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# ASSESSMENT OF DISINTEGRATION AND DISSOLUTION OF DOSAGE FORMS *IN VIVO* USING GAMMA SCINTIGRAPHY

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## ABSTRACT

The measurements of the *in vitro* rate of disintegration and dissolution of dosage forms are considered to be the most available predictors of the behaviour of dosage forms and the plasma concentration - time profile. However, the interaction of the formulation with physiological processes has shown that prediction of bioavailability by such simple tests is inadequate and has highlighted the need to establish methodology which would enable the determination of *in vivo* rates of dissolution and disintegration. Over the past ten years, the technique of gamma scintigraphy has made a significant contribution to the understanding of the behaviour of formulations in the body. This review provides an overview of the technique and its advantages and limitations in

pharmaceutical research, together with illustrations showing some of the applications in the measurement of disintegration and dissolution of dosage forms.

## INTRODUCTION

The bioavailability of a drug from a formulation is influenced by a complex interplay of physiological and physicochemical factors; however it is accepted that the primary determinant of absorption is the rate at which drug is released from the formulation into solution. This, in turn, is determined by the rate of disintegration of the dosage form, which increases the surface area and hence the amount of drug exposed to the medium. The drug must dissolve in the gastrointestinal fluids to be absorbed and hence the the absorption of many drugs, especially those with poor water solubility, is dissolution rate-limited.

The ability to control of the rate of presentation of a drug and achieve a desired *in vivo* behaviour, by manipulation of excipients in the formulation, became a major tool in formulation development and generated the need for *in vitro* tests which would allow the effects of manufacturing variables to be studied. The knowledge that the pH of body fluids changed along the gastrointestinal tract from stomach to colon increased the need for sophistication of the tests and attempts were made to begin to simulate *in vivo* conditions. The majority of drugs are weak acids or bases and the dissolution is therefore dependent upon the pH of the gut fluid. There is considerable variation in the pH within the gastrointestinal tract,

and most physiology texts state that the gastric pH is in the range 1 - 3, with a pH of 5 - 6 in the duodenum, increasing to 7 - 8 in the proximal jejunum and 8 in the large intestine. However, there is some evidence that the pH of the fasting stomach in man may be much higher (Kuna, 1964)

The muscular actions of the gastrointestinal tract stir and agitate the preparation during its transit, thus a paddle was incorporated into the dissolution apparatus to break-up the stagnant diffusion layers of fluid. Levy (1963) found that agitation of tablets in the stomach as observed by x-rays was mild and his observations were used to decide stirring conditions for *in vitro* dissolution tests. Further refinements include conducting the test at body temperature and the addition of digestive enzymes and surfactants such as pepsin, bile salts and lecithins, since these have been shown to affect *in vitro* dissolution (Mayersohn, 1979).

The ability to determine drug levels in body fluids enabled researchers to examine the effect of formulation variables on bioavailability. It soon became clear that the application of simple *in vitro* tests was inadequate to explain the behaviour of some preparations. The dissolution of a dose form and the release of a drug in some instances does not correlate with the absorption of the drug into the systemic circulation (Toothaker and Welling, 1980). The application of various designs of *in vitro* apparatus to simulate absorption was largely unsuccessful and investigators turned to other methods of trying to explain the relationship between the release characteristics of a formulation and the plasma concentration-time profile.

In addition, demand arose for more sophisticated formulations, especially sustained or controlled release preparations. This caused further problems in the establishment of the appropriate *in vitro* test. Interest in controlled release preparations was fuelled by three main objectives. Firstly, there were an increasing number of observations that certain drugs were irregularly absorbed from the gastrointestinal tract. This led to the concept of absorption windows, in which the intestinal contents or nature of the epithelium of specific areas of the gastrointestinal tract optimised absorption, and it became important to the pharmacist to take advantage of this phenomenon to increase bioavailability. Secondly, there was increasing attention paid to the application of enteric coatings and slow release products to avoid local toxicity. Thirdly, there was an attempt to improve patient compliance in multiple daily dosing regimens and the reduction of the minimization of 'peaks and troughs' in the plasma concentration time profile. This led to the development of new systems which attempted to reduce the number of daily doses of a drug, releasing the drug slowly within the gastrointestinal tract over a period of hours. These sustained release preparations can be formulated either as single or multiple unit dose forms. A major concern with sustained release devices is that since they contain up to a whole day's dose of drug in a single unit, they may "dose-dump" with serious consequences for the patient. Thus visualisation of the behaviour of the dosage form within the gastrointestinal tract became an important research goal to aid in the development of new technology systems.

Direct observation of the rate of disintegration for a solid dosage form *in vivo* have involved uncomfortable procedures for the subject.

Early measurements of rates of disintegration were carried out by attaching a string to the tablet, which was then swallowed and periodically recovered and weighed. Alternatively the tablet was recovered by inducing emesis (Steinberg et al., 1965). It is possible to directly observe the behaviour of tablets during endoscopy, but the patient has to be sedated. Dimethicone also has to be administered to prevent frothing of the stomach contents which would obscure the behaviour the the preparation. Such procedures are so invasive that they cannot be regarded as satisfactory as the basis of routine investigative techniques.

X-ray techniques have been widely applied to the study of the physiology of the gastrointestinal tract and the behaviour of tablets containing contrast materials. Roentgenography or fluoroscopy allows the dose form to be followed throughout the gastrointestinal tract; however, the radiation hazard to the subject is too high to permit the position of the dose form to be established with repeated images. The technique has been used to follow the oesophageal transit of dosage forms (Channer and Virjee, 1986) and the dispersion of multiparticulate systems (Galeone et al., 1981). X-ray techniques can be used to establish the time of disintegration of a formulation, but further quantification of the image is not possible. A further consideration is that the high density of the contrast materials e.g. barium sulphate (4.5 x kg $m^{-3}$), is very different to the density of most drugs and excipients (1.0 to 1.5 x kg $m^{-3}$ ); however, studies at Nottingham have shown that density in the range 0.9 to 2.0 x kg $m^{-3}$ does not affect gastrointestinal transit (Bechgaard et al., 1985).

## GAMMA SCINTIGRAPHY

The technique of gamma scintigraphy is well established within the field of nuclear medicine to monitor pathological conditions. Within the last ten years, it is increasingly being used to measure the *in vivo* behaviour of pharmaceutical dosage forms. Gamma scintigraphy allows the passage of the formulation throughout the gastrointestinal tract to be monitored and stasis of a formulation can easily be detected. The position of a formulation and the degree of dispersion within the gastrointestinal tract can be related to the simultaneous plasma concentration for the drug. Simultaneous pharmacokinetic and scintigraphic profiles for a formulation have facilitated the design of suitable dosage forms for drugs with poor bioavailability. The majority of drugs are absorbed from the intestine and factors affecting the delivery to this region, e.g. food, can be studied using a dual isotope technique.

The gamma camera has a large field of view, which can be split up into the equivalent of a matrix of several thousand finely collimated gamma detectors. The principle of operation may be described with reference to Figure 1.

The gamma camera consists of a detector linked to a computer. The radiolabelled formulation is administered to the subject who is positioned in front of the collimator. The gamma rays emitted from the formulation pass through the body and form an image on a 40 cm diameter thallium-doped sodium iodide crystal. A lead collimator is used to absorb the gamma rays which fall obliquely to the crystal. The gamma rays cause the emission of photons within the crystal

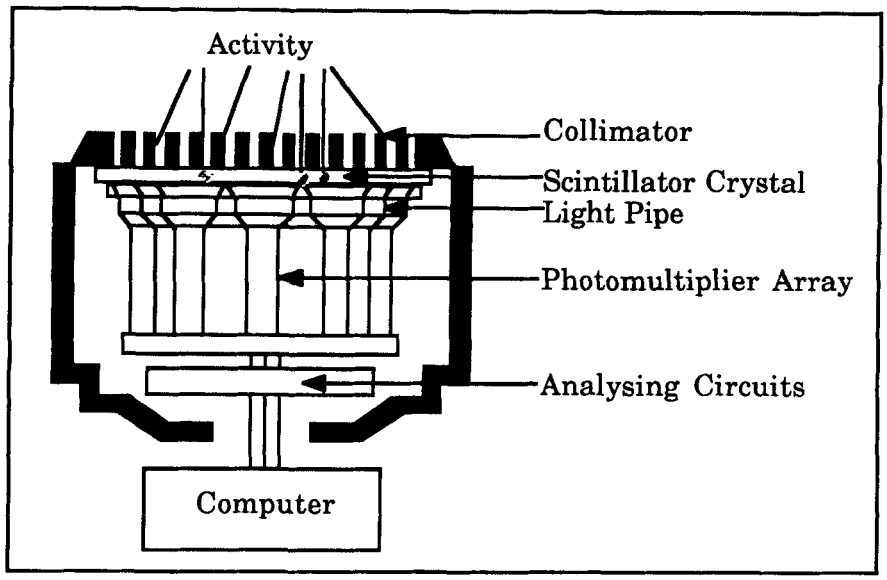


Figure 1 - Schematic of the gamma camera

and a hexagonal array of 37 or 74 photomultipliers mounted behind the crystal converts the light emitted into electrical signals, which are processed to obtain the x and y co-ordinates of the emission. The photomultiplier signal amplitude is related to the energy of the detected gamma photon, thus the photons from different isotopes can be distinguished. Information concerning distribution of the energy is stored as a pixel matrix on a minicomputer for later analysis.

Gamma camera imaging can be carried out using two alternative methods, static imaging in which single acquisitions are stored, and dynamic imaging in which a sequence of data of varying frame time can be obtained. The latter technique is used to follow rapid processes, such as drainage of an aqueous formulation from the eye. Acquisition of data can also be triggered by external events.

The most common applications are following wall motions of the heart, in which a set point in the ECG is used as the start point for a rapid series of short frames or the deposition of an aerosol in the lung using the point between inhalation and expiration as the start of the imaging cycle. It is necessary to add the frames from the same point in the cycle to obtain sufficient counts to form an image. Normally, gastrointestinal transit is sufficiently slow to be resolved by static imaging, however, dynamic imaging is required to study oesophageal transit.

An important advantage of this technique is that the field of view can be arbitrarily divided up into areas and the amount of isotope within these areas can be accurately quantified, and hence the movement and distribution can be followed. The division of an image into regions of interest is illustrated in Figure 2. To facilitate alignment of the images, anatomical markers consisting of small sealed sources are taped to the abdomen opposite the stomach both anteriorly and posteriorly to act as a reference points.

A limitation of the technique of gamma scintigraphy is that very little anatomical information is gained, unless the formulation outlines easily recognised organs such as the stomach and large bowel. When non-disintegrating matrix systems are studied, identification of the position of the object becomes difficult and it is necessary to administer a second radiopharmaceutical to outline the gastrointestinal tract. A radionuclide with a different energy is chosen and it is usually better to use a lower energy than that used to label the preparation, for example a solution of technetium-99m diethylenetriaminepentaacetic acid (DTPA) administered with a

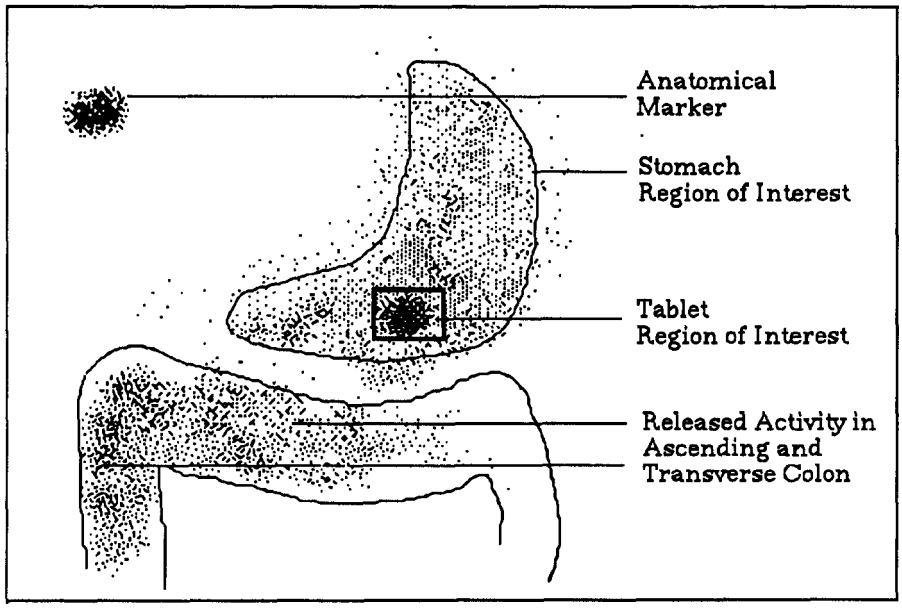


Figure 2 - Division of the image into regions of interest.

tablet labelled with indium-111. These two radionuclides have energies which can be discriminated by the gamma camera and two channels are used to acquire the simultaneous images from each marker. When the "softer" isotope is used to mark the tablet together with the indium as a liquid marker, there is a "scatter-down" of energy from the indium into the technetium channel which has to be corrected. The correction is made by subtracting a fixed proportion of one channel from the other. This correction factor is a fixed calculable function of the isotopes and will not vary within the course of the study.

Attenuation is a problem with "soft" gamma-emitters such as technetium-99m. Air does not attenuate gamma rays, but tissues

attenuate to a variable degree. The combination of attenuation and movement of the isotope in the anterior-posterior plane within the body produces a significant error. The fundus of the stomach lies more posteriorly than the antrum and thus as the material moves from the fundus to the antrum, the count rate in the anterior view rises. The counts in the stomach are greater in the anterior scans than the posterior, but as the tracer moves to the small intestine, the counts from posterior scans increase. The calculation of the geometric mean of anterior and posterior counts allows a partial correction for this error (Hardy and Perkins, 1985; Tothill et al., 1978). Hard gamma emitters such as indium-113m do not have the problem of attenuation, but the counting efficiency is lower.

The stomach and large bowel have a characteristic appearance in the gamma camera image hence the exact position of the formulation can be visualised directly within these areas. The small intestine is more convoluted, folding back on itself and hence the position of a single unit cannot be accurately identified by gamma scintigraphy with anterior- posterior imaging. This limitation was overcome for a single non-disintegrating unit in the study by Kaus and coworkers (1984a) who imaged from the front and the side, and used three dimensional coordinate geometry to calculate the position of the dose form. Images were aligned by placing a square array of markers visible in each image.

The small intestinal transit time (SITT) for single objects is more commonly calculated as the time from the object leaving the stomach to its arrival at the ileocaecal junction. For diffuse sources such as pellets, suspensions or a meal, the SITT is usually defined as the

time difference between 50% of the material leaving the stomach and 50% arrival at the ascending colon. The major disadvantage of this method is the loss of the majority of the information contained in the gastric emptying and colon arrival curves, since only a single point on each is used. An alternative technique used at Nottingham employs the entire data set. When the stomach contains, for example, 90% of its initial contents, 10% of the contents will have entered the small intestine. Consequently, the time at which 10% of the material has arrived at the ileocaecal junction marks the transit of this portion of the activity. Generally, the time difference between x% of the material being in the stomach, and (100-x)% arriving at the ileocaecal junction is a measure of the transit time (Figure 3). If this transit time is measured at intervals (conveniently 10%), the mean SITT can be defined as the average of the set of values obtained. In addition it is possible to detect drug induced changes in the rate of small intestinal transit time occurring over the time course of the experiment which would not be evident using the simple 50% method.

## RELATED TECHNIQUES

There are a number of techniques related to gamma scintigraphy which require different instrumentation. The most familiar of these is tomography, in which the gamma camera is moved around the subject taking images every 10° to 15° of rotation. The subject is supported on a couch inside the yoke of the camera and the detector takes approximately 12 minutes to acquire an image. The data can be processed to show transverse slices through the body at various

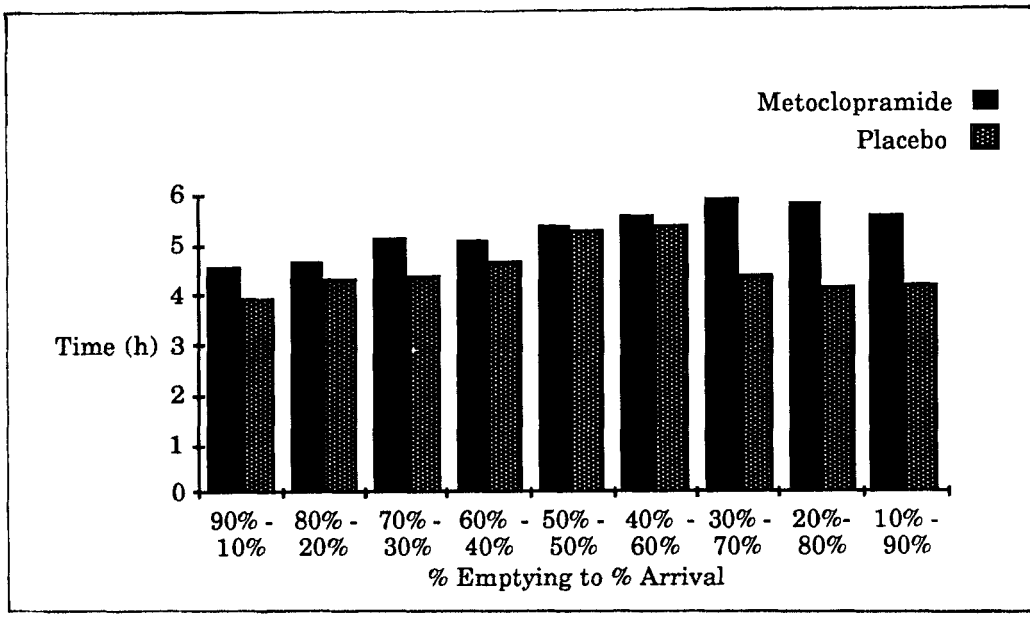


Figure 3 - Deconvolution of the small intestinal transit data

levels and can be used to discriminate overlapping structures, which cannot be resolved by planar scintigraphy. If a flood source emitting gamma rays is mounted opposite the detector with the subject between the two, a transmission tomogram can be obtained. This shows areas of low attenuation e.g. the lung space, since air does not attenuate gamma rays to the same extent as tissues. This technique has been used to study the deposition of aerosols; the total lung space can be seen and if the image of the distribution of the aerosol is superimposed, the efficiency of lung deposition can be assessed (Phipps et al., 1987).

## Positron Emission Tomography

Positron emission tomography (PET) is another scintigraphic method which differs fundamentally from the techniques described

so far and involves the detection of gamma rays emitted by positron emitters. The positron has the same mass but opposite charge to the electron and is sometimes known as an anti-electron. In tissue, the particle rapidly loses its energy and is annihilated on combination with an electron, which results in the simultaneous emission of two 0.51 MeV photons in diametrically opposite directions. This feature is the basis of the positron emission tomography technique described by Ter-Pogossian et al., (1980). As explained below, PET requires the use of cyclotron produced radionuclides and facilities for the rapid synthesis of the radiopharmaceuticals.

## Perturbed Angular Correlation Spectroscopy

None of the imaging techniques described so far are capable of differentiating between label that has been finely dispersed and that which is in solution, i.e. they cannot detect the dissolution process itself. This can be performed by using the perturbed angular correlation technique, which was first applied to this problem by Beihn and Digenis (1981). This is not an imaging method but can usefully be performed concurrently with an imaging study.

The technique is based on the gamma decay cascade of indium-111. This isotope emits a 173 keV photon to form an unstable intermediate nuclear state, which decays with a half-life of 850 nanoseconds and the emission of a 247 keV photon to the ground state. Due to interactions with the nuclear magnetic moment, the two photons are emitted with an angular correlation. If the emitting nucleus is fixed, i.e. is in a rigid or viscous matrix, the correlation between the two photons is preserved. However, if the nucleus is free to rotate, which occurs on a timescale similar to that of the decay of

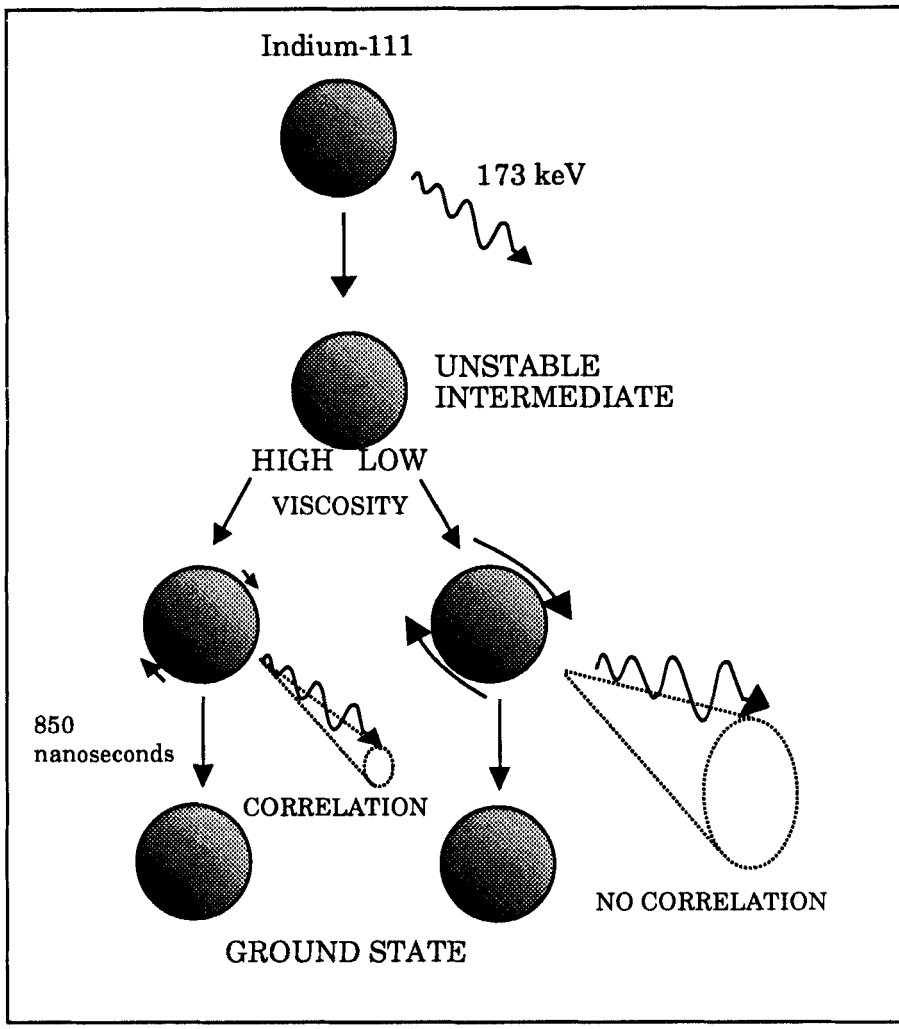


Figure 4 - The principle of perturbed angular correlation

the intermediate state, the nucleus loses its "memory" of its position when the first photon was emitted, and the correlation of the second photon is lost (Figure 4). The correlation can be measured using a suitable arrangement of three gamma detectors and coincidence techniques (Beihn and Digenis, 1981). Thus the dissolution of the isotope from the formulation can be monitored *in vivo* or *in vitro.*

Table 1 - Isotopes used in radionuclide imaging studies.

| Nuclide | Half-Life | Principle Energies (keV) |
|---|---|---|
| *Positron Emitters* | | |
| Carbon 11 | 20.5 min | 511(ß+) |
| Nitrogen 13 | 10.0 min | 511(ß+) |
| Oxygen 15 | 2.0 min | 511(ß+) |
| Fluorine 18 | 110.0 min | 511(ß+) |
| *Gamma Emitters* | | |
| Gallium 69 | 78 hr | 93, 184, 296 |
| Selenium 75 | 118.5 days | 136, 265 |
| Krypton 81m | 13 sec | 190 |
| Technetium 99m | 6.0 hr | 140 |
| Indium 111 | 2.8 days | 171, 245 |
| Indium 113m | 1.7 hr | 393 |
| Iodine 123 | 13 hr | 159 |
| Iodine 131 | 8.05 days | 360(ß-) |
| Xenon 133 | 5.3 days | 81 |
| Thallium 201 | 3.0 days | 69, 83 |

## CHOICE OF LABELS

Direct isotopic labelling describes the process by which a stable atom in a compound is replaced by a radioactive atom of the same element. The majority of drugs contain the elements C, H, N, O, P or S. Hydrogen, phosphorus and sulphur do not have suitable gamma emitting isotopes and the best available isotopes of carbon, nitrogen and oxygen are positron emitters with very short half lives (See Table 1).

Despite the difficulty associated with the rapid synthesis and purification of compounds labelled with these emitters, molecules of

considerable complexity have been produced including $^{11}$C-amphetamine and $^{11}$C-phenytoin. Fluorine-18 is also a positron emitter with a somewhat longer half-life than $^{11}$C. The stability of the C-F bond and the steric similarity of fluorine and hydrogen means that fluorine-18 is an extremely attractive alternative to native molecules since many of the biological features of the tagged molecule are likely to be retained. Fluorine-18 labelled substrates include $^{18}$F- labelled 6-fluoro-dopamine and $^{18}$F-labelled 2-deoxy-2-fluoro-D-glucose. However production of positron emitting isotopes is only available to those centres possessing a cyclotron and it is unlikely that these isotopes will be used for studies of the behaviour of dosage forms. Since native labels are ruled out, the researcher is left with a choice of "foreign" covalent or metal ion nuclide markers.

## Covalent Labels

A covalent label is an atom which has chemically reacted with the drug molecule, usually by addition or exchange processes. The most common label used is iodine which is sufficiently reactive to be easily incorporated in many molecules e.g. by addition across double bonds, iodination of benzene rings or catalysed exchange with existing iodine. Iodine-131 has been used for many years both in radiotherapy and as a diagnostic radiopharmaceutical. However, the ß-radiation from iodine-131 yields high radiation dosimetry and the safer isotope iodine-123 has superceded iodine-131 in imaging studies. Iodine-131 does have the advantage of a longer half-life and therefore is still of value in experiments where the behaviour of a formulation, such as an intra-muscular depot, is to be followed over many days. A fuller review of the subject is covered by Kelly (1984).

## Metal Ion Labels

A number of metal nuclides are suitable for use in human studies. The most useful are those which can be obtained from self-contained generators. Technetium-99m is the most commonly used radionuclide with a monochromatic 140 keV peak, no beta or alpha radiation and a half life of 6.03 hours. The generator contains a molybdenum-99 source (ammonium molybdate adsorbed onto alumina) within a lead-shield. The technetium-99m is eluted as the pertechnetate ion $TcO4^-$ which is relatively unreactive, but reduction of the $Tc^{7+}$ ion in an acidic medium yields the more reactive $Tc^{4+}$ which can be combined with a wide variety of chelating compounds, colloids and lipophilic complexes.

Another generator-produced radionuclide, indium-113m, has great importance in gamma camera studies since its energy can be discriminated from technetium-99m allowing a double-labelling experiment to be performed. The generator contains tin-113 (half-life 118 days) and therefore has a long working life. The half-life of indium-113m is relatively short (1.7 hours) and for many applications the longer-lived isotope indium-111 (half-life 2.8 days) has replaced indium-113m in our studies of drug-formulations, however, indium-111 is produced by a cyclotron and thus cannot be produced on site.

## DOSIMETRY

The use of gamma emitters for clinical or research purposes is an area in which the relative risks due to radiation are poorly understood outside of the hospital or research laboratory. The use of short-lived gamma emitters such as technetium-99m, iodine-123 and

the indium isotopes are associated with a low dosimetry. In the United Kingdom, the dosimetry is calculated as an "effective dose equivalent" and the calculated annual dose is divided into three categories (i) within the natural variations of background radiation (< 0.5 mSv) , (ii) within the dose band for members of the public not involved in handling radioisotopes or x-ray sources (0.5 mSv - 5 mSv) and (iii) the acceptable range for radiation workers (5 mSv - 50 mSv). The effective dose equivalent of technetium used in a typical gastrointestinal study is approximately 0.017 mSv per megabequerel, which can be seen to not significantly increase the radiation burden of a volunteer.

## METHODS OF LABELLING THE DOSE FORM

One of three strategies can be followed to incorporate a radiolabel as a marker in a formulation. Firstly, it is possible to label the drug directly by substitution of a radioactive atom for a native atom in the molecule, for example, replacing iodine-127 by iodine-123 or iodine-131 into iodinated compounds. Rao and co-workers (1983) in our laboratories, have used antimony-125 to prepare radioactive sodium stibogluconate for incorporation into liposomal preparations. A related approach is to use radioisotopes whose chemical and physical properties are similar to the test atom. This approach has been used to radiolabel aluminium containing antacids with a radioisotope of indium since both atoms occur in group IIIb of the periodic table (Washington et al., 1985).

The second method is to radiolabel an inert marker whose physical behaviour mimics that of the drug. Often the materials

used are ion-exchange resins, particles or solutions which are not absorbed, for example, chelates of diethylenetriaminepentaacetic acid (DTPA) with technetium-99m or indium. 'Amberlite' resins, into which radioisotopes can be incorporated by ion exchange, also provide useful radiopharmaceuticals for the study of drug formulations, particularly suspensions and pellets. The final approach is more applicable to the study of pharmacodynamic properties of drugs. Food can be radiolabelled by incorporation of technetium-99m sulphur colloid into egg, liver, mushrooms, bran or other foods. For gastrointestinal transit studies, it is important that the label is not absorbed into the blood pool. Biological systems themselves can be labelled, such as erythrocytes or leucocytes, and the changes in distribution following drug treatment can be monitored (Hardy and Wilson, 1981).

A major disadvantage with the previously discussed techniques of labelling, in which an active isotope is incorporated into a dosage form, is that the active material must be added prior to any manufacturing steps and hence the production apparatus must be located within a radioisotope laboratory. This can be avoided by using the technique of neutron activation of the dosage form. A non-radioactive (stable) isotope of a suitable element is incorporated into the formulation which can then be processed in the normal manner. The formulation is then irradiated with neutrons from an atomic reactor. The stable isotope absorbs the neutrons to produce an unstable isotope whose gamma emission can be detected in the normal way. The factors governing the selection of suitable isotopes for activation have been described by Parr and co-workers (1986). They are a) stability and absence of toxicity, b) low dosimetry of the

radionuclide produced, c) high natural abundance and d) a large neutron capture cross-section. Suitable precursors are barium-138, erbium-170 and samarium-152, although other isotopes have been used (Christensen et al., 1984; Parr et al., 1986). A problem with the technique is that, to ensure predictable dosimetry, only the desired isotope should be activated; radionuclide purity can be tested by gamma ray spectroscopy. Traces of sodium-23 and potassium-41 are strongly activated and are absorbed by the body and hence contamination of the formulations with these elements should be avoided.

Theodorakis and coworkers (1980) described a method of labelling intact tablets with iodine-131 for administration to dogs. The tablet was exposed to vapours of $^{131}I_2$ in carbon tetrachloride for 5 hours to allow the iodine to adsorb onto the tablet surface. The tablets were then administered to anaeasthetised dogs and their behaviour followed by gamma scintigraphy for 1 hour. The dosimetry associated with iodine-131 precludes the use of this technique in man and the absorption of the halide into the bloodstream eventually masks the position of the tablet.

## MEASUREMENT OF THE RATES OF DISSOLUTION OF DOSAGE

### DISPERSION AND DISSOLUTION

Gamma scintigraphy was first used to study the behaviour of capsules *in vivo* by Casey and coworkers in 1976. To date, gamma scintigraphy has been used to investigate the behaviour of a wide variety of dosage forms including tablets, capsules, suspensions,

multiparticulates, aerosols, rectal foams, suppositories, osmotic pumps and ocular inserts.

One of the first studies carried out by our group at Nottingham was the measurement of the *in vivo* and *in vitro* release rates of the radiolabelled marker, $^{99m}$Tc-DTPA, from a matrix tablet composed of hydroxypropyl - methylcellulose (Synchron). $^{99m}$Tc-DTPA was substituted for the antihistamine- drug chlorpheniramine in the commercial preparation and used to study the behaviour of the matrix (Daly et al., 1982). Release of $^{99m}$Tc-DTPA from the tablet was found to be independent of pH between 1 and 8.5 and the *in vitro* release rate agreed with those values determined *in vivo* using gamma scintigraphy.

In later studies, the $^{99m}$Tc-DTPA was incorporated with the drug in the preparation, so that absorption rate could be correlated with the rate of release of the marker (Wilson et al., 1984). The *in vitro* dissolution test (USP method 2) showed a good correlation between the rate of release of the drug and marker in the test preparation, and similar salicylate release in the test and commercial tablets (Figure 5).

Maublant and coworkers (1987) have used the same label to monitor the behaviour of a sustained release theophylline tablet in fasted subjects. Good correlation was noted between the rate of theophylline and radiolabel release using the USP paddle method in pH 7.2 phosphate buffer. *In vitro* and *in vivo* half-times for release of the label were 176 and 156 minutes respectively.

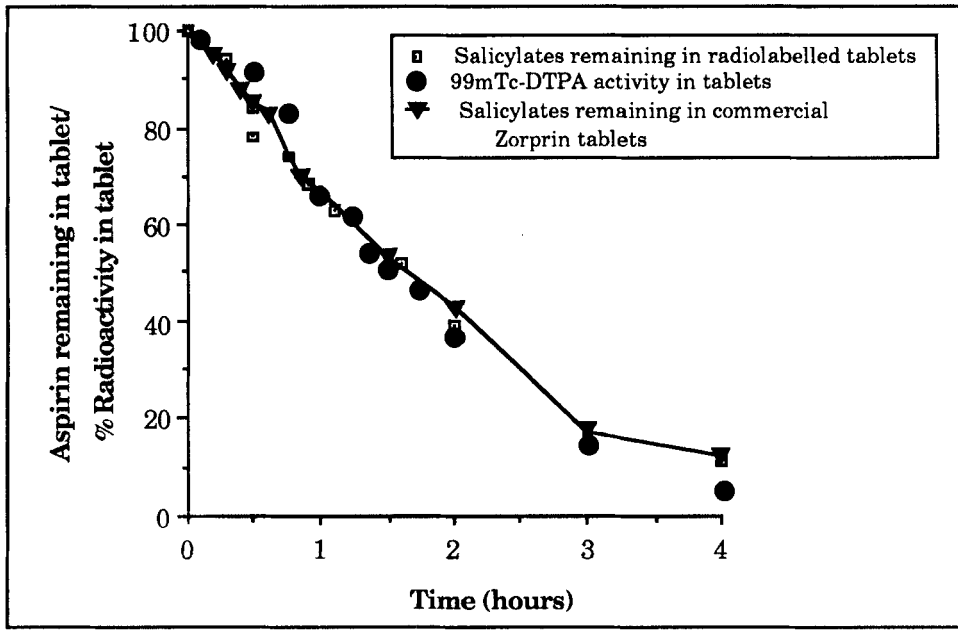


Figure 5 - The rate of release of drug and radiolabel marker from the test preparation, compared to the release characteristics of the drug from the commercial preparation.

A finding which has been confirmed in several studies, is that the rate of release of the marker *in vivo* is significantly different to that observed *in vitro* (Figure 6).

This is probably due to the differences in pH and the stirring conditions in the gastrointestinal tract. Although Levy (1963) found that agitation of tablets in the stomach as observed by x-rays was mild, studies by our group of a 800 mg naproxen tablet (Figure 7) demonstrated considerable movement in the pylorus for several hours in fed subjects as the tablet was pushed to the duodenum then retropulsed to the antrum since it was too big to be emptied (Davis et al., 1986a; Wilson et al., 1987a).

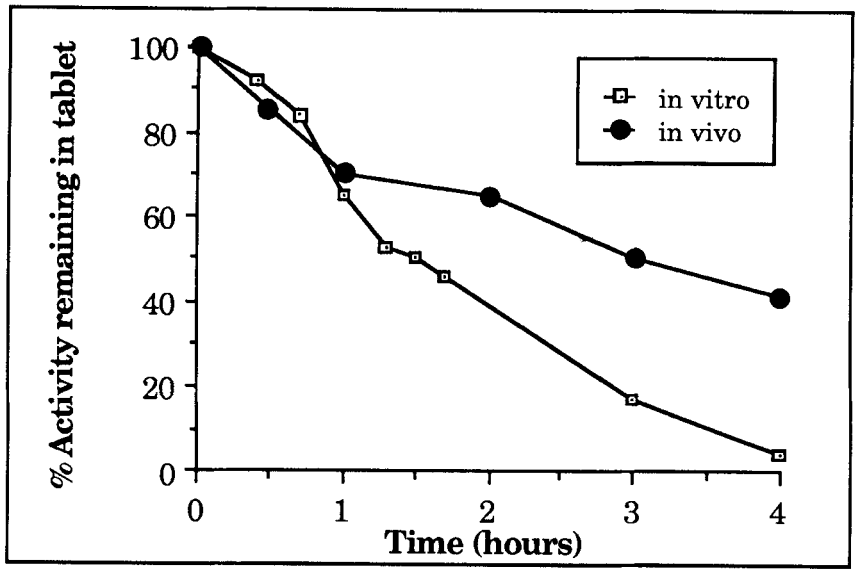


Figure 6 - Rate of release of rabiolabelled marker *in vivo* and *in vitro*

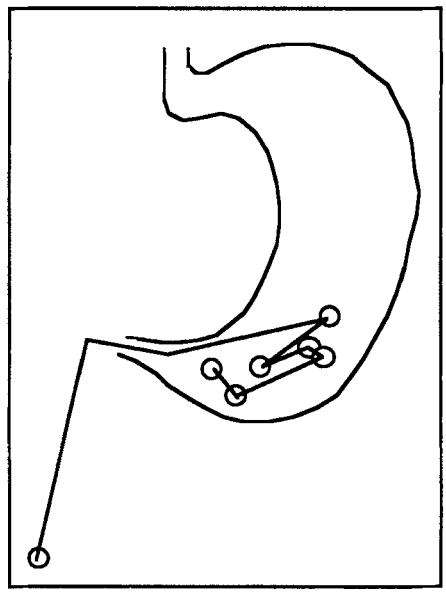

Figure 7 - Movement of tablet in stomach

## Effect of Food

The major complication when studying the dissolution of dosage forms *in vivo* is the presence of food within the gut. Food affects the rate at which dose forms travel through the gastrointestinal tract and the degree of spread of the formulation. The time for which a dose form remains in the stomach can vary enormously depending upon it's size and shape and the amount of food present at the time of administration. Food influences gastric pH and there may be chemical or physical interactions between the food and drug. In addition the food also changes the viscosity of the gastrointestinal fluid in which the drug is presented to the absorbing mucosa.

Some research workers have found that the basal gastric pH can be surprisingly high. Kuna (1964) measured the fasting pH of gastric contents in dogs and man. In 403 tests in dogs, 77% had a gastric pH of 6 or above, compared to 35% in 1556 human tests. Less than 2% of the human subjects had a resting pH below 1.5. In our studies we have found that the basal gastric pH in normal healthy students to be around 1.8. The rate of secretion is approximately 1 to 1.5 ml per minute rising to a maximum rate of 2 to 4 ml after stimulation. Meals markedly alter the pH, which can increase to 3 - 5 after eating, particularly if the meal contains large amounts of easily digested protein. A typical pH trace is shown in Figure 8.

The changes in pH will be especially important when developing products designed to be gastro-resistant, e.g. for acid-labile or potentially irritant drugs and gamma scintigraphy may be combined with *in vivo* pH measurement to investigate the efficiency of enteric-coating. In a recent study reported by Hardy and co-workers (1987a),

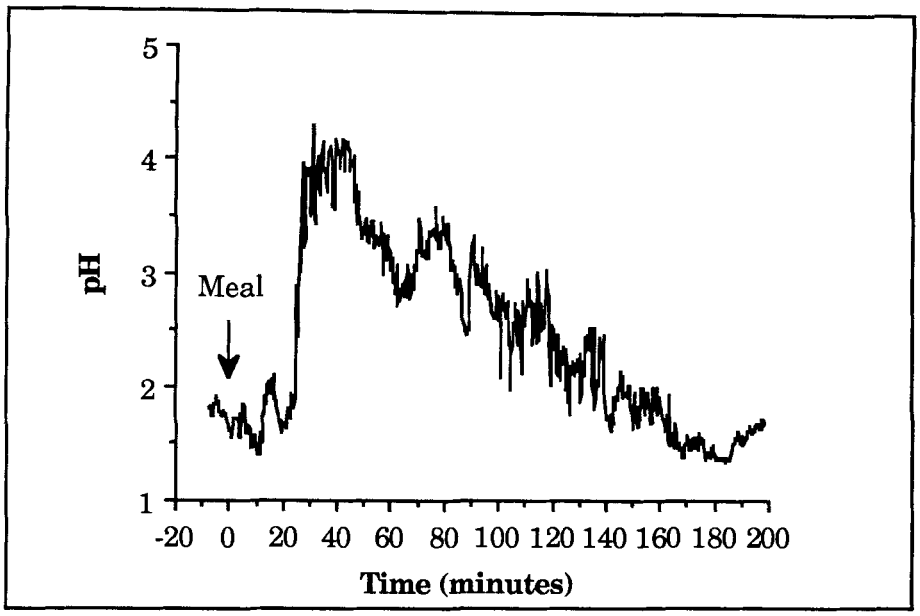


Figure 8 - Typical gastric pH changes observed after an scrambled egg meal



both pH radiotelemetry capsules and enteric coated naproxen tablets were radiolabelled and administered to fed subjects. The local pH and rate of disintegration were monitored simultaneously. The pH remained below 2 within the stomach, except for a transient rise after food. Five tablets disintegrated in the small intestine approximately 1.2 h after gastric emptying, 1 disintegrated in the stomach at pH 1.1 and 1 tablet remained intact in the stomach for 9 h. The median gastric emptying time for the tablets and telemetry capsules were 3.3 h and 4.2 h respectively.

## Tablets for Buccal Delivery

The therapeutic efficacy of glyceryl trinitrate in the treatment of anginal pain is limited by the short half-life of the drug and high

hepatic clearance. Over the past few years there have been several initiatives to develop sustained release formulations to enable the drug to be used prophylactically. One of the newer formulations is a buccal or transmucosal tablet of glyceryl trinitrate which is placed between the teeth and the inside of the lips. The surface of the tablet quickly gels and serves both to anchor the tablet in position and to control the rate of diffusion of the drug. The tablet is based on a matrix of modified hydroxypropylmethylcellulose (Schor, 1980). The tablets are friable and the gel layer breaks on removal, and the advantage of gamma scintigraphy is that the *in situ* dissolution can be measured without disturbing the tablet. Gamma scintigraphy was used to study the inter- and intra-subject variation, the effect of position in the buccal cavity and of chewing and drinking on the rate of release of $^{99m}Tc$ - DTPA from the tablet. With the tablet placed in the upper buccal pouch it was noted that between subjects there were marked differences in the rates of release, whereas within an individual measured on four occasions the variation was quite small. This did not appear to be due to differences in saliva flow rate and the rate of dissolution probably correlates best with the extent to which the subject talked during the experiment. Articulation of the cheek surfaces during speech increases the erosion of the tablet surface releasing the marker or drug into the buccal cavity. However, the rate of release of marker did not increase when the subject drank hot coffee or chewed gum.

Chewable formulations are used for the delivery of antacids where the flavouring agents give the sensation of relief and such a system may be preferred by the patient who has difficulty in swallowing tablets or capsules. The most important physiological

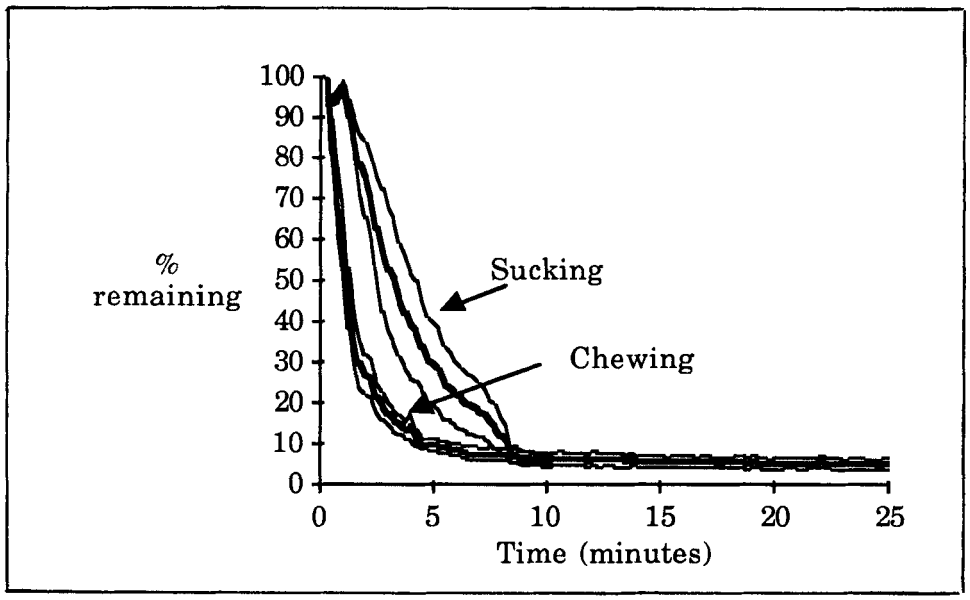


Figure 9 - Effect of chewing and sucking a formulation on the dissolution of the marker.



variable is likely to be whether the subject sucks or chews the formulation, a type of dissolution test which is hard to recreate *in vitro*. The rate of release of $^{99m}$Tc - DTPA from such formulations has been monitored *in vivo* in a group of volunteers who either sucked or chewed capsules containing various excipients. The results are shown in Figure 9 and illustrate the marked effect on dissolution of chewing the capsule.

An alternative strategy for the patient who has difficulty in taking an intact formulation is to use a dose form designed to disintegrate in the buccal cavity such as an Expidet (American Home Products Corporation).

## Expidets

Recently a new type of dosage form based on a freeze-dried mixture of drug and fast-dissolving excipients has been introduced to deliver sedative drugs such as benzodiazepines. Expidets are solid dose forms which do not have to be taken with water and are useful where swallowing is difficult or oesophageal clearance is impaired. Incorporation of technetium-99m labelled micronised "Amberlite" CG400 resin during manufacture enabled the deposition and clearance of these formulations to be followed by gamma scintigraphy (Wilson et al., 1987b). The micronised resin was chosen as a marker since the units are intended for benzodiazepine delivery and the two candidate drugs, lorazepam and oxazepam have low aqueous solubility at the pHs likely to be encountered in the buccal cavity. Two marker loading were used, 2.5 mg and 10 mg, and the effect of incorporating salivary stimulants talin/saccharin and citrate investigated. At the end of each experiment, the head was outlined with a cobalt-57 source. The buccal cavity, glottis and upper oesophagus could then be clearly discriminated (Figure 10).

It was noted that the buccal clearance of the formulation containing the 10 mg resin was significantly faster (50 ± 20 s) than that containing 2.5 mg resin (190 ± 70 s); however, calculation of the total activity remaining after dissolution showed that the amount remaining on the tongue was approximately 1 mg in each case. This probably represents the amount of resin trapped within the papillae of the tongue. Incorporation of salivary stimulants made little difference to the rate of dissolution of the formulation. This was not unexpected since salivary stimulants increase the output of the

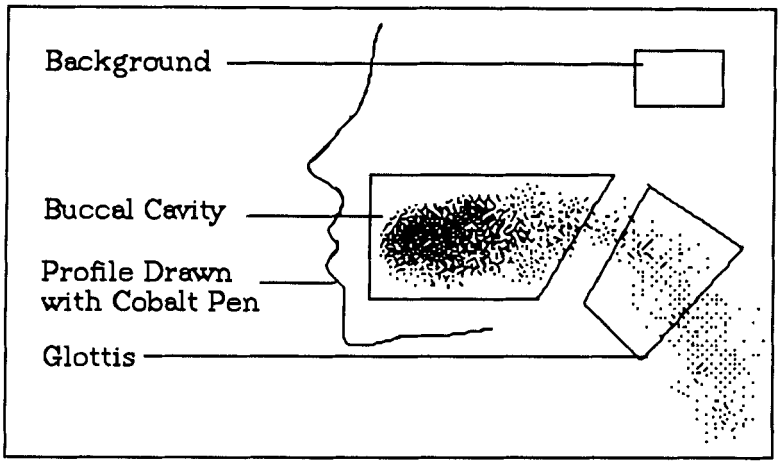


Figure 10 - The clearance of the activity release from the Expidet in the buccal cavity.

submandibular and sublingual salivary glands, which discharge watery secretions onto the floor of the mouth, wetting the side of the tongue and cheek surfaces. The posterior third of the tongue surface contains mucus glands, but the quantity of secretion is relatively small. Thus increased saliva flow may not result in a more aqueous phase available for dissolution of the dosage form from the tongue surface.

## Capsules

Hard gelatin capsules have found a variety of applications in drug formulation. The capsule can be used as a container for powdered drug, multiparticulate systems, a liquid-fill matrix or oily vehicle. The nature of the interior of the fill of the capsule is known to affect the rate of disintegration. A hydrophobic interior, reduces the rate of disintegration compared to that of a water soluble

material. The particle size can also be important as illustrated by the experiments of Hunter and co-workers (1980).

In their experiments, they used Tc-99m labelled 'Amberlite' resin which was graded to three sizes, with geometric means of *a*) 25 μm, *b*) 9 μm *c*) 150 - 210 μm. Sample *b* had been milled down to obtain the appropriate size. 'Amberlite' resin was chosen as it has a similar density to most pharmaceutical materials. The *in vitro* tests showed that capsules containing the powder batches *a* and *c* had shorter disintegration times than *b*. The milled resin was found to be more hydrophobic, decreasing the wettability of the powder and increasing the time to disintegration of the capsule (8 minutes for *b* compared to 2-3 minutes for *a* and *c*). Scintigraphic evidence confirmed the results of the *in vitro* tests. Formulation *b* showed little dispersion suggesting that the gastric emptying of the capsule fill took place with the turnover of gastric mucus. In later experiments (Hunter et al., 1983), the researchers compared formulations *a* and *b* with a third soluble formulation which consisted of [$^{113m}$In] indium chloride recrystallised with sodium chloride. The three formulations were administered to subjects either fasted or with a light breakfast and in both cases, the capsules were administered with 100 ml water. Despite the good *in vitro* disintegration characteristics of formulation *a*, the dispersion in the fasted state was limited and the capsule emptied from the stomach largely undisintegrated. When taken after a meal, the dispersion was improved. Formulation *b* in earlier trials had been demonstrated to be less dispersible. This was confirmed and the activity was observed to leave the stomach in both fasted and fed states as a bolus. For formulation *c* there was no differences in the

behaviour observed in fasted and fed subjects; in both cases the capsule dissolved rapidly and the activity emptied from the stomach in a mono-exponential pattern.

From our own observations and the experiments of Hunter and coworkers (1980, 1982 and 1983) it has been established that the dispersion of the capsule fill is limited in fasted subjects and the material empties from the stomach as a bolus. The dispersion is increased if the capsule is taken with a meal, particularly if the meal has high liquid content. This is of importance since patients are often instructed to take medications with a meal, but it is unclear whether this means before, during or after food.

A recent study in our laboratory has examined the effects of the time of dosing relative to a standard meal (O'Reilley et al., 1987). The behaviour of a multiparticulate dosage form has been followed in six healthy volunteers who received a capsule containing radiolabelled 'Amberlite' beads 10 minutes prior, during and 10 minutes after a meal of a total energy content of 3800 kJ. The particles were released from all capsules within a few minutes. After dosing with the capsule during or after a meal, the pellets tended to remain in the upper half of the stomach. In these cases, the gastric emptying pattern was approximately linear with time. The gastric emptying half-times (T50) were similar for the experiments between 3 - 4 hours; however, over the initial 100 minutes, the particles taken before the meal emptied fastest and the emptying followed an exponential pattern with time.

In a second experiment, the gastric emptying of pellets predispersed in a meal was compared to that of a capsule containing the same number of pellets. This system was analogous to the "sprinkle" formulations which have been suggested for theophylline administration. Although the distribution in the stomach of the predispersed pellets was more even, the gastric emptying following both manoeuvres was similar with no significant differences between the emptying rates (O'Reilly et al., 1987). Two important points were determined in addition to our main findings. First, "sprinkle" systems have to be dispersed into a high viscosity medium e.g. jam or mashed potatoes, otherwise they may fall through the meal prior to eating, with the consequent risk of under-dosing. Particles as large as 800 μm are probably unsuitable as the subjects complained of the sensation of "grittiness", when eating their meal. This increases the desire to masticate and for sustained release formulations would increase the risk of dose-dumping. Thus it is a prerequisite of such systems that they be relatively small:- under 500 μm, for example.

## Soft Gelatin Capsules

There have been relatively fewer studies of the behaviour of soft gelatin capsules in man. From our pilot studies, we have observed that the time of disintegration of soft gelatin capsule formulations is highly variable, particularly if the formulations are given without food. The emptying tends to follow the break up of the capsule in the pylorus. A group at the Welsh School of Pharmacy has compared the dispersion of oils from soft gelatin capsules in man and rabbits (Armstrong et al., 1983) using x-ray techniques and gamma scintigraphy. Soft gelatin capsules were filled with iodinated cotton

seed oil (Lipiodol) for x-ray studies or iodine-123 labelled ethyl oleate for gamma camera studies in humans. The effects of various surfactants was also investigated.

In the rabbit (x-ray) studies, disintegration of the capsule began after 2-3 minutes, swelling into a more isometric shape. This behaviour was observable *in vitro* and was associated with the breakdown of the capsule at the sealing line. Subsequently it was difficult to assess whether the shell had dissolved with the oil as one discrete globule, or whether the oil had emerged from the shell before it had completely dissolved. When 1% polysorbate 80 was added to the formulation, mean disintegration time of the soft gelatin capsule decreased markedly, supporting the findings of Hunter et al., (1980) and Casey et al., (1976). Analysis of variance showed that the presence of surfactant in the formulation to be most important factor influencing dispersion.

From the gamma camera studies in man, the authors defined the disintegration time as the time at which the regular shape of the oil droplet was lost. Three different strategies for calculation of the degree of dispersion were used. First, they used a fixed area of 5 x 4 pixels on the whole field of view; an approach that proved to be invalid since as capsule moved around the stomach, it moved out of the fixed area. The second approach was to use a moveable area of 5 x 4 pixels; however, problems were experienced when the oil divided to give multiple areas of high count rate and it proved difficult to select the area of maximum activity. The third technique involved the automatic generation of contours and is based on the calculation of number of pixels which exhibit activity of greater than 5% of the

maximum activity in the frame. The technique is not subjective and shows a rapid rise at the presumed point of capsule disintegration and liberation of its contents. Spreading was defined as commencing when the area covered by the 5% contour doubled in magnitude. Using the latter technique they determined that the mean time to disintegration was 12.3 ± 6.7 minutes and to spreading 14.3 ± 10.2 minutes.

## Suppositories and Enemas

The spreading area of the suppository determines the release area of the drug from the delivery form. Furthermore, the position of the formulation in the rectum determines how much of the released drug avoids hepatic first pass metabolism since the drainage territories of the inferior haemmorhodial and middle rectal vein differ. Animal species, particularly the rat and dog, have been widely used to measure the dissolution of suppository formulations, usually by the incorporation of a fluorescent dye or coloured marker. Tukker (1983) first described an elegant use of gamma scintigraphy to quantify the spreading of suppositories in recumbent dogs. The author constructed a series of activity profiles, measuring the activity in each of the pixels along the centre line of the image. The subsequent images were then stacked to yield an impression of the way that the suppositories spread with time. The results show that the addition of surfactants markedly affected *in vivo* spreading. Similarly preadministration of neostigmine which increases colonic motility markedly increased the spreading of the Witepsol H15 suppository.

Hardy and coworkers (1987b) have described the spreading behaviour of suppository bases and incorporated suspension. The bases, Witepsol H15 and Labrafil WL2514, were labelled by the incorporation of small amounts of iodine-123 labelled unsaturated markers (arachis oil and Labrafil WL2700 respectively). The suspension consisted of micronised cationic exchange resin incorporated throughout the base at a disperse phase loading of 10% w/v.

The limits of spreading were defined as the edge of the 20% contours, defining 20% of the maximum activity in each frame. Analysis of the data showed that little spreading occurred and both base and suspension tended to move together. Most spread occurred within the first hour after dosing and reached a maximum of 8 to 10 cm. In a few subjects, separation of base and resin occurred particularly in the suppositories composed of the surfactant material WL2514.

Treatment of the proximal bowel is clearly not achieved by use of suppositories and the strategy most commonly employed is the delivery of the drug as a rectal enema. Penetration into the transverse colon is however poor and Hardy et al. (1986) have commented that the optimum enema volume is about 100 ml. Increasing the volume to 200 ml did not enhance dispersion and 50 ml doses showed less spreading. Although administration of the enema or intake of food caused increased motility, neither manoeuvre increased the spreading of the enema.

## Osmotic Pumps

The development of a small osmotically-driven device, consisting of an osmotic core containing drug surrounded by a semi-permeable membrane was first described by Theeuwes (1975). In the operation of an 'Osmet' device developed by Alza Corporation, water is osmotically imbibed across the semi-permeable membrane, swelling the osmotic compartment and squeezing the drug reservoir uniformly along the axis. Since water is incompressible and the semi-permeable membrane is relatively rigid, there is a corresponding amount of drug solution from the reservoir squeezed through the delivery orifice.

It is expected that delivery from such a system should be relatively independent of pH and agitation conditions and this has been tested by gamma scintigraphy (Davis et al., 1984a). The release of In-111 DTPA from the 200μl capacity 'Osmet' with a nominal steady-state delivery of 15 $\mu l\ h^{-1}$ was defined *in vitro*. One of these units, together with a capsule containing a number of technetium-99m labelled 'Amberlite' beads was administered to each of six volunteers with or without food. The release of the radiolabelled marker was unaffected by the presence of food and was similar to that found *in vitro* (Figure 11) confirming the original hypothesis.

An osmotic tablet system ('OROS', Alza Corporation) for delivery of a number of drug candidates has been developed and one such system was marketed for the delivery of indomethacin. Since the interior of the unit is solid, an alternative strategy was needed to identify the site of initial release. In order to follow the behaviour in man, we developed a method to label the position of the tablet and to

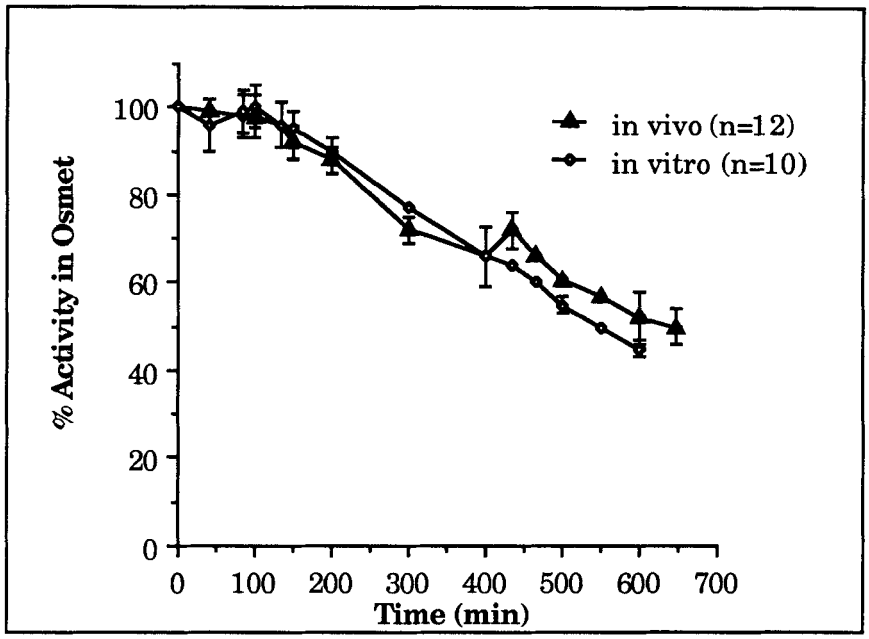


Figure 11 - The release of the radiolabel marker from an "Osmet" *in vivo* and *in vitro*

depth of 7 mm. This was packed with dried indium-111 labelled 'Amberlite' CG 120 cation-exchange resin and sealed with a small blob of 'Araldite' resin containing technetium-99m labelled 'Amberlite' CG 400 anion exchange resin (Figure 12).

The release of indium-111 from the device was observed to follow zero-order kinetics for at least 6 hours in the USP test (method 2) and this method of labelling was used to follow the gastrointestinal transit of the unit. The onset of release of label from the delivery orifice defined the time at which drug was pumped out and helped to establish the position of the unit *in vivo*.

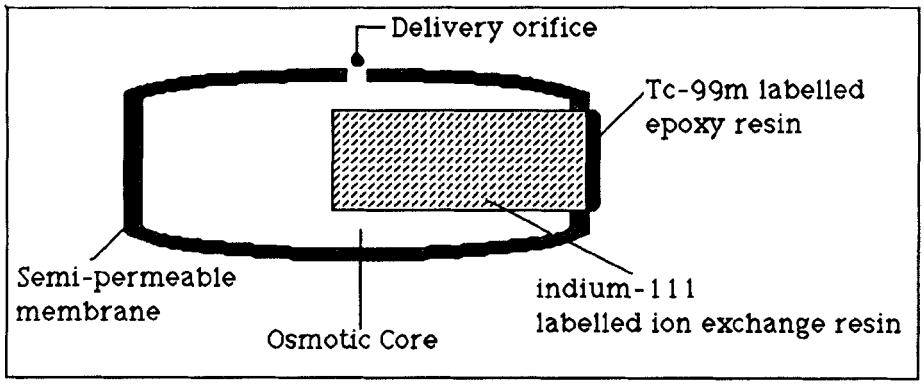


Figure 12 - Labelling of the interior core and exterior surface of an osmotic tablet



## Ophthalmic Formulations

For drugs administered topically in the eye, the sites of intended activity can be intra-ocular as in the treatment of glaucoma with transcorneal penetration the predominant requirement or extra-ocular, for the treatment of conjunctivitis, blepharitis or keratitis sicca. The dosage form most commonly used is the eyedrop, although it has the disadvantage that the majority of the instilled drug is lost due to drainage via the nasolacrimal duct in the first 15 to 30 seconds (Shell, 1982). Much of the present research has been directed towards perfecting sustained release devices to deliver drugs continuously. Three major approaches have been investigated : presoaked matrices typically based on soft-contact lens material soaked in the drug; diffusional devices containing a central reservoir of drug enclosed between rate-controlling polymeric membranes and erodible systems which release drugs at a rate proportional to the dissolution rate of the matrix.

We have developed a gamma scintigraphic technique to investigate the behaviour of polyvinyl alcohol films inserts in man (Fitzgerald et al., 1986; Olejnik and Wilson, 1987). In these experiments we have tried to model the presentation of a suspension of drug which would be released as the matrix erodes. Gohensol GH-17, average molecular weight 98,000 with 87 - 89% hydrolysis was used as the base for the matrix. A sterile solution of the polymer in water was prepared. Technetium-99m labelled sulphur colloid or [$^{99m}$Tc] sodium pertechnetate was added to the concentrated solution and the preparation spread onto a melinex backing sheet. The film was dried under aseptic conditions at 70$^{0}$ C and cut into 25 mm$^{2}$ sections with a scalpel. *In vitro* dissolution tests were carried out in distilled water, with the film supported on a wire mesh. A paddle stirrer was positioned 2 cm above the mesh and rotated at 60 r.p.m. to reduce stagnant layer formation. Samples were removed at intervals and the technetium-99m content of the fluid monitored.

Release of the soluble pertechnetate label occurred rapidly before the matrix had dissolved whereas the sulphur colloid label was released as a function of the square root of time. This indicated that the sulphur colloid was a more appropriate marker for entrapped drug and this radiopharmaceutical was used for the volunteer studies.

The volunteers were positioned 5 cm away from the pinhole collimator with the head supported by an ophthalmic table. A 5 x 5 mm square piece of film was placed under the lower eyelid and images recorded over a period of thirty minutes. The plot of activity versus time followed a monoexponential curve with a mean half time

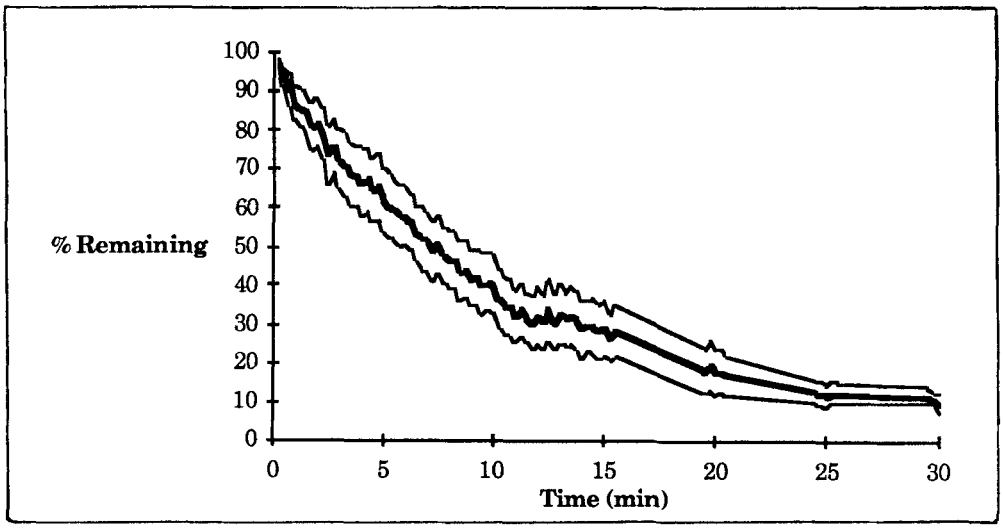


Figure 13 - The precorneal clearance of activity from a polyvinyl alcohol film in man.

of eight minutes (Figure 13), although the correlation coefficient was equally as good for the relationship between activity remaining and and the square root of time (Higuchi plot).

There was great individual variation in rates of clearance with the slowest half time of 23 minutes and the fastest of 3 minutes. The presence of irritant material in the eye causes reflex blinking and increased tear flow so there is a need for the surface to hydrate quickly to minimise corneal sensation. Blinking is probably the most important physiological factor influencing precorneal clearance and increased rates of blinking are associated with increased precorneal turnover.

## TRANSIT OF DOSAGE FORMS THROUGH THE GASTROINTESTINAL TRACT

The period for which a dose form remains in the environment of each region of the gastrointestinal tract is determined by gut motility. Transit through the small intestine is fairly uniform and difficult to alter, however, the residence of a formulation in the stomach can be extremely variable and this can affect the rate of presentation of the drug to the site of absorption.

### Oesophageal Transit

The oesophageal transit of dose forms is extremely rapid, usually in the order of 10 to 14 seconds. It is well recognised that tablets or capsules taken by patients in the supine position may lodge in the oesophagus, causing damage and irritation (D'Arcy, 1984; Channer and Virjee, 1985). If tablets are taken without water, the risk is greatly increased and the units may remain lodged in the lower oesophagus until they disintegrate (Hey et al., 1982). The problem can be aggravated in patients who have cardiac pathologies in which the left side of the heart is enlarged or who are elderly and have oesophageal dysfunction. Retention of the dosage form in the oesophagus has been demonstrated to delay drug absorption, as drugs cannot easily pass through the stratified squamous epithelium of the oesophageal mucosa (Channer and Roberts, 1985).

The hydration of a sticky material against the mucosal epithelium greatly increases the chance of adhesion and has been recognised as a hazard of formulations containing gelatin or cellulose derivatives

(Swisher et al., 1984). The tendency of hydroxymethylcellulose to adhere can be adjusted by incorporation of sucrose which reduces surface stickiness; conversely, addition of lactose or titanium oxide and talc increases the tendency to adhere (Marvola et al., 1983). The interior surface of the oesophagus is moist rather than wet and a dosage form in contact with the mucosa will cause partial dehydration at the site of contact as the unit hydrates, resulting in formation of a gel between the formulation and the mucosa. The unit then disintegrates from its non-contact side. Disintegration of the lodged formulation is slow, first because the amount of dissolution fluid available is low, being dependent on the volume of swallowed saliva and secondly due to the reduced surface area available for dissolution.

Fell (1983) has challenged the belief that gelatin capsules are more likely to stick than tablets, and concludes that the evidence suggests that the two dosage forms should be regarded as having equal potential to adhere. Out of a total of 200 people dosed at Nottingham with various preparations contained in hard gelatin capsules, we have found little evidence of oesophageal lodging or adhesion of the units elsewhere in the gastrointestinal tract.

## Gastric Residence Time of Dosage Forms

The most dramatic effect of food is that it produces significant changes in the gastric motility patterns and a clear discrimination can occur between the gastric emptying of single units and multiparticulates. Food can increase, decrease or delay the absorption of a drug. The absorption of most drugs is slower from the stomach than from the small intestine (Levine, 1970; Heading et al., 1973) and

the rate at which gastric emptying occurs can be a controlling factor in the onset of drug absorption (Heading et al., 1973). Gamma scintigraphy has been used to investigate the gastric emptying time of liquid formulations. It has been demonstrated that 10 to 20 ml of a liquid antacid or anti-reflux agent administered to fasted subjects empties from the stomach within 30 minutes (Jenkins et al., 1983; Washington et al., 1986). Gastric residence of the same formulation can be increased to more than 2 hours by the ingestion of a meal 30 minutes prior to administration of the formulation (May et al., 1984).

The function of the stomach is to provide a reservoir of ingested food and regulate emptying into the intestine to provide a constant calorific input. Digestion and absorption is facilitated by enzymatic action and the milling and grinding movements of the pyloric antrum which triturates food to fine particles. Pressures of up to 60 cm $H_2O$ (43 mm Hg) have been recorded in the antral mill (Quigley and Brody, 1950). Emptying of the pylorus occurs in discrete episodes of 2 - 5 seconds duration and the majority occur as the terminal antrum, pylorus and duodenum relax at the end of each peristaltic cycle (King et al., 1984). The liquid component of a meal empties exponentially, but the emptying of solids is linear after a variable lag time. A transverse mid-gastric band was first noted by William Beaumont in 1833 (republished in 1955) and this has subsequently been found to separate the function of proximal and distal stomach. The distribution of food across the mid-gastric band is believed to be a major component of the lag phase in solid emptying (Moore et al., 1986; Collins et al., 1987). The lag phase is dependent upon the size of the food particles in the stomach, the larger the particles, the longer the stomach requires to

break them down into a size suitable to exit through the pylorus. Eventually, all the digestible material is emptied from the stomach, leaving a residue of mucus and undigested solids. Large tablets or capsules, whether intact or in large fragments, will also be treated by the stomach as an indigestible material since they do not possess a significant calorific value. The migrating myoelectric potential or 'housekeeper wave' serves to remove the debris from the stomach by strong contractions against an open pylorus during the fasted mode. This will sweep undisintegrated tablets and capsules into the intestine. The 'housekeeper sequence' occurs at approximately two to three hourly intervals. If food is given at any time while the stomach is in the fasted mode, it reverts to the fed mode and the 'housekeeper sequence' is suppressed until the stomach is again empty (Figure 14).

A study by Park and co-workers (1984) examined the effect of size and shape of tablets on the rate of their gastric emptying in fasted volunteers. The largest tablet studies was 17.6 x 9.5 mm. It was reported that the physical properties of the tablets did not affect the gastric emptying time and 80% of the dose forms emptied by 2 h. However, the gastric emptying of large single units from fasted volunteers is extremely erratic and can vary from a few minutes to three hours (Kaus et al., 1984a; Wilson et al., 1984). This can explain the variability observed in drug-plasma profiles when large tablets,enteric coated units or sustained release matrix tablets are administered to fasted volunteers. The rationale for using fasted volunteers in clinical trials has been to decrease variability in the onset

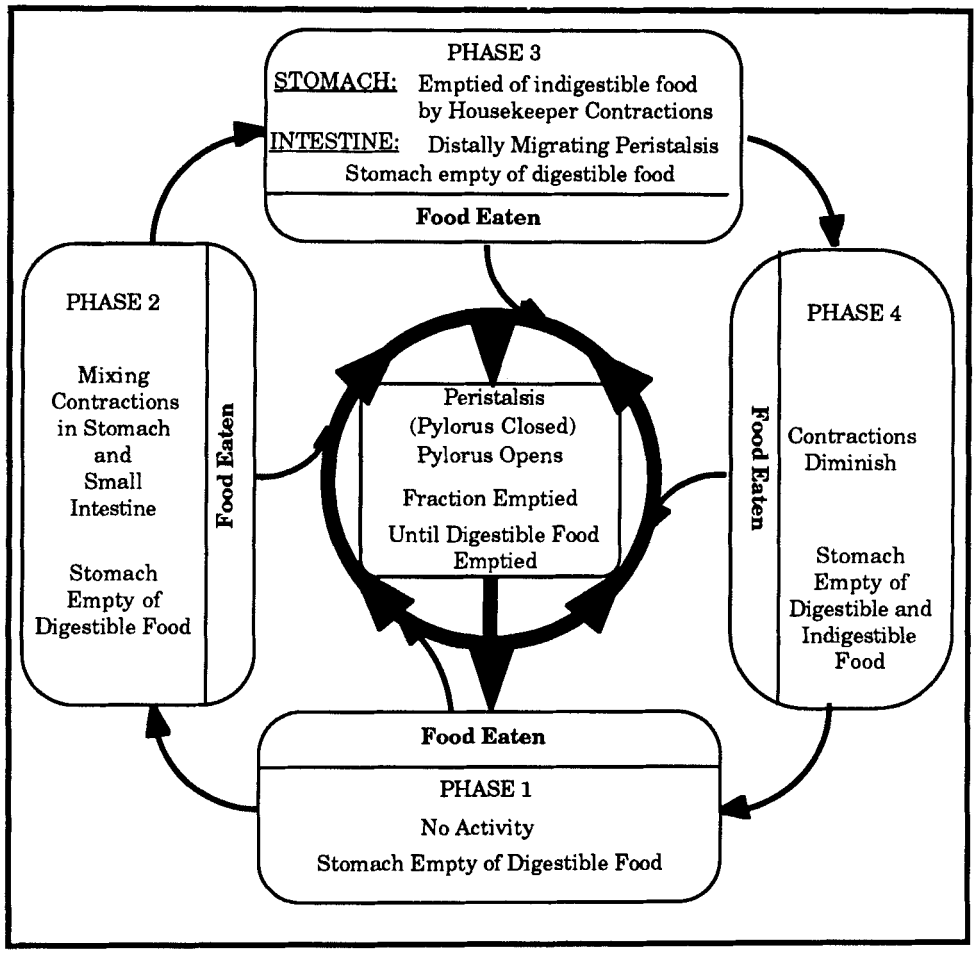


Figure 14 - Motility patterns in the stomach

of drug absorption, but the fasting dosing schedule actually introduces a large source of variation due to unpredictable gastric emptying. This calls in to question the requirement of regulatory authorities of using fasted volunteers in clinical trials. It would be far better to administer single units with a light meal of energy value

no greater than 1500 kJ, which would have the effect of bringing motility patterns into phase. A further point is that the kinetics of gastric emptying and drug absorption are markedly altered by the size of the meal and these effects may be much larger than small changes in bioavailability induced by different formulations.

A popular method of delivering sustained release oral preparations is the multiparticulate or pelleted system contained within a hard gelatin capsule. Davis and coworkers (1985) has described the emptying of pellets from fasted subjects as a random event, with the particles tending to empty as a series of boluses. This, however, is dependent upon nature of capsule and how quickly it disperses, since the volume of fluid available for dissolution is low in the stomach of a fasted individual. The pellets empty more slowly in the presence of food, as the calorific load to the duodenum is controlled which causes the spread of the pellets to be greater in the gastrointestinal tract.

The differences in behaviour between a single unit and a pelleted formulation is illustrated by the study of Davis and coworkers (1984b), who described the simultaneous administration of both formulations. In general, the pellets emptied as a series of boluses from the stomach, ahead of the tablets which were expelled with the onset of the housekeeper sequence. In some cases the pellet formulations failed to disintegrate, and they too were emptied as a single bolus. There have been several studies which have demonstrated that large non-disintegrating tablets can remain in the stomach for up to 12 hours if they are administered with a large breakfast (3600 kJ) and the subject is fed at regular intervals throughout the day (Davis et al.,

1984a; Wilson et al., 1987b). If the tablet is enteric coated, or the drug is not acid soluble, the appearance of the drug in the plasma can be greatly delayed in fed subjects.

One method of prolonging exposure of the upper small intestine to high concentrations of drug is to retain the drug delivery system in the stomach. This also advantageous for drugs which are acid soluble. Muller-Lissner and coworkers (1981) described a floating capsule for sustained delivery of diazepam which has been evaluated by gamma scintigraphy. The capsule contained 10 mg of diazepam-$N_1$-methyl-$^{14}C$ and drug absorption was calculated by collection of $^{14}CO_2$ in expired air. The matrix was labelled by the inclusion of $^{51}Cr$ and $^{57}Co$ labelled microspheres. These systems have no intrinsic property of gastric retention, and rely on flotation on ingested food. Muller-Lissner and Blum (1981) have described a study to investigate the effect of food on the gastric emptying times of non-disintegrating floating and sinking capsules. Both types of capsules were administered simultaneously to each subject. In fasted subjects, both capsules left the stomach within 2.5 h. A high fat meal consisting of 200 ml cream and milk, delayed the emptying of the capsules. Two of the six sinking capsules were evacuated within 2.5 h, with the remainder being emptied by 5 h. The majority of the floating capsules were emptied from the stomach between 2.5 and 5 hours, but in one subject both capsules were emptied after 12 hours and in another, one after 12 h and the second after 24 h. This demonstrates that although the specific gravity of the capsules has little effect on the gastric residence time in fasted subjects, in agreement with the studies by Christensen and coworkers (1984), food increases the effect of capsule density to a variable degree.

## Factors Influencing Gastric Emptying

There are well documented differences in the rate of gastric emptying between normal subjects and patients and gastrointestinal transit may be either faster or slower than normal. The most extreme example is seen in patients who have had vagotomy and pyloroplasty in which 80% of the meal may be emptied in the first 10 minutes of onset of eating (Holt et al., 1982). In the elderly, the differential between solid and liquid emptying is less evident and liquids are emptied more slowly than in younger subjects. Evans (1981) measured the mean gastric emptying half-time (T50) for liquids as 123 minutes in a group average age 77 years, compared to 50 minutes in a younger group of average age 26 years.

There is a statistically significant difference in the gastric emptying times for males and females. A recent study by Datz and coworkers (1987) demonstrated that the T50 for the solid phase of a meal was 59.8 ± 3.7 minutes for males and 92.4 ± 7.5 minutes for females whereas the T50 for the liquid phase was 30.3 ± 2.3 and 53.8 ± 4.9 minutes for males and females respectively. The authors could not fully account for their findings but suspected that the effect is due to sex hormones especially progesterone and oestradiol on gastrointestinal motility.

Drugs which modify motility may be expected to alter the plasma concentration-time profile both of themselves and of coadministered drug, but the effects are sometimes subtle in healthy subjects. Metoclopramide is used to accelerate gastric emptying in pharmacokinetic studies. Kaus and coworkers (1984c) described the transit of a radiolabelled solid perspex capsule after i.v.

administration of metoclopramide (10 mg). The drug had no effect on gastric emptying of the unit but had a variable effect on increasing the transit of the capsule through the first part of the small intestine. The authors conclude that the effect of metoclopramide on gastric emptying may only be important when gastric emptying is abnormally slow, an opinion which our studies tend to support. An explanation for the observed effect of metoclopramide on drug absorption is that the intestinal transit may be altered, decreasing the contact time.

## Intestinal Transit of Dosage Forms

The function of the small intestine is to optimise the digestion and absorption of nutrients. It is often overlooked that there are two distinct patterns of small intestinal motility. During the fed phase, the contractions serve to mix food with enzymes and digestive secretions, circulate the contents to facilitate contact with the intestinal mucosa and finally propel the contents towards the large bowel. The contractions which serve to mix the food are called segmental contractions and locally squeeze the food to enable spreading and contact with the intestinal villi. Coordinated muscular contraction over a length of intestine produces the peristaltic wave which propels the food in a aboral direction. Pellets administered with a meal are emptied more slowly from the stomach, and are more widely distributed within the small intestine, with an average small intestinal transit time of approximately 200 minutes (Davis et al., 1984b, 1987).

The small intestinal transit time for pharmaceutical dosage forms has been reviewed by Davis and coworkers (1986b). The mean transit

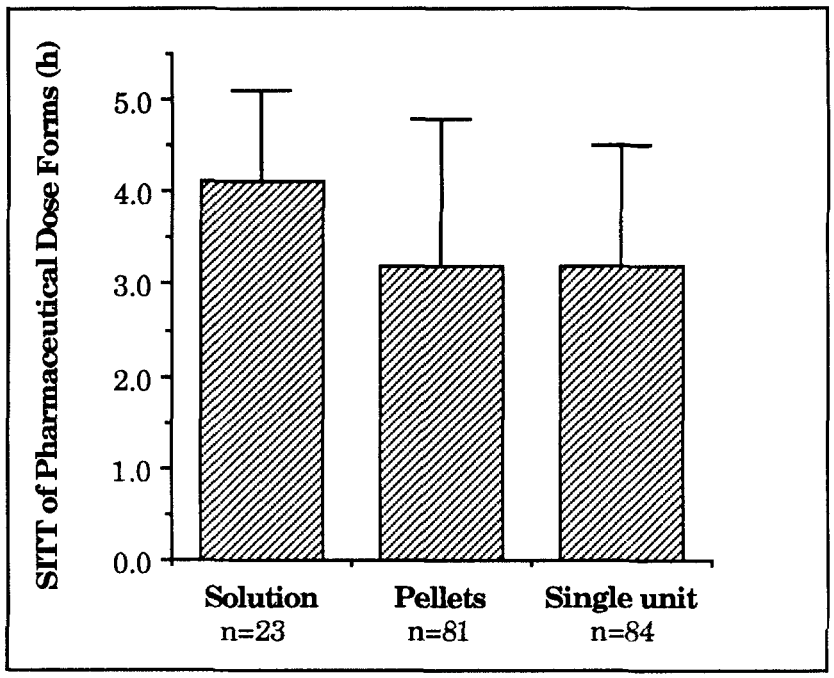


Figure 15 - The small intestinal transit of pharmaceutical dosage forms in man (after Davis et al., 1986b).

time for the formulations studied was between three and four hours (Figure 15). In the past, figures of 5 to 8 hours have been quoted in physiology texts, which have led to overestimates of the time available for drug absorption from the small intestine when formulating sustained release preparations. The data from 201 studies revealed that small intestinal transit time in healthy subjects is not influenced by the physical state, or the size of the dosage form nor by the presence of food; however, transit may be slightly slowed by high calorific loads. Exercise has also been demonstrated not to affect small intestinal transit time (Ollerenshaw et al., 1987). Most physical factors, such as density, appear to be unimportant but the effects of viscosity have not been fully investigated.

The passage of a single non-disintegrating perspex capsule, similar in shape and size to a conventional No. 1 hard gelatin capsule, was measured through the small intestine as described earlier (Kaus et al., 1984a). It was found that the passage of the unit through the duodenum was too rapid to be measured, but the mean transit rate through the small intestine was 4.2 - 5.6 cm $min^{-1}$; gastric emptying of the capsule was erratic and ranged from 15 to 197 min. It is interesting to note, that although drugs are best absorbed from the duodenum, the passage through this area is usually too rapid to allow significant transfer to occur.

## Movement Through the Ileocaecal Junction

Stasis of material at the ileocaecal junction is a normal phenomenon as propulsive peristaltic waves become weaker towards the end of the small intestine. This causes the materials such as suspensions or pellets to bunch at the junction before being swept through into the ascending colon or is seen as a period of stasis of intact tablets. Patients who take non-steroidal anti-inflammatory drugs have an increased incidence of gastric bleeding and peptic ulceration, and there have been attempts to reduce this by enteric coating the formulation or the use of controlled delivery devices. This may only be a partial therapeutic advantage as there is evidence to suggest that non-steroidal anti-inflammatory drugs may cause inflammation of the ileocaecal junction due to local irritant effects. Day (1983) reported two cases in which indomethacin delivered in an osmotic pump was associated with intestinal perforation. In one case it seemed probable that the capsule, being rigid and of the right size to become trapped, lodged in a diverticulum. There has been some confusion in the literature that this behaviour may be attributed

to the film coat but mucoadhesion is only seen in the oesophagus and should be discriminated from stasis.

## Drug Delivery to the Proximal Colon

The ideal system for delivery of a drug to the proximal colon would avoid release of the active compound whilst in the stomach and small intestine, but allow dispersion on reaching the caecum. Dew and coworkers (1982) described a Eudragit-S coated capsule preparation which delivers the encapsulated drug to the ascending colon. Candidate drugs may be 5-aminosalicyclic acid or steroids for the management of ulcerative colitis.

Within the colon, dispersible systems such as pellets become widely distributed (Hardy and Perkins, 1985) but large single units or fragments of tablets travel rapidly through the colon ahead of the smaller pellets (Figure 16) (Hardy et al., 1985, Davis et al., 1984b). This phenomenon is related to the observation that batches of markers of increasing sizes given with successive meals become interdispersed within the large intestine (Halls, 1965). This would be in accordance with the larger particles moving fastest.

The results from the scintigraphic study provide the data upon which to base the design of systems for the delivery of drugs to the proximal colon. The drug should be retained within the preparation for approximately the first 5 hours after administration to the fasted patient, to allow time for gastric emptying and transit through the small intestine. The drug preparation should then disperse into small fragments allowing release of the material over the 10 to 12 hours and dispersion through the ascending and transverse colon.

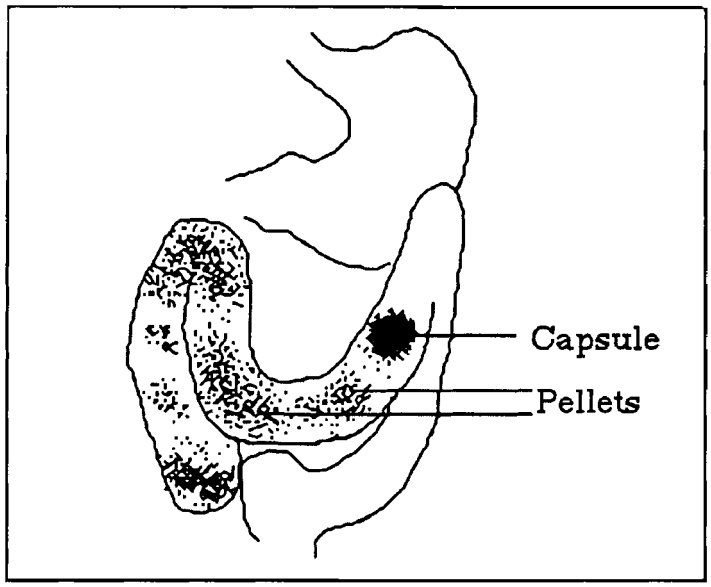


Figure 16 - The movement of pellets and a capsule in the colon. Large intact units travel ahead of the pellets.

It is not reliable to extend the release profile over longer times because of the variability of excretion patterns and the slower diffusion through consolidating faecal material.

## RELATIONSHIP BETWEEN DRUG ABSORPTION AND POSITION OF FORMULATION

One of the most important applications of gamma scintigraphy is the correlation of the plasma concentration-time profile with the position of the formulation since it allows the identification of the 'absorption window', the region of the gastrointestinal tract from which the drug is well absorbed. A further use of the technique is to examine possible sources of variability observed in the plasma

profile, for example erratic gastric emptying of the formulation. The accurate determination of the absorptive capacity, may be carried out by the use of a zero-order release device such as an osmotic pump filled with the drug. The exterior of the unit can be radiolabelled and administered with a non-absorbed radionuclide labelled marker to outline the gastrointestinal tract. This approach has been used to follow the absorption of oxprenolol as shown in Figures 17a and 17b

Two extreme cases are shown in which the units had vastly differing transit times. Figure 17a shows that the drug is well absorbed in the colon for this subject, since blood levels establish a plateau during the transit through the ascending, transverse and descending loops. For subject 4 (Figure 17b), the area under the plasma concentration time profile is considerably less due to the reduced residence time of the unit in the colon. These data emphasize the importance of drug absorption in the large bowel since in this region of the gastrointestinal tract, a considerable portion of the dose has to be absorbed from a sustained release formulation.

A related approach has been used to explain the absorption kinetics of a sustained release aspirin tablet which showed zero-order release characteristics *in vitro*. Incorporation of the non-absorbed marker Tc-99m DTPA into the formulation allowed the dissolution to be followed *in vivo*. As can be seen from Figure 18, the cumulative *in vivo* dissolution profile approximated to zero-order release and correlated well with the absorption phase of the drug.

For sustained release dosage forms with first order release profiles, the plasma concentration time curve is deconvoluted to

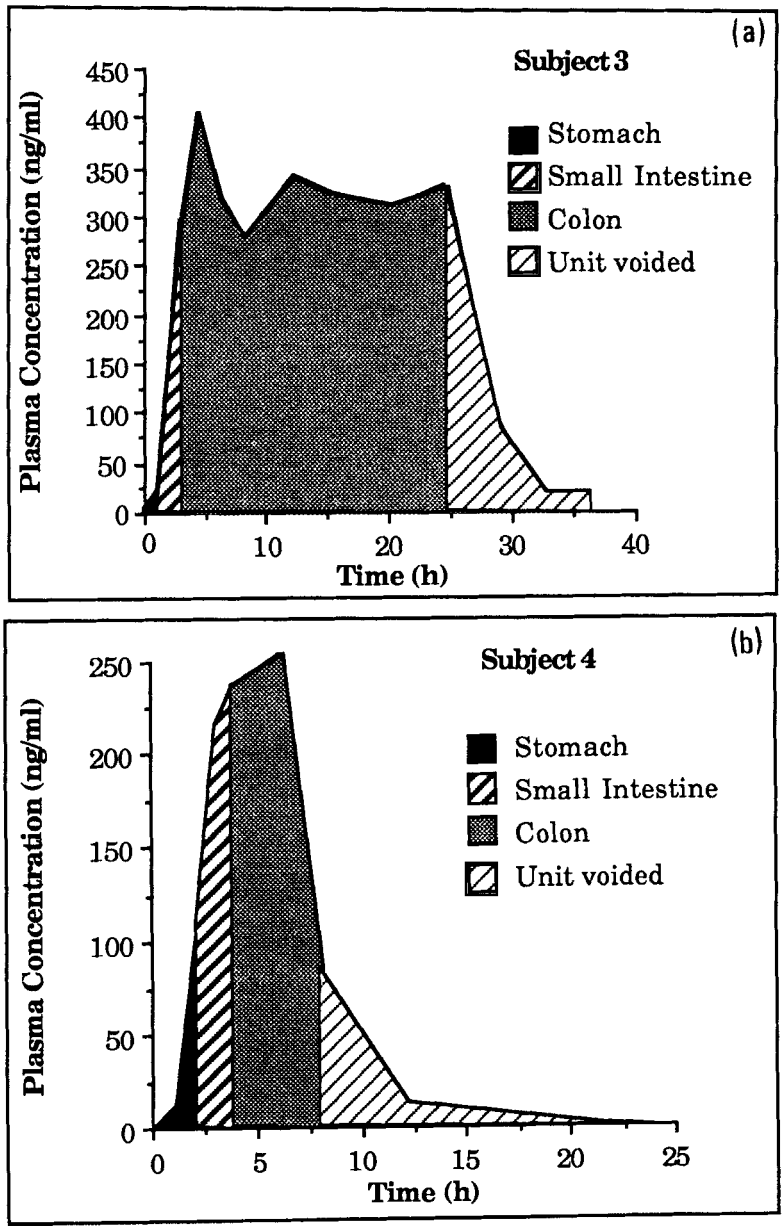


Figure 17 - Relationship between transit of the oxprenolol loaded osmotic pump and the plasma concentration profile for 2 volunteers.

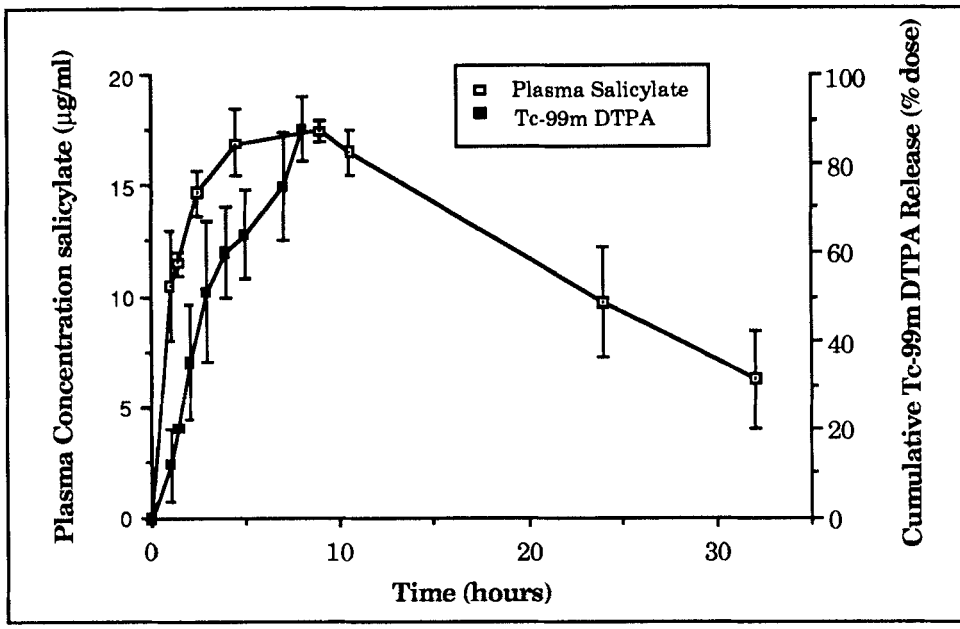


Figure 18 - Comparison of the mean salicylate concentration time profile with the dissolution rate of the tablet.

estimate the amount of drug remaining to be absorbed (Figures 19a & 19b). However, when exploring the relationship between the gastric emptying and absorption, it is important that due allowance for the bioavailability of the drug is made. Low bioavailability alters the correlation between the absorption percentages derived from deconvolution (percentage of drug absorbed) whereas dissolution figures based on gamma scintigraphy data relate to the total amount of material administered. When absorption data is corrected for low bioavailability, the correlation is improved (Ganley et al., 1984).

This technique works satisfactorily with drugs which are well absorbed such as ibuprofen delivered in a sustained release system

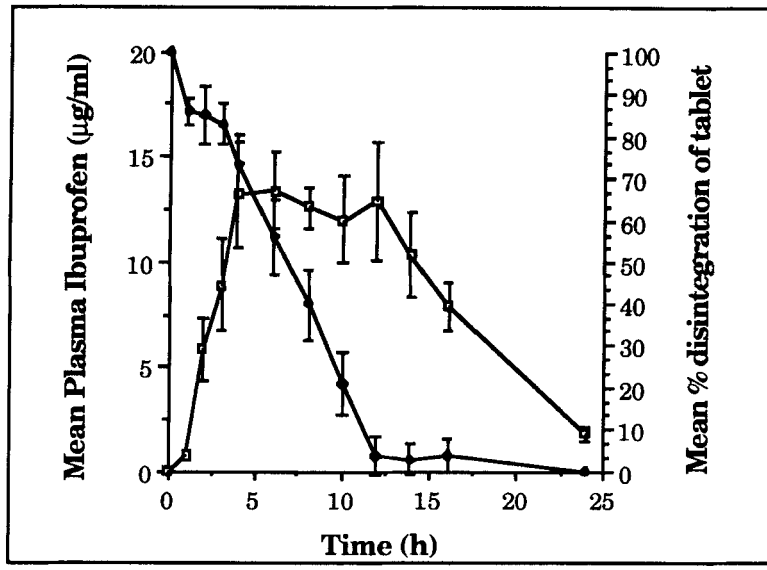


Figure 19 a - Relationship between cumulative dissolution of a sustained release ibuprofen tablet and the plasma concentration profile

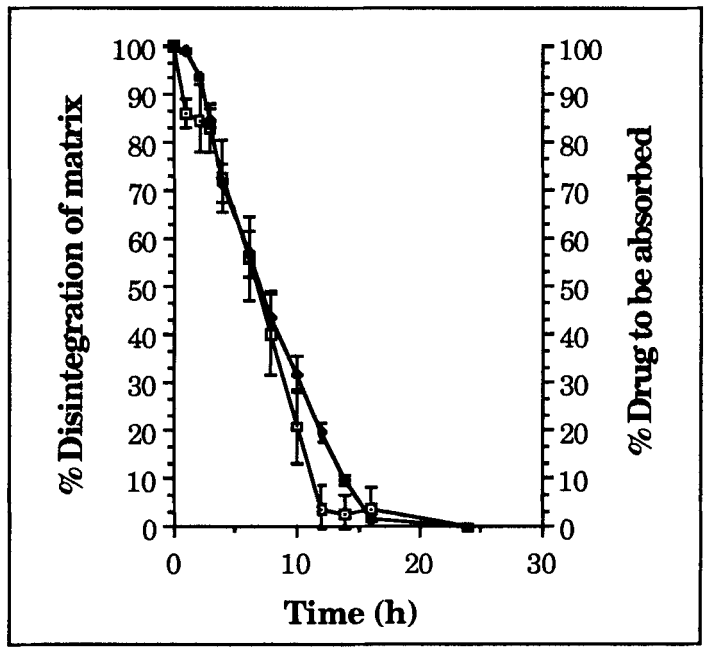


Figure 19 b - Deconvoluted plasma curve and dissolution with time

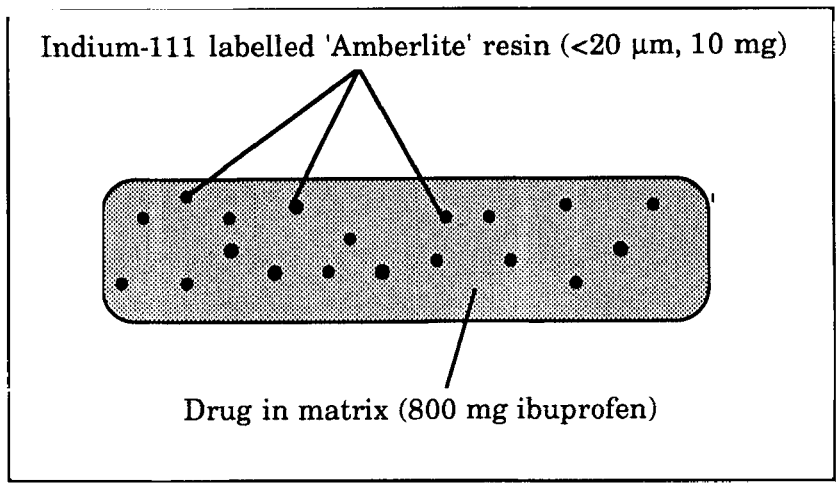


Figure 20 - Indium-111 labelled sustained release ibuprofen tablet.

using micronised indium-labelled 'Amberlite' resin to follow the dissolution of the matrix (Figure 20).

Although in many studies there have been good correlations between the gamma scintigraphic data and the plasma concentration profile, there have been examples in the literature where the results have been completely inexplicable. Bogentoft and coworkers (1984) studied the absorption of acetylsalicylic acid from enteric-coated tablets in relation to gastric emptying and *in vivo* disintegration. Tablets were labelled with $^{51}Cr$ and transit followed in six healthy individuals in fasting and fed conditions by external scintigraphy. In eight of the 12 experiments, the time of onset of absorption correlated well with the time of disintegration. In four other experiments, three in post-prandial state and one under fasting conditions, the absorption of acetylsalicylic acid was delayed more than 10 hours in spite of the fact that complete disintegration and gastric emptying of the tablet seemed to have occurred.

For many drugs, the absorption is dependent upon the rate of disintegration of the dosage form and subsequent emptying into the small intestine. The relationship between the *in vivo* dispersion and gastric emptying on the appearance of glibenclamide in the blood after administration of a rapidly-dissolving liquid-filled capsule formulation has been described by Ganley and coworkers (1984). In the fasting state, the beginning of drug absorption indicated by the first appearance of the drug in the plasma correlated well with the start of *in vivo* disintegration. Food markedly affected the dispersion of the dosage form and delayed the appearance of the drug for an hour, which correlated with the lag time for gastric emptying. Inspection of the images after administration of food indicated that the chief effect of food was to inhibit the dispersion of the dosage form within the stomach.

In order to study the absorption of drugs along the small intestine, Ho, Merkle and Higuchi (1983) modelled the absorption process using a simple first-order model, which led to the prediction of an exponential decrease in drug concentration with length of small intestine. The authors then defined the intestinal reserve length as the distance from the point at which 95% of drug had been absorbed to the distal end of the small intestine. Although intestinal reserve length produces a useful guideline, it makes a number of assumptions, primarily that there is no variation in the absorptive capacity of the small intestine along its length. This assumption may be true for some materials, but in other cases absorption may be carrier mediated or occur at specific places e.g. thiouracil or griseofulvin. Additionally, the selection of 95% absorption as an indicator of "complete" absorption is arbitrary; the authors present

no data to allow such a point to be determined experimentally nor is the available data sufficiently precise to allow extrapolation.

In spite of these shortcomings, the model does provide an explanation of a number of phenomema, notably the variation in absorption with transit velocity, however, the model is only semi-quantitative at best and must be evaluated with its physiological limitations in mind.

A delay in gastric emptying can provide a prolonged period for dissolution which would be expected to increase the availability of a drug such as acyclovir, whose solubility in acidic media is relatively high. As has been discussed, food is the major determinant affecting gastric emptying and therefore the rate of presentation of a suspension of the drug to the small intestine can be controlled by administration with a light or heavy breakfast. Acyclovir (400 mg suspension in 20 ml water), was labelled by inclusion of technetium-99m labelled anion exchange resin and administered to healthy volunteers with either a full English breakfast (3600kJ) or a light continental breakfast (1500kJ). Venous blood samples were collected over a 24 hour period and the subjects imaged for the first 10 hours after dosing. The heavy meal significantly decreased the rate of gastric emptying and caused an increase in the small intestinal transit time; however, the peak plasma concentration and the area under the plasma-concentration-time profile were reduced. The time to peak concentration was not significantly different with the two meals, and occurred within two hours of dosing, suggesting that the site of maximum absorption is situated in the proximal small intestine. These data suggest that the simplistic approach of the

intestinal reserve length theory may be inadequate to predict the behaviour of drugs which show a marked decrease in solubility when transfered from an acidic to a more neutral medium (Wilson et al., 1987c).

## CONCLUDING REMARKS

It is widely appreciated that there is, as yet, no universal dissolution test which in every instance would correlate *in vitro* performance and *in vivo* bioavailability. In view of the information gained from scintigraphic investigations, it is probably unrealistic to expect that a single *in vitro* apparatus will ever be able to model the complex interplay between the formulation and the biological factors. Gamma scintigraphy is a technique which has greatly advanced our understanding of the behaviour of dosage forms and will continue to do so, particularly in combination with pharmacokinetic and telemetric techniques. Ultimately, it should be possible to explain all the factors in the sequence between the release of drug from the formulation to the expression of the pharmacodynamic response.

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