GASTROINTESTINAL TRANSIT OF DOSAGE FORMS

by

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To my parents

"The whole of science is nothing more
than a refinement of everyday thinking."

Einstein

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CONTENTS

ABSTRACT

This thesis describes the results from a series of studies designed to evaluate the gastrointestinal transit of oral dosage forms. The transit of placebo pellet and tablet formulations was monitored using the technique of gamma scintigraphy. The formulations were radiolabelled with either technetium-99m or indium-111. Four parameters, two physiological and two pharmaceutical, were selected for investigation. All the studies were conducted in healthy male volunteers.

The first study examined the influence of the supine position on the gastric emptying of pellets in fasted and fed subjects. There was no marked difference between the supine and control gastric emptying data. As would be expected, food had a significant effect on gastric emptying.

The influence of the time of day of administration on the gastrointestinal transit of pellets was investigated in fasted subjects. Transit of the pellets was not affected by their time of administration.

The effect of the putative bioadhesive, polycarbophil, on the gastrointestinal transit of a pellet formulation was studied in fasted subjects. The pellets emptied from the stomach, rapidly and in an exponential manner.

A set of studies was conducted to evaluate the transit of tablets in fed and fasted subjects. Tablet size did not affect gastric emptying, although there was an increase in the variability of gastric emptying with increasing tablet size. Food had a marked effect on gastric emptying. The rate of emptying was related to the energy content of the meal. Tablet size did not appear to be a determinant of transit through the ileocaecal sphincter. The colon transit and dispersion of the tablets was examined. Neither the ingestion of food nor defecation appeared to alter the rate of transit through the colon.

ABBREVIATIONS

CDD	Colonic Diverticular Disease
CDDS	Controlled Drug Delivery System(s)
CR	Controlled Release
CE	Colon entry
Ct50%	time for 50% to enter the colon
DHSS	Department of Health and Social Security
DTPA	Diethylenetriaminepentaacetic acid
5-ASA	5-aminosalicylic acid
GE	Gastric emptying
GI	Gastrointestinal
GIT	Gastrointestinal tract
IBS	Irritable Bowel Syndrome
ICS	Ileocaecal sphincter
^{111}In	Indium-111
MCt	Mouth to colon transit time
MMC	Migrating myoelectric complex
PAC	Perturbed angular correlation
P:S	Peak-to-scatter ratio
REM	Rapid eye movement
ROI	Region(s) of interest
s.e.m.	standard error about the mean
SIT	Small intestine transit
SR	Sustained release
St50%	time for 50% to empty from the stomach
^{99m}Tc	Technetium-99m

CHAPTER ONE:

INTRODUCTION

1.1 Outline

This introduction provides a review of topics pertinent to my thesis. I shall begin by discussing relevant aspects of gastrointestinal (GI) physiology, with an emphasis on GI motility. Techniques to measure GI transit will be revised, with particular reference to the technique of gamma scintigraphy. Mention will be made of the design and development of controlled release (CR) dosage forms, and I shall consider the import of GI physiology to the design of CR dosage forms. A review of the GI transit of oral dosage forms will be made. Finally, the aims and objectives of the thesis will be discussed.

1.2 Gastrointestinal Physiology

The vast span of this subject forces me to concentrate on the topic of gastrointestinal (GI) motility, with a brief mention of GI anatomy. A more comprehensive discussion of GI physiology and function can be found in several texts (1,2,3).

1.2.1 The Stomach

The first detailed investigation of the human stomach was made by William Beaumont (4). In 1882, he had the opportunity to study the functions of the stomach through a gun-shot wound. Our methods of study, and our knowledge have measurably advanced since then.

1.2.1.1 Structure and function

Material enters the stomach via the oesophagus. Oesophageal transit depends on the physical nature of the bolus and on contractile activity (5). Gravity influences the movement of liquids, whilst other materials rely on repetitive contractions to sweep the bolus into the stomach.

The stomach performs four main functions (6):

i. acts as a reservoir;
ii. mixes ingested material with gastric secretions;
iii. propels material into the small intestine;
iv. acts as an antibacterial barrier.

However, despite the complexity of gastric function, the stomach is not a vital organ.

The stomach accomplishes its motor activity by an interaction of two distinct regions, the proximal and distal regions (7) (Figure 1.1). The dividing line between these regions is determined by myoelectric and motor criteria.

The proximal stomach is primarily concerned with the receipt and storage of food, and transfer of chyme to the duodenum. The contractions of the proximal stomach serve to regulate intragastric pressure, as well as propelling gastric contents and accommodating swallowed food. The proximal stomach has the property of receptive

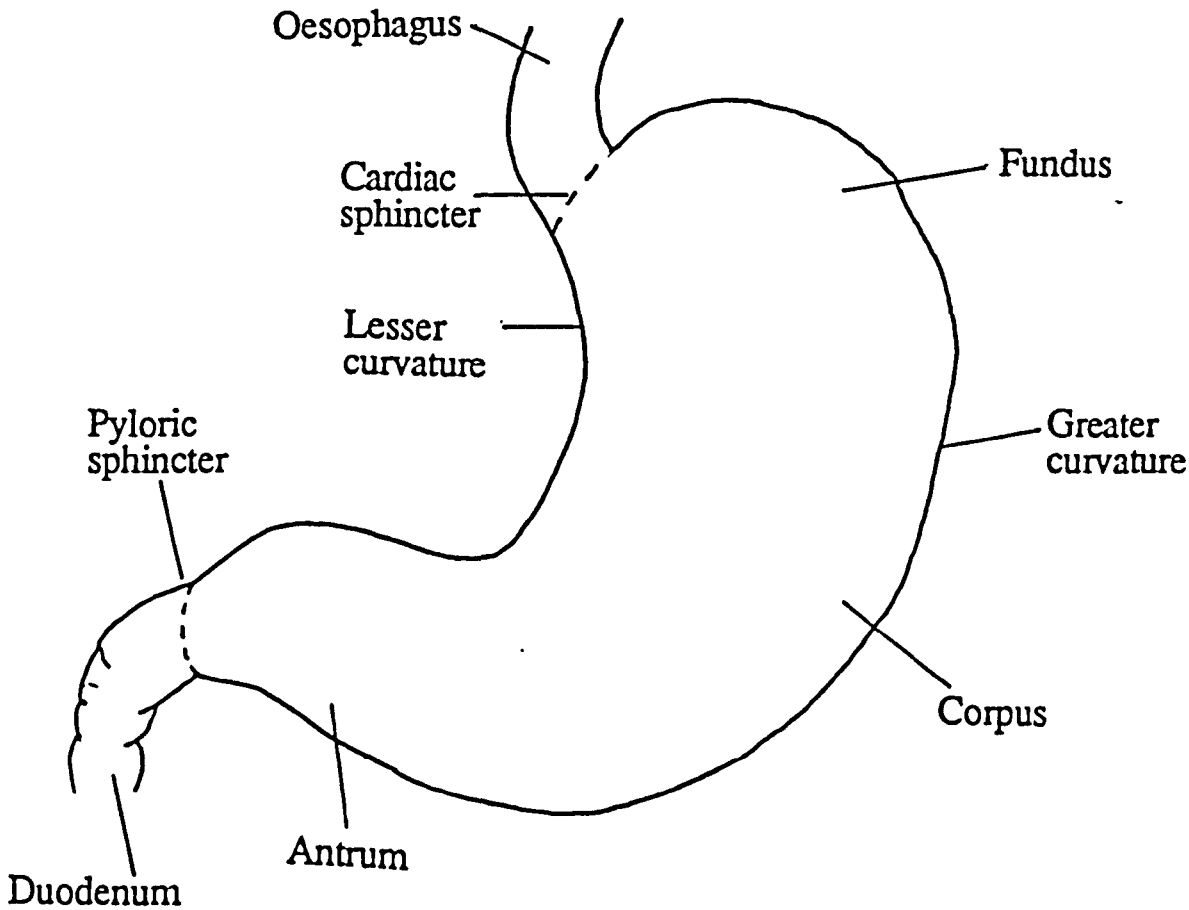


Figure 1.1 Anatomical structure of the stomach

relaxation, which allows the stomach to fill without large increases in intergastric pressure (8). Slow, steady contractions which press contents distally have a major role in emptying liquids. This is thought primarily to be a function of the pressure gradient between the stomach and duodenum (9). Simple solutions have been shown to empty rapidly in either an exponential fashion (10) or as a linear function of the square root of the volume remaining in the stomach (11). The contractions of the proximal stomach are regulated through an inhibitory vagal system (12), hormones (eg. motilin and gastrin) and by locally released substances (eg. histamine).

The main functions of the distal stomach is to mix and triturate gastric contents, and regulate the emptying of solids (Figure 1.2). The characteristic contractions of the distal stomach is the peristaltic wave. As the waves sweep distally, the velocity of propagation increases so the entire gastric wall of the distal antrum appears to contract simultaneously - terminal antral contraction. Postprandial waves do not occlude the gastric lumen, and propel chyme near the gastric wall toward the pylorus, but allow more central contents to pass backward. The contractions are vagally and sympathetically mediated, in response to stretch, mechanical and pH perturbations. Hormones (eg. gastrin)

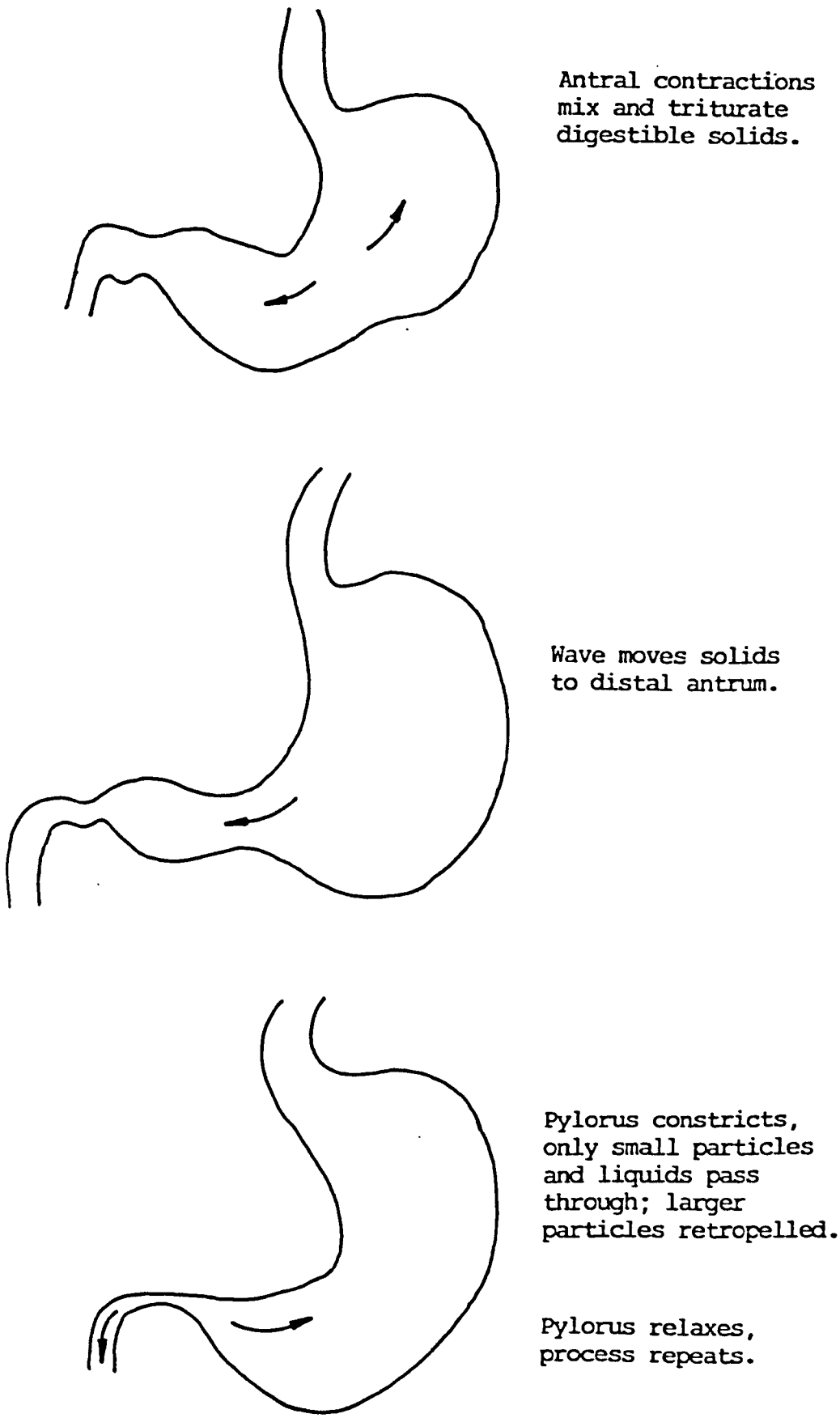


Figure 1.2 Contractions of the fed stomach

and locally released chemicals (eg. histamine) also have a regulatory role.

The consequences of the contractions of the distal stomach are the mixing of gastric chyme with gastric juices, and trituration of gastric solids. Chyme is propelled towards the pylorus, and liquid in the chyme passes through to the duodenum, whilst solids are retained. The terminal antral contraction closes the pylorus, trapping the remaining liquid with the solids. An antral systole compresses the antral contents and causes retropulsion into the corpus of the stomach. This cycle continually repeats, mixing and triturating gastric solids. Eventually, small solid particles, 0.1mm in size, will become suspended in the liquid phase of the chyme and pass through to the duodenum (13). The emptying of solids is largely determined by their resistance to flow across the pylorus, even if a large pressure gradient exists. Antral and pyloric contractions determine the magnitude of the resistance at the junction, and hence their role in the emptying of solids. Digestible solids empty in a linear fashion at a slower rate than liquids (14). They are also subject to a lag phase due to the triturating process. Dozois et al (15) illustrated the importance of the antrum in regulating the gastric emptying (GE) of solids, by performing a distal antrectomy in dogs. The operation resulted in premature and rapid emptying of solids.

The pyloric junction acts as an integral part of the terminal antrum. The small diameter of the lumen provides continence of gastric solids. As solids are swept distally, the junction closes preventing particles larger than about 2mm from leaving the stomach (16). The junction also remains closed when contractions occur in the proximal duodenum, thus preventing retrograde movement of duodenal contents.

1.2.1.2 Determinants of gastric emptying

Factors which modify the pattern of gastric emptying can be divided into three groups, physiological, pathalogical and pharmacological. A number of reviews discussing these influences on gastric emptying are available (16,17,18,19).

The primary determinant of liquid emptying is volume (20). Distension of the stomach is the only natural stimulus that increases the rate of gastric emptying (19). Thus, the greater the ingested volume, the faster the rate of emptying (20). Similarly, increasing the meal weight, at constant caloric content, increases the emptying of solid food (21). Most other factors that influence gastric emptying do so by inhibiting the activity of the gastric pump. This inhibition is mediated through a number of receptors located in the duodenum and jejunum (22) - acid receptors, osmotic receptors, fat receptors and L-tryptophan receptors. The

receptors sense the nature of the just emptied chyme, and activate mechanisms which alter the rate of emptying of subsequent material. This control ensures that the small intestine does not become overburdened.

The composition of chyme, its acidity, osmolarity and fat or amino acid content, probably exerts the most significant effect on gastric emptying. Neutral, isoosmolar and calorically inert solutions empty quite rapidly (23). Hypertonic solutions containing fats, acid and some amino acids all retard gastric emptying by action of the duodenal receptors. Solutions with high acid concentrations cause a more profound inhibitory effect than those of low concentrations (24). The inhibitory effect of an acid can be related to its molecular weight in that, acids with high molecular weight cause less retardation than those with low molecular weight. In general, increasing the osmolarity of a solution results in slower emptying (25). The inhibitory effect of fatty acids is determined by the fatty acid chain length, with chain lengths of 10-14 carbons causing the greatest delay (26). Amino acids exert their effect by the osmolarity of the solution. However, L-tryptophan appears to have a specific inhibitory effect, suggesting the presence of a specific receptor (27).

The greater the energy content of food, the slower the rate of emptying (28). The rate of emptying is such

that the number of calories delivered to the duodenum remains constant. Thus, carbohydrates empty faster than proteins, which empty faster than fats. However, isocaloric amounts of each, empty at the same rate (29). Nevertheless, increasing the caloric content of a meal will not overcome the enhancing effect of meal weight (21). Carbohydrates and amino acids, except L-tryptophan, retard gastric emptying via the osmoreceptors, and fats slow emptying via the fat receptors (22).

The viscosity of a meal appears to be an important factor in gastric emptying (30,31). An increase in viscosity not only slows emptying, but significantly alters gastric sieving (32).

Temperature effects on gastric emptying have not been extensively investigated. Ritschel and Erni (33) found capsules entered the small bowel more rapidly with a cold drink than a warm one. Bateman (34) observed only an initial rapid emptying for cold drinks, with no significant effect on subsequent emptying.

The relationship of body size to the rate of gastric emptying has been investigated. Both body size and body area were inversely proportional to the rate of gastric emptying (35). Another study indicated obese men empty solids more rapidly than non-obese men, whilst both groups had similar patterns of liquid emptying (36). The

slower emptying of solids may have resulted from prolongation of the lag phase in obese subjects (37).

Other factors known to alter gastric emptying include stress (38), posture (39), and sex of the subject (40). A relationship has been shown between gastric emptying and the phase of the menstrual cycle (41), and also the stage of pregnancy (42). Solid and liquid emptying were significantly slower in older subjects than in younger subjects, but this was not considered clinically significant (43). Gastric emptying is retarded by severe exercise, but hastened by mild exercise (44). Furthermore, the extent of retardation is a function of the level of the exercise, and not the type of exercise.

One significant observation with consequences for GI studies, is that gastric emptying time is a variable process in healthy subjects, with significant inter- and intrasubject day-to-day differences (45).

It should be remebered, that the control of gastric emptying not only serves digestion and transit, but is likely to have homeostatic features which influence feeding (46).

Diseases which modify the rate of gastric emptying can be classified as either extrinsic or intrinsic (47). There have been few studies to illustrate the direct effect of extrinsic diseases on gastric emptying. In many cases the drug administered to treat the disease may

affect gastric emptying. However, diseases that apparently delay gastric emptying include diabetes mellitus (48), thyroid disease (49), and migraine (50). The data for intrinsic diseases is more conclusive. The disease states shown to affect gastric emptying include gastric ulceration (51), gastric dyspepsia (52), pyloric stenosis (53) and gastric carcinoma (54).

A number of drugs have been shown to influence the rate of gastric emptying. Some drugs, such as atropine (55), propantheline (56), and morphine (57), reduce gastric motility. Other drugs, such as metoclopramide (58), and domperidone (59), increase the rate of emptying. Cigarette smoking accelerates the rate at which liquids leave the stomach (60), and high nicotine cigarettes delay the emptying of solid foods (61). It has been suggested that wine and beer delay gastric emptying, while spirits may promote emptying (62).

1.2.1.3 Migrating myoelectric complex

The patterns of gastric emptying discussed above relate to the stomach in the postprandial state. During fasting the stomach is ordinarily empty aside from swallowed saliva, mucus and cellular debris. In addition there may be particles of indigestible solid content left from the previous meal. A mechanism termed the migrating myoelectric complex (MMC), first described by Szursweski

(63), exists to empty this fasting content. The MMC exhibits four distinct phases:

phase 1 - 45-60 mins of no contractions;

phase 2 - 30-45 mins of intermittent contractions,

phase 3 - 5-15 mins of powerful distal and proximal gastric contractions;

phase 4 - 5 min transitory period back to phase 1.

Each phase of the cycle migrates distally from the stomach to the terminal ileum, and takes about 2 hours to do so. Thus, when one phase 3 reaches the terminal ileum, another is begining in the stomach. The pylorus remains open when the waves approach allowing liquids and solids to be propelled out. The ability of phase 3 to so completely empty the stomach has earned it the name the "housekeeper wave" of the gastrointestinal tract (GIT). Abolition of the cycle occurs promptly with feeding and a normal meal causes disruption of the MMC for about 3-4 hours (64). The disruption is mediated through both neural and hormonal action (65).

1.2.2 The Small Intestine

Detailed investigations of the small intestine became possible with the advent of radiographic techniques. The studies conducted by Cannon (66) early this century still provide much of our basic understanding of the small intestine.

1.2.2.1 Structure and function

The small intestine is a long tubular structure, 300-400cm, that extends from the stomach to the caecum. Although the small intestine is one continuous organ, it is normally considered as three parts, duodenum, jejunum, and ileum. The diameter of the intestine gradually decreases from the proximal to the distal end.

The small intestine is the major area of absorption of water, nutrients and electrolytes. Contractions of the small intestine musculature bring about:

i. mixing of foodstuffs with digestive enzymes;
ii. circulation of the intestinal contents to ensure contact with the absorptive cells of the mucosa;
iii. net aboral movement of chyme.

The manner of movement depends on the volume and composition of food, although little is known about these characteristics in each region of the intestine. It is known that duodenal contents are more voluminous and less viscous than ileal contents. Nonpropulsive contractions serve to mix and locally circulate the contents by rhythmic segmentation, causing oral and aboral movements, but no net propulsion. Propulsive contractions, or peristalsis, propel the intestinal contents in an aboral direction over varying distances, but cause little mixing (67).

A comprehensive study of small intestine transit times in a number of subjects between the ages of 1-25 years, reported mean transit times of 2.75-3h (68). A detailed study on the flow rate, flow velocity and composition of intestinal contents, suggested that laminar flow occurs in the small intestine (69). Furthermore, a velocity gradient exists down the intestine, with flow rates decreasing in the distal portion of the intestine.

Contractions of the small intestine are due to the activities of smooth-muscle cells. These contractions are dependent on the intrinsic properties of the cells, intrinsic nerve plexuses, extrinsic para- and sympathetic nerves, and locally released chemicals (eg. gastrin, acetylcholine).

1.2.2.2 Determinants of intestinal transit

Unlike the stomach, the small intestine does not differentiate between solids and liquids, and both materials move through the intestine at the same rate (70). However, liquids reach the colon faster than solids, when considering stomach to caecum transit, due to the difference in gastric emptying. Furthermore, changes in intestinal transit can occur independently of changes in gastric emptying (71). These changes are governed by dietary factors.

A recent hypothesis proposes the presence of a feedback mechanism which controls gastric emptying and small bowel transit (72). This "ileal brake" is located in the distal ileum, and would serve to optimise the time available for absorption. The mechanism operates by detecting unabsorbed fat or protein, and via an undetermined mediator, would delay both gastric emptying and intestinal transit (73). Spiller et al (74) gave further credence to the hypothesis, by showing that an infusion of intralipid delayed transit of bromosulphthalein. A similar study illustrated the effect on carbohydrate absorption by the presence of fat in the ileum (75). The importance of the terminal ileum in controlling intestinal transit was described by Neal et al (76). A rapid small bowel transit was observed in patients who had undergone ileal resection.

Apart from the presence of fat or protein in a meal, the amount of unabsorbable carbohydrate (eg.lactulose) in the meal appears to have a profound affect on intestinal motility (77). An accelerated transit time probably resulted from an increase in luminal volume and an osmotic effect.

As with gastric emptying, the menstrual cycle influences intestinal transit, with transit being slower in the luteal phase and faster after menstruation (41). Moderate exercise does not appear to affect small bowel transit (78), whilst stress accelerates transit (38).

Patients suffering from diarrhoea show a significant acceleration in intestinal motility (79), although this could be stress related. Conversely, patients suffering from constipation show delays in small bowel transit (80).

Drugs known to reduce intestinal motility include morphine (81) and loperamide (79). Few drugs have been shown to accelerate intestinal transit, although metoclopramide is regarded to have a significant effect (82). Intravenous administration of metoclopramide caused a
significant increase in the rate of travel of a capsule, but only in the proximal intestine (83).

Finally, the duration of transit of a meal through the small bowel will influence the extent of absorption (84). However, it appears that absorption cannot be predicted solely from transit patterns, but depends on the agent or event that alters the transit (79). Absorption is inhibited to a greater extent by agents that increase intestinal volume, than by agents that directly stimulate propulsion. The implications for drug adminstration are profound.

1.2.2.3 Migrating myoelectric complex

The existence of the MMC was first demonstrated in the small intestine of fasting dogs (63,85), and the basic pattern has been described above. Control of the

MMC is thought to be mediated through hormones, eg. motilin, and extrinsic nerves (86). Wingate et al (87) have proposed the presence of an intrinsic biological clock, possibly located in the small bowel wall, which controls the periodic activity of the intestinal MMC, whereas gastric MMC are controlled by an extragastric mechanism.

Intestinal MMC differ from gastric MMC, in that gastric MMC occur in the fasted state when the stomach is devoid of digestible matter, whilst intestinal MMC appear to have a role in the propulsion of intestinal contents. Code and Schlegel (88) illustrated the interdigestive propulsion of phase 3 using cineradiography techniques. It is accepted that this propulsive activity is not the primary force for transit, but may act to prevent orad transit of contents (89). Another proposal for the propulsive phases is that they are necessary to prevent bacterial overgrowth of the small bowel during fasting (90). Despite the uncertainty about the role of the propulsive phase of the MMC, the pattern of contractions will have a marked influence on intestinal transit and digestion (91).

1.2.3 The Ileocaecal Sphincter

The ileocaecal sphincter (ICS) is an anatomically distinct boundary between the small intestine and colon (91). The ICS was apparently first described by Bauhin,

in 1579, as a musculature structure rather than a mechanical sphincter (92). Interest in the functions of the sphincter was later renewed by Alvarez (93), Cohen (94), and more recently by Quigley and colleagues (95).

1.2.3.1 Structure and function

The ICS is apparent as a thickening of the musculature of the last few centimetres of the ileum. In man, a portion of the ileum projects into the caecum and is surrounded by colonic musculature. The ICS satisfies the four main criteria used to define sphincters of the GIT, ie. it exhibits a segment of tonic pressure; relaxes with distension of the ileum; contracts with distension of the proximal colon; and responds to nerve stimulation differently from adjacent GI smooth-muscle (95). However, some observers have failed to detect a high tonic pressure at the human ICS (96). The tone of the ICS is regulated by electrical activity, neural activity and possibly hormonal action.

The function and importance of the ICS are not confirmed. The sphincter may act to:

i. regulate transit of material from the ileum to the colon;

ii. prevent the reflux of colonic content into the ileum;

iii. serve as a barrier to bacterial reflux from the colon.

The regulatory role controlling flow of material into the colon seems the most likely. However, there is much debate as to the nature of this flow.

Several studies have shown an increased activity in the ileocaecal region within minutes of food ingestion being accompanied by expulsion of ileal contents into the colon - the gastroileal reflex (97,98).

Spiller et al (99) concluded that postprandial flow of material across the ICS was regular and rapid, whilst transit before eating was slow and erratic. They also suggested a reservoir function for the terminal ileum during the low flow rates. Scintigraphic measurements of ileocolonic transit suggest that transit often occurs as a bolus in both the fed and the fasting state (100). The intermittent nature of transit across the ICS influences the colon's ability to absorb dietary residues, secretions, and water (101). Furthermore, the absorptive capacity of the colon is readily overloaded by rapid infusion of fluid (102). These observations point to a regulatory role for the ICS, to achieve maximum colonic absorption.

The terminal ileum differs from the rest of the small intestine with regard to MMC activity. Studies have shown that phase 3 contractions become disorganised in the terminal ileum, and a single propulsive contraction not related to the MMC propels ileal contents into the colon (89). It has been suggested that in the

fasted state, this propulsive contraction could be related to phase 2 activity (100). A comprehensive study on the motility of the terminal ileum not only observed both the absence of phase 3 activity and the presence of a propulsive contraction, but also identified discrete clustered contractions (103). The relevance of these clustered contractions to the transit of ileal contents remains unclear.

The role of the ICS in regulating the flow of material into the colon is not completely defined. Nevertheless, both the postulated reservoir function and bolus movements have implcations for drug delivery to the colon.

1.2.4 The Colon

The colon has been studied less than other portions of the alimentary canal. This has been due to the considerable interspecies variations in the anatomy of the colon, the complexity of its functions, and the presence of microbial flora which complicates the experimental approaches to colonic function (104).

1.2.4.1 Structure and function

The human colon is about 1.5m long and is generally described in several parts: appendix, caecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum and anus (Figure 1.3). Throughout its length, the

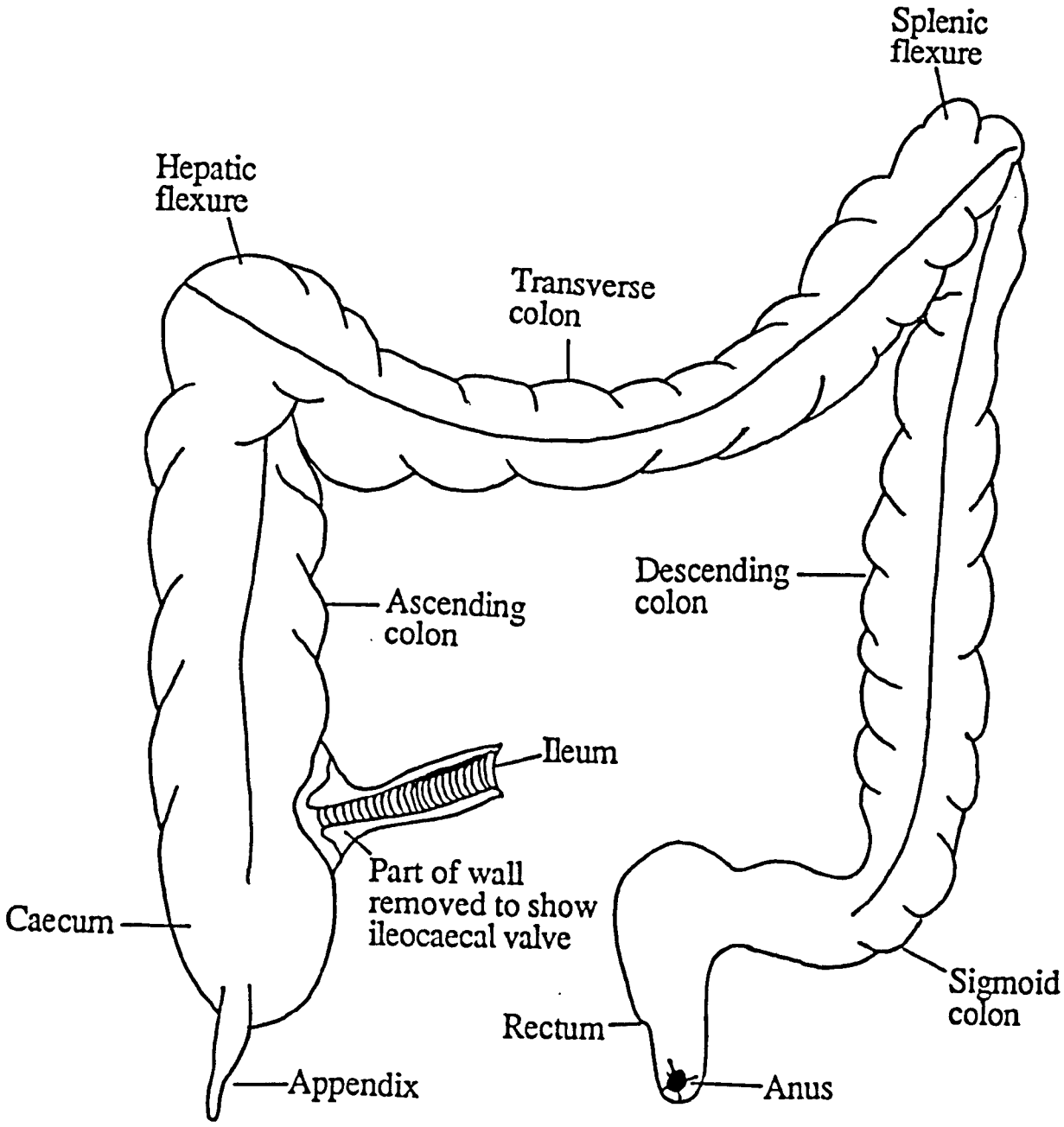


Figure 1.3 Anatomical structure of the colon

colon is a sacculated organ, achieved by the arrangement of the outer muscle coats. The colon has a variety of functions:

i. the maintenance of electrolyte and fluid balance;
ii. provision of an absorption site for nutrients;
iii. digestion and metabolism of dietary material;
iv. formation of faeces;
v. temporary storage of faeces until elimination is convenient.

All segments of the colon have the capacity both to propel and prevent too rapid a progression of contents. This storage function facilitates digestion, reabsorption of ileal fluids and production of faecal mass. Furthermore, this property makes it more appropriate to measure colon transit time in days rather than in hours (105). Ritchie (106) observed that healthy subjects with normal bowel habits moved the contents of the right colon, under resting conditions, at a rate of 1cm/h. Studies have shown that stools are retained in the right half of the colon (107), although a recent study suggests that the transverse colon, is the primary site of storage (108).

The contractions of the colon can be divided into three basic patterns, which occur in distinct regions:

i. Ring contractions of 2-8 minutes occuring at 15 minute intervals, which serve to mix and churn the contents in the caecum. Entry of new material from the ileum causes a brief period of strong contractions in the caecum and ascending colon, pushing the contents towards the rectum.

ii. Co-ordinated peristalsis in the middle part of the colon of segmented or haustral contractions. These contractions are either stationary or propagate very slowly in an oral or aboral direction. However, they have a net propulsive role towards the rectum.

iii. Strong contractions of the sigmoid colon and rectum which move contents slowly towards the anus and serve to empty the colon.

The control of colonic segmental and propulsive activity appears to be very complex, and is mediated through myogenic factors, intrinsic and extrinsic innervation, and hormonal factors (109).

1.2.4.2 Determinants of colonic motility

Ingestion of food is the main physiological stimulus of colonic motor activity, often referred to as the "gastrocolic reflex" (110). A rapid increase in contractile activity occurs after eating, the degree of which depends upon the caloric content and the nature of the nutrients. Fat produces a much stronger stimulation of colonic activity than protein or carbohydrate (109).

Ingestion of crude fibres shortens transit time significantly. However, addition of large amounts of fibre to the diet regulates bowel habits. Thus, subjects with a slow transit time develop a faster one, and vice versa (111).

A number of drugs are known to affect colonic transit. Laxatives (112) and cholinergic agents (113) generate colonic peristalsis which propagate mass movement of contents, and accelerate transit. Calcium antagonists (eg. nifedipine) decrease the postprandial activity (114). A recent paper reports that oleic acid induces accelerated transit and abnormal motility in the colon (115).

Other factors that alter colonic motility include stress, distension of the colon, and many disease states (116).

1.2.4.3 Pathology of the colon

Interest has recently developed in formulating oral drug delivery systems for the local release of drugs used in the treatment of diseases of the colon. A brief outline of common abnormalities of colonic motility would identify those disorders which would benefit from local rather than systemic drug action.

i. Irritable Bowel Syndrome (IBS). This is probably the most common disease of the colon, and leads to abdominal pain, constipation and diarrhoea (117). The

aetiology of IBS is thought to be a disordered motor function of the bowel, caused by stress. Treatment relies on identification and modification of the stress factors, as well as using drugs to treat anxiety, depression and colonic motility.

ii. Colonic Diverticular Disease (CDD). In this disease, small outpouches of the mucosa form through the muscle wall, and there is a raised intraluminal pressure due to disordered muscle activity (110). Its occurence is common in western society, and appears to be related to the amount of fibre in the diet. Treatment consists of a high roughage diet, and the use of antispasmodics (eg. peppermint oil (118)) to reduce pain and discomfort.

iii. Ulcerative Colitis and Crohn's Disease. Both these conditions are similar in their presentation, pathology and treatment. The diseases are possibly immunological in nature, and some evidence suggests a genetic influence (119). Ulcerative colitis involves the rectum, although the diseased area may spread proximally as a continuous band from the rectum. Crohn's disease is often present as a discontinuous inflammation of the bowel. Drug treatment involves the use of corticosteroids, and the local action of 5-aminosalicylic acid (5-ASA) (120).

1.3 Controlled Release Technology

1.3.1 History of Controlled Release

The notion that a dosage form can be other than simply a dose of drug, has only recently attracted attention. Advances in pharmacology and pharmacokinetics have demonstrated the importance of drug release rates and absorption in determining therapeutic results in systemic treatment (121). These advances have led to the development of dosage forms with specified or controlled drug delivery rates.

Dosage forms with modified release rates are not entirely new. The first coated pills can be traced to about A.D. 900, when Rhazes recommended a mucilage coating (122). This technique was adopted by the Europeans in the 10th century, in the form of gold-, silver- and pearl-coated pills. Although these coatings were designed to mask bitter tastes and improve appearance, they did alter the release of drug. Advances in coating technology in the late 1800s saw the advent of sugar-coated and enteric-coated pills. These coating methods led to the development of the repeat action tablet (123), consisting of a core tablet sealed with an enteric material followed by a second drug dose in a sugar-coating layer. It was not until 1938, however, that Lipowski patented the first oral sustained release preparation (124). His formulation consisted of a number

of small coated beads, which gave a slow and constant release of drug. This idea was later developed by Blythe (125), and was the basis for the first marketed sustained release (SR) product in 1952 (126).

Unfortunately, the proliferation of modified release formulations since that date, has created a problem of terminology (127). Controlled release is now the popular term to describe these formulations, since it implies a predictable and reproducible release rate, whilst SR suggests only a prolonged release of drug (128). However, neither term considers the physiological variables, such as GI transit, that will influence drug bioavailability.

The controlled release administration of drug is not restricted to the oral route. Systems have been developed for the transdermal (129), ocular (130), vaginal (131) and parentral (132) routes. These devices provide a localised depot of drug, with a rate-controlled release into the systemic circulation. Physiological influences are minimised due to the very design of the systems. The eventual design of such controlled release delivery systems (CDDS) (133) for the oral route, will require an increased understanding of gastrointestinal tract (GIT) physiology (134).

1.3.2 Rationale for Controlled Release

The primary reasons for developing an oral controlled release formulation are listed below:

i. **Maintain a steady therapeutic drug concentration in the systemic circulation and tissue cells** (135). Conventional dosage forms often require high doses to achieve a therapeutically effective concentration. This massive dosing can elicit undesirable toxicological effects. Furthermore, the peak and trough fluctuations common with conventional drug administration, can lead to periods of no therapeutic effect.

ii. **Reduced frequency of dosing** (136). The advantage of a single daily dose is particularly suitable for psychiatric patients, who have a high failure rate in taking prescribed drugs (137).

iii. **Improved patient compliance** (138). This probably results from the convenient dosing regimes and the reduced side-effects.

iv. **Economic advantage** (139). Initial unit costs of CR formulations are usually greater than conventional dosage forms. However, the average cost of treatment over an extended period of time is less. Economy also results from a decrease in nursing time/hospitalization.

The major disadvantages of oral controlled release formulations are:

i. **Accidental poisoning** (140). This can result if the integrity of the controlled release system is breached, possibly due to incorrect administration by the patient, causing "dose dumping".

ii. **Reduced control of dosing** (141). The flexibility of tailoring drug doses to individual patient requirements is reduced with CR formulations. Inter-patient variation in response to a formulation also becomes more difficult to resolve.

Although the advantages of CR formulations appear to outweigh the disadvantages, not all drugs are ideal candidates for controlled release. Properties of drugs that preclude their use in CR formulations include:

i. **Size of dose** (142). The practical constraints in formulating high dose drugs (eg. aspirin), favours the use of drugs with small doses.

ii. **Site of absorption** (143). The drug should be absorbed throughout the length of the GIT, and not at specific absorption windows in the upper part of the gut (eg. iron).

iii. **Duration of action** (144). Controlled release formulations offer no advantage for drugs whose half-life is longer than about 12 hours (eg. diazepam).

iv. **Rate of metabolism** (145). Drugs with a high first-pass metabolism are poor canditates for CR systems (eg. levodopa). This is because many metabolic processes

are saturable, leading to a dose-dependent loss of drug and a marked reduction in bioavailability.

v. **Toxicity.** Controlled release formulations often contain a large dose of drug. Rapid release of a potent drug with a narrow therapeutic index (eg. digoxin) would result in a systemic toxic reaction.

1.3.3 Oral Controlled Release Systems

Oral controlled release systems are classified as either single-unit or multiple-unit doses (146). Single-unit preparations remain as a non-disintegrating unit throughout the GIT. Multiple-unit preparations are composed of many CR sub-units, formulated either in a capsule or as a tablet, designed to disperse throughout the GIT. These preparations offer a more reproducible GI transit than single-unit systems (147), but are often more expensive to manufacture (148). Liquid CR products have also been developed (149), but the difficulties in formulating such preparations normally makes them commercially nonviable.

Controlled release of drug from the dosage form, either single-unit or multiple-unit, can be achieved by a variety of techniques. Generally, the system consists of a drug reservoir, a source of energy, and a rate controlling device (150). The energy required is provided by a concentration gradient between the drug

core and the surrounding fluid. The rate controlling device relies on specific physical mechanisms:

i. **Diffusion controlled systems.** Drug is either encapsulated in a water-insoluble polymer (151) or dispersed in an insoluble matrix (152). The rate of release is dependent on the rate of drug diffusion from the system and is a zero-order process for encapsulated systems (153) but proportional to the square root of time for matrix systems (154).

ii. **Dissolution controlled systems.** These are similar to the above, but drug dissolution and not diffusion is rate limiting. A constant release rate will be achieved if the surface area, concentration and diffusional pathlength can be maintained (155).

iii. **Osmosis controlled systems.** These systems consist of a drug core, either solid or liquid, surrounded by a semipermeable membrane containing a small orifice (156). Selective entry of water dissolves the drug, and generates an internal pressure which forces the drug solution out of the orifice. Two products relying on this mechanism have been developed by the Alza Corporation, (a) OROS, designed for the delivery of solid drug (157); and (b) OSMET, designed for the delivery of semi-solids and liquids (158). The advantages of these products include their zero-order release rate, which is largely unaffected by the conditions in the GIT, and the

large category of drugs that can be formulated into osmotic systems (121).

In summary, controlled release dosage forms offer a number of advantages over conventional drug administration. Several innovative mechanisms have been developed to achieve a constant and predictable release rate, but scant consideration has been given to the fate of the dosage form in the GIT.

1.4 Techniques to Measure Gastrointestinal Transit

A number of methods has been applied to investigate the performance of dosage forms in the GIT. These methods can be described as either invasive or non-invasive. Invasive techniques interfere with normal physiological processes, which makes them less suitable as investigative tools than non-invasive techniques.

1.4.1 Invasive Techniques

Early studies on the GI behaviour of dosage forms were primarily concerned with evaluating the performance of enteric coated tablets (159). These methods were later applied to the evaluation of other tablet formulations. Techniques such as the Yo-Yo method, which involved the withdrawal of tablets from the gut by means of a string attached to them (160), and induced vomiting (161), would have been particularly unpleasant for the

volunteer subjects. Other tests involved the detection of either dye markers or drug metabolites in the saliva (eg. iodide from potassium iodide tablets (160)); in the urine (162) (eg. methylene blue (163)); and in the blood (164). These methods provided good estimates of drug absorption, but scant information on the GI behaviour of the tablets, other than the tablets must have disintegrated.

The most common method of determining the in vivo performance of tablets was to incorporate radio-opaque material, usually barium sulphate, into the tablets, which enabled visualisation using X-rays (165). The high density of barium sulphate, which could affect gastric emptying, and the problems of safety associated with X-rays are major disadvantages of this method. Nevertheless, roentgenologic methods have been widely used to investigate the fate of timed-disintegration capsules (166), and of pellets (167).

Mouth to caecum transit time can be estimated indirectly by the measurement of pulmonary hydrogen excretion. The method, known as the hydrogen breath test, features the administration of a nonabsorbable carbohydrate, lactulose, which is converted to hydrogen by anaerobic bacteria in the colon. The level of hydrogen excreted in the breath can be measured by gas chromatography (168). The problems associated with this method include the large quantity of lactulose required

to produce a significant rise in hydrogen and the acceleration of intestinal propulsion caused by the strong osmotic stimulus exerted by this large quantity (169). Furthermore, some individuals may lack the intestinal flora required for the degradation of lactulose to produce hydrogen. Modifications to the method have been made with the use of ^{14}C-lactulose, and the measurement of $^{14}CO_2$ in the breath (170). The negligible mass of carrier lactulose required alleviates the problem of accelerated intestinal transit.

Other techniques include those routinely used for clinical investigations of the gut, such as gastroscopy, which allows visualisation of solid doses (171), and intubation methods such as aspiration and perfusion, for liquids and small particles (172, 173). However, these methods can cause much discomfort to the volunteers.

1.4.2 Non-invasive Techniques

An early study to measure GI transit used inert materials which were swallowed and subsequently recovered in the faeces (174). A similar idea was used by Bechgaard and Ladefoged (175), who recovered pellets from ileostomy bags. The problems with this method are that the recovery of the dosage forms maybe incomplete and ileostomy patients may have different GI characteristics from subjects with intact intestines.

Recent advances in diagnostic instrumentation has led to a number of direct, non-invasive methods. Gastric emptying of liquids can be measured by ultrasound (176). Since there are no ionising risks, the technique can be used safely in both men and women (177) and can be repeated on the same subject (178). However, the technique is restricted to measuring the gastric emptying of liquids.

The gastric emptying of liquids can also be determined by measuring epigastric impedance (179). Gastric impedance rises when liquids of low conductivity are swallowed, and then drops as the liquid empties. The technique is regarded simpler and cheaper to operate than most other methods, as well as providing comparable results (180). However, gastric secretions could become a source of impedance error, as could changes in skin resistance due to anxiety or stress. More recently, Avill et al (181) described the use of applied potential tomography to follow the gastric emptying of liquids and semisolids. The method relies on the change in tissue resistivity during gastric emptying.

These methods have little application to the study of the GI transit of solid doses, but provide valuable information about GI motility. The use of radiotelemetric capsules, however, would provide transit profiles that resemble the GI transit of large indigestible solids. These capsules either transmit a

continuous radio signal which is received by an external detector (182) or monitor the pH of the environment (Heidelberg capsule) (183). Gastric emptying of the latter is indicated by a sharp rise in pH, as the capsule moves from the acidic stomach to the more alkaline intestine. The performance of an enteric coated formulation was evaluated by attatching a coated buffer tablet to an Heidelberg capsule (184). Premature rupture of the coating in the stomach was detected by a rise and then a fall in gastric pH prior to gastric emptying. However, these methods can only give reliable information on the GI transit of the device, and cannot be used to determine the transit of multi-particulate formulations.

The use of animal models to measure the GI transit time of dosage forms has been forwarded by Takahashi et al (185). It was reported that rabbits in which gastric emptying and gastric pH were controlled by special diet, had GI transit profiles similar to humans. The authors suggest that these rabbits could be used as a model for estimating the bioavailability of controlled release products in humans.

1.4.3 Gamma Scintigraphy

The technique of gamma scintigraphy has become the most popular method to investigate the GI performance of both food and pharmaceuticals. A gamma emitting isotope is incorporated into the test material, and is monitored

externally by measuring the radiation emitted. Griffiths et al (186), in 1966, were the first to demonstrate this technique, by monitoring the gastric emptying of chromium-51 labelled food using an automatic scintiscanner. Hansky and Connell (187) had previously used chromium-51 to measure total transit times, by administering radiolabelled chromium oxide powder and using a scintillation counter to measure the activity recovered in the stools. However, it was not until 1976 that the technique was used to investigate the fate of pharmaceuticals in vivo. Alpsten et al (188) used two scintillation detectors to monitor the dispersion of radioactively labelled tablets. In an almost simultaneous publication, Casey et al (189) described the use of external scintigraphy to visualise the disintegration of technetium-99m labelled capsules. The same technique was later used to monitor the in vivo disintegration of tablets (190).

1.4.3.1 The gamma camera

Certain materials have the property of emitting a flash of light or scintillation when struck by ionising radiation. A scintillation detector detects ionising radiation by observing the scintillation induced in the material. The head of scintillation or gamma cameras commonly consists of a sodium iodide crystal, 40cm in diameter, activated with thallium, NaI(Tl). Pure sodium

iodide crystals do not normally scintillate at room temperature, but do so after the addition of thallium. The thickness of the crystal is restricted to about 1cm. In a thick crystal, the depth of the flash of light will affect the intensity of light detected, whilst thin crystals will have poor detection efficiency (191). Coupled to the crystal is an hexagonal array of photomultiplier tubes, which detect the light pulses. The whole arrangement is encased in lead to shield the crystal from extraneous radiation. A package of electronics links the photomultiplier tubes to a computer and visual display unit. Information regarding the strength and position of the pulses are stored in the computer for subsequent analysis, and an image can be generated on the display unit (Figure 1.4).

Gamma rays from the source are focused onto the detector by a lead collimator placed directly in front of the crystal. A number of collimators is available, including parallel-hole, converging and pinhole collimators. The latter are suitable for magnifying small objects such as the eye. Parallel-hole collimators are the most commonly used, and give a 1:1 correspondence of object and projection onto the scintillator (191). The collimator consists of many thousands of parallel-sided holes, which ensure that only parallel rays emitted from the source are detected. Parallel-hole collimators are available as low energy, medium energy

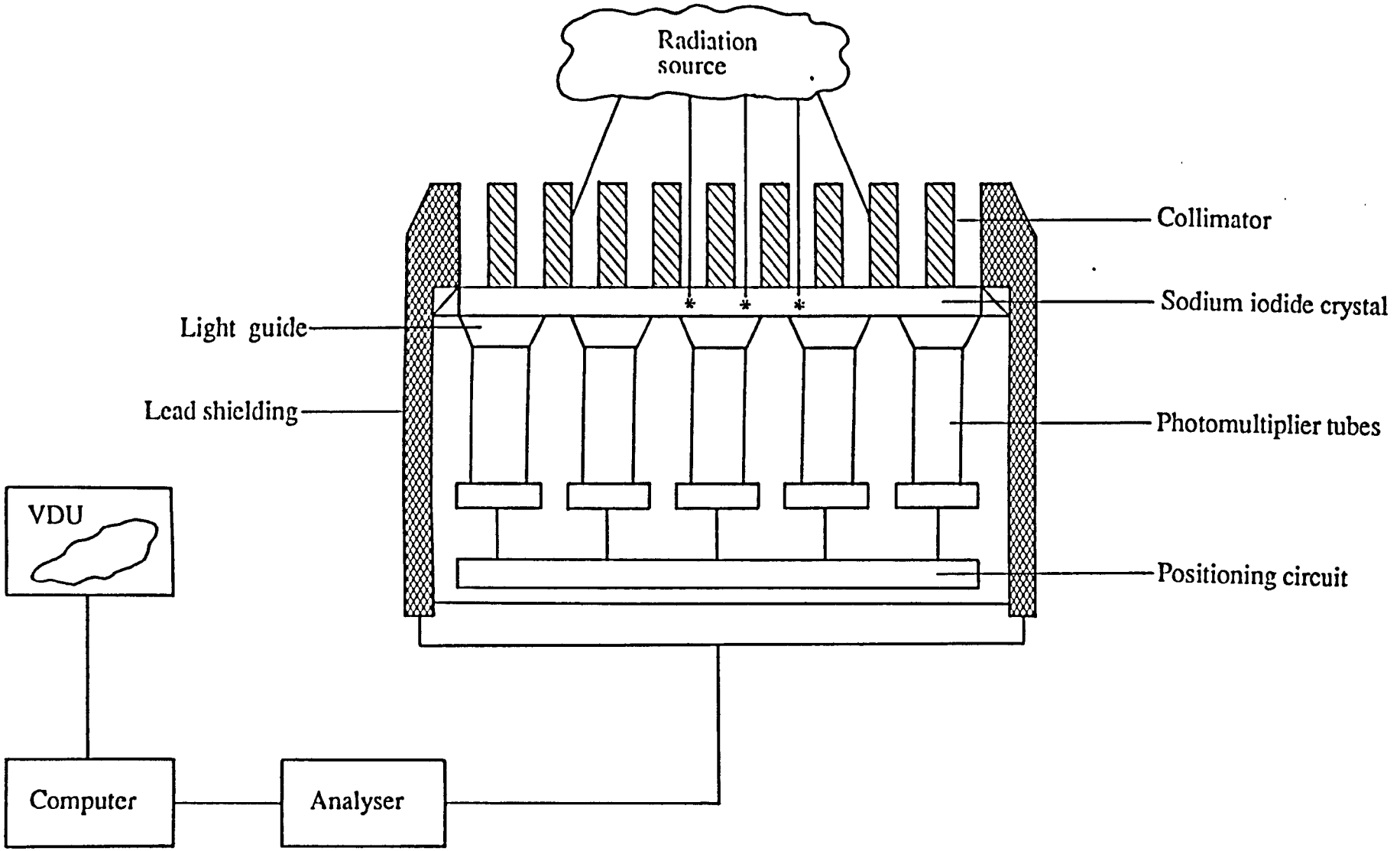


Figure 1.4 Schematic diagram of the gamma camera

and high energy, depending on the thickness of the septa, and hence the number of holes. Low energy collimators have thin septa and thus many holes, which makes them more sensitive. The collimator used will depend on the photon energy of the isotope being used. A comprehensive account of gamma cameras can be found in a number of publications (192, 193).

1.4.3.2 Radiopharmaceuticals

A number of radionuclides are available for imaging purposes, but not all are ideal candidates. Factors such as the radiation energy, half-life, extent of particulate radiation, cost and availability must be considered. Low energy radiation is absorbed by the tissues, whilst high energy radiation raises problems in shielding the detector (194). The ideal energy range is considered to be between 100-250keV, although the use of appropriate collimators can extend this to 70-400keV. The half-life is important not only because of radiation doses to the subject, but must be sufficiently long to allow preparation of the radiopharmaceutical and perform the study (195).

After taking the above criteria into account, only a few radionuclides are suitable for imaging studies. These can be divided into three categories according to their chemistry (194), native labels (eg. ^{11}C); foreign covalent labels (eg. ^{75}Se); and foreign metal-ion label

(eg. ^{99m}Tc). Native labels generally have short half-lifes, and are prepared by a cyclotron. This restricts their use for studies on drug delivery systems, although they have been utilised in studies of tissue disposition of drug (196). Metal-ion nuclides most closely satisfy the essential criteria, which accounts for their extensive use in scintigraphy studies. The most popular of these is technetium-99m. The reasons for this popularity are its versatile chemistry, near ideal energy (140keV), low radiation dose, and suitable half-life (6.0h). Furthermore, it is readily available through the use of a portable generator (197) (Figure 1.5). Other commonly used metal-ion nuclides include indium-111 and indium-113m. A more complete review of radionuclides suitable for imaging has been given by Kelly (194).

Having chosen a suitable radionuclide, an appropriate agent must be selected, which is radiolabelled with the isotope. Gastrointestinal studies require both solid-phase and liquid-phase markers. Apart from being nontoxic, liquid-phase markers should be nonabsorbable and should not adhere to either the GIT or solid food particles (198). Solid markers require efficient binding of the radiolabel throughout the period of study. Early studies incoporated the radionuclide into food (199), but since then a number of radiopharmaceuticals have been used. These include ^{129}Cs

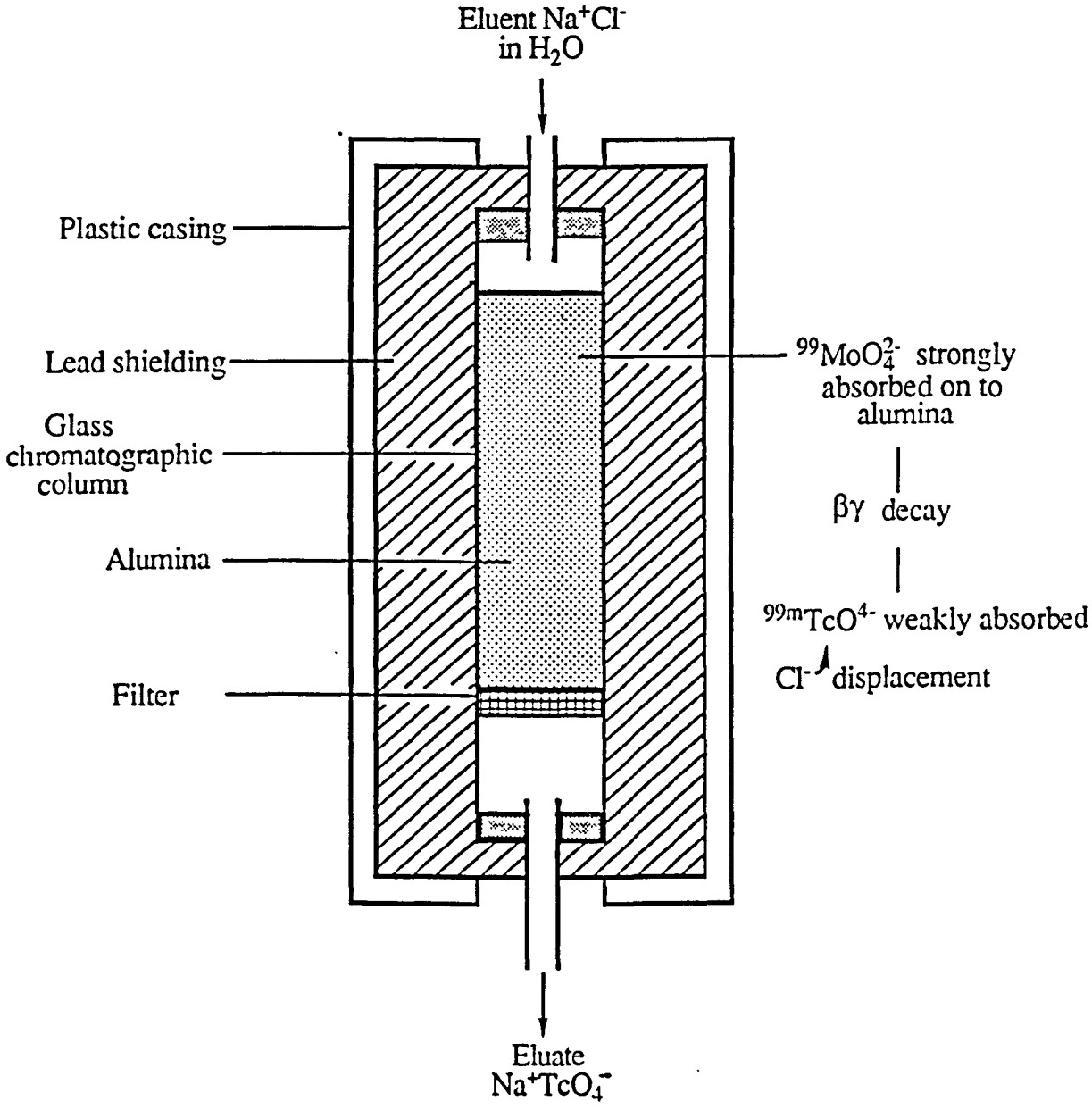


Figure 1.5 Schematic diagram of a ^{99m}Tc generator.

absorbed onto a suspension of zirconium phosphate (200), ^{113m}In-labelled diethylenetriaminepentaacetic acid (DTPA) (201) and ^{131}I-labelled human serum albumin (202). Radiopharmaceuticals labelled with technetium-99m are probably the most widely used, due to the advantages of the isotope. These radiopharmaceuticals include ^{99m}Tc-labelled chelating agents (eg. DTPA (203), EDTA (204)); colloids (eg. sulphur colloid (205)); cells and blood elements (eg. erythrocytes (206)), human serum albumin (207); polystyrene resins (208); and cellulose macromolecules (209). For an excellent discussion of ^{99m}Tc-labelled radiopharmaceuticals, the reader is directed to the review by Eckelman and Levenson (210).

For studies on the GI transit of dosage forms, the radiolabelled marker is either incorporated into the formulation or the marker is used to mimic the behaviour of the dosage form. Conventional methods of labelling require the marker to be incoporated as late as possible, thus reducing the risk of radioactive contamination during manufacture. This has caused problems with enteric-coated formulations. Recently, however, Parr et al (211) described a process to irradiate enteric-coated tablets, containing a small quantity of stable erbium isotope, in a neutron flux, to produce radioactive tablets containing erbium-171.

1.4.3.3 Errors and corrections

The technique of gamma scintigraphy, like many other scientific methods, has a number of inherent errors. These errors are related either to the physical properties of the radionuclides and instruments or to changes in the distribution of the radionuclide within the subject, and can be overcome by applying a number of suitable corrections. Physical corrections include those for radionuclide decay, septal penetration and scatter from high energy gamma rays.

All radiation detectors will record some activity without a source present. This background activity is caused by radiation from natural radio-isotopes and cosmic rays, and by instrument noise. A simple subtraction of the background count from the gross count of the source will give the net count due to the source alone (192).

Gastrointestinal transit studies often extend for many hours, and thus accurate results will require correction for radioactive decay (212).

Modern gamma camera systems allow the activity from two isotopes to be measured concurrently. This property has been used to simultaneously measure the gastric emptying of liquid and solid components of a meal, using ^{113m}In-DTPA as the liquid phase marker and paper impregnated with ^{99m}Tc-labelled sulphur colloid as the solid phase marker (213). However, an appropriate correction for the scatter down from the higher energy

isotope into the lower energy isotope window is required to give meaningful results. This is usually done by administering the high energy isotope first and measuring the counts in the low energy window. This value is then used as factor to correct the low energy counts obtained after administration of the second isotope.

The use of high energy emitters, such as ^{113m}In, also requires a correction for septal penetration of the collimator, using an empirically derived expression (214). The use of a collimator with septa of appropriate thickness will help reduce the errors due to septal penetration.

Radiation from ingested isotopes will be scattered or absorbed by intervening tissues and bone, before reaching the gamma camera, causing the registered radiation to be attenuated (215). Attenuation is more pronounced when measuring gastric emptying, due to the anterior movement of the radiopharmaceutical as it descends from the fundus into the antrum. This movement results in an increase in anterior counts due to decreased tissue attenuation. Tothill et al (216) solved this problem by using a double-headed scanner to obtain anterior and posterior counts, from which they calculated the geometric mean of the counts, (anterior counts x posterior counts)$^{1/2}$. A plot of the corrected counts against time produced a more representative emptying profile. Christian et al (217) later confirmed these

findings using a conventional gamma camera. Moore et al (218) noticed that liquids showed only a slight difference between anterior only counts and geometric mean counts, whereas the difference was more pronounced with solids. This was attributed to the greater attenuation of the low energy of technetium-99m, used as the solid phase marker, compared to the high energy of indium-111, used as the liquid phase marker. Harding et al (219) have, however, suggested that errors in measuring gastric emptying using gamma scintigtraphy are insignificant. Nevertheless, the geometric mean correction is routinely used in gastric emptying studies, and has also been validated for whole bowel transit (220).

Two other methods of correcting for changes in the depth of source and attenuation have been suggested. The first requires anterior peak and anterior scatter counts, from which a peak-to-scatter ratio (P:S) is obtained (221). This ratio is then used to correct the anterior gastric counts and provides a convenient alternative to the geometric mean method. The second method uses a lateral image of the stomach to generate correction factors for posterior only images (222). It was argued that the lateral image method is a practical alternative, since the geometric mean correction is cumbersome and the P:S method is not suitable when using technetium,

Other common errors with gamma scintigraphy include the distance of the subject from the collimator (191), the change in the position of the stomach during emptying (223) and patient motion during imaging (224).

1.4.3.4 Evaluation of oral dosage forms using gamma scintigraphy

Gamma scintigraphy has been extensively used to evaluate gastric emptying for clinical purposes (225). Its application for the evaluation of dosage forms in vivo has, in comparison, been a recent event.

Extensive reviews of the potential of gamma scintigraphy as a tool in the assessment of radiolabelled drug formulations have been presented by Hardy and Wilson (226) and Wilson et al (227). The technique has been used to investigate rectal administration (228), nasal administration (229), parenteral administration (230), tumour targeting (231), tissue uptake and clearance of particles (232), and ocular administration (233). However, it is the application of the technique to investigate the GI fate of oral dosage forms that most concerns this discussion.

The effect of eating and drinking on the buccal release of a model material, ^{99m}Tc-DTPA, from a matrix tablet was measured using the gamma camera (234). Other studies have followed the oesophageal transit of capsules and concluded that capsules are best taken in an upright

position. A preliminary sip of water ensures the capsule does not remain in the oesophagus (235, 236).

The disintegration of hard gelatin capsules in the stomach of fasting and non-fasting subjects was reported on by Hunter et al (237). Another study used the ^{99m}Tc-DTPA model to assess the *in vivo* dissolution rate of a sustained release tablet (238). A good correlation was obtained between the *in vitro* and *in vivo* release profiles. Beihn and Digenis (239) have proposed the use of perturbed angular correlation (PAC) as an alternative technique to measure the dissolution *in vivo* of the water soluble component of a solid dosage form. It is known that some radionuclides decay by emitting two gamma rays, with a unique time delay between the first and second emission, eg. indium-111. PAC involves the time-delayed coincidence counting of two cascading gamma rays that exhibit angular correlation. This angular correlation can be perturbed as a result of interactions between the excited nucleus and its environment, such as occurs during a phase change (solid to liquid), and the degree of perturbation is measured. A modification of this method, known as the summation peak ratio method, provided reliable dissolution data of tablets (240). This method has the advantage of requiring only one camera, as opposed to the three detectors required by PAC. Detailed images of the dissolution *in vivo* of

tablets can be achieved using a gamma camera fitted with a four pinhole collimator (241).

It is not only the gastric performance of solid doses that have been evaluated. Liquid preparations, such as antacids, have also been evaluated (242). The gastric emptying of oils and liquid paraffin has been examined in rats (243). Both the type and volume of the oil altered the rate of gastric emptying.

Gamma scintigraphy has become a potent tool to investigate the total GI transit of dosage forms. Studies have been conducted in both animals (244) and man (245). The influence of factors such as food (246), posture (247) and exercise (248) on the GI transit of pellet formulations has been investigated. Single-unit formulations have also been evaluated (249).

The dual isotope facility has enabled the GI transit of a pellet system and osmotic device to be monitored simultaneously in the same subject (250). The effect of food on the gastric emptying of each formulation was measured, as well as the release of material from the osmotic device. A similar dual isotope study has been conducted on the soluble and insoluble components of a capsule formulation (251).

Scintigraphic studies have recently been coupled with pharmacokinetic studies. This combination of techniques allows the position of the formulation <u>in vivo</u> to be related to plasma and urine drug levels (252). The

influence of food on the disintegration/dispersion and transit of the dose form can also be related to the pharmacokinetic data (253).

It should be remembered, that most of the above studies have been conducted in healthy subjects and thus, their clinical relevance is slightly circumspect. Recently conducted studies evaluating dosage forms in patients, have shown a significant difference in transit times between patients and healthy subjects (254).

Informative reviews on the use of gamma scintigraphy to investigate the behaviour of oral dosage forms have been produced by Davis (255) and by Fell and Digenis (256).

In conclusion, the technique of gamma scintigraphy has a number of distinct advantages over other methods to investigate the GI transit of oral dosage forms:

i. it is a non-invasive technique;
ii. the radiation dose is low;
iii. there is no discomfort to the subjects;
iv. easy labelling of formulations, using readily available isotopes;
v. the transit of the actual dosage form is followed;
vi. data can be quantified and obtained on a continuous basis;
vii. two formulations can be monitored simultaneously.

The technique has the disadvantage of producing images which do not possess the same structural details as X-rays, but probably the major disadvantage is the cost of the instrument.

1.5 The Gastrointestinal Barrier

Oral drug administration has historically been the predominant route of drug delivery. An accurate control of drug bioavailability is necessary in order to optimise this delivery, which, in turn, requires knowledge of both the interactions of the drug with the components of the gut and the performance of the dosage form in controlling these interactions (257).

In this section I shall explain why an understanding of GIT physiology, illustrated by considering drug absorption, and the GI transit of dosage forms, is important to the future design of oral CDDS.

1.5.1 Drug Absorption

The principal site of drug absorption is the small intestine (258). Absorption is facilitated by the large surface area created by surface folds at the macroscopic, microscopic and sub-microscopic levels: Kerckring folds, villi and microvilli (259). Some drugs are absorbed throughout the length of the small intestine, whereas others (eg. riboflavin (260)) are absorbed only at

specific sites, "absorption windows", usually in the jejunum (261). Both the impermeability to small hydrophilic molecules and low surface area of the stomach, and similarly the small absorptive area of the colon, make them unlikely routes of absorption (262).

1.5.1.1 Mechanisms of absorption

Drug molecules are transported across the semipermeable GI mucosa by one or more of the following mechanisms:

i. **Passive diffusion** (263). Most lipid soluble drugs are absorbed by simple diffusion. The rate of absorption is influenced by changes in pH, an observation which led to the classical pH-partition hypothesis (264). Several problems arise in the quantitative application of this hypothesis (265). These include the variability in pH of the stomach, which could affect drug dissolution, and the pattern of water flow in the small intestine.

ii. **Pore transport** (266). Small molecules (eg. urea) can diffuse through the pores associated with biological membranes.

iii. **Active transport** (267). Drug molecules are transported across the membrane, against a concentration gradient, by a carrier substance. The mechanism is saturable, shows specificity, requires a source of energy, is often site specific, and can be inhibited.

iv. **Facilitated transport** (268). This is similar to active transport, but does not occur against a concentration gradient.

v. **Pinocytosis** (159). Substrate particles are enveloped in vacuoles formed by the invagination of the apical cell membrane.

1.5.1.2 Physiological factors affecting absorption

The duration of absorption and of excretion will influence the duration of efficacy of a drug (269). The former cannot be longer than the residence time of the dosage form in the region of absorption. This residence time is itself dependent on the rate of gastric emptying of the formulation (270), and so, gastric emptying rather than permeation is prospectively the primary rate-limiting step in drug absorption (258). Thus, factors that affect gastric emptying (Section 1.2.1.2) could markedly influence drug absorption.

The intake of food exerts a complex influence on bioavailability (271), by either enhancing bioavailability (eg. propranolol (272)) or reducing bioavailability (eg. rifampicin (273)). In other cases, the rate but not the extent of absorption is reduced (eg. paracetamol (274)). These results are often due to the influence of food on processes such as GI motility, and first-pass metabolism (275). Furthermore, changes in the boundary conditions of the gut (276), such as pH,

temperature and osmolality, as a result of food intake, could also affect the mechanism of drug release, drug absorption and the performance of the dosage form (277).

Other physiological factors that affect drug absorption include, administration of the dose at different phases of the MMC (278), disease states (279), and patient variability (eg. age) (275).

1.5.1.3 Pharmaceutical factors affecting absorption

Pharmaceutical variables that exert an effect on drug absorption include the nature of the dosage form, the drug itself, and formulation variables (280). Bogentoft et al (281) demonstrated that the absorption of aspirin from enteric-coated granules was not influenced by food, whereas a corresponding tablet formulation gave lower plasma concentrations. Similarly, the inter-subject variation in plasma concentration was less for a granule formulation of aspirin, than for a tablet product (282). Drugs that either reduce (eg. atropine) or increase (eg. metoclopramide) gastric motility will affect absorption of co-administered drugs. Similarly, drugs affecting mesenteric blood flow, (eg. nifedipine) will influence the absorption rate of a second drug (283). Furthermore, the concomitant administration of a second formulation (eg. antacids) can reduce drug bioavailability (284). Formulation excipients, such as the vehicle, can also affect bioavailability. Soci and

Parrott (285) found that the absorption of nitrofurantoin from various suspensions was dependent on the vehicle. Algin, and guar gum suspensions exhibited delayed absorption compared to aqueous suspensions.

1.5.2 Gastrointestinal Transit of Solid Doses

The duration of drug absorption is partially governed by the GI transit of the formulation. It can be envisaged, that factors influencing GI motility (Section 1.2) will have a bearing on the transit of solid doses. It is also recognised, that the nature of the formulation, single-unit or multiple-unit, will determine its GI transit (146).

1.5.2.1 Gastric emptying

Oral doses administered to a fed stomach have an emptying pattern similar to food. Thus, liquid formulations behave as simple liquids, and show an exponential emptying pattern (286). The drug solution from disintegrating solid doses will have a similar exponential pattern of emptying, after an initial dissolution lag phase (287).

Multiple-unit formulations, composed of sub-units small enough to pass through the constricted pylorus, will exhibit a disintegration lag phase, followed by gradual emptying of the sub-units (288). Gradual emptying ensures the sub-units are dispersed along the

length of the small intestine (289), resulting in lower local drug concentrations, and reduced irritation of the intestinal mucosa (290). The initial gastric dispersion of the sub-units is, however, dependent on the physiological condition of the stomach. Dispersion occurs readily after a meal with a high liquid content, but is limited after administration to a fasting stomach (237). The lack of dispersion results in the bolus emptying of material, which has been observed with both encapsulated powders (237) and pellets (291). O'Reilly et al (292), recently demonstrated a linear emptying pattern for sub-units when the multiple-unit formulation was taken either with or after a meal, but an exponential pattern when taken before a meal. However, emptying half-times of 3-4h, similar to those reported by Bechgaard and Christensen (147), were observed for all the dosing regimes. Hunter et al (293) have rationalised the various emptying patterns observed with capsule formulations into five main types, described by the pattern of the gastric emptying profile.

Investigations into the effect of particle density on the GI transit of multiple-unit systems have produced conflicting results. An initial study in ileostomy subjects, suggested heavy pellets had a slower transit time than light pellets (175). A later study, in healthy subjects, could not confirm this effect of density (294). Christensen et al (295) have reported that light pellets

float in the proximal stomach of healthy subjects, resulting in a longer lag phase before emptying than for heavy pellets. However, the half-times for emptying were similar for both types of pellets. In contrast a second study in ileostomy subjects, reported analogous patterns of emptying for both heavy and light pellets (296). In both studies, the intestinal transit of the pellets was not affected by particle density. An interesting observation, with possible clinical consequences, reported that fed subjects exposed to noise-induced stress exhibited a faster gastric emptying of capsule contents than those not exposed to the stress (297).

Single-unit, non-disintegrating formulations behave like large indigestible solids, and are emptied by phase 3 activity of the MMC (298). Park et al (249) report that enteric-coated tablets empty erratically from the fasted stomach, depending on their time of arrival in the stomach in relation to the occurence of MMC contractions. Emptying was independent of the size, shape and volume of the tablets. A high inter- and intra-subject variation in transit time, attributed to erratic gastric emptying, has also been observed in fed ileostomy subjects (299). Studies on the effect of density have shown tablets of low density to float on top of gastric contents, whereas more dense tablets sink to the distal stomach (300). Thus, the intake of food, and especially the energy content of the meal, will exert a greater influence on

the gastric emptying of single-units than the emptying of multiple-unit systems (301). Therefore, the high inter-subject variation observed in the gastric emptying of single-units must be considered when designing new CR formulations (302).

1.5.2.2 Intestinal transit

There have been few studies in the past on the intestinal transit of dosage forms, largely due to the lack of suitable measuring techniques. An early study by Rosswick et al (303), found the intestinal transit of a capsule to range between 1.5-16h, with a mean value of about 4h.

Recent extensive use of gamma scintigraphy to investigate the GI behaviour of pharmaceuticals, has produced an abundance of suitable data. Davis et al (304) have produced a comprehensive report describing the intestinal transit of solutions, pellets and single-units. They determined a mean transit time of about three hours, which was independent of the dosage form and fed state. This result is in agreement with Malagelada et al (305), who reported transit times of about three hours for both solids and solutions. Studies by Kaus (306), investigating the rate of transit of a non-disintegrating unit, have also shown intestinal transit to be less variable than gastric emptying. Passage through the duodenum was rapid, followed by a

mean transit rate of 4.2-5.6cm/min. This correlates well with the value of 4.7cm/min for the velocity of travel of the MMC down the intestine (307). Exercise has been shown to have no affect on the intestinal transit of a pellet formulation in healthy subjects (248).

1.5.2.3 Colonic transit

The predictable nature of intestinal transit has generated enthusiasm to investigate the suitability of oral administration, rather than rectal, for the local release of drug. Localised systems have the advantage of reduced side-effects and the delivery of effective concentrations of drug to the appropriate site. Commonly used rectal preparations, such as enemas, do not spread regularly within the colon (308), and often fail to reach the transverse colon (309). Efforts in research have been directed to the oral delivery of drugs, such as 5-aminosalicylic acid (5-ASA), to the colon, without loss of drug in the small intestine. A number of coated systems have been developed (310, 311), with varying degrees of success. Other systems rely on the enzymatic activity of bacterial flora in the colon. For example, a polymeric drug has been developed, which is reduced by bacterial enzymes to 5-ASA (312). The molecular size of the polymer precludes intestinal absorption.

These systems, whilst being technically efficient, could be further improved by considering the transit

characteristics of dosage forms, especially in the colon. The knowledge that multiple-units become widely dispersed within the colon (313), led to the development of multiple-unit systems for the delivery of 5-ASA to the colon (314). Hardy et al (315) have suggested that the extent of dispersal is size dependent, since large particles pass through the colon more rapidly than smaller particles. Furthermore, their results indicate that a timed release formulation should retain drug within the preparation for about five hours after administration to a fasted patient. This would allow time for gastric emptying and intestinal transit. Drug released over the next ten hours from a dispersive formulation, would distribute throughout the ascending and transverse colon.

1.5.3 Oral Controlled Drug Delivery Systems

The physicochemical characteristics of the drug, the nature of the delivery system, and the GI transit of the dosage form are criteria that must be considered during formulation. Davis (316) has framed this into the concept of the trinity of drug, dosage form, and destination. Theoretical models, which consider the complex GI environment and formulation variables, are now being used in the rational design of oral CDDS (317). Davis et al have developed (318), and validated (319), a computer simulation, that uses preformulation data,

permeability values and estimates of physiological variables, for the formulation of delivery systems. A similar model approach, developed by Ho et al (320), introduces the concept of the anatomical reserve length, described as the length of small intestine yet available for absorption:

$$RL = L - l^{*}$$

where

RL = anatomical reserve length, cm

L = maximum theoretical reserve length, ie. the length of the human small intestine, 300-350cm

l^{*} = length at which absorption is completed, cm.

Thus, the reserve length of a soluble drug will be larger than that of a poorly soluble drug. In their discussion, the authors stress the necessary quantitative interrelationship of physiological, physicochemical, and pharmaceutical parameters, within the framework of the reserve length, in the development of drug delivery systems. Several examples were provided to support the use of the model.

Currently available CR products boast zero-order release over twelve hours or more. These claims have little meaning, unless the drug is extensively absorbed in the colon, considering the potentially short stomach to caecum transit time in the fasted state. This could result in a reduced systemic level of drug, and a significant fraction of the dose being wasted. Thus, the

future development of CR systems should concentrate on prolonging the GI residence of the dosage form (321), as well as optimising drug release rates. Gastric emptying of dosage forms is variable and influenced by factors such as diet and the type of dosage form (322). Conversely small intestine transit appears to be regular and unaffected by these factors (304). Control of the gastric emptying of dosage forms is, therefore, the preferred option.

A number of pharmaceutical strategies, such as particle size (323) and particle density (290), have been proposed to control gastric emptying. Devices which float on the gastric contents have been developed (324). These systems are either of low density or are rendered buoyant by the liberation of gas into a deformable hollow membrane (325). A recent innovation has even maintained buoyancy in the fasted state (326). The suitability of such systems for prolonging gastric residence is not entirely conclusive (327, 328). Another approach is the use of bioadhesives which adhere to the mucin/epithelial surface of the GIT, to provide a localised platform for drug release (329). The use of fatty acids to delay gastric emptying and improve drug bioavailability has been demonstrated in both humans (330) and rats (331).

Apart from the transit of CDDS, future designs should consider the boundary conditions of the gut, in particular the variations in GI pH. Bechgaard and

Baggesen (332) found lower intra-subject variations in the availability of propoxyphene from a pH-independent multiple-unit system, than from a pH-dependent system. Despite this, Bechgaard et al (333) have developed an alkaline pH-dependent pellet formulation of indomethacin. Drug release occurs only in the lower regions of the intestine, and drug availability is independent of gastric activity (334). A theophylline product consisting of pellets compressed within a slowly disintegrating tablet matrix, has managed to combine the elements relating to single- and multiple-units, is not pH sensitive and is unaffected by gastric activity (335).

These examples suggest that the effects of GI physiological variables on the controlled delivery of drugs to the GIT, can be minimised by appropriate application of formulation procedures. A further understanding of these variables should lead to the development of more reliable dosage forms, and hence more effective drug therapy.

1.6 Thesis Objectives

In the preceding pages I have attempted to illustrate the importance of considering both physiological and pharmaceutical criteria for the future design of oral CDDS.

In this thesis I have identified two physiological parameters, and two pharmaceutical parameters which merit investigation:

i. the influence of posture on the gastric emptying of pellets;

ii. the influence of the time of day of administration on the GI transit of pellets;

iii. the influence of the mucoadhesive, polycarbophil on the GI transit of pellets;

iv. the GI transit of tablets, investigating,
   (a) the effect of tablet size, and
   (b) the influence of food.

The conclusions generated from these investigations, and from future similar studies, should enable the design of oral CDDS which are not only technically elaborate, but also physiologically competent.

CHAPTER TWO:

THE INFLUENCE OF POSTURE

2.1 Introduction

In this chapter I shall present the findings from an investigation to measure the gastric emptying in supine subjects, of a placebo pellet formulation.

The rate of GE will determine the rate of absorption of many orally administered drugs, and factors influencing GE will, in turn, influence drug absorption (Section 1.5). One likely influence on GE is the posture, either supine or upright, of patients. Oral pharmaceuticals are often administered to patients confined to bed, and taken by patients prior to retiring for the night. Evidence suggests that GE patterns in supine patients who have undergone certain forms of surgery, differ from postoperative GE patterns in the upright posture (336,337).

The stomach empties more rapidly in neonates lying either in the prone position or on their right sides, than when supine or on their left sides (338). However, no difference was seen in babies, for the same four positions (339). Hunt et al (39) reported that the GE of liquid test meals was slowed by tipping the subjects into a head down position. Naturally, this is an unreasonably severe posture, but a later study demonstrated the influence of the supine positon on the GE of simple liquids (340). Emptying was faster in subjects lying on the right side, than either on the left side or sitting.

Nimmo and Prescott (341) report a delay in paracetamol absorption in subjects lying on the left side. A similar affect on the absorption of aspirin solution in supine subjects was attributed to a delay in GE (342). Posture is known to affect the oesophageal transit of dosage forms (343), and there is some evidence that body position may alter the GE of pellets in hard gelatin capsules (288). A comparison of two different aminophylline and theophylline pellet formulations suggested differences in theophylline levels between the formulations could become clinically relevant in the supine position at night (344).

Loo et al (345) report a slower GE of liver particles in supine subjects. They suggest a passive redistribution of the meal to the posteriorly located fundus, where no grinding activity is exerted on the food, causing a delay in GE. Thus, a combination of food and body position may have a marked affect on GE.

The above studies have mainly considered the effect of posture on the GE of food. A study was, therefore, designed to investigate the influence of body posture on the GE of pellets in fasted and fed subjects.

2.2 Materials and Methods

2.2.1 Preparation of Formulations

Beads of Amberlite IRA410 (BDH), an anionic ion-exchange resin, were used as the placebo pellet

formulation. Ion-exchange resins need to be washed and regenerated before use, and the following standard procedure was used (346):

i. soak resin in 2N sodium hydroxide (NaOH) solution for 20min;
ii. recover the resin by filtration, and wash with water, methanol, and water again;
iii. soak resin in 2N hydrochloric acid (HCl) for 20min, recover and wash as above;
iv. repeat steps i-iii twice;
v. soak for 30min to regenerate resin, in 2N HCl for cationic exchangers, or 2N NaOH for anionic exchangers.

Only pellets in the size range 0.5-1.0mm were used in the study. These were obtained by sieving about 50g resin in a typical nest of sieves, 10cm diameter sieves (Endecotts Test Sieves Ltd.), assembled in decreasing aperture size in a square root of two geometric progression. The sieves were agitated for 30min on a sieve shaker (EFL1MK11, Endecotts Test Sieves Ltd), and the appropriate fraction collected. The density of the pellets was previously determined as 1.17g/cm^3 using an air pycnometer (Model 930, Beckmann).

The resin was labelled by soaking 6g in 10ml ^{99m}Tc-sodium pertechnetate solution (CIS(UK) Ltd.) for 10min. The resin was recovered and dried in a fan oven

at 70°C. The activity of the recovered resin was measured before and after drying. There was no difference between the values, implying drying did not disrupt the isotope binding. The tenacious nature of isotope binding to resins is well documented. Theodorakis et al (209) studied the binding of technetium-99m to a variety of polymer resins. They found that the isotope had a very stable binding *in vitro* to Dowex resin, another commercial resin similar to Amberlite resin. Copping (347) has tested the binding *in vitro* of technetium-99m to Amberlite IRA410 resin. Labelled resin was soaked in solutions, varying from pH1 to pH14. A maximum of 1.8% of the isotope leached out over a 2h period. On the basis of these results, only a simple binding test was performed on the labelled pellets in this study. About 500mg of labelled resin was added to two separate beakers containing 100ml 0.1N HCl, and 100ml 0.1N NaOH. A magnetic stirrer and "flea" were used to stir the contents of the beakers. A 10ml aliquot was taken from each beaker after 2h, and activity measured in a gamma counter (Intertechnique CG4000). The activity detected was negligible, and the binding was considered to be stable.

Stability *in vitro* does not *a posteriori* imply a stable binding *in vivo*. ^{99m}Tc-pertechnetate is readily absorbed from the small intestine, and accumulates in the thyroid and bladder (348). Thus, if the isotope leached

from the resin, some activity would be detected in these organs. A check of the thyroid region was made during the study to ensure no isotope had been lost from the resin.

The labelled pellets were filled into size 0 hard gelatin capsules (Capsugel), to a notional fill weight of 310mg. The capsules had a disintegration time of less than 10min in 0.1M HCl, as measured by the standard BP test (349). Each filled capsule had an activity of 3MBq technetium-99m at the time of administration. The total radiation absorbed was estimated as 0.603mG/MBq for the stomach and small intestine, and 0.045mG/MBq for the whole body (133,350).

2.2.2 *In-vivo* Study

The study was approved by the Ethical Committee of the University of Nottingham, and conducted in accordance with the declaration of Helsinki Guidelines for Ethics in Research. Approval to administer radiopharmaceuticals was obtained from the Department of Health and Social Security (DHSS). The investigation was performed in two separate stages. The first part was conducted in fasting subjects, and the second part in fed subjects.

The first study involved six male subjects (age 18-25, height 1.7-2.0m, weight 65-75kg), who were non-smokers, were not on any medication, had abstained from alcohol for 24h, and had fasted for 10h before the

study. On the morning of the study, each subject swallowed one capsule with 100ml water, and then lay face upwards on stretcher trolleys. The subjects remained supine for the duration of the study (4h) and were only allowed to leave the trolley when they needed to urinate. They were asked to keep all body movements to a minimum during the study. Anatomical markers, containing 0.1MBq technetium-99m, were taped to the skin, anteriorly and posteriorly, over the liver and to the right of the stomach.

Anterior and posterior images, each of 60s duration, were taken at regular intervals, using a gamma camera (General Electric Maxicamera, Type II) having a 40cm field of view. Since only technetium-99m was being used, the camera was fitted with a low energy (160keV) parallel-hole collimator. Posterior images were recorded after the subjects had rolled over onto their fronts. Images were recorded on a computer (Nodecrest), and stored on magnetic tape for subsequent analysis.

The images were analysed on the computer, by drawing regions of interest (ROI), using an electric cursor, around the position of the stomach. The position of the stomach in each successive image, in relation to the external marker, was determined by referring to the preceding images. A second ROI was drawn on each image, away from the main area of activity, to assess the background counts. The appropriate computer software

enabled the activity in each stomach region to be quantified, corrected for background activity and radioactive decay. The error due to the variation in depth was also corrected on the computer, using the geometric mean of corresponding anterior and posterior views (216). The resultant corrected %activity was then plotted against time.

A control study was conducted a week later, with the subjects remaining in an upright position during and between imaging.

The fed study was conducted in the same manner about twelve months later. A further five male subjects participated (age 18-25, height 1.6-2.0m, weight 60-75kg) under the same constraints as described above. However, in this study, the subjects consumed a light breakfast (1800kJ) consisiting of:

2 slices toast
bowl of cereal
butter and marmalade
120ml milk
100ml orange juice

about 15min before taking the encapsulated pellets. The duration of this study was 7h. A similar control study was conducted one week later, with the subjects in the upright posture.

In neither the fed nor the fasted investigation did the subjects complain of any untoward side-effects.

2.3 Results and Discussion

2.3.1 Fasted Study

Gastric emptying data have been expressed as the time for 50% of the activity to leave the stomach (St50%). The results of the investigation are detailed in Tables 2.1-2.3. Gastric emptying profiles for the supine and control studies are shown in Figures 2.1-2.3, and representative scintiscans are presented in Figures 2.4 and 2.5.

The pellets were released rapidly from the hard gelatin capsule, and the dispersion of the pellets enabled ready identification of the stomach region for subsequent creation of ROI. The scintiscans show the unreleased pellets, the pellets dispersing in the stomach, and gastric emptying of the pellets. An outline of the stomach, and in later chapters of the colon, has been drawn around the pellets to improve visualisation of the images. The anatomical marker is also visible.

Gastric emptying of the pellets generally began within 20min, the time between the first and second images. Subject 4 exhibited a distinct lag phase before emptying commenced, in both the supine and control study (Figure 2.1). The mean emptying profiles (Figure 2.2) indicate that the pellets empty in an exponential manner, in both the supine and control study. However, some individuals exhibited an almost bolus emptying of the pellets, as illustrated by Figure 2.1. This rapid

emptying as a whole has been previously described by Hunter et al (288).

A paired Student t test on the St50% values, suggests there is no significant difference ($p>0.1$) between the supine and upright postures. Few studies of this nature have been conducted, and thus comparison with previous results is difficult. Nevertheless, the mean St50% ($\pm$s.e.m.) for the supine study, 32 (12)min, and for the control study, 52 (16)min, are in close agreement with a previous investigation. Hardy and Perkins (220) report a gastric emptying t50% of 45min (n=4) for pellets given to fasted subjects in the upright position. Sutton et al (180) conducted a study to compare the GE, in supine subjects, of orange flavoured water, measured either by the technique of epigastric impedance or gamma scintigraphy. A mean GE t50% value of 26min was recorded using the impedance method, and 27min using gamma scintigraphy (n=5).

The rapid emptying observed in my investigation can be ascribed to the contractions of the MMC. Administration of the encapsulated pellets during either phase 2 or phase 3 contractions would result in the rapid emptying of the pellets. However, administration during phase 1 of the MMC, when there are no contractions, would result in a slower emptying, with a possible lag phase during which the pellets passively disperse in the stomach. This would explain the lag phase exhibited by

subject 4. Naturally, the subjects would be in different phases of the MMC prior to administration of the capsule, hence the marginally different rates of emptying and the relatively large s.e.m. values on the mean emptying profiles (Figure 2.2).

Subject 6 inadvertently consumed a bowl of cereal on the morning of the supine study, and thus has not been included in the mean values. To allow comparison with the control study, he consumed the same volume of food before taking the capsule on the upright study day. In both cases he shows a distinct lag phase before GE. The GE profiles for subject 6 (Figure 2.3) are also different from the profiles illustrated in Figures 2.1-2.2, exhibiting a more gradual pattern of emptying.

2.3.2 Fed Study

Gastric emptying data and profiles are presented in Tables 2.4-2.6 and Figures 2.6 and 2.9, and representative scintiscans in Figures 2.7.

Dispersion of the pellets again enabled the stomach region to be readily identified. The subjects all exhibited a lag phase before GE began, in both the supine and control study. The pellets exhibited an almost linear pattern of GE, after the lag phase. This linear profile is the characteristic emptying pattern of solid food (216), and indicates that the pellets become mixed with the food before emptying commences (292). A paired

Student t test on the St50% values indicates there is no significant difference ($p>0.5$) between the supine and upright positions. The mean St50% ($\pm$s.e.m.) value of 191 (25)min for the supine study, and 175 (21)min for the control study are similar in magnitude to previous investigations. Davis (322) reports mean GE t50% values of 115 (16)min after a light breakfast, and 225 (38)min after a heavy breakfast. Tiaprofenic acid pellets exhibited a more rapid emptying, with mean GE t50% values of 77min after a light breakfast, and 170min after a heavy breakfast (246).

2.3.3 Supine vs Upright, Fed vs Fasted

In both the fed and fasted investigations, there is no significant difference between the supine St50% values and the upright St50% values. A similar finding was reported by Mannell and Esser (351), who investigated the GE of a solid meal in supine and erect subjects. Bennett et al (352) investigated the influence of posture on the GE of antacids. They noticed that the GE of alginate antacids was faster in subjects lying on their left sides, and slowest in subjects lying on their right sides. More importantly, the emptying, in the supine position, of a liquid meal administered with the antacids, was similar to that measured in subjects in an upright position.

A comparison of fed and fasted results illustrates the effect of food on GE. The mean GE data for both the fasted and fed investigations are illustrated in Figure 2.8. An unpaired Student t test on the St50% values for both the supine studies, indicates there is a significant difference ($p<0.001$) between the fed and fasted values. Similarly a significant difference ($p<0.01$) was found between the fed upright and fasted upright values. The influence of food on GE has been illustrated by Davis (322). As mentioned above (Section 2.3.2), in that study, GE was emptying was slower after a heavy breakfast than after a light breakfast.

An understanding of two physiological processes helps to explain the effect of food on GE. Firstly, the almost bolus emptying of the pellets in the fasted state can be related to the contractions of the MMC, as described above (Section 2.3.1). These contractions are not present in the fed state, resulting in a slower emptying.

Secondly, in the fed state, a lag phase before emptying begins is commonly observed. This reflects a redistribution of food from the quiet fundus to the active antrum, and the preparation of solid food into chyme before emptying can commence (353). Pellets initially remain in the upper half of the stomach, dispersed in the food (292), and then become dispersed throughout the stomach (237), presumably as the food

redistributes. The apparent lag phase before GE in the fed study is a consequence of these processes. The subsequent activity in the antrum would then cause the emptying of these small pellets. The GE of indigestible particles is further discussed in Chapter 5.

Subject 1 participated in both the fed and fasted investigations, and a comparison of the emptying profiles (Figure 2.9) illustrates the influence of food on GE. The pronounced lag phase in the fed supine study is probably a consequence not only of the above described processes, but may reflect the passive redistribution of food from the antrum back to the quiet fundus, as described by Loo et al (345).

In contrast to my findings, Kaus et al (251) did not observe a difference between the emptying rates of the soluble and insoluble components of a formulation in fasting and fed supine subjects. One possible explanation for this difference, is the proportionally larger volume of liquid ingested by the subjects in that study. Hunter et al (293) suggest the dispersion of capsule contents occurs more rapidly with meals of high liquid content. This would result in a faster rate of emptying in the fed state, akin to the rate in the fasted state.

2.4 Conclusions

The following conclusions can be drawn from the results of this investigation:

i. The gastric emptying of pellets is not influenced by the supine position in either the fasted or fed state.

ii. Gastric emptying of pellets is slower in the fed state, in both the supine and upright posture.

iii. In the fed state, pellets empty predictably and gradually, after an initial lag phase.

iv. Pellets empty rapidly and less predictably, in the fasted state.

Table 2.1 Gastric emptying data for the fasted supine study - %activity remaining in the stomach.

Subject	1	2	3	4	5	mean	s.e.m.
Time (min)							
0	100	100	100	100	100	100	-
20	49	35	73	100	37	59	11
60	12	0	0	91	7	22	16
80	11	0	0	58	0	14	10
120	8	0	0	2	0	2	-
140	5	0	0	0	0	1	-
160	0	0	0	0	0	0	-

Table 2.2 Gastric emptying data for the fasted control study - %activity remaining in the stomach.

Subject	1	2	3	4	5	mean	s.e.m.
Time (min)							
0	100	100	100	100	100	100	-
20	63	95	37	100	100	79	13
35	48	0	0	100	100	50	20
50	20	0	0	100	96	43	20
60	0	0	0	100	60	32	18
75	0	0	0	100	56	31	18
90	0	0	0	100	52	30	18
110	0	0	0	18	32	10	6
125	0	0	0	0	0	0	-

Table 2.3 Lag time and Gastric emptying (St50%) values for the fasted supine and control studies.

	Supine study		Control study	
Subject	Lag Time (min)	St50% (min)	Lag Time (min)	St50% (min)
1	<5	20	<5	30
2	<5	15	<5	25
3	<5	25	<5	15
4	40	85	90	100
5	<5	15	35	90
mean	-	32	-	52
s.e.m.	-	12	-	16
6	20	90	20	55

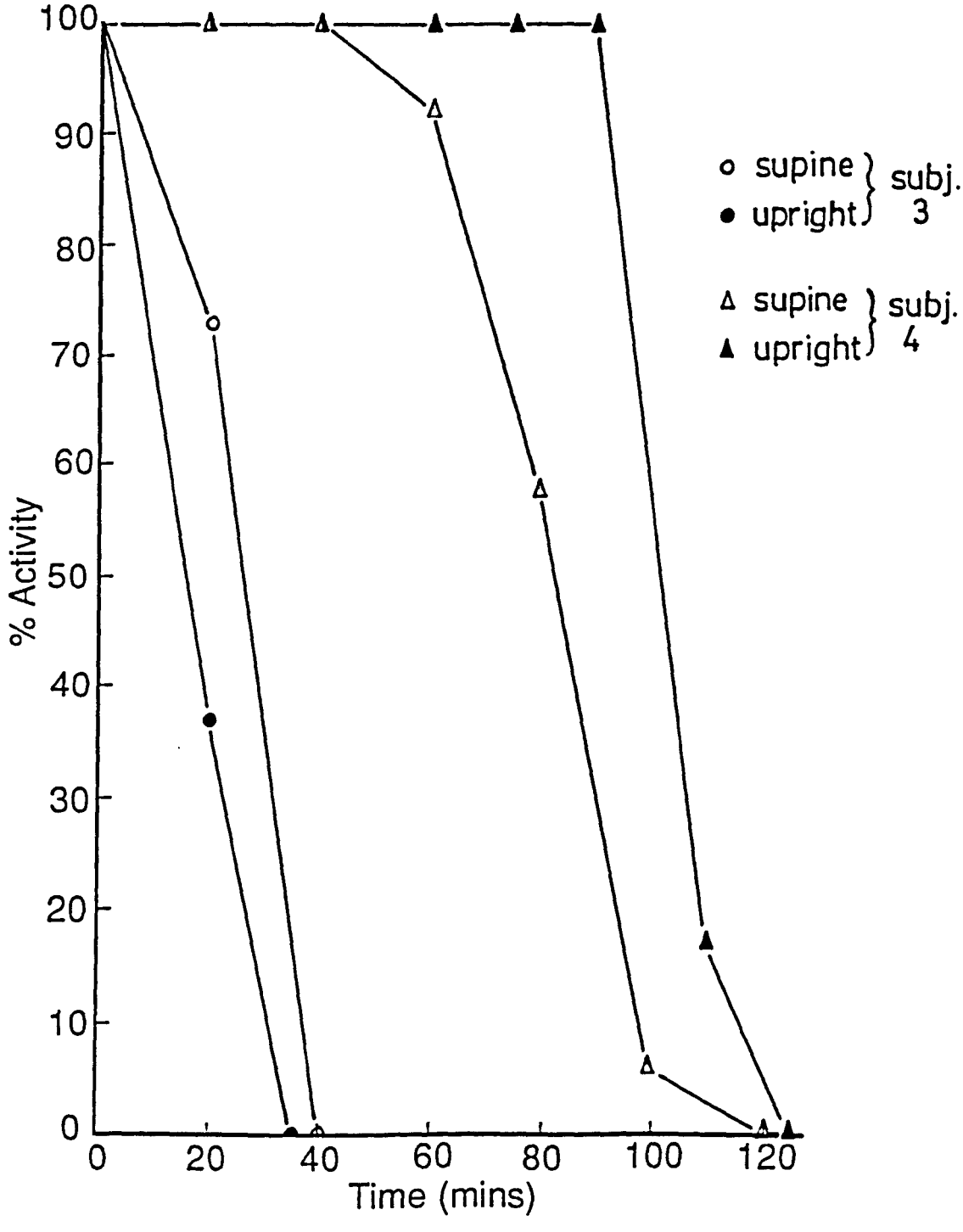


Figure 2.1 Gastric Emptying of Pellets (Subjects 3 + 4) - Fasted.

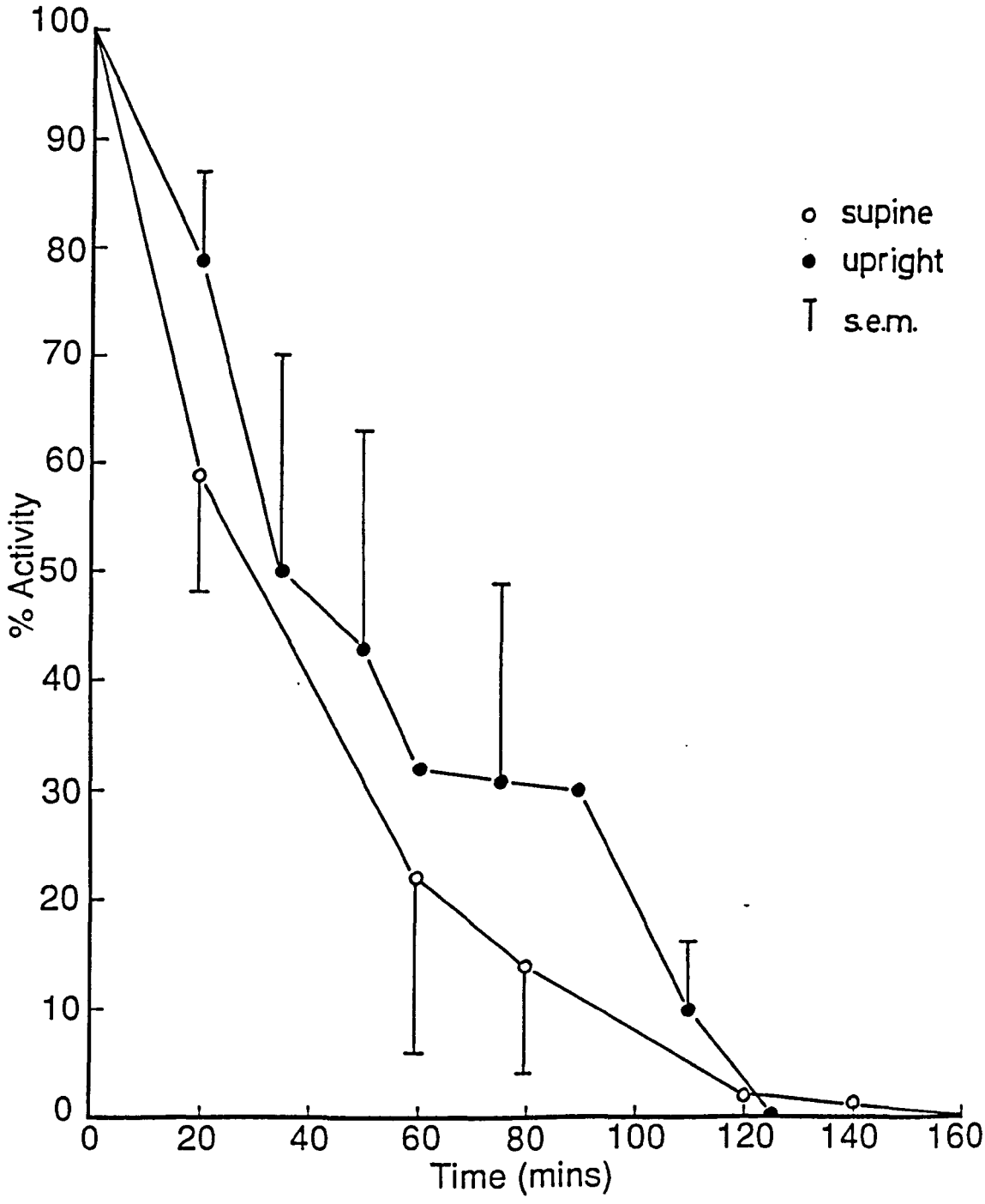


Figure 2.2 Mean Gastric Emptying of Pellets - Fasted.

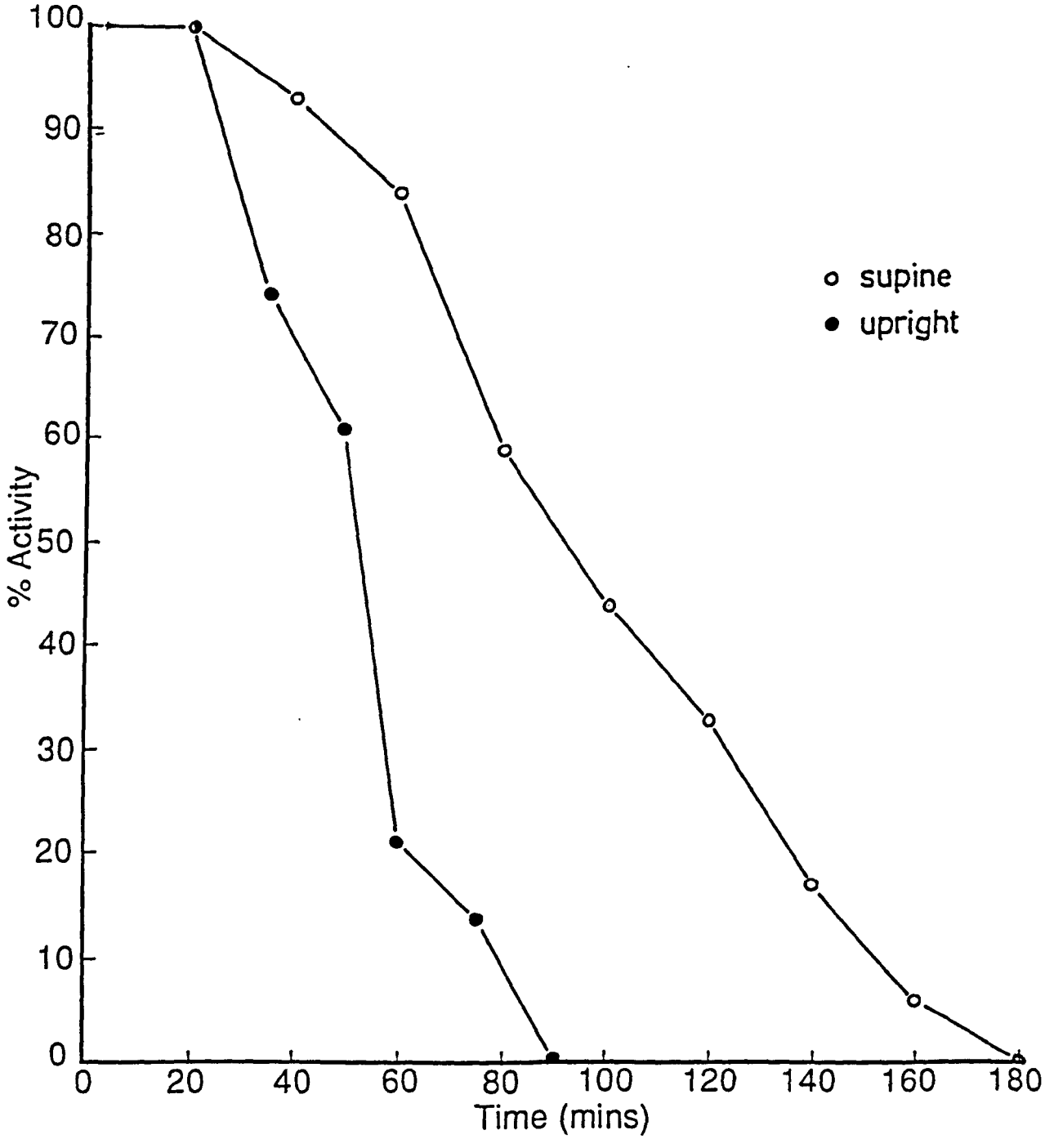


Figure 2.3 Gastric Emptying of Pellets (Subject 6) - Fasted.

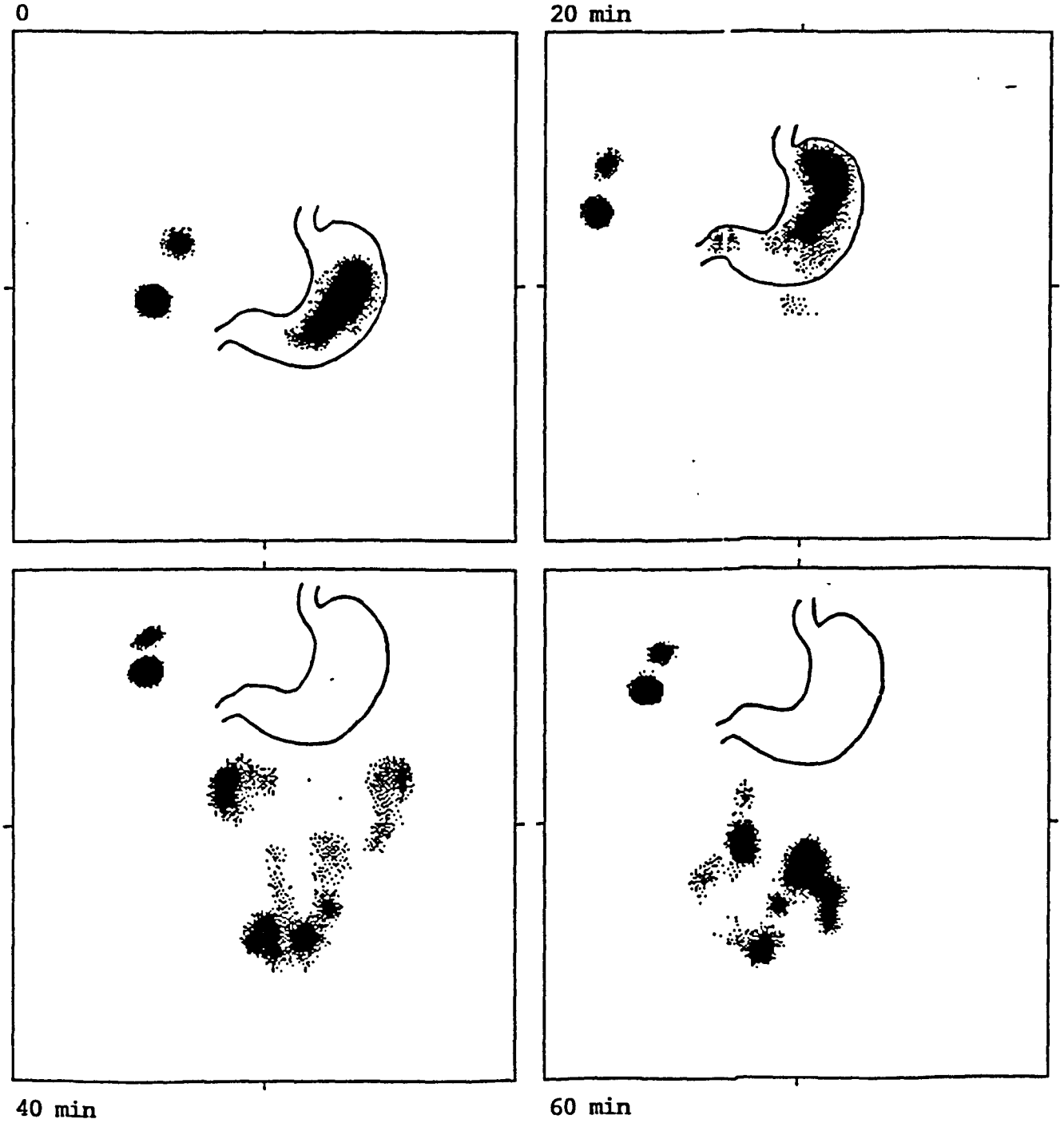


Figure 2.4 Gastric Emptying of Pellets - Subject 1, Supine, Fasted.

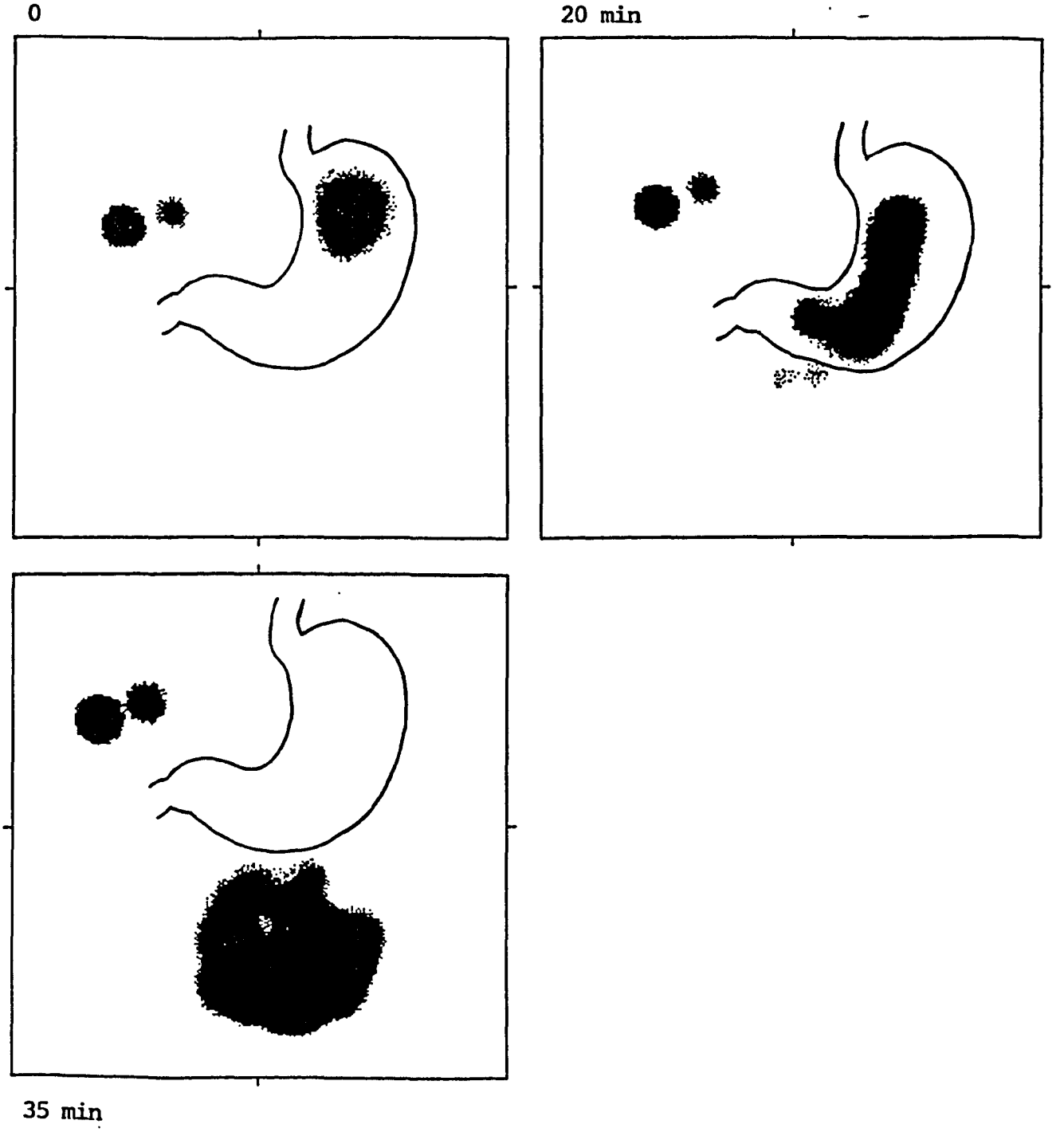


Figure 2.5 Gastric Emptying of Pellets - Subject 1, Upright, Fasted.

Table 2.4 Gastric emptying data for the fed supine study - %activity remaining in the stomach.

Subject	1	2	3	4	5	mean	s.e.m.
Time (min)							
0	100	100	100	100	100	100	-
15	100	100	100	100	100	100	-
30	100	100	100	100	100	100	-
45	100	83	87	90	100	92	3
60	86	60	81	84	100	82	6
75	80	53	81	81	100	79	7
90	79	51	76	76	100	76	7
105	76	48	71	76	100	74	7
120	76	46	71	76	100	74	8
150	71	44	66	76	82	72	7
180	66	31	59	73	39	54	7
210	60	9	49	71	22	42	10
240	44	0	33	68	4	30	11
270	41	0	22	27	0	20	8
300	29	0	0	25	0	11	6
330	0	0	0	0	0	0	-

Table 2.5 Gastric emptying data for the fed control study - %activity remaining in the stomach.

Subject	1	2	3	4	5	mean	s.e.m.
Time (min)							
0	100	100	100	100	100	100	-
15	100	100	100	100	100	100	-
30	100	100	100	100	100	100	-
45	100	100	100	100	100	100	-
60	100	100	100	100	100	100	-
75	76	100	100	100	100	95	4
90	61	100	100	100	100	92	7
105	43	90	100	100	100	87	10
120	31	81	100	100	100	82	12
150	15	65	78	88	81	67	12
180	0	42	30	83	69	45	13
210	0	26	16	66	22	26	10
240	0	14	8	51	15	17	5
270	0	14	0	36	11	12	6
300	0	0	0	32	0	6	6
330	0	0	0	10	0	2	-
360	0	0	0	0	0	0	-

Table 2.6 Lag time and Gastric emptying (St50%) values for the fed supine and control studies.

	Supine study		Control study	
Subject	Lag Time (min)	St50% (min)	Lag Time (min)	St50% (min)
1	120	170	60	100
2	30	95	90	170
3	30	205	120	170
4	30	255	120	245
5	45	230	120	190
mean	51	191	102	175
s.e.m.	16	25	11	21

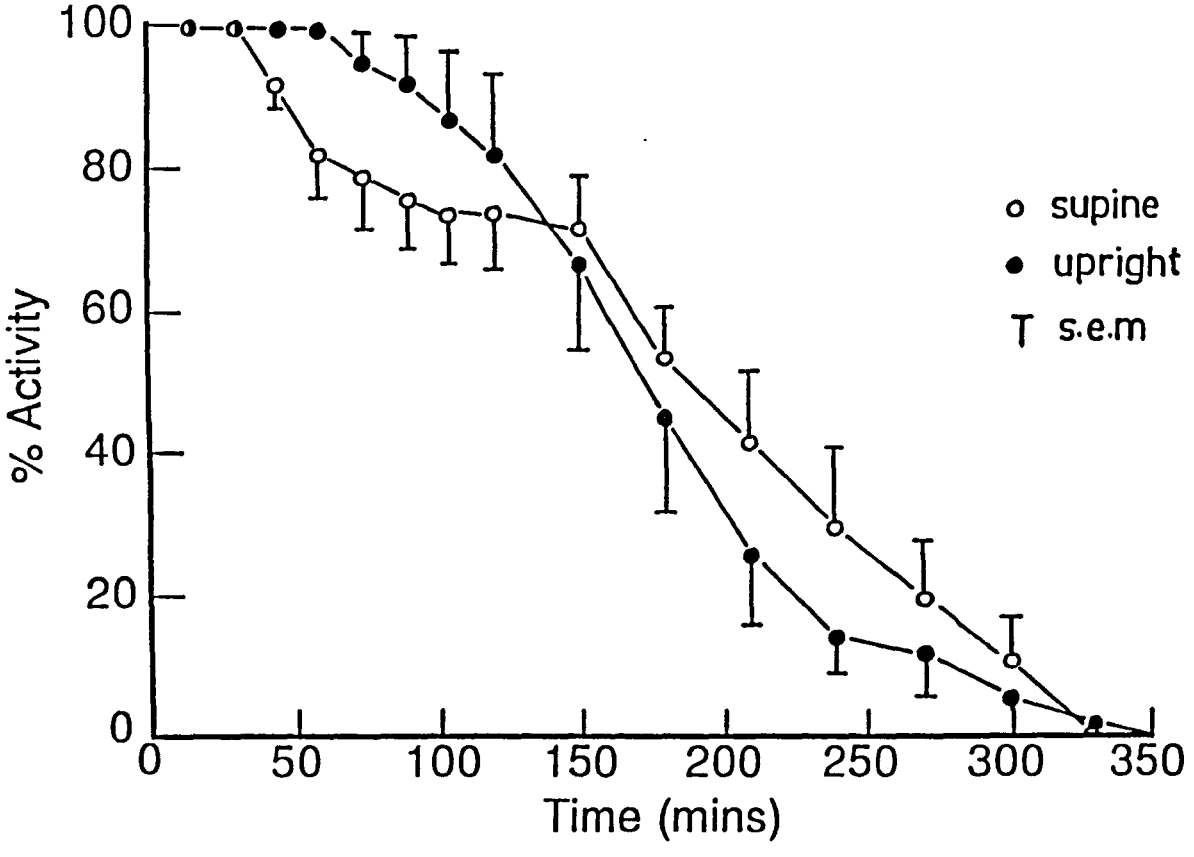


Figure 2.6 Mean Gastric Emptying of Pellets - Fed.

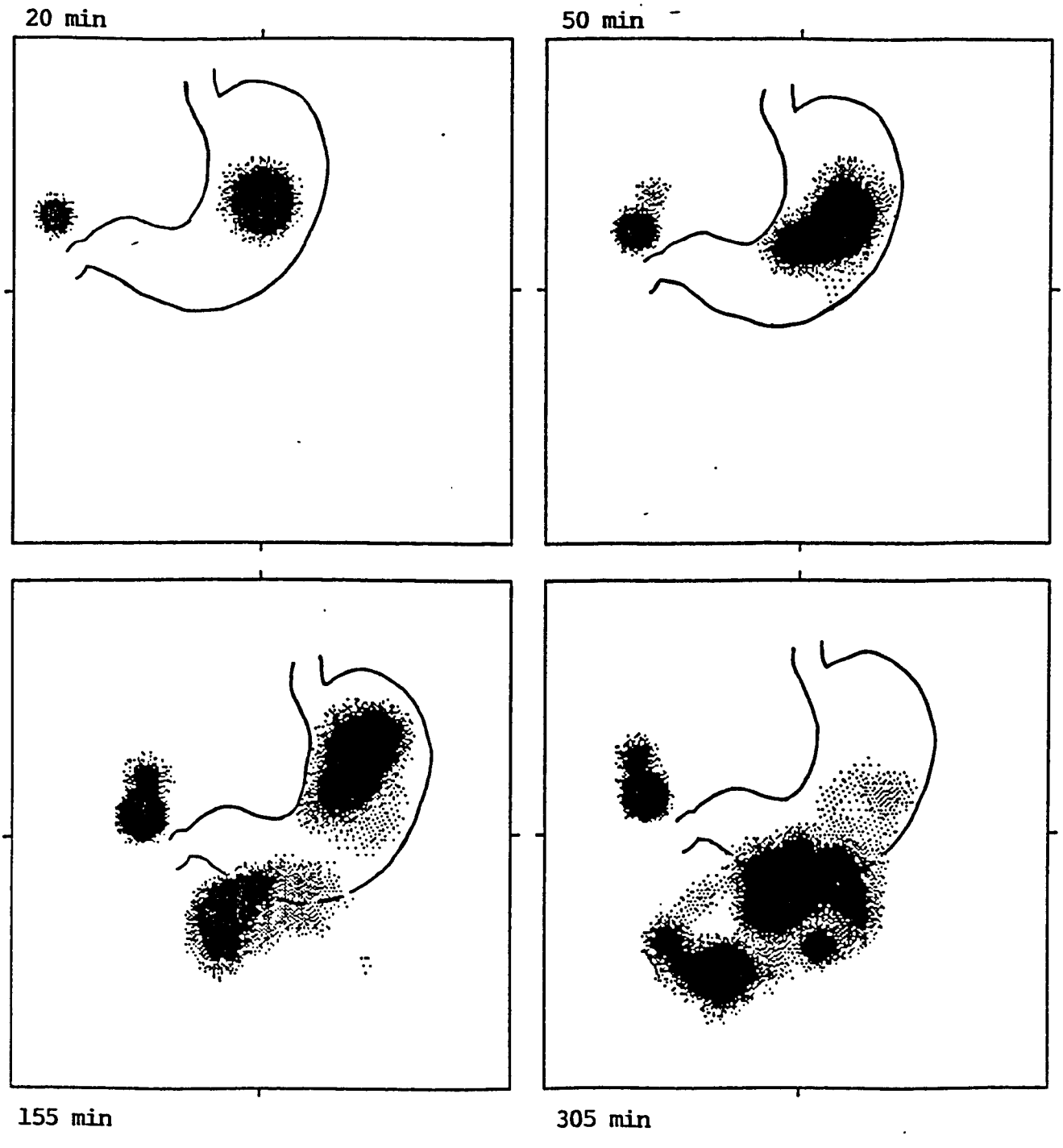


Figure 2.7 Gastric Emptying of Pellets - Subject 2, Supine, Fed.

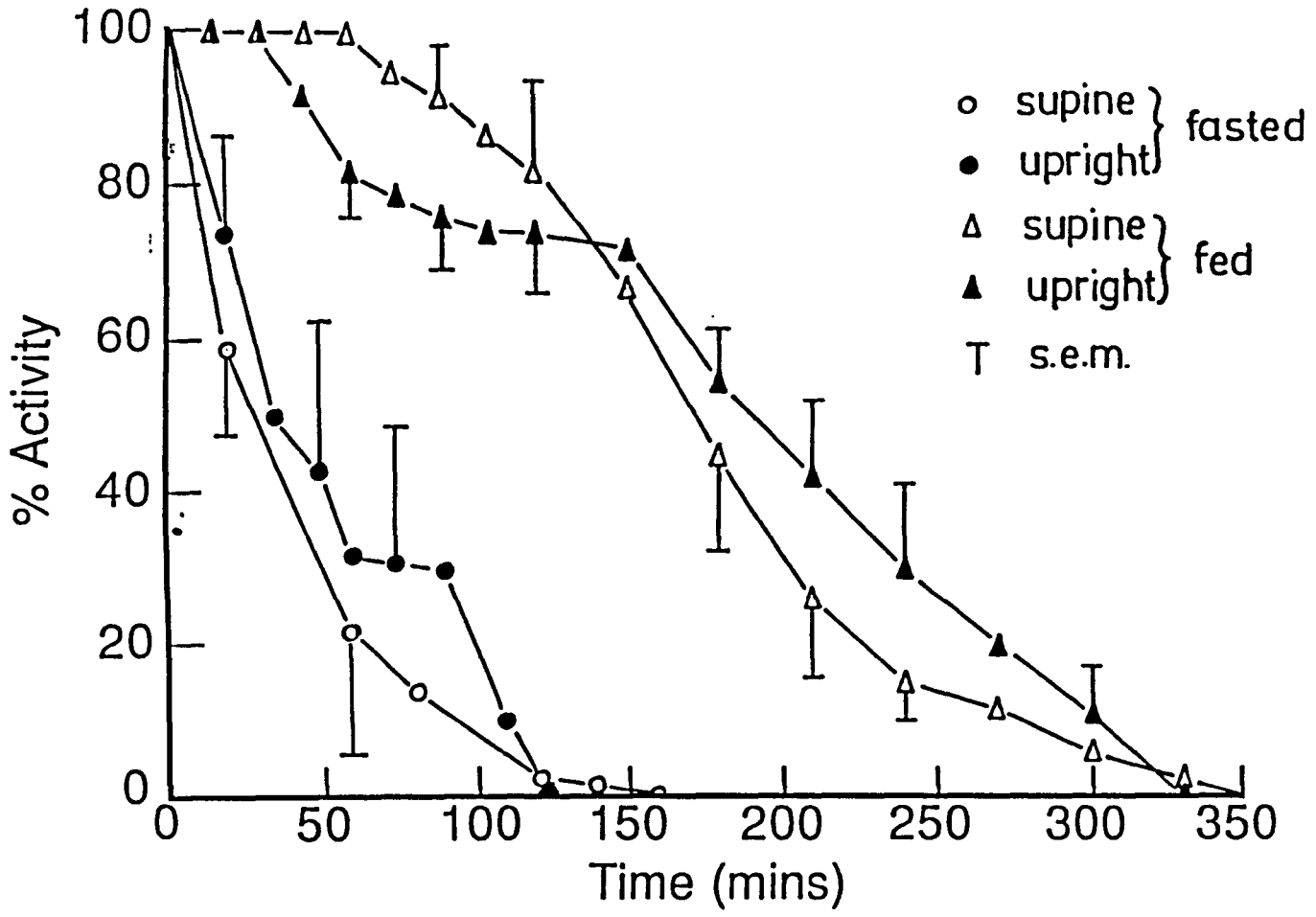


Figure 2.8 Mean Gastric Emptying of Pellets - Fasted and Fed.

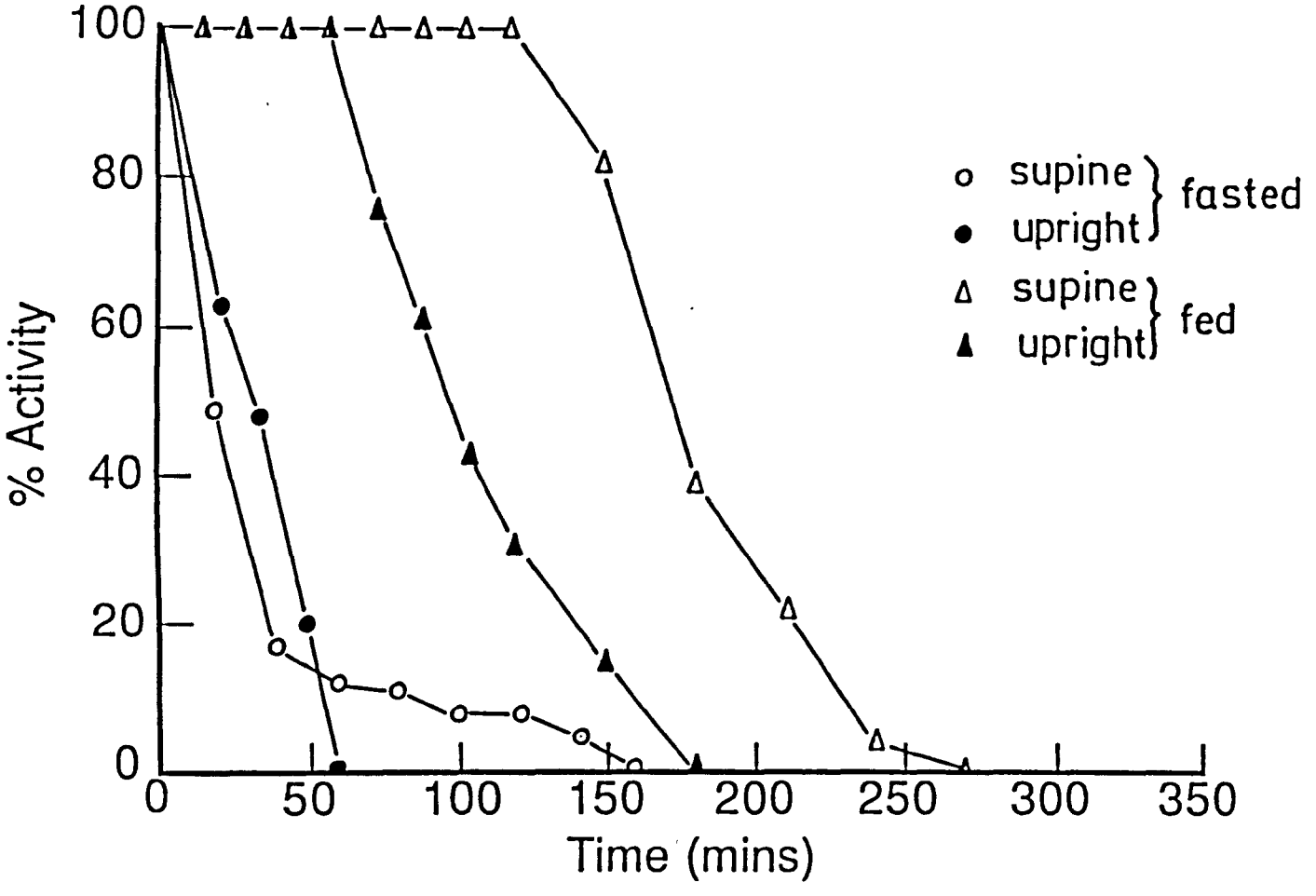


Figure 2.9 Gastric Emptying of Pellets (Subject 1) - Fed and Fasted.

CHAPTER THREE:

TIME OF DAY OF ADMINISTRATION

3.1 Introduction

This chapter describes the findings of an investigation designed to determine the influence of the time of day of administration on the GI transit of a placebo pellet formulation.

3.1.1 Chronobiology

The subject of chronobiology has markedly grown since the investigations, conducted in the 1890s, into the relationship between mental efficiency and the time of day (354). A number of cyclic physiological and behaviourial processes have been identified, eg. rapid eye movement (REM) sleep (355), diurnal changes in body temperature (356), and the menstrual cycle. Attention has been recently directed to investigating physiological functions that exhibit ultradian cycles, ie. cycles that occur with a periodicity of about 90min (357). The REM sleep cycle is one example of an ultradian process, but others include urine flow (358) and alertness (359). Ultradian periodicity has been identified in the eating behaviour of both monkeys (360) and humans (361). However, the function most relevant to this discussion is the cyclic nature of GI contractions in the fasted state.

As early as 1869, Legros and Onimus (362), noted the occurence of rhythmic contractions of the upper and lower segments of the SI in dogs. In 1922, Wada (363) also demonstrated a rhythmicity, of about 100min, in gastric

activity. However, it was not until 1969, that Szursweski (63) rationalised this rhythmic activity, which occurs only in the fasted state, into what is now described as the MMC (Section 1.2.3). A burst of motor activity, with a periodicity of 90-120min, originates in the gastroduodenal region and migrates distally to the terminal ileum. Control of the periodicity of the MMC has not been completely determined, although an oscillator located outside the gut has been proposed (87). The exact anatomic location of this oscillator has yet to be demonstrated, but an oscillatory mechanism within the central nervous system has been suggested (364).

3.1.2 Chronopharmacology

Another area of study that has attracted attention, is the topic of chronopharmacology. Tomlinson (365) has elucidated on the importance of timing of drug arrival at its receptor. The activity of some pharmacological agents depends on the circadian stage at which they are administered. This has been extensively demonstrated for cancer chemotherapy. Mice, inoculated with acute leukaemia, varied in their response to cytosine arabinoside, depending on the dosing schedule (366).

There are several instances in the literature relating drug bioavailability with the time of day of administration (367). One drug that has been

investigated in this context is theophylline. Asthmatic children, receiving conventional theophylline preparations, have to be maintained on a 6h dosing regimen to sustain serum theophylline levels. An investigation into a SR formulation, designed for a twice daily regimen, noticed a circadian variation in theophylline pharmacokinetics (368). It was suggested that, this variation could be related to the fasting or fed state of the children. A temporal variation in theophylline pharmacokinetics, also from a twice daily SR formulation, was observed in adults (369). Serum levels were higher in the morning, than in the evening. Diurnal variation in the clinical features of manic-depressive illness has been widely studied (370). An improvement in response to therapy was achieved by correlating drug dosing regimens with these variations.

The importance of GI transit on drug absorption has been previously discussed (Section 1.5). The importance of the time of day of administration on drug pharmacokinetics and response to therapy is illustrated by the examples cited above. This relationship between drug performance and the time of administration is possibly related to the GI transit of the dosage form. Of particular importance are the strong contractions during the fasted state, which may accelerate the transit of the dosage form. Thus, the advantage of reduced dosing regimens afforded with CR systems, could be

markedly affected by this contractile activity. It was, therefore, considered relevant to conduct an investigation into the effect of the time of day of administration on the GI transit of an oral formulation, during MMC activity.

3.2 Materials and Methods

3.2.1 Preparation of Formulations

Amberlite IRA410 resin (BDH) beads were used as the placebo pellet formulation. The pellets were prepared, labelled with technetium-99m, and encapsulated as previously described (Section 2.2.1). Similar *in vitro* tests and an *in vivo* check confirmed the integrity of the isotope binding to the resin, and the rapid disintegration of the capsules. Each filled capsule had an activity of about 3MBq technetium-99m at the time of administration. The total radiation dose absorbed was estimated as 0.603mG/MBq for the stomach and small intestine, and 0.045mG/MBq for the whole body (133,350).

3.2.2 *In vivo* Study

The study was approved by the Ethical Committee of the University of Nottingham, and conducted in accordance with the declaration of Helsinki Guidelines for Ethics in Research. Approval to administer radiopharmaceuticals was obtained from the DHSS.

The investigation was conducted on three separate days. The morning study commenced at 8.15a.m. on the first day; the afternoon study, six days later, commenced at 1.00p.m.; and the evening study, a further six days later, commenced at 6.00p.m. Five male subjects (age 18-22, height 1.7-1.9m, weight 60-75kg), who were non-smokers, were not on any medication, had abstained from alcohol for 24h, and had fasted for 10h before each study period, participated in the investigation.

At the start of each study period, the subjects each swallowed one capsule, with 100ml water. Anterior and posterior images, each of 60s duration, were taken at regular intervals over an 8h period, using a gamma camera (General Electric Maxicamera, Type II) as previously described (Section 2.2.2). The subjects stood directly in front of the camera during imaging, and were asked to keep body movements to a minimum during imaging. The images were recorded, stored and analysed as described in Section 2.2.2. The same methods of analysis and calculation were applied to the colon images. The subjects remained in an upright position, sitting/standing, throughout the study. About 4h after dosing the subjects received a standard light meal of one cheese roll and 150ml orange juice. The subjects did not complain of any untoward side-effects during the study days.

3.3 Results and Discussion

The data for this investigation are expressed as the time for 50% of the activity to leave the stomach (St50%), and the time for 50% of the activity to enter the colon (Ct50%). The coiled form of the SI, and the overlying of different regions of activity preclude the accurate quantification of the pellets in the SI. Thus, the small intestine transit (SIT) of the pellets was calculated by subtracting St50% values from Ct50% values. A value for the time from ingestion to 100% activity in the colon (MCt) is also given. The results are presented in Tables 3.1-3.5 and Figures 3.1-3.2. Dispersion of the pellets from the capsule enabled ready identification of the stomach. Dipersion of the pellets in the colon enabled definition of the colon region for the purposes of analysis. Representative scintiscans (Figure 3.3) show the pellets dispersed in the stomach, gastric emptying of the pellets into the SI, the pellets entering the colon, and the pellets dispersed in the colon.

Generally, the subjects exhibited a lag phase, of different duration, before emptying began. The duration of the lag phase differed both between subjects and was different for each subject on subsequent study days. Emptying of the pellets occurred rapidly after this lag. The GE profiles for subject 3 (Figure 3.1), which are typical of those observed, illustrate the lag phase and subsequent rapid emptying. A plot of the mean GE values (Figure 3.2), shows the pellets empty rapidly in an

exponential fashion. Entry of the pellets into the colon was generally in the form of a bolus, as illustrated by the steep colon entry (CE) curves (Figure 3.1). The slopes of the mean CE curves (Figure 3.2.) also reflect this rapid entry. Both the rapid GE of the pellets and the bolus entry into the colon, suggest the pellets traverse the SI as a bolus. It is difficult to verify this on the scintiscans, due to the convoluted structure of the SI. In some cases, however, GE did not occur as a complete bolus, whereas CE was in bolus form. This suggests the pellets amass and form a bolus, before entering the colon. It is possible that this bolus forms in the region of the ICJ, and entry into the colon occurs with the next powerful contraction (Section 5).

The mean St50% (s.e.m.), 68 (23)min, 74 (19)min, and 67 (13)min, are similar to those previously reported. Bechgaard and Christensen (147) report GE t50% values of 90-180min, depending on the fasting or non-fasting state. A mean GE t50% value of 45min for pellets given to fasted subjects, was reported by Hardy and Perkins (220). Gastric emptying t50% values ranged from 30-150min, for pellets taken by either fasted subjects or subjects who had received a breakfast (301). It has been suggested that, particles less than about 2mm empty more as a liquid than a solid (16). The exponential pattern of emptying of the pellets illustrated in Figure 3.2, is similar to the GE pattern of liquids (216). Literature

values for the GE t50% of liquids range from 10-50min, depending on the fasting or fed state (289). Radiolabelled orange juice, given to fed subjects, had a mean GE t50% of 37min (371), and radiolabelled water had a mean GE t50% of 18min (295).

As has been previously discussed (Section 2.3), the rapid and almost bolus emptying of the pellets observed in some subjects, is a consequence of the contractions of the MMC. The duration of the lag phase shows an inter- and intra-subject difference, because the subjects are likely to be in different phases of the MMC when the capsule is ingested. The rapid emptying of capsule formulations in fasting subjects, has been previously demonstrated (237). It was suggested, that an adequate volume of liquid should be given with the dosage form, to improve dispersion of capsule contents in the stomach and maximise randomized emptying. However, bolus emptying of part of the formulation may still occur, even after a light breakfast (295). Gastric emptying is a variable process in healthy subjects, with marked inter- and intra-subject day-to-day differences (45). Multiple-unit systems are used as CR preparations to obtain a steady and predictable gastric emptying, thus reducing this variability. However, the results presented here, indicate that multiple-unit preparations given to fasted subjects, do not exhibit a steady and reproducible pattern of emptying.

The mean SIT (±s.e.m.) values of 175 (18)min, 148 (21)min, and 182 (10)min, are similar to literature values. A mean SIT of 2.8h was reported for pellets given to fasted subjects (220). A study investigating the influence of density on the SI transit of pellets in fasted subjects, obtained mean SIT values of 2.9 (0.6)h for low density pellets, and 2.2 (0.5)h for high density pellets (372). In fed subjects, values of 4.7 (0.9)h and 3.1 (0.2)h, were reported for the low and high density pellets respectively. Tiaprofenic acid pellets had a mean SIT of 176min after a light breakfast, and 250min after a heavy breakfast (246). Lactulose solution, labelled with technetium-99m, and administered to fasted subjects, had SIT values ranging from 47-139min (373). The SIT values in the present study are also in close agreement with the SIT time of 3-4h, commonly observed for oral dosage forms, irrespective of the fed or fasted state, reported by Davis et al (304). The consequences of this relatively short intestinal transit on the performance of CR formulations, has been discussed by Davis et al (304) and in Section 1.5 above. Furthermore, the bolus emptying of pellets and subsequent bolus SI transit, observed with fasted subjects, could affect drug release, and hence bioavailability, from multiple-unit preparations designed to disperse throughout the GIT.

The mean Ct50% (±s.e.m.) values of 242 (15)min, 222 (18)min and 249 (20)min for the three study days, are

similar to published results. Pellets administered to fasted subjects had a mean CE t50% of about 4h (220). Pellets administered after a light breakfast had a mean CE t50% of 253 (14)min (246). The colon entry of pellets administered to subjects who had fasted or who had eaten, ranged from 170-700min, depending on the caloric content of the meal (301). A range of CE t50% values of 190-360min was obtained for radiolabelled water, administered to fed subjects (295). It is not entirely clear if entry of the pellets into the colon, in these cited studies, was in the form of a bolus.

The mean (±s.e.m.) mouth to colon transit times of 292 (26)min, 270 (8)min, and 325 (37)min, are of considerable consequence to the design of multiple-unit CR preparations. Many multiple-unit CR products are designed to release drug over 12h. These results indicate, that in fasted subjects, all the sub-units would have entered the colon within 5-6h. Thus, only half the total dose of drug would be released in the SI, considered the major site of drug absorption (258), and the remainder released in the colon. If, as is commonly assumed, drugs are not extensively absorbed in the colon (262), this release in the colon represents a substantial loss of drug. Future studies would need to ascertain the extent of colonic absorption. In the meantime, the future design of CR formulations should endeavour to

control the GI transit of the dosage form, in both the fasted and fed state.

Paired Student t tests were performed on the GI transit data, St50%, Ct50%, SIT and MCt values: morning/afternoon, morning/evening, and afternoon/evening. There was no significant difference ($p>0.1$) between the values for each pair of data. This is also suggested by a simple comparison of the mean and s.e.m. values, and the mean transit profiles (Figure 3.2). Thus, the time of day of administration does not appear to be a major determinant of GI transit. The variation in the theophylline levels cited above (368,369) is possibly related to the different contractile activity during the fasted and fed states. Formulations taken in the morning, possibly on an empty stomach, would be subjected to MMC activity and enter the colon within 6h. This would result in low drug levels in the evening. Formulations taken in the evening, possibly after dinner, would not be subjected to MMC activity until digestion was completed. A longer gastric residence, depending on the caloric content of the meal (301), would ensure a greater proportion of drug released into the SI, and higher drug levels.

3.4 Conclusions

The following conclusions can be drawn from the results of this investigation:

i. The gastrointestinal transit of pellets is not influenced by the time of day of administration of the formulation, in fasted subjects.

ii. Gastric emptying occurs rapidly after a short lag phase, in fasted subjects.

iii. Entry of the pellets into the colon often occurs in the form of a bolus.

iv. Small intestine transit takes about 3h, and mouth to colon transit takes about 6h. These values are of consequence to the design of CR dosage forms.

Table 3.1 Mean (s.e.m.) gastric emptying data - %activity remaining in the stomach.

Time (min)	Morning	Afternoon	Evening
0	100	100	100
15		100	97 (2)
20	79 (18)		
30		88 (5)	73 (20)
35	57 (19)		
45		63 (18)	60 (23)
55	53 (19)		
60		59 (18)	54 (23)
70	42 (17)		
75		36 (17)	49 (24)
90	25 (15)	22 (18)	35 (20)
105	15 (14)	20 (18)	14 (8)
120	14 (12)	15 (14)	12 (8)
150	14 (12)	12 (11)	10 (8)
180	0	0	8 (7)
210	0	0	8 (7)
240	0	0	0

Table 3.2 Mean (s.e.m.) colon entry data - %activity entered colon.

Time (min)	Morning	Afternoon	Evening
150	0	0	0
180	11 (10)	28 (16)	16 (14)
210	27 (17)	31 (17)	20 (17)
240	30 (17)	33 (19)	57 (22)
270		99 (1)	66 (20)
285	97 (3)		
300		100	88 (10)
315	99		
330		100	89 (10)
345	100		
360	100	100	93 (6)
425	100	100	100

Table 3.3 Lag time and Gastric emptying (St50%) data.

	Morning		Afternoon		Evening	
	Lag (min)	St50% (min)	Lag (min)	St50% (min)	Lag (min)	St50% (min)
Subject						
1	0	10	15	65	70	85
2	35	67	60	75	75	87
3	20	27	15	40	90	100
4	20	77	15	35	15	23
5	70	157	105	155	15	40
mean	29	68	42	74	54	67
s.e.m.	10	23	16	19	14	13

Table 3.4 Small intestine transit (SIT) data.

	Morning	Afternoon	Evening
	SIT (min)	SIT (min)	SIT (min)
Subject			
1	168	190	205
2	198	105	210
3	231	215	160
4	170	132	152
5	106	100	185
mean	175	148	182
s.e.m.	18	21	10

Table 3.5 Colon entry (Ct50%) and mouth to colon data.

	Morning		Afternoon		Evening	
	Ct50% (min)	MCt (min)	Ct50% (min)	MCt (min)	Ct50% (min)	MCt (min)
Subject						
1	178	210	255	270	290	420
2	265	390	180	300	297	425
3	258	285	255	270	260	300
4	247	290	167	240	175	240
5	263	285	255	270	225	240
mean	242	292	222	270	249	325
s.e.m.	15	26	18	8	20	37

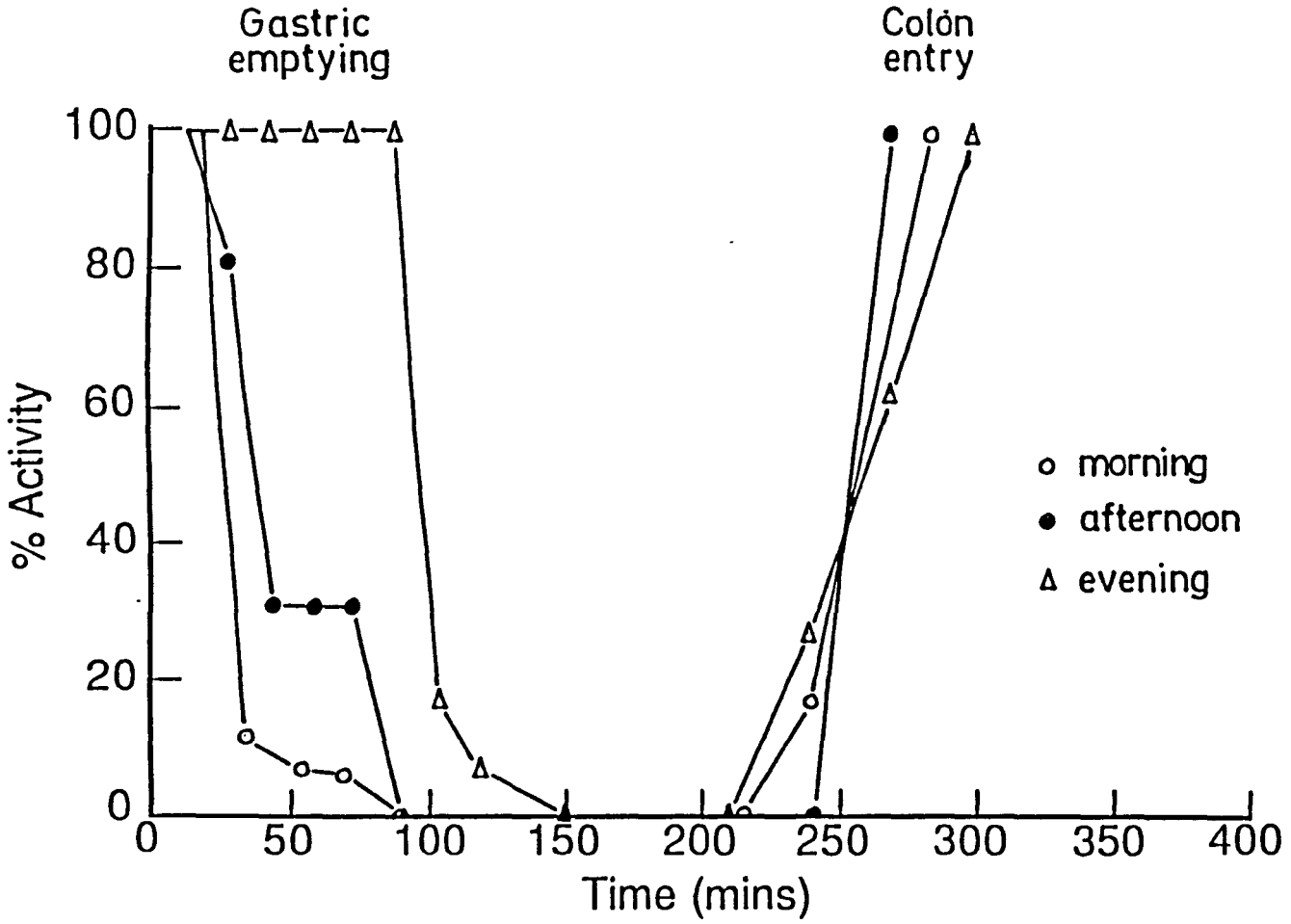


Figure 3.1 Gastric Emptying and Colon Entry of Pellets (Subject 3).

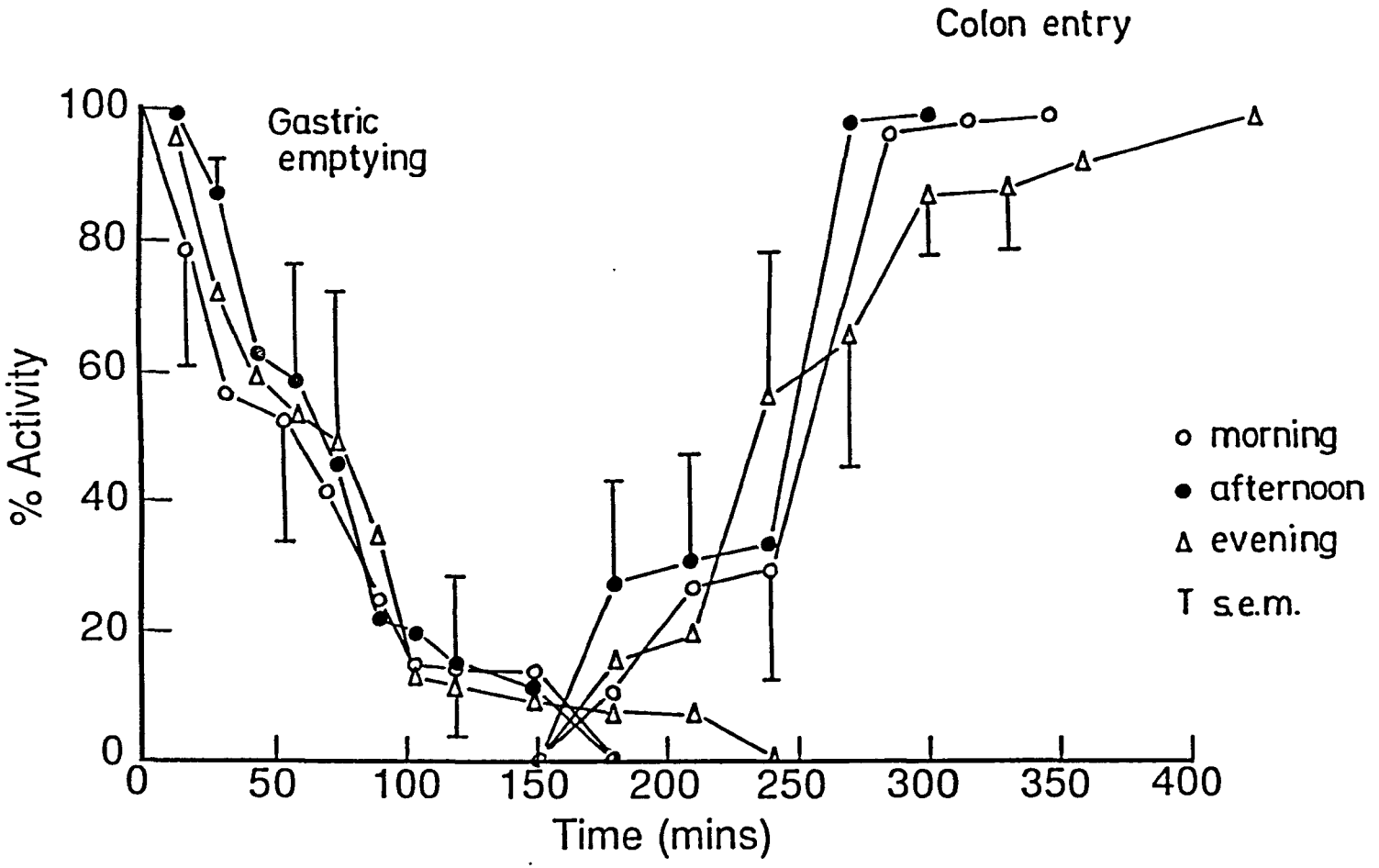


Figure 3.2 Mean Gastric Emptying and Colon Entry of Pellets.

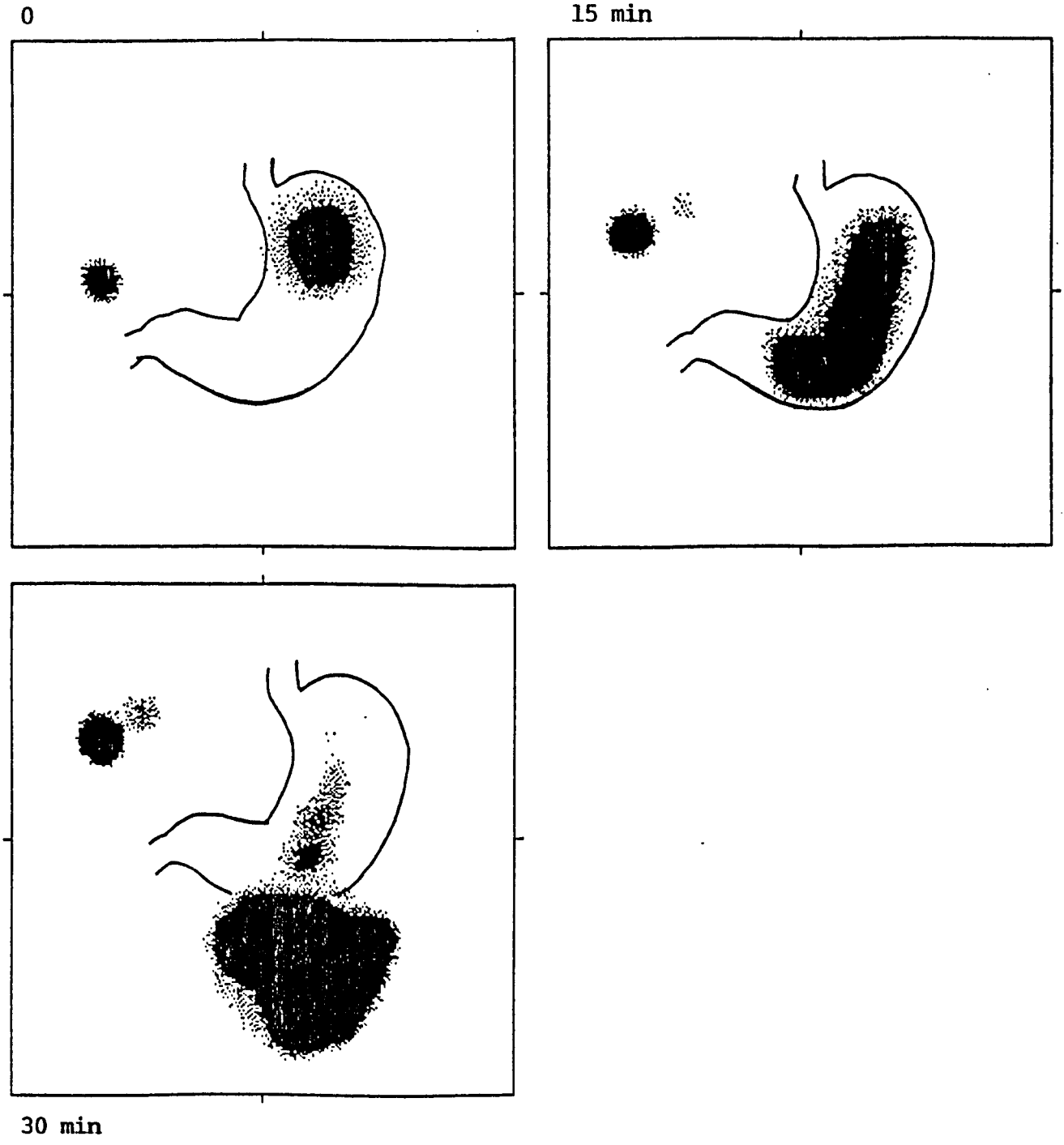


Figure 3.3a Gastric Emptying of Pellets - Subject 4.

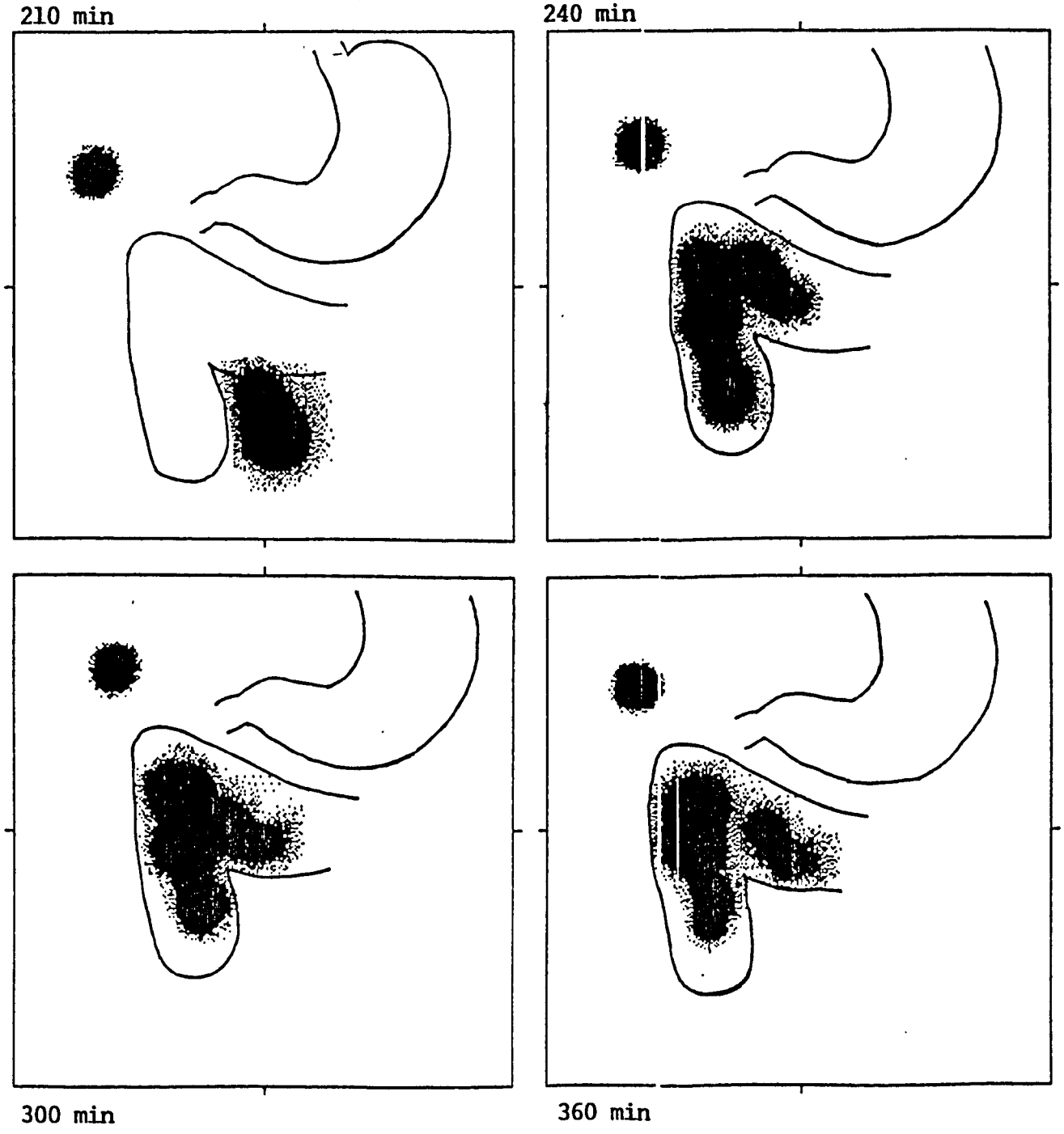


Figure 3.3b Colon Entry of Pellets - Subject 5.

CHAPTER FOUR:

MUCOADHESION

4.1 Introduction

An investigation was conducted to determine the influence of the putative bioadhesive, polycarbophil, on the GI transit of a placebo pellet formulation. The results of the investigation are presented and discussed in this chapter.

The design of oral CR dosage forms continues to attract the attention of formulation scientists. Many technically ingenious systems have been developed (eg. osmotic devices) that are capable of well defined controlled drug release (Section 1.3). The performance of these systems in vivo, however, will be limited to the relatively variable GE times (301) and short SI transit (3-4h) (304) of dosage forms in man. A device designed to deliver its dose over 24h, may have emptied from the stomach, traversed the SI, and entered the colon in half that time. This could result in a reduced systemic level and a significant fraction of the dose being wasted. Control of the GI transit of CR systems would be a clear advantage.

The variable nature of GE of dosage forms, which is influenced by factors such as diet and the type of dosage form administered, has been well documented (374). Conversely, small intestine transit appears to be regular and unaffected by these factors (71,304). Control of the gastric emptying of dosage forms, therefore, represents the preferred option. A number

of strategies have been proposed for this purpose, such as particle size (323), and particle density (175). Another approach is the use of so called bioadhesive polymers, which adhere to the mucin/epithelial surface of the gastrointestinal tract (329). Controlled release devices formulated with such polymers, could provide a "localised platform", in the gastrointestinal tract, for drug release (375). The potential of bioadhesive systems is not restricted to oral drug delivery, but has already been exploited by the dental (376) and opthalmic professions (377). Systems have already been developed for nasal (378), vaginal (379), and buccal (380) drug administration.

Bioadhesion involves the binding together, for an extended period of time, of two materials, one of which is biological in nature (381). Thus, any macromolecular material that adheres to, and is retained on biological tissue, can be termed a bioadhesive. For an extensive discussion of the interactions between polymers and tissues, the reader is directed to the review by Peppas and Buri (382). Very briefly, the postulated mechanisms of bioadhesion are:

i. Mechanical bonding, whereby the bioadhesive occupies empty spaces in the tissue. This is only suitable for fluid bioadhesives that can flow into the crevices.

ii. Primary chemical bonds, generated by chemical reaction of functional groups of the tissue and bioadhesive. Due to their high strength, these bonds are not suitable for drug delivery systems.

iii. Secondary chemical bonds, such as van der Waals interactions and hydrogen bonding. These are considered the most important forces contributing to bioadhesion.

A number of polymeric devices have been investigated for their adhesiveness to mucus (383), and various methods have been applied to evaluate bioadhesion. These tests have largely concentrated on surface analysis and bioadhesive strength. The surface analysis tests have relied on conventional contact angle measurements and a variety of spectroscopic techniques (382). Bond strength tests can be classified into in vitro, in situ, and in vivo methods. Smart et al (384), using an in vitro tensiometric technique, have classified several polymers according to their bioadhesive strength with mucin. Park et al (385) have devised a method to measure polymer binding, using a fluorescent probe (pyrene) in cultured epithelial cells. The Robinson group has also developed a technique which measures the adhesion of polymer to rabbit stomach tissue (386). The force required to detach the polymer from the mucus is

measured. Recently, Mikos and Peppas (387) described an *in vitro* flow method, which should simulate the behaviour of CR devices in contact with mucus *in vivo*. Ch'ng et al (386) measured the GI transit, in rats, of polymers labelled with ^{51}Cr. The distribution of the polymers in the GIT was determined after sacrificing the rats and measuring the distribution of radioactivity. The technique of gamma scintigraphy has now been used to evaluate the bioadhesive performance of a polymer in man (388).

Polymers which show bioadhesive properties can be categorised into three main groups: hydroxyl-containing, carboxyl-containing, and polymers with charged species (389). However, not all of these may satisfy the criteria, defined by Robinson et al (390), for use in CR devices:

i. Polymers should show specificity in their site of adhesion, eg. they should attach to ileal mucin surface and not to jejunal mucin surface.

ii. Polymers should have no intrinsic activity, and should not cause irritation or an immunologic reaction.

iii. Residence time of the polymer on the mucin surface should be controllable.

Few available polymers fulfil these criteria, but anionic, water-insoluble polymers are considered suitable, because of their low toxicity, and greater flexibility of use (329). In particular, polycarbophil, a hydrophilic, granular, acrylate polymer, used as both an antidiarrheal, and a bulk-forming laxative (391), has been shown to adhere to the rat stomach and small intestine (386). Furthermore, a sustained release formulation, containing polycarbophil and albumin beads, provided a longer duration of drug action, in rats, than formulations without the polymer (375). It was suggested that polycarbophil rapidly hydrated *in vivo*, retaining the beads and adhering to the mucin coating of the rat stomach. Toxicity data have revealed no deleterious results from the use of polycarbophil, whilst other studies indicate the polymer was neither absorbed from the rat GIT nor physiologically active (392). Clinical investigations have shown no GI irritation or systemic toxicity in patients who had taken polycarbophil for extended periods (392).

The performance of bioadhesives in the human GIT has not been widely assessed. It was, therefore, considered useful to investigate the GI transit of a polycarbophil pellet formulation in man, using the technique of gamma scintigraphy.

4.2 Materials and Methods

4.2.1 Preparation of Formulations

The formulations were prepared in a manner to mirror the systems employed by Longer et al (375). Pellets, size range 0.5-1.0mm, density 1.17g/cm^3, of Amberlite IRA410 anionic resin (BDH) were labelled by soaking 6g in 10ml ^{99m}Tc-sodium pertechnetate solution (CIS(UK) Ltd, London). A mix of 100mg polycarbophil (0.5-1.0mm) (Lee Laboratories, Petersburg, USA) and dried labelled pellets (310mg), was filled into size 0 hard gelatin capsules (Capsugel). The integrity of the binding of the label to the resin, was checked as described previously (Section 2.2.1). A disintegration test, in 0.1N HCl, was also performed on the test formulation, but containing unlabelled pellets encapsulated with polycarbophil. The polycarbophil began to hydrate as soon as the capsule ruptured, and the pellets became entrapped within the polymer gel. Each capsule had an activity of about 3MBq technetium-99m at the time of administration. The total radiation dose absorbed was estimated as 0.603mG/MBq for the stomach and small intestine, and 0.045mG/MBq for the whole body (133,350).

4.2.2 <u>In vivo</u> Study

The study was approved by the Ethical Committee of the University of Nottingham, and conducted in accordance with the declaration of Helsinki Guidelines

for Ethics in Research. Approval to administer radiopharmaceuticals was obtained from the DHSS.

Three, healthy male volunteers, age range 19-25, height range 1.7-2.0m, weight range 64-75kg, participated with informed consent. Each subject abstained from alcohol for 24h, and had fasted for 10h prior to each study day. The subjects did not smoke, and were not on medication. On the morning of each study day, each subject swallowed one capsule with 100ml water.

Anterior and posterior images, each of 60s duration, were taken at regular intervals, using a gamma camera (General Electric Maxicamera, Type II) having a 40cm field of view and fitted with a low energy (160 keV) parallel hole collimator. The subjects stood in front of the camera for imaging and were asked to keep body movements to a minimum during imaging. During the study, the subjects remained in an upright position, sitting/standing. The images were recorded, and stored on computer (Nodecrest). Anatomical reference markers containing technetium-99m, were taped to the skin, anteriorly and posteriorly, over the liver to the right of the stomach. The volunteers were given a standard light lunch of one cheese roll and 150ml orange juice, after five hours of imaging. After this time they were allowed to eat and drink as normal.

The recorded images were analysed by drawing regions of interest around the position of the stomach and colon, as described previously (Section 2.2.2). The activity in these regions was quantified, and then corrected for background activity and radioactive decay. The error due to the variation in depth of radionuclide in the stomach and colon, was corrected by calculating the geometric mean of corresponding anterior and posterior views (216).

A control study was conducted one week later, using capsules containing pellets only. The subjects did not complain of any untoward side-effects during each study day.

4.3 Results and Discussion

The data for this investigation are expressed as the time for 50% of the activity to leave the stomach (St50%), and the time for 50% of the activity to enter the colon (Ct50%). Due to the coiled structure of the SI and the overlying of different regions of activity, which precludes the accurate quantification of the pellets in the SI, the SIT of the pellets was calculated by subtracting St50% values from Ct50% values. A value for the time from ingestion to 100% activity in the colon (MCt) is also given. Transit data are presented in Tables 4.1-4.5 and Figures 4.1-4.3. Release of the pellets from the capsule

occurred within 15 minutes of administration and the dispersion of the pellets enabled ready identification of the stomach region for subsequent creation of regions of interest. Dispersion of the pellets in the colon enabled definition of the colon region for the purposes of analysis. Representative scintiscans (Figure 4.4) show the pellets dispersed in the stomach, gastric emptying of the pellets into the SI, the pellets entering the colon, and the pellets dispersed in the colon.

A lag phase before GE is only markedly exhibited by subject 3, in both studies (Figure 4.1). As in the previous studies on posture and time, these fasted subjects show a rapid bolus-like emptying of the pellets. The control study GE curve for subject 1 shows a two step emptying pattern, possibly indicating the pellets emptied as two boluses. The mean ($\pm$s.e.m.) St50% time for the polycarbophil formulation, 52 (13)min, and for the control formulation, 66 (18)min, are in good agreement with previous studies that have used gamma scintigraphy to measure gastric emptying. A St50% gastric emptying of 45min (n=4), was reported for pellets given to fasted subjects (220). The mean St50% for pellets given to subjects who had taken a light breakfast, was 99 (7)min (245). Davis et al (301) obtained St50% values ranging from 30-150min (n=6), for pellets taken by subjects who were either fasted or had

received breakfasts of different calorific values. This influence of food on the gastric emptying of pellets has been well illustrated by Davis et al (374). Gastric emptying was slower, 285 (45)min, when the subjects (n=6) received a heavy breakfast, than when given a light breakfast, 119 (15)min. Thus, rapid gastric emptying in the present study, can be attributed to the absence of food in the stomachs of the subjects. This has been adequately discussed in previous chapters (Sections 2.3 and 3.3).

The data show that both formulations empty in an exponential fashion (Figure 4.3). It has been suggested, that particles small enough (<=2mm) to pass through the "closed" pylorus, empty more as a liquid than as a solid (16). The rate of emptying of a liquid can be described as an exponential function, and typical St50% values range from 10-50min (289). Malagelada et al (305) report gastric emptying values between 20-60min for radiolabelled water given to fed subjects. Emptying followed approximately an exponential pattern. Similarly, the mean St50% for radiolabelled water, given to subjects who had received a light breakfast, was 18 (4)min (n=5) (245). The results of the present study suggest, therefore, that the pellets emptied from the fasted stomach in a pattern similar to that for the gastric emptying of liquids.

The similar rate of emptying for both formulations, indicates that their admixture with polycarbophil does not retard the gastric emptying of pellets in fasted subjects. Longer et al (375) investigated the gastrointestinal transit of a similar formulation of polycarbophil and albumin beads in rats. Approximately 90% of the beads remained in the stomach six hours after administration. In the absence of polycarbophil, the beads emptied rapidly. Russell and Bass (393) have reported that only 8% of a polycarbophil meal emptied from the stomachs of dogs within 90min. A further investigation of canine gastric emptying of polycarbophil (394) reported that 50% of a 90g polycarbophil meal emptied within 4h. However, in this study no attempt was made to attribute the slow emptying to adhesion of the polycarbophil to the gastric mucosa. Autopsy of the dogs after the study, revealed particles of polycarbophil located in the stomach which were easily moved. This suggested that they did not adhere to the gastric mucosa. The amounts of polycarbophil used in these studies, in rat and dog, were greater than that used in the present study. These larger amounts may have elicited motor activity of the fed stomach, which would result in a slower rate of gastric emptying (394). About 98% of Amberlite resin particles, with an adsorbed film of poly(acrylic acid), a polymer with bioadhesive

propeties in vitro, were retained in the murine stomach 1h after administration (395). The particles were labelled with technetium-99m, and administered as a suspension. The small particle size of the resin (0.009mm), as well as the nature of the formulation, precludes comparison with the present study. Recently, Fell et al (396) investigated the effect of polycarbophil and Carbopol-934P on the gastrointestinal transit of Amberlite pellets (0.7-1.0mm). The formulations were investigated using a similar method to the present study. Polycarbophil did not alter the gastric emptying of the beads (t50% 33min), whereas Carbopol delayed gastric emptying (t50% 166min). The small intestine transit was similar for the polymer and control formulations.

The mean SIT ($\pm$s.e.m.) values of 160 (14)min for the polycarbophil formulation and 160 (10)min for the control formulation, are in close agreement to the mean value of 3h for oral formulations observed by Davis et al (304). Furthermore, these values are similar to the SIT values observed in the time study, 175 (18)min, 148 (21)min and 182 (10)min. Comparison with other literature values can be found in Section 3.3. The similarity between these SIT values and literature values, suggests polycarbophil does not inhibit SI transit. A similar result was expressed by Fell et al (396). This is in contrast to the results of Ch'ng et

al (386), which indicate the bioadhesion of polycarbophil in the rat SI. They, however, suggest the extent of bioadhesion in the SI will be governed by the number of free binding sites on the surface of the polymer. These are likely to be few, due to the mucin covering the polymer when it is discharged from the stomach. Another study, investigating the effect of guar on the absorption of glucose in rats, suggested an interaction between hydrated guar and mucopolysaccharides of the mucosal surface, which "anchors" the surface layer of gel (397). Preferential adhesion in the SI of rats, was achieved by incorporating amino sugars into copolymers of hydroxypropylmethacrylamide (398). Galactosamine residues caused bioadhesion in the duodenum, whereas fucosylamine improved adhesion in the distal jejunum. The CE curves (Figures 4.2 and 4.3) also reflect the bolus entry that was seen in the time study. The mean Ct50% ($\pm$s.e.m.) values of 212 (22)min for the polycarbophil study and 226 (17)min for the control study, are similar to the time study values (242 (15)min, 222 (18)min and 249 (20)min for the three study days), and to published results (Section 3.3). Similarly, the mean ($\pm$s.e.m.) MCt values, 265 (29)min for the polycarbophil study and 295 (41)min for the control study, are in close agreement with the time of day data (292 (26)min, 270 (8)min, and 325 (37)min).

These results further reflect the relatively short GI transit times of formulations. The error in designing CR systems which release drug over a 12h period, without attempting to control the transit of these systems is further emphasised by these results (see also Section 3.3).

Despite the small sample size, a Students t test was performed on the transit data. In each case no significant difference was observed ($p>0.1$) between the polycarbophil data and the control data. Thus, admixture of pellets with polycarbophil does not reduce GIT transit times. There is possibly one major flaw with the design of the present investigation, namely the position of the polycarbophil in the GIT is not known. Although the investigation was designed to determine the influence of polycarbophil on the GI transit of pellets, it would have been fruitful to have labelled the polycarbophil with another isotope (eg. indium-111). This would indicate if the polymer did remain in the stomach, without entrapping the pellets.

The importance of controlling the GI transit of CR systems has been discussed above. In many instances this would improve bioavailability of the drug. The absorption of digoxin, which occurs largely in the proximal SI, was improved by decreasing GI motility using propantheline (399). However, decreasing GI motility can also decrease absorption by decreasing the

agitation required for solid dissolution (280). The glucose absorption study cited above, noted a decrease in aborption in the presence of guar (397). An increase in resistance of the mucosal diffusion barrier, resulting from an increase in viscosity at the mucosal surface, was provided as an explanation. Thus, the strategy used to control GI transit should not in itself interfere with the processes of dissolution and absorption.

An important caveat, exemplified by the withdrawal of the OSMOSIN system (400), should be considered in our quest to identify suitable bioadhesives for CDDS. Although the OSMOSIN system was not a bioadhesive system, the adverse reactions associated with the formulation could be repeated by bioadhesive drug delivery products. Several workers have also reported on the oesophageal sticking of capsule and tablet formulations as a possible cause to oesophageal ulceration (343,401). Thus, all that sticks is not necessarily safe. Our search for a suitable bioadhesive should not be impaired by these findings, but it may be rewarding to direct our research to understanding the mechanism of bioadhesion exhibited by several bacteria (eg. Escherichia coli) (381).

4.4 Conclusions

The following conclusions can be drawn from the results of this investigation:

i. The gastrointestinal transit of pellets is not influenced by the admixture of polycarbophil.

ii. The pellets emptied rapidly from the stomach, usually as a bolus, and entered the colon in a similar fashion.

iii. Small intestine transit of the pellets, about 3h, was similar to previously quoted values.

Table 4.1 Gastric emptying and colon entry data for the polycarbophil formulation - %activity remaining in the region.

Subject	1	2	3	mean	s.e.m.
Time (min)					
0	100	100	100	100	-
15	94	96	100	97	1
30	88	15	98	67	21
45	85	2	98	62	25
60	8	0	74	28	19
75	6	0	62	23	16
90	6	0	28	11	7
105	0	0	10	3	3
120	0	0	6	2	2
135	0	0	0	0	
150	0	15	0	5	4
165	0	84	0	28	23
180	0	93	18	37	23
195	0	100	20	40	25
210	0	100	22	41	25
255	65	100	78	81	8
285	83	100	100	94	5
315	100	100	100	100	

Table 4.2 Gastric emptying and colon entry data for the control formulation - %activity remaining in the region.

Subject	1	2	3	mean	s.e.m.
Time (min)					
0	100	100	100	100	-
15	100	94	100	97	2
30	95	90	100	95	2
45	95	58	94	82	10
60	94	10	77	59	20
75	69	6	36	37	15
90	41	4	27	24	9
105	38	2	7	15	9
120	38	0	0	13	11
135	35	0	0	12	10
150	35	0	0	12	10
165	0	0	0	0	
180	0	17	0	6	5
195	0	84	0	28	23
210	0	84	28	37	19
245	41	100	100	80	16
260	46	100	100	82	15
275	56	100	100	85	12
305	60	100	100	87	11
335	72	100	100	91	7
365	92	100	100	97	2
395	100	100	100	100	

Table 4.3 Lag time and Gastric emptying (St50%) values for the polycarbophil and control studies.

	Polycarbophil study		Control study	
	Lag Time (min)	St50% (min)	Lag Time (min)	St50% (min)
Subject				
1	<5	53	15	80
2	<5	23	<5	47
3	15	80	15	70
mean	-	52	-	66
s.e.m.	-	13	-	8

Table 4.4 Small intestine transit (SIT) data for the polycarbophil and control studies

	Polycarbophil study	Control study
	SIT (min)	SIT (min)
Subject		
1	192	185
2	134	145
3	153	150
mean	160	160
s.e.m.	14	10

Table 4.5 Colon entry (Ct50%) and mouth to colon data for the polycarbophil and control studies.

	Polycarbophil study		Control study	
	Ct50% (min)	MCt (min)	Ct50% (min)	MCt (min)
Subject				
1	245	315	265	395
2	157	195	192	245
3	233	285	220	245
mean	212	265	226	295
s.e.m.	22	29	17	41

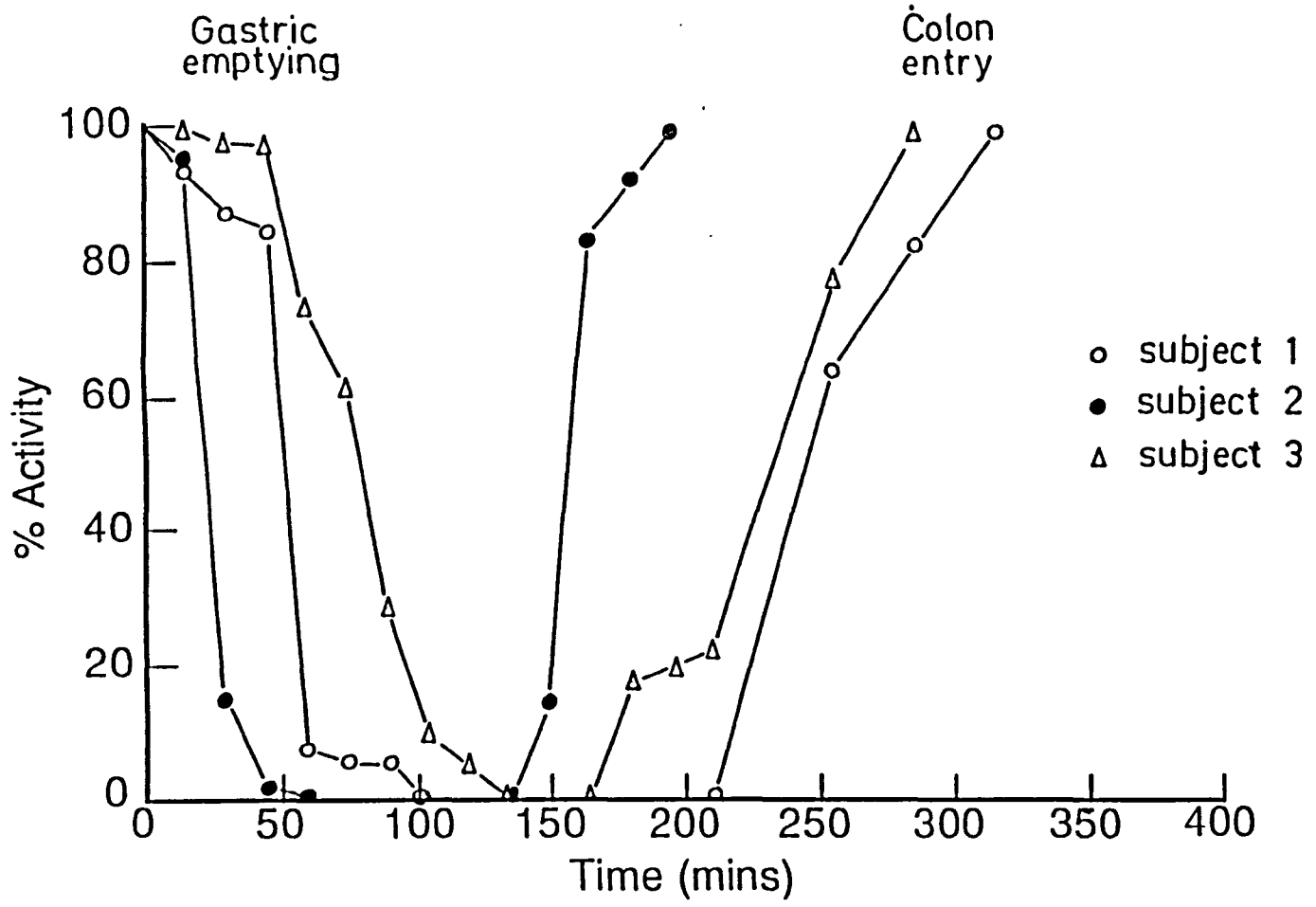


Figure 4.1 Gastric Emptying and Colon Entry of Pellets - Polycarbophil Study.

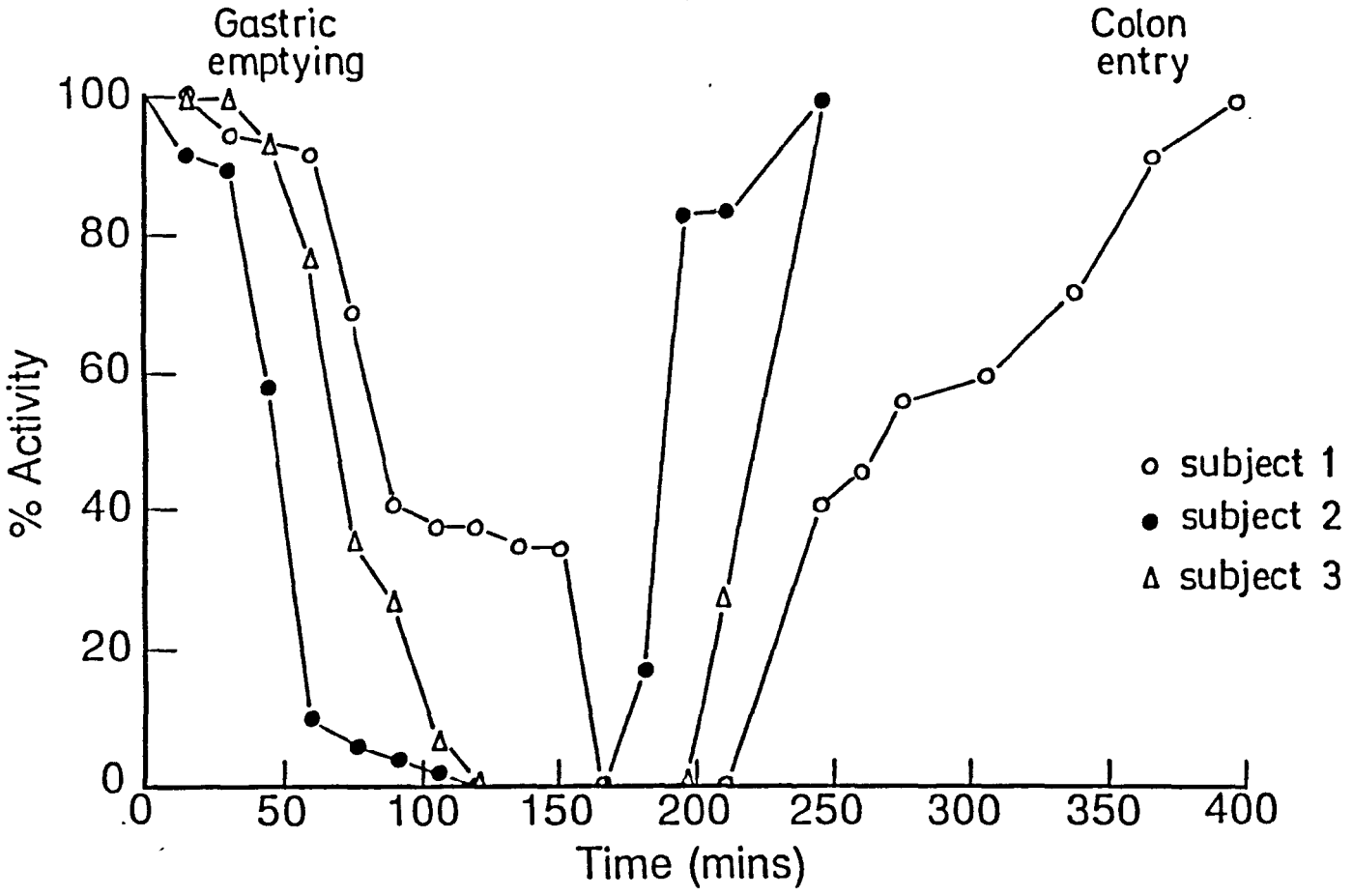


Figure 4.2 Gastric Emptying and Colon Entry of Pellets - Control Study.

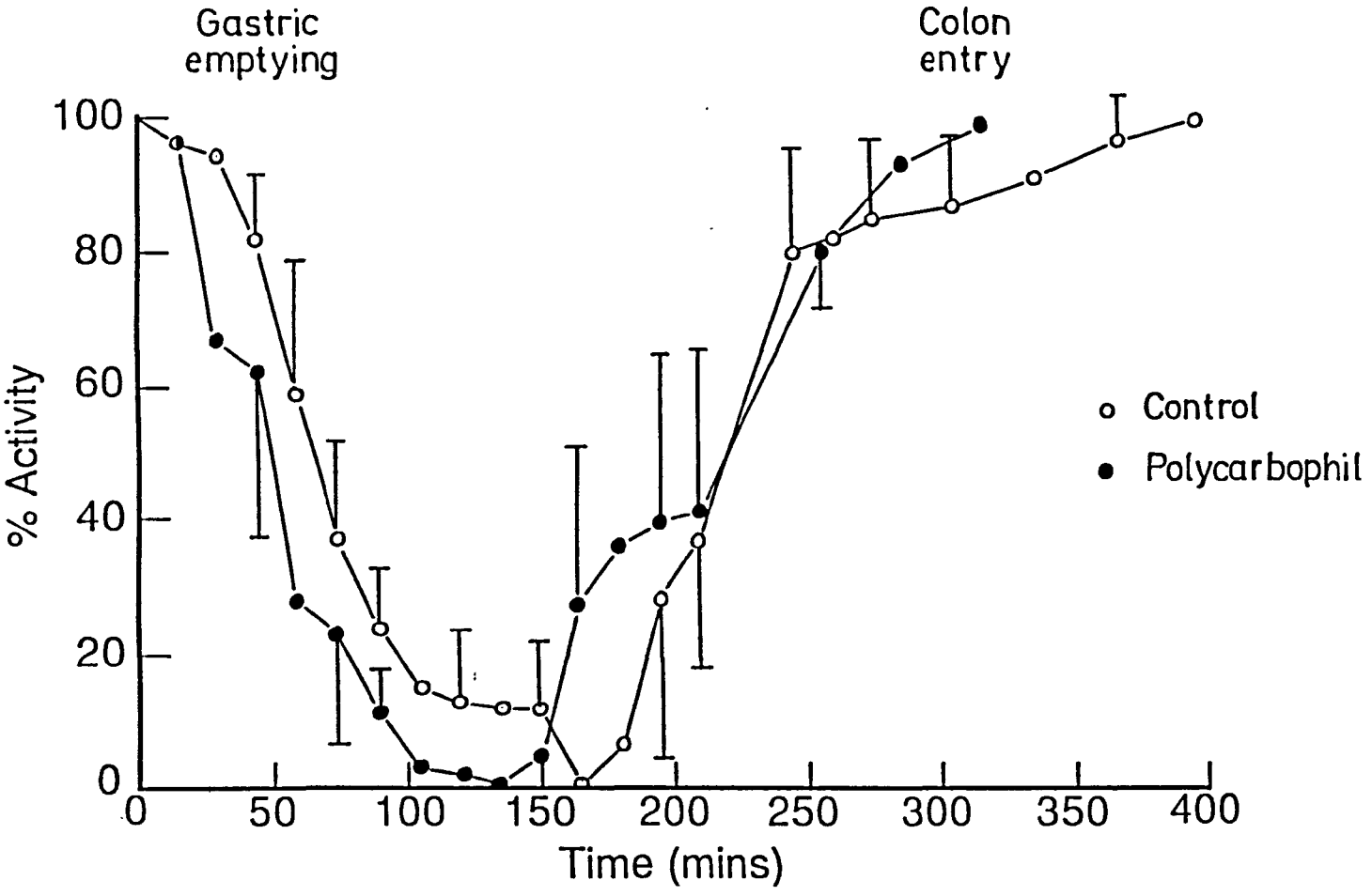


Figure 4.3 Mean Gastric Emptying and Colon Entry of Pellets.

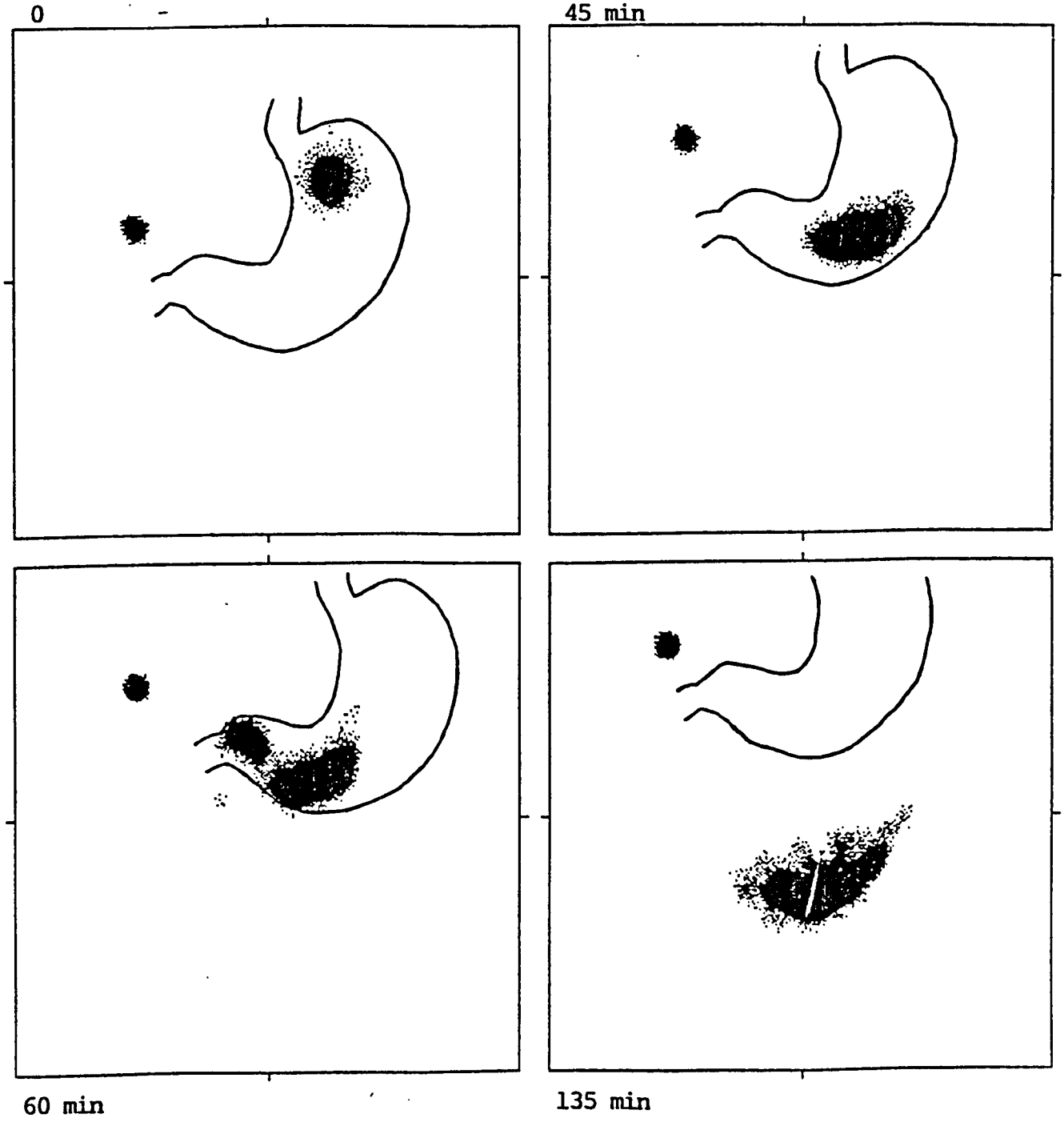


Figure 4.4a Gastric Emptying of Pellets - Subject 3.

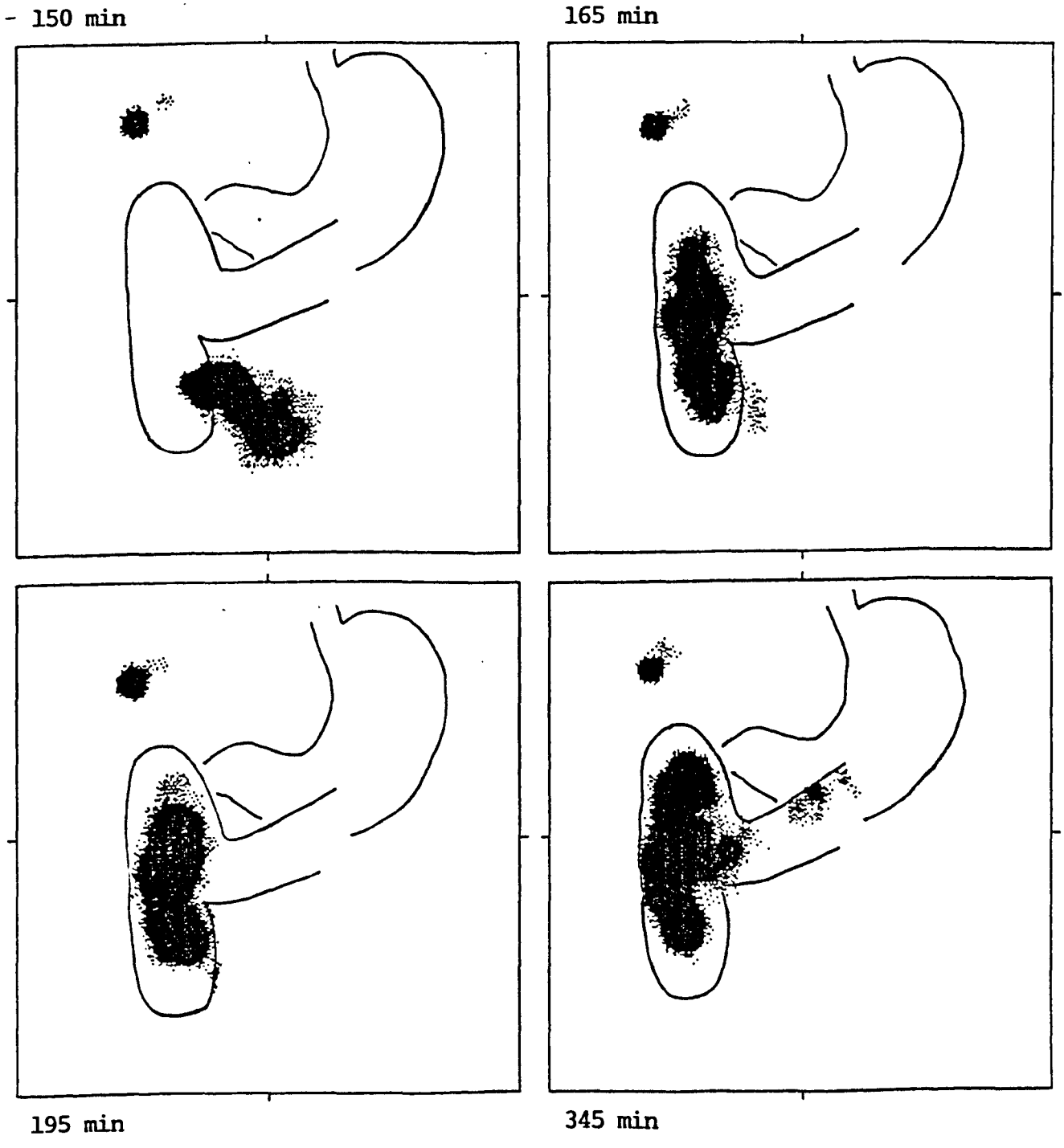


Figure 4.4b Colon Entry of Pellets - Subject 2.

CHAPTER FIVE:

GASTROINTESTINAL TRANSIT OF TABLETS I

5.1 Introduction

In the next two chapters, I shall discuss the results of a series of studies designed to investigate the gastrointestinal transit of tablets. The investigation addressed three themes:

i. the effect of tablet size on GI transit, with particular reference to gastric emptying and transit across the ileocaecal sphincter;
ii. the effect of food on GI transit;
iii. the transit of tablets in the colon (Chapter 6).

The need to control the GI transit of oral dosage forms has been comprehensively discussed in Sections 1.5 and 3.3. It was also suggested, that controlling gastric emptying was the preferred option (Section 4.1). A number of plausible strategies has been proposed for this purpose, such as particle density (175), floating tablets (324), bioadhesives (329), and incorporating fatty acids into formulations (330). However, only a limited success has been achieved using these strategies. One further proposal, is the use of particle size (323). Several studies have suggested that the size of particles is a major determinant of the gastric emptying of solids in the fed state, whereas size does not appear to affect transit through the small intestine (304). It is important to recognise the differences in gastric

emptying patterns of the fed and fasted stomach, and the role of the MMC in emptying large indigestible solids (Section 1.2.1).

Radiolabelled liver, either homogenised or 1cm cubes, together with 7mm plastic spheres, have been administered to dogs (402). Gastric emptying of the respective particles was determined by sampling the duodenal contents. The liver always emptied from the stomach, homogenised liver emptying faster, whereas the spheres were retained. The authors concluded that solids must be reduced to a critical size before they can empty. A similar study illustrated the sieving function of the stomach. Only liver particles of about 1mm, emptied from the intact canine stomach, whereas after gastric surgery, larger particles were able to empty (13). A later study indicated the human stomach also allows only small particles (<1mm) to empty into the duodenum (403). A study using gamma scintigraphy found that subjects emptied 0.25mm liver particles more quickly than 10mm cubes (404). Cortot (405) suggests 0.5mm is the critical diameter for digestible solids, but admits dietary fibres measuring 1-2mm can empty from the fed stomach. Radio-opaque markers (10mm x 2mm) emptied significantly slower than digestible solids, with most markers emptying during the fourth post prandial hour (406). The now commonly accepted size for the diameter of digestible

solids that can empty from the fed stomach is about 2mm (16).

Studies have also been conducted, in man, with dosage forms. Disintegrating tablets formed a mass of 2-3cm, which was retained in the stomach until the mass dispersed into smaller particles (408). Pellets (4mm) taken with food had a linear pattern of emptying, similar to digestible solids, but the rate of emptying was slower than that of the food (338). Another study, however, found pellets of a similar size had a slower rate of emptying, than co-administered food (409). Bechgaard and Ladefoged found no significant change in transit times of pellets, increased in size from 0.5mm to 1.5mm (175). Mini-matrices (3mm diameter) emptied gradually from the stomach of fed subjects, but as a bolus in fasted subjects (410). Park et al (249) found no effect of either size or shape on the rate of gastric emptying of enteric coated tablets (4.7-12.7mm). These studies were, however, conducted in fasted subjects. Riboflavine tablets (10mm and 12mm) were retained in the stomach for a prolonged period, which resulted in an improved bioavailability of the vitamin (411). Size of the tablets was considered the major factor controlling the gastric retention.

Studies recently conducted in dogs, have attempted to specifically address the question of particle size, for indigestible solids, and gastric emptying. Meyer et

al (323), reported that the rate of emptying, in dogs, became progressively faster as sphere diameter was reduced from 5mm to 1mm. Spheres of 0.015mm, however, had a rate of emptying similar to 1mm spheres. A relationship between particle size and gastric emptying was also observed by Itoh et al (407). Gastric residence time progressively increased as particle size increased. This approached an apparent plateau at about 5mm, after which gastric residence was not significantly affected by increases in particle size.

Two conclusions can be deduced from the above examples. Firstly, the fed stomach discriminates between the gastric emptying of solids depending upon particle size. Secondly, the precise size of particles that can empty from the fed stomach is not absolutely determined. It is feasible that there is no definite cut-off size, but a gradation of sizes over which emptying becomes both slower and more variable as particle size increases. An investigation using tablets of a relatively narrow size range would indicate if such a cut-off point exists, and the feasibility of using particle size to control the gastric emptying of oral dosage forms. Therefore, this was a designated objective of the present thesis.

The role of the ICS in regulating the entry of material into the colon is largely unknown. Quigley and colleagues (95) have conducted several studies, which indicate the ICJ controls the passage of chyme into the

colon (see Section 1.2.3). Feely et al (410) suggest that sub-units of a multiple unit system, which have spread in the SI, due to their variable gastric emptying, regroup at the ICS before entering the colon. Information relating particle size and transit across the ICS, would prove useful to the design of dosage forms for directed delivery to the colon.

The transit of dosage forms in the colon has not been extensively studied. A study by Hardy et al (315) has shown a relationship between particle size and the rate of transit in the colon. Further data would help verify this initial finding.

In the light of these past investigations, it was decided to conduct a series of studies to measure the GI transit of tablets in human volunteers, with particular emphasis on the above mentioned themes.

5.2 Materials and Methods

The investigation was conducted as two separate but related parts. The first study investigated the GI transit of ten 3mm, 4mm and 5mm tablets, taken after either a light or heavy breakfast. The second study examined the transit of ten 5mm, 6mm and 7mm tablets taken after a medium sized breakfast, and was conducted as a crossover design. A crossover was not possible in the first study because of the restrictions in giving radiolabelled formulations to human volunteers.

5.2.1 Preparation of Formulations

Non-disintegrating tablets were prepared from ethylcellulose (BDH) and Amberlite IRA410 resin (BDH). The resin was prepared as previously described (Section 2.2.1), and then milled using a conventional ball mill (Pascall Engineering Company). The milled resin was labelled with technetium-99m using the method described in Section 2.2.1. Labelled resin was passed through a 0.09mm screen, and blended with ethylcellulose powder to the following formula:

Amberlite resin	2% w/w
Ethylcellulose	98% w/w.

The powder mix was then directly compressed into tablets using a Manesty F3 single-punch tablet machine. The tablets had a hardness of 8kgF as measured on a CT40 hardness tester (Engineering Systems). Details of the tablets are described in Table 5.1.

All batches of tablets were coated to prevent the leaching out of the radiolabel, and to stop the tablets from disintegrating. Two coating solutions were used:

Ethylcellulose	4.5% w/w
Acetylbutylcitrate (A/S Alfred Benzon)	0.5% w/w
Propan-2-ol (BDH)	95% w/w.

The solution was painted onto each tablet with a small brush and allowed to dry under a stream of warm air. The second coating solution was then applied to the dried tablets in the same way:

Table 5.1 Formulation details

Diameter (mm)	Shape of Punch	Mean Uncoated Tablet Weight (mg)
3.1	Normal curvature	20
4.0	Flat faced	35
5.0	Flat faced	55
6.2	Flat faced	75
7.1	Concave	81

*Cellulose acetate	15% w/w
Solvent	85% w/w
* Dichloromethane (BDH)	80% v/v
Methanol (BDH)	20% v/v.

A simple in vitro dissolution test was performed on each batch of labelled and coated tablets. Five tablets, were added to a beaker containing 50ml 0.1N HCl at room temperature. The contents were stirred using a magnetic stirrer and "flea". The tablets were removed at regular intervals, and activity measured as described in Section 2.2.1. In each case not more than 1.5% of radiolabel was lost after six hours. Thus, the tablet coating prevented any substantial leaching out of the isotopes.

5.2.2 In vivo Studies

The studies were approved by the Ethical Committee of the University of Nottingham, and conducted in accordance with the declaration of Helsinki Guidelines for Ethics in Research. Approval to administer radiopharmaceuticals was obtained from the DHSS.

5.2.2.1 Study 1

Six, healthy male volunteers, age range 19-25, height range 1.69-1.87m, weight range 65-76kg, participated with informed consent. Each subject abstained from alcohol for 24h, and had fasted for 10h prior to each study day. The subjects did not smoke, and

were not on any medication. On the morning of each study day, three subjects consumed a light breakfast (1500kJ):

1 bowl cereal with milk
1 slice toast, butter, marmalade
1 glass orange juice.

The other three subjects took a heavy breakfast (3500kJ):

1 egg
1 rasher bacon
1 sausage
tomatoes
1 slice toast, butter, marmalade
1 glass orange juice.

Immediately after breakfast, the subjects took either ten 3mm, 4mm or 5mm tablets together with 200ml water. Each dose of ten tablets had an activity of about 3MBq. The total radiation dose absorbed was estimated as 0.603mG/MBq for the stomach and small intestine, and 0.045mG/MBq for the whole body (133,350). Anterior and posterior images, each of 60s duration, were taken at regular intervals, using a gamma camera (General Electric Maxicamera, Type II) having a 40cm field of view and fitted with a low energy (160 keV) parallel hole collimator. The subjects stood in front of the camera for imaging and were asked to keep body movements to a minimum during imaging. During the study, the subjects remained in an upright position, sitting/standing. The images were recorded, and stored on computer (Nodecrest). Anatomical reference markers containing technetium-99m, were taped to the skin, anteriorly and posteriorly, over the liver to the right of the stomach. At about 2.5h after dosing the subjects were given a drink of orange

juice. A standard light lunch consisting of one cheese roll, one ham roll and 150ml orange juice, was taken after about 4h. An evening meal of steak, chips, peas, and cheesecake was taken about 9.5h after dosing.

The recorded images were analysed by drawing regions of interest around the position of the stomach and colon, as described previously (Section 2.2.2). The activity in these regions was quantified, and then corrected for background activity and radioactive decay. The error due to the variation in depth of radionuclide in the stomach and colon, was corrected by calculating the geometric mean of corresponding anterior and posterior views (216).

The study was repeated using the same protocol on two further occasions, such that each subject received each size of tablets, after eating the same breakfast they consumed on the first day. The subjects did not complain of any untoward side-effects during each study day.

5.2.2.2 Study 2

A further six, healthy male volunteers, age range 19-25, height range 1.72-1.90m, weight range 59-83kg, participated with informed consent. Each subject abstained from alcohol for 24h, and had fasted for 10h prior to each study day. The subjects did not smoke, and were not on medication. The study used the same protocol

as Study 1, except a medium sized breakfast (2300kJ) was consumed by all six subjects:

1 bowl cereal
2 slices toast, butter, marmalade
1 glass orange juice.

Immediately after breakfast, the subjects took either ten 5mm, 6mm or 7mm tablets together with 200ml water. Each dose of ten tablets had an activity of about 3MBq. The total radiation dose absorbed was estimated as 0.603mG/MBq for the stomach and small intestine, and 0.045mG/MBq for the whole body (133,350). The study was repeated using the same protocol on two further occasions, such that each subject received each size of tablets. The subjects did not complain of any untoward side-effects during each study day.

5.3 Results and Discussion

The data for the investigation have been expressed in a number of ways, and representative examples are given. The St50%, SIT, Ct50% and MCt values are presented in Tables 5.2-5.10. Gastric emptying profiles and colon entry curves are shown in Figures 5.1-5.4 and 5.8-5.9. Representative scintiscans, which illustrate the various phases of transit, are presented in Figure 5.5. The spreading of tablets from the stomach, followed by subsequent regrouping at the ICS was a typical phenomena. In a number of cases, the individual tablets could all be distinguished spread in different regions of

the colon. Histogram plots, which also demonstrate the spreading of the tablets from the stomach and regrouping at the ICS, are given in Figures 5.6, 5.7 and 5.10.

5.3.1 Study 1

The tablets emptied quite rapidly from the stomach, in the light breakfast group, with no appreciable lag phase (Figure 5.3). The linear pattern of emptying exhibited by all three tablet sizes, is typical for digestible soilds (216), and indicates the tablets become dispersed in, and empty with the food (292). A lag phase is more evident with the heavy breakfast, although the 4mm tablets show a rapid initial emptying (Figure 5.4), and emptying appears to have a biphasic pattern. Emptying is linear after the initial lag, followed by a second lag phase and subsequent linear emptying. The total duration of emptying is markedly longer following the heavy breakfast, for all tablet sizes. Both the GE profiles and the St50% data show gastric emptying is not significantly influenced by tablet size ($p>0.1$), for each type of breakfast. However, the difference in emptying patterns between the light and heavy breakfast, suggests the nature of the meal is a determinant of emptying. A Student t test conducted on the St50% data for each breakfast group, irrespective of tablet size, shows a significant difference ($p<0.005$) between the groups.

The St50% values for the tablets are similar to literature values for pellet studies (0.5-1.0mm) conducted in humans: 77min after a light breakfast and 170min after a heavy breakfast (246). Mini-matrices (3mm) had a mean St50% of 130min after a medium sized breakfast (410). However, these results are in contrast to similar studies conducted in animals. Meyer et al (323) report St50% values of 3-4h for 3.2mm spheres given to fed dogs, whilst about 80% of 5mm spheres remained in the stomach 6h after ingestion. Liver particles of these same sizes had St50% values of about 2h. Mean values of 4h and 7h are reported for the emptying of 3mm and 5mm indigestible particles respectively, in fed dogs (407). Prolonged periods of gastric residence (>7h) were also seen for 4.1mm tablets given to gastric emptying controlled rabbits (185). A difference in both GI physiology, and the nature of the administered meals may explain the differences between the animal and human data.

Small intestine transit was not affected by either meal size or tablet size, which is in keeping with previous observations (301). Furthermore, SIT values are in good agreement with the commonly observed 3(1)h SI transit of oral pharmaceutical dosage forms (304).

Colon entry data are similar to pellet data, mean Ct50% values of 253min after a light breakfast and 420min after a heavy breakfast (246). A significant difference

($p<0.001$) is also apparent between the light and heavy breakfast groups, irrespective of tablet size. This simply reflects the difference in gastric emptying between the two groups, and is emphasised by colon entry not reaching 100% for all three tablet sizes in the heavy breakfast group.

5.3.2 Study 2

The pattern of GE is similar for all three tablet sizes ($p>0.1$), although the 7mm tablets appear to have a faster rate of emptying (Figure 5.9). The GE curves are similar in shape to those of the previous study, which suggests that indigestible solids, up to 7mm diameter, can empty from the fed stomach. The mean St50% values, as well as the mean SIT and Ct50% values, are in good agreement with the literature values quoted above. Once again, the present values do not compare with animal data. The gastric emptying of 7.7mm particles was >7h in rabbits (185), and >8h for 8mm spheres in dogs (407). However, in certain cases, in the present study, some tablets did remain in the stomach 10h after ingestion (eg. subject 5, 7mm tablets).

The pattern of transit, illustrated by Figure 5.10, was similar to Study 1 (Figures 5.6-5.7). Tablets spread in the small intestine, as a consequence of their gastric emptying, but regrouped at the ICS, before entering the colon.

5.3.3 General Discussion

5.3.3.1 The effect of tablet size

The GE data for both Study 1 and Study 2 suggest that indigestible solids, up to 7mm in diameter, can empty from the fed stomach. This is in contrast to current literature, which suggests a critical size of about 2mm (16). However, this figure was obtained from work largely conducted in dogs. There are two possible explanations for the results of the present investigation and their contradiction with the animal work.

The first explanation is simply that the critical size in man is greater than 2mm, and the present results indicate that the critical size is larger than 7mm. This is possible considering that the mean resting pyloric diameter in man is 12.8±7mm (411). A difference in GI physiology may account for the discrepancy between human and canine data. However, gastric emptying does not depend on pyloric diameter, but on the pressure gradient between the antrum and duodenum (see Section 1.2.1).

The second explanation considers the contractions of the stomach, and is based on the observations of Dozois et al (16). They noticed that plastic spheres, subject to the contractions of the fasted canine stomach, are normally swept into, and then retropelled from the terminal antrum back into the main body of the antrum. These contractions are likely to be the intermittent

phase 2 contractions of the MMC. Occasionally, spheres became "trapped" in the terminal antrum, and as the next contraction swept towards the terminal antrum, the trapped sphere passed through the partially occluded pylorus into the duodenum. This would be facilitated by the pressure gradient between the antrum and duodenum generated by the approaching contraction. This "trapping" is obviously a random process, but with a large number of particles, there is a greater statistical chance for fortuitous emptying. Blythe et al (413) made a similar observation with radio-opaque enteric coated tablets. Normally the tablets were retropelled back from the pyloric region, but on some occasions, tablets were seen remaining near the pyloric sphincter.

Although the present investigation was conducted in fed subjects, the above scenario is still applicable, since phase 2 contractions are similar to fed state contractions (335,414). Thus, ten tablets given to one subject, will essentially empty in a random fashion from the stomach, but over a given period the emptying appears to be regular. It can be envisaged that both the diameter of the human pylorus and fortuitous emptying are responsible for the present results. The mean GE data for Study 2 suggest that the 7mm tablets empty more rapidly than the 5mm and 6mm, although the differences are not significant. Interestingly, the variability (expressed as s.e.m.) in the data increases as the size

is increased (eg. compare the s.e.m. for the St50% values, 16 for the 5mm, 23 for the 6mm and 35 for the 7mm). This would be expected since the pattern of emptying should become more unpredictable as the size approaches a critical value. It is possible that larger tablets are initially more prone to being trapped, which increases their chance of fortuitous emptying. As the number of tablets in the stomach begins to decrease, the incidence of trapping also decreases, and the tablets are retained largely due to their diameter. Smaller tablets will behave like digestible solids and exhibit a similar pattern of emptying. These results suggest that there is a gradation of sizes which will empty from the fed stomach, rather than a precise cut-off value. Gastric emptying becomes less predictable as tablet diameter increases, and this may reach a plateau at larger sizes. Smith and Feldman (415) noticed no signficant difference between the gastric emptying of 2mm and 10mm radio-opaque markers in fed human subjects. This suggests the critical size of indigestible solids that can empty from the fed human stomach is markedly greater than 2mm. More importantly, their results and the results of the present study, suggest the gastric emptying of indigestible solids does not rely entirely on the phase 3 contractions of the MMC. In contrast, Jonsson et al (416) concluded that size was of importance in the gastric emptying of tablets when taken with food. Two tablets each, of 3mm

and 14mm diameter were administered to eight subjects. The 14mm diameter tablets were retained in the stomach for a significantly longer time (median time >780min) than the 3mm tablets (median time 480min). It is probable that 14mm is larger than the critical diameter, hence the longer duration of gastric residence.

The original rationale for conducting these studies was to determine the size of tablet that would not empty from the fed stomach, and to use this information in the design of CR dosage forms. However, these results bring fresh doubts as to the suitability of using the size of dosage forms as a control on gastric emptying. Furthermore, the obvious practical problems in administering a multiple unit system, consisting of tablets greater than 7mm, would have to be realised. Thus, this method of controlling the gastric residence of oral dosage forms becomes less of a pharmaceutical reality. A further study using tablets larger than 7mm would be of value more for its physiological interest than for its pharmaceutical relevance.

5.3.3.2 The effect of food

The important effect of food on gastric emptying is well illustrated by the St50% data for both studies. The greater the energy content of the meal, the longer the duration of emptying. The mean gastric emptying curves for the tablets are presented in Figures 5.3, 5.4, 5.9.

A careful examination of the curves indicates the nature of the breakfast has a greater influence on emptying than the size of tablet. The tablets (3mm, 4mm, 5mm) taken after the light breakfast empty rapidly, those taken after the heavy breakfast (3mm 4mm, 5mm) empty slowly, and those taken after the medium breakfast (5mm, 6mm,7mm) have an emptying rate between the two. The duration of gastric emptying can be arranged in a similar order. Smith and Feldman (415) also concluded that food had a greater influence on the gastric emptying of indigestible solids than did particle size. The effect of food on the gastric residence of dosage forms has been well illustrated. The mean gastric emptying of a controlled release naproxen tablet (17mmx4mm) was markedly increased if administered after a breakfast (417). Food had a similar effect on 11mm floating and non-floating tablets (418). Food was also the major determinant of the gastric emptying of both light and heavy pellets (0.7-1.0mm), rather than the density of the pellets (328). The mean gastric residence time of an Heidelberg capsule was increased by administering the capsule after a meal, and then prolonged by frequent feeding (183).

The colon entry curves mirror the GE curves, ie. the light breakfast tablets enter the colon before the medium breakfast tablets, which in turn enter the colon before the heavy breakfast tablets. Thus, entry into the colon is determined by the time for gastric emptying, and not

by the time for SI transit. This result reinforces the observation of the consistent nature of SI transit, which is affected neither by the energy content of food (71) nor the dosage form (304).

5.3.3.3 Transit across the ileocaecal sphincter

As mentioned above, the tablets generally regrouped at the ICS, before entering the colon, illustrated by Figures 5.6, 5.7 and 5.10. This stagnation is probably related to the proposed reservoir function of the ICS (99), and has been previously observed for both multiple unit (410) and single unit (419) CR systems. However, no obvious pattern could be found between tablet size and transit across the ICS. Tablets were sometimes seen grouped in the ICS region immediately prior to lunch, but had not always entered the colon after lunch. Thus, the gastroileal reflex noted by some workers (95), is not a generic event. Spiller et al (100) also concluded that the gastroileal reflex is of minor importance to ileocaecal transit. In some cases, entry into the colon was in the form of a bolus (Figure 5.1), but no obvious pattern emerged relating tablet size to bolus entry. Kruis et al (101) suggest that 30-50% of ileocolonic transit is as a bolus, but the remainder occurs as a steady trickle. Bowel movement was considered a likely factor of importance, and this was selected for evaluation in Study 2. The times at which the subjects

defaecated, over the duration of the study, was recorded. However, there was no observable connection between entry into the colon and bowel movements.

The shape of colon entry curves and Ct50% values are considered useful parameters for measuring ICS transit (99). A comparison of the Ct50% values for the tablets, for each type of breakfast, shows no significant difference between the values ($p>0.1$). Further comparison of the data suggests an apparent difference due to the breakfast consumed. This difference in Ct50% values probably reflects the difference in St50% values due to the the breakfast consumed, rather than an affect on ileocaecal transit. However, a detailed examination of the colon entry curves (Figures 5.3, 5.4 and 5.9) shows the light breakfast yields steeper entry curves than the medium and heavy breakfasts. A similar examination of the curves for individual subjects (Figures 5.1, 5.2, and 5.8) also shows a rapid entry after the light breakfast. These steep curves reflect bolus entry of material into the colon, after remaining immobile in the terminal ileum (99). The longer plateau, seen with the medium and heavy breakfast curves, is indicative of episodic colonic inflow. This difference in the rates of entry, may relate to the solid content of the meal, since high residue meals have a slower rate of colonic filling than low residue meals (99). The light breakfast has a relatively larger volume of fluid than

the other two meals, and could be considered a lower residue meal. Another explanation, is that the contractions of the MMC would begin relatively early after the light breakfast, propelling the tablets into the colon. However, the literature suggests that MMC contractions, unlike in dogs, do not have a major role in ileocaecal transit (89). Further studies are required, perhaps taking greater consideration of bowel habits and diet, before a complete
understanding of ileocaecal transit can emerge.

5.4 Conclusions

The following conclusions can be drawn from the results of this investigation:

i. Tablets, upto 7mm in diameter, can empty from the fed stomach, in an apparently linear fashion. There is an increase in variability of emptying as tablet size increases, but no significant difference in gastric emptying due to the size of the tablets.

ii. The energy content of the breakfast consumed, has a marked effect on the rate of gastric emptying of the tablets.

iii. Tablet size does not influence small intestine transit, and colon entry.

iv. The solid content of the meal consumed may have an influence on ileocaecal transit.

Table 5.2a Mean (s.e.m) gastric emptying for the light breakfast group - %activity remaining in the stomach.

Tablet size	3mm	4mm	5mm
Time (min)			
0	100	100	100
15	95(4)	90(10)	100
30	95(4)	83(10)	86(8)
45	90(4)	74(10)	77(8)
60	84(13)	59(18)	65(6)
75	80(13)	39(18)	54(6)
90	78(11)	27(16)	32(9)
105	66(11)	12(4)	15(4)
120	40(11)	8(4)	5(4)
160	13(8)	0	0
190	10(8)	0	0
220	1	0	0
250	0	0	0

Table 5.2b Mean (s.e.m.) colon entry for the light breakfast group - % activity remaining in the colon.

Tablet size	3mm	4mm	5mm
Time (min)			
105	0	0	0
120	0	1	0
160	0	21(17)	0
190	0	30(17)	0
220	17(13)	31(25)	8(7)
250	36(13)	49(25)	29(15)
290	77(2)	84(8)	72(17)
320	90(2)	94(8)	83(17)
350	93(5)	98(1)	86(11)
390	98(2)	100	93(5)
435	100	100	100

Table 5.3a Mean (s.e.m) gastric emptying for the heavy breakfast group - %activity remaining in the stomach.

Tablet size	3mm	4mm	5mm
Time (min)			
0	100	100	100
15	100	87(5)	100
30	100	79(5)	96(2)
45	100	78(5)	96(2)
60	95(4)	74(15)	93(3)
75	95(4)	72(15)	90(3)
90	95(4)	71(15)	88(3)
105	85(4)	70(15)	85(3)
120	69(8)	47(20)	75(6)
160	58(8)	38(20)	54(6)
190	53(8)	35(15)	53(2)
220	43(8)	25(15)	49(2)
250	31(9)	20(16)	38(7)
290	15(9)	13(16)	24(7)
320	9(5)	9(6)	20(7)
350	6(2)	8(6)	16(7)
390	5	8(6)	16(7)
435	5	8(6)	16(7)
510	5	8(6)	11(5)
570	5	3	8(5)
640	0	0	0

Table 5.3b Mean (s.e.m.) colon entry for the heavy breakfast group - %activity remaining in the colon.

Tablet size	3mm	4mm	5mm
Time (min)			
160	0	0	0
190	0	3	0
220	0	4	8
250	7(5)	4	10(8)
290	10(5)	38(9)	24(8)
320	29(5)	60(10)	36(16)
350	41(20)	69(10)	59(13)
390	49(20)	74(10)	67(13)
435	63(20)	82(10)	84(7)
510	88(9)	86(11)	84(7)
570	88(9)	86(11)	84(7)
640	88(9)	86(11)	84(7)

Table 5.4 Lag time and Gastric emptying (St50%) values for the light and heavy breakfast studies.

		3mm		4mm		5mm	
	Subject	Lag (min)	St50%	Lag (min)	St50%	Lag (min)	St50%
LIGHT	1	15	85	5	95	15	70
	2	90	113	5	35	30	73
	3	60	143	30	67	20	83
	mean	52	114	13	66	22	75
	s.e.m.	20	14	7	14	4	3
HEAVY	4	45	250	5	23	45	235
	5	105	207	35	275	105	243
	6	90	123	75	167	15	157
	mean	80	193	38	155	55	212
	s.e.m.	15	30	17	60	22	22

Table 5.5 Small intestine transit (SIT) data for the light and heavy breakfast studies

	Subject	3mm SIT (min)	4mm SIT (min)	5mm SIT (min)
LIGHT	1	175	178	252
	2	164	118	167
	3	77	188	242
	mean	139	161	220
	s.e.m.	25	18	22
HEAVY	4	205	300	158
	5	183	100	102
	6	197	110	136
	mean	195	170	132
	s.e.m.	5	53	13

Table 5.6 Colon entry (Ct50%) and MCt values for the light and heavy breakfast studies.

		3mm		4mm		5mm	
	Subject	Ct50% (min)	MCt	Ct50% (min)	MCt	Ct50% (min)	MCt
LIGHT	1	260	330	273	315	267	300
	2	277	360	153	255	240	285
	3	220	495	255	360	325	420
	mean	252	395	227	310	277	335
	s.e.m.	14	41	31	25	20	35
HEAVY	4	455	555	323	450	393	>640
	5	390	>580	375	>640	345	>640
	6	320	420	277	390	293	360
	mean	388	-	325	-	344	-
	s.e.m.	32	-	23	-	24	-

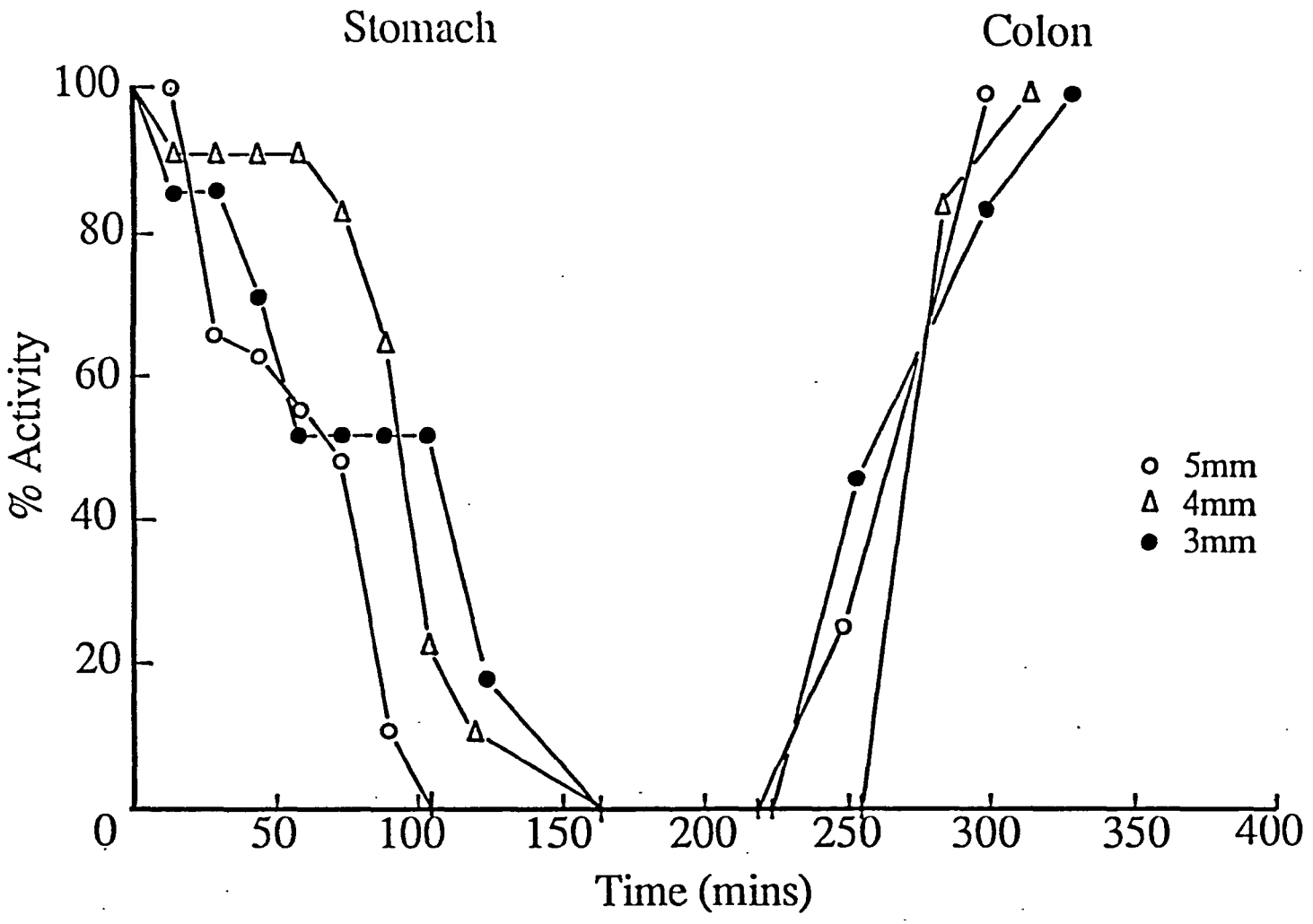


Figure 5.1 Gastric Emptying and Colon Entry of Tablets - Subject 5, Light Breakfast

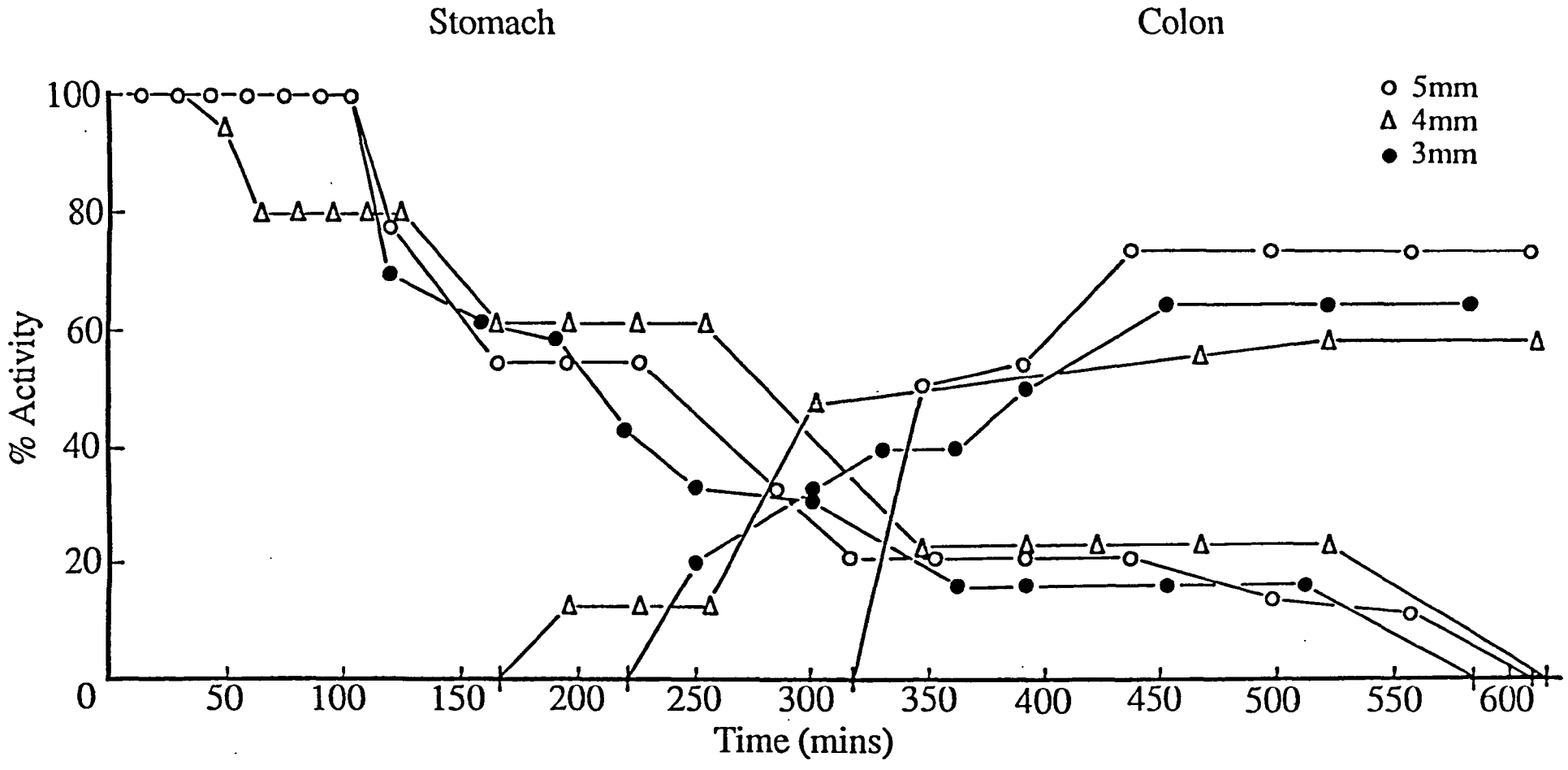


Figure 5.2 Gastric Emptying and Colon Entry of Tablets - Subject 4, Heavy Breakfast

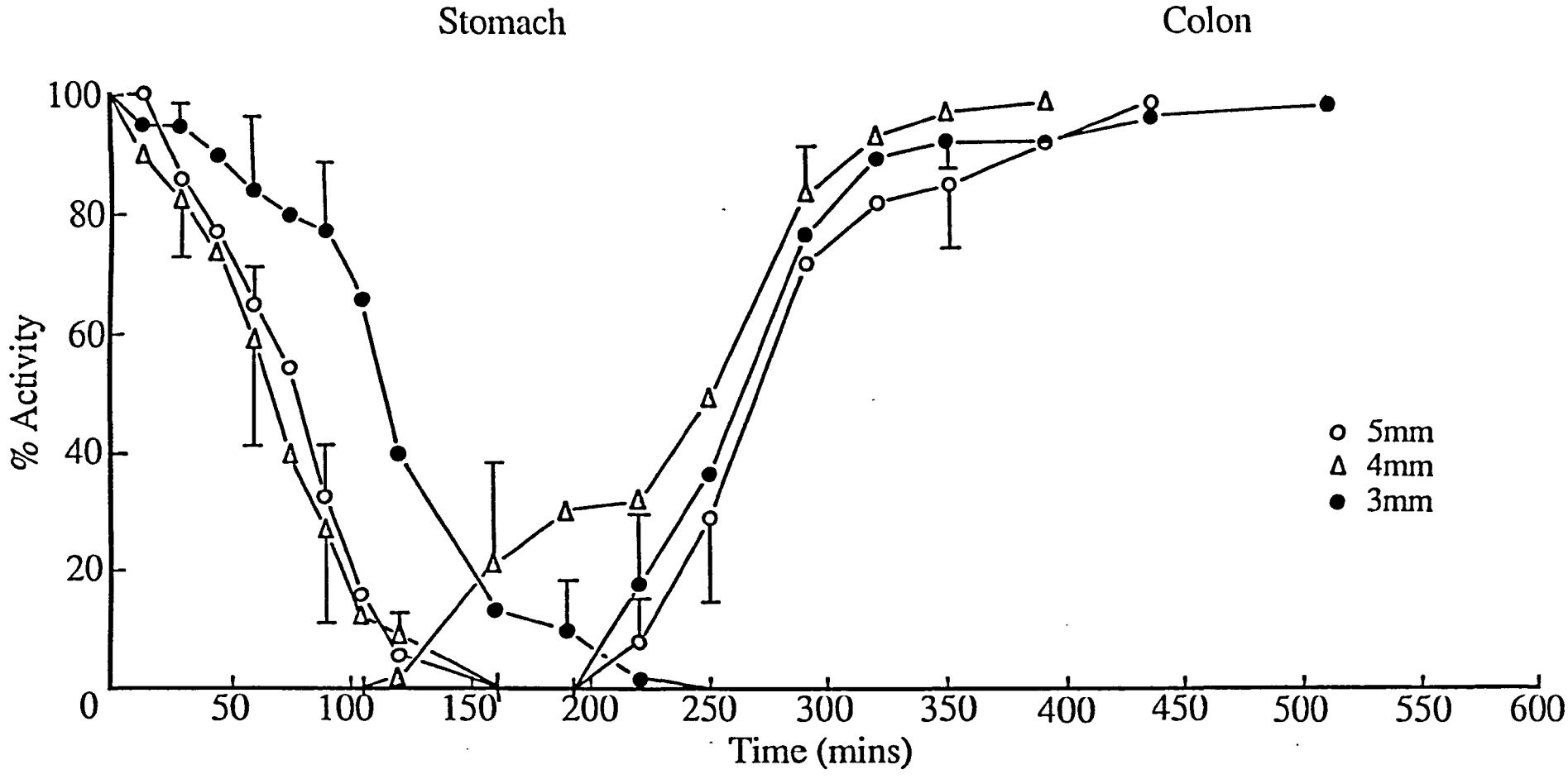


Figure 5.3 Mean Gastric Emptying and Colon Entry of Tablets - Light Breakfast

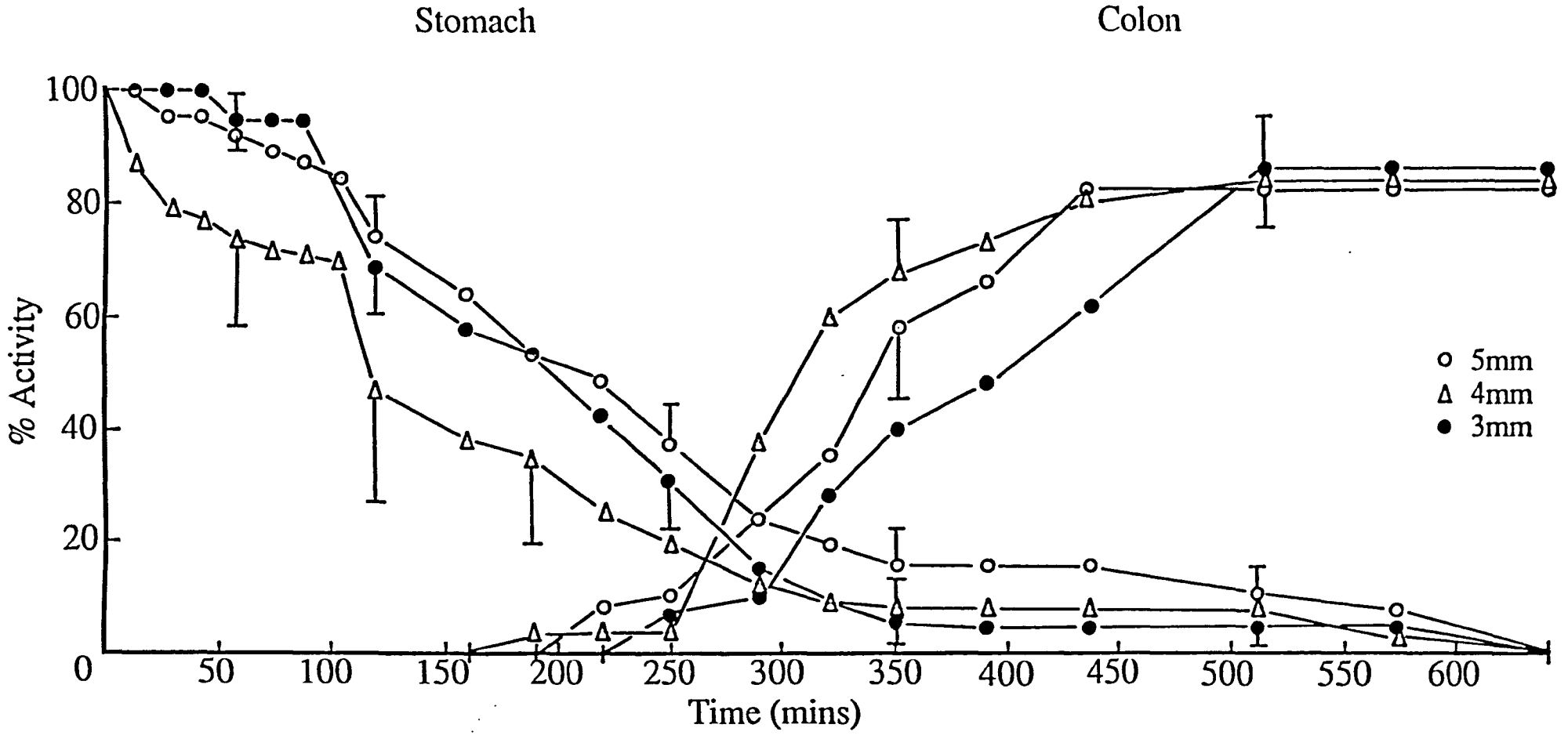


Figure 5.4 Mean Gastric Emptying and Colon Entry of Tablets - Heavy Breakfast

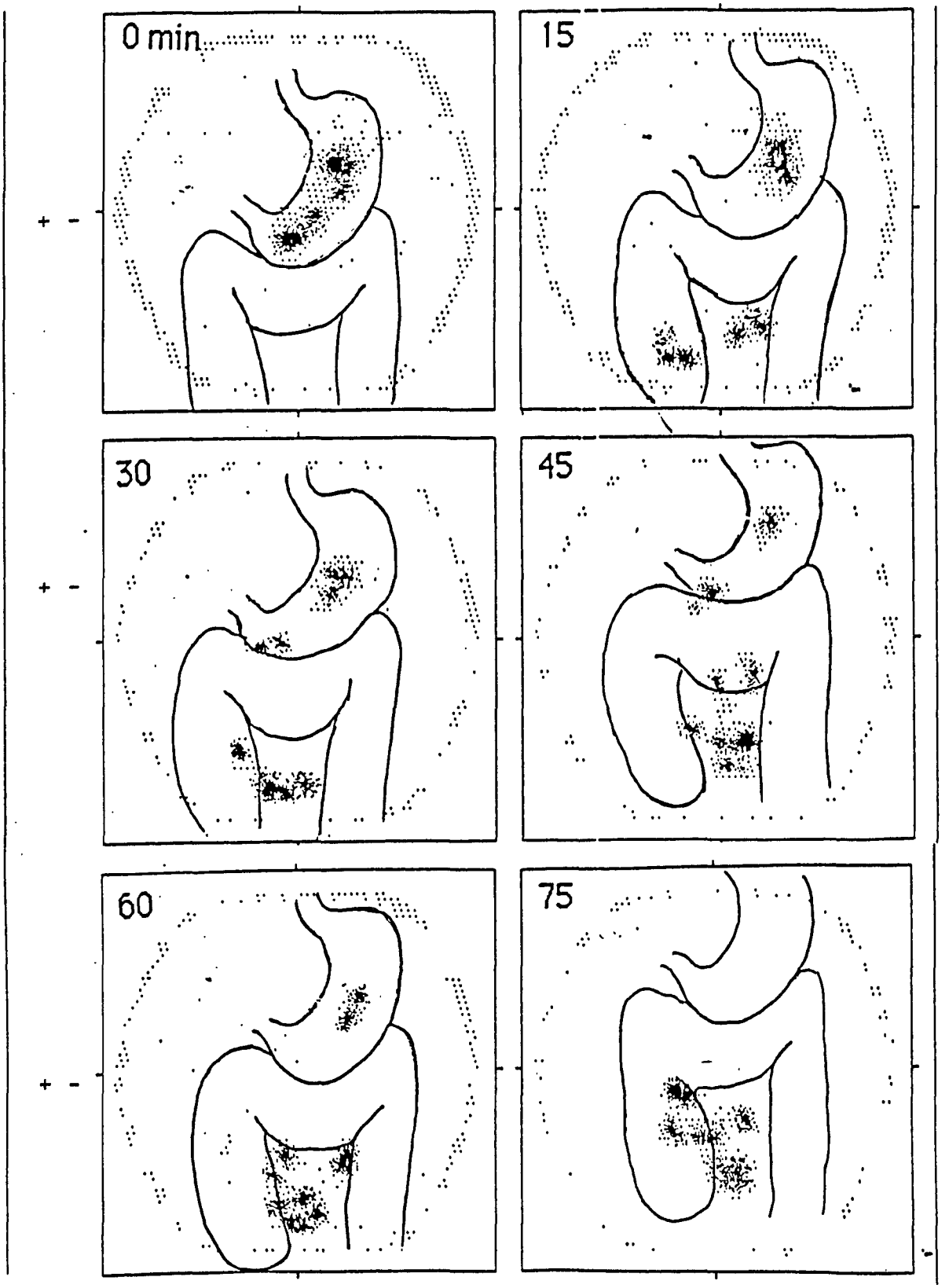


Figure 5.5a Gastrointestinal Transit of 4mm Tablets - Subject 3, Light Breakfast.

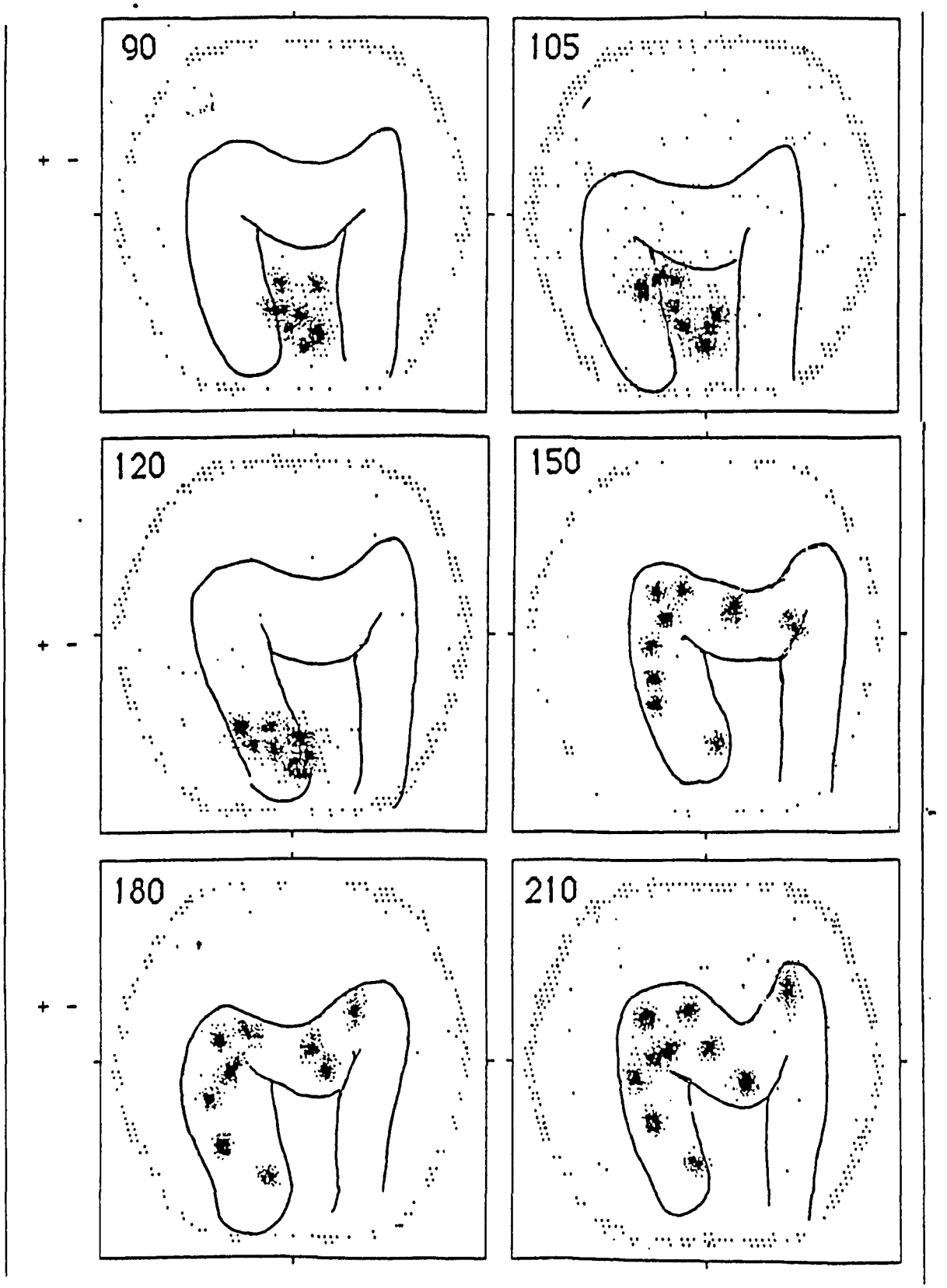


Figure 5.5b Gastrointestinal Transit of 4mm Tablets - Subject 3, Light Breakfast.

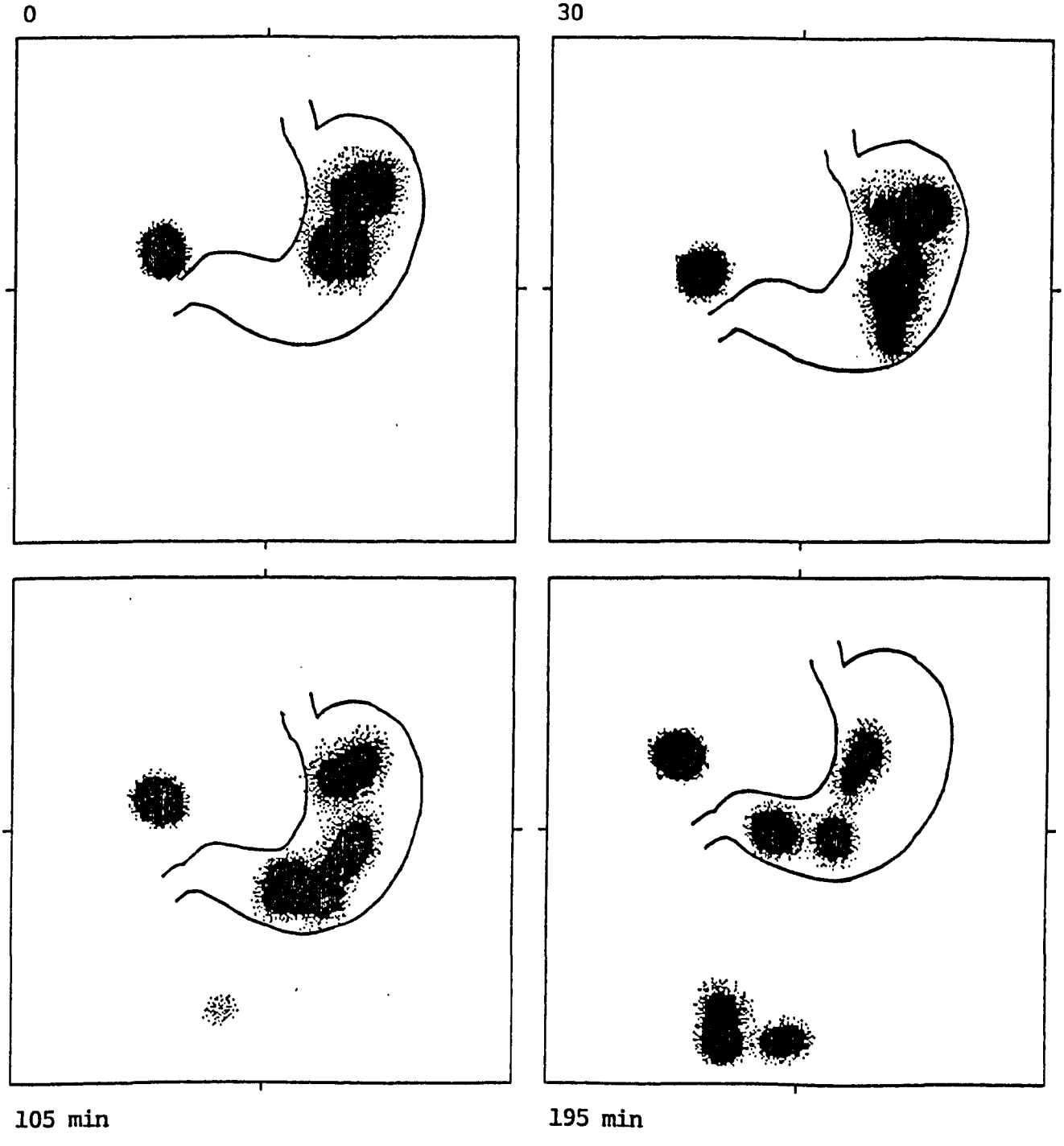


Figure 5.5c Gastric Emptying of 4mm Tablets - Subject 6, Heavy Breakfast.

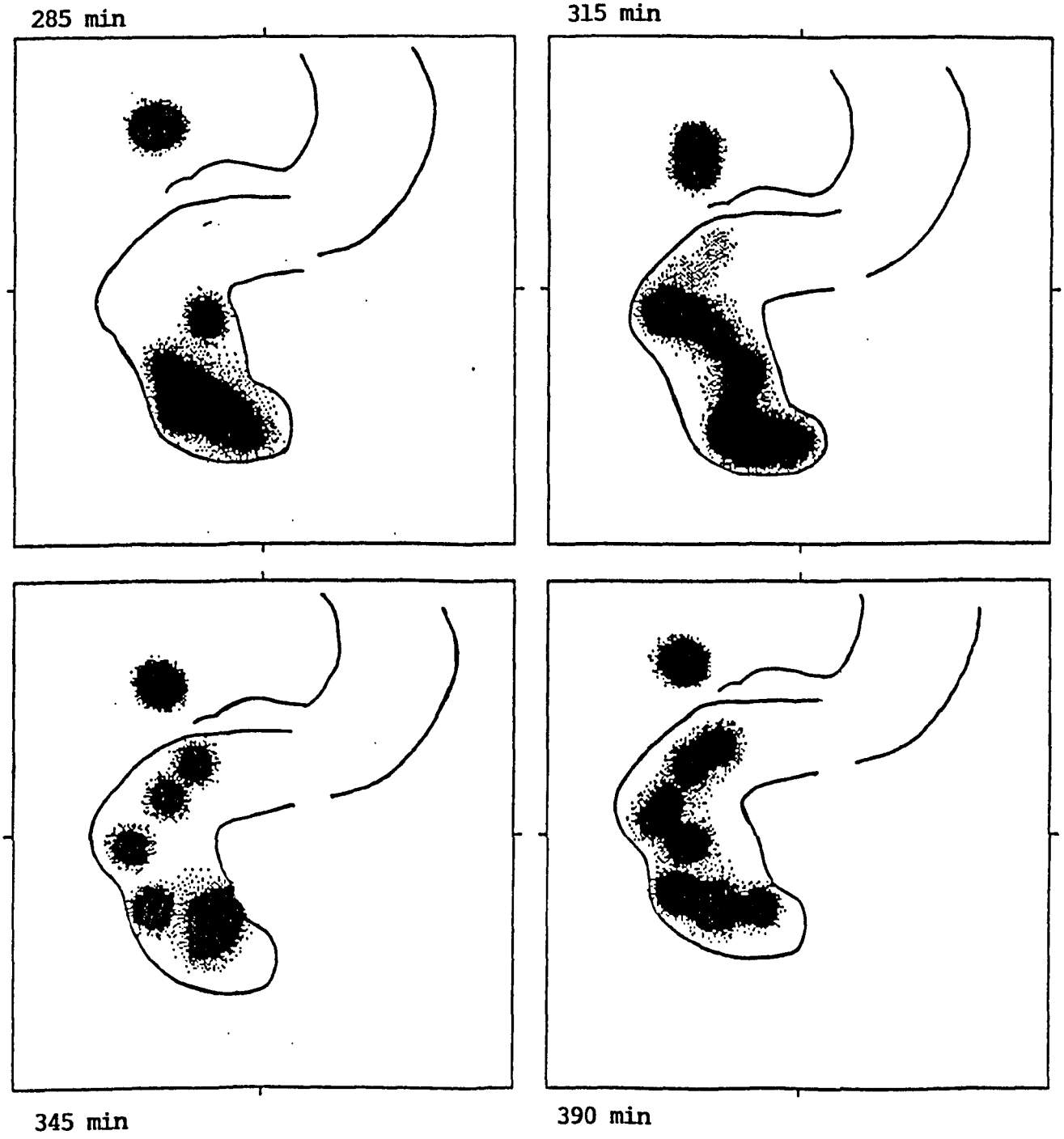


Figure 5.5d Colon Entry of 4mm Tablets - Subject 6, Heavy Breakfast.

Figure 5.6

Histogram plots showing the distribution of tablets in different regions of the gastrointestinal tract after a light breakfast.

KEY

s	-	stomach
si	-	small intestine
icj	-	ileocaecal sphincter
ac	-	ascending colon
tc	-	transverse colon
dc	-	descending colon
sc	-	sigmoid colon

GASTROINTESTINAL TRANSIT OF 10 SMALL TABLETS

SUBJECT 3, LIGHT BREAKFAST, 3 mm tablets

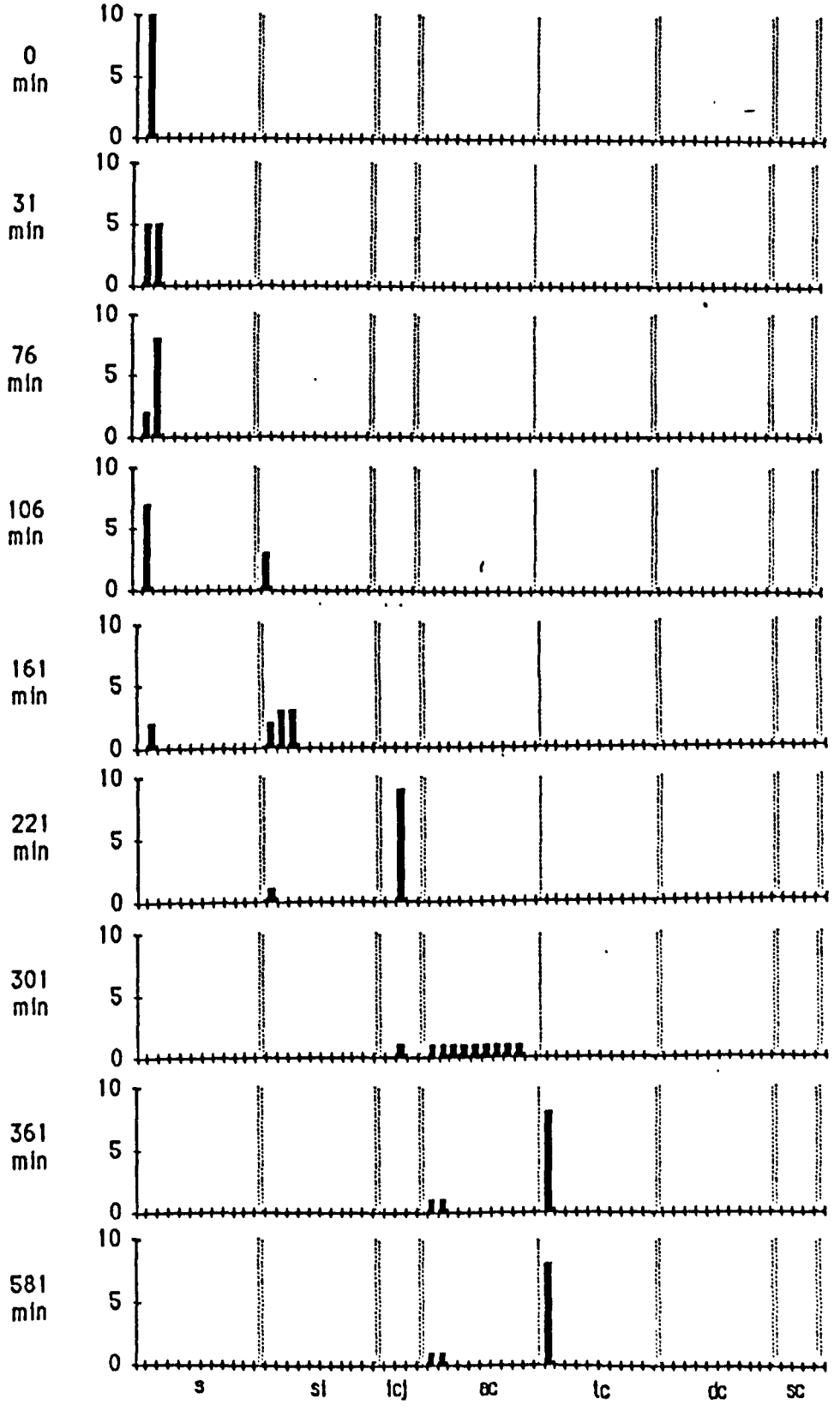


Figure 5.6a

GASTROINTESTINAL TRANSIT OF 10 SMALL TABLETS

SUBJECT 3, LIGHT BREAKFAST, 4 mm tablets

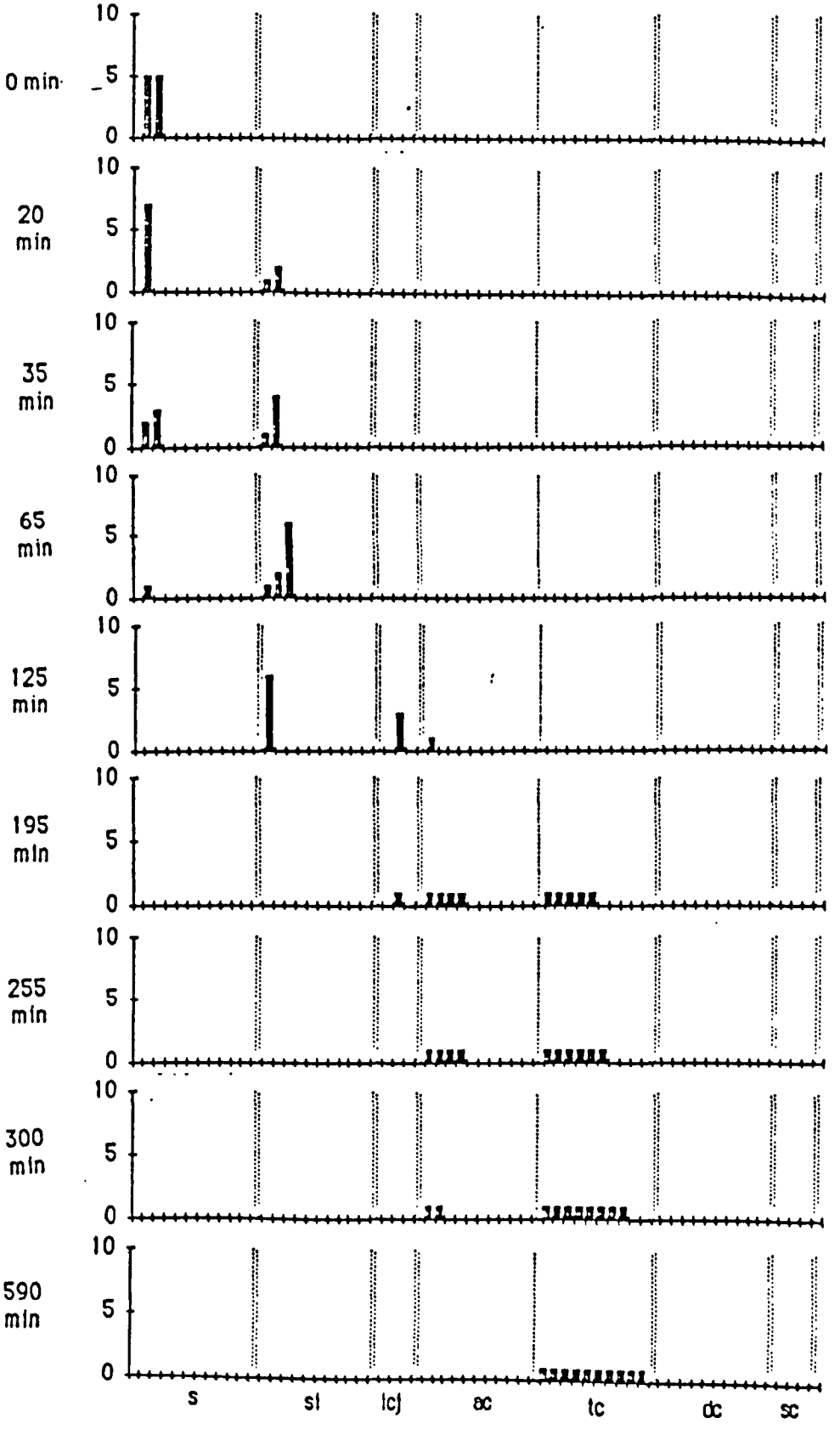


Figure 5.6b

GASTROINTESTINAL TRANSIT OF 10 SMALL TABLETS

SUBJECT 3, LIGHT BREAKFAST, 5 mm tablets

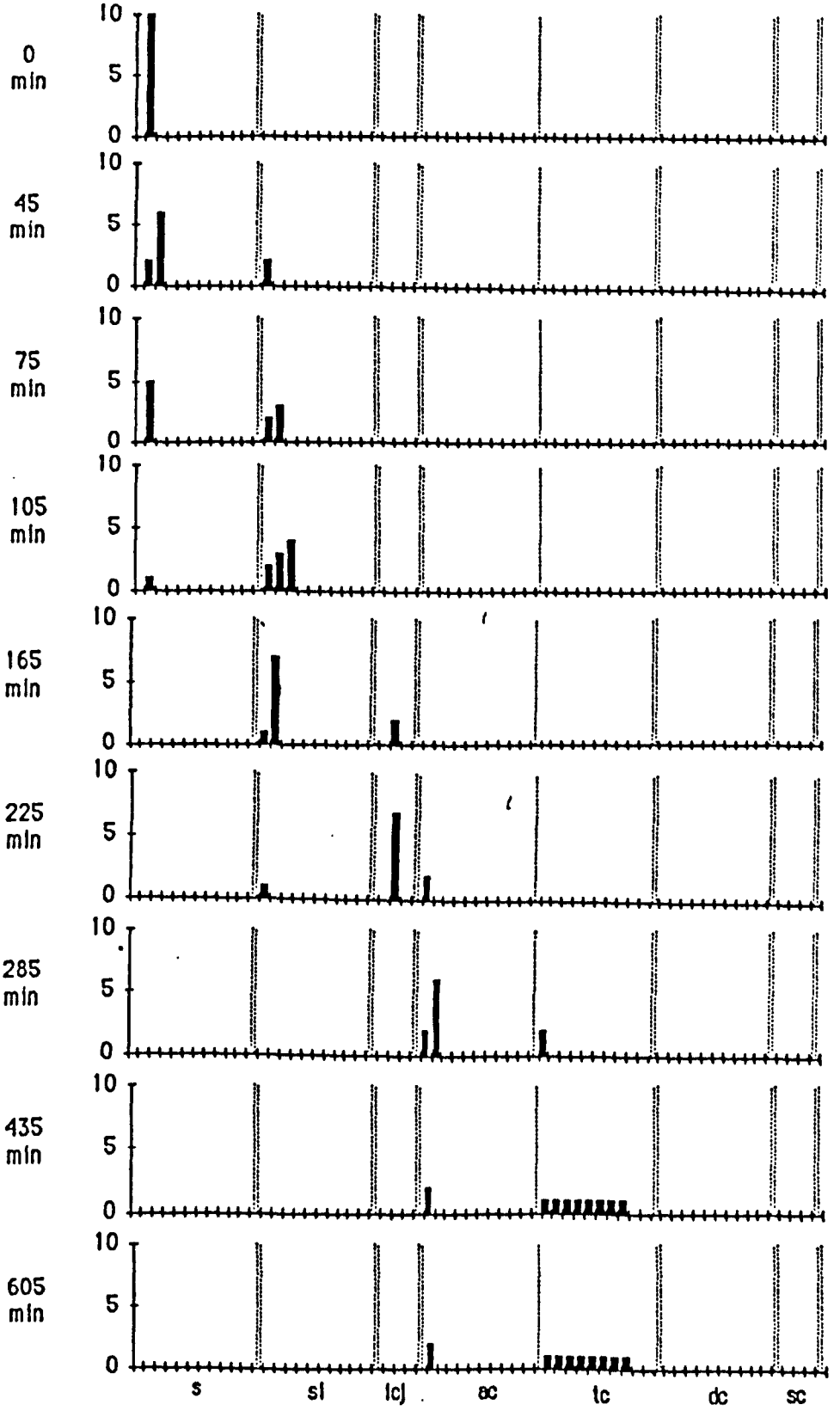


Figure 5.6c

Figure 5.7

Histogram plots showing the distribution of tablets in different regions of the gastrointestinal tract after a heavy breakfast.

KEY

s	-	stomach
si	-	small intestine
icj	-	ileocaecal sphincter
ac	-	ascending colon
tc	-	transverse colon
dc	-	descending colon
sc	-	sigmoid colon

GASTROINTESTINAL TRANSIT OF 10 SMALL TABLETS

SUBJECT 6, HEAVY BREAKFAST, 3 mm tablets

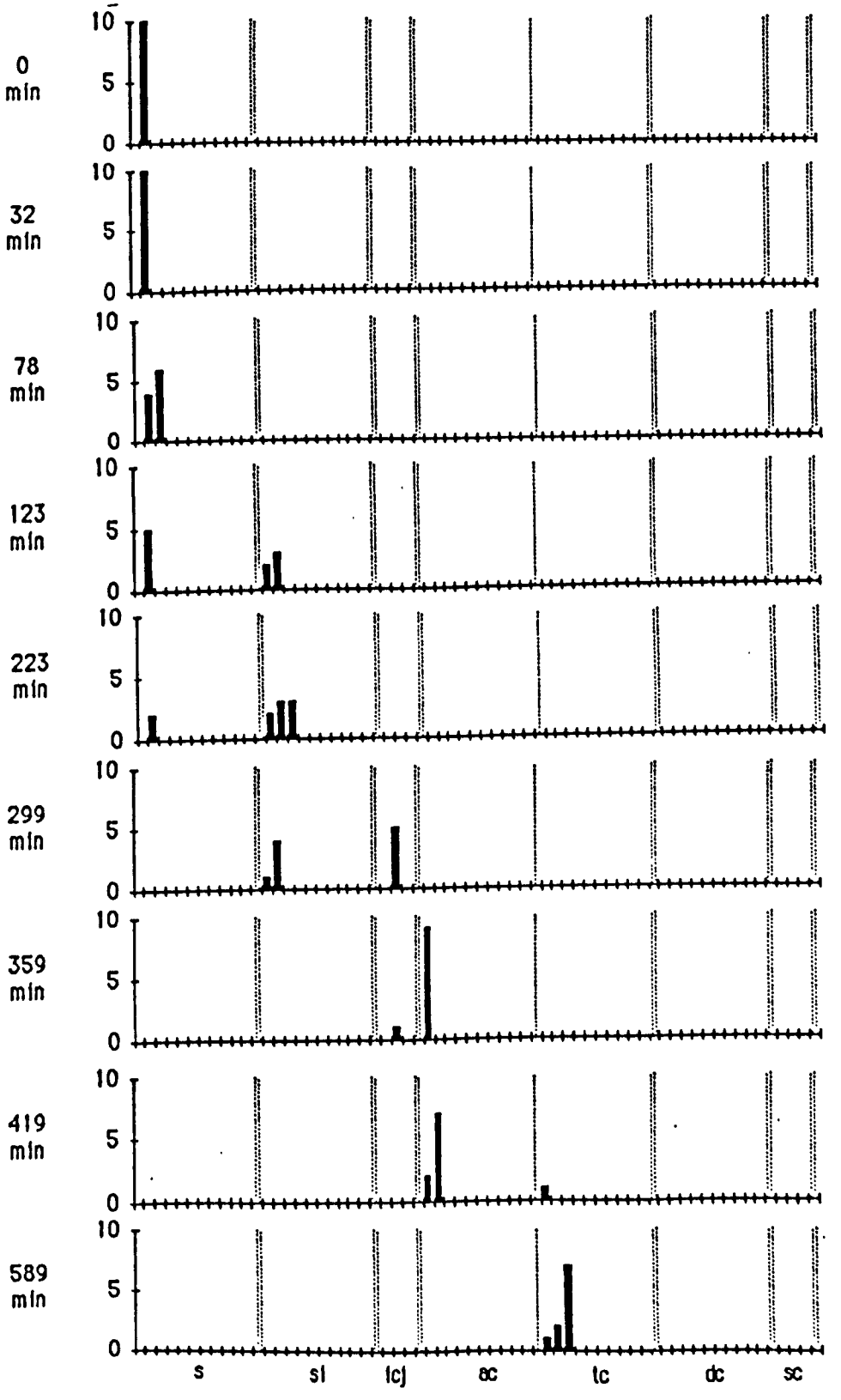


Figure 5.7a

SUBJECT 6, HEAVY BREAKFAST, 4 mm tablets

GASTROINTESTINAL TRANSIT OF 10 SMALL TABLETS

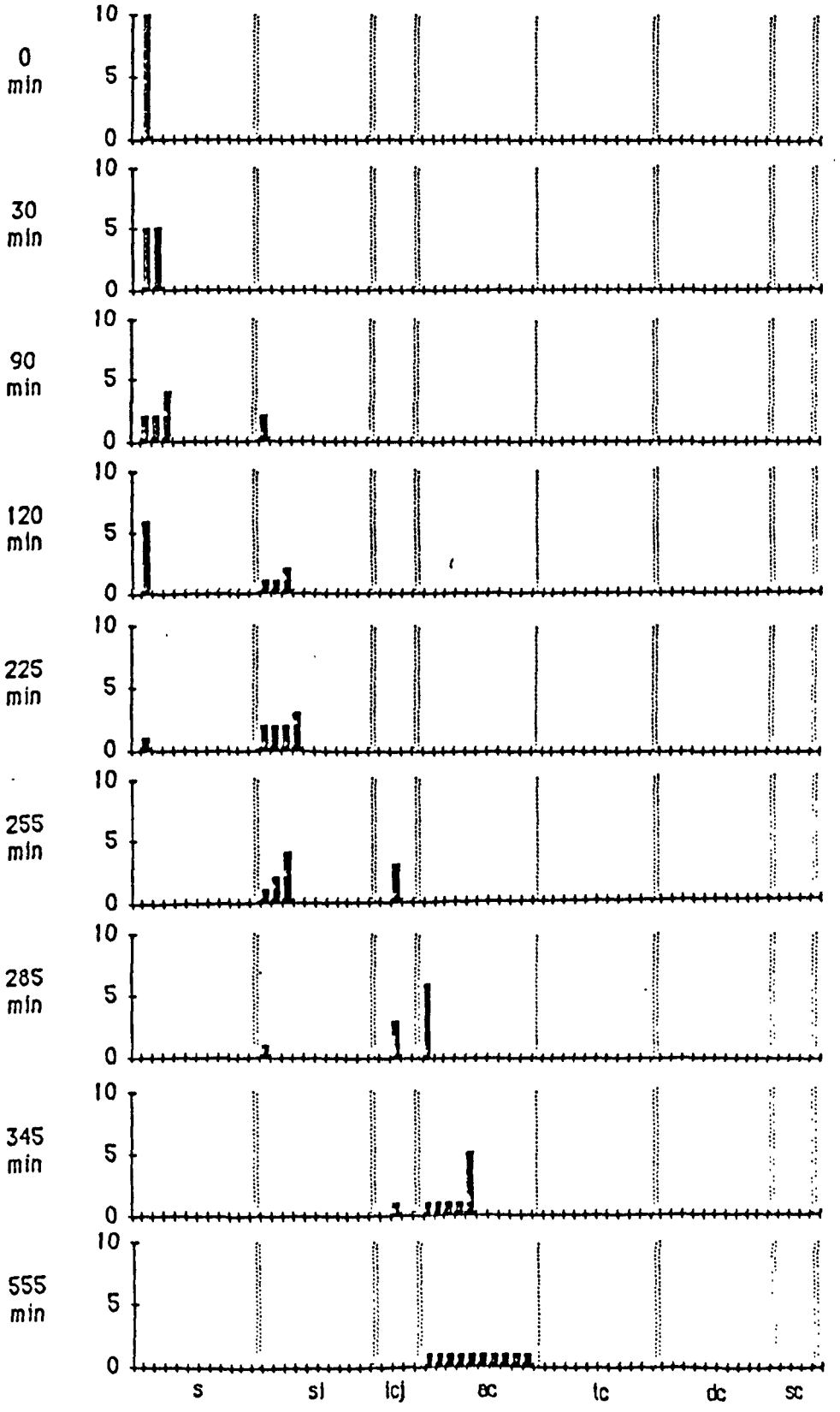


Figure 5.7b

GASTROINTESTINAL TRANSIT OF 10 SMALL TABLETS

SUBJECT 6, HEAVY BREAKFAST, 5 mm tablets

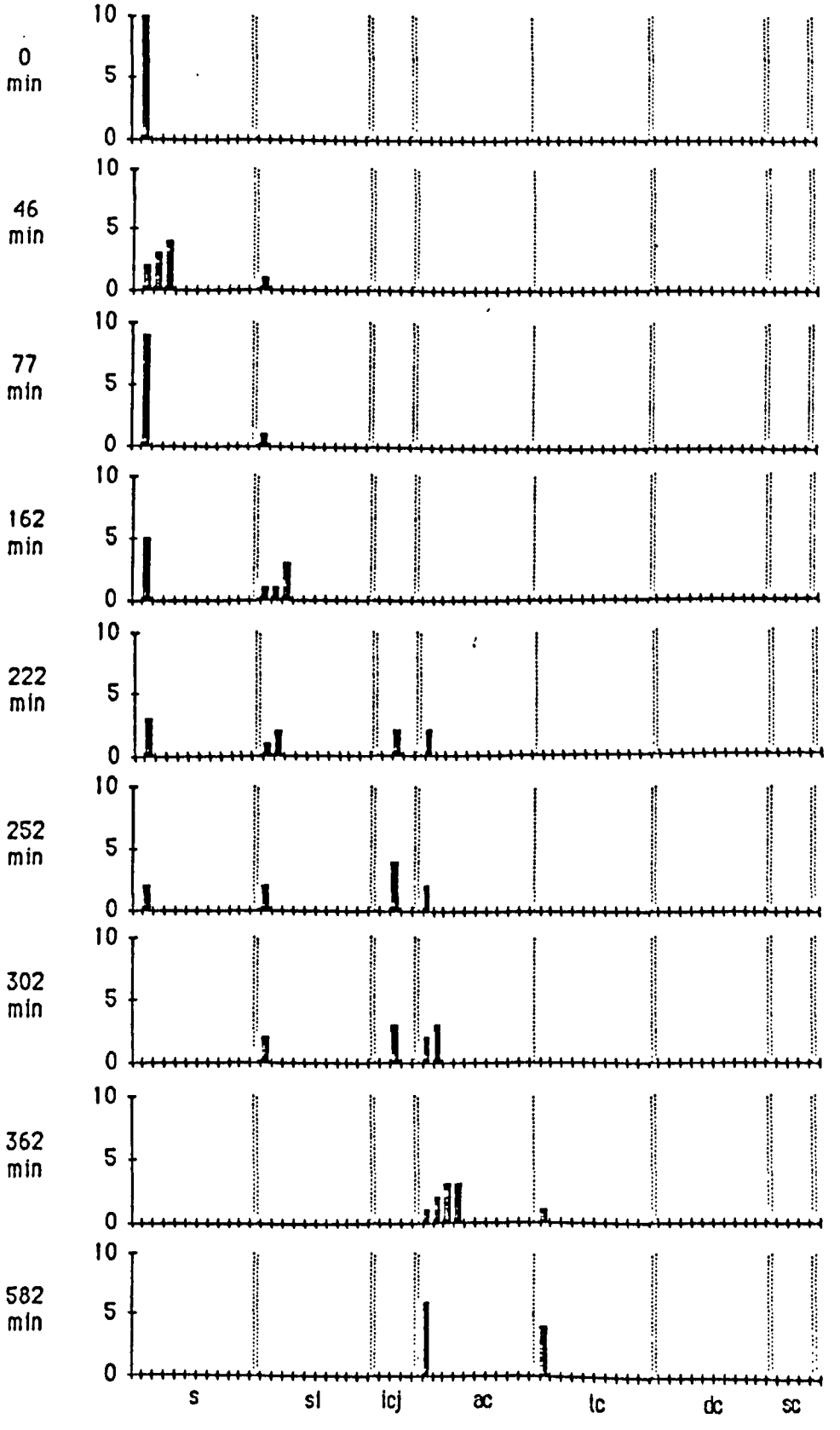


Figure 5.7c

Table 5.7a Mean (s.e.m) gastric emptying for the medium breakfast group - %activity remaining in the stomach.

Tablet size	5mm	6mm	7mm
Time (min)			
0	100	100	100
20	95(3)	98(2)	95(3)
35	94(3)	91(6)	80(9)
50	87(3)	91(6)	66(11)
65	85(4)	87(6)	60(13)
80	82(5)	86(5)	54(15)
95	77(8)	78(8)	52(16)
110	77(8)	69(11)	46(16)
125	73(7)	69(11)	41(17)
155	48(6)	58(12)	32(17)
185	24(7)	38(11)	28(15)
215	11(8)	24(12)	21(11)
245	7(6)	12(7)	17(10)
290	7(6)	9(5)	9(6)
320	7(6)	9(5)	9(6)
350	7(6)	7(4)	9(6)
380	5(5)	3(2)	6(5)
410	5(5)	3(2)	6(5)
455	5(5)	3(2)	6(5)
500	3(2)	3(2)	6(5)
545	0	1	6(5)
605	0	0	6(5)
665	0	0	6(5)
725	0	0	6(5)

Table 5.7b Mean (s.e.m.) colon entry for the medium breakfast group - %activity remaining in the colon.

Tablet size	5mm	6mm	7mm
Time (min)			
95	0	0	0
110	0	0	9(8)
125	0	0	9(8)
155	2(2)	0	17(14)
185	5(5)	0	20(14)
215	6(5)	6(5)	25(14)
245	9(5)	25(9)	38(18)
290	34(12)	34(13)	56(14)
320	50(13)	46(12)	65(16)
350	65(12)	65(16)	68(15)
380	72(13)	66(16)	75(14)
410	72(13)	70(15)	80(13)
455	92(4)	79(11)	80(13)
500	93(3)	79(11)	89(6)
545	93(3)	89(6)	89(6)
605	100	97(2)	95(5)
665	100	97(2)	95(5)
725	100	98(2)	95(5)

Table 5.8 Lag time and Gastric emptying (St50%) values for the medium breakfast study.

	5mm		6mm		7mm	
	Lag (min)	St50%	Lag (min)	St50%	Lag (min)	St50%
Subject						
1	10	90	65	105	20	53
2	35	143	125	225	95	213
3	35	147	10	88	10	123
4	10	157	20	237	10	33
5	20	225	50	140	125	265
6	125	165	155	178	35	60
mean	39	155	71	162	49	125
s.e.m.	16	16	22	23	18	35

Table 5.9 Small intestine transit (SIT) values for the medium breakfast study.

Subject	5mm SIT (min)	6mm SIT (min)	7mm SIT (min)
1	190	153	247
2	292	292	272
3	300	155	104
4	113	206	77
5	60	115	128
6	145	135	200
mean	183	176	171
s.e.m.	36	24	30

Table 5.10 Colon entry (Ct50%) and MCt values for the medium breakfast study.

	5mm		6mm		7mm	
Subject	Ct50% (min)	MCt	Ct50% (min)	MCt	Ct50% (min)	MCt
1	280	605	258	410	300	410
2	435	605	517	725	485	605
3	335	380	243	380	227	243
4	270	455	443	>725	110	150
5	285	605	255	605	393	>725
6	310	380	313	350	260	320
mean	319	505	338	-	296	-
s.e.m.	23	42	43	-	49	-

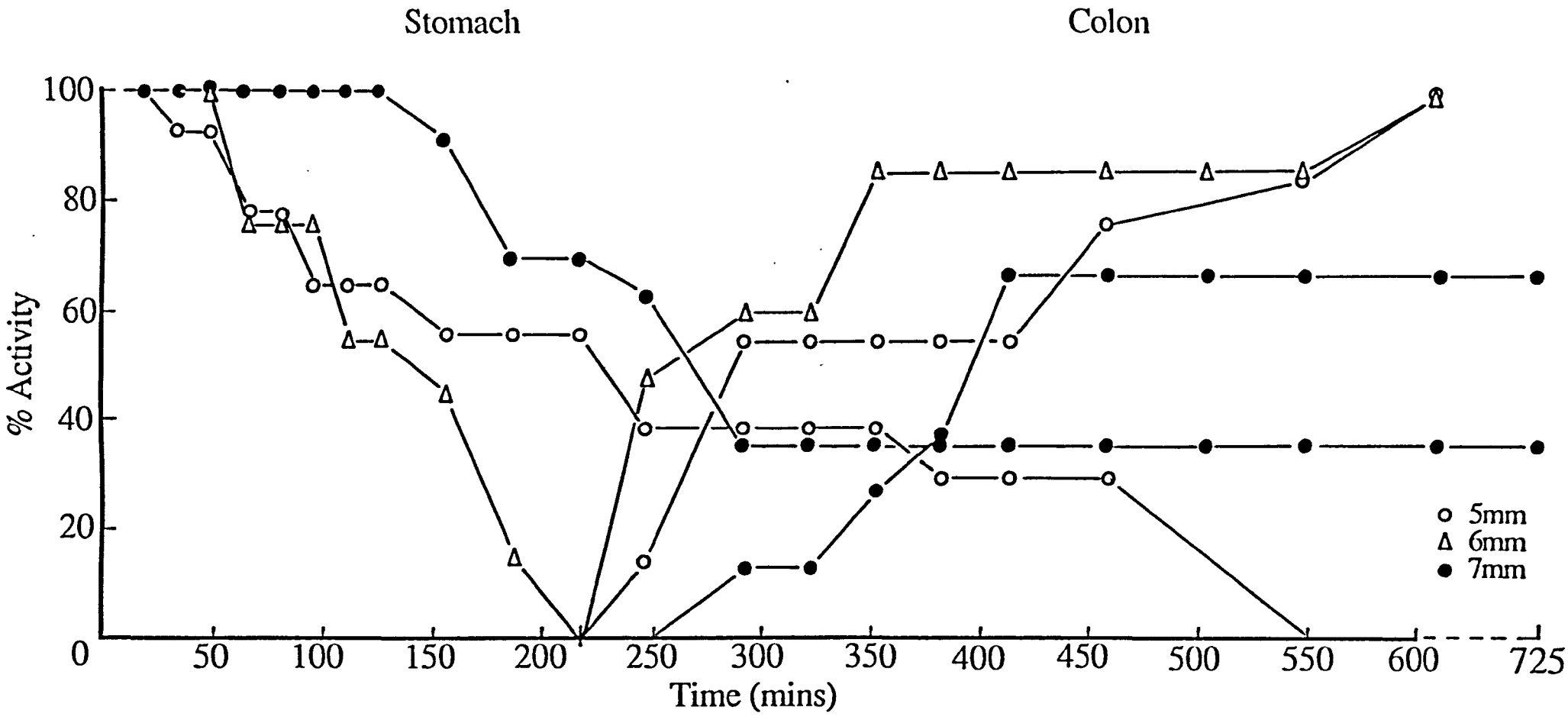


Figure 5.8 Gastric Emptying and Colon Entry of Tablets - Subject 5

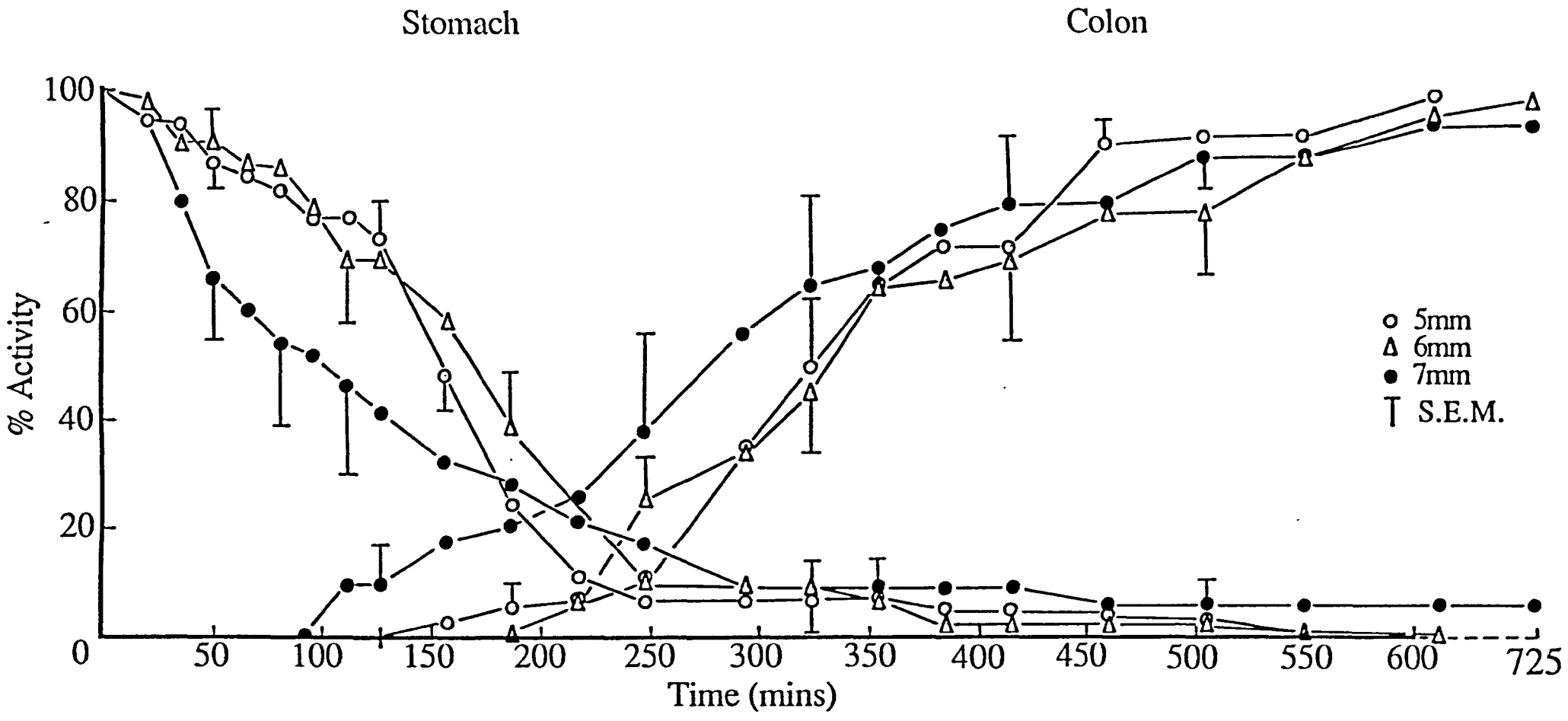


Figure 5.9 Mean Gastric Emptying and Colon Entry of Tablets

Figure 5.10

Histogram plots showing the distribution of tablets in different regions of the gastrointestinal tract after a medium breakfast.

KEY

s	-	stomach
si	-	small intestine
icj	-	ileocaecal sphincter
ac	-	ascending colon
tc	-	transverse colon
dc	-	descending colon
sc	-	sigmoid colon

GASTROINTESTINAL TRANSIT OF 10 SMALL TABLETS

SUBJECT 2, MEDIUM BREAKFAST, 5 mm TABLETS

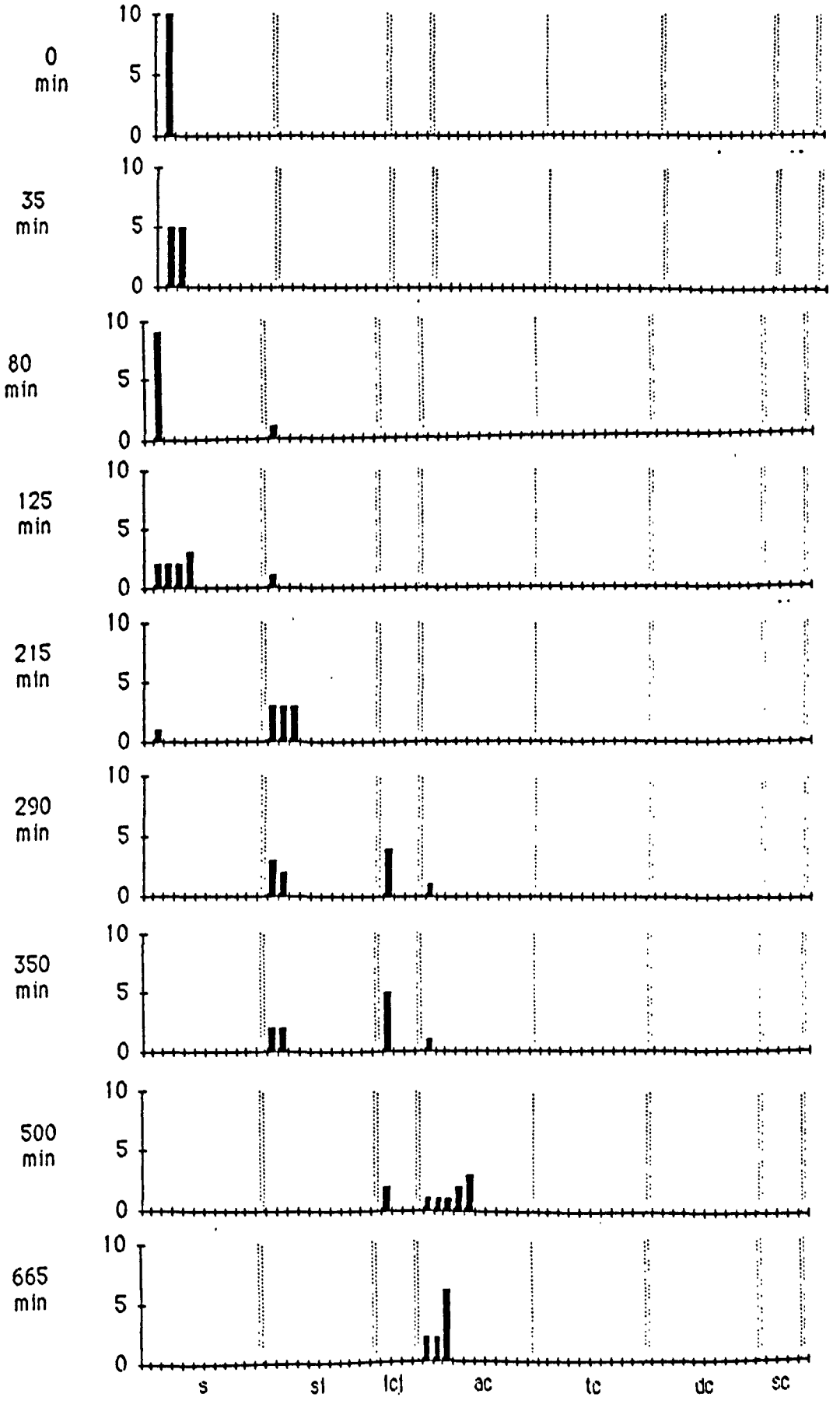


Figure 5.10a

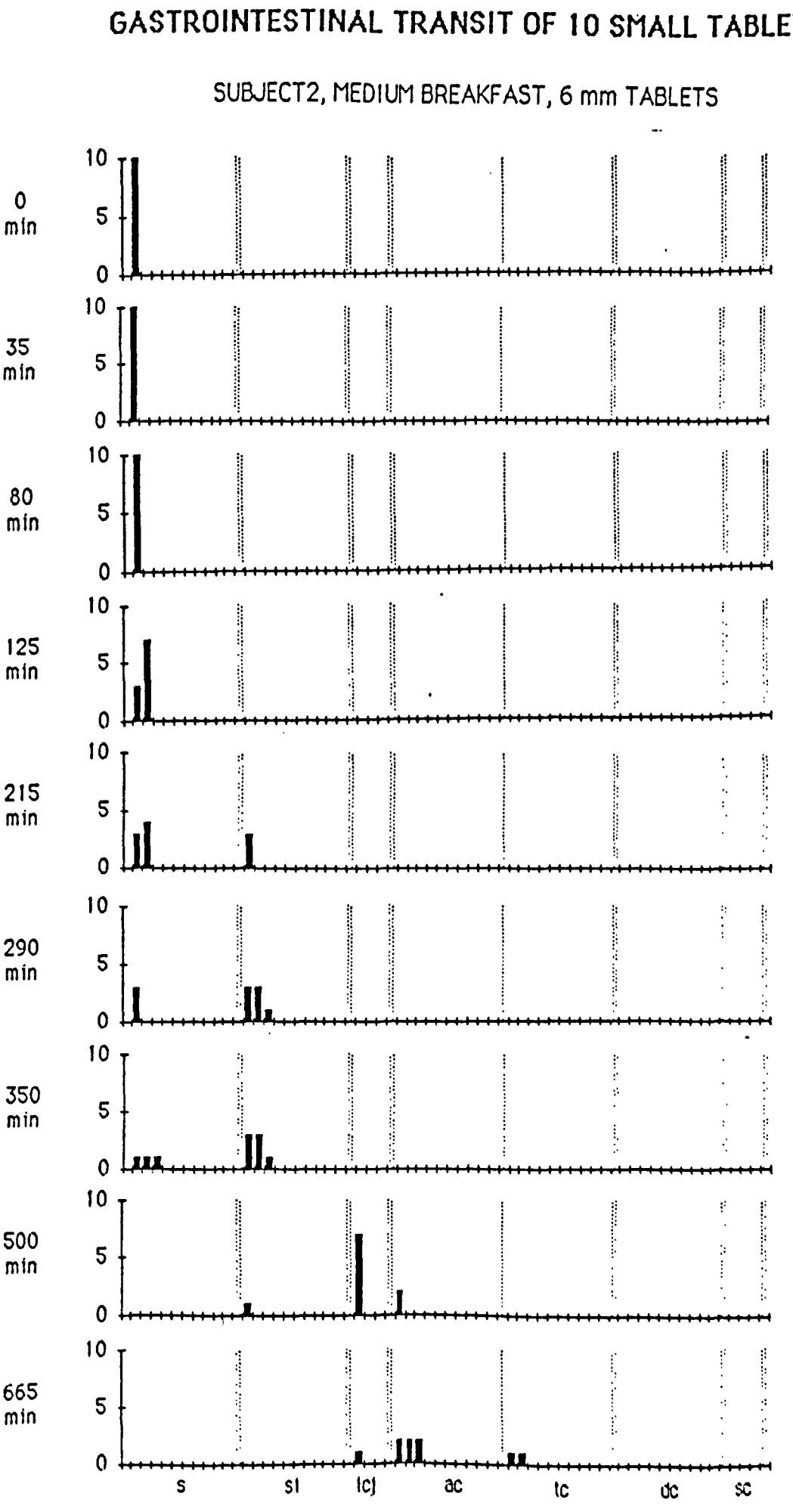

GASTROINTESTINAL TRANSIT OF 10 SMALL TABLETS
SUBJECT2, MEDIUM BREAKFAST, 6 mm TABLETS
0 min
35 min
80 min
125 min
215 min
290 min
350 min
500 min
665 min
10
5
0
s
si
icj
ac
tc
dc
sc

Figure 5.10b

GASTROINTESTINAL TRANSIT OF 10 SMALL TABLETS

SUBJECT 2, MEDIUM BREAKFAST, 7 mm TABLETS

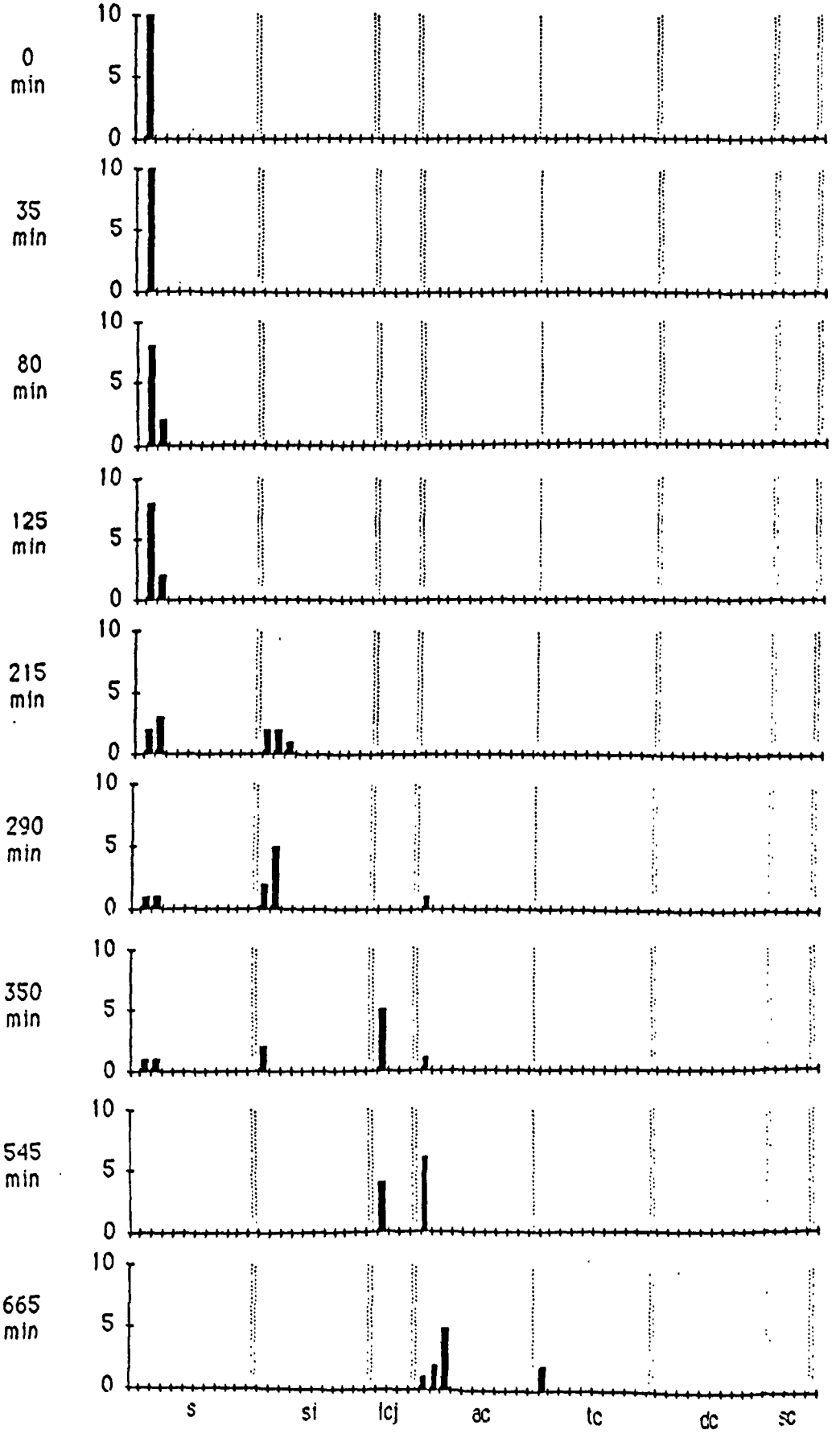


Figure 5.10c

CHAPTER SIX:

GASTROINTESTINAL TRANSIT OF TABLETS II

6.1 Introduction

In chapter 5, I presented the results of a study to evaluate the gastrointestinal transit of tablets, with an emphasis on tablet size. In this chapter I shall discuss the results of a similar study, with an emphasis on the colon transit of tablets. The significance of investigating the transit of dosage forms through the colon has been previously discussed (Section 1.5).

It is generally accepted that, due to its small absorptive area, the colon is not a major site of drug absorption (Section 1.5). However, it has been postulated that, the absorption of drugs in the colon must be greater than has been commonly believed (255). This is conceivable, considering that CR systems achieve extended absorption profiles, even when the dosage form is unlikely to be in the small intestine. The slow transit of dosage forms through the colon would prolong contact between the system and the absorptive surface, resulting in a greater proportion of drug being absorbed than would be predicted. This has been illustrated in a combined bioavailabilty and transit study, conducted in dogs. Dogs that retained the multiple unit formulation in the colon for the longest time, exhibited the highest bioavailability of drug (420). Extensive absorption of drug in the colon was considered probable. A similar study conducted in

man, reported that a large percentage of ibuprofen was absorbed while the dosage form was in the colon (421).

As mentioned before, few studies have been designed to specifically explore the colon transit of dosage forms. Work by Hardy et al (315) has suggested a relationship between particle size and transit through the colon. Another study to evaluate the GI transit of an osmotic device, also suggests particle size is a determinant of colon transit (250). The osmotic device (OSMET, 25mm x 7mm) usually traversed the colon ahead of the released solution.

The design of dosage forms for selective drug delivery to the colon has attracted much attention (section 1.5). Many studies have considered the delivery of corticosteroids (eg. beclomethasone) for use in ulcerative colitis, to the large bowel, via the mouth (422). The rational design of such systems requires extensive evaluation of the colon transit of dosage forms. It was, therefore, considered appropriate to conduct a study designed to investigate the transit of tablets through the colon.

6.2 Materials and Methods

The investigation was conducted on three consecutive days, which enabled both the total transit of the tablets, and the dispersion of tablets in the colon after regular daily dosing to be monitored. In

order to make a comparison with the previous studies, 5mm tablets were used in this investigation.

6.2.1 Preparation of Formulations

The tablets were prepared as described in the previous chapter. However, since the study was conducted over three days, indium-111 (half-life 2.8 days) was used to label the tablets. Amberlite IR120 (BDH) cationic resin, was washed and prepared as described in Section 2.2.1. Milled resin was labelled by soaking in a solution of indium chloride (Amersham International) and recovered as before.

A simple in vitro dissolution test was performed on each batch of labelled and coated tablets. Five tablets, were added to a beaker containing 50ml 0.1N HCl at room temperature. The contents were stirred using a magnetic stirrer and "flea". The tablets were removed at regular intervals, and activity measured as described in Section 2.2.1. In each case not more than 2% of radiolabel was lost after six hours. Thus, the tablet coating prevented any substantial leaching out of the isotopes. Copping (347) reported a total loss of 3.7% indium activity from labelled resin soaked in solutions ranging from pH 1-14. Indium-111 is not significantly absorbed from the GI tract (423), and thus it will not accumulate in any particular organ. This makes it more difficult to confirm the integrity

of the indium label *in vivo*. The technique of pertubed angular correlation (239) could be used, but this requires more than one gamma camera, thus precluding its use. Christensen (198) has described an alternative method to determine the binding of indium-111 to resin *in vivo*. A batch of resin pellets was half labelled with technetium-99m and the other half with indium-111. Using the dual isotope facility of the gamma camera, the gastric emptying of the pellets could be measured simultaneously. The pellets had a similar pattern of emptying. The integrity of the technetium label was confirmed by monitoring both the thyroid and bladder. Differences in gastric emptying between the pellets would suggest the loss of the indium label. Since there was no difference in emptying, it was concluded that the indium remained bound to the resin. Thus, although no specific check *in vivo* was made in the present study, the integrity of the indium label was assumed on the strength of the above result.

6.2.2 *In vivo* Study

The study was approved by the Ethical Committee of the University of Nottingham, and conducted in accordance with the declaration of Helsinki Guidelines for Ethics in Research. Approval to administer radiopharmaceuticals was obtained from the DHSS.

Five, healthy male volunteers, age range 20-25, height range 1.70-1.82m, weight range 57-83kg, participated with informed consent. Each subject abstained from alcohol for 24h, and had fasted for 10h prior to each study day. The subjects did not smoke, and were not on medication. On the morning of each day of the study, the subjects took five 5mm tablets together with 200ml ^{99m}Tc-DTPA labelled water (3MBq). The labelled water enabled ready identification of the stomach and colon. The subjects remained fasted before administration of the tablets to allow a more rapid transit to the colon, and provide data for comparison with the previous 5mm tablet fed studies. Each dose of tablets had an activity of about 1MBq. The total radiation dose absorbed by the subjects was estimated as 0.533mG/MBq for the stomach, 1.066mG/MBq for the small intestine, and 0.128mG/MBq for the whole body (133,350). Anterior and posterior images, each of 60s duration, were taken at regular intervals, using a gamma camera (General Electric Maxicamera, Type II) having a 40cm field of view and fitted with a medium energy (200 keV) parallel hole collimator. The subjects stood in front of the camera for imaging and were asked to keep body movements to a minimum during imaging. During the study, the subjects remained in an upright position, sitting/standing. The images were recorded, and stored on computer (Nodecrest).

Anatomical reference markers containing indium-111, were taped to the skin, anteriorly and posteriorly, over the liver to the right of the stomach. At about 2.5h after dosing the subjects were given a drink of orange juice. A standard light lunch consisting of one ham roll and 150ml orange juice, was taken after about 4h. An evening meal of steak, chips, peas, and cheesecake was taken about 10h after dosing.

The recorded images were analysed by drawing regions of interest around the position of the stomach and colon, as described previously (Section 2.2.2). The activity in these regions was quantified, and then corrected for background activity and radioactive decay. The error due to the variation in depth of radionuclide in the stomach and colon, was corrected by calculating the geometric mean of corresponding anterior and posterior views (216). Careful examination of the colon images enabled the individual tablets to be seen and counted. The dispersion of the tablets provided a good outline of the colon, allowing identification of the various regions.

The study was repeated using the same protocol on the following two days. A record of bowel habits was kept for the period of the study. The subjects did not complain of any untoward side-effects during each study day.

6.3 Results and Discussion

6.3.1 General Discussion

The data for the investigation have been quantified in a number of different ways, and representative examples are given. The St50%, SIT, Ct50% and MCt values are presented in Tables 6.1-6.5. Gastric emptying profiles and colon entry curves are shown in Figures 6.1-6.5. Representative scintiscans, which illustrate the various phases of transit, are presented in Figure 6.6. Diagrams to illustrate the transit of the tablets in the colon are shown in Figures 6.7, 6.9 and 6.11. Histogram plots, which also demonstrate the transit of the tablets in the colon are given in Figures 6.8, 6.10 and 6.12.

Generally, the tablets emptied from the stomach rapidly and as a bolus. This bolus emptying probably relates to the phase 2/phase 3 activity of the MMC, and was observed in the pellet studies described in previous chapters. Feely et al (410) also reported on the bolus emptying of mini-matrix tablets in fasted subjects. In some cases, especially on day 3, the tablets began to empty only after a lag phase (eg. subject 5, Figure 6.2). This lag must relate to the quiescent MMC activity of phase 1. Subject 2 also exhibited a long lag phase (Figure 6.3), before the tablets began to empty. However, emptying of the tablets was interrupted at about 240min, which coincides with lunch. A second lag phase is then

apparent, before the bolus emptying of the remainder of the tablets. This example illustrates the cessation of the MMC contractions by the ingestion of food. Unfortunately, ingestion of food before the tablets had emptied from the stomach, introduced an extra variable which applied only to subject 2. This demonstrates a problem commonly associated with such studies, which should aim to reduce all experimental variables but maintain a real life situation. The St50% values are similar to previously cited results, and also to the pellet data presented in previous chapters. A paired Student t test on the St50% values for the three days shows no significant difference ($p>0.1$) between the results. It is interesting to note, that the variability of the data (s.e.m. value) on day 3 is greater than on the first two days. This is due to the St50% value for subject 2, since the variability is reduced if this value is not included (mean 83min$\pm$21). The gastric emptying profiles (Figure 6.4) illustrate the effect that this result has on the mean GE values, with the day 3 curve extending over a longer period of time. A greater variability in gastric emptying data would have been expected, since the probability of the subjects being in the same phase of the MMC is small. Park et al (249) monitored the gastric emptying of a series of capsules (diameter 4.7-9.5mm, length 9.8-1.76mm) and spheres (diameter 6.0-1.27mm) in fasted

subjects. They concluded that gastric emptying was a very variable process in fasted subjects, and was governed by the time of ingestion of the dosage form in relation to the active phases of the MMC. Gastric residence times varied between 5->140min. However, in another study, the gastric emptying of a single tablet (17x4mm), in fasted old and young subjects, did not exhibit a large interindividual variation (s.e.m. 7-13min) (417). Jonsson et al (416) obtained mean gastric emptying data of 60min for 3mm tablets, and 45min for 14mm tablets. This result suggests that tablet size is not a determinant of gastric emptying in the fasted state. Gruber et al (424) found that >90% of administered particles are emptied from the stomach by one MMC. The remainder require no more than two cycles of the MMC. They also concluded that size, density and surface characteristics do not influence gastric emptying in fasted dogs.

A comparison of the results with the 5mm tablet data for the light, medium, and heavy breakfast studies, further exemplifies the effect of food and the activity of the MMC on gastric emptying. The St50% values for the present study are similar to the St50% values of the light breakfast, but the pattern of emptying is different. In the fasted state, the tablets empty as a bolus, whereas after the breakfast, emptying is slightly more transitory (Figures 6.4 and

6.5). The difference between the fasted data and the medium and heavy breakfast results is well illustrated by the gastric emptying profiles. Smith and Feldman (415) also noted a pronounced effect on the gastric emptying of 10mm tablets due to food. Tablets administered to fasting subjects emptied rapidly, whilst those administered after a meal had a longer gastric residence. The bolus emptying of dosage forms from the fasted stomach is of significance to the performance of multiple unit systems. These systems are designed to spread through the small intestine, by virtue of their gastric emptying. However, in the fasted state, the sub-units could empty as a bolus and traverse the small intestine as a bolus, thus compromising their performance.

The SIT values are similar to the previous pellet data, and in close agreement with the mean small intestine transit value for dosage forms (304). Subject 4 exhibits a very short SIT, on more than one occasion, which may be due to a powerful phase 3 contraction accelerating the tablets to the colon. It was apparent from the recorded images that, the tablets traversed the small intestine as a bolus. There is no significant difference between the results of the three study days ($p>0.1$). These SIT values are similar to the previous 5mm tablet results, which again confirms the invariable nature of small intestine transit.

The CE data are also in close agreement with the previous 5mm light breakfast results, with no significant difference between the three days. The transit of the tablets through the colon will be discussed below.

6.3.2 Colon Transit

It is evident from the colon entry curves (Figures 6.1-6.4) that, entry of the tablets into the colon occurred as a bolus. As mentioned before, entry of material as a bolus is not necessarily due to MMC activity. Steep colon entry curves are indicative of clumping at the ICS, followed by bolus entry into the colon (99). Clumping was apparent on the recorded images and is illustrated in Figure 6.6. The tablets did not remain at the ICS for extended periods, although subject 1 on day 3 did exhibit a long residency at the ICS. This is exemplified by the long SIT value. The mean colon entry curves (Figure 6.4) are similar to the profiles for the 5mm tablets taken after a light breakfast (Figure 6.5). The curve for day 3 suggests a less rapid rate of entry, which can partly be explained by the long gastric residence of subject 2. This would shift the curve to the right. Nevertheless, the tablets, for this subject, did enter the colon as a bolus. The stagnation of the tablets at the ICS, in subject 1, would also broaden the colon

entry curve. Further similar studies would indicate the frequency of extended stagnation at the ICS, in fasted subjects, and determine the generic pattern of colon entry. The similarity between the light breakfast and fasted (day 1 and 2) colon entry curves, provides more evidence that meal residue may influence transit through the ICS. It is unlikely that, the residue from lunch would have affected colon entry, since entry usually began before or within an hour of lunch. Furthermore, the solid content of the meal was relatively small. There was also no demonstrable relationship between the ingestion of food and either colon entry or transit through the colon. Thus, whilst ingestion of food normally causes an increase in colonic activity, the "gastrocolic" reflex (101), this increased activity does not necessarily result in aboral movement of colonic material.

The transit of the tablets through the colon is best illustrated by the results for subjects 1, 2, and 3 (Figures 6.7-12). The tablets usually remained as a bolus in the region of the caecum, began to disperse as they progressed further up the ascending colon, transverse colon and descending colon, before forming a bolus in the sigmoid colon/rectum. It has been previously noted that dispersive systems, such as pellets, become widely distributed within the colon (220). A similar dispersion was also seen of a

radiolabel marker released from an osmotic device (OSMET) (250).

Subject 1 exhibited an extremely slow transit through the colon, with 15 tablets remaining in the colon at the end of day 3. These tablets were distributed throughout the colon. In contrast, subject 2 exhibited a faster rate of transit. Most of the day 2 tablets, had reached the sigmoid colon 420min after entering the colon, and were evacuated before day 3. Subject 3 appeared to have an intermediate rate of transit. Three of the day 1 tablets had been evacuated at the start of day 2. It is interesting to note that, the remaining two tablets were only in the descending colon and not in the sigmoid colon. This suggests a mass movement of material which evacuated the three tablets. The two remaining tablets were evacuated before day 3. Subjects 4 and 5 also exhibited an intermediate rate of transit. It is evident from the histograms that, total transit times of the tablets (mouth to anus) ranged from about 18h (subject 2, day 2 tablets) to more than 72h (subject 1). Hardy et al (315) reported total transit times of 17-72h, for a pellet formulation given to fasted subjects. John et al (425) obtained a median mouth to evacution time of 27.4h, for a single unit system (OROS), in fasted subjects. Individual times, however, ranged from 5.1-58.3h. Transit was measured by recovering the unit

in the faeces. It has been suggested that very short transit times (upto 6h), may relate to a vegetarian diet (418). Further studies detailing the normal diet of the subjects would provide the required evidence for this suggestion.

The histograms suggest that transit of the tablets was not a continuous process, but was interspersed with periods of little movement. Similar observations were made by Hardy et al (315). Defaecation did not generally result in a major progression of the tablets, except to evacuate those tablets in the sigmoid colon/rectum. As mentioned above, a mass movement appears to have occurred in subject 3. Mass movement, at the time of defaecation, is also suggested for subject 2 on day 2 (Figure 6.10); tablets progressed rapidly from the transverse colon down to the sigmoid colon. John et al (425) did not notice a relationship between total transit times and the frequency of bowel movements.

The present results provide further substance to previous comments regarding CDDS designed for drug delivery to the colon (315). The duration of gastric emptying and small intestine transit suggests that, drug should not be released from the system for about 5h after administration to fasted patients. Release of drug, from a dispersive system, over the next few hours would distribute throughout the proximal and transverse

colon. However, the period of drug release is restricted by the apparent intersubject differences in colon transit times. A multiple unit system given on a once daily basis, would be sufficiently dispersed in the colon to provide adequate local delivery of drug for the treatment of common colonic diseases. The results of this study are also of relevance to the general design of CDDS. Total transit times of less than 24h makes once daily dosing redundant, even if drugs are extensively absorbed in the colon. Furthermore, it is still necessary to determine the degree of biotransformation of drugs that occurs in the colon, and more importantly, the extent of drug absorption that does occur in the colon. Conventional bioavailability studies, combined with the technique of gamma scintigraphy would be extremely suitable for such investigations. Efforts should, therefore, be continued in devising systems which have a prolonged gastric residence, especially in the fasted state. Food may extend gastric residence, but this is neither a practical nor pharmaceutical option, and thus other strategies are required.

6.4 Conclusions

The following conclusions can be drawn from the results of this investigation:

i. Tablets (5x5mm) emptied rapidly and as a bolus from the fasted stomach. Transit through the small intestine was also as a bolus.

ii. The tablets amassed at the ileocaecal sphincter, before entering the colon as a bolus. Residency at the ileocaecal sphincter was of a short duration.

iii. The rate of transit through the colon was very different between subjects. However, in all subjects, the tablets did disperse throughout the colon.

iv. There was no relationship between either the ingestion of food or bowel habits, and the movement of the tablets in the colon.

Table 6.1 Mean (s.e.m) gastric emptying values - %activity remaining in the region.

Study day	1	2	3
Time (min)			
0	100	100	100
20	67(16)	80(18)	95(3)
40	36(15)	17(16)	82(8)
60	24(16)	0	50(19)
80	14(13)	0	47(18)
120	0	0	33(19)
160	0	0	31(18)
200	0	0	31(18)
240	0	0	14(8)
280	0	0	7(6)
320	0	0	7(6)
360	0	0	7(6)
420	0	0	7(6)
480	0	0	7(6)
540	0	0	7(6)
600	0	0	0

Table 6.2 Mean (s.e.m) colon entry values - %activity remaining in the region.

Study day	1	2	3
Time (min)			
80	0	0	0
120	0	20(18)	0
160	20(18)	20(18)	16(14)
200	60(22)	20(18)	33(19)
240	60(22)	40(22)	33(19)
280	75(17)	60(22)	39(22)
320	100	97(2)	52(20)
360	100	100	60(19)
420	100	100	86(8)
480	100	100	94(6)
540	100	100	94(6)
600	100	100	94(6)
660	100	100	94(6)

Table 6.3 Lag time and Gastric emptying (St50%) values.

	Day 1		Day 2		Day 3	
	Lag (min)	St50%	Lag (min)	St50%	Lag (min)	St50%
Subject						
1	0	35	0	10	0	43
2	0	10	20	30	200	230
3	0	30	20	30	20	45
4	0	20	20	30	0	100
5	0	28	20	50	40	145
mean	0	25	16	30	52	113
s.e.m.	-	4	4	6	38	78

Table 6.4 Small intestine transit (SIT) values.

Subject	Day 1 SIT (min)	Day 2 SIT (min)	Day 3 SIT (min)
1	135	210	362
2	252	230	173
3	255	270	145
4	115	70	45
5	167	253	167
mean	185	207	178
s.e.m.	29	36	51

Table 6.5 Colon entry (Ct50%) and MCt values.

	Day 1		Day 2		Day 3	
	Ct50% (min)	MCt	Ct50% (min)	MCt	Ct50% (min)	MCt
Subject						
1	170	210	220	240	405	480
2	262	320	260	280	403	-
3	285	320	300	320	190	360
4	135	160	100	120	145	200
5	195	200	303	360	312	420
mean	209	242	237	264	307	-
s.e.m.	25	29	38	41	51	-

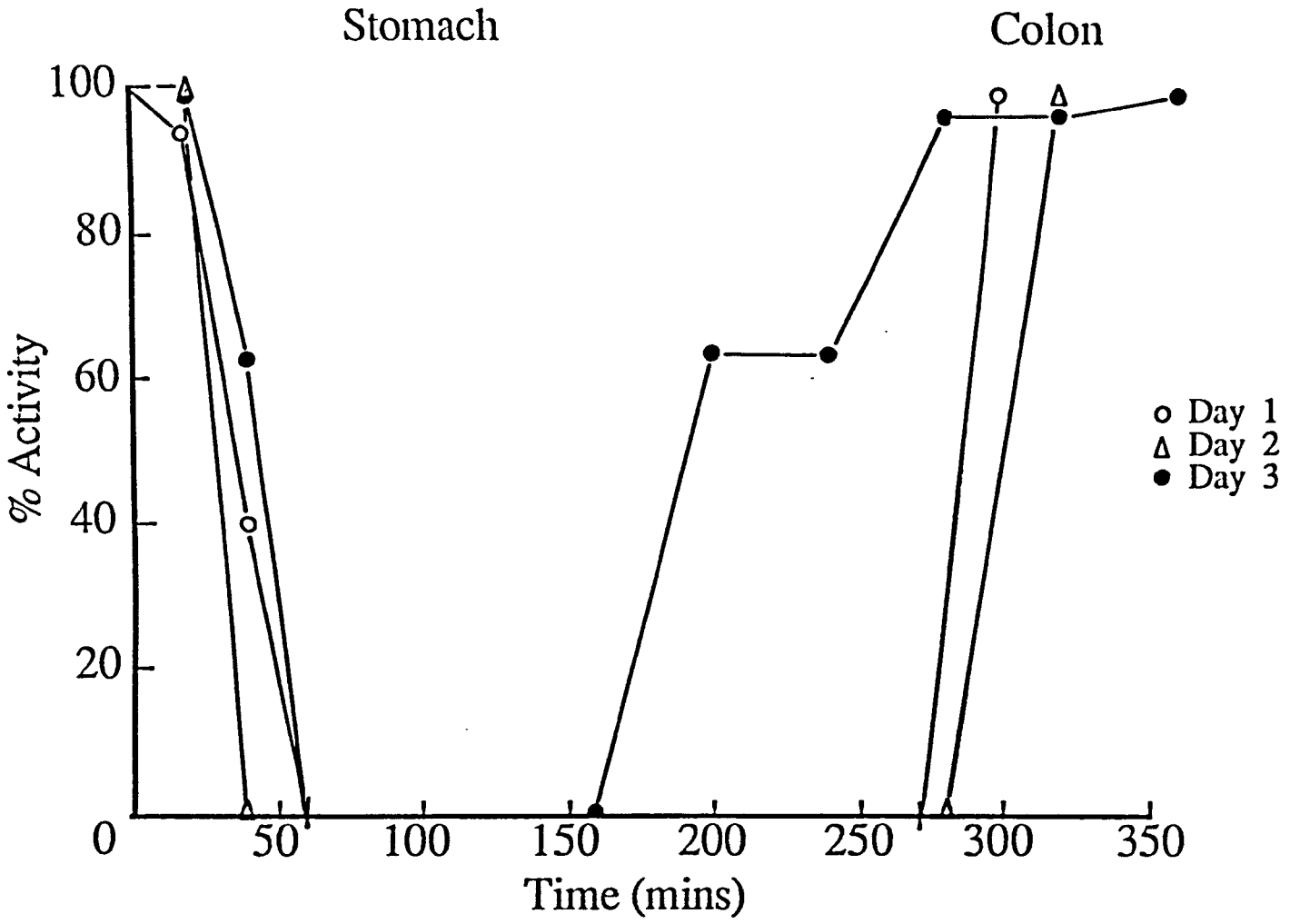


Figure 6.1 Gastric Emptying and Colon Entry of Tablets - Subject 3

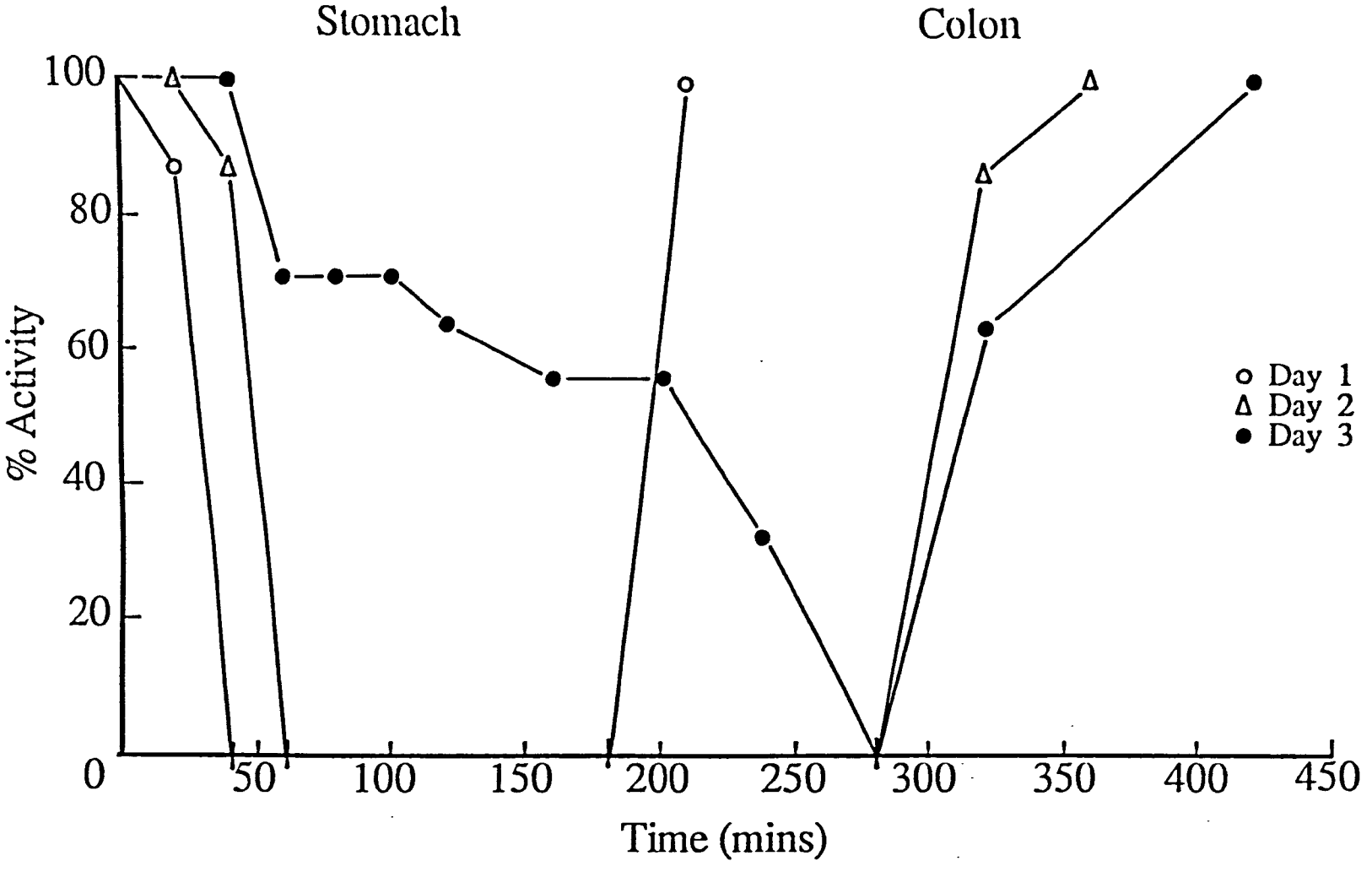


Figure 6.2 Gastric Emptying and Colon Entry of Tablets - Subject 5

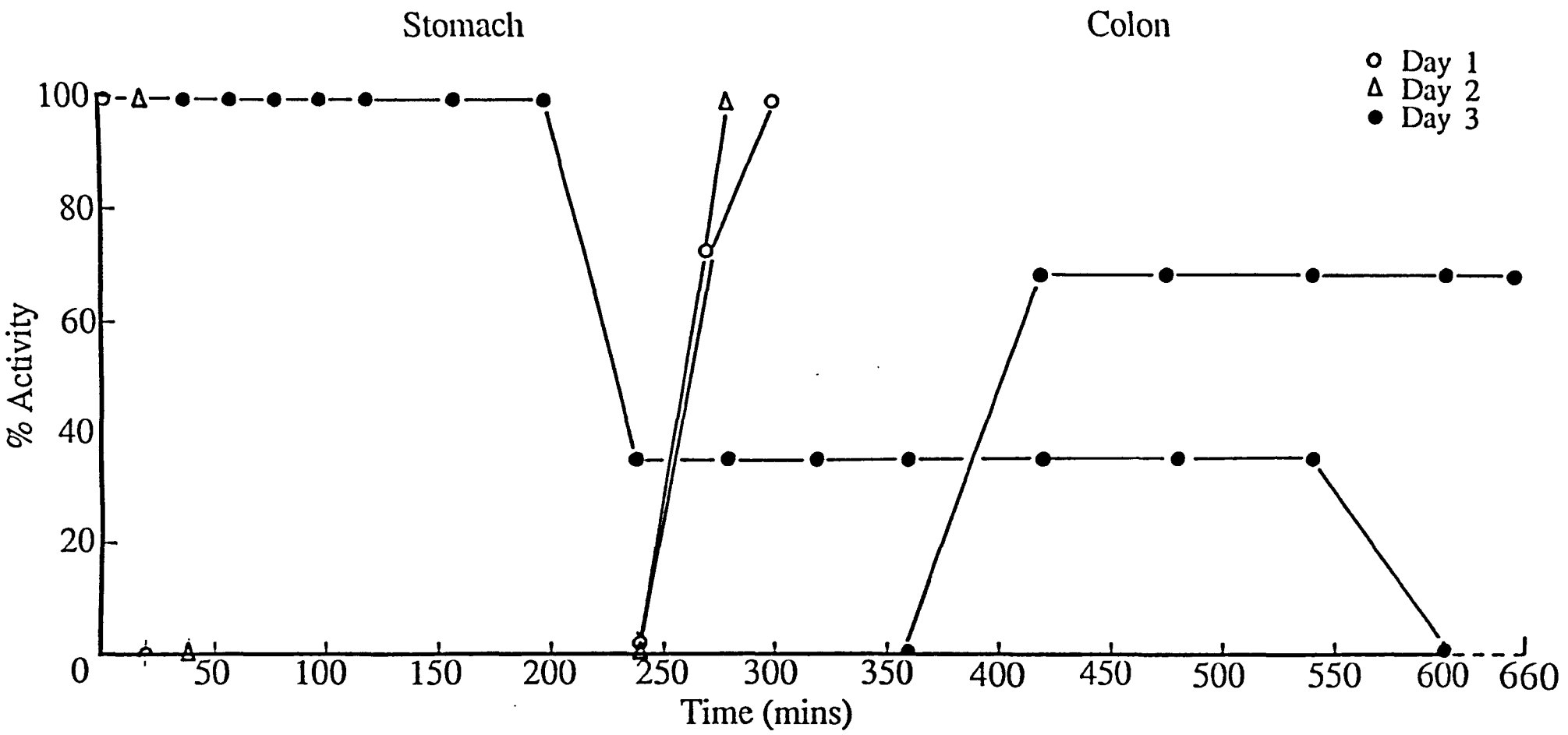


Figure 6.3 Gastric Emptying and Colon Entry of Tablets - Subject 2

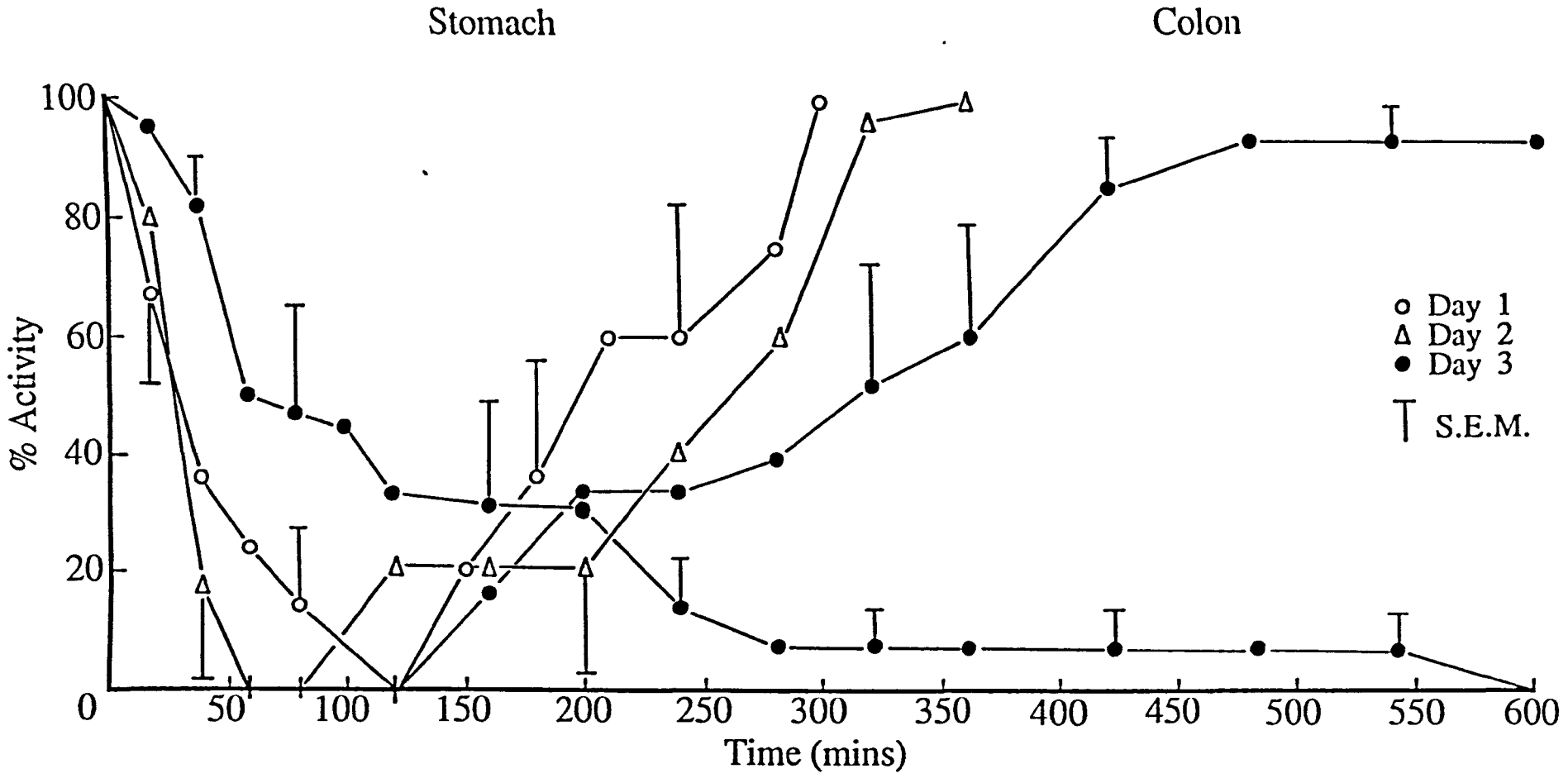


Figure 6.4 Mean Gastric Emptying and Colon Entry of Tablets

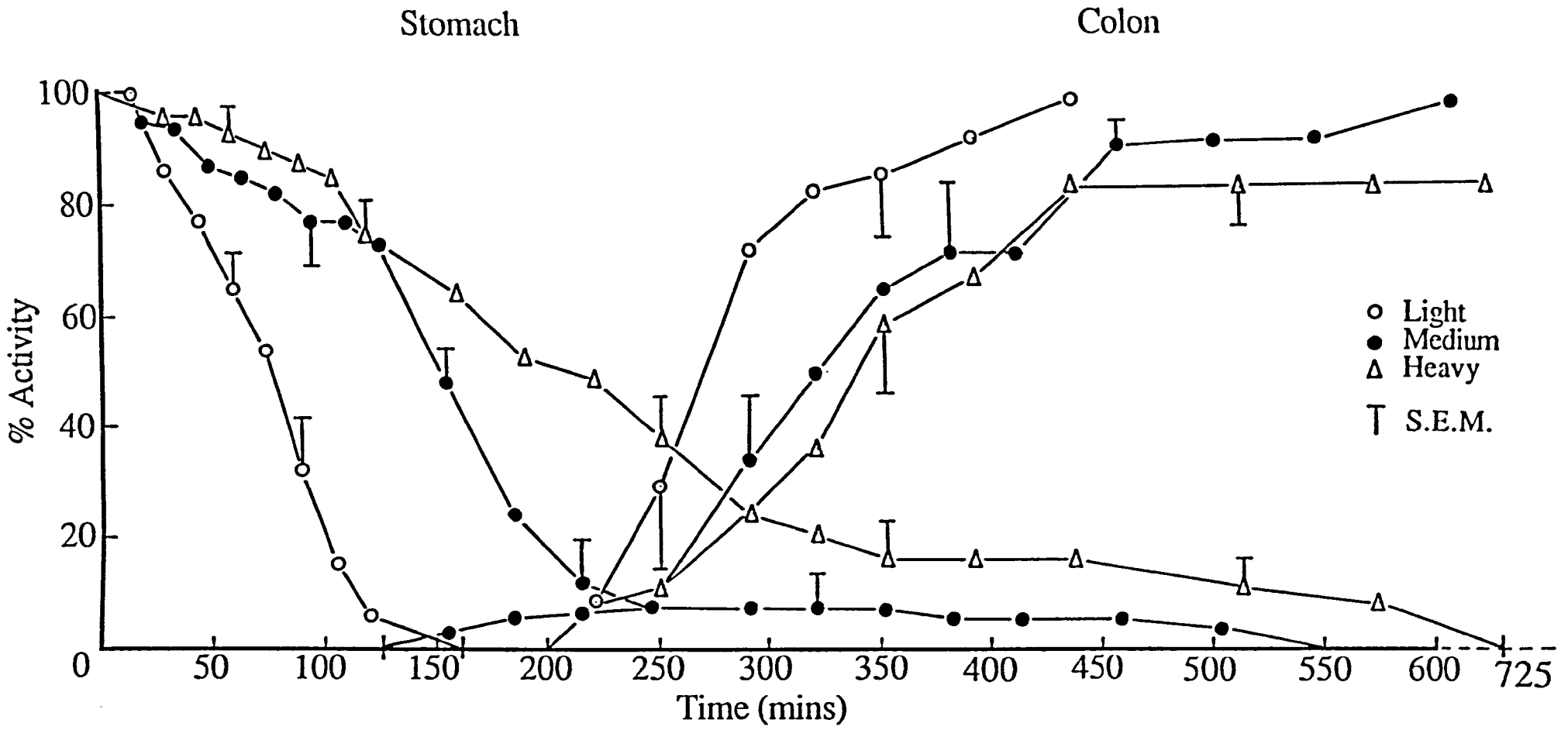


Figure 6.5 Mean Gastric Emptying and Colon Entry of 5mm Tablets

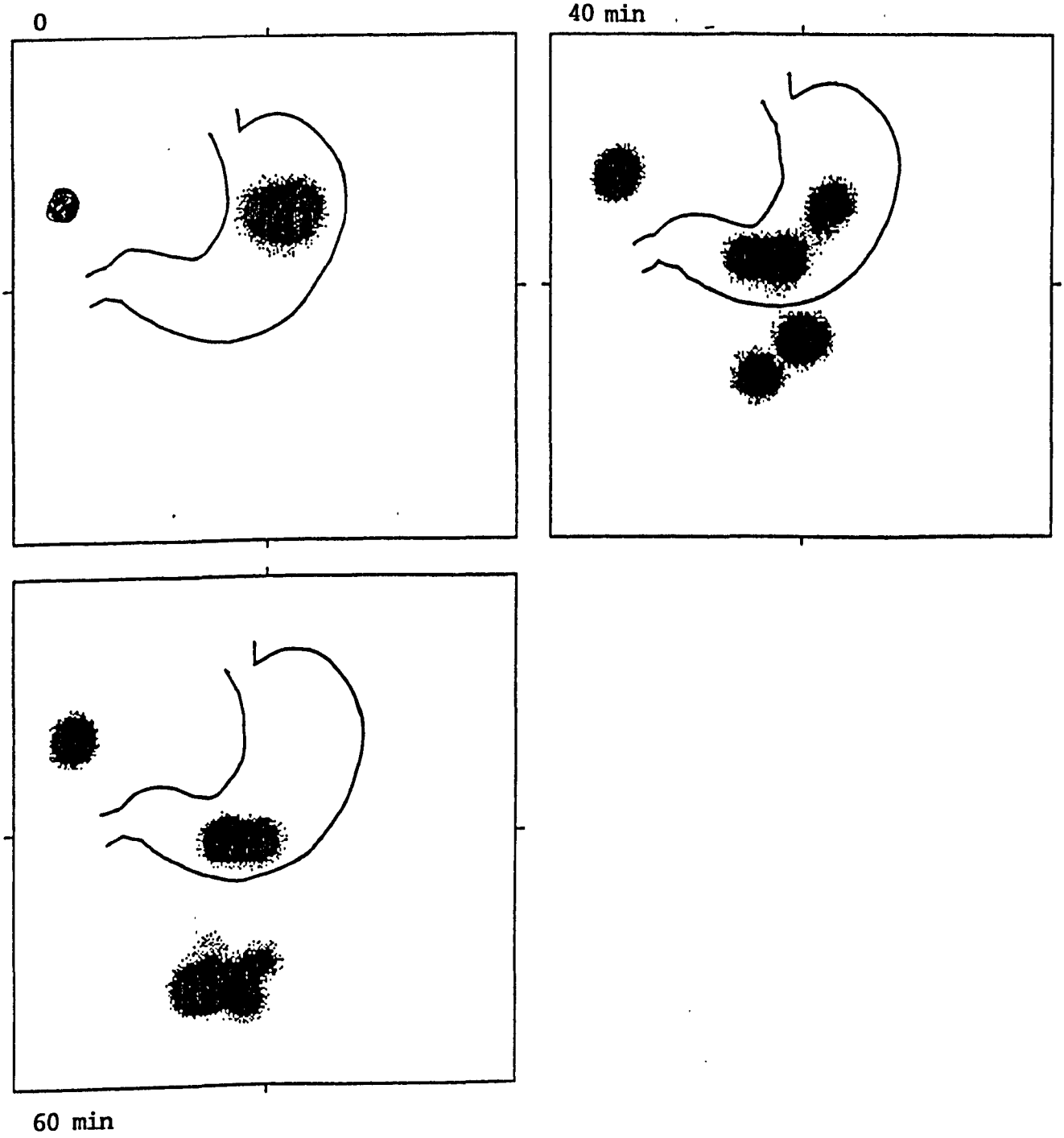


Figure 6.6a Gastric Emptying of Tablets - Subject 1, day 1.

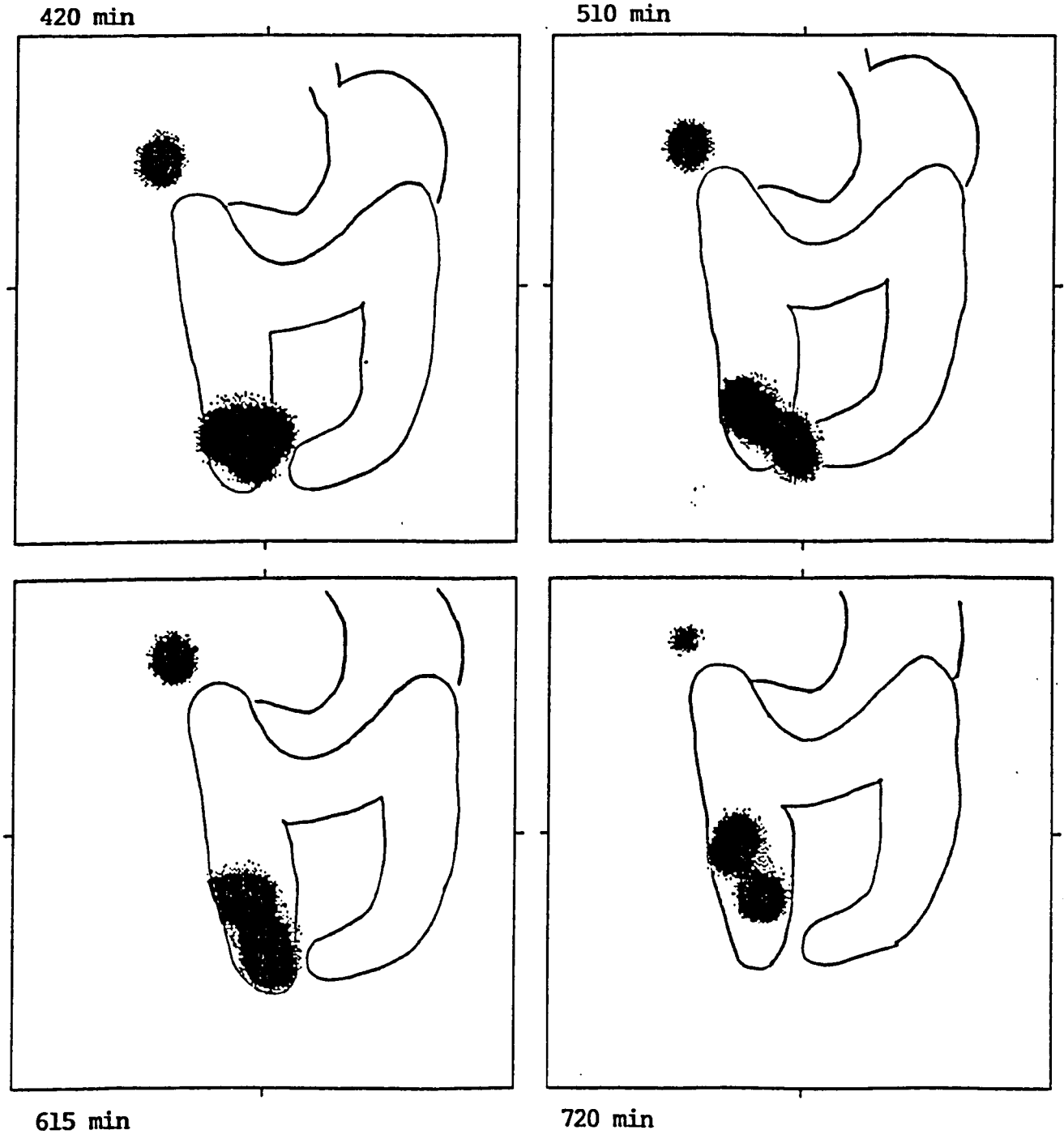


Figure 6.6b Colon Entry of Tablets
Subject 1, day 1.

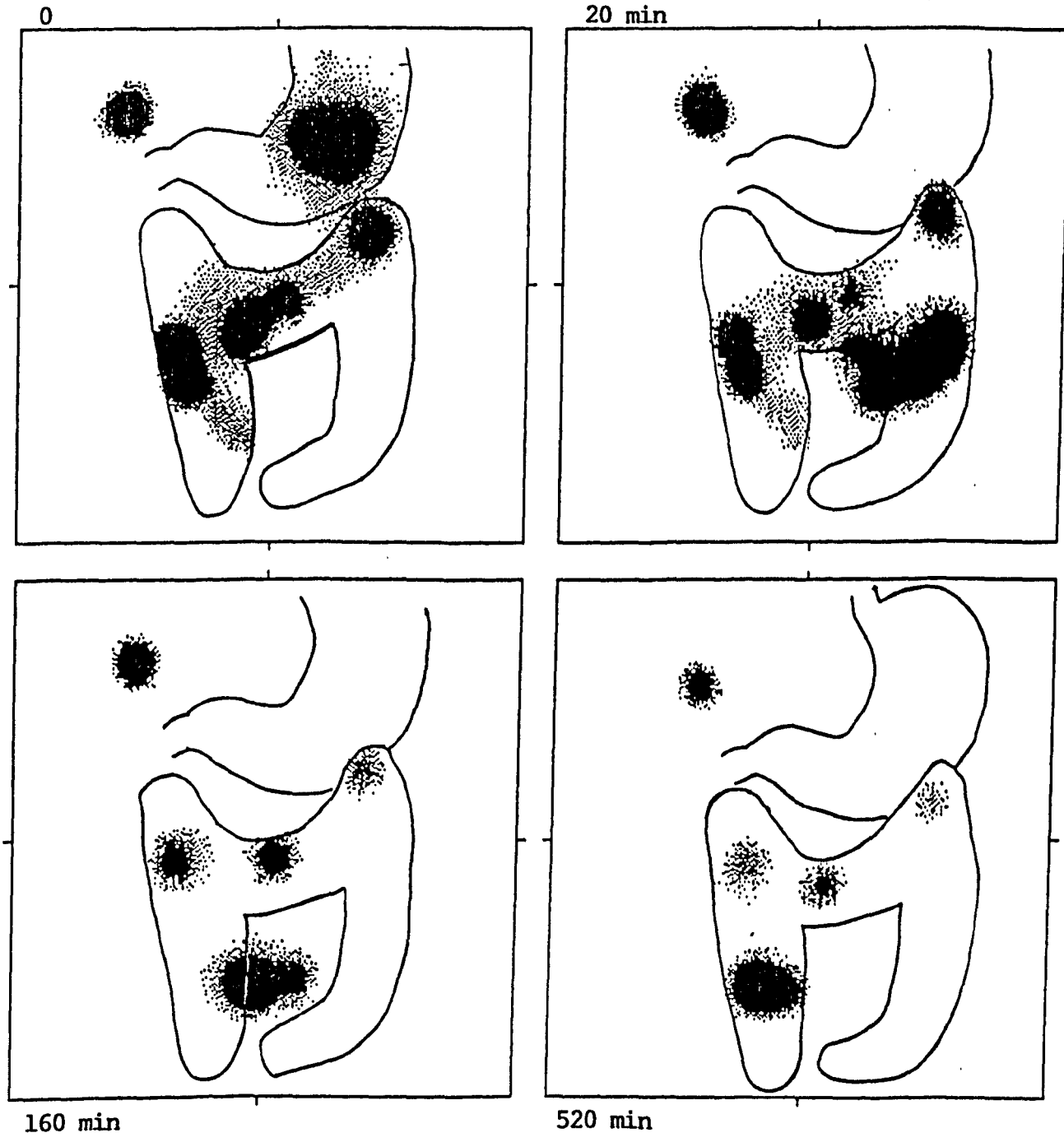


Figure 6.6c Gastrointestinal Transit of Tablets - Subject 1, day 2.

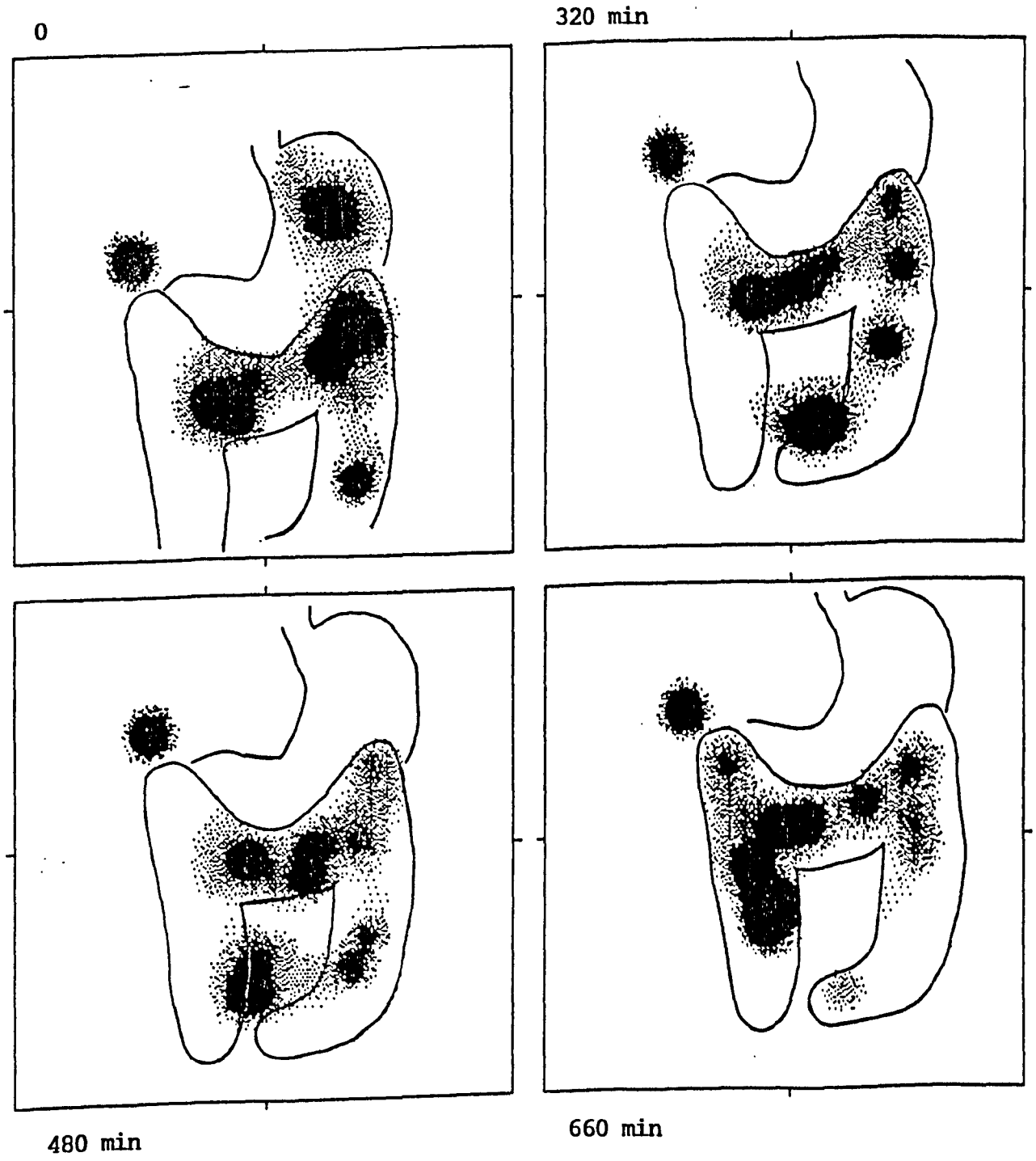
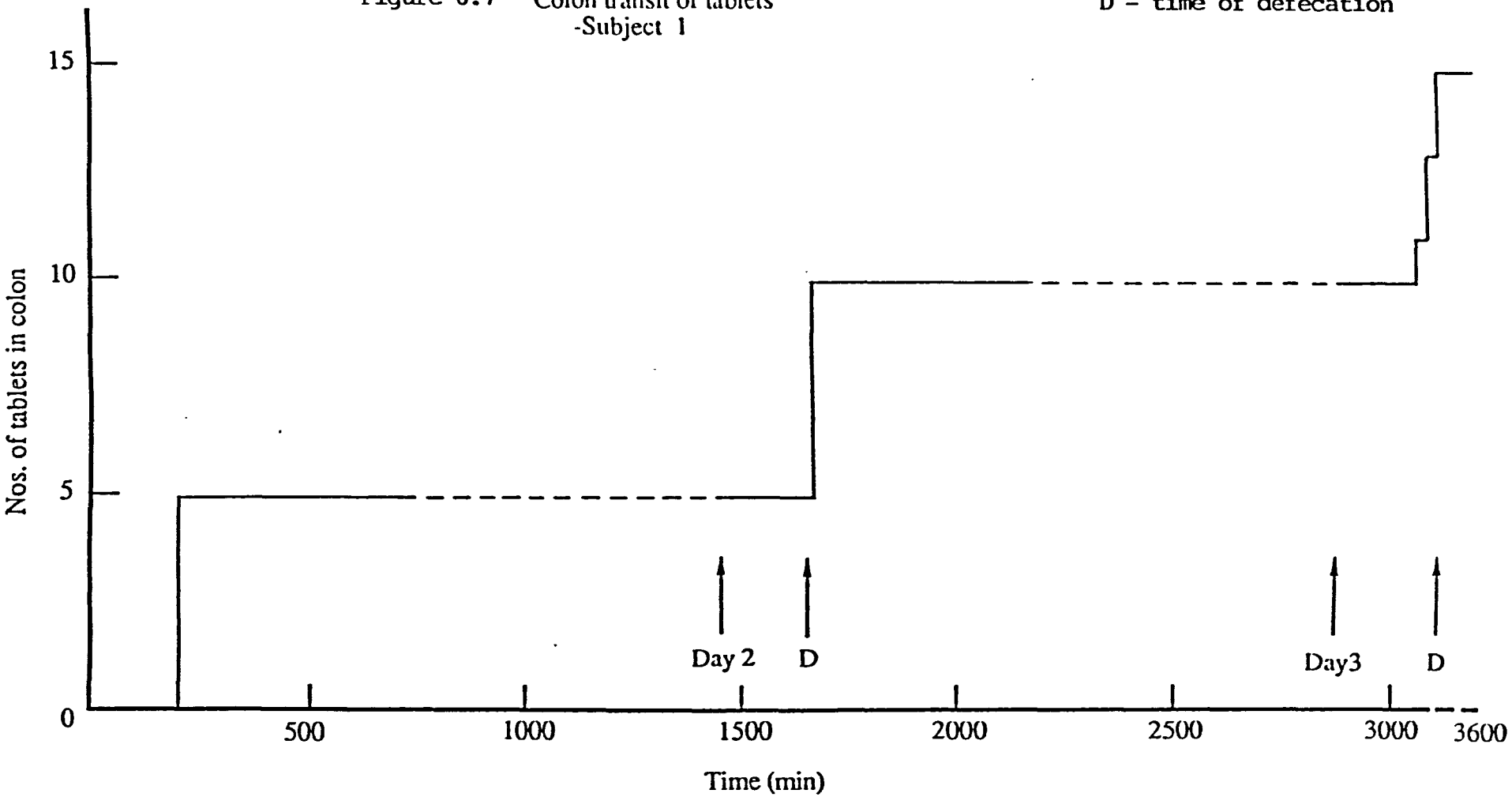


Figure 6.6d Gastrointestinal Transit of Tablets - Subject 1, day 3.

Figure 6.7 Colon transit of tablets
-Subject 1

D - time of defecation



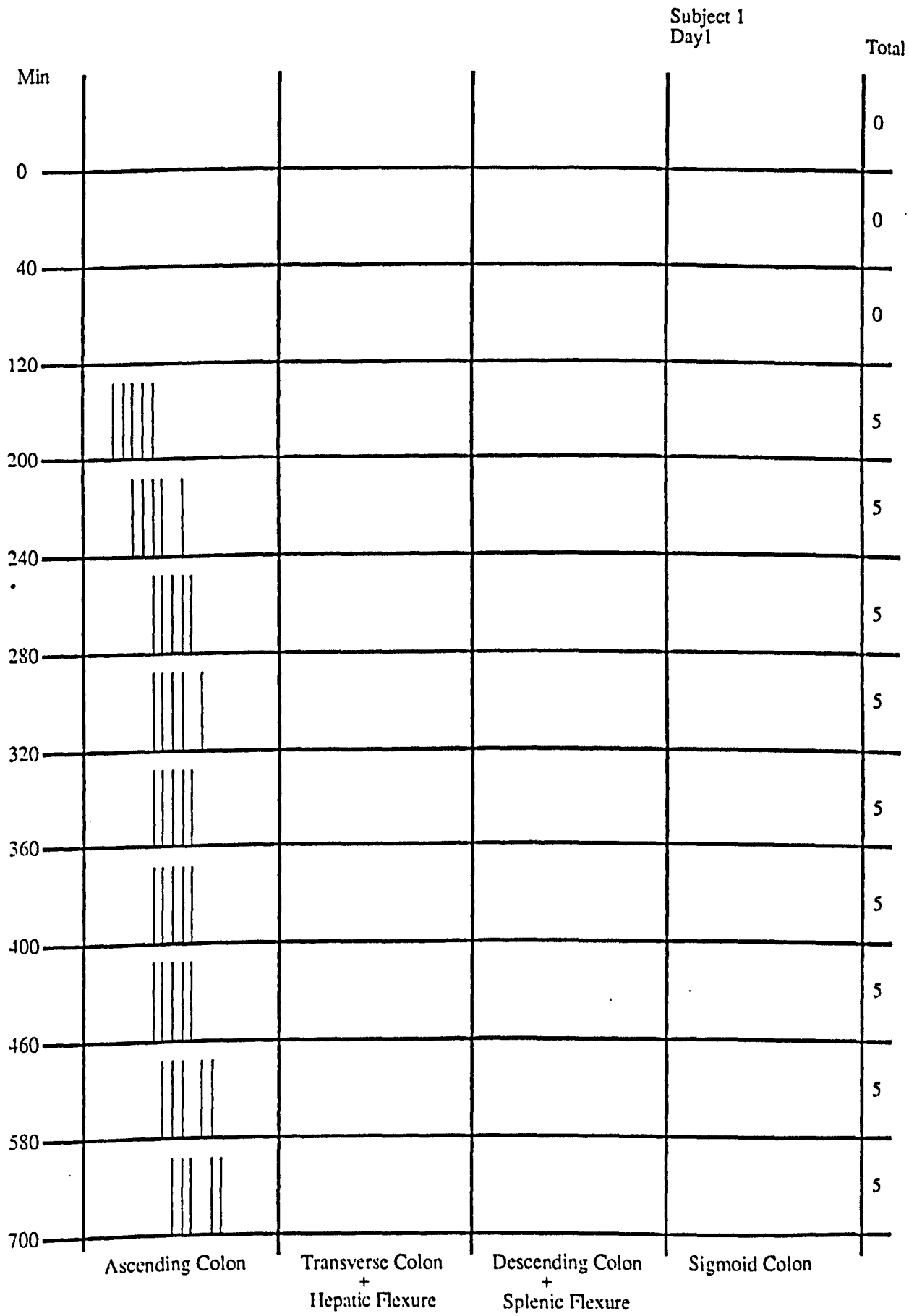


Figure 6.8a Colon transit of tablets.

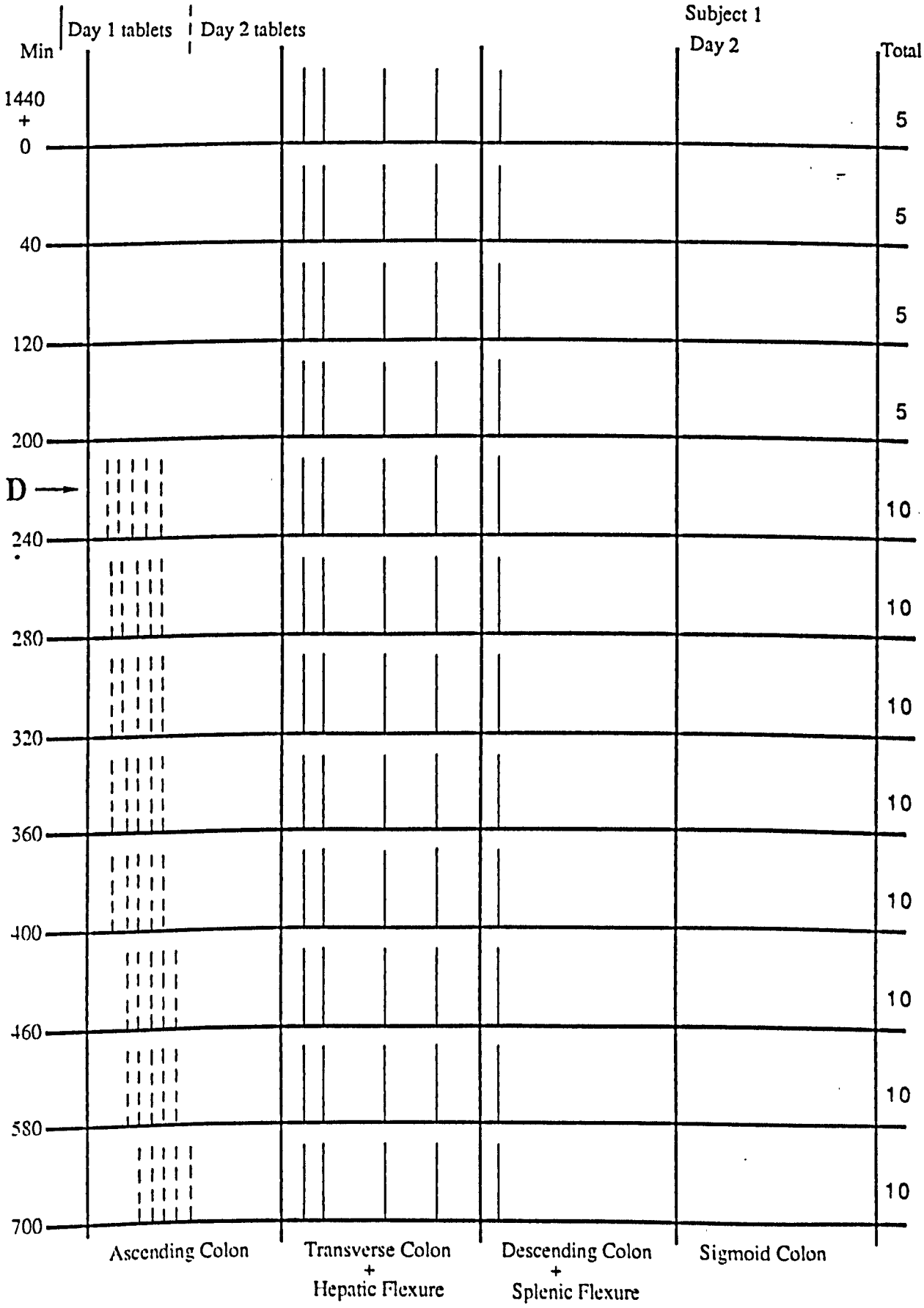


Figure 6.8b Colon transit of tablets.

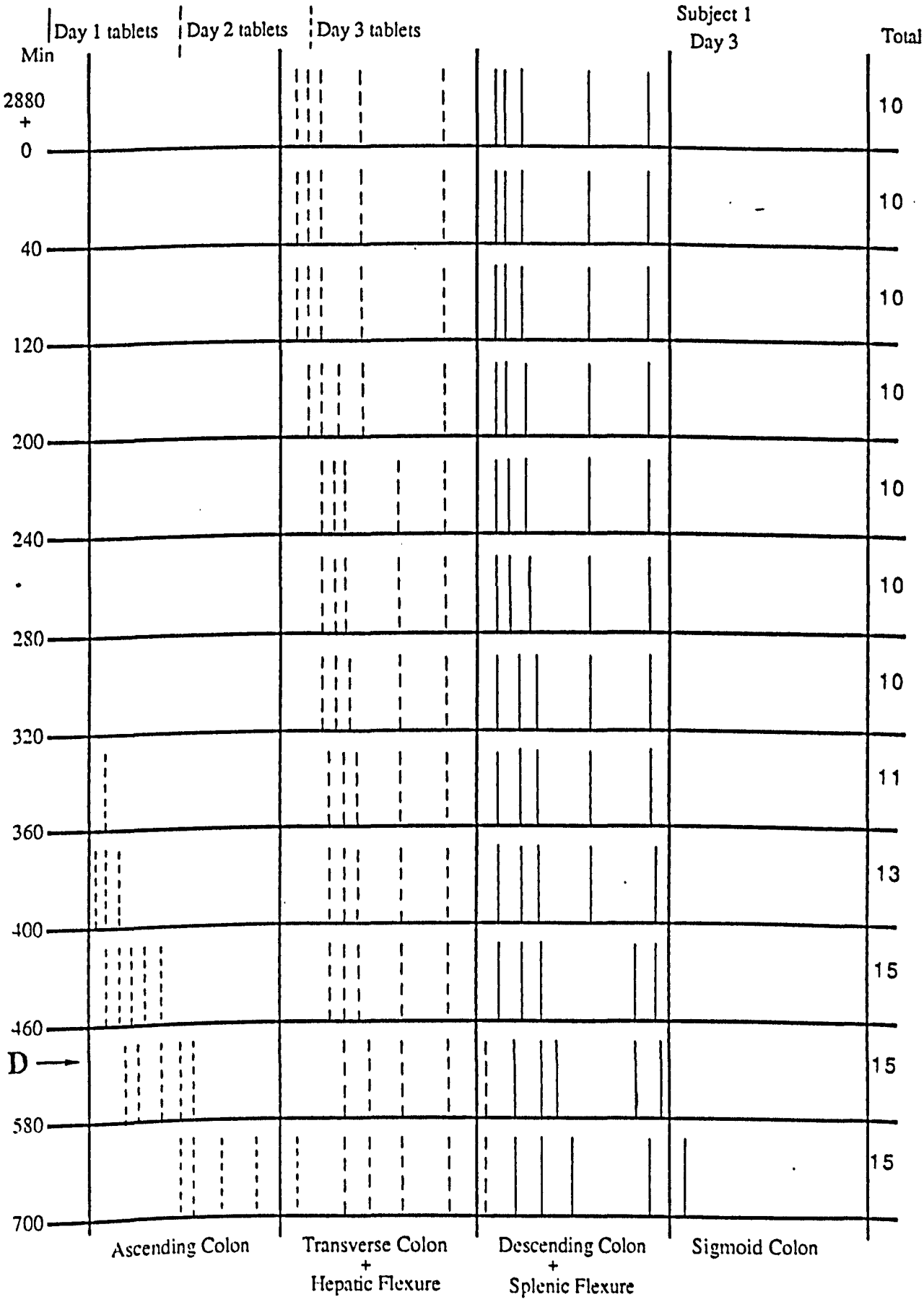


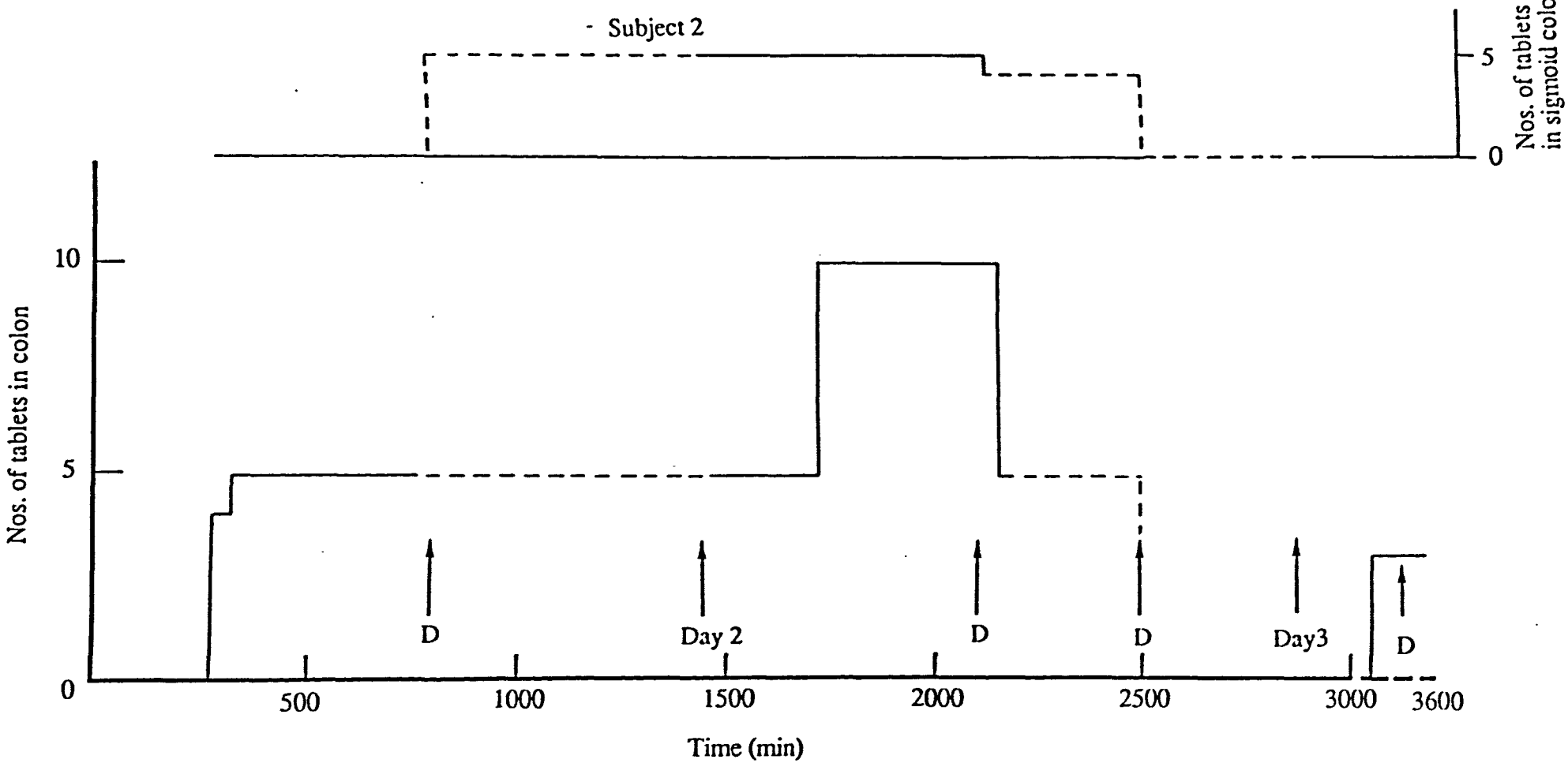
Figure 6.8c Colon transit of tablets.

Figure 6.9

Colon transit of tablets

- Subject 2

D - time of defecation



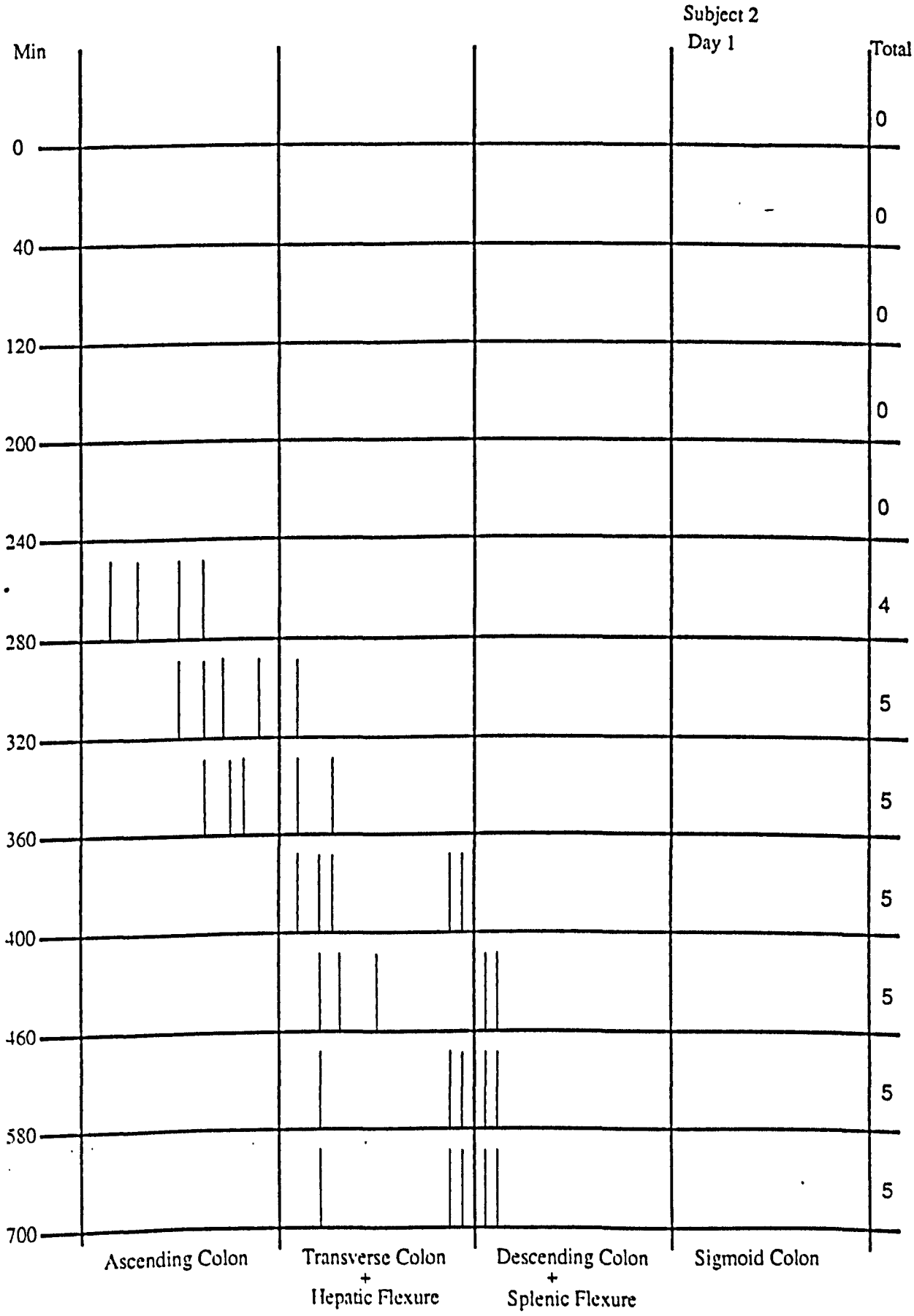


Figure 6.10a Colon transit of tablets.

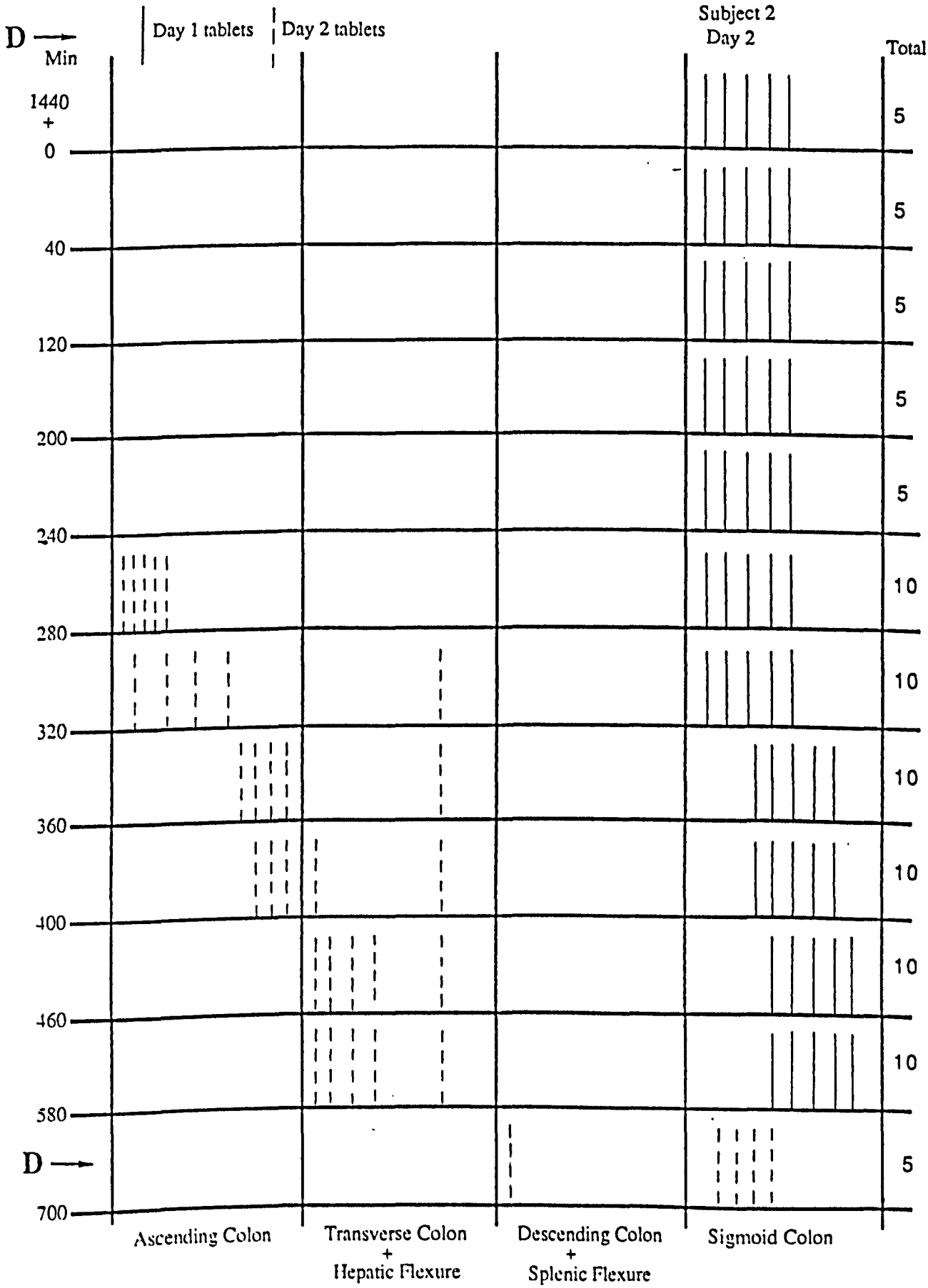


Figure 6.10b Colon transit of tablets.

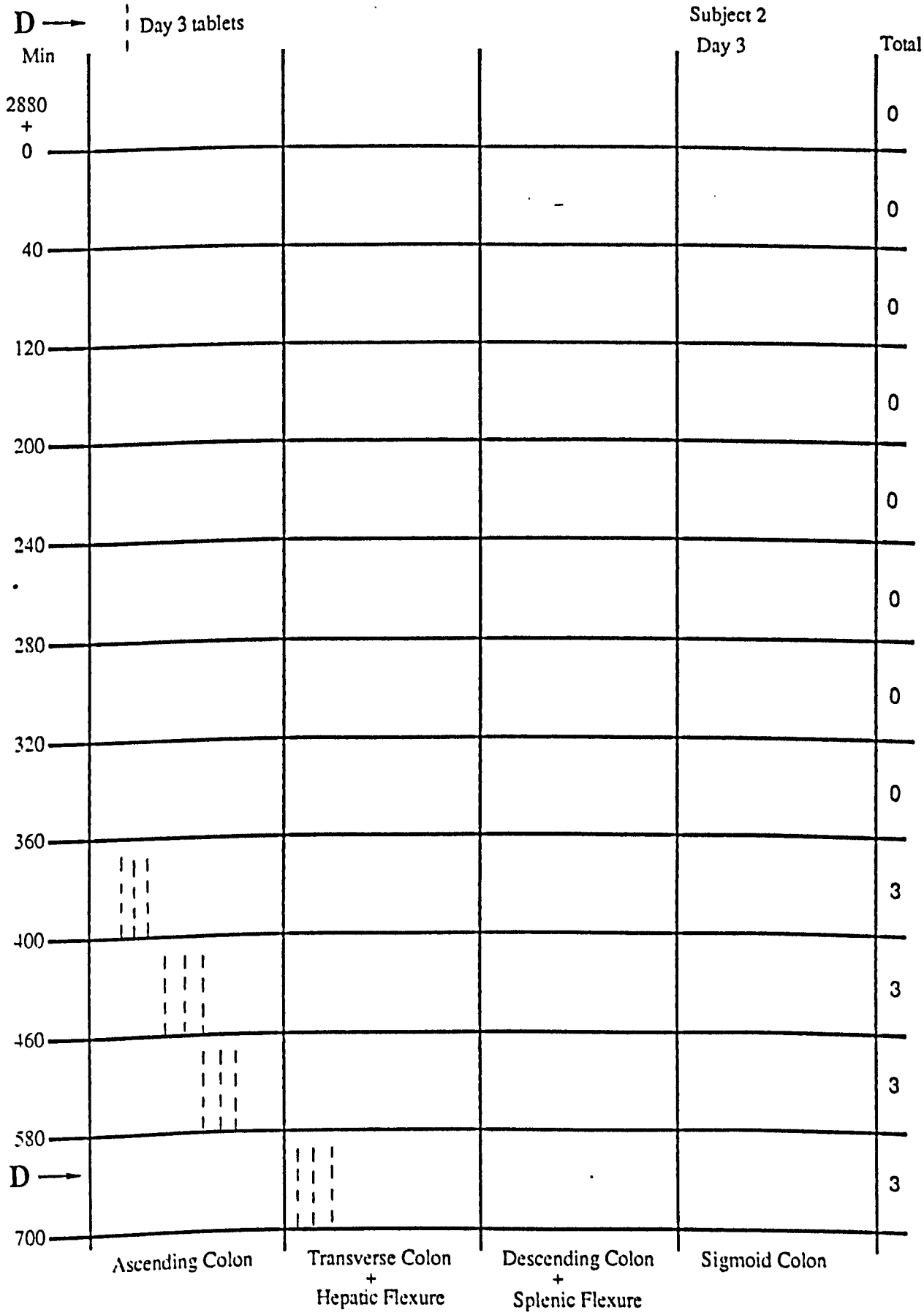
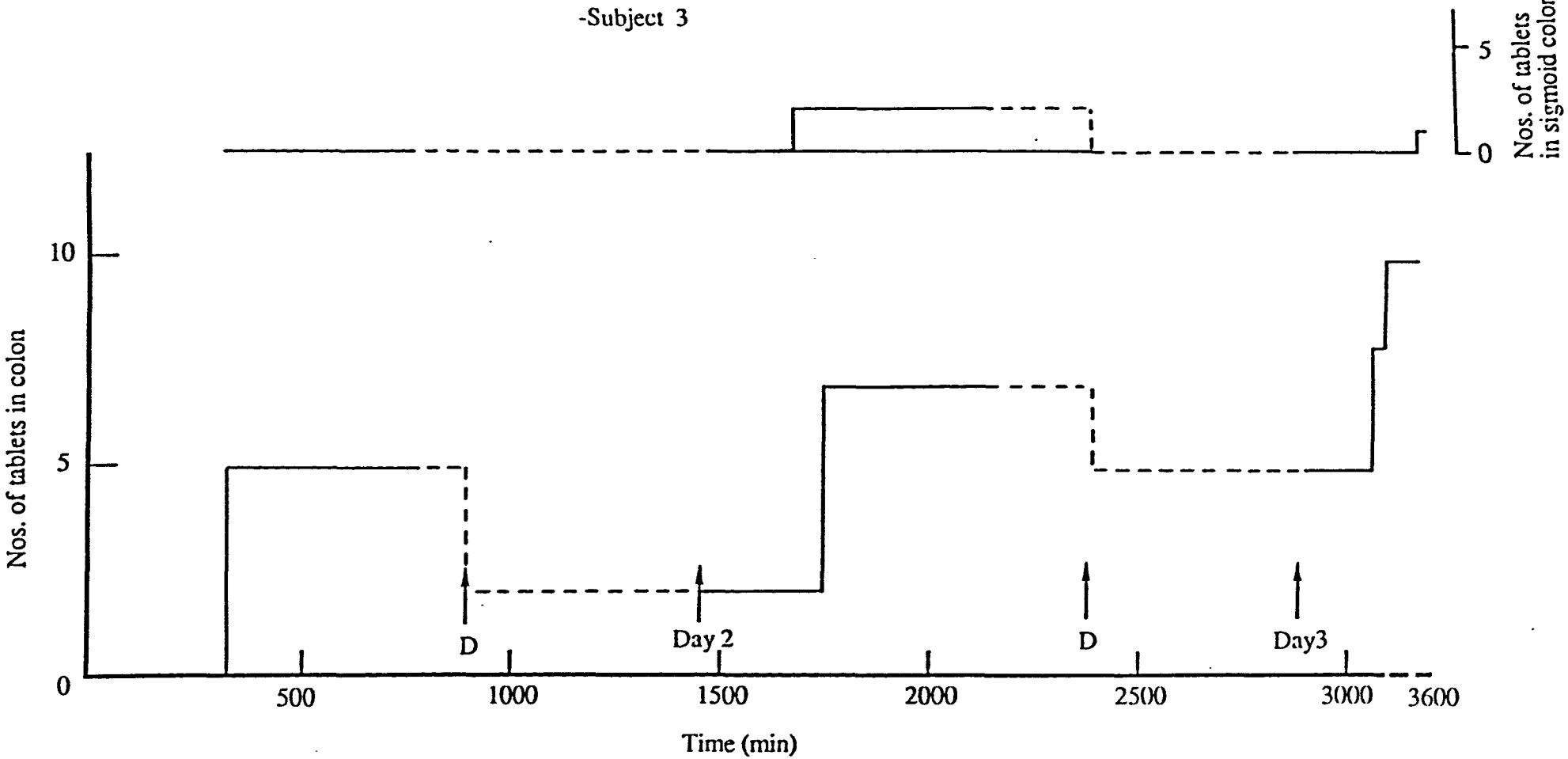


Figure 6.10c Colon transit of tablets.

Figure 6.11 Colon transit of tablets
-Subject 3

D – time of defecation



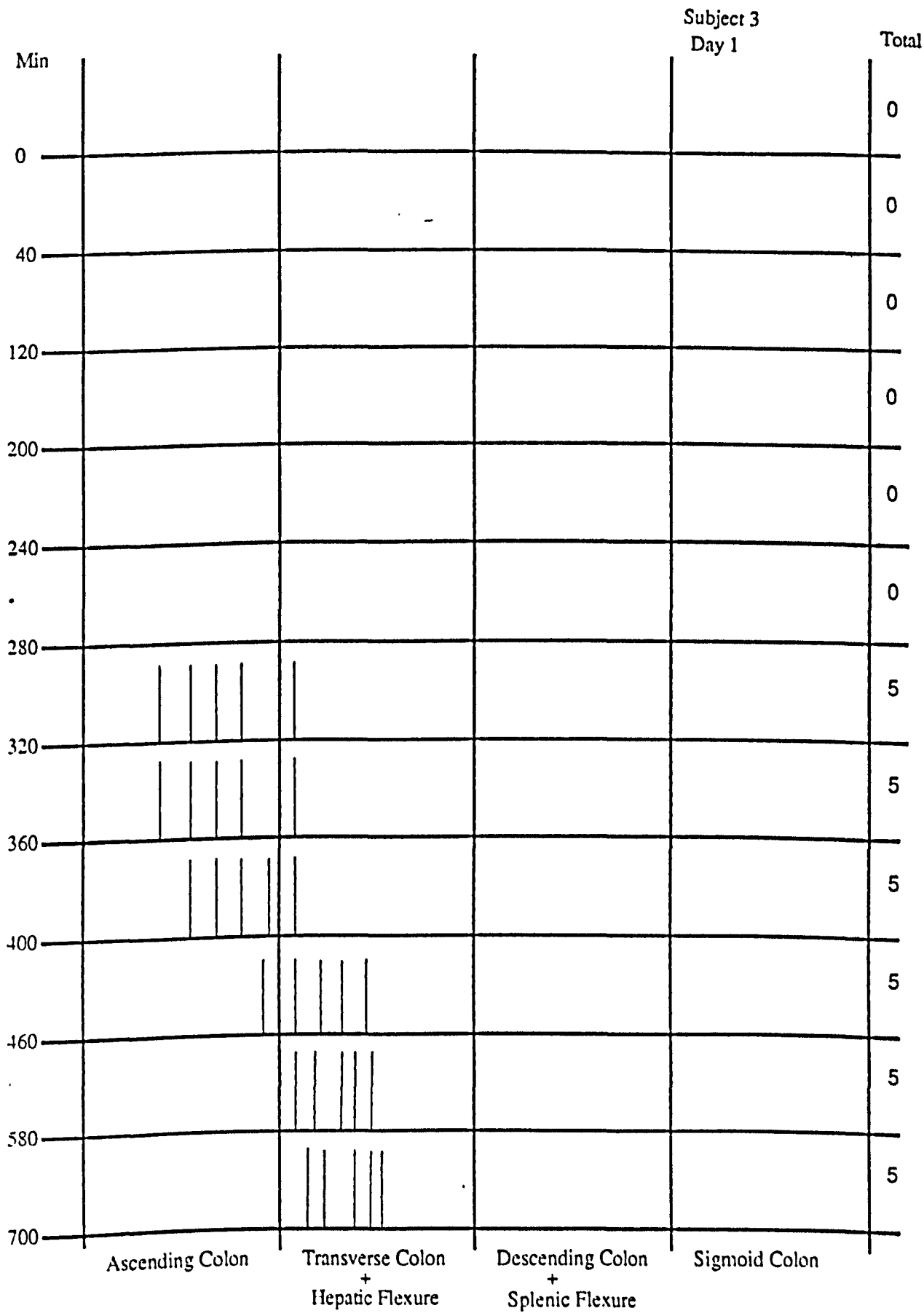


Figure 6.12a Colon transit of tablets.

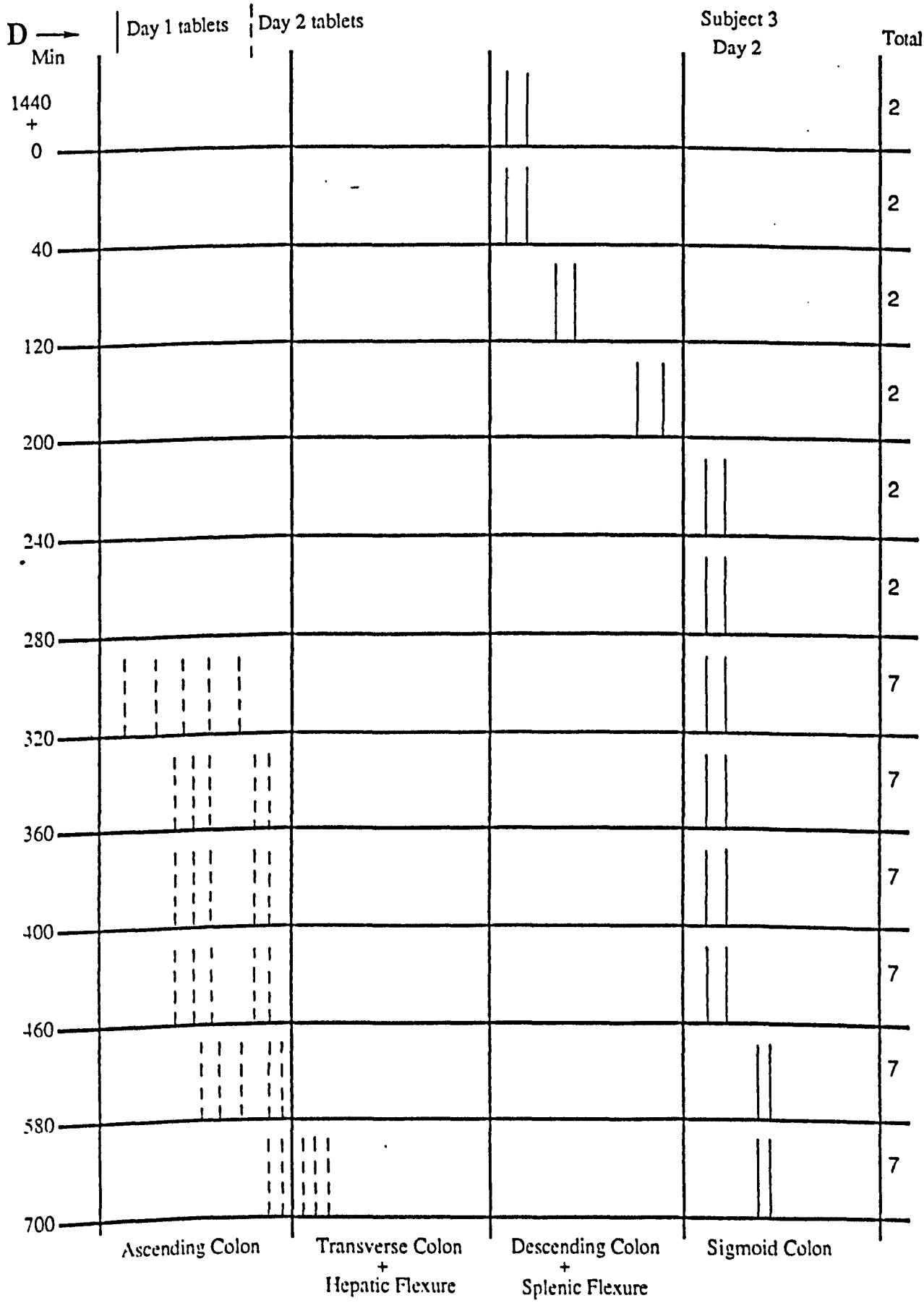


Figure 6.12b Colon transit of tablets.

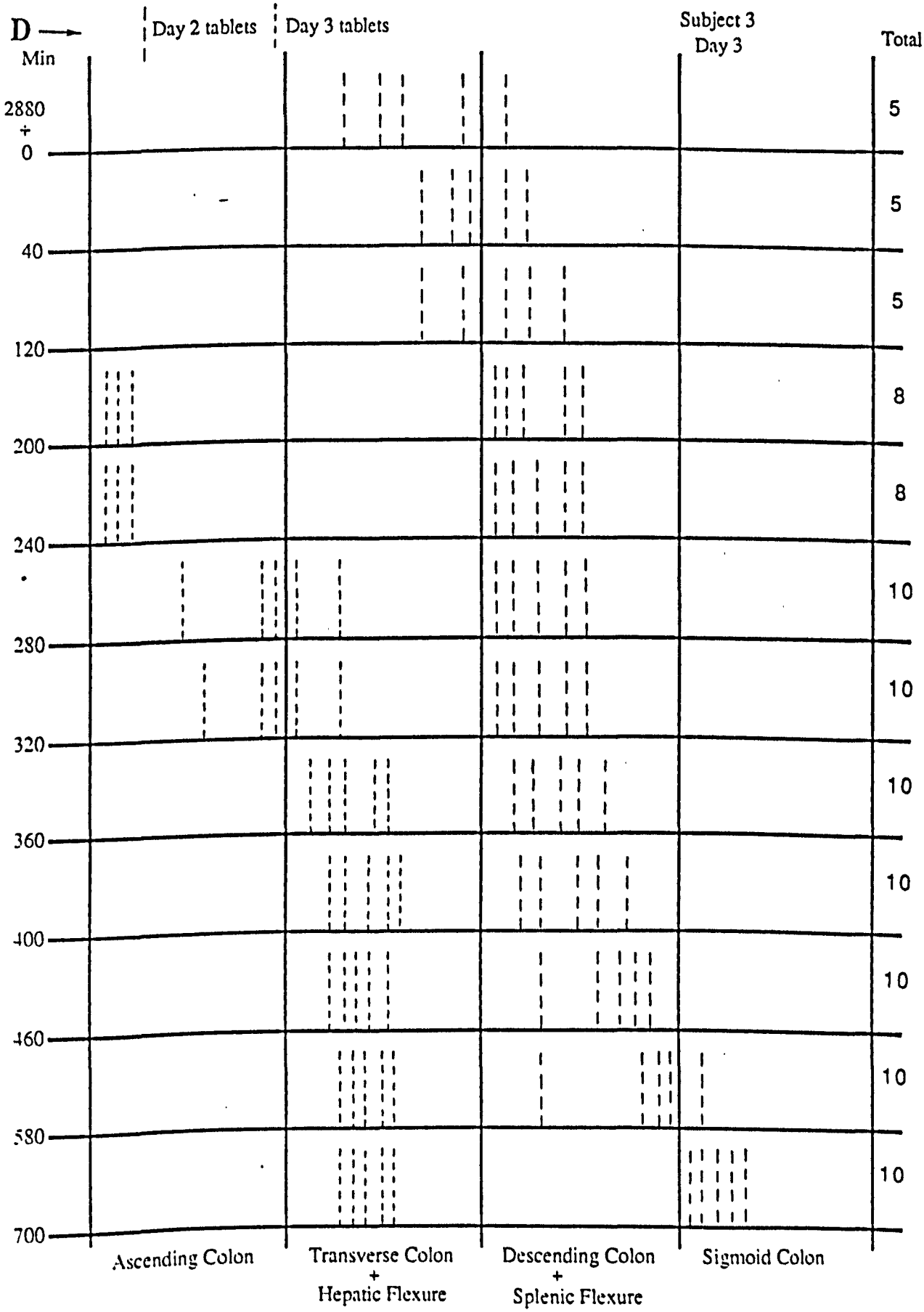


Figure 6.12c Colon transit of tablets.

CHAPTER SEVEN:

FUTURE WORK

7.1 Future Work

The studies described in this thesis form part of a general programme to investigate the gastrointestinal transit of dosage forms. These studies were designed to evaluate the influence of both physiological and pharmaceutical parameters on gastrointestinal transit. The ultimate aim is to rationalise the performance *in vivo* of oral dosage forms, and subsequently design physiologically competent CDDS. The obligation of the pharmaceutical industry to define the gastrointestinal transit of all new formulations, in fed and fasted subjects, has been suitably expressed (426).

The majority of studies to date, have been conducted using healthy subjects. Whilst these studies provide a basic understanding of gastrointestinal transit, their absolute relevance to the clinical environment is fairly questionable. Differences in gastrointestinal motility between patients and healthy individuals, may have a significant effect on the transit and dispersion of CDDS. Future studies, conducted with patient volunteers, would be of considerable value. Similarly, most studies have mainly considered the transit of placebo formulations. Future work should also concentrate on combined bioavailability and transit studies. These would provide information on site-specific absorption, the effect of drugs on motility, and the extent of drug absorption in

the colon. Naturally, the ethical restraints of such studies should be realised.

The need to regulate the gastric emptying of dosage forms has been expressed on a number of occasions. The two methods investigated in this thesis, the size of tablets and mucoadhesion, did not prove successful. The impracticality of using tablet size as a controlling factor has already been mentioned. Further work is required to prove the usefulness of mucoadhesives. Coated systems, as opposed to admixtures, may be more successful. Two other strategies which merit investigation are:

i. incorporate fatty acids (330)/tryptophan (427), which are active at specific duodenal receptors, into formulations; the quantities required to produce a physiological response, in man, may prohibit their use;

ii. the use of gel forming materials, such as guar gum, to increase gastric viscosity (31); however, the quantities required to slow gastric emptying may also restrict their use.

Further studies are also required to investigate the transit of dosage forms through the ileocaecal sphincter and colon .

A major drawback to transit studies is the sample size, in each study. Criticism has been drawn that the

small number of subjects participating in each study, prevents any definitive conclusion being made from the study. However, as more studies are conducted, the accumulated data should provide a representative principle for the transit of dosage forms through the gastrointestinal tract.

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