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Review Article

FLOATING PULSATILE BEADS: AN ORAL MULTIPARTICULATE PULSATILE DRUG DELIVERY SYSTEM - A REVIEW

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ABSTRACT

Pulsatile Drug delivery systems are gaining a lot of interest as they deliver the drug at the right site of action, at the right time and in the right amount, as per the pathophysiological needs of the diseases, resulting in increasing patient compliance. A combination of floating, pulsatile and multiparticulate systems is now widely employed for the treatment of various diseases. Floating pulsatile beads release drug after a lag time with no release during floating in the stomach after which a burst release in the upper part of the g.i.t. so drugs can be delivered at right time, in right amount and at right site of action by use of floating pulsatile beads.

Keywords: floating pulsatile multiparticulate system, beads, ionotropic gelation.

INTRODUCTION

Controlled drug delivery systems have acquired very important role in pharmaceutical Research and Development (R&D) business.[1] The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action. But in case of certain diseases that show chronobiological behaviour which demand site and time specific release of drug in a burst manner after a lag time. The above conditions demand release of drug after a lag time that is a time with no drug release [2]. Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off–release period, i.e., lag time. Here release of drug can be controlled by circadian rhythm, which regulates many body functions in human beings.[3]

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 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. FPDDS showed excellent lag phase followed by burst release in distal part of small intestine which gives site- and time-specific release of drugs acting as per chronotherapy of the diseases. A combination of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in upper GI tract after a defined time period of no drug release.

ADVANTAGES OF FLOATING PULSATILE DRUG DELIVERY

1. For better response keep the drug floated in stomach.
2. To prolong retention of drug in stomach
3. To release drug as per body's clinical need.
4. To avoid dose dumping.
5. Increase bioavailability of drug.

DISADVANTAGES OF FLOATING PULSATILE DELIVERY

1. Drugs which are irritant to gastric mucosa is also not desirable or suitable
2. The dosage form should be administered with a full glass of water (200-250 ml) .

3. Manufacturing this type of dosage form, multiple formulation steps, higher cost of production, need of advanced technology and trained/skilled personal needed for manufacturing.

METHODS OF FLOATING PULSATILE DRUG DELIVERY

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

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 behaviour due to unit to unit variation.

These can be developed in various types of dosage forms like:

i. Pellets
ii. Granules
iii. Microspheres
iv. Beads
v. Nanoparticles
vi. Microsponges [5]

Various types of multiparticulate pulsatile systems are

a. 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.

b. Reservoir systems with soluble or erodible polymer coating

The barrier dissolves or erodes after a specific lag time followed by burst release of drug from the reservoir core. In general, for this kind of systems, the lag time prior to drug release can be controlled by the thickness of the coating layer. However, since from these systems release mechanism is dissolution, a higher ratio of drug solubility relative to the dosing amount is essential for rapid release of drug after the lag period.

c. 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 quarternary ammonium compounds with succinic acid counter ion in the medium.

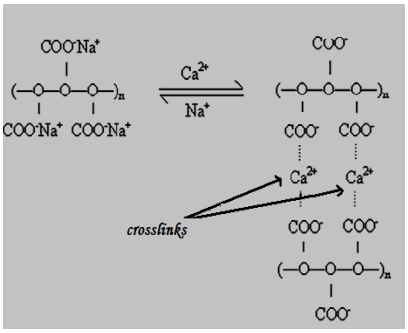
d. Low density floating multiparticulate systems

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.[6]

PREPARATION OF BEADS

IONOTROPIC GELATION TECHNIQUE

Ionotropic gelation involves simply the interaction of an ionic polymer with oppositely charge ion to initiate cross linking and it is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form beads. Various approaches to induce buoyancy in crosslinked beads, some of which include freeze-drying, entrapment of gas or gas forming agents, use of volatile oils or fixed oils, have been used.[7]



Electrostatic interaction between –COO groups of alginate and cross linker Ca++ ions.

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]

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 are examples. They not only provide coating to the drug core but also act as release retardants.

4. Cross linking agent

Acidified solution 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

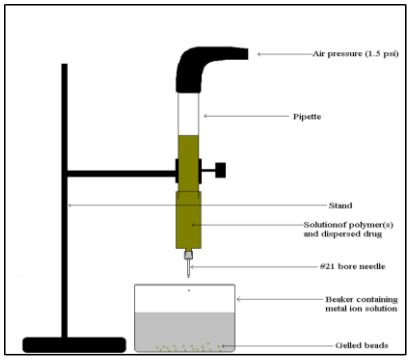
They are used in emulsion gelation method where oils are used to impart buoyancy to the formulation since they have bulk density less than unity. E.g. Light liquid paraffin. The oil phase is emulsified in the water phase containing drug which is extruded into the acidified solution of cross linking agent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

Types of ionotropic gelation

There are two methods differ from each other in the source of the cross linking ion.

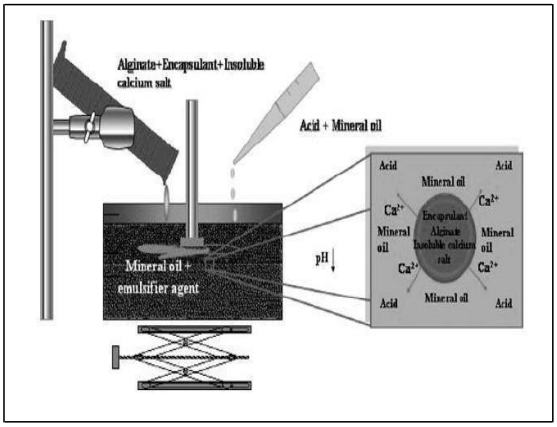
1. External ionotropic gelation

In this method the cross linker ion is positioned externally. The drug and gas forming agent is dispersed in polymer solution which is extruded into acidified solution of cross linking agent. External cross- linking produced thinner films with smoother surface, greater matrix strength, stiffness and permeability than internally cross-linked films. Externally cross-linked micropellets were also capable of greater drug encapsulation efficiency and slower drug release rate.



2. Internal emulsion gelation

In this method the cross linker ion is incorporated within the polymer solution in inactive form. In this method the drug is dispersed in the polymer solution in which oil is dispersed to get emulsion which is extruded to solution of cross linking agent.[7]



DIFFERENT TECHNIQUES OF PREPARATION

Jet cutting method

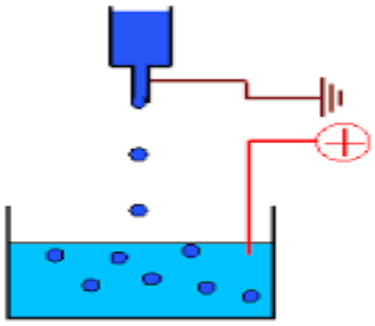
It allows the production of beads in the range of 0.2–3 mm in diameter even from high viscous fluids (e.g. polyvinyl alcohol solutions) at a high production rate and narrow particle size distributions. It uses mechanical forces to break up liquid jet by rotating cutting wire. Jet is cut in to cylindrical segments those attains spherical shapes.

Resonance method

It uses vibration applied at a constant frequency to liquid jet resulting in jet break up in to small uniform droplets. Vibration can be applied to liquid reservoir or nozzle.

Electrostatic method

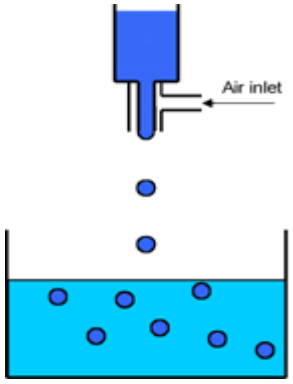
Small alginate beads with a narrow size distribution, ranging in size down to about 150µm, can easily be manufactured by using the electrostatic bead generator. Electrostatic droplet generation uses electrostatic forces to disrupt a liquid surface at capillary/needle tip forming a charge stream of small droplets. In this way liquid exposed to electrical field, introducing electrical charge to liquid surface and a repulsive outside directed force. An electrostatic voltage of a few kV is set between the needle feeding the polymer solution and the gelling bath. The droplet size is also largely determined by selecting an appropriate nozzle size. This lead to lab scale with 1 needle and production scale with 10 needles are available.[9]



Principle of electrostatic method

Co-axial air stream method

In this method coaxial air stream pulls droplets from a needle tip into the gelling bath. Coaxial bead generator works on this principle. This instrument generally uses for production of smaller quantities of spherical alginate beads ranging in size down to around 400 µm .



Principle of coaxial air stream bead generator

The Unit is equipped with two connections one for the hose, which feeds the alginate (or other) solution – the other connection is meant for an air-hose with 4 mm OD. The alginate (or other) solution may be fed into the unit with a syringe, using a syringe pump. A magnetic stirrer is placed underneath the gelling bath to keep the beads separated during gelling.[10]

Characterisation of floating pulsatile beads

a. *Invitro* drug release
b. Micromeritics studies
c. *Invitro* buoyancy study
d. Drug entrapment and drug loading
e. Swelling studies
f. Thermal analysis
g. Stability study

a. *Invitro* drug release

Dissolution studies were performed in using the USP dissolution test apparatus-II at 100 rpm. The dissolution studies of the beads were performed using USP 24 type II dissolution test apparatus .The drug release study was carried out in 0.1 N HCl for initial floating period followed with dissolution in phosphate buffer pH 7.4, each 900 ml, maintained at 37 ± 2 °C and agitated at 100 rpm. Samples were collected periodically and replaced with a fresh dissolution medium each time. Samples, after filtration through muslin cloth, concentration of drug was determined spectrophotometrically.

b. Micromeritic studies

1. Particle size and shape

Fifty floating beads were analyzed for their size distribution by optical microscopy. The mean diameter was determined by measuring the number of divisions covered by the beads using an ocular micrometer previously calibrated using a stage micrometer

2. Scanning electron microscopy (SEM)

The surface morphology and internal structure of the products were observed by scanning electron microscopy. Dry beads were placed on an electron microscope brass stub and coated with gold in an ion sputter. Pictures of the beads were taken by random scanning of the stub.

c. *Invitro* buoyancy study

In-vitro buoyancy studies were done using dissolution test apparatus USP type II (rotating paddle). Fixed number of beads were taken and added to the dissolution flask containing 0.1 N HCl as medium (900 ml). Temperature was maintained at 37 ºC ± 0.5 ºC for 8h. Paddle maintained at 50 rpm. The floating and the settled portion of beads recovered separately. Buoyancy percentage was calculated as the ratio

of the number of beads that remained floating and the total number of beads taken.

Buoyancy percentage =
Number of beads remained floating
Total number of beads

d. Percentage entrapment efficiency and drug loading

Accurately weighed quantities of beads were placed in 100ml phosphate buffer pH 7.4 and mechanically agitated on a shaker at 200 rpm for 24 hrs or 3hrs at 25^{0}C. Then the resultant dispersion were filtered through Whatt's man no. 41 filter paper and analyzed spectroscopically.[11]

Percentage entrapment efficiency (% EE) = AQ *100/TQ

AQ = actual drug content in the beads
TQ = theoretical drug content in the beads

Percentage drug loading (%DL) = WD* 100/WT

WD= weight of drug loaded in the beads
WT = total weight of the beads

e. Swelling studies

Beads were studied for swelling characterization. Prepared formulations were taken and weighed and placed in wire basket of USP dissolution apparatus II. The basket containing beads was put in a beaker containing 100 ml of 0.1 N HCl (pH 1.2) maintained at 37 °C. The beads were periodically removed at predetermined intervals and excess moisture is removed using a blotting paper and the immediately weighed. The same procedure was done with using phosphate buffer pH 6.8. Then the swelling ratio was calculated as per the following formula.

Swelling ratio = Wt/Wo

Wt =weight of beads at t time
Wo = initial weight

f. Thermal analysis

DSC thermo grams of beads with drug loaded beads were recorded on a disc calibrated with indium and zinc. The DSC runs were preformed over a temperature range of 50-250^{o}C at a heating rate of 10^{o}C per minute for bead formulation.

g. Stability studies

The stability studies for beads were done by keeping the sample beads at room temperature for 90 days. The beads were filled in capsules and these capsules were packed in vials. The vials were sealed and stored at room temperature only because the polymer used in preparation of beads i.e sodium alginate is not stable at higher temperature. The samples were put for 90 days. In the interval of each one month the beads were evaluated for different parameters like floating time, swelling ratios and drug release studies.[12]

CONCLUSION

Nowadays pulsatile drug delivery systems are gaining importance in various disease conditions specifically in diabetes where dosing is required at different time points. Among these systems, multi-particulate systems (e.g. pellets, beads) offer various advantages over single unit which include no risk of dose dumping, flexibility of blending them with different release patterns, as well as short and reproducible gastric residence time. Therefore floating pulsatile beads serves as a potential delivey system in the treatment of chronic conditions. However pulsatile drug delivery systems are still in developmental stage and research works are still going on to modify their mechanism.

MARKETED FORMULATIONS [13]

TECHNOLOGY	MECHANISM	*BRAND NAME*	*API*	*DISEASE*
OROS	Osmotic mechanism	Covera-HS ;XL	Verapamil Hydrochloride	Hypertension
Three dimensional	Externally regulated	Their Form	Diclofenac sodium	Inflammation
DIFFUCAPS	Multiparticulate	Innopran;XL tablets	Verapamil, Propranolol HCl	Hypertension
Pulsincap TM	Rupturable system	Pulsincap TM	Dofetilide	Arrhythmia
PULSYS	Multiparticulate	Moxatag TM tablets	Amoxycillin	Infection
TIMERx	Erodible or soluble barrier coating	OPANA ER tablets	Oxymorphone	Pain
CONTIN	Extended release tablets	Uniphyl	Theophylline	Asthma

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