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Review Article

Imaging and behaviour of solid oral dosage forms in vivo

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Introduction

Many studies have been directed towards an understanding of the manufacturing processes and properties of solid oral dosage forms. Despite this, the development of such products is essentially empirical, although increasingly guided by the results of such studies. This empiricism is, however, required as the majority of solid pharmaceutical systems are, of necessity complex. The results of scientific studies on simple, well-defined systems, cannot therefore always be directly applied in practice. In addition, there is a lack of understanding of the behaviour of solid pharmaceuticals after administration.

It may be argued that the ultimate test of a solid oral dosage form is the blood level achieved by the drug. However, if the behaviour of solid dosage forms in the gastrointestinal tract is understood, then it may be possible to formulate in such a way as to maximize the potential of the drug. This is particularly true for sustained release and other novel approaches to solid oral dose formulation. In vitro disintegration and dissolution tests are essential procedures in development and quality control. They cannot, however, mimic in vivo conditions. In order to understand the behaviour of solid dosage forms after administration, it is essential that experiments are carried out, in vivo, in man.

This review is concerned with the techniques available for such studies, and the results achieved.

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General considerations

Solid oral dosage forms are generally swallowed whole with a draught of water. The dose form passes through the oesophagus into the stomach where it will remain for a period of time. During this time it may disintegrate and dissolve to a greater or lesser extent. The residence time in the stomach and the amount of dissolution occurring will be important as drugs must be in solution to be absorbed and the major site of absorption is the small intestine. The absorption of a given drug may not, however, occur equally along the length of the small intestine (Koch-Weser and Schecter, 1979). Hence, the rate of transit through the intestine will also be important.

There are, thus, an enormous variety of physiological and pharmaceutical factors that may influence the ultimate absorption of the drug. The realization of the importance of these factors has been the stimulus for much of the work to be described.

Techniques

An awareness of the value of understanding the behaviour of dosage forms is not new. Earlier workers employed techniques which may appear bizarre, simply because sophisticated imaging equipment was not available.

Direct methods

Several direct methods of observation of solid dosage forms have been published. Gruber et al. (1958) and Steinberg et al. (1965) used tablets which were attached to lengths of string. The tablet could be withdrawn at a given time interval and examined for disintegration. Steinberg et al. (1965) also induced vomiting in volunteers who had swallowed tablets. Recovered tablets could then be examined for changes. Direct observation of a tablet or capsule in the stomach can be achieved by the use of a fiberscope or gastroscope, instruments routinely used for observation of the stomachs of patients with gastric disease. This technique has been employed by Weiss et al. (1961), Steinberg et al. (1965) and Hey et al. (1979).

The use of ileostomy patients in monitoring transit times has been described by Bechgaard and Ladefoged (1978). Examination of the contents of ileostomy bags at timed intervals after administration of a dosage form gave information on transit times.

Imaging techniques

The inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by the use of X-rays. This method was first used by Losinsky and Diver (1933) but has been employed by many subsequent workers (Steinberg et al., 1965; Levy, 1963; Evans and Roberts, 1981). In a similar manner, the inclusion of a gamma-emitting radionuclide in a formulation allows indirect external observation using a gamma camera or scintiscanner. A typical set-up is shown in Fig. 1. Most systems are able to separate emissions on the basis of different photopeak energies

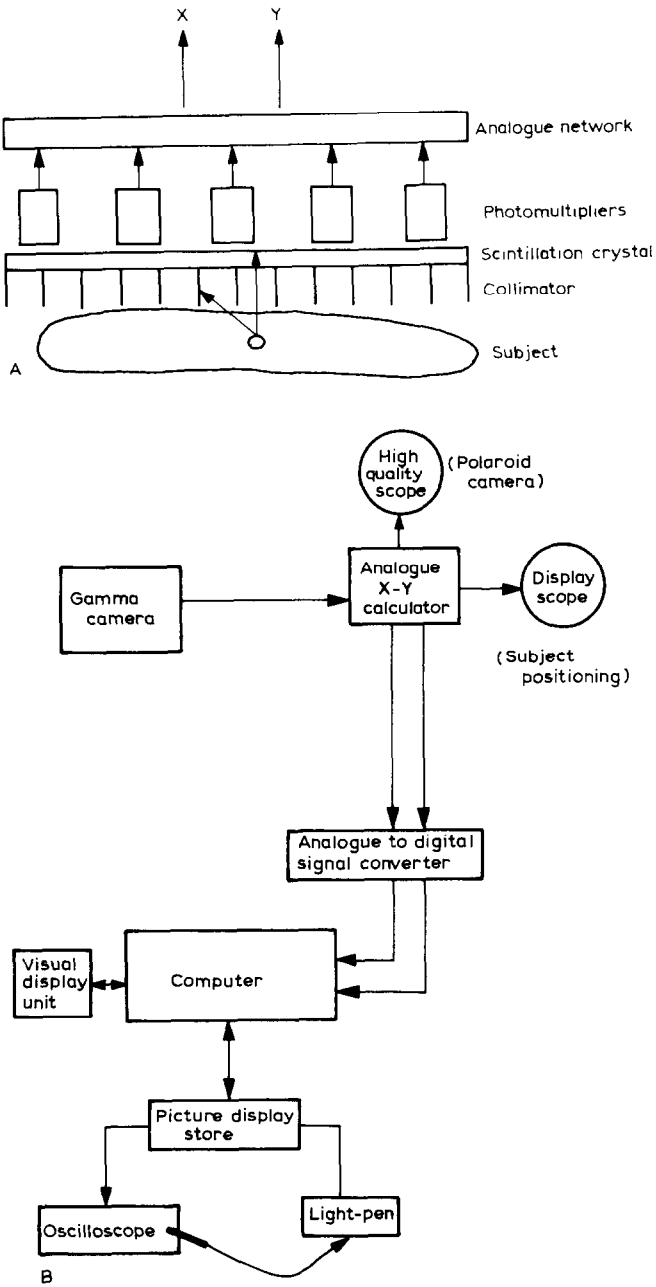

Fig. 1. A typical gamma camera system. A: radiation photons from the source pass through the collimator and strike the sodium iodide cystal. The resultant flash of light is detected by photomultiplier tubes. B: the 'information' determined by the photomultiplier tubes can be displayed on a cathode ray oscilloscope and is digitized so that it can be stored on magnetic disc and subsequent quantitative image processing can be performed.

so that two isotopes may be monitored simultaneously and independently. Although the use of these techniques are widespread and well established in nuclear medicine (Maisey, 1980), it was not until the almost simultaneous publications of Casey et al. (1976) and Alpsten et al. (1976) applying the technique to pharmaceuticals, that interest was aroused. The subsequent growth in the use of this technique can be judged by the holding of two symposia at the University of Nottingham, U.K. (1979, 1981) on the subject and the publications of the collected lectures and posters presented at the second symposium (Wilson and Hardy, 1981).

All of these techniques have their limitations and drawbacks, some of which are immediately obvious. The use of X-rays involves exposing a patient to a fairly high radiation dose as several photographs must be taken. Information cannot be obtained on a continuous basis and radio-opaque materials, such as barium sulphate, have a high density and may not be good models for most pharmaceuticals. Gastroscopy, while providing direct observation of material in the stomach is an invasive procedure which may cause abnormal behaviour of the solid dose form. These objections are overcome by the use of gamma scintigraphy which is non-invasive, exposes the patient to only low radiation doses and obtains information on a continuous and quantitative basis. In general, however, a drug itself cannot easily be labelled and reliance must be placed on a suitable model. Several are available which are close in physical characteristics to many pharmaceuticals (Casey et al., 1976; Hunter et al., 1980; Daly et al., 1981). A further limitation to this technique is that it cannot distinguish between a radionuclide present as a solid, and that present in solution. This may be overcome by the use of perturbed angular correlation studies as described by Beihn and Digenis (1981). Radionuclides which decay by emitting two gamma rays in cascade, such as ^{111}In, emit the rays with a certain angular correlation between them. This can be perturbed if the physical environment of the nucleus changes, for example, by dissolution. Hence, this affords an approach to monitoring the location and dissolution of a dosage form in vivo, by using simultaneous perturbed angular correlation studies and gamma scintigraphy.

Of the techniques that have been used for in vivo studies, that of gamma scintigraphy, perhaps coupled with perturbed angular correlation studies, appears to be the most useful. The majority of work currently undertaken in the field of examining solid dose forms in vivo has adopted this technique and many of the findings discussed in the next section are based on its use.

Studies on in vivo behaviour

The discussion concerning the results obtained using the aforementioned techniques will be divided into oesophageal transit, behaviour in the stomach and gastric emptying and intestinal transit. These are natural divisions although many of the studies address themselves to more than one aspect.

Oesophageal transit

As most solid dosage forms are swallowed with water, it may be considered that transit of material to the stomach should be relatively free of problems. Several

studies have shown that this is not the case. Sticking of tablets and capsules is of consequence as certain drugs are known to cause oesophageal damage, e.g. emepromium bromide, potassium chloride and some antibiotics (Collins et al., 1979). Evans and Roberts (1976) examined the ability of patients to swallow tablets of barium sulphate which were similar in size and shape to those of aspirin. The tablets were found to remain in the oesophagus for over 5 min in half the patients studied. Further studies with capsules (Evans snd Roberts, 1981) showed similar effects, but the propensity for sticking was less. Channer and Virgee (1982) showed that the posture of the patient and the volume of water consumed during administration affected the sticking of capsules, increased volumes of water and an upright posture reducing the number of capsules sticking. Similar results were obtained by Hey et al. (1983) who also noted that the size of the tablet or capsule influenced the rate of sticking. Capsules seemed less prone to stick than tablets and were less influenced by changes in size, posture and fluid volume. All these studies employed tablets and capsules containing barium sulphate and visualization using X-rays and are therefore subject to the drawbacks mentioned earlier. Fisher et al. (1982) used gamma scintigraphy to observe oesophogeal transit of various materials upright and the capsule was swallowed with water. However, the capsules used were filled with radiolabelled filter paper so the relevance to pharmaceutical systems is limited.

This area is of obvious clinical significance and further studies on systems analogous to 'real' pharmaceuticals would be useful.

Behaviour of solid dosage forms in the stomach and gastric emptying

Early work on this subject was concerned with evaluating the success of enteric coatings. Bukey and Rhodes (1935) determined the point and time of disintegration of barium sulphate tablets coated with a variety of enteric coatings. Some disintegrated in the stomach, others in the descending colon. Gruber et al. (1958), using X-rays, showed their enteric coating system to be successful and found that subjects lying on their left sides exhibited delayed gastric emptying compared with when they were erect.

Levy (1963) found that the agitation of tablets in the stomach, observed by X-rays, was mild. This observation was significant not only in deciding on stirring conditions for in vitro dissolution rate tests but also suggested that the behaviour of certain pharmaceutical dosage forms in the stomach could be studied by external scintigraphic techniques. Substantial movement of the dosage forms in the stomach would have resulted in erroneous readings of radioactive emissions by the gamma counter (inverse square law). In addition, tablets that disintegrated rapidly in vitro did not disperse throughout the stomach but remained as aggregates. Similar observations were made by Weiss (1961) using gastroscopy. Aspirin tablets were found, in some cases, to adhere to the mucosa appearing as a white gelatinous mass of granules. In a later study, Hey et al. (1979) observed the behaviour of pivampicillin capsules and tablets, in fasting subjects, by gastroscopy. The material was found to spread to a greater or lesser extent over the gastric mucosa. These studies emphasize that the behaviour of tablets and capsules in the stomach is vastly different from that observed during in vitro disintegration tests. The dosage forms

used in the aforementioned studies all behaved adequately in vitro, and yet, in vivo, the majority of the observations showed that dispersion was limited. Similar observations were made by Digenis et al. (1984) who found that a lack of correlation existed between the in vitro and in vivo disintegration behaviour of a paper dosage form (Digenis, G.A., Goldberg, A., Mlodozeniec A. and Beihn, R., unpublished data). It is significant that all these studies were conducted on fasting subjects and the stomach would therefore contain minimal amounts of fluid.

The application of gamma scintigraphy or scintiscanning to the study of dosage forms has enabled continuous and quantitative assessment of behaviour to be made. Qualitative observations using these techniques have tended to confirm the results of earlier observations. Thus Casey et al. (1976), using capsules loaded with a labelled insoluble polystyrene resin, showed that dispersion of the capsule contents did not commence until 30–40 min after ingestion when the subjects were fasting and 93–120 min on a full stomach. When the capsules contained a water-soluble material, the initial release was more rapid, occurring after 6 min. Hunter et al.

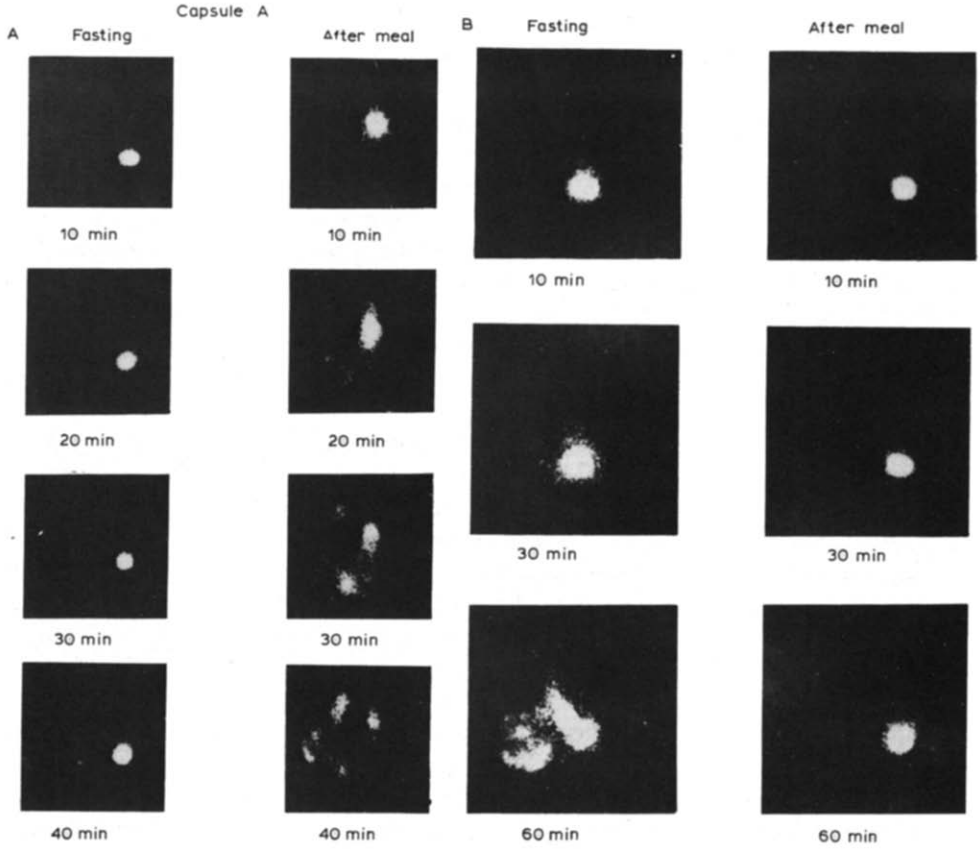

Fig. 2. Scintiphotos of capsules in the fasting and non-fasting states. A: capsule with a rapid in vitro disintegration time (B.P. 2 min). B: capsule with a slow in vitro disintegration time (B.P. 9 min).

(1980), using capsules filled with a labelled insoluble ion exchange resin, showed that dispersion in the stomach was limited when the subjects were fasting, but occurred more readily after the subjects had ingested a meal with a high liquid content. These capsules had rapid in vitro disintegration times. Studies with capsules that had slower in vitro disintegration times showed a lack of dispersion in both the fasting and non-fasting states (Fig. 2). Because of this lack of dispersion, a large proportion of material could be emptied, as a bolus, from the stomach into the duodenum. This was found for conventional powders (Hunter et al., 1980) as well as for beads similar in size to sustained release preparations (Hunter et al., 1982).

Interesting observations on the effect of density have been reported by both Digenis (1982) and Muller-Lissner and Blum (1981). Both found that tablets with low density remained in the fundus of the stomach whereas denser tablets sedimented to the more distal regions.

The data obtained from such studies has been quantified in two ways: the determination of an in vivo disintegration time; and the measurement of gastric emptying.

The determination of a disintegration time involves the selection of an arbitrary end-point, and several have been suggested. Casey et al. (1976) monitored the decrease in activity in a selected area of interest over the dose form and the concomitant increase in activity in a region in the lower pylorus. A typical result is shown in Fig. 3. Problems may occur in some cases using this method as the capsule contents may move as a whole into the pyloric region and a false impression of

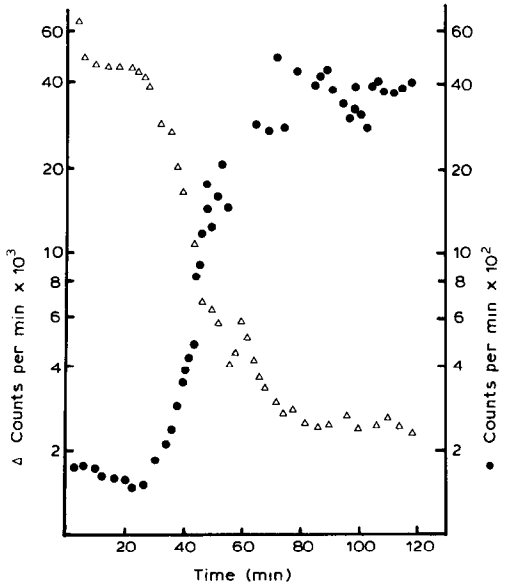

Fig. 3. The release of radioactivity from a hard gelatin capsule in a fasting volunteer showing: (△) the disappearance of activity from the region of the capsule and (●) the increase in activity in the pyloric region of the stomach.

disintegration may be obtained (Fell et al., 1982). More recently a simple mathematical technique has been developed to correct for interference from background radioactivity arising from dissolution of the radionuclide from the dosage form (Goldberg, A., Mlodozeniec, A., Beihn, R. and Digenis, G., unpublished data).

Thus, if it is assumed that the background radiation is uniform over the entire area, then the net dosage form counts (CD) may be found from the following two equations:

$$C1 = CD + F \times CB \tag{1}$$

$$C2 = CD + CB \tag{2}$$

where CB = background counts (not including dosage forms); CD = dosage form counts (not including background); F = ratio of dosage form measurement zone to total area (usually 16 mm/256 mm); C1 is the number of counts from the dosage form plus the number of background counts from the zone of the dosage form; and C2 is the number of counts from the dosage form plus the number of background counts from the total area.

Eqns. 1 and 2 may be solved for CD, and the resulting expression is:

$$CD = \frac{C1 - F \times C2}{1 - F} \tag{3}$$

where CD = dosage form counts (not including background).

The amount remaining in the dosage form is determined from the expression:

$$\text{Amount remaining} = \frac{CD_0 - CD}{CD_0} \times 100\% \tag{5}$$

where the subscript 0 refers to be corrected activity at zero time. Lagas et al. (1980) determined the rate of distintegration in vivo by monitoring the number of radioactive counts in the channels over the dosage form, subtracting this from the total counts in all the channels and dividing by the total counts. This gave a percentage disintegration at a given time. Comparison of capsules containing benorylate, a hydrophobic drug, and benorylate treated to render it hydrophilic showed large differences in the rate of disintegration. This work is interesting as the benorylate was prepared by precipitation in the presence of [^{99m}Tc]tin colloid to produce a 'labelled drug'. Alpsten et al. (1979) considered that disintegration of a capsule had occurred when the shape, as seen on a monitor, changed from punctate to a broadly distributed source. On this basis, the disintegration times of two capsule formulations were determined. These are shown in Table 1. The in vitro disintegration times were 1–2 min (B.P. 1973) or 2–4 min (Pharm Nord). Because both end-points are arbitrary in nature, comparisons such as this must be viewed cautiously. However, these results support those discussed previously in that disintegration and dispersion can be limited when compared with in vitro predictions.

TABLE 1

DISINTEGRATION TIMES OF 2 HARD GELATIN CAPSULE FORMULATIONS IN VIVO (MIN)

Subject	Formulation 1 Acetylsalicylic acid granules	Formulation 2 Acetylsalicylic acid granules Enteric coated
1	25	20
2	8	26
3	20	12
4	8	12
5	–	20
6	12	20
Mean	15	18

Current research into gastric motility and transit distinguishes two separate states: the fed mode and the fasting mode. The fed mode commences when food enters the stomach and is characterized by continuous contractile activity which gives rise to the grinding of food particles, emptying, when these reach a 'liquid' consistency and retropulsion back into the stomach to effect further size reduction. Indigestible solids are held back in the stomach. The fasting mode consists of a period of limited activity which gradually increases to a period of intense contractions, the migrating motor complex, which sweeps the fasting contents out of the stomach and migrates down the intestine. This is sometimes called the housekeeper effect (Hinder and Kelly, 1977; Meyer, 1980).

The use of gamma scintigraphy to quantify gastric emptying is subject to debate as to whether a single-sided measurement is appropriate, or the geometric mean of a front- and rear-view should be used (Tothill et al., 1978; Christian et al., 1983). In addition, problems may occur with regard to the avidity of the label, especially when two labels are used to distinguish between, for example, the solid and liquid components of a meal (Jobin and Jian, 1982). Information on abnormalities in the pattern and rate of gastric emptying is clinically useful. Digenis et al. (1977) pointed out the shortcomings of many materials used to monitor gastric emptying and listed the characteristics of an ideal material as: (1) not influencing the osmolality of the stomach contents; (2) non-absorbable and non-adsorbable; (3) to bind the radionuclide tenaciously and not exchange it with food or the stomach wall; (4) to possess ideal food mixing characteristics and have a particle size comparable to foods; and (5) be non-toxic and inert and give reproducible and non-invasive estimates of the gastric emptying time without exposing the patient to a high radiation dose. Such a material, triethylenetetramine-polystyrene resin, was synthesized by these workers and has since been adopted for the study of gastric emptying abnormalities (Domstad et al., 1980). Quantitation of the gastric emptying of meals or meal components is often achieved through the use of a half-time as emptying is often found to be linear or exponential with time. This is inappropriate for pharmaceuticals which may be emptied partly dispersed and partly undispersed. Because of this, Hunter et al.

(1983) used a gastric emptying index as defined by Grimes and Goddard (1977) to compare the gastric emptying of different capsule formulations. Differences in behaviour were shown for capsules which were poorly disintegrating in vitro, rapidly disintegrating in vitro or soluble. The fasting state of the subject was also important. In addition these authors were able to classify the gastric emptying patterns into the 5 types shown in Fig. 4. Kaus et al. (1984) used the areas under log % radioactivity in the stomach against time curves as a means of quantifying the gastric emptying of the soluble and insoluble components of a capsule formulation. The study showed there was no significant difference in the emptying between the soluble and insoluble components of the formulation chosen.

In normal subjects, liquids empty faster than solids. In these experiments the capsule shell must first rupture or dissolve to allow the soluble material to dissolve in the stomach contents. Much of the liquid swallowed with the capsule will have already emptied and hence emptying of the soluble component will be slower than expected.

The studies described previously have been concerned with dispersion and disintegration but the possibility of measuring dissolution rates in vivo would be of immense value. In specific cases, this can be done using conventional gamma scintigraphy or scintiscanning. Alpsten et al. (1976) measured the release of ferrous

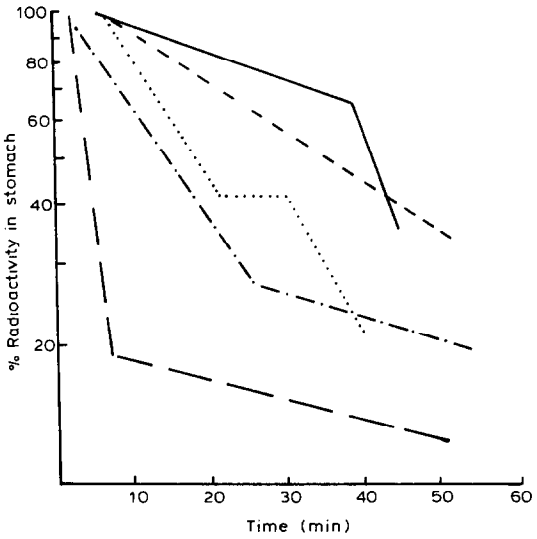

Fig. 4. Classification of gastric emptying patterns observed with hard gelatin capsules. ------, Type 1—monoexponential emptying when the capsule contents were well dispersed in the stomach. ·–·–·, Type 2—biexponential emptying with the first phase faster signifying some dispersion of the capsule's contents. — — —, Type 2-R—biexponential with the first phase very rapid when much of the capsule was emptied as a whole into the duodenum. ———, Type 3—biexponential emptying with the second phase faster than the first due to partial dispersion followed by rapid emptying of the contents as a whole. · · · · · ·, Type 4–a stepwise pattern occurring with little dispersion of the capsule's contents.

sulphate (as ^{59}Fe) from slow release tablets, and found a slower release in vivo than that given in an in vitro test. In this connection enteric coated and uncoated ferrous sulphate tablets (labelled with two different radionuclides) were recently administered to healthy human subjects (Digenis et al., 1984; unpublished data). Prolonged stomach retention times of the coated tablets were observed when the two formulations were administered at the same time. In contrast, however, shorter stomach retention times for the coated tablets were noticed when the fast disintegrating ferrous sulphate tablets were administered one hour after the ingestion of the coated tablets. This discrepancy in the stomach retention times of the coated tablets may be explained by the presence of the ferrous sulphate, in the case of co-administration of the two formulations, which is known to cause slower gastric emptying rates. This may also explain the slower in vivo release of ferrous sulphate from tablets as compared to the in vitro experiments obtained by Alpsten et al. (1976). Daly et al. (1982) used [^{99m}Tc]-labelled diethylenetriamine pentacetic acid (DTPA) as a model for chlorpheniramine in sustained release tablets. The release rates of the two materials in vitro were comparable – in vitro and in vivo release rates for the labelled DTPA were similar.

A more general method would obviously be desirable and the use of combined gamma scintigraphy and perturbed angular correlation measurements offers this possibility (Beihn and Digenis, 1981). A typical result is shown in Fig. 5 showing a delay in the onset of dissolution. The drawback of the method is that it monitors the dissolution of the radionuclide and not the active ingredient. However, the use of appropriate models or the recrystallization of the drug in the presence of the radionuclide to label the drug crystals may make the technique of general value.

Intestinal transit

The measurement of transit rates through the intestine is complicated by the coiled nature of the intestine and the difficulty of locating precisely the object or

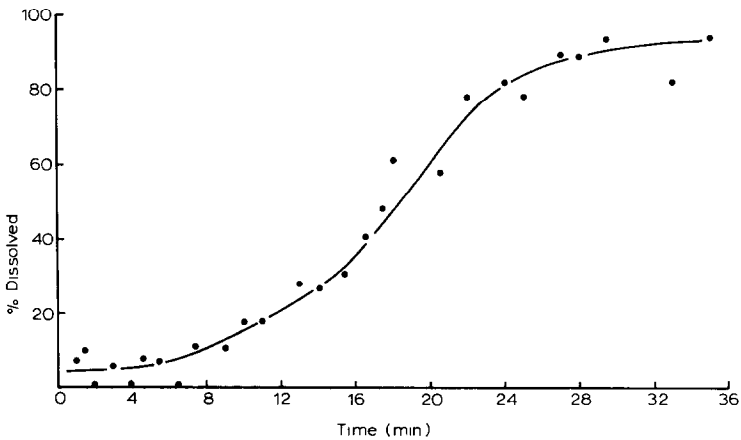

Fig. 5. The dissolution rate of indium-111 chloride from a lactose tablet in a human subject measured using perturbed angular correlation. Note the delay in the onset of dissolution.

objects under study. Several studies have been made on overall transit times and relationships to intestinal motility (Bond and Levitt, 1975; Ruckebusch and Fioramonti, 1975; Jian et al., 1979), but rates of transit in the various regions of the intestine have received less attention (Reed et al., 1980). Studies on pharmaceutical materials or systems allied to pharmaceuticals are few. Rosswick et al. (1967) studied the passage of a 1 cm diameter object through the intestine. Transit times of the small intestine varied from 1.5 to 16 h with a mean of 4 h 38 min. Hinton et al. (1969) examined the passage of pellets of radio-opaque polythene but measured only an overall transit time from the mouth to appearance in the stools. In 25 normal subjects, all passed the first pellets within 3 days and most passed 80% in 5 days.

Bechgaard and Ladefoged (1978) examined the gastrointestinal transit times of pellets of different densities in ileostomy patients. The contents of the ileostomy bags were examined at time intervals for the presence of pellets. The average transit time (time for 50% of the pellets to reach the bag) varied with the density of the material but not the diameter of the pellet. The average time for pellets of density 1.0 was 7 h whereas it was 25 h for pellets of density 1.6. The study did not differentiate between gastric emptying times and intestinal transit. Such large differences in times may be a useful formulation variable, although work by Bogentoft et al. (1981) failed to confirm the finding. In a further study, Bechgaard and Ladefoged (1981) examined the transit of non-disintegrating tablets. These

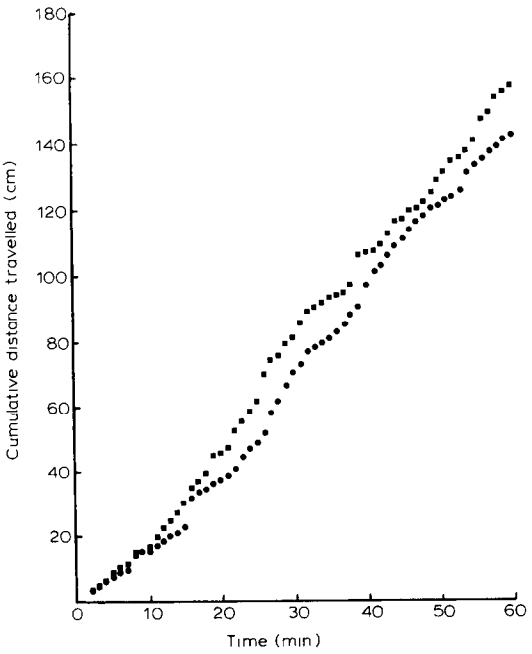

Fig. 6. The cumulative distance travelled down the intestine against time for a non-disintegrating perspex capsule administered to a fasting volunteer. ■ = specific gravity 1.03; ● = specific gravity 1.61.

tablets showed a much greater variability in transit times compared to the pellets, which was regarded as being a result of variable gastric emptying, although this factor was not quantified.

Kaus (1983) used gamma scintigraphy in fasting subjects to monitor transit rates down the small intestines. Using a non-disintegrating perspex 'capsule' containing ^{99m}Tc, images were obtained at alternate 30 s intervals with subject facing the camera and then side on. Comparison with markers taped to the subject allowed the determination of a three-dimensional coordinate for the position of the 'capsule'. Plots of distance travelled against time are shown in Fig. 6 and are essentially linear. The time taken for the 'capsule' to leave the stomach varied greatly both between and within subjects. The rate of travel down the intestine was, however, much less variable. The passage through the duodenum was generally extremely rapid. Following this, the capsule travelled at a mean rate of between 4.2 and 5.6 $cm \cdot min^{-1}$ for the 1 h period of study. This is interesting as it is close to the figure of 4.7 $cm \cdot min^{-1}$ quoted by Kerlin and Phillips (1982) for the velocity of travel of the migrating motor complex down the intestine. Studies for longer periods of time showed that the rate of movement slowed as the capsule progressed down the intestine.

Conclusion

The use of the techniques described in this review, in particular, gamma scintigraphy, have enabled qualitative and quantitative information to be obtained on the behaviour of solid oral dosage forms in vivo. The technique is, of course, not restricted to such dosage forms, but finds application in other areas such as the in vivo melting and rate of dissolution of a drug from a suppository (Jay et al., 1983), in vivo migration of enemas (Hay et al., 1979; Farthing et al., 1979), transcervical migration of polylactic acid microspheres after intravaginal administration (Digenis et al., 1984) and erosion of biopolymer coating materials from pacemaker implants (Jay and Digenis, 1984).

It is expected that as formulation becomes more sophisticated to meet the objective of the controlled and precise release of drugs, so the use of such imaging techniques will increase.

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