The transit of a drug (formulation) through the GI tract will determine how long a compound will be in contact with its preferred absorptive site. A good understanding of gastrointestinal transit in humans and the effect of factors such as food can be helpful in the design of drug delivery systems.

Formulation strategies for absorption windows

Stanley S. Davis

Absorption windows in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of controlled release formulations for important drugs. Methods to increase the residence of drug formulations at or above the absorption window are discussed in this review. Two main approaches are presently being explored: (i) bioadhesive microspheres that have a slow intestinal transit; and (ii) the gastroretentive dosage system, which is based on multiparticulates or large single unit systems. A good understanding of gastrointestinal transit in humans and the effect of factors such as food can be helpful in the design of rational systems that will have clinical benefit.

Oral drug administration still remains the route of choice for the majority of clinical applications. Some drugs have ideal characteristics for good absorption to occur throughout the gastrointestinal (GI) tract, whereas others present difficulties. The Biopharmaceutical Classification System, introduced by the Food and Drug Administration (FDA) in 1995, has categorized drugs in terms of their solubility and intestinal permeability. Class I compounds are defined as those with high solubility and high permeability, and are predicted to be well absorbed when given orally. All other compounds (classes II–IV) suffer from low solubility, low permeability or both, and will present challenges to the development of products with acceptable oral bioavailabilities. An increasing number of new chemical entities are to be found in classes II–IV and many of these display variable absorption in different regions of the human GI tract [1]. Polar compounds and those that rely on some form of facilitated transport process generally display good absorption from the upper GI tract, but are poorly absorbed in the large intestine (or colon). As a consequence, their oral bioavailabilities can be affected by the limited absorptive site. In addition, the development of a modified release product, such as those designed to

Stanley S. Davis
Institute of Pharmaceutical Sciences,
University of Nottingham,
University Park,
Nottingham,
UK, NG7 2RD
e-mail:
stanley.davis@nottingham.ac.uk

STANLEY S. DAVIS

Professor Stanley S. (Bob) Davis obtained his Bachelors degree in Pharmacy from the School of Pharmacy at the University of London in 1964. He remained at the same University to study for a PhD in colloid science. In 1966, he was appointed Assistant Lecturer in Pharmaceutics and then to Lecturer in 1967. He was awarded his Doctor of Science degree (higher doctorate) in 1982. In 1968, he was awarded a one-year Fulbright Scholarship to undertake postdoctoral studies with Professor Takeru Higuchi at the University of Kansas, USA, in the field of solution thermodynamics. In 1970, Davis moved to the University of Aston, Birmingham, UK, as Senior Lecturer and Head of the Pharmaceutics section, where he built an active research group in drug delivery systems. Davis took the position of Lord Trent Professor of Pharmacy at the University of Nottingham, UK, in 1975, where he ran a large research group, studying novel drug delivery systems. Topics of research have included drug targeting (with particular emphasis on colloidal carriers), transmucosal delivery, oral and parenteral systems for controlled release and product evaluation through gamma scintigraphy. He became an Emeritus Professor in 2003. Davis has published over 700 papers and is co-editor of seven books. He is the co-founder of two pharmaceutical companies, Danbiosyst (UK) Ltd (now part of West Pharmaceutical Services) and Pharmaceutical Profiles Ltd. Davis has acted as a consultant to various pharmaceutical companies, and has served on numerous committees and panels, including European Pharmacopoeia, Medicines Commission, Science and Engineering Research Council.

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provide once-daily dosing, will be difficult, if not impossible. Hence, the concept of an 'absorption window' has become popular [2].

Absorption windows

Some drugs display region-specific absorption that can be related to differential drug solubility and stability in different regions of the intestine as a result of changes in environmental pH, degradation by enzymes present in the lumen of the intestine or interaction with endogenous components such as bile [3]. Active transport mechanisms for drugs involving carriers and pump systems have been well described [4]. Compounds such as ACE inhibitors and certain antibiotics exploit peptide transporters. The importance of P450 metabolism in the intestinal mucosa has now been recognized. The isoform P4503A4 (CYP3A4) is dominant in 'gut wall' metabolism and different levels are found in different regions of the intestine. The absorption of drugs can also be limited by efflux mechanisms, especially if compounds are lipophilic in nature. The secretory transporter P-glycoprotein located on the mucosal surface of epithelial cells is responsible for the low and variable bioavailability of various compounds (e.g. propranolol, felodipine) [5]. Some drugs can be substrates for both CYP3A4 and p-glycoprotein (e.g. cyclosporin, itraconazole) [6]. In theory, it should be possible to inhibit efflux and metabolism processes by the use of inhibitors, but such agents are not usually without their own pharmacological effects. The inhibitory effect of grapefruit juice toward intestinal cytochrome P450 is a well known example [7].

Today, it is possible to assess regional differences in intestinal drug absorption by conducting a non-invasive human drug absorption (HDA) study using a remote-controlled delivery capsule [1]. Gamma scintigraphy is used for real-time visualization of capsule location, and a radio frequency signal is used to activate the capsule at the target site. For example, in order to determine the bioavailability and pharmacokinetic profile of faropenem daloxate (a prodrug of a broad-spectrum antibiotic), this drug was delivered in a particulate form to the proximal small bowel, distal small bowel or ascending colon. The pharmacokinetic profiles for delivery to the two sites in the small intestine were similar and comparable to those for a reference tablet (Table 1). Significant absorption was also seen after delivery to the colon, but the area under the curve (AUC) and the maximum plasma concentration (C_{max}) values were markedly reduced.

TABLE 1

Pharmacokinetic parameters for faropenem (free acid) following site-selected delivery to different regions of the human gastrointestinal tract[a]

	IR tablet	Proximal small intestine	Distal small intestine	Ascending colon
AUC (mg hour^{-1} l^{-1})	25.8	22.7	20.1	8.6
C_{max} (mg l^{-1})	15.3	11.8	10.0	2.3

[a]Data obtained from Ref. [1]. Abbreviations: AUC, area under curve; C_{max}, maximum plasma concentration; IR, immediate release.

Gastrointestinal transit

The transit of a drug (formulation) through the GI tract will determine how long a compound will be in contact with its preferred absorptive site. In humans, the small intestine transit time is reasonably constant: at around three hours for a drug formulation (or for a meal) to pass from the stomach to the ileo-caecal junction [8]. Transit through the colon is much longer and can be 20 h or more [9]. Hence, the time a drug will have in its absorption window can be relatively short, more so if the drug is preferentially absorbed in the proximal small intestine (e.g. jejunum) rather than throughout the small bowel. Consequently, the bioavailability of a drug, which is largely or exclusively absorbed from the upper GI tract, will be affected by factors that change GI transit. For example, the presence of food in the stomach will slow the rate of gastric emptying and will thereby keep the drug above or at the absorption window for a longer period of time. An increase in bioavailability might then be expected. However, if formulation excipients are used that increase the rate of transit in the small intestine (e.g. through an osmotic effect), the bioavailability can be reduced as observed with cimetidine, a polar drug that is almost exclusively absorbed from the small intestine [10].

Some important drugs have absorption windows in the small intestine and, as a result, they often display low bioavailability after oral dosing. In addition, they are difficult to formulate into extended release products because on arrival in the colon (or even before), absorption will be low or non-existent (Box 1). Efforts have been made to improve absorption, and various different strategies have been described in the scientific literature and in published patents. This article will review some of the strengths and weaknesses, and outlines some of the more promising current developments.

Preformulation studies

Before one can attempt to solve a problem, it is useful to first understand why a drug displays low and site-specific absorption. Data gathered in preformulation studies will often provide some insight into crucial characteristics, such as drug solubility and drug stability. Similarly, *in vitro* permeability studies using cultured cell systems such as Caco-2 can give an indication of potential problems [11]. Formulation strategies to improve dissolution rate and drug stability can be investigated. For example, Terao *et al.* [12] investigated the feasibility of widening the absorption window of furosemide by controlling the pH in distal parts of the intestine using a methacylate polymer. Good results were obtained with an *in vitro* rat model, but extrapolation to clinical practice is uncertain. Enteric coatings to prevent drug exposure to the adverse conditions

BOX 1

Drugs that would benefit from increased residence in the small intestines or stomach

There are several examples of drugs that would benefit from an increase in the time that a formulated product resides in the stomach or small intestine. These are listed as follows:

- Acyclovir
- Bisphosphonates
- Captopril
- Furosemide
- Metformin
- Gabapentin
- Levodopa
- Baclofen
- Ciprofloxacin

in the stomach are a standard approach. Coating strategies are also available to deliver the drug to a preferred region in the distal intestines where drug stability (physical and metabolic) or even absorption could be better [13].

Poor permeability can sometimes be improved by the use of an absorption enhancer. Current research is focusing on agents that can modify the tight junctions between cells in a transient manner [14]. Interestingly, several materials such as surfactants that are well-known excipients can enhance the absorption of drugs displaying low bioavailabilities. This approach is most relevant to polar compounds, including peptides and proteins.

Methods designed to provide longer contact of the drug or delivery system with the crucial absorption region fall into two different categories: (i) those that attempt to slow down transit through the small intestine; and (ii) those that attempt to hold the drug formulation above the absorption window through gastroretention.

Modification of small intestine transit

Pharmacological methods

It is well known that drugs can alter GI transit. For example, scintigraphic data have indicated that pre-treatment with metoclopramide decreased gastric emptying time and increased GI motility, whereas pre-treatment with propantheline had the opposite effect [15]. The extent of metformin absorption (a drug primarily absorbed from the small intestine) is improved when the GI motility is slowed. Drug combinations that contain gastrokinetic agents such as metoclopramide have been marketed, but it would be difficult to imagine that regulatory authorities would accept the addition of a second drug to improve the bioavailability of another. (Similar considerations apply to the use of inhibitors discussed above.)

Nature's methods

Dietary components such as fats, certain amino acids and peptides can slow gastric emptying and intestinal transit [16,17]. A lesser-known phenomenon is the ileal brake [18]. There are particular dietary components, for example, fats and fatty acids, that are infused into the terminal ileum and can cause a slowing of intestinal transit. This 'braking' mechanism appears to be a feedback process for the improved digestion of dietary components. Studies have been performed in humans to identify optimal ileal brake activators (quality and quantity). One of which investigated whether ileal brake activators could alter the bioavailability of atenolol from the small intestine by slowing intestinal transit and thereby increasing the time available for absorption [19]. Oleic acid and a monoglyceride were formulated into modified release capsules that were targeted to the small intestine. The results showed that, in some volunteers, an increase in small intestine transit time led to an increase in the quantity of drug absorbed. However, drug absorption was related not only to the total time spent by the drug in the small intestine, but also other factors such as the proportion of such time spent at the ileo-caecal junction. This study highlighted the complexities of exploiting natural GI processes to enhance the oral bioavailability of drugs.

Kroening *et al.* have recently reported that tapeworms can slow the transit of intestinal contents [20]. Of the tapeworm-secreted compounds tested, only lumenal infusion of guanosine 3′,5′-cyclic monophosphate (cGMP) induced contractile patterns that mimicked those observed during tapeworm infection. As a consequence, it has been suggested that cGMP might be used in proprietary pharmaceutical formulations to improve drug absorption; 'Wisconsin investigators have filed for a patent on the idea of adding cGMP to drugs to lengthen the amount of time they spend in the gut and thus increase how much medicine a person absorbs' (http://www.sciencenews.org/articles/20030322/fob6.asp).

Unfortunately, the patent position will be less than certain because, in 1982, the *Escherichia coli* heat-stable toxin was reported to activate the cGMP system [21], which altered motor activity thus slowing transit and enabled bacterial proliferation and invasion.

Bacteria have other strategies that help to promote invasion. Fimbriae are long filamentous protein projections on the surface of certain organisms that allow them to adhere to receptors on the brush borders of villous enterocytes [22]. Caston *et al.* investigated the use of purified fimbriae from *E. coli* as a natural bioadhesive [23]. The fimbriae were attached to small microspheres. Encouraging data were reported for a rat model in terms of an increase in small intestine transit, but the system has yet to be investigated in humans. In a similar fashion, various groups have studied the use of plant lectins to target the lumenal surface of the small intestine. Once again, animal studies have been supportive. For example, two plant lectins selected by Montisci *et al.* (*Lycopersicon esculentum L.* and *Lotus tetragonolobus* lectins) were reported to be specific for oligomers of N-acetyl-D-glucosamine and L-fucose, respectively, and were conjugated to small radiolabeled poly (lactide) microspheres [24]. The transport

and distribution of the particles along the intestine, as well as their interactions with the intestinal mucosa, were determined after oral administration in rat. The overall transit of the particles was delayed when the microspheres were conjugated to the lectins, mainly because of gastric retention. A significant fraction of the conjugates adhered to the gastric and intestinal mucosae, but the interaction process appeared to be largely a result of non-specific interactions. Apparently, premature adsorption of soluble mucin glycoprotein limited specific (lectin-mediated) adhesion. Some 15 years ago, a similar conclusion was reached concerning the role of soluble (non-adherent) mucin from studies conducted in humans. Using the technique of gastroscopy, we examined the mucoadhesive properties of small 'bioadhesive' tablets, which carry a net positive charge. *In vitro* studies had shown that such a charge provided a good interaction with the negatively charged sialic acid groups on gastric mucus [25]. The video films obtained demonstrated that it was a easy to attach mucus to the small tablets, but the reverse process of attaching small tablets to the mucus adhering to the stomach wall was a different matter. Mucus adherence and 'turn over' still represents an obstacle when trying to slow small intestinal transit.

Bioadhesion

For years pharmaceutical scientists have been fascinated by the concept of bioadhesion. Various attempts have been made to identify putative bioadhesive or mucoadhesive materials using *in vitro* and *in vivo* tests. Unfortunately, in many cases, such tests have been based on a poor understanding of relevant behavior of the human GI tract. As a result, systems that performed well *in vitro* or in animal models failed to live up to expectations in humans. The rat, dog and pig are not good models for the human GI tract especially where transit processes are concerned.

Bioadhesive microspheres based on the pharmaceutically acceptable cationic polymer chitosan have been of special interest [26]. Chitosan is known to bind well to mucus, and microparticles coated with chitosan adhere well in the intestine of animals [27]. However, good adhesion and delayed transit do not always translate into improved bioavailability of an administered drug. Clearly, with a system like bioadhesive microspheres, the incorporated drug must be released at an appropriate rate and be stable in the lumen to have a chance for absorption. Shimoda *et al*. reported that their chitosan microsphere system showed good adhesion to the intestinal mucosa, but scarcely facilitated absorption of insulin [28]. This is in line with expectation because insulin is very poorly permeable and would be degraded rapidly in the lumen.

Claims of bioadhesion of microparticles in the human GI tract are often based on circumstantial evidence in the form of altered pharmacokinetic profiles rather than the direct measurement of transit using properly labeled formulations and techniques such as gamma scintigraphy. For example, two kinds of sustained-release microspheres, adhesive and non-adhesive, containing furosemide and riboflavin, were prepared and administered to fasted volunteers in hard gelatine capsules [29]. Areas under the plasma concentration–time curves (AUC) were 1.8 times larger for furosemide and the urinary recovery was 2.4 times higher for riboflavin when adhesive microspheres were used as compared with the non-adhesive system. These are interesting results, but no hard data on altered transit were provided.

Flamel Technologies have described the design of a proprietary drug delivery system (Micropump® microparticles) that is claimed to be bioadhesive and which allows an extended transit time in the small intestine with mean residence time in the plasma extended up to 24 h (http://www.flamel.com/micropump.htm). This system is stated to be particularly suitable for short-lived drugs known to be absorbed only in the small intestine. However, as far as can be ascertained, the extended intestinal transit has yet to be demonstrated in humans. Indeed, it is hard to find any published evidence to demonstrate that strategies of bioadhesion will change transit through the small intestine of humans (an effect on gastric emptying has been found, as described below). As aforementioned, the transit of food and pharmaceuticals through the small intestine is reasonably constant in humans with a mean value of around three hours. It is little affected by fed state, age, particle size, shape, density or disease condition [9]. This is not too surprising because the small intestine has a role of moving material to the colon by a process of peristalsis. The mucus that lines the intestine has a protective role and a quick turnover. Moreover, the surface of administered particles can be rapidly conditioned by the adsorption of endogenous components such as non-adherent mucus. Notwithstanding, it has been has been postulated that, because of their size, very small particles could perhaps become trapped between the villae of the small intestine (and also in the folds of the stomach). To test this proposal, Brown *et al*. followed the transit of very small particles (in the ranges of 70–80 μm, 1–10 μm and 500 nm) in the human gut [30] using gamma scintigraphy. The results showed that the particles all had similar transit behaviors and that the measured transit times were in broad agreement with those reported previously for conventional multiparticulate systems such as pellets.

Recently, a new approach to delaying transit has been proposed using super-porous hydrogels that swell rapidly in water and in so doing should slow intestinal transit [31]. Various *in vitro* experiments have been described, together with some data obtained in an animal model (pig) [32]. In the pig model, the hydrogel enhanced the intestinal absorption of insulin. However, human investigations are apparently ongoing and the same type of hydrogel is also being evaluated for its gastroretentive properties.

Gastroretention

In theory, an elegant and simple way to improve drug absorption is to hold a drug delivery system above the absorption window and for the drug to be released at an appropriate rate. Because most absorption windows are thought to be located in the proximal small intestine, the obvious strategy will be to hold the formulation in the stomach (i.e. gastroretention). This concept was advanced many years ago and has been the subject of extensive research, publications and patents filings, with some successes, but many failures. The Holy Grail remains the retention of a delivery system in the fasting human stomach using a system that will be safe and effective.

The process of GI transit in humans and its implications for drug delivery are now well understood (Box 2) [9]. Dosage forms administered to a fed stomach will have delayed emptying. A multiparticulate system, such as one containing microspheres or pellets, can become mixed with the food and, as a consequence, will usually empty with the food over an extended period of time [33]. If the administered particles are large, they will not be able to pass through the constricted pylorus with the digested food, and will have to wait until the stomach is empty and in the fasted state. There has been some debate in the past as to the cut-off size for retention in the fed stomach. Unfortunately, data obtained in the dog have been extrapolated directly to human without any attempt at scaling. In general, particles up to ~10 mm in size can be expected to empty from the fed stomach. Exactly when the particles empty will also depend on their number and their relative positions within the stomach. Hence, a dosage form larger than 15 mm and administered with food is expected to achieve gastroretention. Such a dosage form will then have an opportunity to empty after the food has left the stomach when the fasted state occurs. In the fasted stomach, different levels of activity occur in the form of contractions or waves [9]. One particular wave called the 'housekeeper wave' is very relevant. This wave, as its name suggests, can function to clear undigested material from the stomach through the relaxed and open pylorus into the intestine. Such waves occur about every two hours in humans, but are inhibited by food. Hence, if the stomach is maintained in the fed state, for instance, by repeated administration of small meals, a single unit could have extended retention. Unfortunately, this process of repeated feeding will not be a sensible strategy for achieving gastroretention in a clinical setting.

A single unit system (or a multiparticulate) can empty rapidly from the fasted stomach. Exactly when it will empty will also depend on the timing of the housekeeper wave in relation to dosing. The open pylorus has a diameter of ~15 mm in humans. An object greater than this size will have difficulty in passing into the small intestine in the fasted (or fed) state. Based on this knowledge, various approaches have been devised for gastroretention. These fall into two main classes: (i) small particles that have bioadhesive properties (and also a propensity to float on the stomach contents); and (ii) large swelling objects that will be retained in the stomach because of their size. These swelling systems might also have floating characteristics, usually provided by the generation of carbon dioxide. The early literature on gastroretentive systems has been well-reviewed elsewhere [34,35], and only the more recent developments and strategies will be considered here. Attention will be focused on systems that have been tested in humans. As discussed earlier, promising results obtained *in vitro* and in animal models have not always translated well to human. In many cases, the realities of human gastric emptying have been neglected. Floating systems require fluid in the stomach to function. While this might be the case for the fed stomach, the fasted stomach will contain little fluid and a liquid given at the time of dosing will empty rapidly. Thus, for the fasted state, floating will be transient but might allow other mechanisms to operate such as mucoadhesion. Floating systems could also have their limitations in the fed state because a change in body position to supine will have a direct effect on the floating system and its proximity to the pylorus.

BOX 2

Gastrointestinal transit of pharmaceutical dosage forms

There are many factors that control the gastrointestinal transit of pharmaceutical dosage forms, summarized below:

- Gastric emptying is controlled by feeding status
- Objects less than 10 mm in size can empty from the fed stomach
- Large objects (>20 mm in size) will be retained in the fed stomach
- The transit time in the small intestine is ~3 h
- A dosage form can reach the colon in 4–5 h in fasted subjects
- Transit in the colon is lengthy (~20 h)

Microparticulates

Gastroretentive microparticles have been investigated, but few studies have demonstrated success in clinical investigations. Pivotal studies in Nottingham University, UK, have revealed that oral dose forms containing finely divided ion-exchange resins can provide prolonged gastric residence and uniform distribution within the stomach [36]. For such an effect, the particles will need to be small from a mechanical consideration and of low density so that they might be able to float. A positive charge should also confer an advantage. Adherence to the wall of the stomach will be possible during the emptying process in both the fed and fasted state, assuming that the mucoadhesive properties of the particles have not been modified by the stomach contents, in particular, non-adherent mucus (Figure 1).

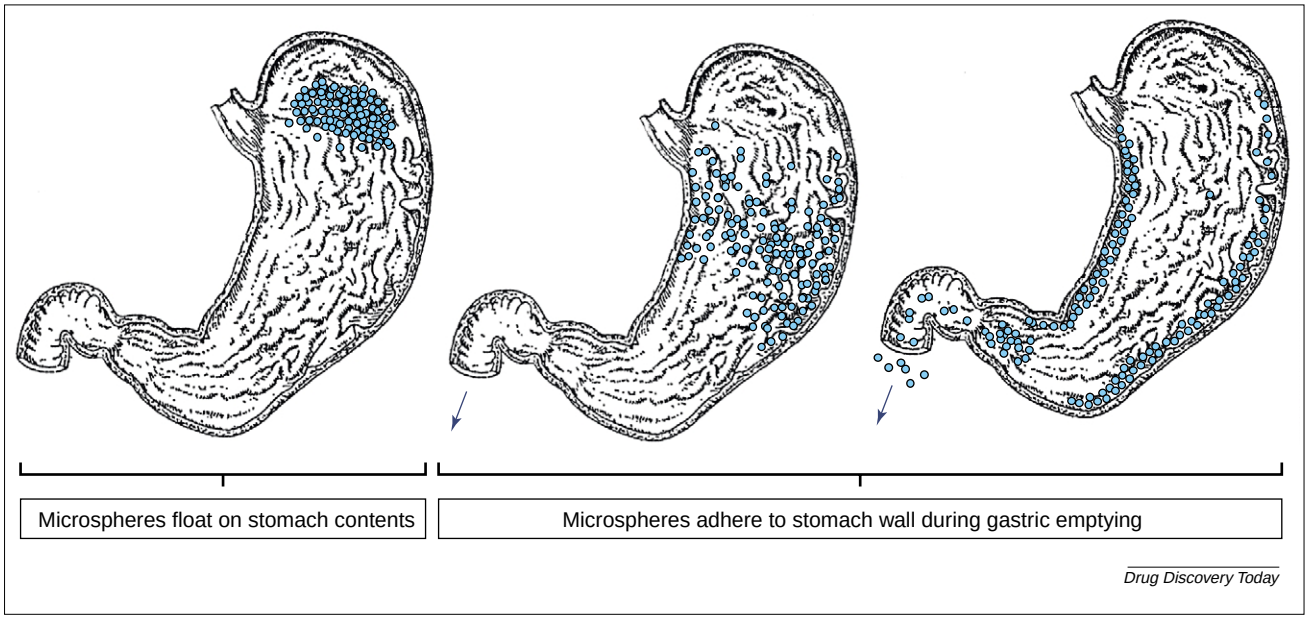

FIGURE 1

Proposed mechanism for retention of bioadhesive microspheres in the human stomach. A capsule containing the bioadhesive microspheres is administered with water and the released microspheres float on the fluid in the stomach. During the process of gastric empyting, a proportion of the bioadhesive microspheres adheres to the stomach wall to provide gastroretention.

Chitosan, a popular choice as a coating material because of its regulatory status and its positive charge, binds to mucus [26] (Figure 2). In constructing controlled release chitosan formulations, it is important to retain the positive nature of the material. Sakkinen *et al*. have described a gamma scintigraphic evaluation of the fate of microcrystalline chitosan granules in the fasted human stomach [37]. The *in vivo* mucoadhesion of the chitosan formulations was better than that of a control but was erratic, and the authors concluded that, in their present form, the formulations studied were not reliable gastroretentive drug delivery systems. No data were provided as to the charged nature of the chitosan, and no attempt was made to provide a floating effect and enhanced contact with the gastric mucosa. Chitosan-based systems for local delivery of antibiotics in the stomach have been described by Torrado *et al*. [38], who studied a swelling chitosan-poly (acrylic) acid-based controlled drug release system in humans. The gastric half-emptying time of the polyionic complex was significantly delayed when compared with that of a reference formulation. An interesting gastroretentive floating chitosan-based system is described by West Pharmaceutical Services (http://www.westpharma.com/drug%20delivery/oral_delivery.asp) in the form of controlled release low-density microspheres. It is stated that 'the microspheres float on the stomach contents, and then adhere to the mucous lining as the stomach empties. The release of drug from the system can be controlled to coincide with the half-life emptying of the system from the stomach'. Full clinical data have yet to be provided.

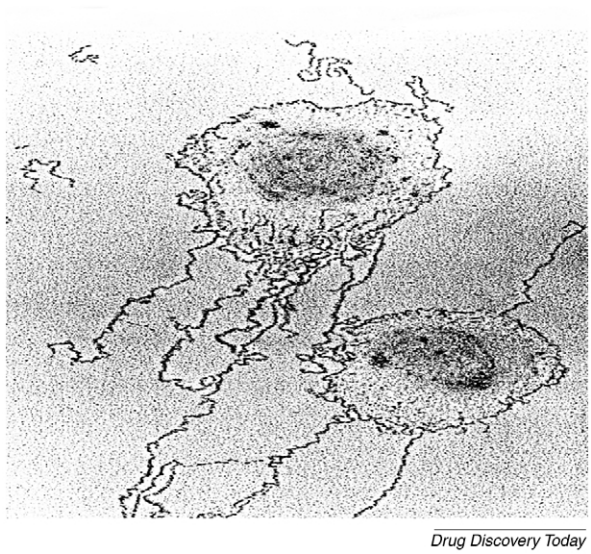

FIGURE 2

Interaction of mucin with chitosan. An enhanced electron micrograph showing mucin as long strands attached to chitosan aggregates. Chitosan interacts with mucin through charge interaction and hydrogen-bonding mechanisms.

Swelling and expanding systems

Perhaps the most promising approach to achieving gastroretention is that of creating a swelling or expanding system *in situ*. This is easier said than done. Any system will need to expand to a size large enough to be retained in the (fasted) stomach, but to do so in a safe and reliable manner. It must not swell or expand in the oesophagus or in the intestines, if it is emptied prematurely from the stomach (e.g. problems could arise from the formation of an insoluble mass known as a bezoar). The gastroretentive system will also need to display controlled release

properties so that the drug is released at an appropriate rate for optimal absorption from the absorption window. The system should have sufficient rigidity to remain intact in the stomach and to withstand the mechanical forces therein. Last but not least, it will need to decrease in size (degrade) after it has performed its function and then transit through the intestines in the normal way. The various systems described in the literature (to include numerous patents) usually achieve an increase in size through processes of expansion or swelling, or through unfolding. Expansion and swelling processes have either involved the generation of gas, in the form of carbon dioxide, or have exploited the properties of compressed porous materials such as hydrogels. Some earlier systems were based on novel geometries, such as long worm-like structures [34,35].

The fasted stomach presents a severe challenge in terms of the limited time available for a size increase and for retention to be achieved. By contrast, the lightly fed stomach can provide sufficient residence time for a suitable size increase. Therefore, it is not surprising to find that the majority of studies conducted on putative gastroretentive systems in human have involved the fed state.

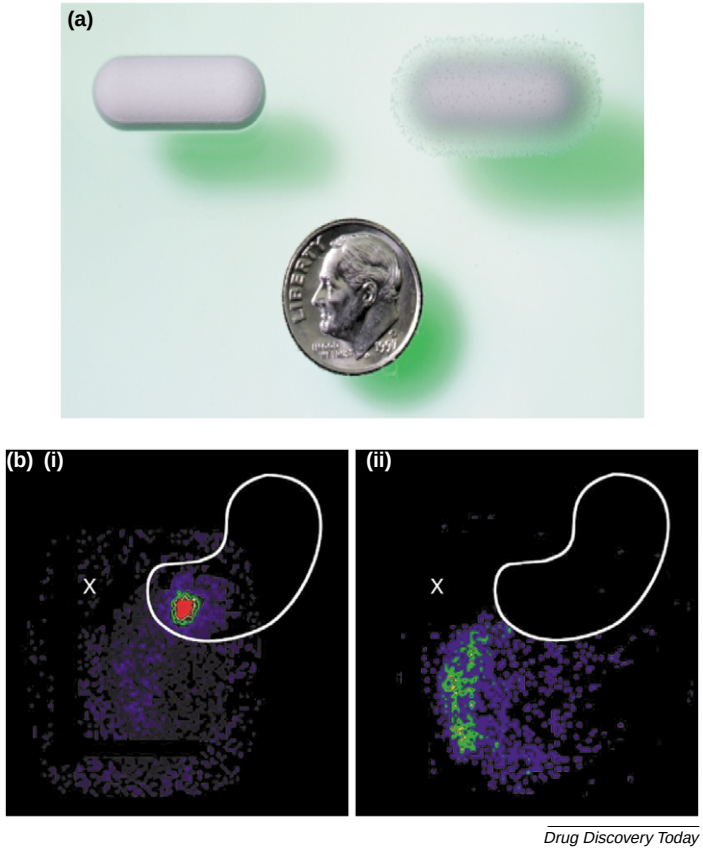

FIGURE 3

The Depomed Gastric Retention (GR™) System. (a) The Gastric Retention (GR™, Depomed) system in the non-swollen and swollen state is indicated, with a coin for comparison. **(b)** Gamma scintiscans showing the retention of the system in the stomach of a healthy volunteer. The formulation was labelled with two radionuclides of different energy characteristics to allow visualization of: (i) the retention of the swollen matrix in the stomach; and (ii) the erosion and gastric empyting of the drug-containing layer.

Super-porous hydrogel composites have been described as a strategy to delay small intestine transit. These devices, which have a very high swelling capacity because of the presence of numerous large pores, have also been investigated as gastroretentive systems [39]. Evaluation has been made in dogs, both under fasted and fed conditions, but these systems have yet to be tested in humans. Under fasted conditions, the composites remained in the stomach of the dog for two to three hours before breaking into two pieces and then emptied. When food was given before the experiment, the composite remained in the stomach for more than 24 h, although the fed condition was maintained only for the first few hours. Such results are encouraging, but I am reminded of our own studies performed some years ago on so-called gastroretentive systems [40]. Tablets formulated using hydrophilic polymers were tested in dogs and were found to have excellent gastroretentive properties (greater than 12 h) even in the fasted state. Sadly, when these systems were tested in human volunteers using scintigraphy, the average time for emptying from the fasted stomach was just 33 minutes. Hence, the dog is not a good model for human. The pig is a better model than dog, but pigs have a longer gastric retention of pellets and tablets than that in humans [41]. The best model for human is human.

The drug delivery company Depomed have described gastroretentive tablets 'that swell in the stomach which treats the tablet like undigested food, and won't let it pass into the small intestine. The tablet is retained by the stomach for several hours, where it can deliver its payload of drug as quickly or slowly as desired' (http://www.depomedinc.com/products_pipeline.htm).

These systems are based on polyethylene oxide (PEO) in combination with hydroxypropyl methylcellulose (HPMC) to produce a sustained-release matrix tablet that can swell. According to the company, candidate molecules include metformin, gabapentin ciprofloxacin and furosemide. Recent press releases state that Depomed has completed Phase III clinical trials with once-daily metformin for the treatment of Type II diabetes and with once-daily ciprofloxacin for the treatment of urinary tract infections, and that new drug applications (NDA) for both products have been filed with the FDA. The company is also conducting a Phase II trial with the diuretic furosemide. No full publications are yet available and, the degree and/or rate of swelling achieved might not be sufficient to allow retention of the dosage form in the fasted state. A recent abstract has described a dual-labelled scintigraphic study of controlled release furosemide gastric

*Louie-Helm, J. *et al.* (2003) Dual-labeled pharmacoscintigraphic study of furosemide gastric retention (GRTM) tablets in healthy volunteers. Abstract no. 118, Proceedings of the Controlled Release Society 30th Annual Meeting held 19–23 July 2003, in Glasgow, UK.

retentive tablets in healthy volunteers*. The dual-labelling procedure permitted separate characterization of the erosion and swelling. The tablets (and an immediate release control) were administered after a high-fat breakfast. Gastric residence of the swelling tablets was sufficiently long to deliver the drug to the upper GI tract (Figure 3). Consequently, the plasma concentration of the drug was extended and, furthermore, unlike previous slow release formulations reported in the literature, there was no reduction in bioavailability. From a standpoint of patient compliance, the gastroretentive tablet provided gradual diuresis and natriuresis, rather than the brief and intense diuresis of short onset time experienced by patients taking conventional immediate release furosemide tablets.

Workers in Israel have developed an interesting unfolding expandable compressed-dosage form comprising an inner polymeric and/or drug matrix layer with two shielding outer layers containing a coating of microcrystalline cellulose to prevent adhesion [42]. The usual type of dog study has been conducted with a demonstration of an enhanced bioavailability for the marker compounds. More importantly, two clinical studies have also been reported where the gastroretentive dosage form containing furosemide was given to volunteers [43]. This provided altered pharmacokinetics and pharmacodynamics, which were related to a longer residence in the stomach. In a second study, the unfolding and physical integrity of the dosage systems were evaluated *in vitro* and *in vivo* (by gastroscopy and radiology) [44]. A combination of rigidity and large dimension of the dosage forms was considered to be a decisive parameter to ensure prolonged gastroretention of five hours or longer. A significant extension of the absorption phase was demonstrated for levodopa; a drug with a narrow absorption window, but it is noteworthy that the system was dosed with a light breakfast.

Further clinical data are awaited with interest for all the systems described above. Data obtained by combining gamma scintigraphy with pharmacokinetics will be decisive in the selection of candidate systems before detailed evaluation takes place in Phase II clinical investigations [45,46].

Conclusions

While recent results from recent clinical studies are promising, convincing results have yet to be presented for a gastroretentive system that displays the necessary performance behaviour (as listed above) and which is retained in the fasted stomach of humans for a sensible period of time after dosing. A swelling or expanding system appears to be the best option, but rapid change in dimensions will have to be achieved in a fail-safe manner. Furthermore, the system will need to retain its integrity for an extended period of time in the harsh conditions present in the human stomach. Alternative approaches, such as attempts to modify small intestine transit using bioadhesion, could be frustrated by the efficient process of peristalsis and the presence of non-adherent mucus.

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