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FLOATING A NEW APPROACH FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Floating drug delivery systems provide local delivery to specific regions like stomach and proximal small intestine and shows better bioavailability, improves patient compliance by increasing the gastric residence time and controlling the drug release. They propose several advantages over conventional dosage forms. The purpose of writing this review article is to introduce the mechanism of floatation in order to attain the gastric retention. In current decades, there have been numerous attempts to overcome the barriers like short gastric residence times and unpredictable gastric emptying times. This article covers different mechanisms, factors affecting, classification and different evaluations of floating drug delivery system. It also includes the advantages, disadvantages and applications of FDDS in detail. This review also summarizes the in vitro techniques to evaluate the drug release from floating system.

Keywords: Bioavailability, Floating drug delivery system, Gastric residence time

INTRODUCTION

Drug delivery system is the way of administering a pharmaceutical compound to attain a therapeutic effect in humans or animals. Changes in drug delivery system can modify drug release profile, absorption, distribution and elimination of the drug and improving product efficacy, safety, patient convenience and compliance[1]. Oral route is mostly use because of high level of patient conformity but it is not much successful due to low bioavailability problem. Oral controlled drug delivery system is developed in order to increase the gastric retention time. Normal gastric retention time range is 5 to 120 minutes. The drugs with short half-life can quickly eliminated from the systemic circulation. Various oral controlled drug delivery systems are developed to reduce these problems

and in order to ensure proper release of drug to maintain the plasma level. The drugs which have poor bioavailability are best candidates for the gastro retentive drug delivery system because their absorption is limited in the upper part of the GIT. There are various physiological difficulties to achieve the gastric retention[2]. To overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs.

Definition

Floating systems are low-density systems that have adequate buoyancy to remain float over the gastric contents and stay buoyant in the stomach without disturbing the gastric emptying rate for a prolonged period of time. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration[3].

Difference between Conventional and Gastroretentive drug delivery system[4]

Table 1: - Difference between conventional and gastroretentive drug delivery system

Conventional drug delivery system	Gastroretentive drug delivery system
- High risk of toxicity	- Very low risk of toxicity
- Less patient compliance	- Improves patient compliance
- Not suitable for delivery of drugs with narrow absorption window in small intestinal region.	- Suitable for delivery of drugs with narrow absorption window in small intestinal region.
- Not much advantageous for	- Very much advantageous for
Drugs having rapid absorption through GIT	Drugs acting locally in the stomach.
Drugs which degrade in the colon.	Drugs which degrade in the colon.
Drugs acting locally in the stomach.	Drugs having rapid absorption through GIT
Drugs which are poorly soluble at an alkaline pH	
- No risk of dose dumping	- Possibility of dose dumping.

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY[5-7]

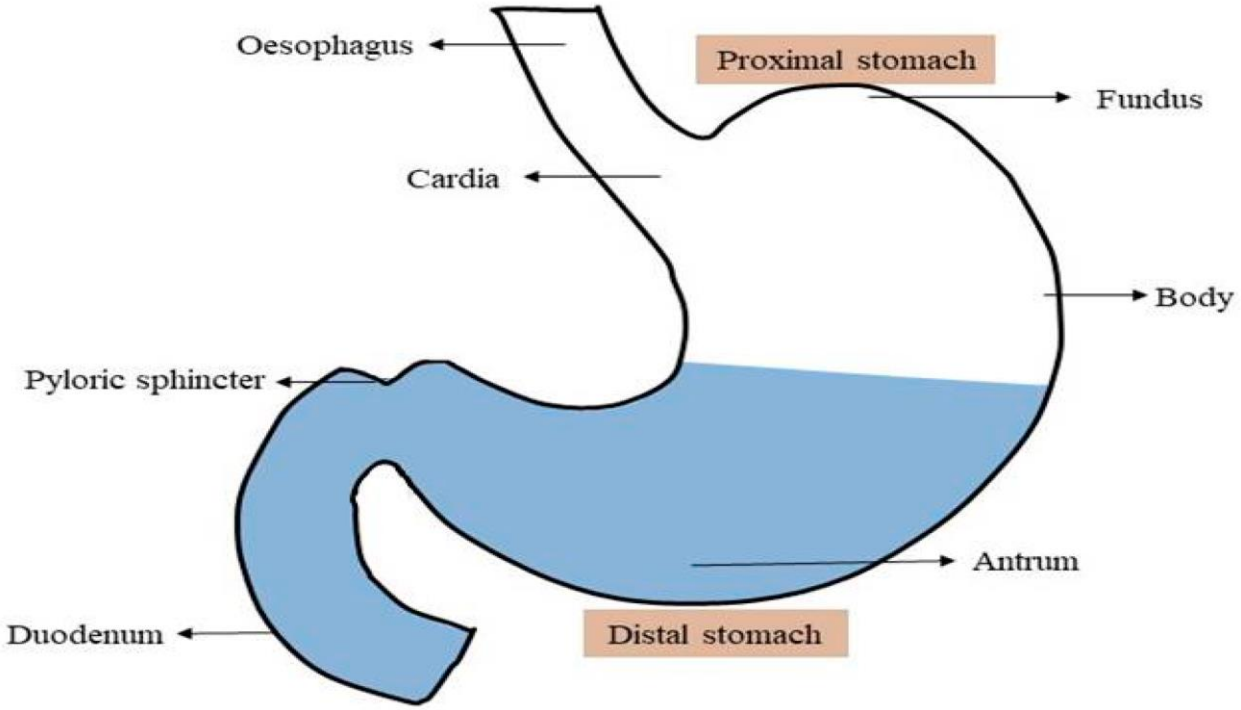

Fig.1: Basic Gastrointestinal Tract Physiology

Anatomically the stomach is mainly divided into 3 regions: fundus, body, and antrum (pylorus). The fundus is proximal part and body acts as a reservoir for undigested material, whereas the main site for mixing motions is antrum and it acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs in fasting as well as fed states. During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine in every 2 to 3 hours. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases:

1. Phase I (basal phase) lasts from 30 to 60 minutes with rare contractions.
2. 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 increases gradually.

3. 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.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

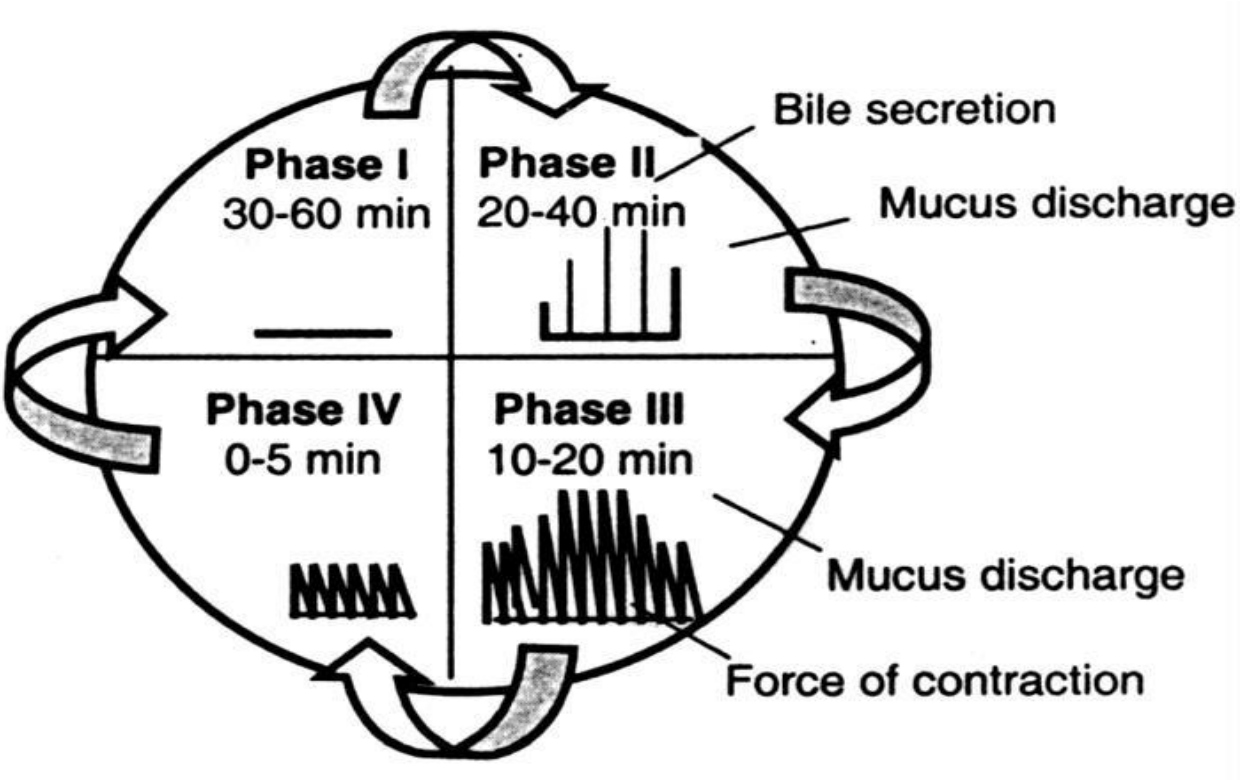

Fig. 2: Migrating Myloelectric Cycle

APPROACHES TO GASTRIC RETENTION [8, 9]

Various types of systems have been developed to increase the GRT of dosage forms by employing range of concepts.

These systems have been classified on the basis of principle of gastric retention.

1. Floating drug delivery systems (FDDS): These systems have low density, so it can float over the gastric contents.
2. Bioadhesive systems: This system binds with stomach mucosa and hence, enables the localized retention of the system.
3. Swelling and expanding systems: This system absorbs water and hence, enlarged size.
4. High density systems: They remain in the stomach for longer period of time, by sedimenting to the folds of stomach.

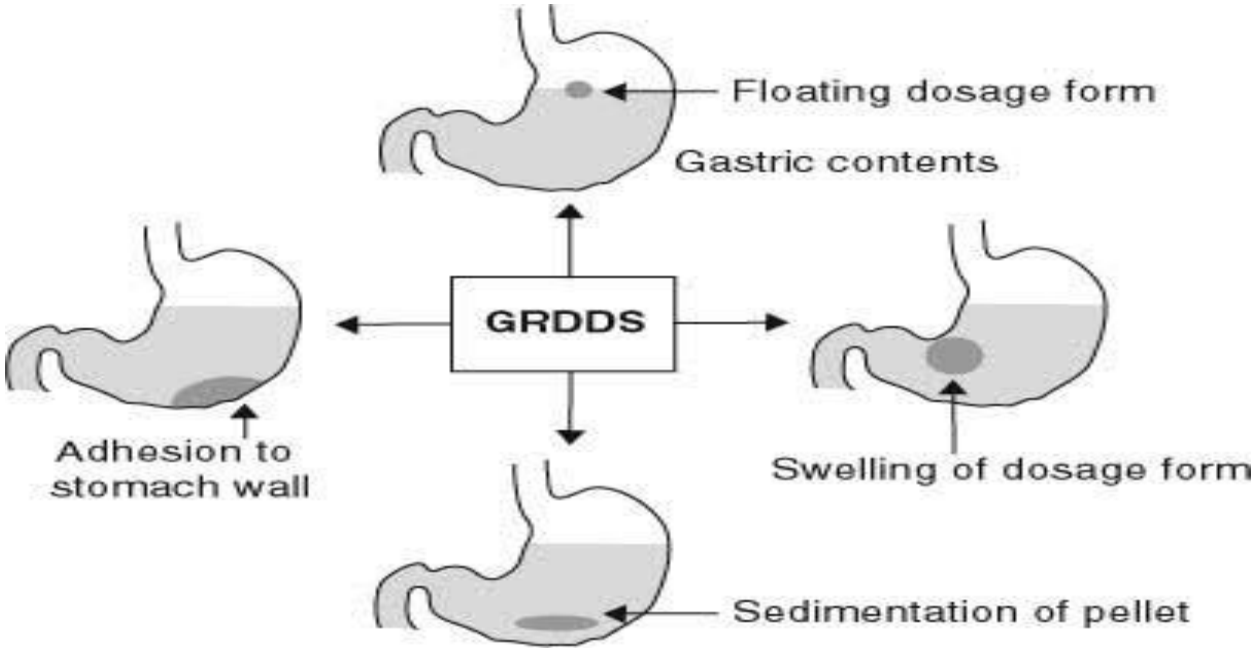

Fig. 3: Approaches to gastric retention

MECHANISM OF FLOATING SYSTEMS [10-12]

Various types of dosage forms are design to increase the retention time of dosage form into the stomach. These attempts include 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. From 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. In FDDS, the drug is release 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. The object floats better if F is on the higher positive side.

F = F buoyancy - F gravity= (Df - Ds) gv

Where,

F= total vertical force, Df = fluid density, Ds = object density, v = volume and g = acceleration due to gravity

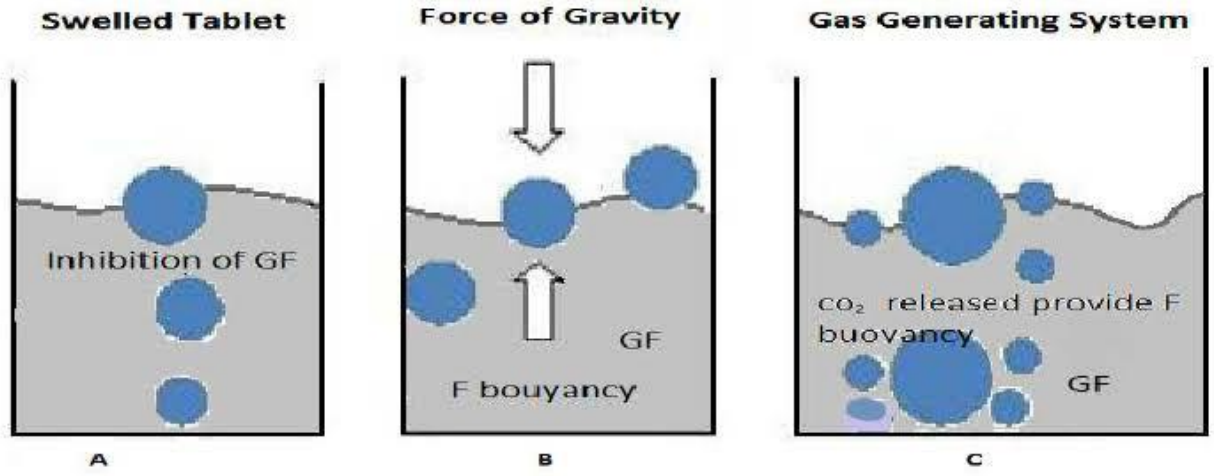

Fig. 4: Mechanism of Floating system

5. ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM [13-15]

1. Advantageous for drugs meant for local action in the Stomach e.g. Antacids.
2. Advantageous for drugs absorbed through the stomach e.g. Ferrous salts, antacids.
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 and then will be available for absorption in the small intestine after emptying of the stomach contents.
4. FDDS provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

5. Certain types of drugs can benefit from using FDDS. These include:
   a) Drugs acting locally in the stomach.
   b) Drugs those are primarily absorbed in the stomach.
   c) Drugs those are poorly soluble at an alkaline pH.
   d) Drugs with a narrow window of absorption.
   e) Drugs absorbed rapidly from the GI tract.
   f) Drugs those degrade in the colon

6. DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEMS [14-16]

1. Floating system is not feasible for those drugs that have solubility or stability problem in GIT.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
3. Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism may not be desirable.
4. Drugs which are irritant to gastric mucosa are not suitable.
5. Drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the system.
6. The dosage form should be administered with a full glass of water (200-250 ml).
7. These systems do not offer significant advantages over the conventional dosage forms for drugs which get absorbed throughout gastrointestinal tract.

FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM [17-19]

1. **Density:** Density of the dosage form should be less than the gastric contents (1.004gm/ml).
2. **Fed or Unfed State:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
3. **Nature of the meal:** Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.
4. **Caloric Content:** GRT can be increased between 4 to 10 hours with a meal that is high in proteins.

5. **CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM** [20-24]
6. The floating drug delivery system can be divided into gas generating and non-effervescent systems.
7. **Gas-Generating Systems:** In this system floatability can be achieved by creation of gas bubbles. CO_2 can be generated in situ by incorporation of carbonates or bicarbonates, which react with acid either the natural gastric acid or co-formulated as citric or tartaric acid. An alternative is to integrate a matrix with entrapped of liquid, which forms a gas at body temperature. This approach has been used for single and multiple unit systems. In single unit systems, such as capsules or tablets, effervescent substances are incorporated in the hydrophilic polymer, and CO_2 bubbles are trapped in the swollen matrix. In vitro, the lag time before the unit floats is <1 min and the buoyancy is prolonged for 8 to10 h. Bilayer or multilayer systems have also been designed. Drug and excipients can be prepared separately and the gas generating unit can be incorporated in any of the layer. Further refinements involve coating the matrix with a polymer which is permeable to water, but not to CO_2. The main difficulty of such formulation is to find a support between elasticity, plasticity and permeability of the polymer.
8. **Non-Effervescent Systems:** Non-effervescent floating dosage forms use a gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of <1g/ml. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass. 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 polycarbonate.

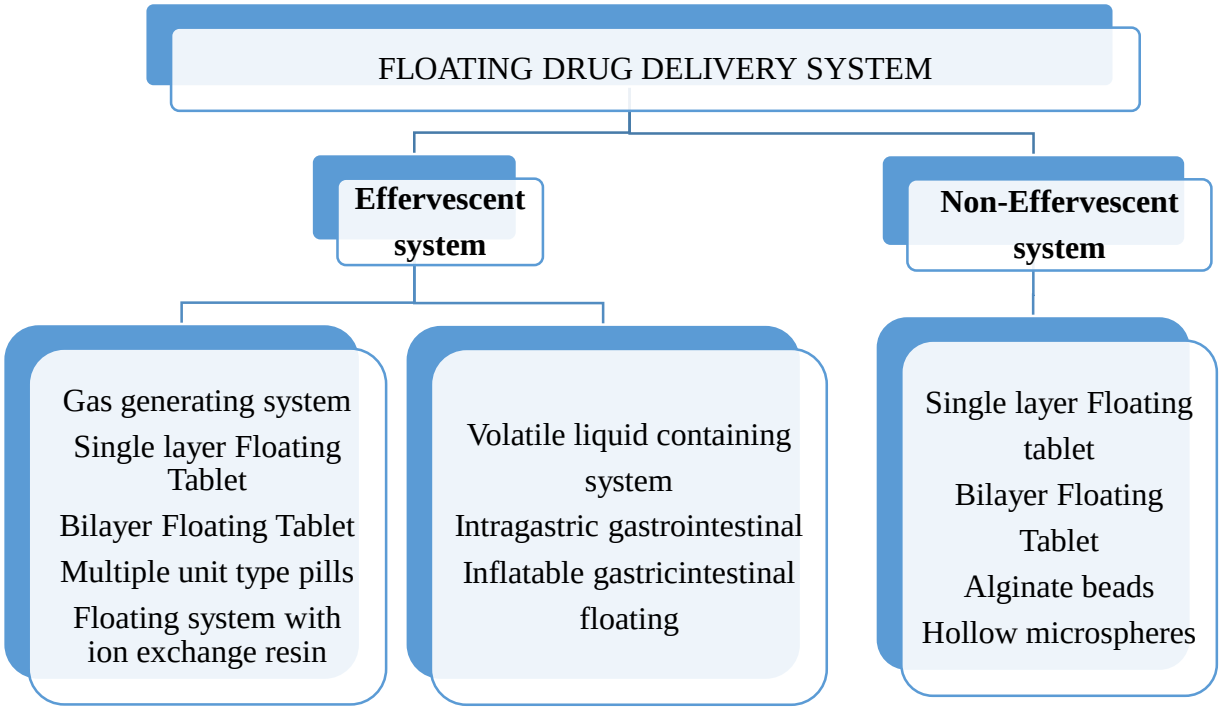

Fig. 5: Classification of floating drug delivery system

EVALUATION OF FLOATING DRUG DELIVERY SYSTEM

Size and shape evaluation [25]

The particle size of the formulation can be determining by using Sieve analysis, Air elutriation analysis, Photo analysis, Optical microscope, Electro résistance counting methods, Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air Pollution Emissions Measurements etc

Buoyancy/Floating test [26]

The time between introduction of the dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant are measured. The time taken for the dosage form to emerge on the surface of a 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).

Swelling Studies[27, 28]

Swelling studies can be determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include ^{1}HNMR imaging, Confocal laser scanning micro- and fats scopy (CLSM), Cryogenic Scanning Electron Microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus (USP dissolution apparatus can be calculated as per the following formula.

%Swelling ratio = (Weight of wet formulation / Weight of formulations) x100

Drug–excipients interaction studies [29]

Pure drug and optimized tablet formulation can be analyzed by Fourier transform infrared (FTIR) spectroscopy.

Drug loading [30]

It is assessed by crushing accurately weighed in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyze by various analytical methods like spectrophotometry. The percentage drug loading is calculated by the formula given below:

%Drug loading = (Amount of drug in the sample/ weight of total formulation) x100

Water uptake study [31]

It is performed by introduction the dosage form in simulated gastric fluid at 37^{o}C and study the dimensional changes, such as diameter and thickness, at regular interval of time. The swollen beads are weighed and water uptake is calculated in the terms of percentage weight gain, as given:

$W_u = (W_t - W_o)/ W_o \times 100$

Where, W_t and W_o are the weight of the tablet after time t and initially, respectively

Drug Release[22]

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.

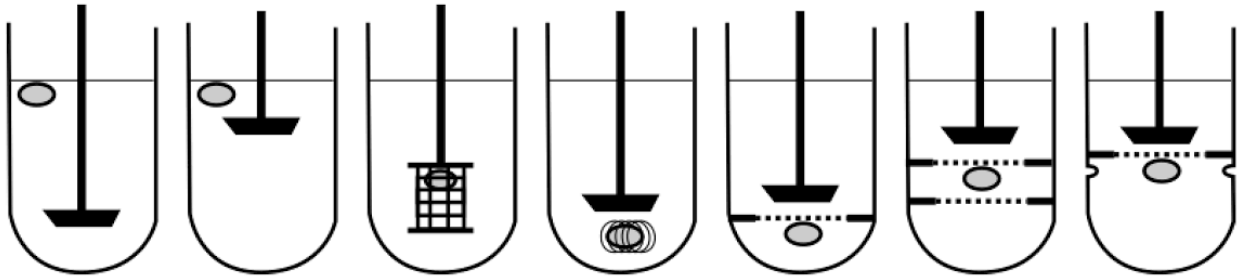

Fig. 6: Different methods of dissolution for the floating dosage form

APPLICATION OF FLOATING DRUG DELIEVERY SYSTEM[13, 32]

- **Enhanced Bioavailability**: The bioavailability of therapeutic agents can be extensively increased mainly for those which get metabolized in the upper GIT by gastroretentive drug delivery approaches in comparison to the administration of nongastroretentive drug delivery.
- **Sustained Drug Delivery**: Oral CR formulations have some problems such as gastric residence time in the GIT. Less drug absorption from oral CR formulations because they have short GRT. These problems can be overcome with the floating systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents.
- **Site Specific Drug Delivery Systems:** The controlled, slow delivery of drug from gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also decrease the dosing rate. Eg: Furosemide and Riboflavin.
- **Absorption Enhancement**: Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby enhancing their absorption.
- **Minimized Adverse Activity at the Colon**: Retention of the drug in the floating systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be reduces.
- **Reduced Fluctuations of Drug Concentration**: Constant input of the drug following controlled release gastroretentive delivery produces systemic drug concentrations within a

narrower range compared to the immediate release oral dosage forms. Thus, fluctuations in drug effects are reduce and concentration dependent adverse effects that are linked with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

Conclusion: From the above review, it has been concluded that the floating system is best approach for the gastro retentive drug delivery system. It can enhance the residence time of the drugs, which are specifically used in upper GIT. This system used for the drugs having low bioavailability and extensive first pass metabolism.

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