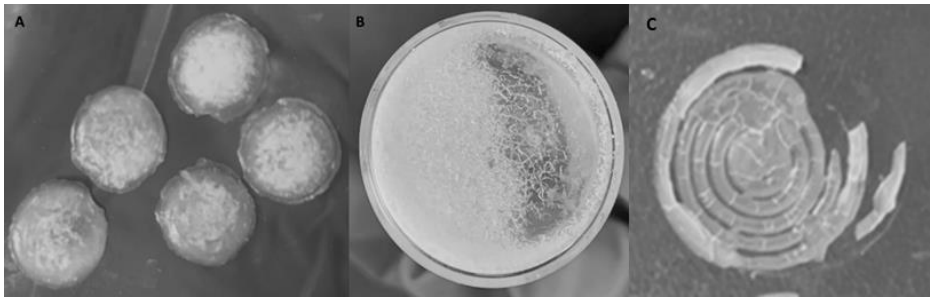


Figure 4.4 A) Observed material separation upon cooling of Gelucire® 44/14 and PEG8000 printed tablet, B) solidification pattern of PEG 8000 alone in a vial, C) single layer printing of F3

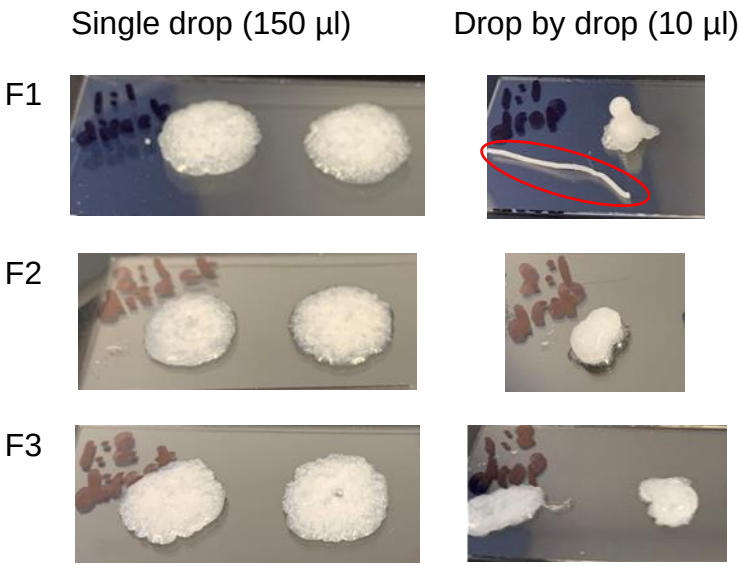


Figure 4.5 Solidification behaviour of a mixture containing different ratios of Gelucire® 44/14 and PEG 8000 (effect of droplet size), printing filament appear in the red oval-shape.

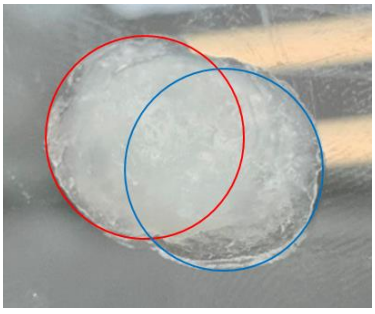


Figure 4.6 Moving of printlet due to nozzle digging (red; original print, blue; migrated print)

Adjustment of the printbed temperature was done by either increasing or decreasing the temperature from ambient to minimize the effect of solidification rate on solidification behaviour, however, separation was still present in the final print when the temperature was increased (Figure 4.7) and difficulty in printing due to nozzle touching the solid printed surface when

temperature decreased from ambient. On basis of melting point, I hence decided to include Gelucire® 50/13 in the formulation, which has a melting point of 50 ºC, intermediate between PEG 8000 and Gelucire® 44/14. To retain the advantage of polymers and lipids and on an effort to maintain the formulation stability I doubled the ratio of PEG 8000 relative to gelucires, since PEG amorphous dispersion is more stable [334] and safer [335] than gelucires.

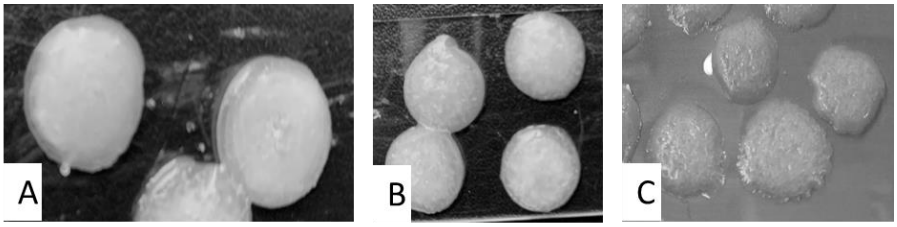


Figure 4.7 Images of printlets with adjustment of printbed temperature. A) Ambient temperature, B) 30 °C, C) 40 °C

Unfortunately, a significant weight variation together with visible phase separation of some preparations was still an issue which affected the physical appearance. This may lead to patient rejection, and from a pharmaceutical view such separation might result in poor drug distribution within the printlet and variability in dissolution. A lower melting point PEG was needed at this point. Since PEG 1450 has a melting point relatively similar to Gelucire® 50/13 and between the melting points of Gelucire® 44/14 and PEG 8000, it was selected. Melting point of an excipient can play a major role in printability. It was noted that a slight change in printhead temperature could result in either over spilling or nozzle blockage. Printing with Gelucire® 44/14 was very challenging as it has a melting range much below 50°C, a temperature at which the thermoplastic printhead cannot print. Adjusting ink composition was hence needed. From a printability view, a ratio of 1:1:1:1 of each excipient was selected to avoid phase separation, filament liquefaction and nozzle blockage. Printing parameters used were as recorded in Table 4.3.

Table 4.3 Immediate release formulation printing parameters using thermoplastic printhead

Temperature	**50 °C**
Printing speed	5 mm/sec
Pressure	8 kPa
Nozzle size	0.4 mm
Printing pattern	Concentric
Infill density	35-45%

From solubility studies, we had an estimation that the selected formulation was capable of accommodating around 20% drug w/w (drug solubility in each excipient/amount of excipient in formulation). Thus, drug loadings below and above this value were examined. 40% w/w drug loading was difficult to print as the viscosity of the ink increased and nozzle clogging was common, together with signs of insolubility of the drug (as would be expected) were visually detected. 16% w/w drug loading was printable; however, I choose 10% w/w drug loading for further analysis for improved printability and to ensure full solubility and avoid potential regions of drug super saturation.

Upon optimizing excipient ratios (1:1:1:1) and drug loading (10% w/w), printlet geometries was tested at different diameter size and number of layers with a target dose of 10 mg (highest usual dose of felodipine) in each tablet (Figure 4.8). The selected infill density was designed that each printed filament was adjacent to the previously printed one to provide a solid print and to prevent the effect of surface area increase that could affect the dissolution rate.

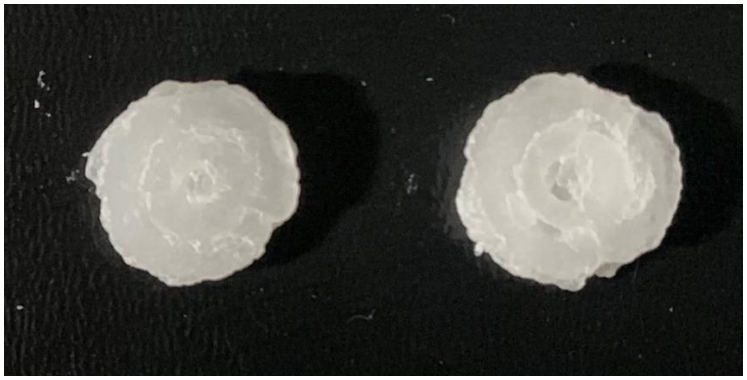


Figure 4.8 3D printed immediate release tablets on stainless steel with selected formulation (equal amount of each excipient, 10% w/w drug loading)

4.4.3 Substrate selection

Spreading of the melted formulation on printing substrate affects the final shape of the printlet. This can be influenced by the substrate surface properties on to which the printing takes place. I hence investigated the contact angle of the formulation on suitable substrates. The higher the contact angle the lower the surface energy, and the lower the spreadability [336]. Less spreadable inks lead to a more uniform printlet shape. The data in Table 4.4 demonstrates the contact angle of the optimized formulation on the selected substrates. The ceramic showed the highest contact angle (Figure 4.9). However, ceramic was not selected as an optimum substrate, since the droplet printed on ceramic and also on glass stuck very strongly and were difficult to remove without damage. Roughness of the surface plays an important role on sample adhesion [337]. Moreover, product finishing affects the roughness of the surface subsequently [338]. Accordingly, the results favour printing on stainless steel, as it has the second-highest contact angle and the printlets were easily removed.

Table 4.4 Measured contact angle of immediate release formulation on different substrates

Substrate	Contact angle(º)
Ceramic (high purity alumina)	144.3
Stainless steel (304)	125.6
Glass (glass slide)	112.3
Aluminium foil	92.1
PET	83.2
PEN	68.6

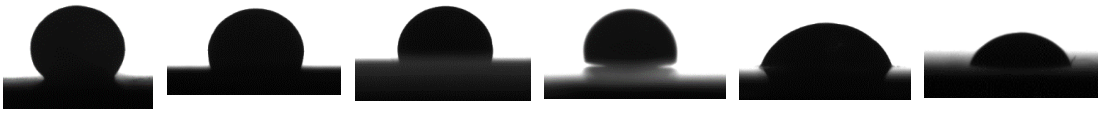


Figure 4.9 Ink droplet contact angle on: A) ceramic, B) stainless steel, C) glass, D) aluminium foil, E) PET, F) PEN

4.4.4 Weight uniformity

The design dimensions were expected to print a 100 mg tablet. Multiple dimensions were tested until the required weight reached. The calculated average tablet weight of twenty tablets was 99.5 mg with an RSD% of 4.5 compared to USP (acceptance criteria 15% RSD) [339].

4.4.5 Analytical Characterization

4.4.5.1 TGA

TGA was done at a processing temperature range sufficient to investigate the degradation temperature of the raw materials and the final formulation. The results are in agreement with literature [340-344] with the mass decay of all raw materials occurring at a much higher temperature than the printing temperature. TGA shows the decomposition temperature of the formulation and its raw ingredients represented in Table 4.5 and Figure 4.10.

Table 4.5 TGA of felodipine, raw materials and immediate release formulation

Material	Decomposition temperature (ºC)
Felodipine	291
PEG 1450	330
PEG 8000	330
Gelucire® 44/14	310
Gelucire® 50/13	335
10% drug loaded formulation	333

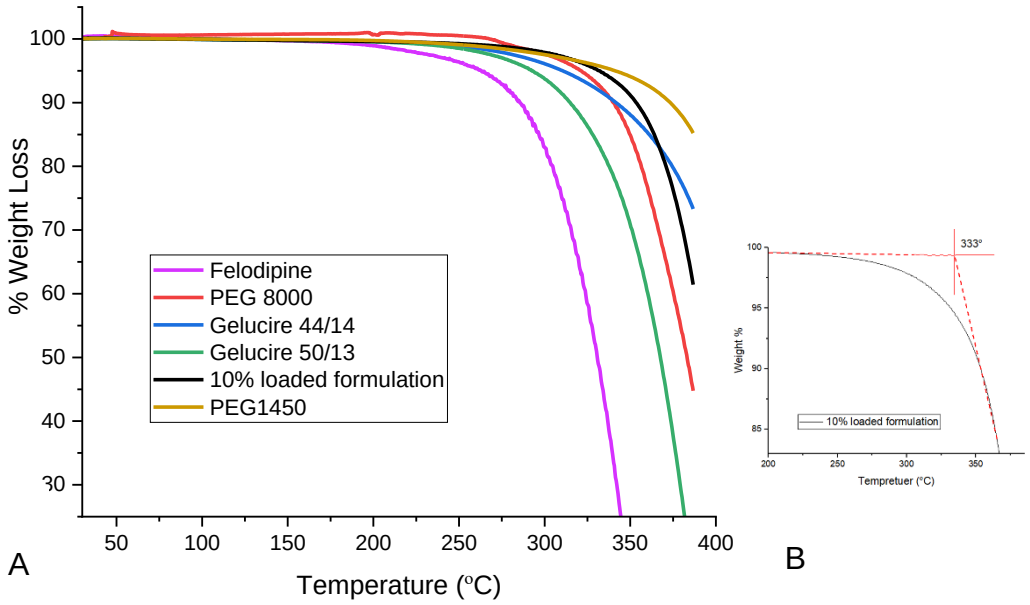


Figure 4.10 A)TGA of felodipine, Gelucire® 44/14, Gelucire® 50/13, PEG 8000, PEG 1450 and immediate release formulation, B) Extrapolation of TGA decomposition temperature.

4.4.5.2 DSC

Thermal analysis was done to reveal possible interactions between formulation components and incompatibilities. All samples were tested in duplicates. Endothermic peaks occurred at 44 ºC, 49 ºC, 47 ºC, 62 ºC, and 149 ºC for Gelucire® 44/14, Gelucire® 50/13, PEG 1450, PEG 8000, and felodipine respectively (Figure 4.11). This is in accordance with literature [211, 234, 345-347]. Smaller exothermic peaks were observed at 150 ºC, 154 ºC, 160 ºC and 188 ºC for PEG 8000, PEG 1450, Gelucire® 44/14, and Gelucire® 50/13 respectively, similar to that described by Leyva-Porras and co-workers as crystallization peaks [348]. The drug loaded formulations showed a broad peak in a range between 38 ºC and 60 ºC, which relates to gelucires and polyethylene glycol with absence of felodipine peak and excipients exothermic peaks. The absence of an API peak demonstrates the conversion of felodipine to an amorphous or dispersed form and the absence of further peaks indicates compatibility with other excipients. The lack of an expected

felodipine characteristic crystalline peak in the high loaded formulation (40%) is at first sight surprising, especially as seen later, XRPD indicates the presence of crystals. This may indicate that the felodipine solubility increases within the formulation with increasing the temperature during the DSC experiment, as rate of heating is consider relatively slow (10 °C/min) which may give drug crystals lattice to be disrupted and further dissolve in the polymeric matrix [349].

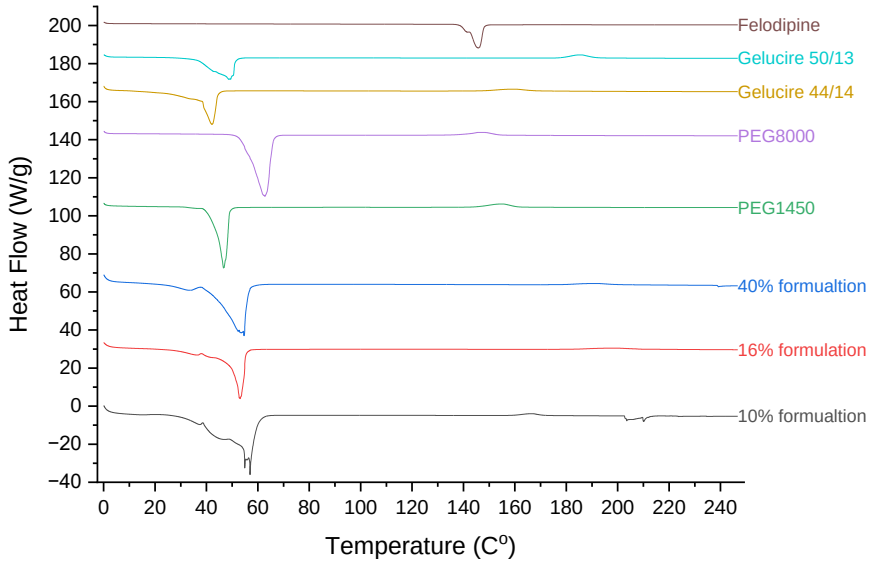


Figure 4.11 DSC analysis of felodipine, Gelucire® 44/14, Gelucire® 50/13, PEG 8000, PEG 1450 and immediate release formulation of variable drug loading (Exo-up)

4.4.5.3 Attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR)

FT-IR analysis was done to certify the chemical stability of felodipine after 3D printing with the excipients. The data in Figure 4.12 displays the FT-IR absorption spectra of pure felodipine, Gelucire® 44/14, Gelucire® 50/13, PEG 8000, PEG 1450, and the 3D printed formulation containing 10% felodipine. Felodipine showed a peak at 3382 cm^{-1} related to N-H stretching, ester C =O at 1684 cm^{-1}, and stretching of C-Cl at 724 cm^{-1} [350]. Both Gelucire® 44/14

and Gelucire® 50/13 share the same spectra characterized by OH stretching (3667-2970 cm^{-1}), C-H (2963-2805 cm^{-1}), C =O stretching (1733 cm^{-1}), C =C stretching (1630 cm^{-1}), C-O stretching (1098 cm^{-1}), C-H bending (959 cm^{-1}), C-C stretching (839 cm^{-1}), and C=C bending (710 cm^{-1}). PEG 8000 spectra showed a characteristic peak at 2867 cm^{-1} corresponding to aliphatic C-H stretching, and at 1125 cm^{-1} related to C-O-H stretching vibrations. Indeed, PEG 1450 showed similar IR spectra with partial shifting. This similarity was also noted by Li *et al.* for variable molecular weights PEGs [351]. All the discussed results are in agreement with literature [235, 350, 352]. For API formulation, the spectra showed lower peak intensities than pure excipients ones, as well as the disappearance of the felodipine peak at 3382 cm^{-1}. This could be as a result of interactions between felodipine and formulation excipients, and could be attributed to hydrogen bonding or overlapping of analogue peaks related to the API and excipients.

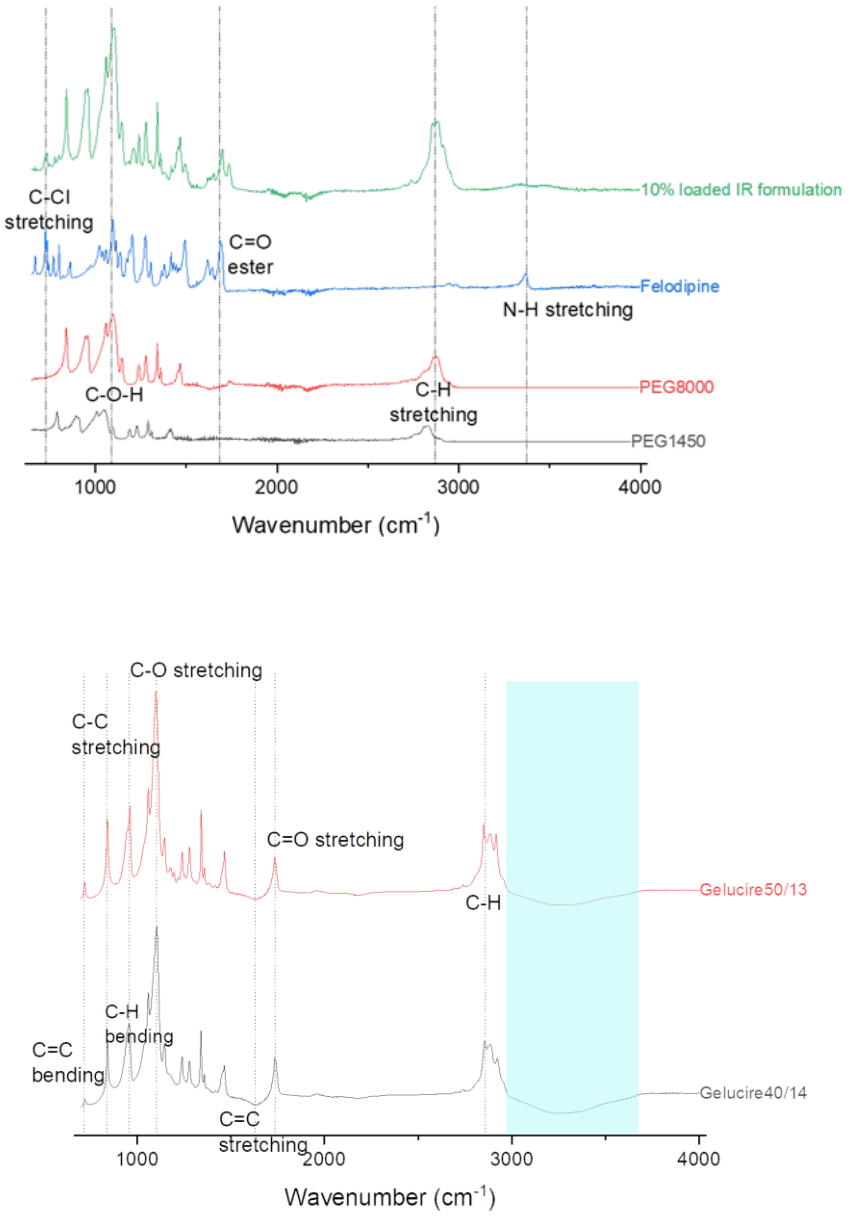


Figure 4.12 FTIR analysis of felodipine, PEG 8000, PEG 1450, immediate release printlet, Gelucire® 44/14 and Gelucire® 50/13

4.4.5.4 XRPD

XRPD of pure felodipine, the excipients (Gelucire® 44/14, Gelucire® 50/13, PEG 8000 and PEG 1450) and felodipine printed optimized formulation was done to inspect physical alteration of the API upon formulation or/and printing

(Figure 4.13). Felodipine diffractogram are equivalent to those known for polymorph I [341], with sharp peaks present at 10.19°, 14.6°, 23.27°, 25.37° and 26.45°. Furthermore, since all the implemented excipients (lipids and PEGs) are PEG based, they share the same characteristic peaks at 2θ= 19.3° and 23.5° with some minor peaks distributed at variable diffraction angles [353-356]. XRPD results of 10% felodipine loaded immediate release formulation represent similar diffraction pattern to excipients which demonstrate the stability of excipients on printing together with amorphisation of felodipine. Higher drug loading printlets (16, 40 %), show a combination of felodipine and excipients peaks, that proven that part of felodipine which above the solubility limit is still crystalline. However, when the amount of felodipine is within the solubility limits, felodipine sharp peaks was absent on XRPD which reveal the conversion of crystalline felodipine into amorphous structure.

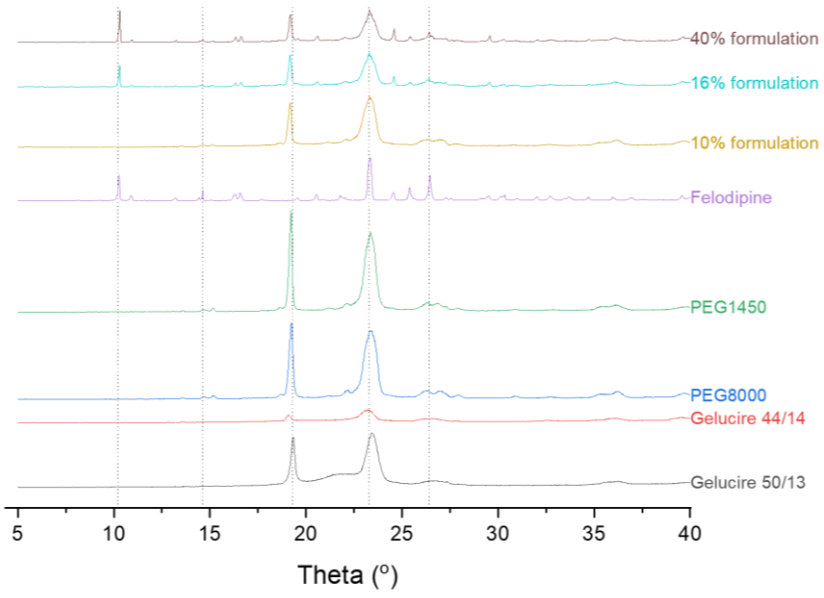


Figure 4.13 X-ray diffractogram of felodipine, Gelucire® 44/14, Gelucire® 50/13, PEG 8000, and variable felodipine loaded immediate release formulations

4.4.6 Drug release studies

The drug release rate from the printed formulations over the first thirty minutes was relatively slow. This is due to poor solubility of felodipine in acidic media [212], however, once the media was changed to alkaline at 30 minutes, the release rate increased from 22% to almost 50% after a further 5 minutes. The pure API control also showed an identifiable increase in the release rate upon media change. This is similar to the results of Abrahamsson *et al.* showing that the basic environment of the intestine is the major site for release and hence subsequent absorption of felodipine [357]. However, Bhole and Patil revealed opposite results in their solubility testing using felodipine with PEG 6000 and PVA. They found that felodipine is more soluble at pH 1.2 than 6.8. However, dissolution testing gave similar results at both pHs [358].

Upon comparison with pure felodipine, the developed formulation showed a significant increase in the effective solubility of felodipine (Figure 4.14). Where it reaches 90% at the end of study (90 min), while the percent solubilized with pure felodipine was below 20%.

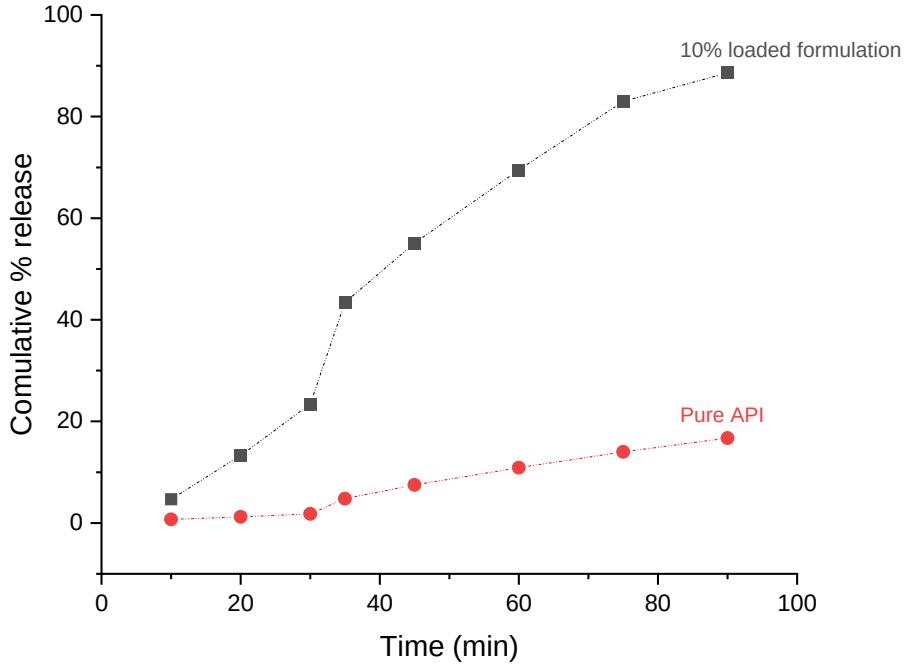


Figure 4.14 Release profile of immediate release formulation and pure felodipine (n=3) (media changed after 30 min from simulated gastric to intestinal media)

Thus, the significant escalation in drug release of the printed tablets is a consequence of inclusion into polymeric-lipid formulation, showing that gelucires and PEGs were able to solubilize the poorly water soluble active. Polymers interact with drugs and affect their physical properties. The PEG monomer contains both polar and non-polar groups, which make them able to build various bonds with drugs [359]. Felodipine has five hydrogen bond acceptor sites and one hydrogen donor site that reflect possibility of a single molecule of felodipine forming six hydrogen bonds with the polymer [360]. Teberekidis and Sigalas confirmed the presence of hydrogen bonding between the nitrogen atom of felodipine with oxygen in PEG [361]. Hydrogen bonding between felodipine and excipients in this study has been proven by FTIR and pXRD at low drug loading when specific felodipine peak disappeared. Moreover, it has been reported that hydrophilic polymers facilitate drug solubility by acting with water. Upon similar reaction, drug-drug

interaction weakens and polymer-drug interaction increases, which result in solubility enhancement [362]. Indeed, the existence of gelucire which act as a wetting agent, synergizes PEG (hydrophilic polymer) solubilisation of felodipine which reflected by dramatic increase of felodipine solubility compared to pure API.

4.5 Conclusions

Polymeric-lipid formulation was produced via extrusion 3D printing to enhance the solubility of felodipine, a poorly water soluble drug in an immediate release form. Lipophilic excipients showed higher solubilizing capacity than hydrophilic ones for a lipophilic drug. Since polymer solidification behaviour influences final printlet appearance, proper selection of materials and their ratios together with rate of cooling adjustment is necessary in heat-based processes to avoid phase separation and further product rejection. In addition, surface properties and roughness of the surface being printed on plays a major role in droplet shape and degree of contact. The selection of an optimal surface for printing, stainless steel here, is essential to maintain printlet shape and geometries. Furthermore, Identification of material decomposition temperature is crucial when using temperature-based processes to avoid loss of activity of API and excipients after printing. Moreover, signal peaks overlapping between materials and concentration below detection limits of instrument are limitations of analytical techniques commonly used (DSC, XRPD etc). On the whole, the developed formulation showed significant increase in felodipine dissolution compared to pure felodipine especially in alkaline media. Besides, 3D printing of polymeric-lipid in an oral solid dosage form is suitable for enhancing the effective solubility of a poorly water soluble drug.

5 Development of sustained release formulations, analytical characterisation, and stability analysis

With the achieved immediate release formulation, I went on to develop lipid-based sustained release formulations, as felodipine is usually manufactured as a sustained release single daily dose.

5.1 Introduction

5.1.1 Aim and objectives

This chapter aims to enhance the effective solubility of felodipine through inclusion in a lipid solid dispersion.

The objectives of this chapter are as follow:

- To produce 3D printed formulation that can deliver felodipine in a sustained release manner.

- To determine the stability of the developed formulations.

5.1.2 Background

As previously mentioned, solubility of active ingredients is directly related to bioavailability. With more than half of newly synthesised small molecules having poor aqueous solubility [363], various solubility enhancing techniques are used in pharmaceutical development.

3D printing of pharmaceuticals is an emerging technology that provides potential innovative solutions to patients and industry. Personalised therapy can be achieved in 3DP through designing versatile release profile and dose

adjustment. Moreover, 3D printing could benefit new drug development and early stage clinical trials, through ease of scalability [167].

Physical and chemical properties of materials (active/non-active) impact stability [364]. Proper selection of excipients is hence essential at early formulation development guided by estimation of potential incompatibility and interactions. Despite the effectiveness of lipid-based excipients in enhancing drug solubility, there are currently limited products available in the market due to their relative physical instability [365].

In this chapter I will discuss the development of sustained release lipid-based oral formulations to enhance the solubility of poorly water soluble compound -felodipine- via extrusion 3D printing. Subsequent chemical and physical analysis of the developed formulations and stability assessment will be carried out.

5.2 Materials

Felodipine was kindly provided by AstraZeneca. Gelucire® 50/13 (Stearoyl polyoxyl-32 glycerides) and Precirol® ATO 5 (Glyceryl distearate) were generously supplied by Gattefossé (GATTEFOSSÉ UK). All other used chemicals were of high chemical grade ((Fisher scientific, UK), (Sigma Aldrich, UK)).

5.3 Methods

5.3.1 Materials selection

Gelucire® 50/13 was selected for its solubility enhancing properties, relatively high melting point (compared to other gelucires) which facilitates delayed release and printability. Moreover, Precirol® ATO5 was chosen as it acts as a matrix to sustain drug release, also it has suitable melting point in relation to Gelucire® 50/13, together with other characteristic such as taste masking (not tested in this study).

The combination of the two materials are used by Quotient Sciences, typically in a ratio of 8:2 Gelucire® 50/13: Precirol® ATO5.

5.3.2 API solubility in excipients

Five milligrams of felodipine were added steadily to two grams of each excipient separately. Precipitation was then assessed visually. The maximum amount of felodipine before precipitation was assigned as the maximum solubility point. Further details are available in 4.3.1.

5.3.3 Ink preparation

In a glass vial, excipients were melted together after weighing in an oven at 75° C. Once in the fully molten state, felodipine was added and stirred over a hotplate for 30 min at the same temperature. When the formulation reached equilibrium (homogeneously mixed), it was allowed to re-solidify at room temperature before transferring to the printer stainless steel cartridge.

5.3.4 Printlet design

TinkerCAD® was used to create .stl file that represent printlet shape and required external geometries (7 mm × 7 mm × 2.3 mm) for 2.5% and 10% w/w drug loaded formulations. Cylindrical shaped tablets were chosen to be printed here as it has the most preference by public as mentioned before in this thesis (3.4.2.3). A concentric, 35- 45% infill pattern was selected. Variable infill densities were chosen depending on the viscosity/degree of melting behaviour of variable formulations.

5.3.5 Extrusion 3D printing

A BIO X extrusion 3D printer (Cellink, Gothenburg, Sweden) was used to prepare sustained release formulations. A thermoplastic printhead was used for all prints of this chapter. The printhead was set at 50 °C and printbed temperature was at ambient.

5.3.6 Printlet weight uniformity

Ten printlets of each formulation were selected, individually weighed, the average weight calculated along with relative standard deviation (RSD%).

5.3.7 Characterisation

5.3.7.1 Differential scanning calorimetry (DSC)

A PerkinElmer DSC 8000 was employed for DSC thermal analysis. Thermal analysis was conducted to assess thermal stability of formulation components upon preparation and printing.

Samples of 5-10 mg of the developed formulations, or raw materials controls were placed in a suitable sealed aluminium sample holder for analysis. Ramp and heat-cool-heat cycles were carried out for different samples under the same heating rate; 10 ºC/min from 0° to 250 ºC, the cooling rate was set at 20 ºC/min, under nitrogen atmosphere of 19 ml/min flow.

5.3.7.2 Attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR)

See 4.3.7.3.

5.3.7.3 X-ray powder diffraction (XRPD)

See 4.3.7.4.

5.3.7.4 Scanning Electron Microscopy (SEM)

SEM was performed on the final printlets to ascertain their surface morphology.

Pre-cut printlets were placed on a double-sided sticky disc, covered by Carbone. These were then coated with a thin gold layer using a Sputter

Coater (108 Manual Sputter Coater, Ted Pella, ink., Redding, CA, USA). The coating process took 90 sec with a current of 26 – 29 mA, and 0.06 mbar pressure in an argon environment.

The coated samples were fixed in a SEM sample holder after adjusting the height. Images were taken using a TM3030 microscope (Hitachi, Tokyo, Japan). SEM studies were carried out under an accelerating voltage of 15 kV. Magnification of focus, contrast, and brightness adjusted as needed.

5.3.8 Friability test

Friability testing was done using a Copley Friability tester FRV 2000 (Copley Scientific Limited, UK). Ten previously weighted tablets were placed in the apparatus and subjected to roll 25 rpm for 4 min in total of 100 rounds. Dust was then brushed away from the tablets. Tablets were reweighed. The percentage of weight loss was calculated, and friability was determined.

5.3.9 Drug release

5.3.9.1 Dissolution medium preparation

In order to prepare 5 L of dissolution media, 24.71 g of monobasic sodium phosphate monohydrate, 13.91 g of dibasic sodium phosphate anhydrous, and 50 g of sodium lauryl sulfate were dissolved in 4 L of water. The pH was then adjusted to 6.5 using sodium hydroxide, and the volume made up to 5L.

5.3.9.2 In-vitro drug release

A type I USP apparatus was used for printed formulations and marketed product, and a type II USP apparatus was used in the dissolution of pure API and physical mixture (in powder form) (personal communication, Quotient Sciences). Dissolution media of 500 ml rotated at 50 rpm at 37.0 ± 0.5 °C. Samples of 1.5 ml were automatically sampled by (Eclipse 5300, Distek, NC) at 0.25, 0.5, 1, 2, 4, 8, 10, 12, 16, 18, and 24 hours. An extra hour of infinite

run at 250 rpm was conducted to further asses the total tablet drug content. Samples were filtered through 45 µL Ultra High Molecular Weight (UHMW) Polyethylene cannula (Dissolution Accessories, Netherlands), before filling to HPLC vial.

5.3.9.3 High performance liquid chromatography (HPLC)

See 4.3.8.3.

5.3.10 Stability study

Stability studies were conducted under two conditions; room temperature RH = 0% for long term studies (up to 12 months), and accelerated conditions at 37 ± 1 °C and RH = 75% for shorter term studies (3 months). The effect of aging at room temperature was studied in multiple sustained release formulations, while the accelerated stability was carried out on a selected formulation (8:2 Gelucire® 50/13: Precirol® ATO5, 10% felodipine). DSC, FTIR, XRPD, SEM/EDS, optical microscopy, Raman and dissolution testing were used to identify stability issues in the samples. Samples were stored in closed glass vials in a desiccator for the long term stability, while for short term stability study samples were kept in an open petri dish inside a closed container of 75% RH in a temperature controlled oven. Analysing interval of samples under accelerated conditions was carried out at day 1, day 2, day 3, day7, day 14, 1 month, 2 months and 3 months. A Day 0 test was also done using variable techniques to confirm the amorphisity of the formulation and to be used as a control reference to tested samples.

The software OriginPro® was used to plot data.

5.3.10.1 Optical microscopy

A Nikon Optical Microscope (Eclipse LV100ND) fitted with polarising filters and connected with Nikon digital sight DS-Fi2 camera, with up to 100X

magnification was used for optical examination. Printlets were mounted on a glass slide and examined under both polarised and non-polarised light.

5.3.10.2 Scanning Electron Microscopy (SEM)/ Energy Dispersive Spectroscopy (EDS)

EDS samples were carbon coated using a Quorum Q150R ES coater (Quorum, UK), at 15 kV, with a working distance of 10 mm by Philips XL 30 (Philips, Japan), Jeol JSM.6490LV (SEM, JEOL Ltd., Japan), and Quanta 650 (FEI, USA). Many instruments were used due to machine availability at testing time.

EDS samples were run by Miss. Lorelei Robertson (nmRC, University of Nottingham).

5.3.10.3 Raman

Micro Raman spectroscopy was performed using a HORIBA LabRAM HR Raman microscope (Kyoto, Japan). Spectra were acquired using a 785 nm laser, a 100x objective, and a 200 µm confocal pinhole. To simultaneously scan a range of Raman shifts, a 300 lines mm^{-1} rotatable diffraction grating along a path length of 800 mm was employed. Spectra were detected using a Synapse CCD detector (1024 pixels) thermoelectrically cooled to −60 °C. Before spectra collection, the instrument was calibrated using the zero-order line and a standard Si (100) reference band at 520.7 cm^{-1}. The spectral resolution is better than 1.7 cm^{-1} in this configuration.

Single point spectra of the references were collected over the range 100-4000 cm^{-1} (4 spectral windows) with an acquisition time of 5-30 seconds and 2 accumulations to automatically remove artefacts, e.g., cosmic rays.

Multispectral images were collected from areas 100x100 µm and 250x250 µm in 2 µm steps (2,601 and 15,876 spectra, respectively) over the range 405-

1725 cm^{-1} (1 spectral window) with an acquisition time of 0.5 seconds and 1 accumulation. The focal plane was maintained by autofocussing using the optical image collected with ViewSharp™ and Mosaic functions. Spectra were despiked using the Despike algorithm within Labspec 6.5 software. False colour images were generated using univariate analysis by plotting the intensity (as peak height) of peaks associated with the API (1590-1675 cm^{-1}) and excipients (1050-1085 cm^{-1}).

Raman data was collected and analysed by Dr. Graham Rance (nmRC, University of Nottingham).

5.4 Results and Discussion

5.4.1 Solubility of felodipine in excipients

Solubility analysis revealed that 1 g of each Gelucire® 50/13 and Precirol® ATO 5 is capable of solubilising 300 mg and 30 mg of felodipine respectively. Such results were anticipated as gelucire is intended to work as a solubiliser and drug carrier, while precirol is a release modifier [366].

Five different formulations were developed by altering excipients ratios and drug loading (Table 5.1) to explore the effect of materials ratio on release rate and degree of solubility enhancement. All formulations were printed using the same printing parameters (Figure 5.1), namely a nozzle size of 0.4 mm diameter, printed at 8 kPa pressure, with a 5mm/sec speed. The printhead temperature was set at 50 °C, while the printbed was at room temperature (19 ± 1° C).

Table 5.1 Sustained release formulation compositions

	Felodipine [a]	Gelucire 50/13 [b]	Precirol ATO5 [b]
F1	10	8	2
F2	10	7	3
F3	10	9	1
F4	10	5	5
F5	2.5	8	2

[a] Percent w/w,[b] Part

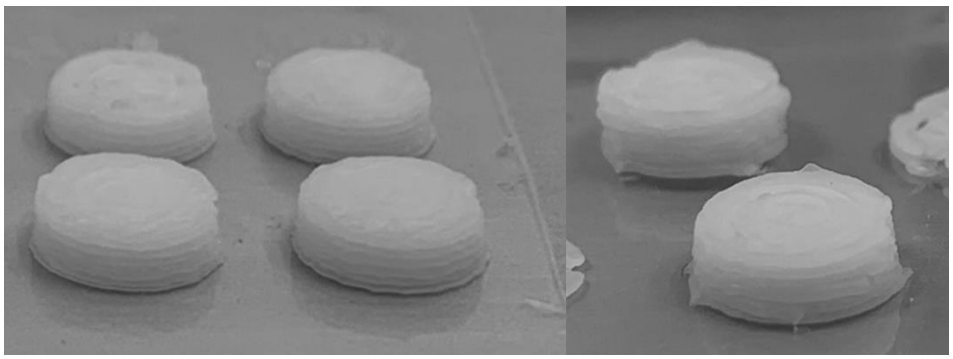


Figure 5.1 Example images of sustained release printed tablet (F1)

5.4.2 Tablet weight uniformity

Table 5.2 Summarises the calculated printlet uniformity of weight for five developed sustained release formulations. All printed developed formulations were within the limits of the British Pharmacopeia of tablets 80-250 mg (%deviation ≤ 7.5) [367].

Table 5.2 Uniformity of weight of printed tablets of different formulation, average weight (mg) and RSD (%) (n=10)

	Average weight	RSD %
F1	103.1	3.69
F2	97.5	5.52
F3	102.3	4.44
F4	100.7	5.61
F5	100.1	6.17

5.4.3 Characterisation

5.4.3.1 Differential scanning calorimetry (DSC)

Thermal analysis was done to examine possible changes of state and interactions between felodipine and excipients. Sharp characteristic peaks of felodipine, gelucire and precirol melting points appeared at 145°C, 51°C and 60°C respectively (Figure 5.2). The felodipine melting peak is similar to literature representing form I which is used in marketed products as it is the most stable form [213, 368, 369]. Both excipients have a melting range rather than a sharp peak. Different batches might have slightly different melting point ranges since the used excipients are a mixture of multiple components together with the mono-, di-, tri-esters of specific oils [199, 370-372]. The various formulations show broad endothermic peaks related to gelucire and precirol between 30°C and 63° C (Figure 5.3). The shape of the peaks differs in each formulation in relation to materials ratio change. Date *et al.* have discussed equivalent findings when using a combination of gelucire and precirol as a lipid nanocarrier [373]. They describe a physical interaction between the two excipients that results in different peak shape [373].

Felodipine characteristic melting peak was absent in all the developed formulations, consistent with an effective dispersion of felodipine within formulations or conversion into an amorphous state, at least below the detectable limit of DSC (reported as approximately 1 to 5% w/w [374]).

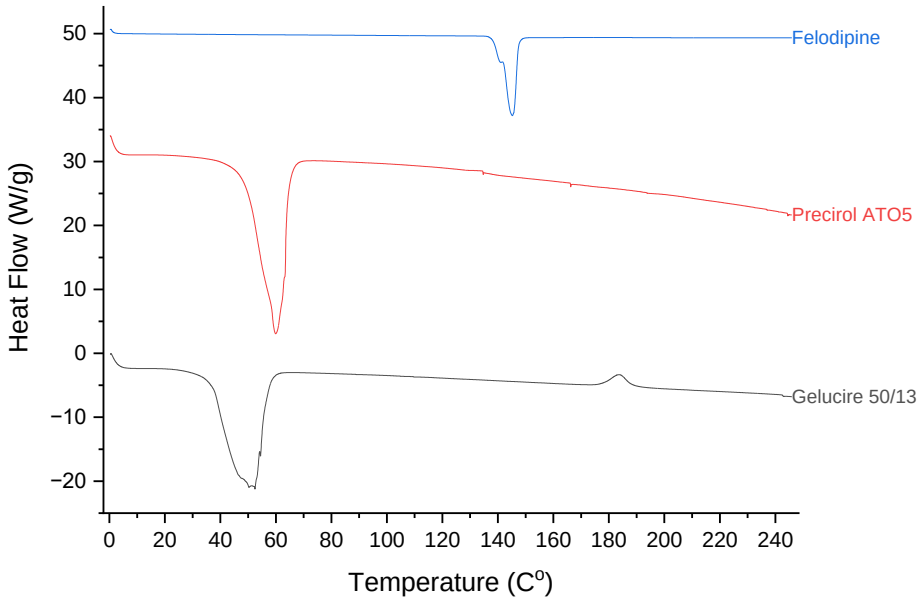


Figure 5.2 DSC of Felodipine, Gelucire® 50/13, and Precirol® ATO 5 (Exo-up)

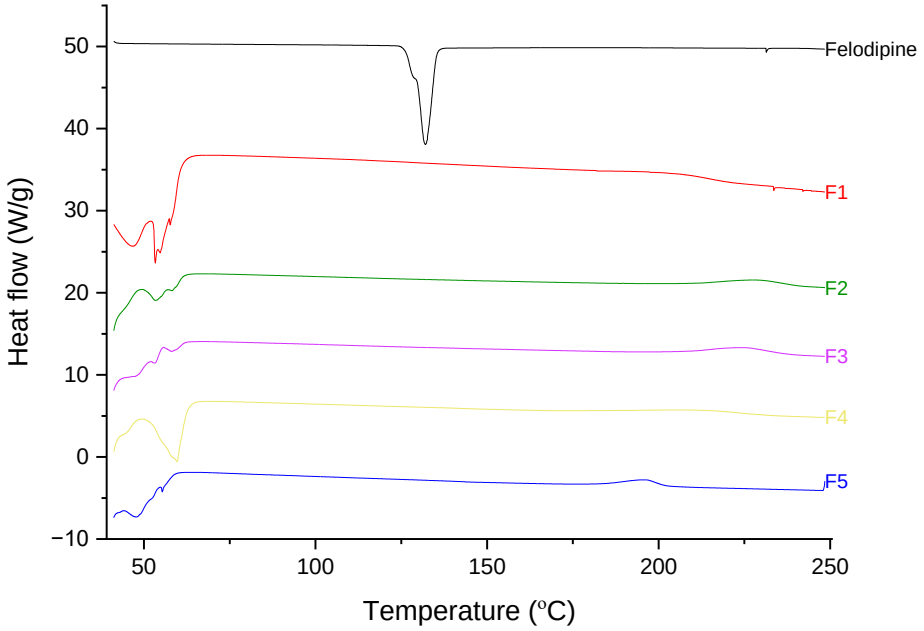


Figure 5.3 DSC of Felodipine, F1, F2, F3, F4 and F5 (Exo-up)

5.4.3.2 Attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR)

The corresponding FTIR spectra of felodipine, Gelucire® 50/13 and precirol were reflective to literature [178, 200, 330] with no detectable shift in the wavenumber of relevant peaks of raw materials or formulations (Figure S5.26). For the prepared formulations there is an overlap between the felodipine and formulation excipients in most peaks, however, a single peak which appears at around 3371cm^{-1} related to N-H stretching unique to felodipine can be identified. All freshly printed five formulations did not show this peak which was present in pure felodipine sample (Figure 5.4). Even though F5 has a low felodipine concentration that is possibly below the limit of detection of the instrument, the consistency of absence of felodipine peak in all other formulations supports the reliability of the results. This suggested hydrogen bond formation between felodipine and the polymer matrix as both have multiple hydrogen acceptor/donor sites, together with dispersion of felodipine within the matrix.

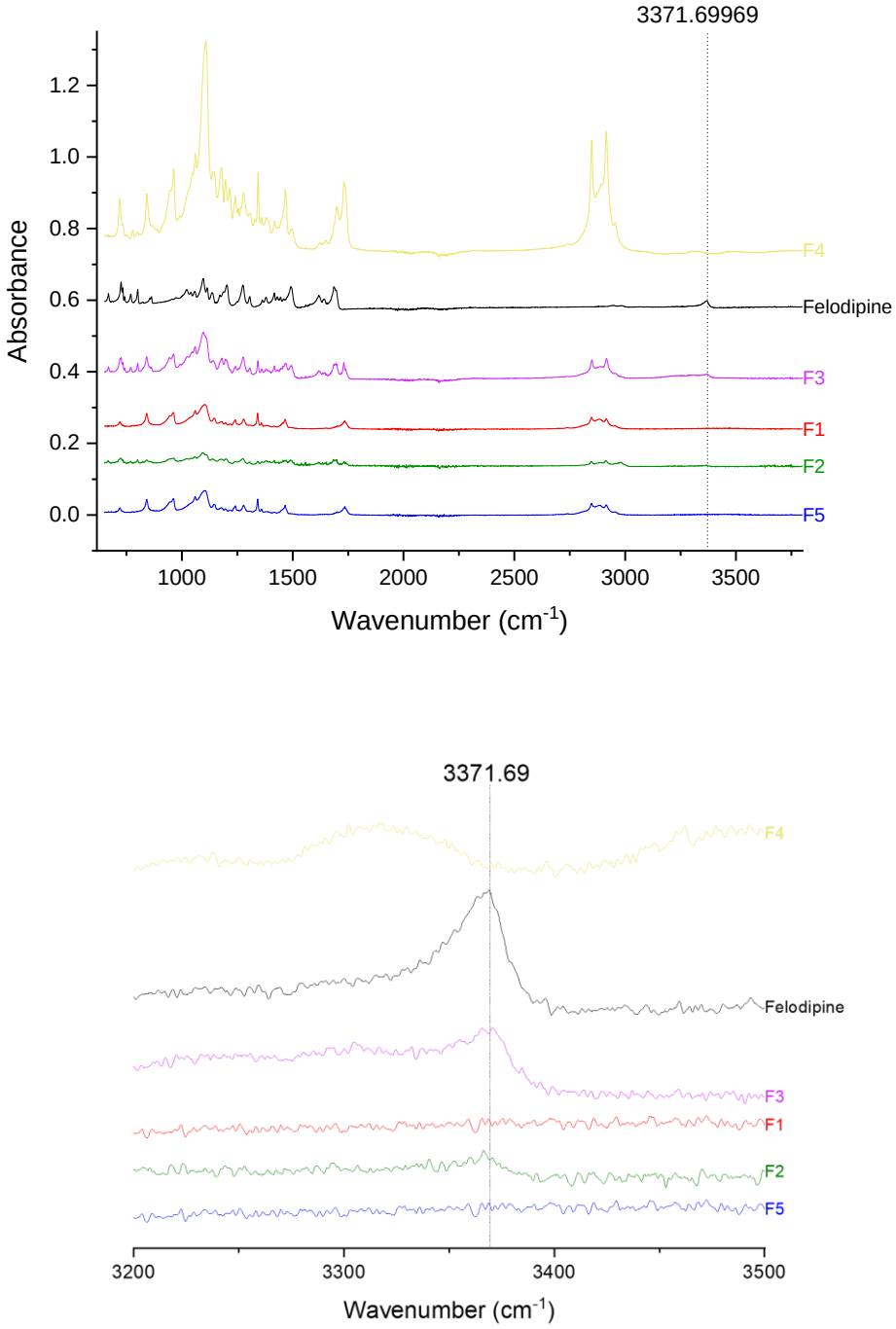
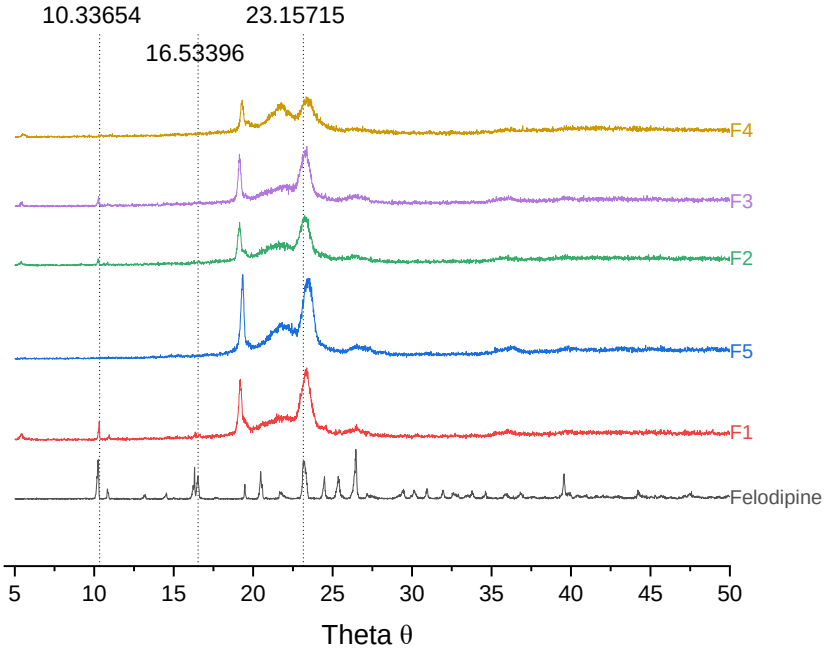


Figure 5.4 FTIR of felodipine and freshly printed sustained release formulations

5.4.3.3 X-ray powder diffraction (XRPD)

Solid-state characterisation of felodipine and other excipients were tested before and after incorporation to the formulations. The XRPD diffractograms (Figure 5.5) show a sharp intense peaks of felodipine at theta 10.3°, 16.53° and 23.15° as stated in literature (Figure S5.27) [215, 375, 376]. The peak at 23.15° from felodipine was not able to be seen in the formulation data, as an overlap with the excipient peaks occurred. Fresh samples of F1, F2, and F3 demonstrated the absence of a felodipine characteristic peak at 16.5° and a decrease in the intensity of the peak at 10.3°. Moreover, F4 and F5 diffractograms show the absence of all felodipine characteristic peaks. The lower drug concentration in F5 is probably the most relevant cause for the absence of felodipine peak, while in F4 with a relatively high amount of precirol might interact with the high proportion of felodipine to inhibit crystallisation. Alternatively, such results could be because of conversion of felodipine to an amorphous state (partial) or ordered material being below the detection limit of the technique [374].



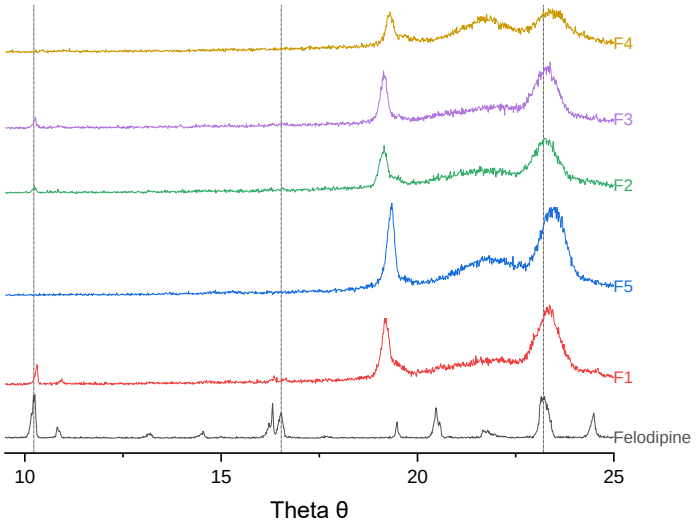


Figure 5.5 XRPD of felodipine and freshly printed sustained release formulations (2nd image is a zoomed area of felodipine specific peaks)

5.4.3.4 Scanning Electron Microscopy (SEM)

The topology of the printed formulations was examined by SEM (Figure 5.6). The internal cross-section displays an arrangement of layers over each other. Moreover, the external side view shows the number of printed layers, however, in certain prints when the extrusion was rapid, the external side shows double the number of expected layers. This could be related to the force required to print at speed and the lamination of a new layer before the latest is dry. Nonetheless, such behaviour did not affect printlet physical characteristics as it has similar weight and dimensions. The top and bottom faces showed the printing pattern. The underside view appears smooth as a result of printing on to a flat substrate, with minor gaps related to the filling pattern of printing. The top surface was affected by nozzle movement together with the effect of solidification in contact to with ambient environment. Similar behaviour can be seen within the internal structure of the printed object, however, printing a new layer before the previous fully solidify minimise such effect. Some cracks at the edges resulted from cavitation of the printing filament which can appear at any part of the print.

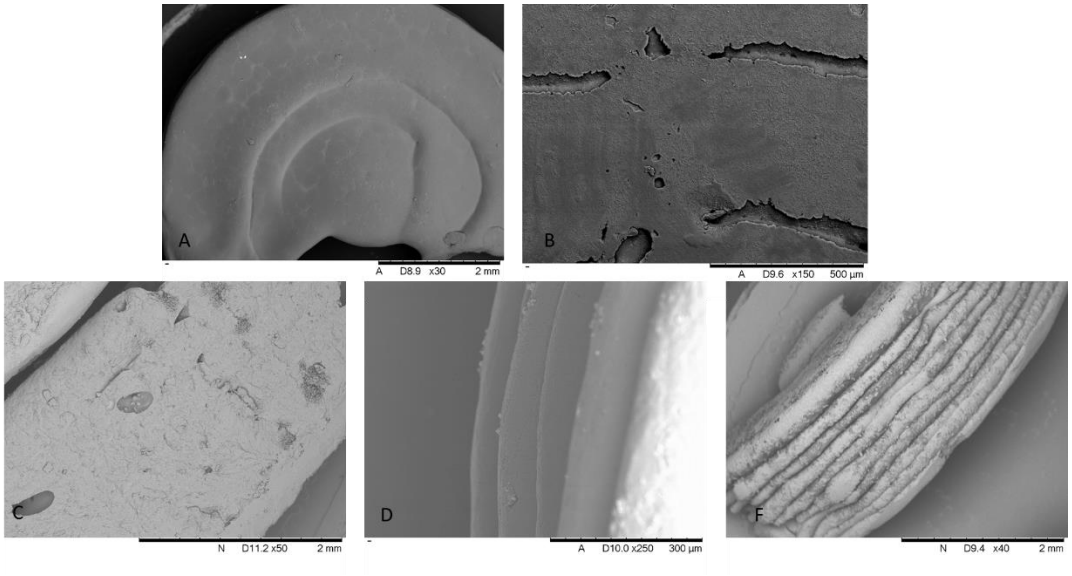


Figure 5.6 SEM of a freshly printed tablet; A) top view (F1), B) bottom view (F1), C) internal section (F3), D) external view (F1) (exact number of printed layers), F) external view (effect of lamination of layers that visually appear as extra number of layers) (F2)

5.4.4 Friability study

Friability testing was done on the F1 (8:2) formulation as a limited number of printed tablets of other formulations was available. The tested samples had a friability weight loss of 0.66 % (Table S5.6), below the 1% that is within the acceptable limit according to USP [377].

5.4.5 Drug release

Drug release was assessed for the five different formulations (Figure 5.7). All formulations exhibited sustained release of felodipine over 24 hours as required. The initial release (around 30%) in the first two hours is proposed to be a result of self-emulsification from the gelucire that present on the surface and partial melting at physiological temperature allowing more drug to be available. As described earlier, gelucire has a melting range of 30-60 °C, when the constituent part that melts at the lower temperature at the surface is exhausted lower release rate is proposed to take place by diffusion of the

drug from the matrix. Moreover, Gattefosse, the excipients manufacturer states that drug release from lipophilic matrices occur by diffusion effect solely and swelling is not a mechanism of its release (unless otherwise stated) (personal communication, Gattefosse).

The amount of felodipine in an individual tablet tested for drug release was from the feed stock ink after establishing each tablet weight.

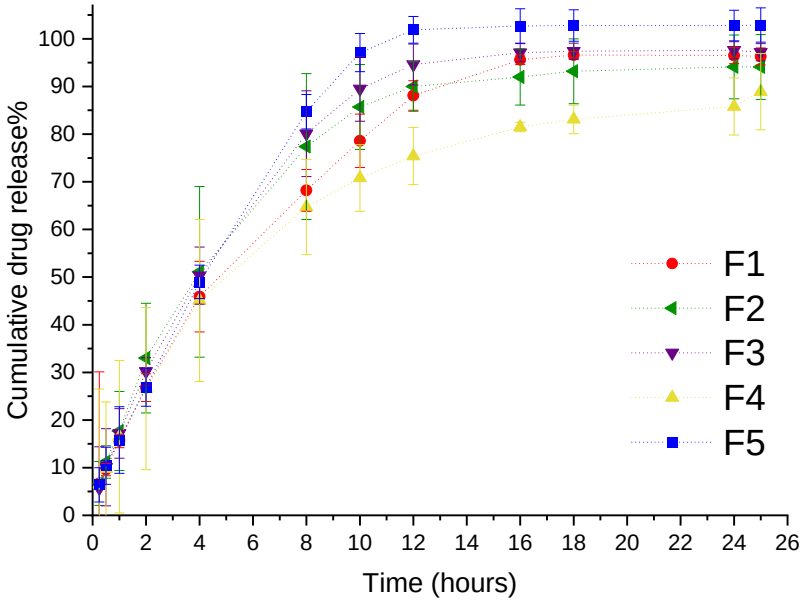


Figure 5.7 Cumulative drug release from sustained release formulations (n=3)

All formulations showed 100% or close to 100% drug release, excluding F4 that contains more precirol – a known release inhibitor material [378]. The release profiles can be attributed to felodipine partitioning towards gelucire than precirol as it is more soluble in gelucire as described in 5.4.1, along with ability of additional gelucire to self-emulsify in high gelucire ratio formulations that increases the felodipine solubility [379]. Nonetheless, part of the tablets remain intact at the end of 24 hours release in the form of a creamy semi-solid matrix, mostly it is proposed to be related to precirol, having lower erosion rate [380]. This remaining part can hold an amount of felodipine entrapped with the precirol and therefore does not release to the media.

Statistically, a significance difference in cumulative felodipine release between F3 and F4 was shown ($p = 0.0352$); owning to the highest and lowest percent of gelucire respectively. This demonstrates an enhancement of the rate of drug release with increasing Gelucire® 50/13 content, consistent with literature [217, 371, 375, 381]. However, in contrast to a published *in vitro* study, drug release rate decreased when the amount of Gelucire® 50/13 was increased for a hydrophilic drug [382]. Mohsin *et al.* defined the need of a substantial quantity of Gelucire® 50/13 alone or in mixture with other lipophilic excipients in order to retain sustain release delivery of a water soluble drug [382]. This could be due to the relatively high melting point of Gelucire® 50/13 that needs much time to dissolve in the physiological temperature, and hydrophilic drug portioning toward hydrophilic polymer (PEG 6000 in that study).

Moreover, a statistically significant result was also revealed between formulations having different felodipine concentrations in the cumulative amount released of felodipine ($p = 0.0415$) (Figure 5.8). Decreasing the amount of felodipine resulted in increasing the total percentage released felodipine. With a high drug loading of 15% (beyond the measured solubility limit), felodipine would tend to be present in an ordered and ultimately crystal form, consequentially decreasing the amount released due to poor solubility of the crystalline form. However, at lower drug loading, felodipine is dispersed within the matrix and is hence available in an effectively more soluble form. Moreover, increasing drug loading even though below the solubility limit can result in particles agglomeration that decrease drug solubility (as shown in 10% loaded formulation vs. 2.5%).

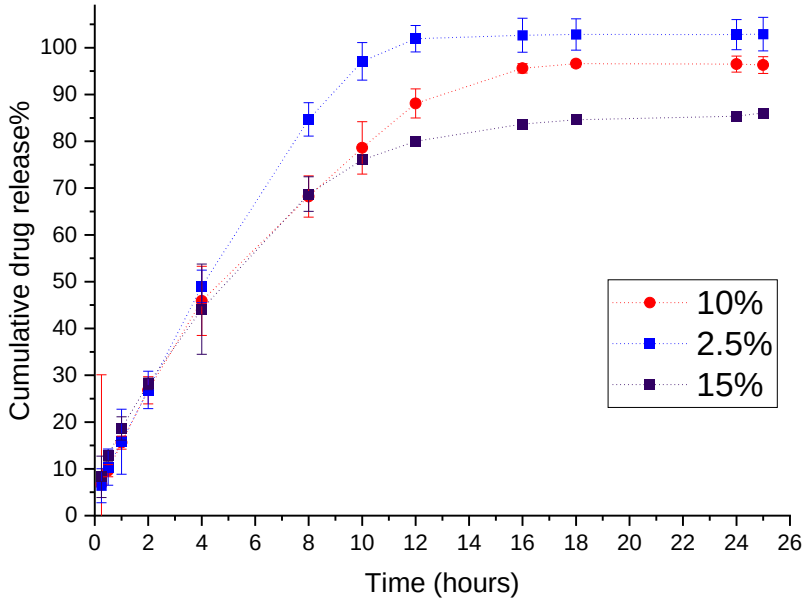


Figure 5.8 Felodipine release from sustained release formulations (effect of drug loading on the release) (n=3)

There were no significant differences in drug release between F1, F2 and F3 when minor changes in excipients ratio were made. F1 was selected as representative for further investigation.

A physical mixture containing the same amount and ratio of constituents as F1 was compared with the pure API and F1 in drug release (Figure 5.9). During the first 4 hours, the printed F1 formulation releases the drug slower than pure API and the physical mixture. This is proposed to be because the printed formulation is in a compact matrix rather than a free powder with a higher surface area, where in printed tablets precirol plays a role in hindering the release of felodipine. Nonetheless, the release from the printed tablet was superior to physical mixture and pure API after 10 hours of dissolution and afterward. This change is due to depletion of apparently solubilised felodipine in powder forms at this time point. Moreover, since pure felodipine is poorly water soluble and not dispersed within the PM, the solubility is limited.

However, in printed tablet, controlled diffusion of felodipine take place by the effect of dispersion and release modification through the matrix affected by precirol. Another observation is that the release rate of the physical mixture and pure felodipine appear to have a similar pattern despite the physical mixture having a higher release rate due to the effect of gelucire in the system which acts as an emulsifier. In the physical mixture, felodipine presents as a free powder without matrix inhibition as API is not dispersed in the excipients matrix, while the presence of the excipients within the mixture promotes felodipine solubility.

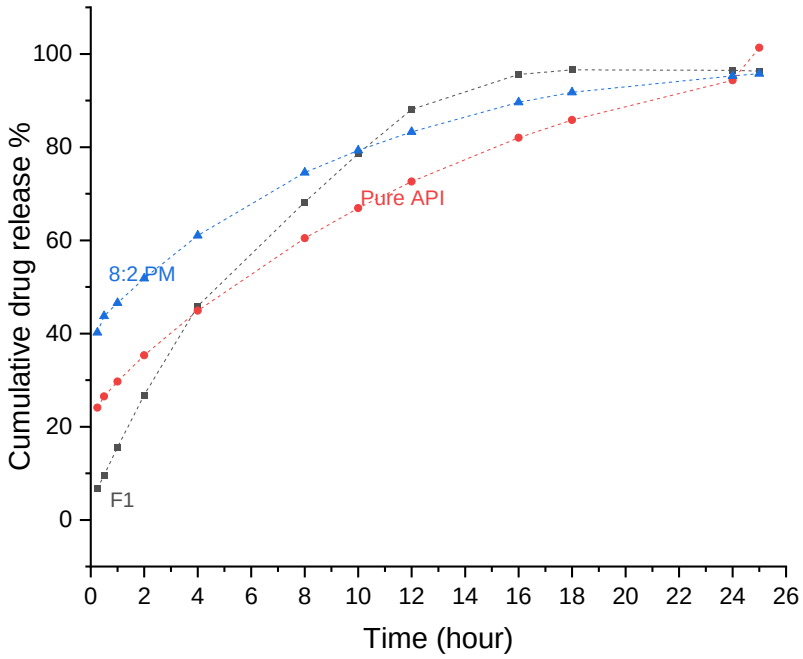


Figure 5.9 Comparison of release profile of F1, physical mixture (same composition to F1), and pure API (n=3)

Marketed drug product contains the same amount of active drug (10 mg/tablet) as in printed formulations was tested using the same method (Figure 5.10). The developed bespoke formulations represent faster release in the first 8 hours, however, both were within the acceptable limits of USP for sustained release felodipine formula (Table 5.3) [289]. Though, there was no

felodipine lipidic formula available in the market, that makes the comparison vague.

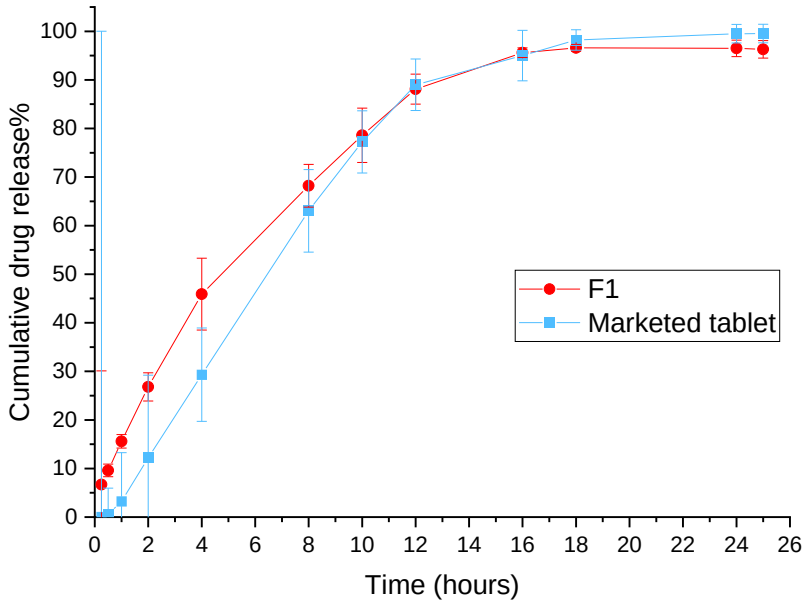


Figure 5.10 Comparison of release profile of felodipine marketed product and F1 (n=3)

Table 5.3 USP acceptance limits of felodipine labelled amount from extended release tablet at specified time [289]

Time (hours)	Amount dissolved %
2	10- 30
6	42- 68
10	≥ 75

5.4.6 Release kinetics

The obtained data of drug release were fitted using zero order, first order, Higuchi, Koresmeyer-Peppas, and Hixson-Crowell models to investigate felodipine kinetics of release from various formulations. Drug release in zero-order release only depends on time, where a constant release continues without any effect of drug concentration. Zero-order can be achieved ordinarily by tablet coating, osmosis of formulation core surrounded by a membrane, matrix (slab) that rely on erosion for drug release and transdermal systems [383, 384]. In first-order release, the release of drug depends on the drug concentration. Porous matrices that hold water soluble ingredient represent an example of formulations able to have first-order release [383, 385]. The Higuchi equation was initially developed to quantify drug release from an ointment film and was later applied to many other controlled release delivery systems [383]. A direct relationship between cumulative drug release and square root of time based on a pseudo-steady-state approach is described in the Higuchi model. Various assumptions have been made in order to use Higuchi model that relies on drug solubility, unidirectional diffusion, dosage form thickness, matrix dissolution, drug diffusion and sink condition [383, 386]. Koresmeyer-Peppas is termed as a Power Law relationship to drug release as function of time and was established specifically for drug release from polymers [383]. Koresmeyer-Peppas is considered to be suitable when multiple release phenomenon are expected. The release behaviour can be classified as Fickian (n= 0.5) (diffusion-based release) or non-Fickian model ($0.5 < n \leq 1$)(polymer swelling, combination of diffusion and swelling) depending on the value of the exponent of release mechanism (n) in function of time [383, 387, 388]. Lastly, Hixson-Crowell found a relation between particle area and its volume. They described the dissolution of solid dosage form that take place in layers parallel to the surface, while the dosage form preserves its geometries. According to particle surface factors the dissolution will be affected, constant for regular shaped particles (sphere and cubic), while deviation appear for irregular ones. Hixson-Crowell model assumes that drug release does not take place by diffusion

(movement of particles according to concentration gradient), but with dissolution velocity (capacity of solvent to move solute molecules apart) [383, 389].

Data fitting to kinetics models gave many indications of drug release pattern of various formulations (Table 5.4) (Figure S5.28). F1, F2 and F3 (of relatively similar constituents) showed comparable correlation coefficient (R^2) on all models, except for zero-order (will be discuss later). F4 best fitted first-order, Higuchi and Koresmeyer-Peppas. While F5 which has lower drug loading best fitted Koresmeyer-Peppas and zero order. Furthermore, all non-fitted data had an $R^2 \geq 0.92$. Additionally, the marketed product best fit is zero-order.

From this study results, it was observed that the excipients and their combination together with the process of 3D printing have yielded multiple release mechanisms that vary subtly with composition. For zero-order drug release, an increase of correlation coefficient (R^2) was observed with decreasing Precirol® ATO5 concentration in different formulations. This is due to precirol main action as a drug release modulator. The high proportion of glyceride (lipophilic material) in precirol minimises the amount of penetrated dissolution media to the matrix, which in turn reduces drug release [390]. A zero-order release is recommended for a sustained release drug delivery system to gain a stable release over the time [391].

From exploring data fitted to the first-order model, low drug loading appears to not fit this model, as the release is mainly dependent on the matrix effect rather than drug concentration.

Based on Higuchi model assumptions, I believe that the assumption of constant drug diffusion most applies in the printed formulations. The 10% loaded formulations fitted this model better than 2.5% (0.996 vs. 0.986 respectively). When considerable amount of drug is available it releases constantly, while when a lesser amount of drug is within the formulation the

release will be slower, showing that the concept of a matrix dissolution effect rather than amount of drug is the primary control of the release pattern.

All five printed formulation fit the Koresmeyer-Peppas model. This was expected from various release mechanisms of lipid matrixes reported in literature (self-emulsification, diffusion, and erosion) [392-394]. Since the tested tablets were cylindrical in shape, together with recorded (n) value in Korsmeyer-Peppas was between 0.5 and 1, the release of felodipine from the formulation followed anomalous non-Fickian transport. The release mechanism is a combination of comparable rates of diffusion and self-emulsification. Time-dependant anomalous effects are result of simultaneous diffusion and slow polymeric chain rearrangement [383].

Assuming all formulations have the same composition (materials) and printed under the same condition (temperature, pressure, speed), variable fitting to Hixson-Crowell model was not expected. Nevertheless, the concept of dissolution velocity might be applied for the high drug loaded system with more gelucire (e.g. F3) where the release appears to be faster due to the high amount of drug (10%) and easier drug escaping from this matrix.

Table 5.4 Kinetic models fit of felodipine release from freshly printed sustained release formulations

	F1 8:2 10mg	F2 7:3 10mg	F3 9:1 10mg	F4 1:1 10mg	F5 8:2 2.5mg	Marketed 10mg
Zero order	y = 7.3565x + 8.8728	y = 8.0753x + 10.712	y = 8.6124x + 8.753	y = 6.6106x + 9.9637	y = 9.4157x + 6.8192	y = 8.1582x - 3.4907
R^2	0.9782	0.9687	0.9798	0.9619	0.9935	0.9989
First order	y = -0.0641x + 1.9903	y = -0.0823x + 1.9965	y = -0.095x + 2.0218	y = -0.0523x + 1.9732	y = -0.1395x + 2.0948	y = -0.0645x + 2.0515
R^2	0.9974	0.998	0.9901	0.9956	0.9248	0.9773

Higuchi	y = 27.742x - 10.086	y = 30.632x - 10.397	y = 32.461x - 13.415	y = 25.146x - 7.4324	y = 35.055x - 16.696	y = 29.93x - 23.13
R²	0.9962	0.9982	0.9968	0.9967	0.9862	0.9627
Korsmeyer-Peppas	y = **0.6954**x + 1.2162	y = **0.7184**x + 1.2651	y = **0.7671**x + 1.2308	y = **0.6817**x + 1.2162	y = **0.746**x + 1.2324	y = 2.2021x + 0.1555
R²	0.9966	0.997	0.9989	0.9978	0.9966	0.9202
Hixson-Crowell	y = -0.1782x + 4.5577	y = -0.215x + 4.5503	y = -0.2397x + 4.608	y = -0.1509x + 4.5186	y = -0.3045x + 4.7206	y = -0.185x + 4.7675
R²	0.9977	0.9983	0.9996	0.988	0.9803	0.9902

5.4.7 Stability studies

Stability studies were carried out to investigate the effect of time and variable storage conditions on the stability of formulations. It is known that lipids are prone to oxidation and blooming (lipid crystallisation) [395, 396]. The blooming effect associated with storage of soft lipids is attributed to migration of lipid toward a surface, which in turn increases drug release due to increases in the effective surface area of flake-like lipid crystals [395, 397]. Blooming of gelucire has been confirmed by SEM, where cracks appeared in the surface and resulted in dissolution enhancement by allowing dissolution media to penetrate easily [398]. There is a debate regarding lipid matrices on whether they undergo polymorphic changes [392, 393], or physical modifications and rearrangements [396, 397, 399, 400]. Indeed, physical rearrangements theory appear to be more suitable from the results of this study and previously mentioned studies [396, 397, 399, 400]. Different lipids have variable tendencies to equilibrium, Precirol® ATO 5 which consist of high glycerides tend to equilibrate with aging, while Gelucire® 50/13 which is a mixture of different components (glycerides and PEG esters) strive to reach equilibrium, since materials of symmetrical components equilibrate more easily than unsymmetrical ones [401].

The development of such a product was challenging. The effect of aging with time (up to 12 months) was studied on samples from different formulations using DSC, FTIR, XRPD and drug release. Those samples were stored in a desiccator (RH=0) at room temperature. In addition, a single formulation F1 (8:2) was tested under accelerated conditions (37 ± 1°C, 75% RH). A limited number of samples of some formulations prevented further analysis.

For samples stored at room temperature, 0% RH, comparable results were seen on DSC peaks with fresh samples, which indicates the presentence of solubilisation efficiency of the matrix with time (Figure 5.11). FTIR spectra show no recrystallisation of felodipine with time (Figure 5.12).

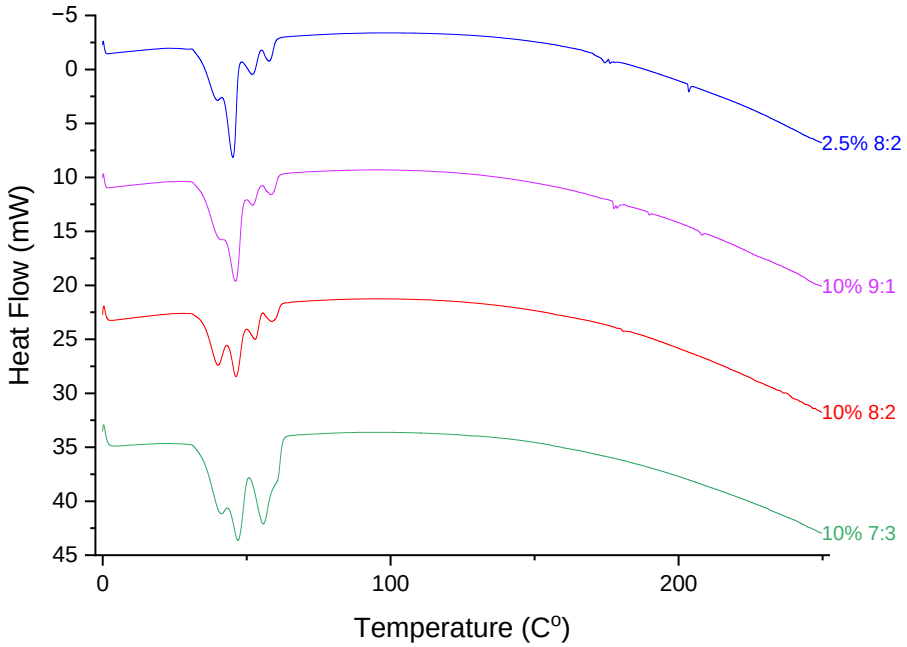


Figure 5.11 DSC of stability samples (from top; F5, F3, F1, F2) (room temperature, 0% RH) (Exo-up)

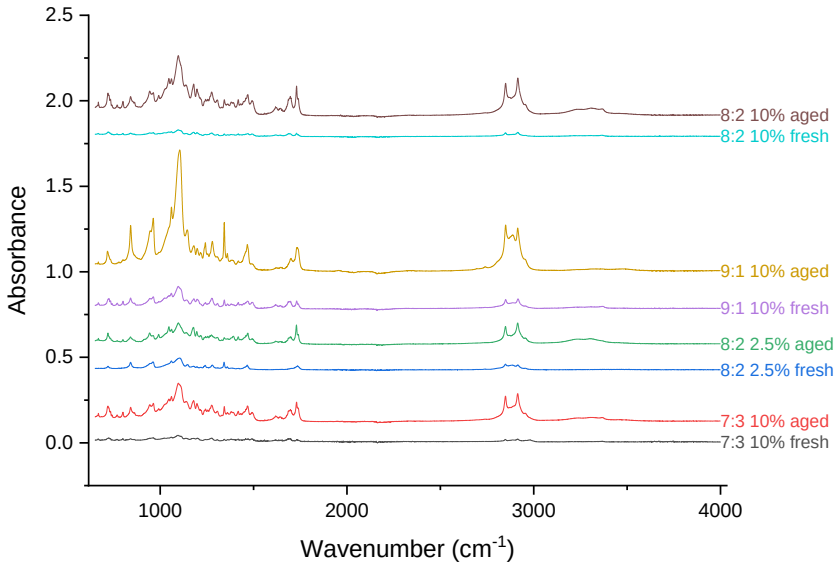


Figure 5.12 FTIR of stability samples (room temperature, 0% RH) (from top: F1, F3, F5, F2)

However, XRPD results indicate a different conclusion, where a felodipine characteristic peak appears at theta 10° and hence demonstrates felodipine crystal growth (Figure 5.13). Further investigation using SEM showed a change of the surface topology from fresh sample suggesting crystallisation of felodipine (Figure 5.14). Though, stabilisation of DSC samples can be as a result of increasing the solubility of the drug with increasing the temperature during thermal analysis. At relatively slow rate of heating of 10 °C/min during DSC experiment, the applied energy has sufficient time to cause some drug molecules to escape from the crystal lattice and be further solubilised within the polymer matrix [402]. Another assumption is the detection limit of DSC technique, where around 20% of the 10% felodipine loaded tablets needs to re-crystallise in order to be detected by the instrument [403]. Along with possible organisation of felodipine in less ordered form that possibly detected by a technique but not another (XRPD vs. DSC). Moreover, the absence of felodipine peaks in FTIR could be related to a low detection limit of the technique, which is limited to 1- 5 % of ordered material [374]. Hence minor recrystallisation of relatively low drug concentration formulations is expected to be below instrument detection limit. Additionally, different analytical testing can fail to differentiate the changes that would occur to samples while other could effectively regarded [404].

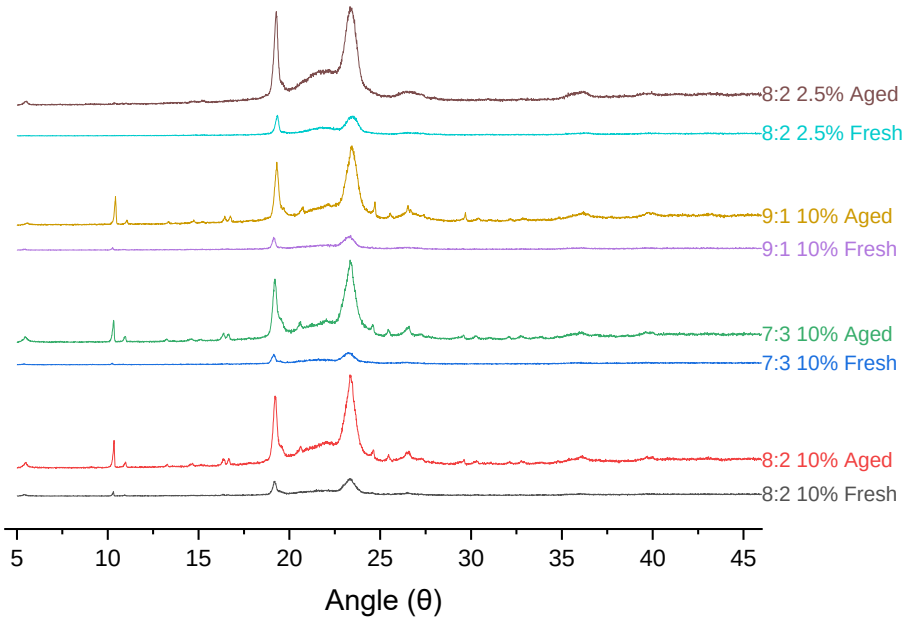


Figure 5.13 XRPD of stability samples (room temperature, 0% RH) in comparison to freshly printed ones (from top: F5, F4, F2, F1)

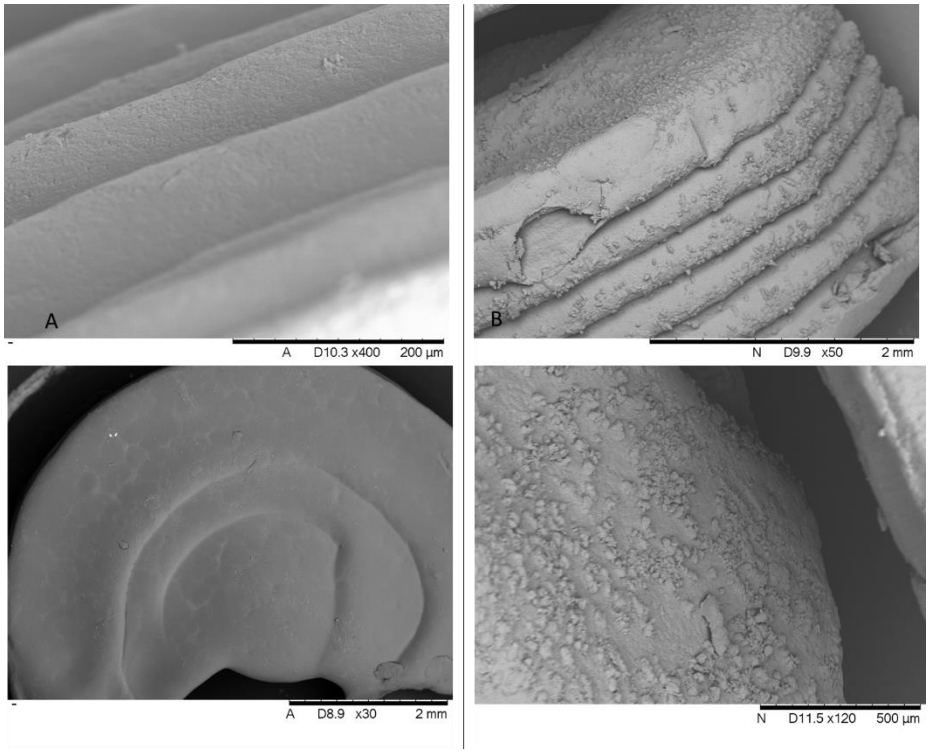


Figure 5.14 SEM of: A) freshly printed, and B) stability samples (room temperature, 0% RH) (F1)

Optical microscopy indicated the crystallisation of both felodipine and matrix (Figure 5.15A). Felodipine appeared as shiny crystals distributed within a yellowish-blue matrix. Polarised microscopy was not be able to be used since samples are not transparent nor thin enough for polarised light to pass through. Since felodipine has a chlorine atom within its chemical structure as a unique element, EDS was used to measure the crystallisation of felodipine and distribution within printlets. The image in Figure 5.16A indicated phase separation together with crystallisation of felodipine at the surface of the printlet. The purple colour in the image represents chlorine within felodipine, while the majority green colour is related to oxygen that is distributed in felodipine and the excipients.

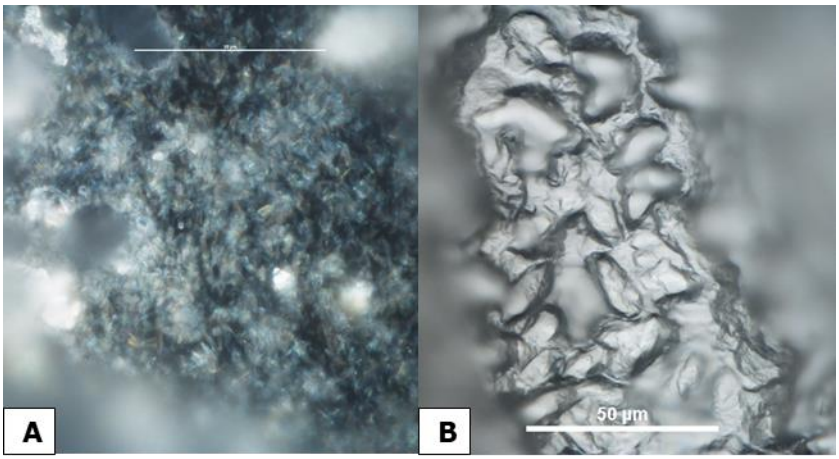


Figure 5.15 Optical images of tablets (F1) stored at A) room temperature (room temperature, 0% RH) , B) 1 month at (37 ± 1°C, 75% RH)

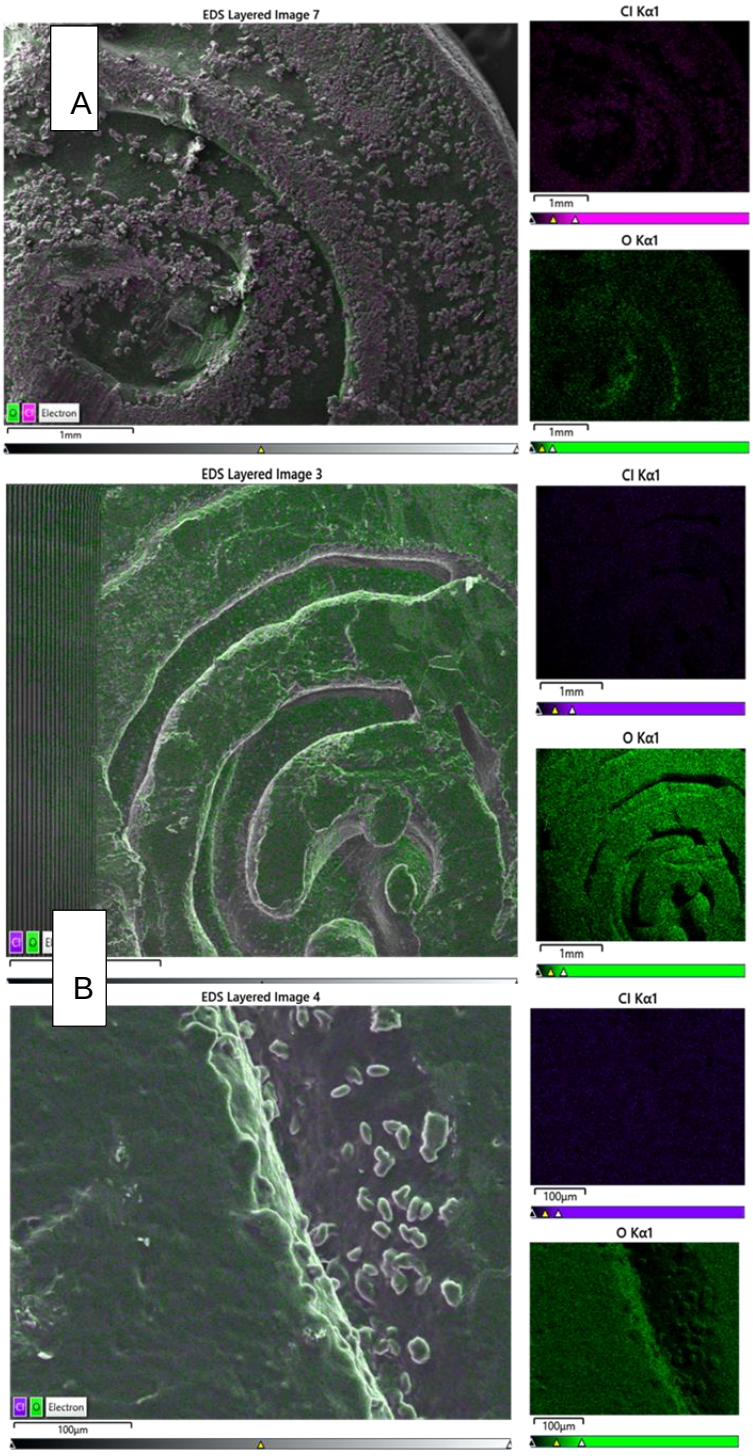


Figure 5.16 SEM/EDS of samples (F1) stored at A) 1 month at room temperature, 0% RH, B) 1 month at 37 ± 1°C, 75% RH

Raman spectroscopy was employed to better assess the API distribution and possible phase separation of the printed matrix. The results indicate some crystallisation of felodipine and phase separation where felodipine is also available in the excipients enriched areas (Figure 5.17). On the ‘heat-map’ in Figure 5.17, areas of enrichment of either felodipine or excipients are present. In the excipient heat-map, yellowish areas indicate the enrichment of excipients, while the blackish area on the same map represents felodipine. From spectra data, felodipine sharp peaks are present in both spectrums (felodipine and excipients enriched areas) where peaks appear to resemble crystalline rather than amorphous state of felodipine.

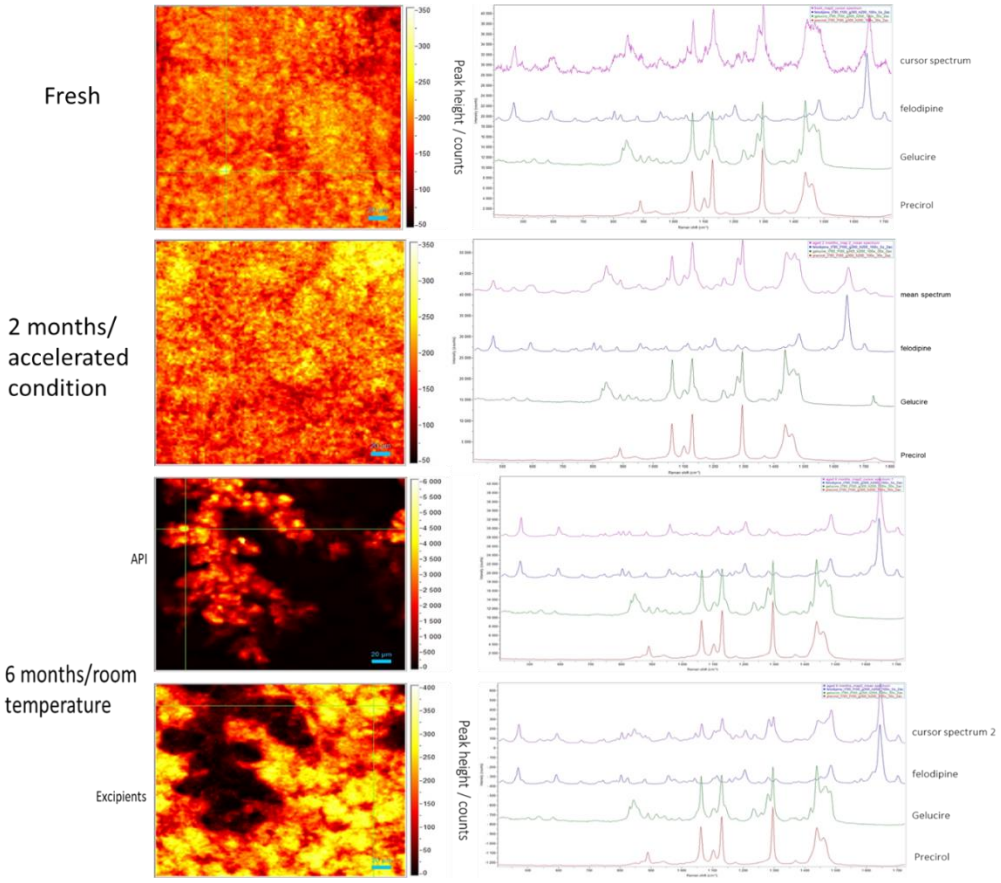


Figure 5.17 Raman spectroscopy heat-maps of freshly printed tablets, 2 months under accelerated conditions (37 ± 1°C, 75% RH) and 6 months at room temperature (room temperature, 0% RH) (F1)

Similar investigations were done on samples under accelerated conditions (37 ± 1°C, 75% RH). Upon analysis using DSC, a separation of the peak related to excipients was found (Figure 5.18), which re-joined in the second heating cycle (Figure S5.33). This represents different components of excipients (PEG esters and glycerides) [392, 405]. In addition, a new peak appeared at around 110°-120° C formed on the first day and absent after one month, indicating product instability. A non-medicated formulation and pure API were tested under the same conditions and no such peak was present (Figure 5.19). A stability study of felodipine and PVP solid dispersion showed a thermographic peak at 124° C, proposed to be either a second glass transition or a depression of the melting point of felodipine within the solid dispersion. This is consistent with the suggestion that the immiscibility induced by moisture is reversible at a high temperature (125 °C) but not lower (room temperature) [406].

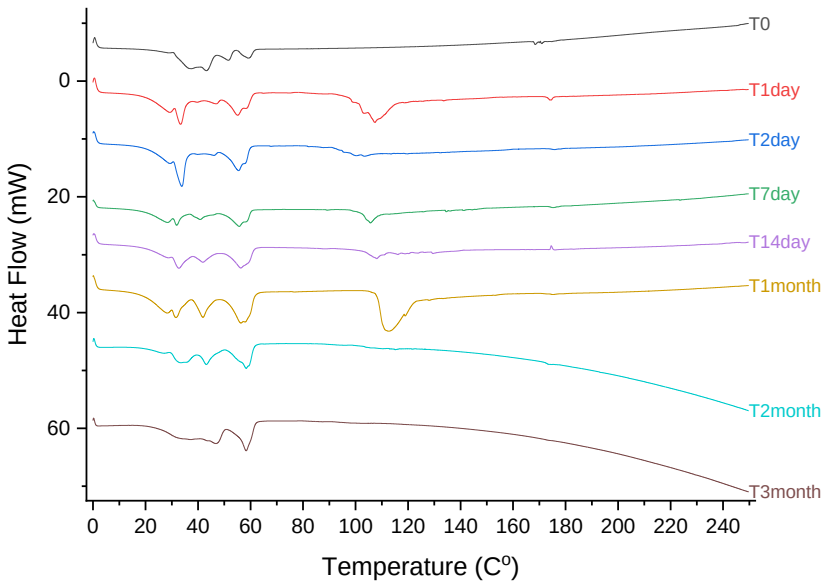


Figure 5.18 DSC of samples stored at accelerated conditions up to 3 months (37 ± 1°C, 75% RH) (Exo-up)

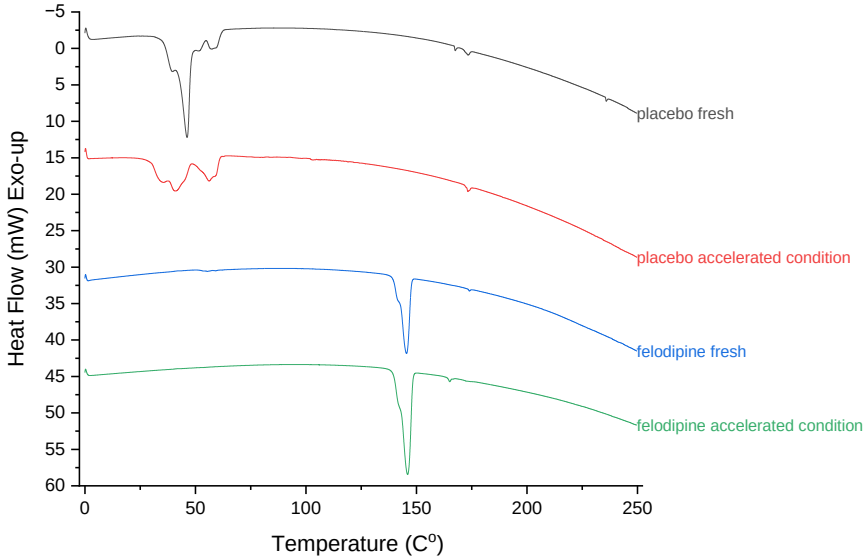


Figure 5.19 DSC of drug-free print and pure felodipine (fresh, 3 days at (37 ± 1°C, 75% RH))

FTIR spectra of stability samples show no changes from fresh samples. This may be because of the limited detection of the technique. X-ray diffraction (Figure 5.20) shows no felodipine related peak, however, a peak related to precirol at angle 5° disappeared after one month indicating a change in stability together with the change in the DSC at the same time point. Additionally, optical images (Figure 5.15B) showed no sign of crystallisation of either API or matrix. This might be due to high surface mobility due to partial melting of the formulation at storage temperature.

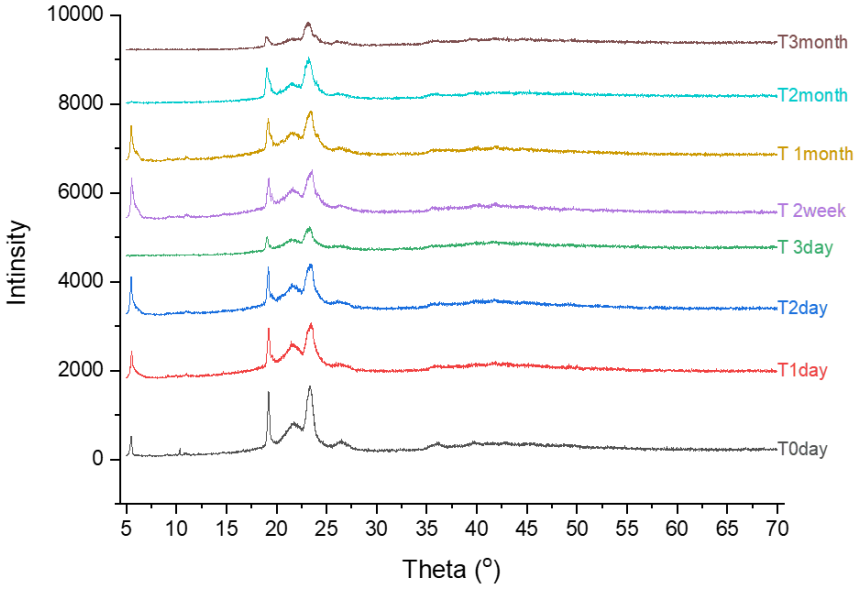


Figure 5.20 XRPD of samples stored at accelerated conditions up to 3 months (37 ± 1°C, 75% RH)

Furthermore, SEM/EDS showed an even distribution of felodipine within the formulation with no crystallisation (Figure 5.16B). Raman spectra results are consistent with EDS, where felodipine appears to be evenly distributed and no crystallisation present (Figure 5.17). The heat-map is similar for API and excipients which is also resembles the fresh sample. Together with coloured map which appear in purple colour as a result of blue and red maps overlap (Figure 5.21).

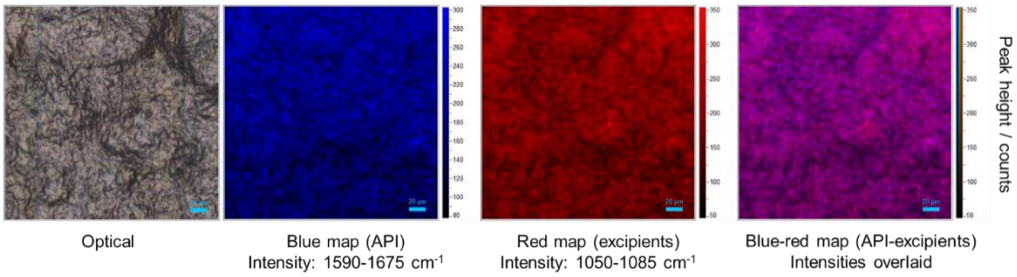


Figure 5.21 Raman map for samples stored at accelerated conditions (37 ± 1°C, 75% RH)

For additional information, 12 month samples were stored at room temperature, 0% RH and were then switched to be stored for 3 days under accelerated conditions (37 ± 1°C, 75% RH), tested by optical microscope (Figure 5.22) and Raman (top surface, cross section (multiple areas)) (Figure 5.23). The presented results resemble the samples stored at 37 ± 1°C, 75% RH for 2 months in drug distribution. It is anticipated that the temperature used in the accelerated study re-solubilised the felodipine in the matrix.

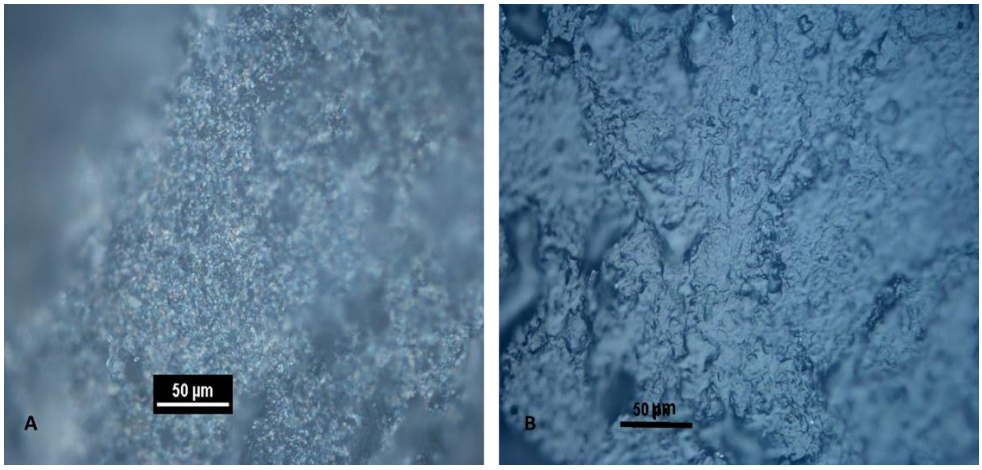


Figure 5.22 Optical microscope images of A) F3 stored at (room temperature, 0% RH) for 12 month, B) same sample stored at (37 ± 1°C, 75% RH) after (A) was collected

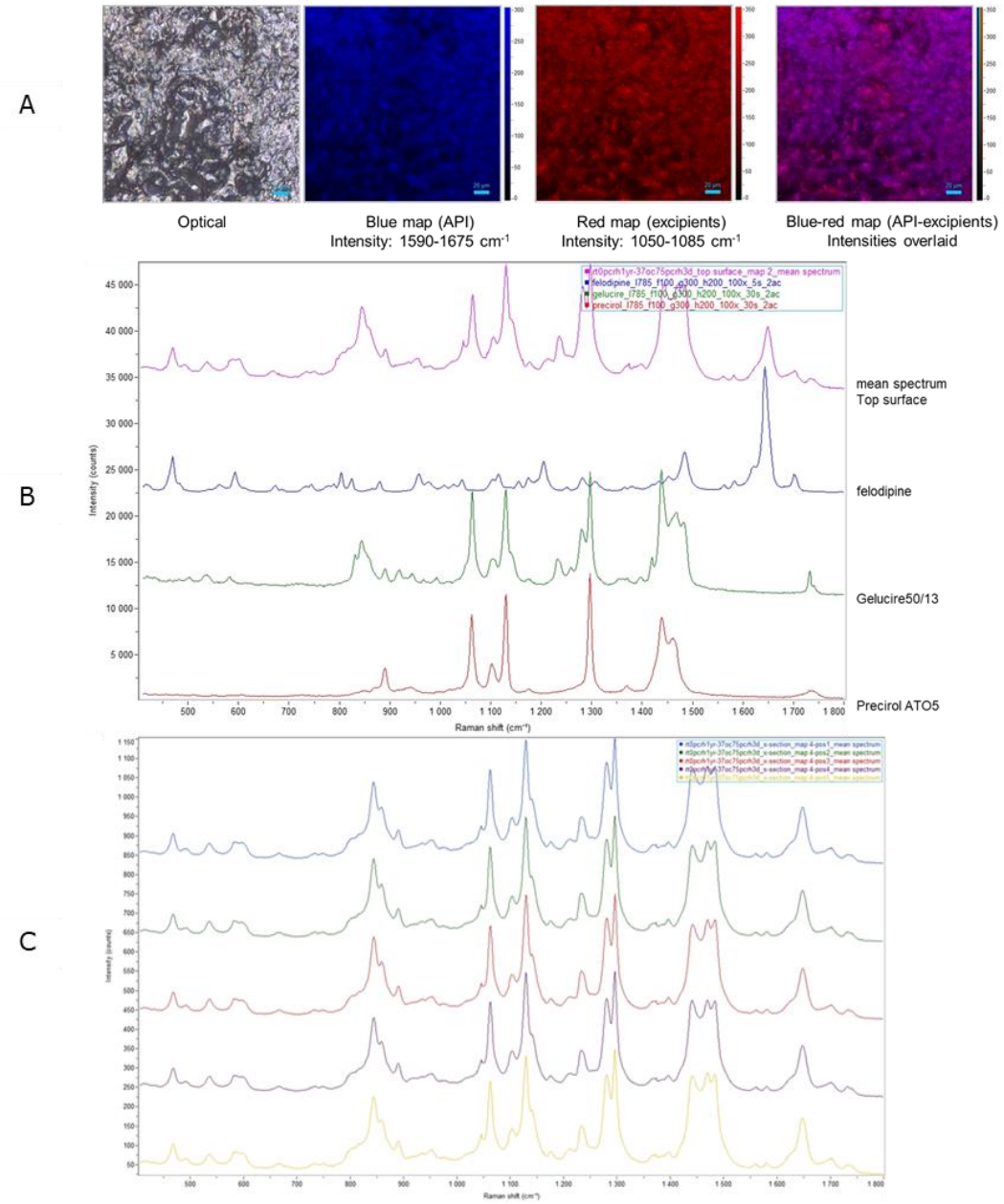


Figure 5.23 Raman spectroscope after storage condition changed from (room temperature, 0%RH) to (37 ± 1°C, 75% RH), A) coloured map of top surface. B) Raman spectra of top surface compared to raw materials. C) Raman spectra of cross-sectional Raman spectra from different sites

The release study presented an increase in the drug release rate of all samples stored at different conditions from fresh samples (Figure 5.24) which is comparable to some other studies [395, 407]. Conversely, one study

demonstrated no change in the release rate on storage [382]. Formulation composition, lipid ratio, API used, and study conditions directly affect possible change in drug release from study to another. The mechanism behind the increase in drug release rate can be describe in different ways for both distinct stability conditions in comparison to freshly printed samples. In samples stored at room temperature, reorganisation of PEG chain and fatty acids ageing results in acceleration in the drug release due to API being dissolved in the lipid matrix with time together with blooming of lipids in flake-shape crystals that increase the surface area [408]. In contrast, for samples exposed to accelerated conditions, at 37° C, part of the excipient was melted which promoted drug solubility within the matrix.

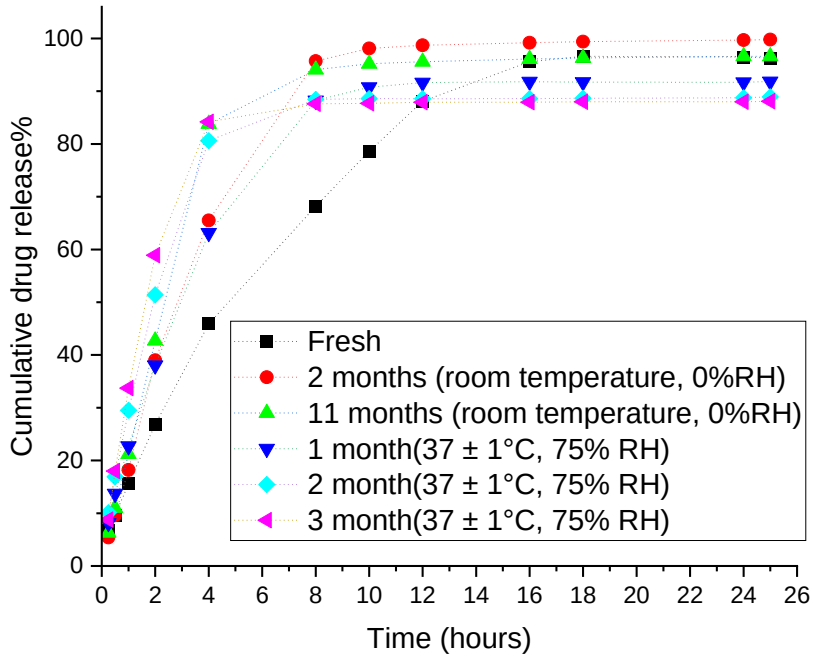


Figure 5.24 Drug release from sustained release formulation (effect of aging and storage conditions) (n=3)

For further investigation, I studied the effect of storage temperature on a higher drug loaded formulation. Drug release from fresh samples 8:2, Gelucire® 50/13: Precirol® ATO5 loaded with 15% felodipine was compared to two months samples stored in either room temperature or fridge (4 - 8° C)

both at 0% humidity. Results demonstrated enhancement of drug release if stored at the higher (room) temperature (Figure 5.25). As previously mentioned, the increase in the dissolution in samples stored at room temperature is due to reorganisation of the matrix. Despite that the manufacturer of the implemented excipients did not specify a storage conditions of below ambient temperature, it has been noted that such excipients need to be stored at 4-8° C to maintain its stability (personal communication, Quotient Sciences).

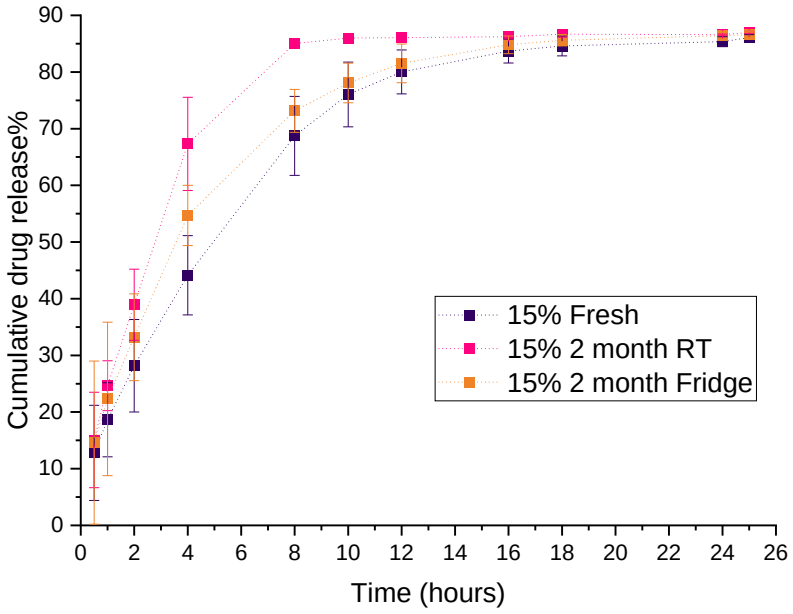


Figure 5.25 Effect of storage temperature in drug release (room temperature, 4-8° C) (n=3)

From all analyses performed on stability study we can summarise the major observations for samples stored at variable conditions in Table 5.5. However, it should be noted that such observed changes may not have an effective therapeutic effect. An *in-vivo* study showed that the bioavailability remain unchanged for a hydrophilic drug combined with Gelucire® 50/13 despite the drastic change in dissolution profile (mean dissolution time) for samples stored for long-term in different storage temperatures [409]. Furthermore, Dennis *et al.* advised that no specific storage requirement for gelucire solid

dispersion, since significant thermographic change have no effect in drug plasma level [410].

Table 5.5 Comparison between samples stored at room temperature, 0% RH and accelerated conditions (37 ± 1°C, 75% RH) using DSC, FTIR, XRPD, Dissolution, SEM, PLM and Raman

	37 ± 1°C, 75% RH	Room temperature, 0% RH	Comments
DSC	A new peak appears from day 1 above 110° C then disappeared at 2 months	Same as fresh	
FTIR	No change from fresh samples in both		
XRPD	Precirol characteristic peak at 5° disappeared after 1 month	A felodipine characteristic peak appeared at 10°	
Release	Increase in rate but decrease in amount than fresh	Increase in rate and amount than fresh	Insignificant difference
SEM	Crystallisation of matrix but not in drug	Crystallisation of the drug	The increase in temperature stabilise the matrix, preventing the drug from nucleation

Optical microscpe	No sign of crystallisation in both matrix and drug	Crystallisation of the matrix with some drug crystals	Same as SEM
Raman	Similar to fresh samples. No phase separation or drug crystallisation. Drug evenly distributed	Phase-separated regions of crystalline API and excipient matrix (the latter often containing a small amount of crystalline API)	

5.5 Conclusions

Wax-based formulations were developed with different ratios of excipients to produce sustained release of felodipine, a poorly water soluble active from printed tablets. The developed formulations show excellent printability and compatibility. Moreover, the release studies demonstrated a significant difference in cumulative drug release between formulations of highest and lowest Gelucire® 50/13 composition (9 vs. 5), and formulations of different felodipine concentrations (2.5, 10, 15%). Furthermore, stability studies revealed that a high storage temperature of 37 °C could prevent crystal growth and maintain the amorphous state. Indeed, stability studies over two months show that storage at 4 -8° C preserves freshly printed tablet release profile. Additionally, felodipine can go back to its amorphous state after recrystallisation when samples are exposed to accelerated conditions (37 ± 1°C, 75% RH) after being at (room temperature, 0% RH) for long time (>1 year).

5.6 Chapter appendix: supplementary information

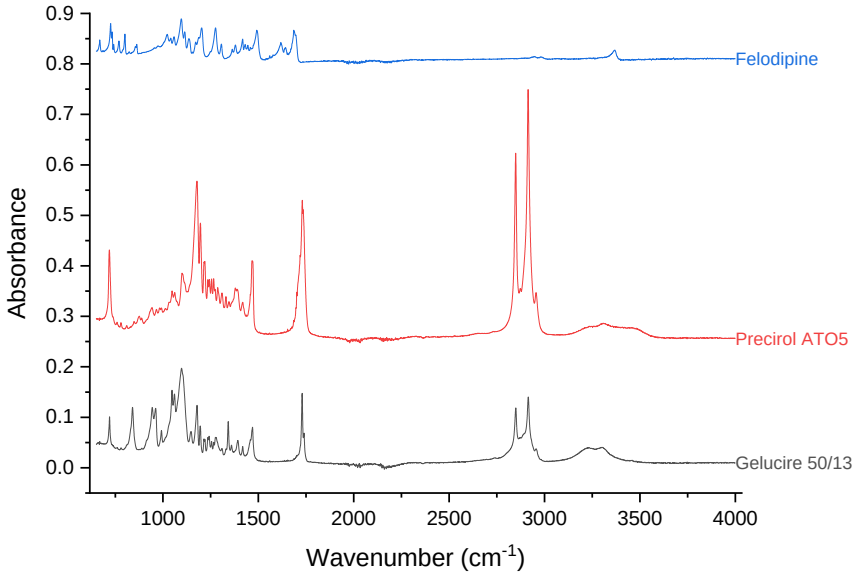


Figure S5.26 FTIR of felodipine, Gelucire® 50/13 and Precirol® ATO5

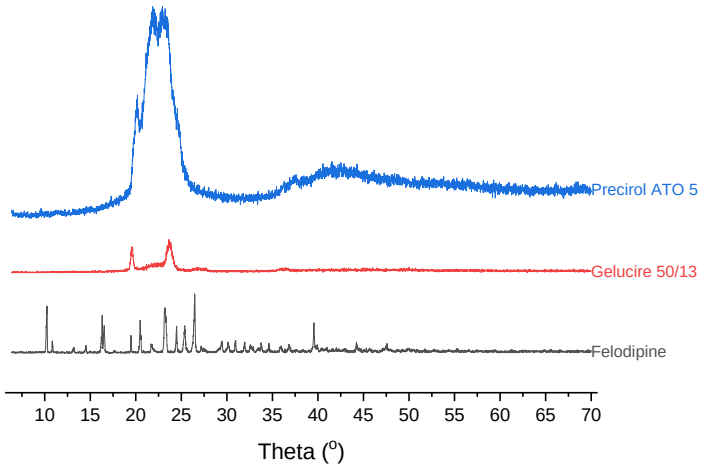


Figure S5.27 XRPD of felodipine, Gelucire® 50/13 and Precirol® ATO5

Table S5.6 Tablet friability data of F1 (8:2 Gelucire® 50/13: Precirol® ATO, 10% felodipine)

Initial weight (g)	Finish weight (g)	Friability (%)
0.9979	0.9913	**0.661**

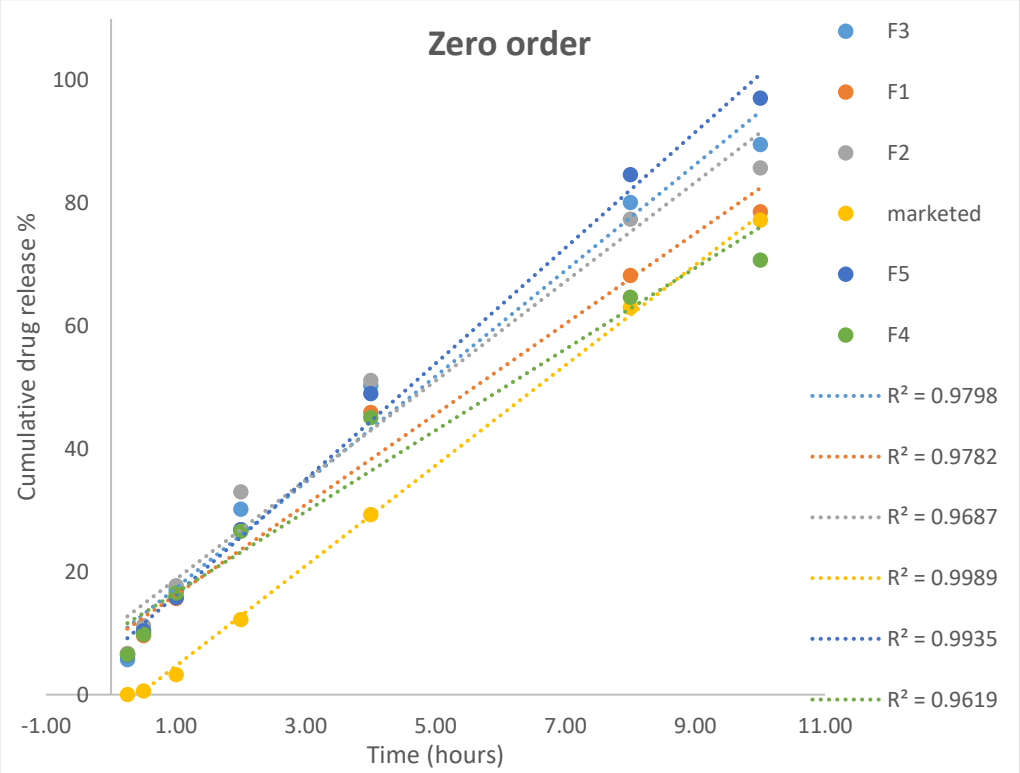


Figure S5.28 Data fitting to zero order kinetics model of felodipine release from sustained release formulations

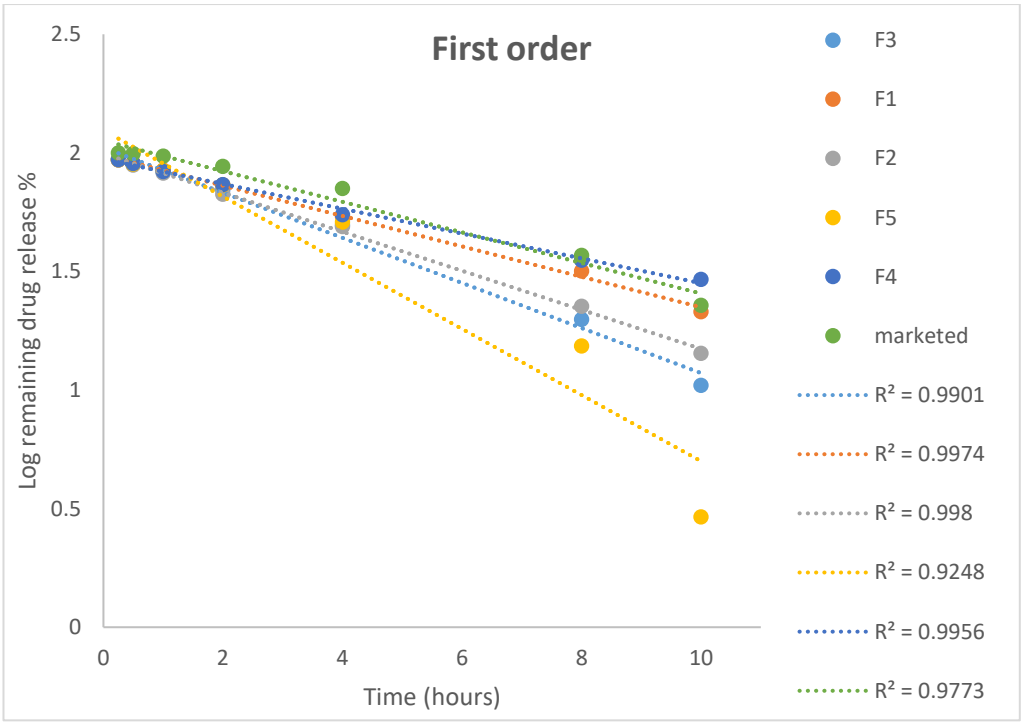


Figure S5.29 Data fitting to first order kinetics model of felodipine release from sustained release formulations

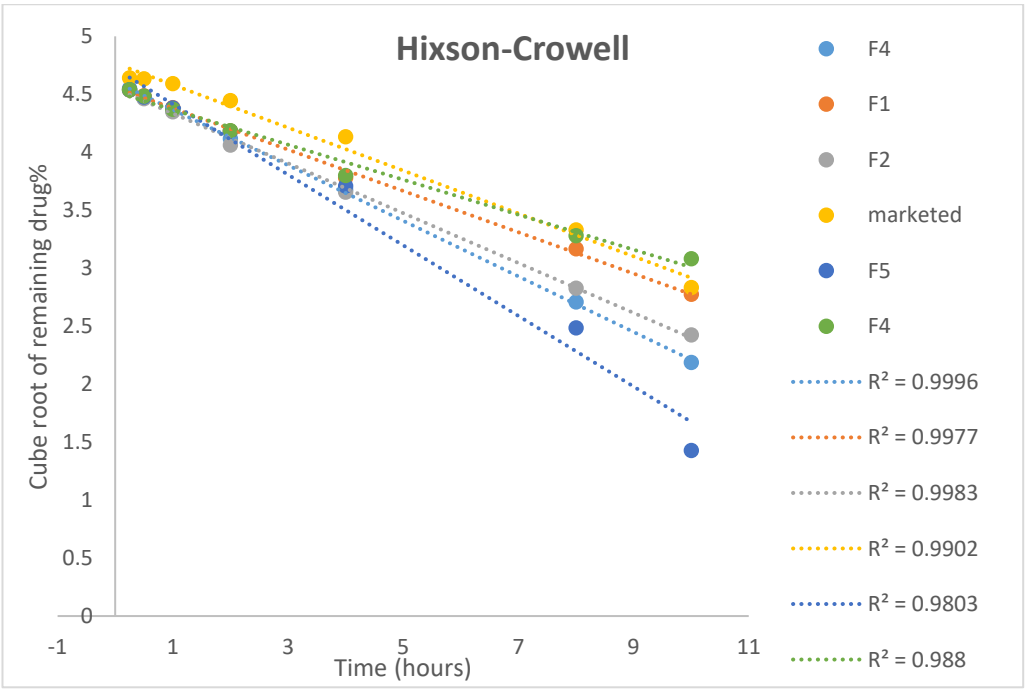


Figure S5.30 Data fitting to Hixon-Crowell kinetics model of felodipine release from sustained release formulations

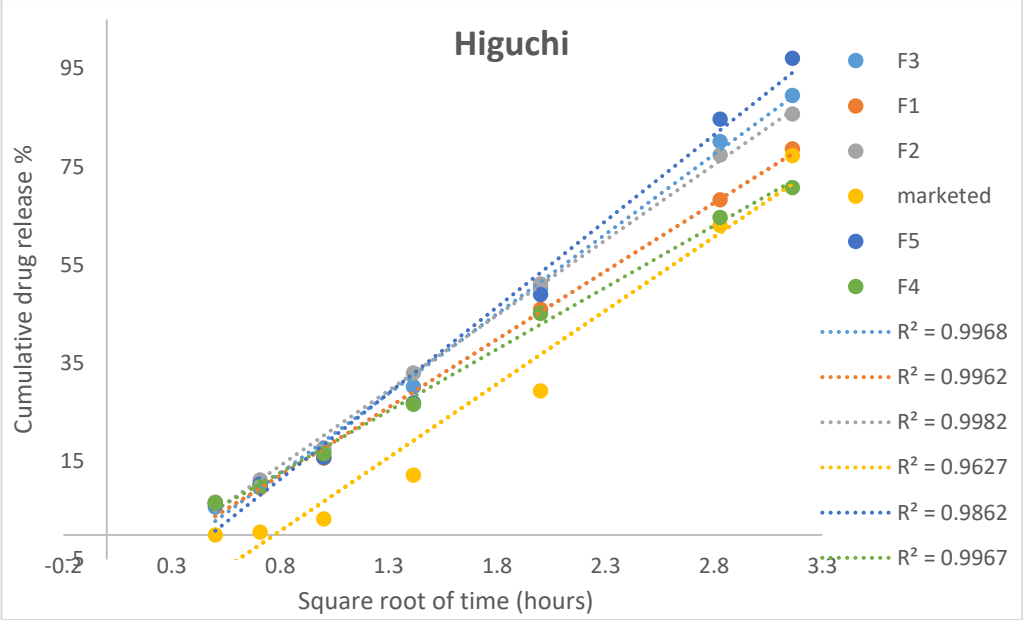


Figure S5.31 Data fitting to Higuchi kinetics model of felodipine release from sustained release formulations

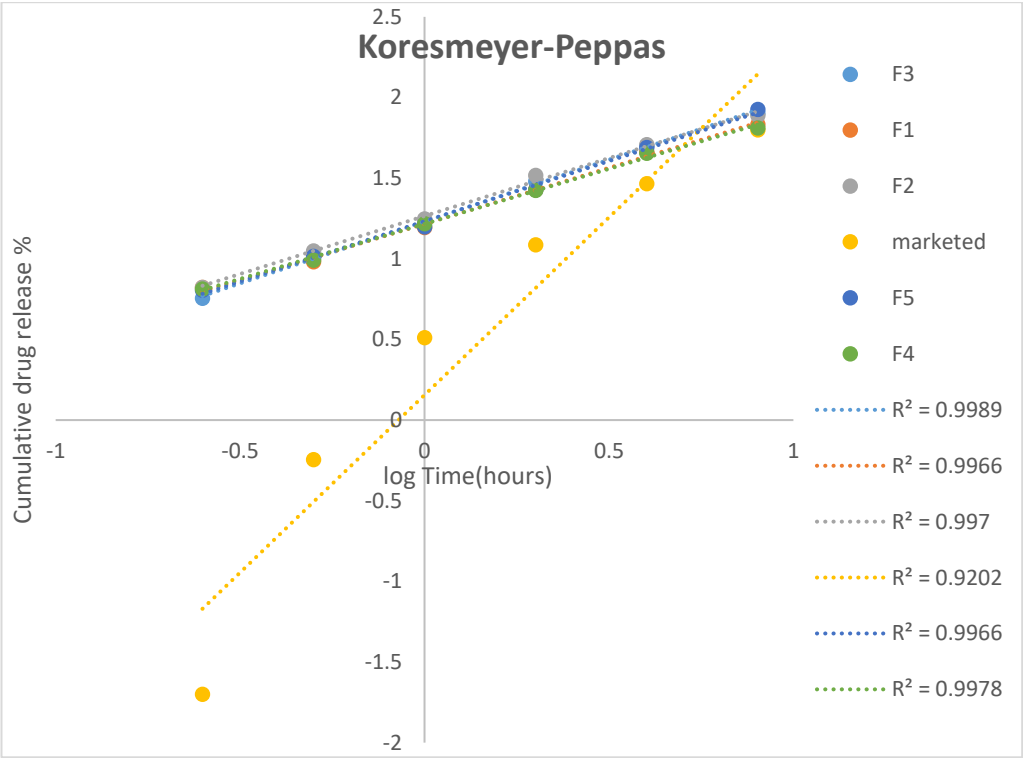


Figure S5.32 Data fitting to Koresmeyer-Peppas kinetics model of felodipine release from sustained release formulations

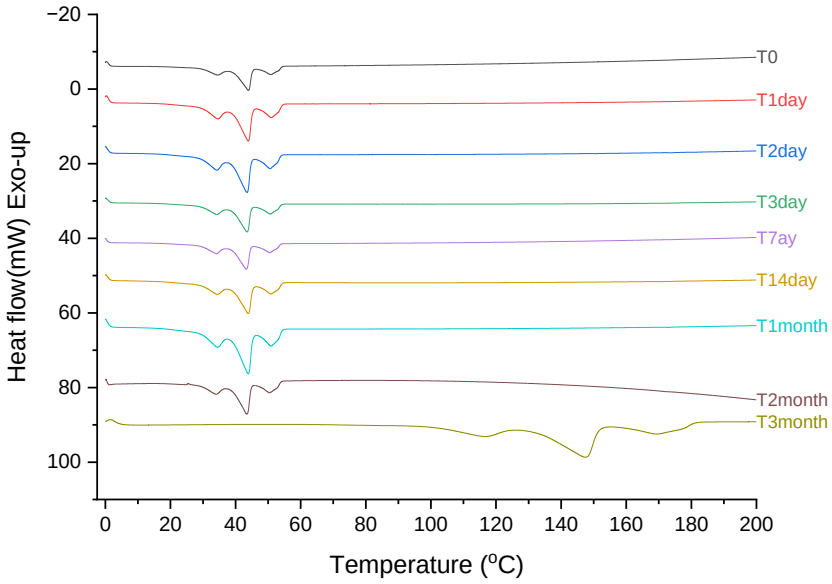


Figure S5.33 DSC 2nd heat cycle of samples stored at (37 ± 1°C, 75% RH)

6 Conclusions and future work

6.1 Conclusions

This thesis brings together a study of public acceptance of 3D printed solid-dosage form medicines and the use of extrusion 3D printing to improve the bioavailability of a poorly water soluble drug in the form of immediate and sustained release lipidic based formulation.

Public acceptance of 3D printed medicines was gathered by focus groups conducting (Chapter 3). Safety concerns of technology misuse and dosage inaccuracy were raised during the discussions along with regulatory issues. Further depth and knowledge about 3D printed medicines investigated the participants preference toward standard shape tablets/capsules of moderate size and lighter colours. Future consumers saw that adaptation to a new technology comes from repeated exposure. This pilot study gives insights to public acceptability of new pharmaceutical manufacturing technology and provides a guide for policy and regulatory innovations.

The outcome of the public consultation was used to guide tablet features in the design of 3D printed medicines to enhance the water solubility of felodipine, a poorly water soluble drug. In Chapter 4, an immediate release formulation was developed by extrusion of pre-melted drug-excipients lipidic based ink. A solid dispersion of the drug was formed in the polymeric-lipid based tablets enhanced the solubility of felodipine.

Sustained release formulations were then developed (Chapter 5) to accommodate felodipine pharmacokinetics. Different ratios of lipid (Gelucire® 50/13) and a release modifier (Precirol® ATO5) were used to study their effect on drug release. A higher amount of drug release modifier (1:1 Gelucire® 15/13: Precirol® ATO5) resulted in significant differences in cumulative drug release, not observed when only minor changes in formulation were applied (9:1, 8:2, 7:3). Felodipine loading in the dosage form also had a significant

difference in the cumulative release from the printed tablets. Due to stability issues that are known to occur with lipids, stability studies were necessary. Multiple storage conditions were studied. Storage at low temperature (4°C) maintained the release rate observed for the freshly printed dosage form. Storage at room temperature and 0% RH resulted in crystallisation of felodipine and the matrix. Additionally, storage at 37 °C and 75% RH seemed to help preserve the amorphous nature of the felodipine. The rate of drug release was increased than freshly printed formulation when stored at room temperature and 37 °C, despite the partial crystallisation of samples at room temperature. Indeed, a storage at 4-8 °C is recommended for semi-solid/solid lipids.

Even though the developed formulations showed instability, such dosage forms could still be implemented in clinical trials where the dosage form could be administered shortly after manufacture, and dosage adjustment can easily be made with the versatility of 3D printing. Additionally, lipids are commonly used in clinical trials for the purpose of solubility enhancement. Furthermore, personalised and on-demand medicines would also be printed freshly when the patient needs them, and the dispensed amount can be adjusted to product stability.

6.2 Future work

Although the primary thesis goal was accomplished, further interventions need to take place to develop suitable pharmaceutical product. Modification of excipients selection or addition of a stabilising material would be an option to maintain product stability over longer time periods. Adjustment of heating and cooling rate during product development is also a choice, however it is challenging from practicality perspective. Additionally, performing an *in-vivo* study would be advantageous to assess if the *in-vitro* release profile change have a significant bioavailability effect.

From the work done and presented in this thesis, public engagement in scientific research is very important to maximise the potential benefits of the research. In addition, adaptability of extrusion 3D printing and its ability to create bespoke drug products of complex geometries opens a new horizon in pharmaceutical manufacturing and personalised medicines.

References

1. Mohammed S. Alqahtani, et al., *Advances in Oral Drug Delivery.* Front Pharmacol, 2021. **12**.DOI: 10.3389/fphar.2021.618411.

2. Deviprasad Sahoo, et al., *Oral drug delivery of nanomedicine*, in *Theory and Applications of Nonparenteral Nanomedicines*, Prashant Kesharwani, Sebastien Taurin and Khaled Greish, Editors. 2021, Academic Press: Science Direct. p. 181-207.

3. Pragasam Viswanathan, Yuvashree Muralidaran and Gokulakannan Ragavan, *Challenges in oral drug delivery: a nano-based strategy to overcome*, in *Nanostructures for Oral Medicine*, Ecaterina Andronescu and Alexandru Mihai Grumezescu, Editors. 2017, Elsevier: Micro and Nano Technologies. p. 173-201.

4. Arpna Indurkhya, et al., *Influence of Drug Properties and Routes of Drug Administration on the Design of Controlled Release System*, in *Dosage Form Design Considerations*, Rakesh K. Tekade, Editor. 2018, Academic Press: Advances in Pharmaceutical Product Development and Research. p. 179-223.

5. Umesh Gupta and Omathanu Perumal, *Dendrimers and Its Biomedical Applications*, in *Natural and Synthetic Biomedical Polymers*, Sangamesh G. Kumbar, Cato T. Laurencin and Meng Deng, Editors. 2014, Elsevier. p. 243-257.DOI: https://doi.org/10.1016/B978-0-12-396983-5.00016-8.

6. Maria Carvalho and Isabel F. Almeida, *The Role of Pharmaceutical Compounding in Promoting Medication Adherence.* Pharm 2022. **15**(9).DOI: 10.3390/ph15091091.

7. Julie A. Mennella and Nuala K. Bobowski, *The sweetness and bitterness of childhood: Insights from basic research on taste preferences.* Physiol. Behav, 2015. **152**(B): p. 502-507.DOI: 10.1016/j.physbeh.2015.05.015.

8. Vangelis Karalis, et al., *Bioavailability and Bioequivalence: Focus on Physiological Factors and Variability*. 2008: Pharm. Res. p. 1956-1962.

9. Ryusuke Takano, et al., *Rate-limiting steps of oral absorption for poorly water-soluble drugs in dogs; prediction from a miniscale dissolution test and a physiologically-based computer simulation.* Pharm Res, 2008. **25**(10): p. 334-2344.DOI: 10.1007/s11095-008-9637-9.

10. Joseph P. O'Shea, et al., *Best practices in current models mimicking drug permeability in the gastrointestinal tract - An UNGAP review.* Eur. J. Pharm. Sci., 2022. **170**.DOI: 10.1016/j.ejps.2021.106098.

11. Yasuhiro Tsume, et al., *The Biopharmaceutics Classification System: Subclasses for in vivo predictive dissolution (IPD) methodology and IVIVC.* Eur J Pharm Sci, 2014. **57**: p. 152-163.DOI: 10.1016/j.ejps.2014.01.009.

12. Ramu Samineni, Jithendra Chimakurthy and Sathish Konidala, *Emerging Role of Biopharmaceutical Classification and Biopharmaceutical Drug Disposition System in Dosage form Development: A Systematic Review.* Turk J Pharm Sci, 2022. **19**(6): p. 706-713.DOI: 10.4274/tjps.galenos.2021.73554.

13. Jiunn H. Lin, Masato Chiba and Thomas A. Baillie, *Is the Role of the Small Intestine in First-Pass Metabolism Overemphasized?* Pharmacol. Rev., 1999. **51**(2): p. 135-158.

14. Gordon L. Amidon, et al., *A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability.* Pharm. Res., 1995. **12**: p. 413–420.DOI: 10.1023/a:1016212804288.

15. Sven Stegemann, et al., *When poor solubility becomes an issue: From early stage to proof of concept.* Eur. J. Pharm. Sci., 2007. **31**(5): p. 249-261.DOI: 10.1016/j.ejps.2007.05.110.

16. Deepak Gupta, et al., *Salts of Therapeutic Agents: Chemical, Physicochemical, and Biological Considerations.* Mol., 2018. **23**(7).DOI: 10.3390/molecules23071719.

17. Daniela Hartmann Jornada, et al., *The Prodrug Approach: A Successful Tool for Improving Drug Solubility.* Mol., 2015. **21**(1).DOI: 10.3390/molecules21010042.

18. Ahmed Almotairy, et al., *Effect of pH Modifiers on the Solubility, Dissolution Rate, and Stability of Telmisartan Solid Dispersions Produced by Hot-melt Extrusion Technology.* J Drug Deliv Sci Technol., 2021.DOI: 10.1016/j.jddst.2021.102674.

19. Phennapha Saokham, et al., *Solubility of Cyclodextrins and Drug/Cyclodextrin Complexes.* Mol., 2018. **23**(5).DOI: 10.3390/molecules23051161.

20. Dóra Csicsák, et al., *The Effect of the Particle Size Reduction on the Biorelevant Solubility and Dissolution of Poorly Soluble Drugs with Different Acid-Base Character.* Pharmaceutics, 2023. **15**(1).DOI: 10.3390/pharmaceutics15010278.

21. Kavita Joshi, et al., *Nanocrystalization: An Emerging Technology to Enhance the Bioavailability of Poorly Soluble Drugs.* Pharm Nanotechnol, 2019. **7**(4): p. 259-278.DOI: 10.2174/2211738507666190405182524.

22. Gislaine Kuminek, et al., *Cocrystals to facilitate delivery of poorly soluble compounds beyond-rule-of-5.* Adv Drug Deliv Rev, 2016. **101**: p. 143-166.DOI: 10.1016/j.addr.2016.04.022.

23. Zun Huang, Sven Staufenbiel and Roland Bodmeier, *Combination of co-crystal and nanocrystal techniques to improve the solubility and dissolution rate of poorly soluble drugs.* Pharm Res, 2022. **39**(5): p. 949-961.DOI: 10.1007/s11095-022-03243-9.

24. Shashi Kiran Misra and Kamla Pathak, *Supercritical fluid technology for solubilization of poorly water soluble drugs via micro- and naonosized particle generation.* ADMET DMPK, 2020. **8**(4): p. 355-374.DOI: 10.5599/admet.811.

25. Avinash Ramrao Tekade and Jyoti Narayan Yadav, *A Review on Solid Dispersion and Carriers Used Therein for Solubility Enhancement of Poorly Water Soluble Drugs.* Adv Pharm Bull, 2020. **10**(3): p. 359-369.DOI: 10.34172/apb.2020.044.

26. Rina J. Chokshi, et al., *Improving the Dissolution Rate of Poorly Water SolubleDrug by Solid Dispersion and Solid Solution—Pros and Cons.* drug Deliv, 2007. **14**: p. 33-45.DOI: 10.1080/10717540600640278.

27. Juan Xu, et al., *Mifepristone polymorph with enhanced solubility, dissolution and oral bioavailability.* Steroids, 2020. **159**.DOI: 10.1016/j.steroids.2020.108649.

28. Anna Karagianni, Kyriakos Kachrimanis and Ioannis Nikolakakis, *Co-Amorphous Solid Dispersions for Solubility and Absorption Improvement of Drugs: Composition, Preparation, Characterization and Formulations for Oral Delivery.* Pharmaceutics, 2018. **10**(3).DOI: 10.3390/pharmaceutics10030098.

29. Alla B. Mirgorodskaya, et al., *Supramolecular systems based on gemini surfactants for enhancing solubility of spectral probes and drugs in aqueous solution.* Colloids Surf. A: Physicochem. Eng. Asp, 2016. **510**: p. 33-42.DOI: https://doi.org/10.1016/j.colsurfa.2016.07.065.

30. Yan Zheng, et al., *Sugar Fatty Acid Esters*, in *Polar Lipids*, Moghis U. Ahmad and Xuebing Xu, Editors. 2015, Elsevier. p. 215-243.DOI: https://doi.org/10.1016/B978-1-63067-044-3.50012-1.

31. William N. Charman, *Lipids, Lipophilic Drugs, and Oral Drug Delivery—Some Emerging Concepts.* J. Pharm. Sci., 2000. **89**(8): p. 967-978.DOI: 10.1002/1520-6017(200008)89:8<967::aid-jps1>3.0.co;2-r.

32. Christopher J H Porter, Natalie L Trevaskis and William N Charman, *Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs.* Nat Rev Drug Discov, 2007. **6**(3): p. 231-248.DOI: https://doi.org/10.1038/nrd2197.

33. Ronak Savla, et al., *Review and analysis of FDA approved drugs using lipid-based formulations.* Drug Dev. Ind. Pharm, 2017. **43**(11): p. 1743-1758.DOI: 10.1080/03639045.2017.1342654.

34. Saba Khan, et al., *Nanostructured lipid carriers: An emerging platform for improving oral bioavailability of lipophilic drugs.* Int J Pharm Investig, 2015. **5**(4): p. 182-191.DOI: 10.4103/2230-973X.167661.

35. Hina Shrestha, Rajni Bala and Sandeep Arora, *Lipid-Based Drug Delivery Systems.* J Pharm (Cairo), 2014.DOI: 10.1155/2014/801820.

36. Akhilesh K. Singh, et al., *Engineering Nanomaterials for Smart Drug Release: Recent Advances and Challenges*, in *Applications of Targeted Nano Drugs and Delivery Systems*, Shyam S. Mohapatra, et al., Editors. 2019, Elsevier: Micro and Nano Technologies. p. 411-449.DOI: 10.1016/B978-0-12-814029-1.00015-6.

37. LianDong Hu, Xing Tang and FuDe Cui, *Solid lipid nanoparticles (SLNs) to improve oral bioavailability of poorly soluble drugs.* J. Pharm. Pharmacol., 2004. **56**(12): p. 1527-1535.DOI: 10.1211/0022357044959.

38. Kanchan Kohli, et al., *Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability.* Drug Discov. Today, 2010. **15**(21-22): p. 958-965.DOI: 10.1016/j.drudis.2010.08.007.

39. Daniela Hartmann Jornada, et al., *The Prodrug Approach: A Successful Tool for Improving Drug Solubility.* Mol., 2016. **21**(1).DOI: 10.3390/molecules21010042.

40. Sandeep Kalepu and Vijaykumar Nekkanti, *Insoluble drug delivery strategies: review of recent advances and business prospects.* Acta Pharm. Sin. B., 2015. **5**(5): p. 442-453.DOI: 10.1016/j.apsb.2015.07.003.

41. Thorsteinn Loftsson and Marcus E Brewster, *Pharmaceutical applications of cyclodextrins: basic science and product development.* J. Pharm. Pharmacol., 2010. **62**(11): p. 1607-1621.DOI: 10.1111/j.2042-7158.2010.01030.x.

42. Smita Salunke, et al., *Oral drug delivery strategies for development of poorly water soluble drugs in paediatric patient population.* Adv. Drug Deliv. Rev., 2022. **190**.DOI: 10.1016/j.addr.2022.114507.

43. Bernd U. Riebesehl, *Drug Delivery with Organic Solvents or Colloidal Dispersed Systems*, in *The Practice of Medicinal Chemistry (Fourth Edition)*, Camille Georges Wermuth, et al., Editors. 2015, Academic Press. p. 699-722.DOI: https://doi.org/10.1016/B978-0-12-417205-0.00029-8.

44. Deepshikha Rawat, et al., *Role of Nanotechnology in Nutrient Delivery.* Nanotechnology Horizons in Food Process Engineering: Volume 3: Trends, Nanomaterials, and Food Delivery, 2023: p. 133.

45. Stéphane Gibaud and David Attivi, *Microemulsions for oral administration and their therapeutic applications.* Expert Opin. Drug Deliv., 2012. **9**(8).DOI: 10.1517/17425247.2012.694865.

46. Yogita R. Gonnade, Kamlesh Niranjane and Arati Ambatkar, *Lipid: an emerging platform for lipid based drug delivery system.* World J Pharm Pharm Sci, 2014. **3**: p. 572-589.DOI: 0.1016/j.ejpb.2009.06.001.

47. Dinesh K. Mishra, Ruchita Shandilya and Pradyumna K. Mishra, *Lipid based nanocarriers: a translational perspective.* Nanomedicine: NBM, 2018. **14**(7): p. 2023-2050.DOI: 10.1016/j.nano.2018.05.021.

48. Angel Tan, Shasha Rao and Clive A. Prestidge, *Transforming Lipid-Based Oral Drug Delivery Systems into Solid Dosage Forms: An Overview of Solid Carriers, Physicochemical Properties, and Biopharmaceutical Performance.* Pharm. Res., 2013. **30**: p. 2993-3017.DOI: 10.1007/s11095-013-1107-3.

49. Elham Nemati, et al., *Ethambutol-Loaded Solid Lipid Nanoparticles as Dry Powder Inhalable Formulation for Tuberculosis Therapy.* AAPS PharmSciTech, 2019. **20**(3).DOI: 10.1208/s12249-019-1334-y.

50. Deepa Nakmode, et al., *Fundamental Aspects of Lipid-Based Excipients in Lipid-Based Product Development.* Pharmaceutics, 2022. **14**(4).DOI: 10.3390/pharmaceutics14040831.

51. Martin Kuentz, *Lipid-based formulations for oral delivery of lipophilic drugs.* Drug Discov. Today Technol., 2012. **9**(2): p. 97-104.DOI: https://doi.org/10.1016/j.ddtec.2012.03.002.

52. Anette Müllertz, et al., *New perspectives on lipid and surfactant based drug delivery systems for oral delivery of poorly soluble drugs.* J. Pharm. Pharmacol., 2010. **62**(11): p. 1622-1636.DOI: 10.1111/j.2042-7158.2010.01107.x.

53. Yingjie Zhai and Guangxi Zhai, *Advances in lipid-based colloid systems as drug carrier for topic delivery.* J. Control. Release., 2014. **193**: p. 90-99.DOI: 10.1016/j.jconrel.2014.05.054.

54. Yvonne Rosiaux, et al., *Solid lipid excipients - matrix agents for sustained drug delivery.* J. Control. Release., 2014. **188**: p. 18-30.DOI: 10.1016/j.jconrel.2014.06.004.

55. Salome Amarachi Chime and Ikechukwu V. Onyishi, *Lipid-based drug delivery systems (LDDS): Recent advances and applications of lipids in*

drug delivery. Afr J Pharm Pharmacol 2013. **7**(48): p. 3034-3059.DOI: 10.5897/AJPPX2013.0004.

56. Piyush Jaiswal, Bina Gidwani and Amber Vyas, *Nanostructured lipid carriers and their current application in targeted drug delivery.* Artif. Cells Nanomed. Biotechnol., 2014. **44**(1): p. 27-40.DOI: https://doi.org/10.3109/21691401.2014.909822.

57. Roohi Kesharwani, et al., *Lipid-Based Drug Delivery System (LBDDS): An Emerging Paradigm to Enhance Oral Bioavailability of Poorly Soluble Drugs.* Biomedical Materials & Devices 2022.DOI: https://doi.org/10.1007/s44174-022-00041-0.

58. Viveksarathi Kunasekaran and Krishnamoorthy Kannan, *Effect of the moist-heat sterilization on fabricated nanoscale solid lipid particles containing rasagiline mesylate.* Int J Pharm Investig, 2015. **5**(2): p. 87-91.DOI: 10.4103/2230-973X.153383.

59. Karen L. Edelblum and Jerrold R. Turner, *Epithelial Cells: Structure, Transport, and Barrier Function*, in *Mucosal Immunology (Fourth Edition)*, Jiri Mestecky, et al., Editors. 2015, Academic Press. p. 187-210.

60. Sabyasachi Maiti, *Nanometric Biopolymer Devices for Oral Delivery of Macromolecules with Clinical Significance*, in *Multifunctional Systems for Combined Delivery, Biosensing and Diagnostics*, Alexandru Mihai Grumezescu, Editor. 2017, Elsevier. p. 109-138.

61. Michael J. Hackett, et al., *Fatty acids as therapeutic auxiliaries for oral and parenteral formulations.* Adv. Drug Deliv. Rev., 2013. **65**(10): p. 1331-1339.DOI: 10.1016/j.addr.2012.07.012.

62. Tuulikki Lindmark, Yukitaka Kimura and Per Artursson, *Absorption enhancement through intracellular regulation of tight junction permeability by medium chain fatty acids in Caco-2 cells.* J Pharmacol Exp Ther, 1998. **284**(1): p. 362-369.

63. Marion Joseph Fedoruk and S. Hong, *Gastrointestinal System*, in *Encyclopedia of Toxicology (Third Edition)*, Philip Wexler, Editor. 2014, Academic Press. p. 702-705.

64. Michael J. Mitchell, et al., *Engineering precision nanoparticles for drug delivery.* Nat. Rev. Drug Discov, 2020. **20**: p. 101-124.DOI: 10.1038/s41573-020-0090-8.

65. Howard S. Kruth, *Receptor-independent fluid-phase pinocytosis mechanisms for induction of foam cell formation with native LDL particles.* Curr Opin Lipidol, 2011. **22**(5): p. 386-393.DOI: 10.1097/MOL.0b013e32834adadb.

66. Helge Ewers and Ari Helenius, *Lipid-Mediated Endocytosis.* Cold Spring Harb Perspect Biol, 2011. **3**(8).DOI: 10.1101/cshperspect.a004721.

67. Joshua J. Rennick, Angus P. R. Johnston and Robert G. Parton, *Key principles and methods for studying the endocytosis of biological and nanoparticle therapeutics.* Nat. Nanotechnol, 2021. **16**: p. 266-276.DOI: https://doi.org/10.1038/s41565-021-00858-8.

68. Xingwang Zhang and Wei Wu, *Ligand-mediated active targeting for enhanced oral absorption.* Drug Discov. Today, 2014. **19**(7): p. 898-904.DOI: 10.1016/j.drudis.2014.03.001.

69. Ramona Khanum and Haema Thevanayagam, *Lipid peroxidation: Its effects on the formulation and use of pharmaceutical emulsions.* Asian J Pharm Sci, 2017. **12**(5): p. 401-411.DOI: 10.1016/j.ajps.2017.05.003.

70. Jasmine Musakhanian, Jean-David Rodier and Masumi Dave, *Oxidative Stability in Lipid Formulations: a Review of the Mechanisms, Drivers, and Inhibitors of Oxidation.* AAPS PharmSciTech, 2022. **23**(5): p. 151.DOI: 10.1208/s12249-022-02282-0.

71. Veerawat Teeranachaideekul, Rainer Helmut Müller and Varaporn Buraphacheep Junyaprasert, *Encapsulation of ascorbyl palmitate in nanostructured lipid carriers (NLC)--effects of formulation parameters on physicochemical stability.* Int J Pharm, 2007. **340**(1-2): p. 198-206.DOI: 10.1016/j.ijpharm.2007.03.022.

72. Yanzhi Song, et al., *The application of EDTA in drug delivery systems: doxorubicin liposomes loaded via NH4EDTA gradient.* Int J Nanomedicine, 2014. **9**: p. 3611-3621.DOI: 10.2147/IJN.S64602.

73. Delphine Marchaud and Sophie Hughes, *Solid dosage forms from self-emulsifying lipidic formulations.* Pharm. Technol. Eur., 2008. **20**(4).

74. Stephan Sacher and Johannes G. Khinast, *An Overview of Pharmaceutical Manufacturing for Solid Dosage Forms*, in *Process Simulation and Data Modeling in Solid Oral Drug Development and Manufacture*. 2016. p. 311-383.DOI: 10.1007/978-1-4939-2996-2_10.

75. Mohamed A Alhnan, et al., *Emergence of 3D Printed Dosage Forms: Opportunities and Challenges.* Pharm Res, 2016. **33**(8): p. 1817-32.DOI: 10.1007/s11095-016-1933-1.

76. Sarah J Trenfield, et al., *3D Printing Pharmaceuticals: Drug Development to Frontline Care.* Trends Pharmacol Sci, 2018. **39**(5): p. 440-451.DOI: 10.1016/j.tips.2018.02.006.

77. Witold Jamróz, et al., *3D Printing in Pharmaceutical and Medical Applications - Recent Achievements and Challenges.* Pharm Res, 2018. **35**(9): p. 176.DOI: 10.1007/s11095-018-2454-x.

78. Shaban A. Khaled, et al., *3D extrusion printing of high drug loading immediate release paracetamol tablets.* Int J Pharm, 2018. **538**(1-2): p. 223-230.DOI: 10.1016/j.ijpharm.2018.01.024.

79. Jonathan Goole and Karim Amighi, *3D printing in pharmaceutics: A new tool for designing customized drug delivery systems.* Int J Pharm, 2016. **499**(1-2): p. 376-394.DOI: 10.1016/j.ijpharm.2015.12.071.

80. Samuel Clark Ligon, et al., *Polymers for 3D Printing and Customized Additive Manufacturing.* Chem Rev, 2017. **117**(15): p. 10212-10290.DOI: 10.1021/acs.chemrev.7b00074.

81. James Norman, et al., *A new chapter in pharmaceutical manufacturing: 3D-printed drug products.* Adv Drug Deliv Rev, 2017. **108**: p. 39-50.DOI: 10.1016/j.addr.2016.03.001.

82. Hideo Kodama, *Automatic method for fabricating a three-dimensional plastic model with photo-hardening polymer.* Rev. Sci. Instrum, 1981. **52**(11).DOI: https://doi.org/10.1063/1.1136492.

83. Antonio Savini and G.G. Savini, *A Short History of 3D Printing, a Technological Revolution Just Started*, in *2015 ICOHTEC/IEEE International History of High-Technologies and their Socio-Cultural Contexts Conference (HISTELCON)*. 2015, IEEE: Tel-Aviv, Israel. p. 1-8.

84. Bethany C Gross, et al., *Evaluation of 3D printing and its potential impact on biotechnology and the chemical sciences.* Anal Chem, 2014. **86**(7): p. 3240-53.DOI: 10.1021/ac403397r.

85. Shende Pravin and Agrawal Sudhir, *Integration of 3D printing with dosage forms: A new perspective for modern healthcare.* Biomed Pharmacother, 2018. **107**: p. 146-154.DOI: 10.1016/j.biopha.2018.07.167.

86. Niki Parikh and Pranav Sharma, *Three-Dimensional Printing in Urology: History, Current Applications, and Future Directions.* Urol. J, 2018. **121**: p. 3-10.DOI: 10.1016/j.urology.2018.08.004.

87. Zuoxin Zhou, et al., *Printability of calcium phosphate: calcium sulfate powders for the application of tissue engineered bone scaffolds using the 3D printing technique.* Mater Sci Eng C Mater Biol Appl, 2014. **38**: p. 1-10.DOI: 10.1016/j.msec.2014.01.027.

88. Weidong Huang, et al., *Levofloxacin implants with predefined microstructure fabricated by three-dimensional printing technique.* Int J Pharm, 2007. **339**(1-2): p. 33-8.DOI: 10.1016/j.ijpharm.2007.02.021.

89. Ramya Alluru and Sai leela Vanapalli, *3D printing technologies in various applications.* Int. J. Mech. Eng., 2016. **7**(3): p. 396-409.

90. Pamela Robles Martinez, et al., *Fabrication of drug-loaded hydrogels with stereolithographic 3D printing.* Int J Pharm, 2017. **532**(1): p. 313-317.DOI: 10.1016/j.ijpharm.2017.09.003.

91. Jiaxiang Zhang, et al., *Pharmaceutical Additive Manufacturing: a Novel Tool for Complex and Personalized Drug Delivery Systems.* AAPS PharmSciTech, 2018. **19**(8): p. 3388-3402.DOI: 10.1208/s12249-018-1097-x.

92. *Stereolithography (SLA) 3D printing: Technology overview*. 2021 22 Aug 2023]; Available from: https://xometry.eu/en/stereolithography-sla-3d-printing-technology-overview/.

93. John R. Tumbleston, et al., *Continuous liquid interface production of 3D objects.* Science 2015. **347**(6228): p. 1349-1351.DOI: 10.1126/science.aaa2397.

94. Marta Kozakiewicz-Latała, et al., *Binder jetting 3D printing of challenging medicines: From low dose tablets to hydrophobic molecules.* Eur J Pharm Biopharm, 2022. **170**: p. 144-159.DOI: 10.1016/j.ejpb.2021.11.001.

95. Ravikumar Tamil Ponni, Mahalingam Swamivelmanickam and Sivagnanam Sivakrishnan, *3D Printing in Pharmaceutical Technology – A Review.* Int. J. Pharm. Investig., 2020. **10**(1): p. 8-12.DOI: 10.5530/ijpi.2020.1.2.

96. Chris Bailey, et al., *3D-printing and electronic packaging*, in *2016 Pan Pacific Microelectronics Symposium (Pan Pacific)*. 2016, IEEE: Big Island, HI, USA. p. 1-7.

97. Johannes Gartner, *Electroninks Finalizes Enhanced Particle-Free Silver Ink Product for Aerosol Jet Printing*, in *ele times* 2022: online.

98. Kah Fai Leong, et al., *Building porous biopolymeric microstructures for controlled drug delivery devices using selective laser sintering.* Int. J. Adv. Manuf. Technol, 2006. **31**: p. 483-489.DOI: 10.1007/s00170-005-0217-4.

99. Hans Rieder, et al., *Online Monitoring of Additive Manufacturing Processes Using Ultrasound*, in *11th European Conference on Non-Destructive Testing (ECNDT 2014)*. 2014: Prague, Czech Republic. p. 2194-2201.

100. Sanna M. Peltola, et al., *A review of rapid prototyping techniques for tissue engineering purposes.* Ann. Med., 2008. **40**(4): p. 268-280.DOI: https://doi.org/10.1080/07853890701881788.

101. Andrea Alice Konta, Marta García and Dolores R Serrano, *Personalised 3D Printed Medicines: Which Techniques and Polymers Are More Successful?* Bioeng., 2017. **4**(79): p. 1-16.DOI: 10.3390/bioengineering4040079.

102. Shaban A Khaled, et al., *Extrusion 3D Printing of Paracetamol Tablets from a Single Formulation with Tunable Release Profiles Through Control of Tablet Geometry.* AAPS PharmSciTech, 2018. **19**(8): p. 3403-3413.DOI: 10.1208/s12249-018-1107-z.

103. Shaban A Khaled, et al., *Desktop 3D printing of controlled release pharmaceutical bilayer tablets.* Int J Pharm, 2014. **461**(1-2): p. 105-11.DOI: 10.1016/j.ijpharm.2013.11.021.

104. Mohammed S. Algahtani, Abdul Aleem Mohammed and Javed Ahmad, *Extrusion-Based 3D Printing for Pharmaceuticals: Contemporary Research and Applications.* Curr. Pharm. Des., 2018. **24**: p. 1-18.DOI: 10.2174/1381612825666190110155931.

105. Yumin Zhang , et al., *Ceramic green tape extrusion for laminated object manufacturing.* Mater. Lett., 1999. **40**(6): p. 275-279.DOI: https://doi.org/10.1016/S0167-577X(99)00089-0.

106. Abbas Razavykia, et al., *An Overview of Additive Manufacturing Technologies—A Review to Technical Synthesis in Numerical Study of Selective Laser Melting.* J. Mater., 2020. **13**(17).DOI: 10.3390/ma13173895.

107. Athina Liaskoni, Ricky D Wildman and Clive J Roberts, *3D printed polymeric drug-eluting implants.* Int J Pharm, 2021. **597**: p. 120330.DOI: 10.1016/j.ijpharm.2021.120330.

108. Tharmalingam Sivarupan, et al., *A review on the progress and challenges of binder jet 3D printing of sand moulds for advanced casting.* Addit. Manuf., 2021. **40**.DOI: 10.1016/j.addma.2021.101889.

109. M.A. León-Cabezas, Asunción Martínez-García and F.J. Varela-Gandía, *Innovative functionalized monofilaments for 3D printing using fused deposition modeling for the toy industry*, in *Manufacturing Engineering Society International Conference 2017, MESIC 2017*. 2017, Elsevier B.V.: Vigo (Pontevedra), Spain. p. 738-745.

110. Luisa Menano, et al., *Integration of 3D Printing in Art Education: A Multidisciplinary Approach.* Computers in the Schools, 2019. **36**(3): p. 222-236.DOI: https://doi.org/10.1080/07380569.2019.1643442.

111. Iman Dankar, et al., *Assessing Mechanical and Rheological Properties of Potato Puree: Effect of Different Ingredient Combinations and Cooking Methods on the Feasibility of 3D Printing.* Foods, 2019. **9**(1).DOI: 10.3390/foods9010021.

112. Adam M. Pringle, Mark Rudnicki and Joshua M. Pearce, *Wood Furniture Waste–Based Recycled 3-D Printing Filament.* For. Prod. J., 2018. **68**(1): p. 86-95.DOI: 10.13073/FPJ-D-17-00042.

113. Guy A. Bingham, et al., *Rapid manufactured textiles.* Int. J. Comput. Integr. Manuf., 2007. **20**(1): p. 96-105.DOI: 10.1080/09511920600690434.

114. Karnyupha Jittivadhna, Pintip Ruenwongsa and Bhinyo Panijpan, *Beyond textbook illustrations: Hand-held models of ordered DNA and protein structures as 3D supplements to enhance student learning of helical biopolymers.* Biochem Mol Biol Educ, 2010. **38**(6): p. 359-64.DOI: 10.1002/bmb.20427.

115. *RepRap*. [cited 2023 09 August]; Available from: https://reprap.org/wiki/RepRap.

116. Flavia Laffleur and Valérie Keckeis, *Advances in drug delivery systems: Work in progress still needed?* Int. J. Pharm., 2020. **590**.DOI: 10.1016/j.ijpharm.2020.119912.

117. Ajit S. Narang and Sai HS. Boddu, *Excipient Applications in Formulation Design and Drug Delivery*, in *Excipient Applications in Formulation Design and Drug Delivery*, Ajit S. Narang and Sai HS. Boddu, Editors. 2015, Springer, Cham. p. 1-10.DOI: https://doi.org/10.1007/978-3-319-20206-8_1.

118. Shanshan Wang, et al., *A Review of 3D Printing Technology in Pharmaceutics: Technology and Applications, Now and Future.* Pharmaceutics, 2023. **15**(2).DOI: 10.3390/pharmaceutics15020416.

119. Wiebke Kempin, et al., *Immediate Release 3D-Printed Tablets Produced Via Fused Deposition Modeling of a Thermo-Sensitive Drug.* Pharm Res, 2018. **35**(6).DOI: 10.1007/s11095-018-2405-6.

120. Yazhou Wang, et al., *A novel controlled release drug delivery system for multiple drugs based on electrospun nanofibers containing nanoparticles.* J. Pharm. Sci., 2010. **99**(12): p. 4805-4811.DOI: 10.1002/jps.22189.

121. Sena Harmanci, et al., *Production of 3D Printed Bi-Layer and Tri-Layer Sandwich Scaffolds with Polycaprolactone and Poly (vinyl alcohol)-Metformin towards Diabetic Wound Healing.* Polymers, 2022. **14**(23).DOI: 10.3390/polym14235306.

122. Alice Melocchi, et al., *3D printing by fused deposition modeling (FDM) of a swellable/erodible capsular device for oral pulsatile release of drugs.* J Drug Deliv Sci Technol., 2015. **30**: p. 360-367.DOI: 10.1016/j.jddst.2015.07.016.

123. Shaban A. Khaled, et al., *3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles.* J Control Release., 2015. **217**: p. 308-314.DOI: 10.1016/j.jconrel.2015.09.028.

124. Patricio López-Jaramillo, et al., *Polypill: an affordable strategy for cardiovascular disease prevention in low–medium-income countries.* Ther Adv Cardiovasc Dis, 2018. **12**(6): p. 169–174.DOI: 10.1177/1753944718764588.

125. Denise Tiemi Uchida and Marcos Luciano Bruschi, *3D Printing as a Technological Strategy for the Personalized Treatment of Wound Healing.* AAPS PharmSciTech, 2023. **24**(1).

126. Martyna Nizioł, et al., *3D Printing of Thermoresponsive Hydrogel Laden with an Antimicrobial Agent towards Wound Healing Applications.* Bioeng., 2021. **8**(6).DOI: 10.3390/bioengineering8060079.

127. Cristiane Patricia Pissinato Pere, et al., *3D printed microneedles for insulin skin delivery.* Int. J. Pharm., 2018. **544**(2): p. 425-432.DOI: 10.1016/j.ijpharm.2018.03.031.

128. Thapakorn Charoenying, et al., *Development of a novel tablet-shaped floating 3D-printed device with adjustable floating time as floating drug delivery systems provided zero-order release kinetics.* J Drug Deliv Sci Technol., 2023. **84**.DOI: 10.1016/j.jddst.2023.104506.

129. David Hutton, *ARVO 2023: 3D printing breakthroughs to accelerate ocular drug delivery, biodegradable contact lenses and pharma research*, in *Opthalmology times*. 2023: https://www.ophthalmologytimes.com.

130. Shiva Kumar, et al., *Reduction in drop size of ophthalmic topical drop preparations and the impact of treatment.* J Adv Pharm Technol Res, 2011. **2**(3): p. 192-194.DOI: 10.4103/2231-4040.85540.

131. Sadikalmahdi Abdella, et al., *3D printed bilayer mucoadhesive buccal film of estradiol: Impact of design on film properties, release kinetics and predicted in vivo performance.* Int. J. Pharm., 2022. **628**.DOI: 10.1016/j.ijpharm.2022.122324.

132. Sarah Teworte, et al., *Mucoadhesive 3D printed vaginal ovules to treat endometriosis and fibrotic uterine diseases.* Eur. J. Pharm. Sci., 2023. **188**.DOI: 10.1016/j.ejps.2023.106501.

133. Sabana Kotta, Anroop Nair and Nimer Alsabeelah, *3D Printing Technology in Drug Delivery: Recent Progress and Application.* Curr. Pharm. Des., 2018. **24**(42): p. 5039-5048.DOI: 10.2174/1381612825666181206123828.

134. Mengsuo Cui, et al., *Fabrication of high drug loading levetiracetam tablets using semi-solid extrusion 3D printing.* J Drug Deliv Sci Technol., 2020. **57**.DOI: https://doi.org/10.1016/j.jddst.2020.101683.

135. Alvaro Goyanes, et al., *3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems.* J. Control. Release., 2016. **234**: p. 41-48.DOI: 10.1016/j.jconrel.2016.05.034.

136. Maren Preis and Heidi Öblom, *3D-Printed Drugs for Children—Are We Ready Yet?* AAPS PharmSciTech, 2017. **18**: p. 303-308.DOI: 10.1208/s12249-016-0704-y.

137. Shrawani Lamichhane, et al., *Complex formulations, simple techniques: Can 3D printing technology be the Midas touch in pharmaceutical industry?* Asian J. Pharm. Sci., 2019. **14**(5): p. 465-479.DOI: 10.1016/j.ajps.2018.11.008.

138. Yash Kapoor, et al., *Flexible Manufacturing: The Future State of Drug Product Development and Commercialization in the Pharmaceutical Industry.* J. Pharm. Innov., 2020.DOI: 10.1007/s12247-019-09426-z.

139. Alvaro Goyanes, et al., *Patient acceptability of 3D printed medicines.* Int J Pharm, 2017. **530**(1-2): p. 71-78.DOI: 10.1016/j.ijpharm.2017.07.064.

140. Basel Arafat, et al., *Tailored on demand anti-coagulant dosing: An in vitro and in vivo evaluation of 3D printed purpose-designed oral dosage forms.* Eur J Pharm Biopharm, 2018. **128**: p. 282-289.DOI: 10.1016/j.ejpb.2018.04.010.

141. Mustafa Alomari, et al., *Personalised dosing: Printing a dose of one's own medicine.* Int. J. Pharm., 2015. **494**(2): p. 568-577.DOI: 10.1016/j.ijpharm.2014.12.006.

142. Sarah J Trenfield, et al., *Binder Jet Printing in Pharmaceutical Manufacturing*, in *3D Printing of Pharmaceuticals*, Abdul W. Basit and Simon Gaisford, Editors. 2018, Springer International Publishing: Cham. p. 41-54.DOI: 10.1007/978-3-319-90755-0_3.

143. Ian Gibson and Dongping Sh, *Material properties and fabrication parameters in selective laser sintering process.* Rapid Prototyp. J., 1997. **3**(4): p. 129-136.DOI: https://doi.org/10.1108/13552549710191836.

144. Jian-Yuan Lee, Jia An and Chee Kai Chua, *Fundamentals and applications of 3D printing for novel materials.* Appl. Mater. Today, 2017. **7**: p. 120-133.DOI: 0.1016/j.apmt.2017.02.004.

145. Yasmin Thabet, Rok Sibanc and Joerg Breitkreutz, *Printing pharmaceuticals by inkjet technology: Proof of concept for stand-alone*

and continuous in-line printing on orodispersible films. J. Manuf. Process., 2018. **35**: p. 205-215.DOI: https://doi.org/10.1016/j.jmapro.2018.07.018.

146. Rowan Rimington, et al., *Biocompatible 3D printed polymers via fused deposition modelling direct C2C12 cellular phenotype in vitro.* Lab Chip, 2017. **17**(17): p. 2982-2993.DOI: 10.1039/c7lc00577f.

147. Thierry Rayna and Ludmila Striukova, *From rapid prototyping to home fabrication: How 3D printing is changing business model innovation.* Technol Forecast Soc Change, 2016. **102**: p. 214-224.DOI: 10.1016/j.techfore.2015.07.023.

148. Michael Hay, et al., *Clinical development success rates for investigational drugs.* Nat. Biotechnol, 2014. **32**: p. 40-51.DOI: https://doi.org/10.1038/nbt.2786.

149. Mohammed Maniruzzaman, *3D and 4D Printing in Biomedical Applications : Process Engineering and Additive Manufacturing*. 2019, Newark, GERMANY: John Wiley & Sons, Incorporated

150. Pan Tian, et al., *Applications of excipients in the field of 3D printed pharmaceuticals.* Drug Dev. Ind. Pharm., 2019. **45**(6): p. 905-913.DOI: 10.1080/03639045.2019.1576723.

151. *Nourished*. [cited 2023 27 September]; Available from: https://get-nourished.com/?gclsrc=aw.ds&&tw_source=google&tw_adid=663507972205&tw_campaign=20304773246&gad=1&gclid=EAIaIQobChMI8qKcloPLgQMVx9vtCh3BLAYWEAAYASAAEgLeq_D_BwE.

152. Cynthia A. Challener, *Continuous Hot-Melt Extrusion for Poorly Soluble APIs.* Pharm. Technol. Eur., 2023. **47**(5): p. 18-20.

153. Mohammed Maniruzzaman and Ali Nokhodchi, *Continuous manufacturing via hot-melt extrusion and scale up: regulatory matters.* Drug Discov. Today, 2017. **22**(2).DOI: 10.1016/j.drudis.2016.11.007.

154. Lawrence X. Yu, et al., *Understanding Pharmaceutical Quality by Design.* AAPS Journal, 2014. **16**(4): p. 771-783.DOI: 10.1208/s12248-014-9598-3.

155. Thomas O'Connor, *Scientific Considerations for Continuous Manufacturing Processes* in *2nd FDA/PQRI Conference on Advancing Product Quality*. 2015, PQRI.

156. Abdulsalam A Alqahtani, et al., *3D Printed Pharmaceutical Systems for Personalized Treatment in Metabolic Syndrome.* Pharmaceutics, 2023. **15**(4).DOI: 10.3390/pharmaceutics15041152.

157. Andrus Maandi, James Porteus and Ben Roberts, *OsteoFab® Technology*. 2020, Oxford Performance Materials, Inc., South Windsor, Connecticut 06074.

158. *https://www.triastek.com/*. 30/06/2023]; Available from: https://www.triastek.com/.

159. *Aprecia, The 3D Pharmaceutical Company*. [cited 2023 11.07]; Available from: https://www.aprecia.com/.

160. Achim Schneeberger, *3D Screen Printing Enables Application of Integrated QR Codes on Pharmaceutical Dosage Forms in Mass Production – A Game Changer.* Biomed J Sci Tech Res, 2022. **41**(4).DOI: 10.26717/bjstr.2022.41.006630.

161. Marcel Enke, et al., *3D screen printing technology enables fabrication of oral drug dosage forms with freely tailorable release profiles.* Int J Pharm, 2023. **642**.DOI: 10.1016/j.ijpharm.2023.123101.

162. Jan Witowski, et al., *From ideas to long-term studies: 3D printing clinical trials review.* Int. j. comput. assist. radiol. surg, 2018. **13**: p. 1473-1478.DOI: 10.1007/s11548-018-1793-8.

163. Laura E Diment, Mark S Thompson and Jeroen H M Bergmann, *Clinical efficacy and effectiveness of 3D printing: a systematic review.* BMJ Open, 2017. **7**(12).DOI: 10.1136/bmjopen-2017-016891.

164. Dipak Kumar Gupta, et al., *3D printing technology in healthcare: applications, regulatory understanding,IP repository and clinical trial status.* J. Drug Target., 2022. **30**(2): p. 131-150.DOI: 10.1080/1061186X.2021.1935973.

165. Nicolas Martelli, et al., *Advantages and disadvantages of 3-dimensional printing in surgery: A systematic review.* Surg. J., 2016. **159**(6): p. 1485-1500.DOI: 10.1016/j.surg.2015.12.017.

166. Edward Weaver, Collette O'Hagan and Dimitrios A Lamprou, *The sustainability of emerging technologies for use in pharmaceutical manufacturing.* Expert Opin Drug Deliv, 2022. **19**(7): p. 861-872.DOI: 10.1080/17425247.2022.2093857.

167. Timothy Tracy, et al., *3D printing: Innovative solutions for patients and pharmaceutical industry.* Int J Pharm, 2023. **631**.DOI: 10.1016/j.ijpharm.2022.122480.

168. C. Huls. *Digitalizing the production of pills*. in *3D medical printing conference*. 2021. online.

169. Derrick Smith, et al., *3D printed capsules for quantitative regional absorption studies in the GI tract.* Int J Pharm, 2018. **550**(1-2): p. 418-428.DOI: 10.1016/j.ijpharm.2018.08.055.

170. George Z Cheng, et al., *Three-dimensional Printing and 3D Slicer: Powerful Tools in Understanding and Treating Structural Lung Disease.* Chest, 2016. **149**(5): p. 1136-42.DOI: 10.1016/j.chest.2016.03.001.

171. Christine M. Madla, et al., *3D Printing Technologies, Implementation and Regulation: An Overview*, in *3D Printing of Pharmaceuticals*, Abdul W. Basit and Simon Gaisford, Editors. 2018, Springer International Publishing AG: ProQuest Ebook Central.

172. Akm Khairuzzaman, *Regulatory Perspectives on 3D Printing in Pharmaceuticals*, in *3D Printing of Pharmaceuticals*, Abdul W. Basit and Simon Gaisford, Editors. 2018, Springer International Publishing AG: ProQuest Ebook Central. p. 215-236.DOI: 10.1007/978-3-319-90755-0_11.

173. *Distributed Manufacturing and Point-of-Care Manufacturing of Drugs*, FDA, Editor. 2022, U.S. food & drug administration

174. *Consultation on Point of Care manufacturing*, Medicines & Healthcare Regulatory Agency, Editor. 2023: GOV.UK.

175. Bhanu P. Sahu and Malay K. Das, *Nanosuspension for enhancement of oral bioavailability of felodipine.* Appl. Nanosci., 2014. **4**: p. 189–197.DOI: 10.1007/s13204-012-0188-3.

176. Jiannan Lu, et al., *Solid-state characterization of Felodipine–Soluplus amorphous solid dispersions.* Drug Dev. Ind. Pharm., 2015. **42**(3): p. 485-496.DOI: 10.3109/03639045.2015.1104347.

177. Boyu Jing, et al., *Enhanced oral bioavailability of felodipine by novel solidself-microemulsifying tablets.* Drug Dev. Ind. Pharm., 2016. **42**(3): p. 506-512.DOI: 10.3109/03639045.2015.1058816.

178. Amit Tapas, Pravin Kawtikwar and D.M. Sakarkar, *Enhanced dissolution rate of felodipine using spherical agglomeration with Inutec SP1 by quasi emulsion solvent diffusion method.* Res Pharm Sci, 2009. **4**(2): p. 77-84.

179. Osama Mahmah, et al., *A comparative study of the effect of spray drying and hot-melt extrusion on the properties of amorphous solid dispersions containing felodipine.* J Pharm Pharmacol, 2014. **66**(2): p. 275-84.DOI: 10.1111/jphp.12099.

180. Hayder Kadhim Drais and Ahmed Abbas Hussein, *Investigation of Lipid Polymer Hybrid Nanocarriers for Oral Felodipine Delivery: Formulation,*

Method, In-vitro and Ex-vivo Evaluation. Iraqi J. Pharm. Sci., 2022. **31**(1): p. 119-129.DOI: 10.31351/vol31iss1pp119-129.

181. Yingmeng He, et al., *Enhanced Oral Bioavailability of Felodipine from Solid Lipid Nanoparticles Prepared Through Effervescent Dispersion Technique.* AAPS PharmSciTech 2020. **21**.DOI: 10.1208/s12249-020-01711-2.

182. Trideva Sastri and Radha Gadela, *Development of self nano-emulsifying drug delivery system for an anti-hypertensive agent felodipine: a systematic approach for lipidd nano-formulation with improved oral bioavailability* Int. J. Appl. Pharm., 2020. **12**(3).DOI: 10.22159/ijap.2020v12i3.37203.

183. Kasitpong Thanawuth, et al., *Controlled Release of Felodipine from 3D-Printed Tablets with Constant Surface Area: Influence of Surface Geometry.* Pharmaceutics, 2023. **15**(2).DOI: https://doi.org/10.3390/pharmaceutics15020467.

184. Rares Iuliu Iovanov, et al., *3D printing of prolonged-release oral solid dosage forms containing felodipine.* Farm., 2023. **71**(3): p. 480-490.DOI: https://doi.org/10.31925/farmacia.2023.3.5

185. Muqdad Alhijjaj, Peter Belton and Sheng Qi, *An investigation into the use of polymer blends to improve the printability of and regulate drug release from pharmaceutical solid dispersions prepared via fused deposition modeling (FDM) 3D printing.* Eur J Pharm Biopharm. , 2016. **108**: p. 111-125.DOI: 10.1016/j.ejpb.2016.08.016.

186. Nikolaos Scoutaris, et al., *Inkjet printing as a novel medicine formulation technique.* J. Control. Release., 2011. **156**: p. 179-185.DOI: 10.1016/j.jconrel.2011.07.033.

187. Iria Seoane-Viaño, et al., *3D printed tacrolimus suppositories for the treatment of ulcerative colitis.* Asian J. Pharm. Sci., 2021. **16**(1): p. 110-119.DOI: 10.1016/j.ajps.2020.06.003.

188. María Eugenia Barberis, et al., *Mathematical and Pharmacokinetic Approaches for the Design of New 3D Printing Inks Using Ricobendazole.* Pharm. Res., 2022. **39**: p. 2277–2290.DOI: 10.1007/s11095-022-03320-z.

189. Atabak Ghanizadeh Tabriz, et al., *Personalised Tasted Masked Chewable 3D Printed Fruit-Chews for Paediatric Patients.* Pharmaceutics, 2021. **13**(8).DOI: 10.3390/pharmaceutics13081301.

190. Kapilkumar Vithani, et al., *A Proof of Concept for 3D Printing of Solid Lipid-Based Formulations of Poorly Water-Soluble Drugs to Control Formulation Dispersion Kinetics.* Pharm Res, 2019. **36**(7): p. 102.DOI: 10.1007/s11095-019-2639-y.

191. Nicolaos Scoutaris, Steven A. Ross and Dennis Douroumis, *3D Printed "Starmix" Drug Loaded Dosage Forms for Paediatric Applications.* Pharmaceutical Research, 2018. **35**.DOI: 10.1007/s11095-017-2284-2.

192. Azizah M. Malebari, et al., *Development of Advanced 3D-Printed Solid Dosage Pediatric Formulations for HIV Treatment.* Pharmaceuticals 2022. **15**(4).DOI: 10.3390/ph15040435.

193. Dinesh Choudhury, et al., *Stereolithography-assisted fabrication of 3D printed polymeric film for topical berberine delivery: in-vitro, ex-vivo and in-vivo investigations.* J. Pharm. Pharmacol., 2022. **74**(10): p. 1477-1488.DOI: 10.1093/jpp/rgab158.

194. Mohammed Elbadawi, *Rheological and Mechanical Investigation into the Effect of Different Molecular Weight Poly(ethylene glycol)s on Polycaprolactone-Ciprofloxacin Filaments.* ACS Omega, 2019. **4**(3): p. 5412-5423.DOI: 10.1021/acsomega.8b03057.

195. Sruti Biswal, Jagannath Sahoo and Padala Narasimha Murthy, *Characterisation of Gliclazide-PEG 8000 Solid Dispersions* Trop. J. Pharm. Res., 2009. **8**(5): p. 417-424.DOI: 10.4314/tjpr.v8i5.48085.

196. Madhuri Newa, et al., *Enhancement of Solubility, Dissolution and Bioavailability of Ibuprofen in Solid Dispersion Systems.* Chem. Pharm. Bull., 2008. **56**(4): p. 569-574.DOI: 10.1248/cpb.56.569.

197. Ivan I. Krasnyuk Jr, et al., *Effect of Solid Dispersions on the Dissolution of Ampicillin.* J. Bionanosci. , 2017. **7**: p. 340-344.DOI: 10.1007/s12668-016-0342-6.

198. Ivan I. Krasnyuk Jr, et al., *Effect of Solid Dispersions with Polyethylene Glycol 1500 on the Solubility of Indomethacin.* Pharm. Chem. J., 2018. **52**: p. 241-244.DOI: 10.1007/s11094-018-1799-0.

199. Surajit Das, et al., *Formulation design, preparation and physicochemical characterizations of solid lipid nanoparticles containing a hydrophobic drug: effects of process variables.* Colloids Surf B Biointerfaces, 2011. **88**(1): p. 483-9.DOI: 10.1016/j.colsurfb.2011.07.036.

200. Muhammad Farhan Ali Khan, et al., *Hydrogel Containing Solid Lipid Nanoparticles Loaded with Argan Oil and Simvastatin: Preparation,In Vitro and Ex Vivo Assessment.* gels, 2022. **8**(277).DOI: 10.3390/gels8050277.

201. *Guideline on pharmaceutical development of medicines for paediatric use.* European Medicine Agency, 2013.

202. F. Ruiz, et al., *Standardized method to assess medicines' acceptability: focus on paediatric population.* J Pharm Pharmacol, 2017. **69**(4): p. 406-416.DOI: 10.1111/jphp.12547.

203. S. Sapkota, et al., *A systematic review of interventions addressing adherence to anti-diabetic medications in patients with type 2 diabetes--impact on adherence.* PLoS One, 2015. **10**(2): p. e0118296.DOI: 10.1371/journal.pone.0118296.

204. Robert Ternik, et al., *Assessment of swallowability and palatability of oral dosage forms in children: Report from an M-CERSI pediatric formulation workshop.* Int J Pharm, 2018. **536**(2): p. 570-581.DOI: 10.1016/j.ijpharm.2017.08.088.

205. Fang Liu, et al., *Patient-centred pharmaceutical design to improve acceptability of medicines: similarities and differences in paediatric and geriatric populations.* Drugs, 2014. **74**(16): p. 1871-1889.DOI: 10.1007/s40265-014-0297-2.

206. Maria Rautamo, et al., *Benefits and Prerequisites Associated with the Adoption of Oral 3D-Printed Medicines for Pediatric Patients: A Focus Group Study among Healthcare Professionals.* Pharmaceutics, 2020. **12**(3).DOI: 10.3390/pharmaceutics12030229.

207. Mark Møller Fastø, et al., *Perceptions, preferences and acceptability of patient designed 3D printed medicine by polypharmacy patients: a pilot study.* Int J Clin Pharm, 2019. **41**(5): p. 1290-1298.DOI: 10.1007/s11096-019-00892-6.

208. Fang Liu, et al., *Acceptability of oral solid medicines in older adults with and without dysphagia: A nested pilot validation questionnaire based observational study.* Int J Pharm, 2016. **512**(2): p. 374-381.DOI: 10.1016/j.ijpharm.2016.03.007.

209. Sejal R Ranmal, Anne Cram and Catherine Tuleu, *Age-appropriate and acceptable paediatric dosage forms: Insights into end-user perceptions, preferences and practices from the Children's Acceptability of Oral Formulations (CALF) Study.* Int J Pharm, 2016. **514**(1): p. 296-307.DOI: 10.1016/j.ijpharm.2016.07.054.

210. Hasso Scholz, *Pharmacological aspects of calcium channel blockers.* Cardiovasc. Drugs Ther., 1997. **10**: p. 869–872.DOI: 0.1007/BF00051613.

211. Utpal Jana, et al., *Felodipine loaded PLGA nanoparticles: preparation,physicochemical characterization and in vivo toxicity study.* Nano Converg., 2014. **1:31**.DOI: 10.1186/s40580-014-0031-5.

212. Tuan-Tu Le, et al., *Delivery of Poorly Soluble Drugs via Mesoporous Silica: Impact of Drug Overloading on Release and Thermal Profiles.* Pharmaceutics, 2019. **11**(6).DOI: 10.3390/pharmaceutics11060269.

213. Artem O. Surov, et al., *Crystallization and Polymorphism of Felodipine.* Cryst. Growth Des., 2012. **12**: p. 4022-4030.DOI: https://doi.org/10.1021/cg300501u.

214. *National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 3333, Felodipine*. August 1, 2023]; Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Felodipine.

215. Samridhi Verma, et al., *Formulation by design of felodipine loaded liquid and solid self nanoemulsifying drug delivery systems using Box-Behnken design.* Drug Dev Ind Pharm, 2014. **40**(10): p. 1358-70.DOI: 10.3109/03639045.2013.819884.

216. *Physicochemical data for felodipine. AB Hässle Subsidiary of AB Astra. 20 September 1985*.

217. Kahnu Charan Panigrahi, et al., *Gelucire: A versatile polymer for modified release drug delivery system.* Future J. Pharm. Sci., 2018. **4**(1): p. 102-108.DOI: 10.1016/j.fjps.2017.11.001.

218. Mohamed Abbas Ibrahim and Mahmoud El-Badry, *Formulation of immediate release pellets containing famotidine solid dispersions.* Saudi Pharm J, 2014. **22**(2): p. 149-156.DOI: 10.1016/j.jsps.2013.01.011.

219. Sunil K. Jain and Anuj Gupta, *Development of gelucire 43/01 beads of metformin hydrochloride for floating delivery.* AAPS PharmSciTech, 2009. **10**(4): p. 1128-1136.DOI: 10.1208/s12249-009-9302-6.

220. *Gelucire® 44/14*. Available from: https://www.gattefosse.com/pharmaceuticals-products/gelucire-4414.

221. André B. da Fonseca Antunes, et al., *Gelucire 44/14 based immediate release formulations for poorly water-soluble drugs.* Drug Dev. Ind. Pharm., 2013. **39**(5): p. 791-798.DOI: 10.3109/03639045.2012.709251.

222. Jeetendra Prasad Kushwaha, Debjani Baidya and Sharvil Patil, *Harmine-loaded galactosylated pluronic F68-gelucire 44/14 mixed micelles for liver targeting.* Drug Dev. Ind. Pharm., 2019. **45**(8): p. 1361-1368 DOI: 10.1080/03639045.2019.1620267.

223. Ayşegül Karataş, Nilüfer Yüksel and Tamer Baykara, *Improved solubility and dissolution rate of piroxicam using gelucire 44/14 and labrasol.* Il Farmaco, 2005. **60**(9): p. 777-782.DOI: 10.1016/j.farmac.2005.04.014.

224. Sanjeevani Deshkar, et al., *Effect of Gelucire 44/14 on Fluconazole Solid Lipid Nanoparticles: Formulation, Optimization and in vitro Characterization.* Drug Deliv. Lett., 2015. **5**(3): p. 173-187.DOI: 10.2174/2210303105031604011211141.

225. Deepak Khobragade, et al., *A novel practical approach for enhancement of bioavailability of a poorly water soluble drug by hot melt coating technique.* Int. J Pharm Sci Rev Res, 2014. **26**(1): p. 258-263.

226. Sun Woo Jang, Young Wook Choi and Myung Joo Kang, *Preparation of Solid Dispersion of Everolimus in Gelucire 50/13 using Melt Granulation Technique for Enhanced Drug Release.* Bull Korean Chem Soc 2014. **35**(7): p. 1939-1943.DOI: 10.5012/bkcs.2014.35.7.1939.

227. Jammula Sruti, et al., *Improvement in the dissolution rate and tableting properties of cefuroxime axetil by melt-granulated dispersion and surface adsorption.* Acta Pharm. Sin. B., 2013. **3**(2): p. 113-122.DOI: https://doi.org/10.1016/j.apsb.2013.01.001.

228. Srinivas Reddy Devireddy and Prabhakar Reddy Veerareddy, *Solubility and Bioavailability Improvement of Glcclazide by Solid Dispersions Using Novel Carriers.* Int. J. Drug Deliv., 2012. **4**(4): p. 455-461.

229. Arijit Baral, Prashant Upadhyay and Tanmoy De, *Formulation and development of floating multiparticulate drug delivery system of antidiabetic drug by hot melt technique.* Int J Adv Pharm Sci, 2013. **4**(4): p. 587-601.

230. Richard B. Greenwald, *PEG drugs: an overview.* J. Control. Release., 2001. **74**(1-3): p. 159-171.DOI: 10.1016/s0168-3659(01)00331-5.

231. Abid Mehmood Yousaf, et al., *Silymarin-laden PVP-PEG polymeric composite for enhanced aqueous solubility and dissolution rate: Preparation and in vitro characterization.* J. Pharm. Anal., 2019. **9**(1): p. 34-39.DOI: 10.1016/j.jpha.2018.09.003.

232. Md Saquib Hasnain and Amit Kumar Nayak, *Solubility and dissolution enhancement of ibuprofen by solid dispersion technique using PEG 6000-PVP K 30 combination carrier.* Bulg. J. Sci. Educ. Policy, 2012. **21**(1): p. 118-132.

233. Aruna Roby, Suna Erdogan and Vladimir P. Torchilin, *Enhanced in vivo antitumor efficacy of poorly soluble PDT agent, meso-tetraphenylporphine, in PEG-PE-based tumor-targeted immunomicelles.* Cancer Biol Ther 2007. **6**(7): p. 1136-1142.DOI: 10.4161/cbt.6.7.4345.

234. Tippabattini Jayaramudu, et al., *Preparation and characterization of poly(ethylene glycol) stabilized nano silver particles by a mechanochemical assisted ball mill process.* J. Appl. Polym. Sci., 2016. **133**(7).DOI: 10.1002/app.43027.

235. Kenneth C. Ofokansi, et al., *Improved dissolution and anti-inflammatory activity of ibuprofen-polyethylene glycol 8000 solid dispersion systems.* Int J Pharm Investig, 2016. **6**(3): p. 139-47.DOI: 10.4103/2230-973X.187344.

236. *Technical Information Kollisolv® PEGs*, BASF, Editor.

237. *Precirol® ATO 5*. 17 August 2023]; Available from: https://www.gattefosse.com/pharmaceuticals-products/precirol-ato-5.

238. Fred M. Newmann, *Higher order thinking in teaching social studies: a rationale for the assessment of classroom thoughtfulness.* J. Curric. Stud., 1990. **22**(1): p. 41-56.DOI: 10.1080/0022027900220103.

239. Alan Bryman, et al., *Social Research Methods*. 1 ed. 2022: OUP USA

240. Ellie Fossey, et al., *Understanding and Evaluating Qualitative Research.* Aust. N. Z. J. Psychiatry, 2002. **36**(6): p. 717-732.DOI: 10.1046/j.1440-1614.2002.01100.x.

241. Barbara DiCicco-Bloom and Benjamin F Crabtree, *The qualitative research interview.* Med. Educ., 2006. **40**(4): p. 314-321.DOI: 10.1111/j.1365-2929.2006.02418.x.

242. Wendy Moyle, *Unstructured interviews: challenges when participants have a major depressive illness.* J. Adv. Nurs., 2002. **39**(3): p. 266-273.DOI: https://doi.org/10.1046/j.1365-2648.2002.02273.x.

243. Shazia Jamshed, *Qualitative research method-interviewing and observation.* J Basic Clin Pharm, 2014. **5**(4): p. 87-88.DOI: 10.4103/0976-0105.141942.

244. Mohd Nor Rashidi, et al., *The Conduct of Structured Interviews as Research Implementation Method.* J. Adv. Res.design, 2014. **1**(1): p. 28-34.

245. Tim Freeman, *'Best practice' in focus group research: making sense of different views.* J. Adv. Nurs., 2006. **56**(5): p. 491-497.DOI: 10.1111/j.1365-2648.2006.04043.x.

246. Fok-Han Leung and Ratnapalan Savithiri, *Spotlight on focus groups.* Can Fam Physician, 2009. **55**(2): p. 218–219.

247. Sharique Ahmad, et al., *Qualitative v/s. Quantitative Research- A Summarized Review.* J. Evid. Based Med. Healthc., 2019. **6**(43): p. 2828-2832.DOI: 10.18410/jebmh/2019/587

248. Julia Levashina, et al., *The Structured Employment Interview: Narrative and Quantitative Review of the Research Literature.* Pers. Psychol., 2013. **67**(1): p. 241-293.DOI: https://doi.org/10.1111/peps.12052.

249. Hamed Taherdoost, *Sampling Methods in Research Methodology; How to Choose a Sampling Technique for Research.* IJARM, 2016. **5**(2): p. 18-27.DOI: http://dx.doi.org/10.2139/ssrn.3205035.

250. *BIO X* Cellink, Editor.

251. Sameh M.I. Saad and August Wilhelm Neumann, *Axisymmetric Drop Shape Analysis (ADSA): An Outline.* Adv. Colloid Interface Sci., 2016. **238**: p. 62-87.DOI: https://doi.org/10.1016/j.cis.2016.11.001.

252. Thomas Moriarty, et al., *Bacterial Adhesion and Biomaterial Surfaces*, in *Comprehensive Biomaterials II*, Paul Ducheyne, Editor. 2017, Elsevier. p. 101-129.DOI: 10.1016/B978-0-08-100691-7.00106-3.

253. James Gomes, et al., *Monitoring and Control of Bioethanol Production From Lignocellulosic Biomass*, in *Waste Biorefinery*, Thallada Bhaskar, et al., Editors. 2018, Elsevier. p. 727-749.DOI: https://doi.org/10.1016/B978-0-444-63992-9.00025-2.

254. Sina Ebnesajjad, *Surface and Material Characterization Techniques*, in *Surface Treatment of Materials for Adhesion Bonding*, Sina Ebnesajjad, Editor. 2006, William Andrew Publishing. p. 43-75.DOI: https://doi.org/10.1016/B978-1-4377-4461-3.10004-5.

255. Jiji Abraham, et al., *Thermoanalytical Techniques of Nanomaterials*, in *Characterization of Nanomaterials*, Oluwatobi Samuel Oluwafemi Sneha Mohan Bhagyaraj, Nandakumar Kalarikkal, Sabu Thomas, Editor. 2018, Woodhead Publishing: Micro and Nano Technologies. p. 213-236.DOI: https://doi.org/10.1016/B978-0-08-101973-3.00008-0.

256. Mahmoud Nasrollahzadeh, et al., *Plant-Mediated Green Synthesis of Nanostructures: Mechanisms, Characterization, and Applications*, in *Interface Science and Technology*, Mahmoud Nasrollahzadeh, et al., Editors. 2019, Elsevier. p. 199-322.DOI: https://doi.org/10.1016/B978-0-12-813586-0.00006-7.

257. Roque Alfredo Osornio-Rios, Jose Alfonso Antonino-Daviu and Rene de Jesus Romero-Troncoso, *Recent Industrial Applications of Infrared Thermography: A Review.* IEEE Trans. Industr. Inform., 2019. **15**(2): p. 615-625.DOI: 10.1109/TII.2018.2884738.

258. J.O. Hill, *Thermal Analysis | Temperature-Modulated Techniques*, in *Encyclopedia of Analytical Science (Second Edition)*, Paul Worsfold, Alan Townshend and Colin Poole, Editors. 2005, Elsevier. p. 22-29.DOI: https://doi.org/10.1016/B0-12-369397-7/00613-0.

259. Rupinder Singh, et al., *Investigations for Development of Feed Stock Filament of Fused Deposition Modeling From Recycled Polyamide*, in *Reference Module in Materials Science and Materials Engineering*. 2018, Elsevier.DOI: 10.1016/B978-0-12-803581-8.10391-1.

260. Pooria Gill, Tahereh Tohidi Moghadam and Bijan Ranjbar, *Differential Scanning Calorimetry Techniques: Applications in Biology and Nanoscience.* J Biomol Tech, 2010. **21**(4): p. 167-193.

261. Sabine Petit and Jana Madejova, *Fourier Transform Infrared Spectroscopy*, in *Developments in Clay Science*, Gerhard Lagaly Faïza Bergaya, Editor. 2013, Elsevier. p. 213-231.DOI: https://doi.org/10.1016/B978-0-08-098259-5.00009-3.

262. Niamh Nic Daeid, *Forensic Sciences | Systematic Drug Identification*, in *Encyclopedia of Analytical Science (Second Edition)*, Alan Townshend Paul Worsfold, Colin Poole, Editor. 2005, Elsevier. p. 471-480.DOI: https://doi.org/10.1016/B0-12-369397-7/00197-7.

263. Jayato Nayak and Sankha Chakrabortty, *MOFs-based advanced materials for gaseous adsorption: Sustainable environmental remediation*, in *Novel Materials for Environmental Remediation Applications*, Dimitrios A. Giannakoudakis, Lucas Meili and Ioannis Anastopoulos, Editors. 2023, Elsevier. p. 185-205.DOI: https://doi.org/10.1016/B978-0-323-91894-7.00005-0.

264. Derek Peak, *Fourier Transform Infrared Spectroscopic Methods of Soil Analysis*, in *Reference Module in Earth Systems and Environmental Sciences*. 2013, Elsevier.DOI: 10.1016/B978-0-12-409548-9.05170-8.

265. Randa S.H. Mansour, Pran Kishore Deb and Rakesh K. Tekade, *Role of Amorphous State in Drug Delivery*, in *In Advances in Pharmaceutical Product Development and Research*, Rakesh K. Tekade, Editor. 2018, Academic Press: Dosage Form Design Parameters. p. 105-154.DOI: https://doi.org/10.1016/B978-0-12-814421-3.00004-X.

266. Daniel Louër, *Powder X-Ray Diffraction, Applications*, in *Encyclopedia of Spectroscopy and Spectrometry (Third Edition)*, John C. Lindon, George E. Tranter and David W. Koppenaal, Editors. 2017, Academic Press. p. 723-731.DOI: 10.1016/B978-0-12-803224-4.00257-0.

267. Harry G. Brittain, *Malic Acid.* Anal. profiles drug subst. excip., 2001. **28**: p. 153-195.

268. Daniel Louër, *Powder X-Ray Diffraction, Applications*, in *Encyclopedia of Spectroscopy and Spectrometry*, John C. Lindon, Editor. 1999, Elsevier. p. 1865-1875.

269. Nidhi Raval, et al., *Importance of Physicochemical Characterization of Nanoparticles in Pharmaceutical Product Development*, in *In Advances in Pharmaceutical Product Development and Research*, Rakesh K. Tekade, Editor. 2019, Academic Press: Basic Fundamentals of Drug Delivery. p. 369-400.DOI: https://doi.org/10.1016/B978-0-12-817909-3.00010-8.

270. Akira Yoshida, Yutaka Kaburagi and Yoshihiro Hishiyama, *Scanning Electron Microscopy*, in *Materials Science and Engineering of Carbon*, Michio Inagaki and Feiyu Kang, Editors. 2016, Butterworth-Heinemann. p. 71-93.DOI: https://doi.org/10.1016/B978-0-12-805256-3.00005-2.

271. Goerg H. Michler, *Scanning Electron Microscopy (SEM)*, in *Electron Microscopy of Polymers*. 2008, Springer: Splaboratory. p. 87-120.DOI: https://doi.org/10.1007/978-3-540-36352-1_5.

272. Meisam Omidi, et al., *Characterization of biomaterials*, in *Biomaterials for Oral and Dental Tissue Engineering*, Lobat Tayebi and Keyvan Moharamzadeh, Editors. 2017, Woodhead Publishing. p. 97-115.DOI: https://doi.org/10.1016/B978-0-08-100961-1.00007-4.

273. Hollis Williams, *SEM for conductive and non-conductive specimens.* Phys. Educ., 2021. **56**(5).DOI: 10.1088/1361-6552/ac1503.

274. Aviva Burnstock and Chris Jones, *Scanning electron microscopy techniques for imaging materials from paintings*, in *Radiation in Art and Archeometry*, D.C. Creagh and D.A. Bradley, Editors. 2000, Elsevier Science B.V. p. 202-231.DOI: https://doi.org/10.1016/B978-044450487-6/50056-0.

275. Seifollah Nasrazadani and Shokrollah Hassani, *Modern analytical techniques in failure analysis of aerospace, chemical, and oil and gas industries*, in *Handbook of Materials Failure Analysis with Case Studies from the Oil and Gas Industry*, Abdel Salam Hamdy Makhlouf and Mahmood Aliofkhazraei, Editors. 2016, Butterworth-Heinemann. p. 39-54.DOI: https://doi.org/10.1016/B978-0-08-100117-2.00010-8.

276. William J. Wolfgong, *Chemical analysis techniques for failure analysis: Part 1, common instrumental methods*, in *Handbook of Materials Failure Analysis with Case Studies from the Aerospace and Automotive Industries*, Mahmood Aliofkhazraei Abdel Salam Hamdy Makhlouf, Editor. 2016, Butterworth-Heinemann. p. 279-307.DOI: https://doi.org/10.1016/B978-0-12-800950-5.00014-4.

277. Lorraine Gibson, *Archaeometry and antique analysis: (b) metallic and ceramic objects*, in *Encyclopedia of Analytical Science (Second Edition)*, Paul Worsfold, Alan Townshend and Colin Poole, Editors. 2004, Elsevier. p. 117-123.

278. Dong Qian, et al., *Mechanics of carbon nanotubes.* Appl Mech Rev 2022. **55**(6): p. 495-533.DOI: https://doi.org/10.1115/1.1490129.

279. Stephen J.B. Reed *Introduction to Energy Dispersive X-ray Spectrometry (EDS)*. 1995.

280. Anupam Das and Huiyuan Guo, *Raman spectroscopy*, in *Encyclopedia of Soils in the Environment (Second Edition)*, Michael J. Goss and Margaret

Oliver, Editors. 2023, Academic Press. p. 497-509.DOI: https://doi.org/10.1016/B978-0-12-822974-3.00031-8.

281. Delphine D. Le Pevelen, *NIR FT-Raman*, in *Encyclopedia of Spectroscopy and Spectrometry (Third Edition)*, John C. Lindon, George E. Tranter and David W. Koppenaal, Editors. 2017, Academic Press. p. 98-109.DOI: https://doi.org/10.1016/B978-0-12-409547-2.12150-X.

282. Andreas Synetos and Dimitris Tousouli, *Invasive Imaging Techniques*, in *Coronary Artery Disease*, Dimitris Tousoulis, Editor. 2018, Academic Press. p. 359-376.DOI: 10.1016/B978-0-12-811908-2.00018-0.

283. Ashok K. Adya and Elisabetta Canetta, *Nanotechnology and Its Applications to Animal Biotechnology*, in *Animal Biotechnology*, Anchal Singh Ashish S. Verma, Editor. 2014, Academic Press. p. 247-263.DOI: https://doi.org/10.1016/B978-0-12-811710-1.00014-8.

284. William E. Brown, *Tablet Friability*, in *USP29-NF24*. USP: Pharmacopeial Forum.

285. Harekrishna Roy, et al., *Formulation and design of sustained release matrix tablets of metformin hydrochloride: Influence of hypromellose and polyacrylate polymers.* Int J Appl Basic Med Res, 2013. **3**(1): p. 55-63.DOI: 10.4103/2229-516X.112242.

286. Xiaoming Xu, Deval Patel and Ying Zhang, *Adaptive Perfusion: A Novel In Vitro Drug Release Testing Method for Complex Drug Products*, U.S. Food & Drug Administration, Editor. 2021.

287. Jordan L. Cohen, et al., *The Development of USP Dissolution and Drug Release Standards.* Pharm. Res., 1990. **7**: p. 983-987.DOI: 10.1023/a:1015922629207.

288. Lukas Roth, et al., *Monographs for medicines on WHO's Model List of Essential Medicines.* Bull World Health Organ, 2018. **96**(6): p. 378-385.DOI: 10.2471/BLT.17.205807.

289. *Felodipine Extended-Release Tablets*, The United States Pharmacopeial Convention, Editor. 2009: Revision Bulletin.

290. T. Itoh and Haruki Yamada, *Antibiotics | Liquid Chromatography*, in *Encyclopedia of Separation Science*, Ian D. Wilson, Editor. 2000, Academic Press. p. 2067-2077.DOI: https://doi.org/10.1016/B0-12-226770-2/01441-1.

291. Seneca, *Alkaloid Chemistry*, in *Alkaloids - Secrets of Life*, Tadeusz Aniszewski, Editor. 2007, Elsevier. p. 61-139.DOI: https://doi.org/10.1016/B978-044452736-3/50004-0.

292. Pulok K. Mukherjee, M. Venkatesh and Arunava Gantait, *Ayurveda in Modern Medicine: Development and Modification of Bioactivity*, in *Comprehensive Natural Products II*, Hung-Wen (Ben) Liu and Lew Mander, Editors. 2010, Elsevier. p. 479-507.DOI: 10.1016/B978-008045382-8.00655-9.

293. Jeff G. McDonald, Pavlina T. Ivanova and H. Alex Brown, *Approaches to Lipid Analysis*, in *Biochemistry of Lipids, Lipoproteins and Membranes (Sixth Edition)*, Neale D. Ridgway and Roger S. McLeod, Editors. 2016, Elsevier. p. 41-72.DOI: https://doi.org/10.1016/B978-0-444-63438-2.00002-X.

294. *High Performance Liquid Chromatography (HPLC) Basics*. 17 August 2023]; Available from: https://www.ssi.shimadzu.com/service-support/faq/liquid-chromatography/knowledge-base/hplc-basics/index.html#:~:text=Introduction%20to%20HPLC&text=A%20liquid%20sample%20is%20injected,they%20flow%20through%20the%20column.

295. Murali Monohar Pandey, et al., *Determination of pKa of felodipine using UV–Visible spectroscopy.* Spectrochim Acta A Mol Biomol Spectrosc, 2013. **115**: p. 887-890.DOI: 10.1016/j.saa.2013.07.001.

296. Füsun Gedil (Üstün), Osman Üstün and Okan Atay, *Quantitative determination of felodipine in pharmaceutics by high pressure liquid chromatography and UV spectroscopy.* Turkish J. Pharm. Sci, 2004. **1**(2): p. 65-76.

297. Namdeo R. Jadhav, Ramesh S. Kambar and Sameer J. Nadaf, *RP-HPLC Method for Simultaneous Estimation of Atorvastatin Calcium and Felodipine from Tablet Dosage Form.* J. curr. pharma res, 2012. **2**(4): p. 637-642.

298. Allison Tong, Peter Sainsbury and Jonathan Craig, *Consolidated criteria for reporting qualitative research (COREQ) a 32-item checklist for interviews and focus groups.* Int J Qual Health Care, 2007. **19**(6): p. 349- 357.DOI: https://doi.org/10.1093/intqhc/mzm042.

299. Christina Karavasili, et al., *Pediatric-friendly chocolate-based dosage forms for the oral administration of both hydrophilic and lipophilic drugs fabricated with extrusion-based 3D printing.* Eur J Pharm Sci, 2020. **147**: p. 105291.DOI: 10.1016/j.ejps.2020.105291.

300. Virginia Braun and Victoria Clarke, *Using thematic analysis in psychology.* Qual Res Psychol, 2006. **3**(2): p. 77-101.DOI: 10.1191/1478088706qp063oa.

301. *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules Guidance for Industry*, U.S. Department of Health and Human Services Food and Drug Administration, Editor. 2015, Pharmaceutical Quality/CMC.

302. *Guideline on pharmaceutical development of medicines for paediatric use*, in *805880*, European Medicines Agency, Editor. 2013.

303. Klaudia Englezos, et al., *3D printing for personalised medicines_ implications for policy and practice* Int. J. Pharm., 2023. **635**(122785).DOI: 10.1016/j.ijpharm.2023.122785.

304. Netta Beer, et al., *Scenarios for 3D printing of personalized medicines - A case study.* Explor Res Clin Soc Pharm, 2021. **4**: p. 100073.DOI: 10.1016/j.rcsop.2021.100073.

305. Patricija Januskaite, et al., *I Spy with My Little Eye: A Paediatric Visual Preferences Survey of 3D Printed Tablets.* Pharmaceutics, 2020. **12**(11).DOI: 10.3390/pharmaceutics12111100.

306. Ambuj Roy, Nitish Naik and K. Srinath Reddy, *Strengths and Limitations of Using the Polypill in Cardiovascular Prevention.* Curr Cardiol Rep., 2017. **19**(45).DOI: 10.1007/s11886-017-0853-y.

307. Kumud Kumar Padhee, et al., *Stable pharmaceutical composition for atherosclerosis*, European Patent Office, Editor. 2010, Cadila Pharmaceuticals Ltd.

308. William H Polonsky and Robert R Henry, *Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors.* Patient Prefer Adherence, 2016. **10**: p. 1299-307.DOI: 10.2147/PPA.S106821.

309. Malte Bogdahn, et al., *Influence of the geometry of 3D printed solid oral dosage forms on their swallowability.* Eur J Pharm Biopharm, 2021. **167**: p. 65-72.DOI: https://doi.org/10.1016/j.ejpb.2021.07.009.

310. A.B.A. Overgaard, et al., *Patients' evaluation of shape, size and colour of solid dosage forms.* Pharm World Sci, 2001. **23**(5): p. 185-188.DOI: 10.1023/a:1012050931018.

311. Louise Bracken, et al., *Creating Acceptable Tablets 3D (CAT 3D): A Feasibility Study to Evaluate the Acceptability of 3D Printed Tablets in Children and Young People.* pharmaceutics, 2022. **14**(516).DOI: 10.3390/pharmaceutics14030516.

312. Anna Lion, et al., *Customisable Tablet Printing: The Development of Multimaterial Hot Melt Inkjet 3D Printing to Produce Complex and Personalised Dosage Forms.* pharmaceutics, 2021. **13**(1679).DOI: 10.3390/pharmaceutics13101679.

313. Alvaro Goyanes, et al., *Effect of geometry on drug release from 3D printed tablets.* Int. J. Pharm., 2015. **494**: p. 657-663.DOI: 10.1016/j.ijpharm.2015.04.069.

314. Alvaro Goyanes, et al., *Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: First single-centre, prospective, crossover study in patients.* Int J Pharm, 2019. **567**: p. 118497.DOI: 10.1016/j.ijpharm.2019.118497.

315. Bertie Hazell and Ross Robson, *Pharmaceutical waste reduction in the NHS* 2015, NHS.

316. J. DALE PRINCE, *3D Printing_ An Industrial Revolution.* J. Electron. Resour. Med. Libr., 2014. **11**(1): p. 39-45.DOI: 10.1080/15424065.2014.877247.

317. Douglas S. Thomas and Stanley W. Gilbert, *Costs and Cost Effectiveness of Additive Manufacturing A Literature Review and Discussion.* NIST Special Publication, 2014. **1176**.DOI: 10.6028/nist.sp.1176.

318. Moe Elbadawi, Abdul W. Basit and Simon Gaisford, *Energy consumption and carbon footprint of 3D printing in pharmaceutical manufacture.* Int. J. Pharm., 2023. **639**(122926).DOI: 10.1016/j.ijpharm.2023.122926.

319. Venkatewara Reddy, et al., *First FDA Approved 3D Printed Drug Paved New Path for Increased Precision in Patient Care.* Appl. Clin. Res. Clin. Trials Regul. Aff., 2020. **7**: p. 93-103.DOI: 10.2174/2213476X07666191226145027.

320. Mohammed S. Algahtani, *Assessment of Pharmacist's Knowledge and Perception toward 3D Printing Technology as a DispensingMethod for Personalized Medicine and the Readiness for Implementation.* pharmacy, 2021. **9**(68).DOI: 10.3390/pharmacy9010068.

321. Odelia Goh, et al., *Preferences of Healthcare Professionals on 3D-Printed Tablets: A Pilot Study.* Pharmaceutics, 2022. **14**(1521).DOI: 10.3390/pharmaceutics14071521.

322. Tomasz Chmiel, et al., *The impact of lipophilicity on environmental processes, drug delivery and bioavailability of food components.* Microchem J, 2019. **146**: p. 393-406.DOI: https://doi.org/10.1016/j.microc.2019.01.030.

323. Salwa K Poole and Colin F Poole, *Separation methods for estimating octanol–water partition coefficients.* J. Chromatogr. B 2003. **797**(1-2): p. 3-19.DOI: 10.1016/j.jchromb.2003.08.032.

324. Jannes van der Merwe, et al., *The Role of Functional Excipients in Solid Oral Dosage Forms to Overcome Poor Drug Dissolution and Bioavailability.* Pharmaceutics, 2020. **12**(5).DOI: 10.3390/pharmaceutics12050393.

325. David J Hauss, *Oral lipid-based formulations.* Adv Drug Deliv Rev, 2007. **59**(7): p. 667-76.DOI: 10.1016/j.addr.2007.05.006.

326. Dong-Han Won, et al., *Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process.* Int. J. Pharm, 2005. **301**(1-2): p. 199-208.DOI: 10.1016/j.ijpharm.2005.05.017.

327. Renuka Nair, S Gonen and Stephen W Hoag, *Influence of polyethylene glycol and povidone on the polymorphic transformation and solubility of carbamazepine.* Int. J. Pharm, 2002. **240**(1-2): p. 11-22.DOI: 10.1016/s0378-5173(02)00083-2.

328. Sandhiya Jatwani, et al., *Solubility and dissolution enhancement of simvastatin using synergistic effect of hydrophilic carriers.* Der Pharmacia Lettre, 2011. **3**(6): p. 280-293.

329. Stephen K. Dordunoo, James L. Ford and Michael H. Rubinstein, *Solidification studies of polyethylene glycols, gelucire 44/14 or their dispersions with triamterene or temazepam.* J. Pharm. Pharmacol., 1996. **48**(8): p. 782-789.DOI: 0.1111/j.2042-7158.1996.tb03974.x.

330. Cesáreo J. Jiménez de los Santos, et al., *Enhancement of albendazole dissolution properties using solid dispersions with Gelucire 50/13 and PEG 15000.* J Drug Deliv Sci Technol., 2017. **42**: p. 261-272.DOI: 10.1016/j.jddst.2017.03.030.

331. Prashant Upadhyay, Jayanta Kumar Pandit and Arun Kumar Wahi, *Gelucire: An alternative formulation technological tool for both sustained and fast release of drugs in treating diabetes mellitus type II disease.* J Sci Ind Res, 2013. **72**: p. 776-780.

332. Kazunori Iwanaga, et al., *Enhancing mechanism of intestinal absorption of highly lipophilic compounds using microemulsion- Quantitative analysis of the partitioning to the mesenteric lymph in intestinal cells.* Asian J. Pharm. Sci., 2014. **10**(3): p. 186-193.DOI: https://doi.org/10.1016/j.ajps.2014.12.005.

333. *Biorelevant*. 30 Aug 2023]; Available from: https://biorelevant.com/fassif-fessif-fassgf/buy/.

334. Shui-Mei Khoo, Christopher J.H. Porter and William N. Charman, *The formulation of Halofantrine as either non-solubilising PEG 6000 or solubilising lipid based solid dispersions: Physical stability and absolute bioavailability assessment.* Int. J. Pharm., 2000. **205**(1-2): p. 65-78.DOI: 10.1016/s0378-5173(00)00485-3.

335. Claudia Fruijtier-Pölloth, *Safety assessment on polyethylene glycols (PEGs) and their derivatives as used in cosmetic products.* Toxicology, 2005. **214**(1-2): p. 1-38.DOI: 10.1016/j.tox.2005.06.001.

336. A. Kozbial, et al., *Study on the surface energy of graphene by contact angle measurements.* Langmuir, 2014. **30**(28): p. 8598-606.DOI: 10.1021/la5018328.

337. Bo Persson. and Michele Scaraggi, *Theory of adhesion: Role of surface roughness.* J. Chem. Phys, 2014. **141**.DOI: https://doi.org/10.1063/1.4895789.

338. Gülcan Coşkun Akar, et al., *Effects of surface-finishing protocols on the roughness, color change, and translucency of different ceramic systems.* J. Prosthet. Dent., 2014. **112**(2): p. 314-321.DOI: 10.1016/j.prosdent.2013.09.033.

339. USP, *Uniformity of Dosage Units* in <*905*> USP–NF, Editor. 20–Apr–2007.

340. Chaoming Wang, et al., *Thermal behavior of polyethylene glycol based phase change materials for thermal energy storage with multiwall carbon nanotubes additives.* Energy, 2019. **180**: p. 873-880.DOI: 10.1016/j.energy.2019.05.163.

341. Wei Guo, et al., *Thermal properties of drug polymorphs: A case study with felodipine form I and form IV.* J. Saudi Chem. Soc., 2020. **24**(6): p. 474-483.DOI: 10.1016/j.jscs.2020.04.003.

342. Basmah Nasser Abdullah Aldosari, *Development and evaluation of self-nanoemulsifying drug delivery systems for oral delivery of indomethacin*, in *School of Pharmacy*. 2018, University College London. p. 306.

343. Rahul V. Haware, et al., *Physical properties and solubility studies of Nifedipine-PEG 1450/HPMCAS-HF solid dispersions.* Pharm Dev Technol, 2019. **24**(5): p. 550-559.DOI: 10.1080/10837450.2018.1519573.

344. Stefania Cometa, et al., *In vitro investigations on dopamine loaded Solid Lipid Nanoparticles.* J Pharm Biomed Anal, 2020. **185**: p. 113257.DOI: 10.1016/j.jpba.2020.113257.

345. Sarah O Otun, et al., *The use of quasi-isothermal modulated temperature differential scanning calorimetry for the characterization of slow crystallization processes in lipid-based solid self-emulsifying systems.* Pharm Res, 2015. **32**(4): p. 1316-24.DOI: 10.1007/s11095-014-1535-8.

346. Suresh Bandari, et al., *Enhancement of Solubility and Dissolution Rate of Loratadine with Gelucire 50/13.* J. Pharm. Innov., 2014. **9**(2): p. 141-149.DOI: 10.1007/s12247-014-9181-6.

347. Ali Dabbagh, et al., *Low-melting-point polymeric nanoshells for thermal-triggered drugrelease under hyperthermia condition.* Int. J. Hyperthermia, 2015. **31**(8).DOI: 10.3109/02656736.2015.1094147.

348. César Leyva-Porras, et al., *Application of Differential Scanning Calorimetry (DSC) and Modulated Differential Scanning Calorimetry (MDSC) in Food and Drug Industries.* Polymers (Basel), 2019. **12**(1).DOI: 10.3390/polym12010005.

349. Daniela Gramaglia, et al., *High speed DSC (hyper-DSC) as a tool to measure the solubility of a drug within a solid or semi-solid matrix.* Int. J. Pharm., 2005. **301**(1-2): p. 1-5.DOI: 10.1016/j.ijpharm.2005.04.038.

350. Kunal P Pagar and Pradeep R Vavia, *Felodipine beta-cyclodextrin complex as an active core for time delayed chronotherapeutic treatment of hypertension.* Acta Pharm, 2012. **62**(3): p. 395-410.DOI: 10.2478/v10007-012-0023-0.

351. Ruilong Li, et al., *Effect of molecular weight of polyethylene glycol on crystallization behaviors, thermal properties and tensile performance of polylactic acid stereocomplexes.* RSC Adv, 2020. **10**(69): p. 42120-42127.DOI: 10.1039/d0ra08699a.

352. Mohamed A. Shaker, *Dissolution and bioavailability enhancement of Atorvastatin: Gelucire semi-solid binary system.* J Drug Deliv Sci Technol., 2018. **43**: p. 178-184.DOI: 10.1016/j.jddst.2017.10.003.

353. Nrupa Patel, et al., *Development of Solid SEDDS, II: application of Acconon® C-44 and Gelucire® 44/14 as solidifying agents for self-emulsifying drug delivery systems of medium chain triglyceride.* J. Excipients and Food Chem, 2012. **3**(2): p. 54 – 66.

354. Josimar de Oliveira Eloy, et al., *Solid Dispersion of Ursolic Acid in Gelucire 50/13: a Strategy to Enhance Drug Release and Trypanocidal Activity.* AAPS PharmSciTech, 2012. **13**(4): p. 1436-1445.DOI: 10.1208/s12249-012-9868-2.

355. Melisa K. Barron, et al., *Investigation of Processing Parameters of Spray Freezing Into Liquid to Prepare Polyethylene Glycol Polymeric Particles for Drug Delivery* AAPS PharmSciTech 2003. **4**(2).DOI: 10.1208/pt040212.

356. Rahul V Haware, et al., *Physical properties and solubility studies of Nifedipine-PEG 1450/HPMCAS-HF solid dispersions.* Pharm Dev Technol., 2018. **24**(5): p. 550-559.DOI: 10.1080/10837450.2018.1519573.

357. Bertil Abrahamsson, et al., *Absorption, gastrointestinal transit, and tablet erosion of felodipine extended-release (ER) tablets.* Pharm Res, 1993. **10**(5): p. 709-14.DOI: 10.1023/a:1018959732744.

358. P. G. Bhole and V. R. Patil, *Enhancement of water solubility of felodipine by preparing solid dispersion using poly-ethylene glycol 6000 and poly-vinyl alcohol.* Asian J. Pharm., 2009. **3**(3): p. 240.DOI: 10.4103/0973-8398.56305.

359. Alex Bunker, *Poly(ethylene glycol) in drug delivery, why does it work, and can we do better? All atom molecular dynamics simulation provides some answers.* Phys. Procedia, 2012. **34**: p. 24-33.DOI: https://doi.org/10.1016/j.phpro.2012.05.004.

360. *Felodipine physico-chemical properties*. [cited 2023 28 September]; Available from: https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=4190.

361. Vasilios I. Teberekidis and Michael P. Sigalas, *Theoretical study of hydrogen bond interactions of felodipine with polyvinylpyrrolidone and polyethyleneglycol.* J. Mol. Struct., 2007. **803**(1-3): p. 29-38.DOI: https://doi.org/10.1016/j.theochem.2006.09.016.

362. Man Zhou, et al., *Recent Advances in Stimuli-Sensitive Amphiphilic Polymer-Paclitaxel Prodrugs.* Front Bioeng Biotechnol, 2022. **10**.DOI: 10.3389/fbioe.2022.875034.

363. Ketan T. Savjani, Anuradha K. Gajjar and Jignasa K. Savjani, *Drug solubility: importance and enhancement techniques.* ISRN Pharm, 2012. **2012**: p. 195727.DOI: 10.5402/2012/195727.

364. Mittal A. Darji, et al., *Excipient Stability in Oral Solid Dosage Forms: A Review.* AAPS PharmSciTech 2017. **19**: p. 12-26.DOI: 10.1208/s12249-017-0864-4.

365. Caroline Alvebratt, et al., *In Vitro Performance and Chemical Stability of Lipid-Based Formulations Encapsulated in a Mesoporous Magnesium Carbonate Carrier.* Pharmaceutics, 2020. **12**(5).DOI: 10.3390/pharmaceutics12050426.

366. *Gattefossé*. Available from: https://www.gattefosse.com/.

367. Chiara R. M. Brambilla, et al., *3DP Printing of Oral Solid Formulations: A Systematic Review.* Pharmaceutics, 2021. **13**(3).DOI: 10.3390/pharmaceutics13030358.

368. Artem O. Surov, et al., *Crystal architecture and physicochemical properties of felodipine solvates.* CrystEngComm, 2013. **15**(30): p. 6054.DOI: 10.1039/c3ce40715b.

369. Shasha Li, et al., *Solid–Liquid Phase Equilibrium and the Thermodynamic Correlation of Felodipine Form I in Pure and Mixed Solvents.* J. Chem. Eng., 2022. **67**(2): p. 284-490.DOI: 10.1021/acs.jced.1c00566.

370. Shamkant L Shimpi, et al., *Stabilization and improved in vivo performance of amorphous etoricoxib using Gelucire 50/13.* Pharm Res, 2005. **22**(10): p. 1727-34.DOI: 10.1007/s11095-005-6694-1.

371. Swati Jagdale, et al., *Preparation and in vitro evaluation of Allopurinol-Gelucire 50/13 solid dispersions.* Int. j. adv. pharm. sci., 2010. **1**(1): p. 60-67.DOI: 10.5138/ijaps.2010.0976.1055.01007.

372. Ana Milanovic, et al., *Hot-melt coating with Precirol ATO 5 in a fluidized-bed apparatus: Application of experimental design in the optimization of process parameters.* J Drug Deliv Sci Technol., 2018. **46**: p. 274-284.DOI: 10.1016/j.jddst.2018.05.030.

373. Abhijit A Date, et al., *Lipid nanocarriers (GeluPearl) containing amphiphilic lipid Gelucire 50/13 as a novel stabilizer: fabrication, characterization and evaluation for oral drug delivery.* Nanotechnology, 2011. **22**(27): p. 275102.DOI: 10.1088/0957-4484/22/27/275102.

374. Mark S'ari, et al., *Characterization of Amorphous Solid Dispersions and Identification of Low Levels of Crystallinity by Transmission Electron Microscopy.* Mol. Pharmaceutics, 2021. **18**(5): p. 1905-1919.DOI: https://doi.org/10.1021/acs.molpharmaceut.0c00918.

375. M. El-Badry, G. Fetih and M. Fathy, *Improvement of solubility and dissolution rate of indomethacin by solid dispersions in Gelucire 50/13 and PEG4000.* Saudi Pharm J, 2009. **17**(3): p. 217-25.DOI: 10.1016/j.jsps.2009.08.006.

376. Saeed Ghanbarzadeh, et al., *Enhanced stability and dermal delivery of hydroquinone using solid lipid nanoparticles.* Colloids Surf B Biointerfaces, 2015. **136**: p. 1004-10.DOI: 10.1016/j.colsurfb.2015.10.041.

377. William E. Brown, *TABLET FRIABILITY*, in *1216*, USP, Editor. 2016: www.usp.org/.

378. Graţiela Popa, et al., *Formulation and preparation of orally disintegrating tablets using innovative binder.* Farmacia, 2013. **61**(1): p. 1131-1136.

379. *Gelucire® 50/13*. Available from: https://www.gattefosse.com/pharmaceuticals-products/gelucire-5013.

380. Venkata Raman Kallakunta, et al., *Effect of formulation and process variables on lipid based sustained release tablets via continuous twin screw granulation: A comparative study.* Eur J Pharm Sci, 2018. **121**: p. 126-138.DOI: 10.1016/j.ejps.2018.05.007.

381. Sabeeh Mohsin, et al., *Suitability of Gelucire 50/13 for controlled release formulation of salbutamol sulphate.* Pak. J. Pharm. Sci., 2012. **25**(1): p. 35-41.

382. Sabeeh Mohsin, et al., *Suitability of Gelucire 50/13 for controlled release formulation of salbutamol sulphate.* Pak. J. Pharm. Sci, 2012. **25**(1): p. 35-41.

383. Marcos Luciano Bruschi, *Mathematical models of drug release*, in *Strategies to Modify the Drug Release from Pharmaceutical Systems* 2015, Elsevier. p. 63-86.DOI: 10.1016/b978-0-08-100092-2.00005-9.

384. Jörn E. Möckel and Bernhard C. Lippold, *Zero-Order Drug Release from Hydrocolloid Matrices.* Pharm. Res., 1993. **10**: p. 1066-1070.DOI: 10.1023/a:1018931210396.

385. Arthur A. Noyes and Willis R. Whitney, *The rate of solution of solid substances in their own solutions.* J. Am. Chem. Soc., 1897. **19**: p. 930-934.

386. Juergen Siepmann and Nicholas A Peppas, *Higuchi equation: derivation, applications, use and misuse.* Int J Pharm, 2011. **418**(1): p. 6-12.DOI: 10.1016/j.ijpharm.2011.03.051.

387. V. Jannin, *Analysis of Fickian and non-Fickian drug release from polymers.* Pharm. Acta Helv., 1985. **60**(4): p. 110-111.

388. Richard W. Korsmeyer, et al., *Mechanisms of solute release from porous hydrophilic polymers.* Int. J. Pharm, 1983. **15**(1): p. 25-35.DOI: https://doi.org/10.1016/0378-5173(83)90064-9.

389. A. W. Hixson and J. H. Crowell, *Dependence of Reaction Velocity upon surface and Agitation.* Ind. Eng. Chem. Res., 1931. **23**(8): p. 923-931.DOI: https://doi.org/10.1021/ie50260a018.

390. Rakesh K Deore, Kunchu Kavitha and Theetha G Tamizhmani, *Preparation and evaluation of sustained release matrix tablets of tramadol hydrochloride using glyceryl palmitostearate.* Trop. J. Pharm. Res., 2010. **9**(3): p. 275-281.DOI: 10.4314/tjpr.v9i3.56289.

391. Xiaosi Li, Qi Li and Chao Zhao, *Zero-Order Controlled Release of Water-Soluble Drugs Using a Marker Pen Platform.* ACS Omega, 2021. **6**: p. 13774-13778.DOI: https://doi.org/10.1021/acsomega.1c01141.

392. Wanchai Sutananta, *The physical characterisation of complex glyceride mixtures*, in *School of Pharmacy*. 1993, University of London: ProQuest LLC.

393. Karin Becker, Sharareh Salar-Behzadi and Andreas Zimmer, *Solvent-free melting techniques for the preparation of lipid-based solid oral formulations.* Pharm Res, 2015. **32**(5): p. 1519-45.DOI: 10.1007/s11095-015-1661-y.

394. Pradeep R. Patil, Shailesh V. Biradar and Anant R. Paradkar, *Extended Release Felodipine Self-Nanoemulsifying System.* AAPS PharmSciTech, 2009. **10**(2): p. 515-523.

395. Nurzalina Khan and Duncan Q.M. Craig, *Role of blooming in determining the storage stability of lipid-based dosage forms.* J Pharm Sci, 2004. **93**(12): p. 2962-71.DOI: 10.1002/jps.20210.

396. V. Jannin, J. Musakhanian and D. Marchaud, *Approaches for the development of solid and semi-solid lipid-based formulations.* Adv. Drug Deliv. Rev., 2007. **60**: p. 734-746.

397. Carolina Corzo, et al., *Novel approach for overcoming the stability challenges of lipid based excipients. Part 1: Screening of solid-state and physical properties of polyglycerol esters of fatty acids as advanced pharmaceutical excipients.* EUR J PHARM BIOPHARM 2020. **148**: p. 134-147.DOI: 10.1016/j.ejpb.2020.01.012.

398. Sally Galal, et al., *Study of In-Vitro Release Characteristics of Carbamazepine ExtendedRelease Semisolid Matrix Filled Capsules Based on Gelucires.* Drug Dev. Ind. Pharm., 2004. **30**(8): p. 817-829.DOI: 10.1081/ddc-200030497.

399. Georgia I. Sakellari, et al., *Formulation design, production and characterisation of solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for the encapsulation of a model hydrophobic active.* Food Hydrocoll. Health., 2021. **1**(100024).DOI: 10.1016/j.fhfh.2021.100024.

400. *Gelucire 44/14 Self emulsifying excipient for solubility and oral bioavailability enhancement*. 2019.

401. Wanchai Sutananta, Duncan Q.M. Craig and John Michael Newton, *The effects of ageing on thermal behaviour and mechanical properties of pharmaceutical glycerides.* Int. J. Pharm., 1994. **111**: p. 51-62.DOI: https://doi.org/10.1016/0378-5173(94)90401-4.

402. Daniela Gramaglia, et al., *High speed DSC (hyper-DSC) as a tool to measure the solubility of a drug within a solid or semi-solid matrix.* Int. J. Pharm., 2005. **301**(1-2): p. 1-5.DOI: 10.1016/j.ijpharm.2005.04.038.

403. kazunori Kaddota, et al., *Quanti cation of the Amorphous Content of Ursodeoxycholic Acid by Pulsed NMR.* J. Pharm. Sci. Technol., 2016. **76**(2): p. 117-122.

404. Xiang Li, et al., *Effects of preparing techniques and aging on dissolution behavior of the solid dispersions of NF/Soluplus/Kollidon SR: identification and classification by a combined analysis by FT-IR spectroscopy and computational approaches.* Drug Dev Ind Pharm, 2015. **41**(1): p. 2-14.DOI: 10.3109/03639045.2014.938080.

405. Nurzalina Khan and Duncan Q.M. Craig, *The influence of drug incorporation on the structure and release properties of solid dispersions in lipid matrices.* J Control Release., 2003. **93**(3): p. 355-368.DOI: 10.1016/j.jconrel.2003.09.006.

406. Patrick J Marsac, et al., *Effect of temperature and moisture on the miscibility of amorphous dispersions of felodipine and poly(vinyl pyrrolidone).* J Pharm Sci, 2010. **99**(1): p. 169-85.DOI: 10.1002/jps.21809.

407. Julia Krause, Markus Thommes and Jörg Breitkreutz, *Immediate release pellets with lipid binders obtained by solvent-free cold extrusion* Eur J Pharm Biopharm, 2009. **71**: p. 138-144.DOI: 10.1016/j.ejpb.2008.08.020.

408. Gábor Vasvári, et al., *Development and Characterisation of Modified Release Hard Gelatin Capsules, Based on In Situ Lipid Matrix Formation.* AAPS PharmSciTech, 2018. **19**(7): p. 3165-3176.DOI: 10.1208/s12249-018-1146-5.

409. Y W Choy, Nurzalina Khan and Kahhay Yuen, *Significance of lipid matrix aging on in vitro release and in vivo bioavailability.* Int. J. Pharm., 2005. **299**: p. 55-64.DOI: 10.1016/j.ijpharm.2005.04.030.

410. Andrew B. Dennis, et al., *In vivo evaluation of rapid release and sustained release Gelucire capsule formulations.* Int. J. Pharm., 1990. **65**(1-2): p. 85-100.DOI: https://doi.org/10.1016/0378-5173(90)90013-T.