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Review Article

FLOATING DRUG DELIVERY SYSTEM OF NSAIDS TO INCREASE GASTRIC RETENTION TIME IN UPPER PART OF GASTROINTESTINAL TRACT: A REVIEW

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ABSTRACT

Floating drug delivery system was to organize the recent journalism with unique focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single unit and multiple unit floating systems. In the recent decades, there have been numerous attempts to overcome the barrier like short gastric residence times and unpredictable gastric emptying times. This review also summarizes the in –vitro technique of evaluation, all the pre-formulation and post formulation evaluations criteria. These systems are useful to several problems encountered during the development of pharmaceutical dosage form. In this review, the technologies of formulation and mechanism of drug release, advantage, application in drug delivery of floating systems are discussed.

Keywords: FDDS, gastric retention, gastric emptying time, floatation, in-vitro techniques

INTRODUCTION

The design of an oral controlled drug delivery system should be primarily aimed at achieving more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localize the drug delivery system within desired regions of the gastrointestinal tract and the highly variable nature of gastric emptying process. The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. These systems have more advantages due to patient acceptance and ease of administration. [1]

The total gastrointestinal residence time of the dosage form is increased by prolonging the gastric residence time, improved patient compliance. Floating drug delivery system provides buoyancy in stomach for extended time period thereby extended gastric residence time for the dosage form ensuring maximum bioavailability. [2]

The residence time of the dosage form in the stomach depends upon various factors like pH, size of the dosage form, food intake, and biological factors which include age, body weight gender, posture, and diseased states (hepatic failure, diabetes, chrons disease).[2] Table no.1 shows the various drugs in GRDDS formulation.

Basic Gastrointestinal Tract Physiology [3]

It is well recognized that the stomach may be used as a depot for sustained release dosage forms both in human and veterinary applications. The stomach is anatomically divided in to three parts fundus, body, and pylorus. The proximal stomach made up of the fundus and body regions, serves as reservoir for food materials

The gastrointestinal motility is characterized by a cyclic pattern that consists of four distinct phases:

Phase I (Basal phase) lasts from 30 to 60 minutes with rare contractions.

Phase II (Preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increase gradually.

Phase III (burst phase) lasts for 10 to 20 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.

Phase IV lasts for 0 to 5 minutes and occurs between phases III and first second consecutive cycles.

Factors affecting the gastric retention time

- Density
- Size
- Shape
- Nature of meal
- Posture
- Age and Gender
- Frequency of Feed

Types of gastroretentive forms [4,5, 6]

- Floating systems
- High density systems
- Expandable systems
- Superporous hydrogel

- Mucoadhesive or bioadhesive systems

Floating Systems

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. Floating system mechanism as shown in figure 1. [3]

Floating dosage form with prolonged residence time in stomach is highly desirable for drug-

- That is locally active in stomach
- That have absorption window in stomach or in upper small intestine
- That is unstable in intestinal or colonic environment has low solubility at high pH value.

Mechanism of Floating system: [7,8,9]

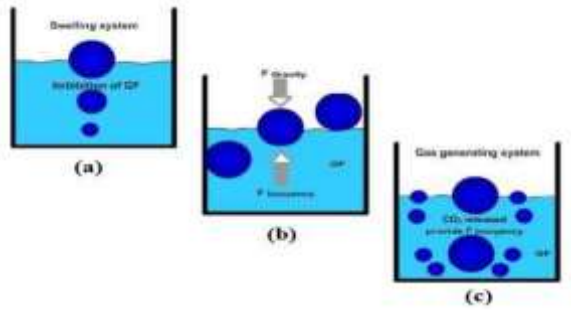

Fig 1: Mechanism of floating system.[7,8,9]

High density systems

Gastric contents have a density close to water (1.004 g/cm3). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g/cm3 seems necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.

Expandable systems [10,11,12]

A dosage form in the stomach will withstand gastric transit if it is bigger than the 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, three configurations are required: a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release. Unfoldable and swellable systems have been investigated. Unfoldable systems are made of biodegradable polymers. The concept is to make a carrier, such as a capsule, incorporating a compressed system which extends in the stomach.

Superporous Hydrogels

These are swellable systems, they differ sufficiently from the conventional types. With pore size ranging between 10 nm and 10 Am, absorption of water by conventional hydrogel is a very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Superporous hydrogels, average pore size >10 Am, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover, they swell to a large size and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction.

Mucoadhesive or bioadhesive systems [12,13,14]

The basis of mucoadhesion is that a dosage form can stick to the mucosal surface by different mechanisms. Different theories are invoked to explain these mechanisms. Firstly, the electronic theory proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material. Secondly, the adsorption theory suggests that bioadhesion is due to secondary forces such as Van der Waals forces and hydrogen bonding. The wetting theory is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucus layer

Classification of floating drug delivery system

Based on the mechanism of buoyancy, FDDS can be classified into:

- Effervescent system (gas-generating system).
- Non-effervescent system.

Effervescent system

In effervescent systems a gas generating agent usually sodium bicarbonate or sodium carbonate is mixed with matrices prepared with swellable polymers, when the systems come in contact with gastric fluids, the carbon dioxide is liberated by the acidity of gastric contents and the gas is entrapped in the viscous hydrocolloid. Thus, produces an upward motion of the system maintaining buoyancy. [6]

Non-effervescent system

In non-effervescent FDDS, the drug mixes with a gel forming hydrocolloid, polymers such as polycarbonates, polyacrylates etc. Gel forming hydrocolloid swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and the bulk density of less than one within gastric environment.

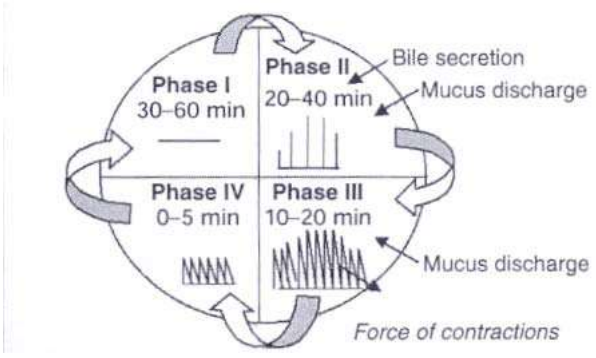

Fig. 2: Motility pattern in GIT (source www.ijopjournal.com)

Advantages of floating drug delivery system [15-17]

- The gastroretentive systems are advantageous for drugs absorbed through the stomach e.g. ferrous salts, antacids.
- Acidic substances like aspirin cause irritation on the stomach wall when they come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
- The gastro retentive systems are advantageous for drugs meant for local action in the stomach e.g. Antacids.

Disadvantages of floating drug delivery system

- Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
- 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.
- The drugs that are significantly absorbed throughout the gastrointestinal tract, which undergo significant first pass metabolism are only desirable candidates.
- Some drugs present in the floating system causes irritation to gastric mucosa.

Table 1: Commonly Used Drugs in Formulation of GRDD

DOSAGE FORMS	DRUGS
Floating Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbide mononitrate, p- Aminobenzoic acid (PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil
Floating Capsules	ChlordiazepoxideHCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin
Floating Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Floating Granules	Diclofenac sodium, Indomethacin, Prednisolone
Powders	Several basic drugs
Films	Cinnarizine

Applications of floating drug delivery system [18]

1. Enhanced bioavailability
2. Sustained Drug Delivery
3. Site-Specific Drug Delivery
4. Absorption Enhancement
5. Minimized adverse activity at the colon
6. Reduced fluctuations of drug concentration

EVALUATION PARAMETERS OF FDDS (TABLET)

Precompression parameters

Angle of repose

It defines as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.[18]

Procedure

The angle of repose of granules was determined by the funnel method. The accurately weight powder was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder. The powder was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured, and angle of repose was calculated by using the following formula

$$\tan\theta = h/r$$

Where, h = height of pile, r = radius of the base,
θ = angle of repose

Compressibility Index

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size of a powder. The compressibility of a material can be estimated from the tap and bulk density measurements.

Carr's Compressibility Index for the prepared granules was determined by the following formula.

$$\text{Carr's Index (\%)} = \text{TBD} - \text{LBD/TBD} \times 100$$
$$\text{Hausner Ratio} = Vb/Vt$$

Where, Vb = initial or bulk volume, Vt = final or tapped volume

Bulk density and Tapped density

Bulk density is the ratio of the weight of a powder to the volume it occupies. It is expressed as gm/ml. Volume occupies by powder includes volume of the solid portion of the particle and voids between the particles. Bulk density is important in determining the size of the container needed for handling and processing.

$$\text{Bulk density} = W/V_o$$

Where, W= weight of the powder, V_o= initial volume,
V_f= final volume

Post Compression Parameters

***In vitro* buoyancy studies**

In vitro buoyancy was determined by floating lag time. The tablets were placed in a 100 ml glass beaker containing 0.1N HCL. The time required for the tablet to float to the surface and float was determined as floating lag time. The total floating time also determined.[19]

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of tablets was determined using a validated dial type hardness tester. It is expressed in kg/cm^2. Three tablets were randomly selected from each batch and analyzed for hardness. The mean and standard deviation were also calculated.

Weight Variation test

Twenty tablets were selected randomly and weighed individually. Calculate average weight and compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in table and not more than deviate by more than twice the percentage.

Friability test

Friability was performed by using Roche friabilator; normally pre weighed six tablets were placed in the plastic chamber of friabilator. This was then operated for 100 revolutions. Tablets are then dusted and reweighed. Loss of less than 1% in weight is considered to be acceptable.

$$F = \text{initial wt} - \text{final wt.} 100$$

Drug content uniformity

Five tablets were weighed and taken in a mortar and crushed to powder from. A quantity of powder weighing equivalent to 40 mg of Lornoxicam was taken in a 100 ml volumetric flask and 0.1N HCL was added. It was then heated at 60 ^{0}C for 30 minutes. The solution was filtered using What man filter paper and then its absorbance was measured at 379nm. The amount of drug was calculated using calibration curve.

***In-vitro* Dissolution studies**

One tablet was placed in dissolution basket. The study was carried in 900ml of 0.1N HCl for duration of 6 hours (75 rpm); the

temperature was maintained at 37± 2˚C. Aliquots of 1 ml were withdrawn at specific time intervals. At each time of withdrawal, 1ml of fresh medium was replaced into the dissolution flask.[20]

CONCLUSION

Floating drug delivery system have been come forward as an efficient means of enhancing the bioavailability and controlled delivery of drugs. The advancements in delivery technology will lead to the development of large number of floating delivery systems to optimize the delivery of molecules that exhibit absorption process, low bioavailability and extensive first pass hepatic metabolism. Drug absorption in the gastrointestinal tract is a highly variables procedure and prolonging gastric retention of the dosage form extends the time for drug absorption.

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