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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF CHRONOMODULATED DRUG DELIVERY OF BARICITINIB

Mayuri Bodige[1], Agaiah Goud B[2] and Bhagavan Raju M[3]

[1,3]Srivenkateshwara College of Pharmacy, Madhapur, Hyderabad
[2] SRR College of Pharmacy, Valbapur, Karimnagar

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A B S T R A C T

Rheumatoid arthritis is an auto immune disease which requires chronotherapy as it occurs during early morning. Baricitinib used to treat rheumatoid arthritis. The aim of the present investigation was to develop 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.

INTRODUCTION

A pulsatile release profile is characterized by a lag time followed by rapid and complete drug release. Pulsatile drug delivery systems are designed according to the circadian rhythm of the body[1]. Chronomodulated system is also known as pulsatile system or sigmoidal release system related to biological rhythms. Circadian rhythm regulates many functions in human body like metabolism, physiology, behavior, sleep pattern, hormone production. Many diseases such as cardiovascular, asthma, peptic ulcer, arthritis etc. follow the body's circadian rhythm and shows circadian pattern[2]. These conditions could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. These systems are designed in a manner that the drug is available at the site of action at the right time in the right amount[3]. Disease conditions where constant drug levels are not preferred but need a pulse of therapeutic concentration in a periodic manner acts as a push for the development of pulsatile drug delivery system. A time delayed release profile is characterized by a lag time followed by rapid and complete drug release[4].

Corresponding author:* **Mayuri Bodige
Srivenkateshwara College of Pharmacy, Madhapur, Hyderabad

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[5,6]. 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[7,8]. 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[9-11].

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[12].

Table 4 Coating solution (Trail 3)

S.no	Ingredients	Quentity
1	Eudragit L-100	24.5g
2	Acetone	100Ml

Pre formulation studies

Bulk density, Tapped density, Hausners ratio, Void volume, Total porosity, Angle of repose was studied[13].

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 Korsemeyer model (log cumulative % drug release versus log time).

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	Quentity
1	Eudragit L-100	6.5g
2	Acetone	100Ml

Table 3 Coating solution (Trail 2)

S.no	Ingredients	Quentity
1	Eudragit L-100	12.5g
2	Acetone	100Ml

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 $40^{O}C \pm 2^{O}C$ / 75% RH ± 5% for 30 days.

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

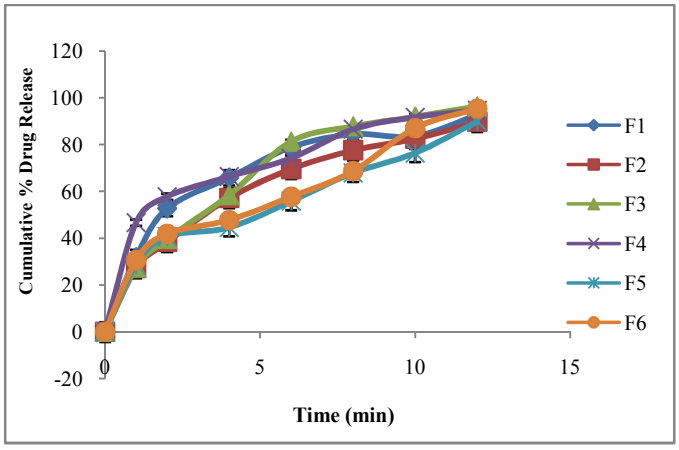

Figure 1 in *vitro* Drug Release Profile for immediate release tablet of Baricitinib F1-F6

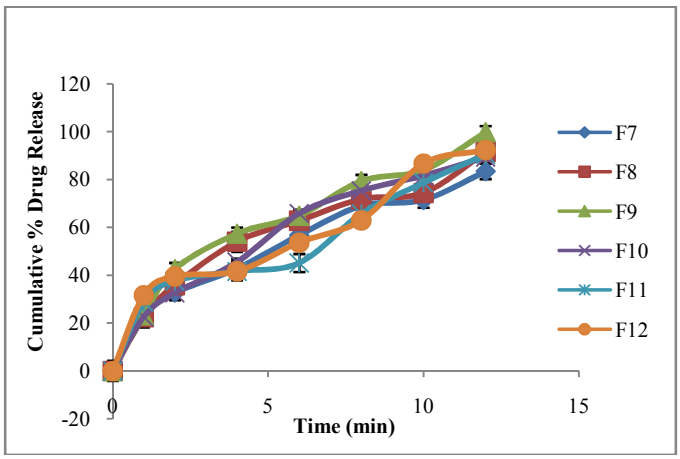

Figure 2 in *vitro* Drug Release Profile for immediate release tablet of Baricitinib F7-F12

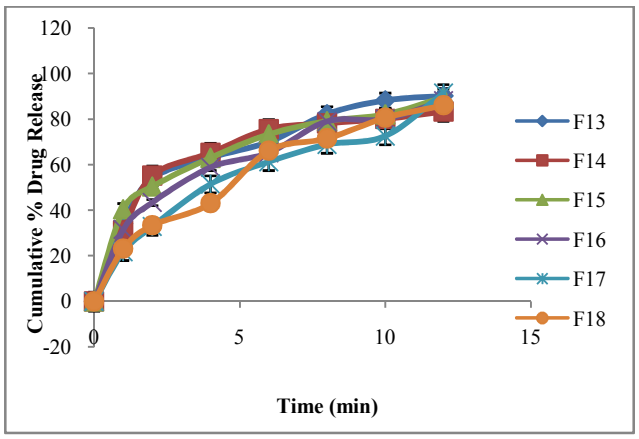

Figure 3 *in vitro* Drug Release Profile for immediate release tablet of Baricitinib F13-F18

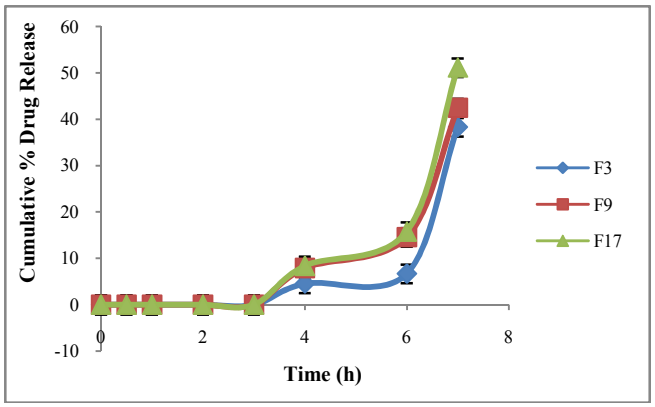

Figure 4 *in vitro* Drug Release Profile for Trail 1 Prepared middle active layer of Baricitinib tablets F3, F9, F17

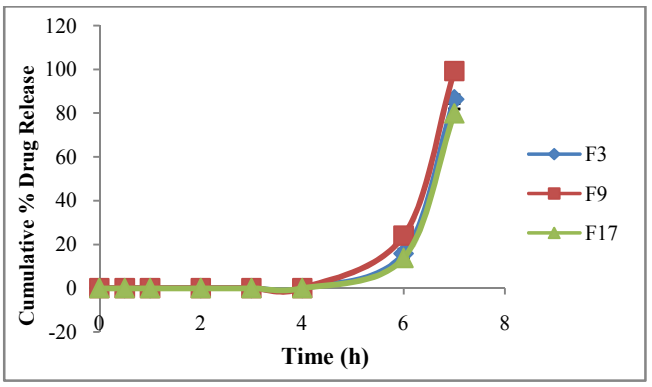

Figure 5 *in vitro* Drug Release Profile for Trail 2 Prepared middle active layer of Baricitinib tablets F3, F9, F17

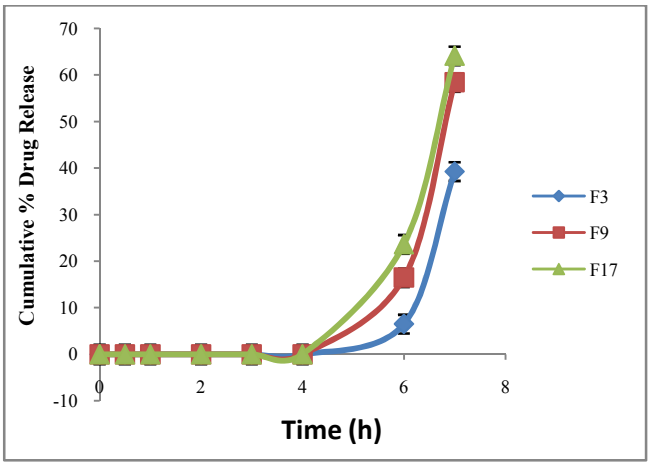

Figure 6 in *vitro* Drug Release Profile for Trail 3 Prepared middle active layer of Baricitinib tablets F3, F9, F17

Kinetic Analysis of Dissolution Data

The release rate kinetic data of optimized formulation F9 are shown in table

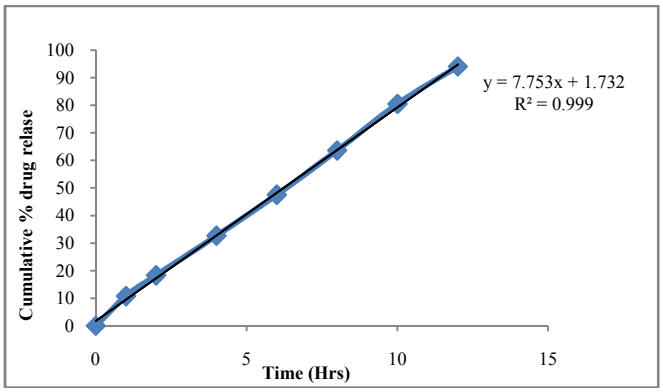

Figure 7 Zero order Graph for Kinetic Data of Optimized Formulation F9

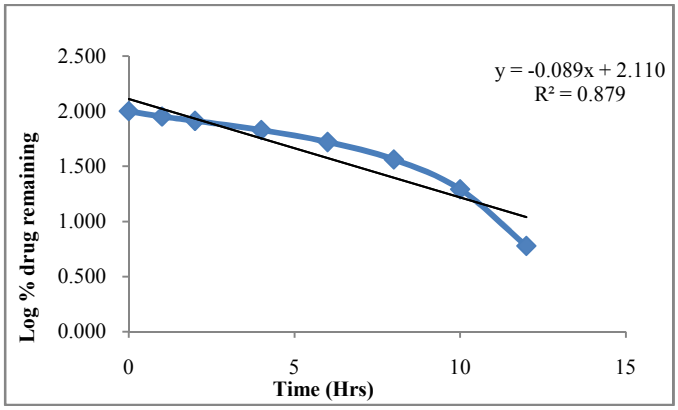

Figure 8 First order Graph for Kinetic Data of Optimized Formulation F9

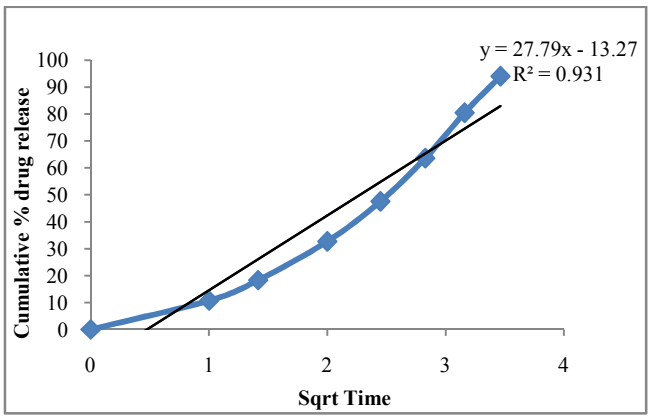

Figure 9 Higuchi Equation Kinetic Data of Optimized Formulation F9

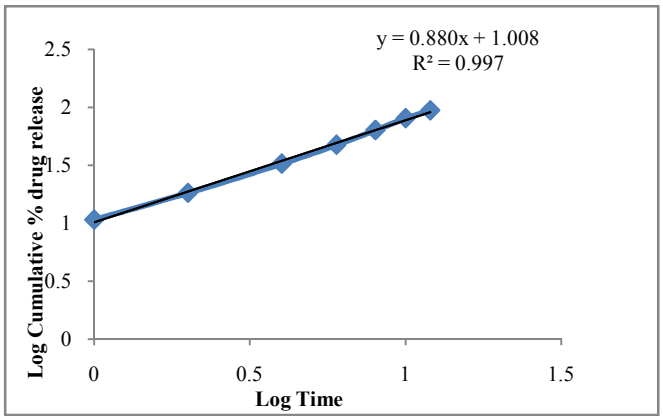

Figure 10 Korsemyer-Peppas Graph for Kinetic Data of Optimized Formulation F9 Drug Release Kinetics of Optimized (F9)

Table 6 Comparison of Kinetic Data of Optimized Formulation F10

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

Table 7 Stability studies

Parameters	Time (Months)			
	0(Initial)	1st month	2nd month	3rd 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
In-vitro drug release	98.43	98.65	98.83	98.73

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 trial 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 (r2=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 40^0C + 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.

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

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