A Review on current approaches in gastro retentive drug delivery system

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Abstract:

Oral controlled release delivery systems are programmed to deliver the drug in predictable time frame that will increase the efficacy and minimize the adverse effects and increase the bioavailability of drugs. It is most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. In fact the buoyant dosage unit enhances gastric residence time(GRT) without affecting the intrinsic rate of emptying. Unfortunately floating devices administered in a single unit form (Hydrodynamically balanced system) HBS are unreliable in prolonging the GRT owing to their ' all- or-nothing' emptying process and, thus they may causes high variability in bioavailibity and local irritation due to large amount of drug delivered at a particular site of the gastrointestinal tract. One of the most widely gastro retentive drug delivery system. The present paper highlights the current approaches and another aspect of the GRDS.

Key-words:-*Gastro-retentive drug delivery system, physiology of stomach, current approaches in GRDDs, Evaluation parameters.*

Introduction

Drug Delivery system is becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biological parameters pertinent to their performances. Controlled Drug Delivery System provides drug release at a predetermined, predictable and controlled rate to achieve high therapeutic efficiency with minimal toxicity. Despite tremendous advancement in drug delivery, oral route remains the preferred route for the administration of therapeutic agents and oral drug delivery is by far the most preferable route of drug delivery because of low cost of therapy and ease of administration leads to high levels of patient compliance as well as the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes, consequently much effort has been put into development of strategies that could improve patient compliance through oral route[1]. 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. 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[2].

Conventional oral dosage forms such as tablets, capsules etc provide specific drug concentration in systemic circulation without offering any control over drug delivery and also great fluctuations in plasma drug levels, by comparison oral controlled drug delivery systems provide a release profile predominantly controlled by the design of

the system itself[2,3] . The release of active agents is, therefore, largely independent of external factors. For oral solid delivery systems, drug absorption is unsatisfactory and highly variable between the individuals. An important requisite for the successful performance of oral controlled release drug delivery system is that the drug should have good absorption throughout the gastrointestinal tract (GIT). The major problem is the physiological variability such as gastrointestinal transit in addition to gastric retention time, as the later plays a dominating role in the over all transit of the dosage form[4]. Another problem associated with the performance of oral controlled release systems is that even though the slow release can be achieved, the drug released after passing the absorption site (upper position of small intestine) is not fully utilized; this is because the GRT of the delivery system is less than 12 hours. Therefore, it is not possible to deliver the drug for more than 12 hours through the oral route. This has prompted researchers to retain the drug delivery systems in the stomach for prolonged and predictable time, such a prolonged gastric retention not only controls the time but also the space in the stomach by maintaining the delivery system positioned at a steady site and thereby properly delivering the drug. It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists 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[4,5].

Dosage forms that can be retained in the stomach are called gastroretentive drug delivery systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability[1,4,6].

Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low-density systems. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.

Furthermore, improved bioavailability is expected for drugs that are absorbed readily upon release in the GI tract. These drugs can be delivered ideally by slow release from the stomach. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine[7].

Certain types of drugs can benefit from using gastric retentive devices. These include:

- Drugs acting locally in the stomach
  E.g. Antacids and drugs for H. Pylori viz., Misoprostol
- Drugs that are primarily absorbed in the stomach
  E.g. Amoxicillin
- Drugs that is poorly soluble at alkaline pH
  E.g. Furosemide, Diazepam, Verapamil, etc.
- Drugs with a narrow window of absorption

E.g. Cyclosporine, Methotrexate, Levodopa, etc.

- Drugs which are absorbed rapidly from the GI tract.
  E.g. Metonidazole, tetracycline.
- Drugs that degrade in the colon.
  E.g. Ranitidine, Metformin HCl.
- Drugs that disturb normal colonic microbes
  E.g. antibiotics against Helicobacter pylori[8].

Physiology Of The Stomach:

The Gastrointestinal tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), esophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the Gastrointestinal tract has the same general structure throughout most of its length from the esophagus to the anus, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents.

Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH 1–3) and air. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. The GI tract is in a state of continuous motility consisting of two modes, interdigestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract. The interdigestive motility pattern is commonly called the 'migrating motor complex' ('MMC') and is organized in cycles of activity and quiescence[8].

Gastrointestinal transit time and motility*:*

Based on fasted and fed states of stomach, there are two distinct patterns of gastrointestinal motility. The fasted state is associated with some cyclic contractile events commonly known as Migrating Myoelectric Complex (MMC). Liquid components easily pass through the partially constricted sphincter. On the contrary, an "antral-sieving" process retains the large undigested materials. Usually a series of interdigestive events takes place in stomach. The Migrating Myoelectric Complex (MMC), which governs the gastrointestinal motility pattern has been described as an alternating cycles of activity and quiescence. Apparently there are four consecutive phases of activity in MMC[9,10].

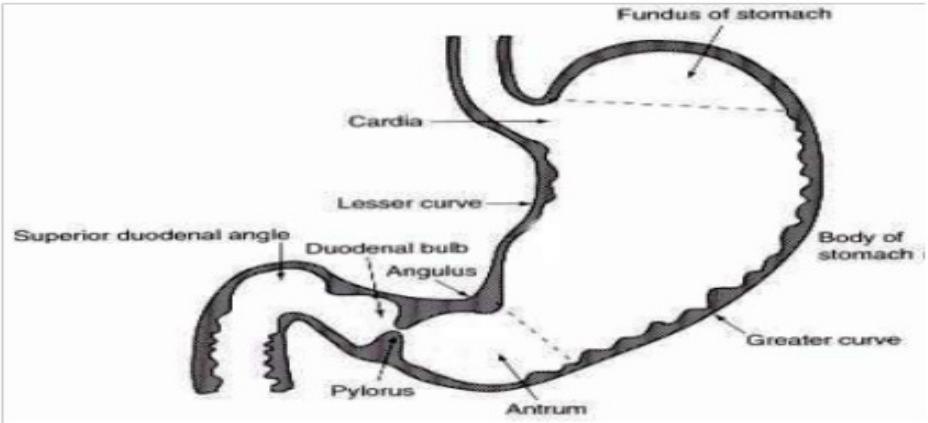


Fig. 1 : Anatomy of Stomach

- Phase I: It is a quiescent period lasting from 30 to 60 minutes with no contractions.
- Phase II: It consists of intermittent contractions that gradually increase in intensity as the phase progresses and it lasts about 20 to 40 minutes.
- Phase III: This is a short period of intense distal and proximal gastric contractions (4 to 5 contractions per minute) lasting about 10 to 20 minutes; these contractions, also known as "housekeeper wave" sweep gastric contents down to small intestine.
- Phase IV: This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase I.

The fasted-state emptying pattern is independent of the presence of any indigestible solids in the stomach. Patterns of contractions in the stomach occur such that solid food is reduced to particles of less than 1mm diameter that are emptied through the pylorus as a suspension. The duration of the contractions is dependent on the physiochemical characteristics of the ingested meal[11].

Generally, a meal of ~450kcal will interrupt the fasted state motility for about three to four hours. It is reported that the antral contractions reduce the size of food particles to ≤1mm and propel the food through the pylorus. However, it has been shown that ingestible solids ≤7mm can empty from the fed stomach in humans.TableNo.1

Section	Length (m)	Transit time (h)	pH	Microbial count	Absorbing surface area (m2)	Absorption pathway
Stomach	0.2	Variable	1-4	<103	0.1	P, C, A
Small Intestine	6-10	3 ± 1	5-7.5	103 – 1010	120-200	P, C, A, F, I, E, CM

P – Passive diffusion, C – Aqueous channel transport, A – Active transport

F – Facilitated transport, I – Ion-pair transport, E – Entero-or pinocytosis

CM – Carrier mediated transport

Different features of stomach:-

Gastric pH: Fasted healthy subject 1.1 ± 0.15

Fed healthy subject 3.6 ± 0.4

Volume : Resting volume is about 25-50 ml

Gastric secretion: Acid, pepsin, gastrin, mucus and some enzymes about 60 ml with approximately 4 mmol of hydrogen ions per hour.

Effect of food on Gastric secretion: About 3 liters of secretions are added to the food. Gastro intestinal transit time .

Requirements For Gastric Retention:-

Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

Factors affecting gastric retention time of the dosage form:-[12,13]

1**. Density**:- GRT is a function of dosage form buoyancy that is dependent on the density. The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.

2**. Size & Shape of dosage form**:- Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of non floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric.

3. **Single or multiple unit formulation**:- Multiple unit formulations show a more Predictable release profile and insignificant impairing of performance due to failure of units allow co- administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

4**. Fed or unfed state**:- under fasting conditions: GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

5**. Nature of meal**:- feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

6. **Caloric content**:- GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

7. **Frequency of feed**:- the GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

8. **Gender**:- Male- 3.4□}0.6hr to Female-4.6□}1.2hr.

9. **Age**:- Elderly people, especially those over 70, have a significantly longer GRT.

10**. Posture**: GRT can vary between supine and upright ambulatory states of the patient.

11. **Concomitant drug administration**:-

- ✓ Anticholinergic like atropine, propentheline-increase GRT.
- ✓ Metoclopramide and cisapride-decrease GRT.

12. **Disease state**:-
   - ✓ Gastric ulcer, diabetes, hypothyroidism increase GRT.
   - ✓ Hyperthyroidism, duodenal ulcers decrease GRT.

Advantages of gastro retentive delivery systems[14]:-

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 in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. E.g. b-lactam antibiotics (penicillins and ephalosporins)
3. For drugs with relatively short half life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient Compliance.
4. They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.
5. Gastro retentive drug delivery can produce prolongs and sustains release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.
6. The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable Effects of side effects.
7. Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.
8. Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.
9. Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.

LIMITATIONS:-

- ✓ Require a higher level of fluids in the stomach.
- ✓ Not suitable for Drugs that...
  - ➢ Have solubility problems in gastric fluid.E.g. phenytoin
  - ➢ Cause G.I irritation. E.g.NSAIDS.
  - ➢ Are unstable in acidic environment.
- ✓ Drugs intended for selective release in the colon E.g. 5- amino salicylic acid and corticosteroids etc.
- ✓ The floating systems in patients with achlorhydria can be questionable in in case of swellable system.
- ✓ Retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.
- ✓ The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

Approaches to achieve gastric retention:-

Floating – A low density approach:-

Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention time and a better control of fluctuations in the plasma drug concentration in some cases.

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3- 4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Many results have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved clinical situations. These results also demonstrate that the presence of gastric content is needed to allow the proper achievement of the buoyancy retention principle. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxypropyl methylcelluloses. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy[15,16].

Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performances of floating forms.

These assessments were realized either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the form transit in the GI tract. When a floating capsule is administered to the subjects with a fat and protein meal, it can be observed that it remains buoyant at the surface of the gastric content in the upper part of the stomach and moves down progressively while the meal empties. The reported gastric retention times range from 4 to 10 hours. Pharmacokinetic and bioavailability evaluation studies confirm the favorable incidence of this prolonged gastric residence time[17].

The Floating drug delivery system (FDDS) can be divided into effervescent and Non-effervescent systems.

(A) Effervescent systems:-

These are matrix type of systems prepared with the help of sellable polymers such as Methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

- **Volatile liquid containing systems:-**

These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach.

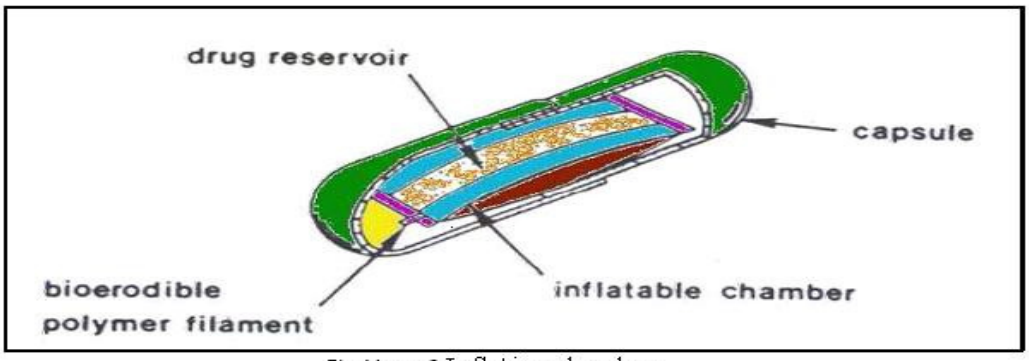


Fig No : - 2 Inflation chamber

These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid.

- **Gas generating systems:-**

These buoyant systems utilised matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach. Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC) and floating systems based on ion exchange resin technology, etc[18].

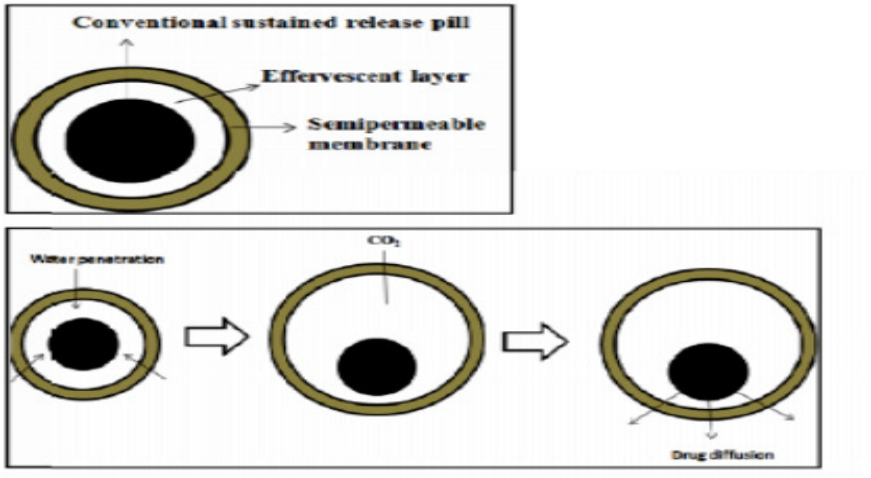


Figure No:-3 Effervescent pill

Matrix Tablets:-

Single layer matrix tablet is prepared by incorporating bicarbonates in matrix forming hydrocolloid gelling agent like HPMC, chitosan, alginate or other polymers and drug. Bilayer tablet can also be prepared by gas generating matrix in one layer and second layer with drug for its SR effect. Floating capsules also prepared by incorporating such mixtures. Triple layer tablet also prepared having first swellable floating layer, second sustained release layer of 2 drugs (Metronidazole and Tetracycline) and third rapid dissolving layer of bismuth salt. This tablet is prepared as single dosage form for Triple Therapy of H.Pylori.

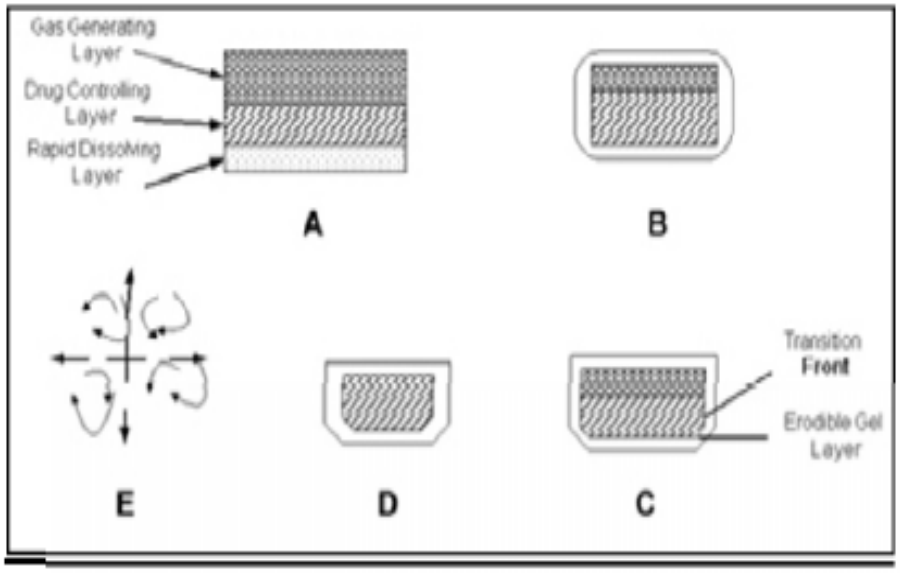


Fig-4Tripal layer matrix tablet

(B) Noneffervescent system:-

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

➢ **Hydrodynamically balanced systems**:-

Sheth and Tossounian[19] first designated these 'hydrodynamically balanced systems'. These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these

systems[20,21] . The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form [21]. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Madopar LPR, based on the system was marketed during the 1980's[22] . Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile several strategies have been tried and investigated to improve efficiencies of the floating hydrodynamically balanced systems[21,22].

- **Microballoons / Hollow microspheres**:-

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion evaporation methods[21] (Figure 1) to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours [23]. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

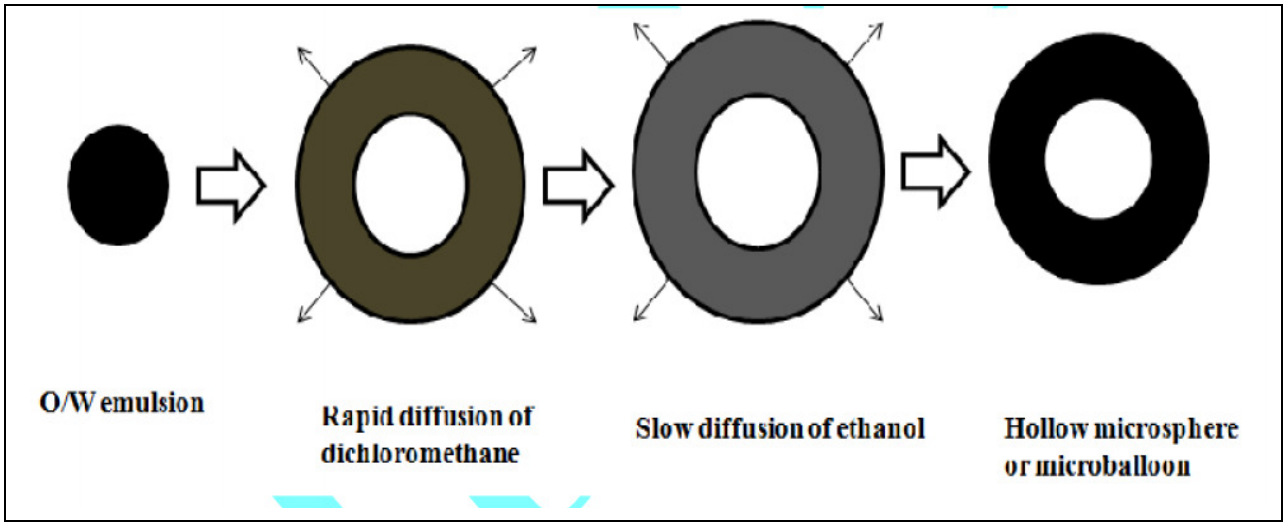


Figure 5. Formulation of floating hollow microsphere or microballoon

- **Alginate beads:-**

Talukdar and Fassihi[24] recently developed a multiple-unit floating system based on cross-linked beads. They were made by using Ca2+ and low methoxylated pectin (anionic polysaccharide) or Ca2+ low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric etention time (GRT) more than 5.5 hrs[23,25] . Microporous compartment system: This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with

pores along its top and bottom walls[26] . The peripheral walls of the device were completely sealed to present any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid[27]. Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption.

(c) Bioadhessive systems:-

Bio/mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the Gastro retention of drug delivery system (DDS). in the stomach by increasing the intimacy and duration of contact of drug with the biological membrane. A bio/muco-adhesive substance is a natural or synthetic polymer capable of producingan adhesive interaction based on hydration–mediated, bondingmediated or receptor mediated adhesion with a biological membrane or mucus lining of GI mucosa[28,29].

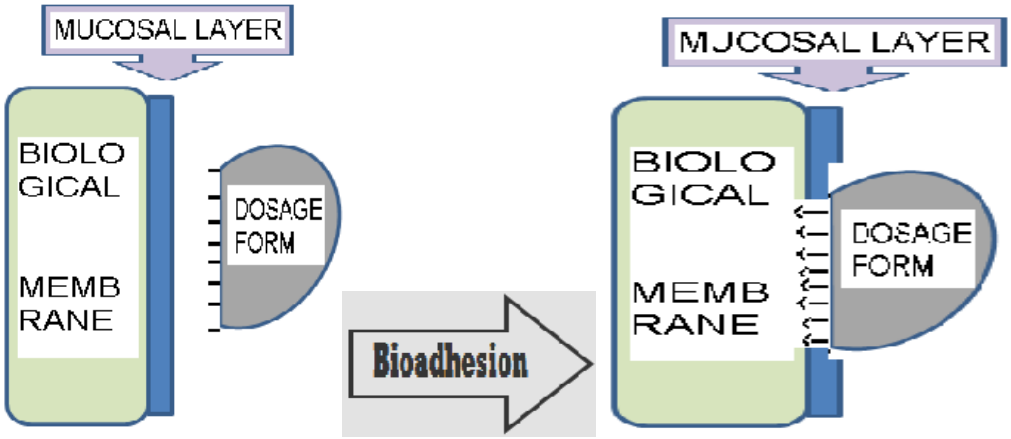


Fig.6 bioadhesive system

(d) Swelling systems:-

These are the dosage forms, which after swallowing, swells to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be named as 'plug type systems'. Sustained and controlled drug release may be achieved by selection of polymer of proper molecular weight and swelling of the polymer retards the drug release. on coming in contact with gastric fluid, the polymer imbibes water and swells.

(e)High density systems:-

These systems with a density of about 3 g/cm3 are retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements. The only major drawbacks with such systems is that it is technically difficult to manufacture such formulations with high amount of drug (>50%) and to achieve a density of about 2.8g/cm3. It is necessary to use diluents like barium sulfate, zinc oxide, titanium dioxide, iron powder etc. to manufacture such high density formulations. Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations[30,31].

(f) Raft forming systems:-

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO2. Usually, the 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. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of helicobacter pylori (H. Pylori) infections in the GIT. The composition contained drug, alginic acid, sodium bicarbonate, calcium carbonate, mannitol and a sweetener. These ingredients were granulated, and citric acid was added to the granules. The formulation produces effervescence and aerates the raft formed, making it float[14,32,33,].

(g)Expandable system:-

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus[32]. As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. As dosage form coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical crosslink's in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of crosslinking retards the swelling ability of the system and maintains its physical integrity for a prolonged period. On the other hand, a low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer[14]. An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion[33]. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration[14].

The expandable GRDFs are usually based on three configurations:

- A small collapsed configuration which enables sufficient oral intake.
- Expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter.
- A smaller form that is achieved in the stomach when the retention is no longer required i.e. after the GRDF has released its active ingredient, thereby enabling evacuation.

The expansion can be achieved by

i) Swelling system
ii) Unfolding system

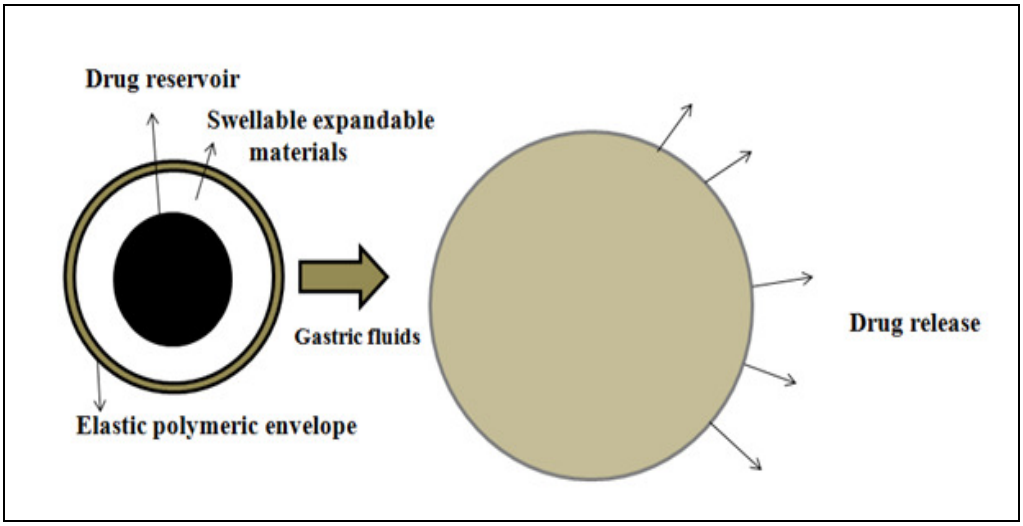


Fig-7 Swellable system

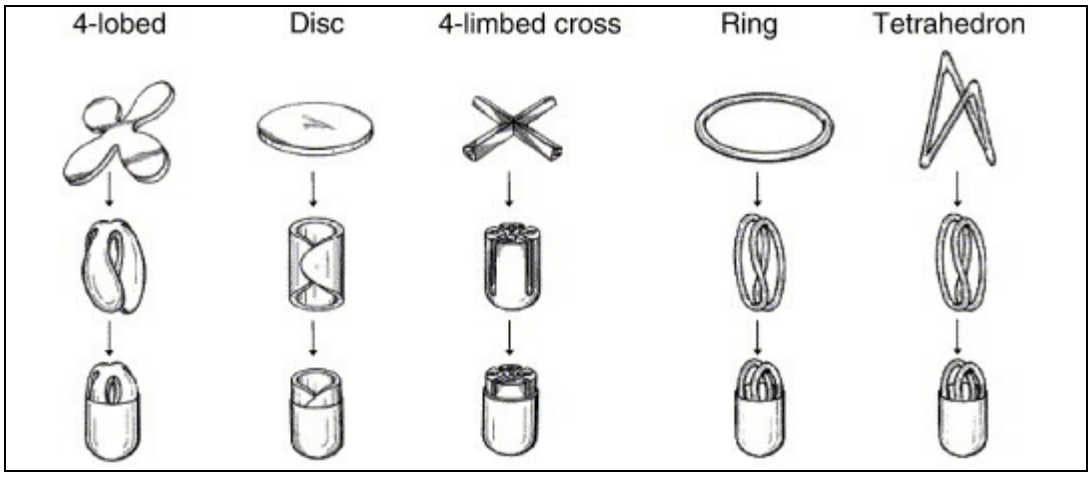


Fig-8 various geometric form of unfolding system.

Magnetic systems:-

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. Ito etal. used this technique in rabbits with bioadhesives granules containing ultrafine ferrite (g-Fe2O3). They guided them to the esophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 h [34]. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance [35].

Evaluation of gastroretentive dosage form:-

A) In-Vitro Evaluation:-[36,37]

i) Floating systems:-

a) Buoyancy Lag Time:-[38]

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:-[39]

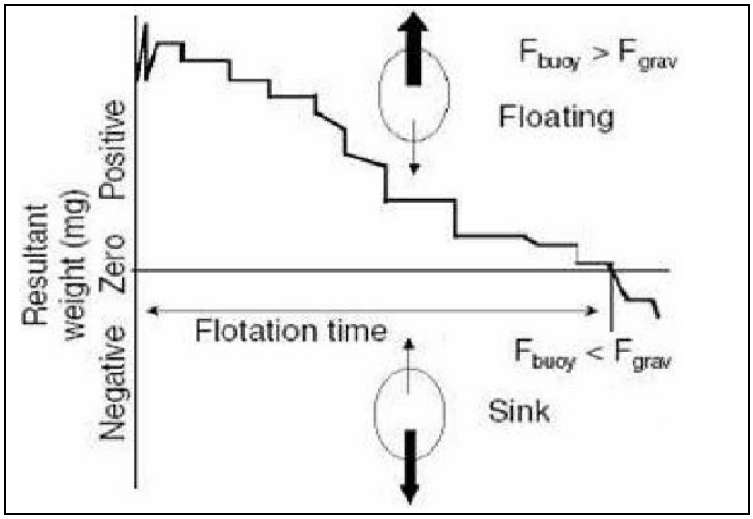
Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 370C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

c) Specific Gravity / Density:-

Density can be determined by the displacement method using **Benzene** as displacement medium.

d) Resultant Weight:-[40]

Now we know that 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 (Fbuoy) and gravity force (Fgrav) acting on dosage form .



F = Fbuoy - FgravF = Df g V – Ds g V F = (Df – Ds) g V

F = (Df – M/V) g V

Where,

F = resultant weight of object

Df = Density of Fluid
DS = Density of Solid object
g = Gravitational force
M = Mass of dosage form
V = Volume of dosage form
when Ds, density of dosage form is lower, F force is positive gives buoyancy and when it is Ds is higher, F will negative shows sinking.

ii) Swelling systems:-

a) Swelling Index:-

After immersion of swelling dosage form into SGF at 370C, 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 asWeight Gain.

$$\textbf{Water uptake = WU = (Wt – Wo) * 100 / Wo}$$

Where, Wt = weight of dosage form at time t.
Wo = initial weight of dosage form.

B) IN-Vitro Evaluation Test:-[39,41]

1. 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. In order to prevent such problems, various types of modification in dissolution assembly made are as follows.
2. 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.

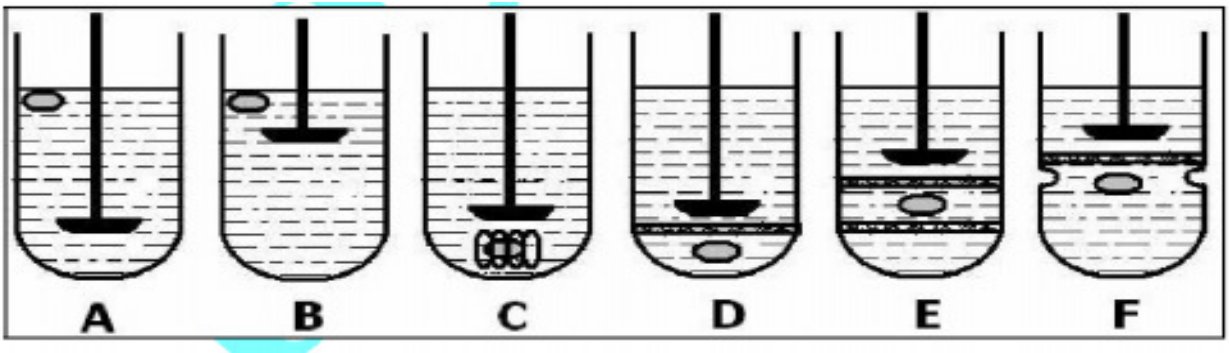


Fig-9dissolution of floating dosage form

3. 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.
4. 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.

5. Other method suggests placing dosage form between 2 ring/meshes.
6. 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 indentedprotrusions, this gives more area for dosage form.
7. Inspite of the various modifications done to get the reproducible results, none of themshowed co-relation with the in-vivo conditions. So a novel dissolution test apparatuswith modification of Rossett-Rice test Apparatus was proposed.

C) IN-Vivo Evaluation Test:-

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) 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:-

13C Octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates CO2 gas which comes out in breath. The important Carbon atom which will come in CO2 is replaced with 13C isotope. So time up to which 13CO2 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 CO2 release. So this method is cheaper than other.

Conclusions:-

In the field of gastric retention, we have seen that there are many obstacles that need to be overcome in order to be able to claim true gastric retention. Considering the advantages for improved delivery of drugs, some companies have undertaken the considerable task of developing these types of devices, some with success and others with failure due to the unpredictability of the human GI tract. However, we are as close as we have ever been to seeing a greater transition of gastric retention devices from developmental level to the manufacturing and commercial stage.

Future Prospects:-

While the control of drug release profiles has been a major aim of pharmaceutical research and development in the past two decades, the control of GI transit profiles could be the focus of the next two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. Soon, the so-called ‘once-a-day’ formulations may be replaced by novel gastroretentive products with release and absorption phases of approximately 24 hours.

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