Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Chronotherapy and chronotherapeutic formulations of NSAIDs in the management of rheumatoid arthritis

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ARTICLE HISTORY

Received: 21.04.2017

Accepted: 30.05.2018

Available online: 30.06.2018

Keywords:

Ketoprofen (KP), NSAIDs, chronotherapy, Pulsatile Drug Delivery System (PDDS), rheumatoid arthritis

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ABSTRACT

Oral controlled drug delivery systems are the most common type of controlled drug delivery systems for oral route of drug administration with obvious benefits. These are usually designed in such a way that aimed at constant, variable, sustained drug release or targeting the drug to a particular site, tissue or organ. However, recently there are certain conditions for which conventional release pattern is not apt and it needs some type of timely release of drugs at specific sites. Chronopharmaceutics is a branch of pharmaceutics dedicated to the design and assessment of drug delivery systems that release the active ingredient at a rhythm that ideally matches in real time, the biological demand for a given illness therapy or prevention. These are conditions which demand release of medicament after a lag time. Ketoprofen (KP) is a promising drug candidate for fabrication of Pulsatile Drug Delivery System (PDDS) in many ways in the management of rheumatoid arthritis through chronotherapy.

INTRODUCTION

The relation of many conditions and body functions on circadian rhythm is widely established. Particular rhythms in the onset and extent of symptoms were observed in conditions like bronchial asthma, myocardial infarction, angina, arthritis, ulcer, diabetes, and hypercholesterolemia and in high blood pressure. The treatment of such conditions relies on chronopharmacotherapy[1].

Chronopharmaceutics is a branch of pharmaceutics dedicated to the design and assessment of drug delivery systems that release the active ingredient at a rhythm that ideally matches in real time, the biological demand for a given illness therapy or prevention. These are conditions which demand release of medicament after a lag time.

In alternative words, it's needed that the drug should not be released at all throughout the initial phase of dosage form administration. This kind of release pattern is termed as "Pulsatile release". PDDS or Pulsatile drug delivery system is often outlined as a system where the drug is released immediately after a well-defined lag period according to the circadian rhythm of the malady[2]. Arthritis or inflammatory disease state with pathological symptoms like stiffness and swelling of joints and limited mobility. Within the morning hours, all these symptoms are at their peak.

Majority of Pulsatile delivery platforms involve coated formulations where the applied polymer serves as the drug release-controlling mediator[3]. Once exposed to liquid medium, the coating at the outset performs as a protecting barrier and, afterwards, undergoes a timely collapse based on miscellaneous mechanism depending on its physico-chemical and formulation character.

DISCUSSION

Nonsteroidal anti-inflammatory drugs (NSAID) present a vital therapeutic category used to alleviate pain and inflammation. Based upon their chemical structure, NSAIDs may be more classified: salicylate derivatives, propionic and acetic acid derivatives, fenamic and enolic derivatives, COX-2 inhibitors, sulphonanilides etc. KP (Ketoprofen) comes under propionic acid derivative class of NSAIDs.

Common side-effect shared by all NSAIDs in including KP is gastric intolerance (hemorrhage), during which incidence of ulcers in stomach persist even with the administration of single therapeutic dose. However, there is still a call for developing the risk free profile for these drugs by improving the efficiency of therapy[4]. One such latest approach is chronotherapy, within which the drug release is matched with circadian rhythms. The chronotherapeutic strategy has rumored promise in some therapeutic conditions, together with the managing of nocturnal bronchial asthma, hypertension, nocturnal acid breakthrough, nighttime angina and allergic rhinitis.

KP is called as 2-(3-benzoyl phenyl) propionic acid. It's known effects are analgesic, anti-inflammatory, and antipyretic. It is employed in a broad range of severe and chronic inflammatory diseases and in the management of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and abdominal cramps in connection with menstruation. Recently, additional interest in KP lies within their possible therapeutic edges in the bar of various cancers including colorectal and respiratory organ cancers also as in the treatment of nerve degenerative disorders like Alzheimer's disease and, Parkinson's disease. The drug is currently available in capsule, tablet, solution, injectable solution, suppository, and topical gel formulations [5].

Chronobiology and Chronotherapy

The dependence of many disease conditions and body function on circadian rhythm is well recognized. A hereditary control of a master clock situated in the nucleus Suprachiasmaticus has been recently projected. Numerous studies conducted, suggests that pharmacokinetics, drug efficiency and adverse reactions is tailored by following treatment corresponding the biological tempo[6] Specificity in delivering higher quantity of drug in a burst manner at circadian rhythms associated with particular pathological conditions can be a key issue to attain maximum drug effects. Particular rhythms in the beginning and level of symptoms were found in diseases such as asthma attack, myocardial infarction angina pectoris, arthritis, ulcer, diabetes, attention deficit hyperactivity disorder (ADHD), hypercholesterolemia and hypertension. The management of these conditions depends on chronopharmacotherapy, dosage regimen based on the circadian rhythm[7].

Chronobiology is the study of biological rhythms, their mechanisms and it's clearly applicable in the fields of pharmacology, medicine, and delivery of drugs. Notably, the term "chrono" essentially refers to the study that each metabolic happening follows rhythmic changes in time. Circadian Rhythms (CRs) are, endogenous oscillations that occur with a cyclic nature of about 24 h and regulate several body functions like-metabolism, sleep pattern, hormone production etc.

Chronotherapy is the study of circadian or other systemic changes in the susceptibility and sensitivity of the target system to a drug chronotherapy refers to a treatment technique in which *in-vivo* drug availability is timed to match rhythms of disease so as to optimize therapeutic outcomes and minimize side effects. Chronopharmaceutics is a branch of pharmaceutics dedicated to the fabrication and evaluation of drug delivery systems that release a drug at a rhythm that ideally match in real time the biological necessity for a given disease therapy[8].

Circadian Rhythms

Circadian rhythms are endogenous rhythm (biological rhythm) pattern that cycles a daily (approximately 24 hour) basis under normal circumstances. The circadian cycle controls changes in performance, endocrine rhythms, behavior and sleep time. Additionally these rhythms control the wake -sleep cycle, body temperature, blood pressure, time of reaction, alertness level, hormone secretion, and digestive functions[9]. It is often referred to as the pacemaker because of the great amount of control of the circadian rhythm cycle. Morning and evening types are two explicit forms of time unit rhythms commonly discussed in research arena. Majority of the people falls someplace among the two types.

Rheumatoid arthritis and Chronotherapeutics

Rheumatoid arthritis (RA) is a malady in which body's own immune structure starts to attack body's tissue. Attack is directed not only to joints but also on different body parts. In RA injury mostly happens to the joint lining and cartilage resulting in wearing away of two opposing bones. Varied level of pain, swelling, joint stiffness and constant ache around the joints are the common symptoms[10]

RA is a chronic inflammatory autoimmune condition characterized by immunological abnormalities like hypergammaglobulinaemia, the occurrence of immune complexes and rheumatoid factors within the serum, and lymphocytic penetration of the synovium. The prime signs of RA are stiffness, swelling and pain of one or more joints typically most severe in the morning. RA shows a noticeable circadian deviation in its symptoms. The above situations require release of drug after a lag time. In different words, it is required that the drug must not be released in the least amount during the initial part of dosage form administration. This kind of release pattern is called as "pulsatile release". So Pulsatile DDS release a drug at a rhythm that ideally matches the biological requirement of a given therapy of disease.

Pulsatile Drug Delivery Systems

Pulsatile DDS delivers a drug in rapid and burst manner within a short period of time directly past a programmable lag part. With the progression of technologies within the pharmaceutical field drug therapy has changed its path. In conventional therapy, the drug is released straight after administration. Therefore, the drug amount in the plasma is raised and usually it is over the virulent level. Sustained and controlled release devices are not appropriate in some cases like time-programmed administration of hormones and some other drugs. The conclusion from the new science of chronobiology clearly exposes that biological functions and processes are not static over time. Thus, these systems are not appropriate for the proper treatment of the diseases exhibiting circadian path. PDDS has fulfilled this requirement [11].

Advantages of Pulsatile Drug Delivery System:

There are several advantages of pulsatile dosage form over conventional dosage form.

1. Improves absorption and bioavailability of drugs than conventional immediate or sustained release dosage forms due to its capability to release drug in a burst manner, at target site of absorption.

2. Site targeting permits delivery of poorly bioavailable drugs that would get destroyed in higher alimentary canal environment e.g. (peptide and protein molecules)

3. Reduces dose of drug without decrease in therapeutic effects.

4. Decreases side effects.

5. Low drug interaction due to lower cytochrome P450 isoenzymes.

6. Decreases changes occurring in bioavailability of drug administered with food.

7. Improved compliance.

8. Programmed chronotherapy delayed release provides paramount treatment of diseases.

9. Pulse release permits multiple dose administration in a single dose form.

10. Site-specific release for local management of diseases can be obtained. Change in pH of GIT will not affect release of drug, viscosity of lumen contents, and stir rate of alimentary canal.

11. Several solid dosage forms like granules, microspheres, micro particles, tablets, capsules, and pellets can be fabricated into Pulsatile DDS.

Drug release profiles from pulsatile drug delivery

The pulsatile effect, i.e., the release/ discharge of drug as a "pulse" after a lag time has to be planned in such a way that a complete and rapid drug release should follow the lag time. Such systems are also referred to as time-controlled, as the drug released is independent of the environment.

Pulsatile DDS are gaining a lot of interest these days. These systems have a particular mechanism of delivering the drug rapidly and fully after a “lag time” i.e., a period of “no drug release”.

Mechanism of drug release from pulsatile drug delivery systems

The mechanism of drug release from PDDS is often occurring in the following ways:

Diffusion, erosion and osmosis are the popular mechanism involved in the drug release from PDDS

Methodologies for Pulsatile Drug Delivery

Several methodologies are developed and applied to design chronotropic systems for desired pulsatile drug release. These methodologies can be generally classified into three major categories:

1. Time controlled pulsatile release system
2. Stimuli induced pulsatile drug delivery systems
3. Externally regulated pulsatile drug delivery systems

CHRONOTHERAPEUTIC FORMULATIONS OF KP IN RHEUMATOID ARTHRITIS

The following approaches are commonly followed in the preparation of chronotherapeutic formulations of ketoprofen[12].

1) Press coated tablets

This drug delivery system is designed to deliver the drug at such a time when it might be most necessary to patient of rheumatoid arthritis. The press coated tablets contain ketoprofen in the inner core formulated by direct compression method with an outer coating of various amounts of hydroxyl propyl methyl cellulose (HPMC K4M)

Usually prepared by direct compression method. The core tablet contains ingredients of ketoprofen, sodium starch glycolate, ludipress and magnesium stearate. HPMC K4M, Ludipress (directly compressible lactose) and magnesium stearate were used to coat the core tablet.

The lag time and time-controlled release behavior of KP from press-coated tablets could be modulated by varying the concentration of polymer in outer coating layer and thickness of the compression coating. For rheumatoid arthritis the optimal time for an NSAID to be taken is after the evening meal. Considering this the preferable lag time would be of six hr.

2) Compression coated tablets

Core tablets of ketoprofen can be prepared using the wet granulation method . Core tablets can be coated with Eudragit S100 and Eudragit L100 by compression coating methodology to achieve desired lag time.

The composition of core tablet can consist of microcrystalline cellulose, sodium starch glycolate, magnesium stearate, talc and polyvinyl pyrollidone. The drug and excipients can be mixed and granulated using PVP K30 solution as the granulating agent. The wet mass is passed through sieve no. 30 and also the granules were dried and compressed into tablets employing a tablet machine equipped with 6.5 mm diameter punch.The core tablets are coated using Eudragit S100 (10%) by the compression coating methodology. The complete compression coated tablet is prepared by placing 500th of the outer layer powder mixture in the die, manually centering the previously prepared core tablets on the powder within the die & loading the remaining 500th of the outer layer powder mixture into the die, the contents are then compressed using a single press tableting machine fitted with a 8 mm diameter concave punch set. Thus, pulsatile release of ketoprofen can be achieved from compression coated tablets using Eudragit® polymers.

Pulsatile release multiparticulate systems-pH responsive dual pulse multiparticulate dosage forms

Preparation of ketoprofen core pellets

Drug-containing core pellets were prepared by extruder spheronizer. Ketoprofen, spheronizing agent Avicel pH 101, filler lactose, superdisintegrant croscarmellose sodium, and osmogent sodium chloride were mixed to form a uniform blend. The binder solution PVP K30 (2.5%, w/v in 50:50 alcohol:water) was slowly additional within the powder mixture to achieve a consistency of the damp mass appropriate for further extrusion spheronization process. The ready mass was in real time passed through a screw-type extruder exploitation one millimeter diameter screen with the speed set at 15 rpm. The extrudates were then transferred to spheronizer for 1520 minutes at a rotation speed of 750 rpm. The resultant pellets were dried at 50°C in an oven for 30 minutes. Preparation of initial dose pellets

Preparation of second dose pellets

The core pellets were coated with a second pH-responsive polymer of methacrylic acid and methyl methacrylate Eudragit® S100. The polymer was sprayed onto the core pellets using a spray gun in a pan coater to achieve a weight gain in the range of 2.57.5%. The conditions for coating are as follows: pellets charged 25 g, preheating temperature 50°C, preheating time 10 minutes, and outlet blower temperature 65°C. Pellets were dried in coating chamber for 15 minutes at 50°C after a desired weight gain.

It would be all over that the pH-dependent dual pulse release coated pellets would be a promising drug delivery system for general administration of NSAIDs for RA. The pellets were designed to prevent drug release in stomach and to release drug rapidly after the predetermined lag time. The system consists of a core containing a drug (ketoprofen), a swelling agent of croscarmellose Na, osmogen sodium chloride, and a coating film of Eudragit® L100-55. For the first dose, Eudragit® L100-55 coating gets dissolved in an environment of pH above 5.5 and causes the swelling agent to expand and release the drug. The second dose pellets were coated with Eudragit® S100 polymer

desired to dissolve after a lag time of 5 hours.

Novel core-shell Chronotherapeutic system

Matrix systems fabricated from a pectin matrix and double layered particles (core-shell systems) made of a core of pectin and a shell of Eudragit S100® is developed. Pectin-Ketoprofen particles showing the best technological properties were selected as starting core material for the production of core shell systems, covering the drug particles with Eudragit S100® an anionic copolymer of methacrylic acid and methyl methacrylate insoluble in acid pH.

Ketoprofen loaded beads

A weighed amount of pectin can be dissolved in deionized water at room temperature under light stirring in order to get polymer solution (6% w/w). Afterwards, different amounts of ketoprofen were suspended into the polymer solution and stirred for 2 h so as to obtain three different drug/ polymer ratios in the pectin solution (1:20, 1:10 and 1:5 w/w). Beads were manufactured by a vibrating nozzle device, equipped with a syringe pump, pumping the drug/polymer solution through a nozzle 400 mm in diameter. A stroboscopic lamp was set at the same amplitude as the frequency, so as to visualize the falling droplets. These latter can be jellified under light stirring. The beads were held into the gelling solution for 5-10 min at room temperature then recovered with a sieve and thoroughly rinsed with deionized water. Finally, the beads can be dried at room temperature by exposure to air.

Core-shell systems

The core-shell system developed can be able to keep ketoprofen in the acid simulated environment and to prolong the release in intestinal simulated environment until 5 h. This formulation is therefore feasible and probably effective as a dosage form appropriate for the chronotherapy of early morning pathologies that is demanding to have drug products to be taken at bedtime and able to act in the early morning.

Ketoprofen-loaded pH-triggered colon targeted microspheres

The weighed amounts of ketoprofen and Eudragit S-100 is dissolved in equal ratio of mixed solution of ethanol and dichloromethane. The resulting drug-polymer solution is poured into PVA solution under predetermined stirring speed and was continued till the translucent emulsion globules became opaque harden microparticles. The harden microparticles were separated by filtration and washed with few ml of distilled water for three times. The resulting microparticles were dried under room temperature for one day.

Inclusion of ketoprofen into pH-triggered polymer, eudragit S-100 microsphere formulation may present a prominent way to intentional delayed absorption/release of drug following oral administration to accomplish chronotherapy of early morning symptoms of RA.

CONCLUSION

The symptoms of rheumatoid arthritis are always worse in the morning. Taking long-acting NSAID like ketoprofen at bedtime optimizes their therapeutic impact and minimizes or averts their side effects. 12-hour sustained-release NSAIDs that are taken twice daily must include a night or bedtime intake time to ensure adequate control of the prominent morning symptoms of rheumatoid arthritis.

Pulsatile drug delivery is one such system that, by delivering a drug at right time, right place, and in right amounts, holds sensible promises of benefit to the patients suffering from chronic problem like rheumatoid arthritis. Immediate release formulation and extended release formulations are not economical in treating the diseases especially diseases with chronological pathophysiology, for which, Pulsatile drug delivery is helpful. The drug is delivering in this system when its actual concentration is required as per chronological need, therefore pulsatile release systems should be promising in the future.

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