Gelucire mediated gastric floating drug delivery systems

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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, 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 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 have been discussed.

Keywords: Floating drug delivery system, gelucire, gastric residence time, gastroretentive

INTRODUCTION

Oral route of drug administration remains the most favoured preference for majority of therapeutic applications, with obvious advantages including ease of administration, patient compliance and flexibility in formulation [1]. Numerous oral controlled drug delivery systems have been investigated which provide drug release at a predetermined, predictable rate and also optimize the therapeutic effect by controlling the drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility [3]. Gastric emptying time in humans which normally averages 2-3 h through the main absorption area can result in an incomplete drug release from controlled drug delivery system thus leading to diminished efficacy of an administered dose [4]. The ability of a dosage form to prolong and control the gastric emptying time is a valuable asset for drugs acting locally in GIT [5]. These considerations led to the development of gastroretentive dosage forms possessing gastric retention capabilities for prolonged period of time and thus minimizing dosing frequency of the drug [4].

Gastroretentive dosage forms are one of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the GIT [6]. These are designed to be retained in the stomach for an extended duration in order to improve the residence time of dosage forms, thereby leading to enhanced bioavailability of the drug [7,8]. They enable oral therapy for drugs with a narrow absorption window in the upper part of GIT or drugs with a poor stability in the colon. Furthermore, the drug can act locally within the stomach and prolonged intimate contact with absorbing membrane increases its efficacy [9]. These dosage forms are also particularly appropriate for drugs with low solubility at high pH values [10]. Over the past few decades, several dosage forms have been designed to prolong gastric residence time (GRT) of the drug. These include high density system, floating systems, expandable systems, superporous hydrogel systems, muco/bioadhesive systems magnetic systems, etc. Out of above different approaches, the most convenient, economical and logical one is gastric floating drug delivery systems [11]. Incorporation of the drug in the floating dosage form provides a mean to utilize all the pharmacokinetic and
The pharmacodynamic advantages of controlled release dosage forms [12]. Floating drug delivery systems (FDDS) can be formulated by employing various excipients of natural or synthetic origin. Several floating dosage forms that have been explored may include granules, powders, capsules, tablets, laminated films, hollow microspheres, etc. [7]. Also, there are several commercial preparations available in the market based on gastroretentive approach; some are illustrated in Table 1 [13,14].

**Table 1: Marketed products based on gastroretentive approach**

<table>
<thead>
<tr>
<th>Marketed product</th>
<th>Drug</th>
<th>Company</th>
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<tbody>
<tr>
<td>Glumetza</td>
<td>Metformin</td>
<td>Depomed</td>
</tr>
<tr>
<td>Gabapentin GR</td>
<td>Gabapentin</td>
<td>Depomed</td>
</tr>
<tr>
<td>Cytotec</td>
<td>Misoprostol</td>
<td>Pharmacia</td>
</tr>
<tr>
<td>Valrelease</td>
<td>Diazepam</td>
<td>Roche</td>
</tr>
<tr>
<td>Madopar HBS</td>
<td>L-Dopa + Benserazide</td>
<td>Roche</td>
</tr>
<tr>
<td>Baclofen ER</td>
<td>Baclofen</td>
<td>Sun Pharma</td>
</tr>
<tr>
<td>Cifran OD</td>
<td>Ciprofloxacin</td>
<td>Ranbaxy</td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Ranbaxy</td>
</tr>
<tr>
<td>Coreg CR</td>
<td>Carvedilol</td>
<td>Flamel</td>
</tr>
<tr>
<td>Liquid Gaviscon</td>
<td>Antacid</td>
<td>Glaxo Smith Klein</td>
</tr>
<tr>
<td>Topalkan</td>
<td>Antacid</td>
<td>Pierre Fabre Drug</td>
</tr>
<tr>
<td>ProQuin</td>
<td>Ciprofloxacin</td>
<td>Depomed</td>
</tr>
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**Factors Affecting Gastric Retention [15-21]**

Several factors which influence the gastric retention of drugs are shown in the following section:

- **Effect of density:** Systems having a density higher than gastric contents sink to the bottom of the stomach while low density drug delivery systems float on the surface.
- **Effect of size:** Timmermans et al found that floating units with a diameter equal to or less than 7.5 mm had longer GRT as compared to non floating units.
- **Effect of shape:** Tetrahedron and ring shaped devices have a better GRT as compared with other shapes.
- **Effect of nature of meal:** Oily layers formed by fats on gastric contents are emptied later than the other.
- **Effect of caloric value:** Increase in acidity and caloric value slows down the gastric emptying rate.
- **Effect of food:** Sangekar et al found that presence of food in the stomach appears to significantly prolong the gastric retention of floating dosage forms.
- **Effect of gender:** Generally females have a slower gastric emptying rate than males.
- **Effect of volume ingested:** Larger the volume, faster is the emptying. Fluids taken at body temperature leave the stomach more quickly than colder or warmer fluids.
- **Effect of posture:** GRT can vary between supine and upright ambulatory states of the patient.
- **Effect of concomitant drug administration:** Drugs like anticholinergics (Atropine); opiates (Codeine); prokinetic agents (Metoclopramide, Cisapride); laxatives and purgatives affect the GRT. Diseased states like diabetes, Crohn’s disease also affect the gastric emptying rate.
- **Effect of age:** Young people have faster gastric emptying rate as compared to elderly subjects.

**FLOATING DRUG DELIVERY SYSTEMS**

Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time [22,23]. This results in an enhanced gastric retention time along with a better control of the fluctuations in plasma drug concentration [24]. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films, hollow microspheres, etc. It is pertinent to note that presence of gastric content is needed to allow the proper achievement of buoyancy retention principle [25]. Based on the mechanism of buoyancy, these systems can be effervescent or non-effervescent in nature [26]:

- **Effervescent systems:** These buoyant systems utilize matrices prepared with swellable polymers such as methocel (HPMC), polysaccharides, e.g. chitosan and various effervescent components, e.g. sodium bicarbonate, citric acid and tartaric acid or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated that is entrapped in the gellified hydrocolloid which produces an upward motion of the dosage form and maintains its buoyancy.

- **Non-effervescent systems:** The most commonly used polymers for the preparation of these systems are gel forming or highly swellable type hydrocolloids, polysaccharides and matrix forming polymers like polycarbonate, polyacrylate, polymethacrylate and polystyrene. The formulation approach involves intimate mixing of drug with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration and attains a bulk density of less than unity. The air entrapped within the swollen polymer matrix provides buoyancy to the dosage.
form. Moreover, swollen gel structure acts as a reservoir and allows sustained release of drug through the gelatinous barrier.

ADVANTAGES OF FDDS
Gastroretentive floating drug delivery system offers numerous advantages over conventional drug delivery system [12,27]. These advantages include:

- Improved drug absorption, due to increased GRT.
- Controlled delivery of drugs.
- Site specific drug delivery.
- Delivery of drugs for local action in the stomach.
- Minimizing the mucosal irritation due to release of drug at a controlled rate.
- Treatment of gastrointestinal disorders such as gastro-oesophageal reflux.
- Convenient equipments for manufacture.
- Minimizes or eliminates the side effects by delivering the drugs at the active site.
- Ease of administration and better patient compliance.

EVALUATION OF FDDS
Several techniques are available for evaluation of gastroretentive performance of floating drug delivery systems. These include determination of floating behaviour, floating lag time, floating kinetics, in vitro dissolution studies, swelling characteristics and stability studies. Evaluation parameters of tablets include characterization of hardness, weight variation, drug content and friability. In case of multiparticulate drug delivery systems, differential scanning calorimetry, particle size analysis, flow properties, surface morphology and mechanical properties are performed additionally so as to determine the morphological characteristics of the formulation. In vivo gastric retention of floating dosage form is usually determined by gamma-scintigraphy, roentgenography, magnetic resonance imaging etc. [12,21,28].

LIPIDIC CARRIER-GELUCIRE IN FLOATING SYSTEMS
For more than two decades, considerable use of polymeric materials to deliver bioactive agents has attracted attention of various investigators throughout the scientific community. Polymer chemists, chemical engineers along with pharmaceutical scientists are highly engaged in bringing out the design and development of various controlled drug delivery systems [29]. 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 [30]. Numerous materials have been studied extensively in the design of drug delivery systems [31] 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 [32] 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 [33]. 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 [34]. In the designation of its name, for example, Gelucire 54/02, 54 indicates melting point while 02 indicates its HLB value [35]. The lipidic materials such as Gelucire are considered as an alternative to other polymers employed in sustained release formulations because of following advantages [36,37] 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 tri-glycerides are lipophilic in nature [38]. 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 [35]. 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 [39]. The hydrophilic property of the polymer is quite useful in the dissolution enhancement as well as in control release formulations [33].
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 [35].

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:

Chauhan et al prepared and evaluated floating risedronate sodium-Gelucire 39/01 matrices using melt solidification method. The sustained release floating matrices were evaluated for in vitro and in vivo floating ability and in vitro drug release. Owing to extreme hydrophobicity and low density, Gelucire 39/01 may be considered an appropriate carrier for designing sustained release floating drug delivery systems. SEM, HSM and DSC showed that ageing of Gelucire 39/01 is responsible for an increase in drug release [40]. Working on similar grounds, Siripuram et al formulated floating sustained-release matrices of metoprolol succinate using Gelucire 43/01 and Gelucire 44/14 by melt solidification technique. The in vitro and in vivo characteristics of the prepared matrices were evaluated. Drug release data were analyzed by various mathematical models, and the mean dissolution time, dissolution efficiency and similarity factor were determined in optimizing formulations. DSC and FTIR spectroscopy showed no chemical interaction between drug and carriers. Results indicated that Gelucire 43/01 is an appropriate carrier for the development of sustained-release floating drug delivery systems and Gelucire 44/14, a highly hydrophilic and lipophilic balance (HLB) excipient acts as release enhancer in the formulations [41].

Furthermore, 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-hyperglycemic drugs for controlled delivery [42]. Similarly utilizing the same grade of material, Thakkar et al fabricated and evaluated levofloxacin hemihydrate 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 [43].

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 [44]. 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 [45]. Furthermore, Shah et al prepared gatifloxacin lipid granules by the melt granulation technique and evaluated for in vitro floating and drug release. Ethyl cellulose was taken as release rate modifier. A 3^2 full factorial design was used for optimization by taking the amounts of gelucire 39/01 (X_1) and ethyl cellulose (X_2) as independent variables, and the percentage drug released in 1 (Y_1), 6 (Y_6) and 12 (Y_12) h as dependent variable. The study indicated that the hydrophobic lipid, Gelucire 39/01 can be considered an effective carrier for design of a multiunit floating drug delivery system for gatifloxacin [46].

Soberanez et al explored the application of gelucire 39/01 for the design of sustained release multi-unit and single-unit floating systems of metronidazole. Metronidazole-gelucire 39/01 granules were prepared by melt granulation technique, alone and after addition of HPMC K15M or sodium cross-linked carboxymethylcellulose (Carmacel). The formulations were evaluated in vitro for their floating ability and drug release. It was observed that increasing proportions of gelucire decrease the initial fast release of the drug that stabilizes and practically come to an end thereafter. The granules floating time were greater than 6 hours. It was concluded that gelucire 39/01 can be considered as a carrier for design of floating drug delivery systems only when mixed with dissolution enhancers that increase the permeability of the almost impermeable matrix [47]. Agrawal et al formulated and evaluated floating microspheres of orlistat, lipase inhibitor used as an antiobesity agent. Drug loaded carrier (DLC) was used to prepare microspheres (MDLC) by hydrophobic congealable disperse-phase encapsulation method using gelucire 43/01 as wax phase. Similarly drug loaded microspheres without calcium silicate (MDL) were also prepared using only gelucire 43/01. The effects of formulation and process variables on particle size, buoyancy, entrapment efficiency and drug release from microspheres were studied and optimized. The designed formulation (MDLC) was found to be floating in gastric fluid and orlistat release was found to prolong significantly [48]. In another research endeavour, Shah et al prepared in situ cubic phase transforming system of glyceryl monooleate which offers protection to the metaloenzyme, seratiopeptidase (STP) in gastric environment and provides delayed and controlled release with no initial burst after oral administration. Effect of magnesium trisilicate (MTS) on floating, proteolytic activity and drug release was studied. Gelucire 43/01 was incorporated in the system to provide prolonged lag time. The release of STP was decreased with increasing amount of MTS in the matrix. The rate of STP release from these matrices was very slow due to incorporation of gelucire into lipid bilayers, which provided resistance to movement of STP [49].

From enormous scientific advancements in the field of floating technology utilizing this novel material, it may be concluded that gelucire can be considered as an effective carrier for the design of a floating drug delivery systems for wide variety of active ingredients. Recent developments and appropriate utilization of this substance reflect the several exciting opportunities in the arena of gelucire mediated gastric floating drug delivery systems.

CONCLUSION

Floating drug delivery technology has emerged as an efficient approach for enhancing the bioavailability and controlled delivery of various therapeutic molecules. 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 systems in the near future.

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REFERENCES


