Review Article ISSN:2321-2624

International Journal of Medicine and Pharmaceutical Research
www.pharmaresearchlibrary.com/ijmpr

Chronopharmacokinetics: As Targetted Drug Delivery for Rheumatoid Arthritis by PDDS

A. Srikanth[1*], Y. Prasanna Raju[2], N. Devanna[3], Kambham Venkateswarlu[4]

[1]*Department of Pharmacology, Oil Technological Research Institute, Anantapur-515001, Andhra Pradesh, India.*
[2]*Department of Pharmaceutics, Sri Vidyanikethan College of Pharmacy, Rangampet, Tirupati-517102, A.P, India.*
[3]*Department of Chemistry, Oil Technological Research Institute, Anantapur-515001, Andhra Pradesh, India.*
[4]*Department of Pharmaceutics, Oil Technological Research Institute, Anantapur-515001, Andhra Pradesh, India.*
Received: 7 April 2014, Accepted: 29 May 2014, Published Online: 10 June 2014

Abstract

The main aim of this review is "how to target the Rheumatoid Arthritis by Pulsatile Drug Delivery System through chronopharmacokinetic information". The patients who are suffering from Rheumatoid Arthritis will have pain at morning time. Due to this chronopharmacokinetic studies, this gives the information about variation in drug plasma levels as a function of time usually 24 hours and the mechanism responsible for that time dependent variation. So now the targeted drug delivery will happen in that patients and they will be free from the pain rapidly. PDDS releases the drug for prolonged period of time, especially after the lag time.
Key words: Chronopharmacokinetics, Rheumatoid Arthritis, PDDS.

Contents

***Corresponding author**
A. Srikanth
JNTUA-Oil Technological Research Institute, Anantapur-515 001, A.P, India
E-mail: srikanthvbcops@gmail.com
Manuscript ID: IJMPR2066

PAPER-QR CODE

1. Introduction

Since fourth century BC, the Alexander the Great's scribe Androsthenes had noted leaves of certain tress opened during day times but closed during night time. This time based reaction is called as rhythmicity. The French astronomer Jean Jacques had conducted the first experiment on biological rhythms, in 1729. Many drugs efficiency and toxicity mainly depends on the rhythmicity [24 hours] of body and dosing schedule. Rhythms are nothing but biochemical, physiological and behavioural processes. Some several drugs cause changes in rhythms of body can takes place, so this may leads to severe adverse reactions. To minimize this, should maintain optimum dosing schedule with optimum dose. All the drug delivery systems designed for getting the constant release rate [1, 2, 3, 18, 19].

II. Chronopharmaceutics:

To understand Chronopharmaceutics, the meaning of the following terms should be known. Those are

A. Chronobiology
B. Pharmaceutics [3, 4, 5, 6]

A. Chronobiology:

The name itself indicates the study of biological rhythms and their mechanisms.
The meaning of biological rhythms means a number of characteristics.
Rhythms types:

A. Ultradian
B. Circadian
C. Infradian[3, 4, 5, 6]

B. Pharmaceutics:

It deals with the design and evaluation of pharmaceutical dosage forms. Based on previous definitions, chronopharmaceutics is nothing but a branch of pharmaceutics which is devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of given disease therapy. Chronopharmaceutical drug delivery system is also called as a time controlled and site specific delivery system[3, 4, 5, 6].

II. Ideal characteristics of Chronopharmaceutical drug delivery system:

a. Should be non-toxic.
b. Should have the feedback control system [self-regulation]
c. Should have specific triggering biomarker for respective disease.
d. Should be easy to administer
e. Should be easy to manufacture
f. Should be biocompatible[3, 4, 5, 6]

IV. Biological rhythms:

The study of biological rhythms and mechanisms of biological time keeping is called as chronobiology. Biological rhythms defined as the characteristics of period, level, amplitude and phase [6, 7].

Period:

The time required to complete a single cycle is called as period.
Short term biological rhythms occur within seconds.
An intermediate biological rhythm occurs for about few hours.
Long term biological rhythms occur for about days [7].

Level:

It represents a baseline, around this baseline rhythmic variation occurs [7].

Amplitude:

This is nothing but a measurement of magnitude of predictable in-time variability due to biological rhythms. The amplitude of rhythms may changes with aging [7, 8].

Phase:

It is defined as the clocking of specific features of a rhythm relative to the corresponding time scale [7].

Mechanism of biological timekeeping:

A Suprachismatic nucleus controls the circadian rhythms by its master clock network. Suprachismatic nuclei present in in the hypothalamus and pineal gland [7, 9].

V. Chronopharmacology:

It is the study of kinetics and dynamics of medications which are directly affected by endogenous biological rhythms and also how the time of dosing of medication affects the biological time keeping is called as the chrono-pharmacology[6, 7, 10].

Two types:

A. Chronokinetics
B. Chronodynamics

A. Chronokinetics:

It is the study of differences in absorption, distribution, metabolism, elimination with corresponding to the dosing time is called as the Chronokinetics [7, 10].

B. Chronodynamics:

It is the study of differences in effectiveness of medications with relation to dosing time called as Chronodynamics [7, 10].

VI. Rheumatoid arthritis:

It means pain at the joints. In Rheumatoid arthritis, there is a evidence of circadian rhythm in the plasma concentration of c-reactive protein and interleukin-6. Different types of drugs used for treatment of rheumatoid arthritis but different drugs having different pharmacological actions and adverse effects. These effects might be depending on the time of day of administration and time at which drug was released. Patients who are suffering with osteoarthritis may have pain at night time and less pain at morning time. So to treat this disease, the drug should

release at night time more and at day time less concentration. In case of Rheumatoid arthritis, the pain will be high at morning time but decreases throughout the day. So to treat this disease, the drug concentration should be more in blood at morning time and less at day time. If drug concentration maintains like this means there may be less adverse effects and optimum therapeutic activity will be obtained. So for treating diseases which changes their nature with time can be treated by Pulsatile Drug Delivery System [3, 11, 12, 17].

VII. Pulsatile Drug Delivery System (PDDS):

Now a day the Pulsatile Drug Delivery System (PDDS) is gaining much popularity. It has designed to release a drug for prolonged period of time. It has an advantage i.e after a lag time it can release the drug immediately and completely. Lag time defined as the time between when dosage form is placed in aqueous environment and the time at which the active ingredient gets to release from dosage form [13, 14, 15].

Drug release profile from Pulsatile drug delivery system:

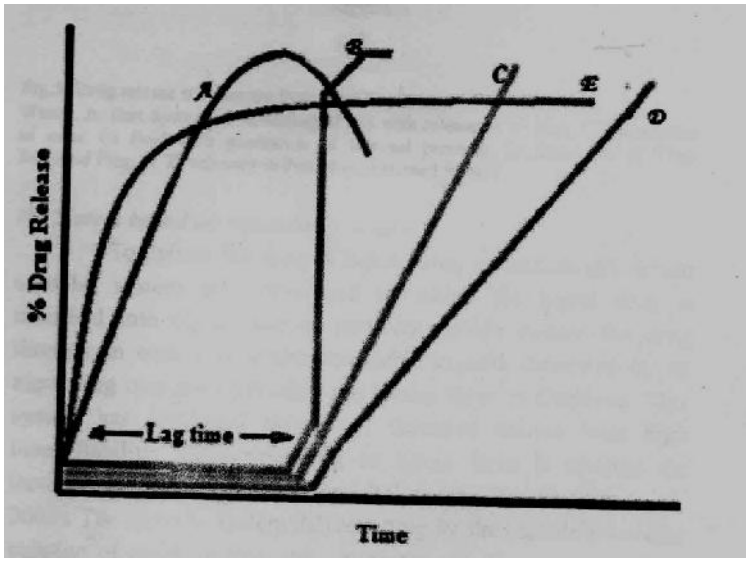

Figure 1. Drug release profile from Pulsatile drug delivery system

A. Convetional release profile
B. Burst release of drug after lag time
C. Delayed release profile after lag time
D. Constant release profile in prolonged period after lag time
E. Extended release profile without lag time[13]

2. Types of PDDS

1. Time controlled PDDS
2. Externally regulated PDDS
3. Multiparticulate system
4. Stimuli induced PDDS[13, 14, 15]

1. Time controlled PDDS:

In this system the pulsatile drug release is obtained after a specific time interval.

This system contains two components:

A. Immediate release type: which releases the drug immediately there by shows its pharmacological action.
B. Pulsed release type: which releases the drug slowly thereby shows its pharmacological action. [13, 14]

Types:

1.1. Single unit pulsatile system
  1.1.1. Pulsincap system [Capsule based system]
1.2. Delivery systems with ruptured coating layer
1.3. Delivery systems provided with erodible coating layers
1.4. Capsule shaped system provided with release controlling plug
1.5. Pulsatile system based on osmosis [13, 14]

1.1. Single unit pulsatile system:

1.1.1. Pulsincap system [Capsule based system]:

Mostly all the single unit systems are developed in capsule especially Pulsincap System.
It has three components which are

- Outer [top] soluble portion [Cap]
- Middle swellable portion [Plug]
- Inner drug portion

Plug controls the lag time.
The capsule is water insoluble in nature.
When the capsule comes into contact with dissolution medium, the capsule gets swell.
After a lag time, the plug itself pushes out; thereby drug comes out from the capsule [13, 14].

Design of Pulsincap:

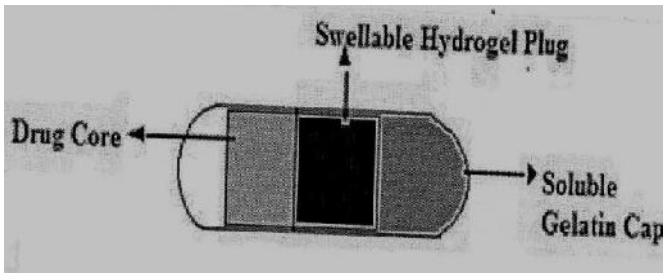

Figure 2

Mechanism of release of drug:

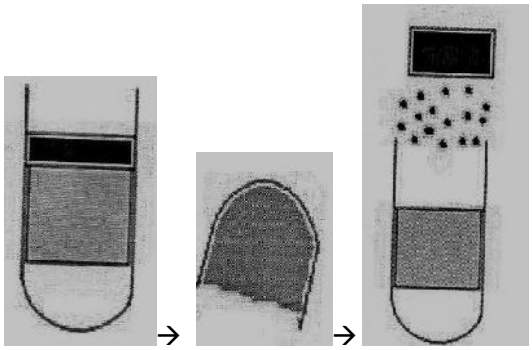

Figure 3

1.2. Delivery systems with ruptured coating layer:

It has three components, which are

A. Outer rupturable layer
B. Middle swellable layer
C. Inner drug core

When this system comes into contact with dissolution medium, the middle swellable layer gets swell there by outer layer gets rupture. Now drug will be released rapidly. The rupture may be induced by swelling [14, 15,16].

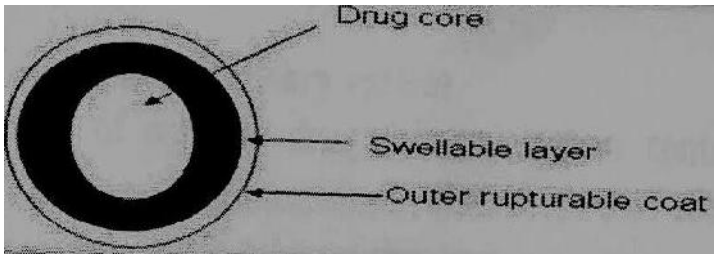

Figure 4

1.3. Delivery systems provided with erodible coating layers:

In this system, the core tablet is coated with erodible coating layer.
So now the time dependent release of drug will be attained.
The time dependent release of drug is depend on the thickness of the outer erodible layer [14, 15].

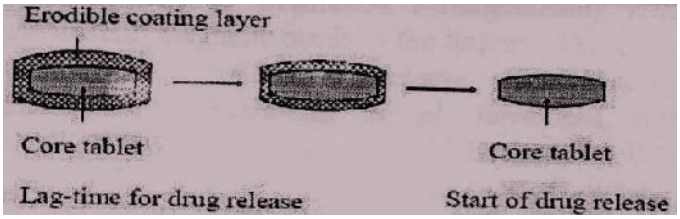

Figure 5

1.4. Capsule shaped system provided with release controlling plug:

This system consists of plug which was placed between immediate phase and pulsed release phase.

On contact with dissolution fluid, the outer cap rapidly dissolves there by immediate release component will be released followed by pulsed release component [14, 15].

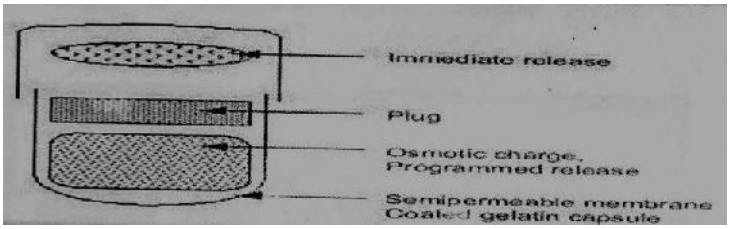

Figure 6

1.5. Pulsatile system based on osmosis:

In this system, the capsule coated with semipermeable membrane.

It has a plug which contains osmotically active agent.

On contact with dissolution medium, first immediate release phase released followed by drug[14, 15].

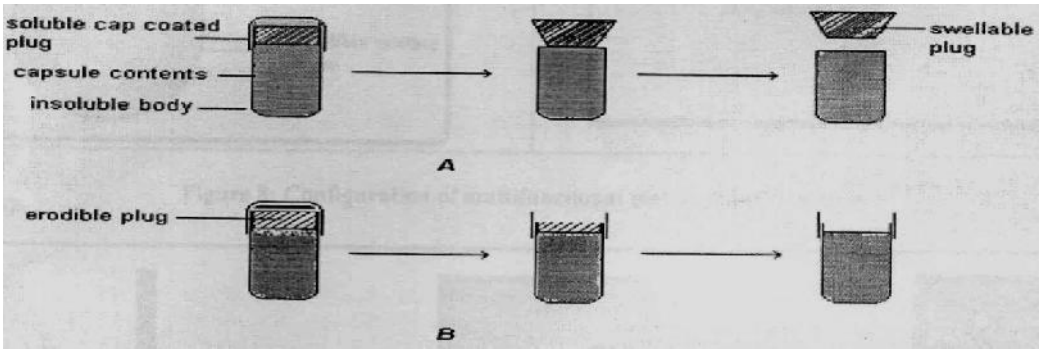

Figure 7

PORT System:

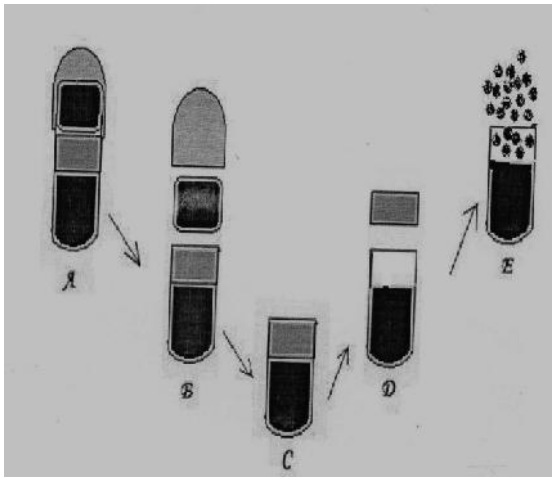

Figure 8

A. PORT System
B. Swelling of cap with release of 1st dose
C. Permeation of more GI fluid with generation of internal pressure
D. Expulsion of time released plug
E. Second dose released in pulsed or sustained form [14, 15].

2. Externally regulated PDDS:

The drug release is controlled by using external stimuli like irradiation, magnetism and electrical effect etc.
Eg:
If the drug release is controlled by magnetism, this system the magnetic beds in implants. When the magnetic field applied the drug release occurs due to the magnetic beads [14, 15].

3. Multiparticulate system:

This system is most suitable for achieving controlled or sustained release of oral dosage forms. This is reservoir type, in which outer layer is either rupturable or coating film and has capsular body. The main purpose of designing this multiparticulate system is to develop a reliable formulation which all the advantages [14, 15].

4. Stimuli induced PDDS:

In this type of system, the drug released is controlled by biological factors like temperature and other chemical stimuli like pH etc.

4.1. Temperature induced system:

Eg: Thermo-responsive hydrogel system
In this system swelling or deswelling happens in response to the temperature whether increased or decreased. This type of system consists of two components, which are immediate release type and pulsed release type phases. Pulsed release phase releases the drug according to changes in pH. The human gastrointestinal tract consists of different pH at different parts. So in this system selectivity of location is appreciable [14, 15].

Merits:

a. Patient compliance is appreciable.
b. PDDS improves the bioavailability.
c. PDDS cause a limited risk of local irritation.
d. It causes no risk of dose dumping.
e. It improves the stability.
f. There was a less inter and intra-subject variability.
g. It decreases the side effects.
h. Its characteristic of pulse release allows multiple dosing in a single dosage form.
i. In case of Chronotherapy, the programmed delayed release provides optimal treatment of diseases.
j. It gives the site specific release of drug for local treatment of diseases.
k. It also causes a less food effects [13, 14, 15].

Limitations of PDDS:

a. Withdraw of drug is not possible.
b. Drug load is low.
c. Drug release is somewhat incomplete.
d. *In vivo* variability.
e. Manufacturing steps high.

Diseases which require PDDS:

- Asthma
- Arthritis
- Diabetes mellitus
- Cardiovascular diseases
- Peptic ulcer

Examples of marketed technologies of pulsatile drug delivery system:

- CODAS
- Pulsincap
- DIFFUCAP[13, 14, 15]

3. Conclusion

The PDDS has many advantages when compared to other formulations. Circadian rhythm of the body is the important concept for knowing the optimum need of the drug in the body. With PDDS, patient compliance can be improved and the frequency of administration can be minimized. Due to its pulsatile mode, it can release the drug after a programmable lag phase. So adverse effects minimized and treatment will be optimized. These drug delivery

systems are now in early stage of development, so there will be a much scope to develop a clinical alternative by continuing the research on PDDS.

4. References

1. C.S. Pittendrich, Temporal organisation: reflections of a Darwinian clock-watcher, Annu. Rev. Physiol. 55, **1993**, 16-54.
2. M. Menaker, Circadian rhythms. Circadian photoreception, Science, **2003**, 294: 2511-2515.
3. Bi-Botti C. Youan, Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery?, journal of controlled release, 2004, **98**: 337-353.
4. M.H. Smolensky, G.E. D'Alonzo, Biologic rhythms and medicine, Am. J. Med., **1988**, 85, 34-46.
5. W.J. Hrushesky, Tumour Chronobiology, J, Control. Release, **2001**, 74: 27-30.
6. Singh Haribansh Narayan, Saxena Shivangi, Yadav Ajit Kumar, Singh Sunil, Chronotherapeutics: Clinical Science Based on the Circadian Rhythms**,** *International Journal of Medicine and Pharmaceutical Research***, 2013**, 1 (2): 226-234.
7. Michael H. Smolensky, Nicholas A. Peppas, Chronobiology, drug delivery, and chronotherapeutics, Advansed Drug Delivery Reviews, **2007**, 59: 828-851.
8. M.H. Smolensky, B. lemmer, A.E Reinberg, The chronobiology and chronotherapy of allergic rhinitis and bronchial asthma, Adv. Drug, Deli, Rev., **2007**, 59: 852-882.
9. E.Maronde, J.H. Stehle, The mammalian pineal gland: known facts, unknown facets, Trends Endocrinal. Metab., **2007**, 18, 142-149.
10. B.Lemmer, Chronopharmacology: cellular and biochemical interactions, Marcel Dekker, Inc., New Yark, **1989**, 720.
11. S.E. Auvil-Novak, The chronobiology, chronopharmacology and chronotherapeutics of pain, Annu. Rev. Nurs. Res., **1999**, 17, 133-153.
12. K.J. Vener, A. Reddy, Timmed treatment of the arthritis diseases: a review and hypothesis, Semin. Arthritis Rheum. 22, 1992, 83-97.
13. Anamika Singh, HarikeshDubey, InduShukla, Darmchand P. Singh, Pulsatile drug delivery system: an approach of medication according to Circadian Rhythm, Journal of applied pharmaceutical science, **2012**, 2 (3): 166-176.
14. B. Venkateswara Reddy, P. Sandeep, K. Navaneetha, P. Ujwala, Pulsatile Drug Delivery System–A Review, *International Journal Of Medicine and Pharmaceutical Research*, **2014,** 2(1): 479-487
15. Mayee RV, Shinde PV, Mane PP, A review: current reported technologies used in pulsatile drug delivery system, *International Journal of Pharmacy Review And Research*, **2012**, 2 (1): 23-30.
16. Kambham Venkateswarlu, A. Shanthi. Formulation and Evaluation of Sustained Release Glipizide Matrix. *IOSR Journal of Pharmacy and Biological Science*, **2012**, 2(5): 17-23.
17. K. Venkateswarlu. Pharmacological evaluations (Analgesic Activity) of 'Piper betel.' *International Journal of Pharmamedix India*, **2013**, 2(2): 688-693.
18. Kambham Venkateswarlu, N.Devanna. A Text Book of General and Dispensing Pharmacy, Edition-I, Pharmamedix India Publications, **2014**, pp. 18-33, 57-61.
19. Kambham Venkateswarlu. A Text Book of Pharmaceutical Dosage Forms: Evaluation Tests & Problems, Edition-I, Pharmamedix India Publications, **2014**, pp. 30-35.