Raft Technology for Gastro Retentive Drug Delivery

Keywords: Gastro Retentive Drug Delivery, Absorption window, Prolonged gastric residence time, Raft Technology

ABSTRACT

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Gastro Retentive Drug Delivery are the most commonly formulated but still offer highest attention in the area of novel drug delivery systems. This system can also help in optimizing oral controlled delivery of drugs having ‘absorption window’ by continuously releasing drug prior to absorption window, for prolonged period of time thus causing optimal bioavailability. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Prolonged gastric residence time (GRT) within the GI tract helps to reduce dosing frequency and total dose, improve patient compliance and convenience, maintain a less fluctuating plasma level, as well as reduce GI side effects. Prolonging the GRT of therapeutic agents by raft technology is thought to be beneficial especially under several circumstances such as for drugs acting topically on the gastric region, for drugs with a narrow therapeutic window or for drugs with the major absorption site in the upper GI tract. Raft forming systems incorporate alginate gels. These have a carbonate components and upon reaction with gastric acid, bubbles form in gel, enabling the floating. In this review, we summarize the raft technology for Gastro Retentive Drug Delivery.
INTRODUCTION

In recent years there has been a growing interest in the development, design and evaluation of sustained or controlled release systems. Many controlled release systems have been developed for maintaining a therapeutically effective concentration of drug in systemic circulation for longer period of time as well as to reduce side effects\(^1\). Oral delivery of drugs is by far the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation and handling of these forms. Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems\(^2\). The high level of patient compliance has been observed in taking oral drug delivery systems\(^2\). Although a lot of advancements have been made this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). To modify the GI transit time is one of the main challenge in the development of oral controlled drug delivery system\(^3\).

Oral controlled release drug delivery system has drawn considerable attention as these systems provide drug release at a predetermined, predictable and controlled rate. However some drugs show poor bioavailability because of incomplete absorption or degradation in the G.I.T. Therefore to overcome such problems, gastroretentive drug delivery systems are designed to prolong the gastric retention time of the drugs which are:

- Locally active in the stomach.
- Unstable in the intestinal environment.
- Have narrow absorption window in the GIT.
- Have low solubility at the high pH regions\(^4\).

Development of oral controlled release system has been a challenge to formulation scientists because of their inability to restrain and localize the system in the targeted area of the gastrointestinal tract\(^5\).

A major constraint in oral controlled drug delivery is that, not all drug candidates are absorbed uniformly throughout the Gastrointestinal Tract (GIT). Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional

\(^{1,2,3,4,5}\)
dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. The extent of GIT drug absorption is related to contact time with the small intestinal mucosa[^6].

Conventional drug delivery system maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day[^7]. Success of oral drug delivery system depends on its degree of absorption through GIT. Thus, the idea of enhancing drug absorption pioneered the idea of development of Gastroretentive drug delivery system (GRDDS)[^8]. On the basis of the mechanism of mucoadhesion, floatation, sedimentation or by the simultaneous administration of pharmacological agents, the controlled gastric retention of solid dosage forms may be achieved, which delay gastric emptying[^9].

The single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly which results in more reproducible absorption and risk of irritation is reduced[^10].

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach low density (floating) systems that causes buoyancy in gastric fluid mucoadhesive systems that causes bioadhesion to stomach mucosa unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, superporous hydrogel systems, magnetic systems etc.[^11].

Pharmaceutical field is now focusing towards such drugs which require site specificity. Gastroretentive delivery is one of the site specific deliveries for the delivery of drugs either at stomach or at intestine. It is obtained by retaining dosage form into stomach and drug is being released at controlled manner to specific site either in stomach, duodenum and intestine[^12].
A simple meaning of Raft is a flat structure, typically made of planks, logs, or barrels, that floats on water and is used for transport or as a platform for swimmers\textsuperscript{13}. In the raft forming systems, a gel forming solution on contact with gastric contents or fluid swells and forms a viscous cohesive gel containing entrapped carbon dioxide bubbles on and forms a layer which resembles same as a raft in river, and floats on the contents of stomach. The gel layer is of very low bulk density due to generation of carbon dioxide within system which makes layer to float on gastric contents. The gel forming agents are from alginate category; also include antacids like aluminium hydroxide for reduction of gastric acidity\textsuperscript{14}.

**RATIONALE FOR GASTRO RETENTION**

A. Low density form of the DF that causes buoyancy in gastric fluid.
B. High density DF that is retained in the bottom of the stomach.
C. Bioadhesion to stomach mucosa.
D. Slowed motility of the gastrointestinal tract by concomitant administration.
E. Expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter.
F. Drugs that are absorbed from the proximal part of the gastrointestinal tract.
G. Drugs that are less soluble or degraded by the alkaline pH they encounter at the lower part of GIT.
H. Drugs that are absorbed due to variable gastric emptying time.
I. Local or sustained release drug delivery to the stomach and proximal small intestine to treat certain conditions.
K. Taste masking
L. Patient compliance
M. Increased therapeutic efficacy\textsuperscript{15}.

**DEFINITION**

**GRDDS**

Dosage forms with a prolonged gastric residence and controlled drug delivery are called as GRDDS.\textsuperscript{16}
IDEAL PROPERTIES OF GRDDDS

- Efficient retention in stomach.
- Sufficient drug loading capacity.
- Controlled drug release profile.
- Full degradation and evacuation after drug release.
- No effect on gastric motility including emptying pattern.
- No other local effects\textsuperscript{[17]}.

ADVANTAGES OF GASTRO RETENTIVE DELIVERY SYSTEMS

1. Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide.
2. Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation of therapeutic levels.
3. Minimizing the risk of resistance especially in case of antibiotics. e.g. B-lactam antibiotics (penicillin and cephalosporin).
4. Prolongation of gastric residence time is desired for following class of drugs:
   - Drugs acting locally in the stomach.
   - Drugs those are primarily absorbed in the stomach.
   - Drugs those are poorly soluble at an alkaline pH.
   - Drugs with a narrow window of absorption.
   - Drugs that get degraded in the colon.
5. Enhanced first pass metabolism.
6. Reduced frequency of dosing.
7. Targeted therapy for local ailments in upper GIT.
8. Improved receptor activation selectivity.
9. Extended time over critical concentration.
10. Reduced counter activity of the body.
11. Site specific drug delivery.
LIMITATIONS OF THE GASTRORETENTION TECHNIQUES

1. 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.

2. 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.

3. Not suitable for drugs that may cause gastric lesions e.g. Non-steroidal anti inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the gastrointestinal tract.

4. The drugs which are absorbed throughout GIT, which undergo significant first pass metabolism, are not desirable candidate.

5. Not suitable for the drugs that have solubility or stability problem in GIT.

6. Drugs that are irritant to gastric mucosa are not suitable.

7. Drugs that are unstable in acidic environment are not suitable. [18-19]

POTENTIAL DRUG CANDIDATES FOR STOMACH SPECIFIC DRUG DELIVERY SYSTEMS

1. Drugs those are locally active in the stomach e.g. misoprostol, antacids etc.

2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-dopa, para amino benzoic acid, furosemide, riboflavin etc.

3. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.

4. Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.

5. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

6. Drugs those are unsuitable for stomach specific drug delivery systems.

7. Drugs that have very limited acid solubility e.g. phenytoin etc.

8. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.

9. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid.
POTENTIALLY ACTIVE DRUG CANDIDATES SUITABLE FOR GASTRORETENTION

a. The suitable candidates for gastroretentive drug delivery system are molecules that possess poor absorption but are characterized by better absorption.
b. Drugs that have narrow absorption window in gastrointestinal tract. e.g. riboflavin.
c. Drugs that are primarily absorbed from stomach and upper part of gastrointestinal tract. e.g. calcium supplements, chlordiazepoxide and cinnarazine.
d. Locally active drugs in the stomach. e.g. antacids and misoprostol.
e. Drugs which degraded or unstable in the colon. e.g. ranitidine HCl and metronidazole.
f. Drugs that disturb normal colonic bacteria or microbes. e.g. amoxicillin trihydrate

DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

a. Drugs that have very limited acid solubility e.g. phenytoin etc.
b. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
c. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids.

COMPARISON OF CONVENTIONAL DRUG DELIVERY SYSTEM AND GRDDS

Table no.1: Comparison of conventional drug delivery system and GRDDS:

<table>
<thead>
<tr>
<th>CONVENTIONAL DRUG DELIVERY SYSTEM</th>
<th>GASTRORETENTIVE DRUG DELIVERY SYSTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk of toxicity</td>
<td>Low risk of toxicity</td>
</tr>
<tr>
<td>Less patient compliance</td>
<td>Improves patient compliance</td>
</tr>
<tr>
<td>Not suitable for the delivery of the drugs with narrow absorption window in small intestine</td>
<td>Suitable for the delivery of the drugs with narrow absorption window in small intestine</td>
</tr>
<tr>
<td>Not much advantageous for : -Drugs that are poorly at alkaline pH -Drugs that degrade in colon -Drugs having rapid absorption through GIT -Drugs which act locally in stomach</td>
<td>Very much advantageous for : -Drugs that degrade in colon -Drugs having rapid absorption through GIT -Drugs which act locally in stomach</td>
</tr>
<tr>
<td>No risk of dose dumping</td>
<td>Possibility of dose dumping</td>
</tr>
</tbody>
</table>

APPROACHES TO GASTRO RETENTION \[23\]

In vitro Picturisation of the gastroretentive formulations

Orally administered controlled release dosage forms suffer from mainly two adversities:
1. The short gastric emptying time (GRT).
2. The unpredictable gastric emptying time (GET).

These problems can be overwhelmed by altering the gastric emptying time. \cite{25}

Various approaches have been made to increase the retention of an oral dosage form in the stomach.

![Figure no. 5: Various approaches \cite{26}]

**RAFT FORMING SYSTEMS**

Raft forming systems incorporate alginate gels. These have a carbonate component and upon reaction with gastric acid, bubbles form in gel, enabling the floating. The raft floats because of the buoyancy created by carbon dioxide formation. The mechanism involves the formation of cohesive gel in contact with gas fluids wherein each portion of liquid swells forming a continuous layer called raft. Raft floats on the gastric fluids because of low bulk density created by carbon dioxide (CO$_2$) formation. It contains a gel forming agent and alkaline bicarbonates or carbonates responsible for formation of CO$_2$ to make the system less dense and float on gastric fluids. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus.
Gastric reflux is the passage of small amounts of highly acidic gastric juice and bile acids from the stomach into the lower part of the oesophagus. This causes the pain of heartburn and can inflame or damage the oesophagus. Gastric reflux may be symptomatic of a variety of disorders such as ulcers or biliary conditions.

Preparations which are known to treat gastric reflux comprise a substance which when exposed to the acid contents of the stomach forms a gel which floats on the surface of the stomach contents as a raft due to a lower bulk density. The lower bulk density is achieved by entrapment of gas bubbles within the gel structure. The gas is generated by a material which produces gas in the acidic conditions of the stomach as the gel is being formed, for example a carbonate or bicarbonate which produces carbon dioxide. The gel raft acts as a physical barrier to gastric reflux. The raft, which is located in the upper part of the stomach (fundus), also protects the oesophagus if reflux does occur as on reflux the raft contacts the oesophagus before the gastric juices, providing some further protection [27-28].

MARKETED PREPARATIONS

1. ALGICON ® (Rorer)
2. GASTROCOTE ® (Boeringer Mannheim)
3. BISODOL ® (White Hall)
4. GASTRON ® (Sanofi Winthrop)
5. LIQUID GAVISCON ® (Reckitt Benckiser Healthcare)
6. GAVISCON ADVANCE TABLETS ® (Reckitt and Colman) [29]
MARKETED PREPARATION: GAVISCON

Gaviscon advance is an extra strength treatment for heartburn and indigestion including hiatus hernia and gastro oesophageal reflux disease also known as GERD. It does not cure the condition but rather is used to control the unpleasant symptoms and for me it works a treat. Gaviscon advance is a thick creamy suspension that is available in two flavours: Peppermint flavor and aniseed. It is quite pleasant to taste but a lot of people cannot bear the taste of aniseed.

MECHANISM OF ACTION OF GAVISCON

The Gaviscon liquid is a thick suspension that on swallowing slides down the oesophagus into the stomach. It forms a barrier over the top of the stomach contents preventing the acid from rising into the oesophagus. However it has quite high sodium content, so it will reduce their sodium intake. It is sugar and gluten free. It is safe to use in pregnancy and during breast feeding. Some people may be allergic to some of the ingredient.

WHAT DOES IT CONTAIN PER 10ml DOSE?

1g of Sodium Alginate (Derived from seaweed)
200 mg of Potassium bicarbonate
Calcium Carbonate
Carbomer
Methyl & propyl hydroxybenzoates (E218 & E216)
Sodium Saccharin \(^{[29]}\)

SODIUM ALGINATE

Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrant; it has been used as a diluent in capsule formulations. Sodium alginate has also been used in the preparation of sustained release oral formulations since it can delay the dissolution of a drug from tablets, capsules, and aqueous suspensions. The effects of particle size, viscosity and chemical composition of sodium alginate on drug release from matrix tablets have been described. In topical formulations, sodium alginate is widely used as a thickening and suspending agent in a
variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions. Recently, sodium alginate has been used for the aqueous microencapsulation of drugs, in contrast with the more conventional microencapsulation techniques which use organic solvent systems. It has also been used in the formation of nanoparticles. The esophageal bioadhesion of sodium alginate suspensions may provide a barrier against gastric reflux or site-specific delivery of therapeutic agents. Therapeutically, sodium alginate has been used in combination with an H2-receptor antagonist in the management of gastroesophageal Reflux. Also used in formulations for the treatment of *Helicobacter pylori*.

**POTASSIUM BICARBONATE**

As an excipient, potassium bicarbonate is generally used in formulations as a source of carbon dioxide in effervescent preparations, at concentrations of 25–50% w/w. It is of particular use in formulations where sodium bicarbonate is unsuitable, for example, when the presence of sodium ions in a formulation needs to be limited or is undesirable. Potassium bicarbonate is often formulated with citric acid or tartaric acid in effervescent tablets or granules; on contact with water, carbon dioxide is released through chemical reaction, and the product disintegrates. On occasion, the presence of potassium bicarbonate alone may be sufficient in tablet formulations, as reaction with gastric acid can be sufficient to cause effervescence and product disintegration.

Potassium bicarbonate has also been investigated as a gas forming agent in alginate raft systems. Therapeutically, potassium bicarbonate is used as an alternative to sodium bicarbonate in the treatment of certain types of metabolic acidosis. It is also used as an antacid to neutralize acid secretions in the gastrointestinal tract and as a potassium supplement.

**CALCIUM CARBONATE**

It is used as buffering agent, as a diluents, aid in dispersion tablets. Therapeutically it is used as an antacid.

**CARBOMER**

Lightly crosslinked carbomers (lower viscosity) are generally more efficient in controlling drug release than highly crosslinked carbomers (higher viscosity). Carbomers copolymers are also

*Citation: Ramdas T. Dolas et al. Ijppr.Human, 2015; Vol. 3 (1): 232-252.*
employed as emulsifying agents in the preparation of oil-in-water emulsions for external administration. Carbomer 951 has been investigated as a viscosity-increasing aid in the preparation of multiple emulsion microspheres, also used in the sustained release matrix beads.

**METHYL AND PROPYL HYDROXYL BENZOATES**

They are used as preservatives. Owing to the poor solubility of the parabens, the paraben salts, particularly the sodium salt, are frequently used in formulations. This may cause the pH of poorly buffered formulations to become more alkaline.

**SODIUM SACCHARINE**

Used as an artificial sweetener [30].

**ADVANTAGES OF RAFT SYSTEMS**

- They are used for the symptomatic treatment of heartburn and oesophagitis. It can be used in LPR. GERD, Laryngopharyngeal Reflux (LPR) refers to the backflow of stomach contents into the laryngeal and pharyngeal region.
- It does not interfere with the activity of promotility agent, antisecretory agents such as cimetidine.
- Rapid and Long-duration of action can easily achieved by raft formation. It may show its action within seconds.
- It will not interfere with function of pyloric sphincter.
- Better patient compliance can be achieved and it is well tolerated.

**ADVANCES IN RAFT FORMING APPROACH**

Alginates are established among the most versatile biopolymers, used in a wide range of applications. The conventional use of alginate as an excipient in drug products generally depends on the thickening, gel-forming, and stabilizing properties. Alginate-based raft-forming formulations have been marketed worldwide for over 30 years. They are used for the symptomatic treatment of heartburn and oesophagitis, and appear to act by a unique mechanism which differs from that of traditional antacids. In the presence of gastric acid, alginates precipitate, forming a gel. Alginate-based raft-forming formulations usually contain sodium or
potassium bicarbonate; in the presence of gastric acid, the bicarbonate is converted to carbon dioxide which becomes entrapped within the gel precipitate, converting it into foam which floats on the surface of the gastric contents, much like a raft on water. Both *in vitro* and *in vivo* studies have demonstrated that alginate-based rafts can entrap carbon dioxide, as well as antacid components contained in some formulations, thus providing a relatively pH-neutral barrier. The alginate raft can preferentially move into the oesophagus in place, or ahead, of acidic gastric contents during episodes of gastro-oesophageal reflux; or the raft can act as a physical barrier to reduce reflux episodes. Although some alginate-based formulations also contain antacid components which can provide significant acid neutralization capacity, the efficacy of these formulations to reduce heartburn symptoms does not appear to be totally dependent on the neutralization of bulk gastric contents. The strength of the alginate raft is dependent on several factors, including the amount of carbon dioxide generated and entrapped in the raft, the molecular properties of the alginate, and the presence of aluminium or calcium in the antacid components of the formulation. Raft formation occurs rapidly, often within a few seconds of dosing; hence alginate-containing antacids are comparable to traditional antacids for speed of onset of relief. Since the raft can be retained in the stomach for several hours, alginate-based raft-forming formulations can additionally provide longer-lasting relief than that of traditional antacids\[^{30}\].

EVALUATION PARAMETERS

A) *IN VITRO* EVALUATION

i) Floating systems

a) Buoyancy Lag Time

It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

b) Floating Time

Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 37\(^{0}\)C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

c) Specific Gravity / Density
Density can be determined by the displacement method using Benzene as displacement medium.

d) Resultant Weight

The bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. For example a matrix tablet with bicarbonate and matrixing polymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form. The magnitude and direction of force/resultant weight (up or down) is corresponding to its buoyancy force (\(F_{\text{buoy}}\)) and gravity force (\(F_{\text{grav}}\) acting on dosage form

\[
F = F_{\text{buoy}} - F_{\text{grav}} = D_f g V - D_s g V
\]

\[
F = (D_f - D_s) g V
\]

\[
F = (D_f - M/V) g V
\]

Where,
- \(F\) = resultant weight of object
- \(D_f\) = Density of Fluid
- \(D_s\) = Density of Solid object
- \(g\) = Gravitational force
- \(M\) = Mass of dosage form
- \(V\) = Volume of dosage form

So when \(D_s\), density of dosage form is lower, \(F\) force is positive gives buoyancy and when it is \(D_s\) is higher, \(F\) will show negative sinking.
Plot of $F$ vs. Time is drawn and floating time is time when $F$ approaches to zero from positive values.

**ii) Swelling systems**

**a) Swelling index**

After immersion of swelling dosage form into SGF at $37^\circ$C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

**b) Water Uptake**

It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time. So it is also termed as Weight Gain.

\[
\text{Water uptake} = \text{WU} = \frac{(W_t - W_0) \times 100}{W_0}
\]

Where, $W_t =$ weight of dosage form at time $t$

$W_0 =$ initial weight of dosage form

![Figure No. 8: Water swelling study](image)

While we remove dosage form out and measure dimensions, the outer gel layer is disturbed which can create a problem. So new idea came into picture by which swelling index and water uptake can be measured without disturbing tablet.

In this assembly, concentric circles with various diameters are drawn in computer and print out is laminated to make hydrophobic. This laminated piece is attached with some system which can facilitate up and down movement of assembly.

*Citation: Ramdas T. Dolas et al. Ijprr.Human, 2015; Vol. 3 (1): 232-252.*
This assembly is placed in beaker and tablet is placed exactly at center and then there is no disturbance given to tablet. Tablet is allowed to swell on laminated paper and diameter can be easily noted without removing out. To determine water uptake/weight gain, whole assembly can bring out. Weighing of assembly done after wiping off water droplets adhered at surface of assembly and then can be placed back as it is without touching to tablet. Rate of water penetration is also important parameter for swelling matrix, that how fast swelling occurs is determined by equation:

c) Continuous monitoring of water uptake
Although previous method has advantage of un-disturbance of swollen tablet, but for measuring water uptake one has to remove whole assembly out of beaker, so process in not continuous. In this apparatus, swelling tablet is placed on glass filter as support in one hollow cylinder with smooth surface inside, and one light weight punch is placed on it to prevent floating. This cylinder is placed pre-heated in dissolution medium. Another dissolution medium reservoir beaker is placed on digital balance and both are connected with media filled U tube as shown in figure and medium level is kept equal. As swelling of tablet started, it absorbs water and water level in outer part of cylinder goes down. The decrease in water level is maintained by importing extra medium via U tube from reservoir beaker. As medium is transferred from reservoir, amount of water transferred can be determined by observing loss in weight by digital balance.

B) IN VITRO DISSOLUTION TESTS
a. In vitro dissolution test is generally done by using USP apparatus with paddle and GRDDS is placed normally as for other conventional tablets. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results.

b. To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.

c. Floating unit can be made fully submerged, by attaching some small, loose, non-reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release.
d. Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit.

e. Other method suggests placing dosage form between 2 ring/meshes.

f. In previous methods unit have very small area, which can inhibit 3D swelling of swellable units, another method suggest the change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form.

g. Inspite of the various modifications done to get the reproducible results, none of them showed co-relation with the in vivo conditions. So a novel dissolution test apparatus with modification of Rossett-Rice test Apparatus was proposed.

Rossett-Rice test is used for predicting in vitro evaluation of directly acting antacid (action by chemical neutralization of acid), where HCl is added gradually to mimic the secretion rate of acid from the stomach. It has side arm from bottom of beaker such that it maintains volume of 70 ml in beaker and fresh SGF is added from burette at 2 ml/min rate. Thus sink condition is maintained along with easy sampling. Stirring is done by magnetic stirrer at 70-75 RPM. Thus this apparatus mimics in vivo condition for GRDDS.

Figure no.9: Rossett-Rice test
C) IN VIVO EVALUATION

a) Radiology
X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, BaSO4 is incorporated inside dosage form and X-ray images are taken at various intervals to view GR.

b) X-Scintigraphy
Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99Tc.

c) Gastroscopy
Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

d) Magnetic Marker Monitoring
In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.

e) Ultrasonography
Used sometimes, not used generally because it is not traceable at intestine.

f) $^{13}$C Octanoic Acid Breath Test
$^{13}$C Octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates CO$_2$ gas which comes out in breath. The important Carbon atom which will come in CO$_2$ is replaced with $^{13}$C isotope. So time upto which $^{13}$CO$_2$ gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no CO$_2$ release. So this method is cheaper than other.$[^31]$

CONCLUSION

Gastroretentive multiparticulates have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. Multiparticulate drug delivery systems provide greater flexibility and adaptability of microparticulate dosage forms which gives clinicians and those engaged in product development powerful new tools to optimize therapy. Based on the literature survey, it can be concluded that, gastroretentive drug delivery offers

various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. It can serve the best for treatment of diseases related to the GIT, GERD and for extracting a prolonged action from a drug with a short half-life. The raft system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO₂ to make the system less dense and float on the gastric fluids. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus. Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Raft forming system promises to be a potential approach for heartburn and oesophagitis.

REFERENCES
2. Monica Katwara, Upendra Jain, Jaspreet Ramana, International journal of recent advances in pharmaceutical research, recent advances in floating microspheres as gastro retentive drug delivery system, july 2012, 2(3) page no:5.
15. Monali C. Gorde, a review of gastro retentive drug delivery system, PRES’s college of pharmacy (For Women) chincholi, 2009-2010, page no: 5.