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GASRTORETENTIVE DRUG DELIVERY SYSTEM: AT A GLANCE

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ABSTRACT

In recent years scientific and technological advancements have been made in the research and development of oral drug delivery. Because oral route provide ease of administration. Oral sustained drug delivery has limited gastric residence times. Differences in gastric physiology, such as gastric pH and motility exhibit both intra- and inter- subject variability which has significant impact on the gastric retention time and drug delivery behavior. Because of this formulation of stomach specific dosage forms are taken into consideration. Gastro retentive drug delivery systems (GRDDS) are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Gastro retention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients. Controlled gastric retention of solid dosage form may be achieved by the mechanisms of floatation, mucoadhesion, sedimentation, expansion or by a modified shaped system. Several approaches are currently being used to prolong the GRT, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, high-density systems, and other delayed gastric emptying devices. In this review, the current and recent developments of FDDS, including patented delivery systems and marketed products, are discussed.

KEYWORDS: Floating drug delivery system, Hydrodynamically balanced system, Gastroretention, Evaluation of FDDS.

INTRODUCTION

Gastric emptying of a dosage form is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms which resides in the stomach for

longer period of time than conventional dosage forms. Gastro retentive systems can remain in gastric region for several hours and hence significantly prolong the residence time of drugs. Due to prolonged retention of drug bioavailability increases, reduce drug waste, and solubility improves for those drugs which are less soluble in the high pH environment. The controlled gastric retention of solid dosage forms can be achieved by the mechanism of mucoadhesion, floatation, sedimentation, expansion, modified systems and/or by the administration of pharmacological agents which delays gastric emptying. So floating drug delivery system seems to be the promising delivery systems for the controlled drug release.

FDDS

FDDS described by Davis in 1968. FDDS have bulk density less than gastric fluids and because of that they remain buoyant in the stomach without affecting the gastric emptying rate for the prolonged period of time. When system floats on the gastric fluid, the drug released slowly at the desired rate system eliminated from the stomach after release of the drug. This causes an increased GRT and better control of fluctuations in plasma drug concentration. The FDDS dosage forms exhibit most of the characteristics of hydrophilic matrices and are also known as Hydro dynamically balanced systems (HBS).

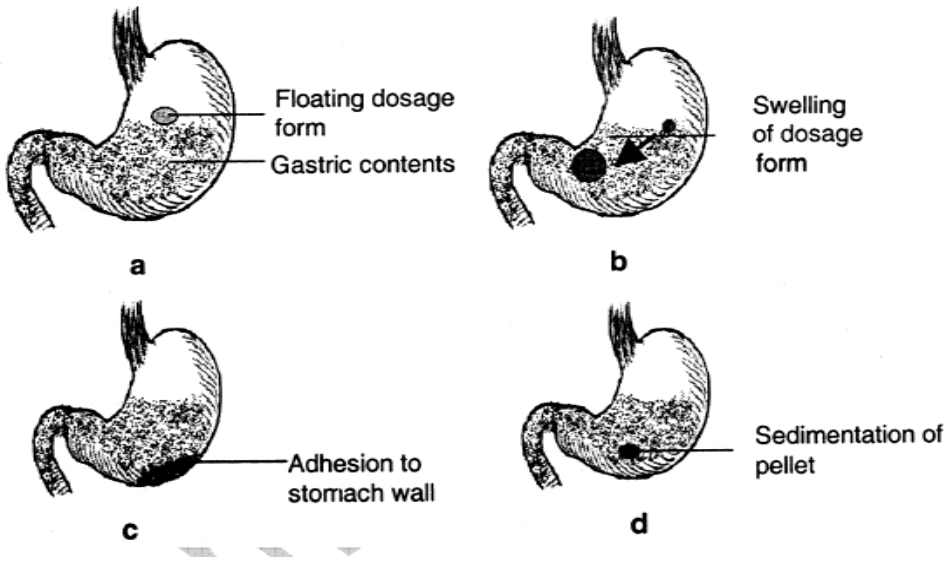

Figure 1. Approaches of gastric retention.

Since they are able to maintain their low apparent density because polymer hydrates and builds a gel like barrier at the outer surface. These forms are expected to remain buoyant in gastric content for 3-4 hours without affecting the intrinsic rate of emptying because bulk density of floating dosage form is less than the gastric content. Different hydrocolloids are

recommended for the buoyancy retention effect among them cellulose ether polymers are the most popular especially HPMC. Fatty materials with bulk density less than one may be added to the formulation to decrease the water intake rate and increase buoyancy. Many buoyant systems have been developed based on granules, powders, tablets, laminated films, and hallow microspheres. List of drugs that are formulated as FDDS is given below.

Drugs used in the formulation of floating drug delivery system

Floating microspheres: Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Tranilast, Terfinadine etc.

Floating granules: Diclofenac sodium, Indomethacin, Prednisolone etc.

Films: Cinnarizine, Albendazole etc.

Floating tablets and pills: Para amino benzoic acid, Piretanide, Theophylline, Verapamil HCl, Chlorpheniramine maleate, Aspirin, Calcium carbonate, Fluorouracil, Prednisolone, Sotalol, Pentoxyphilline and Diltiazem HCl, Acetaminophen, Acetylsalicylic acid, Amphicillin, Amoxycillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate etc.

Floating capsules: Chlordizepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid, Pepstatin, Propranolol etc.

Potential Drug Candidate for GRDDS:

1. Drugs having narrow absorption window in GIT. Ex. L-DOPA, PABA, Furosemide, Riboflavin etc.
2. Drugs which are unstable in intestinal or colonic environment. Ex. Captopril, Ranitidine HCl, Metronidazole.
3. Drug which are locally effective in the stomach. Ex. Mesoprostol, Antacid etc.
4. Drugs that disturb normal colonic microbes. Ex. Antibiotic against H. Pylori.
5. Drugs that exhibit low solubility at high pH values. Ex. Dizepam, Chlordizepoxide, Verapamil HCl.

Drugs Those Are unsuitable for GRDDS

1. Drugs having very limited acid solubility. **Ex.** Phenytoin etc.
2. Drugs which are unsuitable in the gastric environment. Ex. Erythromycin.
3. Drugs intended for selective release in the colon. Ex. 5-amino salicylic acid, Corticosteroids.

Advantages

FDDS is advantageous for drugs meant for local action in stomach. Ex. Antacids.

Floating dosage forms (Tablet and Capsules) will remain in the gastric fluid for prolonged time even at alkaline pH of intestine.

FDDS is advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a better response. Acidic substance like Aspirin causes irritation on the stomach wall when come in contact with it.

FDDS advantageous for drug absorbed through stomach. Ex. Ferrous salt, antacids.

FDDS improves patient compliance by decreasing dosing frequency.

Bioavailability enhances despite first pass effect because fluctuation in plasma drug concentration is avoided; a desirable plasma drug concentration is maintained by continuous drug release.

Better therapeutic effect can be achieved for drugs having short half-life.

Because of buoyancy gastric retention time is increased.

Absorption of drugs which are solubilize only in stomach is enhanced.

No risk of dose dumping because microspheres releases drug uniformly.

FDDS avoid gastric irritation, because of sustained release effect, floatability and uniform release of drug through multiparticulate system.

Disadvantages

Drugs having solubility and stability problem in GIT are not compatible for FDDS.

FDDS requires a high level of fluid in the stomach to float and work efficiently.

The drugs which are significantly absorbed throughout GIT and which undergo significant first pass metabolism are only desirable candidates.

Some drugs delivered by FDDS causes irritation to gastric mucosa.

The drugs which are not stable in an acidic environment of the stomach are not suitable candidate to incorporate in to the system.

Classification of gastroretentive drug delivery system:

1. 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. A density close to 2.5 g/cm^3 seems necessary for significant prolongation of gastric residence time as

barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients. Although encouraging results are reported in ruminants, effectiveness in human beings is not observed and no system has been marketed.

2. Floating systems

These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy.

2. a) Hydrodynamically balanced systems

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. HPMC is the most common used excipient, although hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), sodium carboxymethylcellulose (NaCMC), agar, carrageenans or alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, hydration and swelling of the surface polymers produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy. Incorporation of fatty excipients gives low-density formulations and reduced penetration of water, reducing the erosion.

2.b) Gas-generating systems

Floatability can also be achieved by generation of gas bubbles. CO_2 can be generated *in situ* by incorporation of carbonates or bicarbonates, which react with acid either the natural gastric acid or co-formulated as citric or tartaric acid. An alternative is to incorporate a matrix with entrapped liquid, which forms a gas at body temperature. The approach has been used for single and multiple unit systems.

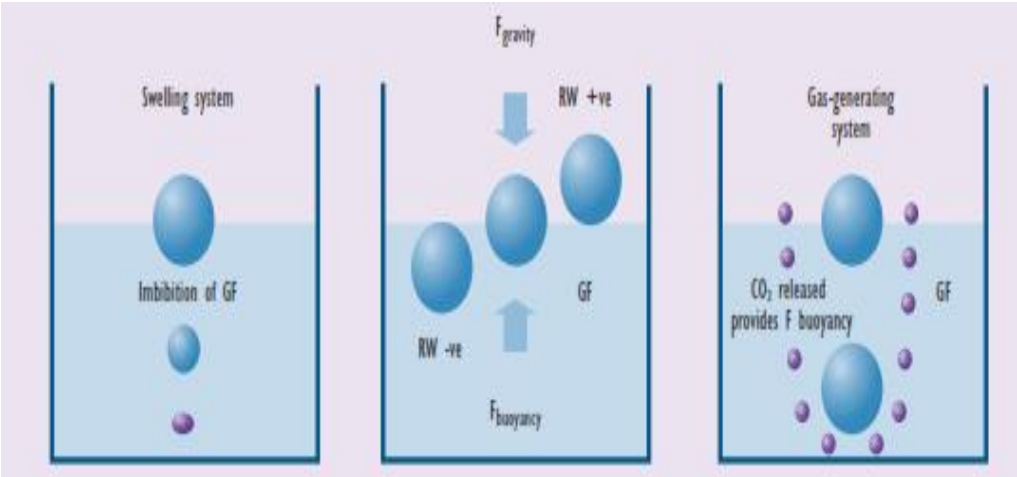

Figure 2 b. Gas generating system.

In single unit systems, such as capsules or tablets, effervescent substances are incorporated in the hydrophilic polymer and CO_2 bubbles are trapped in the swollen matrix. Bilayer or multilayer systems have also been designed. Drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers. Further refinements involve coating the matrix with a polymer which is permeable to water, but not to CO_2.The main difficulty of such formulation is to find a good compromise between elasticity, plasticity and permeability of the polymer. Multiple unit system comprises an inner effervescent layer (bicarbonate and tartaric acid) and an outer swellable membrane (polyvinyl acetate and shellac).

2.c) Raft-forming systems:

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium chloride to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment. The gels formed have bulk density less than the gastric fluids so they remain buoyant in the gastric region. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system.

2.d) Low-density systems

It involves use of low density materials, entrapping oil or air. It involves multiple unit systems such as microspheres, microballoons, microsponges etc.

2. Expandable 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, three configurations are required: a small configuration for oral intake, an expanded gastro retentive form and a final small form enabling evacuation following drug release.

Unfoldable systems are made of biodegradable polymers. The concept is to make a carrier, such as a capsule, incorporating a compressed system made of bioerodible polymer which extends in the stomach. Another approach involves use of swellable systems which are retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids. The bulk enables gastric retention and maintains the stomach in a ‘‘fed’’ state, suppressing housekeeper waves.

4. Superporous hydrogels

Though these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification. With pore size ranging between 10 nm and 10 µm, absorption of water by conventional hydrogel is a very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Superporous hydrogel, average pore size >100 µm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover, they swell to a large size and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is achieved by co-formulation of a hydrophilic particulate material, Ac-Di- Sol (croscarmellose sodium).

4. Mucoadhesive or bioadhesive systems

The basis of mucoadhesion is that a dosage form can stick to the mucosal surface by different mechanisms. Different theories are invoked to explain these mechanisms. Firstly, the electronic theory proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material. Secondly, the adsorption theory suggests that bioadhesion is due to secondary forces such as Van der Waals forces and hydrogen bonding. The wetting theory is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucus layers and finally, the diffusion theory proposes physical entanglement of mucin strands and the flexible polymer chains, or an interpenetration of

mucin strands into the porous structure of the polymer substrate. Materials commonly used for bioadhesion are poly (acrylic acid) (Carbopol/polycarbophil), chitosan, Gantrez (Polymethyl vinyl ether/maleic anhydride copolymers), cholestyramine, tragacanth, sodium alginate, HPMC, sephadex, sucralfate, polyethylene glycol, dextran, poly (alkyl cyanoacrylate) and polylactic acid.

6. Magnetic systems

This system is based on a simple idea: the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach assists in gastric retention.

Evaluation parameters of stomach specific FDDS

Different in-vitro studies exhibiting gastric retention exhibit the prolonged gastric residence in-vivo. However it should be noted that, good in-vitro floating behavior alone is not sufficient proof of efficient gastric retention in-vivo. Because the simultaneous presence of food and the complex motility of the stomach are difficult to assess, so only the in-vivo studies can provide definite prof that prolonged gastric retention obtained.

1. Measurement of buoyancy capabilities of the FDDS

Floating behavior was evaluated by using resultant weight measurements. The experiment carried out in two different media, deionized water and a simulated meal, for monitoring possible differences. The result shows that higher molecular weight polymers with a slower rate of hydration exhibit enhanced floating behavior and this is more in simulated meal medium as compare to deionized water.

2. Floating time and duration

Floating time measurement is performed in simulated gastric fluid or in 0.1mol/1HCl maintained at 37^0C in dissolution apparatus, containing 900ml 0.1mol/1HCl as dissolution medium at 37^0C. The time taken by the dosage form to float in gastric fluid is termed as the floating lag time and the time for which the dosage form floats in the gastric fluid is termed as floating time / floatation time.Recently, Gohel *et al* proposed a more relevant*in vitro* dissolution method to evaluate a floating drug delivery system (for tablet dosage forms). A 100-ml glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker could hold 70 ml 0.1 mol/l HCl dissolution medium and allowcollection of samples. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic the gastric acid secretion rate. The performance of the modified

dissolution apparatus was compared with that of USP dissolution Apparatus 2 (Paddle). A problem involving adherence of the tablets to the shaft of the paddle was observed with the USP dissolution apparatus. The tablets did not stick to the agitating device in the proposed dissolution method and the observed drug release followed zero-order kinetics. A similarity in the dissolution curves was observed between the USP method and the proposed method at a 10% difference level ($f2 = 57$). The proposed test may exhibit a good *in vitro-in vivo* correlation since an attempt was made to mimic the *in vivo* conditions, such as the gastric volume, gastric emptying, and gastric acid secretion rate.

3. Drug release

Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

4. Content uniformity, Hardness, Friability (for tablets)

5. Drug loading, Drug entrapment efficiency, Particle size analysis, Surface characterization (for floating microspheres and beads)

For assessment of drug loading the accurately weighed sample of beads or microspheres are taken and crushed and added to the appropriate dissolution medium, which then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. Percentage drug loading is a ratio of amount of drug in the sample and the weight of total beads or microspheres. Particle size and size distribution of beads or microspheres is determined by optical microscopy method in dry state. Surface characterization is done by Scanning electron microscopy (SEM).

6. X-Ray / Gamma Scintigraphy

It is a very popular evaluation parameter for floating dosage form now a days. By using X-ray / gamma scintigraphy, the dosage form can be located in GIT and by which one can predict and correlate the gastric emptying time and passage of dosage form in the GIT. Radio-opaque material is included into solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a gamma emitting radionuclide in the formulation allows indirect external observation using gamma-camera or scinti-scanner (Harries and Sharma, 1990). This technique is helpful to monitor the location of the dosage form in the GIT, because the gamma rays emitted by the radionuclide are focused on a camera (Timmermans et. al., 1989).

7. Pharmacokinetic studies

Pharmacokinetic studies are the integral part of the in-vivo studies. In pharmacokinetic study of any of the pellets containing drug filled into a capsule and compared with the conventional tablet. Cmax, Tmax and AUC valuesof both the forms are compared. Tmax and AUC of pellets containing drug in capsule is higher than conventional tablet, and no much more difference for Cmax was found. So this suggest that the bioavailability of the floating pellets is improved.

Future Potential

FDDS can be used for various active agents having narrow absorption window like antiviral, antifungal and antibiotics (quinolones, sulfonamides, penicillin, cephalosporine, aminoglycosides, tetracyclines). Some unresolved critical issues related to the rational development of FDDS includes quantitative development of FDDS systems in both conditions (fasted and fed), and correlation between prolonged GRT and sustained release characteristics. Promising area of research for gastro retentive drug delivery system is eradication of H. pylori, which causes gastritis and peptic ulcer because complete eradication of microorganisms requires high concentration of antibiotics for prolongrd period of time. This drug delivery system can be used in the oral drug delivery of proteins and peptides such as calcitonin, erythropoietin, vasopressin, insulin, heparin etc, so that the continuous supply of drug to its more efficient site can be achieved.

CONCLUSION

GRDDS comprised of mainly floating, bioadhesive, swelling, high density and magnetic systems used to enhance bioavailability of the drug and controlled delivery of the drugs that exhibit an narrow absorption window, low bioavailability and extensive first pass metabolism. By prolonging the gastric emptying time of the dosage form, controlled release of the dosage form and optimal absorption both can be achieved. Thorough understanding of the physicochemical properties of the drugs, physiological events of the GIT and formulation strategies are the important aspects in designing GRDDS.

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