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# RECENT TRENDS IN CONTROLLED RELEASE ORAL DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW

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**ABSTRACT**

In recent decades different modern technological attempts have been explored in the research and development of controlled release oral drug delivery systems to cross the barriers of physiological adversities, like unpredictable gastric emptying times (GET) and short gastric residence times (GRT). The most successful approaches in the reigon of oral delayed release drug delivery is gastroretentive drug delivery system (GRDDS). Drugs with a narrow absorption window and having well to moderate solubility in gastric fluids are rapidly eliminated from stomach due to rapid gastric transit. GRDDS delay the retention time of dosage forms in the stomach or proximal part of gastro intestinal tract (GIT), so that it enhances solubility, ultimately bioavailability of drugs and therapeutic efficacy of the dosage form as well. Various methodologies have been adopted to enhance the gastric residence time of drugs, such as floating system, sedimentation or high density system expanding or swelling systems, bio/mucoadhesive system, hydro dynamically balanced system, geometry or modified shape system. This article aims to review the current & recent developments of gastric floating drug delivery systems to provide basic principles useful to overcome the difficulties associated with formulation design carrying wide range of drugs.

**Keywords:** Raft forming system, Gastric emptying time, Mucoadhesive systems, Floating lag time, Hydrodynamically balanced system.

## INTRODUCTION

Oral route is the highly preferred and convenient route of administration for drug delivery. The main goal of any drug delivery system is to afford a desired therapeutic concentration of drug to the targeted site in the body to attain promptly, and then maintain the desired concentration of drug. In Oral drug delivery system some drugs are not well absorbed uniformly throughout the gastrointestinal tract (GIT). Some drugs are absorbed in a particular portion of gastrointestinal tract. The phenomenon of absorption of drugs from selective region of GIT is termed as narrow absorption window. Oral controlled release drug delivery systems have been recently increasing interest in pharmaceutical field to achieve enhanced therapeutic advantages, such as patient compliance, ease of dose administration and flexibility in formulation. Drugs which posses well absorption from gastrointestinal tract (GIT) and have short half-lives were rapidly eliminated from the body. Frequent dosing of these drugs is necessary to achieve desired therapeutic activity. To overcome this limitation, the development of oral sustained - controlled release formulations is one of the attempt to release the drug slowly into the GIT and maintain the effective drug concentration in the systemic circulation for a prolonged period of time. After oral administration, such a drug delivery system would be accommodated in the stomach for a prolonged period of time and release the drug in a controlled manner continuously to the effective absorption sites in the GIT [1].

Gastro retentive floating drug delivery have ability to achieve better availability of drug products with suitable therapeutic activity and substantial benefits for the patients. This mode of floating drug delivery would result in achieving best pharmacokinetic and pharmaco dynamic advantages of controlled release dosage forms [2].

To design a successful gastro retentive drug

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delivery system various techniques are currently used such as, magnetic systems [3-5]. Raft systems having alginate gels [6-8]. Bioadhesive or mucoadhesive systems [9], high density systems [10-12], super-porous hydrogels [13]. Floating drug delivery system/ Hydro dynamically balanced systems (HBS) [14].

**High density systems, low density systems [15-17]**

Gastro retentive drug delivery systems (GRDDS) suffer from mainly two adversities: the low gastric retention time (GRT) and unpredictable rapid gastric transit which results in incomplete drug release from the dosage form in the absorption site (stomach or upper part of small intestine) leading to diminished efficacy of administered dose [18].

Gastro retentive dosage forms has become a modern trend in novel sustained drug delivery systems and their application can be advantageous in case of drugs that are absorbed mainly from the stomach and upper part of GIT or unstable in the alkaline $p^H$ of distal intestinal regions. They can also be used beneficially in the treatment of local infections in the stomach and upper intestinal regions.

**Basic anatomy of Stomach and its physiology**

Anatomically the stomach is divided into 3 regions:

1) Fundus
2) Body
3) Antrum (pylorus).

The proximal region of gastric cavity made of fundus and body acts as a reservoir for undigested material, capable of providing large surface area to accommodate food without much increase in intragastric pressure. Whereas the antrum is the major site for mixing motions and act as a pump for gastric emptying by propulsion mechanism. Under unfed state the stomach is collapsed bag with residual volume of 50 ml and contains a small amount of gastric fluid and air. Mucosal lining is covered throughout the stomach below this layer specialized cells which were secret gastric juice into gastric cavity.

**Gastric juice consists of:**

- Water
- Intrinsic factor
- Mucus- glycoprotein
- Gastric enzymes (pepsin, gastric lipase, gastrin, renin and other enzymes)
- Sodium, calcium, potassium, chloride, bicarbonate, phosphates and Hydrochloric acid.

Normal gastric residence time usually ranges between 5 minutes to 2 hours. In the fasted state the electrical activity in the stomach – the inter digestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and the transit of dosage forms.

**Requirements of gastricretention**

To achieve gastric retention, the dosage form must full fill certain requirements. One of the key requirement is that the dosage form must be able to withstand the forces exerted by peristaltic waves in the stomach and the constant contractions and grinding and churning moments . To function as a gastric retention dosage form, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be easily evacuated from the stomach.

**Unsuitable Drugs For Gastroretentive Drug Delivery Systems**

1) Drugs that having poor acidic solubility
   e.g. Phenytoin etc.
2) Colon targeting Drugs
   e.g. Corticosteroids and 5- amino salicylic acid etc.
3) Drugs those are unstable in the gastric environment
   e.g. Erythromycin etc.

**Suitable Drug Candidates for Gastroretention**

(a) Drugs those are less soluble in alkaline pH.
   e.g. Diazepam, Verapamil, Furosemide, etc.
(b) Drugs that act locally in the stomach
   e.g., Antacids and Misoprostol.
(c) Drugs that have a narrow absorption window.
   e.g., Levodopa, Cyclosporine, Riboflavin, and Methotrexate.
(d) Drugs that are having primary absorption in the stomach.
   e.g. Calcium supplements and Cinnarazine , Metronidazole,
   Chlordiazepoxide, and Tetracycline.
(e) Drugs with variable bioavailability.
   e.g. Sotalol HCl
(f) Drugs that is unstable in the intestinal or colonic environment.
   e.g. Ranitidine HCl and Metronidazole.

**Factors Affecting Gastric Retention Time [19-21]**

**1. Single or multiple unit formulation** – Multiple unit formulations show a predictable release pattern and insignificant impairing of performance due to failure of units, which allows the co-administration of units with different release profiles or containing incompatible substances and allows a larger margin of safety against dosage form failure compared with single unit dosage forms.

**2. Density:** GRT is a function of dosage form buoyancy that is dependent on the specific gravity. The density of a dosage form also affects the gastric emptying rate and determines the position of the system in the stomach. Dosage forms having lower density than the gastric contents can float on the surface, and high density systems sink to bottom of the stomach. Both positions may seperate the dosage form from the pylorus. A density of $< 1.0$ gm/ $cm^3$ is required to exhibit buoyant tendency.

**3. Size & Shape of dosage form**: Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm. Tetrahedron as well as ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square

inch (kpsi) are reported to have good GRT 90% to 100% retention at 24 hours compared with other shapes.

**4. Concomitant drug administration:**
Anticholinergic drugs like atropine, propentheline- increase GRT.
Metoclopramide and cisapride- decrease GRT.

**5. Caloric content:** GRT has been increased by 4 to 10 hours with a meal that is high in proteins and fats.

**6. Nature of meal:** Feeding of indigestible materials or fatty acid salts can alter the motility pattern of the stomach , thus decreases the gastric emptying rate and prolonging drug release.

**7. Disease state:**
Hyperthyroidism and duodenal ulcers reduces GRT.
Gastric ulcer, diabetes and hypothyroidism increases GRT.

**8. Frequency of feed:** the GRT can increase by over 400 minutes, when successive meals is given compared to a single meal because of the low frequency of MMC.

**9. Gender:** Male- 3.4 ± 0.6hr and to Female- 4.6 ± 1.2hr.

**10. Fed or unfed state:** Under unfed conditions GI motility is characterized by the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC evacuates undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short.

**11. Age:** Elder people, especially those having age over 70years have a significantly longer GRT.

**12. Posture:** GRT can vary between supine and upright ambulatory positions of the patient.

**Approaches to Gastric Retention**

**1) Floating Dosage forms :A Low Density Approach**

**A) Effervescent systems**

***a) Gas Generating systems***

1. Tablets
2. Capsules
3. Floating systems with ion-exchange resin
4. Multiple unit type floating pills

***b ) Volatile liquid/ Vacuum systems***

1. Intragastric osmotically controlled drug delivery systems
2. Inflatable gastrointestinal drug delivery systems
3. Intra gastric gastrointestinal drug delivery systems

**B) Non-Effervescent systems**

1. Single layer Floating Tablet
2. Bilayer Floating Tablets
3. Hollow microspheres
4. Alginate beads

**Mucoadhesive systems**

**1) Magnetic systems**
**2) High density systems**
**3) Self Unfolding systems**
**4) Swelling and Expandable systems**
**5) Super porous hydro gels**
**6) Raft forming systems**

**LOW DENSITY APPROACH VIA FLOATING DRUG DELIVERY SYSTEMS**

Hydro-dynamically balanced systems are also known as floating drug delivery systems (FDDS). These systems have a specific gravity lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. While these systems are floating on the gastric contents, the drug is released slowly at a predetermined rate from the stomach. After the drug release the residual system must empty from the stomach. This results in enhancing the gastric retention time and a better control of fluctuations in the plasma concentration of drug in some cases.

**Types of floating drug delivery systems**

Based on the floating mechanism two different technologies have been utilized for the development of FDDS.

***1) Non-Effervescent FDDS***

The Non-effervescent FDDS is designed based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most widely used polymers in non-effervescent FDDS are gel forming agents or highly swellable cellulose derivatives like hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polyacrylate, polycarbonate polymethacrylate, polystyrene as well as bioadhesive polymers such as carbopol and Chitosan.

**The various types of floating system are as follows:**

***A. Single Layer Floating Tablets***

They are formulated by uniform mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains spefic gravity less than one. They are formulated by blending of drug with low-density enteric materials such as cellulose acetate pthalate, hydroxyl propyl methyl cellulose etc.

***B. Bi-layer Floating Tablets***

A bi-layer tablet contain two layers one immediate release layer which releases loading dose from system while the another is sustained release layer which releases maintainence dose by absorbing gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a specific gravity less than unity and thereby it remains buoyant in the stomach .

C***. Hollow Microspheres***

Another name of hollow microspheres also termed as microballoons. These are loaded with drug in their outer shells that are prepared by various approaches, most widely used method is novel emulsion-solvent diffusion method. In this method the dichloromethane: ethanol solution of the drug and an enteric acrylic polymer is poured into an

agitated aqueous solution of PVA that is thermally controlled at $40^0$C. The gas phase produced in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float for more than 12 hours over the surface of acidic dissolution media containing surfactant.

***D. Alginate Beads***

Spherical beads having approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a buoyancy force for over 12 hours, and these floating beads gave a prolonged gastric residence time of more than 5.5 hours .

***(2) Effervescent systems***

These are matrix type of systems formulated by using 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 upon contact of dosage form with the gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which aids buoyancy to the dosage forms.

***i) Gas generating systems***

The most widely used approach for preparing these systems involves usage of resin beads loaded with bicarbonates and coated with ethylcellulose. The coating, which is insoluble allows the permeation of water. Thus, carbon dioxide is released, causing the buoyancy of beads to float in the stomach. These floating systems were widely prepared with swellable polymers like methocel, and polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid.. One of the best stoichiometric ratio of sodium bicarbonate and citric acid for gas generation is reported to be 1: 0.76.

***2) Volatile liquid containing systems***:

These systems are osmotically controlled floating systems having a hollow deformable unit. There are two chambers in the system first chamber contains the drug and the second chamber contains the volatile liquid.These have an inflatable chamber which contains volatile liquid e.g. ether, cyclopentane,etc, which release gas at body temperature to cause the inflation of the chamber in the stomach.

**Super porous hydrogel systems**

To achieve prolong gastric retention time (GRT) super porous hydrogels of average pore size >100 micro meter is mandatory, Super porous hydrogel swell to equilibrium size within a minute due to rapid uptake of water by capillary wetting through numerous interconnected open pores [22]. They swell to a huge size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure created by gastric contraction.

**Magnetic Systems**

Magnetic Systems based on the simple principle that the dosage form contains a small internal magnet, and another magnet placed on the abdomen over the position of the stomach. However magnetic system seems to work, the external magnet must be positioned with a degree of precision [24].

**Mucoadhesive systems**

In this approach involves the usage of bioadhesive polymers that can be adhere to the epithelial surface of the GIT. This systems are used to localize a delivery device within the lumen of stomach to enhance the drug absorption process in a site-specific manner. The mechanisms of bio adhesive systems involves by the formation of hydrogen and electrostatic bonding at the mucus polymer boundary.

**Raft forming system**

The mechanism present in this system includes the formation of viscous cohesive gel upon contact of dosage form with gastric fluids in which each portion of the liquid swells forming a continuous layer called a raft. Buoyancy of system is achieved by the liberation of $CO_2$. Usually the system ingredients having a gel forming agent along with alkaline bicarbonates or carbonates which are responsible for the formation of $CO_2$ bubbles in the gel, enabling floating of raft on gastric fluid. Biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system and difficult to industrialize and not cost effective.

**High-density Systems**

A density close to 2.5 gm/$cm^3$ seems necessary for significant prolongation of gastric residence time [23]. sedimentation have been employed as a retention mechanism for pellets that are small enough to be accomidate in the folds or rugae of the stomach body near pyloric region, which is a region of stomach with the lowest position in an upright posture. Sedimentation depends more on density than on diameter of the pellets. Most widely used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder. Dense pellets (approximately 3g/cm3) settled in rugae and also have ability to withstand againest the peristaltic movements produced by the stomach wall. With the high dense systems, the GI transit time can be enhanced from an average of 5.8–25 hours.

**Unfoldable, Expandable and Swellable systems**

To withstand gastric transit, a dosage form in the stomach should be bigger than pyloric sphincter. And the dosage form must be small enough to be swallowed, and should not cause gastric obstruction. Unfoldable systems are formulated with biodegradable polymers.

They are available in various geometric forms like ring, tetrahedron or planner membrane of bio erodible polymer compressed within a capsule which extends in the stomach [25].

Swellable systems are retained in the gastric cavity due to their mechanical properties. The swelling due to osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid.

**Formulation considerations for GRDDS**

1) Dosage form should have full degradation and evacuation of the system once the drug release is completed
2) Dosage form should have sufficient drug loading capacity.
3) Dosage form should control the drug release profile.
4) Dosage form should not have other local adverse effects.

## POLYMERS EMPLOYED IN GRDDS

***Mucoadhesive polymers***

Poly ethylene oxide Esters of haluronic acid, Polyvinyl acetate, Polylactide-co-glycolides, Polycaprolactones, Polyalkyl cyanoacrylates, Polyphosphoesters, Chitosan [26]. Polylactides, Polyglycolides, Ethylene glycol etc.

***Natural polymers***

Tragacanth, Locust gum, Gelatin, Isapgulla (Psyllium) [27]. Sodium Alginate, Pectin, Guar gum, Carrageenan, Okra gum, Chitosan Tamarind gum, Hibiscus rosasinensis, etc.

***Synthetic polymers:***

Sodium Carboxy methyl cellulose ,Polyalkylene glycols, Esters and halides Polymethacrylic acid, HPMC K4M, HPMC K 100M, Carbopol 934 p, Ethyl cellulose Methyl cellulose, Polyvinyl alcohol, Polyamides, Polycarbonates, Polymethyl Methacrylic acid, HPC, HEC etc.,

## EVALUATION PARAMETERS FOR FDDS

***Hardness***

Hardness or tablet crushing strength (fc ), it is the force required to break a tablet in a diametric Compression was measured using Monsanto or Pfizer tablet hardness tester. It is expressed in kg/cm2.

***Thickness***

Thickness and diameter of ten tablets were measured using vernier calipers.

***Weight variation:***

20 tablets were selected at random, weigh Individually and weight together for the determination of average weight of tablets.

***Friability***

The friability test was carried out in Roch Friabilator. Ten tablets were weighted (Wo) initially and kept in a rotating drum. Then the tablets were subjected to 100 falls from a height of 6 inch. After completion of 100 rotation, the tablets were again weighted (W1).

% Weight loss or friability (f) = $(1 - w1/ w0) \times 100$

***Buoyancy lag time***

A tablet was introduces in to beaker containing 100ml of 0.1N HCL. The time taken by the tablet to come up to the surface and floated was taken as the buoyancy lag time. An average of three determinations from each batch was considered.

***Content uniformity***

The drug content in each formulation was determined by triturating 20 tablets and 10 mg weight of powder was taken in volumetric flask and make up the volume of 100ml with solvent, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically in UV.

***Floating time***

The test for floating time measurement is usually performed in stimulated gastric fluid or 0.1N HCl maintained at $37^0$C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 N HCl as the dissolution medium , the time for which the dosage form floats is termed as the floating or flotation time.

***X-Ray/gamma scintigraphy***

X-Ray/Gamma Scintigraphy helps to locate dosag e form in the gastrointestinal tract (GIT), by which one can i nterprit and correlate the gastric emptying time and the pass age of dosageform in the GIT. Here the inclusion of a radio-opaquematerial Barium sulphate into a solid dosage form enables it to be visualized by X-rays. In case of γ-scintigraphy, the γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GIT [28].

***Disintegration time***

In vitro disintegration time was determined using disintegration test apparatus. tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube and disintegration medium was placed in apparatus. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured.

***Dissolution studies***

Dissolution tests are performed using the dissolution apparatus containing 900 ml of 0.1 N Hcl maintained at $37^0$C as the dissolution medium. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

## CONCLUSION

Buoyant mechanism has been utilized in the development of different anti-reflux formulations. Floating delivery system has been considered as a most effective strategy for the treatment of localised infections in stomach or duodenum and drastically declines the fluctuations in the plasma drug concentrations that results from delayed gastric emptying. Floating drug delivery system efficiently increases the bioavailability of drugs that are having narrow absorption window. FDDS promises to be a potential approach for gastric retention for the effective treatment of local infections in stomach and upper segment of intestine.

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