A Novel Technique in Gastroretentive Drug Delivery System- A Review
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Abstract: Various attempts have been made globally in the development of gastroretentive dosage forms to overcome physiological adversities, such as short gastric residence time, unpredictable gastric emptying time etc. These dosage forms can be retained in the stomach for prolonged period of time in a predetermined manner. Among various gastroretentive techniques such as high density system, floating drug delivery system, expandable drug delivery system, magnetic system, super porous hydrogel system etc floating drug delivery system is one of the promising approaches providing local delivery to the stomach and proximal small intestine revealing better bioavailability, improved therapeutic activity with substantial benefits for patients. This manuscript outlines the techniques for gastroretention with their mechanisms and which polymers can be used in this and also potential applications of gelucire in the design of floating drug delivery systems. Owing to its various beneficial properties, it is a favoured candidate for utilization in the floating dosage forms. Several recent attempts and advanced approaches exploiting gelucire as a potential carrier in the development of gastroretentive floating dosage forms and other gastroretentive approaches have been discussed.

Keywords: Gastroretentive Drug Delivery System, Novel Technique of Drug Delivery System,Review.

Introduction
Oral administration is the most convenient mode of drug delivery and is associated with superior patient compliance as compared to other modes of drug intake. However, oral administration has only limited use for important drugs, from various pharmacological categories, that have poor oral bioavailability due to incomplete absorption and/or degradation in the gastrointestinal (GI) tract. Some of these drugs are characterized by a narrow absorption window (NAW) at the upper part of the gastrointestinal tract. This is because the proximal part of the small intestine exhibits extended absorption properties (including larger gaps between the tight junctions, and dense active transporters). Despite the extensive absorption properties of the duodenum and jejunum, the extent of absorption at these sites is limited because the passage through this region is rapid. Enhancing the gastric residence time (GRT) of a NAW drug may significantly improve the net extent of its absorption.\(^1\)

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. The small intestinal transit time is an important parameter for drugs that are incompletely absorbed.\(^2\)

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also
for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.\(^3\)

Figure 1: (a) Conventional Dosage Form and (b) Gastric Retentive Drug Delivery System

Anatomy & Physiology of Stomach:

The stomach is divided into three anatomical region; Fundus, Body and Pylorus (or antrum). \(^4\) The proximal stomach consisted of Fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric content for gastric emptying. Gastric emptying occurs both in fasting as well as fed states. In case of fasted state an interdigestive series of electrical events occurs in cyclic manner both through the stomach and small intestine every 2 to 3 hours. The interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and the transit of dosage forms. It is characterized by four Phases:

Phase I – Period of no contraction (30-60 minutes)

Phase II – Period of intermittent contractions (20-40 minute).

Phase III – Period of regular contractions at the maximal frequency also known as housekeeper wave (10-20 minutes).

Phase IV – Period of transition between Phase III and Phase I (0-5 min.)\(^5\)

Fig. 2 Gastric motility pattern
Factors controlling gastric retention of dosage forms:

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm \(^6\). The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include:

1. **Density of dosage forms:**

   Density of the dosage form should be less than the gastric contents (1.004 gm/ml).

2. **Shape and size of the dosage form:**

   Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kiloponds per Square inch (KSI) is reported to have better GIT retention 90 to 100 % retention at 24 hours compared with other shapes.

3. **Food intake and its nature:**

   Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms. \(^3\)

4. **Effect of gender, posture and age:**

   Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down \(^7\).

**Suitable Drug Candidates for gastroretention:**

In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

- Narrow absorption window in GI tract, e.g., riboflavin and levodopa
- Primarily absorbed from stomach and upper part of GI tract, e.g., calcium supplements, chlordiazepoxide and cinnarazine
- Drugs that act locally in the stomach, e.g., antacids and misoprostol
- Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole
- Drugs that disturb normal colonic bacteria e.g., amoxicillin trihydrate \(^8\)

**Approaches for gastroretentive drug delivery system:**

To formulate a successful gastro-retentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS)/ floating drug delivery system, raft systems incorporating alginate gels, bioadhesive or mucoadhesive systems, high density systems, super porous hydrogels and magnetic systems. \(^9\)

1. **High density (sinking) system or non- floating drug delivery system:**

   This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm\(^3\)). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. The materials increase density by up to 1.5- 2.4 gm/cm\(^3\). A density close to 2.5 gm/cm\(^3\) seems necessary for
significant prolongation of gastric residence time. But, effectiveness of this system in human beings was not observed [10].

2. Bioadhesive or Mucoadhesive drug delivery systems:

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bioadhesive polymers are used and they can adhere to the epithelial surface in the stomach. Thus, they improve the prolongation of gastric retention. The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms are wetting theory, diffusion theory, absorption theory & electron theory.

Materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polyactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT). [11]

3. Expandable, unfoldable and swellable systems:

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system to prolong gastric retention time (GRT):
1) A small configuration for oral intake,
2) An expanded gastroretentive form, and
3) A final small form enabling evacuation following drug release from the device.

Thus, gastroretentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastroretentive drug delivery. 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. Swellable systems are also retained in the gastrointestinal tract (GIT) due to their mechanical properties. [2]

4. Super porous hydrogel systems:

These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size > 100 micro miter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material [12].

5. Magnetic Systems:

This approach to enhance the gastric retention time (GRT) 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. [8]

6. Floating drug delivery system (FDDS):

FDDS is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability [13]. This system is desirable for drugs with and absorption window in the stomach or in the upper small intestine. [14] This have a less density then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate flora prolonged period and the drug is released slowly as a 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 fluctuation in plasma drug concentration. [14]
a) Effervescent Systems:

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach; CO$_2$ is released, causing the formulation to float in the stomach. \[^{[15]}\]

1. Volatile liquid containing systems:

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the Inflatable systems from the stomach.

2. Gas generating system:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO$_2$, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime. \[^{[15]}\] How the dosage form float is shown in the following figure.

![Fig 3: mechanism of gas generating system](image)

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. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl 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: \[^{[16]}\]

1. Colloidal gel barrier system.
2. Microporous compartment system.
3. Alginate beads.
4. Hollow microspheres or Microballoons.

1. Colloidal gel barrier system:

The most commonly used excipient in noneffervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polycrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating
dosage forms involves intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration 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.

Sheth and Tossounian developed a HBS capsule containing a mixture of a drug and hydrocolloids. Upon contact with gastric fluid, the capsule shell dissolved; the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time.\textsuperscript{[13]}

![Fig:4 Working principle of the hydrodynamically balanced system (HBS). The hard gelatine capsule contains a special formulation of hydrocolloids, which swell into a gelatinous mass upon contact with gastric fluids.]

2. 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. 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 flotation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the gastric fluid to an extent that it prevents their exit from the drug and carries the dissolved drug for continuous transport across the intestine for absorption.\textsuperscript{[17]}

3. Alginate beads:

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at \(-40^\circ\text{C}\) for 24 hours, leading to the formation of porous system, which can maintain a floating force over 12 hours.\textsuperscript{[18]}

4. Hollow microspheres:

Hollow microspheres (microballoons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40\(^\circ\text{C}\). The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours in vitro.\textsuperscript{[9]}

c) Lipidic carrier-gelucire in floating system:

For more than two decades, considerable use of polymeric materials to deliver bioactive agents has attracted attention of various investigators throughout the scientific community. Polymers are generally
employed in the development of floating drug delivery systems so as to target the delivery of drug at a specific region in the GIT i.e. stomach. Numerous materials have been studied extensively in the design of drug delivery systems and one of the favoured excipients is Gelucire. Gelucire is a family of vehicles derived from mixtures of mono-, di- and tri-glycerides with polyethylene glycol (PEG) esters of fatty acids. They are inert, semi-solid, waxy amphiphilic excipients that are enormously used in controlled-release matrices in order to enhance the physicochemical properties of drug. Gelucire can be used for different purposes according to their chemical composition. Gelucire 44/14 possesses surfactant and self emulsifying properties which can be used as meltable binder by melt granulation of poorly water-soluble active substances. In contact with aqueous fluids it forms a fine emulsion which solubilises the active substances and hence increases its oral bioavailability.

Gelucire having low HLB value can be used to reduce the dissolution rate of drugs on the other hand, Gelucire with high HLB value can be used for faster release of drugs. In the designation of its name, for example, Gelucire 54/02, 54 indicates melting point while 02 indicates its HLB value. The lipidic materials such as Gelucire are considered as an alternative to other polymers employed in sustained release formulations because of following advantages such as

- Low melt viscosity, thus obviating the need of organic solvents for solubilisation.
- Absence of toxic impurities such as residual monomer catalysts and initiators.
- Potential biocompatibility and biodegradability.
- Prevention of gastric irritation by forming a coat around the gastric irritant drug.

Physicochemical properties

Each component of gelucire presents different affinity for water and act as surfactant and co-surfactant. Di- and triglycerides are lipophilic in nature. Certain gelucires are produced by the reaction of hydrogenated palm kernel oil and polyethylene glycol, PEG 33 (Gelucire 44/14). It contains PEG 33 esters, glycerides, unreacted PEG 33 and a small amount of glycerol. The different kinds of gelucires are characterized by a wide range of melting points from about 33°C to about 64°C, and most commonly from about 35°C to about 55°C and by a variety of HLB values from about 1 to about 14, most commonly from about 7 to about 14. The hydrophilic property of the polymer is quite useful in the dissolution enhancement as well as in control release formulation.

Recent Research Endeavours

Extensive research efforts have been undertaken worldwide for the development of gelucire based gastric floating drug delivery systems. Different grades of gelucire have been utilized by investigators for the formulation of various single and multiple units floating dosage forms. Important research endeavours undertaken by several investigators globally exploiting gelucire as a potential carrier in floating dosage forms are discussed in the subsequent section:

1. Gelucire Beads:

Jain et al developed beads of metformin hydrochloride for floating delivery using Gelucire 43/01. The beads were evaluated for particle size, surface morphology, percent drug entrapment, percent yield, DSC, in vitro floating ability, and in vitro drug release. Ageing effect on storage was evaluated using HSM, DSC, SEM and in vitro floating ability. Formed beads were sufficiently hard and spherical in shape and demonstrated favourable in vitro floating ability. Prepared formulations showed better controlled release behaviour when compared with its conventional dosage form and comparable release profile with marketed sustained release product. From the observations, it may be concluded that beads of Gelucire 43/01 could be served as an effective carrier for highly water soluble anti-hyperglycaemic drugs for controlled delivery.

2. Gelucire Tablet:

Thakkar et al fabricated and evaluated levofloxacin hemihydrates floating formulation. Nine formulations of floating tablets were prepared by direct compression method using Gelucire 43/01 (hydrophobic) and hydroxypropyl methylcellulose (hydrophilic) polymer in different ratios. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyancy and in vitro release studies. Various models were used to estimate kinetics of drug release. The criteria for selecting the most appropriate model were based on the goodness-of-fit test and lowest sum of square residual and Fischer’s
ratio. Release rate of drug was decreased by increasing the proportion of Gelucire 43/01, 5 to 40%. The release rate of drug from matrices was found to be function of hydrophilic and hydrophobic polymer ratio. \[^{29}\]

3. Gelucire Granules:

Patel et al developed floating granules of ranitidine hydrochloride using Gelucire 43/01 and optimized the formulation employing factorial design. The multiunit floating system of a highly water soluble drug i.e. ranitidine hydrochloride was developed using compritol, Gelucire 50/13 and Gelucire 43/01 as lipid carriers and by employing melt granulation technique. Ethyl cellulose, methyl cellulose and hydroxypropyl methyl cellulose were evaluated as release rate modifiers. A 32 full factorial design was used for optimization by taking the amounts of Gelucire 43/01 (X1) and ethyl cellulose (X2) as independent variables, and the percentage drug released in 1st (Q1), 5th (Q5) and 10th (Q10) hours as dependent variables. Results revealed that the moderate amount of Gelucire 43/01 and ethyl cellulose provides desired release of ranitidine hydrochloride from a floating system. \[^{30}\]

In another study employing the similar formulation technique, Shimpi et al prepared and evaluated diltiazem hydrochloride-Gelucire 43/01 floating granules by utilizing melt granulation technique. The granules were evaluated for in vitro and in vivo floating ability, surface topography and in vitro drug release. Aging effect on storage was evaluated using SEM, HSPM, DSC and in vitro drug release. Granules were retained in stomach for at least 6 hours. Surface topography, HSPM, DSC study of the aged samples showed phase transformation of gelucires causing significant increase in drug release. It was concluded that gelucire 43/01, hydrophobic lipid can be considered as an effective carrier for design of multiunit floating drug delivery system. \[^{31}\]

Characterization of gelucire containing formulations

In order to characterize gelucire containing formulations, several parameters can be studied including the physical stability of drug in the matrix systems. Moreover, crystallinity and polymorphic and/or pseudo-polymorphic form of drug in a matrix containing gelucire can be assessed by differential scanning calorimetry (DSC) and powder X-ray diffractometry (PXRD). Diffuse reflectance Infrared Fourier Transform spectroscopy (DRIFTS) can also be employed to identify the nature of interactions between drug and the constituents of the polymeric matrix. However, several other techniques such as hot stage microscopy (HSM), hot stage polarizing microscopy (HSPM), scanning electron microscopy (SEM), and saturation solubility of formulation are available by which gelucire containing formulations can be analyzed. \[^{24}\]

Evaluation parameters of stomach specific DDS \[^{[3, 16, 32-36]}\]

Weight variation:

Uniformity of Weight according to Indian pharmacopoeia, 20 tablets were selected at random, weight together and individually for the determination of weight of tablets. The mean and standard deviations were calculated.

Hardness:

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric Compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm\(^2\).

Thickness:

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

Friability:

Friability The friability test was carried out in Roche Friabilator. Ten tablets were weighted (Wo) initially and put in a rotating drum. Then the tablets were subjected to 100 falls of 6 in. height. After completion of rotation, the tablets were again weighted (W).

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\% \text{ Weight loss or friability (f)} = (1 - \frac{w}{w_0}) \times 100
\]
Disintegration time:

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

Buoyancy time:

A tablet was introduced into a 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 time. An average of three determinations from each batch was taken for the floating forms.

Floating time and dissolution:

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

Drug release:

Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

Content uniformity:

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of solvent, followed by stirring for 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically in UV.

Conclusion:

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. GRDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention. Outstanding scientific progress has made, demonstrating the potential applications of gelucire in gastroretentive floating approaches. Gelucire has been successfully utilized by many investigators globally in the development of floating dosage forms. These lipidic carriers have emerged as promising and efficacious agents with myriad spectrum of desired characteristics for effective drug delivery. It is further anticipated that the use of gelucire as an indomitable excipient will expand the scope of new drug delivery system.

References


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