REVIEW ON GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT
Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels. The purpose of writing this review on gastroretentive drug delivery systems was to compile the recent literature with special focus on various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention. Afterwards, we have reviewed various gastroretentive approaches designed and developed until now, i.e. high density (sinking), floating, bio- or mucoadhesive, expandable, unfoldable, super porous hydrogel and magnetic systems. Finally, advantages of gastroretentive drug delivery systems were covered in detail.

KEYWORDS: Gastroretentive, Drug, Oral route.

INTRODUCTION
Oral controlled release (CR) dosage forms (DFs) becoming an interesting topic of research for the past 3 decades due to their considerable therapeutic advantages (Hoffman 1998). However, this approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the gastrointestinal tract i.e. stomach and small intestine. This is due to the relatively short transit time of the DF in these anatomical segments. Thus, after only a short period of less than 6 h, the CR-DF has already left the upper gastrointestinal tract and the drug is released in non-absorbing distal segments of the gastrointestinal tract. These results in a short absorption phase that is often accompanied by lesser bioavailability. The drugs categorised with narrow absorption window are mostly associated with improved absorption at the jejunum and ileum due to their enhanced absorption properties e.g. large surface area, in comparison to the colon; or because of the enhanced solubility of the drug in the stomach as opposed to more distal parts of the gastrointestinal tract. It was suggested that compounding
narrow absorption window drugs in a unique pharmaceutical DF with gastroretentive properties would enable an extended absorption phase of these drugs. After oral administration, such a DF would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs for these drugs.

The stomach is divided into three anatomical regions: Fundus, Body, and Pylorus (or antrum). The proximal stomach consists of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric content for gastric emptying. Gastric emptying occurs both in fasting as well as fed states. In case of fasted state an inter-digestive series of electrical events occurs in a cyclic manner both through the stomach and small intestine every 2 to 3 hours.

The delivery of drugs to the stomach takes advantage of several features of this organ, particularly the ones related to its physiology like the low pH, motility or gastric emptying time. By affecting the physiology, formulation variables including concomitant administration of other materials, such as food, one can retain a dosage form in the stomach or improve its displacement to the duodenum. The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in GRDFs that were designed in large part based on the following approaches (Hwang et al. 1998): (a) low density form of the DF that causes buoyancy above gastric fluid (Singh et al. 2000); (b) high density DF that is retained in the bottom of the stomach; (c) bioadhesion to the stomach mucosa (Moes 1993); (d) slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients (Rubinstein et al. 1994); (e) expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter. Changes on the density of the dosage forms (e.g. high porosity, swelling or expansion, super porous hydrogels) after administration, bioadhesion and changes on geometry of dosage forms (Hwang et al., 1998; Gangadharappa et al., 2007). Floating, magnetic retention or geometry changes of the dosage form can be achieved with the aim of increasing the bioavailability of the carrying drug by prolonging the gastric residence time. The current review deals with the expandable GRDF approach that has recently become the leading methodology in this field.

**APPROACHES TO GASTRIC RETENTION**
A number of oral controlled release systems have been developed to improve the delivery of drugs to the systemic circulation. Although such systems can control precisely and predictably the drug release rate for extended periods of time, even over a number of days, they do not always perform satisfactorily if they pass through the drug absorption site, e.g. the small intestine, before the release of loaded drug is complete. Thus attention must be given to prolonging the residence time of the system to achieve complete drug release in the gastrointestinal (GI) tract (stomach or small intestine) as well as to modulating the drug release rate as predicted by the system in order to obtain an ideal oral controlled release system. Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floating systems (Deshpande et al 1997), swelling and expanding systems (Urquhart et al 1984; Mamajek et al 1980), bioadhesive systems (Alvisi et al 1996; Lenaerts et al 1990; Lehr 1994; Ponchel et al 1998), modified-shape systems (Cargill et al 1988; Caldwell et al 1988; Caldwell et al 1988; Caldwell et al 1988; Fix et al 1993; Kedzierewicz et al 1999), high-density systems (Rednick et al 1970; Bechgaard et al 1978; Davis et al 1986), and other delayed gastric emptying devices (Gro¨ning et al 1984; Gro¨ning et al 1989). Swelling type dosage forms are such that after swallowing, these products swell to an extent that prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred to as "plug type systems" since they exhibit a tendency to remain lodged at the pyloric sphincter. Bioadhesive systems are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner (Lenaerts et al 1990). The approach involves the use of bioadhesive polymers that can adhere to the epithelial surface of the GI tract. The proposed mechanism of bioadhesion is the formation of hydrogen- and electrostatic bonding at the mucus-polymer boundary (Wilson et al 1989). Rapid hydration in contact with the mucoepithelial surface appears to favor adhesion, particularly if water can be excluded at the reactive surfaces (Wilson et al 1989). Modified-shape systems are nondisintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modulus of the drug delivery device (Cargill et al 1988; Caldwell et al 1988; Caldwell et al 1988; Caldwell et al 1988; Fix et al 1993; Kedzierewicz et al 1999).

High-density formulations include coated pellets, which have a density greater than that of the stomach contents (1.004 g/cm). This is accomplished by coating the drug with a heavy inert material such as barium sulfate, zinc oxide, titanium dioxide, iron powder, etc. Other delayed
gastric emptying approaches of interest include sham feeding of indigestible polymers (Russell et al 1985; Russell et al 1985; Leung et al 1993) or fatty acid salts (Gro¨ning et al 1984; Gro¨ning et al 1989; Heun 1987) that change the motility pattern of the stomach to a fed state, thereby decreasing the gastric emptying rate and permitting considerable prolongation of drug release. Floating drug delivery systems or hydrodynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in plasma drug concentrations in some cases.

Floating drug delivery systems were first described by Davis in 1986. These systems were used to prolong the gastric residence time of drug delivery systems. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. A floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract (GIT), are unstable in lower parts of GIT, or are poorly absorbed in the intestine (Martinez et al 2008). A problem frequently encountered with conventional controlled release dosage forms is the inability to increase their residence time in the stomach and proximal portion of the small intestine. Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time, thereby, resulting in improved oral bioavailability of the basic drugs that have poor solubility in higher pH, as well as, drugs susceptible to circadian variations (Menon et al., 1994; Whitehead et al., 1998; Fell, 1999; Baumgartner et al., 2000). A number of oral controlled release systems have been developed to improve the delivery of drugs to the systemic circulation. Although such systems can control precisely and predictably the drug release rate for extended periods of time, even over a number of days, they do not always perform satisfactorily if they pass through the drug absorption site, e.g. the small intestine, before the release of loaded drug is complete. Thus attention must be given to prolonging the residence time of the system to achieve complete drug release in the gastrointestinal (GI) tract (stomach or small intestine) as well as to modulating the drug release rate as predicted by the system in order to obtain an ideal oral controlled release system. Limited gastrointestinal (GI) transit time often restricts the complete absorption of oral drugs, or limits the duration of absorption. Thus dosage of a few times a day is generally needed (Khosla and Davis, 1989).

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS
**Enhanced bioavailability**

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption (Klausner et al 2003).

**Enhanced first-pass biotransformation**

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input (Garg et al 2008).

Sustained drug delivery/reduced frequency of dosing

For drugs with relatively short biological halflife, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

**Targeted therapy for local ailments in the upper GIT**

The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

**Reduced fluctuations of drug concentration**

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index (Hoffman 1998).

**Improved selectivity in receptor activation**

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

**Reduced counter-activity of the body**

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.
**Extended time over critical (effective) concentration**

For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

**Minimized adverse activity at the colon**

Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganisms resistance.

**Site specific drug delivery**

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine (Hoffman et al 1999). The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

**GASTRORETENTIVE DELIVERY SYSTEMS**

Multunit rastroretentive drug delivery systems Shaji et al 2009 prepared a multiunit gastroretentive microspheres can be utilized to provide a more reliable and long lasting release of drug in the stomach for local and systemic action and thus altering the absorption of drug, thereby enhancing bioavailability. Famotidine, being a poorly bioavailable drug due to reasons unrelated to hepatic metabolism, is ideally suited to be delivered through a controlled release floating multiunit dosage form for slow release in the stomach and subsequent complete absorption in the intestine. In the present study, non-aqueous solvent evaporation technique was employed to develop polymethylmethacrylate (PMMA) microspheres of famotidine. A multi-unit floating gel bead was synthesized with calcium alginate, sunflower oil, and a drug of interest through an emulsification/gelation process. Three kinds of drugs with different hydrophilicities, ibuprofen, niacinamide and metoclopramide HCl, were tested in the study (Tang et al 2007). Kagan et al 2006 developed an Accordion Pill™ (AP), a novel controlled release gastroretentive unfolding dosage form (DF), to increase the bioavailability of riboflavin (RF) in humans. The AP
is composed of three layers: two envelope membranes that “sandwich” between them the third layer composed from the frame that affords the physical properties to the device and the drug reservoir in the center. Jain et al 2005 prepared a multi-unit gastro-retentive dosage form of Repaglinide to be used as controlled-release drug delivery systems to increase its residence time in the stomach without contact with the mucosa and it was achieved through the preparation of floating microspheres by the emulsion solvent diffusion technique consisting of (i) calcium silicate (FLR) as porous carrier; (ii) Eudragit S as polymer.

**Floating Drug Delivery System**

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non-effervescent and gas-generating system:

(a) **Non-effervescent systems**

This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier (Hilton et al 1992). The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

(b) **Gas-generating (Effervescent) systems**

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid) (Rubinstein et al 1994). The system is so prepared that upon arrival in the stomach, carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate (Stockwell et al 1986), multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin.
technology, etc. El-Gibaly I., 2002 prepared floating (F) microcapsules containing melatonin (MT) by the ionic interaction of chitosan and a negatively charged surfactant, sodium diocetyl sulfosuccinate (DOS). In this approach chitosan microparticles containing MT were prepared by a capillary extrusion procedure (Shiraishi et al., 1993). Joseph et al, 2002 achieved over 95% of incorporation efficiencies for the encapsulation by preparing a floating type dosage form (FDF) of piroxicam in hollow polycarbonate (PC) microspheres capable of floating on simulated gastric and intestinal fluids was prepared by a solvent evaporation technique. Hollow microspheres (microballoons) floatable on solution \{(300 ml, pH 1.2, 378C) containing Tween 20 (0.02 w/v \%)} were developed as a dosage form capable of floating in the stomach.

Hollow microspheres were prepared by the emulsion solvent diffusion method using enteric acrylic polymers with drug in a mixture of dichloromethane and ethanol (Sato et al 2003). Sauzet et al 2009 developed an innovative floating gastro retentive dosage form (GRDF) by use of state of the art wet granulation manufacturing process. The technology induces a low-density dosage form containing high active pharmaceutical ingredient (API) concentration i.e. Theophylline by using a hydrophobic dusty powder excipient under specific conditions. Ali et al 2007 developed a hydrodynamically balanced system of metformin as a single unit floating capsule. Various grades of low-density polymers (Different grades of the poly ethylene oxide (PEO) of grades-WSR 1105, WSR 301, WSR 303, WSR 60 K, WSR N80, and HPMC K4 M) were used for the formulation of this system. They were prepared by physical blending of metformin and the polymers in varying ratios. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in simulated fed state gastric fluid (citrate phosphate buffer pH 3.0).

Effect of various release modifiers was studied to ensure the delivery of drug from the HBS capsules over a prolonged period. Sungthongjeen et al 2008 prepared a Floating multi-layer coated tablets of Anhydrous theophylline based on gas formation. The floating tablets using direct-compressed cores had shorter time to float and faster drug release than those using wet-granulated cores. The tablet was coated with a protective layer (hydroxypropyl methylcellulose), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane (Eudragit RL 30D due to its high flexibility and high water permeability), respectively. The obtained tablets enabled to float due to the CO_{2}-gas formation and the gas entrapment by polymeric membrane. The effect of formulation variables on floating properties and drug release was investigated.

**Matrix floating tablet**

A Matrix floating tablet of captopril was prepared from Metolose SH 4000 SR/sodium bicarbonate by varying the proportions of Metolose and bicarbonate (Martinez et al 2008).
compressed matrix tablet of Metformin based on pH-sensitive poly (ethylene oxide) (PEO)–Eudragit L100 (EUD L) compounds was prepared by Colo et al 2002 by following co-evaporation procedure.

**Mucoadhesive and Bioadhesive Microspheres**

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach (Moes1993). Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucus by the gastric mucosa to replace the mucus that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc. According to the Vasiret al., 2003 microspheres with bio-adhesive polymer incorporated could contribute to improve absorption and enhance bioavailability of the drugs due to an intimate contact with the mucus layer, prolonged retention in the gastrointestinal tract, or specific targeting of drugs to the absorption site, etc. If the bio-adhesive interactions occur primarily with the mucus layer of a mucous membrane, the phenomenon is referred to as “muco-adhesion” (Gu et al., 1988). Muco-adhesion can be obtained by either nonspecific or specific interactions with surface ligands at a mucosal surface and hence Tao et al 2009 prepared acyclovir-loaded muco-adhesive microspheres (ACV-ad-ms) using Ethylcellulose as matrix and Carbopol 974P NF as muco-adhesive polymer (prepared by emulsion solvent evaporation method) for the purpose of improving the oral bioavailability of acyclovir.

**Mislenuous Gastroretentive Drug Delivery Systems**

Whitehead et al., 1998 developed a freeze-dried calcium alginate multiple-unit of floating dosage forms (FDFs) which demonstrate favorable in vitro floating characteristics. The aim of this study was to investigate the in vivo behaviour of this system compared to a multiple-unit non-floating dosage form manufactured from identical material. Murata et al 2000 prepared two types of alginate gel beads capable of floating in the gastric cavity were prepared. The first, alginate gel bead containing vegetable oil (ALGO), is a hydrogel bead and its buoyancy is attributable to vegetable oil held in the alginate gel matrix. The model drug, metronidazole (MZ), contained in ALGO was released gradually into artificial gastric juice, the release rate being inversely related to the percentage of oil. The second, alginate gel bead containing chitosan (ALCS), is a dried gel
bead with dispersed chitosan in the matrix. The drug-release profile was not affected by the kind of chitosan contained in ALCS. Roy et al. 2009 worked on a conceptualizes specific technology, based on combining floating and pulsatile principles to develop drug delivery system, intended for chronotherapy in nocturnal acid breakthrough. In this approach a programmed delivery of ranitidine hydrochloride from a floating tablet with time-lagged coating was used. In this study, investigation of the functionality of the outer polymer coating to predict lag time and drug release was statistically analyzed using the response surface methodology (RSM). RSM was employed for designing of the experiment, generation of mathematical models and optimization study. Fukuda et al. 2006 prepared a controlled release hotmelt extruded (HME) tablets containing Eudragit® RS PO and/or Eudragit® E PO and the purpose behind this formulation was to investigate the influence of sodium bicarbonate on the physicochemical properties of controlled release hotmelt extruded (HME) tablets. Acetohydroxamic acid and chlorpheniramine maleate were used as model drugs. Sodium bicarbonate was incorporated into the tablet formulations and the drug release properties and buoyancy in media for HME tablets and directly compressed (DC) tablets were investigated. The crosssectional morphology of the HME tablets showed a porous structure since CO2 gas was generated due to the thermal decomposition of sodium bicarbonate in the softened acrylic polymers at elevated temperature during the extrusion process. Chavanpatil et al. 2005 prepared a sustained release (SR)-gastroretentive dosage forms (GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. A new strategy is proposed for the development of gastroretentive dosage forms for ofloxacin preferably once daily. The design of the delivery system was based on the sustained release formulation, with floating and swelling features in order to prolong the gastric retention time of the drug delivery systems. Different polymers, such as psyllium husk, HPMC K100M, crospovidone and its combinations were tried in order to get the desired sustained release profile over a period of 24 h.

**CONCLUSION**

Controlled release gastroretentive dosage forms (CR-GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. CR-GRDF provides a means to utilize all the pharmacokinetic (PK) and pharmacodynamics (PD) advantages of controlled release dosage forms for such drugs. Based on the literature surveyed, it may be concluded that drug absorption in the gastrointestinal tract is a highly variable process.
and prolonging gastric retention of the dosage form extends the time for drug absorption. Thus gastroretentive dosage forms provide an additional advantage for drugs that are absorbed primarily in the upper segments of gastrointestinal tract, i.e. stomach, duodenum and jejunum. Due to the complexity of pharmacokinetic and pharmacodynamic parameters, in vivo studies are required to establish the optimal dosage form for a specific drug. For a certain drug, interplay of its pharmacokinetic and pharmacodynamic parameters will determine the effectiveness and benefits of the CRGRDF compared to the other.

REFERENCES


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