A REVIEW ON GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

This review explains the recent advances in gastroretentive drug delivery systems with special focus on floating drug delivery systems. Oral route is the most convenient and painless technique of drug delivery. Gastroretentive drug delivery systems have been developed which overcome physiological conditions in gastrointestinal tract such as short gastric resident time (GRT) and unpredictable gastric emptying times (GET). Various approaches used for prolonging GRT are mucoadhesive systems (Bioadhesive Systems), High Density Systems, Expandable Systems (Swelling Systems), Floating Drug Delivery systems (FDDS). formulations of floating tablets were prepared using direct compression technique with low viscosity polymer such as HPMC K100LV, high viscosity polymers such as HPMC K4M, K15M, and carbopol in different ratios. The evaluation results revealed that all formulations comply with the specification of official pharmacopoeias and/or standard reference with respect to general appearance, content uniformity, hardness, friability and buoyancy. Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. Incorporation of the drug in a controlled release gastroretentive dosage forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices.

Key words:-Gastric retention time, Gastro retentive systems; floating drug delivery system; Effervescent; non effervescent.
INTRODUCTION
Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulation, require frequent dosing. To avoid this problem, the oral controlled release (CR) formulations have been developed in an attempt to release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation. Therefore, prolonged gastric retention is important in achieving control over the GRT because this helps to retain the CR system in the stomach for a longer time in a predictable manner. The development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in systemic circulation for a long time. These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine).

The residence time of the dosage form in the stomach depends upon various factors like pH, size of the dosage form, food intake, and biological factors which include age, body mass index, gender, posture, and diseased states (hepatic failure, diabetes, chronis disease). Other techniques for gastro retentive dosage forms involve swelling, mucoadhesion, sedimentation, microballoons and low density systems. Out of all systems available, the floating beads, floating tablets and floating microspheres have gained major importance. FDDS possess lower bulk density than the gastric fluid exerting buoyancy in the stomach leading to slow drug release in an extended manner before it reaches absorption window.

In this present formulation, dual benefits of buoyancy as well as sustained action is achieved with an intention to maintain the steady state of drug release. Hydrophilic matrix system is one of the easiest approaches for developing modified and sustained release dosage forms. A polymer like hydroxyl propyl methyl cellulose (HPMC) function as a pH independent Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems. Thus the real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs for more than 12h but to prolong the residence time of dosage forms in the stomach or somewhere in the upper small intestine or until all the drug is retained for the desired period of time. Therefore, it is desirable, to
formulate a controlled release dosage form that gives an extended GI residence time. Extended release dosage forms with prolonged residence time in stomach are highly desirable for drugs: that are locally active in stomach, that have an absorption window in the stomach or in the upper small intestine, that are unstable in the intestinal or colonic environment, have low solubility at high pH values. The single-unit floating systems are more popular but have a disadvantage owing to their "all-or-nothing" emptying process leading to high variability of the gastrointestinal transit time. Still, the multiple-unit dosage forms may be better suited because they are claimed to reduce the inter subject variability in absorption and lower the probability of dose dumping. Such a dosage form can be distributed widely throughout the gastrointestinal tract (GIT), affording the possibility of a longer lasting and more reliable release of the drug from the dosage form. [1,2,3]

Objective
The present study attempts to give an insight into the gastro retentive drug delivery systems, and gastric floating tablets, in particular. These have attracted the interest of many formulators due to their advantages over the conventional drug delivery systems, recently. The study highlights these advantages with reference to the various types of gastro retentive drug delivery systems, as well as provides an overview of the recent advances that have taken place in this arena. [14]

BASIC PHYSIOLOGY OF STOMACH

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas
PHYSIOLOGICAL PROBLEMS

Gastric emptying

It is well recognized that the stomach may be used as a ‘depot’ for controlled-release (CR) dosage forms, both in human and veterinary applications. The stomach is anatomically divided into three parts: fundus, body, and antrum (or pylorus). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying. The oral route is the first-pass effect, which leads to reduced systemic bioavailability of a large number of drugs. Overall, the relatively brief GI transit time of most drug products, which is approximately 8–12 h, impedes the formulation of a once daily dosage form for most drugs. These problems can be exacerbated by alterations in gastric emptying that occur due to factors such as age, race, sex, and disease states, as they may seriously affect the release of a drug from the DDS. It is, therefore, desirable to have a CR formulation’s that exhibits an extended GI residence and a drug release profile independent of patient related variables.

Methods

Effervescent Floating tablets containing Amlodipine besylate were prepared by direct compression technique using varying concentrations of different grades of polymers with Sodium bicarbonate and citric acid. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except Magnesium stearate all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, Magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine. The weights of the tablets were kept constant for all formulation.

Approaches to design floating dosage forms

Two types of floating systems are available. These are single unit dosage forms and multiple unit dosage forms. Single-unit dosage forms are exemplified by hydrodynamically balanced systems capsules and floating tablets. Multiple unit dosage forms include hollow microspheres (microballoons), granules, mini-tablets and pellets. In listed below represented
the multiple-unit effervescent (gas generating) oral floating drug delivery system and similarly represented the working of a triplelayer system.[14]

CHARACTERIZATION OF FDDS

Flow properties

The flow properties of powder blend (before compression) were characterized in terms of angle of repose, Carr index and Hausner ratio. For determination of angle of repose (θ), the powder blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The powder blend was poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The tan-1 of (height of the pile / radius of its base) gave the angle of repose.

Powder blend were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess powders were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated. Hausner ratio (HR) and Carr index (IC) were calculated according to the two equations given below:

HR = ρt/ρb
IC = (ρt– ρb)/ρt

Hardness and friability test

The crushing strength (Kg/cm²) of tablets was determined by using Monsanto type hardness tester. Friability was determined by weighing 10 tablets after dusting, placing them in the friabilator (Roche Friabilator) and rotating the plastic cylinder vertically at 25 rpm for 4 min. After dusting, the total remaining weight of the tablets was recorded and the percent friability (PF) was calculated using formula.

PF = (Weight original – Weight final) / Weight original X 100.

Uniformity of weight and drug content

Uniformity of weight was determined with the help electronic balance. Uniformity of drug content was determined by taking 5 tablets in a glass mortar and powdered; 100 mg of this powder was placed in a 100 mL stoppard conical flask. The drug was extracted in double distilled water with vigorous shaking on a mechanical shaker (100 rpm) for 5 hours and filtered into 50 Ml volumetric flask through cotton wool and filtrate was made up to the mark.
by double distilled water through filter, further appropriate dilution were made and absorbance was measured at 256 nm using double distilled water as blank solution by UVVisible double beam spectrophotometer (EI, India).[4]

Classification Of Floating System

FLOATING DRUG DOSAGE SYSTEM
1. Single Unit Floating Dosage Systems
   a) Effervescent system
2. Multiple Unit Floating Systems
   b) Non effervescent system
   c) Hollow microsphere
3. Raft forming GF system

1). Single Unit Floating Dosage Systems
a) Effervescent systems: Effervescent floating drug delivery systems generate gas (CO2), thus reduce the density of the system, and remain buoyant in the stomach for a prolonged period of time and release the drug slowly at a desired rate. The main ingredients of effervescent system include swell able polymers like chitosan, methyl cellulose and effervescent compounds such as citric acid, sodium bicarbonate, citric acid and tartaric acid (11). Penners et al prepared an expandable tablet containing mixture of polyvinyl lactams and polyacrylates that swells rapidly in an aqueous environment and thus, stays in stomach over an extended period of time. In addition to this, gas-forming agents were also incorporated so as soon as the gas Formed, the density of the system was reduced and thus, the system tended to float in the gastric environment (12). M.Jaimini et al. prepared the effervescent floating tablet of famotidine. They found that the addition of gel-forming polymer methocel (K100 and K15M) and gas-generating agent sodium bicarbonate along with citric acid was essential to achieve in vitro buoyancy. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed 13.

b) Non effervescent system
Non-effervescent systems commonly use gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid (14). Prior to formulation of floating tablets, nimodipine was incorporated into poloxamer-188 solid
dispersion after which it was directly compressed into floating tablets. It was observed that by increasing the HPMC and decreasing the PEG 6000 content, a decline in in vitro release of nimodipine occurred. The main drawback of such system is “all or none” phenomenon. In such cases, there is a danger of passing of the dosage form to intestinal part at the time of house-keeper waves. To overcome this difficulty multiple, unit dosage forms are designed 15.

2) Multiple Unit Floating Systems

Multiple unit dosage forms may be an attractive alternate since they have been shown to reduce inter and intra-subject variability’s in drug absorption as well as to lower the possibility of dose dumping. Various multiple unit floating systems have been developed in different forms, and using principles such as air compartment multiple unit system, hollow microspheres prepared by emulsion solvent diffusion method, beads prepared by emulsion gelation method. Use of effervescent and swellable polymer is another approach for preparing multiple unit FDDS 16.

a) Effervescent System

Ichikawa et al developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into two sublayers to avoid direct contact between the two agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37°C, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO2 was generated by the neutralization reaction between the two effervescent agents, producing swollen pills (like balloons) with a density less than 1.0/ml.

b) Non effervescent systems:Not many reports were found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio17.
c) Hollow Microspheres
Both natural and synthetic polymers have been used to prepare floating microspheres. Joseph et al. Developed a floating dosage form of piroxicam based on hollow polycarbonate microspheres. The microspheres were prepared by the solvent evaporation technique. Encapsulation efficiency of ~95% was achieved. *In vivo* studies were performed in healthy male albino rabbit.

3) Raft forming GF system
Raft forming systems have received much attention for the drug delivery for gastrointestinal 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 CO2. Usually, the system ingredients includes a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids. Jorgen et al described an antacid raft forming floating system. The system contains a gel forming agent (e.g. sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), which when comes in contact with gastric fluids, the raft floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) intomthe esophagus by Acting as a barrier between the stomach and esophagus Jorgen et al described an antacid raft forming floating systems.

**CURRENT APPROACHES TO GRDDS**
1. Floating drug delivery systems (FDDS)
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. FDDS are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. Floating systems can be classified as effervescent and noneffervescent systems.

i) Effervescent systems
These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. Flotation of a drug delivery system in the stomach can be achieved by
incorporating a floating chamber filled with vacuum, air, or an inert gas. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the CO2 produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float. Recently a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed.

ii) Noneffervescent systems

Noneffervescent systems incorporate a high level (20–75% w/w) of one or more gel-forming, highly swellable, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose [HPMC], and sodium carboxymethylcellulose), polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules. Upon coming into contact with gastric fluid, these gel formers, polysaccharides, and polymers hydrate and form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density of and confers buoyancy to the dosage form.

2. Bio Mucoadhesive systems

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. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving bioavailability. A bio mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bio-adhesive 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. Furthermore, they must be nontoxic and non-absorbable, form noncovalent bonds with the mucin–epithelial surfaces, have quick adherence to moist surfaces, easily incorporate the drug and offer no hindrance to drug release, have a specific site of attachment, and be economical. The binding of polymers to the mucin-epithelial surface can be subdivided into three broad categories.
a. Hydration-mediated adhesion
b. Bonding-mediated adhesion

a. Hydration-mediated adhesion
Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

b. 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., vander Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyland carboxylic groups.

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.

4. Swelling/ Expanding Systems
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.

These polymeric matrices remain in the gastric cavity for several hourseven in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. As dosage form coming in contact with gastric fluid, the polymer imbibes water and swells. 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.
5. High-density systems
Gastric contents have a density close to water (~1.004 g/cm³). 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. Sedimentation has been employed as a retention mechanism for high density systems. A density ~3 g/cm³ seems necessary for significant prolongation of gastric residence time. Barium sulphate, zinc oxide, iron powder, titanium dioxide may be used to formulate such high density systems due to their high density. 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/cm³.

6. Magnetic systems
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-Fe₂O₃). 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 h.

7. Raft systems
Raft systems incorporate alginate gels these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating.⁷,¹²

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORM
The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include

1) Density of dosage forms
Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/cm³ is required to exhibit floating property.

2) Shape and size of the dosage form
In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum. Dosage forms having a diameter of more than 7.5 mm show a better gastric
residence time compared with one having 9.9 mm. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.

3) **Food intake and its nature**
Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the GIT influences the GRT of the dosage form. Usually the presence of food in the GIT improves the GRT of the dosage form. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms.

4) **Fed or Unfed state**
Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

5) **Caloric content**
GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

6) **Frequency of feed**
The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

7) **Gender**
Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

8) **Age**
Elderly people, especially those over 70, have a significantly longer GRT.

9) **Posture**
GRT can vary between supine and upright ambulatory states of the patient.

10) **pH**
The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large
volume of water administered with an oral dosage form raises the pH of stomach contents to 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.15

11) Volume
The resting volume of the stomach is 25 to 50 ml. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is Faster.11,10

Advantages of FDDS
1. The Floating systems are advantageous for drugs meant for local action in the Stomach e.g. Antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
3. The Floating systems are advantageous for drugs absorbed through the stomach. V. E.g. Ferrous salts, antacids.
4. 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 emptying of the stomach contents.
5. 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.
6. FDDS provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
7. Certain types of drugs can benefit from using FDDS.

These include:
a) Drugs acting locally in the stomach.
b) Drugs those are primarily absorbed in the stomach.
c) Drugs those are poorly soluble at an alkaline pH
d) Drugs with a narrow window of absorption.
e) Drugs absorbed rapidly from the GI tract.
f) Drugs those degrade in the colon
Disadvantages of FDDS

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Some drugs present in the floating system causes irritation to gastric mucosa.[8,11]

I. Pre-Compression Evaluation Parameters

(a) Angle of Repose

The angle of repose of powder blend was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using following formula.

\[ \tan \theta = \frac{h}{r} \]

Where, h and r are the height and radius of the powder cone.

(b) Bulk density

Both loose bulk density (LBD) and tapped bulk density (TDB) was determined. A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

\[ \text{LBD} = \frac{\text{Weight of powder blend}}{\text{Untapped volume of packing}} \]
\[ \text{TDB} = \frac{\text{Weight of powder blend}}{\text{Tapped volume of packing}} \]

(c) Tapped density

A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further
change in volume was 15,16 noted. Tapered density was calculated using the following equations.

\[ \text{Tapped density} = \frac{W}{V_f} \]

Where, \( W \) = wt. of powder, \( V \) = final volume. 

(d) Compressibility index

The Compressibility Index of the powder blend was determined by Carr’s compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr’s Index is as below:

\[ \text{Carr’s index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100 \] \[ ^{[4,5]} \]

II. Post-Compression Parameters

(a) Tablet Dimensions

Thickness and diameter of five tablets randomly selected were measured using vernier calipers. The Pharmacopoeia states that the extent of deviation in a batch of tablet should not exceed the limit of ± 5% of their determined standard values.

(b) Hardness Test

The crushing strength kg/cm of prepared tablets was determined for tablets of each batch by Monsanto tablet hardness tester. Hardness indicates the ability of a tablet to withstand mechanical shocks while handling.

(c) Friability Test

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets randomly selected were initially weighed (W initial) and 0 transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W final). The percentage friability (%F) was then calculated by

\[ \%F = (1 - \frac{W}{W'}) \times 100 \]

Where, \( W \) = weight of tablet before test, 0
\( W' \) = weight of tablet after test.

(d) Weight Variation Test

Twenty tablets were selected randomly from each batch and weighed individually using electronic balance to check for weight variation.
(e) Drug Content Estimation

Ten tablets were randomly selected and powdered. A quantity of powder equivalent to 60 mg of diltiazem hydrochloride was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in 0.1 N HCl and the volume was made with 0.1 N HCl (pH 1.2). The flask was shaken on a flask shaker for 24 h and was kept for 12 h for the sedimentation of undissolved materials. The solution was filtered through Whatman filter paper. 1 ml of the above solution was transferred to a 100 ml volumetric flask and diluted to 100 ml with 0.1 N HCl and the absorbance was measured at 236 nm using UV / visible spectrophotometer (Shimadzu UV – 1600/1700).

The percentage of diltiazem hydrochloride was determined using calibration curve.

(f) In Vitro Buoyancy Test

The prepared tablets were subjected to in vitro buoyancy test by placing them in 250 ml beaker containing 200 ml of 0.1 N HCl (pH 1.2, temp. 37±0.5 °C). The time between introduction of the dosage form and its buoyancy in the medium and the floating durations of tablets was calculated for the determination of lag time and total buoyancy time by visual observation. The Time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

(g) In Vitro Dissolution Studies

The dissolution study was carried out using USP II (paddle method) apparatus in 900 ml of 0.1 N HCl (pH 1.2) for 12 h. The temperature of the dissolution medium was kept at 37±0.5 °C and the paddle was set at 100 rpm. 10 ml of sample solution was withdrawn at specified interval of time and filtered through Whatman filter paper. The sample was replaced with fresh dissolution medium. The sample diluted to a suitable concentration with 0.1 N HCl.

(h) Stability Studies

The stability studies of all the formulations were studied at different temperatures using the reported standard procedure. The tablets were wrapped in aluminum foil and placed in Petri dishes. These containers were stored at ambient humid conditions, at room temperature (27 ±2 °C), oven temperature (40 ± 2 °C) and in refrigeration temperature (7 ± 2 °C) for a period of 8 weeks.[6,9]
CONCLUSION
Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Dosage forms with a prolonged GRT will bring about new and important therapeutic options. The currently available polymer-mediated Noneffervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. Number of commercial products and patents issued in this field are the evidence of its. The FDDS become an additional advantage for drugs that are absorbed primarily in the upper part of GI tract, i.e., the stomach, duodenum, and jejunum. Some of the unresolved, critical issues like the quantitative efficiency of floating delivery systems in the fasted and fed states, role of buoyancy in enhancing GRT of FDDS and more than that formulation of an ideal dosage form to be given locally to eradicate H.Pylori, responsible for gastric ulcers worldwide. Due to the complexity of pharmacokinetic and pharmacodynamic parameters, in vivo studies are required to establish the optimal dosage form for a specific drug. Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will ensure the development of increase number of gastroretentive drug delivery to optimize the delivery of molecules that exhibits absorption window, low bioavailability of extensive first pass metabolism.

REFERENCE


9. M Seth, DS Goswami, H Dhaliwal, N Uppal, S Kashyap and KD Sharma, design and characterization of floating tablets of anti-diabetic drug international journal of research in pharmacy and chemistry 2013, 3(3) 605-611

10. V.K Sharma, meloxicam loaded floating sustained release matrix tablet journal of advanced pharmacy education & research (2012) 2 (1) 18-24


12. Ganesh N. S., Suraj Mahadev Ambale, Ramesh B., Kiran B. Deshpande an overview on limitations of gastroretentive drug delivery system, may – june 2011; volume 8, issue 2, article-023,133-139
