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FLOATING DRUG DELIVERY SYSTEM-REVIEW

K. Malleswari,* R.B. Desi Reddy, J. Vijaya Ratna, M. Srilatha

Department of Pharmaceutics, Nalanda institute of Pharmaceutical sciences, Kantepudi, Guntur, Andhra Pradesh, India.

Department Pharmaceutical Sciences, College of Pharmacy, Andhra University, Visakhapatnam.

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***Corresponding Author**
K. Malleswari
Department of Pharmaceutics, Nalanda institute of Pharmaceutical sciences, Kantepudi, Guntur, Andhra Pradesh, India.

ABSTRACT

The aim of writing this review on gastro retentive and floating drug delivery system was to compile the new literature with the principle mechanism of floatation to acquired gastric retention. Technological attempts have been made in the research and development of rate-controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). It is known that differences in gastric physiology, such as, gastric pH, and motility exhibit both intra-as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behaviour. This triggered the attention towards formulation of stomach specific (gastro retentive) dosage forms. This dosage forms will be very much useful to deliver 'narrow absorption window' drugs. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed.

KEYWORDS: gastric residence time, floating drug delivery system, hydrodynamically balanced system, effervescent, noneffervescent.

INTRODUCTION

The gastric emptying time and the variation in pH in different segments of gastrointestinal tract (GIT) are the major challenging task for the development of oral controlled release drug

delivery system. Various attempts have been made to enhance the residence time of the dosage form within the stomach. Gastro retentive system can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of the drug in the GIT. Potential drug candidates for gastro retentive drug delivery system (GRDDS) are drugs, which are locally active in the stomach eg. Misoprostol, antacids etc., and drugs that have narrow absorption window in GIT eg. L-DOPA, paraamino benzoic acid etc. It is characterized by four phases: Phase I–Period of no contraction (40-60 minutes), phaseII – Period of intermittent contractions (20-40 minutes), phase III–Period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave. (10-20 minutes) and phase IV–Period of transition between phase III and phase I (0-5 minutes).[1] Gastric emptying is unpredictable if there are physiological problems and other factors like the presence of food. Drugs having a short half-life are eliminated quickly from the blood circulation. Various oral controlled delivery systems have been designed which can overcome these problems and release the drug to maintain its plasma concentration for a longer period of time. This has led to the development of oral gastroretentive dosage forms. Gastroretention is essential for drugs that are absorbed from the stomach, drugs that are poorlysoluble or degraded by the higher pH of intestine, and drugs with an absorption which can be modified by changes in gastric emptying time. Gastroretentive dosage forms are also useful for local as well as sustained drug delivery systems.

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, lowdensity systems[2], raft systems incorporating alginate gels[3], bioadhesive or mucoadhesive systems[4], high density systems[5-6], superporous hydrogels[7] and magnetic systems.[8-9]

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 [10]

F = F buoyancy - F gravity

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

Where, F= total vertical force, Df = fluid density,

Ds = object density, v = volume and

g =acceleration due to gravity

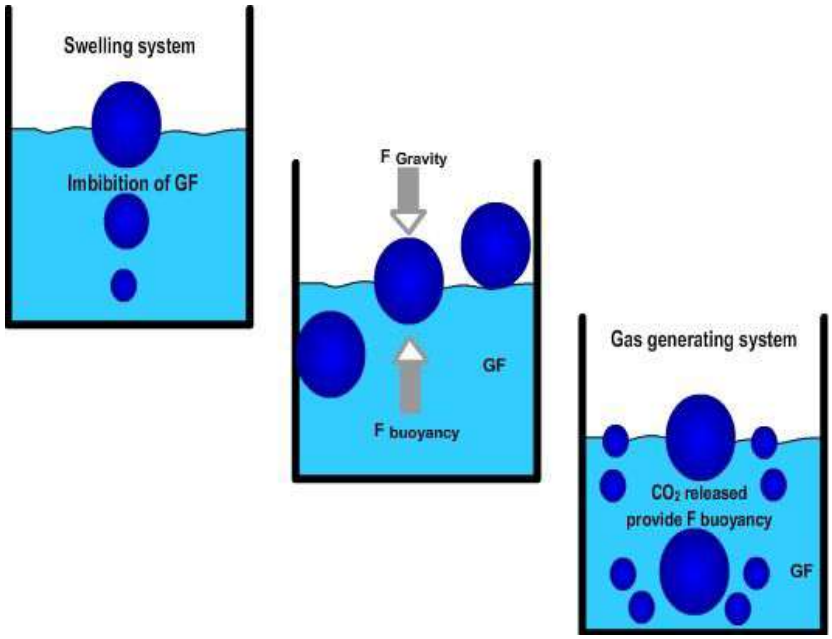

Figure 1. Mechanism of floating systems, gf= gastric fluid

Based on the mechanism of buoyancy FDDS can be classified into

A. Single Unit Floating Dosage Systems

a) Effervescent Systems (Gas-generating systems

b) Non-effervescent Systems

B. Multiple Unit Floating Dosage Systems

a) Non-effervescent Systems

b) Effervescent Systems (Gas-generating Systems)

c) Hollow Microspheres

C. Raft Forming Systems

A. Single Unit Floating Dosage Systems

a) Effervescent Systems (Gas-generating Systems):

Effervescent systems

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas.

i. **Volatile liquid containing systems**

These have 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. These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid.

Gas generating systems

These buoyant delivery systems utilizes effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 , which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chime. A multiple unit type of floating pills, which generate CO_2, have also been developed. The system consists of a sustained release (SR) pill as seed, surrounded by double layers. The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer is of a swell able membrane layer containing PVA, shellac etc. Another effervescent system consisting of a collapsible spring, which controls the release of drug from the polymer matrix, has also been developed. The common approach for preparing these systems involves

resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating which is insoluble but permeable, allows permeation of water. Thus, carbon-dioxide is released, causing the beads to float in the stomach.

B Non-effervescent systems

i. Colloidal gel barrier systems

Hydrodynamically balanced system (HBS), which contains drugs with gel forming hydrocolloids, was first designed by Sheth and Tossounian in 1975. These systems incorporate a high level (20- 75%w/w) of one or more gel forming, highly swellable, cellulose type hydrocolloids, polysaccharides and matrix forming polymers. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug.

ii. Micro porous compartment systems

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the un dissolved drug.

iii. Multiparticulate system: Floating Beads

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Thus multi particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet.

iv. Microballoons

There are various approaches in delivering substances to the target site in a controlled release fashion. One such approach is using polymeric microballoons as carrier for drugs. Hollow microspheres are known as the microballoons. Microballoons were floatable in vitro for 12 hrs, when immersed in aqueous media. Radio graphical studies proved that microballoons

orally administered to human were dispersed in the upper part of stomach and retained there for three hr against peristaltic movement.

C. Raft Forming Systems

Raft forming systems have received much attention for the delivery of antacids and 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 contains 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[11]Jorgen et al described an antacid raft forming floating system. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed 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. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of helicobacter pylori (H. Pylori) infections in the GIT. The composition contained drug, alginic acid, sodium bicarbonate, calcium carbonate, mannitol and a sweetener. These ingredients were granulated, and citric acid was added to the granules. The formulation produces effervescence and aerates the raft formed, making it float.

Advantages of FDDS

1. Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:
2. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
3. Controlled delivery of drugs.
4. Delivery of drugs for local action in the stomach.
5. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
6. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
7. Simple and conventional equipment for manufacture.
8. Ease of administration and better patient compliance.

9. Site-specific drug delivery.

Disadvantages of FDDS[12]

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process.
4. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.

Drugs Used In the Formulations of Stomach Specific Floating Dosage Forms

- Floating microspheres – Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol Tranilast[13] and Terfinadine[14]

- Floating granules - Diclofenac sodium, Indomethacin and Prednisolone.
- Films – Cinnarizine[15], Albendazole.
- Floating tablets and Pills - Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate[16], Para- aminobenzoic acid, Piretanide[17], Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol[18], pentoxyfilline and Diltiazem HCl.
- Floating Capsules - Chlordiazepoxide hydrogen chloride, Diazepam[19], Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid[20] and Pepstatin, and Propranolol.

Polymers and other ingredients

Following types of ingredients can be incorporated into HBS dosage form in addition to the drugs:

- Hydrocolloids (20%-75%): They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. Eg. Acacia, pectin, Chitosan,agar, casein, bentonite,

veegum, HPMC(K4M, K100M and K15M),Gellan gum(Gelrite®), Sodium CMC, MC, HPC

- Inert fatty materials(5%-75%): Edible, inert fattymaterials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. Eg. Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.
- Effervescent agents: Sodium bicarbonate, citricacid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).
- Release rate accelerants(5%-60%): eg lactose,mannitol
- Release rate retardants (5%-60%): eg Dicalciumphosphate, talc, magnesium stearate
- Buoyancy increasing agents(upto80%): eg. ethylcellulose
- Low density material: Polypropylene foam powder (Accurel MP 1000®).

Evaluation Parameters of Stomach Specific FDDS

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro floating behaviour show prolonged gastric residence in vivo. However, it has to be pointed out that good in vitro floating behaviour alone is not sufficient proof for efficient gastric retention in vivo. The effects of the simultaneous presence of food and of the complex motility of the stomach are difficult to estimate. Obviously, only in vivo studies can provide definite proof that prolonged gastric residence is obtained.

1. Measurement of buoyancy capabilities of the FDDS

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

2. Floating time and dissolution

The test for floating time measurement is usually performed in stimulated gastric fluid or 0.1 mole.lit-1 HCl maintained at 370C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 mole.lit-1 HCl as the dissolution medium at 370C. 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 [14.] Recently Gohel et al[15] proposed a more relevant in vitro dissolution method to evaluate a floating drug delivery system (for tablet dosage form). A 100-mL glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 ml of 0.1 mole.lit-1 HCl dissolution medium and allow collection of samples. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic gastric acid secretion rate. The performance of the modified dissolution apparatus was compared with USP dissolution Apparatus 2 (Paddle). The problem of adherence of the tablet to the shaft of the paddle was observed with the USP dissolution apparatus. The tablet did not stick to the agitating device in the proposed dissolution method. The drug release followed zero-order kinetics in the proposed method. Similarity of dissolution curves was observed between the USP method and the proposed method at 10% difference level (f2=57). The proposed test may show good in vitro-in vivo correlation since an attempt is made to mimic the in vivo conditions such as gastric volume, gastric emptying, and gastric acid secretion rate.

3. 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.

4. Content uniformity

Hardness, Friability (Tablets) Drug loading, drug entrapment efficiency, particle size analysis, surface characterization (for floating microspheres and beads).

5. Drug loading

Is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. The particle size and the size distribution of beads or microspheres is determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done byscanning electron microscope (SEM).[19]

6. X-Ray/Gamma Scintigraphy

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form now a day. It helps to locate dosage form in the g.i.t. and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner . In case of γ scintigraphy, the γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract.

7. Pharmacokinetic studies

Pharmacokinetic studies are the integral part of the in vivo studies and several works has been on that. Sawicki studied the pharmacokinetics of verapamil, from thefloating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The tmax and AUC (0-infinity) values (3.75 h and 364.65 ng.ml-1h respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (tmax value 1.21 h, and AUC value 224.22 ng.ml-1h). No much difference was found between the Cmax values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. An improvement in bioavailability has also been observed with piroxicam in hollow polycarbonate microspheres administered in rabbits. The microspheres showed about 1.4 times more bioavailability, and the elimination half-life was increased by about three times than the free drug.

CONCLUSION

The currently available polymer-mediated Non effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. Number of commercial products and patents issued in this field are the evidence of it. The FDDS become an additional advantage for drugs that are absorbed primarily in the upper part of GI tract, i.e., the stomach, duodenum, and jejunum. Some of the unresolved, critical issues like the quantitative efficiency of floating delivery systems in the fasted and fed states, role of buoyancy in enhancing GRT of FDDS and more than that formulation of an ideal dosage form to be given locally to eradicate H.Pylori, responsible for gastric ulcers worldwide. With an increasing understanding of polymer behaviour and the role of the biological factors

mentioned above, it is suggested that future research work in the FDDS should be aimed at discovering means to control accurately the drug input rate into the GI tract for the optimization of the pharmacokinetic and toxicological profiles of medicinal agents. It seems that to formulate an efficient FDDS is sort of a challenge and the work will go on and on until an ideal approach with industrial applicability and feasibility arrives.

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