Review Article

A Comprehensive Review on Development and Investigational Strategies for Biphasic Site-Specific Floating Cum Bioadhesive Drug Delivery System

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ABSTRACT

The purpose of this review is to compile the recent literature with special focus on characterization of both, *in vitro* and *in vivo* parameters for gastric behavior of biphasic floating cum bioadhesive site specific drug delivery system. This review consists of different types of bilayer floating drug delivery systems, one of the type, biphasic gastroretentive drug delivery system gives better patient compliance (by reducing both dose and dosing frequency) and increases the efficacy of drug therapy. Few drugs have narrow absorption window in GIT, so have poor absorption and there by leads to low bioavailability via conventional sustained release drug delivery system. Thus, few researchers have developed biphasic floating drug delivery system which becomes more promising approach in gastroretentive drug delivery system. It consists of immediate release layer to release the drug in a very short period for quick onset of action while another floating bioadhesive sustained release layer, to release the maintenance dose of drug with sustained fashion in stomach for desired period. We have focused on calculation of both doses such as loading and maintenance dose. Floating drug delivery systems are having bulk density less than gastric fluids therefore it remain buoyant in the stomach for a desired period of time, releasing the drug slowly but promptly at the desired rate from the systems. This review includes various sophisticated *in vitro* and modern *in vivo* evaluation techniques for biphasic floating bioadhesive site-specific drug delivery system including stability studies.

Keywords: Bilayer floating tablets, bioadhesion, biphasic release tablets, gastro retention, *In vivo* study, kinetic models

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INTRODUCTION

Despite of considerable advancements in drug delivery, the oral route is the most convenient, predominant, and remains the preferable way to administer the medication. Oral controlled release dosage forms have been developed over the past two-three decades due to their considerable therapeutic benefits such as ease of administration, high level of patient compliance, low cost of the therapy, and flexibility in formulation. It provides drug release at a predetermined, predictable, controlled rate, and drawn considerable attention. However, due to incomplete absorption or degradation of many drugs in the lower gastrointestinal tract (GIT), controlled release (CR) dosage forms must be maintained in the upper GIT, preferably in the stomach, while the medications are delivered to the region of the GIT where they are best absorbed [1,2]. This approach is having physiological problem such as inability to restrain and locate the controlled drug delivery system (CDDS) within the desired region of the GIT due to variable gastric emptying and motility. In

addition, the relatively short gastric emptying time (GET) in humans which normally ranges 2-3 h through the major absorption zone i.e., stomach and upper part of the GIT. The short GET may result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose [3].

Gastro retentive drug delivery system (GRDDS) are primarily controlled release drug delivery systems (CRDDS), which get retained in the stomach for longer period, thus helping in absorption of drug for the intended duration. This in turn improves bioavailability, reduces drug wastage, and improves solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drugs like papaverine, domperidone). It also helps in achieving local delivery of drugs to the stomach and proximal small intestine. Gastro retentive drug delivery (GRDD) devices can be useful for the spatial and temporal delivery of many drugs. Thus this approach is also called as oral targeted drug delivery system for stomach.

Time controlled oral drug delivery systems offer several advantages over immediate release dosage forms, including the minimization of fluctuations in drug concentrations in the plasma and at the site of action over prolonged period, resulting in optimized therapeutic concentrations and reduced side effects; a reduction of the total dose administered (providing similar therapeutic effects) and a reduction of the administration frequency leading to improved patient compliance [4, 5].

Overview of GIT

The GIT is not in a uniform structure; it is composed of several regions differing in anatomy, biochemical environment, pH, microbial flora, expression of transporters, and absorption characteristics (**Table 1**). Drug absorption from the GIT is a complex procedure and is subject to many variables [6, 7].

The main function of the stomach is to temporarily store food, start its digestion and to release the resulting chyme slowly through the pylorus into the duodenum. Because of the small surface area of the stomach, absorption into the systemic circulation is restricted. The jejunum and ileum are the most important sites for absorption of nutrients and drugs. In the colon, mainly water and ions are absorbed, as well as certain drugs that show significant absorption due to the long residence time in the colon. The process of gastric emptying is characterized by a distinct cycle of electromechanical activity known as the interdigestive migrating myoelectric complex. This series of events that cycle through the stomach and small intestine every 1.5 – 2 h is divided into four consecutive phases [4] as

1. Phase I (45 – 60 min), the most quiescent, develops few or no contractions;
2. Phase II (30 – 45 min) consists of intermittent action potentials and contractions, which gradually increase in intensity and frequency as the phase progresses;
3. Phase III (5 – 15 min) is a short period of intense contractions and peristaltic waves, involving both the proximal and distal gastric regions ('housekeeper waves'). In this phase, indigestible solids are removed from the fasted stomach;
4. Phase IV (0 – 5 min) is a transition period of decreasing activity until the next cycle begins.

In order to study the parameters affecting the process of gastric emptying, various methods have been applied, such as γ-scintigraphy, radiography, endoscopy, radiotelemetry and magnetic marker monitoring. Furthermore, indirect information on gastric emptying could be gained by comparing the pharmacokinetics of drugs administered in oral dosage forms of different size [4].

Approaches for GRDDS

There are several approaches used to retain the dosage form in the stomach. These include bioadhesive systems, swelling and expanding systems, floating systems, modified shape system, and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time (GRT) for the dosage form and sustained drug action [8]. Recently, combination of both mechanisms i.e. floating and bioadhesive called as floating cum bioadhesive drug delivery system (FBDDS) have promising advantages

Table 1: Parameters of Various Segments of the GIT [6, 7]

Parameters	Stomach	Small Intestine	Colon
Length (cm)	20	350–700	90–150
pH range	1–3	6–7	6–8
Bacterial count (CFU/mL)	10^2–10^4	10^3–10^4	10^{11}–10^{12}
Absolute surface area (m^2)	0.1-0.2	200	0.35
Transit time (h)	0–2	3 ± 1	> 20

CFU = Colony forming units

than earlier mentioned any one single approach.

Current trends and advancements in FDDS: Dual working systems

These systems are based on the two working principles such as floating and bioadhesion. FDDS are formulated to persist floating on the gastric fluid when the stomach is full after a meal. However, as the stomach empties and the tablet reaches the pylorus, the buoyancy of the dosage form may be hindered. So that the dosage unit may pass through the pylorus into the small intestine. Thus, the buoyancy of an FDDS in the stomach may be limited to only 3–4 h. In a bioadhesive drug delivery system, it is quite likely that the system becomes dislodged from the stomach mucosa wall when the system is full and the semi liquid contents are churning around due to the effect of peristalsis. A dual working system would overcome drawbacks associated with alone bioadhesive, or floating system, and would have a significant effect on improving the therapeutic effect of the drug involved. Several researchers have developed FBDDS exhibiting a unique combination of floatation and bioadhesion to prolong residence in the stomach such as [9, 10, 11] and many as described by [12].

Bilayer tablets

Bilayer tablets are generating great interest recently as they can achieve controlled delivery of different drugs with pre-defined release profiles. This bilayer compacting technology has gained more popularity in recent times, as the bilayer tablets offer several advantages over the conventional tablets. Key advantages include the physical separation of chemically incompatible active pharmaceutical ingredients (APIs); and also to enable the development of different drug release profiles of the same active pharmaceutical ingredient (API) in a single dosage form [13]. Bilayer tablet is also suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release (IR) as initial dose and second layer is maintenance release (MR) dose [14]. Bilayer tablets may be prepared by direct compression, wet granulation, or dry granulation method.

Quality and GMP requirements of bilayer tablets

A quality bilayer tablet can be produced in a validated and GMP way provided that the selected press is capable of [15]:

1. Preventing capping and separation of the two individual layers that constitute the bilayer tablet
2. Providing sufficient tablet hardness
3. Preventing cross contamination or mixing between the two layers
4. Producing a clear visual separation between the two layers
5. High percentage of yield
6. Accurate and individual weight control of the two layers

Bilayer floating drug delivery system (BFDDS)

Recently bilayer floating tablets become of increased interest within the researchers due to the tailored release profiles of APIs that may be obtained. Various types of bilayer floating tablets as per previous literature are listed in **Table 2**. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve. For many drugs, absorption is moderately slow in the stomach, rapid in the proximal intestine, and declining sharply in the distal segment of the intestine. As a result, a

constant plasma concentration may not be obtained even though a dosage form with a zero order *in vitro* release is administered. Therefore, it is conceivable that a delivery system which can provide a release profile exhibiting an initial burst release followed by a relatively steady release at late stage may offer a better solution. This concept can be used to produce a biphasic delivery system combining a fast release together with the slow release component of the drug. This system can produce a rapid rise in the plasma concentrations for some drugs that are requested to promptly exercise the therapeutic effect, followed by a prolonged release phase in order to avoid repeated administrations. Over the past decades, many pharmaceutical researches have witnessed the boost of biphasic delivery system. This system concerns with a high control over the release rate of the drug combined with a high flexibility on the adjustment of both the dose and the release of drugs [16].

Table 2: Types of Bilayer Floating Drug Delivery Systems

Sr. No.	Type	Description	Specification
1	Type I	Biphasic drug delivery system consisting of one layer as IR dose and another layer as MR dose	One or two drugs in two different layers
2	Type II	Biphasic drug delivery system consisting of both layers with different drugs	Two different drugs in two different layers
3	Type III	Bilayer drug delivery system consisting of one layer as drug release layer and another layer is floating or osmotic layer or any other type	One drug in one layer while another layer is floating or osmotic layer or any other type

Overview aspect of biphasic tablet dosage form

This new biphasic release system for slightly soluble drugs has been of practical interest. To enhance the dissolution rate, the drug has milled with a superdisintegrant. Then, double layer tablets has prepared. In which the first layer is formulated to obtain a prompt release of the drug (prime/first/loading dose), with the aim of reaching an enough or sufficient serum concentration in a short period of time. The second layer is a prolonged release hydrophilic matrix, which is designed to maintain an effective plasma level for a desired period [15,17].

The biphasic system is used mostly when maximum relief needs to be achieved quickly and it is followed by a sustained release phase. It also avoids repeated administration of drugs like coronary vasodilator, antihypertensive, antihista-minic, analgesic, antipyretics and antiallergic agents [18].

Drug selection criteria for BRT

Drugs which satisfy the selection criteria of FDDS should also posses one of the following characteristics to formulate into BRT

1) Drugs having narrow therapeutic range ex. Theophylline [19],

2) Drugs having low solubility ex. Ciprofloxacin [10,20,21],

3) Several antibiotics ex. Ofloxacin [11,21,22].

Formulae for calculation of loading dose and maintenance dose

There are several formulae to calculate loading and maintenance dose few are discussed below [23-25]

I) The total dose of drug, D_t, in a prolonged action preparation comprises the normal (prompt/ loading) dose, D_n and the sustaining (maintenance) dose D_s i.e.,

$D_t = D_n + D_s$ (Eq. 1)

If the first order elimination rate constant is k, the rate at which drug is eliminated when a normal dose is given is D_nk which is the rate at which drug must be replaced if the peak blood level is to be maintained. Given a maintenance period t the maintenance dose (D_s) is D_nkt. The total dose is therefore:

$D_t = D_n + D_s$ (Eq. 1)

$D_t = D_n + D_nkt$ (Eq. 2)

$D_t = D_n (1 + kt)$ (Eq. 3)
$Dt = D_n (1 + 0.693\ t/t_{½})$ (Eq. 4)

II) The amount of drug required in an extended release dosage form to provide a sustained drug level in the body is determined by the pharmacokinetics of the drug, the desired therapeutic level of the drug, and the intended duration of action. In general, the total dose required (D_{tot}) is the sum of maintenance dose (D_m) and the initial dose (D_I) released immediately to provide a therapeutic blood level.

$D_{tot} = D_I + D_m$ (Eq. 5)

In practice, D_m (mg) is released over a period of time and is equal to the product of t_d (the duration of drug release) and the zero order rate k^0_r (mg/h). Therefore, Eq. 5 can be expressed as

$D_{tot} = D_I + k^0_r\ t_d$ (Eq. 6)

Ideally, the maintenance dose (D_m) is released after D_I has produced a blood level equal to the therapeutic drug level (C_p). However, due to the limits of formulations, D_m actually starts to release at t = 0. Therefore, D_I may be reduced from the calculated amount to avoid "topping".

$D_{tot} = D_I - k^0_r\ t_p + k^0_r\ t_d$ (Eq. 7)

Eq. 7 describes the total dose of drug needed, with t_p representing the time needed to reach peak drug concentration after the initial dose.

For a drug that follows a one compartment open model, the rate of elimination (R) needed to maintain the drug at a therapeutic level (C_p) is

$R = kV_D\ C_p$ (Eq. 8)

Where k^0_r must be equal to R in order to provide a stable blood level of the drug. Eq. 8 provides an estimation of the release rate (k^0_r) required in the formulation. Eq. 8 may also be written as

$R = C_p\ Cl_T$ (Eq. 9)

Where, Cl_T is the clearance of the drug. In designing an extended release product, D_I would be the loading dose that would raise the drug concentration in the body to C_p, and the total dose needed to maintain therapeutic concentration in the body would be simply

$D_{tot} = D_I + C_p\ Cl_T$ (Eq. 10)

III) Here the doses are calculated as follows

Total Dose (D) = (D_0) + (D_I) (Eq. 11)

$D_0 = C_p \times Cl_T \times T$ (Eq. 12)

$D_I = C_p \times V_d$ (Eq. 13)

Where,
D = Total dose
D_0 = Maintenance dose
D_I= Immediate release dose
V_d = Volume of distribution (70 kg)
C_p = Plasma drug level
T = Time duration of release
Cl_T = Total body clearance

IV) As per the zero order release principle, the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. The release from the dosage form should follow zero-order kinetics, as shown by the following equation:

K^o_r = Rate in = Rate out = $k_e.C_d.V_d$ (Eq. 14)

Where,
K^o_r = is the zero order rate constant for drug release (amount/time),
k_e = first order rate constant of overall drug elimination (h^{-1})
C_d = desired drug level in the body (amount/volume),
V_d = volume in which the drug is distributed

For a system in which the maintenance dose releases drug by a zero order process for a specified period of time, the total dose is as follows:

$W = (D_i - K^o_r\ T_p) + K^o_r\ T_d$ (Eq. 15)

Where,
W = total dose
Di = initial dose
K^o_r = is the zero order rate constant for drug release (amount/time),
T_d = total time desired for sustained release from 1 dose

V) For oral administration during calculation of loading dose absolute bioavailability should be considered, since 100% bioavailability is not possible by oral route, in such a case following simple equation can be used to determine loading dose [7]

$X_{0,L} = C_{ss,av}\ V_d\ /F$ Eq. 16)

Where, $X_{0,\ L}$ is loading dose, $C_{ss,\ av}$ is the average drug concentration at steady-state, F is the absolute bioavailability.

Formulation of bilayer floating tablets

Bilayer floating tablets or BRT can be prepared in two stages. First stage involves formulation of immediate release layer tablet (IRLT). IRLT mixture is prepared by mixing the IR dose of the drug, one of the

superdisintegrants, and DCP (Dicalcium phosphate, widely used as diluent in IRLT) if required, mixed geometrically, transferred into die cavity, and slightly compressed as shown in **Fig. 1.** Second stage involves formulation of floating bioadhesive sustained release layer tablet (FBSRLT) over the IRLT. The MR dose of the drug, release retarding polymer, bioadhesive or mucoadhesive polymer, sodium bicarbonate, citric acid, and lactose or MCC (microcrystalline cellulose) as diluent are mixed geometrically, transferred over the slightly compressed IRLT mixture as shown in **Fig. 1** while **Table 3** shows various types of BFDDS reported as per previous literature. Diagrammatic representation of preparation of bilayer tablets using normal tablet machine is shown in **Fig. 1**.

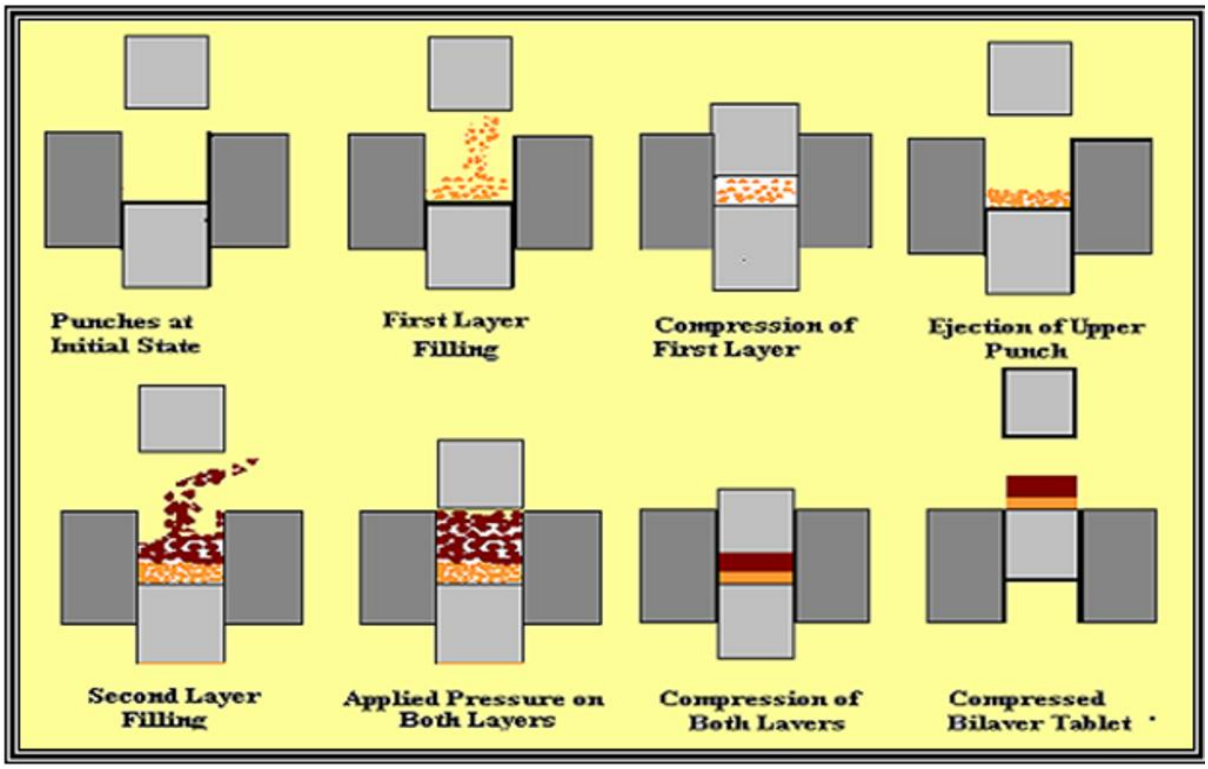

Fig. 1: Compression cycle for preparation of bilayer floating tablets.

Various steps involved in bilayer tablet preparation are as follows

1. Filling of IR powder (first layer) in to dies;
2. Slightly compression of IR powder (first layer) in dies (manually half rotation of tablet machine);
3. Ejection of upper punch;
4. Filling of floating release powder (second layer) over earlier compressed IR powder (first layer) in to same die;
5. Compression of both layers;
6. Ejection of bilayer tablet from die.

Table 3: Various types of BFDDS reported as per previous literature

Sr. no.	Model drugs	Ref. no.	Type of BFDDS
1	Sodium riboflavin 5 phosphate	26	Type III
2	Atenolol	27	Type III
3	Theophylline	28	Type I
4	Furosemide	29	Type III
5	Cisapride	30	Type III
6	Captopril	31	Type III

7	Metoprolol tartrate	32	Type I
8	Cefuroxime axetil	33	Type I
9	Rosiglitazone maleate	9	Type III
10	Alfuzosin HCl	34	Type III
11	Tizanidine HCl	35	Type III
12	Anhydrous theophylline	36	Type III
13	Atorvastatin calcium and nicotinic acid	37	Type I
14	Salbutamol and theophylline	38	Type I
15	Metoclopramide HCl and ibuprofen	14	Type I
16	Atenolol and lovastatin	39	Type I
17	Acyclovir	40	Type I
18	Famotidine	41	Type III
19	Fenoverine	42	Type I
20	Amoxicillin trihydrate	43	Type III
21	Ranitidine	44	Type I
22	Verapamil HCl	45	Type I
23	Isosorbide mononitrate	46	Type I
24	Glimepride and metformin HCl	47	Type I
25	Metformin HCl and pioglitazone HCl	48	Type II
26	Metformin HCl and glimepiride	49	Type I
27	Propranolol HCl	50	Type III
28	Trifluoperazine HCl	51	Type I

Evaluation parameters for BRT

The various evaluation parameters applicable for IRLT, FBSRLT, and BRT are reported in **Table 4** and explained here as follows

Table 4: Various applicable evaluation parameters for IRLT, FBSRLT, and BRT

Evaluation parameters	IRLT	FBSRLT	BRT
Appearance	✓	✓	✓
Tablet thickness	✓	✓	✓
Tablet hardness	✓	✓	✓
Tablet friability	✓	✓	✓
Tablet porosity	✓	✓	✓
Tablet density	✓	✓	✓
Weight variation	✓	✓	✓
Disintegration test	✓	-------	✓ *
Content uniformity	✓	✓	✓
Floating characteristics	-------	✓	✓ **
***In vitro* dissolution study**	✓	✓	✓
Kinetic modeling	-------	✓	✓
Swelling studies	-------	✓	✓
Bioadhesion test	-------	✓	✓
***In vivo* study (like X-ray Study)**	-------	✓	✓
***In vitro in vivo* correlation**	-------	✓	✓
Stability studies	✓	✓	✓

*** Indicates that disintegration test is only applicable to IRL from BRT.**
**** Indicates that buoyancy study is only applicable to FBSRLT from BRT.**

Appearance

The tablet should be free from cracks, depressions, pinholes etc. The color of the tablet should be uniform on whole surface. The surface of the tablets should be smooth [52].

Tablet thickness

Crown thickness of tablet is important for uniformity of tablet size. It is measured using Dial caliper, digital Vernier caliper, or starrett portable dial hand micrometer and expressed in mm. It is measured individually for 10 tablets; average is calculated with SD. The average thickness and SD should be reported [49].

Tablet hardness

The resistance of tablets to shipping or breakage, under the conditions of storage, transportation, and handling before usage depends on its hardness. The hardness of tablet is measured by Monsanto hardness tester. The hardness is measured in terms of kg/cm^2 [35].

Tablet friability

Friability is measured with the device called as Roche friabilator. This device measures the combine effect of abrasion and shock on the tablets during the handling of manufacturer, packaging shipment, and consumer use. Roche friabilator is consist of plastic chamber that revolves at 25 rpm (revolutions per min), dropping the tablets from a distance of six inches with each revolution.

Randomly 20 tablets are selected and weighed them (initial weight, W_0), transferred to plastic chamber of Roche friabilator, which is then operated for 100 revolutions (i.e. rotated at 25 rpm for 4 min), then dusted and reweighed (final weight, W) to determine the loss in weight. Then % friability is calculated by using the following formula [49, 53]

$$\text{Friability (\%)} = \frac{W_0 - W}{W_0} \times 100 \quad \text{(Eq. 17)}$$

Where, W_0 is the initial weight (before revolutions) of tablets where as W is the final weight (after revolutions) of tablets.

Tablet porosity

Tablet porosity is calculated as follows [54]

$$\varepsilon = 1 - m/(\rho t \times V) \quad \text{(Eq. 18)}$$

Where, ε is the porosity, ρt is true density, m and V are the weight or mass and volume of the tablet, respectively.

Tablet density

For a floating dosage form, density is an important parameter to predict its floatability. Tablet density is the ratio of tablet weight (w or m) to tablet volume (V). Tablet volume is calculated by measuring tablet height (h) and radius (r) using a micrometer gauge. The density of tablets can be determined by Eq. 19 where as the volume of the tablet can be determined by Eq. 20 as follows [55,56].

$$d = m/V \quad \text{(Eq. 19)}$$

$$V = \pi r^2 h \quad \text{(Eq. 20)}$$

Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention. A density of <1.0 gm/cm^3 is required to exhibit floating property.

However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium [3].

Before immersing the tablet in SGF or 0.1 N HCl, its density has to be determined. If this density is less than 1 gm/cm^3, it will float immediately in SGF or 0.1 N HCl without taking FLT/BLT, this type of gastroretentive approach is called as HBS (hydrodynamically balanced system) and differs from FDDS. Thus in HBS, effervescent agents are not required.

In FDDS, always the density of tablet before immersion in SGF or 0.1 N HCl is ⍰1 gm/cm^3. After immersion of tablet in SGF or 0.1 N HCl, especially effervescent agents react with each other (sodium bicarbonate i.e. base and citric, tartaric acid, or 0.1 N HCl i.e. acid) to precede acid base reaction. This reaction yields generation of carbon dioxide gas in tablet. This FDDS consist of hydrophilic matrix polymers such as HPMC (Hydroxypropyl methyl cellulose), Carbopol, or Na CMC (sodium carboxy methyl cellulose), which swells in the presence of 0.1 N HCl or SGF and the generated air or gas trapped by the swollen polymer to confers buoyancy of tablet [3]. Over all in this mechanism, because of dissolution of effervescent agents, the mass of tablet becomes decreased, whereas swelling of polymer causes expansion of system and generated gas increases the volume of the tablet in comparison with before immersion of tablet in dissolution media, subsequently density of tablet decreases than 1 gm/cm^3 (as per density calculation, Eq. no. 19) and system becomes in floating state [20].

Weight variation

A tablet is designed to contain a specific amount of drug in a specific amount of tablet formula. To check the proper amount of drug in tablet the weight of tablet is routinely measured by weight variation test. It is performed as follows -

Randomly 20 tablets are selected from each batch and weighed them individually in mg or gm on an analytical balance. Calculated the average weight, and compared the individual tablet weight to the average. The tablets meet the test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The weight variation tolerances for the uncoated tablets differ depending on average tablet weight and described in **Table 5** [57].

In general the tablet compression machine is required to be adjusted suitably to produce tablets of uniform weight [49].

Table 5: Weight Variation Tolerances for Uncoated Tablets

Sr. no.	Average weight of tablets (mg)	Maximum percent difference allowed
1	130 or less	10
2	130–324	7.5
3	More than 324	5

Disintegration test

A generally accepted maxim is that if a drug should be readily available to the body, it must be present in solution form. For most tablets, the first important step toward solution is breakdown of tablet into smaller particles or granules, a process known as disintegration. The time that it takes to disintegrate a tablet is measured in a device described in USP/NF called as disintegration tester or apparatus. Research has established that one should not automatically expect a correlation between disintegration and dissolution. However, since the dissolution of a drug from the fragmented tablet appears to control partially or completely the appearance of the drug in the blood, disintegration is still used as a guide to the formulator in the preparation of an optimum tablet formula and as an in process control test to ensure batch to batch uniformity.

This test is applicable to only for IRLT and BRT. Randomly six tablets from each batch are selected for disintegration test. Disintegration test can be performed in SGF at 37 ± 2°C using disintegration test apparatus. Disintegration time can be measured by using stop watch. Then mean ± SD of six tablets is calculated [14, 57].

Content uniformity

A physically sound tablet may not produce the desired effects. To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet and to batch to batch, and a measure of the tablets ability to release the drug needs to be ascertained [57]. Randomly 20 tablets from each batch are selected, weighed, and powdered them. Accurately weighed powder equivalent to 10 mg or 100 mg (as per monograph of drug in official books) of drug and dissolved in the buffer 1.2 pH (0.1 N HCl), diluted it, if necessary and estimated the drug content by using suitable (such as UV Spectrophotometry or HPLC etc) analytical technique [53].

The potency of the tablets is expressed in terms of gm, mg, or µg (for some potent drugs) of drug per tablet and is given as the label strength of the product. Official compendia or other standards provide an acceptable potency range around the label potency. For highly potent, low dose drugs such as digitoxin, this range is usually not less than 90% and not more than 110% of the labeled amount. For most other larger dose drugs in tablet form, the official potency range that is permitted is not less than 95% and not more than 105% of the labeled amount [57].

Three factors can directly contribute to content uniformity problems in the tablets, 1) non uniform distribution of drug substance throughout the powder mixture or granulation, 2) segregation of the powder mixture or granulation during

various manufacturing procedures, and 3) tablet weight variation. The use of weight variation test cannot be used as potency indicator, except perhaps when the active ingredient is 90 to 95% of the total tablet weight. In tablets with smaller doses, a good weight variation does not ensure good content uniformity, but a large weight variation precludes good content uniformity [57].

Floating characteristics

The floating lag time (FLT), density, and total floating time (TFT) are now considered as essential parameters for the majority of evaluations describing the floating capability or characteristics of dosage forms. However, although the density value may indicate whether an object will float or not, it does not reflect the magnitude of floating force produced by the object. The changes in weight and volume of dosage form due to the dissolution of drug, swelling, and erosion of polymer as a function of time yields continuous variation in density of the dosage form, which affects the floating capability and thus cannot be predicted by a single determination of density [55]. The same thing also discussed in density aspect of tablet. Floating characteristics study is only applicable to FBSRLT and BRT. FLT and TFT should be determined in triplicate in conjunction with the *in vitro* dissolution study.

A) FLT/BLT

Buoyancy lag time (BLT) is also FLT. It is the time required for the tablet to rise towards surface and float. The buoyancy of tablets is studied in a USP dissolution testing apparatus at 37 ± 0.5 °C in 900 mL of 1.2 pH buffer (SGF without enzyme i.e. pepsin) to mimic *in vivo* conditions. The duration of buoyancy is observed visually and recorded by using stop watch.

The FLT should be less; few researchers concluded that ideal floating system should float within 3 min, as this time increases from 3 min to above the ideality of dosage decreases and vice versa. The ability of hydrogel to absorb water or dissolution medium is due to the presence of hydrophilic groups. The hydration of these functional groups results in water or dissolution medium entry into the polymer network leading to expansion and consequently an ordering of the polymer chains. It has assumed that behaviour of these hydrophilic tablets starts with water diffusion into the glassy HPMC material where the water plasticizes the polymer and reduces its glass transition temperature (Tg). When Tg has decreased to ambient temperature, a transformation from a glassy state to a rubbery state occurs. As the water or dissolution medium continues to enter the tablet, a highly concentrated polymer solution is formed, denoted as a gel layer. The solvent continues to penetrate the tablet, and the gel layer and the dimensions of the swollen tablet increase, a process normally referred to as the swelling process [2,35,45,53].

B) TFT

The time period that tablet constantly float on the surface of gastric media is called as TFT. It is also studied in a USP dissolution testing apparatus at 37 ± 0.5 °C in 900 mL of 1.2 pH buffer (SGF without enzyme i.e. pepsin) to mimic *in vivo* conditions. The duration of TFT is observed visually and recorded by using stop watch [2,35,45,53]. Always FLT is depending on concentration of effervescent agent while TFT is depending on concentration of hydrophilic polymer. This is because the amount of gas or air generation is governed by effervescent agent while the same amount of gas or air entrapped in polymer mass of tablet is governed by concentration and type of polymer (ex. HPMC K 4M, K15 M, K 100M and K 200M i.e. different viscosity grades of polymer etc).

C) Resultant Buoyancy

Timmermans and Moes [58, 59] have developed an apparatus for the *in vitro* determination of real floating capabilities in terms of 'resultant weight' as a function of time. The resultant weight apparatus consists of a force transmitter device (FTD) connected to a weighing balance. The lower extremity of FTD holds the dosage form into the dissolution medium and transmits reacting force; either upward or downward forces, to the electromagnetic measuring module of a weighing balance. The lower extremity of FTD is interchangeable for different types of floating dosage forms (i.e., needle-like or mesh-like holders). The resultant weight apparatus operates by

measuring the force equivalent to resultant weight F required to maintain the object totally submerged in the fluid. The magnitude and direction of force F corresponds to the vectorial sum of buoyancy force ($F_{buoyancy}$) and gravity force ($F_{gravity}$) acting on the dosage form, as shown in Eq. 21.

$F = F_{buoyancy} - F_{gravity} = (D_f - D_s)\, g\, V$ (Eq. 21)

Where, F is total vertical force (resultant weight of an object), D_f is fluid density, D_s is object density, V is volume, g is acceleration due to gravity. The values are used to draw floating curves.

The floating curves are obtained by plotting a continuous resultant weight of the floating dosage form as a function of time. A positive resultant weight signifies that the F is exerted upward and that the object is able to float, whereas a negative value describes downward movement of the object.

The crossing of the zero base line by the floating curve from positive towards negative value indicates the transition of the dosage form from floating to non floating conditions. The intersection of lines on a time axis corresponds to the floating time of the dosage form. Recently several researchers have utilized this apparatus for evaluation and optimization of various GRDDS [35,55,60].

D) Floating kinetics

Parikh and Amin, [55] described a continuous floating monitoring system which is based on the method to access the mucoadhesive force measurement. It has a floating measuring probe consisting of a stainless steel basket, is connected to a metal string, suspended from an electronic balance. The floating dosage form is kept in the basket and immersed at a fixed depth into the dissolution apparatus.

The upward force can be measured by the balance and this measure is transmitted to an online computer by RS-232C cable. The data obtained are used to plot a floating kinetic curve where the floating kinetics is plotted against time at each 30 sec interval.

***In vitro* dissolution study**

The *in vitro* drug release from floating tablets (n = 6) can be determined by using USP. Dissolution testing apparatus USP 1 and USP 2 are widely used for the same purpose. The dissolution test is performing by using 900 mL of dissolution media with or without enzymes and surfactants (SGF, 0.1 N HCl, or pH 1.2), at 37 ± 0.5° C and at reported rpm of that model drug. A sample (5 mL) of the solution will be withdrawn from the dissolution apparatus at specified time intervals and the samples will be replaced with same volume of fresh prewarmed same dissolution medium.

The samples are filtered through a 0.45 micron membrane filter and diluted to a suitable concentration with above dissolution media. Absorbance of these solutions is measured at suitable wavelength (λ_{max}) of model drug using a UV/Visible double beam spectrophotometer or any other suitable analytical technique. Calculate cumulative percentage drug release using an equation obtained from a standard calibration curve of model drug [44].

Kinetics modeling

To study the release kinetics, data obtained from *in vitro* drug release studies can be subjected to various kinetic models: zero order (Eq. 22) as cumulative amount of drug released Vs time, first order (Eq. 23) as log cumulative percentage of drug remaining Vs time, Higuchi's model (Eq. 24) as cumulative percentage of drug released Vs square root of time, and Korsmeyer Peppas model (Eq. 25) as log cumulative percentage of drug released Vs log time, and the exponent n was calculated through the slope of the straight line [14,25,61,62].

$C = K_0 t$ (Eq. 22)

Where, K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in h. A graph of concentration Vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

$\text{Log } C = \text{Log } C_0 - Kt/2.303$ (Eq. 23)

Where, C is the concentration of the drug in time t, C_0 is the initial concentration of drug, K is the first order constant, and t is the time.

$Q = Kt^{1/2}$ (Eq. 24)

Where, K is the constant reflecting the design variables of the system and t is the time in h.

$M_t = M_0 + K_k t^n$ (Eq. 25)

Where, M_t is the amount of drug released in time t, M_0 the initial amount of drug, K is

respective release constant (may be zero or first order) and n is the release exponent, which characterizes the mechanism of drug release.

Swelling studies

The swelling index represents the swelling capacity of the polymer when it comes into contact with the dissolution media. It play vital role in maintaining buoyancy of the floating dosage forms.

The swelling properties of the tablet can be determined by placing it in the dissolution test apparatus, in 900 mL of 0.1 N HCl at 37 ± 0.5°C. The tablets are removed periodically from dissolution medium, immediately wipe with a paper towel to remove surface droplets, measured for weight gain. The swelling index or water uptake (Q) of swellable tablets can be determined using Eq. 26 as

$$Q = \frac{(Ws - Wd)}{Wd} * 100 \text{ (Eq. 26)}$$

Where Ws and Wd represent the weight of the swollen tablet and weight of the dry tablet (i.e. initial weight of tablet before swelling), respectively. The formulator has to design the dosage form by balancing the swallowability by the patient and the gastroretentive capability. Thus, higher swelling index values are desired for GRDDS based on the swelling system and the expandable type of system. The data should be represented mean ± SD, n = 3 [2,40,55].

Bioadhesion test

Bioadhesive or mucoadhesive drug delivery system (BDDS or MDDS) are based on extensive research carried out to find polymers that bind mucosal membranes in *in vitro* or *ex vivo*. It is studied by following ways -

I) *In vitro* test (Tablet Adhesion Retention Test)

Recently Tadros, [63] has described a new *in vitro* method for measurement of bioadhesive strength of bioadhesive tablet. An agar plate (1%, w/w) is prepared in 0.1 N HCl (pH 1.2). A side of the tablet is wetted with 50 µL of 0.1 N HCl and attached to the center of agar plate by applying a light force with a finger tip for 20 sec.

Five min later, the agar plate is further attached to a USP disintegration test apparatus and moved up and down in 0.1 N HCl (i.e. pH 1.2) at 37 ± 0.5° C. The adhering tablet on the plate is immersing into the solution at the lowest point and get out of the solution at the highest point. The retention period of the tablet on the plate can be noted down visually [63].

II) *Ex vivo* Test (Detachment stress/force or Modified balance method)

The mucoadhesive forces of the bilayer tablets are determined by means of mucoadhesive force measuring device shown in **Fig. 2**.

The pieces of fundus tissues of sheep are stored frozen in saline solution and thawed to room temperature before use. For performing test, a section of tissue (5) is secured, keeping the mucosal side out, on to upper glass vial (3) using a rubber band and an aluminum cap. The diameter of each exposed mucosal membrane is around 1 cm. The vials with the fundus tissue are stored at 37° C for 10 min. Next, one vial with a section of tissue (5) is connected to the balance (1) and the other vial is fixed on a height adjustable pan (7). To the lower vial, a bioadhesive (bilayer) tablet (4) is applied with the help of adhesive tape (6). The height of the vial is adjusted so that the tablet could adhere to the mucosal tissues of vial. A constant force is placed on the upper vial and applied for 2 min, after which it is removed and the upper vial is then connected to the balance. Water (8) is added slowly to the pan containing the specific gravity bottle (2) on the other side of the modified balance until the two vials are separated. The bioadhesive force, expressed as the detachment stress in dyne/cm^2, is determined from the weight of water that detached the two vials using the following equation [9, 35, 64].

$$\text{Detachment stress (dyne/cm)}^2 = \text{m} \times \text{g/A} \text{ (Eq. 27)}$$

Where, m is the weight of water added to the specific gravity bottle in balance (gm), g is acceleration due to gravity, A is area of sheep fundus tissue exposed and is equal to πr^2 (r the radius of the circular hole in the aluminum cap).

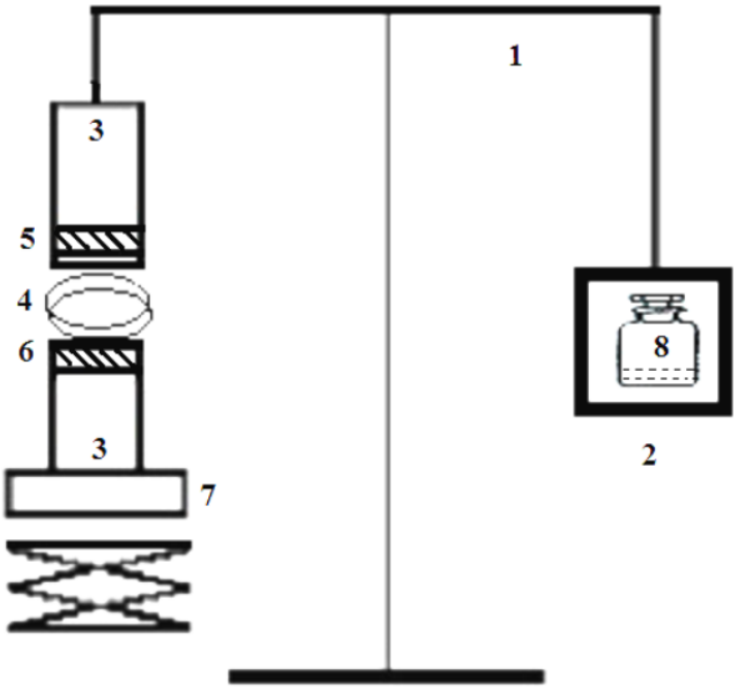

Fig. 2: Mucoadhesive strength measuring device (Modified balance method)

Where, (1) modified balance; (2) specific gravity bottle for measuring exact weights by using water; (3) glass vial; (4) bioadhesive tablet; (5) piece of fundus tissues of sheep or suitable animal fundus tissue; (6) supportive adhesive tape; (7) height adjustable pan; (8) water added to specific gravity bottle for exact measure.

***In vivo* study**

Previously reported *in vivo* studies for GRDDS were carried out on beagle dogs. In India, now a day's it is quite difficult to choose beagle dogs for performing *in vivo* study as per CPCSEA guidelines. Therefore as an alternative animal, rabbits are suitable for performing *in vivo* study. Larger size tablets cannot be administered to rabbits. Thus, human dose tablets can be prepared to small sized (100 mg) tablets without changing the percentage of release retarding or bioadhesive polymer, and effervescent agent. Drug can be replaced by diluents except bioavailability studies i.e. pharmacokinetic studies. It can be performed by various ways as follows -

I) Gamma scintigraphy

Gamma scintigraphy is used for monitoring the *in vivo* behavior of the oral dosage forms. Among the methods available, gamma scintigraphy is the most widely used noninvasive technique for studying the *in vivo* behavior of oral dosage forms under normal physiological conditions. The common radio nuclides used to correlate the GI behavior of dosage forms with their pharmacokinetic parameters, i.e. correlation of the location of the dosage forms in a certain region of the GIT to maximum plasma concentration, are Technetium-99 m (^{99m}Tc) and Indium 111 (^{111}In). In this technology a stable radioisotope is formulated within the developed system and administered in healthy human volunteers or animal models to correlate the location of FDDS. Technetium-99 m is the most widely used radionuclide in nuclear medicine. It has a very short half life of 6 h and emits photons but not particulate radiation (β rays harmful to tissues). A dose of 6 MBq ^{99m}Tc can be incorporated into the tablet blend during manufacture to facilitate scintigraphic imaging. The tablet is prepared without drug and administered along with 100 mL water after taking a light breakfast in the morning. The dosage form is visualized using a gamma camera. Major drawbacks with such a technique are associated ionization radiations, limited topographic information, low resolution, and complicated and expensive preparation of radiopharmaceuticals [9,12,55,65].

II) Roentgenography

This method includes pre-clinical estimation of gastro retention. X-ray technique is the most widely used method for examination of internal body systems. In comparison to γ-scintigraphy, radiology is a more simple and cost effective technique. However, limitations regarding exposure to X-rays decline its popularity because for optimum evaluation of buoyancy a high amount of contrasting agent (radio opaque marker), barium sulphate ($BaSO_4$) is generally required. For better exemplification of GRDDS by radiology, a high concentration of barium sulfate (25-40% or in some cases more) is required, which would require changes in the formulation of GRDDS. This problem can be overcome by incorporation of radio-contrast aluminum threads obtained from surgical gauze pads. Radiographs can be taken after ingestion of the dosage form, to locate the floating and non-floating (fabricated) dosage forms at various periodic time intervals. The major drawback of this technique is the amount of exposure of human volunteers to X-rays, which depends on exposure time, frequency, and repetitions required to assess the efficacy. Higher exposures to X-rays lead to a hazardous risk to the human body [12, 55].

III) Gastroscopy

Gastroscopy is a small part in endoscopy. Where endoscopy looks at all the structures of the human body from joint spaces to the lower intestines, gastroscopy only involves the upper GIT. Gastroscopy is a peroral endoscopy technique used with fibre optics or video systems. It is used to inspect visually the effect of prolongation of the dosage form in the stomach. It can also allow the withdrawal of the GRDDS from the stomach for thorough evaluation. GRDDS are intended to remain in the stomach for about 8-12 or more h. In order to assess the gastro-retentive performance by peroral endoscopy, the video system has to enter into the body of the volunteer at regular time intervals, making the procedure inconvenient to the volunteer, as well as necessitating the presence of a gastroenterologist for the entire evaluation study. Active uncontrolled bleeding, retained blood in the stomach, and retained food or antacids may also lead to an inadequate study. These factors have lead to the limited use of gastroscopy [12,55,56].

IV) Ultrasonography

In this technique, ultrasonic waves are used images of body structures. The waves travel through tissues and are reflected back where density differs. The reflected echoes are received by an electronic apparatus that measures their intensity level and the position of the tissue reflecting them. The results can be displayed as still images or as a moving picture of the inside of the body. However, this method is not popular due to lack of ultrasound traceability at the intestine. Another drawback of this method is some of the dosage forms may not exhibit a sharp acoustic mismatch. Therefore, ultrasonography is not routinely used for the evaluation of FDDS [12, 55].

V) Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a noninvasive, especially diagnostic technology. It uses a powerful magnetic field, radio frequency pulses, and a computer to produce detailed pictures of organs, soft tissues, bone, and virtually all other internal body structures. The images can then be examined on a computer monitor, transmitted electronically, and printed or copied to a compact disk (CD). It does not use ionizing radiation (X-rays), thus it is less hazardous than previous methods. In the last couple of years, MRI was shown to be valuable tool in GI research for the analysis of gastric emptying, motility and intra gastric distribution of macronutrients and drug models. The other advantages of MRI include high soft tissue contrast, high temporal and spatial resolution. Also, harmless paramagnetic and supra magnetic MRI contrast agents can be applied to specifically enhance or suppress signal of fluids and tissues of interest and thus permit better delineation and study of organs. However, the technique is not widely used because it requires formulative changes, that are incorporation of iron powder, which has higher density and may affect the performance of GRDDS [12,55,67,68].

VI) Bioavailability studies (Pharmacokinetic study)

The tablets are administered to the suitable animal models, which are housed individually under environment conditions (25° C, 12 h of light and dark cycle) or human volunteers. They should be fasted overnight but have free access to drinking water. Periodically either blood samples or urine samples should be collected and analyzed by using suitable analytical technique to know the drug concentration. Further calculate % of bioavailability by using kinetic software [44, 69].

***In vitro in vivo* correlation (IVIVC)**

A simple *in vitro* dissolution test on the drug product will be insufficient to predict its therapeutic efficacy. Convincing correlation between *in vitro* dissolution behaviour of a drug and it's *in vivo* bioavailability must be experimentally demonstrated to guarantee reproducibility of biological response. Here *in vitro* dissolution parameters such as percent drug dissolved, rate of dissolution, rate constant for dissolution etc can be correlated with parameters such as percent drug absorbed, rate of absorption, C_{max}, t_{max} obtained from plasma level data or correlated to the amount of drug excreted unchanged in the urine, cumulative amount of drug excreted as a function of time from urinary excretion data. This correlation should be linear. Results of bioadhesion test and TFT (*in vitro* tests) are also correlated with γ scintigraphy, X –ray, Gastroscopy, ultrasonography study to confirm the gastric retention [7].

Stability studies

It is always advisable to perform stability studies on optimized formulation or best selected formulations.

A stability study is carrying out according to ICH (international conference on harmonization) guidelines. Tablets of optimized formulations are sealed in aluminium packaging coated inside with polyethylene, and samples can be kept in humidity chamber at 40 ± 2° C and 75 ± 5 % RH (relative humidity) for 3 months. At the end of each month, samples are analyzed for drug content, floating characteristics, hardness values, and *in vitro* dissolution studies [39]. If all the above evaluated parameters are found to be in satisfactory limit then the stored formulation can be claimed to be robust and vice versa.

At the end of studies, the comparison of release profiles of initial and after stability samples are need to be done. For the same purpose, the "similarity factor" f_2, are calculated.

The similarity factor (f_2) is a logarithmic transformation of the sum of squared error of differences between the test T_j and the reference products R_j at over all time points. It is calculated using the Eq. 28.

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{j=1}^{n} W_j\left|R_j - T_j\right|^2\right]^{-0.5} \times 100\right\} \quad \text{(Eq. 28)}$$

Where, w_j is an optional weight factor and other terms are as defined earlier. The two dissolution profiles are considered to be similar, if f_2 value is more than 50 i.e. between 50 -100) [40,42,61,62].

CONCLUSION

Increased GRT in sustained or CDDS has important practical aspect. A CDDS with gastro retentive ability can significantly improve the drug utilization (bioavailability) and thereby improve efficacy of medical therapy. Detailed ideas about the formulation of bilayer tablet have been integrated in the manuscript.

On the basis of literature survey, in this article we classified three different types of approaches of bilayer floating drug delivery system. Emphasis was given more on formulation and evaluation aspects of biphasic floating cum bioadhesive tablets. We tried to provide suitable platform for the calculation of loading and maintenance dose for desired h with different formulae. Different *in vitro* and *in vivo* evaluation parameters for an exhaustive study of BRT belonging to FDDS have well discussed. Researchers may adopt suitable technique to ensure optimum performance of region selective drug delivery system in formulation and evaluation of FDDS. In characterization, special emphasis is given on *in vivo* studies.

The techniques mentioned in this article will provide easy access to researchers while formulating and evaluating GRDDS

and also ensures the success of dosage form during clinical trial.

Declaration of Interest/Conflict of Interest

The authors state no conflicts of interests and have not received payment in the preparation of this manuscript. We alone are responsible for the content and writing of this manuscript.

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ABBREVIATIONS

GIT	Gastro intestinal tract
CR	Controlled release
CDDS	Controlled drug delivery system
CRDDS	Controlled release drug delivery system
GET	Gastric emptying time
GRDDS	Gastro retentive drug delivery system
GRDD	Gastro retentive drug delivery
FDDS	Floating drug delivery system
FBDDS	Floating-bioadhesive drug delivery system
BFDDS	Bilayer floating drug delivery system
BFT	Bilayer floating tablets
IR dose	Immediate release dose
MR dose	Maintenance release dose
IRLT	Immediate release layer tablets
FBSRLT	Floating bioadhesive sustained release layer tablets
BRT	Biphasic release tablets
BLT	Buoyancy lag time
FLT	Floating lag time
TFT	Total floating time
SGF	Simulated gastric fluid
APIs	Active pharmaceutical ingredients
API	Active pharmaceutical ingredient
MCC	Microcrystalline cellulose
DCP	Dicalcium phosphate
GRT	Gastric retention time
HBS	Hydrodynamically balanced system
h	Hours
min	Minutes
sec	Seconds
mm	Millimeter
cm	Centimeter
gm	Gram
mg	Milligram
Eq.	Equation
Sr. no.	Serial number
HPMC	Hydroxypropyl methyl cellulose
USP	United States Pharmacopeia
SD	Standard deviation
HCl	Hydrochloric acid
UV spectrophotometry	Ultra violet spectrophotometry
HPLC	High performance liquid chromatography
GMP	Good manufacturing practices
FTD	Force transmitter device

Vs	Versus
BDDS	Bioadhesive drug delivery system
MDDS	Mucoadhesive drug delivery system
mL	Millliter
µL	Microliter
MBq	Megabecquerel
MRI	Magnetic Resonance Imaging
CD	Compact disc
IVIVC	*In vitro in vivo* correlation
C_{max}	Peak plasma concentration
t_{max}	Time of peak plasma concentration
ICH	International conference on harmonization
CFU	Colony forming units

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