JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

A Review on Gastroretentive Drug Delivery System

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ABSTRACT:

Gastroretentive drug delivery system comprised mainly of floating, bioadhesive, swelling, high density and magnetic systems have emerged as a current approaches of enhancing the bioavailability and controlled delivery of drugs that exhibit an absorption window. By prolonging the gastric emptying time of the dosage form, these systems not only provide controlled release of the drug for a prolonged period but also present the drug in an absorbable form at regions of optimal absorption. CR-GRDF provides a means to utilize all the pharmacokinetic (PK) and pharmacodynamic (PD) advantages of controlled release dosage forms for such drugs. Due to the complexity of pharmacokinetic and pharmacodynamic parameters, *in vivo* studies are required to establish the optimal dosage form for a specific drug. For a certain drug, interplay of its pharmacokinetic and pharmacodynamic parameters will determine the effectiveness and benefits of the CRGRDF compared to the other dosage forms.

KEYWORDS: floating, bioadhesive, swelling, high density and magnetic systems

Article history:
Received 18 Apr 2012
Accepted 05 May 2012
Available online 13 Jun 2012

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INTRODUCTION:

1. GASTRORETENTIVE TECHNIQUES

GRDDS prepared by using following methods: [1]

- By using gel forming hydrocolloids such as hydrophilic gums, gelatin, alginates, cellulose derivatives, etc.
- By using low density enteric materials such as methacrylic polymer, cellulose acetate phthalate.
- By reducing particle size and filling it in a capsule.
- By forming carbon dioxide gas and subsequent entrapment of it in the gel network.
- By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.
- By incorporation of inflatable chamber which contained in a liquid e.g. solvent that gasifies at body temperature to cause the chambers to inflate in the stomach.

Various techniques were used to encourage gastric retention of an oral dosage form as follow:

1.1 Floating drug delivery system,

1.2 Bio / Mucoadhesive systems,

1.3 Swelling/ Expanding Systems,

1.4 High-density systems (sedimentation/sinking system)

1.5 Magnetic systems

1.1 Floating drug delivery system: [2-8]

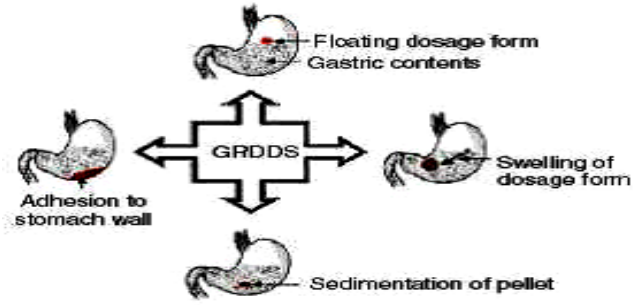

Figure 1: Classification of gastroretentive drug delivery system

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

1.1.1 Effervescent System, and
1.1.2 Non-Effervescent System.

1.1.1 Effervescent System:

Effervescent systems include use of gas generating agents, carbonates(ex. Sodium bicarbonate) and other organic acid(e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide(CO_2) gas, thus reducing the density of system and making it float on the gastric fluid.

These effervescent systems further classified into two types.

1.1.1.A Gas generating systems
1.1.1.B Volatile liquid/Vacuum systems.

1.1.1.A Gas-generating Systems:
Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS):

These are as shown in Figure 2 and formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. This leads to an increase in the gastroretention time and a better control over fluctuation in plasma drug concentration.

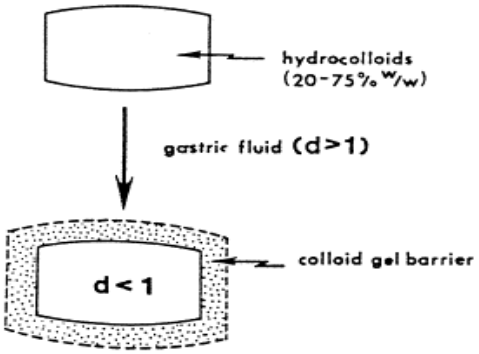

Figure 2: Intragastric floating tablet

Intra Gastric Bilayer Floating Tablets:

These are also compressed tablet as shown in Figure 3 and containing two layer i.e.,

- Immediate release layer
- Sustained release layer.

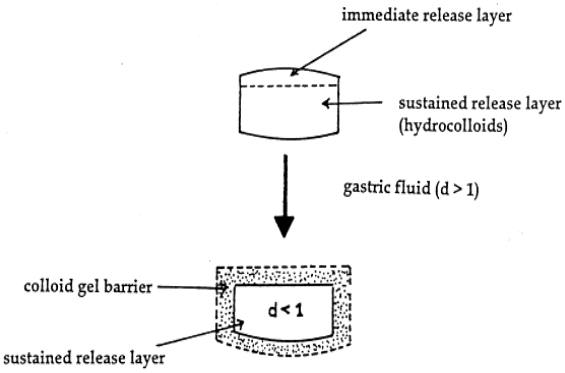

Figure 3: Intragastric floating bi-layer tablet

Multiple Unit type floating pills:

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. This lower density is due to generation and entrapment of CO_2 within the system.

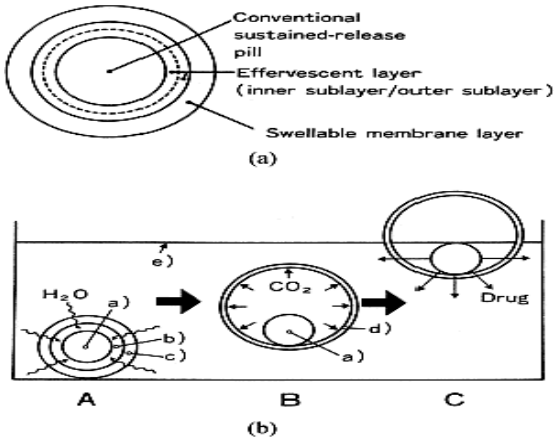

Figure 4: (a) multiple-unit oral floating dosage system. (b) Stages of floating

Mechanism

1.1.1.B Volatile Liquid / Vacuum Containing Systems:

Intragastric Floating Gastrointestinal Drug Delivery System:

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment, as shown in Figure 5

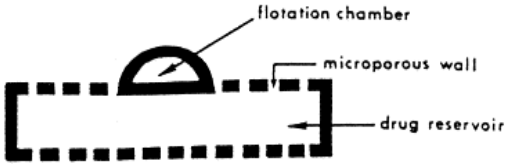

Figure 5: Intragastric floating drug delivery device

Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The system is shown in Figure 6

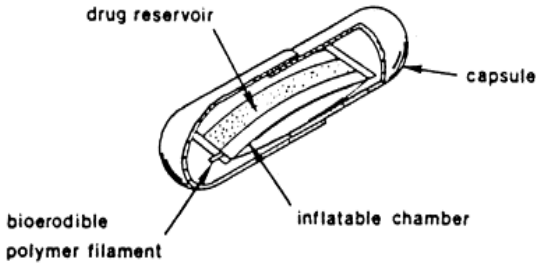

Figure 6: Gastro-inflatable drug delivery device

Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery device .In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device contains a liquid that gasifies at body temperature to inflate the bag, given in figure 7

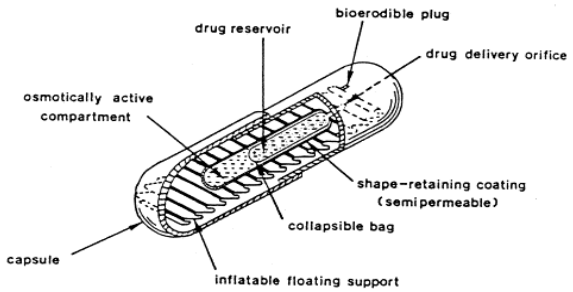

Figure 7: Intragastric osmotic controlled drug delivery system

1.1.2 Non-Effervescent System:

The non effervescent FDDS 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, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The various types of this system are as follows:

Single Layer Floating Tablets:

They are formulated by intimate mixing of drug wit gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

Bilayer Floating Tablets:

A bilayer tablet contain two layer immediate release layer which release 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.

Raft systems incorporate alginate gels:

Raft forming systems have received much attention for the drug delivery for gastrointestinal infections and disorders. Usually, the system ingredients includes a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids.

Hollow Microspheres:

Hollow microspheres (microballons), loaded with drug in their outer polymer shells were prepared by a novel emulsion solvent diffusion method. The ethanol:dichloromethane solution of drug and enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 400 C. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro.*

1.2 Bio / Mucoadhesive systems: [9]

Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and increase the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane.

Mucus is a viscoelastic, gel-like, stringy slime comprised mainly of glycoproteins. The primary function of mucus is to protect the surface mucosal cells from acid and peptidases

The epithelial adhesive properties of mucin are well known and have been applied to the development of GRDDS through the use of bio/mucoadhesive polymers. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving bioavailibility.

A bio/mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bioadhesive polymer) or the mucus lining of the GIT (mucoadhesive polymer). The characteristics of these polymers are molecular flexibility, hydrophilic functional groups, and specific molecular weight, chain length, and

conformation.The binding of polymers to the mucin-epithelial surface can be subdivided into three broad categories:

1.2.1 Hydration-mediated adhesion
1.2.2 Bonding-mediated adhesion
1.2.3 Receptor-mediated adhesion

1.2.1 Hydration-mediated adhesion:

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

1.2.2 Bonding-mediated adhesion:

The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Physical-mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., van der waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

1.2.3 Receptor-mediated adhesion:

Certain polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx.

1.3 Swelling/ Expanding Systems: [9]

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter.

The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration.

1.4 High-density systems (sedimentation/ sinking system): [9]

Gastric contents have a density close to water. When high density pellets is given to the patient, it will sink to the bottom of the stomach and are entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. The only major drawbacks with this systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm^3.

1.5 Magnetic systems: [9]

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. Ito et al.used this technique in rabbits with bioadhesives granules containing ultrafine ferrite (g-Fe_2O_3). They guided them to the oesophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 hr.

2. MATERIALS [1]

Following types of the ingredients can be incorporated in to HBS dosage form:

Hydrocolloids

Suitable hydrocolloids are synthethics, anionic or non ionic like hydrophilic gums, modified cellulose derivatives. E.g. Acacia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used.

Release rate accelerant

The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5-60% by weight.

Buoyancy increasing agents

Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80 % by weight.

Excipients

Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

3. Evaluation

3.1 Evaluation of powder blend: [10]

3.1.1 Angle of repose:

Lower the angle of repose, better the flow properties. The angle of repose may be calculated by measuring the height (h) of the pile and the radius of the base(r) with ruler.

$$\text{Tan } \theta = h/r \qquad \text{..... (1)}$$

3.1.2 Bulk density:

$$\text{Bulk Density} = W/BV \qquad \text{..... (2)}$$

Where, W = Weight of powder,
BV = Bulk Volume

3.1.3 Percentage porosity:

Porosity provides information about hardness, disintegration, total porosity etc.

$$\% \text{ porosity} = v.v / _{B.V} * 100 \quad \text{.....(3)}$$

$$\% \text{ porosity} = (^{B.V. - T.V.} / _{T.D.}) * 100 \quad \text{.....(4)}$$

Where,V.V. – void volume, B.V.- bulk volume, T.V.- true volume, T.D.- true density.

3.2 Evaluation of granules: [11]

3.2.1 Flow Properties of Granules:

The flow properties of granules (before compression) were characterized in terms of angle of repose, Carr index and Hausner ratio

$$HR = \rho t/\rho b \quad \text{.....(5)}$$

$$IC = (\rho t - \rho b)/\rho t \quad \text{.....(6)}$$

Where ρb -Bulk density, ρt -tapped density, HR -Hausner ratio and IC -carr index.

3.3 Evaluation of floating tablets: [12,13,14]

3.3.1 Measurement of buoyancy capabilities of the FDDS:

The experiment is carried out in two different media, de-ionized water and simulated meal. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behavior and it was observed more in simulated meal medium compared to de-ionized water.

3.3.2 *In Vitro* floating and dissolution behavior:

A small, loose piece of nonreactive material with not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float.

3.3.3 Weight variation:

The USP provides the weight variation test by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit, and if no tablet differs by more than 2 times the percentage limit.

3.3.4 Hardness & Friability:

Conventional compressed tablets that lose less than 0.5 to 1.0 % of their weight are generally considered acceptable.

3.3.5 Particle size analysis, surface characterization (for floating microspheres and beads):

The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM).

3.3.6 X-Ray:

It helps to locate dosage form in the gastrointestinal tract (GIT), 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 radio-opaque material into a solid dosage form enables it to be visualized by X-rays.

3.3.7 Pharmacokinetic studies:

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).

3.4 Evaluation of bioadhesive system: [15]

The bioadhesive strength of a polymer can be determined by measuring the force required to separate the polymer specimen sandwiched between the layers of either an artificial (e.g., cellophane) or biological (e.g., rabbit stomach tissue) membrane. This force can be measured by using a modified precision balance or an automated texture analyzer.

3.5 Evaluation of swelling systems: [16]

3.5.1 Weight gain and water uptake (WU):

The study is done by immersing the dosage form in simulated gastric fluid at 37^0C and determining these factors at regular intervals. The dimensional changes can be measured in terms of the increase in tablet diameter and/or thickness over time. WU is measured in terms of percent weight gain, as given by the equation 7

WU = ([W.sub.t] - [W.sub.0]) x 100/[W.sub.0] …….(7)

Where [W.sub.t] and [W.sub.0] are the weights of the dosage form at time t and initially

3.5.2 Gastroretention:

The inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. The use of X-rays involves exposing a patient to an X-ray beam, thus permitting the visualization of the GI transit of the dosage form.

3.5.3 Dissolution/drug release:

The major requirement for the dissolution test is to allow a dosage form to sink to the bottom of the vessel before the rotation of the paddle.

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