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A Comprehensive Overview on Gastroretentive Drug Delivery System for Improving Drug Bioavailability

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ABSTRACT

Gastroretentive Drug Delivery System (GRDDS) helps in the treatment of gastritis and peptic ulcer disease. The most advantageous approach of the gastroretentive drug delivery system improves the drug bioavailability and patient compliance by increasing the gastric residence time and controlling the drug release. Recently, many new and old drug molecules are modified and even the combination product are formulated as gastroretentive drug delivery systems. Other development methods include floating, swelling, mucoadhesive and high-density system have been developed to increase the gastric retention time of the dosage form. Gastroretentive drug delivery system has become a leading methodology in site-specific orally administered controlled release drug delivery system, which are unstable in alkaline pH, soluble in acidic pH, having a narrow absorption window, site of action specific to the stomach can be developed by using this technique.

INTRODUCTION:

Oral controlled release drug delivery systems have recently been of increasing interest in the pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance, and flexibility in formulation. Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve a suitable therapeutic activity. (1) To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT). These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of the small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolonged gastric residence time by the drug delivery. (2) Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the solubility of drugs that are less soluble in a high pH environment. (3) 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. (4) 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 have been being designed and developed, including high density (sinking) systems that are retained in the bottom of the stomach, low density (floating) systems that cause buoyancy in gastric fluid, mucoadhesive systems that cause bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limit emptying of the dosage forms through the pyloric sphincter of stomach, super porous hydrogel systems, magnetic systems, etc. (5)

1.1 Potential drug candidates for gastroretentive drug delivery systems: (6)

- Drugs that are locally active in the stomach, particularly useful for the treatment of peptic ulcers caused by H. Pylori Infections. e.g. misoprostol, antacids, etc.

- Drugs that have a narrow absorption window in the gastrointestinal tract e.g. L-DOPA, para-aminobenzoic acid, furosemide, riboflavin, etc.
- Drugs that are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
- Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
- Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

1.2 Drugs that are unsuitable for gastroretentive drug delivery systems:

- Drugs that have very limited acid solubility e.g. phenytoin.

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

- Drugs intended for selective release in the colon e.g. 5- aminosalicylic acid and corticosteroids.

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 stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents. The stomach is divided into 4 sections, each of which has different cells and functions. (7) The sections are shown in fig 1:

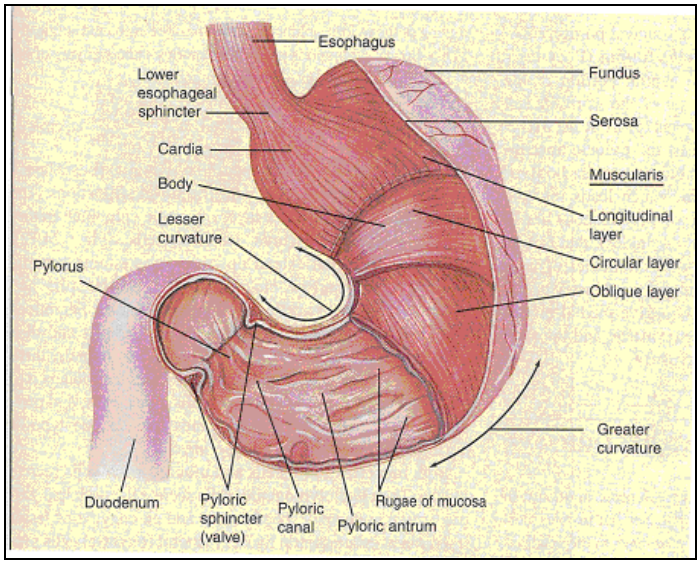

Figure No. 1A: Structure of stomach

Cardia- Where the contents of the oesophagus empty into the stomach.

Fundus- Formed by the upper curvature of the organ.

Body or Corpus- The main, central region.

Pylorus - The lower section of the organ that facilitates emptying the contents into the small intestine.

Figure No. 1B: Different parts of stomach with function

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 wall of the stomach has four layers: (8)

1. The mucosa – this is the name for the lining of the stomach. It contains glands that produce chemicals (enzymes and acid) that make gastric juices.
2. The submucosa – a layer underneath the mucosa.
3. The muscular – a layer of muscle beneath the submucosa.
4. The serosa – this is a strong membrane that forms the outer layer of the stomach. (7)

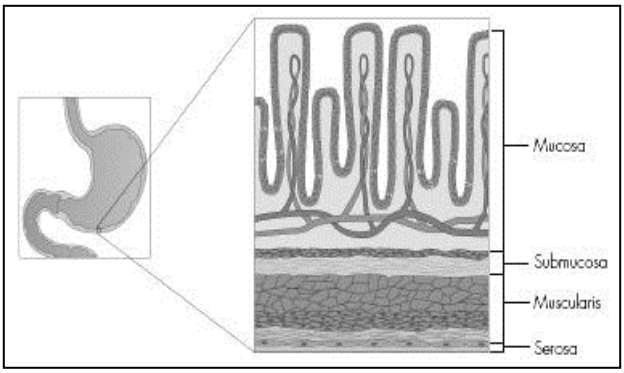

Figure No. 2: Structure of the stomach wall

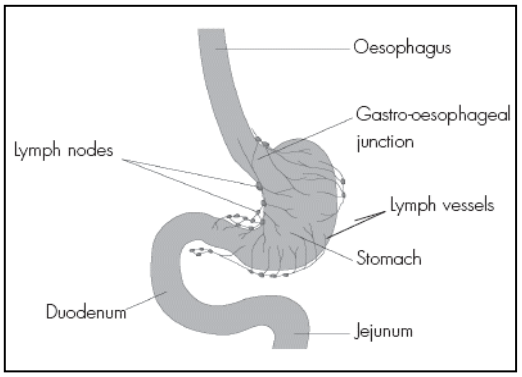

Figure No. 3: Lymphatic system of stomach

As well as being part of the digestive system the stomach is also connected to the lymphatic system. The lymphatic system has two main roles. It helps to protect the body from infection and it drains fluid from the tissues. All the tissue layers of the stomach are bathed in a fluid called lymph. This fluid drains through tiny tubes (lymph vessels) in the stomach layers, which are connected to small bean-like structures (lymph nodes). The lymph nodes filter debris (such as old cells or bacteria) from the fluid before returning it through larger lymph vessels to the main blood circulation. (8)

Section	Length (m)	Transit time (hr)	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

2.1 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.

2.2 Gastric intestinal motility pattern:

Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50 ml 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 inner digestive 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. (9)

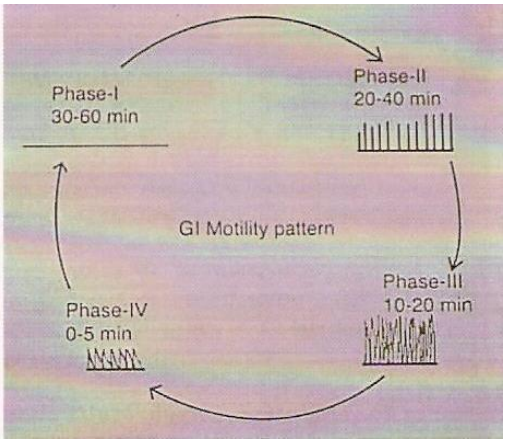

Figure No. 4: Gastro intestinal motility pattern

Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone in the blood controls the duration of the phases. In the inner digestive or fasted state, and MMC wave migrates from the stomach down the GI tract every 90–120 minutes. The interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), is further divided into the following 4 phases as described by Wilson and Washington. (10)

1. Phase I (basal phase) lasts from 30 to 60 minutes with rare contractions.

2. Phase II (pre burst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increase gradually.

3. Phase III (burst phase) lasts for 10 to 20 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 lasts for 0 to 5 minutes and occurs between phases III and me of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fast to that of a fed state. This is also known as the digestive motility pattern and comprises continuous contractions as in phase II of the fasted state. (11) These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in a slowdown of gastric emptying rate. The digestive or fed state is observed in response to meal ingestion. It resembles the fasting Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the inner digestive MMC. It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern or by the presence of food**.**

3. Advantages of Gastroretentive Delivery Systems: (12)

I. Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose. e.g. furosemide

II. 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 cephalosporins)

III. Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time thereby increasing the bioavailability of sustained-release delivery systems intended for once-a-day administration. e.g. ofloxacin. (13)

4. Limitations of the Techniques of Gastroretention:

I. The floating systems in patients with achlorhydria can be questionable in the case of swellable systems, faster-swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.

II. 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.

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

IV. The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

V. For all the above systems the physical integrity of the system is a very important and primary requirement for the success of such gastroretentive systems. (12)

5. Factors controlling gastric retention of dosage forms:

The stomach anatomy and physiology parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of food intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes, etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide, cisapride.). The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters. (6)

I. The density of dosage forms

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 the bottom of the stomach. Both positions may isolate the delivery system from the pylorus. A density of < 1.0 gm/ cm^3 is required to exhibit floating property.

II. Shape and size of the dosage form

The shape and size of the dosage form are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of nonfloating 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 retention time (GRT) as the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time. Ring-shaped and tetrahedron-shaped devices have better gastric retention as compared with other shapes.

III. Food intake and its nature

Food intake, viscosity, and volume of food, caloric value, and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) alters the gastric retention time (GRT) of the dosage form. Usually, the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form, and thus, the drug absorption increases by allowing its stay at the absorption site for a longer period. Again, the increase in acidity and caloric value slows down gastric emptying time (GET), which can improve the gastric retention of dosage forms.

IV. Effect of gender, posture, and age

Generally, females have slower gastric emptying rates than males. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in the upright, ambulatory, and supine state. In the case of elderly persons, gastric emptying is slowed down.

6. Approaches To Achieve Gastric Retention: (14)

Various techniques have been used to encourage gastric retention of an oral dosage form. Floating systems have low bulk density so that they can float on the gastric juice in the stomach. The problem arises when the stomach is completely emptied of gastric fluid. In such a situation, there is nothing to float on. Different techniques used for gastric retention are illustrated in fig 5:

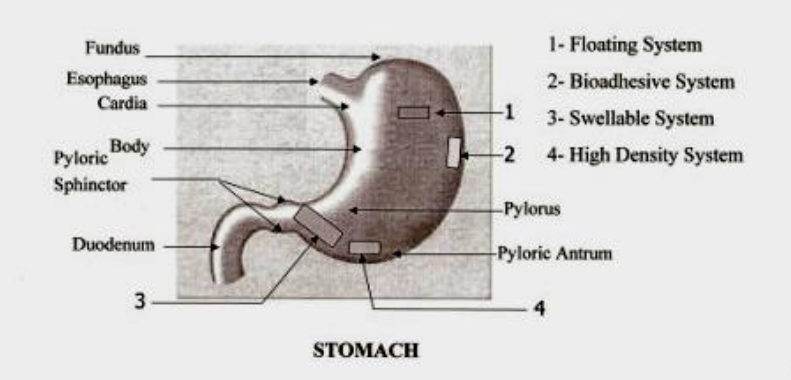

Figure No. 5: Various approaches to achieve gastric retention

I. High density (sinking) system or non-floating drug delivery systems

This approach involves the formulation of dosage forms with a density that exceeds the density of normal stomach content (~ 1.004 gm/cm3). These formulations are prepared by coating the drug on a heavy core or mixed with inert materials such as iron powder, barium sulfate, zinc oxide, and titanium oxide, etc. (15)

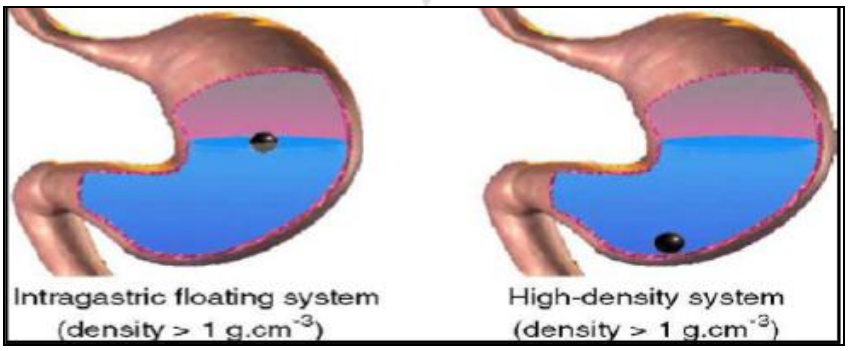

Figure No. 6: Schematic localization of an intra-gastric floating system and a high density system in the stomach.

The materials increase density by up to 1.5- 2.4 gm/cm3. A density close to 2.5 gm/cm^3 seems necessary for significant prolongation of gastric residence time. But, the effectiveness of such systems in human beings has not been observed and no such system has been marketed. (15)

II. Floating drug delivery systems

A floating drug delivery system is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability**.** Such delivery systems are desirable for drugs with an absorption window in the stomach or the upper small intestine. This system has

a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period and 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. (16) The major requirements for floating drug delivery systems are:

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).
- It must form a cohesive gel barrier.

The inherent low density can be provided by the entrapment of air (e.g. hollow chambers) or by the incorporation of low-density materials (e.g. fatty materials or oils, or foam powder). These approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of polypropylene foam powder, the matrix-forming polymers, drug, and filler. The acceptable floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produce irritation. On the other hand, multiple-unit floating systems may be an attractive alternative since they have been shown to reduce inter-and intra- subject availabilities in drug absorption as well as to lower the possibility of dose dumping. (16)

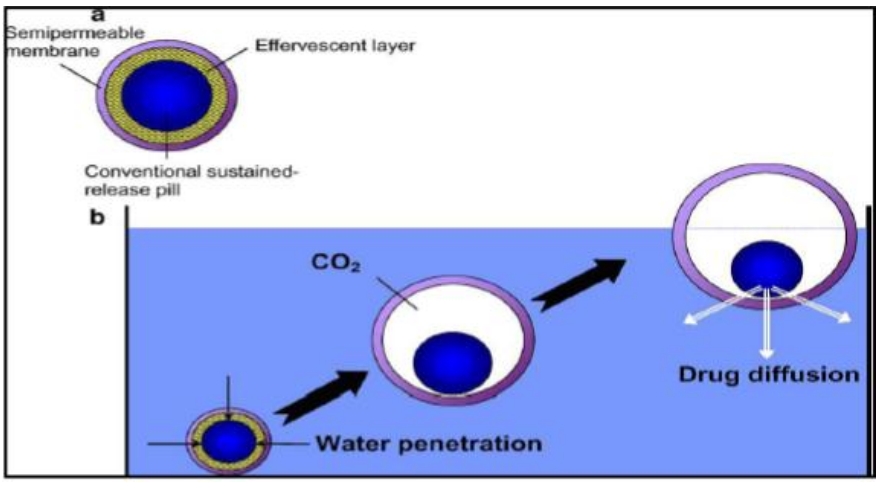

Figure No. 7 (a): Schematic representation of ‘‘floating pill’’.

(b) The penetration of water into effervescent layer leads to a CO2 generation and makes the system float.

Various multiple-unit floating systems like air compartment multiple-unit system, hollow microspheres (micro balloons) prepared by the emulsion solvent diffusion method microparticles based on low-density foam powder, beads prepared by emulsion gelation method, etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer-lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery systems.

A. Non-effervescent Systems

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose. In one approach, intimate mixing of drug with a gel-forming hydrocolloid results in contact with gastric fluid after oral administration and maintains relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to such dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide, and polycarbonates. Such a system can be divided into the sub-types:

i. Hydrodynamically balanced systems:

Sheth and Tossounian first design such as „hydrodynamically balanced systems". Such systems contain drugs with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. (17) The polymer is mixed with drugs and administered in a hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and the mixture swells to form a gelatinous barrier, which imparts buoyancy to a dosage form in gastric juice for a long period. Continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to the dosage form. Incorporation of fatty excipients gives low-density formulations reducing erosion. Madopar LP®, based on this system was marketed during the 1980"s. 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. (17)

ii. Micro balloons / Hollow microspheres:

Micro balloons / hollow microspheres loaded with drugs in their outer polymer shell were prepared by simple solvent evaporation or solvent diffusion/evaporation methods to prolong the gastric retention time of the dosage form. (18)

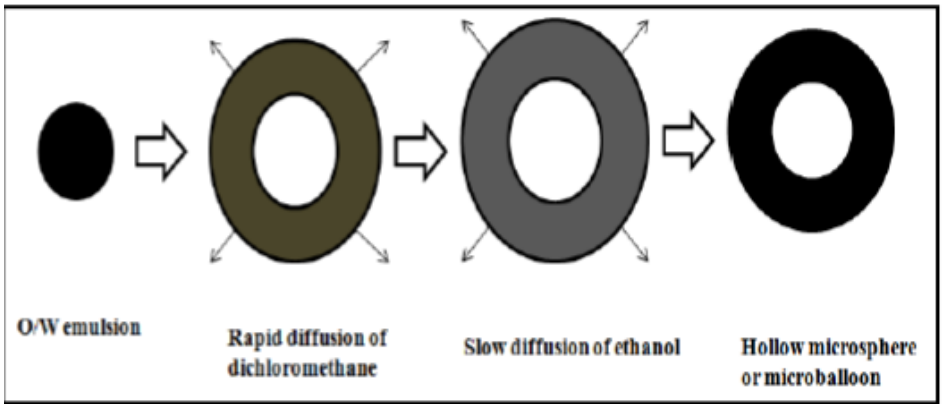

Figure No. 8: Formulation of floating hollow microsphere or microballoon

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 the number of polymers, the plasticizer polymer ratio, and the solvent used for formulation. At present hollow microspheres is one of the most promising buoyant systems because they combine the advantages of a multiple-unit system and good floatability.

iii. Alginate beads:

Alginates beads are 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, a sodium alginate solution is dropped into an aqueous solution of calcium chloride and causes the precipitation of calcium alginate. (19) 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 retention time by more than 5.5 hrs.

iv. 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**.** The peripheral walls of

the device were completely sealed to prevent 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. Gastric fluid enters through the aperture, dissolves the drug, and causes the dissolved drug for continuous transport across the intestine for drug absorption. (20)

B. Effervescent (gas generating) systems

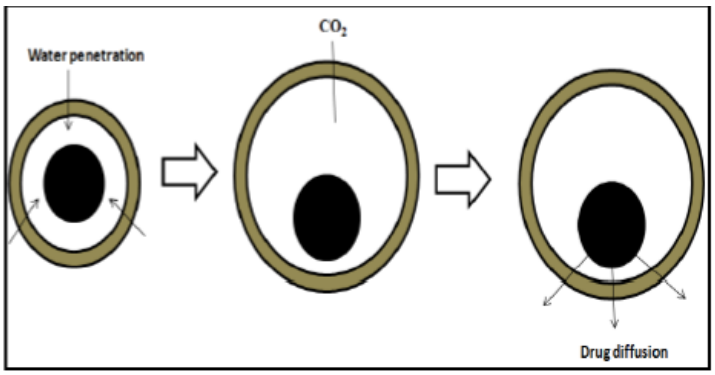

Figure No. 9: Drug release from effervescent (gas generating) systems

Floatability can be achieved by the generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid, or tartaric acid)**.** The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. In this system carbon dioxide is released and causes the formulation to float in the stomach.

Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple-unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose, and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC), and floating system based on ion exchange resin technology, etc. Bilayer or multilayer systems have also been designed. Drugs and excipients can be formulated independently and the gas generating material can be incorporated into any of the layers. Further modifications involve coating the matrix with a polymer that is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise between elasticity, plasticity, and permeability of the polymers. (21)

III. Bioadhesive or Mucoadhesive drug delivery systems

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bioadhesive polymers are used and they can adhere to the epithelial surface in the stomach**.** Thus, they improve the prolongation of gastric retention. The basis of adhesion is that a dosage form can stick to the mucosal surface by different mechanisms. These mechanisms are based on:

- The wetting theory, which depends on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
- The diffusion theory, which proposes physical entanglement of mucin strands in the flexible polymer chains, or interpenetration of mucin strands into the porous structure of the polymer substrate.
- The absorption theory, suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
- The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material. (22)

Materials commonly used for bioadhesion are polyacrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acid, etc. Even though some of these polymers are effective at producing bioadhesion, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).

IV. Expandable, unfoldable, and swellable systems

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system to prolong gastric retention time (GRT):

- A small configuration for oral intake
- An expanded gastroretentive form, and
- A final small form enabling evacuation following drug release from the device.

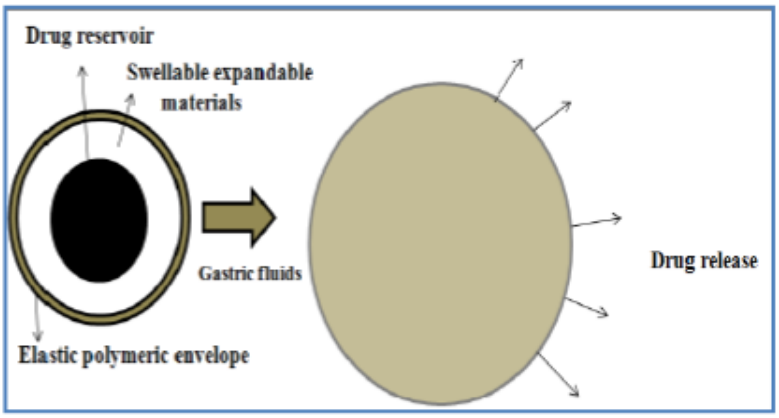

Figure No. 10: Drug release from swellable systems

Thus, gastroretentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastroretentive drug delivery. Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like a tetrahedron, ring, or planner membrane (4 - label disc or 4 - limbed cross form) of bioerodible polymer compressed within a capsule that extends in the stomach. (23)

Swellable systems are also retained in the gastrointestinal tract (GIT) due to their mechanical properties. The swelling usually results from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid. Expandable systems have some drawbacks like problematical storage of many easily hydrolyzable, biodegradable polymers relatively short-lived. Mechanical shape memory for the unfolding system is most difficult to industrialize and is not cost-effective. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion, and gastropathy.

V. Super porous hydrogel systems

These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve Gastric Retention Time (GRT) super porous hydrogels of average pore size >100 micrometer, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient

mechanical strength to withstand the pressure by gastric contraction. This is achieved by co-formulation of hydrophilic particulate material. (20) (9)

VI. Magnetic Systems

This approach to enhancing the gastric retention time is based on the simple principle that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. Although the magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance. (20)

7. Evaluation of Gastroretentive Dosage Forms:

A. For Single Unit Dosage Forms (tablets)

i. Floating lag time: It is the time taken by the tablet to emerge onto the surface of the dissolution medium and is expressed in seconds or minutes.

ii. In-vitro drug release and duration of floating: This is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37 ± 0.2 °c in simulated gastric fluid (pH 1.2 without pepsin). Aliquots of the samples are collected and analyzed for the drug content. The time (hrs) for which the tablets remain buoyant on the surface of the dissolution medium is the duration of floating and is visually observed.

iii. In-vivo evaluation for gastro-retention: This is carried out utilizing X-ray or Gamma scintigraphic monitoring of the dosage form transition in the GIT. The tablets are also evaluated for hardness, weight variation, etc.

B. For Multiple Unit Dosage Forms (ex: microspheres) Apart from the in-vitro release, duration of floating and in-vivo gastro-retention tests, the multiple unit dosage forms are also evaluated for –

i. Morphological and dimensional analysis with the aid of scanning electron microscopy (SEM). The size can also be measured using an optical microscope.

ii. % yield of microspheres: This is calculated from the following formula,

% yield of microspheres = [weight of microspheres obtained / Total weight of drug and polymer] ×100

iii. Entrapment efficiency: The drug is extracted by a suitable method, analyzed, and is calculated from the following equation:

Entrapment efficiency = [Practical amount of drug present / Theoretical drug Incorporated] ×100

iv. In vitro floating ability (Buoyancy %): A known quantity of microspheres are spread over the surface of a USP (Type II) dissolution apparatus filled with 900 ml of 0.1 N HCl containing 0.002% v/v Tween 80 and agitated at 100 rpm for 12 hours. After 12 hours, the floating and settled layers are separated, dried in a desiccator, and weighed. The buoyancy is calculated from the following formula.

$$\text{Buoyancy (\%)} = Wf / (Wf + Ws) * 100$$

Where Wf and Ws are the weights of floating and settled microspheres respectively.

v. Drug-excipient (DE) interactions: This is done using FTIR. The appearance of a new peak, and/or disappearance of the original drug or excipient peak indicate the DE interaction.

Apart from the above-mentioned evaluation parameters, granules are also evaluated for the effect of aging with the help of Differential Scanning Calorimeter or Hot stage polarizing microscopy.

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