Available online on 15.12.2020 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

A Comprehensive Review on Floating Drug Delivery System (FDDS)

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Abstract

The main goal of any drug delivery system is to achieve desired concentration of the drug in blood or tissue, which is therapeutically effective and non-toxic for a prolonged period. Current pharmaceutical scenario focuses on the formulation of floating drug delivery system (FDDS). FDDS are low density systems that float over the gastric contents and remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. The aim of writing this review is to compile the current literature with special focus on the principal mechanism of floatation to attain gastric retention. Effervescent FDDS release CO_2 gas, thus reduce the density of the system and remain buoyant in the stomach for a prolonged period of time and released the drug slowly at a desired rate so it can be used to prolong the gastric residence time in order to improve the bioavailability of drug. The review briefly describes the mechanism, types of floating system, advantages, limitation, factors affecting floating system, drug candidates suitable for floating, evaluation parameters and application of the system. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form and the future potential of FDDS.

Keywords: Floating drug delivery system, Absorption Window, Effervescent system, floating lag time.

Article Info: Received 07 Oct 2020; Review Completed 26 Nov 2020; Accepted 03 Dec 2020; Available online 15 Dec 2020

Cite this article as:

Bhosale AR, Shinde JV, Chavan RS, A Comprehensive Review on Floating Drug Delivery System (FDDS), Journal of Drug Delivery and Therapeutics. 2020; 10(6):174-182 http://dx.doi.org/10.22270/jddt.v10i6.4461

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INTRODUCTION:

Despite tremendous advancement in drug delivery, oral route of administration has received the more attention and success because the gastrointestinal physiology offers more flexibility in dosage form design than other routes. Hence, research continuously keeps on searching for ways to deliver drugs over an extended period of time, with a well-controlled release profile [1]. The solid oral dosage forms like capsules, tablets gives specific drug concentration in Systemic blood circulation without getting any control over drug delivery system and also cause major fluctuations in plasma drug concentrations. There are numerous attempts are performed to develop prolonged (sustained) release preparations with extended clinical effects and reduced frequency of dose. A problem continuously encountered with conventional sustained release dosage forms is that the duration in stomach is unable to extend and there's no control over drug delivery of drug which leads to fluctuations in plasma drug concentration level [2]. Recent approaches to extend the gastric duration of drug delivery systems include bioadhesive systems, floating systems (low density systems), non-floating systems (high density systems), magnetic systems, swelling systems, unfoldable and expandable systems, raft forming systems and superporous systems, Biodegradable hydrogel systems [3].

FLOATING DRUG DELIVERY SYSTEM:

Floating drug delivery system (FDDS) is a class of gastroretentive drug delivery system [4]. By virtue of their low densities (<1.004 g/cm3), Floating systems or hydrodynamically controlled systems remain and provide continuous release of the drug [5, 6].

MECHANISM OF FLOATING DRUG DELIVERY SYSTEMS [3, 7, 8]:

The system is floating on the gastric contents (see in figure 1(a)), the slow drug release is accompanied with requisite rate during the system flow on the gastric contents. The release is followed by removal of the residual system from the stomach. But, along with the appropriate level of floating force (F), minimum levels of gastric contents are needed to permit achievement of buoyancy retention principle and also to keep dosage form buoyant over meal surface. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW) has been reported in the literature. Its operation constitutes of measuring a force equivalent to F (with respect to time) which keeps the object submerged. The object floats better if RW is on the higher positive side (see in figure 1(b)).This apparatus optimizes FDDS and prevents its drawbacks unforeseeable intragastric buoyancy capability variations, related to stability and durability.

$$RW \text{ or } F = F_{buoyancy} - F_{gravity} = (D_f - D_s)\, gV$$

Where, F= total vertical force, D_f = fluid density, D_s = object density, V = volume and g = acceleration due to gravity.

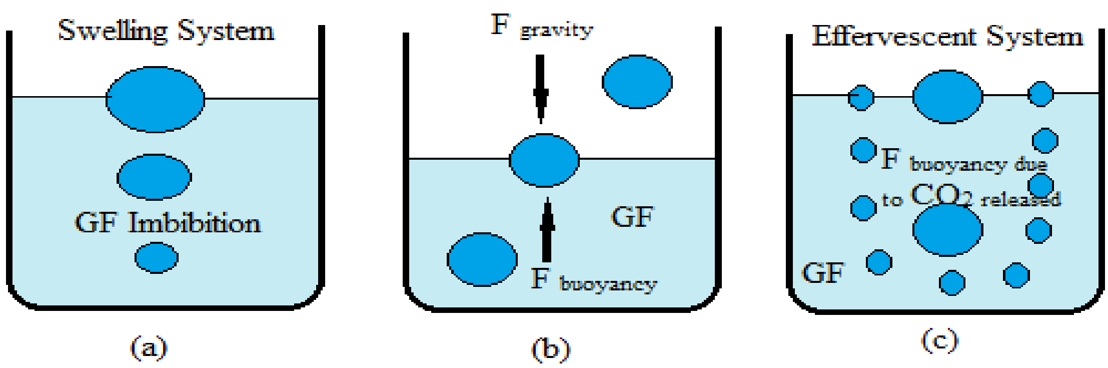

FIGURE 1: Mechanism of FDDS, GF: Gastric Fluid, CO_2: Carbon Dioxide [3]

ADVANTAGES OF FDDS [1, 2, 9]:

- Increases the oral bioavailability of drug.
- Enhanced first pass biotransformation.
- Sustained drug delivery/ reduced frequency of dosing.
- Reduced fluctuations of plasma drug concentration.
- Improved receptor activation selectivity.
- Provide higher efficiency due to reduced counter-activity of body.
- Extended time over critical (Effective) concentration.
- Minimized adverse activity at the colon.
- Targeted therapy for local ailments within the upper GIT.
- Site specific Drug Delivery.

LIMITATIONS OF FDDS [10-14]:

- Drugs having solubility or stability problem in GIT aren't suitable for FDDS.
- Drugs like Nifedipine, Propranolol etc. which are well absorbed throughout GIT and which undergoes first pass metabolism aren't be desirable candidate.
- Drugs which are irritant to Gastric mucosa also are not desirable.
- Drugs that are unstable in the acidic environment of the stomach aren't suitable in this type of systems.
- High level of fluid in the stomach is required for maintaining buoyancy; float and work efficiently.

RATIONALE FOR DRUG SELECTION [15]:

The rationale for drug choice becomes quite important for this drug delivery system. The selection criteria for floating systems involve numerous physicochemical characters of drug. Biopharmaceutical system (BCS) is vital criteria for drug to be chosen. BCS classification relies on solubility and permeability of drug. For FDDS, solubility of drugs ought to be very soluble in abdomen to understand better bioavailability. The dissociation constant of the drug of choice ought to be >2.5 for acidic drug, therefore as which can stay unionised at gastric pH and drug get absorb within the abdomen. For lipophilicity, the partition constant of the drug ought to be >1 for quick absorption across lipoidal membranes. The half –life of drug ought to be shorter (2 -6, preferably). The drug that possesses acid stability can exclusively be developed as FDDS.

DRUG CANDIDATES SUITABLE AND UNSUITABLE FOR FLOATING DRUG DELIVERY SYSTEMS [3, 16, 17]

The suitable and unsuitable medication candidates for FDDS are listed in Table 1 and Table 2 severally.

TABLE 1: Drug candidates suitable for floating Drug Delivery system.

S. No.	Suitable Drug Candidates	Example
1.	Medication with narrow absorption window in GIT.	Methotrexate, Levodopa, Repaglindine, Riboflavin, Furosemide, Cyclosporine, Atenolol, Theophyllin, Para-aminobenzoic Acid.
2.	Medication acting regionally within the stomach.	Antacids, Anti-ulcer medication, Misroprostol
3.	Medication having low solubility at high nucleon concentration values.	Diazepam, chlordiazepoxide, verapamil HCL, Furosemide
4.	Medication having unstable properties within the enteral or colonic atmosphere.	Captopril, ranitidine HCl, metronidazole, Metformin HCl.
5.	Medication caused imbalance of normal colonic microbes.	Antibiotics against H. Pylori, Amoxil Trihydrate, Tetracycline, Clarithromycin

TABLE 2: Drug candidates unsuitable for floating Drug Delivery System.

S. No.	Unsuitable Drug candidates	Example
1.	Medication having terribly restricted acid solubility.	diphenylhydantoin
2.	Medication that suffers instability among the gastric environment.	Erythromycin
3.	Medication that are used for selective release in the colon.	mesalamine and corticosteroids

FACTORS CONTROLLING FDDS [3,7, 9,11-13,18]:

Factors controlling FDDS are shown in Figure 2 and some of the factors are enumerate-

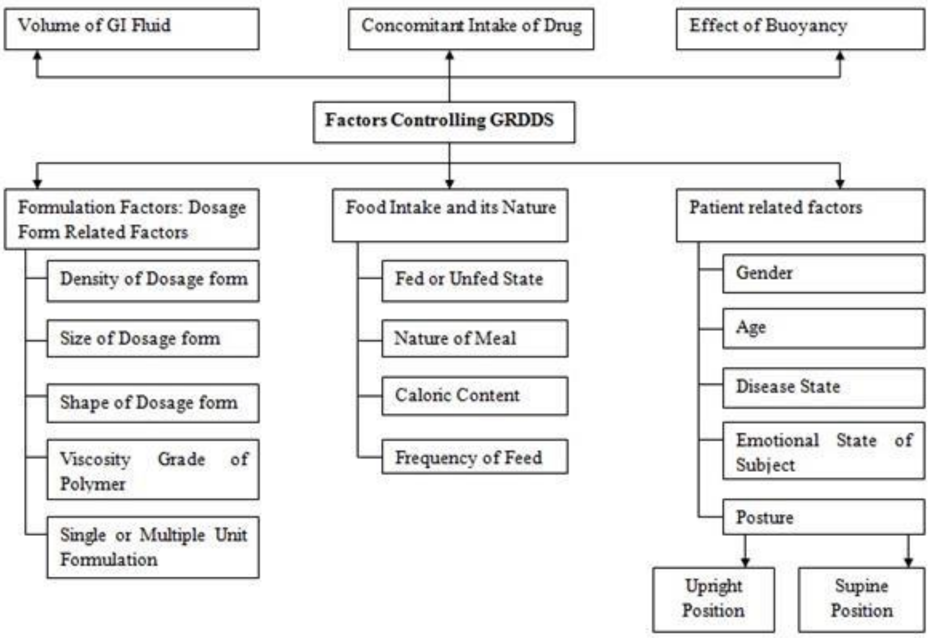

FIGURE 2: Factors controlling FDDS

- **Density:** Density of the dosage form ought to be less than the stomachic contents (1.004gm/ml).
- **Size and Shape:** dosage form unit with a diameter of more than 7.5 millimeter are reported to possess an enhanced GRT competed to with those with a diameter of 9.9 mm. The dosage type with a form tetrahedron and ring form devises with a flexural modulus of forty eight and 22.5 kilo-pond per sq in (KSI) are reported to possess higher gastrointestinal tract for ninety to 100 percent retention at twenty four hours compared with alternative shapes.
- **Viscosity Grade of Polymer:** Drug unleash and floating properties of FDDS are greatly plagued by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be additional helpful than high viscosity polymers (e.g., HPMC K4M) in rising floating properties. additionally, a decrease within the unleash rate was ascertained with a rise in polymer viscosity.

- **Fed or Unfed State:** under abstinence conditions, the GI motility is characterised by periods of sturdy motor activity or the migrating myoelectric complexes (MMC) that happens each 1.5 to 2 hours.
- **Caloric content:** GRT are usually increased by 4–10 h with a meal that is more in proteins and fats.
- **Frequency of feed:** The GRT will increase by over 40 minutes when sequential meals are given compared with a single meal because of the low frequency of Migrating Myoelectric Complex(MMC).
- **Gender:** It absolutely was ascertained that mean GRT in males (3.4±0.6 h) is a smaller amount than the female subjects (4.6±1.2 h) of same age and race. Females empty their abdomen slowly as compared to male candidates, despite their weight, height, and body area.
- **Age:** Older individuals, particularly those over seventy, have a considerably longer gastrointestinal residence time (GRT).
- **Posture:** GRT will vary between supine and upright ambulant states of the patient. For the floating systems it absolutely was rumored that when subjects were kept within the upright ambulant position the dosage type stayed unceasingly on stomachic content as compared to the supine state of the patients. Thus, inside the upright position of the patients floating drug delivery system protected against post-prandial evacuation.
- **Concomitant drug administration:** Antihypertensive drug like clonidine, lithium, nicotine, progesterone, anti-cholinergics like atropine and propantheline, and opiates like codeine prolong gastric residence time. On the alternative hand, Erythrocin and octreotide enhance the stomachic evacuation
- **The amount of the GI Fluid:** the amount of liquids administered affects the stomachic evacuation time. when the amount is large, the evacuation is faster . Cold fluids delay stomachic evacuation whereas hotter fluids fasten stomachic evacuation.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS [19]:

Two distinctly different technologies have been utilized in the development of FDDS, according to the mechanism of buoyancy [20].

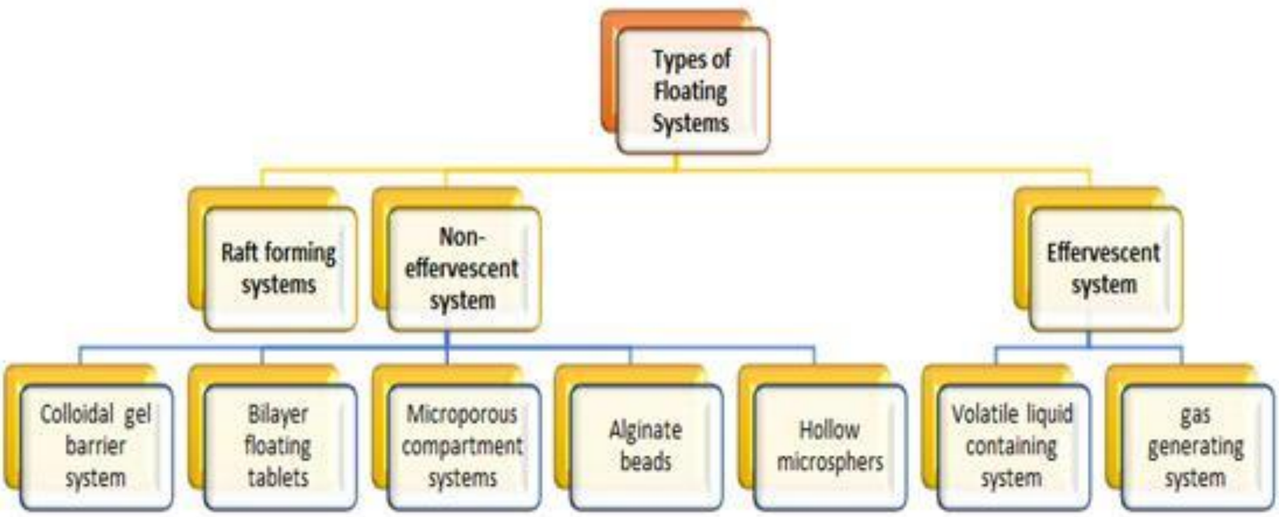

FIGURE 3: Classification of floating system [20]

Non-Effervescent Floating Drug Delivery System [3, 21, 23]:

Once ingested, these systems get swelled up by the imbibitions of gastric fluid to such an extent that their exit from the stomach is delayed. Usually, a gel, which swells when gets in contact with the gastric fluid is used in the formulation of these systems which helps in maintaining a relative integrity and a bulk density of <1 within the outer gelatinous barrier. The buoyancy of these systems depends upon air entrapped by the polymer. HPMC, carbopol, polyacrylate polymers etc. are the most commonly used polymers in the formulation of these systems. These systems are further classified as-

1. Colloidal gel barrier system / Hydrodynamically balanced systems (HBS)
2. Microballoons / Hollow microspheres
3. Alginate beads
4. Microporous compartment systems
5. Layered tablets

a. Single layered floating tablets

b. Double layered floating tablets

Effervescent floating drug delivery systems [11, 22]:

Flotations of a drug delivery system within the stomach are often achieved by incorporating a floating chamber stuffed with vacuum, air, or an noble gas. Gas are often introduced into the floating chamber by the volatilization of an organic solvent (e.g. ether or cyclopentane) or by the carbon dioxide produced as a result of an effervescent reaction between organic acids (e.g., citric acid and tartaric acid) and carbonates (e.g.,Sodium bicarbonate). These effervescent systems further classified into following types-

I. Gas Generating systems

II. Volatile Liquid/Vacuum Containing Systems

I. Gas generating system [3, 12, 23, 24]:

Gas bubble generation helps to attain floatability. The swellable polymers viz. methylcellulose and chitosan and numerous effervescent compounds, e.g. sodium bicarbonate, tartaric acid and citric acid, facilitate in making matrix form of such systems. For gas generation, the optimum stoichiometric ratio of citric acid and sodium bicarbonate is rumored to be 0.76:1. reported created in an exceedingly manner that upon contact with stomachic contents carbonic acid gas is discharged finally entrapping in swollen hydrocolloids, that creates dosage forms buoyant. Gas generating systems includes-

1. Intra gastric single layer floating tablets
2. Intra gastric bi-layer floating tablets
3. Multiple unit type floating pills

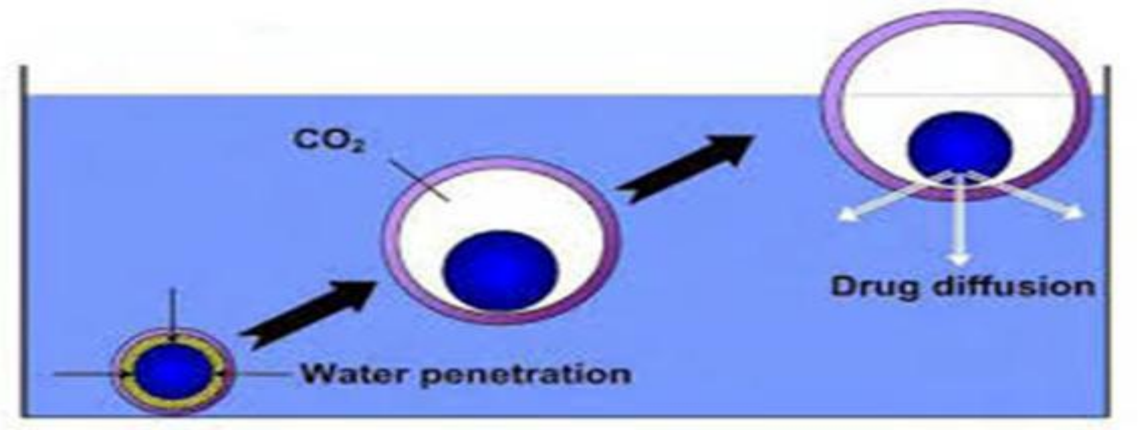

FIGURE 4: Gas generating system [12]

II. Volatile liquid containing systems [16, 25]:

These have an inflatable chamber that contains a liquid e.g. ether, cyclopentane, that gasifies at blood heat to cause the inflation of the chamber within the abdomen. These systems are osmotically controlled floating systems having a hollow deformable unit. There are 2 chambers within the system initial contains the drug and also the second chamber contains the volatile liquid. These systems are further classified as-

1. Intragastric floating gastrointestinal drug system.
2. Inflatable gastrointestinal delivery system
3. Intragastric-osmotically controlled drug delivery system

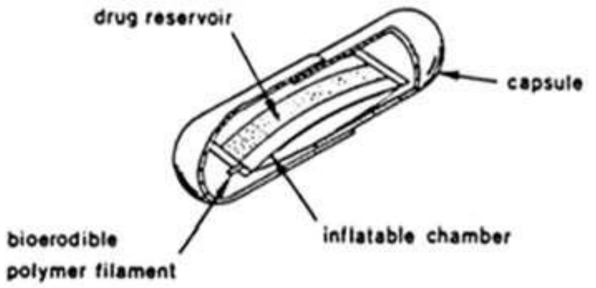

FIGURE 5: Volatile liquid containing systems [16]

FORMULATION [26]:

Excipients mainly used in floating tablets are as-

1. Hydrophilic Polymers: Hydroxy propyl methylcellulose (HPMC)
2. Carrier matrix: Gelucire.
3. Gel forming hydrocolloids / Matrix Formers: Polycarbonate, Polyacrylate, Polymethacrylate and polystyrene.
4. Swellable polymers: Chitosan and sodium bicarbonate and citric acid or tartaric acid.
5. Matrix forming polymers: HPMC, Polyarcylates, cargeenan gum, guar gum, Arabic
6. Fillers: Lactose, microcrystalline cellulose.
7. Lubricant: Magnesium stearate, purified talc.
8. Buoyancy Agents: Cellulose, gums, polysaccharides, starch, gelatin.
9. Diluents: Lactose, mannitol, glucose, microcrystalline cellulose, starch, di-calcium phosphate.
10. Porosity Agents: Lactose.

METHOD OF PREPATRATION OF FLOATING EFFERVESCENT TABLETS:

1. Direct Compression Method [27, 28]:

Involve compression of tablets directly from powdery material whereas not modifying the physical nature of the material itself. Direct compression vehicles or carriers ought to have good flow and compressible characters these properties are imparted by predisposing these vehicles to slugging, spray drying or crystallization. most ordinarily used carriers are di-calcium phosphate trihydrate, tri-calcium phosphate etc. Direct compression technique is particularly used within the formulation of floating effervescent tablet and for all moisture sensitive products.

2. Wet Granulation [28]:

This technique is most generally used and most common method for preparation of tablets. The acid and carbonate parts of the bubbling formulation are often granulated either separately or as in a combination with water, ethanol (possibly diluted with water), iso-propanol or other solvent. When granulating either with solvents containing water or pure water, the bubbling reaction will start. Care must be taken to take care of adequate control of the method . Vacuum processing is usually beneficial because of the ability to control the bubbling reaction and therefore the drying process.

3. Dry Granulation [9]:

The process involves compaction of powder particles into large pieces or compacts which are subsequently broken down into granules to produce granules that can be further processed into dosage forms. When ingredients employed in tablet formulation is sensitive to moisture then slugging may use. Slugging of the material is completed by using heavy-duty tableting equipment or with roller compaction.

4. Hot-Melt Extrusion (HME) Method [24]:

It is the strategy of embedding drug throughout a polymeric carrier. Specifically, HME dosage forms are complex mixtures of API, functional excipients, and processing aids, that are homogenised uniformly. The calculated quantity of beeswax (melting aid) was dissolved in a china dish. To this, geometrical mixture blend of polymers, diluents was added followed by the Active pharmaceutical ingredient (API).Mix it well before solidifying and later the mass was faraway from hot plate by scrapping till it attains room temperature and thus the coherent mass passed through sieve no.36 to form granules. The formed granules were then created to undergo sieve no.100 to get eliminate any fines. The formed granules are then mixed with calculated quantity of glidant and lubricants for the process operations and therefore the granules then are compressed using rotary tablet punching machine to get the floating tablet.

EVALUTION OF FLOATING DRUG DELIVERY SYSTEM [9]:

Following parameter used in evalution of effervescent floating tablet-

- **Bulk density [7]:**

Bulk density denotes the entire density of the material. It includes truth volume of interparticle spaces and intraparticle pores. The packing of particles is especially liable for bulk. Bulk density is defined as:

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume of powder}}$$

When particles are packed, it's potential that an oversized quantity of gaps could also be present between the particles. Therefore, trapping of powder permits the particles to shift and take away the voids to minimum volume. the volume occupied by the powder during this condition represents the bulk volume. substituting this volume for a given weight of powder in equation provides the bulk density.

- **Tapped density [2]:**

Tapped density used to verify flowability and packing geometry of formulation. tapped density is that the ratio of weighed quantity of sample and volume of powder determined by tapping using measuring cylinder. Tapped density is calculated by-

$$\text{Tapped density} = \frac{\text{weight of the powder}}{\text{Tapped volume of powder}}$$

- **Carr's index/ Compressibility index [25, 29]:**

The flowability of powder can be evaluated by comparing the bulk density (ρo) and tapped density (ρt) of powder and the rate at which it packed down. Compressibility index was calculated by –

$$\text{Compressibility index (\%)} = \frac{\rho t - \rho o}{\rho t} \text{x } 100$$

Where, ρo = Bulk density ρt = Tapped density

- **Angle of Repose [7, 25]:**

The resistance forces during a loose powder or granules are usually measured by angle of repose. Angle of repose is outlined as "the maximum angle possible between the surface of the pile of powder and so the horizontal plane." Lower the angle of repose, higher the flow properties. The granules were allowed to flow through the funnel mounted to a stand at definite height (h). The angle of repose was then calculated by measurement of the height and radius of the heap of granules fashioned.

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

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

TABLE 3: Relationship between angle of repose and powder flow

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

- **Percentage Porosity [7]:**

Whether the powder is porous or nonporous, the entire porosity expression for the calculation remains an equivalent . Porosity gives information about hardness, disintegration, total porosity, etc.

$$\text{\% porosity, €} = \frac{\text{Void volume}}{\text{Bulk volume}} \times 100$$

$$\text{\% porosity, €} = \frac{\text{(Bulk volume-true volume)}}{\text{True density}} \times 100$$

- **Thickness, Uniformity of weight, Content uniformity, Hardness, Friability and Assay [9]:**

All these tests can be performed as per the procedures mentioned in the official monographs.

- **Floating lag time and total floating time determination [14]:**

The time between the start of the dosage type into the medium and its go up to higher one third of the dissolution vessel is termed as floating lag time (FLT) and also the time that the dosage type floats is termed as the floating time (FT). These tests are typically performed in simulated stomachic fluid or 0.1 mole/liter HCl maintained at 37° C in USP dissolution equipment containing 900 millilitre of 0.1 molar HCl as the dissolution medium.

- **In-vitro Drug release Studies [30]:**

The test for in vitro drug release studies are typically applied in simulated stomachic and enteric fluids maintained at 37° C. Dissolution tests are performed using the USP dissolution equipment. Samples are withdrawn periodically from the dissolution medium, replaced with constant volume of fresh medium on every occasion, then analyzed for their drug contents after an appropriate dilution. Recent methodology as represented in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started. A small, loose piece of non-reactive material like less than many turns of wire helix could also be hooked up to the dosage units that may otherwise float. However, standard Dissolution methods supported the USP or British pharmacopoeias (BP) are shown to be poor predictors of in vitro performance for floating dosage forms.

- **Swelling Study** [29]**:**

The swelling behaviour of a dosage type was measured by finding out its weight gain or water uptake. The dimensional changes can be measured in terms of the rise in tablet diameter and/or thickness over time. Water uptake was measured in terms of % weight gain, as given by the equation-

$$\text{Water Uptake} = (W_t - W_o) / W_o \times 100$$

Where,

W_t = Weight of dosage form at time t.

W_o = Initial weight of dosage form.

- **Differential Scanning Calorimetry (DSC)** [5]**:**

DSC is employed to characterize water of hydration of prescribed drugs .Thermo grams of developed formulations were obtained using DSC instrument equipped with an intracooler. Metallic standards such as indiun / Zinc were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermitically sealed in an aluminum pan and heated at a constant rate of 10ºC/min; over a temperature vary of 25º C - 65º C. Inert atmosphere was maintained by purging nitrogen gas at the rate of flow of 50ml/min.

- **X-ray/ Gamma scintigraphy** [31]**:**

X-rays are mostly used for internal body examination using radioopaque marker like barium sulphate in dosage forms instead drug and thus the gastroretentive imaging is completed by X-rays at different time intervals such as 0, 1, 6, 12, and 24 hrs. several researchers used X-ray pictures in gastroretentive dosage forms for assessing numerous parameters for their availability. One will conclude and correlate the route of dosage type and stomachic empting time inside the GI tract. to identify availability of dosage type in abdomen, typically X-ray pictures are helpful tools to evolve whether the dosage type accessible or not. Gamma scintigraphy, γ-camera or scinti scanner is utilized for the indirect observation of a formulation by the involvement of a γ-emitting radio nucleotide. In γ-scintigraphy, the γ-rays emitted by the nucleotide are directed on a camera that aids to focus and examine to find the situation of the dosage type inside the alimentary tract. Peroral endoscopy is additionally stated as gastroscopy used with video systems or fiber optics and wont to observe visually the analysis of GRDDS and results of prolongation inside the abdomen to conclude.

- **Gastroscopy** [32]**:**

Gastroscopy involves visual observation of dosage type within the abdomen using optic-fibers and a video camera retained blood or food within the abdomen might cause poor study results.

- **Ultrasonography** [32]**:**

Ultrasonic waves are mainly used to produce pictures of body structures. The waves travel through tissues and are mirrored back wherever density differs. The mirrored echoes are received by an electronic equipment that measures their intensity level and conjointly the position of the tissue reflecting them. The results are going to be displayed as pictures or as a motion picture of the inside of the body.

- **Specific Gravity** [14, 33]**:**

The specific gravity of floating system is determined by displacement methodology by using benzene as a displacing medium.

APPLICATION OF THE FLOATING DRUG DELIVERY SYSTEM [4, 5, 7, 13, 24, 34, 35]:

Several variety of application of floating drug delivery system are following as-

- **Maximize the bioavailability-**

Gastro retentive floating drug delivery system is applied for extended the activity of the dosage type, drug to extended action bioavailability is maximized.

- **Action sustained drug delivery-**

The oral controlled unleash formulation are skirmished with difficulties that's stomachic residence in gastro intestinal tract. To defeat with floating drug delivery system will keep in the abdomen for very long time of the stomachic fluid.

- **Drug Delivery System act on specific site-**

Gastro retentive floating drug delivery system act properly in specific location of drug delivery system and provides appropriateness action that Vantages for dosage type by these system that is in distinction from other absorbed from the abdomen. Controlled drug delivery system is lower and furnish the amount which will fulfill a requirement local curatives levels and boundary the systemic vulnerability to the elements to the dosage type. Drug in blood circulation is cause minimize the adverse effect. furnished the accessibility stomachic from spot directed delivery system might also decrease the dose frequency e.g., furosemide and vitamin B2.

- **Minimize the absorption-**

The dosage types have less bioavailability specific site absorption from the upper part of GIT, enhancing the absorption of the dosage type.

- **Decrease the adverse activity of the colon-**

Holding of the dosage type within the gastro retentive system, decrease the quantity of drug that arrives the colon.

CONCLUSION:

Formulation of FDDS is an efficient and potential approach for gastric retention of dosage forms to improve bioavailability and also to achieve controlled release of dosage form. The most important criteria which has to be looked into for the formulation of a FDDS is that the density of the dosage form should be less than that of gastric fluid. And therefore, it is concluded that these dosage forms serve the most effective in the treatment of diseases associated with the GIT and for extracting a prolonged action from a drug with a short half-life. Inspite of number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing towards commercializing this technique. Number of economic products and patents issued in this field are evident of it.

TABLE 4: Patents on floating drug delivery systems.[21]

Sr. No.	Patent No.	Type of Formulation	Approach	Year
1.	US 5769638	Buoyant controlled release powder formulation	This system includes a floating controlled release powder formulation which can be filled into capsules and release a basic character drug at a controlled rate irrespective of the pH of the surroundings	1992
2.	US 5198229	Self-retaining GIT delivery device	This system includes a drug delivery device having a first, low density that it delivers the drug while floating in the gastric fluids and having a second, higher density to remove the device from the stomach	1993
3.	US 5232704	Sustained release bilayer buoyant dosage form	The dosage form contains a capsule including a non-compressed bi-layer formulation, one of which is controlled release layer and another is a floating layer. The dosage form has a large diameter in relation to its size and an initial density of less than 1	1993
4.	US 5626876	Floating system for oral therapy	The invention relates to a floatable, oral, therapeutic system which is specifically lighter than the gastric fluid, float on the latter and can only with difficulty reach the lower-lying pylorus	1997
5.	US 6207197	Gastro-retentive controlled release microspheres	This system includes a microsphere containing an active ingredient in the inner core and a rate controlling layer of a water-insoluble polymer	2001
6.	US 8277843	Programmable buoyant delivery technology	This system comprised of a core, one or more layers containing the drug-coated over the core and a preformed hollow space. This system provided drug delivery which is both spatially and temporally programmable	2012
7.	US 8808669	GR extended release composition of the therapeutic agent	This approach includes a controlled release omposition having floating and swelling property at acidic pH and delivers the drug for a prolonged period of time	2014
8.	US 9314430	Floating GR dosage form	This approach includes a cylindrical shaped elongated dosage form having two opposing ends, which floats due to its specific shape and size	2016
9.	US 9561179	Controlled-release floating pharmaceutical compositions	The present invention comprised of a plurality of controlled-release coated microparticles containing a drug deposited on the surface of floating core and a controlled release coating	2017

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