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GASTRORETENTIVE DRUG DELIVERY SYSTEMS - A REVIEW

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ABSTRACT

This review is an attempt to discuss various pharmaceutical techniques which improve the gastric residence time (GRT). Gastroretentive drug delivery systems (GRDDS) are fabricated for increasing the gastric emptying time and release the drug at predetermined rate. These systems are often designed for improved drug dissolution in gastric fluid which may enhance the drug absorption in the upper tract of gastrointestinal tract (GIT) and improve the bioavailability of the drugs. In GRDDS various approaches have been used for instance, hydrodynamically balanced systems, floating drug delivery systems, bioadhesive systems, raft systems, magnetic systems, swelling and expanding systems. This review also summarizes the mechanism, advantages and limitations along with the recent advances and application areas of such GRDDS.

KEYWORDS: **Gastroretentive drug delivery systems, Bioadhesive systems, Swelling and Expanding systems, Floating systems, Magnetic systems.**

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INTRODUCTION

ORAL DRUG DELIVERY SYSTEMS

Oral route is one of the most preferred and convenient route for drug delivery. Oral route is considered an ideal drug delivery system because of high levels of patient compliance, ease of administration and low cost of the therapy,[1] in spite of some shortcomings/ limitations of this route.

CONTROLLED RELEASE DRUG DELIVERY SYSTEMS (CRDDS)

CRDDS are those in which the rate of drug release is controlled, or the site of drug release is controlled or both. CRDDS offer numerous benefits over the conventional dosage forms, such as improved patient compliance, reducing the dose frequency, control over rate and site of release, more consistent and prolonged therapeutic effect, decrease intensity of adverse effect and better drug utilization.[2]

GASTRORETENTIVE DRUG DELIVERY SYSTEMS (GRDDS)

These systems can stay in the stomach for several hours and hence notably extend the GRT of drugs.[3] Extended gastric retention often increases solubility results in increase in bioavailability for BCS II and BCS IV class of drugs, e.g., Dipyridamol, Clarithromycin, Furosemide, etc. GRDDS are improved accessibility of new products with new therapeutic uses.[4]

SUITABLE DRUG CANDIDATES FOR GRDDS

A number of drugs have been fabricated into GRDDS owing to one or another reasons. The rationale for selection of drugs for GRDDS is shown in table 1.

Table 1
Rationale for selection of drug for GRDDS [5]

Rationale for gastro-retention	Name of Drug
Mainly act on the stomach	Antacids and Misoprostol
Primarily absorbed in stomach	Furosemide, Chlordiazepoxide and Calcium supplements.
Degrade at higher pH	Captopril
Not stable in colon or intestine	Metronidazole and Ranitidine HCl
Weakly basic drugs or drugs with better solubility at lower pH	Cefpodoxime proxetil, Rosiglitazole maleate, Verapamil, Diazepam, Dipyridamole and Cinnarizine,

Unsuitable Drug for GRDDS:-There are some drugs which are unsuitable for designing GRDDS which are summarized in table 2

Table 2
Example of unsuitable drugs for GRDDS [6]

Unsuitable for gastroretention drug delivery systems	Name of Drug
Unstable in the gastric media	Erythromycin
Mainly act on the colon	5- amino salicylic acid and corticosteroids
Less acid solubility	Phenytoin

Approaches of GRDDS
Various approaches of GRDDS are shown in figure 1.

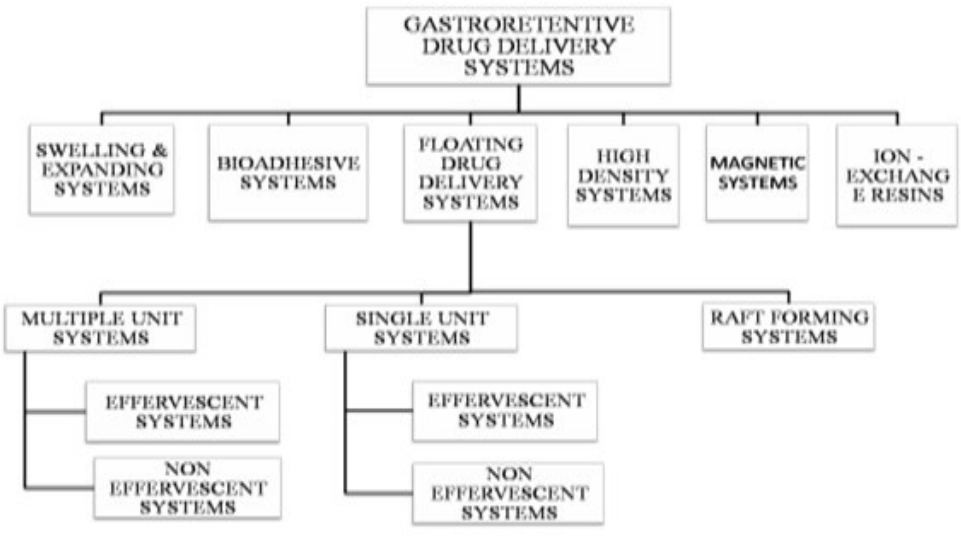

Figure 1
Approaches of various GRDDS

APPROACHES OF VARIOUS GASTRORETENTIVE DRUG DELIVERY SYSTEMS

SWELLING AND EXPANDING SYSTEMS

This system is based on the swelling properties of the polymers. As the size of the system is expanded (due to swelling), the system is confined to the stomach, as (due to increased size) it cannot pass through the pyloric sphincters. So this system is also called as "Plug type system". In the system polymers are used with the appropriate molecular mass and swelling properties which (in addition to imparting floatation) also result in controlled and sustained drug release. This network makes contact with gastric media; the polymer absorbs water and swells, shown in figure 2.[1] Chen *et al.,* (2010) developed swelling systems of Losartan tablets using sodium bicarbonate, sodium carboxy methyl cellulose (Na CMC), and hydroxyl ethyl cellulose (HEC). The optimized formulation showed swelling to 2 cm in diameter within 3 h and floating time more than 16 h.[7] El Zahaby *et al.,* (2014) fabricated swelling systems of levofloxacin hemihydrates using gel forming polymers including: sodium alginate, gellan gum, pectin and xanthan gum. Effect of cross-linkers: aluminum and calcium chloride, on the drug release was also studied.[8]

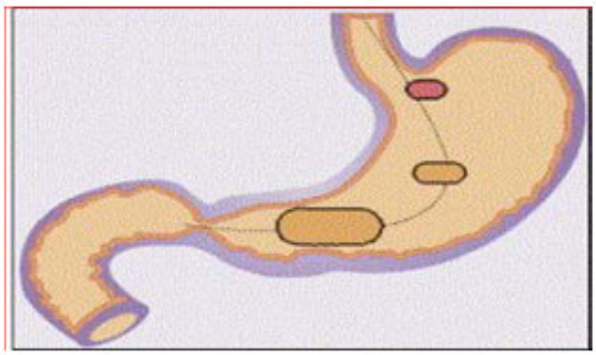

Figure 2
Swellable tablets in stomach [9]

BIOADHESIVE SYSTEMS

These systems usually contain a synthetic and natural polymer that are accomplished of binding on the mucus lining, gastric epithelial cell surface and enlarge the GRT. These systems use the natural and synthetic polymers, i.e., hydrophilic gelling constituents by forming hydrogen bond with many groups, such as sulfate, hydroxyl, carboxyl and amide groups (e.g., cross linked carrageenan, sodium alginate, Na CMC and polyacrylic acids) that can stick on the epithelial surface of the GIT.[5] Chavanpatil *et al.,* (2006) fabricated bioadhesive systems of Ofloxacin tablets using hydroxypropyl methyl cellulose (HPMC K100M), crospovidone and psyllium husk polymers. Optimized formulations showed the drug released for 24 h.[10] Birajdar *et al.,* (2013) fabricated floating mucoadhesive systems of Dipyridamole tablets using HPMC K4M and carbopol 934P. The optimized formulations showed 99.92 % drug released at 12 h.[11]

FLOATING DRUG DELIVERY SYSTEMS

Davis in 1968 first described the FDDS. These systems are low density systems. Due to low density systems, it provides enough buoyancy to float the drug in gastric media in the stomach for a extended time. The network floats in the gastric media and the drug is slowly delivered at the desirable rate that results in enlarged GRT along with decreased fluctuations in plasma drug concentration. It has three types, i.e., Raft forming systems, Effervescent systems and Non effervescent systems.[12] Rao *et al.,* (2013) made FDDS of Cefuroxime Axetil tablets using various grades of HPMC. *In vivo* radiographic studies of the optimized formulations were also conducted in five healthy human volunteers which showed 6 h gastroretention.[13] Shakya *et al.,* (2013) fabricated gastroretentive floating systems of Ofloxacin tablets using HPMC K100M and sodium bicarbonate polymers utilizing Box Behnken designs. *In vitro* studies of the optimized formulations showed the drug release above 12 h and excellent buoyancy properties: floating lag time less than 1 min, floating time more than16 h.[14] Vo *et al.,* (2016) prepared floating pellets of Theophylline by hot melt extrusion techniques using the ammonio - methacrylate (Eudragit RSPO) copolymer. Optimized formulation was showing the increased floating potency after 30 min due to matrix swelling.[15] Mantry *et al.,* (2013) prepared floating bioadhesive systems of Ondansetron Hydrochloride tablets. These tablets were prepared using different concentration of extending rate releasing polymer Na CMC and HPMC for the drug release in upper GIT. Optimized formulation showed better results for buoyancy and content uniformity.[16]

EFFERVESCENT SYSTEMS

These systems are made with swellable polymers for instance; polysaccharides (e.g., chitosan) or methocel and effervescent agents, e.g., citric acid or tartaric acid and sodium bicarbonate or matrices containing reservoirs of liquid are which evaporate at the body temperature. The matrices are made so that upon contact with gastric fluid, carbon dioxide is released by the acidity of gastric content and entrapped in the gel hydrocolloid. This makes the upward motion and

maintains the buoyancy.[17] Jagdale *et al.,* (2012) prepared effervescent matrix tablets of water soluble drug Tapentadol Hydrochloride using xanthan gum and chitosan polymers utilizing the 3^2 full factorial designs. Optimized formulations showed sustained drug release pattern. X ray studies of the optimized formulations showed gastroretention for 6 h.[18]

NON EFFERVESCENT SYSTEMS

These systems are made by using gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polystyrene, polymethacrylate, polyacrylate and polycarbonate. In the system the dosage form swells when comes in contact with gastric fluids and attains a bulk density of less than 1 g/ml. The air entrapped within the swollen matrix imparts buoyancy to the dosage form.[19] Deshpande *et al.,* (2014) developed non-effervescent low density floating systems of Cefpodoxime Proxetil tablets by direct compression method using Accurel® MP1000, gum dammar and HPMC K15M polymers. *In vivo* studies of the optimized preparations in rabbit were carried out by using barium sulphate radio opaque marker.[20]

RAFT FORMING SYSTEMS

These systems contain a gel-forming solution (e.g., Sodium alginate solution containing bicarbonates or carbonates) which swell and form a viscous cohesive gel containing trapped CO_2 bubbles in contact with gastric fluid, shown in figure 3. These systems are used in the antacid formulation because a layer produce sat the top of gastric fluids in the raft forming systems. Therefore, such systems are useful in for gastro-oesophageal reflux treatment.[3] Patel *et al.,* (2015) developed a raft forming systems of Nizatidine using sodium alginate and pectin as raft forming components and used sodium bicarbonate as gas generating agent utilizing 3^2 full factorial design. *In vitro* studies of the optimized formulation exhibited the drug release of 98.86 % in 12 h and showed the maximum raft strength.[21]

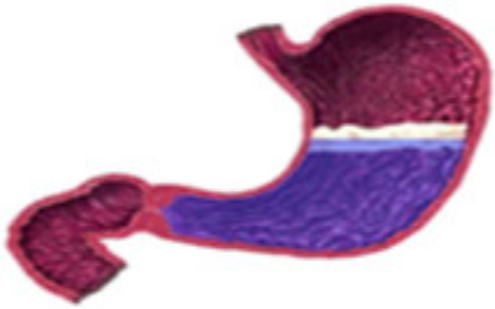

Figure 3
Raft forming systems [5]

HIGH DENSITY SYSTEMS

This system is made by coating the drug or mixed with heavy inert material such as titanium dioxide, barium sulfate, iron and zinc oxide powder. In the system the formulation density exceeds with the normal stomach content (1.004g/ml), shown in figure 4. The resulting pellets can be coated with a suitable polymer in order to obtain desired release profile.[22] Mane *et al.,* (2013) developed floating osmotic drug delivery systems of Diltiazem Hydrochloride tablets using potassium chloride and HPMC K4M polymers utilizing the 3^2 factorial design. *In vitro* studies showed that FDDS offers a promising drug delivery system for improvement of bioavailability of Diltiazem Hydrochloride.[23]

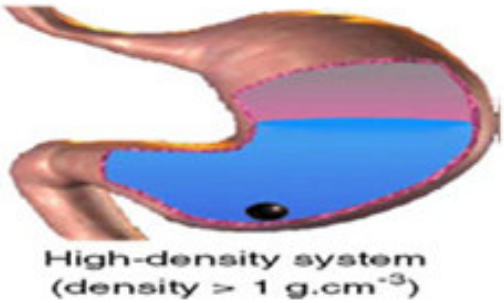

Figure 4
High Density Systems [24]

MAGNETIC SYSTEMS

In these systems, a small internal magnet in the system and a magnet located on the abdomen above the position of the stomach, is employed. In this system an extracorporeal magnet is used which increased the GRT of the dosage form.[22] Fujimori *et al.,* (1995) investigated a magnetic system of acetaminophen tablets. These tablets were prepared by direct compression method using ultra fine ferrite, microcrystalline cellulose and hydroxypropyl cellulose-H polymers. The authors

studied the result of gastric residence of acetaminophen magnetic tablets on drug bioavailability; an enduring magnet (neodymium iron- boron magnet) was applied to the stomach of beagle dogs for 8 h after administration of the magnetic tablets.[25]

ION-EXCHANGE RESINS

Ion-exchange resins are filled with bicarbonate and bound to a negative charge drug. The resulting beads are encapsulated in a semipermeable membrane to overcome the fast loss of carbon dioxide. After arriving in the stomach, an exchange of bicarbonate and chloride ion takes place. As a result of this reaction carbon dioxide is released and is entrapped in the membrane carrying the beads towards the gastric media and producing a floating layer of resin to distinguish the uncoated beads, which will be sink rapidly. [17] Yeong *et al.,* (2012) produced anion exchange resin system of Samarium-152 (III) chloride hexahydrate capsule. It was coated with biocompatible polymer Eudragit TM L100. *In vitro* disintegration studies of optimized formulations showed that all the capsules remained intact in the simulated gastric fluid for 72 h and started to disintegrate in less than15 min when in the simulated intestinal fluid.[26]

ADVANTAGES OF GRDDS

Advantages of GRDDS are shown in table 3.

Table 3
Advantages of GRDDS [16-17, 27-32,]

	Advantages	Drugs
Bioavailability	These systems enhanced bioavailability of the drug.	Furosemide, Diltiazem
Dosing	These systems have reduced the frequency of dosing.	Metformin, Clarithromycin
Action	Targeted action in the upper tract in local ailments.	Famotidine, Ondasetron
Consistency	Patient consistence.	Nizatidine
Diseases	These systems are used in the treatment of gastro esophageal reflux diseases.	Omperazole
Dissolution	These systems prolong the dissolution rate of drugs in gastric media.	Furosemide, Famotidine

LIMITATIONS OF GRDDS

Limitations of GRDDS are shown in table 4.

Table 4
Limitation of GRDDS [17]

High level of fluid	GRDDS required a sufficient amount of media in the stomach for the floating and work competently on the systems. Sufficient amount of water (200-250ml) need to be administered for efficient of working FDDS. [33]
Solubility	Drugs which have solubility problem in the gastric media are not suitable for these systems.
Stability	Drugs which have stability problems in the gastric media are not suitable for these systems.
First pass Metabolism	Drugs absorbed in stomach, undergo first-pass metabolism and may not be suitable candidates for GRDDS because slow gastric emptying would reduce systemic bioavailability, e.g., Nifedipine.
Irritations	Those drugs which cause lesions and irritation to gastric mucosa are not suitable to be formulated as GRDDS.

SINGLE UNIT FLOATING DOSAGE SYSTEMS

These systems are simplest to build up and have the trouble of losing their effects due to “all or none rule” emptying from the abdomen part; they may cause local irritation due to large amount of drug delivered at a particular site of the GIT and high variability in bioavailability.[3]

MULTIPLE UNIT FLOATING SYSTEMS

These systems reduce the intra and inter–subject inconsistency of the drug absorption and minimize the dose clearance. These systems have been prepared indifferent forms and using principles for example emulsion solvent diffusion method by preparing hollow microspheres, emulsion gelation method by preparing beads, air compartment multiple unit system, etc. For preparing multiple unit FDDS uses the swellable and effervescent polymer are used in other approaches.[34] Various multiple unit floating formulations have been summarized in table 5.

Table 5
Formulations of Multiple Unit Floating Drug Delivery Systems [4]

Dosage form	Drug
Floating Microparticles	Verapamil Hydrochloride and Ketoprofen
Hollow Microspheres	Nifedipine
Floating Microspheres	Piroxicam and Acetohydroxamic acid
Low Density Multiparticulate Systems	Meloxicam
Foam Based Floating Microparticles	Diltiazem Hydrochloride, and Theophylline
Floating Micropellets	Lansoprazole
Floating Granules	Ranitidine Hydrochloride
Granules	Residronate Sodium
Floating Beads	Metronidazole

POLYMERS

Numerous polymers and carriers have been utilized for fabrication and to control the drug release in gastric environment, which have been categorically summarized in table-6.

Table 6
Polymers used in preparations of GRDDS [8-9, 20-21, 26, 30, 35-37]

Polymer & Ingredients	Examples
Polymers	HPMC 4000, HPMC 100, HPMC K4M, CMC, PVA, Calcium alginate, Carbopol, Ethyl cellulose, Eudragit RS and RL, acrylic polymer
Buoyancy increasing agents	Ethyl cellulose
Release rate accelerants	Mannitol, Lactose
Release rate retardants	Magnesium Stearate, Dicalcium phosphate, Talc
Low density materials	Polypropylene foam powder
Inert fatty materials	Fatty acids , Bees wax,
Effervescent agents	Tartaric acid, Citric acid, Sodium bicarbonate, Citroglycine

PATENTS ON GRDDS

Patents on GRDDS have been summarized in table 7.

Table 7
Patents on GRDDS [38-45]

S. No	Patents	Patent no
1	Gastrorentevive dosage form systems and process of preparation thereof.	US20140271871846
2	Gastrorentevive sustained and pulsatile drug delivery systems.	W02013051036 A1
3	GRDDS and their dosage form their method of preparation using calcium carbonate.	W02014057086 A1
4	A novel gastro retentive drug delivery of macrolide.	W02011125075 A3
5	Gastrorentevive controlled release microsphere for improved drug delivery.	US6207197 B1
6	Extended release gastro retentive oral drug delivery systems for valsartan.	EP2061438 A1
7	GRDDS.	W02009089665 A2
8	GRDDS comprising an extruded hydratable polymer.	US8586083 B2

SUMMARY

GRDDS are employed to increase the gastric emptying time and specific target site drug release. Systems like hydrodynamically balanced systems, floating drug delivery systems, bioadhesive systems, magnetic systems, raft systems and swelling and expanding systems have potential to delay the GRT of several drugs, thus increasing their therapeutic potential. The inclusion of specific polymers offers increased avenues of gastroretention. GRDDS are now – a -days widely chosen by the researchers to improve therapeutic efficacy of the drugs in use.

CONFLICT OF INTEREST

Conflict of interest declared none.

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