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THE DESIGN AND EVALUATION OF CONTROLLED RELEASE SYSTEMS FOR THE GASTROINTESTINAL TRACT*

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The design and evaluation of delivery systems for the gastrointestinal tract requires knowledge about three inter-related topics, the drug, the delivery system and the destination intended. Preformulation data describing the physicochemical characteristics of a drug molecule need to be considered in relation to known physiological variables such as gastrointestinal pH gradients and transit times. The drug progabide, which is unstable under acid conditions, is used to illustrate the delicate balance between physical and physiological variables and the use of physical models describing the biopharmaceutics and pharmacokinetic events for the design of an appropriate delivery system. Similarly, the use of in vitro *dissolution tests and diffusion experiments can provide essential information on the mechanisms of drug release but are not necessarily good predictors of the* in vivo *situation. The non-invasive technique of gamma scintigraphy has been used to follow* in vivo *release rates and to relate these to pharmacokinetic parameters. The same scintigraphic method has been used to follow the gastrointestinal transit of a variety of controlled release systems to include pellets, matrix systems and osmotic pumps. The effect of dosage characteristics and physiological variables, particularly diet, can be evaluated. Large (>5 mm) units will be retained in a fed stomach while smaller units can empty in a similar way to liquids. Small intestine transit time is short (3 h ± 1 h) for all systems studied. This result has implications for the design of controlled release delivery systems for drugs with poor absorption in the large intestine, as well as for the development of positioned release systems (colon targeting).*

INTRODUCTION

Controlled release systems for oral use include those designed simply to delay the release of a drug (for example an enteric coated system), as well as more complicated systems in the form of matrix tablets, coated pellets, osmotic pumps, etc., designed to release the drug over an extended period of time, either in a continuous manner (sustained release) or as a series of pulses (timed release). Delivery systems, for positioned release at specific sites close to so-called "absorption windows" or for localized treatment can also be considered under the general title of controlled release systems.

The rational design and evaluation of effective controlled release delivery systems needs to take into account the trinity of *drug*, *delivery* and *destination*. Each one is interrelated to the other two and it is essential to consider all aspects and constraints for the successful development of a new system. Factors such as the solubility and stability of the

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drug, its absorption from the different regions of the gastrointestinal tract, the release characteristics of the delivery system *in vitro* and *in vivo* and gastrointestinal transit all need to be evaluated.

Each of the three parts of the trinity will be considered in turn. In doing so it is assumed that the pharmacokinetics of the drug have been well characterised and a controlled release dosage form is required to fulfil a well defined clinical need, for example to change the dosage regimen, improve patient compliance, enhance the total bioavailability, reduce adverse reactions and side effects, etc.

Hopefully, data on the relationship between pharmacokinetic profile, the drug and response (pharmacodynamic and clinical) will be available to the pharmaceutical scientist. However, it is not unknown for controlled release systems to be requested and even developed, without reference to effective blood (and tissue) levels and the therapeutic index of the drug, or the unavailability of same!

DRUG – CHARACTERISTICS OF THE CHEMICAL ENTITY

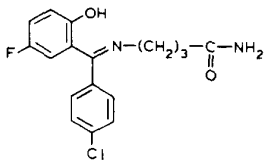
Preformulation studies

The physicochemical characteristics of a drug relevant to its biological availability are determined at the preformulation stage of drug development. Data on such factors as pK_a, pH, stability, solubility and partition (distribution) profiles, can be obtained by standard physicochemical methods. The relevance of some of these values to the biological situation has been questioned, particularly with regard to partition (distribution) data and its use in predicting drug absorption. The studies of Ho and others [1] on membrane permeability and the role of unstirred layers have shown conclusively that a large partition (distribution) coefficient (K_D) does not necessarily lead to enhanced permeability, since at a limiting value of K_D the process of diffusional control changes from one associated with the membrane to one associated with the aqueous unstirred layers adjacent to the membrane. Consequently the effect of mucus layer in the gastrointestinal tract (and the glycocalyx) on drug transport is now receiving attention [2]. Others [3] have questioned the use of 1-octanol as the solvent of choice in distribution experiments and have proposed that liposome systems may be more valid, although more difficult to use experimentally.

Preformulation tests more relevant to the biological environment, such as those based on perfused (*in situ*) intestinal loops in the rat, can provide valuable insight into the absorption behaviour of a compound in different regions of the gastrointestinal tract, and the existence of absorption windows or processes for facilitated transport [4]. As will be shown below, a significant and reliable absorption of a compound from the large intestine may be a prerequisite for the successful development of a controlled release system intended for once daily administration, particularly if the drug has a short half-life. The cannulation of thoracic (or mesenteric) lymph vessels can show whether the compound is transported lymphatically to any significant extent and whether this route, that has the advantage of avoiding first pass metabolism by the liver, has any benefit through the use of appropriate lipid containing oral formulations or through the prodrug approach by making more lipophilic derivatives [5].

Physical models

Preformulation data and information on physiological function need to be correlated so as to provide a rational approach to the choice of a delivery system. The new anticonvulsant progabide is an interesting example of the need to consider physiology as well as physical chemistry. Preformulation information for progabide is provided in Table 1 [6]. The drug is a weak base with a pK_a of



Progabide — (1-(4-chlorophenyl)-1-(3-fluoro-6-hydroxyphenyl))4-methylenimino butyramide
General formula: $C_{17}H_{16}ClFN_2O_2$. Molecular weight: 334.78.

TABLE 1

Progabide — Preformulation profile (data at 37°C)

pK_a	3.41
Distribution coefficient (free base) (octanol/water)	933
Stability in aqueous solution ($t_{1/2}$) (min)	18 (pH = 2.2) 130 (pH = 6.3)
Solubility in aqueous buffers (mg/l)	9093 (pH = 2.2) 44 (pH = 6.3)
Absorption rate constant (k, min^{-1})	
(rat gut loop, pH 6)	0.0854
(salicylic acid)	0.101

3.41 at 37°C. It is reasonably soluble at pH values below 3.0 but is very poorly soluble above pH 4.0. The compound is hydrolysed to release GABA and a benzophenone. The pH—hydrolysis profile is in the form of a bell-shaped curve, maximum stability being found at around pH 6.3. At pH 2.2 the half-life of the compound at 37°C is about 18 min. The octanol—water distribution coefficient of the compound is in the region of 10^3. *In situ* intestinal loop studies have shown that the compound is rapidly absorbed in the small intestine ($t_{1/2}$ = 8.1 min, cf. salicylic acid, $t_{1/2}$ = 6.9 min). In view of the poor stability of the compound at gastric pH a controlled release system was developed in the form of an enteric coated soft gelatin capsule that contained the drug as micronized powder (300 mg dose) dispersed in vegetable oil. However, bioavailability studies conducted in man (Table 2) revealed low levels of the drug and its metabolites in the blood following oral administration. Thus, while the enteric coat had been effective in protecting the drug

TABLE 2

Progabide — Bioavailability (mean ± s.e.m. (n = 6); dose = 600 mg)

Formulation	Drug size	AUC (mg ml^{-1} h)
Capsule	micronized	9836 ± 2950
Capsule	coarse	4508 ± 655
Tablet	micronized	8607 ± 819
Gastroresistant tablet	micronized	4590 ± 1393

from degradation in the stomach, the delivery of the undissolved powder into the intestines, to a pH where it has minimal solubility, was even more disadvantageous. An alternative strategy was considered that took into account the high solubility of the drug at the acid pH of the resting stomach and the rapid emptying of the resultant solution of the drug from the stomach ($t_{1/2} < 1$ h) that could minimize losses due to degradation. The bioavailability of the drug in the unprotected form was indeed better than for the enteric coated system (Table 2).

This necessary compromise between solubility and stability considerations and the importance of physiological factors, has been incorporated into a physical model [7] (Fig. 1) that takes into account not only the factors discussed above, but other issues such as the precipitation of a proportion of the dissolved drug as it enters the intestines and the redissolution of the fine particles so created. Measured or estimated values of the various rate constants can be used to derive blood level—time profiles not only for progabide but also for other drugs with similar stability problems and to assess the changes that would occur if formulation, dosage or physiological parameters were altered.

The model has been validated in the rabbit by following the effects on the bioavailability of change in the particle size of administered progabide as well as the suppression of acid in the stomach by the use of an H_2-antagonist [6]. Both experiments indicated the overriding importance of the dissolution step for

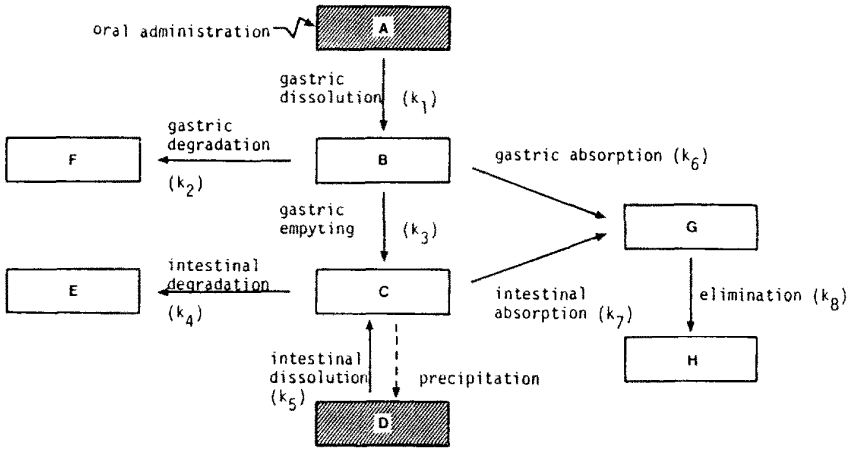


Fig. 1. Pharmacokinetic/biopharmaceutical model for drug absorption following oral administration. (Open boxes — drug in solution; shaded boxes — drug in suspension.)

the compound, for instance increasing the stomach pH by an H_2-antagonist gave a marked reduction in bioavailability contrary to what would be predicted from stability considerations alone (Fig. 2).

Ho, Higuchi and others [8] have developed a similar type of model approach, but have restricted this to the small intestine. Here the inter-relationships between particle dissolution, drug permeability and intestinal transit have been considered. A unifying concept of the "reserve length" was introduced, this being the length of absorptive surface (small intestine) available *after* the drug had been absorbed. Thus, a drug that is rapidly and effectively absorbed in the small intestine would have a large reserve length. An equation was presented whereby it is possible to determine the required particle size of a drug suspension, so that it would dissolve and be absorbed within the absorptive length of the small intestine (about 300 cm). A similar approach was proposed for the calculation of the release characteristics of a controlled release pellet system so that it too would deliver its drug load uniformly within the length of the small intestine. The various physiological factors, namely flow rates in

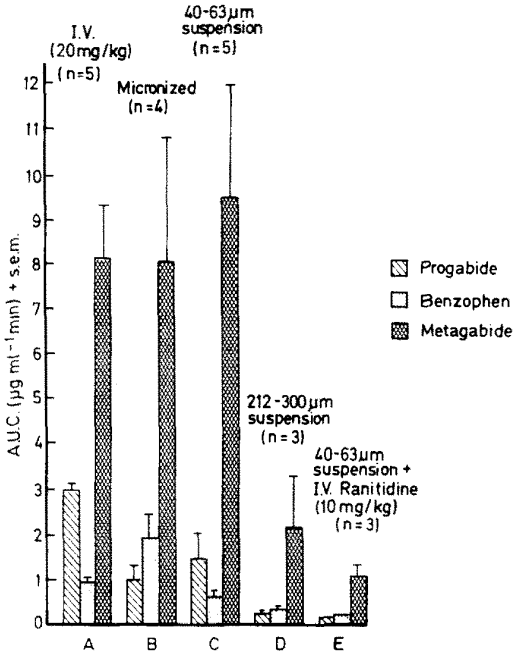


Fig. 2. Bioavailability of progabide and metabolites in rabbit — oral administration (200 mg/kg). A: i.v. (20 mg/kg) (n = 5); B: micronized (n = 4); C: 40—63 µm suspension (n = 5); D: 212—300 µm suspension (n = 3); E: 40—63 µm suspension + i.v. ranitidine (10 mg/kg) (n = 3).

the different segments of the small intestine, the spreading of a particulate system during transit and transit times for passage from duodenum to ileocaecal valve, were taken from the limited information available in the literature on foodstuffs. The transit and spreading behaviour of pharmaceutical dosage forms is discussed further below.

DELIVERY – CHARACTERISTICS OF THE DOSAGE FORM

The range of systems available for the controlled delivery of drugs to the gastrointestinal tract is huge, and it is not the intention to review these here. Instead it will be stressed that the nature of the delivery system will be dictated by the properties and dose of the drug, the purpose for controlling the release of the drug and the interaction of constraining physiological and pathological factors. For example, as will be discussed further below, there is little point in attempting to develop a once daily, multiparticulate system for a compound that is not absorbed from the large intestine, or has an absorption window in the duodenum or jejunum.

Hydroxypropylmethylcellulose (HPMC)

In recent years we have been investigating the use of hydroxypropylmethylcellulose (and its modifications in the form of Synchron) for use as a controlled release system [9]. A variety of polymers of different molecular weight is available. As a means for making controlled release formulations the system has the advantage of needing no special machinery and is extremely robust. Wide tolerancies can be permitted in production factors such as compaction pressure. The release profile of a drug incorporated into the matrix can be altered by change in the polymer content as well as its molecular weight, the addition of soluble or insoluble excipients, surface active agents, etc. [10]. While simple systems conform to the well known matrix release profile (linear plot of quantity released versus square root of time), zero-order release can be achieved by the addition of complexing agents that not only alter the solubility of the drug but also the viscosity of the hydrated polymer [10] (Fig. 3). Reasonable quantities of polymer (> 10%) may be required for an effective controlled release system based upon a dry direct compression matrix system, while much smaller quantities are necessary if a granulation step is included in the production process. The actual process of release of a drug from an HPMC matrix is a complex one involving water penetration into the drug matrix; hydration and gelation of the polymer, diffusion of the dissolved drug in the resultant gel and erosion of the gel layer [11]. The modelling of these processes is further complicated by the swelling of the system [12]. A conventional dissolution test will provide the resultant of these many separate processes, different ones being the rate controlling at various stages of the release process. Recently we have examined the diffusional properties of HPMC systems by means of a novel ultrasound method [13]. The penetration of water into the drug matrix was extremely slow and was affected by the presence of dissolved solutes. The diffusion of water in a hydrated gel system was also quite slow (> 1×10^{-6} cm^2 s^{-1}) but solutes dis-

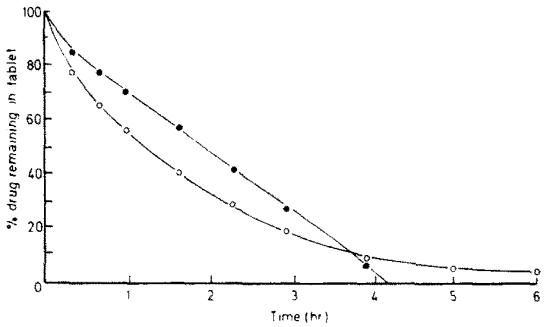


Fig. 3. The release of chlorpheniramine (5%) from Methocel E15 matrix tablets. Legend: ○, no additive; ●, 15% sodium dodecyl sulphate.

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