Introduction
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Oral drug delivery has been known for decade as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. The reason that the oral route achieved such popularity because of the traditional belief that by oral administration the drug is as well absorbed as the foods stuffs. Pharmaceutical products designed for oral delivery are mostly immediate release type, which are designed for immediate-release of the drug for rapid absorption. Because of the clinical advantages over immediate release, sustained release pharmaceutical products came in market. Recently, a new generation of pharmaceutical products called controlled release drug delivery systems has received regulatory approval for marketing. Their superiority over other products has been increasingly recognized. The scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects:

i) Physiochemical, pharmacokinetic and pharmacodynamic characteristics of drug,

ii) The anatomical and physiological characteristics of GIT, and

iii) Physiochemical characteristics and the drug delivery mode of the dosage form to be designed.

It is desirable that the duration of the drug action become more a design property of a rate control dosage form, and less, or not at all, a property of the drug molecules inherent kinetic properties.

Various controlled release formulations containing single drug or multi drug have been designed and developed successfully. While designing controlled release systems, a thorough understanding of the pharmacokinetics and pharmacodynamics of the drugs is essential.

Multi-component Drug Delivery System

Over the years, multi-component drug delivery system is gaining more significance in clinical field of pharmaceutical products. The use of multi-component drug delivery is explored due to superiority over single drug delivery system in terms of, clinical need, disease state, effective treatment, patient compliance and better disease management. There are various diseases which need two or more drugs concomitant treatment for better control over the disease. Few examples of such classes of the drugs are mentioned below.

i) Antihypertensive and diuretics

ii) Antihypertensive and antilipidemics

iii) Antiulcercular

iv) Antibiotics

v) NSAIDS’s

vi) Antibiotics and anthelmintics

vii) Antiemetics and H2-blokers etc.

Ideal Characteristics of multicomponent Formulations

i) Formulation should release the drugs according to predetermined goals, i.e. some drugs need immediate release and or conventional release and or sustained release and or controlled release.

ii) In case of biphasic release systems, formulation should selectively release the drug(s) at desired pre-determined rate at appropriate site in body.

iii) Drugs used should be compatible with each other. Formulation processes should encourage the compatibility of the drugs.

iv) Formulation excipients should be compatible with the drugs.

v) Formulation should facilitate easy packaging and labeling.

vi) The presence of one drug should not hamper the release of co-drug(s).

vii) Should have desired physicochemical properties.

Multicomponent formulation Considerations
While formulation of multicomponent drug delivery system following basic parameters have to be handled carefully.

- Half life of drug(s)
- Extent of absorption and mechanism
- Metabolism
- Elimination
- Side effects of drugs
- pKa
- Disease state
- Hydrophilicity / Lipophilicity
- Bioavailability
- First pass metabolism
- Synergistic/ antagonistic effects

Cardiovascular disease (hypertension, congestive heart failure etc.) is one of the leading causes of the mortality and morbidity. Heart disease causes more than 5,00,000 deaths every year worldwide. One of the causes for cardiovascular disease is high level of cholesterol in body, the condition called hypercholesterolemia. Dyslipidemia is a term often used to describe a group of syndromes or conditions involving imbalances or extremes in blood lipid levels. It encompasses hyperlipidemia and hypercholesterolemia and other lipid disorders. These conditions may lead to various kinds of disorders like, atherosclerosis, myocardial infarction, cardiac arrhythmia, acceleration of progression of glomerular injury etc.

Hyperlipidemia is a major player in atherogenesis. Its relative contribution to cardiovascular risk has been proven if beyond doubt & measured by many, either alone or as fact of group of risk factors. Hypertension is also one of the primary risk factor for atherosclerosis. When non insulin dependant diabetes mellitus (NIDDM) or dyslipidemia is associated with high blood pressure, the risk (& incidence) of major cardiovascular events rises dramatically. The significant reduction of fatal & nonfatal events observed in trials of primary & secondary prevention has confirmed that HMG-COA reductase inhibitors reduce the risk of cardiovascular events well beyond the hypolipidemic effects.

Treatment of modifiable cardiovascular risk factors is essential to reducing the incidence of cardiovascular disease (CVD). Hypertension & dyslipidemia are too frequently co morbid risk factors; these conditions contribute substantially to the burden of CVD indeed, >50% of the conditions, known as metabolic syndrome can be attributed to elevated blood pressure & elevated lipid levels.
Endothelial dysfunction is characterized by vascular endothelium from a smooth nonthrombogenic surface to one whose cells respond abnormally to stimuli of vasodilation while, also expressing adhesion molecules that bind circulating leukocytes. As endothelial dysfunction progresses, there is loss in the production of functional nitric oxide (NO) along with its atheroprotective actions. Endothelial dysfunction leads to smooth muscle cell proliferation & increased level of thromboxane, A_2, a potent stimulus of platelet aggregation. Concomitantly with other signs of endothelial dysfunction, there is evidence of increased endothelial permeability to low-density lipoproteins (LDL). Finally, potent vasoconstrictors such as endothelin I are released, further compromising normal haemodynamics.

Hypertension and hypercholesterolemia frequently coexist and may require concomitant drug treatments. Various researchers have conducted clinical trials for combination therapy for the treatment of hypertension and hypercholesterolemia. These studies indicate a clinical need of combined treatment with statins and antihypertensive drugs like β1 blockers, angiotensin converting enzyme inhibitors and calcium channel blockers.

J. L. Pool and coworkers studied the clinical effects of Lovastatin and coadministered antihypertensive/cardiovascular agents (calcium channel blockers, beta 1 blockers, angiotensine converting enzyme inhibitors and diuretics). They revealed that coadministration of Lovastatin and antihypertensive agents have synergistic or additive effects, further they found no any indication of interaction among the drugs.

In one research study, it was found that, when Lovastatin was coadministered with Diltiazem HCl (sustained release tablets 120 mg), it resulted in 3-4 times increase in mean Lovastatin AUC. And there was no significant effect on Diltiazem HCl plasma levels.

An Indian based Pharmaceutical company (Dr. Reddy's Lab.) has started clinical trial of Simvastatin coadministered with Atenolol ("Polypill") for the treatment of hypertension associated with hypercholesterolemia.

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed. However, it is a well-accepted fact that
it is difficult to predict the real in vivo time of release with solid, oral controlled release dosage forms.

Forms that are retained in the stomach for a prolonged and predictable period of time exist today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT). Dosage forms with a prolonged GRT, i.e. gastroretentive dosage forms (GRDFs), will provide new and important therapeutic options.

Prolonging the gastric retention of a delivery system is sometimes desirable for achieving therapeutic benefits of drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT) or that are less soluble in or are degraded by the alkaline pH they encounter at the lower part of GIT. GRDFs are thus beneficial for such drugs by improving their bioavailability, therapeutic efficacy and by possible reduction of dose. Apart from these advantages, these systems offer various pharmacokinetic advantages like maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics.

Conventional Dosage Form
It requires administration in a particular dose at a particular frequency.

Limitations of Conventional dosage forms

1. Frequent dosing
It requires frequent dosing, which increases the chances of missing the dose of drug especially with the drugs having short half life.

2. Poor patient compliance
Due to the frequent dosing patient compliance for the oral conventional drug delivery is very poor.

3. Typical peak-valley plasma concentration-time profile
Conventional drug delivery shows unavoidable fluctuations in drug concentrations with low and high values from the therapeutic concentration range.

In certain cases in which “therapeutic window” of the drug is small, overmedication or higher therapeutic values yield toxic or adverse effects.

Need For Gastroretention

1. Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT) mainly can effectively be given.

2. Drugs that are less soluble in or are degraded by the alkaline pH are the best suitable candidates for GRDDS, e.g. Captopril.

3. Drugs that are erratically absorbed due to variable gastric emptying time can be administered as GRDFs so that their absorption can be increased as the drug remains in stomach for a longer time.

4. Local or sustained drug delivery to the stomach and proximal small intestine to treat a certain condition is also possible.

5. GRDFs can be particularly useful for the treatment of peptic ulcers caused by H. Pylori infections.

Physiology of Gastrointestinal Tract
Anatomically the stomach is divided into 3 regions: fundus, body and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as in fed states. The pattern of motility is however distinct in the two states.
Table 1. Anatomical and physiological features of human GIT

<table>
<thead>
<tr>
<th>Section</th>
<th>Average length (cm)</th>
<th>Diameter (mm)</th>
<th>pH</th>
<th>Major constituents</th>
<th>Transtub time of food (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>15–20</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Eosophagus</td>
<td>25</td>
<td>2.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Stomach</td>
<td>20</td>
<td>15</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Duodenum</td>
<td>25</td>
<td>5</td>
<td>+</td>
<td>Passive diffusion, convective transport</td>
<td>1–2</td>
</tr>
<tr>
<td>Jejunum</td>
<td>300</td>
<td>6</td>
<td>++</td>
<td>Passive diffusion, convective transport, active transport, facilitated transport, ion pair, pinocytosis</td>
<td>6.3–7.3</td>
</tr>
<tr>
<td>Ileum</td>
<td>300</td>
<td>2.5–5.0</td>
<td>++</td>
<td>Passive diffusion, convective transport, active transport, facilitated transport, ion pair, pinocytosis</td>
<td>7.5</td>
</tr>
<tr>
<td>Cecum</td>
<td>10–30</td>
<td>7</td>
<td>+</td>
<td>Passive diffusion, convective transport, active transport, facilitated transport, ion pair, pinocytosis</td>
<td>7.5–8.0</td>
</tr>
<tr>
<td>Colon</td>
<td>150</td>
<td>5</td>
<td>–</td>
<td>Passive diffusion, convective transport</td>
<td>7.9–8.9</td>
</tr>
<tr>
<td>Rectum</td>
<td>15–19</td>
<td>2.5</td>
<td>–</td>
<td>Passive diffusion, convective transport, pinocytosis</td>
<td>7.5–8.0</td>
</tr>
</tbody>
</table>

* In the "Villi present" column, ‘–’ indicates villi are absent, ‘+’ indicates villi are scarcely present, and ‘++’ indicates villi are abundantly present.

Figure 2. Anatomy of stomach

Gastrointestinal motility and Migrating motor complex (MMC)14
During the fasting state, an interdigestive series of electrical events take place, which cycle both through stomach and intestine for every 2 to 3 hours, this is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases.

1. **Phase I (basal phase):**
   It lasts for 40 to 60 minutes with rare contractions.

2. **Phase II (preburst phase):**
   It lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3. **Phase III (burst phase):**
   It lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

4. **Phase IV:**
   It lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in suspension form.

During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications, short gastric residence time and unpredictable gastric emptying rate.

**Gastric residence: an overview**

Gastric residence time of an oral dosage form is affected by several factors. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach does not get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting one.

The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals also helps to determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying.
time. Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron’s disease) influence gastric emptying. Studies have shown that the gastric residence time (GRT) can be significantly increased under the fed conditions since the MMC is delayed. Several formulation parameters can affect the gastric residence time. More reliable gastric emptying patterns are observed for multiparticulate formulations as compared with single unit formulations, which suffer from “all or none concept.”

**Different Techniques Of Gastroretention**

1. Floating System
2. Bioadhesive System
3. Swellable System
4. High Density System

**Figure 4. Different approaches of gastric retention**

<table>
<thead>
<tr>
<th>System</th>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling systems</td>
<td>The drug optimises the food effect of drug retention in the gut</td>
<td>Depomed’s gastric retention technology</td>
</tr>
<tr>
<td>Floating systems</td>
<td>The drug floats above the food in the stomach</td>
<td>Generally used in conjunction with other systems</td>
</tr>
<tr>
<td>Expansion systems</td>
<td>Where laminate containing drug is folded into a capsule</td>
<td>Intec Pharma’s gastric retention dosage form</td>
</tr>
<tr>
<td>Muco-adhesion</td>
<td>Where polymers stick to the mucous on the stomach wall</td>
<td>Spherics’ bio-adhesive-based oral dosage form</td>
</tr>
</tbody>
</table>

**Floating Systems**

As the name indicates the drug formulation remains floating on the GI contents due to its lower bulk density, than that of the gastric contents (density of gastric content is 1) at any time.
These are hydrodynamically balanced systems [HBS]

**Two commonly used techniques:**

A. **Gas generating systems (Effervescent systems):**

It contains carbonates or bicarbonates that generate carbon dioxide gas in presence of gastric acid and/or the added organic acid.

The carbon dioxide gas thus gets entrapped into the matrix of the formulation, reducing its density and imparting floating property.

1. **Volatile liquid containing systems:**-

   The gastric retention of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, etc. that gasifies at body temperature to cause the inflation of the chamber in the stomach.

   These devices are osmotically controlled floating systems containing a hollow deformable unit that can convert from a collapsed to an expandable position, and returns to the collapsed position after an extended period.

   The deformable system consists of two chambers separated by an impermeable, pressure responsive, movable bladder. The first chamber contains the drug and the second chamber contains the volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid.

   The device may also consist of a biodegradable plug made up of Polyvinyl acetate, 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 system from the stomach.

2. **Intragastric osmotically controlled drug delivery systems**

   They consist of an osmotic pressure controlled drug delivery device and a floatable support in a biodegradable capsule. When the device reaches the stomach, bioerodible capsule quickly disintegrates to release the drug delivery system. The floating support is made up of a deformable hollow polymeric bag containing a liquid that gasifies at body temperature to inflate the bag.

   Osmotic pressure controlled part consists of two compartments, a drug reservoir compartment, and an osmotically active agent compartment.

   The drug reservoir compartment is enclosed in a pressure responsive collapsible bag, which is impermeable to vapors and liquid, and has a drug delivery orifice. The osmotic compartment contains an osmotically active salt, and is enclosed within a semi permeable housing. In stomach, water is absorbed through the semi permeable membrane into the osmotic compartment to dissolve the salt. An osmotic pressure is thus created, which acts on the collapsible bag, and in turn forces the drug reservoir compartment to reduce its volume and release the drug solution through the delivery orifice. The floating support also contains a biodegradable plug that erodes after a predetermined time to deflate the support, which is then excreted from the stomach.

3. **Gas generating systems**

   These floating delivery systems utilize effervescent reaction between carbonate /bicarbonate salts and citric/tartaric acid to liberate CO₂, which gets entrapped in the gellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it to float over chime. These tablets may be either single layered wherein the CO₂ generating components are intimately mixed within the tablet matrix, or they may be bilayered in which the gas generating components are compressed in one hydrocolloid containing layer, and the drug in other layer formulated for a SR effect.

   Another effervescent system consists of a collapsible spring, which controls the release of drug from the polymer matrix, has also been developed. The device consists of a body made up of a non-digestible, acid resistant and high density polymer and a gelatin cap. The lower end of the body consists of an orifice to control the drug release. This orifice is occluded by a drug polymer compact of negligible porosity. A rubber disc with horizontal orifice supporting a collapsible spring and a
rubber balloon housing the bicarbonate granules lies above its drug polymer compact. In aqueous environment, the gelatin cap and a water soluble tape supporting the rubber balloon dissolves. This is followed by an effervescent reaction between the bicarbonate granules and the acid surrounding the spring, thus leading to the generation of CO$_2$ and inflation of rubber balloon providing necessary floating to the dosage form.

Figure 5. The mechanism of floating systems

A minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW) has been reported in the literature. The RW apparatus operates by measuring continuously the force equivalent to F (as function of time) that is required to maintain the object submerged. The object floats better if RW is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

B. Non-gas generating systems (non effervescent systems)

These are highly porous and highly swellable systems that expand in gastric contents reducing their density and thus imparting floating properties.

1. Colloidal gel barrier system:

These are hydrodynamically balanced systems. This system contains drugs with gel forming hydrocolloids meant to remain floating on the stomach contents. Generally a high level [20-75%W/W] of one or more gel forming, highly swellable, cellulose type hydrocolloids e.g. hydroxy ethyl cellulose (HEC), hydroxyl propyl cellulose (HPC), hydroxy propyl methylcellulose (HPMC), sodium carboxy methyl cellulose (Na-CMC), polysaccharides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene are being incorporated in either tablet or capsules.

On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms 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. As shown in figure 6.
As the exterior surface of the dosage form goes into the solution, the gel layer is maintained by the adjacent hydrocolloid solution being hydrated.

**Microporous compartment system**

This system is based on the encapsulation of the drug reservoir inside a microporous 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. In stomach, the floatation chamber, containing entrapped air, causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

**Alginate beads:**

Multiunit floating dosage forms are being developed by using alginate beads. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate. The beads are then separated, snap frozen in liquid nitrogen and freeze dried at -40°C for 24 h. It gives a porous system which can maintain a floating force for over 12 hours.

**Swelling and expanding Systems**

These types of systems can be referred as Plug-Type systems. Polymers in these systems swell at a very faster rate and with higher degree to form a swollen matrix of which size is greater than that of the pylorus. The rate and extent of swelling are important parameters. The rate of swelling and rate of erosion are also important. The integrity of the system is also crucial to prevent the disintegration of the system and to withstand the powerful waves from the stomach. The expandable GRDFs are usually based on three configurations: a small ('collapsed') configuration which enables convenient oral intake; expanded form that is achieved in the stomach and thus prevention of passage through the pyloric sphincter; and finally another small form that is achieved in the stomach when retention is no longer required i.e. after the GRDF has released its active ingredient, thereby enabling evacuation. The expansion can be achieved by swelling or by unfolding in the stomach. Swelling usually occurs because of osmosis. Unfolding takes place due to mechanical shape memory i.e. the GRDF is fabricated in a large size and is folded into a pharmaceutical carrier e.g. a gelatin capsule, for convenient intake. In the stomach, the carrier is dissolved and the GRDF unfolds or opens out to achieve extended configuration. The unfolding occurs when polymeric matrices, known or designed to have suitable mechanical properties, are used with some emphasis on appropriate storage conditions of the GRDF.
The storage should maintain unfoldable properties for extended time spans.

Factors Affecting Performance of GRDDS

1. Formulation factors (density, shape and size of dosage form):

FDDS are being retained in the stomach by virtue of their floating tendency for which their density should be less than that of gastric contents. The effects of various geometric shapes on GRT of dosage form have been well studied. Six shapes (ring, tetrahedron, clove leaf, string, pellet and disc) were screened in vivo for their gastric retention potential. The tetrahedrons and rings exhibited nearly 100% retention in 24 hours than other shapes.

Size of the dosage form can also be a controlling factor behind its gastric emptying. Small sized tablets are emptied from the stomach during the digestive phase, while the larger size tablets are expelled during the housekeeping waves. Variations in the gastric emptying times were observed for non-disintegrating tablets of different sizes. Longest gastric emptying time was observed for 13mm tablets followed by 11mm and 7mm.

These results are in accordance with the aperture of resting pylorus, 12.8±7mm. So this can be taken as the critical value for GI transit of different size dosage forms.

Idiosyncratic Factors:

Presence of food is known to modify the GRT of the dosage form. GRT increases in the presence of food, leading to the increase in the dissolution of the drug and a longer residence of a dosage form at the most favorable sites of absorption.

Further the nature, caloric content and the frequency of intake of food affect the GRT of the dosage form. Co-administration of GI motility decreasing drugs can increase the gastric emptying time. On the contrary, these drugs should be contraindicated with mucoadhesive systems as they reduce the gastric secretion and induce the drying of the mucous membrane.

Different In-Vivo Techniques To Access Gastroretention

1. Gamma-scintigraphic technique:

Using this technique the transit of a dosage form through its intended site of delivery can be non-invasively imaged in vivo via the judicious introduction of an appropriate short lived gamma emitting radioisotope. The extent and location of gastroretentive system can be determined very effectively.

2. Radioanalytical technique using radio-opaque material:

In this technique the radio-opaque material can be included into the formulation and the in-vivo performance can be traced by scanning the subject in X-ray region.

In Vitro Evaluation Techniques

Evaluation of a drug product is a tool to ensure

1. Performance characteristics
2. Control batch to batch quality.

Apart from routine tests like general appearance, hardness and friability, drug content, weight variation, uniformity of content, disintegration time drug release etc. GRDDS need to be evaluated for gastroretentive performance by carrying out specific tests.

1. Floating system

Floating time

The test for floating is usually performed in simulated gastric and intestinal fluids maintained at 37°C. The floating time is determined by using the USP dissolution apparatus containing 900ml of 0.1 N HCl as the testing medium maintained at 37°C. The time for which the dosage form floats is termed as the floating time.

Specific gravity:

It is determined by the displacement method using benzene as a displacing medium.

Resultant weight:
The need for the determination of resultant weight arises from the fact that only density will not reflect the magnitude of floating forces produced by the object. Also, a single density determination made before emersion does not enable one to forecast the floating force evaluation of the dosage form, while dry material, of which it is made, progressively reacts or interacts within the fluids to release its drug contents.

Therefore, an in vitro measuring apparatus has been conceived for determining the real floating capabilities exhibited by buoyant dosage forms as a function of time. It operates by measuring the force equivalent to \( F \) required to maintain the object totally submerged in the fluid. This force determines the resultant weight of the object in immersed conditions and may be used for the quantification of its floating or nonfloating capabilities.

The magnitude and direction of the force and hence the resultant weight, corresponds to the vector sum of buoyancy \( (F_{\text{buoy}}) \) and gravity \( (F_{\text{grav}}) \) forces acting on the object.

By convention, a positive resultant weight signifies force \( F \) exerted vertically upwards and that the object is able to float, whereas a negative resultant weight means that the force \( F \) acts vertically downwards and that the object sinks.

The crossing of the zero base line by the resultant weight curve from positive towards negative values indicates transition of dosage form from floating to nonfloating conditions.

**Limitations of Gastroretentive Delivery Systems**

- These systems are not suitable for drugs that may cause gastric lesions, e.g., Non-steroidal anti-inflammatory drugs.
- Drugs those are unstable in the strong acidic environment cannot be formulated as the GRDDS.
- These systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the gastrointestinal tract.

**Disadvantages of GRDDS**

More predictable and reproducible floating properties should be achieved in all the extreme gastric conditions. The floating systems in patients with achlorhydria can be questionable. In case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.

Bioadhesive systems should have sufficient bioadhesive property to get gastroretention property under powerful migrating waves in the stomach. Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique.

Similarly, retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.

In all the above systems, the physical integrity of the system is very important and is the primary requirement for the success of these systems.

**Some of the marketed Formulations are listed as follows:**

- Valrelease® – floating capsule of diazepam;
- Madopar® – benserazide and L-Dopa Combination formulation;
- Liquid Gaviscon® – floating liquid alginate preparations;
- Topalkan® – aluminium – magnesium antacid preparation; and

Hence, we have attempted to prepare a multidrug novel formulation comprising essentially a statin (Lovastatin) and an antihypertensive drug (B1 blockers-Atenolol and Propranolol HCl, calcium channel blocker-Diltiazem HCl). Lovastatin was loaded in immediate release layer and antihypertensive drugs in controlled release layer in the formulation of bilayer tablets. We have designed the formulation to release both the drugs in stomach by applying the gastroretentive approach.
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3. US Patent No. 60/580,734.


12. www.fda.gov/cardiazem SR_PT.


