



CODEN [USA]: IAJPBB

ISSN : 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<http://doi.org/10.5281/zenodo.4773935>Online at: <http://www.iajps.com>

Research Article

**FORMULATION AND *IN VITRO/ INVIVO* EVALUATION OF
CHRONOMODULATED DRUG DELIVERY OF BARICITINIB**Mayuri Bodige¹, B. Agaiah Goud², M. Bhagavan Raju³^{1&3} Sri Venkateshwara College of Pharmacy, Madhapur, Hyderabad. -500081² SRR College of Pharmaceutical Sciences, Valbapur, Warangal-Urban-505476

Article Received: April 2021

Accepted: April 2021

Published: May 2021

Abstract:

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic joint inflammation which ultimately leads to severe disability and premature mortality. It has a global prevalence of around 1% with the incidence among women being 2–3 times more than in men. The pathogenesis of the disease involves preclinical RA, genetic factors, and environmental factors. The RA has no known cure and the primary aim of treatment remains to attain lowest possible disease activity and recovery if possible. The aim of the present investigation was to formulate and evaluate chronomodulated drug delivery system of Baricitinib such that it releases the drug early in the morning, during which the symptoms of rheumatoid arthritis worsen. To develop chronomodulated drug delivery system of Baricitinib, initially core tablets of Baricitinib were prepared using three different supradisintegrants followed by coating with pH dependent polymer of Eudragit S100. The prepared core tablets are evaluated for physical parameters and an optimal system was identified. Further, coating composition of Eudragit L-100 was optimized and coating tablets of Baricitinib was prepared. The prepared coated tablets were evaluated for the *in vitro* release studies in 0.1N HCl, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer. Formulation with 12.5% of coating solution had shown a significant drug release after a lag time of 3 h (in pH 6.8 medium), 6 h (in pH 6.8 medium) and 8 h (in pH 7.4 medium), respectively. Thus, chronomodulated drug delivery system of Baricitinib was formulated and that if a tablet is administered around 9 pm to 10 pm, the drug release starts after a lag time of 6 h i. e., around 3am to 4 am.

Keywords: Baricitinib, chronomodulated, supradisintegrants**Corresponding author:****Mayuri Bodige,**

M. Pharmacy (Ph. D),

Assistant Professor,

Department of Pharmaceutics,

Sri venkateshwara College of Pharmacy,

Madhapur, Hyderabad.

Email: mayuri.smk@gmail.com, Phone no: 9000349289

QR code



Please cite this article in press Mayuri Bodige et al., *Formulation And In Vitro/ In vivo Evaluation Of Chronomodulated Drug Delivery Of Baricitinib.*, Indo Am. J. P. Sci, 2021; 08(05).

INTRODUCTION:

Over the last 30 years the pharmaceutical market has been demonstrated increasing preferably for controlled and targeted drug delivery system. Such systems have been focused on constant, variable; sustain drug release and/or targeting the therapeutic agent to a specific site/tissue/ organ. However, recently there are certain conditions for which such release pattern is not suitable. Such conditions that lead to the requirements of a time programmed therapeutic system, which capable of releasing drug after predetermined time delay and maintain constant drug levels through the day. To introduce the concept of chronotherapeutics, it is important to define the following concepts [1-3].

Chronobiology: [4, 5]

Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure. "Chrono" pertains to time and "biology" pertains to the study, or science, of life.

Chronopharmacology: [4, 5]

Chronopharmacology is the science concerned with the variations in the pharmacological actions of various drugs over a period of time of the day.

Chronopharmacokinetics: [4, 5]

Chronopharmacokinetics involves study of temporal changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH can play role in time dependent variation of drug plasma concentrations.

Chronotherapy: [4, 5]

Co-ordination of biological rhythms and medical treatment is called chronotherapy.

Chronotherapeutics: [6]

Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past.

Biological rhythms: [7, 8]

Ultradian Rhythms: Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24 h). E.g. 90 minutes sleep cycle.

Infradian Rhythms: Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24 hours). E.g. Monthly Menstruation.

Circadian rhythms: Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours. Interestingly, the term circadian is derived from the Latin *circa* which means "about" and *dies* which can be defined as "a day". Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle.

Rheumatoid arthritis is a chronic inflammatory autoimmune disorder. The cardinal signs of rheumatoid arthritis are stiffness, swelling and pain of one or more joints of the body characteristically most severe in the morning. Rheumatoid arthritis shows a marked circadian variation in its symptoms. A group of British volunteers self-assessed the pain and stiffness of affected finger joints every 2 to 3 h daily for several consecutive days. They also measured the circumference of the arthritic joints to gauge the amount of their swelling, and they performed grip strength tests to determine the effect of the arthritic condition on the hands [9, 10]. Ratings of the severity of joint pain swelling and stiffness were about 3 times higher between 08:00 and 11:00 am than at bedtime. In contrast, hand strength was lower by as much as 30% in the morning than at night. This is typical of rheumatoid arthritis sufferers [11, 12, 13].

The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, asthma, cancer, cardiovascular diseases, and peptic ulcer disease.

MATERIALS AND METHODS:

Materials baricitinib was chosen as a model drug and obtained from Chandra labs as a gift sample. Poly vinyl pyrrolidone k30, Croscarmellose Sodium, Microcrystalline cellulose used as super disintegrants, magnesium stearate, talc obtained from Vijlak Pharma Limited, and obtained from Hetero Drugs, Eudragit S 100, used as P^H sensitive polymers and obtained from Chandra labs.

Preparation of Baricitinib core tablet by direct compression method:

All the ingredients (Baricitinib, Crospovidone,

Croscarmellose Sodium, Microcrystalline cellulose) were triturated individually in a mortar and passed through #60 sieve. Then required of all ingredients were weighted for a batch size of 50 tablets and mixed Uniformly in a mortar except talc and magnesium stearate. Finally magnesium stearate and talc were added as lubricant and glident. This uniformly mixed blend was compressed in to tablets containing 30 mg drug using 5mm flat face surface punches on a cemach rotary tablet machine by direct compression method total weight of tablet was kept 100mg.

Three different weights 6.5gms, 12.5gms and 24.5grms of Eudragit L-100 was weighed and transferred into 100mL beaker to it 50mL of

acetone was added and it was thoroughly mixed for 10min then add remaining amount 50mL of acetone to it then it forms 12.5%(w/v) of Eudragit L100 coating solution. This coating will be dissolved in acidic pH and releases the drug at pH 6-7.

It was done by using the standard coating pan, where fixed numbers of tablets were coated each time by atomizing the polymeric coating solution through the means of spray gun. The scale-up variables including pan loading, pan speed, number of spray guns, spray rate, and inlet airflow etc. were considered. About 50 tablets of Baricitinib tablet were taken and allow to coatings in pan coater at 30 rpm and 50oC temperature. Coating was carried out with praying method and dried with same [14].

Table 1: formulation of Pulsatile Release Tablet of Baricitinib

ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Baricitinib	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Croscarmellose sodium	2	4	6	8	10	12	-	-	-	-	-	-	-	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	1	2	4	5	6	7	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	-	-	-	-	2	4	6	8	10	12
Micro crystalline cellulose	92	90	88	86	84	82	93	92	90	89	88	87	92	90	88	86	84	82
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Coating solution:**Table 2: Coating solution (Trail 1)**

S.NO	INGREDIENTS	QUANTITY
1	Eudragit L-100	6.5g
2	Acetone	100MI

Table 3: Coating solution (Trail 2)

S.NO	INGREDIENTS	QUANTITY
1	Eudragit L-100	12.5g
2	Acetone	100MI

Table 4: Coating solution (Trail 3)

S.NO	INGREDIENTS	QUANTITY
1	Eudragit L-100	24.5g
2	Acetone	100MI

Pre formulation studies

Bulk density, Tapped density, Hausners ratio, Void volume, Total porosity, Angle of repose was studied.

***In-vitro* release studies:**

In-vitro drug release of PDDS capsule was determined using USP dissolution apparatus II (paddle type) (electrolab TDT-08L). The dissolution studies were carried out in 0.1N HCl for 2 hrs, then 4 hrs in pH 6.8 phosphate buffers and finally 1hr in pH 7.4 phosphate buffer at every specific interval 5mL sample were withdrawn and it was replaced by fresh medium with respect to medium at the time to maintain the volume constant. After appropriate dilution, the sample solution was analyzed at 250 nm for Baricitinib by a UV-spectrophotometer. The amount of drug present in the sample was calculated with the appropriated calibration curve. Also the study was carried out in triplicates.

Kinetic Data /Model Fitting of Drug Release from Formulated Matrix Tablets

Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence there in vivo performance. The diffusion data obtained is fitted to mathematical models and the best fit is obtained to describe the release mechanism of the drug.

A number of mathematical models have been developed to describe the drug dissolution kinetics from controlled release drug delivery system as follow as Higuchi (cumulative % drug release versus square root of time), First order (log cumulative % drug remaining versus time), Zero order (cumulative % drug release versus time) and Peppas and Korsmeyer model (log cumulative % drug release versus log time).

Accelerated stability studies:

Stability of drug has defined by Lachman L (1987) the ability of particular formulation, in specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug products varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-tested and self-life to be established.

ICH specific the length of study and storage

conditions: Accelerated testing $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\%$ RH $\pm 5\%$ for 30 days.

In vivo* study of Baricitinib:*Animal Preparation**

Twelve New Zealand white rabbits of either sex rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25°C, RH 45% and 12h alternate light and dark cycle with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee (IAEC NO: CPCSEA/1657/IAEC/CMRCP/19-78).

***In vivo* Study design [15]**

Rabbits were randomly divided into two groups each group contains six animals. The Group A rabbits were fed with Pulsatile tablets of Baricitinib (optimized formulation F9), Group B fed with Marketed drug with equivalent dose to animal body weight. Blood samples (approximately 0.5ml) were obtained with syringes by marginal ear vein at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20 and 24h post dose. During collection, blood sample has been mixed thoroughly with heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5min and stored frozen at -20°C until analysis.

Preparation of Plasma Samples for HPLC Analysis

Rabbit plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re-suspended with 1 ml of Acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10min), the Acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a stream of nitrogen at room temperature.

Determination of cimetidine in Rabbit plasma by HPLC method [16]

The bioanalytical procedure involves extraction of Baricitinib and Methotrexate (internal standard, IS) from Rabbit plasma with a simple liquid-liquid extraction process. RP18 (150x4.6mm, 5.0 µm) column using 0.1% Tri ethyl amine in water adjusted pH-2.5 with OPA and Acetonitrile in simple gradient at a flow rate 1.0 ml/min. The column effluents were monitored by a photodiode array detector set at 224nm. Baricitinib and IS (Methotrexate) eluted at 10 and 8.3 min, respectively.

Pharmacokinetic Analysis:

The pharmacokinetic parameters, peak plasma concentrations (C_{max}) and time to reach peak concentration (t_{max}) were directly obtained from concentration time data. In the present study, AUC_{0-t} refers to the AUC from 0 to 24h, which was determined by linear trapezoidal rule and $AUC_{0-\infty}$ refers to the AUC from time at zero hours to infinity.

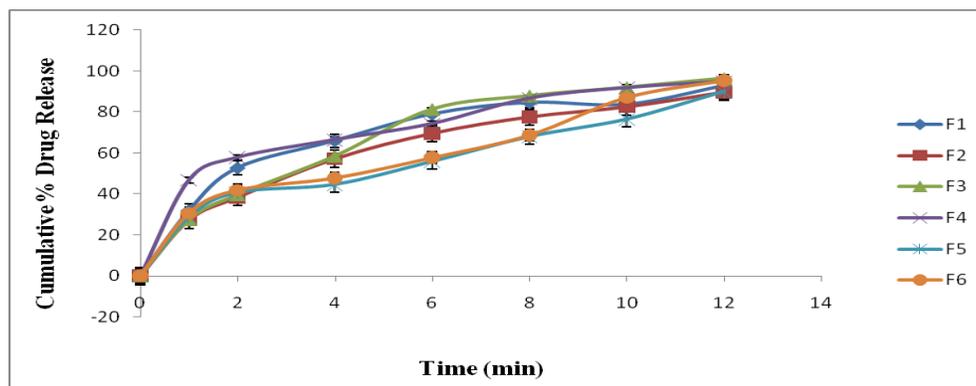
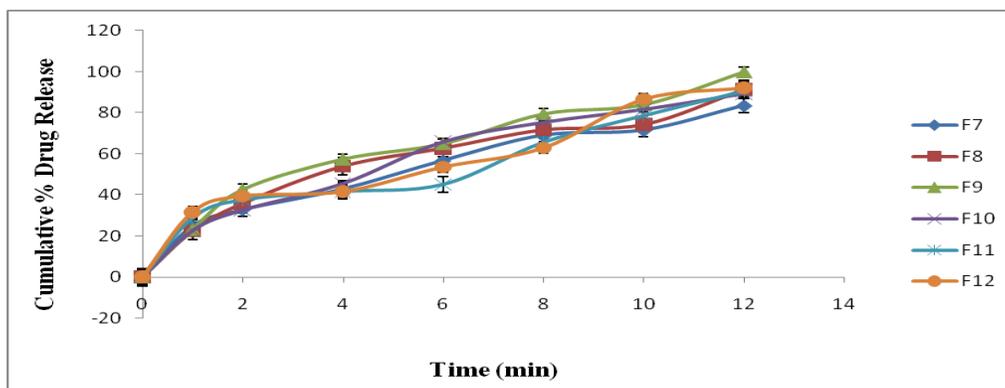
The $AUC_{0-\infty}$ was calculated using the formula $AUC_{0-t} + [C_{last}/K]$ where C_{last} is the concentration in µg/ml at the last time point and K is the elimination rate constant.

Various pharmacokinetic parameters like area under the curve [AUC], elimination half life ($t_{1/2}$), Volume of distribution (V_d), total clearance (Cl_T) and mean residence time for each subject using a non compartmental pharmacokinetic program. The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean ±SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION:**Table 5: Bulk density, Tapped density, Carr's index, Hausner ratio, Angle of repose, %drug content**

F code	Bulk density (mg/ml)	Tapped density (mg/ml)	Angle of repose	Carr's index	Hausners Ratio	%Drug content
F1	0.62±0.04	0.55±0.05	26.43±2.21	10.13±0.43	1.56±0.01	96.92±1.02
F2	0.63±0.03	0.57±0.07	23.83±2.43	10.63±0.76	1.76±0.03	99.92±1.34
F3	0.64±0.02	0.53±0.01	24.63±2.34	10.52±0.76	1.54±0.05	98.72±1.63
F4	0.64±0.05	0.53±0.05	23.53±2.54	12.53±0.57	1.32±0.01	97.21±1.84
F5	0.64±0.04	0.57±0.08	21.24±2.65	13.87±0.35	1.86±0.07	97.57±1.26
F6	0.65±0.03	0.55±0.00	24.84±2.65	12.75±0.75	1.43±0.09	96.92±1.58
F7	0.63±0.07	0.53±0.06	23.67±2.86	11.65±0.46	1.23±0.03	96.21±1.14
F8	0.62±0.06	0.52±0.07	22.43±2.89	10.34±0.74	1.54±0.05	99.92±1.25
F9	0.63±0.05	0.51±0.09	27.52±2.94	10.89±0.37	1.23±0.07	99.93±1.14
F10	0.64±0.03	0.52±0.08	22.62±2.95	12.87±0.38	1.78±0.01	97.31±1.84
F11	0.68±0.02	0.52±0.06	26.35±2.54	13.96±0.47	1.87±0.02	99.52±1.43
F12	0.67±0.01	0.53±0.00	22.54±2.32	12.97±0.85	1.87±0.04	96.92±1.52
F13	0.63±0.01	0.51±0.08	28.22±2.86	11.65±0.85	1.43±0.06	96.21±1.14
F14	0.65±0.02	0.52±0.07	24.23±2.84	11.78±0.46	1.43±0.08	95.78±1.45
F15	0.63±0.04	0.51±0.06	23.44±2.45	11.85±0.98	1.43±0.09	99.96±1.17
F16	0.62±0.03	0.52±0.05	22.16±2.32	12.85±0.96	1.33±0.02	96.92±1.06
F17	0.62±0.06	0.52±0.09	22.65±2.32	11.25±0.74	1.45±0.01	98.25±1.34
F18	0.66±0.01	0.51±0.01	24.34±2.98	12.76±0.35	1.43±0.03	98.72±1.62

Above parameters are communicated as Average ± Standard Deviation; (n=3)

***In vitro* dissolution study:****Figure 1: *in vitro* Drug Release Profile for immediate release tablet of Baricitinib F1-F6****Figure 2: *in vitro* Drug Release Profile for immediate release tablet of Baricitinib F7-F12**

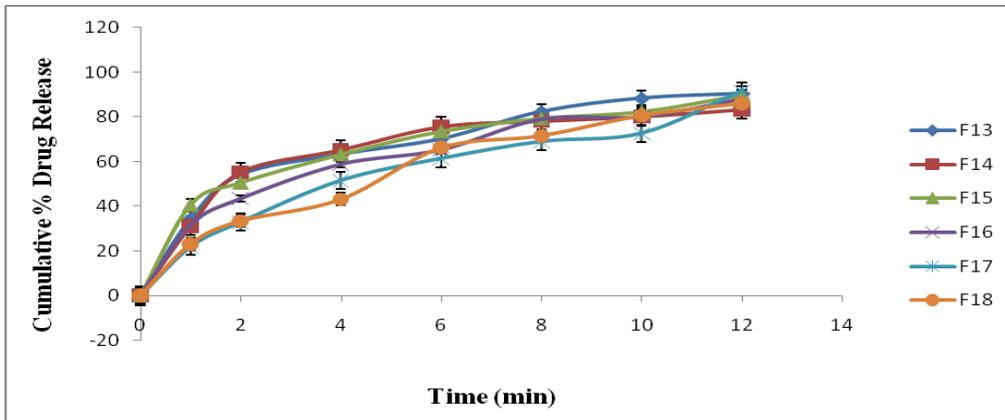


Figure 3: *in vitro* Drug Release Profile for immediate release tablet of Baricitinib F13-F18

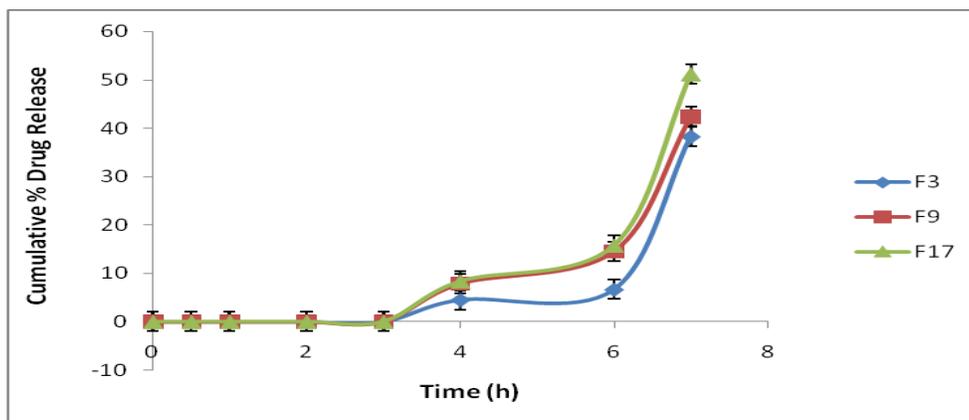


Figure 4: *in vitro* Drug Release Profile for Trail 1 Prepared middle active layer of Baricitinib tablets F3, F9, F17

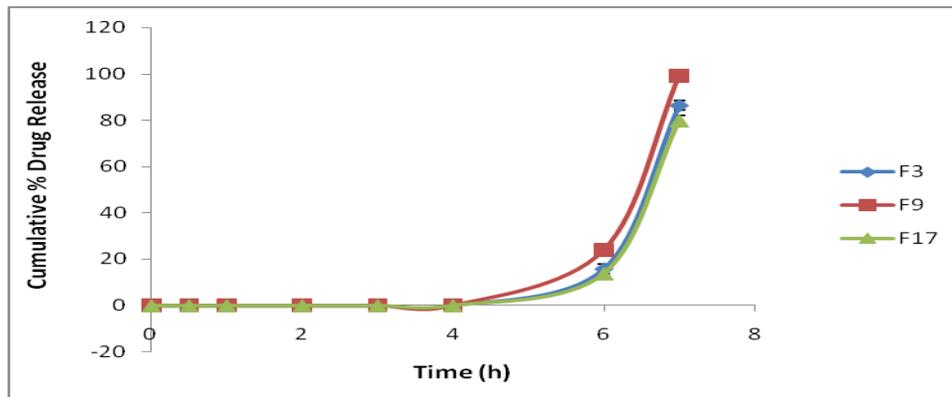


Figure 5: *in vitro* Drug Release Profile for Trail 2 Prepared middle active layer of Baricitinib tablets F3, F9, F17

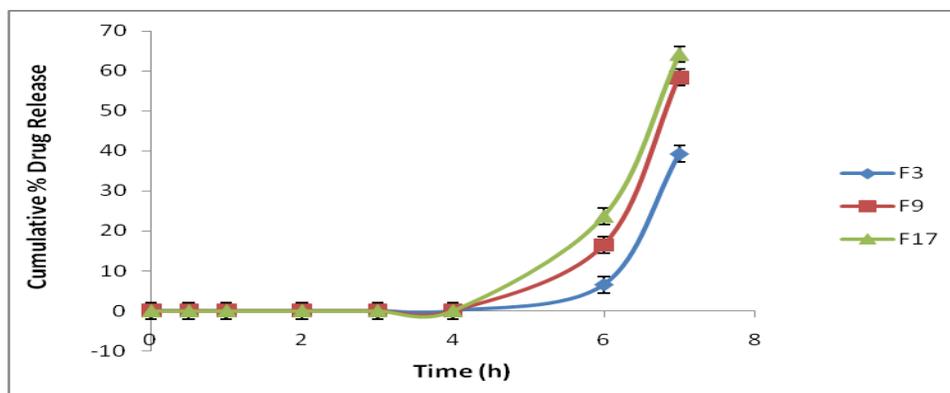


Figure 6: *in vitro* Drug Release Profile for Trail 3 Prepared middle active layer of Baricitinib tablets F3, F9, F17

Table 2: Comparison of Kinetic Data of Optimized Formulation F10

Formulation Code	Correlation Coefficient (r^2)				Diffusional Exponent (n)	Inference
	Zero Order	First Order	Higuchi Equation	Korsmeyer - Peppas		
F9	0.999	0.879	0.931	0.997	1.009	Zero order and Super Case II Transport

Table 3: Stability studies

Parameters	Time (Months)			
	0(Initial)	1 st month	2 nd month	3 rd month
Strength	No Change	No Change	No Change	No Change
Color	No Change	No Change	No Change	No Change
Drug Content (%)	99.34 ± 1.53	99.45 ± 2.98	98.23 ± 2.48	97.92 ± 2.54
<i>In-vitro</i> drug release	98.43	98.65	98.83	98.73

Pharmacokinetic studies:

Baricitinib and IS (Methotrexate) eluted at 10 and 8.3 min, respectively.

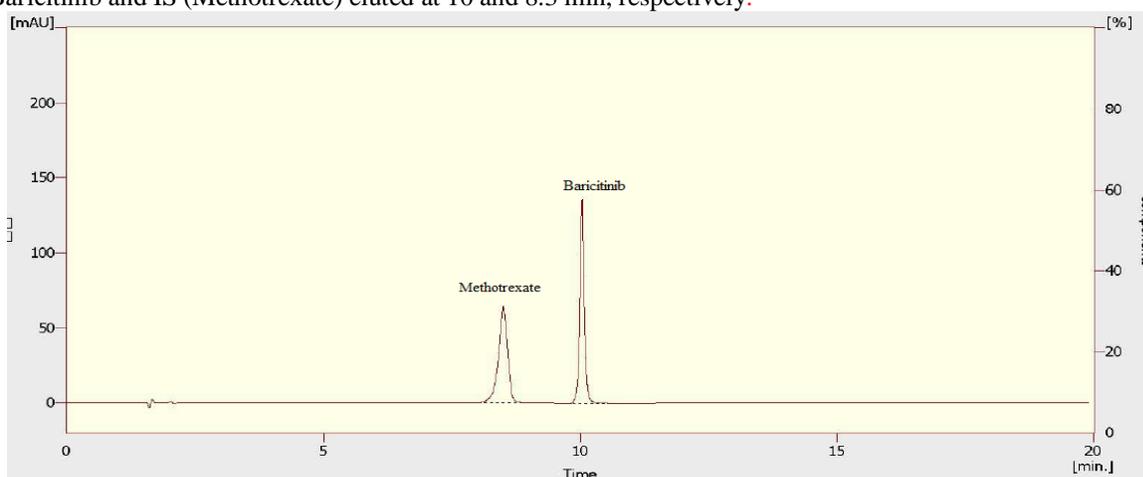


Figure 7: Standard chromatogram of Baricitinib in Rabbit plasma

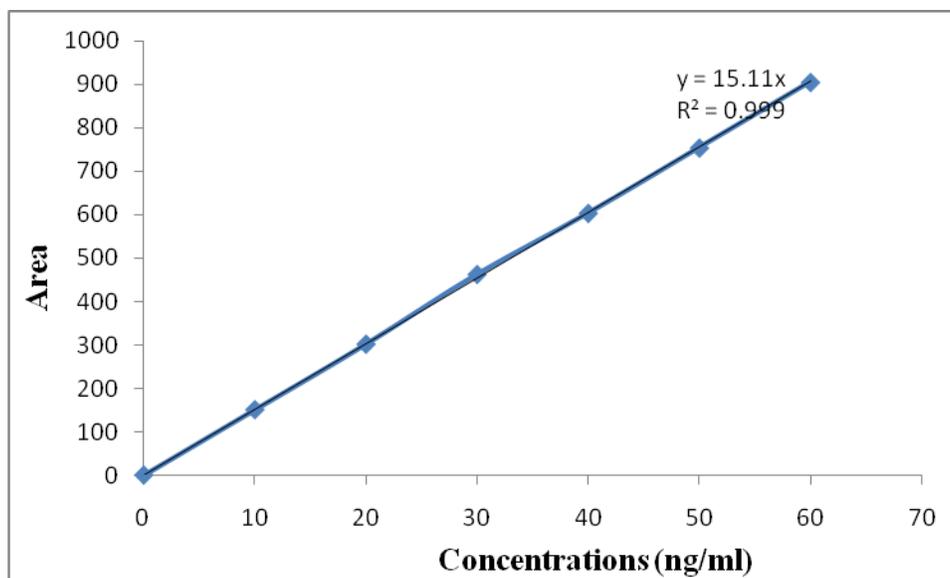


Figure 8: Standard graph of Baricitinib in Rabbit plasma

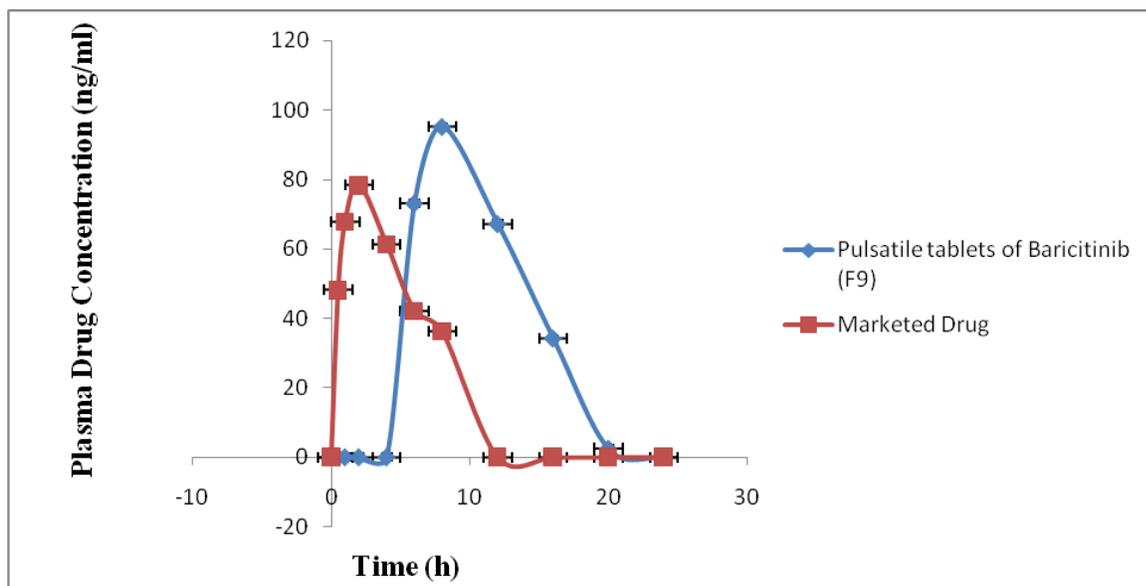


Figure 9: Plasma Concentrations of Pulsatile tablets of Baricitinib (F9) and Marketed drug at different time intervals (Mean \pm SD, n = 6)

Table 4: Comparison of Pharmacokinetic parameters of pulsatile tablets of Baricitinib (F9) and Marketed drug

Parameters	Pulsatile tablets of Baricitinib (F9)	Marketed drug
C_{max} (ng/ml)	95.20 \pm 7.35	78.44 \pm 3.29
AUC _{0-t} (ng h/ml)	743.21 \pm 8.87	441.76 \pm 8.87
AUC _{0-∞} (ng h/ml)	922.89 \pm 8.78	612.65 \pm 9.87
T_{max} (h)	8.00 \pm 0.15	2.00 \pm 0.15
$t_{1/2}$ (h)	10.00 \pm 0.05	4.5 \pm 0.14

DISCUSSION:

The immediate release tablets were prepared by using different types and different concentration of super disintegrating agents like Croscarmellose, Crospovidone and sodium starch glycolate. For immediate release tablets dissolution studies were performed in that three best formulations were selected (F3, F9, F17) for pulsatile release formulation. Selected three formulations were coated with three trails were of different weights of coating material used for trail 1 6.5gm of coating material was used, trail 2 12.5gm of coating material was used and trail 3 24.5gm of coating material was used. Trial 2 was showed good release pattern, the polymer Crospovidone shows good drug release profile than Croscarmellose and sodium starch glycolate. The 5% Crospovidone shows better results. Formulations prepared by using Croscarmellose 8 % showed the maximum amount of drug release 84.24% after 7th hour in pulsatile release formulations. Formulations prepared by using Crospovidone 5% showed the maximum amount of drug release 99.24±1.23 after 7th hour in pulsatile release formulations. The coating polymer Eudragit L-100(50% weight gain) produces the lag time of 6hrs. From the above drug release profile, the F9 was selected as best formulation. The corresponding plot (Log Cumulative Drug Release Vs Log time) for Korsmeyer – Peppas equation indicated a good linearity ($r^2=0.997$). The diffusional exponent “n” was 1.009, which appears to indicating the release of drug polymer matrix formulations was found to be super case-II transport, i.e., drug release by more than one mechanism. Super case II transport generally refers to erosion of polymeric chain and anomalous transport. The stability of this optimized formulation was known by performing stability studies for three months at accelerated conditions of 40°C ± 75 % RH on optimized formulation. The formulation was found to be stable, with no change in the weight variation, thickness, and friability, hardness, drug content and *In vitro* drug release pattern.

***In vivo* evaluation studies in Rabbit.**

The ability of pulsatile tablets as a drug delivery system to release drugs in a predetermined time release manner was investigated in Rabbits after oral administrations was investigated. The pulsatile drug delivery system tablet prepared under laboratory conditions release the drug *in vitro* in a uniform and reliable manner, these data indicated that the optimized formulation should be suitable for *in-vivo* evaluation in animals. Mean plasma drug concentration curve v/s time for both the groups of rabbits was studied for comparing various pharmacokinetic parameters. Maximum drug plasma

concentration (C_{max}) and the time to maximum value (T_{max}) were obtained directly from the drug plasma profile for each animal following administration of all the three above mentioned dosage formulations. The AUC_{0-t} for animals Group A given Pulsatile tablets of Baricitinib was found to be 743.21±8.87ng/ml/hr whereas the AUC_{0-t} for animals administered with Marketed drug was 441.76±8.87ng/ml/hr. MRT is defined as the mean time for the intact drug molecule to transit through the body and involved a composite of all kinetic processes including release from the dosage form, drug absorption into the body and drug disposition. MRT can be used in a comparative way to evaluate the *in vivo* performance of a pulsatile release dosage form. Therefore, the increase in the MRT from 4.5 to 10.00 h following Bricitinib Marketed drug and pulsatile drug, respectively, was mainly due to the change in drug release and elimination. The average t_{max} values were found to be 2.00 ± 0.15h, and 8.00 ± 0.15h for Marketed drug Baricitinib and pulsatile drug respectively. Marketed drug formulation showed low value of t_{max} (2h) which indicates faster absorption of the drug as compared to pulsatile drug formulation. As per the summary of pharmacokinetic parameters as given in **Table 4** one can predict that Marketed drug Baricitinib showed pattern of drug absorption and pulsatile drug formulation showed a lag time of 3 hours before finally showing maximum concentration (C_{max}) at 8 hours, which correlated with the *in-vitro* release (8 hours) One way analysis of variance (ANOVA) using Dunnett multiple comparison test on computer program Graphpad InStat 3 was used, the differences were considered significant at p value equal or less than 0.05($p \leq 0.05$).

CONCLUSION:

Baricitinib given in form of modified chronomodulated should be advantageous for patients suffering from rheumatoid arthritis, and it provides better patient compliance and effective mode of treatment in a disguised manner. Formulation F9 appears suitable for further Pharmacodynamic and Pharmacokinetic to evaluate clinical safety of these modified chronomodulated drug delivery of Baricitinib in suitable animal and human models

REFERENCES:

1. Janugade BU, Patil SS, Patil SV, Lade PD. Pulsatile drug delivery system for chronopharmacological disorders: an overview. Journal of pharmacy research 2009; 2 (1): 132-143.
2. Parmar RD, Parikh RK, Vidyasagar G, Patel DV, Patel CJ and Patel BD. Pulsatile Drug Delivery

- Systems: An Overview. *International Journal of Pharmaceutical Sciences and Nanotechnology* 2009; 2(3): 605.
3. Nitin Saigal, Sanjula Baboota, Alka Ahuja and Javed Ali. Site Specific Chronotherapeutic Drug Delivery Systems: A Patent Review. *Recent Patents on Drug Delivery & Formulation* 2009; 3: 64-70.
 4. Jha N, Bapat S. Chronobiology and chronotherapeutics, *Kathmandu University Medical Journal* 2004; 2(8): 384-388.
 5. Bruguolle B, Lemmer B. Recent advances in chronopharmacokinetics: methodological problems, *Life Science* 1993; 52: 1809-1824.
 6. URL:http://www.uspharmacist.com/oldformat.asp?url=newlook/files/Feat/ACF2F15.cfm&pub_id, accessed on 15/9/10.
 7. Botti B, Youan C. Chronopharmaceutics: Gimmick or clinically relevant approach to drug delivery. *Journal of Control Release* 2004: 337-353.
 8. Kowanko IC, Pownall R, Knapp MS. Circadian variations in the signs and symptoms of rheumatoid arthritis and in the therapeutic effectiveness of flurbiprofen at different times of the day. *British J Clin Pharma.* 1981; 11: 477-84.
 9. Kowanko IC, Knapp MS, Pownall R, Swannell AJ. Domiciliary self-measurements of in rheumatoid and the demonstration of circadian rhythmicity. *Annals of the Rheumatic Diseases* 1982; 41: 453- 455.
 10. Swannell AJ. Biological rhythms and their effect in the assessment of disease activity in rheumatoid arthritis. *British J Clin Practice* 1983; 38(33): 16- 19.
 11. Harkness JAL, Richter MB, Panayi GS. Circadian variation in disease activity in rheumatoid arthritis. *British Medical J.* 1982; 284: 551-554.
 12. Huskisson EC and GP Velo ed. *Chronopharmacology of anti-rheumatic drugs with special reference to indomethacin in: Inflammatory Arthropathies.* *Excerpta Medica* 1976: 99-105.
 13. Javed Qureshi, Alka Ahuja, Sanjula Baboota, Krishna Chutani, Sanyog Jain, Javed Ali, Development and evaluation of a time-specific pulsatile-release tablet of aceclofenac: a solution for morning pain in rheumatoid arthritis, *Exp Clin Pharmacol.* Jan-Feb 2009; 31(1):15-23.
 14. Raghavendra K, Marina Koland, An In-Vivo Evaluation of Chronotherapeutic Drug Delivery System for the Treatment of Hypertension, *Saudi Journal of Medical and Pharmaceutical Sciences*, Vol-3, Iss-6B (Jun, 2017):643-647.
 15. S. Mohan, N. Srinivasarao, K. Lakshmi, Development and Validation of a Stability indicating Related Substances of Baricitinib by RP-HPLC and its Degradation, *International Journal of Management and Humanities (IJMH)*, Volume-4 Issue-2, October 2019, 1-9.