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Review Article

Various Perspectives of Gastroretentive Drug Delivery System: A Review

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ABSTRACT

The most popular route of administration for systemic action is oral route. It is probable that at least 90% of all the drugs given by oral route .There are different drug deliveries to give drug by oral route .Gastro retentive drug delivery system plays a vital role among novel drug delivery systems. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance Therefore, extended release DDS possessing gastric retention properties may be potentially useful. In this review we summarised approaches and various perspectives of Gastro retentive drug delivery system.

Keywords: Gastric residence time, Gastroretentive, Floating, Mucoadhesive, Effervescent; non-effervescent etc.

INTRODUCTION

The most popular route of administration for systemic action is oral route. It is probable that at least 90% of all the drugs given by oral route. Solid dosage form represents the preferred class of product among the drugs that are given orally. Oral route is the mostly prescribed route since it has patient compliance, ease of ingestion, pain avoidance & versatility to accommodate various type of drug.[1]

The short gastric retention time and unpredictable short gastric emptying time are the two problems of drug delivery systems. Decrease response of dose Due to incomplete drug release from the dosage form in the absorption zone .[2,3]

Drug absorption is unsatisfactory and highly variable among and between individuals due to physiological and usually affected by the GI transit of the form, especially its gastric residence time, which appears to be one of the major causes of the overall transit time variability.[4] In delivery of drugs with narrow absorption windows in the small intestinal region the gastric retention will provide advantages.

GRDDS can be defined as a system which retains in the stomach for a sufficient period of time and releasing active moiety in a controlled manner, and finally metabolized in the body. Over the last two decades, numbers of GRDDS have been designed to

prolong GRT. The main aim of preparing GRDDS is to minimize the problem associated with existing oral sustained release dosage form and to develop patient benefited drug delivery[4].

Gastroretentive drug delivery is prepared with the intention to retain drug in the gastric region for prolonged time and release incorporated drug candidates and thereby enable sustained and prolonged input of the drug to the upper part of the GIT thus leading its optimal bioavailability. Gastroretentive dosage forms greatly improved the pharmacotherapy of the GIT through local drug release, leading to high drug concentrations at the gastric mucosa making it possible to treat various diseases of GI. Gastroretntive drug delivery get popularity from last two decades leading to its potential application to improve oral delivery of some important drugs for which prolonged gastro retention can greatly improve their oral bioavailability.GRDDS not only prolong the dosing intervals, but also increase the patient compliance beyond the level of existing controlled release dosage form[5].

Factors Affecting the Gastro retentive System

Researchers not only using old approaches but also using modified approaches to retain the dosage form in the stomach as a way of increasing the retention time. Like use of floating dosage forms , mucoadhesive systems, high-density systems, modified shape systems, gastric emptying delaying devices and co-administration of gastric-emptying delaying drugs, Raft forming system . While using these approaches GRDDS affected by various factors like[6]

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 reported to have an increased GRT compared with those with a diameter of 9.9 mm.
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 and

prokinetic agents like metoclopramide and itopride.

Requirements for Gastric Retention

Sucessesful gastric retention is possible when the dosage form must obey following requirements.

1. Dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms.
2. To function as a gastric retention device, it must resist premature gastric emptying.
3. If its purpose has been served, the device should be removed from the stomach with ease[9].

Criteria for selection of drug for Gastroretentive drug delivery system[10]

1. Drugs those are locally active in the stomach (e.g. misroprostol, antacids)
2. Drugs that have narrow absorption window in GIT (e.g. L-DOPA, p-aminobenzoic acid, furosemide, riboflavin).
3. Drugs those are locally active in the stomach (e.g. misroprostol, antacids).
4. Drugs exhibit low solubility at high pH values (e.g. diazepam, chlordiazepoxide, verapamil).
5. Drugs that disturb normal colonic microbes such as tetracycline, clarithromycin, amoxicillin
6. Drugs those are unstable in the intestinal or colonic environment.

Advantages of Gastroretentive drug delivery system

1. Reduced frequency of dosing with improved patient compliance for drugs with relatively short half life.
2. There is increase in bioavailability drugs that metabolized in the upper GIT by this Gastroretentive drug delivery approach in comparison to the administration of other drug delivery.
3. They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time as well as the gastric emptying time.
4. Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects.
5. By using this drug delivery we can prolong and sustain release of drugs from dosage.
6. This site-specific drug delivery reduces undesirable effects of side effects.
7. This drug delivery do Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.
8. Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency[11]

Drugs those are unsuitable for Gastroretentive drug delivery systems[12,13].

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.

Limitations of the Techniques of Gastroretention[14,15,16,17]

1. Not suitable for drugs that that are unstable in the strong acidic environment and drugs that causes gastric lesions.
2. Bio adhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique.
3. The floating systems in patients with Achlorhydria can be questionable in case

of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.

Approaches To Achieve Gastric Retention[18,19,20]

1. Low density approach:
   A. Effervescent system:
   a. Gas generating system: Single layer floating tablet, Bilayer floating tablet, Multiparticulate system.
   b. Volatile liquid/vaccum containing system: Intragastric floating gastrointestinal drug delivery, Inflatable gastrointestinal drug delivery, Intragastric osmotically controlled drug delivery.
   B. Non effervescent system: a. Colloidal gel barrier systems, b. Microporous Compartment System, c. Alginate beads, d. Hollow microspheres.

2. High density approach.
3. Mucoadhesive approach
4. Expansion by swelling approach and
5. Raft forming system

1. Low-Density Systems

To avoid premature evacuation of drug through the pyloric sphincter low density system (<1 g/cm3) with immediate buoyancy have 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.

Floating Approach -Floating Drug Delivery Systems[21,22,23,24]

This is mostly used approach of Gastroretntive drug delivery system .Floating drug delivery systems also known as hydro-dynamically balanced systems.

Have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention time and a better control of fluctuations in the plasma drug concentration in some cases.

These dosage forms are also known as gas powered system, which can float in the contents of the stomach and release the drug in a controlled manner for prolonged periods of time.

Based on formulation FDDS are classified in to following Types 25

a) Non-effervescent FDDS

Floating non effervescent matrix tablets were prepared by direct compression method employing various polymers like polypropylene foam powder (Accurel® MP 1000), Karaya gum and Chitosan ,gelicure is used for this system .Floating dosage forms involves intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier.

b) Effervescent FDDS

Non only synthetic polymers but also natural polymers are used for this sysyem.These are matrix type of systems prepared with the help of swellable polymers such as Methylcellulose and chitosan and various effervescent compounds, e.g. sodium

bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the gastric contents, CO2 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

2. High-Density Systems

These systems, which have a density of ~3 g/cm3, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. Above a threshold density of 2.4–2.8 g/cm3, such systems can be retained in the lower part of the stomach.

3. Bio/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 GRDDSthrough 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.

There are various types of mucoadhesion like,

a) Hydration-Mediated Adhesion

This achieved by using hydrophilic polymers which imbibe large amount of water and become sticky, thereby acquiring mucoadhesive properties. The prolonged gastro retention of the bio/mucoadhesive drug delivery system is further controlled by the dissolution rate of the polymer.

b) Bonding-Mediated Adhesion

The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical–mechanical bonding and chemical bonding. Physical–mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature.

c) Receptor-Mediated Adhesion

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.

Polymers used in Gastroretentive mucoadhesive drug delivery system

(1) Synthetic polymers

(a) Various gardes Poly ethylene oxide like WSR 301, 301, N10, Coagulants.
(b) Cellulose derivatives (methylcellulose, ethylcellulose, +ydroxy-ethylcellulose, Hydroxyl propyl cellulose, hydroxy propyl methylcellulose, sodium carboxy methylcellulose.
(c) Poly (acrylic acid) polymers (carbomers, polycarbophil).
(d) Poly (hydroxyl ethyl methyl acrylate).
(e) .Poly (vinyl pyrrolidone).
(f) Poly (vinyl alcohol).

(2) Natural polymers

(a) Tara gum
(b) Sodium alginate
(c) Karaya gum
(d) Guar gum
(e) Xanthan gum
(f) Locust bean gum[26]

4. Swelling system

After taking these swelling system it swell to a size that prevents their passage through the pylorus so that 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 crosslinks in the hydrophilic polymer network.[27]

5. Raft-forming System

Raft forming system is not only helpful for sustained drug delivery but also convenient for pediatric and geriatric patients. This system is helpful as an alternative of oral solid dosage form with the advantages of liquid dosage form. Sustained and prolonged release of the drug, good stability and bioavailability characteristics make the raft forming system very suitable candidate for gastric retention of the drug. Thus the raft forming system promises to be the potential approach for gastric retention drug delivery system

In this gel forming solution (e.g., Sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Nowadays Raft Forming Systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders.[27]

Recent combinational approaches for Gastroretention[28,29]

Currently following combination approaches used in GRDDS

1. Swellable and floating.
2. Bioadhesive and floating.
3. Bioadhesion and swelling.
4. Bioadhesion and High density,
5. Floating pulsatile system.

Methods used for Gastric retention[30]

1. By reducing particle size and filling it in a capsule.
2. By utilising gel forming hydrocolloids such as hydrophilic gums, gelatin, alginates, cellulose derivatives, etc.
3. By Using low density enteric materials such as methacrylic polymer, cellulose acetate phthalate.
4. By forming carbon dioxide gas and subsequent entrapment of it in the gel network.

5. By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.

Various dosage form of GRDDS[31,32]

1. Floating microspheres Rosiglutazone, cefpodoxime, cefuroxime axitel, Nateglinide
2. Floating granules Lacidipine, Ranitidine, simvastatin metopropalol atorvastatin
3. Films Cinnarizine
4. Floating capsules celecoxib ,pioglutazone, diazepam, furosemide, misoprostol, L-dopa, benserazide, ursodeoxycholic acid and pepstatin
5. Floating tablets Alfuzosin, Losarten ,proapnalol, ofloxacin, glipizide, loratidine
6. Mucoadhesie system venlafaxine, famotidine, metformin, metopropalol[33].

CONCLUSION

Growing understanding of impact of GIT physiology on drug delivery will ensure development of an increasing number of drug delivery system to optimize drug delivery of molecules exhibiting regional variability in drug absorption. The increasing sophistication of delivery technology will ensure the development of increase number of gastro retentive drug delivery to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism. Based on the literature surveyed, we concluded that Gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability . Gastroretentive drug delivery system gives maximum benefit to patient so that maximum patience compliance associated with it.

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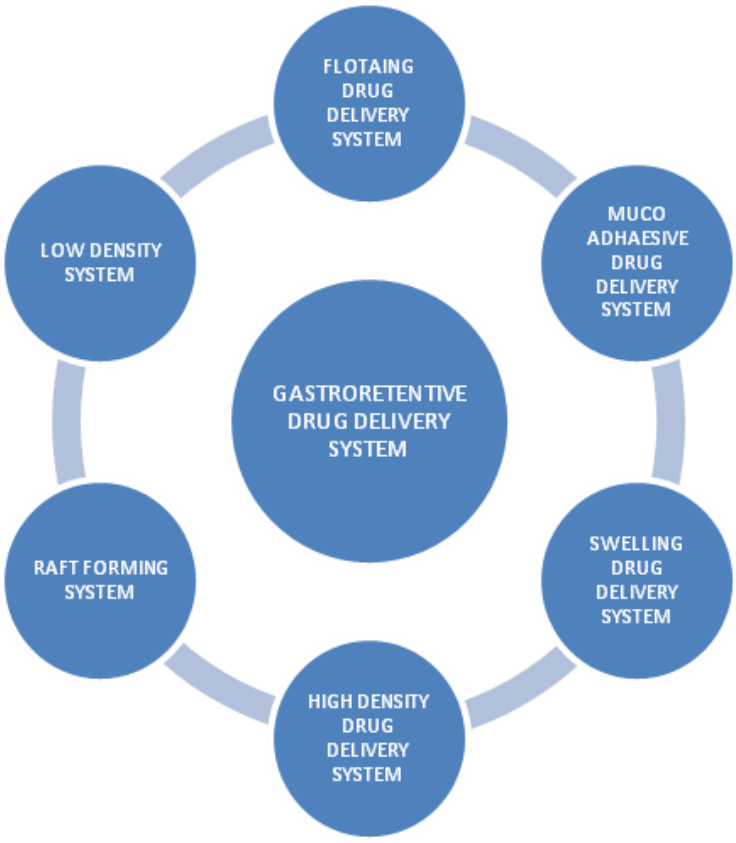

Fig. 1