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FLOATING DRUG DELIVERY SYSTEM – AN OVERVIEW

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ABSTRACT

Oral route drug administration has been the most successful route used for controlled delivery of drugs. Controlled release of drug delivery system optimizes the biopharmaceutical, pharmacokinetic, pharmacodynamics, properties of drugs and to reduce the side effects and to designed to deliver the drug in such a way that the levels are maintained within the therapeutic window effective for a long period till the system continuous to deliver the drug at a particular rate. The aim of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with particular focus on the main floating mechanism to achieve gastric retention. This review includes the physiology, factors controlling gastric retention time, excipient variables influencing gastric retention, approaches to designing single-unit, hydro-dynamically balanced system and multi-unit floating structure, and aspects of their classification, formulation and evaluation are discussed in detail, and few applications of these systems.

KEYWORDS: Floating drug delivery system, micro particles, Gastric empting, Hydrodynamicaly balance system etc.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. The high level of patient compliance in taking oral dosage forms is due to the ease of administration, patient compliance, flexibility in formulation and handling of these forms. However the oral route of administration suffers with certain drawbacks mainly short residence time of the dosage form in the GI tract, unpredictable gastric emptying and degradation of the drug due to highly reactive nature of GI contents. Gastric emptying is a complex process and makes in vivo performance of the drug delivery system uncertain. Formulation of floating drug delivery systems is an useful approach to avoid this variability with increased gastric retention time of the drug delivery system.[1]

Floating drug delivery systems (FDDS) are invented to retain the drug in the stomach and applicable for drugs with poor solubility and low stability in intestinal fluids. The basis behind FDDS is making the dosage form less dense than the gastric fluids to make it float on them. FDDS are hydro-dynamically controlled low-density systems with 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. The residual system is emptied from the stomach with the release of the drug. This results in enhanced gastric residence time and good control over plasma drug concentration fluctuations. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.[2]

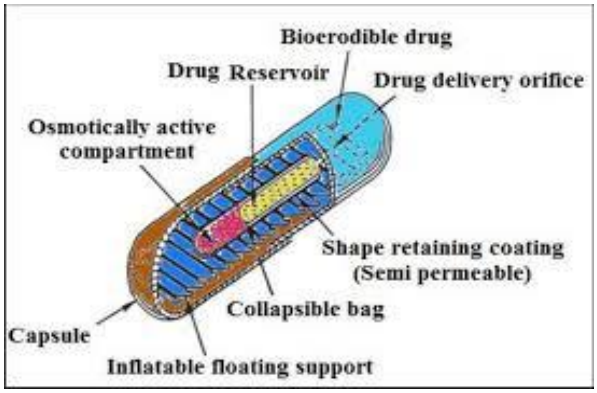

Figure 1: Floating drug delivery system.

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 are the 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, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is eliminated 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 effect, a minimal level of floating force (F) is also required to maintain the buoyancy of the dosage form 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 a submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and sustainability of floating forces produced in order to prevent any unforeseeable variations in intragastric buoyancy.[3]

F = F buoyancy – F gravity = (Df – Ds) g v

Where, F = total vertical force,
Df = fluid density,
Ds = object density,
v = volume and
g = acceleration due to gravity.[4]

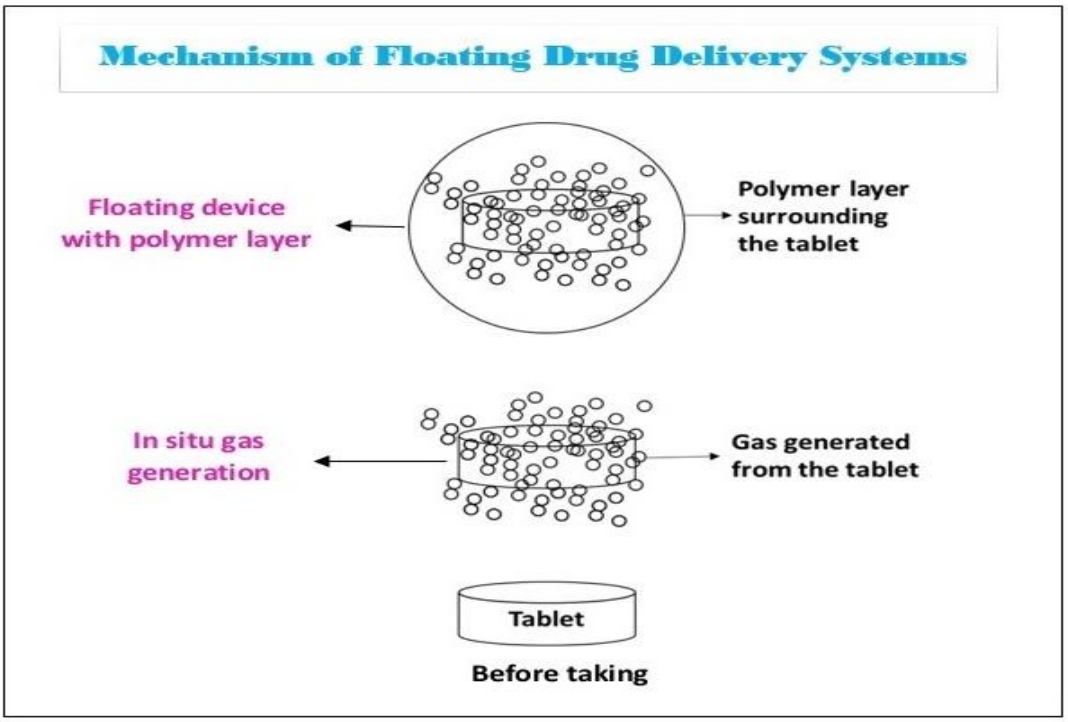

Figure 2: Mechanism of floating system.[5]

Advantages of FDDS[6,7]

- Improved drug absorption, because of increased gastric residence time and more time spent by the dosage form at its absorption site
- Simple and conventional technique for formulation
- Site-specific drug delivery.
- FDDS are advantageous for drugs meant for local action in the stomach eg: Antacids
- When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, 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.
- FDDS improves patient compliance by decreasing dosing frequency.
- Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.
- Gastric retention time is increased because of buoyancy
- Enhanced absorption of drugs which solubilize only in stomach.

Disadvantages of FDDS[8]

- Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
- 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.
- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

- Certain drugs present in the floating system may causes irritation to gastric mucosal linings

Applications of floating drug delivery system[9]

- FDDS are perfect HBS dosage form to provide better delivery of drugs and reduced its GI side effects
- FDDS served as an excellent drug delivery system in the eradication of Helicobacter pylori, blamed for chronic gastritis and peptic ulcers.
- FDDS is site-specific drug delivery: These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine, e.g., Riboflavin and Furosemide.
- In case of Parkinson patient, FDDS is effective in absorption of the drug over a period of 6-8 h and maintained substantial plasma concentration.
- FDDS are claimed for the increased efficacy of drugs as recent studies show that the administration of Diltiazem floating tablets twice a day would be more effective compared to normal tablets in hypertensive patients.

Suitable Drug Candidates for FDDS[10]

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. In general, appropriate candidates for FDDS are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT

- Drugs with narrow absorption window in GIT, e.g., Riboflavin and Levodopa
- Drugs that primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, chlordiazepoxide and cinnarazine.
- Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
- Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., Amoxicillin Trihydrate.

CLASSIFICATION[11]

A. Effervescent FDDS

1. Gas generating system
2. Volatile liquid containing system

B. Non-Effervescent FDDS

1. Colloidal gel barrier system
2. Bi-layer floating tablets
3. Microporous compartment system
4. Floating Beads/ Alginate Beads
5. Micro balloons/ Hollow Microspheres

C. Raft forming system

A. Effervescent FDDS

This system makes use of a floating chamber filled with water, vacuum, air, or inert gas. CO2 which is formed as a result of an effervescent reaction between the organic acid (citric acid) and the carbonate / bicarbonate salts can be introduced into the floating chamber. Such a system uses matrix prepared with swellable polymers such as chitosan-like polysaccharides, effervescent materials such as citric acid, sodium bicarbonate, and tartaric acid, or chambers containing a liquid that gasifies at the body temperature.

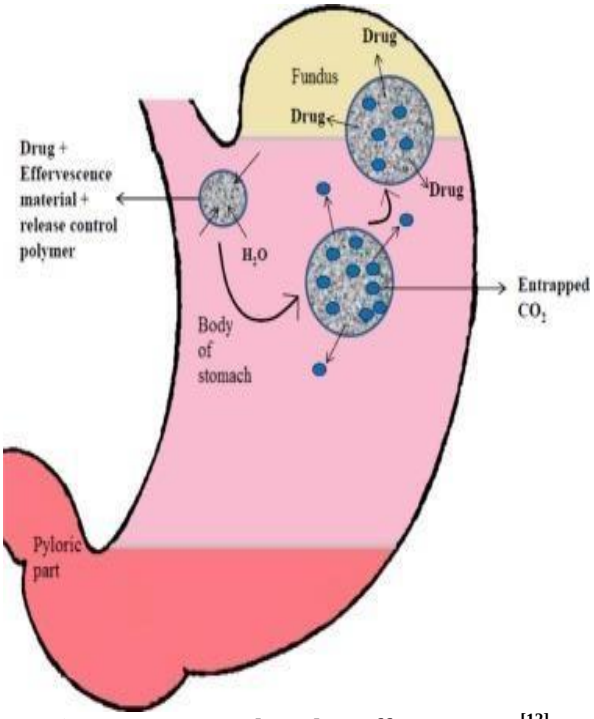

Figure 2: GRDDS based on effervescence.[12]

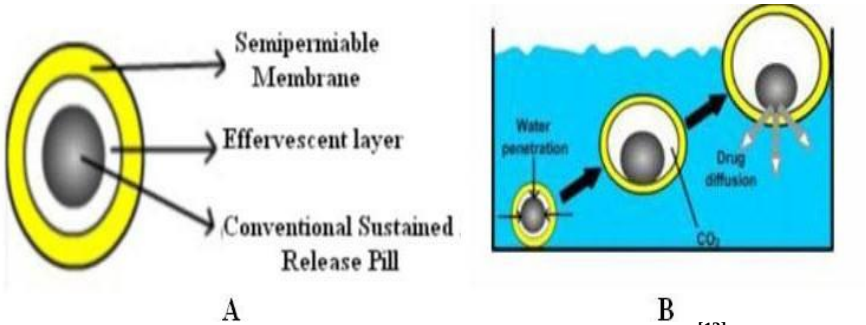

Figure 3: Multiple-unit oral drug delivery system.[13]

1. Gas generation system
This buoyant delivery system uses effervescence reaction between citric acid / tartaric acid and carbonate / bicarbonate salts to release CO2 which further reduces its specific gravity and makes it float over chime.

2. Volatile liquid storage system
These contain an inflatable chamber consisting of a liquid, e.g. cyclopentane, ether, which gasifies at body temperature to induce inflation of the chamber in the stomach. The system consists of two chambers the first chamber consisting of the drug, and the volatile liquid in the second chamber.

B. Non-Effervescent FDDS
In GI tract, the non-effervescent FDDS is based on the mechanism of polymer swelling or bioadhesion to the mucosal layer. The excipients most frequently used in non-effervescent FDDS are:

- Hydrophilic gums
- Gel forming or highly swellable cellulose type hydrocolloids
- Polysaccharides and matrix forming materials such as polymethacrylate, polycarbonate, polystyrene, polyacrylate, as well as bioadhesive polymers such as Carbopol and Chitosan.

1. Colloidal gel barrier systems / Single layer floating tablets
Such systems contain a high degree of one or more gel forming, cellulose type hydrocolloids, polysaccharides, and polymers forming matrix, which are extremely swellable.

2. Bi-layer floating tablets
A bi-layer tablet comprises of two layers with first layer is the immediate release layer, which releases the initial dose from the system while the other is the sustained release layer which absorbs the gastric fluid, creating an impermeable colloidal gel barrier on its surface and retaining a bulk density of less than 1.

3. Micro porous compartment systems
This technology is based on a drug reservoir being encapsulated within a micro porous compartment with apertures along its top and bottom walls.

4. Multi particulate system: Floating beads / Alginate beads
Multi-particulate drug delivery systems are often oral dosage types consisting of a multiplicity of small discrete units.

5. Micro balloons/Hollow microspheres
Hollow microspheres, also known as micro balloons when immersed in aqueous media they were found to float in vitro for 12 hrs.

C. Raft Forming System
For the delivery of antacid and other medications for gastro-infection and gastro intestinal disorders, a Raft forming systems are mostly considered. Upon contact with gastric fluid the gel forming solution swells and creates a viscous compact gel containing an entrapped CO2 bubbles forming raft layer on top of gastric fluid that gradually releases the drug substance into the stomach.

Approaches to Design Floating Drug Delivery System[14]
For Single Unit Dosage Forms (Ex: Tablets)
A. Floating Lag Time: Time taken for the tablet to emerge onto the dissolution medium surface and is measured in seconds or minutes.

B. In-vitro drug release and floating duration: This is calculated by the use of USP II devices (paddle) stirring in simulated gastric fluid (pH 1.2 without pepsin) at a speed of 50 or 100 rpm at 37±0.20C.the samples are then frequently collected and analyzed for the drug content.

The time (hrs) during which the tablets remain buoyant on the dissolution medium surface is the floating duration and is observed visually.

C. In-vivo Gastro-Retention Assessment: This is done by X-ray or gamma-scintigraphic testing of the dosage form transition in GIT. The tablets are also tested for hardness, variation in the weight etc.

Hydrodynamically Balanced System
The delivery system are designed to extend the stay of medication types in the gastro intestinal tract, and to help enhance absorption. HBS system produces drugs which have a greater solubility in acidic conditions and also have a particular absorption site in the upper part of the small intestine. For the drug to retain in stomach for an extended period of time the dosage form should have the bulk density of less than '1' and release the drug constantly from the dosage form.

For Multiple Unit Dosage Forms (Ex: Microspheres)
a) Morphological and dimensional analysis, using electron microscopy (SEM) scanning. An optical microscope can also be used to determine the dimension.
b) In-vitro floating potential (Buoyancy level): A known quantity of microspheres is distributed over the surface of a USP (Type II) dissolution system filled with 900ml 0.1 N HCl containing 0.002 level v / v Tween 80 and agitated at 100 rpm for 12 h. After 12 hours, the floating layer and settled layers are separated, then dried in a dessicator and are weighed.

The buoyancy is calculated from the following formula.

$$\textbf{Buoyancy (\%)} = Wf / (Wf + Ws) \times 100$$

Where,

Wf and Ws are the weights of floating and settled microspheres, respectively.
Drug-excipient (DE) interactions: This is usually done by using FTIR. The appearance of a new peak, and/or disappearance of original drug or excipient peak indicates the Drug-excipent interaction.

Methods of Developing Floating Drug Delivery System[15,16]

- **Direct compression technique**

It means compressing tablets directly from powder content without altering the substance's physical structure itself. Dicalcium trihydrate phosphate, tricalcium phosphate, etc. are the most widely used carriers.

- **Effervescent Technique**

An effervescent reaction between organic acid (citric acid) and bicarbonate salts will fill the floating chamber of the drug delivery system with inert gas (CO2).

- **Wet granulation technique**

Involves wet powder massaging, milling or drying. Wet granulation shapes the granules by binding the powders together with an adhesive rather than compacting them.

- **Ionotropic Gelation Technique**

Gelation of anionic polysaccharide sodium alginate, the primary polymer of natural origin, was accomplished with opposite charged calcium ions (counter-ions) with the objective of forming instantaneous micro particles.

- **Solvent evaporation technique**

Continuous phase ability is inadequate to remove the entire amount of liquid dispersal solvent. Solvent evaporates from the dispersal surface to receive hardened microspheres.

- **Spray Drying Technique**

Involves dispersing the core layer into the liquefied coating content and spraying the core coating mixture into the environment so that the coating is solidified by rapidly evaporating in which the coating material is solubilized.

- **Melt Solidification Technique**

This method involves emulsifying the molten mass in the aqueous phase followed by cooling it to solidify. Lipids, waxes, polyethylene glycol, etc. are the carriers used for this technique.

- **Melt Granulation Technique**

This is the method that agglomerates the pharmaceutical powders using a meltable binder and does not use water or organic solvents for granulation.

Excipients Incorporated in Different Floating Dosage Form[17]

- **Effervescent Agents:** E.g. citric acid, tartaric acid, sodium bicarbonate, Di-SGC (Disodium glycine carbonate), CG (Citroglycine).
- **Release rate Retardants:** Some substances such as, Talc, Dicalcium phosphate, Magnesium stearate are used for retarding the release rate.
- **Inert Fatty Materials:** E.g. Long chain fatty alcohols, Beeswax, Fatty acids, Gelucires 39/01 and 43/01.
- **Release rate Accelerants:** E.g. Mannitol, lactose, etc.
- **Hydrocolloids:** E.g. Acacia, β-cyclodextrin, Gelatin, Alginates, Pectin, HPMC, Carbopol etc.
- **Buoyancy increasing Agents:** E.g. Ethyl Cellulose and Polypropylene Foam Powder (Accurel MP 1000).

Evaluation of Floating Drug Delivery System[18, 19]

- **Bulk Density**

It is the ratio of total mass of powder (m) to the bulk volume (Vo) of powder.

$$Db=m/Vo$$

- **Tapped Density**

It is the ratio of total mass of powder (m) to the tapped volume (Vi) of powder.

$$Dt = m/Vi$$

- **Compressibility Index**

The flowability of powder can be evaluated via evaluating the bulk density (ρB) and tapped density (ρT) of powder and the rate at which it packed down. Compressibility index calculated by means of

$$CI=100[(\rho T-\rho B)/\rho B]$$

Where,
ρT = Bulk density g/ml,
ρB = Tapped density g/ml.

- **Hausner's Ratio**

It is evaluated by means of taking Tapped density and it divided by Bulk density by the usage of following formula.

Hausner's Ratio= Tapped density / Bulk density

- **Angle of Repose**

The frictional forces in a loose powder or granules can be measured via angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules are allowed to flow through the funnel fixed to a stand at fixed height (h). The angle of repose, then calculated by measuring the height and radius of the heap of granules formed.

$$\tan\theta = (h/r)$$
$$\theta = \tan^{-1}(h/r)$$

θ = angle of repose
h = height of the heap
r = radius of the heap

Table 1: The relationship between Angle of repose and powder flow.

Angle of repose	Powder flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

- **Tablet Dimensions**

Thickness and diameter were measured using a calibrated Vernier Caliper. Three tablets of each formulation have been picked randomly and thickness were measured separately.

- **Hardness**

Hardness shows the capability of a tablet to face up to mechanical shocks while handling. The hardness of the tablets was evaluated using Monsanto hardness tester. It was expressed in kg/cm2. Three tablets have been randomly picked and hardness of the tablets was decided.

- **Friability test**

The friability of tablets was evaluated by using Roche Friabilator. It was expressed in percent (%). Ten tablets had been to start with weighed (W) and transferred into friabilator. The friabilator were operated at 25 rpm for 4 minutes or run as much as 100 revolutions. The tablets have been weighed again (Wo). The % friability was then calculated by using formula–

%F = 100 (1-Wo/W)

% Friability of tablets less than 1% was considered desirable.

- **Tablet Density**

Tablet density was an excellent parameter for floating tablets. The tablet could floats most effective when its density turned into much less than that of gastric fluid (1.004). The density was determined by the usage of following formula.

$V = \pi r^2 h$

d = m/v

Where,

v = volume of tablet (cc)

r = radius of tablet (cm)

h = crown thickness of tablet (g/cc)

m = mass of tablet

- **Weight Variation Test**

Ten tablets were selected randomly from each batch and weighed separately to test for weight variation. A little variation was allowed in the weight of a tablet through U.S. Pharmacopoeia.

Table 2: Percentage deviation in weight variation.

Average weight of a tablet	Percentage deviation
130mg or less	10
>130mg and <324mg	7.5
324mg 0r more	5

- **Determination of Buoyancy lag time**

The buoyancy lag is the time required for tablet to come out towards surface & float. The buoyancy of tablets was studied at 37±0.5ºc in 900ml of simulated gastric fluid. The buoyancy lag time was determined by the usage of stop watch and overall floating time was observed visually.

- **Floating time**

Floating time was measured by the use of USP dissolution apparatus-II at 50 rpm using 900ml of 0.1N HCl and temperature was set at 37±0.5ºC, throughout the study. The duration of floating (floating time) is the time the tablet floats within the dissolution medium (including floating lag time, which is the time required for the tablet to rise to the surface) is measured by visual observation.

- **Swelling Index[20]**

Swelling study was carried out for the floating sustained release layer tablets. The accurately weighed tablets were placed in USP dissolution apparatus II containing 900ml of 0.1N HCL maintained at 37±2ºC and allowed to swell up to constant weight. The tablets had been removed, blotted with filter paper, and changes in weight were determined. The experiments were performed in triplicate. The degree of swelling (Swelling index) was then determined from the formula.

$$\text{Swelling index} = \frac{W_s - W_d}{W_d}$$

Where,

W_d = initial weight of tablet

W_s = weight of tablet at equilibrium swelling in the medium.

- **Drug Content**

Five tablets were chosen randomly from a batch, weighed and powdered in a mortar. An accurately weighed quantity of powdered tablets equivalent to 100 mg was taken in a standard flask and the volume was filled up to the mark with 0.1 N HCL; the solution was filtered through a 0.45 um membrane paper. Analysis was done by the usage of spectrophotometric method.

- **In-vitro dissolution studies[21]**

The release rate of floating tablets was determined by the usage of USP dissolution testing apparatus II (Paddle type). The dissolution test was carried out using 900 ml 0.1N HCL, at 37 ± 0.5°C. A sample (5ml) of the solution was taken from the dissolution apparatus at every hour for 12 h, and the samples were replaced with fresh dissolution medium. The samples were passed via Whatman's filter paper and the absorbance of these solutions was measured.

Table 3: Recently Reported Drugs for Floating Drug Derlivery System.

AUTHOR	DRUG	METHODS	REMARKS
Lingam M *et al* (2008)	Captopril	Direct compression	Prolonged gastric residence time and increased bioavailability.[22]
Neha A *et al* (2019)	Azithromycin	Wet granulation	The effervescent based floating drug delivery was a promising approach to achieve in vitro buoyancy.[23]
Kharia A *et al* (2010)	Acyclovir	Wet granulation	Increased gastric residence time and bioavailability[24]
S S Patel *et al* (2006)	Clarithromycin	Wet granulation	Improved bioavailability[25]
Radha Krishna M *et al* (2012)	Amoxyciillin	Direct compression	Sustained release over 2hr[26]

CONCLUSION

Several formulation approaches have been explored in the development of floating drug delivery system. Floating tablet as floating drug delivery System has gained importance for the delivery of the drug in the stomach because of their increase enhanced permeability, increase biocompatibility, and higher stability.

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