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Research Article

PROGRESS IN STOMACH SPECIFIC DRUG DELIVERY SYSTEM FEATURES AND FACTS

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ABSTRACT

Oral route is the most preferable route of administration but it has certain limitation for those drugs which absorb from upper part of GI tract or having narrow absorption window. The bioavailability of these drugs can be improved by increasing the residence of the dosage form in the stomach. The gastric residence time of the dosage form can be improved by formulating them as floating drug delivery system. The current & recent developments of Stomach Specific FDDS are discussed in this review.

Keywords: Stomach specific drug dilevery.

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. From immediate release to site-specific delivery, oral dosage forms have really progressed (Garg and Sharma, 2003).

However, oral administration has only limited use for important drugs, from various pharmaceutical categories, that have poor bioavailability due to incomplete absorption and/or degradation in the GI tract. Some of these drugs are characterized by narrow absorption window at the upper part of gastrointestinal tract. This is because the proximal part of small intestine exhibits extended properties. Despite the extensive absorption properties of the duodenum and jejunum, the extend of absorption at these site is limited because the passage through this region is rapid. Enhancing the gastric residence time of a narrow absorption window drug may significantly improve the net extent of its absorption. To increase the GRT of drugs, a gastroretentive dosage form can be developed (Hoffman *et al*., 2004).

Dosage forms with a prolonged GRT, i.e., gastroretentive dosage forms (GRDFs), will provide us with new and important therapeutic options (Garg and Sharma, 2003).

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients (Arora *et al*., 2005). Gastroretentive systems not only prolong the dosing intervals, but also increase patient compliance beyond the level of exiting controlled release dosage form. This application is especially effective in delivery of sparingly soluble and insoluble drugs. It is known that, as the solubility of the drug decreases, the time available for drug dissolution become less adequate and thus the transit time becomes a significant factor affecting drug absorption (Garg and Sharma, 2003).

There are certain situations where gastric retention is not desirable. Aspirin and non steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of these drugs in the stomach is unwanted. Thus, the drugs that may irritate the stomach lining or unstable in its acidic environment should not be formulated in gastroretentive system. Certain types of drugs can be benefit from using gastric retention device. These include

- Drugs acting locally in the stomach;
- Drugs that are primarily absorbed in the stomach;
- Drugs that are poorly soluble at an alkaline pH;
- Drugs absorbed rapidly from GI tract; &
- Drugs that degrades in colon (Gutierrez-Rocca *et al*., 2003).

The retention of dosage form in the stomach can be achieved by formulating as floating system which floats in the stomach.

Floating systems

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 (Chawala *et al*., 2003). After release of drug, the residual system is emptied from the stomach (Mayavanshi & Gajjar, 2008).

The floating drug delivery system and bioadhesive drug delivery are widely used technique for gastroretention (Sharma and Pawar, 2006) and floating systems in particular has been extensively researched, mainly because the floating system does not adversely effect the motility of GI tract (Tang et al., 2006).

Floating drug delivery systems offer the most effective and rational protection against early and random gastric emptying compared to other methods proposed for prolonging the GRT of solid dosage forms (Goole et al., 2006).

Floating systems can also be classified as effervescent and non-effervescent systems.

Effervescent systems

Floatation 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. 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 (Chawala et al., 2003).

Noneffervescent systems

Noneffervescent systems incorporate a high level (20–75 % w/w) of one or more gel-forming, highly swellable, 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 a 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 polymer lowers the density and confers buoyancy to the dosage form (Chawala et al., 2003).

The following approaches used in designing intra-gastric floating systems (Bardonnet et al., 2006).

Hydrodynamically balanced systems

These are single unit dosage form, containing one or more gel forming hydrophilic polymers, HPMC is the most commonly used excipient, although HEC, HPC, NaCMC, agar and alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsules rapidly dissolve in the gastric fluid, and hydration and swelling of the surface polymer produce a floating mass. Drug release is controlled by the formation of hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layer, maintaining surface hydration and buoyancy. Incorporation of fatty excipients give low density formulations and reduce penetration of water, reducing the erosion. The main draw back is the passivity of operation. It depends on the air sealed in the dry mass centre following hydration of gelatinous surface layer and hence the characteristics and amount of polymer. Effective drug delivery depends on the balance of drug loading and effect of polymer on its release profile (Bardonnet et al., 2006).

Gas generating system

Floatability can also be achieved by generation of gas bubbles. CO_2 can be generated in situ by the incorporation of carbonates or bicarbonates, which react with acid- either the natural gastric acid or co-formulated as citric or tartaric acid. The optimum stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. An alternative is to incorporate a matrix with entrapped of liquids, which forms a gas at body temperature. These approaches have been used for single and multiple unit system (Bardonnet et al., 2006).

Raft-forming System

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 on contact with gastric fluid. Formulations also typically contain antacids such as aluminum 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 the treatment of gastroesophageal reflux treatment (Bardonnet et al., 2006).

Low-Density Systems

Gas-generating system inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density system (<1 g/cm^3) with immediate buoyancy have therefore been developed. They are made of low-density materials, entraping oil or air. Most are multiple unit systems, and are also called "microballoons" because of low-density core (Bardonnet *et al.,* 2006).

Floating drug delivery system can be formulated as single unit system

Table 1: List of Drugs Formulated in Multiple Unit Forms of Floating Drug Delivery Systems.

Drug	Dosage Form	Reference
Verapamil Hydrochloride	Floating Microparticles	Streubel *et al*., 2002
Ketoprofen	Floating Microparticles	Kamel *et al*., 2000
Ranitidine Hydrochloride	Floating Granules	Patel *et al*., 2007
Metronidazole	Floating Beads	Patel *et al*., 2006
Lansoprazole	Floating Micropellets	Muthusamy *et al*., 2005
Meloxicam	Low density multiparticulate system	Sharma & Pawar, 2006
Diltiazem Hydrochloride, Theophylline & Verapamil Hydrochloride	Foam Based Floating Microparticles	Streubel *et al*., 2003
Nifedipine	Hollow Microsphere	Soppimath *et al*., 2006.
Acetohydroxamic Acid	Floating Microsphere	Umamaheshwari *et al*., 2003
Piroxicam	Floating Microsphere	Joseph *et al*., 2002
Residronate Sodium	Granules	Chauhan *et al*., 2005
Diltiazem Hydrochloride	Granules	Shimpi *et al*., 2004
Chlorpheniramine maleate	Microparticles	Streubel *et al*., 2003a
Diltiazem Hydrochloride, Theophylline and Verapamil Hydrochloride		
Repaglinide	Microsphere	Jain *et al*., 2006.
Ibuprofen	Beads	Sher *et al*., 2006
Orlistst	Microsphere	Jain *et al*., 2006
Metformin Hydrochloride	Microsphere	Patel *et al*., 2006
Ibuprofen, Niacinamide and Metaclopramide	Beads	Tang et al., 2006
Levodopa	Minitablets	Goole *et al*., 2006
Theophylline	Beads	Sungthongjeen et al., 2006
Furesamide	Multiple unit FDDS.	Iannuccelli et al., 2000.
P-Aminobenzoic acid	Floating Pills	Ichikawa *et al*., 1991

Practical approaches in the development of Multiple-Unit Floating Drug Delivery Systems

Various approaches are used in the preparation of multiple-unit floating drug delivery system by many scientists. Some of the approaches are given below.

Floating Granules

Inouye *et al.*, 1989, prepared sustained release floating granules of prednisolone using chitosan of different degrees of deacetylation (Chitosan H and L). The granules were prepared by a method involving deacidification, had internal cavities, were immediately

buoyant in both acidic and neutral fluids and gave sustained release of prednisolone.

Yuasa *et al.*, 1996, prepared the intragastric floating granules using calcium silicate (Florite, FLR) as a floating carrier which has floating ability due to air included in the pores when they are covered with a polymer. The granules showed a longer floating time and they suggested that the FLR is a useful carrier for the development of a floating and sustained release preparation.

Takashima *et al*., 1998, investigated the preparation of floating granules using hollow glass beads (G.B) as carrier and oxprenolol hydrochloride as model drug. The prepared granules were evaluated for density, floating property and drug release profile. The density of all type of formulations containing G.B was less than 1 gm/cm^3. These granules floated for long time in test fluid and rate of drug release from the granules was decreased with decreased G.B contents.

Shimpi *et al.,* 2004, prepared floating granules of Diltiazem Hydrochloride using Gelucire 43/01 by melt granulation technique. The granules were retained in stomach for 6 hours and approximately 65 to 85 % drug was released over 6 hours with initial fast release from the surface.

Shimpi *et al*., 2004, prepared the floating granules of Diltiazem Hydrochloride using Gelucire 43/01 by melt granulation technique. The formed granules were evaluated for *in-vitro* and *in-vivo* floating ability, surface topography and in-vitro drug release. The result showed that the granules remain in the stomach for at least six hours and approximately 65 to 85 % drug was released in 6 hours with initial fast release from the surfaces. They concluded that the hydrophobic lipid, Gelucire 43/01 can be use as an effective carrier for the development of a multiple unit floating drug delivery systems.

Jain *et al*., 2007, prepared the porous carrier (calcium silicate) based floating granular drug delivery system of Repaglinide and evaluated for gastroretentive and controlled release properties. The optimized formulation demonstrated favorable *in- vitro* floating and release characteristics. Prolonged gastric residence time of over 6 hours was achieved in all subjects and the relative bioavailability of repaglinide loaded floating granules increased 3.8 times in comparison to that of its marketed capsule.

Floating Microparticles

El Kamel *et al.,* 2001 flaoting multi particulate drug delivery system. The system consisted of microparticles containg drug prepared by emulsion solvent diffusion technique using four different ratio of Eudragit S100 and Eudragit RL. The encapsulation efficiency was decreased with the increased in ERL content. They demonstrated that formulation in a ratio of two polymers (1:1) gave the best floating ability.

Streubel *et al*., 2003, developed low density foam (Polypropylene) based microparticles using diltiazem hydrochloride, theophylline or verapamil hydrochloride as model drug and eudragit RS or polymethyl methacrylate as polymer. The floating micro particle showed a good *in- vitro* floating behavior and a broad variety of drug release pattern depending upon the drug loading and polymer used.

Floating Matrices

Dave *et al*., 2004, reported preparation of Gastroretentive drug delivery system containing Ranitidine hydrochloride using Guar gum, Xanthum gum, HPMC and Sodium bicarbonate as gas generating agent. The effect of citric acid and stearic acid on drug release profile and floating properties were investigated. The results indicated that a low amount of citric acid and a high amount of stearic acid favored sustained release of Ranitidine HCl.

Chauhan *et al*., 2005, prepared the single and multiple unit floating matrices of residronate sodium using Gelicure 43/01 by melt solidification and melt granulation technique. Both single and multiple unit system showed increase in drug release on aging due to changes in the properties of Gelicure 43/01.

Floating Microsphere

Jain *et al*., 2006a, evaluated the gastro-retentive performance and pharmacokinetic parameter of optimized floating microsphere consisting Calcium Silicate (CS) a porous carrier, repaglinide (Rg) and Eudragit S (ES). The optimized microspheres showed prolong gastric residence time (6 hrs) in all animals and the relative bioavailability of Rg loaded microsphere was found to be 3.17 times in comparison with marketed tablets.

Jain *et al*., 2006b, reported the floating micro sphere of Orlistat an oral anti obesity agent using calcium silicate as porous carrier and Eudragit S as polymer by solvent evaporation technique. The microspheres were found to be regular in shape and highly porous. The microspheres containing 200mg calcium silicate, showed the best floating ability in simulated gastric fluid.

Patel *et al*., 2006, prepared the Floating microspheres of Metformin hydrochloride by non-aqueous emulsification solvent evaporation technique using ethycellulose as rate controlling polymer. The drug release from the microspheres was found to be 47 to 85 % in 8 hours.

Floating minitablets

Goole *et al.,* 2006, developed a multiple unit floating drug delivery system (minitablets) by melt granulation and subsequent compression and evaluated the importance of composition and manufacturing parameter on the floating and dissolution properties of minitablets. They reported that the composition and diameter of minitablets had the great influence on the drug release, which was sustained for more than 8 hours.

Xiaoqiang *et al.,* 2006, prepared a floating matrix dosage form of Phenoporlamine HCl based on gas generation technique using HPMC K4M, Carbapol 971 P NF and sodium bicarbonate. The dissolution profile of all the tablets showed non-Fickian diffusion in simulated gastric fluid and *in vivo* study in six healthy human volunteer suggested that floating matrix tablet containing more carbapol was capable of sustained delivery of the drug for longer periods with increased bioavailability.

Sungthogjeen *et al.,* 2006, developed a multiple unit floating drug delivery system (pellets) in order to prolong the gastric residence time and to increase the overall bioavailability of dosage form by extrusion-spheronization process based on gas formation technique. They reported that the optimized dosage form remained buoyant for over a period of over 24 hours and drug release was sustained.

Floating beads

Iannuccelli, *et al.,* 1998, formulated a air compartment multiple unit system and optimized their *in vitro* floating ability. They showed that the floating ability increased with increased in PVA concentration and molecular weight and it was found to be excellent when using PVA 100000 at a concentration of at least 5%.

Iannuccelli, *et al.,* 1998a, assayed the intragestric behavior of floating multiple unit system. The floating units used in this study, composed of a calcium alginate core separated by an air compartment from a calcium alginate/polyvinylalcohol membrane. They conducted the *in vivo* study by administering to each at the same time both floating and control systems, loaded with barium sulphate, and monitored them in the gastric region at determined time intervals using X- ray apparatus and reported that the floating system remained buoyant on gastric content under both fastened and fed state.

Murata *et al.,* 2000 preparedc the floating alginate beads for stomach specific drug delivery. They prepared two type of alginate beads. The first alginate gel beads containing vegetable oil, held in a alginate gel matrix. The model drug was released gradually in to artificial gastric juice, the release rate being inversely related to the percentage of oil. The second alginate beads containing chitosan was deried gel beads with dispersed chitosan in the matrix.

Patel *et al.,*2006 prepared the calcium alginate beads of water soluble drug Metronidazole using 3^2 factorial design. They showed

that the entrapment efficiency of prepared beads was in the range of 81% to 96% w/w. which decreased with decrease in polymer conceration. The beads were spherical with size range between 1.4to 1.9 mm and swelling ratio was 200% in 30 min.

Patel *et al., 2006* prepared floating calcium alginate beads containing water soluble drug metronidazole using 3^2 factorial design.

CONCLUSION

Drug absorption from the gastrointestinal is highly complex and variable. GRDDS have great potential in improving the bioavailability of drugs that exhibit an absorption window, but with certain limitations. The single unit dosage form increase the bioavailability of some drugs but have some disadvantages and these disadvantages can be overcome by formulating the drug in multiple unit floating drug delivery system which have all the advantage of single unit system.

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