

ORAL MULTIPARTICULATE PULSATILE DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

Pulsatile drug delivery aims to release drugs in a planned pattern i.e. at appropriate time and/or at a suitable site of action. Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimising side effects. However, in recent pharmaceutical applications involving pulsatile delivery, multiparticulate dosage forms are gaining much favour over single-unit dosage forms because of their potential benefits like predictable gastric emptying, least risk of dose dumping, flexible release patterns and increased bioavailability with minimum inter- and intra-subject variability. Based on these, the present review aims to study multiparticulate pulsatile delivery systems, for which the Reservoir systems with rupturable polymeric coatings and Reservoir systems with erodible polymer coatings are primarily involved in the control of release. Multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development. 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.

KEYWORDS: Pulsatile release, multiparticulate, chronotherapeutics.

INTRODUCTION

Oral controlled drug delivery represents the popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration, such system release the drug with constant or variable release rates. These dosage form offer many advantage such as nearly constant drug level at the site of action, prevention of peak valley, fluctuation with reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance^{1,2,3}. However there are certain conditions for which such a release pattern is not suitable. These conditions demands complete release of drug after a lag time. Chronopharmacotherapy, the drug regimen based on circadian rhythm is recently gaining much attention worldwide, various diseases like asthma, hypertension and acidity. These activities shows circadian variation that demands time scheduled drug release for effective drug action, e.g. inflammation associated with morning body stiffness^{4,6,7}. Asthma is one such disease where pulsatile drug delivery system can be useful. Circadian changes are seen in normal lung function which reaches a low point in the early morning hours. In case of cardiovascular disease, several functions e.g. blood pressure, heart rate, stroke volume, cardiac output, blood flow to the cardiovascular system are subjected to circadian rhythms². Osteoarthritis where the pain is more intense during night, rheumatoid arthritis where the pain peaks at morning hours, duodenal ulcer where the highest gastric secretion is in the night times and hypercholesterolemia where the cholesterol synthesis is higher at the night. Diseases with time

structure other than circadian rhythm are also possible e.g. diabetes follow the secretion of insulin stimulated by meal or tumour growth in cancer states, that follows body changes in blood flow. Menstrual cycle and the corresponding hormonal flux are also following cyclic patterns.

To follow this principle one has to design a dosage form such that it can be given at a convenient time e.g. bed time for the above mentioned diseases with the drug release in the morning.

Drug pharmacokinetics show circadian variation for various inflammatory drug like indomethacin, ketoprofen and diclofenac sodium which have greater absorption in the morning as compared to evening and site specific absorption from the small intestine. Therefore to develop dosage form for chronopharmacotherapy the desired drug release should be time specific as well as site specific.

Various techniques are available for the pulsatile delivery, broadly classified as single unit and multiple unit system. Single and multiple unit system work on the basic principle of erosion or dissolution, swelling and rupturing system. However single unit pulsatile drug delivery system may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology, that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action^{4,5}. In recent pharmaceutical application involving pulsatile delivery multiparticulate dosage forms are gaining favour over single unit dosage form.

Few advantages of multiparticulate pulsatile drug delivery systems⁵.

1. Less inter and intra subject variability
2. Low risk of local irritation
3. Least risk of dose dumping
4. Improved patient compliance
5. Improved stability
6. Improved bioavailability
7. Reduced adverse effects
8. Flexibility in design

Few drawbacks of multiparticulate system are

1. Several formulation steps
2. Higher cost of production
3. Low drug loading
4. Require advanced technology
5. Proportionally higher need for excipients
6. Lack of manufacturing reproducibility and efficacy
7. Large number of process variables
8. Trained/skilled individual needed for manufacturing

RECENT APPROACH TO PULSATILE DRUG DELIVERY: FLOATING PULSATILE DRUG DELIVERY

Floating pulsatile is gaining much popularity in advance drug delivery mentioned under chronotherapy. Multiparticulate pulsatile release dosage forms have longer dwelling time in the gastrointestinal tract, due to high unpredictable nature of gastric emptying process, may result in in-vivo variability and bioavailability problems. In converse, low density floating multiparticulate pulsatile dosage forms reside in stomach only and is not affected by local environment, varying pH or gastric emptying rate.

V. G. Somani, et al. prepared floating pulsatile hollow calcium pectinate beads. Hollow calcium pectinate beads containing Aceclofenac were prepared by a single ionotropic gelation technique with insitu action of buoyancy. Floating beads provided lag phase release in the alkaline pH useful for rheumatoid arthritis and osteoarthritis. Beads remained buoyant for 7-12 hrs⁷. Atmaram P. Pawar et al. developed Novel/Conceptual Floating Pulsatile System using high internal phase emulsion based porous material intended for chronotherapy. The objective of the work was to develop and evaluate a floating pulsatile system by inducing drug adsorption via solvent evaporation, owing to its simplicity, on the porous material synthesized by using high internal phase emulsion (HIPE) technique. Optimization of drug loading and subsequent drug release was done by employing 3² factorial design with solvent volume

and drug amount as selected variables. Ibuprofen, categorized as NSAID, was selected as model drug used in the treatment of arthritis showing circadian variation⁸. Pawar and Sher had reported a hollow calcium pectinate bead for floating-pulsatile release of diclofenac sodium intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. To overcome the limitations various approaches for imparting buoyancy as hollow/porous beads were prepared by simple acid-base reaction during ionotropic crosslinking. The floating beads provided two-phase release pattern with initial lag time during floating in acidic medium followed by rapid pulsed release in phosphate buffer. This approach suggested the use of hollow calcium pectinate microparticles as promising floating-pulsatile drug delivery system for site specific and time specific release of drugs for chronotherapeutic release of various diseases. The floating beads obtained were porous (34% porosity), hollow with bulk density <1 ⁹. Shaji J, Vishal P. Prepared multiunit (pellet) floating pulsatile drug delivery system for obtaining no drug release during floating in the proximal small intestine followed by pulsed, rapid drug release in distal small intestine to achieve chronotherapeutic release of indomethacin. The system developed consists of drug containing core pellet prepared by extrusion-spheronization process. Materials used were microcrystalline cellulose, eudragit S 100, sodium carbonate and HPMC K 100 M¹⁰. A. Pawar, S. Sharma. prepared low density multiparticulate system for pulsatile release of meloxicam. A multiparticulate floating drug delivery system was prepared by using porous calcium silicate and sodium alginate for time and site specific release of meloxicam¹¹. M. Gaikwad et al. developed a floating, pulsatile, multiparticulate drug delivery system intended for chronopharmacotherapy of arthritis. Cross-linked beads were prepared using low methoxylated pectin (LM104AS), sodium alginate, and low methoxylated pectin (LM104AS) along with sodium alginate by acid-base reaction during ionotropic gelation. Beads were dried in oven at 50°C for 4hrs. Aceclofenac was used as a model drug for encapsulation¹².

OTHER APPROACHES TO MULTIPARTICULATE DRUG DELIVERY SYSTEMS

The purpose of multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulations and yet devoid of the danger of variation in drug release profile and formulation behaviour due to unit to unit variations, change in gastro-luminal pH and enzyme population. A generally accepted view is that multiparticulate systems perform better in vivo than single unit system, as they spread out through the length of the intestine causing less irritation, enjoying a slower transit through the colon and a more reproducible drug release.

(a) Reservoir Systems with Rupturable Polymeric Coatings

These systems are based on a reservoir system coated with a rupturable membrane. Upon water access, the drug is released from the core after rupturing of the adjoining polymer layer, due to pressure build-up inside the system. The pressure required to rupture the coating can be achieved with swelling agents, gas-producing effervescent excipients or amplified osmotic pressure. Water soluble drugs are mainly released by diffusion while for water insoluble drug; the release is dependent on dissolution of the drug.

The time controlled explosive system (TES) is a multiparticulate system, in which the drug is in the inner core followed by swellable layer and an insoluble outer polymeric layer. Upon water entry, the swellable layer expands resulting in the film rupturing with subsequent rapid drug release. The release is to be independent of the environmental pH¹³⁻¹⁶. Hartman Kok et al. formulated a multiparticulate pulsatile release system, where release properties were dependent on the swelling of an UV cross-linked coating and its release properties were described by a mathematical model. The core consists of microcrystalline cellulose and sodium chloride coated with co polymer of ethylacrylate and methacrylic acid containing trifunctional acrylic monomer pentaerythritol triacrylate as crosslinking agent and photo indicator 2, 2-dimethoxy-2-phenyl-acetophenone. As water ingress, the coating swelled to such a degree that the diffusion coefficient of water increased. The lag time of drug release can be controlled by amount of crosslinking, duration of UV crosslinking and coating thickness¹⁸. Dashevsky et al. formulated rupturable pulsatile multiparticulate drug delivery system consisting of insoluble water permeable polymer coating Aquacoat[®] ECD, a swelling layer, comprising of binder and superdisintegrants and drug core. Lag time was controlled by coating level of the outer membrane and it was found to be brittle. This rupture was

sufficient to ensure fast drug release. Talc increased the brittleness of the membrane. As water enters there is swelling of swellable layer, result in rupturing of water membrane layer with rapid drug release. Author performed in vitro and in vivo evaluation of pulsatile system to investigate its drug release, using model drug acetaminophen¹⁹.

T.Guo.et al. formulated diclofenac sodium pulsatile release pellets which were prepared by extrusion spheronization technology and were coated in a mini fluidized bed spray coater having swelling material, as the inner coating and ethyl cellulose aqueous dispersion, as the outer coating. The lag time was influenced by the swelling material, the coating level of the inner swelling layer and outer controlled layer. The lag time for pulsed delivery of diclofenac was done and was found in good agreement for in vitro and in vivo release²⁰.

Schultz and Kleinebudde. developed the use of osmotically active agent that does not undergo swelling. When water imbibed through the coating, solution in the core is created. The drug molecules dissolve in the imbibed water, creating osmotic pressure inside the system. The osmotic pressure distinguishes between the core and the external medium providing the driving force for efflux through the pores in the coating. The lag time of the formulation was depended on the coating thickness and the core volume. The sodium chloride in the core influences the desired fast release. In absence of sodium chloride, sustained release was obtained after a lag time due to low degree of core swelling, which results in small fissures, while coat was not completely ruptured²¹.

S.H. Chew et al. formulated multiparticulate pellets, containing neutral core pellets containing intermediate HPMC layer and an outer insoluble diffusion layer consisting of Eudragit RS. They found that addition of sodium chloride to HPMC layer decreases the rate of swelling and thus delayed the bursting of pellets²³.

(b) Reservoir Systems with Erodible Polymer Coatings

In this type of system the drug release is controlled by erosion or dissolution of coat and this system is pH sensitive. The coatings have been employed because of their increased solubility at some area in the gastrointestinal tract. The sensitivity has been utilized for complete release in the intestine and prevent release in the stomach.

C. Kao et al. studied the films hydrations of various thicknesses in an attempt to deliver drugs to various sites in the gastrointestinal (GI) tract. In a theoretical simulation, it was found that the lag time could be controlled by varying the thickness of the coating polymer, which was equivalent to the amount of polymer coated assuming that the density of the dry polymer was constant. Diltiazem hydrochloride was selected as a model drug with high pH-independent water solubility²⁴. H N. Shivakumar et al. prepared a pH sensitive multiparticulate system intended to approximate the chronobiology of angina pectoris proposed for colonic targeting. The formulation comprising of eudragit S-100 coated pellets was designed for cronotherapeutic delivery of diltiazem hydrochloride. The drug loaded core pellets were produced by aqueous extrusion spheronisation technique using microcrystalline cellulose as the spheronizing agent and PVP K 30 as the binder. Different coat weights of eudragit S-100 were applied to the drug loaded pellets in the automatic coating machine to produce the pH sensitive coatings²⁵.

CONCLUSION

Drug delivery system with sustained release is not well-organized in treating diseases, especially with chronic pathophysiology, for which, pulsatile drug delivery is beneficial. Various advanced methods has been employed for developing pulsatile drug delivery like floating pulsatile drug delivery, rupturable polymeric coatings, erodible polymer coating systems etc. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place and in right amounts, holds good promises for the benefit of patients suffering from chronic problems like arthritis, asthma, hypertension etc. Thus designing of proper pulsatile drug delivery will enhances the patient compliance; optimise drug delivery to the target site and minimizing the undesired side effects. From technological point of view, multiparticulate systems seem to be more efficient than single-unit dosage forms in achieving pulsatile drug delivery and it can become even more sophisticated when coating technologies are incorporated.

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Table 1: Diseases requiring Pulsatile Drug Delivery

Disease	Chronological behaviour	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and at night	H2 blocker
Asthma	Precipitation of attacks during night time or early morning hours.	β 2 agonist, antihistaminics
Cardiovascular diseases	Blood pressure is low during the sleep cycle and rises steeply during the early morning awakening period.	Nitroglycerine, calcium channel blocker, ACE inhibitors etc.
Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Attention deficit syndrome	Increase in DOPA level in afternoon	Methylphenidate
Hypercholesterolemia	Cholesterol synthesis is generally higher during day time	HMG CoA reductase inhibitors