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CONTROLLED GASTRORETENTIVE DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of the administration, patient compliance and flexibility in formulations etc., from the immediate releaseto the site specific delivery, oral dosage forms have really progressed. More than 50% of the delivery systems available are to be administered through oral route. During the last decade, many studies have been performed concerning the sustained release dosage forms of the drug, which have aimed at the prolongation of gastric emptying time(GET). Oral sustained release gastro-retentive dosage forms (GRDFs) offer many advantages for drugs with absorption from upper parts of gastrointestinal track and for those acting locally in the stomach, improving the bioavailability of the medication by enhancing the gastric retention time of the dosage form. GRDDS comprising mainly of the floating, bio adhesive and swellable systems. The purpose of this paper is to review the recent literature and current technology used in the development of gastroretentive dosage forms.

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drugdelivery due to the ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed[1]. More than 50% of the drug delivery systems available are to be administered through oral route[2]. In oral delivery conventional oral dosage forms offer no control overdrug delivery, leading to fluctuations in plasma drug level[3]. And oral sustained drug delivery formulations show some limitations connected with the gastric emptying time. Variable and too rapid gastrointestinal transit could result in incomplete drug release from the device into the absorption window leading to diminished efficacy of the administered dose. It is evident from the recent research 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[4]. During the last decade, many studies have been performed concerning the sustained release dosage forms of the drug, which have aimed at the prolongation of gastric emptying time (GET).

PHYSIOLOGY OF THE STOMACH

The GI 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 GI 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 isan 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 50 ml and contains a small amount of gastric fluid (pH1–3) 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[5].

Modification of the GI transit time is one of the main challenges in the development of oral controlled drug delivery system. Gastric emptying of pharmaceuticals is highly variable and dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence

time usually ranges between 5 minutes to 2 hours. In the fasted state the electrical activity in the stomach – the interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and the transit of dosage forms. It is characterized by four Phases:

Phase I– Period of no contraction (30-60 minutes)

Phase II– Period of intermittent contractions (20-40 minutes)

Phase III– Period of regular contractions at the maximal frequency also known as housekeeper wave (10-20 minutes)

Phase IV– Period of transition between Phase III and Phase I (0-5 minutes)[6].

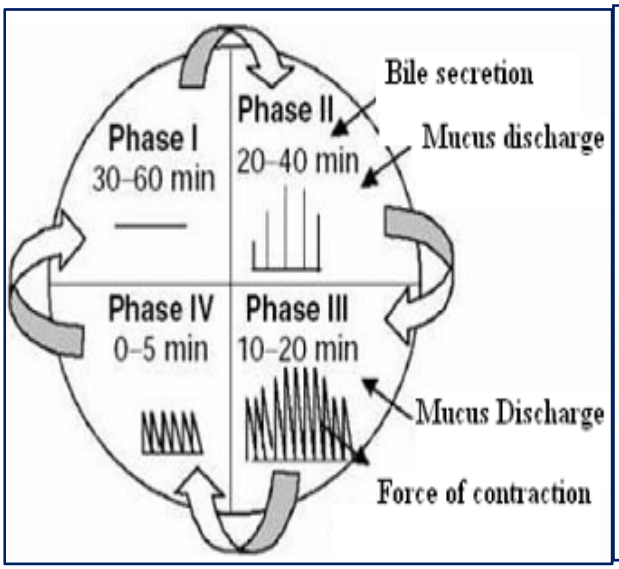


Fig. 1: Gastrointestinal motility pattern

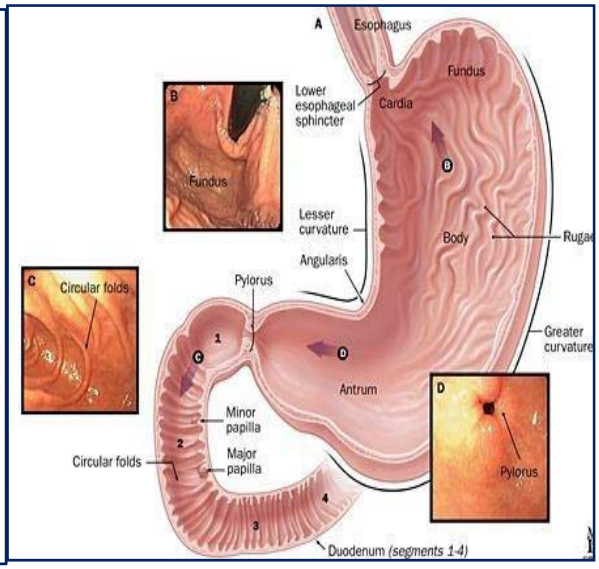


Fig. 2: Physiology of the stomach

GASTRORETENTION

Gastro retentive systems can remain the drugs in the gastric region for several hours and hence significantly prolong the gastric residence time[7]. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment[2]. Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need of repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited[8, 3].

ADVANTAGES.[9,10,11.]

- The gastro retentive systems are advantageous for drugsabsorbed through the stomach. E.g. Ferrous salts, antacids.
- FDDS reduces the drug concentration fluctuation that makes it possible to obtain certain selectivity in the exact pharmacological effect of drugs that are supposed to activate different types of receptors at different concentrations.
- Slow release of the drug into the body reduces the counter activity to minimum level leading to higher drug efficiency.
- Administration of prolonged release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
- Retention of the drug in the gastric formulation at stomach minimizes the amount of drugs that reaches the colon, thereby preventing the degradation of drug that degrades in the colon.
- GRDDS is highly advantageous in case of drugs having local action e.g. Antacids
- The bioavailability of many drugs increases when formulated as Floating dosage form.e.g. Riboflavin Controlled release Gastro retentive Dosage form (CR-GRDF) is highly bioavailable than non GRDF-CR polymeric formulations.
- When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
- Drugs (acidic substances) like aspirin that cause irritation to gastric mucosa when come in contact with it. Therefore to overcome this formulation of such drugs is prepared for administration.

DISADVANTAGES.[2, 6.]

- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- Not suitable for drugs that have solubility or stability problem in GIT.

- This system is not suitable for drugs that irritate the gastric mucosa and the drugs that are not stable in the stomach's acidic environment.
- These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.
- Certain drugs get well absorbed along the gastric tract and undergo significant first pass metabolism, may not be suitable for floating systems because of the slow gastric empting that leads to reduced systemic bioavailability.

SUITABLE DRUG CANDIDATES FOR FLOATING GASTRO-RETENTION [2,12.]

In general, appropriate candidates for CRGRDF are

- ✓ Drugs which have Narrow absorption window in GI tract, e.g., Riboflavin in a vitamin Deficiency and Levodopa.
- ✓ Drugs which are primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, Chlordiazepoxide and Scinnarazine.
- ✓ Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
- ✓ Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
- ✓ Drugs that disturb normal colonic bacteria, e.g., Amoxicillin trihydrate.

Drugs Unsuitable For Gastroretention[13]

Some of the drugs are not suitable to formulate gastro retentive systems they are:

- ❖ Drugs having very limited acid solubility. e.g. phenytoin, etc.
- ❖ Drugs observed with instability in the gastric environment. e.g. erythromycin
- ❖ Drugs which should release specifically in the colon. e.g. 5- amino salicylic acid and corticosteroids, etc.

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS. [12, 2.]

The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, biological factors such as age, sex, sleep, disease state of the individual (e.g.,gastrointestinal diseases and diabetes)

1. DENSITY OF DOSAGE FORM

Dosage forms having a density lower than thatof gastric fluid experience floating behavior and gastric retention. A density of <1.0gm/cm^3 is required to exhibit floating property. However, the floating tendency of the dosageform usually decreases as a function of time, as the dosageform gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium[14].

2. SIZE AND SHAPE

The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. Thus the size of the dosage form appears to be an important factor affecting gastric retention[15].

3. FOOD & PHYSICAL STATE OF FOOD[2]

Food intake, the nature of the food, caloric content, and the frequency of feeding have a profound effect on the gastric retention of dosageforms.The presence or absence of food in the stomach influences the GRT of the dosage form. Usually, the presence of food increases the GRT of the dosageform and increases drug absorption by allowing it to stay at the absorption site for a longer time. There is a difference seen between gastric empting time of liquid, digestible solid, and indigestible solid. It was suggested that the emptying of large (91 mm) indigestible objects from stomach was dependent upon interdigestive migrating myoelectric complex (MMC). When liquid and digestible solids are present in the stomach, it contracts ~3 to 4 times per minute leading to the movement of the contents through partially opened pylorus. Indigestible solids larger than the pyloric opening are propelled back and several phases of myoelectric activity take place when the pyloric opening increases in size during the housekeeping wave and allows the sweeping of the indigestible solids. Studies have shown that the gastric residence time (GRT) can be significantly increased under the fed conditions since the MMC is delayed.

4. pH

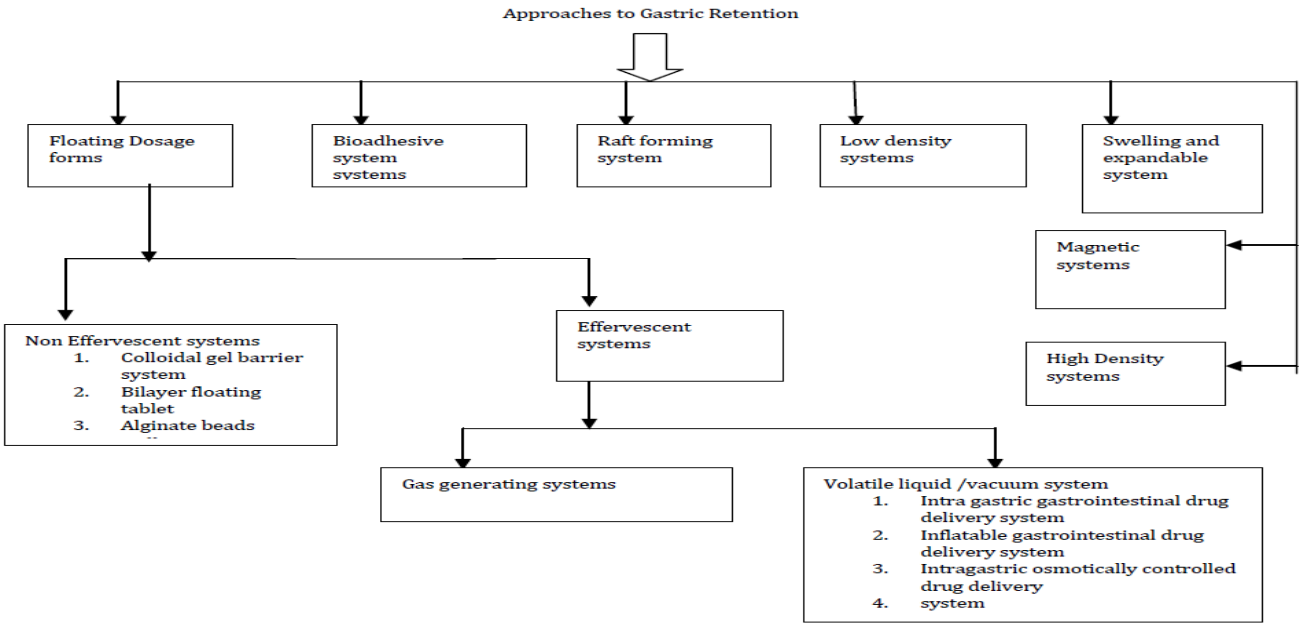
In fasting state, the pH of stomach is approximately 1.5 to 2.0 and in fed state is 2.0 to 6.0. Therefore, a large volume of water has to be administered with an oral dosage form due to which the pH rises from 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state.

5. BIOLOGICAL FACTORS

Factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. A study by Mojaverian et al[16] found that females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men. The authors also studied the effect of postureon GRT, and found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. Stress increases gastric emptying rates while depression slows it down. Gansbeke et al[17], the floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of similar size[18].

APPROACHES TO GASTRIC RETENTION

Various approaches have been followed to encourage gastric retention of an oral dosage form.



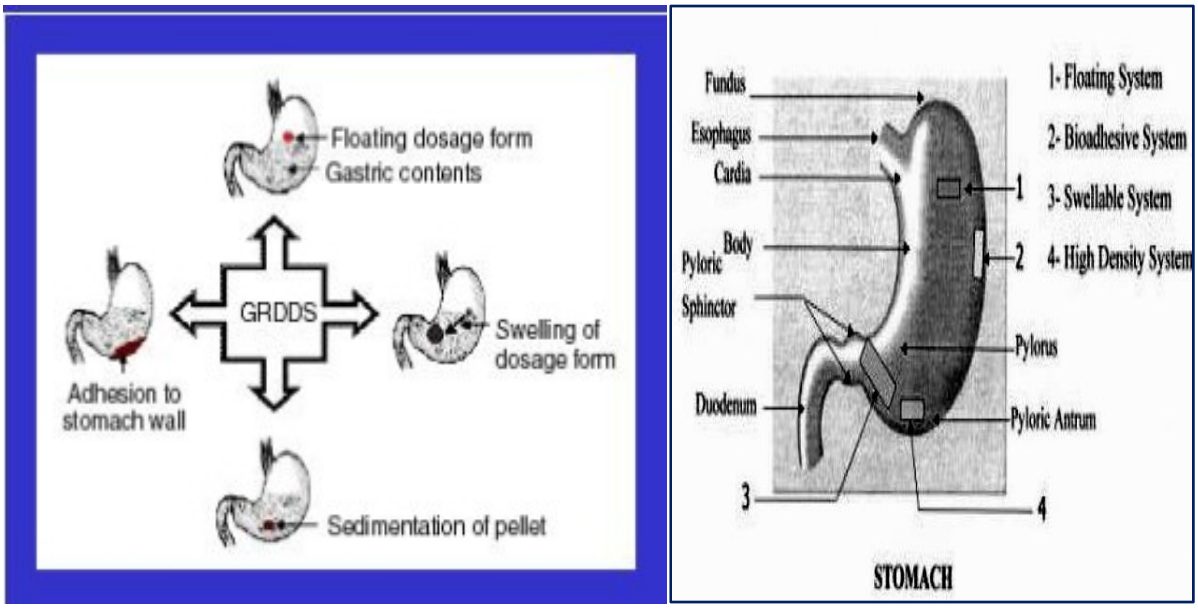


Fig: 3,4: different types of gastro retentive dosage forms

FLOATING DRUG DELIVERY SYSTEMS

Floating systems was first described by Davis in 1968. FDDS is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. Floating systems have low bulk density so that they can float on the gastric juice in the stomach[19]. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach[20]. Floating drug delivery system is also called the hydrodynamically balanced system (HBS)[21]. The problem arises when the stomach is completely emptied of gastric fluid. In such a situation, there is nothing to float on[19]. Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

i. Effervescent systems and
ii. Non-effervescent systems.

I. EFFERVESCENT DOSAGE FORMS:

These are matrix types of systems prepared with the help of swellable polymers such as methyl cellulose 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 acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms[22].

These effervescent systems further classified into two types.

a. Gas generating systems
b. Volatile Liquid/Vacuum containing systems.

A) GAS GENERATING SYSTEMS:[23, 24]

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime.

B) VOLATILE LIQUID/VACUUM CONTAINING SYSTEMS: [23]

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

II. NON-EFFERVESCENT SYSTEMS:

Non-effervescent floating dosage forms are prepared by using a gel forming or swellable cellose type of hydrocolloids, polysaccharides, and matrix forming polymers like polycarbonate, polyacrylate, ploymethacrylate, 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 the 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[22].

This can again divided into the following types:

A) COLLOIDAL GEL BARRIER SYSTEM

These Hydrodynammically balanced systems (HBS) are first designed by Sheth and Tossounian[25]. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This helps in prolongation of GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC),

polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface[12].

B) BILAYER FLOATING TABLETS

A bi-layer tablet contain two layers, one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach[26].

C) **ALGINATE BEADS**

Multiunit floating dosage forms have been developed from freeze dried calcium alginate[27]. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate by ionotropic gelation method. Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form beads. Since, the use of Alginates, Gellan gum, Chitosan and Carboxymethyl cellulose for the encapsulation of drug and even cells, ionotropic gelation technique has been widely used for this purpose[28]. The natural polyelectrolytes inspite, having property of coating on the drug core and acts as release rate retardants contains certain anions on their chemical structure. These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations[3].

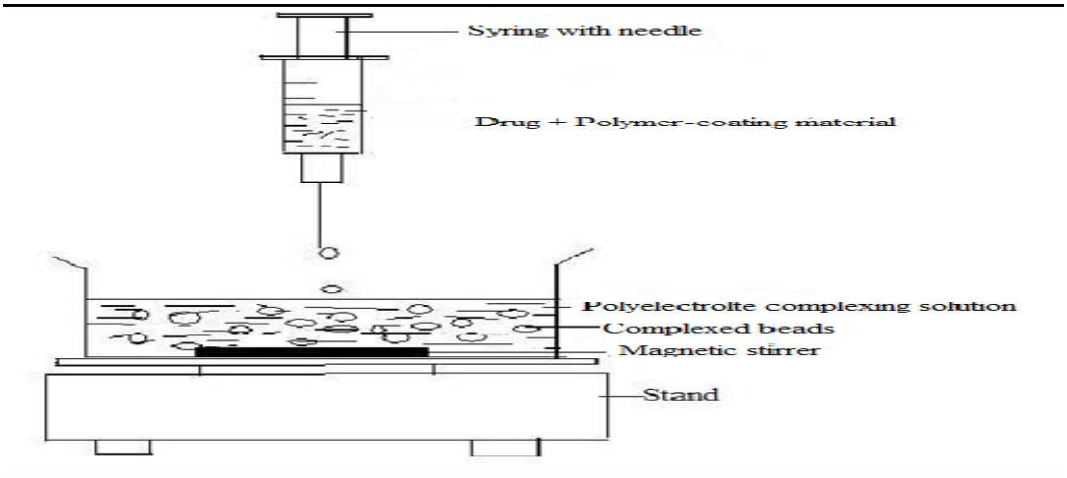


Figure 5: Ionotropic gelation method (Reprinted from)

D) HOLLOW MICROSPHERES

Hollow microspheres (so-called 'microballoons') with drug in their outer polymer shell are prepared by novel emulsion solvent diffusion method. In the emulsion solvent diffusion method a solution of polymer and drug in ethanol methylene chloride is poured into an agitated aqueous solution of poly (vinyl alcohol). The ethanol rapidly partitions into the external aqueous phase and the polymer precipitates around methylene chloride droplets. The subsequent evaporation of the entrapped methylene chloride leads to the formation of internal cavities within the microparticles. Microspheres have different microstructures. These microstructures determine the release and the stability of the carrier[29, 30].

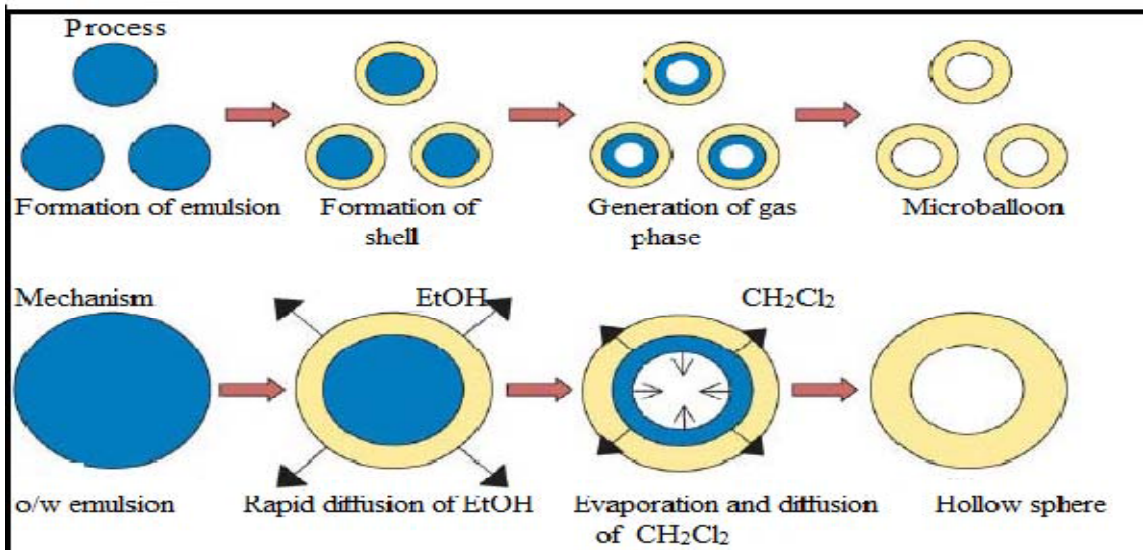


Fig 6: Mechanism of hallow microspheres

BIOADHESIVE SYSTEMS

The term bioadhesion is defined as adhesion to biological surface i.e. mucus and/or mucosal surface. These Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a sitespecific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach[31]. The thickness of the mucin gel layer varies in different regions of the GIT with thickness ranging between 50-500µm in stomach to 15-150µm in the colon. Cohesion of the mucin gel is dependent upon the glycoprotein concentration. The mucus layer is created biologically to play a number of important functions of protecting the underlying tissues from various diffusing/corrosive elements such as enzymes, acid and other toxic molecules[32]. Some of the most promising

excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc. Gastricmucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force[12].

RAFT FORMING SYSTEMS

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastro intestinal 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 CO_2[32]. Raft systems incorporate alginate gels – these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating.[33, 5]

HIGH DENSITY SYSTEMS

Gastric contents have a density close to water (1.004 g /cm^3). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall.[2] Thus sedimentation has been employed as a retention mechanism for pellets[12]. A density close to 2.5 g/cm^3 seems necessary for significant prolongation of gastric residence time. With these pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets[34]. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm^{-3}.

SWELLABLE AND EXPANDABLE SYSTEMS

Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water[2]. Expandable gastroretentive dosage forms (GRDFs) have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach[35]. Gastroretentivity is enhanced by the combination of

substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach.

APPLICATIONS

GRDDS offers several applications for drugs having poor bioavailability, some of the important applications are given below they are:

ENHANCEMENT OF ABSORPTION & BIOAVAILABILITY:

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

e.g. The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

SUSTAINED DRUG DELIVERY:

GRDDS can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

SITE-SPECIFIC DRUG DELIVERY:

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.

REDUCED FLUCTUATIONS OF DRUGCONCENTRATION:

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

CONCLUSION

Gastroretentive drug delivery systems are the most preferable system in order to deliver the drugs which have a narrow absorption window near the gastric region. Now a days number of

drug delivery devices are being developed which aim at releasing the drug at gastric region. GRDDS comprising mainly of the floating, bioadhesive and swellable systems; these are utilized for enhancing the bio availability and controlled release of the drugs by increasing the gastric residence time of the dosage form. Even through these drug delivery systems have several advantages they also have disadvantages like the invitro-invivo correlation is very less.

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