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Review Article

Hydrodynamically Balanced System: A Review

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Abstract

The most suitable drug delivery route is oral delivery due to its easily administration, patient adherence/ patient capacitance etc. Several approaches have been made for maximizing the G.R.T such as high-density system, floating system, swelling & expanding system and mucoadhesive & bio adhesive system etc. the main motive of reviewing the article is to focus on the mechanism of HBS system, classification with new system such as raft forming system and hollow microsphere, its application, marketed preparation and evaluation study. The procedure of gastric emptying is a complex and may leads to uncertainty for *in vivo* performance of the DDS. To prevent this type of complex formation and uncertainty, hard work has been done to expand the retention time of DDS for half of the day. The FDDS are beneficial in such process.

Keywords: HBS system, GRDDS, gastric residence time (G.R.T), raft forming systems, floating formulations, evaluation study.

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Introduction:

HBS is nothing but floating drug delivery system, till now various process has been done on the primary buoyancy process to gain gastric retention. HBS system is very useful for those medicaments which have problems. The most suitable drug delivery route is oral delivery due to its easily administration, patient adherence/ patient capacitance etc.[1], and it is most preferred and convenient and any medicament distribution to the systemic circulation is easy and relaxed.

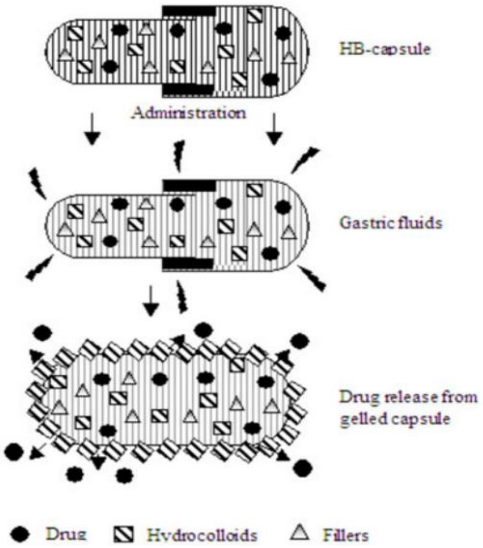


Figure 1: Demonstration of HBS system.

There are various methods which are used to control the release of medicaments by floating system in stomach by preparing the lower density than gastric fluid density. Generally oral controlled drug delivery is based on three aspects-

a) The physicochemical characteristics of medicaments [2].
b) Structure and function of GIT.
c) Characteristics of dosage forms [3].

Gastroretentive DDS:

Gastroretentive system is the preferable system to get enhances release of a medicament after administering it orally. The aim of GRDDS is to enhance the dosage form by residence time in the stomach which is generally called as gastric residence time.

Gastroretentive system basically divided into three systems-

a) System based on floating.
b) Systems based on high-density.
c) Expandable system.

According to the gastric motility in fasted and fed state it can be given in four phases and jointly called the interdigestive myoelectric motor complex (IMMC).

Generally, four phases are-

a) Basal state (nearly 45 min. to 1 hour)
b) Pre-burst state (nearly half an hour to 45 min.)
c) Burst state (nearly 5 to 15 min.)
d) Less time of no contraction (5min) [4].

GDDS system related to density of medicament to gastric fluid is that if the gastric fluid density is more than that of medicament then it will float on proximal surface of the stomach content, which results in maximum life time to release drug before it gets emptied out into the small intestine. Density of gastric fluid is 1g/cm^3. Lesser the density of medicament than gastric fluid then it floats otherwise vice versa i.e., more density of medicament than gastric fluid then it will not float [5].

Mechanism of HBS system-

Several approaches have been made for maximizing the G.R.T which include high-density system, floating system, swelling & expanding system and mucoadhesive & bio adhesive system etc., among these floating systems is used most commonly. Gastric fluid should contain more density as compare to bulk density of HBS system and should remain float/swim inside the belly not with disturbing the G.E.R for maximum time of period when system is on the upper part on gastric contents, the rate of the medicament is steadily released from the bloodstream at the optimal rate [6]. at last, when drug is released, the remaining part get exited from the belly. This all result in the increase in G.R.T and a good command on the changes in rate of fluid medicament.

Minimal gastric content required proper technique of the floating retention principled theory; floating forces (F) level is minimal to stay the medicament smoothly float upon the area of the food. To calculate the buoyancy force kinetics, novel equipment which determines the final result of weight has been given in the literature. By constantly estimating the force equal to F (as time function), it operates which is needed to maintain the entity submerged. If F is on the higher side of the positive, then the subject swims good, this system useful in appropriate HBS w.r.t stability and time period of buoyancy forces in order to stop the benefits of unforeseeable intragastric buoyancy [7].

$F = F_{Buoyancy} - F_{Gravity} = (DF - DS)\, gV$

Where, 'F' is complete vertical power, 'Df' is density of fluid, 'Ds' is density of object, 'g' is gravity-due acc^n and 'v' is volume.

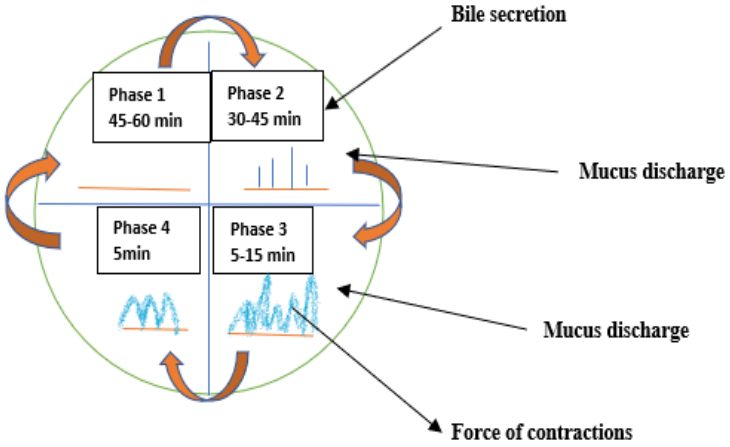


Figure 2: Migrating myoelectric cycle [8]

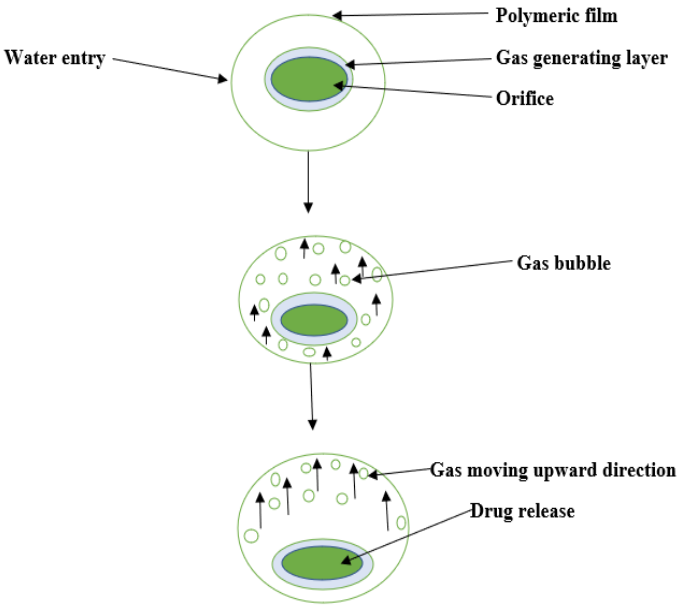
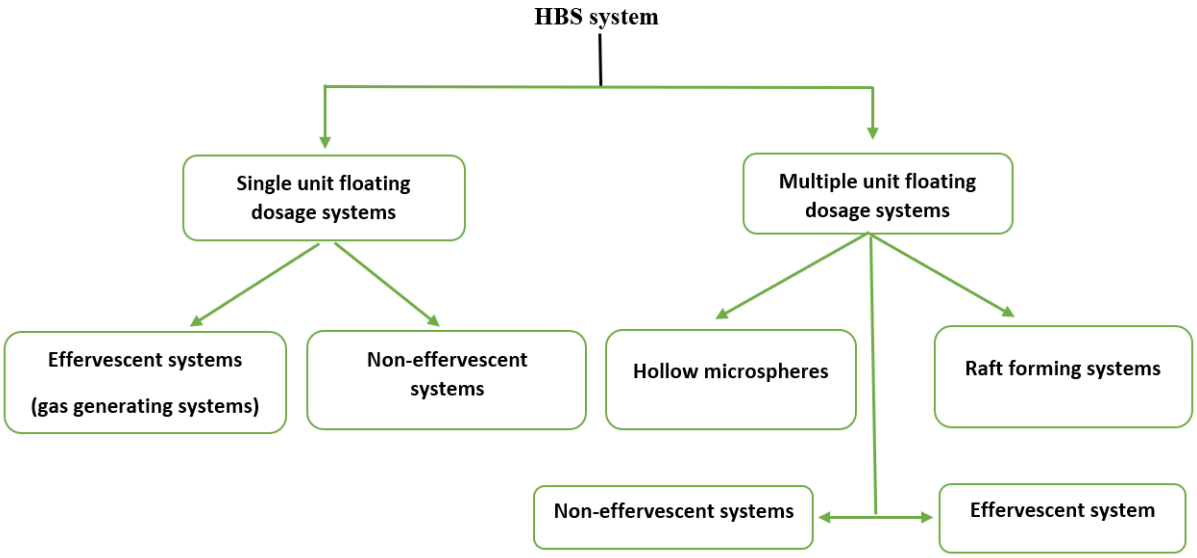


Figure 3: Mechanism of floatation via CO_2 liberation [9]

Classification of HBS system -



A) Dosage systems for single unit floating -

a) Effervescence systems (gas producing systems) –

To float on upper part of system it requires matrices which prepared with Hypromellose as swellable polymer, chitosan as polysaccharides, $NaHCO_3$ effervescent components, citric acid ($C_6H_8O_7$) and tartaric acid ($C_4H_6O_6$), other polymers is Hypromellose (HPMC) and it should also contain chambers which consist of liquid and easily gets gasifies at human body temperature. For this, the gas generations of citric acid and $NaHCO_3$ optimal stoichiometric ratio are 0.76:01. For preparation of these systems, it requires beads in which bicarbonate is loaded & ethyl cellulose coating is there. The coating may be insoluble, but it is permeable, helping to impregnate water. At that time, due to releasing of CO_2 beads start to swim in the belly. Generally used components are Hypromellose, sodium chloride, polyethylene oxide, polycarbonate, sodium alginate, Carbopol, polyvinyl acetate and polyacrylate polymers [10,11].

b) Non-effervescence systems-

In this type of system, after engulfment its start to swell in gastric fluid which allows stopping or remaining in the stomach. "plug type system" mostly referred to this system because they have capacity to stay there close to the pyloric sphincter. In this mainly FDDS systems involved barrier of colloidal gel, alginate beads, micro sporous system of compartment and hollow microspheres and another is floating chamber which is filled with fluid [12], assimilation of a floatation chamber filled with gas into a micro sporous portion that leads to a drug reservoir. The liquid present may be air, under partial vacuum which have an inert behavior as well as an appropriate specific gravity. By overall mechanism it starts to swell and then begins to float. A newer floatable asymmetric configuration DDS self-correcting [13]. There is a modern self-correcting floatable asymmetric configuration drug delivery system that has 3-layer matrices to monitor drug release to resolve old systems. In order to modulate the degree of release and achieve zero-order release kinetics, the 3-layer concept was improvised by creating an asymmetric DDS structure by first retaining a steady region on the diffusing front with eventual dissolution or degradation toward the completion of the release process. The agenda for preparation of this system is to get float for longer G.R.T *in-vivo,* which result in for increasing total transit time within GIT tract surrounding with capacity of maximum absorption and greater bioavailability. Basically, the formulation which have narrow absorption window, solubility of pH-dependent and active transport absorption either by upper/lower part of the smaller intestine is mostly applicable for this system [10,14].

B) Floating dosage system with multiple-unit -

The main motive about this system is to overcome the circumstances which were involved such as by reducing the intersubjective variability & prevent dose dumping. For this both systems prepared of effervescent and non-effervescent multiple floating system [15]. This system also involves hollow microspheres and raft forming type of systems.

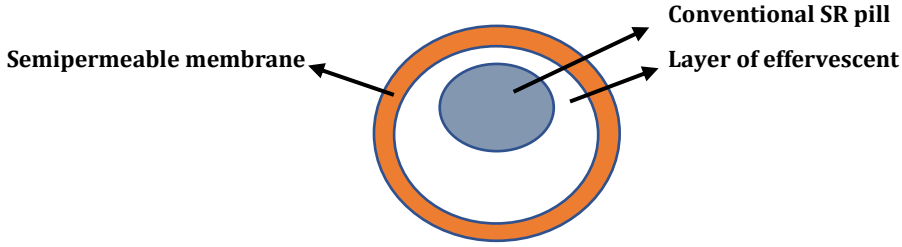


Figure 4: Multiple units of oral FDDS

For the preparation of non-effervescent & effervescent multiple unit systems the reports have been issued. Most focused-on research and innovators are still expanding the nature of hollow microspheres, gastric fluid's swimming capacity & have great gastric retention properties.

a) Effervescence systems (system of gas-generating):

SR swimming granules including tetracycline HCl reports have been produced. Granules are a mixture of two-step medication granulates, i.e. A and B, of which A consists of 60 Hypromellose components, 40 polyacrylic acid components and 20 medical components, Whereas B comprises 70 NaHCO3 components and 30 tartaric acid components. 60 components and 30 components by weight of step A granules and by weight of step B granules, respectively, are combined and mixed together with a lubricant and filled into capsules. Capsule shells begin to dissolve and then granules begin to escape in dissolution media that displayed more than 8 hours of floating time and 80 percent specific drug release in around 6.5 hours[16]. Pepstatin swimming minicapsules with a length of 0.1-0.2 mm have been submitted. They mainly consist of central core & coating. The central center contains granules containing NaHCO3, lactose and a hypromellose polymer coated binder. On above the Hypromellose layer pepstatin is coated. Due to release of CO_2 in gastric fluid system starts to float and the remaining of pepstatin in the belly for longer time. In multiple unit system alginates have acquired more attention for the development of this system [17].

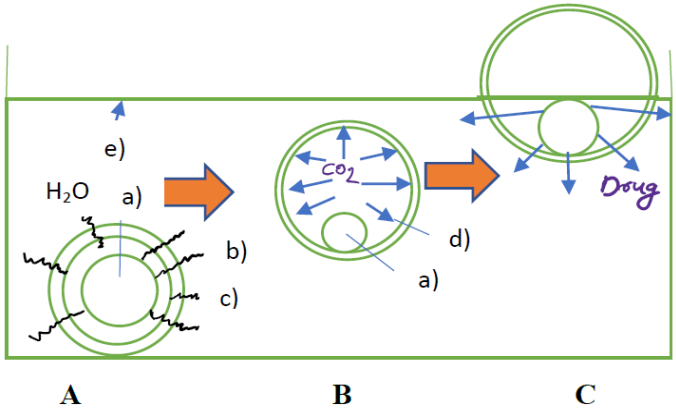


Figure 5: floating mechanism steps: A) Penetration of water; B) generation of CO2 and starts to float; C) drug dissolution. Key: a) sustained release pills(conventional); b) layer of effervescent; c) layer of swellable; d) layer of swellable membrane is expanded; e) beaker containing water surface (37°C).

b) Non-effervescent systems –

There is no more information about non-effervescent systems if comparing to effervescence systems. A number of workers, however, have mentioned the possibility of using indomethacin with polymeric excipients such as chitosan to create this system. By extrusion process a multiple unit hydrodynamically balanced system containing model drug as indomethacin is reported[18]. In this a drug mixture, acetic acid and chitosan is extrudate is cut and that extrudate is dried. In acidic medium hydration of chitosan and starts to float and required drug release obtained by changing the drug-polymer ratio [19,20].

c) Hollow microspheres –

This system is said to be one of the important superior multiple unit floating system. This system has most convenient floating systems due to hollow space in the center which is inside the microsphere. Some methods used in these systems may be method of simple solvent evaporation & diffusion of solvent & method of evaporation (figure.VI). The release of the drug and good floating properties depend primarily on the quality of the polymer, plasticizer and solvent required for the formulation. To prepare hollow microspheres generally polymers are used such as eudragit, polycarbonate, cellulose acetate etc. & by maximizing the polymer-plasticizer ratio and polymer amount, the release of the drug can be justified. For this system generally griseofulvin, aspirin and para nitroaniline were taken as model drugs. In SR swimming microspheres using polycarbonate were produced and technique involved in this is solvent evaporation technique [24].

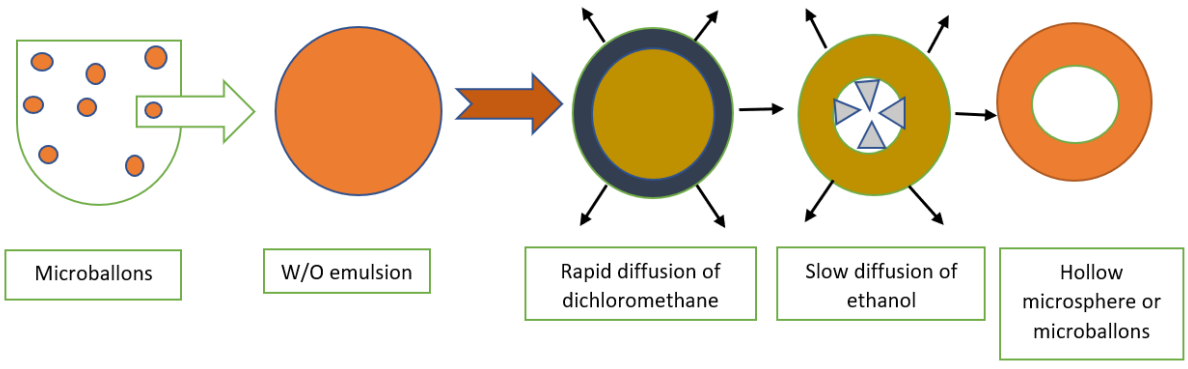


Figure 6: formulation of floating hollow microspheres or microballons

d) Raft forming systems:

Another system and most superior system which comes under multiple unit floating system regarding to antacids and supplies of medicine for GI diseases and disabilities. The process used in formation of raft involves the presence of cohesive viscous gel in interaction with gastric fluids, where every part of solution starts to swell and forms a continuous layer called as raft (fig.VII). the underlying theory of floating is the buoyancy produced by the formation of carbon dioxide which acts as a fence to avoid the reflux of gastric material into the esophagus, such as hydrochloric acid and enzymes. In gastric fluids to make the medicament float and less dense generally it requires alkaline bicarbonates or carbonates and a gel forming agent [25].

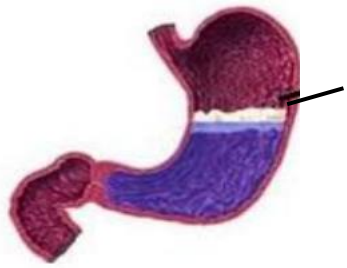


Figure 7: Raft forming system.

Applications of FDDS:

Floating drug delivery has many uses for drugs with poor bioavailability due to the limited absorption window in the upper portion of the digestive tract. At the absorption site, it retains the form of the dosage and thus increases bioavailability. Generally given as;

a) Sustained delivery of drug
b) Drug delivery at specific-site
c) Absorption enhancement

1) Sustained drug delivery-

For long stretches, hydrodynamically balanced systems may stay in the belly. The drug can therefore be released for a longer time of period. Consequently, an oral controlled release formulation can be found with this framework, conquering the problem of brief duration for gastric residence. these structures have a density that is less than 1 because of which the gastric contents will float. In these, the dosage is high in size and passes from the pyloric openings are restricted. Sustained new release Nicardipine hydrochloride floating capsules were produced *in vivo* and measured. Of plasma the time curves for focus sees a longer period for administration (16 hours.) during prolonged floating release capsules comparing to conventional capsules of MICARD (eight hrs.) [21]. Likewise, a comparative analysis [22,23] between the normal Madopar Hydrodynamically balanced system & standard Madopar it was understanding that the medication was released by formulation *in vitro* for 8 hrs. in the previous case & the completely release in the above case in less than ½ hour.

2) Site-specific drug delivery-

For medicines that are directly ingested from the belly or the upper area of the tiny part of the stomach, then these mechanisms are especially helpful, e.g., riboflavin. The main absorption of furosemide is from the belly, followed by the duodenum. it has been verified that a monolithic floating dosage form with extended gastric residence time has been developed and bioavailability has been enhanced. The AUC extracted from floating tablets was about 1.8 times that of conventional furosemide tablets[24].

For the local distribution of misoprostol, a non-natural precursor of prostaglandin E1 used as a preventive agent against gastric ulcers caused by NSAID administration, a bilayer floating capsule was made. Slow administration of misoprostol to the stomach is aimed at maintaining the therapeutic level of target dosage and reducing drug diversion[23,25].

3) Absorption enhancement-

Medicaments with low bioavailability are valuable candidates to be administered as FDDS owing to site-specific absorption from the proximal portion of the GIT tract, therefore it increases the absorption. Compared to the currently produced tablets of LASIX (33.4 percent) and LASIX (enteric coated) long product (29.5 percent), an important increase in the bioavailability (42.9 percent) of floating drug types has been achieved[24,26].

Table 1: Commercially available formulations of floating [27].

Name of the product	Active Ingredient	Category	Name of Company
Madopar® HBS Capsule	Levodopa (100mg) and Benserazide (25 mg)	Anti-parkinsonial	Roche, USA
Valrelease® Capsule	Diazepam (15 mg)	Anti-anxiety	Hoffmann-La Roche, USA
Liquid Gaviscon	Al hydroxide (95 mg). Mg carbonate (358 mg)	Antacid (in reflux esophagitis)	Glaxo Smithkline, India
Cytotec Bilayer capsule	Misoprostol (100 mcg/200 mcg)	-	Pharmacia, USA
Topalkan®	Alginic acid, Aluminium and Magnesium salts	Antacid	Pierre Fabre Drug, Frabce
Almagate flowcoat	Al-Mg antacid	Antacid	Ranbaxy, India

Evaluation study of Floating drug delivery systems –

Several types of studies published in the novel suggest that sustained gastric residence *in vivo* is evidenced by dosage forms pharmaceutically displaying *in vitro* floating activity of gastric residence.

Some evaluation parameters of FDDS are given below:

1) Tablet hardness determination:

Several instruments are used to check hardness of tablet such as Pfizer hardness tester, Monsanto hardness tester, strong cobb hardness tester. Procedurally from each batch of formulation sampled 20 tablets are used for checking of hardness. The unit for tablet hardness is kg/cm^2 [28].

2) Weight variation determination:

According to the United States of Pharmacopoeia, this experiment is processed by taking weights of 20 tablets individually and calculating the individual tablet's weight with an average one. The weight variation value determination is given in % and given in formula as

$$\text{Weight variation} = (WI - WA) / WA \times 100\%$$

Where,

WI = weight of Individual

WA = Weight of average

flow properties and the degree of separation are variables responsible for weight differences.

3) Tablet thickness determination:

Instruments which are used for determination of thickness of tablet are generally Vernier caliper and micrometer and it is determined by the diameter of the tablet. Thickness of tablet should be overcome within ±5% variation of standard value. Factors which affect tablet thickness are generally size and size distribution and compression force etc. [29].

4) Determination of floating lag period:

It is determined by the period when tablet is introduced in the dissolution media & its floats to upward by 1/3 of the dissolution vessel is stated as swimming lag period and the time required when it swims is stated as floating or floating time. These tests are generally done in gastric fluid or 0.1 mole.lit-1 hydrochloric acid kept at 37°C, by using USP dissolution instrument containing 0.1 molar HCl of 900 ml as the dissolution media. Floating lag period is expressed in sec. or minutes [30].

5) Measurement of floating capacity:

Three singles are putted in separate flask having 400 ml of 0.1N hydrochloric acid solutions. Then it measures the time taken for individual tablets to move from the down to the up position of the flask (floating lag time) and the time at which the tablet floats continuously on the water surface (floating duration) calculated. The sample mean and S.D are then calculated. It is expressed in seconds or minutes [31].

6) Simple funnel method:

To determine the flow properties simple funnel method is used and it is also called as angle of repose. This is the highest potential angle between the granules and the horizontal plane of the surface. The granules are passed through funnel which is fixed to one stand at particular height (h) from where granules have to be passed. For calculation of angle of repose measurement of height and radius is required and it is expressed by the equation,

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

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

where,

θ = repose angle

h = height (cm).

r = radius (cm). [32]

7) *in vitro* dissolution study determination:

Floating monitoring and *in vitro* release of drug trials are normally conducted in simulated gastric and Int. fluid preserved at body temperature. Using the USP dissolution apparatus containing 900 ml of 0.1 N HCl as a testing medium held at body temperature, floating potential is determined. The time taken to float the dosage form of the hydrodynamically balanced method is measured as floating time[33].

8) Specific gravity:

The displacement process is used as a displacement medium to assess the specific gravity of the floating device using compound benzene [34].

9) X Ray/ Gamma scintigraphy:

the important floating system evaluation parameter regarding *in vivo* studies. For the process of experiment animals were allowed only to get water with no feed overnight, in a formulation allows indirectly by seeing through naked eyes using **γ** camera. The most important work of **γ** scintigraphy is association of ionising radiation for the patient, the restricted topographic data, the low resolution inherent in the process and the complex and costly radiopharmaceutical preparation [35].

Others parameters include such as incompatibility study, bulk density, Carr's index, Hausner's ratio, tapped density[36] etc.

Conclusion:

Gastroretentive system is the preferable system to get enhances release of a medicament after administering it orally. This system is most preferable than other system due to it's easily administration, patient capacitance etc. Density of gastric fluid is $1mg/cm^3$, Lesser the density of medicament than gastric fluid then it floats otherwise vice versa i.e., more density of medicament than gastric fluid then it will not float. FDDS plays a vital role to get actual release of medicament. Although there is need of more work to cover up different functions and pharmaceutical barrier to produce innovative medicament. In coming new days, it should be suggested that in FDDS the dose must be accurate to be input in the gastrointestinal tract to get proper ADME process and toxicological profile of medicament.

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