WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 4, Issue 4, 1439-1460. Review Article ISSN 2277– 7105

FLOATING DRUG DELIVERY SYSTEM: AN OVERVIEW

Kalyani Y Kshirsagar*, D.M. Shinkar and R.B.Saudaagar

Department of Pharmaceutics, R.G Sapkal College of Pharmacy, Anjaneri Nashik 422213, Maharashtra, India.

Article Received on
04 Feb 2015,

Revised on 01 March 2015,
Accepted on 26 March 2015

***Correspondence for Author**
Kalyani Y Kshirsagar
Department of Pharmaceutics, R.G Sapkal College of Pharmacy, Anjaneri Nashik 422213, Maharashtra, India.

ABSTRACT

Management of illness through medication is entering a new era in which growing number of novel drug delivery systems are being employed and are available for therapeutic use. Oral sustained release gastro-retentive dosage forms (GRDFs) offer many advantages for drugs with absorption from upper parts of gastrointestinal tract and for those acting locally in the stomach, improving the bioavailability of the medication. Floating Drug Delivery Systems (FDDS) is one amongst the GRDFs used to achieve prolonged gastric residence time. The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and applications of these systems.

KEYWORDS: Floating drug delivery systems, Approaches of fdds, Factors of floating dosage form, mechanism, type of fdds, evaluation.

INTRODUCTION

Drug delivery systems are used for maximizing therapeutic index of the drug and also for reduction in the side effects. Oral route remains the prefer route for the administration of therapeutic agents because low cost of therapy and ease of administration leads to higher level of patient compliance. Approximately 50% of the drug delivery systems available in the

market are oral drug delivery system. The oral route is considered as the most promising route of the drug delivery and effective oral drug delivery may depend upon many factors such as gastric emptying process, gastrointestinal transit time of the dosage form, drug release from the dosage form and site of absorption of drug. The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. Although a lot of advancements have been seen in oral controlled drug delivery system in the last few decades, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). To modify the GI transit time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of pharmaceuticals is highly variable and dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence time usually ranges between 5 minutes to 2 hours. In the fasted state the electrical activity in the stomach – the interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and the transit of dosage forms. It is characterized by four Phases.

Phase I– Period of no contraction (30-60 minutes)
Phase II– Period of intermittent contractions (20-40 minutes)
Phase III– Period of regular contractions at the maximal frequency also known as housekeeper
wave (10-20 minutes)
Phase IV– Period of transition between Phase III and Phase I (0-5 minutes)

APPROACHES OF GRDDS: To formulate a successful stomach specific or gastroretentive drug several techniques are currently used such as:

a) Hydrodynamically balanced systems (HBS)

1. Hydrodynamically

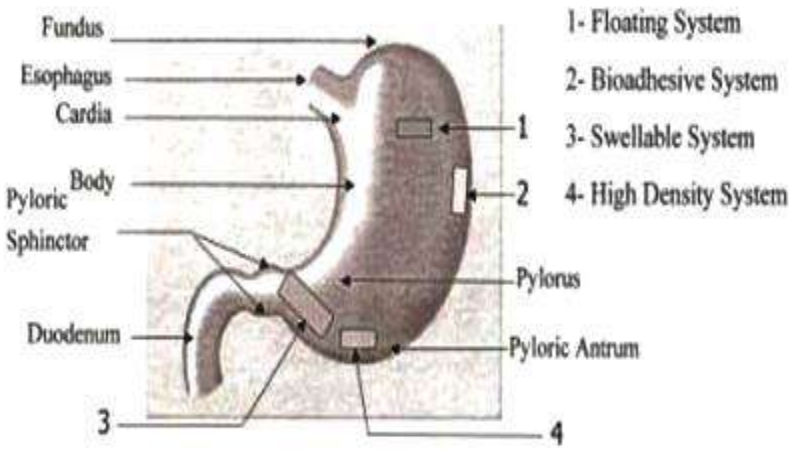
b) Raft systems incorporating alginate gels reaction with gastric acid, bubbles form in the gel, enabling floating.

c) Bioadhesive or Mucoadhesive systems device within the lumen and cavity of the body to in a site-specific manner. are used that can be adhere to the epithel mechanism of bioadhesive is the formation of hydrogen and electrostatic bonding at the mucus polymer boundary.

d) Modified shape systems silastic elastomer or exuded from polyethylene blends and extended the the principal mechanism of floa its potential for oral controlled drug delivery. delivery system In these approaches involve the use of bioadhesives epithelial surface of the GIT. floatation and (GRDDS) hese.[8, 9] polymersial The proposed gastric transit time (GTT) depending on the size, shape and flexural modul device.

e**) High density systems** the stomach content (1.004 gm/cm heavy inert material such as barium sulphate, ZnO, titanium dioxide. This formulation of high-density pellet is based on assumption that heavy pellets might remain longer in the stomach, since they are position in the lower part

f) Swelling system- These the stomach through the pylorus. period of time. These systems may be referred exhibit tendency to remain logged in the pyloric.



g) Magnetic systems- These are the systems whi field for site specific delivery. the dosage form to achieve site

h) Floating drug delivery system

Bulk density lower than that of the gastric fluid prolong period.[2] Swelling delivery systems prevents their passage through the pylorus. Upon coming in contact with gastric fluid, the polymer imbibes water and stomach for a longer period of time

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve in to the

small intestine the particle size should be in the range of 1 to 2 mm.[6] The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include:

1. Density of dosage forms

Density of the dosage form should be less than the gastric contents (1.004gm/ml).

2. Shape and size of the dosage form

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kiloponds per Square inch (KSI) is reported to have better GIT retention 90 to 100 % retention at 24 hours 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 gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms.

4. Effect of gender, posture and age

Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down.

EXCIPIENTS USED IN FDDS

1. Polymers: The following polymers used in preparations of FDDS -HPMC K4 M, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin,HPMC 4000, HPMC 100, CMC, Polyethylene glycol,polycarbonate, PVA, Polycarbonate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4M and Carbopol.

2. Inert fatty materials (5%-75%): Edible, inert fatty material having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Beeswax, fatty acids, long chain fatty alcohols, Gelucires 39/01 and 43/01.

3. Effervescent agents: Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).

4. Release rate accelerants (5%-60%): eg. Lactose, mannitol.

5. Release rate retardants (5%-60%):
eg.Dicalciumphosphate, talc, magnesium stearate.

6. Buoyancy increasing agents (upto80%): eg. Ethyl cellulose.

7. Low density material: Polypropylene foam powder (AccurelMP 1000).

MECHANISM OF FLOATING SYSTEMS

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (given in the Figure 1 (a)), 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 GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side

(Figure 1(b)). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations

F = Fbuoyancy - Fgravity

F = (Df - Ds) gV

Where,

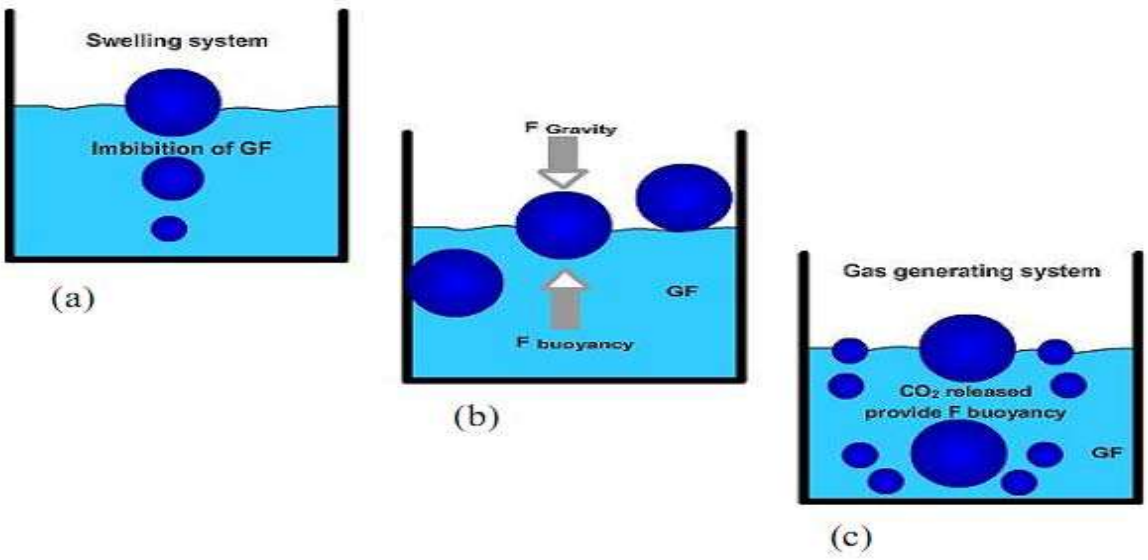
F = Total vertical force in N,

Df = Fluid density in Kg/m3,

Ds = Density of object in Kg/m3,

V = Volume of the object m3,

g = Acceleration due to gravity m/s



TYPES OF FLOATING DRUG DELIVERY SYSTEMS

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include:

A. Floating systems

B. Bioadhesive systems

C. Swelling and expanding systems

D. High density systems and

E. Modified systems

A. Floating drug delivery systems

Floating drug delivery system is also called the hydrodynamically balanced system (HBS). Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

This delivery system is further divided into in to non effervescent and effervescent (Gas-generating system).

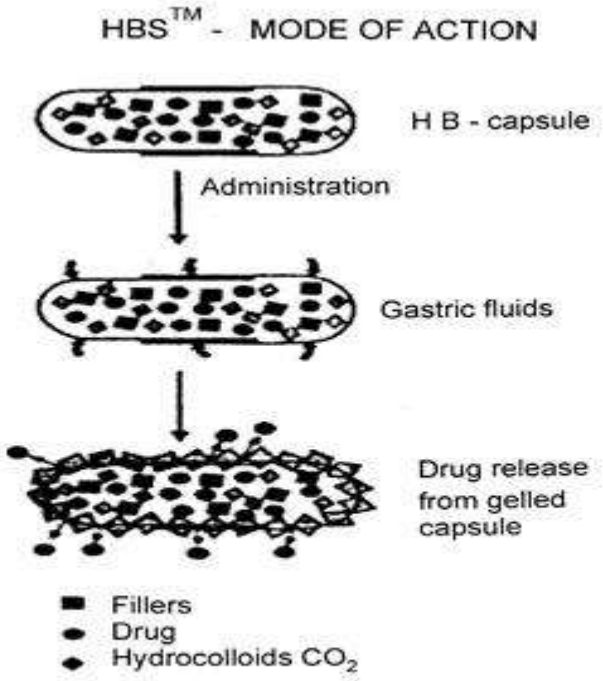
Non-effervescent systems

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

I. Colloidal gel barrier systems / Single Layer Floating Tablets

Hydrodynamically balanced system (HBS), which contains drugs with gel forming hydrocolloids, was first designed by Sheth and Tossounian in 1975. These systems incorporate a high level (20-75%w/w) of one or more gel forming, highly swellable, cellulose type hydrocolloids, polysaccharides and matrix forming polymers. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug.



II. 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.

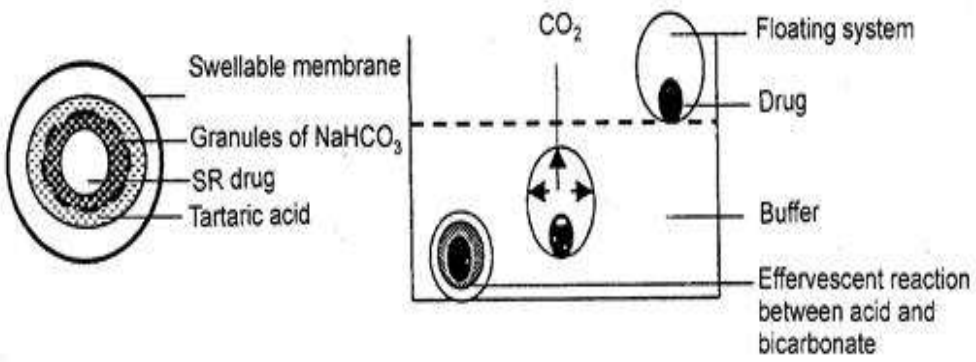
III. Micro porous compartment systems

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the un dissolved drug.

IV. Multi particulate system: Floating Beads / Alginate Beads

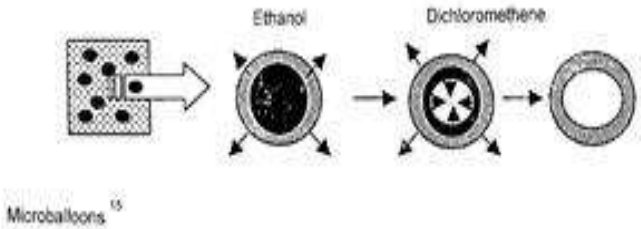
Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Multi-unit floating dosage forms were developed from freeze- dried calcium alginate. Spherical beads 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. Thus multi particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet. Multiple unit type of floating pills and it's floating behavior



V. Micro balloons / Hollow Microspheres

There are various approaches in delivering substances to the target site in a controlled release fashion. One such approach is using polymeric microballoons as carrier for drugs. Hollow microspheres a r e known a s t h e micro balloons. Micro balloons were floatable in vitro for 12 hrs, when immersed in aqueous media. Radio graphical studies proved that microballoons orally administered to human were dispersed in the upper part of stomach and retained there for three hr against peristaltic movements.



Effervescent systems

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas.

I. Volatile liquid containing systems

These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid.

II. Gas generating systems

These buoyant delivery systems utilizes efferves reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chime. A multiple unit type of floating pills, which generate CO_2, have also been developed. The system consists of a sustained release (SR) pill as seed, surrounded by double layers. The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer is of a swell able membrane layer containing PVA, shellac etc. Another effervescent system consisting of a collapsible spring, which controls the release of drug from the polymer matrix, has also been developed. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating which is insoluble but permeable, allows permeation of water. Thus, carbon-dioxide is released, causing the beads to float in the stomach.

MARKETED PRODUCTS OF FDDS

Sr No.	Product	Active Ingredient
1	Madopar	Levodopa and benserzide
2	Valrelease	Diazepam
3	Topalkan	Aluminium magnesium Antacid
4	Almagate flatcoat	Antacid
5	Liquid gavison	Alginicacid and sodium bicarbonate

POLYMERS AND OTHER INGREDIENTS USED IN PREPARATIONS 0F FLOATING DRUGS

1.Polymers: The following polymers used in preparations of floating drugs - HPMC K4 M, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbo-nate, Sodium

alginate, HPC-L, CP 934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4 M and Carbopol.

2.Inert fatty materials (5%-75%): Edible, inert fatty material having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Beeswax, fatty acids, long chain fatty alcohols, Gelucires 39/01 and 43/01.

3.Effervescent agents : Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).

4. Release rate accelerants (5%-60%): eg. lactose, mannitol.

5. Release rate retardants (5%-60%): eg. Dicalcium phosphate, talc, magnesium stearate.

6. Buoyancy increasing agents (upto80%): eg. Ethyl cellulose.

7. Low density material: Polypropylene foam powder (Accurel MP 1000).

ADVANTAGE

1. Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
2. FDDS are advantageous for drugs meant for local action in the stomach eg: Antacids.
3. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a relatively better response.
4. Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
5. The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
6. Controlled delivery of drugs. Minimizing the mucosal irritation due to drugs,by drug releasing slowly at controlled rate.
7. Treatment of gastrointestinal disorders such as gastroesophageal reflux.
8. Ease of administration and better patient compliance
9. Site-specific drug delivery.

7. DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEMS

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. One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.

4. These systems also require the presence of food to delay their gastric emptying.

5. 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.

6. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

7. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.

8. EVALUATION TECHNIQUES

In-vitro evaluation of floating tablets

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

I. Pre-compression parameters

a) Angle of Repose

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

a) Angle of repose

The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

tan = h/r

b) Compressibility Index

The flow ability of powder can be evaluated by comparing the bulk density (ρo) and tapped density (ρt) of powder and the rate at which it packed down. Compressibility index was calculated by –

II. Post-compression parameters

a) Shape of Tablets

Compressed tablets were examined under the magnifying lens for the shape of the tablet.

b) Tablet Dimensions

Thickness and diameter were measured using a calibrated varniear caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

c) Hardness (Hilton AK et al.1992)

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

d) Friability test (Shoufeng L et al. 2001)

The friability of tablets was determined by using Roche Friabilator. It was expressed in percentage (%). Ten tablets were initially weighed (W in itial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). The % friability was then calculated by – **% of Friability = 100 (1-W0/W)** % Friability of tablets less than 1% was considered acceptable.

e) Tablet Density (Ozdemir N et al.2000)

Tablet density was an important parameter for floating tablets. The tablet would floats only when its density was less than that of gastric fluid (1.004). The density was determined using following relationship. V = r 2 h d = m/v **v** = volume of tablet (cc) **r** = radius of tablet (cm) **h** = crown thickness of tablet (g/cc) **m** = mass of tablet.

f) Weight Variation Test (Shoufeng L et al. 2001)

Ten tablets were se lected r a n d oml y f rom each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet by U.S. Pharmacopoeia. The following percentage deviation in weight variation was allowed **Percentage deviation in weight variation.**

g) Buoyancy / Floating Test

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. 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).

h) Swelling Study

The swelling behavior of a dosage form was measured by studying its weight gain or water untake 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 = (W1 – W0) x 100

j) *In-vitro* drug release studies

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 37°C. The time required to float the HBS dosage form is noted as floating (or floatation) time.

9. CHARACTERIZATION PARAMETERS

1. Size and shape evaluation

The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability**.** The particle size of the formulation was determined using Sieve analysis, Air elutriation analysis, Photo analysis, Optical microscope ,Electro résistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air Pollution Emissions Measurements etc (Vedha hari b.n.et al 2010).

2. Floating properties

Effect of formulation variables on the floating properties of gastric floating drug delivery system was determined by using continuous floating monitoring system and statistical experimental design (Choi BY et al.2002).

3. Surface topography

The surface topography and structures were determined using scanning electron microscope (SEM, JEOL JSM – 6701 F, Japan) operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic force microscopy (AFM), Contact profiliometer. (Ichikawam et al.1991).

4. Determination of moisture content

The water content per se is seldom of interest. Rather, it shows whether a product intended for trade and production has standard properties such as

1. Storability
2. Agglomeration in the case of powders
3. Microbiological stability
4. Flow properties, viscosity
5. Dry substance content
6. Concentration or purity
7. Commercial grade (compliance with quality agreements)

Thus moisture content of the prepared formulations was determined by Karl fisher titration, vacuum drying, Thermo gravimetric methods, Air oven method, Moisture Meters, Freeze drying as well as by physical methods.

5. Swelling studies

Swelling studies were performed to calculate molecular parameters of swollen polymers**.** Swelling studies was determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include H1NMRimaging, Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus (USP dissolution apparatus (usp-24) labindia disso 2000) was calculated as per the following formula (Ferdous Khan et al.2008).

Swelling ratio = Weight of wet formulation / Weight of formulations

6. Determination of the drug content

Percentage drug content provides how much amount of the drug that was present in the formulation. It should not exceed the limits acquired by the standard monographs. Drug content was determined by using HPLC, HPTLC methods, Near infrared spectroscopy (NIRS), Microtitrimetric methods, Inductively Coupled Plasma Atomic Emission

Spectrometer (ICPAES) and also by using spectroscopy techniques. (Yuvarej Singh Tanwar et al.2007).

7. Percentage entrapment efficiency

Percentage entrapment efficiency was reliable for quantifying the phase distribution of drug in the prepared formulations. Entrapment efficiency was determined by using three methods such as Micro dialysis method, Ultra centrifugation, and pressure Ultra filtration. (Sunil kumar Bajpai et al.2007).

8. *In-vitro* release studies

In vitro release studies (USP dissolution apparatus (usp-24) lab India disso 2000) were performed to provide the amount of the drug that is released at a definite time period. Release studies were performed by using Franz diffusion cell system and synthetic membrane as well as different types of dissolution apparatus. (Shweta Arora et al.2005).

9. Powder X-ray differaction

X-ray powder diffraction (Philips analytical, model-pw1710) is the predominant tool for the study of polycrystalline materials and is eminently suited for the routine characterization of pharmaceutical solids. Samples were irradiated with α radiation and analyzed between 2 ºC and 60 ºC .The voltage and current used were 30KV and 30mA respectively.(Girish S.Sonar et al.2007).

10. Fourier transform infrared analysis

Fourier transform infrared spectroscopy (FTIR, Shi-madzu, Model-RT-IR-8300) is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, polymer and drugloaded polymer formulations were obtained on FTIR. The pelletswere prepared on KBr-press under hydraulic pressure of 150kg/cm2; the spectra were scanned over the wave number range of 3600 to 400 cm-1 at the ambient temperature.

11. Differential Scanning Calorimetry (DSC)

DSC (Shimadzu, Model-DSC-60/DSC-50/ Metler Toldeo) are used to characterize water of hydration of pharmaceuticals .Thermo grams of formulated preparations were obtained using DSC instrument equipped with an intercooler. Indium/Zinc standards were used to calibrate

the DSC temperature and enthalpy scale. The sample preparations were hermitically sealed in an aluminum pan and heated at a constant rate of 10°C/min; over a temperature range of 25°C – 65°C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50ml/min.

10. APPLICATION OF FLOATING DRUG DELIEVERY SYSTEM

1. Enhanced Bioavailability

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

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. (Moursy NM et al.2003).

3. Site specific drug delievery 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.

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.

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.

REFERENCES

1. Ansel HC, Allen LV, Popovich NG. Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia, Lippincott Williams and Wilkins Chapter -3, 2003; 23-31.
2. Mayavanshi AV, Gajar SS. Floating drug delivery system to increase gastric retention of drug: A Review J. Pharm. Res, 2008; 1940: 345-348.
3. Vachhani savan R, Patel Dipen, Prajapati ST, Patel CN.;J Chem.Pharma Res, 2010; 2(2): 57 64.
4. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review. J Pharm Tech, 2008; 1(14): 345-348.
5. Whitehead L, Collet JH, Fell JT, Sharma HL, Smith AM. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. J Control Release, 1998; 55: 3-12. Hilton AK, Desai PB. In vitro and in vivo evaluation of an oral sustained release floating dosage form of amoxicillin trihydrate. Int J Pharm, 1992; 86: 79-88.
6. Sheth PR, Tossounian JL, 1978; US 4,126,672.
7. Kawashima Y, Nima T, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci (USA), 1998; 81: 135-140.
8. Iannuccelli V, Coppi G, Cameroin R. Air compartment multiple unit system for prolonged gastric residence. II. In vivo evaluation. Int J Pharm, 1998; 174: 55-62.
9. Gholap SB, Banarjee SK, Gaikwad DD, Jadhav SL. Thorat RM, Hollow microspheres: A Review. Int J Pharm Sci R and Res, 2010; 1(1): 74-79.

10. Paterson RS, O‟mahony B, Eccleston GM, Stevens HNE, Foster J & Murray JG. An assessment of floating raft formation in a man using magnetic resonance imaging. J Pharm Pharmacol, 2008; 8(2).
11. Grabowski SR. Principles o f Anatomy and Physiology. New York: JohnWilley and Sons; 10; 2002.
12. KRW, Waugh A. Anatomy and Physiology in Health and Illness. London: Churchill Livingstone; 9; 1996.
13. Thanoo BC, Sunny MC and Jayakrishnan A. Oral Sustained-release Drug Delivery Systems using Polycarbonate Microspheres Capable of Floating on the Gastric Fluid, J.Pharm. Pharmacol, 1993; 45: 21- 24.
14. Kawashinia Y, Niwa T. Takcuchi H. Hino T, Itoh Y. HallowMicrospheres for use as a Floating Controlled Drug Delivery System in the Stomach. J Pharm Sci, 1992; 81(2): 135- 140.
15. Deshpande AA, Shah NH, Rhodes CT, Malick W. Pharm Res, 1997; 14: 815-819.
16. Davis S S, S t o c k w e l l A F , T a y l o r M J . P h a r m . Res, 1986; 3: 208-213 Lehr CM. Crit Rev Ther. Drug Carrier Syst, 1994; 11: 119-160.
17. Groning R, Heun G. Drug D e v I n d. Pharm, 1984; 10: 527-539.
18. Klausner EA, Lavy E, Friedman M, Hoffman A. J Cont Rel, 2003; 90: 143-162.
19. Floating drug delivery system; journal of current pharmaceutical research, 2011; 7(1): 6-20.
20. Ichikawa M, Watanabe S, Miyake Y. A new multiple unit oral floating dosage system. I: Preparation and in vitro evaluation of floating and sustained release kinetics. J Pharm. Sci, 1991; 8: 1062-1066.
21. Shivkumar HG; Vishakante Gwdaand D; Pramod Kumar TM. *Indian J Pharm Educ*, 2004; 38(4): 172-179.
22. Shah SH; Patel JK; Patel NV. *Int J Pharm Tech Res*, 2009; 1(3): 623-633 Singh BM; Kim KH. *Cont J Rel*, 2000, 63, 235-259. [4] Hirtz J. *Br J Clin Pharmacol*, 1985; 19: 77S-83S. [5] Agyilirah GA; Green M; DuCret R; Banker GS.
23. International Journal of Pharmaceutics, 1991; 75: 241-247. [6] Iannuccelli V; Coppi G; Sansone R; Ferolla G. *International Journal of Pharmaceutics*, 1998, 174(1–2), 55–62. [7] Jimenez-Castellanos NR; Zia H; Rhodes CT. *Drug.*
24. Development and Industrial Pharmacy, 1993; 19: 143. [8] Baumgartners S; Kristal J; Vrecer F; Vodopivec P; Zorco B. International Journal of Pharmaceutics, 2000; 195(1-2): 125-135.

25. Rosa M, Zia H, Rhodes TC. Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application.International Journal of Pharmaceutics, 1994; 2: 65-70.
26. Prasad SK, Tanwar M, Sharma A, Singhal M, Sharma A. Preparation and optimization of oral floating Alginate gel beads of famotidine. International Journal of Pharmaceutical Studies and Research, 2012; 3: 04-08
27. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int. J. Pharm, 1996; 136: 117–139.
28. Longer MA, Ch'ng HS, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery III: Oral delivery of chlorothiazide using a bioadhesive polymer. J. Pharm. Sci, 1985; 74: 406–411.
29. Alvisi V, Gasparetto A, Dentale A, Heras H, Felletti- Spadazzi A, D'Ambrosi A. Bioavailability of a controlled release formulation of ursodeoxycholic acid in man. Drugs Exp. Clin. Res, 1996; 22: 29–33.
30. Hirtz, The GIT absorption of drug in man: a review of current concepts and method of investigation, British Journal of Clinical Pharmacology, 1985; 19: 77-83.
31. Singh B, Kim KH., Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Rel, 2000; 69: 235-259.
32. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: *A Review. Research J. Pharm. And Tech*, 2008; 1: 345-348.
33. Narang N. An updated review on: floating drug delivery system (FDDS). International Journal of Applied Pharmaceutics, 2011; 3: 01-07.
34. Chein YW. Novel Drug Delivery Systems, 2nd edition, Marcel Dekker, New York, 2005; 157-63.
35. Kumar R, Philip A. Gastroretentive Dosage forms for prolonging gastric residence time. Int J Pharm Med, 2007; 21(2): 157-71.
36. Vyas SP, Khar RK. Controlled Drug Delivery: Concept and Advances 1st ed. Vallabh Prakashan; Delhi; 2002.
37. Smriti K, Dheeraj G, Rakesh P, Ahmad FJ. Recent Advances in Floating Drug Delivery System. The Ind Pharmacist, Sep 2007; 1724.
38. Chatterjee CC. Human Physiology. Vol I, Medical Allied Agency; Kolkata, 2004; 435-38.
39. Waugh A, Grand A. Ross and Wilson Anatomy and Physiology: In Health and Illness. 10th edi, Churchill Livinstone Elsevier; Edinburgh, 2006; 293-95.

40. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics.
41. Kale RD, Tayade PT. A Multiple Unit Drug Delivery System of Pyroxicam Using Eudragit Polymer. India J Pharm Sci, 2007; 69(1): 120-23.
42. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and Evaluation of Ketoprofen Floating Oral Delivery System. Int J Pharmaceutics 2001; 220: 13-21.
43. Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, Khar RK, et al. Formulatin and development of hydrodynemically balanced system for metformin; In vitro and in vivo evaluation. Eur J of Pharmaceutics and Biopharmaceutics 2007; 67: 11.
44. Choia BY, Park HJ, H wangb SJ, Parkc JB. Preparation of alginate Beads for floating Drug Delivery System: Effects of CO2 Gas – Forming Agents. Int J Pharmaceutics 2002 Jan.
45. Gu T.H. Pharmacokinetics and pharmacodynamics of diltiazem floating Available online at *www.ijpras.com28* tablets. Chung Kao Yao Li Hsuesh Pao.1992; 13: 527-531. 24. 24. Rouge N, Cole E.T, Doelker E, Buri P. Buoyancy and drug release patterns of floating mini tablets containing piretanide and atenolol as model drugs. *Pharm. Dev. Technol*, 1998; 3: 73-84.
46. Cheuh H.R, Zia H, Rhodes C.T.Optimization of Sotalol floating and bioadhesive extended release tablet formulation. *Drug Dev. Ind. Pharm,* 1995; 21: 1725-1747. 26. Nur A.O, Zhang J.S.Captopril floating and/or bioadhesive tablets: design and release kinetics. *Drug Dev Ind Pharm*, 2000; 26: 965-969.
47. Baumgartner S, Kristl J, Vrecer F. Optimization of floating matrix tablets and evaluation of their gastric residence time. *Int J Pharm*, 2000; 195: 125-135.
48. Srivastava AK, Ridhurkar DN, Wadhwa S. Floating microspheres of cimetidine: formulation, Characterization and *in vitro* evaluation. *Acta Pharm*, 2005; 55: 277–285. excipients used in controlled release technology. *Drug Dev Ind Pharm,* 1993; 19: 1061-1081.
49. Whitehead L, Collet JH, Fell JT, Sharma HL, Smith AM. Floating dosage forms: an *in vivo* study demonstrating prolonged gastric retention. *J Control Release*, 1998; 55: 3-12.
50. Gansbeke BV, Timmermans J, Schoutens A, Moes AJ. Intragastric positioning of two concurrenly ingested pharmaceutical matrix dosage forms. *Nucl Med boil*, 1991; 18: 711-718.

51. Klausner EA, Lavy E, Stepensky D, Cserepes E, Batra M, Freidman M & Hoffman A. Furosemide pharmacokinetics and pharmacodynamics following gastroretentive dosage form administration to healthy volunteers. *J Clin Pharmacol*, 2003; 43: 711-720.
52. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. *J Pharm Sci*, 1994; 83:239- 245.
53. Rouge N, Allémann E, and Gex-Fabry M, etal. Comparative pharmacokinetic study of a floating multiple unit capsule, a high density multiple unit capsule and an immediate release tablet containing 25 mg atenolol. *Pharm Acta Helv*, 1998; 73: 81-87.
54. Tanwar YS, Naruka PS, Ojha GR. Development and evaluation of floating microspheres of verapamil hydrochloride. *Brazilian J of Pharm Sci*, 2007; 43: 529-534.
55. Singh BN, Kim KH. Floating drug delivery system: An approach to the controlled drug delivery via gastric retention. *J Control Release*, 2000; 63: 235-259.