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An overview on Gastroretentive drug delivery systems

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ABSTRACT

Administration of drugs through oral route is the most preferable route of drug delivery as it is simple, easy to administer and have greater patient compliance. But its advantages have become limited in case of drugs with low absorption window. There has been considerable research over the past few years on the possibility of controlled and site specific delivery to the GIT by controlling the gastrointestinal transit of orally administered dosage forms using gastroretentive drug delivery system (GRDDS). A wide range of dosage forms have been developed for the drugs which have narrow absorption window, stability and solubility issues at GI pH, and having stomach as a site of action. The present review briefly describe the gastro retentive drug delivery (GRDD), various approaches for GRDDS, factors controlling gastric retention, merits, demerits and applications of gastroretentive drug delivery systems.

Keywords: Gastro retentive, Floating systems, Bioadhesive, Effervescent

INTRODUCTION

As oral drug delivery is simple, most convenient, safest, noninvasive and most economical, it continues to be the preferential route of administration and researchers are seeking ways to incorporate various technologies in oral formulations; even small improvements in drug delivery technology can make significant differences in enhancing patient compliance and drug bioavailability [1]. Some drugs show poor bioavailability because of incomplete absorption or degradation in the GIT [2]. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) [3]. These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose [4].

So the main challenge in oral drug delivery is to develop gastric retention platforms for long-term (ranging from 6 to 24 h) delivery of drugs by oral administration [1]. Therefore to overcome such problems gastroretentive drug delivery systems are designed to prolong the gastric retention time of the drugs [5].

Prolonged gastric retention improves bioavailability, increases the duration of drug release,

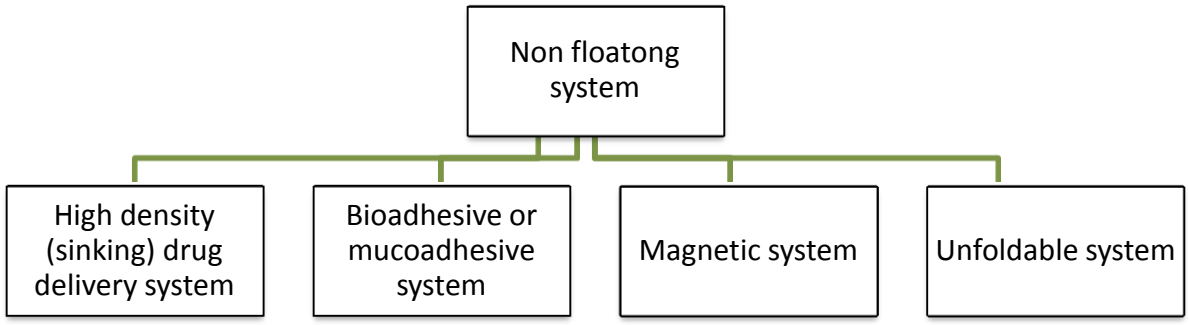
reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment [6, 7]. Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc. Apart from these advantages, these systems offer various pharmacokinetic advantages like, maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels [8].

Approaches

Various approaches have been applied to increase the retention of oral dosage forms in the stomach. Some are formulated as single component whereas others are formulated as multicomponent dosage forms. GRDDS can be broadly categorized into floating and non-floating system [9-12].

Non-floating system

These gastro retentive drug delivery systems do not float in the stomach however they remain retained there by different mechanisms. Non-floating system is further divided into



High Density (Sinking) Drug Delivery System

These systems, which have a density of ~3 g/cm^3, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. In this approach, formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulfate, zinc oxide and titanium oxide so that the density of the formulation exceeds the density of the normal gastric content [13]. Above a threshold density of 2.4–2.8 g/cm^3, such systems can be retained in the lower part of the stomach.

Depending on density, the GI transit time of pellets can be extended from an average of 5.8 to 25 hours. But effectiveness of this system in human beings was not observed [14] and no formulation has been marketed.

Bioadhesive or mucoadhesive system

In this system, drugs 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. The mucus not only protect the surface mucosal cells from acid and peptidases but also acts as a lubricant for the passage of solids and as a barrier to antigens, bacteria, and viruses. A bio/ mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane or the mucus lining of the GIT. 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 bioavailability [15].

The chemicals used for the mucoadhesion purpose include polycarbophil, carbopol, lectin, chitosan, carboxy methyl cellulose, gliadin etc. [16].

Novel adhesive material derived from fimbrae of bacteria or its synthetic analogues have also been tried for the attachment to the gut [17, 18].

Magnetic system

This approach to enhance the gastric retention time (GRT) and is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance [19].

Unfoldable system

Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach [20, 21].

The drug delivery system unfolds and increases in size and it remains lodged at sphincter avoiding its exit from the stomach. For this the system should be small enough to be swallowed but unfold itself when it comes in contact with gastric fluid, and after a certain period of time its size should become small so that it will be easily evacuated.

Floating drug delivery system (FDDS)

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability [22]. Floating drug delivery systems are also known as low density systems.

In contrast to the high density drug delivery system, floating systems have density less than the gastric content thus remains buoyant in the stomach for a prolonged period of time without affecting the gastric contents.

After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration. The major requirements for floating drug delivery system are [13]

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm^3).
- It must form a cohesive gel barrier.

Floating drug delivery system can be divided into

- Effervescent system
- Noneffervescent system: Noneffervescent systems can be further classified as follows

Effervescent System

Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid) [23]. The optimal stoicheometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1 [24].

They are formulated in such a way that when in contact with the gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy.

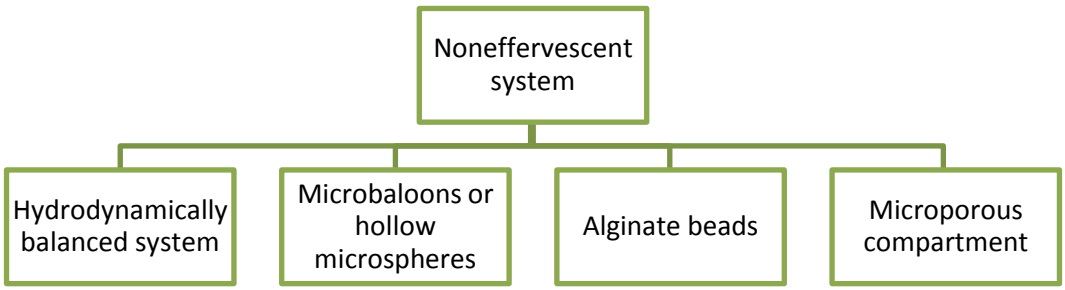
A decrease in specific gravity causes the dosage form to float on the chime. Steps involved in floating of dosage form 1) Penetration of water 2) Generation of CO_2 and floating 3) Dissolution of drug

When the system comes in contact with gastric fluid, it releases carbon dioxide causing the formulation to float in the stomach [25]. This system is further divided as single unit matrix tablets or multiple unit pills. Single unit matrix tablet may be single or multilayer type. Floating system with ion exchange resins has also been reported.

Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC), and floating system based on ion exchange resin technology etc [6]. Bilayer or multilayer system has also been

designed [26, 27]. Drugs and excipients can be formulated independently and the gas generating material can be incorporated in to any of the layers. Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise between elasticity, plasticity and permeability of the polymers.

Non-effervescent system



Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment [28]. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Superporous hydrogels are an excellent example working in this approach. The dosage form swells significantly to several times of original volume upon contact with gastric fluid, the gastric contraction pushes the dosage form to the pylorus but due to larger size of the dosage form, the contractions slips over the surface of the system, due to which the dosage form pushes back into the stomach [29].

Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates [6].

Non-effervescent system can be further divided in to: hydrodynamically balanced system, microbaloons, alginate beads, and microporous compartment.

Hydrodynamically balanced system

The hydrodynamically balanced system (HBS) was first designed by Sheth and Tossounian [30]. HBS contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage forms, and contains one or more gel forming cellulose type hydrocolloid e.g., hydroxypropyl methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, agar, carrageen or alginic acid. It also contains matrix forming polymers such as polycarbophil, polyacrylate and polystyrene [31, 32]. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form [32]. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Madopar LP®, based on the system was marketed during the 1980's [33].

Microbaloons or hollow microspheres

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells, are prepared by emulsion-solvent diffusion method. The microballoons float continuously over the surface of

acidic dissolution media containing surfactant for more than 12 hours [34].

Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours [6]. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

Alginate beads

Freeze dried calcium alginates have been used to develop multi-unit floating dosage forms [37]. By dropping sodium alginate solution into aqueous solution of calcium chloride spherical beads of about 2.5 mm diameter can be prepared. These beads are separated and air dried. This results in the formation of a porous system which remains buoyant in the stomach.

Microporous compartment

In this system, drug reservoir is encapsulated inside a microporous compartment having pores along its top and bottom walls. The floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug in stomach and proximal part of the small intestine for absorption [35].

Factors affecting the gastro retentive system

While using these approaches GRDDS is affected by various factors like

1. Density – Gastric retention time is a function of dosage form buoyancy that is dependent on the density.
2. Size – Dosage form units with a diameter of more than 7.5 mm are to have an increased GRT compared with those with a diameter of 9.9 mm.
3. 3. Shape of dosage form – Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes. 7, 8
4. Fed or unfed state – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes that occurs every 1.5 to 2 hours.
5. Nature of meal – Presence of food affect GRDDS Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
6. Caloric content – If the meal contain high in proteins and fats GRT can be increased by 4 to10 hours.
7. Frequency of feed – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
8. Gender – Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
9. Age – Significantly longer GRT Elderly people, especially those over 70.
10. Posture – GRT can vary between supine and upright ambulatory states of the patient.
11. Biological factors – Diabetes and Crohn's disease, etc.
12. Concomitant drug administration – Floating time is affected by Anticholinergics drugs like atropine and propantheline, opiates like codeine andprokinetic agents like metoclopramide and itopride.

Merits of gastroretentive drug delivery system (GRDDS)

1. The GRDDS has the following advantages
2. Enhanced bioavailability: The bioavailability of the drugs having absorption in the upper part of the GIT like riboflavin, levodopa has tremendously been increased than that of the conventional dosage forms [36, 37].
3. Sustained drug delivery and reduced frequency of dosing. This improves patient compliance.

4. Targeted delivery of the drug at the upper part of the GIT making it suitable for the local treatment of the disease of the region eg; antacids, anti-ulcer drugs, antibacterial for H. pylori infection [38, 39].
5. Suitable for the drugs which have pH dependent absorption from stomach eg., Furosemide [40], Captopril [41], Diazepam, Verapamil, Cefpodoxime proxetil [42].
6. Suitable for the drugs which degrade in the intestine or column [43] eg., Ranitidine hydrochloride.
7. Drug level fluctuation is not observed and maintains the optimal therapeutic plasma and tissue concentrations over prolonged time period. This avoids sub-therapeutics as well as toxic concentration and minimizes the risk of failure of the medical treatment and undesirable side effects. .

Demerits of GRDDS

1. Not suitable for the drugs which are not stable in acidic environment.
2. Not suitable for the drugs which are absorbed better in the lower part of GIT.
3. Difficulty to attain the desired outcome and problem of the dose dumping.
4. Gastric retention is influenced by many factors like gastric motility, pH and presence of food. Hence, the dosage form must be able to withstand the grinding and churning force of peristaltic wave of stomach.
5. Poor in vitro and in vivo correlation.
6. Higher cost of formulation.
7. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reaction.

Potential Drug Candidates For Gastroretentive Drug Delivery Systems

1. Drugs those are locally active in the stomach e.g. misroprostol, antacids etc.
2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, para aminobenzoic acid, furosemide, riboflavin etc.
3. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
4. Drugs that disturb normal colonic microbes e.g.antibiotics against Helicobacter pylori.
5. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

Drugs Those Are Unsuitable For Gastroretentive Drug Delivery Systems

1. Drugs that have very limited acid solubility e.g. phenytoin etc.
2. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
3. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

CONCLUSION

GRDDS have emerged as a current approach of controlled drug delivery of drugs that exhibit an absorption window. Various approaches can be used with their own advantages and disadvantages. To design a successful GRDDS, it is necessary to take into consideration the physicochemical properties of the drug, physiological events in the GIT, formulation strategies, and correct combination of drug and excipients.

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