Review Article

Gastric Retentive Controlled Drug Delivery: An Overview

Bharati V. Bakde[1*], Madhuri Channawar[1], Anil V. Chandewar[1]and B. Mishra[2]

[1]Pataldhamal Wadhwani College of Pharmacy Yavatmal, Maharashtra, India.
[2]Banaras Hindu University, Varanasi, Uttar Pradesh, India.

ABSTRACT
The promise of gastric retentive drug delivery systems has propagated numerous inventions. The therapeutic window of many drugs is limited by their short circulating half-life and absorption via a defined segment of the GI tract. Four technologies have involved a substantial number of human clinical trials: floating, mucoadhesion, density modification, and expansion. The floating drug delivery system can remain in the gastric region for several hours via float on the gastric contents and hence significantly prolong the gastric residence time of drugs. Here the stomach may be used as a 'depot' for sustained release (SR) dosage forms which can be affected by gastric emptying time. Region-specific and narrow absorption and poor bioavailability of drug promoted the invention of floating drug delivery system. Although the goal remains valuable, the promise of gastric retentive drug delivery systems can be fulfilled in near future.

Keywords: gastric retentive drug delivery systems, floating drug delivery system, sustained release.

INTRODUCTION

Oral ingestion has long been the most convenient versatile and commonly employed route of drug delivery due to its advantages like ease of administration, high patient compliance, least sterility constraints and flexibility in the design of the dosage form.

However, the therapeutic window of many drugs is limited by their short circulating half-life and absorption via a defined segment of the GI tract. Such pharmacokinetic limitations in many cases lead to frequent dosing of these medications to achieve the required therapeutic effect. This result in "pill burden" and consequently, decreased patient compliance. The phenomena of absorption via a limited part of the GI tract have been termed the "narrow absorption window". Once the dosage form passes the absorption window, the drug will be neither bioavailable nor effective. In extreme cases, drugs that are insufficiently absorbed cannot be delivered entirely, and are either given by a parental route, or the development of such medication, which is otherwise safe and effective.[1]

Scientists make a success to develop a system that can overcome such problems and this has led to the development of oral gastro retentive floating drug delivery system. The floating drug delivery system can remain in the gastric region for several hours via float on the gastric contents and hence significantly prolong the gastric residence time of drugs. The pharmaceutical dosage form with gastro retentive properties would enable an extended absorption phase of those drugs with narrow absorption window. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract.[2]

It is well recognized that the stomach may be used as a 'depot' for sustained release (SR) dosage forms which can be affected by gastric emptying time. The process of gastric emptying occurs both during fasting and fed states; however, the pattern of motility differs markedly in these two states. In the fasted state, it is characterized by an interdigestive series of electrical events which cycle both

through the stomach and small intestine every 2-3 h[3]. This activity is called the interdigestive myoelectric cycle or migrating myoelectric complex (MMC), which is often divided into four consecutive phases as described by Wilson and Washington.[7]

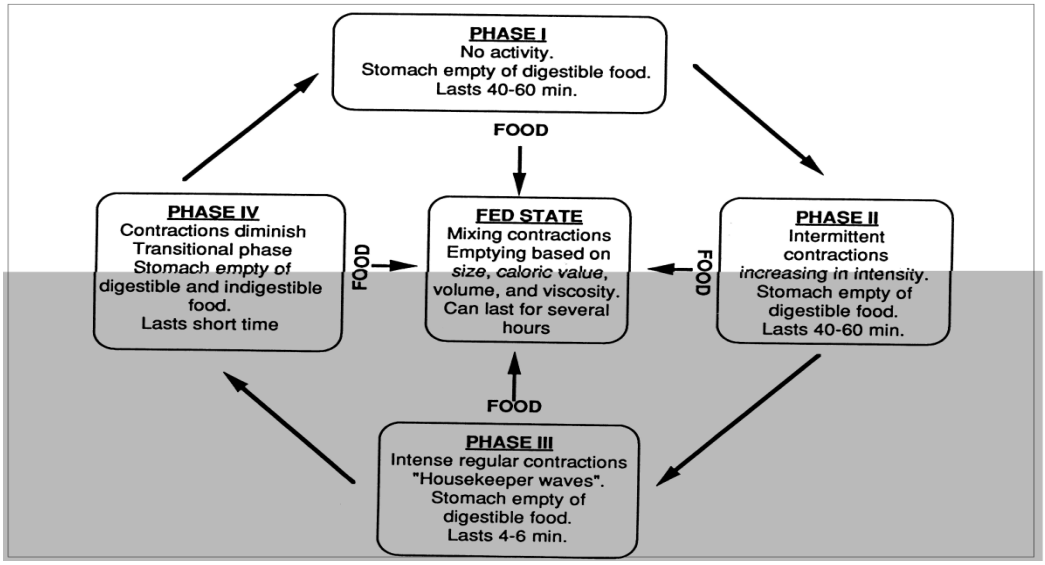

Fig. 1: Interdigestive myoelectric cycle

Need for Gastroretention

- Some drugs display region-specific absorption that can be related to differential drug solubility and stability in different regions of the intestine as a result of changes in environmental pH, degradation by enzymes present in the lumen of the intestine or interaction with endogenous components such as bile.[4]
- Many drugs show poor bioavailability (BA) in the presence of intestinal metabolic enzymes like cytochrome P450 (CYP3A), abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with levels rising slightly from the duodenum to the jejunum and declining in the ileum and colon. [5]
- An absorption window exists because of physiological, physicochemical, or biochemical factors. Drugs having site-specific absorption are difficult to design as oral CRDDS because only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. [6]
- After crossing the absorption window, the released drug goes waste with negligible or no absorption. This phenomenon considerably decreases the time available for drug absorption after its release and expose the success of the delivery system
- The GRDDS can improve the controlled delivery of the drugs which exhibit an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site, thus ensuring its optimal bioavailability

Approaches to Increase Gastric Residence Time [7, 8]

A number of systems have been used to increase the gastric retention time (GRT) of dosage forms by employing a variety of concepts. These systems have been classified according to the basic principles of gastric retention

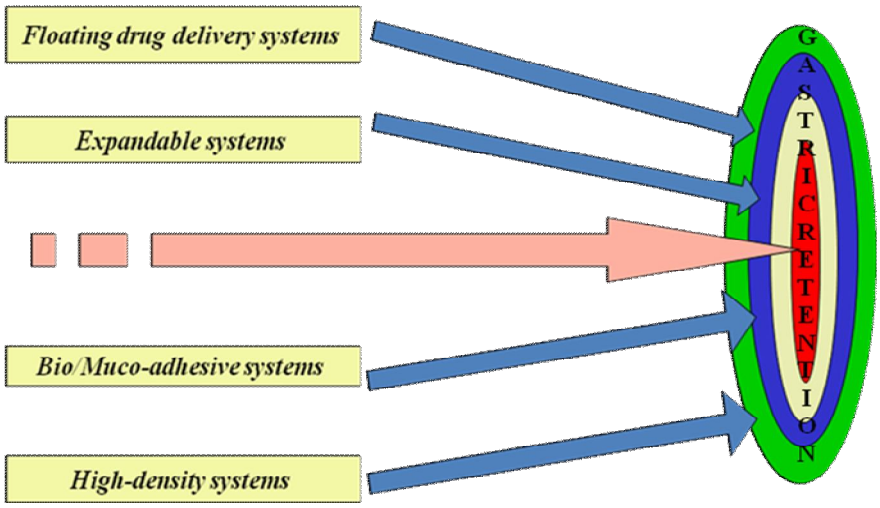

Fig. 2: Different approaches of gastric retention

Floating Drug Delivery Systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids (<1 g/cm^3) and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

Classification of Floating Drug Delivery[9]

Based on the mechanism of buoyancy FDDS broadly classified into two main classes: effervescent and non-effervescent floating systems.

(a) Effervescent Floating system

These are matrix types of systems prepared with the help of swelleble polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to dosage forms.

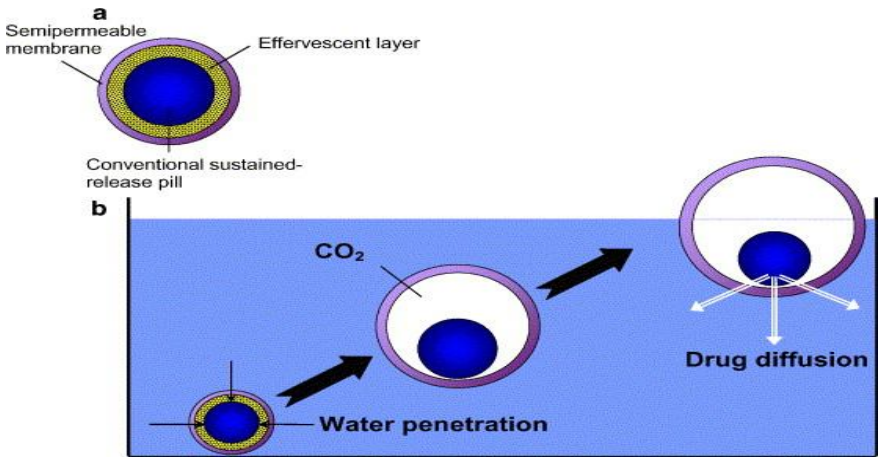

Fig. 3: Effervescent Floating Drug Delivery System

(b) Non-Effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. [10] The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxy propyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

This system can be further divided into four sub-types:

(i) Colloidal Gel Barrier System

Sheth and Tossounian first designated this 'Hydrodynamically balanced system.'[11]such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., Hydroxy Propyl Cellulose, Hydroxy Ethyl Cellulose, Hydroxy Propyl Methyl Cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

Swellable Matrices as Systems for Oral Delivery

Monolithic devices or matrices represent a substantial part of the drug delivery systems. Matrices containing swellable polymers are referred to as hydrogel matrices, polymeric matrices involving moving boundaries, swellable controlled release systems or hydrophilic matrix tablets. Swellable matrices for oral administration are commonly manufactured as tablets by the compression of hydrophilic micro particulate powders. Therefore, the most appropriate classification for these systems is swellable matrix tablets. They are constituted of a blend of drug and one or more hydrophilic polymer. In general drug release from swellable matrix tablets is based on glassy-rubbery transition of polymer as a result of water penetration into the matrix.

Whereas the primary factors which can influence drug release rate to greater or lesser degree are interactions between water, polymer and drug and various formulations variables, such as

- polymer grade,
- drug/polymer ratio,
- drug solubility, and
- drug and polymer particle size

However the central element of the mechanism of drug release is the gel layer (rubbery polymer) which is formed around the matrix. The gel layer is capable of preventing matrix disintegration and further rapid water penetration.

Phenomena determining gel layer thickness are water penetration, polymer swelling, and drug dissolution, diffusion and matrix erosion.

Finally, drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer. In order to follow gel layer dynamics during drug release in swellable matrices, the boundaries of such a layer have to be defined. It is well known that gel layer is physically separated by two sharp fronts. The boundaries separating swollen matrix from solvent and glassy from rubbery polymer. However the possibility of the presence of a third front inside the gel layer has also been described. This additional front was termed undissolved drug front or diffusion front and turned out to be a function of drug solubility and loading. Its presence can create conditions such that the release will be more controlled by drug dissolution than by polymer swelling. Thus in swellable matrix tablet three fronts could be expected:

1) The swelling front - The boundary between the still glassy polymer and its rubbery state.

2) The diffusion front - The boundary in the gel layer between the solid, has yet undissolved drug and the dissolved drug.
3) The erosion front - The boundary between the matrix and the dissolution medium.

(ii) Microporous Compartment System

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. [12] The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, 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 for continuous transport across the intestine for absorption.

(iii) Alginate Beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. [20] Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

(iv)Hollow Microspheres / Microballoon

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. [21] The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h.

Expandable Systems

Expandable gastroretentive dosage forms (GRDFs) have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach. [13] Gastroretentivity is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach. Positive results were obtained in preclinical and clinical studies evaluating the GRT of expandable GRDFs. Narrow absorption window drugs compounded in such systems have improved *in vivo* absorption properties.

Bio / Muco-Adhesive Systems

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site- specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. [14] Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc.

High-Density Systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rogue or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately $3g/cm^{3)}$ trapped in rogue also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. [15] Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to $1.5–2.4g/cm^{3.}$

Mechanism of Floating Systems

When floating drug delivery system (FDDS) are administered orally, they retained in the stomach for a prolonged period of time by virtue of their floating properties, which can be acquired by several means. One of the basic mechanisms beside the floatation can be explained by the concept of density. Mathematically density may be defined as; [16]

Density (ρ) = mass (m) / volume (v)

In case of effervescent floating dosage form which is composed of gas generating agents and swelleble polymers when come in contacts with acidic content of the stomach, CO_2 is librated and is trapped in gellified hydrocolloid, which creates upward motion of dosage form and thus reducing the density of system and making it float on gastric content.

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so 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 the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of gastric contents.

The floating force (F) can be mathematically expressed as; [17]

F = F buoyancy - F gravity

Equation 1 can be rewritten as,

$$F = (D_f - D_s)\, g\, v$$

Where,

F= total vertical force,
D_f = fluid density,
D_s = object density,
v = volume
g = acceleration due to gravity.

Drug Candidates Criteria for Formulation of Floating Oral Sustained Release Systems: [18, 19]

- Desirable Half-Life (2 -8 h)
- High Therapeutic Index of the drug
- Small Dose of the drug
- Aqueous Solubility of the drug
- GI Absorption of the drug
- Drug Stability to Wide pH Range, GI Enzymes and Flora
- First Pass Clearance of the drug

Advantages of Floating Drug Delivery Systems [20- 22]

- Enhanced Bioavailability
- Enhanced First-Pass Biotransformation
- Sustained Drug Delivery/Reduced Frequency Of Dosing
- Targeted Therapy For Local Ailments In The Upper GIT
- Reduced Fluctuations of Drug Concentration

- Improved Selectivity In Receptor Activation
- Reduced Counter-Activity of The Body
- Extended Time Over Critical (Effective) Concentration
- Minimized Adverse Activity at the Colon
- Site Specific Drug Delivery

PATENTS ON GRDDS

Table 1: List of some patent gastro retentive drug delivery systems

US Patent Number	Patent Title
6,207,197	Gastro retentive controlled-release microspheres for improved drug delivery
5,972,389	Gastric retention , oral drug dosage forms for the controlled release of sparingly soluble drugs and insoluble matter
5,443,843	Gastro-retentive systems for controlled-release
5,232,704	Sustained-release , bilayer buoyant dosage form
5,169,638	Buoyant controlled-release powder formulation
6,814,179	Floating sustained-release therapeutic composition
4,767,627	Drug delivery device that can be retained in the stomach for a controlled period of time.
4,167,558	Novel sustained-release formulations
4,126,672	Sustained-release pharmaceutical capsules
20030232895	Hydro gels having enhanced elasticity and mechanical strength properties
6,776,999	Expandable gastro retentive therapeutic system with prolonged stomach retention time
6,685,962	Gastro retentive controlled release pharmaceutical dosage forms
5,076,107	Apparatus and method for resultant-weight measuring system
4,844,905	Granule remaining in stomach
20020119192	Controlled release formulations for oral administration
20030021846	Active ingredient-containing floating forms comprising polyvinyl acetate and polyvinylpyrrolidone , their use and production
20030138486	Methods and dosage forms for improving the bioavailability of therapeutic agents

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