AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Formulation and Evaluation of Naproxen Sodium pulsatile Tablets for Chrono modulated Drug Delivery

Indira Kilari[1]*, Baby Sravani Guduru[1], Ramana Gangireddy[1]

1. Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada-10, Andhra Pradesh, India.

ABSTRACT

The objective of present investigation was to prepare a chrono-modulated drug delivery system for Naproxen sodium to meet chrono pharmacological needs of Arthritis. Press coated tablets is a novel oral pulsatile release drug delivery system in which the drug is released after certain period of lag time generally due to the erosion of barrier layers. Tablets were prepared by direct compression method. The core tablet was formulated using super-disintegrants like sodium starch glycolate, crosspovidone and crosscarmellose sodium. Whereas, the barrier layer contains polymers like carrageenan gum (Viscarin GP-209), xanthan gum in different concentrations and lactose anhydrous as channeling agent for maintaining lag time. The drug-excipient compatibility was confirmed by using FTIR, predicted that there was no chemical interactions between the drug and excipients. The tablets prepared were evaluated for micromeritic properties. *In-vitro* drug release studies were carried out using pH 1.2 buffer for initial 2hrs and in pH 7.4 phosphate buffer for remaining 10hrs. All the formulations followed first order release kinetics. From the obtained results it was found that the F9 formulation of immediate release core tablets (10% of Crosspovidone) showed optimized *in vitro* disintegration time and wetting time respectively. In case of press-coated tablets PCT 8 formulation with hydrophilic polymers 19.2% carrageenan gum, 19.2% xanthan gum and 7.69% lactose anhydrous as channeling agent has shown 6hrs of lag time is considered as optimum formulation and is successful in resisting different RPM pressures for designing into pulsatile delivery for treatment of Arthritis.

Keywords: Naproxen Sodium**,** Pulsatile drug delivery system, lag time, press coated tablets.

*Corresponding Author Email: indukilari@gmail.com

Received 22 May 2015, Accepted 30 July August2015

Please cite this article as: Kilari I *et al*., Formulation and Evaluation of Naproxen Sodium pulsatile Tablets for Chronomodulated Drug Delivery. American Journal of PharmTech Research 2015.

INTRODUCTION

In recent years, biological control of drug delivery has been of interest to achieve improved drug therapies. Changes in the biological rhythms of the human body (ie, chronobiology) may precipitate serious medical conditions, eg: mycordial infaction or stroke, in addition to the manifestation and severity of symptoms of chronic diseases, including allergic rhinitis, asthama, nocturnal acid reflux, and Arthritis. For such chrono pathological conditions chrono therapeutic systems play an important role, because these formulations take into account probable time-dependent variation in risk or symptoms of diseases. Such systems are designed to enable a pulsatile release of drug after a predetermined off–release period (lag time) which mimics the chrono pathological symptoms. Recently, novel systems have been developed that release the drug after a programmable lag time. The required amount of drug should be released from the drug delivery system at the required time of night or early morning. Medications have been formulated, and dosing schedules were established, in an attempt to provide appropriate concentration of a drug in the target area of the body where the drug is mostly needed. Chronobiology[1] is the study of biological rhythms and their mechanisms. The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons. Chronotherapeutics[2] refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. Naproxen Sodium (widely used NSAID) was frequently used for treating rheumatoid Arthritis, which had apparent circadian rhythms and peak symptoms in the early morning. When orally administering Naproxen Sodium conventional formulation, it was difficult to achieve the desired clinical effect, because it elicited patients incompliance of administration in the early morning to coordinate the rhythm of rheumatoid Arthritis, due to rapid absorption of the conventional formulation. However, Naproxen Sodium pulsatile delivery[3-5] is not only effective, but also more convenient for administration than the conventional formulation to get the drug release after desired time period. This system when administered in night was aimed to achieve an elevated Naproxen sodium levels overnight where the risk of Rheumatoid Arthritis was found to be maximum. People with rheumatoid Arthritis (RA), usually experience peak pain in the morning, which decreases throughout the day. In this scenario, an evening once-a-day non-steroidal anti-inflammatory drug (NSAID) schedule is

recommended. If pain is worse during early afternoon or at night, however, a morning or an evening once a day NSAID schedule may be recommended. The exact dose depends on the severity of the patient's pain and their individual physiology. In our study, a pulsatile system containing Naproxen sodium was developed to overcome the morning stiffness in Arthritis patients. This is a time dependent formulation; by administering the formulation at 10.00 pm, symptoms that are experienced early in the morning are avoided. To get immediate release of the drug after a desired lag time, press-coated systems with a rupturable coat have been suggested. In addition, press coating overcomes the draw backs of liquid coating because it does not required use of a solvent and requires a relatively shorter manufacturing process. With newer technologies, tablet compression and press coating can be achieved in a single step. In addition it is possible to control lag time by changing the coating thickness and composition.

MATERIALS AND METHOD

Naproxen sodium was received as a gift sample from Aurobindo Pharma, Hyderabad, India. sodium starch glycolate, crosscarmellose sodium and crosspovidone were obtained from Colorcon Asia pvt. Ltd, Goa, India. Lactose anhydrous, magnesium Stearate, talc were obtained from Sd fine chemicals Ltd, Mumbai. Xanthan gum was obtained from CP Kelco, USA. Carrageenan Gum was obtained from Signet Chemical corporation pvt. Ltd, Mumbai, India.

Experimental methodology

Solubility determination

Excess of Naproxen sodium was added to 5ml of each fluid in a 25 ml stopper conical flasks and the mixtures were shaken for 24 hours at room temperature ($25\pm1^{o}C$) on a rotary flask shaker. After 72 hours of shaking 1 mL aliquots were withdrawn and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for naproxen sodium by measuring absorbance at 332nm. Shaking was continued until three consecutive estimations were same. The solubility experiments were run in triplicate.

FTIR spectral analysis[6]

Samples were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500 cm^{-1} at a resolution of 1.0 cm^{-1}. The powdered sample is simply placed on to the ATR crystal and the sample spectrum is collected. The sample is then cleaned from the crystal surface and the accessory is ready to collect the additional spectra. ATR analysis is less complicated than using KBR pellets, it is fast and very small amount of the sample is needed.

Development of naproxen sodium pulsatile tablet

Formulation of core tablets[7]

Compressed tablets of Naproxen Sodium using different super disintegrants (Sodium starch glycolate, Crosspovidone, Crosscaramellose sodium) were prepared by direct compression method as per formulae given in Table 1. Accurately weighed quantities of API, super disintegrants were passed through sieve no #40 and remaining ingredients were added to the blend in a polybag and mixed for 10 minutes. The resulting powder blend was compressed on single punch tablet press (Cadmach, India) using 10mm round punches to round tablets weighing 350mg with a hardness of 3-5 kg/cm^2.

Table 1: Formulae for Naproxen Sodium Core Tablet

S.NO	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Naproxen Sodium	275	275	275	275	275	275	275	275	275
2	Lactose Anhydrous	47.5	39	30	47.5	39	30	47.5	39	30
3	SSG	17.5	26	35	-	-	-	-	-	-
4	CCS	-	-	-	17.5	26	35	-	-	-
5	Crospovidone	-	-	-	-	-	-	17.5	26	35
6	Talc	5	5	5	5	5	5	5	5	5
7	Mg. Stearate	5	5	5		5	5	5	5	5

Formulation of press coated tablets[8]

The core tablets were press coated with barrier blend as per formulae given in Table 2. Accurately weighed half of the amount of the barrier layer material was transferred into a 12mm die, then the core tablet was placed manually at the center. The remaining amount of the barrier layer material was added into the die and compressed at a pressure of 5 tons for 3min using KBr hydraulic press with a hardness of 3-5 kg/cm^2.

Table 2: Formula for Barrier layer of press coated pulsatile tablet

S.NO	Ingredients	PC T1	PC T2	PC T3	PC T4	PC T5	PC T6	PC T7	PC T8
1	Carrageenan gum	200	150	-	-	50	100	125	125
2	Xanthan gum	-	-	200	150	150	100	125	125
3	Lactose anhydrous	-	-	-	-	-	-	-	50

Preformulation studies[9]

The following micromeritic properties were performed on powder blend

Bulk density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$D_b = M/V_0$$

Where, M is the mass of powder, V_0 is the Bulk volume of the powder.

Tapped density (D_t):

Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed.

$$D_t = M/V_0$$

Where, M is the mass of powder, V_0 is the Bulk volume of the powder.

Carr's Index (I):

It indicates the ease with which a material can be induced to flow and powder compressibility. It is expressed in percentage and is given by

$$I = (D_t - D_b)/D_t \times 100$$

Where, D_t is the tapped density of the powder, $D_b$is the bulk density of the powder.

Angle of repose:

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and horizontal plane.

$$\text{Tan } \Theta = h/r$$

$$\Theta = \text{Tan}^{-1} h/r$$

Where, Θ = angle of repose, h = height, r = radius

A funnel was fixed at a height of approximately of 2-4 cm over the platform. The sample was slowly passed along the wall of funnel, till the cone of the powder formed. Angle of repose was determined by measuring the height of the cone of powder and radius of the heap of powder.

Hausner's ratio:

The ratio of tapped density to the bulk density of the powders is called the Hausner's ratio.

Hausner's ratio = Tapped Density/ Bulk Density

Post compression parameters evaluation[10]

All the prepared Naproxen Sodium press coated tablets were evaluated for Average weight, Hardness, friability, drug content, *in-vitro* disintegration time, wetting time and *in-vitro* dissolution.

Hardness

Six tablets from each batch were selected and hardness was measured using Monsanto hardness tester.

Friability (%F)

Twenty tablets from each batch were selected randomly and weighed. These pre weighed tablets were subjected to friability testing using Roche friabilator for 100 revolutions. The tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability.

$$\%F = 1-(\text{loss in weight}/\text{ initial weight})* 100$$

Weight variation

The weight variation test was conducted by weighing 20 randomly selected tablets individually, calculating the average weight and comparing the individual tablet weights to the average.

Drug content uniformity

The drug content was determined by taking the powder equivalent to 10mg, then it was dissolved in distilled water and absorbance was taken against the blank at 332nm.

***In-vitro* dissolution rate studies[11-14]**

Dissolution rate study for all press coated tablets using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with paddle. The dissolution fluid was 900ml of pH 1.2 and pH7.4 buffers respectively. The dissolution study was done at speed of 50 rpm and at a temperature of 37 ± 0.5^0c. Samples of 5ml were withdrawn for every hour up to 12 hr and the lag time was observed for every batch tablet and the collected samples were analyzed for drug spectrophotometrically at 332nm in order to know the order of drug release and whether the formulations shown pre expected lag time and then drug release. Again the optimized formula was checked for reproducibility at different RPM's like 50, 75 and 100.

Study of release kinetics and release mechanisms:

The various release kinetic equations in which the experimental data can be fitted and drug release rate can be predicted as a function of some variable are mentioned below. The suitability of the equation is judged on the basis of best fit into the equation using statistical indicators like R^2 values.

Zero order-release rate constant

This equation describes the systems where the release rate is independent of the concentration of the dissolved species. The dissolution data are fitted into the zero order equation:

$$X = X_0 - K_0t$$

Where,

X = Amount of drug released at time t, X_0 = Amount of drug released initially

K_0 = Zero order rate constant

A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and the intercept at the origin of the axes. The zero order plots is derived from plotting the cumulative percent drug dissolved vs. time.

First order-release rate constant

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

Release behaviour generally follows the following first order release equation:

$\ln X = \ln X_0 - K_1 t$

Where,

M is the amount of drug undissolved at time t,

M_0 is the amount of drug undissolved at t = 0 and

K_1 is the corresponding release rate constant.

A graph of log concentration of drug remaining vs. time yields a straight line with a negative slope.

RESULTS AND DISCUSSION

The aim of the present study is to formulate and evaluate orally applicable single pulse delivery system based on press coated tablet preparation of Naproxen Sodium in order to treat one of the chronopathological diseases that is Arthritis. A simple sensitive UV-spectrophotometric method was used for the estimation of naproxen sodium which was measured UV-spectrophotometrically at a λ_{max} of 332nm. The regression values obtained indicates a good linear relationship and the selected method is found to be sensitive, accurate, precise and reproducible.

Solubility determination

The order of solubility of Naproxen sodium was Water > 7.4pH buffer > 0.1N HCL. But in the present investigation the dissolution studies were carried out in 0.1 N HCl for the initial 2 hrs and later in 7.4 pH buffer to mimic the in-vivo conditions. The drug showed its highest solubility in water. The results were shown in Figure 1.

FT-IR spectral studies:

The spectral studies of Naproxen sodium pulsatile tablet formulations exhibited no changes in the principal peaks and all the peaks were observed at specific wave number as that of their pure drug. Thus these studies indicated that there were no interactions between the functional moieties of

drug molecule with the polymers incorporated in the formulations. The spectra of various polymers, super disintegrants used, and optimized core and press coated tablet formulations were taken individually. The spectra of Naproxen sodium pure drug and various pulsatile tablet formulations are shown in Figure 2-4.

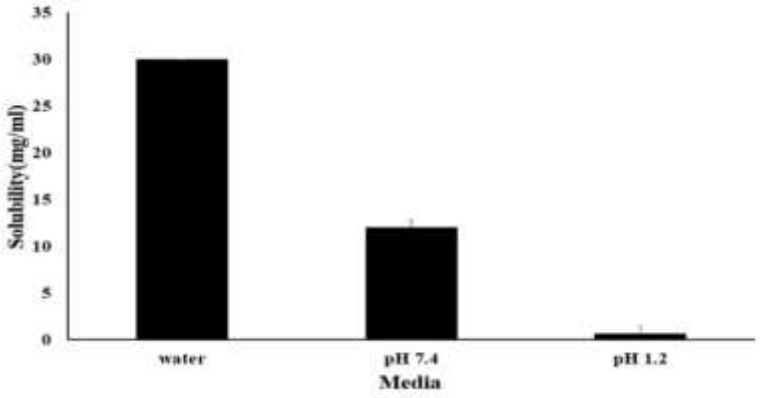

Figure 1: Solubility of Naproxen Sodium in Different media

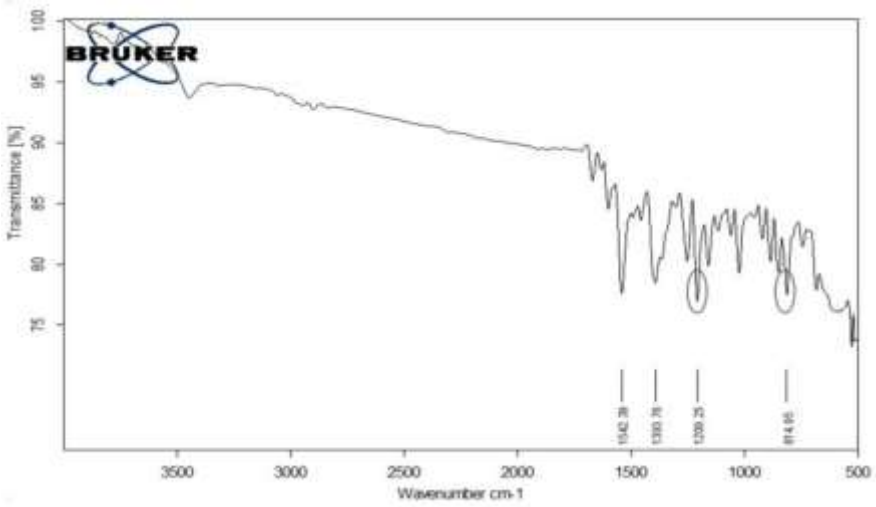

Figure 2: FTIR Spectrum of pure drug Naproxen sodium

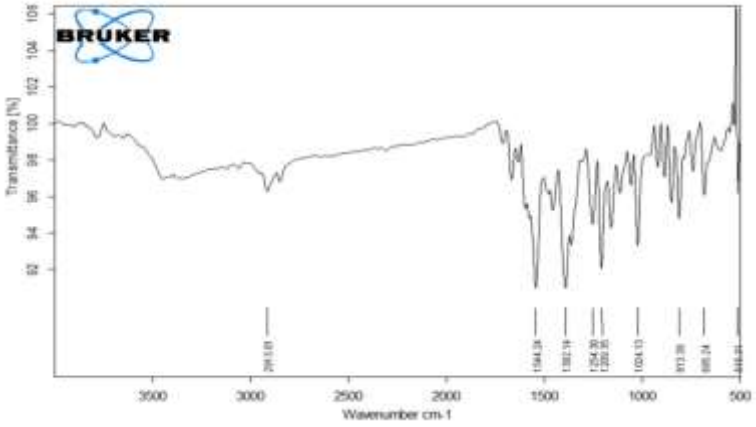

Figure 3: FTIR Spectrum of Optimized Core Tablet

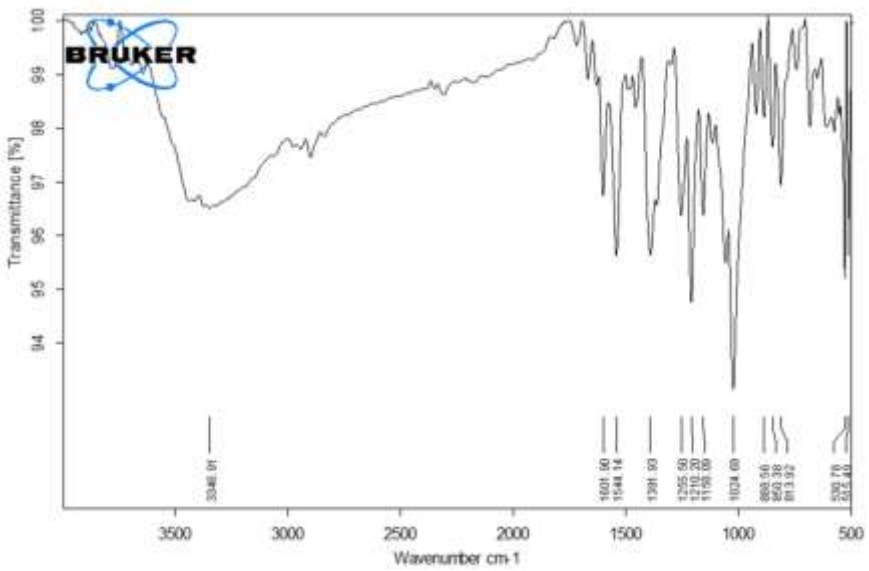

Figure 4: FTIR Spectrum of Optimized Press Coated Tablet

Evaluation of Pre-compression parameters of directly compressible powder blends of core and pulsatile tablets

All the powder blends were evaluated for flow properties such as Carr's index, angle of repose, bulk density, tapped density, compressibility index, Hauser's ratio and flow ability prior to the compression of tablets. The flow properties of the prepared powder blends were good and found to be within the limits.

Evaluation of Post compression properties of immediate release core tablets and Press coated pulsatile tablets

All the prepared tablets were subjected to evaluation of post compressional parameters like weight variation, hardness, friability, *in-vitro* disintegration time, drug content, wetting time. All the prepared tablets were found to exhibit satisfactory tablet characteristics and were within the limits. The results were given in Table 3 and 4.

Table 3: Evaluation of Post compression properties of immediate release core tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation(mg)±SD	349.8±0.2	350.1±0.51	349.8±0.2	351.5±0.26	349.1±0.26	349.1±0.51	350.16±0.5	349.15±0.5	351.56±0.25
Hardness(kg/cm^2)±SD	3.0± 0.12	3.5±0.34	3.5± 0.34	3.0± 0.22	3.0± 0.25	3.0± 0.25	3.0± 0.32	3.0± 0.31	3.5± 0.32
Friability (%)	0.19±0.02	0.21±0.01	0.18±0.02	0.17±0.01	0.20±0.02	0.19±0.01	0.18±0.02	0.16±0.02	0.16±0.02
In-vitro disintegration time(min)	17± 1.0	15± 0.5	14± 1.0	13± 0.5	12± 1.0	11± 0.5	10± 0.5	9± 1.0	7± 0.5
Drug content (%)	98± 2.0	99± 2.0	99± 1.0	98± 2.0	99± 1.0	98± 2.0	99± 2.0	98± 2.0	99± 2.0
Wetting time(sec)	22± 2.0	21± 2.0	22± 1.0	19± 2.0	18± 2.0	19± 2.0	17± 1.0	16± 2.0	15± 1.0
Drug dissolved in 20min (%)	65± 2.0	70± 2.0	77± 2.0	76± 2.0	82± 2.0	89± 2.0	78± 2.0	85± 1.0	99± 1.0

Table 4: Evaluation of Post compression properties of Press coated pulsatile tablets

Formulation	Average weight mg± SD	Flow ability	Hardness (kg/cm^2)	Friability (%)
PC T1	550 ± 0.35	Good	5.0 ± 0.12	0.21 ± 0.14
PC T2	500 ± 0.25	Good	5.0 ± 0.34	0.11 ± 0.09
PC T3	550 ± 0.28	Good	5.0 ± 0.34	0.11± 0.10
PC T4	500 ± 0.31	Good	5.0 ± 0.22	0.14 ± 0.11
PC T5	550 ± 0.24	Good	5.0 ± 0.26	0.12 ± 0.08
PC T6	550 ±0.36	Good	5.0 ± 0.25	0.13 ± 0.05
PC T7	600 ± 0.39	Good	5.0 ± 0.32	0.10 ± 0.07
PC T8	600 ± 0.37	Good	5.0 ± 0.32	0.10 ± 0.24

***In-vitro* dissolution studies**

For immediate release Naproxen sodium core tablets

In the present work release profile of F-9 having 10% Crospovidone in direct compression method was found to have maximum release of 99.39 %±1.95% at the end of 20 minutes. The drug release from all batches was found to be concentration dependent. Hence the formulation of F-9 fulfills the objective of the present study and is suitable as core tablet that can be formulated into press coated pulsatile tablets. The results were shown in Figure 5 and 6.

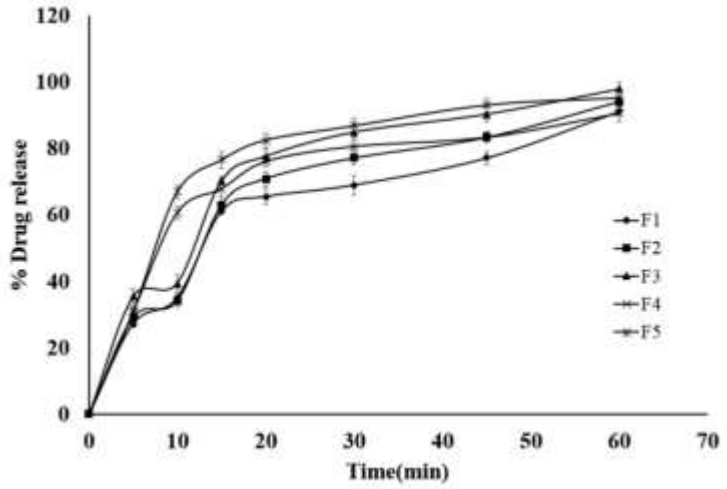

Figure 5: Dissolution profiles of F1, F2, F3, F4, F5 core tablets (n=3 ± mean SD)

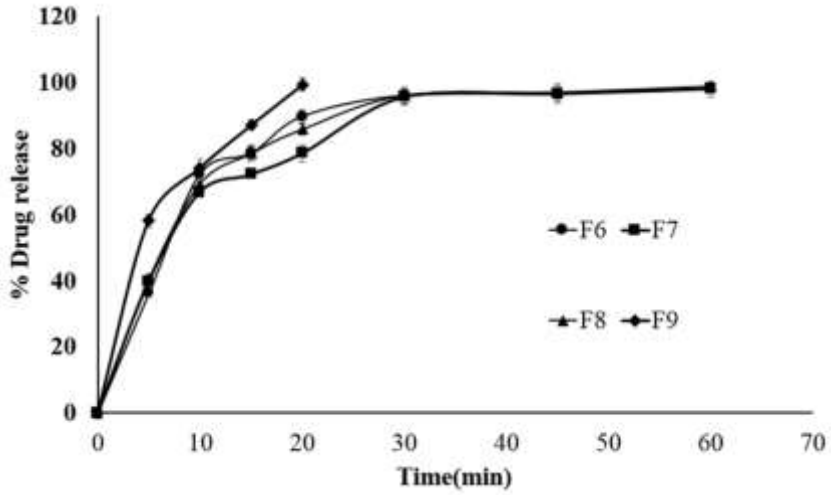

Figure 6: Dissolution profiles of F6, F7, F8, F9 core tablets (n=3 ± mean SD)

For Press coated Naproxen sodium pulsatile tablets

All the press coated formulations were subjected to drug release studies. Naproxen sodium release from the pulsatile tablets were studied in 1.2 pH acidic buffer for the first two hours followed by 7.4 pH phosphate buffer as medium over a period of 12hrs. The drug release from the press coated pulsatile tablets containing polymers were found to be slow and spread over long period of time.

The objective in the dissolution testing of press coated tablets was to identify a suitable ratio and coating level of polymers which releases the drug after a predetermined lag time of at least 6 hrs. Based on the study criteria, a suitable formulation should provide adequate lag time in pH 1.2 dissolution media but immediately release naproxen sodium in pH 7.4 dissolution media. In all the press coated formulations, it was found that neither Carrageenan gum nor Xanthan gum could not individually target the naproxen sodium release within the assumed lag time. Also, it was found that as the concentration of Carrageenan gum was decreased or Xanthan gum was increased, or when both of the polymers when used in combination were unable to release the drug at a predetermined lag time. Thus, formulation PC T8 having 19.2% carrageenan gum, 19.2% xanthan gum, 7.69% lactose anhydrous as changeling agent in press coated direct compression method was found to have maximum release of 98.42% ± 1.37% at 7hrs in pH 7.4 buffer facilitating no drug release upto assumed lag time of 6hrs has met the desired criteria. The results were shown in Figure 7 and 8.

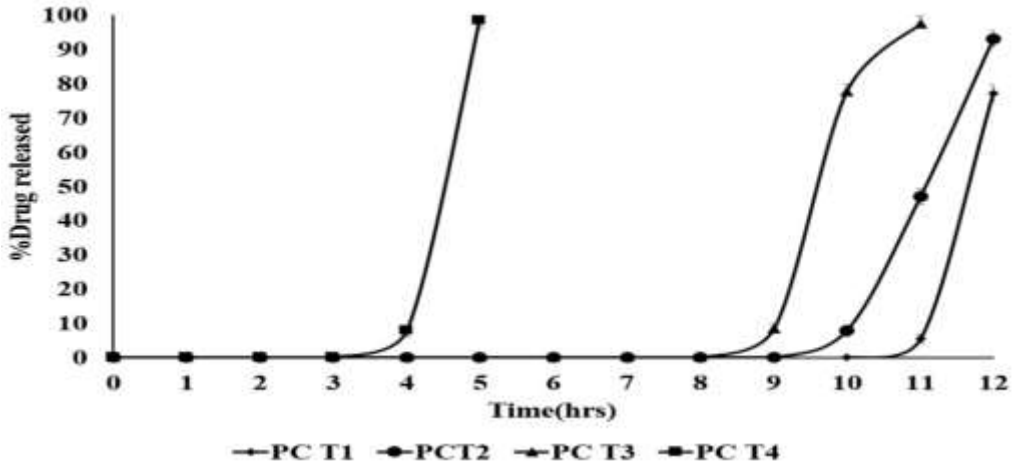

Figure 7: Dissolution profiles of PC T1, PC T2, PC T3, PC T4 (n=3 ± mean SD)

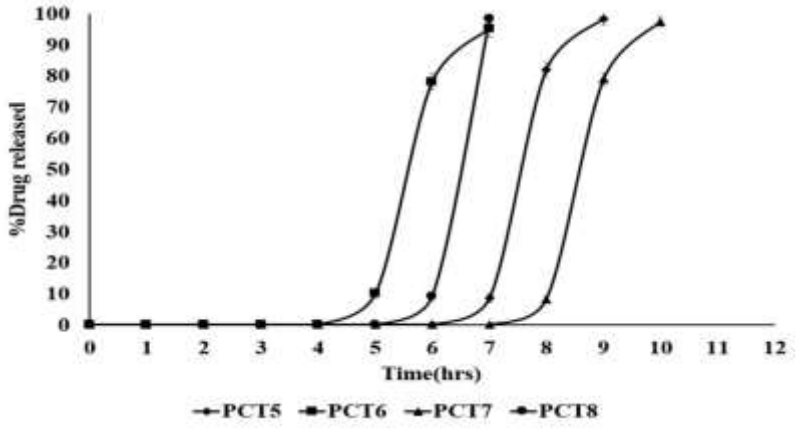

Figure 8: Dissolution profiles of PC T5, PC T6, PC T7, PC T8 (n=3 ± mean SD)

Naproxen sodium drug release studies from press coated pulsatile tablets at different rpm:

The final formula was checked for reproducibility at different RPM's like 50, 75 and 100 in different dissolution mediums. The optimized formulation PC T8 was found to resist the RPM pressure and has shown the 6 hrs lag time. The results were shown in Figure 9.

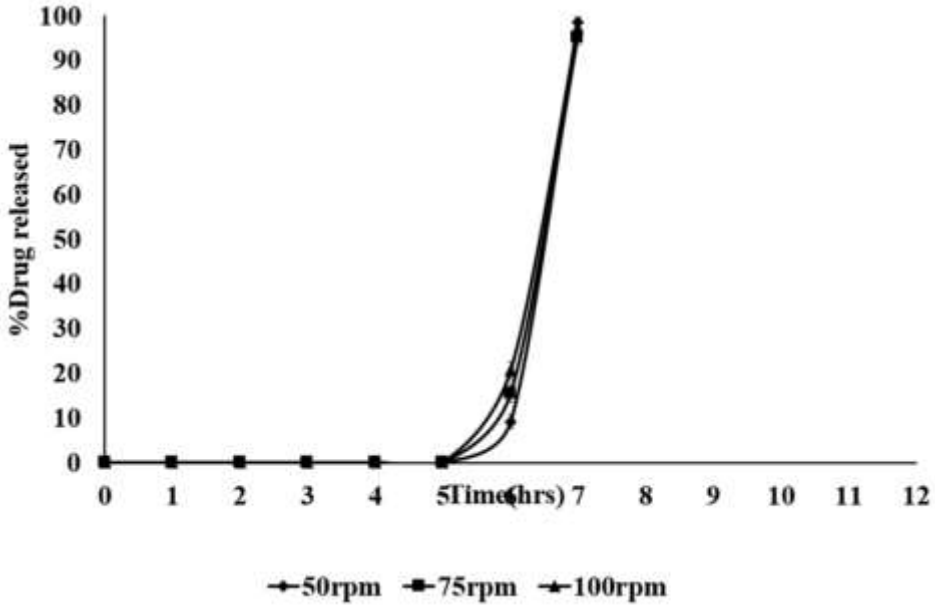

Figure 9: Dissolution profile of Optimized formula PC T8 at different rpm (n=3±meanSD)

***In-vitro* release kinetics data**

The various release kinetic equations in which the experimental data can be fitted and drug release rate can be predicted as a function of some variable (example time) .The suitability of the equation is judged on the basis of best fit into the equation using statistical indicators like R^2 values. From the correlation coefficient (R^2) values of all formulations (F1-F9) and (PC T1- PC T8) it was found that the core tablets and press coated tablets have followed the first order kinetics. The results obtained were given in Table 5.

Table 5: *In vitro* release kinetic parameters for press coated tablets

Formulation	Lag time (hrs)	Zero order model		First order model	
		r^2	k_0(µg/ml)	r2	k_1(hr^{-1})
PC T1	11	0.2413	2.688	0.947	0.060
PC T2	10	0.4038	4.5315	0.773	0.055
PC T3	9	0.4569	6.3912	0.809	0.048
PC T4	4	0.4823	14.726	0.706	0.463
PC T5	7	0.5306	9.1093	0.977	0.125
PC T6	5	0.6366	12.929	0.922	0.056
PC T7	8	0.4906	7.5284	0.946	0.040
PC T8	6	0.3863	8.7504	0.930	0.058

CONCLUSION

From the present investigation it can be concluded that, formulation F9 of immediate release core tablet having 10% Crosspovidone in direct compression method was found to have maximum release of 99.39 %±1.95% at the end of 20 minutes& formulation PC T8 of press coated pulsatile tablet of naproxen sodium having 19.2% carrageenan gum, 19.2% xanthan gum, 7.69% lactose anhydrous as channeling agent in press coated direct compression method was found to have maximum release of 98.42% ± 1.37% at 7hrs in pH 7.4 buffer facilitating no drug release upto assumed lag time of 6hrs has met the desired criteria and is successful in resisting different RPM pressures were selected as they meet the demand of chrono biological need of the disease providing a better pharmacological effect, thus can be effectively used in management of reducing the morning stiffness in Arthritis.

ACKNOWLEDGEMENTS

The authors are thankful to Aurobindo Pharma Hyderabad, for providing Naproxen sodium as gift sample for carrying out research work. The authors are also thankful to Principal and Management, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, for providing all the facilities required for the completion of the research work successfully.

REFERENCES

1. Jha N and Bapat S. Chronobiology and chronotherapeutics. Katmandu University Medical Journal.2004; 2(8): 384-388.
2. Micheal H. Chronobiology, drug delivery, and chrono therapeutics, Advanced Drug Delivery Reviews. 2007; 59, 31 (9, 10):828-851.
3. Shweta Arora, Ali J, Alka Ahuja, Sanjula Baboota and Qureshi J. Pulsatile drug delivery systems: An approach for Controlled drug delivery, Indian J Pharma Sci 2006; 68(3): 295-300.
4. Ganesh Rasve, Ganesh Borade, Siddheshwar Deshmukh and Amol Tagalpallewar. Pulsatile Drug Delivery System: Current Scenario. Int J Pharma and Bio Sci 2011; 2(3): 332-343.
5. Gajbhiye ND, Vilasrao JK, Kisan RJ and Anand UK. Pulsatile Drug Delivery System. J Pharm Res 2010; 2(1):120-123.
6. Gandla Swetha. Formulation and Evaluation of Naproxen Pulsatile Tablets for Chronomodulated Drug Delivery Using Core In Cup Metho. Int J Pharma Chem Biological Sci 2014; 4(4):867-873.

7. Ralph F.S. Compressed tablets by direct compression, Lieberman HA, Lachman L, Schwartz JB, eds. Pharmaceutical Dosage forms: Tablets. Vol 1. New York, NY; Marcel Dekker Inc, 1990, 195-245.
8. Bajpai A K and Sandeep Shukla. Water sorption through a semi-interpenetrating polymer network (IPN) with hydrophilic and hydrophobic chains reactive and functional polymers. Int J Pharm Pharma Sci 2002; 50(1):9-21.
9. Martin A. Micromeritic in Physical pharmacy (Martin A, Baltimore M. Deds) Lippincott Williams and willkins: Philadelphia. 2001; 154:2-19.
10. Lieberman HA, Lachman L and Schwartz JB. Pharmaceutical dosage forms: Tablets. Marcel Dekker, New York. 1990; 2nd edition volume 2:201- 43.
11. Krishnaveni G. Development and Evaluation of Pulsatile Drug Delivery System containing Montelukast Sodium by press coated tablet using natural polysaccharides. Int J Adv Pharm Gen Res 2013; 1(2):41-51.
12. Ashish Babulal Rane, Surendra Ganeshlal Gattani, Vinayak Dinayak Kadam and Avinash Ramarao Tekade. Formulation and Evaluation of press coated tablets for pulsatile delivery using hydrophilic and hydrophobic Polymers. Chem.Pharm.Bull.2009; 57(11):1213-1217.
13. Kamat Akshay Ramesh, Shabaraya A.R, Azharuddin Mohd and Krishnananda Kamat K. Formulation and Evaluation of pulsatile delivery system containing Indomethacin using natural polymers. Int Res J Pharm. 2013; 4(2):111-114.
14. Grover Chandani, Bhatt Ganesh and Kothiyal Preeti. Evaluation and characterization of different polymers based drug Theophylline in pulsatile drug delivery system. The Pharma Innovation.2012; 1(7):105-112.