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Formulation, characterization and drug release kinetics of floating drug delivery systems

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ABSTRACT

The purpose of writing this review on floating drug delivery systems (FDDS) is to pile up the recent literatures with special focus on formulation, characterization and the prime mechanism of floatation to achieve gastric retention, including kinetic consideration for FDDS. Drugs showing absorption window at a particular region has limited surface area for absorption after oral administration. To overcome the limitations different dosage forms are formulated and it was observed that FDDS has the ability to be retained in the gastric environment for longer period of time, favoring the absorption of drugs showing absorption window at gastric region. This paper summarizes current approaches in the research and development, evaluation, along with formulation benefits and limitations, and drug candidates suitable to be formulated into ideal floating drug delivery systems. For predictability and reproducibility in designing an efficient floating dosage form, some kinetic studies and plots are mentioned, and the drug release mechanism from floating drug delivery systems is discussed.

Key words: floating drug delivery, gastric residence, polymers, release kinetics, kinetic plots.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve immediate and then maintain the desired drug concentration [1]. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion. Drugs that have narrow absorption window in gastrointestinal tract (GIT) will have poor absorption. For these drugs, gastro retentive drug delivery systems offer the advantages in prolonging the gastric emptying time. Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), that includes: floating drug delivery systems (FDDS), low- density systems, raft systems incorporating alginate gels, bioadhesive or mucoadhesive systems, high-density systems, super porous hydrogels and magnetic systems. The current review focuses briefly about the FDDS that is one of the most leading methodologies in gastro retentive drug formulations [2-8].

Floating Drug Delivery System (FDDS)

Floating drug delivery system is also called the hydro dynamically balanced system (HBS). FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting 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 emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. Floating Drug Delivery system is further divided into non-effervescent and effervescent (gas-generating system). A simple classification of floating drug delivery systems is given as schematic under Figure 1.

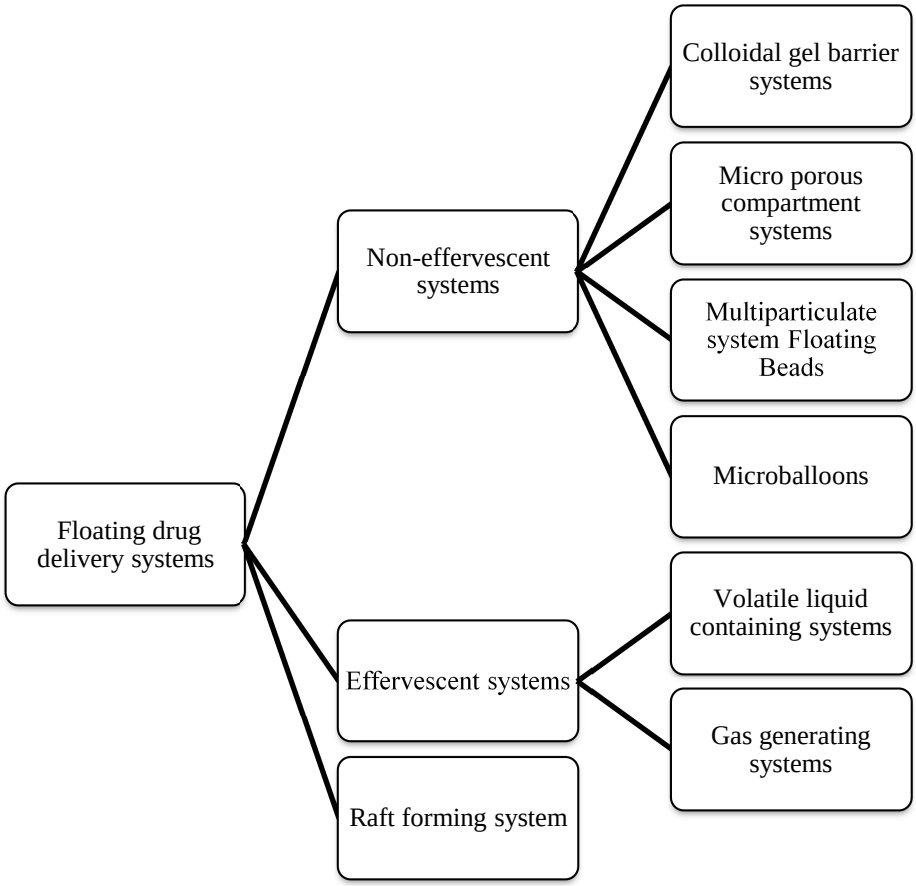

Figure 1: Classification of floating drug delivery systems

Non-effervescent systems

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bio- adhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as chitosans and carbopols.

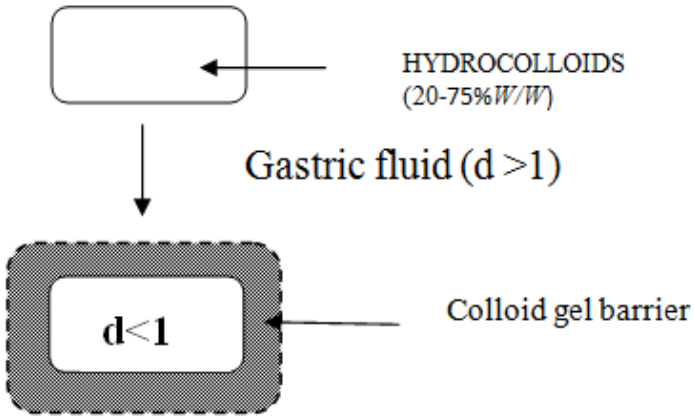

Figure 2: Non Effervescent system (Colloidal gel barrier)

Colloidal gel barrier systems

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. A schematic of non effervescent system is shown under Figure 2.

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 undissolved drug.

Multiparticulate system Floating Beads

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 0.05-2.00 mm. 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.

Microballons

various approaches are made 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 movements.

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, or may be a gas generating system. A schematic of effervescent system is shown under Figure 3.

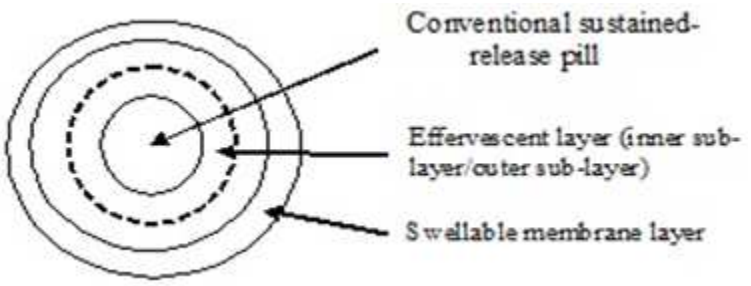

Figure 3: Single unit Effervescent FDDS

Volatile liquid containing systems: The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g., ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up off polyvinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach [9].

Gas generating systems: These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme [10].

Raft forming system

Raft forming systems have received much attention for the drug delivery for gastro intestinal infection and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluid, where in each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluid because of low bulk density created by the formation of CO_2 Usually, the system ingredients includes a gel- forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluid.

Advantages of FDDS:

1. The Floating systems are advantageous for drugs meant for local action in the stomach. e.g., antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
3. The Floating systems are advantageous for drugs absorbed through the stomach e.g., Ferrous salts, antacids.
4. 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 would be available for absorption in the small intestine after emptying of the stomach contents.

5. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

Disadvantages of FDDS:
1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
3. Drugs showing absorption window at stomach region are only considered to be better candidates.

Drug Candidates Suitable for FDDS
1. Drugs that have narrow absorption window in GIT (e.g., L-DOPA, p- aminobenzoic acid, furosemide, riboflavin) [11]
2. Drugs those are locally active in the stomach (e.g., misroprostol, antacids) [12]
3. Drugs those are unstable in the intestinal or colonic environment (e.g., captopril, ranitidine HCl, metronidazole) [13]
4. Drugs that disturb normal colonic microbes (e.g., antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin) [14]
5. Drugs that exhibit low solubility at high pH values (e.g., diazepam, chlordiazepoxide, verapamil) [15]

A List of dosage forms and drugs used in floating drug delivery system are given under Table 1.

Table 1: List of dosage forms and drugs used in floating drug delivery system [52-54]

Sr.No	DOSAGE FORMS	DRUG CANDIDATES
1	Tablets	Furosemide, Ciprofloxacin, Captopril, Acetylsalicylic acid, Nimodipine, Amoxycillin trihydrate, Verapamil HCI, Acetaminophen, Ampicillin, Cinnarazine, Dilitiazem, Florouracil, Prednisolone,
2	Capsules	Nicardipine, Chlordiazepoxide HCL, Furosemide, Misoprostal, Diazepam, Propranlol, Urodeoxycholic acid.
3	Microspheres	Aspirin, Griseofulvin, p-nitroanilline, Ketoprofen, Iboprufen, Terfenadine.
4	Granules	Indomethacin, Diclofenac sodium, Prednisolone
5	Films	Cinnarizine

Factors Affecting Gastric Residence Time of FDDS
A schematic lay out on factors affecting gastric residence time of FDDS is given under Figure 4

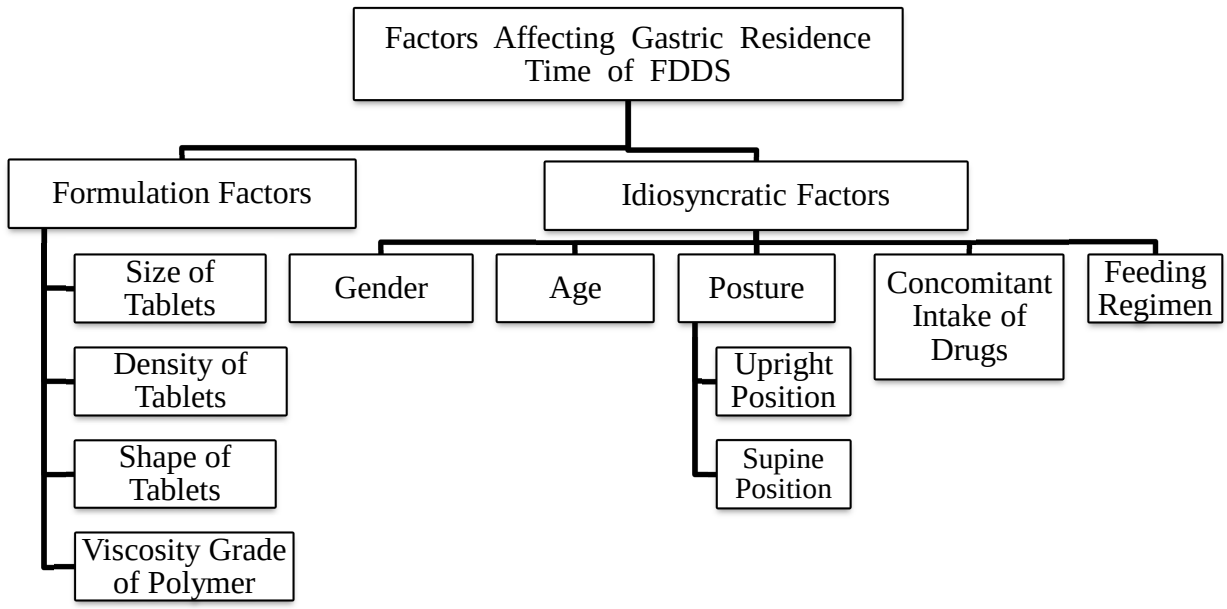

Figure 4: Layout of Factors affecting Residence time of FDDS

Formulation Factors
The design of novel floating dosage forms should take into account three important criteria, i.e., drug, delivery, and destination.

Size of Tablets [48]: The size of the dosage form influences gastric retention. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. Thus the size of the dosage form appears to be an important factor affecting gastric retention.

Density of Tablets [50]**:** Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. A density of less than 1.0 g/ml i.e., less than that of gastric contents has been reported. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities [16].

***Shape of Tablets* :** The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, cloverleaf, string, pellet, and disk) were screened *in vivo* for their gastric retention potential. The tetrahedron (each leg 2 cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr [17].

Viscosity Grade of Polymer: Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity [18].

Idiosyncratic Factors [19-21]
Idiosyncrasy is genetically determined abnormality to a chemical. The drug interacts with some unique feature of the individual, not found in majority of subjects, and produces the uncharacteristic reaction. The type of reaction is restricted to individuals with a particular genotype. It may also depends on-

Gender: Women have slower gastric emptying time than men. Mean ambulatory GRT in meals (3.4±0.4 hours) is less as compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

Age: Low gastric emptying time is observed in elderly than do in younger subjects. Intra subject and inter subject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT.

Posture:
Upright Position: An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by astral peristaltic movements.

Supine Position: This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects.

Concomitant Intake of Drugs: Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anti cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of FDDS. The co-administration of GI-motility decreasing drugs can increase gastric emptying time [21].

Feeding Regimen: Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. A GRT of 4-10 hrs has been reported after a meal of fats and proteins [21].

Formulation of Floating Dosage Form

The following types of the ingredients can be incorporated in to FDDS [22].

1. Hydrocolloids
2. Inert fatty materials
3. Release rate accelerants
4. Release rate retardant
5. Buoyancy increasing agents
6. Miscellaneous

Hydrocolloids: Suitable hydrocolloids are synthethics, anionic or non ionic like hydrophilic gums, modified cellulose derivatives. e.g., Acacia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e., gastric fluid is having pH 1.2.Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydro-dynamically balanced to have a bulk density of less than one to assure buoyancy.

Inert fatty materials: Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increases the buoyancy e.g., Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and mineral oils can be used.

Release rate accelerant: The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5-60 % by weight.

Release rate retardants: Insoluble substances such as di-calcium phosphate, talc, magnesium stearate decreases the solubility and hence retard the release of medicaments.

Table 2: Polymers and their Applications in FDDS

Name of the polymer	Pharmaceutical Applications	Application in FDDS	References
Pectin	Adsorbent; emulsifying agent; gelling agent; thickening agent; stabilizing agent.	Pectin gel beads have been shown to be an effective medium for controlling the release of a drug within the gastrointestinal (GI) tract.	[23]
Acacia	Emulsifying and suspending agent; binder; viscosity- enhancer	Used in novel tablet formulations and modified release tablets	[24,25]
Agar	Emulsifying agent; stabilizing agent; suppository base; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.	It has been investigated in a number of experimental pharmaceutical applications including as a sustained-release agent in gels, beads, microspheres, and tablets.	[26-28]
Gelatin	Coating agent; film-former; gelling agent; suspending agent, tablet binder; viscosity-increasing agent.	Low-molecular-weight gelatin has been investigated for its ability to enhance the dissolution of orally ingested drugs. Ibuprofen–gelatin micro pellets have been prepared for the controlled release of the drug.	[29-30]
Alginic Acis	Stabilizing agent; suspending agent; sustained release adjuvant; tablet binder; tablet disintegrant; viscosity-increasing agent	Alginate gel beads capable of floating in the gastric cavity have been prepared, the release properties of which were reported to be applicable for sustained release of drugs, and for targeting the gastric mucosa.	[31]
Chitosan	Coating agent; disintegrant; film-former; mucoadhesive; binder; viscosity-increasing agent.	Chitosan has been processed into several pharmaceutical forms including gels, films, beads, microspheres, tablets and coatings for liposomes.	[32-35]
Ethylcellulose	Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.	Studies have also suggested ethylcellulose for use in floating microparticles based on low-density foam powder, for gastro retentive drug delivery systems	[36]
Polycarbophil	Adsorbent; bioadhesive; controlled-release tablet binder; emul-sifying agent; thickening agent; suspending agent.	Floating-bioadhesive microspheres coated with poly carbophil have been found to be a useful gastro retentive drug delivery system for the treatment of Helicobacter pylori.	[37]
Sodium bicarbonate	Alkalizing agent; therapeutic agent.	Sodium bicarbonate has been used as a gas-forming agent in alginate raft systems and in floating, controlled-release oral dosage forms of furosemide and cisapride.	[38-42]

Buoyancy increasing agents: Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80 % by weight.

Miscellaneous: Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporates in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems.

A list of Polymers and their Applications in FDDS are given in Table 2.

Evaluation of Floating Drug Delivery System:
Evaluation of a formulation and parameters to be evaluated is a critical aspect in formulation technology. A schematic on evaluation of FDDS is shown under Figure 5.

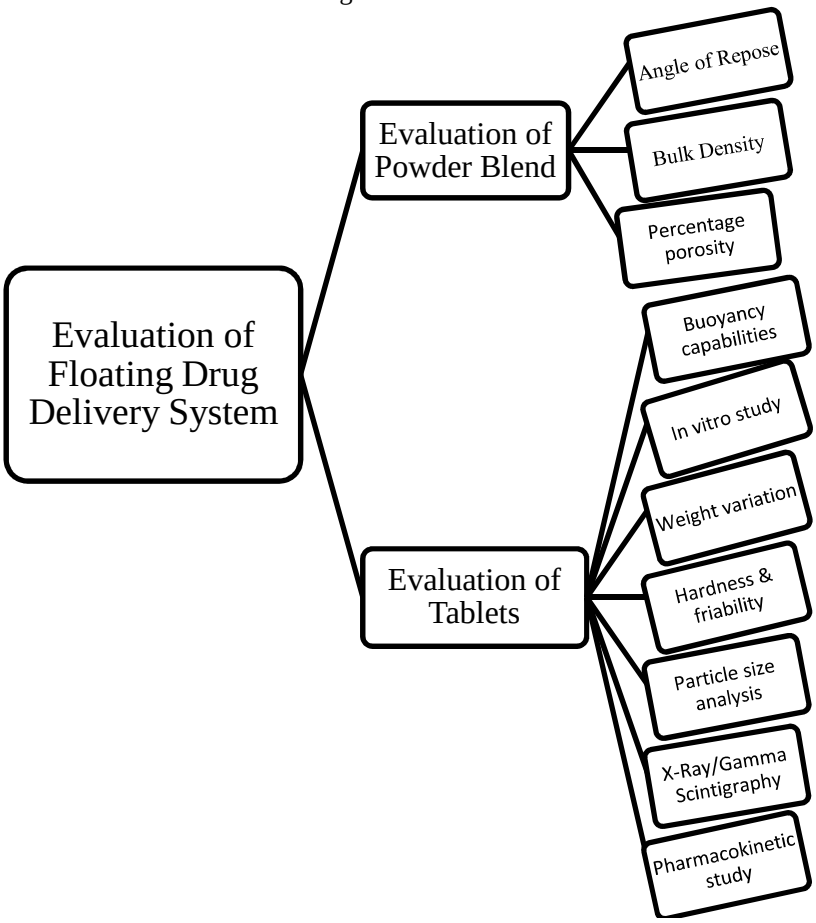

Figure 5: Schematic Diagram of Evaluation of Floating Drug Delivery System

Evaluation of Powder Blend
Angle of Repose: Angle of repose is defined as 'the maximum angle possible between the surface of the pile of powder and the horizontal plane'. Lower the angle of repose, better the flow properties. A value of θ less than 25 indicates excellent flow and more than 40 indicates very poor flow. Angle of repose is obtained from formula-

$\tan\theta = \frac{h}{r}$ OR $\theta = tan^{-1}\frac{h}{r}$

Where, h is height of the pile and r is the radius of pile base.

Bulk Density
Bulk density is obtained by:

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

When particles are packed, it is possible that a large amount of gaps may be present between the particles. Therefore, trapping of powder allows the particles to shift and remove the voids to minimum volume. The volume occupied by the powder in this condition represents the bulk volume. Substituting this volume for a given weight of powder in equation it gives the bulk density.

Percentage Porosity: Porosity provides information about hardness, disintegration, total porosity etc.

$$\%\ porosity\ (€) = \frac{void\ volume}{Bulk\ volume} \times 100$$

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

Evaluation of Floating Tablets

Measurement of Buoyancy Capabilities of the FDDS: The experiment is carried out in two different media, deionised water and simulated meal. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behavior and it was observed more in simulated meal medium compared to deionised water [43].

In vitro drug release studies

The dissolution tests are generally performed on various drugs using USP dissolution apparatus. USP 28 states "the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started". A small, loose piece of nonreactive material with not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float. However, standard USP or BP methods have not been shown to be reliable predictors of *in vitro* performance of floating dosage forms [31].

The test for buoyancy and *in vitro* drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37 °C.

Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replenished with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution.

Weight Variation Test [44]**:**

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet by U. S. Pharmacopoeia. The following percentage deviation in weight variation is allowed. A permissible limit for weight variation as per USP and IP is given under Table 3.

Table 3: Limit for weight variation as per U.S.P and I.P

Average weight of a tablet as per U.S.P	Percent deviation	Average weight of a tablets as per I.P	Percent deviation
130 mg or less	10.0	80 mg or less	10
>130mg and <324mg	7.5	>80mg and <250mg	7.5
324 mg or more	5.0	250 mg or more	5.0

Hardness test [45]**:** Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Friability test [46]**:** The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator is operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final})
The % friability is then calculated by-

$\%F = 100\ (1\text{-}W_{initial}/W_{final})$

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

Particle Size Analysis, Surface Characterization (for floating microspheres and beads):

The particle size and the size distribution of beads or microspheres are determined in the dry state using the optical microscopy method. The external and cross sectional morphology (surface characterization) is done by scanning electron microscope (SEM) [49].

X-ray/ Gamma Scintigraphy [47]**:** X-ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form nowadays. It helps to locate dosage form in the gastrointestinal tract (GIT), 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 GIT.

DRUG RELEASE KINETICS FOR FLOATING DRUG DELIVERY SYSTEMS [55-57]

The kinetic studies in designing a pharmaceutical floating dosage form depends on a good understanding of the drug release mechanism and kinetics. As the qualitative and quantitative changes in a formulation design could change drug release and *in vivo* performance of a dosage form, it seems very essential to have a thorough insight into the mechanisms of drug release kinetics. Different of approaches used for kinetic investigations are: model-dependent methods comprising a variety of kinetic models expressing dissolution profiles and overall release of drug from the formulations. Zero-order, first-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Baker-Lonsdale, Weibull, and regression models are the commonly used models for clarifying the mechanism of drug release. Some of the mathematical equations and kinetic models that are commonly used for evaluating the release kinetics are outlined under Table 4. Studying drug release kinetics is often useful in obtaining one or two physically meaningful parameters that are used for comparative purposes and relating the release parameter with important parameters such as dissolution and bioavailability. For example, the n value is generally used in the Korsmeyer- Peppas model to characterize different release mechanisms. This equation has two distinct physical realistic meanings in the two special cases of $n = 0.5$ and $n = 1$, indicating diffusion-controlled drug release for the former and erosion controlled drug release for the latter. More to the point, an n value between 0.5 and 1 could be regarded as an indicator for the superposition of both phenomena (anomalous transport). In the case of the Weibull model, according the exponent of time b is linearly related to the exponent n of the power law derived from the analysis of the first 60% of the release curves. The value of the exponent b is an indicator of the mechanism of transport of a drug through the polymer matrix. Estimations for b less or equal to 0.75 indicate Fickian diffusion, whereas a combined mechanism (Fickian diffusion and Case II transport) is associated with b values in the range $0.75 < b < 1$. For values of $b > 1$, drug transport follows a complex release mechanism. With this, the authors have tabulated some kinetic data to have an overview on release kinetics and give a rule in relation to drug release kinetics from floating dosage forms. Different ingredients in the relative matrix tablets appeared to be the key factor responsible for the multiplicity of the models fitting the dissolution data and also the differences in drug release patterns. Also, different models in analyzing the drug release data in each study made it difficult to acquire a general rule in proposing a model for the best fit of dissolution data. The use of kinetic models is often helpful in elucidating release mechanisms which in turn can be useful in controlling drug release. Another advantage of the kinetics is to represent several release data with one or two parameters.

TABLE 4: The usual kinetic models with their mathematical equations for analysis of drug release data [56]

SrNo.	Mathematical model	Mathematical equation	Terms used in equation
1	Zero order	$Q_t = Q_O - K_O t$	Q_t =amount of drug remaining as a solid state at time t Q_0 = initial amount of drug in the pharmaceutical dosage form K_0= zero-order release rate constant
2	First-order	$logQ_t = logQ_o - \frac{k_1 t}{2.303}$	Q_t =amount of drug remaining as a solid state at time t Q_0 = initial amount of drug in the pharmaceutical dosage form K_1= First-order release rate constant
3	Higuchi	$Q_t = K_H t$	Q_t =amount of drug released in time t K_H =Higuchi's release rate constant Q_t =amount of drug remaining as a solid state at time t
4	Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = k_s t$	Q_0 = initial amount of drug in the dosage form K_s= Release rate constant
5	Baker–Lonsdale	$\frac{3}{2}\left[1 - \left(1 - \frac{Mt}{M\infty}\right)^{\frac{2}{3}}\right] - \frac{Mt}{M\infty} = \frac{3D_m C_{ms}}{r_0^2 c_0} t$	M_t= amount of drug released at time t M_a =amount of drug released at an initial time; D_m=diffusion coefficient Cms =drug solubility in the matrix r_0 = radius of the spherical matrix C_0= initial concentration of drug in the matrix
6	Korsmeyer–peppas	$\frac{Mt}{M\infty} = at^n$	Mt/M∞= fraction of drug released at time t a=kinetic constant n=diffusional release exponent
7	Hopfenberg	$\frac{Mt}{M\infty} = 1 - [1 - \frac{K_0}{C_0 a_0}]^n$	Mt/M∞= fraction of drug dissolved K_0 =erosion rate constant C_0 =initial concentration of drug in the matrix a_0= initial radius for matrix n =1, 2 and 3 for a slab, cylinder and sphere, respectively. dM/dt=drug release rate
8	Poiseuille's law of laminar flow	$\frac{dM}{dt} = \frac{\pi C}{8}\frac{r^4}{\eta}\frac{p_1 - p_2}{n}$	C= concentration of drug in matrix r = radius of orifice η= viscosity of matrix P_1– P_2 =pressure difference between inside and side out of membrane
9	Weibull	$\log[-\ln(1-\mathrm{m})] = blog(t - Ti) - loga$	m =fraction of the drug in solution at time t a= time scale of the process b= shape parameter Ti =lag time

Plot of different kinetic models are shown in Figure 6

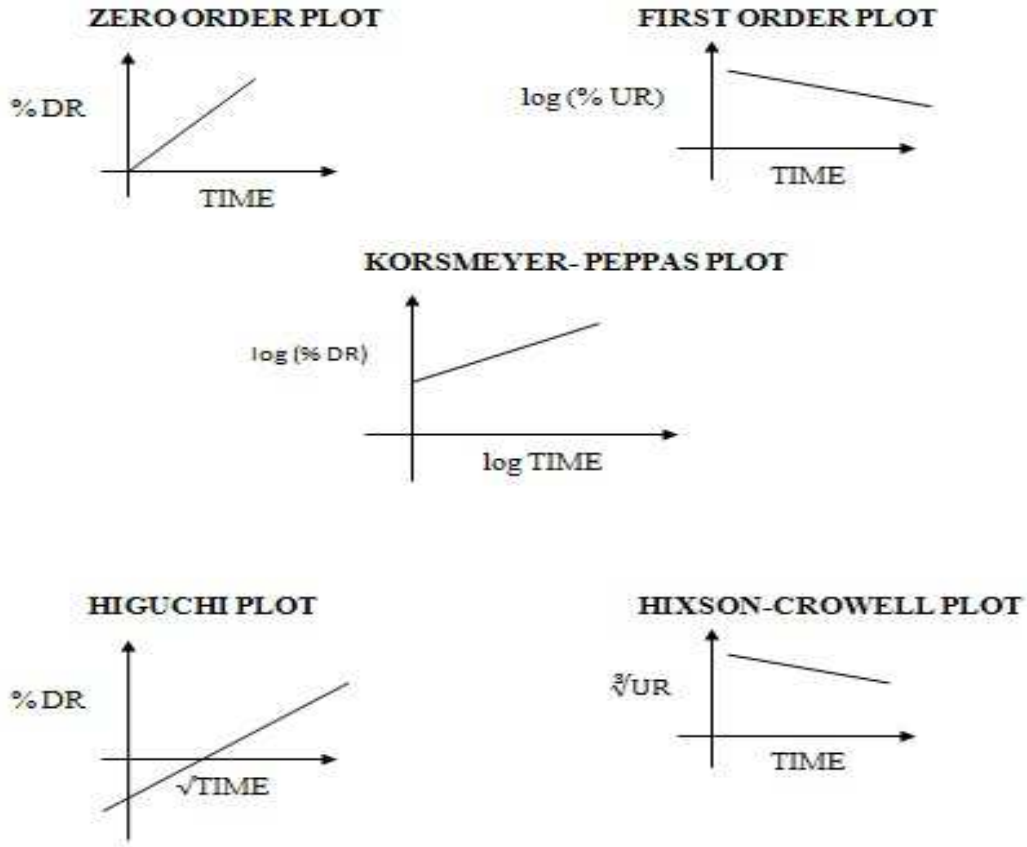

Figure 6: Plot of Different Kinetic Models

Future Prospects and Conclusions

The development of FDDS products is currently one of the most important challenges in pharmaceutical research. From the above review we conclude that FDDS products by virtue of formulation and product design provide drug release in a modified form distinct from that of the conventional dosage forms mainly at stomach region, aptly applicably to drugs showing absorption at stomach site. The physicochemical properties of the drug, polymer and the drug to polymer ratio govern the release of drug from the formulation. The use of one kind of polymer or another can affect the release kinetics, the presence of burst effect and the mechanisms involved in the release. Other factors have been shown to be involved in the release of drugs, such as the percentage and mixtures of polymer and the dimensions of the matrix (geometry and thickness). All this, together with the use of mathematical models as tools for estimating the kinetics of drug release allows floating formulations to be optimized and the pre-formulation phases during drug development to be shortened. However some disadvantages of floating formulations are retrieval of the dose is difficult in case of toxicity and extremes of drug properties. The kinetic study of drug release helps in obtaining meaningful parameters which are employed for comparative purposes and relating the release parameter with important parameters such as bioavailability which further aids in studying the influence of formulation factors on the drug release for optimization.

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