CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1249923

Available online at: http://www.iajps.com Research Article

FORMULAITON AND PHARMACOKINETIC EVALUATION OF NAPROXEN SODIUM MODIFIED RELEASE TABLET

Socorrina Colaco[1], Ramesh. N[2], Ramakrishna Shabaraya[2]

[1]Department of Pharmacology, GITAM Institute of Medical Sciences & Research, Visakhapatnam.

[2]Department of Pharmaceutics, Srinivas College of Pharmacy, Farengipete Post, Mangalore-574143, Karnataka, India.

Abstract:

The objective of the study was to develop naproxen sodium SR tablets were prepared by direct compression method using hydroxy propyl methyl cellulose (HPMC K 100). To know the effect of polymer concentration invitro study performed it has been observed that as the polymer concentration increases, the drug release rate decreases, and bioavailability study carried out in healthy human subject by administering the developed sustained release and marketed immediate release tablet. The developed naproxen sodium showed confirmed longer time to reach peak concentration than marketed immediate release table, controlled and constant drug delivery system, maintains better plasma concentration than conventional tablet by which it overcome the shortcoming of conservative treatment. The rate and extent of absorption of naproxen sodium SR tablets were higher than the marketed immediate release tablet shows more competent and controlled drug release which would sustain plasma concentration level throughout and produce desired effect. Further evidenced with lower elimination rate and higher half life.

Keywords: *Naproxen sodium SR tablets, Marketed immediate release tablet, HPMC, LCMS-MS, Bioavailability study*

Corresponding Author:

Dr. Socorrina Colaco

Associate Professor,
Department of Pharmacology,
GITAM Institute of Medical Sciences & Research
GITAM, Rushikonda, Visakhapatnam – 530 045
Andhra Pradesh, India.
E-mail: drsc77@gmail.com
Fax: + 91 891- 2538 444
Ph: + 91 891-2866 450,Ph: + 91 824 2232700,Fax: + 91 824 2274725

QR code

Please cite this article in press Socorrina Colaco et al., ***Formulaiton and Pharmacokinetic Evaluation of Naproxen Sodium Modified Release Tablet,*** *Indo Am. J. P. Sci, 2018; 05(05).*

1. INTRODUCTION:

Naproxen is a propionic acid derivative related to the aryl acetic acid group of nonsteroidal anti-inflammatory drugs. Naproxen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Naproxen is widely bound to plasma albumin, so it may be more efficient to deliver this drug in its sustained-release dosage form. The dosage of naproxen sodium is usually two to three times a day. Sustained release dosage forms are developed to minimize frequent dosage administration which in turn increase patient compliance and cost effective. Sustained release (SR) formulations are designed to carry prolonged therapeutic plasma concentration from a single dose and sustain the level for predetermined time [1]. Most commonly used method for developing sustained release formulations for acive ingridents to include in matrix tablets [2].

Several types of oral sustained release formulation have been developed to increase efficacy of drugs and patient compliance in case of drug having short half life. The matrix tablet naproxen of using hydroxypropyl methylcellulose derivatives controls the drug release effectively for 24 h; hence, the formulation can be considered as once daily sustained release tablet of naproxen in order to improve patient compliance [3]. The study indicates that the rate of dissolution of Naproxen sodium SR tablet can be considerably improved with Kollidon SR. tablets of naproxen, by using a combination of polymers Kollidon SR and Avicel PH 102 [4]. The objective of the present study was to inspect the Invitro and invivo correlation of directly compressed SR tablets by mixing HPMC and ethyl cellulose and blended with magnesium stearate and talc to prepare the sustained release dosage form containing naproxen sodium. To know the effect of polymer concentration invitro study will be performed and bioavailability study would be carried out in healthy human subject by administering the developed sustained release and marketed immediate release tablet.

2. MATERIALS AND METHODS:

2.1 Chemicals and reagents

Naproxen sodium supplied as gift sample by by Strides Arcolab Limited, Bangalore, India. HPMC K100M was provided as gift sample by Colorcon Asia Pvt. Limited, Goa, India. All ingredients used like talc, magnesium stearate, ethyl cellulose were purchased from local vendor.

2.2 Preparation of tablets by direct compression [5]

Weighed amount of naproxen sodium, polymers (HPMCK100M/ EC), diluent (MCC) mixed by using glass pestle to get uniform mixture. The mixture blended for 5 min with magnesium stearate and talc. The powder mixtures are compressed into tablets by using single punching machine. Punch Details: 10 mm bi-flat round shaped punches. Compression Machine: single station electrically operated tablet compression machine, Cadmach, India. The composition of the tablets are presented in Table 1.

Table 1: Composition of Naproxen Sodium Formulation (F1-F6)

Formulation	Naproxen sodium	HPMC K100M	Talc (1.5%)	Magnesium Stearate (1.5%)	Talc (1%)	Magnesium Stearate (1%)	Ethyl cellulose
F1	375	75 mg	-	-	4.50 mg	4.50 mg	-
F2	375	150 mg	-	-	5.25 mg	6.00 mg	-
F3	375	225 mg	-	-	5.25mg	6.00 mg	-
F4	375	37.5 mg	6.75 mg	6.75 mg	-	-	37.5 mg
F5	375	37.5 mg	7.87 mg	7.87 mg	-	-	37.5 mg
F6	375	37.5 mg	9.00 mg	9.00 mg	-	-	37.5 mg

2.3 Precompression Properties [6]
Precompression properties were evaluated for Angle of repose, Loose bulk density, Tapped bulk density and Carr's compressibility index (%) and Hausner's ratio.

2.4 Evaluation of Tablets Properties [7-9]

The weighr variation, thickness by using vernier calipers, Hardness testing performed by using Monsanto Hardness tester and expressed in Kg/cm^2, The friability of the tablets determined by using Roche Friabilator. Three tablets weighed crushed by using mortar & pestle, accurately weighed 100 mg of powder exteacted with pH 6.8 phosphate buffer, the solution filtered, diluted and the drug content determined at 309 nm using a UV/Vis spectrophotometer.

2.5 Dissolution study
Dissolution of developed naproxen sodium tablets were determined by using dissolution apparatus (type II, paddle), at 50 and 75 rpm. The dissolution media used pH 1.2, 4.5, 5.5, 6.8 and 7.2 buffer solutions maintained at 37±0.5 ˚C. Dissolution tests performed on six tablets. Four ml of the samples withdrawn at 0.0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24.0 hours. Equal quantity of the medium was replaced to the jar after each sampling. The amount of the drug released is estimated by using UV-Visible spectrometer at 332 nm [10]. Cumulative percentage release at various time intervals will be calculated and compared.

2.6 Drug Release Kinetics Mechanism
The in vitro drug release profiles will be plotted according to zero - order, first- order, Higuchi [11]and Peppas [13] equations to know the mechanism of drug release and to compare the dissimilarity in the release profile of developed batches of naproxen sodium SR tablets.

2.7 Clinical Study and Bioanalysis
This was a single center, randomized, single-dose, open-label, four way crossover, bioavailability study to compare the rate and extent of absorption of a naproxen sodium 375 mg SR tablets (i.e. Slow, Medium & Fast) and naproxen sodium 500 mg tablet (marketed immediate release), under fasting conditions. Test or Reference was administered as per the randomization schedule. The blood samples were collected at pre-dose (0.00) and post-dose at 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 hours post dose sample. A washout period of 7 days between the dosing of four periods [17]. Subjects were continuously monitored for well being; and standard diet was provided. The concentration of naproxen sodium in plasma samples were estimated by using validated LCMS/MS method. Pharmacokinetic and statistical analyses were performed on obtained drug concentration data by using Phoenix 6.4.0 version software.

2. RESULT AND DISCUSSION:

Pre compression studies are intended to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical, and analytical investigation in support of promising experimental formulations. Data from pre compression studies gives information on the necessary groundwork for formulation attempts [8]. All the compositions of different tablet batches showed satisfactory values of angle of repose, carr's index (%) and Hausner's ratio refer Table. 2. FTIR and DSC studies indicate the absence of any chemical interactions between naproxen sodium and the excipients used.

Table 2: Pre compression parameters of Naproxen Sodium Formulation (F1-F6)

Formulation	LBD(g/ml)	TBD (g/ml)	Angle of repose (θ°)	Carr's Index	Hausner Ratio
Naproxen (1% T+1% MS)	0.4725	0.6694	34.21	29.41	1.42
Formulation (F1) 1.5% T+1.5% MS	0.4651	0.5405	24.70	13.95	1.16
Formulation (F2) 1.5% T+1.5% MS	0.4543	0.5359	21.80	15.22	1.18
Formulation (F3) 1% T+1% MS	0.4255	0.5000	22.78	14.89	1.18
Formulation (F4) 1.5% T+1.5% MS	0.4782	0.5641	21.80	15.22	1.18
Formulation (F5) 1.5% T+1.5% MS	0.4545	0.5263	19.79	13.64	1.16
Formulation (F6) 1.5% T+1.5% MS	0.5333	0.6486	22.78	17.78	1.22

Table 3: Physicochemical Evaluation of Naproxen Sodium Tablets

Formulations	Hardness (kg/cm^2)	Weight Variation (g)	Thickness (mm)	Friability (%)
F1	4.03	105.2305 ± 2.3627	3.15	<1%
F2	4.23	107.6635 ± 1.1623	3.46	<1%
F3	4.63	82.035 ± 4.5743	3.89	<1%
F4	5.07	98.8755 ± 1.7966	3.17	<1%
F5	5.20	113.9 ± 1.0543	3.56	<1%
F6	4.97	85.1055 ± 0.671	4.23	<1%

Thickness of the tablets among the different batches prepared was uniform. All the batches passed the weight variation as not more 2 tablets in a batch were out of the range of ±5%. The drug content for all the formulations was in the range of 98-101%. Friability of all formulations was found to be less than 1%. The tablets prepared by direct compression showed acceptable physiochemical properties [7-9] and complied with the specifications for weight variation, hardness, friability and drug content refer Table. 3.

The in vitro drug release studies were performed at different pH conditions (namely pH 1.2, 4.5, 5.5, 6.8 & 7.4) to select appropriate pH condition . The results of dissolution studies at different pH conditions with 50 rpm for F1-F6; SR tablets are pH 1.2 and 50 rpm, drug release was incomplete and a maximum of up to about 11% was released within 3 hours. At pH 4.5, the drug release was very slow over the period of 24 hours. At pH5.5 and 50 rpm, there was uniform and slow release of drug from all the 6 tablets (F1-F6; SR tablets) over the period of 24 hours. Almost 80.59-99.86% of drug was released slowly during 24 h time period. However the drug release was different for different formulations at the end of 24 hours which could be due to differences in the composition of the tablets. At pH 6.8 and 7.4 with 50 rpm, although about 86.79-97.32% and 86,95-95.81% release of drug was observed. And to select, appropriate rpm, the dissolution studies were also performed by using 75 rpm in addition to 50 rpm. The in vitro drug release profiles were not much altered when the rpm was increased to 75 from 50. Moreover USP prefers 50 rpm for dissolution studies. Hence pH 5.5 and 50 rpm were optimized conditions for in vitro dissolution studies of naproxen sodium SR tablets. Based on the in vitro dissolution studies of F1 to F6 sustained release formulations in pH 5.5 and 50 rpm F2, F4 and F5 were considered as slow rate releasing, fast rate releasing and medium rate releasing formulations. Furhter invitro study performed for naproxen sodium SR Tablets (F2 Slow, F5 Medium & F4 Fast)as per the USP method i.e. pH 7.4 pH condition at 50 rpm. The percentage cumulative release of naproxen sodium SR tablets are shown in Fig. 1. No significant changes were observed during six month stability study evaluation. The direct relationship was observed between swelling index and polymer concentration, and as polymer concentration increases, swelling index was increased.

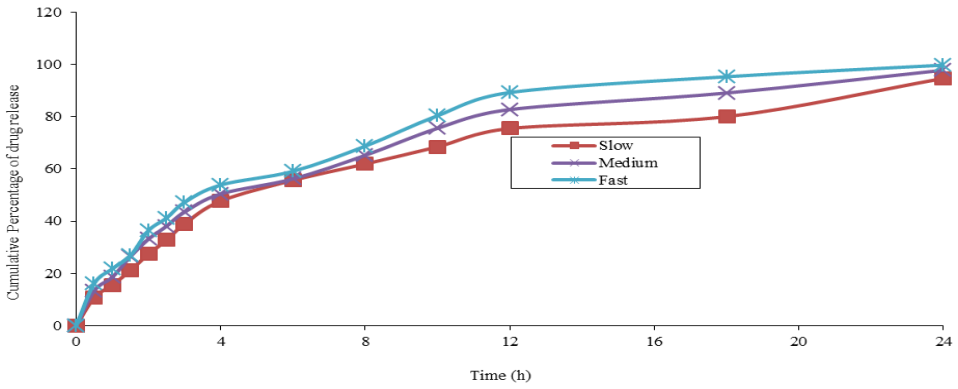

Fig. 1: Percentage Cumulative Release of Optimized Naproxen Sodium SR Tablets (Slow, Medium & Fast)

The regression values obtained with Zero order plots were better those obtained with First order equation refer Fig. 2-5. Further it was found that the in vitro drug release of naproxen sodium sustained release was best explained by Higuchi's equation (32), as the plots showed the highest linearity (r2 = 0.9697 (F5 Medium), 0.968 (F2 slow), and 0.9596 (F4 Fast), followed by zero order (r2 = 0.8464 (F4 Fast), 0.8623 (F5 Medium), 0.8623 (F2 slow) & and first order (r2 = 0.6768 (F4 Fast), 0.667 (F5 Medium) & 0.6548 (F2 slow). Hence Fickian diffusion (as per Higuchi's plots) is the dominant mechanism of drug release associated with Zero order kinetics. However to confirm the mechanism, the data was plotted using Koresmeyer-Peppas equation and the graphs shows good linearity [14] . The slope (n) value obtained with all these 3 formulations ranged between 0.4971 – 0.5725. Since the slope values are near to 0.5 the dominant mechanism for drug release is Fickian diffusion [16]. Reddy et al [15] observed similar results with a matrix tablet of nicorandil with an n value of 0.71 and Fassihi and Ritschel [12] with a matrix tablet of theophylline with an n value of 0.7. However, drug release was also found to be very close to zero-order kinetics, indicating that the concentration was nearly independent of drug release. Hence, mixed order drug release kinetics observed with naproxen sodium sustained release tablets.

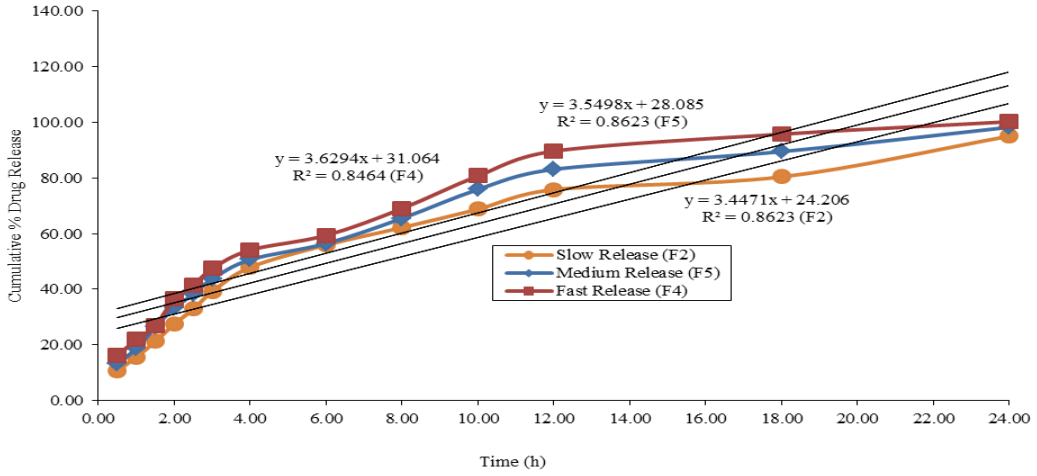

Fig. 2: Zero order Release Profile of Naproxen Sodium SR Tablets (i.e. F2 Slow, F5 Medium & F4 Fast)

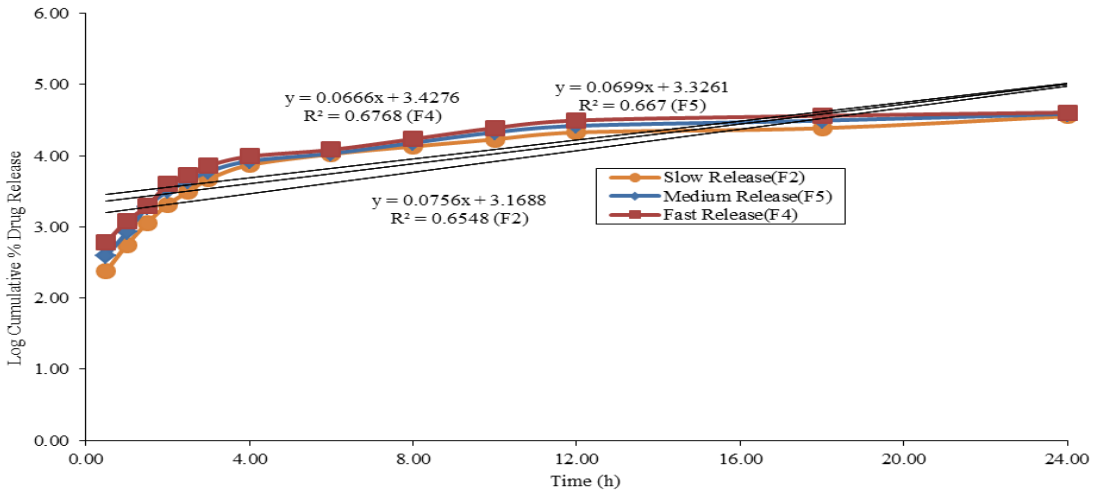

Fig. 3: First Order Release Profile of Naproxen Sodium SR Tablets (i.e. F2 Slow, F5 Medium & F4 Fast)

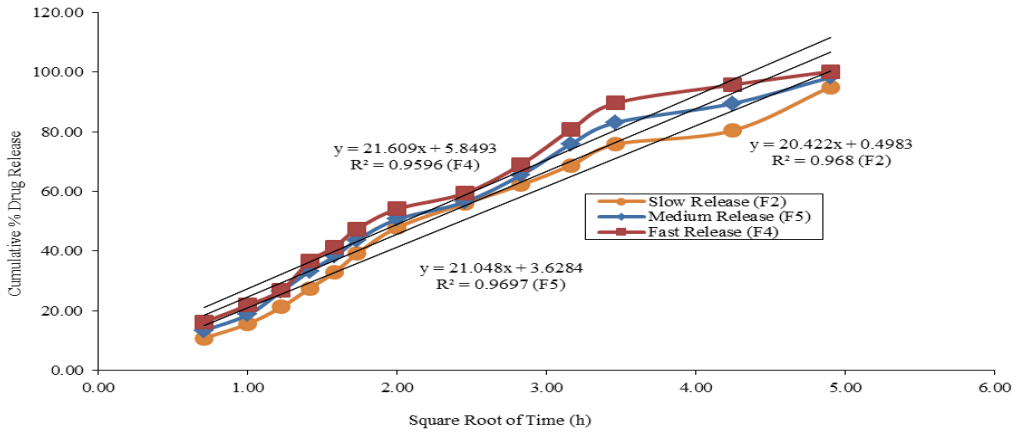

Fig. 4: Higuchi Kinetics Release Profile of Naproxen Sodium SR Tablets (i.e. F2 Slow, F5 Medium & F4 Fast)

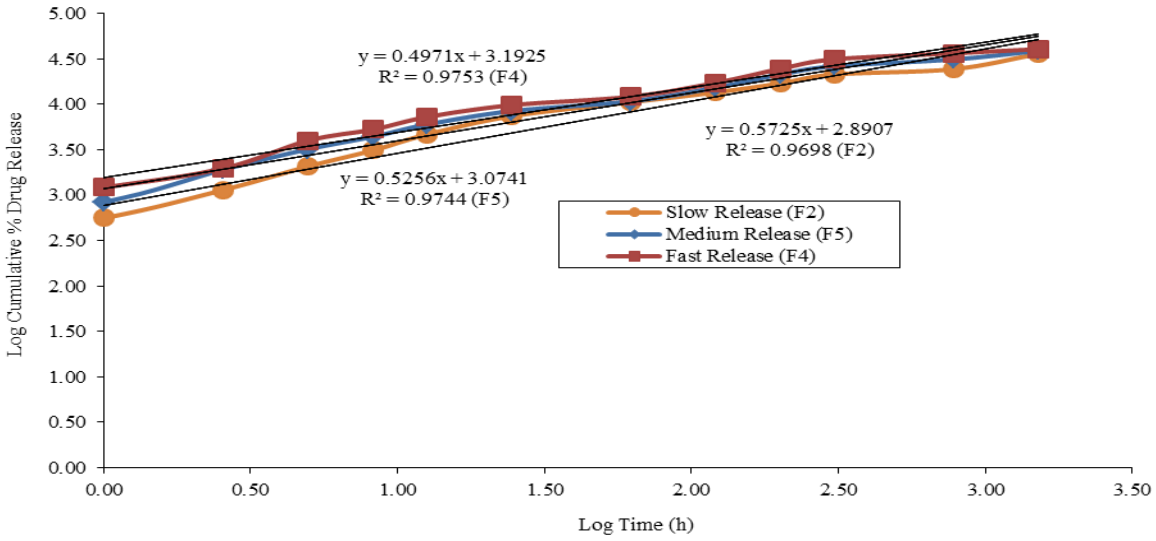

Fig. 5: Korsmeyer-Peppas Kinetics Release Profile of Naproxen Sodium SR Tablets (i.e. F2 Slow, F5 Medium & F4 Fast)

The bioavailability four way crossover, bioavailability study conducted to compare the rate and extent of absorption of a naproxen sodium 375 mg SR tablets (i.e. Slow, Medium & Fast) and naproxen sodium 500 mg tablet (marketed immediate release), under fasting conditions. Test or Reference was administered as per the randomization schedule. The developed naproxen sodium 375 mg SR tablets (i.e. Slow, Medium & Fast) confirmed longer time to reach peak concentration than marketed immediate release tablet and showed more consistent refer Table 6 and Fig. 6. AUClast and AUCINF_obs values for developed naproxen sodium 375 mg SR tablets (i.e. Slow, Medium & Fast) were higher than the marketed immediate release tablet shows more competent and controlled drug release which would sustain plasma concentration level throughout and produce desired effect. Furhter evidenced with lower elimination rate and higher half life.

Table 4: Pharmacokinetic Parameter of Naproxen Sodium for Marketed Immediate Release and Sustained Release Tablet (Fast, Medium & Slow)

Formulation		Kel (1/hr)	Half life (hr)	Tmax (hr)	Cmax (ug/mL)	AUClast (hr*ug/mL)	AUCINF_obs (hr*ug/mL)
Immediate Release Tablet	Mean	0.350	2.203	1.833	54.209	144.237	147.483
	SD	0.109	0.883	0.258	10.685	35.146	36.265
Fast Sustained Release Tablet	Mean	0.186	3.840	2.167	73.767	301.557	307.561
	SD	0.030	0.776	0.258	4.889	8.145	7.775
Medium Sustained Release Tablet	Mean	0.134	5.464	2.667	68.879	373.548	391.273
	SD	0.039	1.230	0.258	4.562	73.928	82.259
Slow Sustained Release Tablet	Mean	0.192	3.722	3.583	63.199	383.289	391.499
	SD	0.038	0.710	0.376	3.141	64.036	69.217

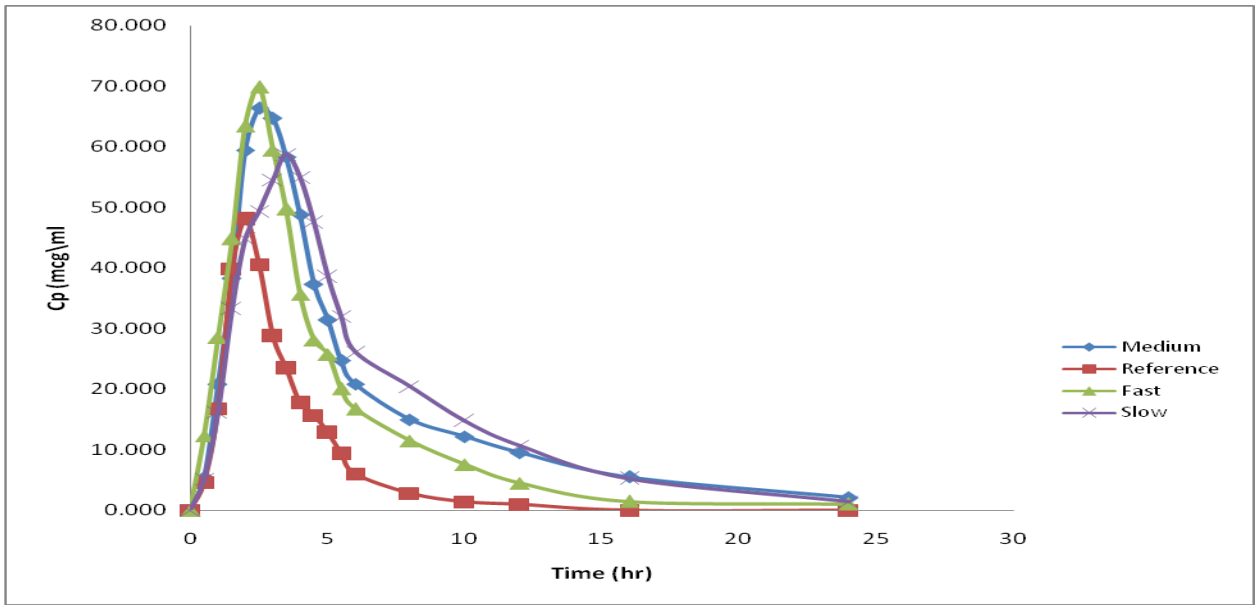

Fig.6: Mean plasma concentrations versus time of Naproxen Sodium for Marketed Immediate Release and Sustained Release Tablet (Fast, Medium & Slow)

3. CONCLUSION:

The rate and extent of absorption of developed naproxen sodium sustained release tablet (i.e. Slow, Medium & Fast) were higher than the marketed immediate release. The present study showed controlled and constant drug delivery system for developed naproxen sodium which maintains better plasma concentration than conventional tablet by which it will overcome the shortcoming of conservative treatment.

ACKNOWLEDGEMENT:

The authors articulate the gratefulness to the management of Srinivas College of Pharmacy, SeQuent Research Limited & Strides Arcolab Ltd, Phoenix Winonlin Certara software Hyderabad for providing necessary support to carry out the work.

REFERENCES:

1. Cardinal JR. Matrix systems. In: Langer RS, Wise DL, editors. Medical Applications of

Controlled Release Systems. Boca Raton, FL: CRC Press Inc, 1984. 43–44.
2. DeHaan P, Lerk CF. Oral controlled release dosage forms. A review. Pharm Weekbl Sci. 1984. 6(2):57-67.
3. Harun R, Abul KLK. Md. Zakir H, Abu SSR. Design and Formulation of Once Daily Naproxen SustainedRelease Tablet Matrix from Methocel K 15M CR and Methocel K 100M CR. Iranian Journal of Pharmaceutical Sciences Autumn 2009: 5(4): 215-224.
4. Dilshad Y, Md. RR, Morshada A. Formulation development of directly compressed Naproxen SR tablet using Kollidon SR and Avicel PH 102 polymer. Yasmin et al., International Current Pharmaceutical Journal. 2013: 2(6): 112-114.
5. Pather S, Russell I, Syce J, Neau S. Sustained release theophylline tablets by direct compression, Part 1: formulation and In vitro testing. Int J Pharm.1998;164:1-10.
6. Martin A. Micrometrics. In: Physical Pharmacy. Baltimore, MD: Lippincott Williams & Wilkins. 2001. 423–454.
7. Pharmacopoeia of India. New Delhi: Ministry of Health and Family Welfare, Government of India, Controller of Publications. 1996.
8. Leon Lachman, Herbert Lieberman A. The theory and practice of industrial pharmacy. Special Indian edition 2009: 293-373.
9. Wells J. Pharmaceutical preformulation: The physiochemical properties of drug substances. In: Aulton ME, editor. Pharmaceutics the science of dosage form design. London: Churchill Livingstone. 2002. 247.
10. United States Pharmacopeia and national formulary USP 37-NF 32; The United States Pharmacopoeial Convention, Inc: Rockville MD; 2014
11. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of release rate of solid drugs dispersed in solid matrices. J Pharm Sci. 1963: 52: 1145-1149.
12. Fassihi RA, Ritschel WA. Multiple-layer, direct-compression, controlled-release system: in vitro and in vivo evaluation. J Pharm Sci. 1993; 82(7):750-4.
13. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev. 2001; 48 (2-3):139-157.
14. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15(91): 25-35.
15. Reddy KR, Mutalik S, Reddy S. Once-daily sustained-release matrix tablets of Nicorandil: formulation and in vitro evaluation. AAPS PharmSciTech. 2003; 4(4): 480-488.
16. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv. 1985; 60(4):110-1.
17. Dymphy RH, David JM, Meindert D, and Oscar EDP. Correlation between in vitro and in vivo concentration–effect relationships of naproxen in rats and healthy volunteers. Br J Pharmacol. 2006; 148(4): 396–404.