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FLOATING DRUG DELIVERY SYSTEM: A CRITICAL REVIEW

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ABSTRACT

The purpose of writing this review on floating drug delivery systems (FDDS) is to compile the recent literature with special focus on the approaches to achieve gastric retention. Floating Drug delivery systems offers numerous advantages specially the drugs having narrow absorption window in GIT, primary absorption in the stomach, stability problem in the intestine, poor solubility at alkaline pH, local activity in stomach, and property to degrade in colon. In recent years scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are currently being utilized in the prolongation of the GRT, including floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices.The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, FDDS types, advantages, disadvantages, evaluation and applications are also reviewed in this article.

KEYWORDS: Gastric retention, floating drug delivery systems, Effervescence and Buoyancy.

INTRODUCTION

Oral route of administration is the most convenient and preferred means of any drug delivery to the systemic circulation. The high level of patient compliance in taking oral dosage forms is due to the ease of administration and flexibility in formulation. However the oral route of administration suffers with certain drawbacks mainly short residence time of the dosage form in the GI tract and unpredictable gastric emptying. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT) by the development of controlled release gastro retentive dosage form (CRGRDFs). Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment.

Floating drug delivery system is a gastroretentive drug delivery system, has bulk density less than gastric fluids and so remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is flowing on 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. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration.[1]

BIOLOGICAL ASPECTS OF CRGRDFS

Stomach Physiology

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae (Fig. 1)[2]

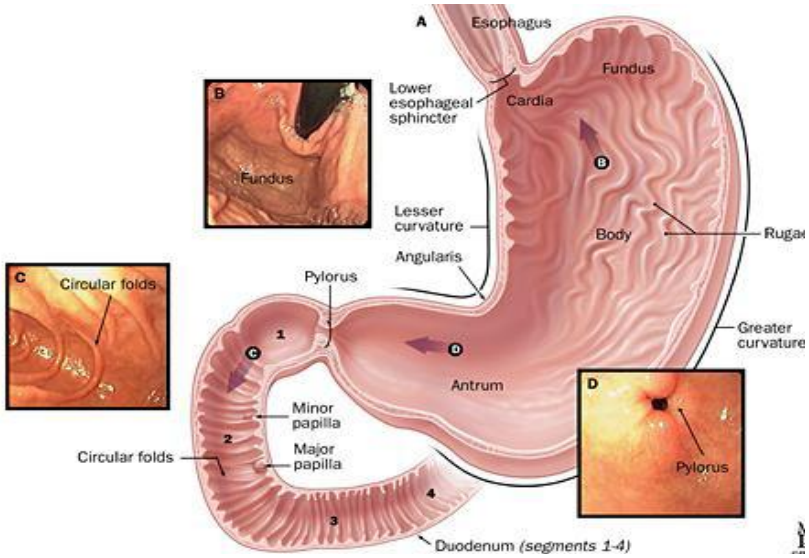

Fig: 1 Physiology of stomach

Gastric emptying rate[3,4,5]

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.

1. Phase I (Basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (Preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2. Consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state.

This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate**.**

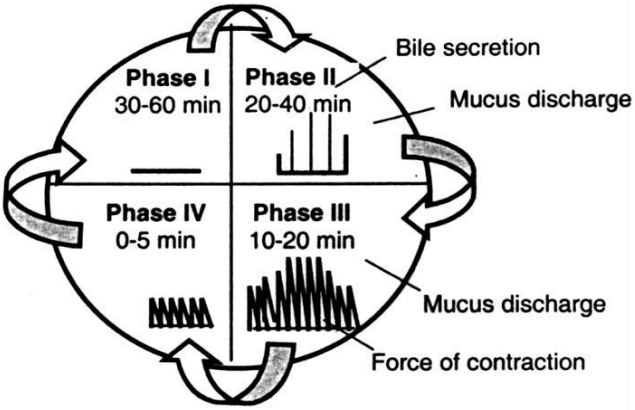

Fig. 2: Motility pattern in gastrointestinal tract.

APPROACHES TO GASTRORETENTION

Several techniques are reported in the literature to increase the gastric retention of drugs.

1) High density systems

These systems, which have a density of ~3g/cm3, are retained in the stomach and capable of withstanding its peristaltic movements.[6, 7] The major drawback with these systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and achieve required density of 2.4-2.8g/cm3. Diluents such as barium sulphate (density= 4.9), zinc oxide and titanium oxide must be used to manufacture such high-density formulation.[8] Sedimentation has been employed as a retention mechanism for high density systems.

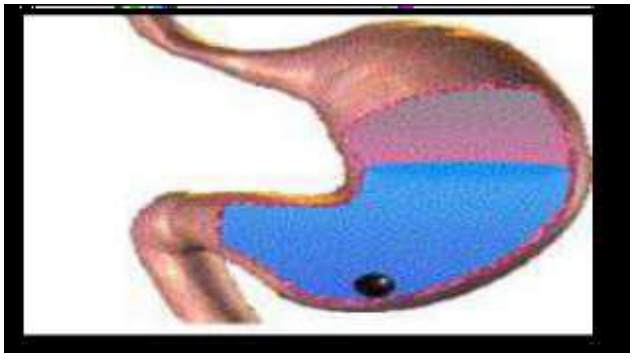

Fig. 3: High density systems

2) Swelling and expanding systems

This system is also called as "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters. The polymeric matrices remain in the gastric cavity for several hours. The polymer of molecular weight and swelling properties controlled and sustained drug. [9]

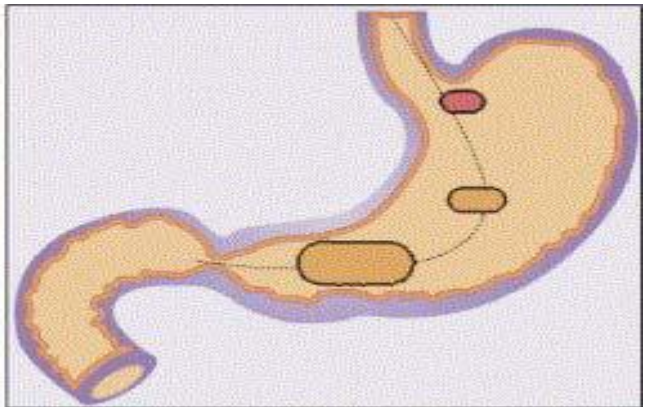

Fig. 4: Swellable tablet in stomach

By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon 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 cross links in the hydrophilic polymer network. These cross link prevents the dissolution of polymer and thus maintain the physical integrity of the dosage form. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer.[10]

3) Incorporating delaying excipient

Delayed gastric emptying approach of interest include feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and prolongation of the drug release with the help of delivery system incorporating delaying excipient like trietanolamine myristate in a delivery system.[11]

4) Modified systems

The non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modules of drug delivery device.[12]

5) Mucoadhesive & Bioadhesive systems

The Bioadhesive delivery systems are used to localize a delivery device within the lumen to increase the drug absorption in a site specific manner. Some of the most promising excipient that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin etc.[13,14]

6) Floating systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids though the system is floating on the gastric contents. After release of drug, the residual system is emptied from the stomach. Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas.[15]

7) Ion Exchange Resins

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.[16]

8) Osmotic Regulated Systems

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.[17]

TYPES OF FLOATING DRUG DELIVERY SYSTEMS

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS.

❖ **Non-Effervescent FDDS[18,19,20,21]**

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate,

polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol.

The various types of this system are as.

- **Single Layer Floating Tablets**

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

- **Bi-layer Floating Tablets**

A bi-layer tablet contain two layer 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.

- **Alginate Beads**

Multi-unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

- **Colloidal gel barrier systems**

These types of HBS system contains drug with gel forming or swellable polymers like cellulose type hydrocolloids, polysaccharides etc. They contain high levels (20 to 75 % w/w) of one or more gel forming highly polymers incorporated either in tablets or capsules. After intake of such systems, the hydrocolloid gets hydrated in gastric fluid and forms a colloidal gel barrier around its surface. The air trapped inside the swollen polymer maintains the density less than unity and confers buoyancy to these dosage forms.

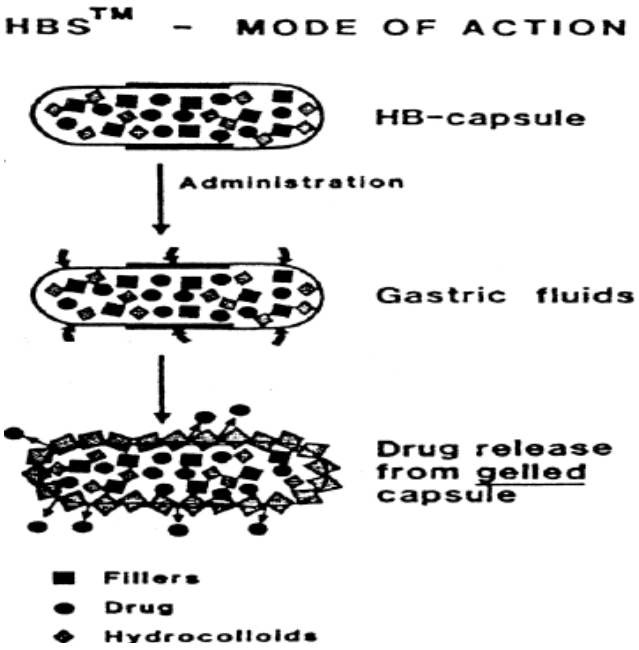

Fig. 5: Colloidal gel barrier systems

This gel barrier controls the rate of the fluid penetration into the device and hence, release of drug. With time the exterior surface of the dosage form goes in to the solution, the adjacent hydrocolloid layer becomes hydrated and thus maintains the gel layer. The HBS must fulfill the three basic criteria's:

1. It must have sufficient structure to form cohesive gel barrier.
2. It must maintain an overall specific density lower than that of gastric contents.
3. It should dissolve slowly enough to serve as reservoir for the delivery system.

Based upon this principle, a bilayer tablet containing one immediate release and other sustained release layer can be prepared. Immediate release layer delivers the initial dose whereas the other layer absorbs gastric fluid and forms a colloidal gel barrier on its surface.

A multi-layer, flexible, sheath-like device buoyant in gastric juice showing sustained release characteristics have also been developed. This device is consisted of at least one dry self-supporting carrier film, made up of water insoluble polymer matrix containing drug in either dispersed or dissolved forms and a barrier film overlaying the carrier film. Both carrier and barrier films are sealed together along their periphery and in such a way as to entrap a plurality of small air pockets, which bring about the buoyancy to the laminated films.

- **Hollow Microspheres**

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane

solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40 °C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.

❖ **Effervescent FDDS**

Effervescent systems include use of gas generating agents like carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types.

1. Gas generating systems.
2. Volatile liquid or vacuum containing systems.

1) Gas generating systems

a) Tablets

Intragastric single layer floating tablets or hydrodynamically balanced system (HBS)

These formulations have bulk density lower than gastric fluids and thus float in the stomach that increases the gastric emptying rate for a prolonged period. These are formulated by intimately mixing the gas (CO2) generating agents and the drug within the matrix tablet. The drug is released slowly at a desired rate from the floating system and the residual system is emptied from the stomach after the complete release of the drug. This leads to an increase in the gastric residence time (GRT) and a better control over fluctuations in plasma drug concentration.

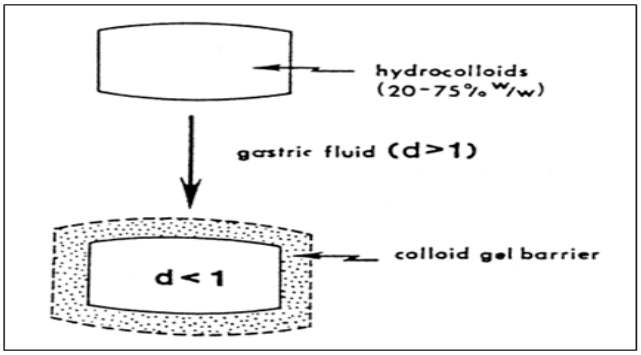

Fig: 6 Intragastric single layer floating tablet

Intragastric Bilayer Floating Tablets

These are also compressed tablets containing two layers:

Immediate release layer

Sustained release layer

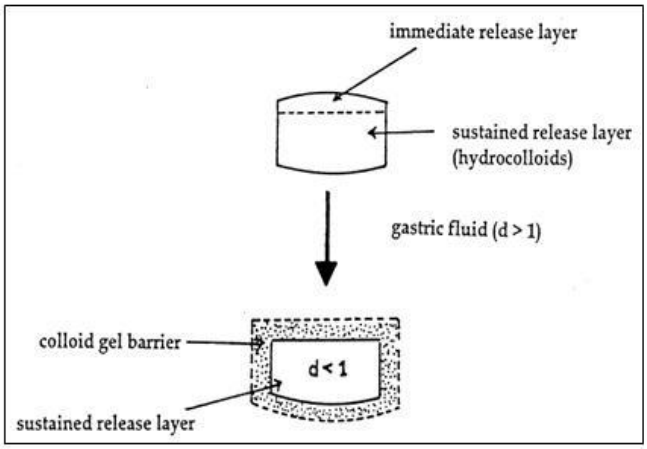

Fig.7: Intragastric bilayer tablet

b) Floating capsules

These floating capsules are formulated by filling with a mixture of sodium alginate and sodium bicarbonate. The systems float as a result of the generation of CO2 that was trapped in the hydrating gel network on exposure to an acidic environment.

c) Multiple unit type floating pills

These multiple unit type floating pills are sustained release pills known as seeds, which are surrounded by two layers. The outer layer is of swellable membrane layer while the inner layer consists of effervescent agents. This system sinks at once and then it forms swollen pills like balloons which float as they have lower density, when it is immersed in the dissolution medium at body temperature. The lower density is due to generation and entrapment of CO2 within the system.

d) Floating system with ion-exchange resins

Floating system using bicarbonate loaded ion exchange resin was made by mixing the beads with 1M sodium bicarbonate solution, and then the semi-permeable membrane is used to surround the loaded beads to avoid sudden loss of CO2. On the contact of gastric contents the exchange of bicarbonate and chloride ions taken place that results in generation of CO2, and

that carries beads towards the top of gastric contents and producing a floating layer of resin beads.

2) Volatile liquid or Vacuum Containing Systems

a) Intragastric floating gastrointestinal drug delivery system

This systems float in the stomach because of floatation chamber, which is vacuum or filled with a harmless gas or air, while the drug reservoir is encapsulated by a microporous compartment.

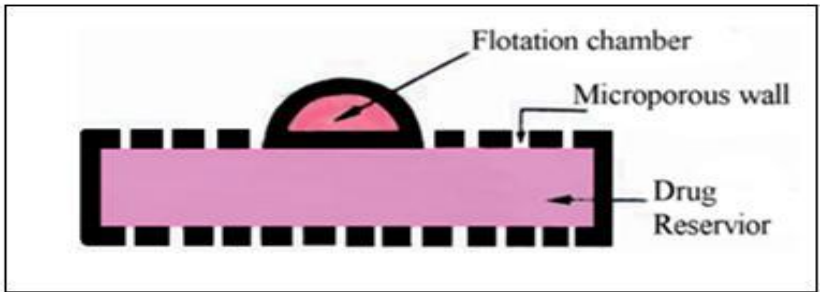

Fig: 8 Intragastric floating gastrointestinal drug delivery system

b) Inflatable gastrointestinal delivery system

Inflatable chamber are incorporated, which contains liquid ether that gasifies at body temperature to inflate the chamber in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug is released continuously from the reservoir into gastric fluid.

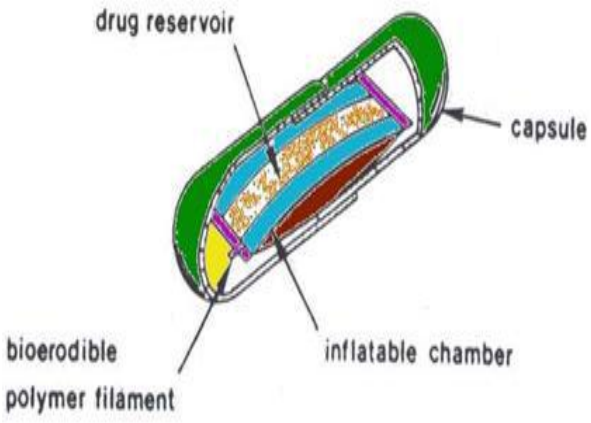

Fig.9: Inflatable gastrointestinal delivery system

c) Intragastric osmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components, drug reservoir compartment and an osmotically active compartment. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.[22, 23]

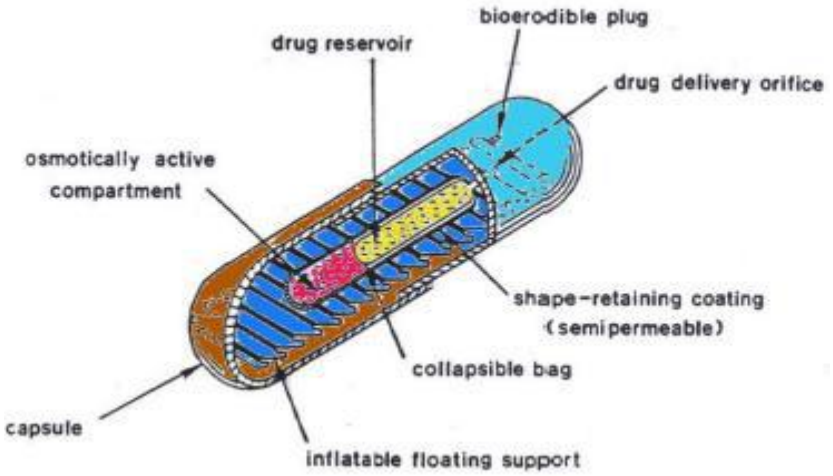

Fig: 10 Intragastric osmotically controlled drug delivery system

ADVANTAGES OF FDDS SYSTEM[24, 25, 26]

1. The gastroretentive systems are advantageous for drugs absorbed through the stomach, e.g. ferrous salts, antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence, HBS formulation may be useful for the administration of aspirin and other similar drugs.
3. Administration of prolongs 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 empty-ing 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.

4. The gastro retentive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.
5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, 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.
6. FDDS improves patient compliance by decreasing dosing frequency.
7. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.
8. Better therapeutic effect of short half-life drugs can be achieved.
9. Gastric retention time is increased because of buoyancy.
10. Enhanced absorption of drugs which solubilise only in stomach.
11. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
12. Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.

Disadvantages of FDDS[27, 28, 29]

1. 1. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
2. Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
3. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
4. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS

Various parameters that need to be evaluated in gastroretentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential

scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed.

1. Buoyancy / Floating Test[30, 31]

The test for buoyancy is usually determined in 900 mL of simulated gastric (HCl/NaClwith 0.02% Tween 80, pH 1.2) or intestinal fluids (KH2PO4/NaOH buffer with 0.02% Tween 80, pH 7.4) maintained at 370C using the USP dissolution apparatus. These fluids simulate the surface tension of human gastric juice (35–50 mN/m2).The amount of time the dosage form floats is termed the floating time. In the case of floating microparticles, the number of floating particles and the time during which they remain buoyant on the test solution can be determined. The floating process depends on the balance between the weight and volume of the dosage form. An increase in the buoyancy force caused by the increased volume causes a resultant weight increase and leads to dosage-form flotation.

2. Swelling Study[30, 31]

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation:

$$WU = \frac{(W1 - W0)}{W0} \times 100$$

Wt= Weight of dosage form at time t.

W0 = Initial weight of dosage form

3. In Vitro Drug Release Studies[30, 31, 32]

The test for buoyancy and in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37oC. In practice, floating time is determined by using the USP dissolution apparatus containing 900ml of 0.1 HCl as a testing medium maintained at 37oC. The time required to float the HBS dosage form is noted as floating (or floatation) time.

Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replenished with the same volume of fresh mediumeach time, and then analyzed for their drug contents after an appropriate dilution.

4. In vivo methods

a) X-Ray method/gamma-Scintigraphy[32,33]

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form now a days. It helps to locate dosage form in the g.i.t. and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radioopaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radio-nucelide in a formulation allows indirect external observation using a γ- camera or scintiscanner41. In case of γ- scintigraphy, the γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract.

b) Pharmacokinetic studies[34]

Pharmacokinetic studies are the integral part of the in vivo studies and several works has been on that. Sawicki studied the pharmacokinetics of verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The tmax and AUC (0- infinity) values (3.75 h and 364.65 ng.ml-1h respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (tmaxvalue 1.21 h, and AUC value 224.22 ng.ml-1h). No much difference was found between the Cmax values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. An improvement in bioavailability has also been observed with piroxicam in hollow polycarbonate microspheres administered in rabbits.

The microspheres showed about 1.4 times more bioavailability, and the elimination half-life was increased by about three times than the free drug.

APPLICATIONS OF FDDS

1. Enhanced Bioavailability

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDFCR 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.[35]

2. Sustained drug delivery

Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the

stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is prohibited.[36]

3. Site specific drug delivery systems

These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency. Eg: Furosemide and Riboflavin.[37]

4. Absorption enhancement

Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.[38]

5. Minimized adverse activity at the colon

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This Pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam Antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism‟s resistance.

6. Reduced fluctuations of drug concentration

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.[39]

CONCLUSION

Floating drug delivery system have come forward as an efficient means of enhancing the bioavailability and controlled delivery of drugs. The advancement in delivery technology will lead to the development of large number of floating delivery system to optimize the delivery

of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism. To develop an efficient gastroretentive dosage form is a real challenge to pharmaceutical technology. Indeed, the drug delivery system must remain for a sufficient time in the stomach, which is not compatible with its normal physiology. In the future, it is expected that they will become of increasing importance, ultimately leading to improved efficiencies of various types of pharmacotherapies.

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