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# A Review: Gastroretentive Drug Delivery Systems and its Rational in Peptic Ulcer Treatment.

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**ABSTRACT:**

Controlled release (CR) 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. CR-GRDF provides a means to utilize all the pharmacokinetic and pharmacodynamic advantages of controlled release dosage forms for such drugs. GRDF provides a mean for controlled release of compounds that are absorbed by active transport in the upper intestine. It also enables controlled delivery for paracellularly absorbed drugs without a decrease in bioavailability. Prolonged gastric retention can be achieved by using floating, swelling, bioadhesive, or high-density systems. Recent advances in polymer science and drug carrier technologies have promulgated the development of bioadhesive systems that have boosted the use of "bioadhesion" in drug delivery. The development of mucus or cell-specific bioadhesive polymers and the concepts of cytoadhesion and bioinvasion provide unprecedented opportunities for targeting drugs to specific cells or intracellular compartments. H2Receptor antagonists (H2RAs) have become first-line therapy for acid related peptic disease and GRDF especially designed for H2RAs and drugs against Helicobacter pylori (H. Pylori), including specific targeting systems and leading to a marked improvement in the quality of life for a large number of patients. In this connection, new formulations with better absorption, better bioavailability and better acid-suppressing regimens are welcome.

**KEY WORDS:** Mucoadhesion, H2 Receptor antagonist, porous carrier.

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## INTRODUCTION:

CR delivery systems provide a uniform concentration/amount of the drug at the absorption site and thus, after absorption, allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. CR products are formulations that release active drug compounds into the body gradually and predictably over a 12 to 24 hour period and that can be taken once or twice a day. Typically, these products provide numerous benefits compared with immediate release drugs, including greater effectiveness in the treatment of chronic conditions, reduced side effects, greater convenience, and higher levels of patient compliance due to a simplified dosing schedule. Because of the above advantages, such systems form the major segment of the drug delivery market. A number of techniques are used to achieve controlled release of drugs via the oral cavity. GRDF is the one of these techniques reviewed briefly in this review.

Many clinically used drugs could benefit from CR dosage forms. A common property of conventional CR technologies is that a large part of the drug load is released in the colon, where the dosage forms stays for a relatively long time period. This delivery approach, while suitable for many molecules, was found to be inappropriate for drugs that are poorly absorbed from the lower part of the GI tract[1].

The concept of CR-GRDF was introduced in order to enable continuous delivery to the upper part of the GI tract, while minimizing the limitation of poor absorption from the colon. These dosage forms are designed to be retained in the stomach for a prolonged time period while releasing their content in a continuous and controlled manner. The gastric retention is attained by preventing the dosage forms from passing through the pyloric sphincter. Detailed discussion regarding the different technological approaches to achieve gastric retention can be found elsewhere[2-6].

A number of alterations in pharmacokinetic and pharmacodynamic profiles of drugs have been reported following drug administration in GRDFs[7, 8].

This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome[9].

Bioadhesives may be able to delay the gastric emptying and intestinal transit of pharmaceutical dosage forms via their interaction with either the mucus lining or mucosa of the GIT[10].

Bioadhesive retentive system involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the GIT. Using bioadhesive would be achieved increase GI transit time and increase in bioavailability. Ahmed[11] studied GRDFs made of naturally occurring carbohydrate polymers and containing riboflavin in vitro for swelling and dissolution characteristics as well as in fasting dogs for gastric retention.

It is also reported that oral treatment of gastric disorders with an H2RA like ranitidine or famotidine, used in combination with antacids, promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion[12].

In particular, H. pylori lives deep within the gastric mucus layer[13] and prolonged local application of drug is needed for sufficient to diffuse to the bacteria. Moreover, efficacy of topical application of antibiotics can sometimes be enhanced by absorbed by the gastric wall, followed by resecretion into the lumen[14, 15].

The contribution of low-density porous carrier in the development of this drug delivery system associates major significance by (a) ensuring the retention of dosage form in the stomach for an extended period without using any excipients for enhancing floating, (b) simultaneous least release all through this period (resembling lag phase) suited for NSAID drugs to avoid gastric irritation, (c) choice of drug loading (melt and solvent evaporation), and(d) limit/overcome various formulation variables by acting as a drug-loading core using single formulation step when compared with other approaches/methods, which need multiple steps by using various polymers and excipients to achieve such release profile.

**Gastroretentive Drug Delivery Systems**

Dosage forms that can be retained in the stomach are called GRDFs[16]. GRDFs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site[17] thus ensuring its optimal bioavailability[18,19].

GI motility patterns affecting dosage form retention. The complex anatomy and physiology of the GIT, including variations in acidity, bile salts, enzyme content, and the mucosal absorptive surface, significantly influence the release, dissolution, and absorption of orally administered dosage forms.

Table 2 lists the anatomical and physiological characteristics of the GIT[20]. Two distinct patterns of GI motility and secretion exist, corresponding to the fasted and fed states[21]. As a result, the bioavailability of orally administered drugs will vary depending on the state of feeding. The fasted state is associated with various cyclic events, commonly referred to as the migrating motor complex (MMC), which regulates GI motility patterns. The MMC is organized into alternating cycles of activity and quiescence and can be subdivided into basal (Phase I), pre-burst (Phase II), and burst (Phase III) intervals (see Figure 1). Phase I, the quiescent period, lasts from 30 to 60 min and is characterized by a lack of secretory, electrical, and contractile activity.

Phase II exhibits intermittent action for 20–40 during which contractile motions increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of Phase II and throughout Phase III. Phase III is characterized by intense, large, and regular contractions, termed housekeeper waves, that sweep off undigested food and last 10–20 min. Phase IV is the transition period of 0–5 min between Phases III and I. This series of electrical events originates in the foregut and continues to the terminal ileum in the fasted state, repeating every 2–3 h[22].

Feeding sets off a continuous pattern of spike potentials and contractions called postprandial motility. The particular phase during which a dosage form is administered influences the performance of peroral CR and GRDFs[23]. When CR systems are administered in the fasted state, the MMC may be in any of its phases, which can significantly influence the total gastric residence time (GRT) and transit time in the GIT. This assumes even more significance for drugs that have an absorption window because it will affect the amount of time the dosage form spends in the region preceding and around the window. The less time spent in that region, the lower the degree of absorption. Therefore, the design of GRDDS should take into consideration the resistance of the dosage form to gastric emptying during Phase III of the MMC in the fasted state and also to continuous gastric emptying through the pyloric sphincter in the fed state. This means that GRDDS must be functional quickly after administration and able to resist the onslaught of physiological events for the required period of time.

Several techniques, including floating[24], swelling, Effervescent/non-effervescent systems, Raft forming systems, bioadhesion [25-28] and swelling system have been explored to increase the gastroretention of dosage forms.

**Floating systems:** Floating systems, first described by Davis in 1968, are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period[29, 30]. While the system floats over the gastric contents, the drug is released slowly at the desired rate [31, 32], which results in increased GRT and reduces fluctuation in plasma drug concentration[33]. Floating systems can be classified as effervescent and non-effervescent systems.

These are single unit dosage forms, containing one or more gelforming hydrophilic polymers. Hydroxypropylmethylcellulose (HPMC) is the most common used excipient, although hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), sodium carboxymethyl cellulose (NaCMC), agar, carrageenans or alginic acid are also used[34,35].The polymer is mixed with drug and usually administered in a gelatine capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy (Figure 2)

Oth et al. produce d a bilayer formulation of misoprostol against gastric ulcers[36]. Chitnis et al. formulated a bioadhesive floating system by coating tablets with Carbopol or a synthetic bioadhesive crosslinked polymer of methacrylic and acrylic acids[37].

**Effervescent systems:** Flotation of a drug delivery system in the stomach can be achieved by incorporating a floating chamber filled with vacuum, air, or an inert gas. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the $CO_2$ produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts[34]. These devices contain a hollow deformable unit that converts from a collapsed to an expanded position and returns to the collapsed position after a predetermined amount of time to permit the spontaneous ejection of the inflatable system from the stomach.

Drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers (Figure 3). Further refinements involve coating the matrix with a polymer which is permeable to water, but not to $CO_2$[38].

**Raft-forming systems:** Here, a gel forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped $CO_2$ bubbles (Figure 4) on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment[39-42] as with Liquid Gaviscon (GlaxoSmithkline).

**Noneffervescent systems:** Noneffervescent systems incorporate a high level (20–75% w/w) of one or more gel-forming, highly swellable, cellulosic hydrocolloids (e.g., HEC, HPC, HPMC, and NaCMC), polysaccharides, or matrix forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules[43]. Upon coming into contact with gastric fluid, these gel formers, polysaccharides, and polymers hydrate and form a colloidal gel barrier[44] that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density of and confers buoyancy to the dosage form.

Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion/evaporation methods. Polycarbonate, Eudragit, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer – polymer ratio and the solvent used[45].

The polypropylene foam particles acted like microsponges, absorbing the organic liquid, and becoming free flowing, low density microparticles following solvent evaporation (Figure 5).

Based on a similar approach, the same group developed a single unit, floating system, consisting of low density polypropylene foam powder, matrix forming polymers (HPMC, polyacrylates, sodium alginate, corn starch, carrageenan, agar, guar gum, Arabic gum), drug and filler.

**Bio/mucoadhesive systems:** “Bioadhesion” in simple terms can be described as the attachment of a synthetic or biological macro-molecule to a biological tissue. An adhesive bond may form with the epithelial cell layer, the continuous mucus layer or a combination of the two. The term “mucoadhesion” is used specifically when the bond involves mucous coating and an adhesive polymeric device, while “cytoadhesion” is the cell specific bioadhesion. The mechanism of bioadhesion has been reviewed extensively [47, 48].

Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The concept is based on the self-protecting mechanism of the GIT. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. Mucus is a viscoelastic, gel-like, stringy slime comprised mainly of glycoproteins. The thickness of the mucus layer decreases from the membrane surface to the GI lumen. The primary function of mucus is to protect the surface mucosal cells from acid and peptidases. In addition, it serves as a lubricant for the passage of solids and as a barrier to antigens, bacteria, and viruses[49]. The epithelial adhesive properties of mucin are well

known and have been applied to the development of GRDFS through the use of bio/mucoadhesive polymers[50]. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving bioavailability[51].

A bio/mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bioadhesive polymer) or the mucus lining of the GIT (mucoadhesive polymer). The characteristics of these polymers are molecular flexibility, hydrophilic functional groups, and specific molecular weight, chain length, and conformation. Furthermore, they must be nontoxic and nonabsorbable, form noncovalent bonds with the mucin–epithelial surfaces, have quick adherence to moist surfaces, easily incorporate the drug, and offer no hindrance to drug release, have a specific site of attachment, and be economical. The binding of polymers to the mucin–epithelial surface can be subdivided into three broad categories: hydration-mediated adhesion, bonding-mediated adhesion, and receptor mediated adhesion[52].

Different theories (Figure 6) are invoked to explain these mechanisms. Firstly, the electronic theory proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material. Secondly, the adsorption theory suggests that bioadhesion is due to secondary forces such as Vander Waals forces and hydrogen bonding. The wetting theory is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucus layers, and finally, the diffusion theory proposes physical entanglement of mucin strands and the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate[53–55]. Materials commonly used for bioadhesion are poly (acrylic acid) (Carbopol\,polycarbophil), chitosan, Gantrez (Polymethyl vinyl ether /maleic anhydride copolymers), cholestyramine, tragacanth, sodium alginate, HPMC, sephadex, sucralfate, polyethylene glycol, dextran, poly(alkyl cyanoacrylate) and polylactic acid. Even though some of these polymers are effective at producing bioadhesion, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract.

**Swelling systems**: After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus[56]. As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state.

Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical–chemical crosslink in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of crosslinking retards the swelling ability of the system and maintains its physical integrity for a prolonged period. On the other hand, a low degree of crosslinking results in extensive swelling followed by the rapid dissolution of the polymer[57]. An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion[58]. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration[56].

**High-density systems**: These systems, which have a density of ~3 g/cm$^3$, are retained in the rogue of the stomach[11] and are capable of withstanding its peristaltic movements[59]. Above a threshold density of 2.4–2.8 g/cm$^3$, such systems can be retained in the lower part of the stomach[60]. If this phenomenon is confirmed by clinical studies, these heavy pellet formulations may appear on the market in the near future. The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm$^3$. Diluents such as barium sulphate (density = 4.9), zinc oxide, titanium dioxide, and iron powder must be used to manufacture such high density formulations.

**Hydrodynamically Balanced systems**: These are single-unit dosage forms, con-taining one or more gel-forming hydrophilic polymers[61, 62]. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy[61].

Now a day GRDF systems covers more research orientation[63] and Table 3 represents recent scenario towards the same.

**Peptic Ulcer Treatments**

Antacids, such as sodium bicarbonate, calcium carbonate, aluminium hydroxide, magnesium hydroxide, or combined preparations, promptly provide effective pain relief via neutralization of intraluminal acid. The effective time for antacids to last in the human stomach, however, is too short to exert a neutralizing effect. Moreover, given that more potent and safe antisecretory drugs, such as H2RAntagonists and acid pump inhibit ors, are readily available, antacid therapy is not commonly utilized for current peptic ulcer treatment. To prolong the effect of antacids, anticholinergic drugs, such as propantheline bromide and benactidine methobromide, have been concurrently administered to delay emptying of the agents into the duodenum. Anticholinergics can also inhibit acid secretion by themselves. Similar to antacids, however, the use of anticholinergic drugs is generally limited, as anticholinergics delivered at dosages capable of inhibiting acid secretion almost invariably induce adverse effects, such as dry mouth, blurred vision, tachycardia, and

bladder dysfunction.

In patients with H. pylori -infection, PPI therapy causes corpus-predominant gastritis, which is frequently found in the background mucosa in patients with gastric cancer. PPIs may modulate not only gastric H+/K+-ATPase activity, but also v-type H+-ATPase activity, which are widely distributed in a variety of cells in the human body. Among these, the acid-producing systems in osteoclasts and leukocytes are well developed for maintaining bone turnover and exhibit bactericidal roles and promote tissue destructive inflammation. Therefore, there is still much potential for research on the pharmacological and clinical aspects of PPI treatment[64]. However, there are studies suggesting that proton pump inhibitors may not control the gastric acidity effectively during the night, especially in gastroesophageal reflux disease. It has therefore been suggested that H2 receptor blockers should be added to the therapy. Combination therapy with H2 receptor blockers and proton pump inhibitors seemed to control intra-gastric pH better than proton pump inhibitors alone[65]. Mostly PPIs absorption takes place from the intestinal environment and thereby not suitability for GRDFs.

**GRDFs containing H2RAs:** Higher doses and more frequent dosing of H2RAs are more effective, both in symptomatic relief and in healing esophagitis. Healing esophagitis is inversely related to the degree of esophagitis[66].

The combination of daily PPIs and night time H2RAs may prevent the nocturnal decrease in pH[67] and may help patients who have nocturnal symptoms. However, the combination of prokinetic drugs and either H2 RAs or PPI has been disappointing.

By modifying the chemical structure of cimetidine, the potent H2RAs like RNT, famotidine (FMT), and nizatidine were all developed, resulting in remarkable treatment for acid related disease, including reflux esophagitis. These new compounds were later found to inhibit gastric acid secretion stimulated by not only histamine, but also carbachol and gastrin in both humans and animals. These findings suggest that H2R stimulation might be required for the effect of such secretagogues. Now a day, H2RAs has become first-line therapy for acid related peptic disease, leading to a marked improvement in the quality of life for a large number of patients. Paralleling the development of such pharmacotherapy, there has been a dramatic reduction in the use of surgical intervention for ulcer treatment[68]. Interestingly, in the beginning of clinical application, many physicians expressed concern over potential regurgitation of intestinal bacteria into the stomach, as the antisecretory effect of H2RAs is much more powerful than conventional anticholinergic drugs. Sustained inhibition of gastric acid might predispose to gastric bacterial contamination, resulting in an increase in Nitrosamine, a metabolite of ingested nitrites and a known carcinogen. Accordingly, the use of H2RAs initially was limited to only 4 weeks. Nonetheless, long term clinical experience has demonstrated that such a risk was a groundless fear. In fact, H2RAs are currently even considered safe enough to be marketed as over-the-counter pharmaceuticals.

Animal studies demonstrated that cimetidine and other representative H2RAs had little or no effect on pharmacologic agent induced necrotizing gastric mucosal damage[69]. In contrast, the FMT was found to have a cytoprotective effect for gastric mucosa against pharmacologic agent induced necrotizing damage in animal studies.

These drugs FMT and RNT reduce basal secretion of acid and also secretion stimulated by food, neural and hormonal influences[70]. Transport of histamine, acetylcholine, and ions (chloride, bicarbonate, potassium, sodium and calcium) has been studied in the presence of liquid membranes generated by surface active FMT. Research indicates that the liquid membranes generated by FMT may play a significant role in their biological action[71].

The surface active nature of the drugs has been discussed with relevance to their pharmacological effects.

It has been reported that the oral treatment of gastric disorders with H2RAs like FMT or RNT used in combination with antacids promotes the local delivery of these drugs to the receptor of parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion. Hence, this principle may be applied for improving the systemic as well as local delivery of FMT, which would efficiently reduce gastric acid secretion[72] and it may be achieved by floating with mucoadhesion.Recently, bedtime H2 blockers have been recommended to provide control of GERD symptoms.

FMT is potent histamine H2Rantagonist used to treat peptic ulceration, reflux esophagitis, Zollinger– Ellison syndrome, and other conditions where reduction of gastric acid is beneficial[73]. It is not absorbed uniformly throughout the gastrointestinal tract (GIT) but mainly at a specific absorption site[74] leading to incomplete and variable absorption[75]. So, a dosage form that achieves gastric retention would be presented at the absorption site over a prolonged period improving its bioavailability and reducing its wastage[76]. Moreover, being a weak base, FMT with a pKa of 7.06 (BP, 1998) has pH dependant solubility and its gastric retention would allow adequate time for its dissolution, the rate limiting step in drug absorption[77]. Different FMT gastroretentive systems were lately formulated including gastroretentive controlled release microspheres[77], mucoadhesive granules compressed to tablets[78], floating osmotic device, and recently floating tablets based on effervescent mechanism. Although multiple unit dosage forms distribute uniformly along the GIT resulting in longer lasting effect s and reduced inter subject variability, single unit tablets still have the advantages of ease of production, cost effectiveness, and lack of using hazardous organic solvents in some production techniques of multiple units.

The pH independent swelling and mucoadhesion behaviour of polypropylene foam powder and polyethylene oxide (PEO)

makes them reliable polymer for floatation and mucoadhesion in the stomach. Such systems are expected to immediate floatation and reside in the stomach for relatively longer duration than the solution dosages, disintegrating type solid formulations, and other conventional formulations, improving the absorption of drugs that show preferential absorption in the stomach or upper part of intestine.

**GRDFs against H. Pylori:** In most countries, H. pylori infection is associated with a four to six fold increased risk of gastric cancer: this means that the majority of gastric carcinomas in the world are related to H. Pylori infection. Because of the high level of antibiotic resistance to H. pylori and the poor patient compliance[79] Given that the bacterium lives deep in the gastric mucus , a logical way to improve the effectiveness of therapeutics is to develop gastroretentive dosage forms in order to release drugs as long as possible in the ecological niche of the bacterium.

Amoxycillin (α-amino-hydroxybenzylpenicillin) is a semi-synthetic, orally absorbed, broad-spectrum antibiotic. It is still widely used in the standard eradication treatment of gastric and duodenal ulcers, which are associated with H. pylori infection combined with a second antibiotic and an acid-suppressing agent[80-82]. Increase in the residence time may reduce the treatment time of such diseases. Therefore, some researchers had prepared and reported new amoxicillin formulations such as float tablets, mucoadhesive tablets, pH-sensitive excipients composition microspheres, etc., which were able to reside in the gastrointestinal tract for an extended period of time for a more effective treatment[83,84]. This would lead to improvement in the bioavailability of the drug. In this way it stands an advantage over conventional dosage form, which needs to be administered twice or thrice a day.

Among a variety of hydrophilic polymers, PEO, HPC and HPMC are frequently used candidates in pharmaceutical formulation, mainly because of its non-toxicity, high water solubility and swellability, mucoadhesive strength, insensitivity to the pH of the biological medium and ease of production[85-90]. Chitosan, a popular choice as a coating material because of its regulatory status and its positive charge, binds to mucus[91]. Chitosan based systems for local delivery of antibiotics in the stomach have been studied and found that 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.

The author s of the latter study also formulated floating bioadhesive microspheres. The microballoons (made by a quasi emulsion solvent diffusion method) were coated with 2% (w/v) solution of polycarbophil by an air-suspension coating method. In vitro floating studies, detachment force measurements and in vivo growth inhibition studies demonstrated the potential of this device, which combines bioadhesive and floating properties[92].

Researchers have formulated mucoadhesive microspheres containing amoxicillin. They dispersed the drug and bioadhesive polymers (carboxyvinyl polymer and curdlan[apolys accharide]) in melted hydrogenated castor oil. Microsphere s of 250 to 335 Am in diameter were obtained by a spray chilling method followed by sieving. They compared these microspheres with an amoxicillin suspension in infected Mongolian gerbils under feeding condition s. The microspheres with an amoxicillin dose of 1.0 mg/ kg provided the same clearance rate (20%) as the amoxicillin suspension with a dose of 10 mg/ kg. This means that the amoxicillin microspheres provided 10 times greater anti H. pylori activity than the amoxicillin suspension. Moreover, adhesion of microspheres on the stomach wall was observed (¨47% and ¨ 20%remained in the stomach after 2 and 4 h, respectively). The authors concluded that these mucoadhesive microspheres containing an appropriate antimicrobial agent should be useful for the eradication of H. pylori[93]. Recently, It has been also published a study on mucoadhesive microspheres containing amoxicillin. They prepared them by an emulsification/evaporation method, using ethyl cellulose as matrix and carbopol 934P as a mucoadhesive polymer and demonstrated that free amoxicillin was rapidly degraded in acidic medium; however, amoxicillin entrapped in the microspheres kept stable.

**Conclusion**

GRDFS, comprised mainly of floating, bioadhesive, and swellable systems, have emerged as an efficient means of enhancing the bioavailability and CR of drugs that exhibit an absorption window. By prolonging the gastric emptying time of the dosage form, these systems not only provide controlled release of the drug for a prolonged period, but also present the drug in an absorbable form at regions of optimal absorption. These systems achieve this by retaining the dosage form in the gastric region, from where the H2RAs and antibacterial like amoxicillin and others are presented at the absorption window. Designing GRDFs found suitability for H2RAs and Amoxicillin for the treatment of Peptic ulcer and in the treatment of H. Pylori infection. A careful consideration of the interplay of these parameters can help in designing a successful GRDFS for the same. Growth in the understanding of the effect of GI physiology on drug delivery and the increasing sophistication of delivery technology will ensure the development of an increasing number of GRDFS to optimize delivery of drug molecules that exhibit regional variability in intestinal absorption.

While recent results from recent clinical studies are promising, convincing results have yet to be presented for GRDFs 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.

Based on the literature surveyed, it may be concluded that floating with bioadhesion offers various potential advantages for drug like H2RAs and Antibiotics like amoxicillin and others. CR drug delivery of these drugs significantly improve therapeutic efficacy. Both natural and synthetic polymers have potential advantages in GRDFs. Several polymers from plant origin have been successfully used and others are being investigated as excipients in the design of dosage forms for effective CR drug delivery. The use of natural gums for pharmaceutical applications is attractive because they are economical readily available, non toxic and capable of chemical modifications.

Furthermore, it is expected that in addition to the already marketed drugs, this CR-GRDF approach may be used in the developmental stage for novel drugs of narrow absorption window in the upper parts of the gastrointestinal tract.

**Tables:**

**Table 1:** Transit times of various dosage forms across the segments of the GIT.

| Dosage form | Transit time (h) | | |
|---|---|---|---|
| | Stomach | Small intestine | Total |
| Tablets | 2.7 ± 1.5 | 3.1 ± 0.4 | 5.8 |
| Pellets | 1.2 ± 1.3 | 3.4 ± 1.0 | 4.6 |
| Capsules | 0.8 ± 1.2 | 3.2 ± 0.8 | 4.0 |
| Solution | 0.3 ± 0.07 | 4.1 ± 0.5 | 4.4 |

**Table 2:** Anatomical and physiological characteristics of the GIT.

| Section | pH | Diameter (cm) | Length (cm) | Absorption mechanism |
|---|---|---|---|---|
| Oral | 5.2-6.8 | 10 | 15-20 | Passive diffusion and convective transport |
| Oesophagus | 5-10 | 2.5 | 25 | ---------- |
| Stomach | 1.2-3.5 | 15 | 20 | Passive diffusion and convective transport |
| Duodenum | 4.6-6.0 | 5 | 25 | Passive diffusion, convective transport, active transport, facilitated transport, pair, pinocytosis |
| Jejunum | 6.3-7.3 | 5 | 300 | Passive diffusion, convective transport, active transport, facilitated transport |
| Ileum | 7.6 | 2.5-5.0 | 300 | Passive diffusion, convective transport, active transport, facilitated transport, pair, pinocytosis |
| Cecum | 7.5-8.0 | 7 | 10-30 | Passive diffusion, convective transport, active transport, pinocytosis |
| Colon | 7.9-8.0 | 5 | 150 | Passive diffusion and convective transport |
| Rectum | 7.5-8.0 | 2.5 | 15-19 | Passive diffusion and convective transport, pinocytosis |

**Table 3:** Current scenario to the various GRDF approach.

| Dosage form | Drug | Polymers/ excipients | References |
|---|---|---|---|
| Tablets | Tizanidine HCl | HPMC K4M, HPMC K15M, $NaHCO_3$ | Adimoolam Senthil et al. (2011) |
| | Glimepiride | Carbopol 934P HPMC K4M, HPMC K100M, $NaHCO_3$ | C. Rubina Reichal et al. (2011) |
| | Dipyridamol | HPMC K4M, Citric acid, $NaHCO_3$ | Gottimukkala Jayapal Reddy et al. (2011) |
| | Aceclofenac | Eudragit, HPMC E4M and $NaHCO_3$ | Ambati Brahma Reddy et al. (2011) |
| | Domperidone | Eudragit L100, HPMC K4M | Shah et al. (2010) |
| | Ranitidine (RNT) HCl | Karaya gum | Shreenivasa Reddy et al. (2010) |
| | Metoprolol succinate | Xanthan gum and karaya gum | V N Deshmukh et al. (2009) |
| Microspheres | 5- Flurouracil | PVA, dichloromethane and acetonitrile | Behera A J et al. (2011) |
| | Metformin HCl | Na CMC, HPMC | Ram Chand Dhakar et al. (2010) |
| | Amoxicillin | Carbopol 934P | Patel J K et al. (2009) |
| Insitu gel | Metoclopramide | Guar gum, sodium alginate, calcium carbonate | Vinay wornorkar et al. (2011) |
| | RNT HCl | Sodium alginate, calcium carbonate | Patel R P et al. (2011) |
| | Clarithromycin | Gellan gum, calcium carbonate | Dipen Bhimani et al. (2011) |
| | Baclofen | Sodium alginate, calcium carbonate | Rishad Jivani et al. (2010) |
| Beads | Mosapride | Sodium alginate and HPMC | Kumuran et al. (2010) |

**FIGURES:**

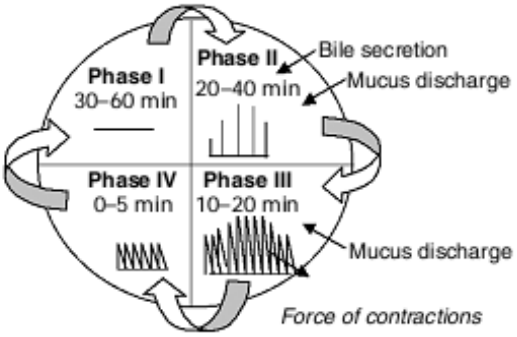


**Figure 1:** Motility Patterns of the GIT in the fasted state

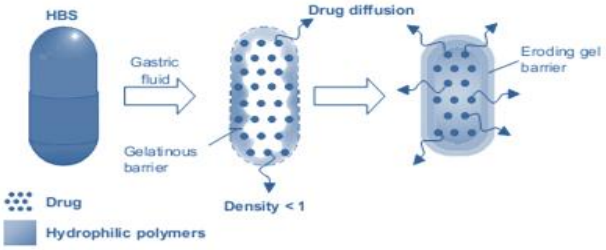


**Figure 2:** Drug release mechanisms by diffusion and erosion from hydrophilic polymer's swelled gel barrier

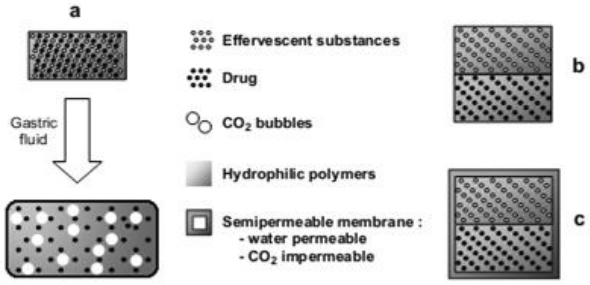


**Figure 3:** Effervescent systems. Schematic monolayer drug delivery system [a] bilayer with [c] or without [b] semipermeable membrane.

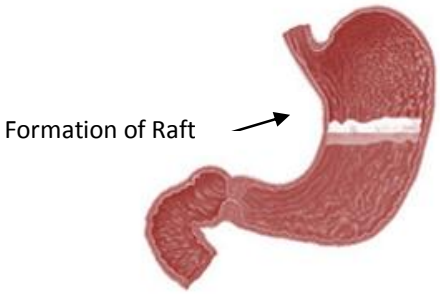


**Figure 4:** Raft forming system in GIT

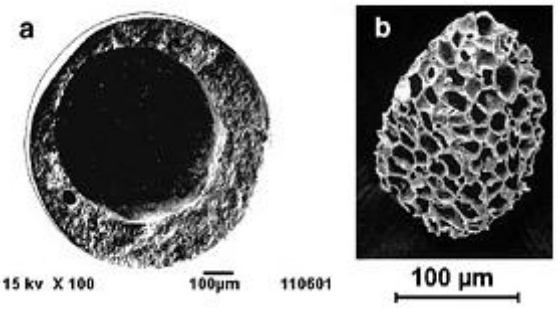


**Figure 5:** Microbaloons [a] and [b] from foam particles[46]

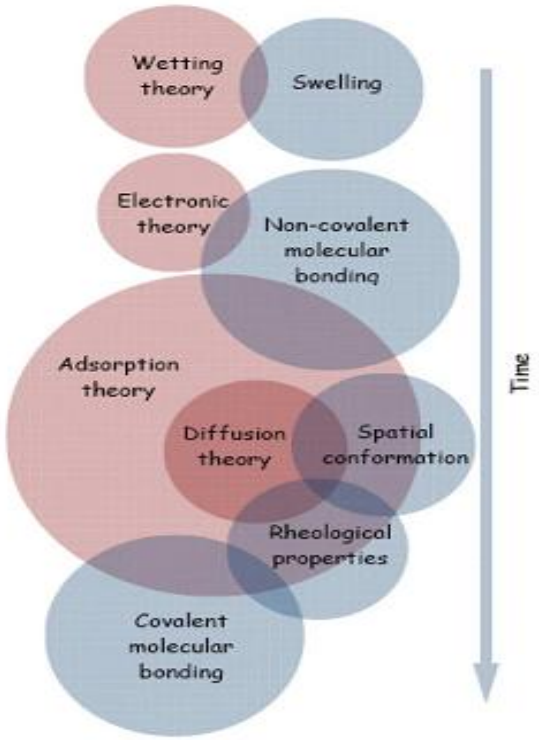


**Figure 6:** Different mechanisms of bioadhesion.

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