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GASTRO RETENTIVE DRUG DELIVERY SYSTEMS

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ABSTRACT

Management of illness through medication is entering a new era in which growing number of Novel drug delivery systems are being employed and are available for therapeutic use. Oral Sustained release gastro-retentive dosage forms (GRDFs) offer many advantages for drugs with Absorption from upper parts of gastrointestinal tract and for those acting locally in the stomach, Improving the bioavailability of the medication.

Keywords: Novel drug delivery system, gastro-retentive dosage forms, sustained release.

INTRODUCTION

The control of gastrointestinal transit of orally administered dosage forms using gastro retentive drug delivery systems (GRDDS) can improve the bioavailability of drugs that exhibit site specific absorption. Prolonged gastric retention can be achieved by using floating, swelling, bio adhesive, or high –density systems (1). In some cases gastro retention is achieved by concomitant administration of drugs or excipientswhich slows the motility of GIT. Despite tremendous advancement in drug delivery, the oral route remains the preferred route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance.

Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. Controlled-release drug delivery systems (provide drug release) at predetermined, predictable, and controlled rate (2). An important requisite for successful performance of oral GRDDS is that the drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion, to

ensure continuous absorption of the released drug. The average time required for a dosage unit to traverse the GIT is 3-4 h, although slight variations exist among various dosage forms. Per orally administered drugs are absorbed by passive diffusion processes and by non-passive diffusion processes. Drugs absorbed by active and facilitated transport mechanisms show higher regional specificity because of the prevalence of these mechanisms in only certain regions of the GIT (3). Many drugs show poor BA because of the presence of enzymes and efflux pumps. In intestinal metabolic enzymes primarily, phase 1 metabolizers such as cytochrome P 450 (CYP3A)-are abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with levels rising slightly from the duodenum to the jejunum and declining in the ileum and colon. This non-uniform distribution of CYP3A causes regional variability in the absorption of drugs that are substrates of that enzyme. In addition, carriers involved in the secretion of organic molecules from the blood into the intestinal lumen may affect drug absorption (4). An example of such a secretory transporter is P-glycoprotein (P-gp), which is present in the villus tip of enterocytes and has the capacity to interact with a vast variety of drugs. P-gpsends the absorbed drug from the cytoplasm of the enterocyte back to the intestinal lumen, thus reducing the drug's BA. The enzyme metabolizes the drug molecule absorbed into the enterocyte. Then that portion of the drug is transported from the enterocyte back into the intestinal lumen by the action of P-gp, following which it is reabsorbed and again subjected to metabolism and efflux. Therefore the drug is continually cycled between the enterocyte and the gut lumen, which allows the enzyme to have repeated access to the drug molecule, thus reducing absorption. Drugs having site –specific absorption are difficult to design as oral CRDDS because only the drug released in the region preceding and in close vicinity to the absorption windowis available for absorption. After crossing the absorption window, the released drug goes to wastewith negligible or no absorption.

Gastro retentive drug delivery systems

Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment of small intestine. It has applications also for local drug delivery to the stomach and proximal small intestines. In spite of having a lot of potential benefits floating drug delivery is associated with certain limitations. Drugs that irritate the gastric mucosa, those that have multiple absorption sites in the gastrointestinal tract, which undergo significant first pass metabolism and those that are not soluble and stable at gastric pH are not suitable candidates to be formulated as floating

dosage forms. Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems (GRDDS) 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 (5). Some drugs are absorbed in a particular portion of the GIT only or are absorbed to a different extent in various segments of the GIT. Such are said to have an absorption window, which identifies the drug's primary region of absorption in the GIT, Because most drugs are absorbed by passive diffusion of the unionized form, the extent of ionization at various pH levels can lead to non-uniform absorption or an absorption window. The presence of certain enzymes in a particular region of the GIT also can lead to regional variability in the absorption of drugs that are substrates of those enzymes (6).

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.

Anatomically the stomach is divided into 3 regions

Fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions(7).

Two distinct patterns of gastrointestinal (GI) motility and secretion exist, corresponding to the fasted and fed states. As a result, the BA 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 1), pre-burst (phase II), and burst (phase III) intervals.

Phase 1, the quiescent period, last 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 min, 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 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 (8). 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 per oral CRDDS and GRDDS (9). When CRDDS 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 considerationthe 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.

Gastro retentive techniques

Several techniques, including floating, swelling, inflation, and adhesion, have been explored to increase the gastro retention of dosage forms.

Floating systems

When the drug is formulated with a gel forming polymer such as semisynthetic derivative of cellulose, it swells in the gastric fluid with a bulk density less than one. It then remains buoyant and floats in the gastric fluid, affecting a prolonged gastric residence time (GRT). This floating dosage form is known as a hydro dynamically balanced system (HBS).(6)Hydro dynamically balanced systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration. Floating systems can be classified as effervescent and non-effervescent systems.

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 CO2 produced as a result of an effervescent reaction between an organic acids and carbonate-bicarbonate salts. 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 timeto permit the spontaneous ejection of the inflatable system from the stomach.

Noneffervescent systems.

Noneffervescent systems incorporate a high level (20-75% w/w) of one or more gel-forming, highly swell able, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose [HPMC], and sodium carboxymethylcellulose), polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules. Upon coming into contact with gastric fluid, these gel formers, polysaccharides, and polymers hydrate and form colloidal gel barrier 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 polymers lowers the density of and confers buoyancy to the dosage form.

Bio/mucoadhesive systems

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 biological membrane. The concept is based on the self –protecting mechanism of the GIT. Mucus secreted continuously by the goblet cells located throughout the GIT plays a cytoprotective role. Mucus is a viscoelastic gel-like, stringy slime comprised mainly of the glycoproteins. The thickness of the mucus layerdecreases from the membrane surface to the GI lumen. The primary function of the mucus is to protect the surface mucosal cells from acid & peptidases. In addition, it serves as a lubricant for the passage of solids and as a barrier to antigens, bacteria and viruses.

The epithelial adhesive properties of mucin are well known and have been applied to the development of GRDDS through the use of bio/mucoadhesive polymers. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving BA.

Abio/mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bioadhesive polymer). The characteristics of these polymers are molecular flexibility. Hydrophilic functional groups, and specific molecular weight, chain length, and conformation.Further more they must be nontoxic andnonabsorbable, form noncovalent bonds with the mucin-epithelial surfaces, have quick adherence to moist surfaces, easily incorporate the drug, offer no hinderance to moist surfaces, easily incorporate the drug, offer no hinderance to drug release, have a specific site of attachement, and be economical. The binding of polymers to the mucin-epithelial surface can be subdivided into three board broad categories: hydration- mediated adhesion, bonding –mediated adhesion, and receptor mediated adhesion. Hydration mediated adhesion.

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties. The prolonged gastroretention of the bio/mucoadhesive drug delivery system is further controlled by the dissolution rate of the polymer.

Bonding mediated adhesion

The adhesion of polymer to a mucus or epithelial cell surface involves various bonding mechanism. Including physical-mechanical bonding and chemical bonding .

Receptor mediated adhesion

Certain polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx. Bioadhesives polymers can also be classified on the basis of their charge. A few examples of bioadhesives polymers are:

Cationic:polybrene, poly-L- lysine, polylysine, polyvinyl methyl imidazole

Anionic : CMC, Dextran sodium, polyacrylic acid

Neutral: Bovine serum albumin, dextran, ficoll, polyethylene glycol.

Swelling Systems

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus, 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.

High Density Systems

These systems, which have a density of ~3g/cm^3, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements.

DRUG CANDIDATES SUITABLE FOR FLOATING DRUG DELIVERY

Drugs which have site-specific absorption in the stomach or upper parts of the small intestine (furosemide, riboflavine-5- phosphate), drugs required to exert local therapeutic action in the stomach (antacids, anti-H.pylori agents, misoprostol), drugs unstable in the lower part of Gastro-intestinal tract (captopril), drugs insoluble in intestinal fluids (quinidine, diazepam), drugs with variable bioavailability (satololHCl). (Baichwal and Kawashima Y et al.,1992)

LIST OF DRUGS EXPLORED FOR VARIOUS FLOATING DOSAGE FORMS

Microspheres Tablets /Pills: Chlorpheniramine maleate, Aspirin, griseofulvin, Acetaminophen, p-nitroaniline, Acetylsalicylic acid, Ibuprofen, Amoxycillintrihydrate, Terfenadine, Ampicillin, Tranilast,Atenolol, Theophylline,Captopril, Isosorbide di nitrate, Sotalol, Isosorbidemononitrate, verapamil HCL.

POLYMERS AND OTHER INGREDIENTS USED INPREPARATIONS OF FLOATING DRUGS

Polymers: The following polymers used in preparations offloating drugs –HPMC K4 M, Calcium alginate, Eudragit S100, Eudragit RL,Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin,HPMC 4000, HPMC 100, CMC, Polyethylene glycol,polycarbonate, PVA, Polycarbo-nate, Sodium alginate, HPC-L, CP934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H,HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4 Mand Carbopol.

Inert fatty materials (5%-75%) : Edible, inert fatty materialshaving a specific gravity of less than one can be used to decreasethe hydrophilic property of formulation and hence increasebuoyancy. e.g. Beeswax, fatty acids, long chain fatty alcohols,Gelucires 39/01 and 43/01.

Effervescent agents : Sodium bicarbonate, citric acid, tartaricacid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).

Release rate accelerants (5%-60%) :eg. lactose, mannitol

Release rate retardants (5%-60%): eg. Dicalcium phosphate,talc, magnesium stearate.

Buoyancy increasing agents (upto80%) :eg. Ethyl cellulose.

Low density material : Polypropylene foam powder (AccurelMP 1000).

ADVANTAGES OF FDDS

1. Floating dosage forms such as tablets or capsules will remains inthe solution for prolonged time even at the alkaline pH of theintestine.
2. FDDS are advantageous for drugs meant for local action in thestomach eg: Antacids
3. FDDS dosage forms are advantageous in case of vigorousintestinal movement and in diarrhea to keep the drug in floatingcondition in stomach to get a relatively better response.
4. Acidic substance like aspirin causes irritation on the stomachwall when come in contact with it hence; HBS/FDDS formulationsmay be useful for the administration of aspirin and other similardrugs.
5. The FDDS are advantageous for drugs absorbed through thestomach eg: Ferrous salts, Antacids.

DISADVANTAGES OF FDDS

1. Floating systems are not feasible for those drugs that havesolubility or stability problems in gastric fluids.

2. Drugs such as Nifedipine, which is well absorbed along theentire GI tract and which undergo significant first-passmetabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemicbioavailability. Also there are limitations to the applicability ofFDDS for drugs that are irritant to gastric mucosa.

3.One of the disadvantages of floating systems is that they requirea sufficiently high level of fluids in the stomach, so that the drugdosages form float therein and work efficiently.

4. These systems also require the presence of food to delay theirgastric emptying.

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