ejpmr, 2017,4(9), 203-212

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW: FLOATING PULSATILE DRUG DELIVERY SYSTEM

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Article Received on 06/07/2017 **Article Revised on 27/07/2017** **Article Accepted on 16/08/2017**

ABSTRACT

In the recent years, scientific and technological advancements have been made in the research and development of novel drug delivery systems by overcoming physiological troubles for e.g.as short gastric residence times and unpredictable gastric emptying times. Several approaches are currently utilized in the prolongation of the gastric residence times, including floating drug delivery systems, swelling and expanding systems, polymeric bio adhesive systems, modified shape systems, high-density systems and other delayed gastric emptying devices. By using floating drug delivery help in avoiding dose dumping gives desirable release as controlled & delayed. A blend of floating and pulsatile principles of drug delivery system seems to present the advantage that a drug can be released in the upper GI tract after a definite time period of no drug release. Floating pulsatile drug delivery system (FPDDS) concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. Diseases wherein FPDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, and attention deficit syndrome in children. To overcome limitations floating and lag controlling were prepared by floating pulsatile delivery systems, for which time controlling system like swelling and rupturablemembranes, soluble or erodible coating, capsule shaped system and multiparticulate system are primarily involved in the control of release.

KEYWORDS: Gastric residence time, Floating drug delivery system, Chronotherapeutic, lag time, avoid dose dumping.

INTRODUCTION

Controlled drug delivery systems have gained very important role in pharmaceutical Research and Development (R&D) business. Such systems offer control over the release of drug &gives target site release of release of a drug so it is having much more imp.[1], The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, more patient compliance and flexibilityin formulation, etc.[2] During the past few decades, numerous oral drug delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a specific period of time at a predetermined and controlled rate.[3] It is evident from the recent scientific and patent literatures that an increased interest in novel oral controlled release dosage forms that designed to be retained in the gastrointestinal tract(GIT) for a prolonged and predictable period of time exists today.[4] Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS), low-densitysystems[5], raft systems incorporating alginate gels[6], bio adhesive or mucoadhesive systems[7], high-density systems[8], superporous hydrogels[9] and magnetic systems.[10] The current review addresses briefly about the FDDS that is one of the most leading methodologies in gastro retentive drug formulations. Oral drug delivery has been known for decades as the most widely utilized route of administration. It can be classified in three categories,

A. Immediate release- which is designed for fast release of drug for rapid absorption.
B. Sustained release- designed on the basis of retardation technology for extended absorption.
C. Controlled and targeted drug delivery system- which are more of pharmaceutical and clinical superiority over conventional immediate release pharmaceutical products to give control dose to target.

Oral drug delivery is one of the most desired drug delivery for achieving systemic and local effects. It is most preferred due to ease of administration, cost effectiveness and flexibility in administration. The development of controlled release formulations continues to be a big success for pharmaceutical industry due to its

ease of manufacturing process and reproducibility of desirable pharmaceutical properties. Controlled drug delivery systems are receiving more and more attention as they control the rate of drug release and reduces the duration of therapy.[11] Site- and time-specific oral drug deliveries have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific or time specific drug release in upper gastrointestinal (GI) tract.[12,13] Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floating system[14,15] which decrease in density upon contact with gastric fluids based on swelling of polymer or carbon dioxide (CO2) generation, mucoadhesive systems which adhere to mucosal surfaces,[16,17] modified-shape systems,[18,19,20] expandable(size-increasing),[21] high-density systems,[22] and other delayed gastric emptying devices.[23]

The dosage forms possessing gastric retention capabilities have a bulk density lower than gastric fluids and thus remain floating in the stomach without affecting the gastric emptying rate for a prolonged period of time. Floating approach has been used for gastric retention of pulsatile dosage form. Floating-pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage form scan remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastro retentive drug delivery approaches being designed and developed, including: high density (sinking)systems that is retained in the bottom of the stomach, low density (floating) systems that causes floating in gastric fluid, mucoadhesive systems that causes Bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, superporous hydrogel systems, magnetic systems etc.[23]

Pulsatile Drug Delivery System

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release. A pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release. Drug release profile of pulsatile drug delivery system presently pulsatile drug delivery systems are gaining interest now a days. Since many diseases are known to show predictable humans rhythms, moreover the timing of rhythms can be used to deliver drugs at the desired time. Oral drug delivery of drugs is the largest segment of drug delivery market and the most preferred route of drug administration. An oral control release system which tends to show a typical pattern of drug release to maintain the drugs in the therapeutic window for the longer duration of time and thereby ensuring sustained action. But there are certain conditions where sustain or controlled release of medication is not required in other way a pulsatile drug delivery are required.[24]

The pulsatile drug delivery is gaining a lot of interest because it release the drug after specific lag time and shows no drug release during the lag time, the total &immediate of drug is released after the desired lag time. Pulsatile drug delivery or can also be known as time and site-specific drug delivery provides a spatial and temporal delivery of drug and thus increase patient compliance. Pulsatile drug delivery is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined no-released period, i.e., lag time, or these systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time, i.e., a period of no drug release. Such a release pattern is known as pulsatile release.[25]

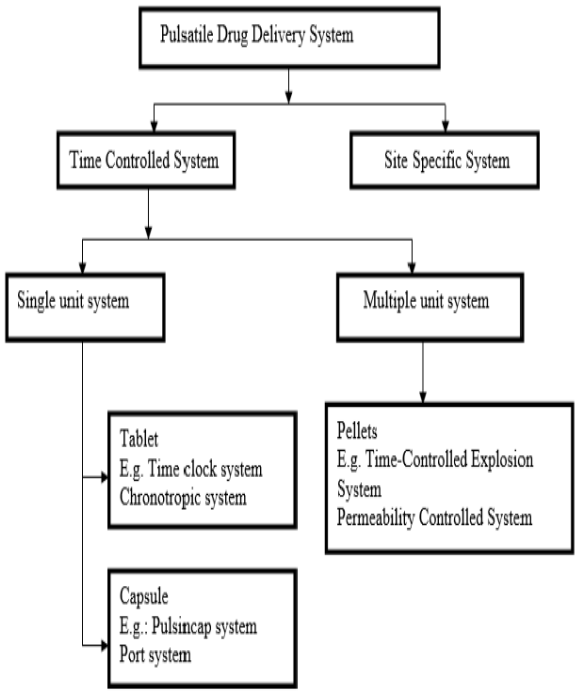

Fig. No. 1: Classification of Pulsatile drug delivery system[39]

1. FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric retention time (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 floating 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 . Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.

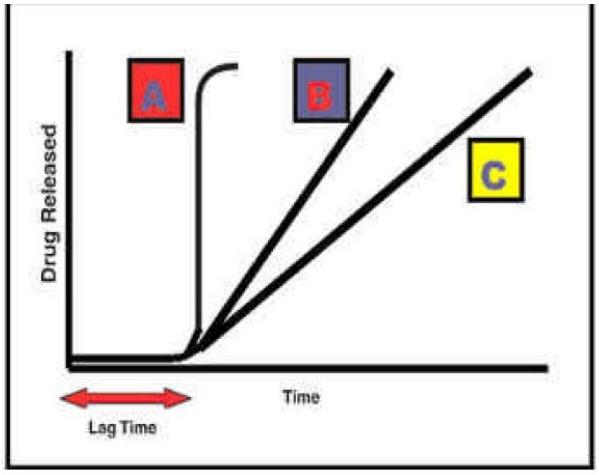

Figure No. 2: Drug release profile of pulsatile drug delivery system.

A: Ideal Sigmoidal Release
B&C: Delayed Release after Initial Lag Time
(Patterns B & C in Figure).

In this context, the aim of the research was to achieve a so-called sigmoid release pattern (pattern An in Figure). The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once. Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time.[26]

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This delivery system is desirable for drugs with an absorption window in the stomach or in the upper small intestine. This have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration.
The major requirements for floating drug delivery system are:
• It should release contents slowly to serve as a reservoir.
• It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).
• It must form a cohesive gel barrier.

The inherent low density can be provided by the entrapment of air (e.g. hollow chambers) or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder. These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler. The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produce irritation. On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce inter and intra-subject availabilities in drug absorption as well as to lower the possibility of dose dumping.

Various multiple-unit floating system like air compartment multiple-unit system, hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method micro particles based on low density foam powder beads prepared by emulsion gelatin method etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery system.[26]

1.1. Drug Candidates Suitable for FDDS

- Drugs that have narrow absorption window in GIT (e.g. L-DOPA, para aminobenzoicacid, furosemide, riboflavin).
- Drugs those are locally active in the stomach (e.g. misroprostol, antacids).
- Drugs those are unstable in the intestinal or colonic environment (e.g. captopril, ranitidine HCl, metronidazole).
- Drugs that disturb normal colonic microbes (e.g. antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin).
- Drugs that exhibit low solubility at high pH values (e.g. diazepam, chlordiazepoxide, verapamil).

Table No.1: Examples of various drugs formulated as different forms of FDDS.

Dosage forms	Drugs
Floating Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorourac, Isosorbide dinitrate, Isosorbid mononitrate, p- Aminobenzoic acid(PABA), Nimodipine, Sotalol, Theophylline, verapamil
Floating Capsules	Chlordiazepoxide HCl, Diazepam, furosemide, L-DOPA and Benserazide, Pepstatin Nicardipine, Misoprostol, Propranolol,
Floating microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Floating granules	Diclofenac sodium, Indomethacin, Prednisolone
powders	Several basic drugs
Films	Cinnerzine

1.2 Types of Floating Drug Delivery Systems

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

i) Non-Effervescent FDDS: 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 no 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 bio adhesive polymers such as Chitosan and Carbopol. The various types of this system are as:

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

b. 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.

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

d. Hollow Microspheres

i) Hollow microspheres (micro balloons): It is loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40 °C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug.

ii) Effervescent FDDS

a. *Volatile liquid containing system:* The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodiable plug made up of Poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

b. *Gas-generating Systems:* These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.[27,28]

DESIGN OF FLOATING PULSATILE DRUG DELIVERY SYSTEM

The purpose of designing by which the drug is released from dosage form depends on the type of coating; insoluble coating underall physiological conditions, pH-dependent coating whose solubility changes dramatically at some point in GI tract, and slowly erodible coating. The method of application and processing conditions may influence the porosity of the coating and consequently the release mechanism. Less obvious but also important to the kinetics of release are the influences of the core formulation, in terms of both physical properties and amounts of the drug and excipients materials present, and physiological environment to which the drug is released. In multiparticulate pulsatile

delivery systems, the swelling and rupturing; dissolution or erosion; and changed permeability of the coating membrane are primarily involved in the control of release.The development of low-density floating Multiparticulate pulsed release dosage forms possessing gastric retention capabilities has also been addressed with increasing focus on the upcoming Multiparticulate pulsatile technologies being exploited on an industrial scale.[29]

METHODS OF FLOATING PULSATILE DRUG DELIVERY

1. Time controlled floating pulsatile drug delivery.
2. Reservoir system with rupturable coating.
3. Reservoir system erodible polymer.
4. Capsule shape system with release controlling plug
5. Multiparticulate system

1. Time-controlling floating pulsatile drug delivery

Time-dependent dosage forms are formulated to release their drug load after a predetermined lag time. The release mechanisms employed include bulk erosion of the polymer, in which drug by diffusion is restricted, surface erosion of layered devices composed of altering drug-containing and drug-free layers, and osmotically controlled erosion coating layer.

2. Reservoir systems with rupturable polymeric coating

Upon water ingress, drug is released from the core after rupturing of the surrounding polymer layer, due to pressure build-up within the system. The pressure necessary to rupture the coating can be achieved with swelling agents, gas-producing effervescent excipients or increased osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time. Water soluble drugs are mainly released by diffusion; while for water insoluble drug, the release is dependent on dissolution of drug.

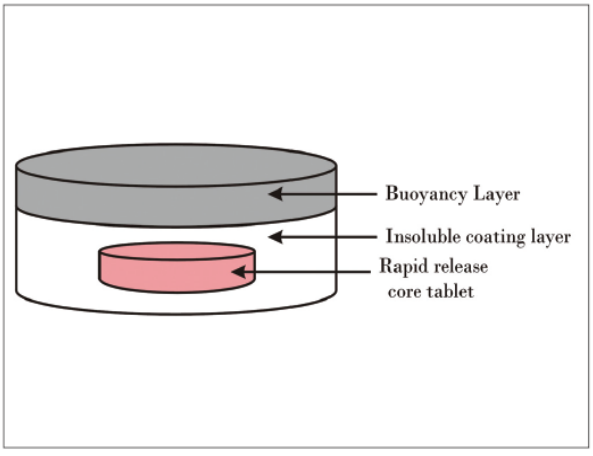

Figure No. 3: Schematic diagram of the floating pulsatile release delivery system with rupturable coatinglayer.

3. Reservoir systems with eroding polymer orsoluble barrier coatings

A pulsatile–floating drug delivery system consists of three different parts, a core tablet, containing the active ingredient; an erodible outer shell; and a top cover buoyant layer, as shown in Figure 1.One layer is for buoyancy and the other for drug pulsatile release.The pulsatile release system with various lag times was prepared by compression with different erodible polymeric layers. Combined usage of hydroxypropyl methylcellulose (HPMC) and carborain a gastric floating or mucoadhesive drug delivery system has been reported to improve the floating properties or mucoadhesiveness of the combined system. The novel system could result in a floating dosage form with a prolonged gastric residence time andina pulsatile dosage form, in which the drug is released rapidly in a time-controlled manner after rupturing of the coating.Floating–pulsatile concept was applied to increase the gastricresidence of the dosage form having lag phase followed by a burst release. We generated the system which consisted of three different parts, a core tablet, containing the active ingredient; an erodible outer shell; and a top cover floating layer.

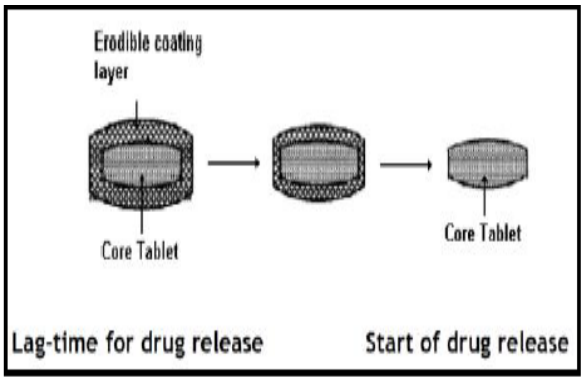

Figure No. 4: Schematic diagram drug delivery with erodible coating layer.

4. Capsule-shaped system provided with releasecontrolling plug

The novel system consists of a drug tablet placed within an impermeable polymeric cylinder closed with an erodible drug-free plug and floating material filled at the bottom. When in contact with the aqueous fluids, the erodible drug-free plug is responsible for a lag phase preceding the onset of release and the floating material filled at the bottom is responsible for buoyancy properties of the formulation. A blend of floating and pulsatile principles of drug delivery system seems to present the advantage that a drug can be released in the upper GI tract after a definite time period of non drug release.System was to develop and evaluate a floating and pulsatile drug delivery system based on an impermeable cylinder. Pulsatile capsule was prepared by sealing the drug tablet and the buoyant material filler inside the impermeable capsule body with erodible plug. The drug delivery system showed typical floating and pulsatile release profile, with a lag time followed by a rapid release phase. The lag time prior to the pulsatile

drug release correlated well with the erosion properties of plugs and the composition of the plug could be controlled by the weight of the plug. The buoyancy of the whole system depended on the bulk density of the dosage form. Gamma-scintigraphic evaluation in human beings was used to establish methodology capable of showing the subsequent *in vivo* performance of the floating and pulsatile release capsule.

The pulsatile release capsule we prepared could achieve a rap release after lag time *in vivo*, which was longer than that *in vitro*. The scintigraphic evaluation could confirm qualitatively that the system with *in vitro* lag time of 4.0 hours provided, with relatively high reproducibility, a pulsatile release occurred around 5.0 hours after administration. A multifunctional drug delivery system based on HPMC-matrices (tablets) placed within an impermeable polymeric cylinder was developed. Depending on the configuration of the device, extended release, floating or pulsatile drug delivery systems could be obtained. The release behavior of the different devices was investigated as a function of its viscosity grade, HPMC content, type of drug (chlorpheniramine maleate or ibuprofen), matriweight, position of the matrix within the polymeric cylinder, addition of various fillers (lactose, dibasic calcium phosphate, or microcrystalline cellulose), and agitation rate of the release medium. The release was fairly independent of the agitation rate, the position of the tablet within the polymeric cylinder, and the length of the cylinder. With the pulsatile device, the lag time prior to the drug release could be controlled through the erosion rate of the matrix (matrix weight and composition).

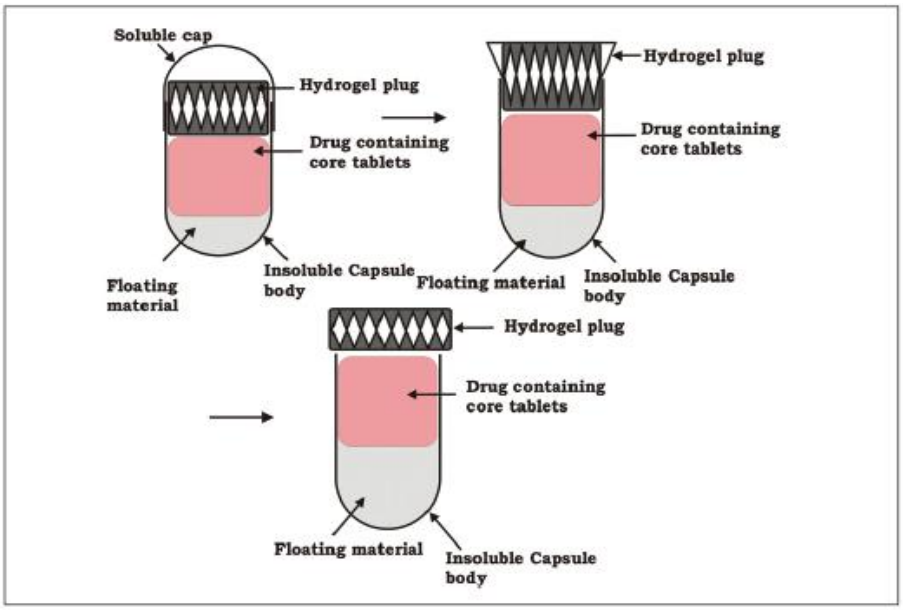

Figure No. 5: Schematic diagram of the floating pulsatile release delivery system with release controlling plug

5. Multiparticulate drug delivery system

Functional membranes (referred to as lag-time coating) are formed of a typical pellet or bead in a multiparticulate system with bi-modal pulse. It comprises of an external water-insoluble polymer (e.g., EC)or enteric polymer (e.g., hypromellose phthalate) over an immediate release drug layer, followed by a release control polymer over the timed pulsatile release drug layer applied on core granules.Multiparticulate systems are made by using this type of methods as systems based upon change in membrane permeability, systems with soluble or eroding polymer coatings, and systems based upon rupturable coating [Figure 6]. Multiparticulate pulsatile release dosage forms like reservoir systems with reputable polymeric coatings, soluble or eroding polymer coatings and changed membrane permeability are having longer residence time in the GI tract and due to highly variable nature of gastric emptying process, may result in poor and bioavailability problems *in vitro/in vivo* relationship. In contrary, floating multiparticulate pulsatile dosage forms reside in stomach only and are not affected by variability of pH, local environment, or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach, requiring local action, or distal part of small intestine.

Overall, these considerations led to the development of Multiparticulate pulsatile release dosage forms possessing gastric retention capabilities. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by burst release.[30]

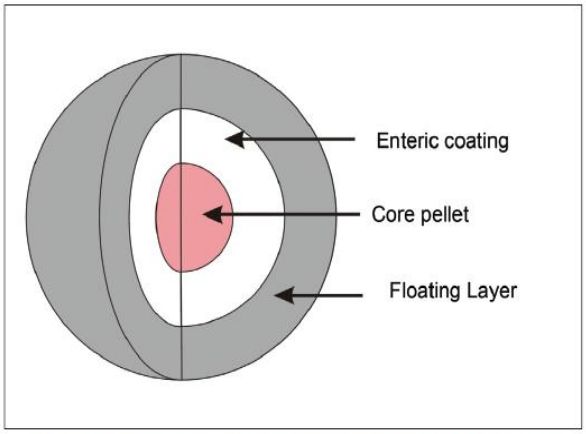

Figure No. 6: Schematic diagram of the floating multiparticulate pulsatile drug delivery system with multiple coating.

DESIGN OF MULTIPARTICULATE SYSTEM

The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulation and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation.[31]

These can be developed in various types of dosage forms like
i. Pellets.
ii. Granules.
iii. Microspheres.
iv. Beads.
v. Nanoparticles.
vi. Microsponges.

VARIOUS TYPES OF MULTIPARTICULATE PULSATILE SYSTEMS

a. Systems with changed membrane permeability

Sigmoidal release pattern is therapeutically beneficial for timed release and colonic drug delivery, and is observed in coated systems. A sigmoidal release pattern is reported based on the permeability and water uptake of Eudragit RS or RL, influenced by the presence of different counter-ions in the release medium When succinic acid was incorporated into the core of Eudragit RS-coated theophylline beads, the drug release profile showed a typical sigmoidal pattern due to the hydration by the interaction of quaternary ammonium compounds with succinic acid counter ion in the medium.

b. Low density floating multiparticulate systems

Low density floating multiparticulate pulsatile dosage forms reside in stomach only and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach. Overall, these considerations led to the development of multiparticulate pulsatile release dosage forms possessing gastric retention capabilities.

1.2 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 whencome in contact with it. Hence FDDS may be useful for the administration ofaspirin and other similar drugs.
3. The Floating systems are advantageous for drugs absorbed through the stomach. 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 dissolvein 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. For better response keep the drug floated in stomach.
7. To prolong retention of drug in stomach
8. To release drug as per bodies clinical need.
9. To avoid dose dumping.
10. Increase bioavailability of drug.[32]

1.3 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 throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Drugs which are irritant to gastric mucosa is also not desirable or suitable
5. The dosage form should be administered with a full glass of water (200-250 ml).
6. Manufacturing this type of dosage form, multiple formulation steps, higher cost of production, need of advanced technology and trained/skilled personal needed for manufacturing.

COMPONENTS OF FLOATING PULSATILE BEADS

The main components of floating pulsatile beads are as follows:

1. Drug

Drug selection based on the following criteria:
1. Drugs with short half life and thus repeated dosing.
2. Used in chronic conditions.
3. Large metabolism degradation.
4. Drugs exhibit tolerance.
5. Increases toxicity with constant release 4.

2. Gas forming agents

They are added to impart buoyancy to the beads. Carbonate salts are used as gas forming agents like sodium bicarbonate, potassium bicarbonate, calcium carbonate, sodium carbonate etc. They react with acidic solution to evolve CO2 which increases pores in the beads and decreases the bulk density < 1.10.8 Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).

3. Polymer

Natural pH dependent swellable polymers are used. They remain protonated in the acidic media but show good swelling and solubility in the intestinal ph. Sodium alginate, chitosan, guar gum, LM Pectin is examples. They not only provide coating to the drug core but also act as release retardants.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 etc.

4. Cross linking agent

Acidified solutions of divalent cations are used as cross linking agents. Calcium chloride acidified with glacial acetic acid is widely used. They form cross linked gels by interaction with polymers. Unlike simple monomeric ions, the interaction of polyanion with cations (or polyanion with polycation) cannot be completely explained by the electro-neutrality principle. The three dimensional structure and presence of other groups influence the ability of cations (or anions) to conjugate with anionic (or cationic) functionalities.

5. Fixed oils/ mineral oils

They are used in emulsion gelation method where oils are used to impart buoyancy to the formulation since they have bulk density less than unity. E.g. Light liquid paraffin. The oil phase is emulsified in the water phase containing drug which is extruded into the acidified solution of cross linking agent to produce beadsEdible, 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.[33]

6. Release rate accelerants (5%-60%): e.g. lactose, mannitol.

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

8. Buoyancy increasing agents (upto80%): e.g. Ethyl cellulose.[34]

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS

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 (Bahco TM) analysis, Photo analysis, Optical microscope, Electro résistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air Pollution EmissionsMeasurements etc.

2. FLOATING PROPERTIES

Effect of formulation variables on the floating properties of gastric floating drug delivery system wasdetermined by using continuous floating monitoring system and statistical experimental design.

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 meterAtomic force microscopy (AFM), Contact profiliometer.

4. DETERMINATION OF MOISTURE CONTENT

The water content per se is seldom of interest. Rather, it shows whether a product intended for tradeand production has standard properties such as. Thus moisture content of the prepared formulations was determined by Karl fisher titration, vacuumdrying, Thermo gravimetric methods, Air oven method, Moisture Meters, Freeze drying as well byphysical 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), Cryogenicscanning electron microscopy (Cryo SEM), Light scattering imaging (LSI) etc. The swelling studies byusing Dissolution apparatus (USP disso-lution apparatus (usp-24) lab India disso 2000) wascalculatedas per the following formula.

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), Micro titrimetric methods, Inductively Coupled Plasma Atomic Emission Spectrometer (ICPAES) and also by using spectroscopy techniques (Elico Limited, Hyderabad).

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.

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.

9. POWDER X-RAY DIFFRACTION

X-ray powder diffraction (Philips analytical, model-pw1710) is the predominant tool for the study ofpoly-crystalline 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.

10. FOURIER TRANSFORMS INFRARED ANALYSIS

Fourier transform infrared spectroscopy (FT-IR, Shimadzu, 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 drug loaded polymer formulations were obtained on FT-IR. The pellets were prepared on KBR press under hydraulic pressure of 150kg/cm2; the spectra were scanned over the wave number range of3600 to 400 cm-1 at the ambient temperature.

11. DIFFERENTIAL SCANNING CALORIMETRY (DSC)

DSC (Shimadzu, Model-DSC-60/DSC-50/ MetlerToldeo) 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.[35,36]

APPLICATION OF FLOATING DRUG DELIVERY SYSTEM

1. Recent study indicated that the administration of Diltiazem floating tablets twice a day may be more effective compared to normal tablets compared to normal tablets in controlling the B.P. of hypertensive patients.
2. Modapar R HBS containing L-Dopa and Benserazide, here the drug was absorbed over aperiod of 6-8 hours and maintained substantial plasma concentration for Parkinsonianpatients. CytotechR- containing Misoprostol, synthetic prostaglandin –EL analogue, forprevention of gastric ulcer caused by non-steroidal anti inflammatory drugs (NSAIDS).
3. As it provides high concentration of drug within gastric mucosa, it is used to eradicate *H.pylori* (a causative organism for chronic gastritis and peptic ulcers).
4. Fluorouracil has been successfully evaluated in the patients with stomach neoplasm.
5. Developing HBS dosage form for tacrin provide better delivery systems and reduced its GIside effects.
6. Treatment of gastric and duodenal ulcer.
7. Enhanced bioavailability.
8. Sustained drug delivery.
9. Absorption enhancement.
10. Site specific drug delivery system.[37]

CONCLUSION

The various disease which arises from change in the circadian rhythm of human body are get treated by time specific &site specific i.e .controlled and targeted drug delivery system. Hence floating concept is used to retard the dissolution at lag time and gives burst and complete release at specific or predetermined time. So that FPDDS is more advantageous than regular pulsatile drug delivery system.

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