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REVIEW ARTICLE

A Review of Gastroretentive Drug Delivery System on Different Absorption Windows

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ABSTRACT

In recent years scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. In this review, the current technological developments of FDDS including patented delivery systems and marketed products, and their advantages and future potential for oral controlled drug delivery are discussed.

Keywords : Intragastric floating systems, Hydrodynamically balanced systems, gastroretentive systems, buoyant delivery systems.

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INTRODUCTION

In 1968, Davis firstly discovered the concept of floating drug delivery system (FDDS) after experience gagging or choking by some persons while swallowing medicinal pills. The GI-tract is the most important route for the delivery of drugs to the systemic circulation. After peroral administration the rate and extent of drug absorption depend on the transit time of the drug or dosage form through the absorbing area of the gastrointestinal tract. Only a few drug substances like theophylline, rivastigmine and metoprolol arecompletely absorbed from lower parts of the gastrointestinal tract. Drugs like acyclovir, levodopa, nitro-furantoin and riboflavin are only absorbed form the upper part of the small intestine. If preparations of such drugs reach lower regions of the gastrointestinal tract before the drug is completely released,drug absorption is reduced. For drug substances which are only absorbed from the upper part of the GI-tract we can try to develop gastroretentive drug delivery systems to achieve a more complete and longer lasting absorption [1]. After ingestion the drug is released from these systems into the stomach for a prolonged period of time. From the stomach the drug is delivered to the absorbing area of the small intestine. In the last decade different types of dosage forms with prolonged gastric residence time have been developed.

The researchers suggested that such difficulty could be overcome by providing pills having the density of less than 1.0g/ml so that the pill will float on water surface since then several approaches have been proposed for ideal floating delivery system. The process and ability to prolonged and control the emptying time is a valuable asset for dosage forms [2].

Floating dosage forms remain in the stomach due to their low density. The drug preparation should swim on the gastric content. Other approaches have been made using bioadhesive or swelling dosage forms. Drug carriers have been designed which unfold or expand in the stomach to form complex geometric shapes. Peroral sustained release dosage forms with an internal magnet and extracorporal guidance have been developed for controlled gastrointestinal transit Gastrointestinal passage may also be prolonged by physiologically active substances such as salts of myristic acid which are responsible for the transit delay, if fatty rich meals are ingested. If these substances are released from drug preparations, they induce a change of the motility pattern of the stomach. A prolonged gastric residence time is obtained. If riboflavin or nitrofurantoin containing preparations are swallowed, the absorption of riboflavin or nitrofurantoin is enhanced. It was the aim of the present investigations to develop new gastroretentive systems for controlled drug release. The dosage forms should be biodegradable to reduce the risk of obstruction of the lumen of intestinal segments [3].

Anatomically the stomach is divided into 3 regions namely

1. Fundus 2. body 3. antrum(pylorus)

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During fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2-3 hours. this is called the migrating myloelectric cycle (mmc) which is further divided into 4 phases.

- Phase-i (basal phase)
- Phase-ii (pre-burst phase)
- Phase-iii (burst phase)
- Phase-iv

orally administered controlled release dosage forms suffer from mainly two adversities:

1. Short gastric retention time (grt)
2. Unpredictable gastric emptying time

FACTORS AFFECTING GASTRIC RETENTION [4]

- Gastric retention time (GRT) is affected several factors including sizr and shape of dosage forms, density, intake of food and drugs such as anticholinergic agents, prokinetic agents and opiates.
- Biological factors which affect gastric emptying include age, gender, posture, body weight and disease state.
- For HBS dosage form to floating stomach it should have the density less than the gastric contents.
- Food has major effect on GRT dosage form by depending on its nature, caloric contents and the frequency of intake which has major effect on gastric emptying than specific gravity.
- FDDS demonstrated that a GRT of four to ten hours could be achieved after a fat and protein meal.
- Size of dosage form is one of the factors among the other determinants of gastric retention

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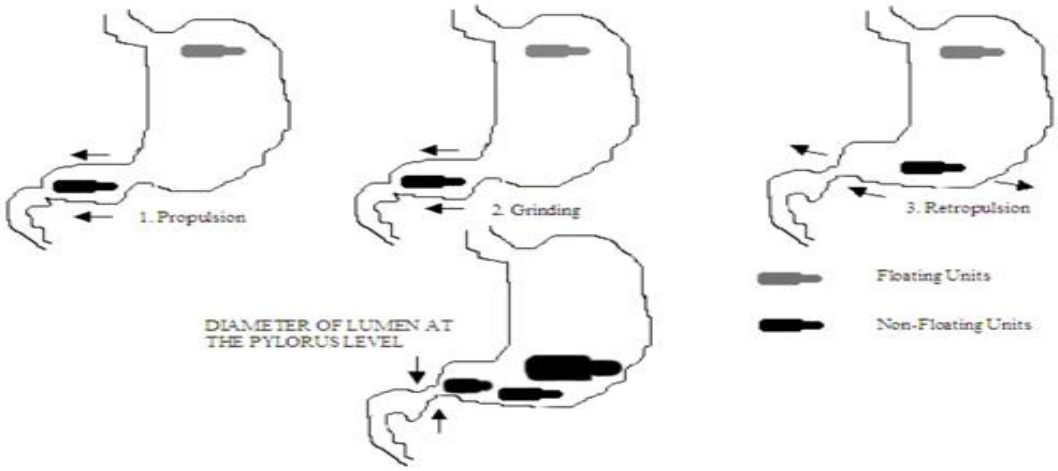

Fig.1 Intragastric Residence Positions of Floating & No floating units

Approaches to Design Floating Dosage Forms

The following approaches have been used for the design of floating dosage form of single and multiple unit system.

SINGLE UNIT DOSAGE FORMS

In low density approach the globular shells apparently having lower density than that of Gastric Fluid can be used as a carrier for drug for its controlled release. Fluid filled floating chamber type of dosage forms includes incorporation of a gas filled floatation chamber into a micro porous component that houses a drug reservoir [5]. The success of HBS capsule as a better system is best exemplified with chlordiazeopoxide hydrochloride. The drug is a classical example of a solubility problem where in it exhibits a 4000 fold difference in solubility going from pH 3-6 Fig.2 .

Hydro dynamically balanced systems (HBS) are designed to prolong the stay of dosage form in the gastro intestinal tract and in enhancing the absorption Fig.4. The 3 Layer principle has been improved by development of an asymmetric configuration drug delivery system in order to modulate the release extent and achieve zero order release kinetics by initially maintaining a constant area at the diffusing front with subsequent dissolution toward the completion of the release process. Single unit processes are associated with problem such as sticking together or being obstructed in the gastrointestinal tract which may have a potential danger of producing irritation[6].

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Multiple Unit Dosage Forms

The purpose of designing multiple unit dosage form is to develop a reliable formulation that has all the advantageous of single unit form and also is devoid of any of the above mentioned disadvantages. In pursuit of this endeavor many multiple unit floatable dosage forms have been designed Fig.2. Micro Spheres have high loading capacity and may polymers have been used such as albumin, gelatin, starch, polymethacrylate**,** polyacrylamine and polyalkylcyanoacrylate [7].

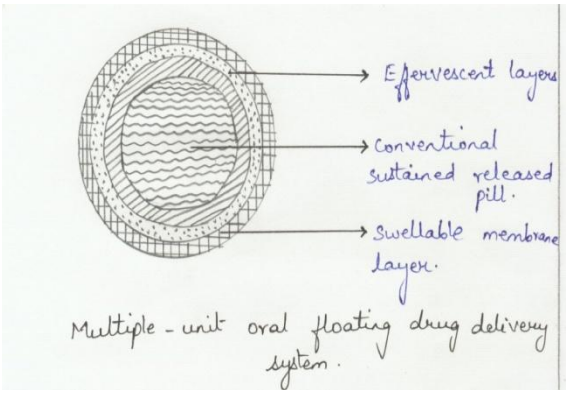

Fig.2 Multiple unit oral floating drug delivery system

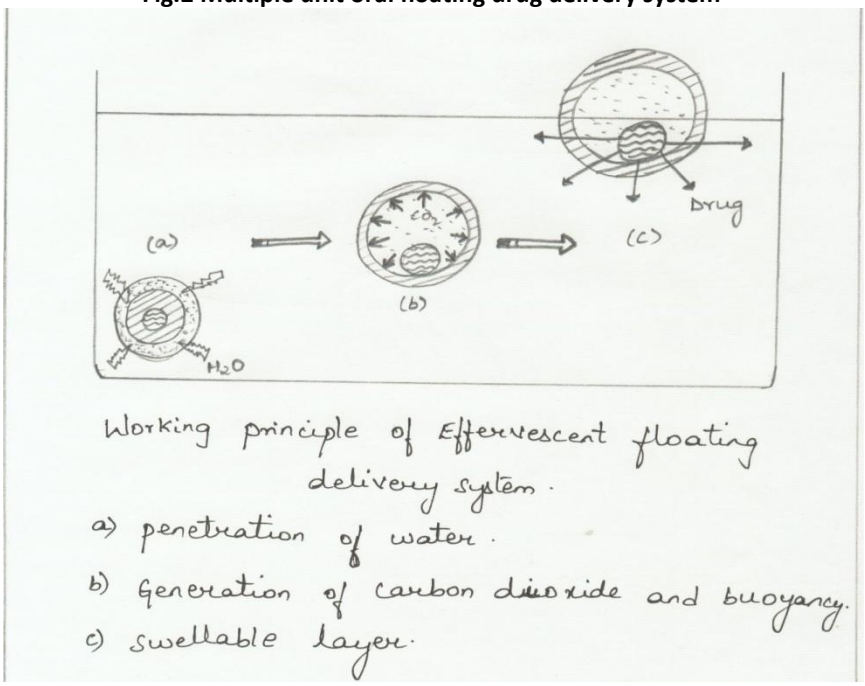

Fig.3 Working prnciple of effervescent floating delivery system

NON-EFFERVESCENT FLOATING DOSAGE FORMS

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- Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides and matrix forming polymers like polycarbonate, polyacrylate, polymethacrylate and polystyrene.
- The formulation method includes a simple approach of thoroughly mixing the drug and the gel forming hydrocolloid [8].

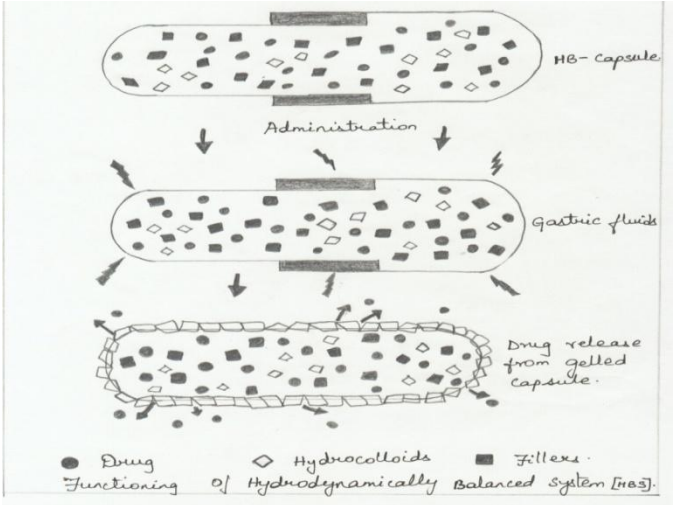

Fig.4 Functioning of Hydrodynamically balanced system

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 [9]. Active transport mechanisms for drugs involving carriers and pump systems have been well described. 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 mecha-nisms, 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. pro-pranolol, felodipine) . Some drugs can be substrates for both CYP3A4 and p-glycoprotein (e.g. cyclosporin, itra-conazole). 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 phar-macological effects. 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 [10]. 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 Ampicilin (free acid) following site-selected delivery to different regions of the human gastrointestinal tract

PARAMETERS	IR TABLET	PROXIMAL SMALL INTESTINE	DISTAL SMALL INTESTINE	ASCENDING COLON
AUC(mg hr^{-1}	26.3	30	20.8	9
Cmax(mg 1^{-1}	15.8	12.1	10.3	2.5

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 . Transit through the colon is much longer and can be 20 h or more . Hence, the time a drug will have in its absorption window can be relatively short, more so if the drug is pref-erentially 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 [11]. 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 .

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 dif-ficult to formulate into extended release products because on arrival in the colon (or even before), absorption will be low or non-existent [12].

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 . Formulation strategies to improve dissolution rate and drug

stability can be investigated. 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 . Poor permeability can sometimes be improved by the use of an absorption enhancer [13]. Current research is focusing on agents that can modify the tight junctions between cells in a transient manner. 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,
(ii) Those that attempt to hold the drug formulation above the absorption window through gastroretention.

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

Modification of small intestine transit [14]:
Pharmacological methods

It is well known that drugs can alter GI transit. For example, scintigraphic data have indicated that pre-treat-ment with metoclopramide decreased gastric emptying time and increased GI motility, whereas pre-treatment with propantheline had the opposite effect .

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.

Bioadhesion [18]

For years pharmaceutical scientists have been fascinated by the concept of bioadhesion. Various attempts have been made to identify putative bioadhesive or mucoadhe-sive 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. Chitosan is known to bind well to mucus, and microparticles coated with chitosan adhere well in the intestine of animals. However, good adhesion and delayed transit do not always translate into improved bioavailability of an administered drug.

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 [19]. 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.

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. Moreover, the surface of administered particles can be rapidly conditioned by the adsorption of endogenous components such as non-adherent mucus. Not with standing, it has been postulated that, because of their size, very small particles could perhaps become trapped between the villae of the small intestine [20]. To test this proposal, It followed the transit of very small particles (in the ranges of 70–80 µm, 1–10 µm and 500 nm) in the human gut using gamma scintigraphy.

Various *in vitro* experiments have been described, together with some data obtained in an animal model. 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.

Based on this knowledge, various approaches have been devised for gastroretention. These fall into two main classes:

(i) small particles that have bioadhesive properties.

(ii) large swelling objects that will be retained in the stomach because of their size.

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 rela-tive 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 contrac-tions or waves . One particular wave called the 'house-keeper 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 gastro-retention in a clinical setting. A single unit system (or a multiparticulate) can empty rapidly from the fasted stomach.

Gastrointestinal transit of pharmaceutical dosage forms [21]

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)

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, and only the more recent developments and strategies will be considered here. 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.

Microparticulates

Gastroretentive microparticles have been investigated, but few studies have demonstrated success in clinical investigations. They have revealed that oral dose forms containing finely divided ion-exchange resins can provide prolonged gastric residence and uniform distribution within the stomach. An interesting gastroretentive floating chitosan-based system is described by West Pharmaceutical Services in the form of controlled release low

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density microspheres. 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. 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. Chitosan, a popular choice as a coating material because of its regulatory status and its positive charge, binds to mucus. The *in vivo* mucoadhesion of the chitosan formulations was better than that of a control but was erratic, and the vauthors concluded that, in their present form, the formulations studied were not reliable gastroretentive drug delivery systems.

Chitosan-based systems for local delivery of antibiotics in the stomach have been described by who studied a swelling chitosan-poly (acrylic) acid-based controlled drug release system in humans.

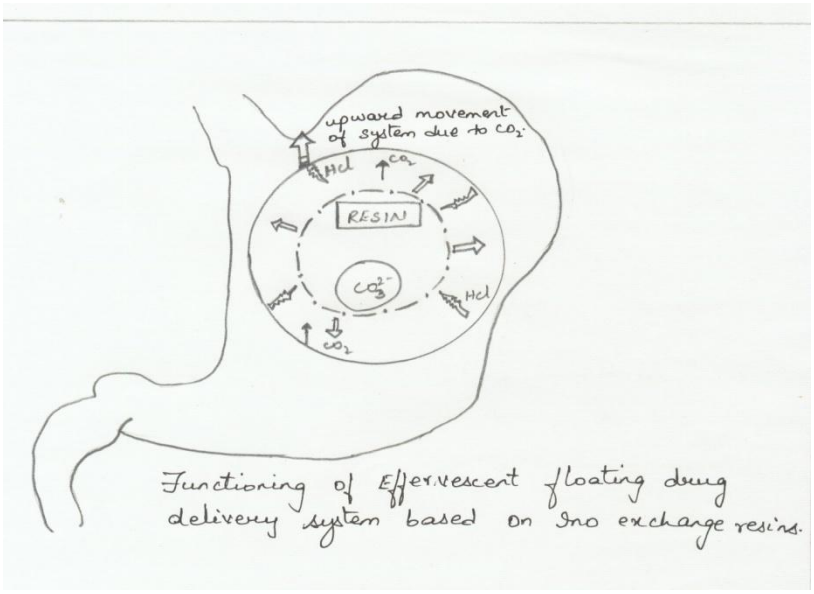

Fig. Functioning of effervescent floating drug delivery system based on Ion exchange resins

Swelling and expanding systems

Perhaps the most promising approach to achieving gastroretention is that of creating a swelling or expanding system *in sit*u. 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 [22]. The system should have sufficient rigidity to remain in-tact in the stomach and to withstand the mechanical forces therein.

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. 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. Super porous hydrogel composites have been described as a strategy to delay small intestine transit.

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 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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