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Review Article

A NOVEL FLOATING DRUG DELIVERY SYSTEM

Kumar Neeraj*, Niranjan S.K, Irchhaiya R, Vishwakarma Ku. Sanjay, Akhtar Ali
Institute of Pharmacy, Bundelkhand University, Jhansi (U.P), India

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*Email: neeraj.kumar.bu@gmail.com

ABSTRACT

Drugs with narrow absorption window in the gastrointestinal tract have poor absorption. Therefore, gastroretentive drug delivery systems (GRDDS) have been developed, which prolong the gastric emptying time. Several techniques such as floating drug delivery system, low density systems, raft systems, mucoadhesive systems, high density systems, superporous hydrogels and magnetic systems, have been employed. Floating drug delivery systems have a bulk density less than gastric fluids and so, remain buoyant in the stomach for a prolonged period of time, releasing the drug slowly at the desired rate from the system. Dosage forms available as gastric floating systems include tablets, capsules, granules and microspheres. Floating system has been considered as one of the imperative categories of drug delivery system gastric retentive behaviour. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and applications of these systems.

Key words: Floating tablets, Gasteroretentative, Effervescent, and Mechanism.

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day[1]. This results in a significant fluctuation in drug levels. Recently, several technical advancements have led to the development of several novel drug delivery systems (NDDS) that could revolutionize method of medication and provide a number of therapeutic benefits[2]. The most important objectives of these new drug delivery systems are: First, it would be single dose, which releases the active ingredient over an extended period of time. Second, it should deliver the active entity directly to the site of action, thus, minimizing or eliminating side effects. To overcome the limitations of conventional drug delivery system, floating tablets have been developed. Drugs that have narrow absorption window in the gastrointestinal tract (GIT) will have poor absorption. For these drugs, gastroretentive drug delivery systems offer the advantages in prolonging the gastric emptying time. To formulate a successful stomach specific or gastroretentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS) / floating drug delivery system[3].

The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion, floatation, sedimentation, expansion, modified shape systems or by the administration of pharmacological agents, that delaying gastric emptying. Based on these approaches, floating drug delivery systems seems to be the promising delivery systems for control release of drugs (Vedha hari b.n.et al, 2010, Drs Jose Gutierrz Rocca et al, 2003).

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

Anatomically the stomach is divided into three regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions[4]. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours[5]. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington[6].

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

DEFINITION

Floating systems or dynamically controlled systems are low-density systems that have sufficiently 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 (Yie W. Chein et al, 1992). This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration. Many buoyant systems have been developed based on granules, powders, capsules, tab-lets, laminated films and hallow Microspheres[7].

FLOATING DRUG DELIVERY SYSTEM:

Floating systems or Hydrodynamically controlled 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. 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[8].

MECHANISM OF FLOATING SYSTEMS

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-

generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. 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 (given in the Figure 1 (a)), 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 the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Figure 1(b)). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations [9].

F = F buoyancy - F gravity

F= (Df - Ds) gv--- (1)

Where,

F= total vertical force,

Df = fluid density,

Ds = object density, v = volume and

g = acceleration due to gravity.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery systems are classified depending up on the two formulations variables Effervescent and Non-effervescent systems (Vedha hari b.n.et al, 2010, Drs Jose Gutierrz Rocca et al, 2003).

1). Single Unit Floating Dosage Systems

a) Effervescent system

b) Non-effervescent Systems

2). Multiple Unit Floating Dosage Systems

a) Effervescent Systems

b) Non-effervescent Systems

c) Hollow microspheres

3). Raft forming system

SINGLE UNIT FLOATING DOSAGE SYSTEMS

Effervescent floating dosage forms

Effervescent floating drug delivery systems generate gas (CO2), thus reduce the density of the system, and remain buoyant in the stomach for a prolonged period of time and release the drug slowly at a desired rate. The main ingredients of effervescent system include swellable

Polymers like chitosan, methyl cellulose and effervescent compounds such as citric acid, sodium bicarbonate, citric acid and tartaric acid[10].

These are matrix type systems prepared with the help of swellable polymers such as hydroxypropyl methyl-cellulose or polysaccharides and chitosan and various effervescent components like sodium bicarbonate, calcium carbonate, citric acid or tartaric acid. These dosage forms are developed in such a way that, when they come in contact with gastric juice in the stomach, Carbon dioxide is liberated and is trapped in the swollen hydrocolloids. This provides buoyancy to the do-sage form. The liberated carbon dioxide may intimately get mixed within the tablet matrix in case of single layered tablet.[11].

The multiparticulate floating reservoir types of delivery systems may contain double or triple layers. The triple layered tablets may be prepared, which contains swell-able gas generating layer, sustainable approach was utilized in the development of floating or pulsatile drug delivery system based on the coated effervescent core. The dosage form had two layers, first layer consisted of drug, cellulose acetate or HPMC as a sustained release core and second layer consisted of effervescent agents, PEG 4000 (4%based on the weight of the second layer) and lactose or microcrystalline cellulose as filler. Sodium bicarbonate and citric acid were used as an effervescent agent in a ratio of 1:0. in the concentration of 30-50 % of the w/w of the core. The carbon dioxide is generated upon contact with the medium and gets entrapped in the polymeric matrix, which provides buoyancy to the dosage form. It was observed that addition of 10-20% w/w of HPMC significantly retarded drug release compared to the dosage form without HPMC4. Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. The main drawback of such system is “all or none” phenomenon. In such cases, there is a danger of passing of the dosage form to intestinal part at the time of house-keeper waves. To overcome this difficulty multiple, unit dosage forms are designed.

Chen *et al* studied the effect of formulation variables on in vitro performance of floating sustained release of verapamil. The formulations were comprised of variables like polymers excipients, polymer content, density of capsule and amount of effervescent agents[12].

Method of preparation of floating effervescent tablet[13]

By direct compression

By wet granulation

By hot melt extraction

Non effervescent FDDS

The non-effervescent FDDS works on the mechanism of polymer swelling, bioadhesion of the polymer to mu-cosal layer of GI tract. The most commonly used excipients for the preparations of non-effervescent FDDS are gel forming or swellable type hydrocolloids, polysaccharides and matrix forming polymers like polyme-thacrylates, polycarbonates, polyacrylates polystyrenes and bioadhesion polymers like chitosan and carbopols. One of the approaches in the development of such floating dosage forms involves thorough mixing of drug and gel forming hydrocolloids. After oral administration, the dosage form comes in contact with gastric fluids and gets swollen, form a gelatinous barrier at the surface. The swollen dosage form maintains a relative integrity of shapes and bulk density less than 10. The air entrapped within the swollen polymer matrix imparts buoyancy to the dosage forms[14].

Thanoo et al developed polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated biofluids as evidenced by scanning electron microscopy (SEM). High drug loading was achieved and drug-loaded microspheres were able to float on gastric and intestinal fluids. It was found that increasing the drug to polymer ratio increased both their mean particle size and release rate of drug[15].

MULTIPLE UNIT FLOATING SYSTEMS

Multiple unit dosage forms may be an attractive alternate since they have been shown to reduce inter and intra-subject variabilities in drug absorption as well as to lower the possibility of dose dumping. Various multiple unit floating systems have been developed in
different forms, and using principles such as air compartment multiple unit system, hollow microspheres prepared by emulsion solvent diffusion method, beads prepared by emulsion gelation method. Use of effervescent and swellable polymer is another approach for preparing multiple unit FDDS.

Effervescent system:

Ichikawa *et al* developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into two sublayers to avoid direct contact between the two agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified
shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO2 was generated by the neutralization reaction between the two effervescent agents,
producing swollen pills (like balloons) with a density less than 1.0 g/ml. It was found that the system had good floating ability independent of pH and viscosity and the drug (Para-amino benzoic acid) released in a sustained manner as shown in fig.2 (a), (b)[16].

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Sheth *et al.* developed hydrodynamically balanced capsules containing mixture of drug and hydrocolloids containing a homogeneous mixture of drug and the hydrocolloid in a capsule,
which upon contact with gastric fluid acquired and maintained a bulk density of less than 1, thereby being buoyant on the gastric contents of stomach, until all the drug was released as shown in fig.3[18].

Hollow microspheres

Both natural and synthetic polymers have been used to prepare floating microspheres.

Joseph *et al.* developed a floating dosage form of piroxicam based on hollow polycarbonate microspheres. The microspheres were prepared by the solvent evaporation technique. Encapsulation efficiency of ~95% was achieved. *In vivo* studies were performed in healthy male albino rabbits. Pharmacokinetic analysis was derived from plasma concentration versus time plot and revealed that the bioavailability from the piroxicam microspheres alone was 1.4 times that of the free drug and 4.8 times that of a dosage form consisting of microspheres plus the loading dose and was capable of sustained delivery of the drug over a prolonged period[19].

Raft forming system

Raft forming systems have received much attention for the drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO2. Usually, the system ingredients includes a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids . Jorgen *et al* described an antacid raft forming floating system. The system contains a gel forming agent (e.g. sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), which when comes in contact with gastric fluids, the raft floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus[20].

FACTOR AFFECTING

1. Density – gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density;
2. Size – dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm;
3. Shape of dosage form – tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes;
4. Single or multiple unit formulation – multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms;

ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEMS

The following advantages of the floating drug delivery systems[21, 22]

1. The gastroretensive systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
4. The gastroretensive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.
5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response

DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEMS

1. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.

2. Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.

3. One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.

4. These systems also require the presence of food to delay their gastric emptying.[21]

APPLICATION OF FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Eg. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).[22]

Site-Specific Drug Delivery:

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide.

Eg. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.[22]

Absorption Enhancement:

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

Eg. A significantly increase in the bioavailability of floating dosage forms(42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).[23]

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. FDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

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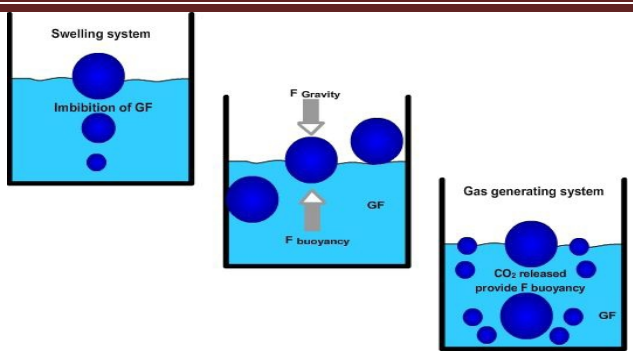
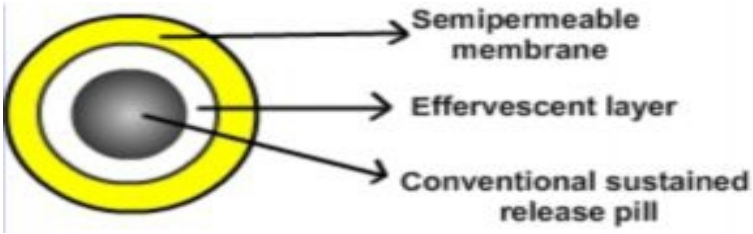


Fig.1 Mechanism of floating systems, GF= Gastric fluid



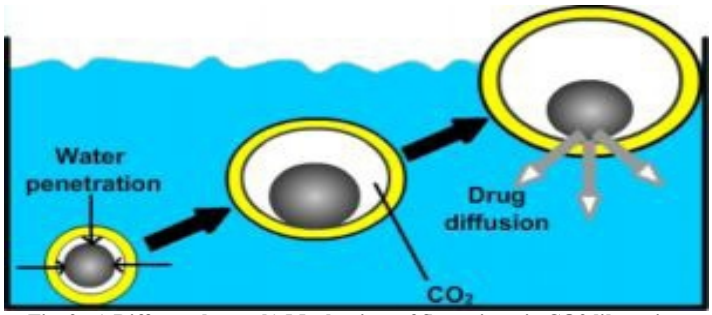


Fig. 2: a) Different layers b) Mechanism of floatation via CO2 liberation

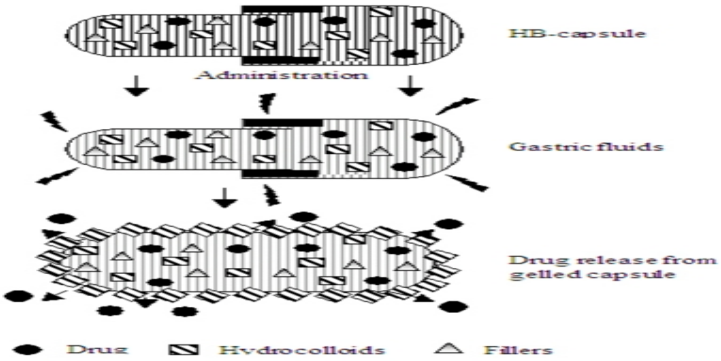


Fig. 3: Working principle of hydrodynamically balanced system

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