International Journal of Research in Pharmacology & Pharmacotherapeutics

ISSN Print: 2278-2648 IJRPP |Vol.9 | Issue 4 | Oct - Dec - 2020
ISSN Online: 2278-2656 Journal Home page: www.ijrpp.com

Research article Open Access

Cardiovascular drug delivery: development and characterization of captopril chronomodulated drug delivery system for the management of hypertension

Kannan C[1]*, Senthilkumar N[2], Thirumurthy R[1]

[1]*SunRise University, Alwar – 301030, Rajasthan, India.*
[2]*JKK Munirajah Medical Research Foundation college of Pharmacy, B.Komarapalam-638183, Tamilnadu, India.*

***Corresponding author: Kannan C**

ABSTRACT

The main objective of the present study was to design development and evaluate a press coated pulsatile drug delivery system of captopril for the effective treatment of hypertension. The core was prepared by direct compression using various super disintegrates such as Crospovidone XL 10, Sodium Starch Glycolate and Croscarmellose in different ratios with the drug and chosen the best core formulation. The outer pulsatile coat formulation was prepared by using various polymers such as HPMC K4M, K15M and K100M by varying compression force in terms of ton pressure. The polymers were studied individually and studied the influence of compression force on lag time further obtaining the lag time. All the preliminary studies were evaluated for various post compression parameters along with the dissolution study that was performed using USP paddle method at 50 rpm in 0.1 N HCl and phosphate buffer pH 6.8. The formulation attain a predetermined lag time of 6 h with effective release is selected as the best formulation.

Keywords: Hypertension, Captopril, Chronopharmaceutics, Chronobiology, HPMC, Crospovidone, Lagtime.

INTRODUCTION

To attain the required therapeutic effect the drug must be given in the right dosage, where the active pharmaceutical ingredient is absorbed/reached to the effective target site at the right time[1, 2]. For this purpose, many fruitful efforts have been made for the design, development and production of oral controlled systems. Oral controlled drug delivery systems epitomize the most popular form of drug delivery systems compared to classical conventional dosage forms for the noticeable advantages of oral route of drug administration.

However, there are certain conditions for which such a release design is not suitable like cardiovascular diseases, Diabetes mellitus, Asthma, Arthritis, Peptic ulcer etc. In such cases chrono therapy delivery system is used in which release drug on programmed pattern i.e. at appropriate time & at appropriate site of action. A major aim of chronopharmaceutics is to deliver the drug in higher concentrations during the time of greatest need and in

lesser concentrations when the need is less to minimize side effects[2].

Chronobiology is the science that studies biological rhythms characterized by their current, regular intervals and the cyclic physical, biochemical, and behaviouralphenomena that occuring all living organisms[3-5]. There are many types of biological rhythms governing the bodies of living beings, including the frequency domain, which can be classified into ultradian, circadian and in fradian rhythms [5].

The phrase "circadian rhythm" was first described by Halberg and Stephens in 1959[6]. Circadianrhythms (Latincircadiem, meaning "About a day") have a duration of approximately 24hours. Rhythms that exceed 24hours are considered in fradianrhythms and include the menstrual cycle and the rate of production of blood platelets. The in fradianperiod can range from approximately seven days to 100 years in the extreme case of their productive cycle of Chinese bamboo. Cycles that have duration of less than 24hours are called ultradianrhythms. These include high-frequency oscillations with periodslessthan 20hours, including periods in the order of milliseconds, such as the firing rate of neurons, or in the order of minutes, such as the rhythm of heartbeats[7]. Temporalintegrationof the internal and external rhythm is coordinated by the suprachiasmaticnucleus(SCN) of the hypothalamus through the monitoring of temporal signals called Zeitgebers (a German neologism meaning time marker), which may be temperature, food intake and the sleep/wake cycle [3].

Chronotherapeutics refers to a treatment method in which *in vivo* drug availability is timed to match rhythms of disease, in order to optimise therapeutic outcomes and minimise side effects [8].

Captopril is a sulfhydryl-containing analogy of proline, can be used in the treatment of hypertension. Captopril is a potent, competitive inhibitor of angiotensin-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII). ATII regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS).

MATERIALS AND METHODS

Captopril was purchased from Yarrow chem products, Mumbai; Hydroxyl propyl methyl cellulose K4M, K15M, K100M was supplied by fourrts India Pvt. Ltd., Chennai. Crospovidone XL 10, Sodium Starch Glycolate supplied by Piramal Enterprises Limited, Mahad. Croscarmellose Sodium and Micro Crystalline Cellulose procured from Loba Chemise Pvt, Ltd., Mumbai. Magnesium Stearate and Lactose was purchased from S.D. Fine-Chem. Ltd., Ahmedabad, India. All the ingredients purchased were of analytical grade.

Preformulation studies

Preformulation studies are the first step in the rational development of dosage form. The preformulation study which includes solubility analysis, melting point determination, angle of repose, bulk density, tapped density, compressibility index, hausner ratio and assay.

Drug and Drug – Excipient Physical Compatibility Studies

The Active ingredients and excipients were mixed and taken in 2 ml glass vials and sealed. These glass vials are kept at room temperature and 40°C / 75% RH for about 1 month. At the interval of 10 days, the samples were withdrawn and analysed for colour change.

Drug excipient compatibility study FTIR

The drug and excipient compatibility study was observed using Fourier Transform - Infra Red spectroscopy (FT-IR). The FT-IR spectra obtained from SHIMADZU (Shimadzu Corporation) FT-IR was utilized in determining any possible interaction between the pure drug and the excipients in the solid state. The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about 8 t/in^2. The spectra were recorded over the wave number of 4000 to 500 cm^{-1}.

Determination of λmax for Captopril

Determination of analytical wavelength of Captopril in 0.1N HCl and pH 6.8 phosphate buffers can be done by taking 1 ml from 100 µg/ml standard stock solutions in 10 ml volumetric flask separately. The volume was made up to 10 ml with buffer solution. The resulting solutions containing 10µg/ml

was scanned between 200 to 400 nm using UV Visible spectrophotometer and their absorbance were foundas212 and 205 nm.

Preparation of Pulsatile press coated tablet of Captopril

The design and development of pulsatile press coated tablet was carried out in two major steps [11] First, the rapid release core tablet is formulated using various super disintegrates by using direct compression process [12, 13]. Core tablet formulations will then be optimized or selected based on their dissolution profile. Next, the optimized core tablet will then further processed for press coating by using various semisynthetic polymers and further optimized [11].

TableNo.1.Rapid Release Core Tablets (RRCT)

S.No	Ingredients	C1	C2	C3	C4	C5	C6	C7	C8	C9
1	Captopril	25	25	25	25	25	25	25	25	25
2	Sodium Starch Glycolate	5	10	15		-	-	-	-	-
3	Croscarmellose Sodium	-	-	-	5	10	15			-
4	Crospovidone XL 10	-	-	-	-	-	-	5	10	15
5	Micro Crystalline Cellulose	28	23	18	13	28	23	18	13	28
6	Magnesium Stearate	2	2	2	2	2	2	2	2	2
Total		60	60	60	60	60	60	60	60	60

Formulation of Rapid Release Core tablets

The rapid release tablets of captopril were formulated by incorporating with super disintegrates like Crospovidone XL 10, Sodium Starch Glycolate and Croscarmellose Sodium in various ratios with the drug[14]. Furthermore, microcrystalline cellulose was used as diluent and magnesium stearate utilized as gliding and as well as lubricant[15, 16]. The content of each tablet is listed in Table No.1. All the ingredients were weighed accurately and transferred to a clean mortar and pestle except magnesium stearate. The powder blend was mixed for 10 min after which magnesium stearate was added to the blend and the mixing was continued for another 10 minutes. After obtaining a uniform blend, it was passed through sieve#60 and was prepared for direct compression. The compression of the powder blend was carried out using 10 station punching machine (Proton mini press) by employing concave punches of 6 mm diameter and adjusting thickness and hardness accordingly.

Table No. 2. Compression Coated tablets

S. No	Formulation	Force Compression (Ton)	Ingredients						
			Core Tablets	HPMC K4M	HPMC K15M	HPMC K100M	Lactose	Mg. Stearate	Total
1	F1	1 Ton	60	75	-	-	173	2	310
2	F2		60	150	-	-	98	2	310
3	F3		60	225	-	-	23	2	310
4	F4		60	-	75	-	173	2	310
5	F5		60	-	150	-	98	2	310
6	F6		60	-	225	-	23	2	310

7	F7		60	-	-	75	173	2	310
8	F8		60	-	-	150	98	2	310
9	F9		60	-	-	225	23	2	310
10	F10		60	75	-	-	173	2	310
11	F11		60	150	-	-	98	2	310
12	F12		60	225	-	-	23	2	310
13	F13		60	-	75	-	173	2	310
14	**F14**	2 Ton	60	-	150	-	98	2	310
15	F15		60	-	225	-	23	2	310
16	F16		60	-	-	75	173	2	310
17	F17		60	-	-	150	98	2	310
18	F18		60	-	-	225	23	2	310
19	F19		60	75	-	-	173	2	310
20	F20		60	150	-	-	98	2	310
21	F21		60	225	-	-	23	2	310
22	F22		60	-	75	-	173	2	310
23	F23	3 Ton	60	-	150	-	98	2	310
24	F24		60	-	225	-	23	2	310
25	F25		60	-	-	75	173	2	310
26	F26		60	-	-	150	98	2	310
27	F27		60	-	-	225	23	2	310

Formulation of Pulsatile press coated tablets

Coat layer blend for coating the core tablet was prepared by dry blending using different ratios of the synthetic polymers such as Hydroxy propyl methyl cellulose K4M, K15M and K100Mas shown in TableNo.2. These powders were dry blended for 10 minutes with the lactose as diluent and the mixture is then used as dry coating material for the optimized batch of the core tablet to prepare press coated pulsatile tablet [17, 18]. The core tablets were press-coated with coat blend where, half of the coating material was weighed and transferred to tablet machine then the core tablet was placed manually at the centre of the die and the remaining quantity of the coating material was added into the die over the core tablet. Then compressed at various compression forces from 1 to3 tons by Proton mini-press tablet machine using 9 mm die size [19, 20].

Precompression Properties

Precompression studies were performed for the core and coating mixture such as Angle of repose, Bulk density, Tapped density, Compressibility index and Hausner ratio.

Evaluation of Core and press coated tablets

The core and coated tablets ware evaluated by performing following studies such as Weight variation, friability, hardness, Thickness, Drug Content, Disintegration test and dissolution test.

Dissolution test

The *in vitro* drug release from core tablets was carried out using United States Pharmacopoeia (USP) paddle apparatus at 50 rpm and 37 ± 0.5ºC, phosphate buffer (pH 6.8).

The *in vitro* drug release from coated tablets was carried out using United States Pharmacopoeia (USP) paddle apparatus at 50 rpm and 37 ± 0.5ºC. HCl (0.1N) and phosphate buffer (pH 6.8) were used as the dissolution medium. Initially, tablets were subjected to dissolution in 0.1N HCl for 2 hours and after that media were changed to phosphate buffer (pH 6.8). The samples were withdrawn at regular intervals and analysed by UV spectrophotometer at 212 nm for 0.1 N HCl& 205 nm for 6.8 pH phosphate buffer for the presence of the drug (n = 3).

Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives.

The International Conference on Harmonization (ICH) Guidelines titled "Stability Testing of New Drug Substance and Products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions. The stability studies were performed for core as well as press coated tablets for a period of 3 months at an interval of 30, 60 & 90 days.

RESULTS AND DISCUSSION

Preformulation studies

All the preformulation studies were performed for the pure drug results are given in the TableNo.3. From the preformulation studies shows that it complies as per the specification.

TableNo. 3. Preformulation studies of Captopril.

Nature of the drug	Specification of the drug	Observation
Colour & Nature	White to off-white, crystalline powder	Complies
odour	Slight sulphurous odor	Complies
Melting Point	103-104^{0}C	Complies
Solubility	Freely soluble in water (approximately 160 mg/ml), Freely soluble in alcohol, chloroform, methylene chloride; sparingly soluble in ethyl acetate	Complies
Angle of repose	27.14^0	--

Drug excipient compatibility study FTIR

Drug and excipient compatibility was confirmed by comparing spectra of FTIR analysis of pure drug with that of various excipients used in the formulation. It was found that there was no chemical interaction between captopril and excipients used because there were no changes in the characteristic peaks of captopril in the IR spectra of mixture of the drug and excipients as compared to IR spectra of pure drug. This can be observed in Figure No.1& table No. 4.

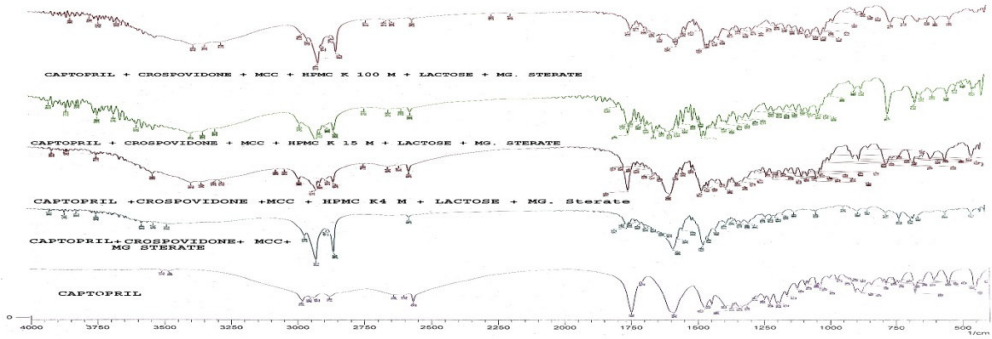


Figure. no.: 1 FTIR Graph of pure drug captopril Vs Optimized Formulations C9, F7, F14 & F 21

TableNo.4. FTIR interpretation of pure drug captopril Vs Optimized Formulations

S.No.	Type of bond	Actual frequency (cm^{-1})	Observed frequency (Captopril) (cm^{-1})	Observed frequency (cm^{-1}) F7	Observed frequency (cm^{-1}) F14	Observed frequency (cm^{-1}) F19
1	N-H Str Amide	3400-3500	3500.56 3476.45	3382.91 3339.51	3587.35 3382.91	3525.63 3382.91
2	C-H Str Alkane	2850-2960	2949.92	2917.13	2918.10	2917.13
3	S-H Str	2550-2600	2566.11	2566.11	2565.15	2566.11
4	C=O Str Ketone	1730-1760	1748.35	1748.35	1747.39	1748.35
5	N-H Ben Amino Salt	1575-1600	1589.23	1578.63	1592.13	1590.20
6	C-H Ben Alkane	1440-1485	1473.51	1465.80	1471.59	1471.59
7	C-O Str Alcohol	1260-1350	1347.19	1339.47	1338.51	1339.47
8	C-N Str Aliphatic Amine	1020-1220	1228.57 1202.53 1190.96	1117.67 1094.53 1071.38	1202.53 1165.89 1142.74	1202.53 1190.96 1164.92

Precompression Properties

Core tablets dry blend

The flow properties of different core formulation blend are shown in the Table No. 5. The results obtained for angle of repose (θ) vary from 21°.58' to24°87' which fall within <25 the official range for good flow i.e. <30. Therefore the blends have good flow property based on their compressibility index ranges from 11.43 to 14.76and Hausner index ranges from 1.12. to 1.18.

Evaluation of core tablets

All the evaluated parameters for core tablets are shown in the Table No.6. The individual weight of different batch tablets was within the official limits (±7.5%) of % deviation and passes the uniformity of weigh test. The hardness of core tablets in each formulation batch ranges from 1.5-1.9 kg/cm^2, therefore ensuring appropriate strength. The thickness observed was 2.6 mm and is even for all batches.

The disintegration time of core tablet with different super disintegrates was in range of 40 ± 0.69 to 140 ± 1.2 sec. The least disintegration time was provided by core tablet formulation C9. The % drug content of all the core tablet formulation ranged from 97.3 ± 2.2% to 100.2 ± 1.6% all within the acceptable limits.

Dissolution study of core tablets

Based on the results obtained from the dissolution study of core tablets in phosphate buffer (pH 6.8) shown in TableNo.7, and FigureNo.2.The core tablet formulation C9 formulated with crosspovidone provided a burst release of 29% within 1^{st} min and therefore was selected to continue with press coating of tablets.

TableNo.5. Evaluation of Precompression parameters of core powder blend

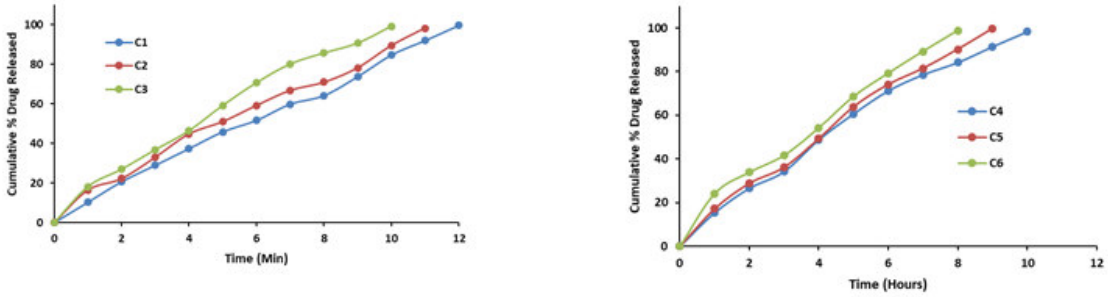
Batch. N0.	Angle-of Repose(^{0})	Bulk Density(g/ml)	Tapped bulk density(g/ml)	Carr's index (%)	Hausner's Ratio
C1	22°31'	0.518	0.622	14.33	1.13
C2	23°12'	0.533	0.634	13.28	1.12
C3	22°27'	0.540	0.628	14.76	1.14
C4	24°87'	0.521	0.626	13.24	1.16
C5	21°.66'	0.533	0.633	13.37	1.13
C6	24°.71'	0.541	0.631	12.59	1.12
C7	21°.58'	0.532	0.629	12.47	1.18
C8	23°.14'	0.538	0.630	11.43	1.17
C9	22°.33'	0.522	0.629	13.22	1.12

TableNo.6. Physical parameters of core tablets

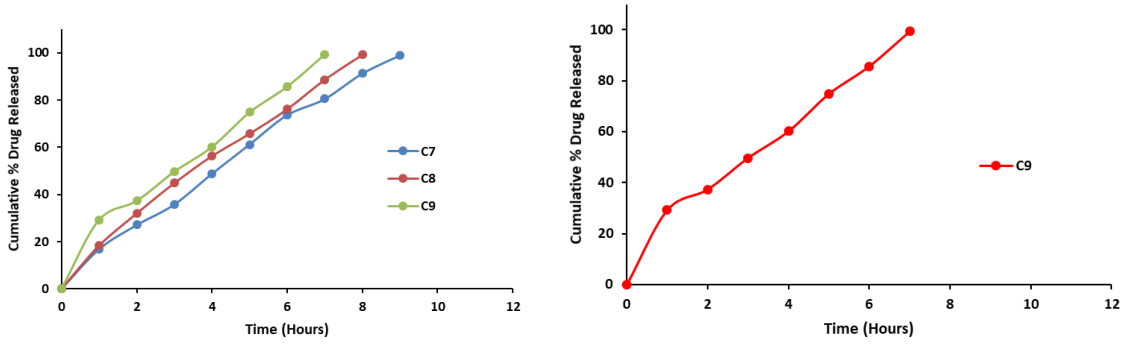
Batch. No	Weight Variation (%)	Friability (%)	Thickness (mm)	Hardness (Kg/cm^2)	Wetting Time (Sec)	Disintegration Time (seconds)
C1	61.1±1.22	0.61	2.2	2.22	101	140
C2	60.7±1.38	0.50	2.2	2.33	92	138
C3	61.2±1.34	0.59	2.2	2.26	85	98
C4	60.8±1.29	0.63	2.2	2.23	71	95
C5	60.8±1.41	0.55	2.2	2.33	66	83
C6	61.2±1.28	0.66	2.2	2.25	59	77
C7	60.6±1.26	0.51	2.2	2.31	62	85
C8	59.8±1.24	0.68	2.2	2.26	29	56
C9	60.3±1.46	0.69	2.2	2.27	25	42

TableNo.7. Cumulative % Release of Core Formulation C1-C9

Time in Minutes	C1	C2	C3	C4	C5	C6	C7	C8	C9
0	0	0	0	0	0	0	0	0	0
1	10.32	16.49	18.24	15.41	17.22	24.16	16.82	18.34	29.21
2	20.69	22.31	27.04	26.62	28.91	33.89	27.11	31.97	37.32
3	29.04	33.08	36.92	34.28	36.24	41.65	35.76	44.84	49.69
4	37.42	44.85	46.47	48.87	49.37	54.22	48.78	56.27	60.14
5	45.92	51.08	59.24	60.72	63.92	68.56	61.19	65.75	74.82
6	51.74	59.22	70.65	71.29	74.12	79.23	73.64	76.14	85.69
7	59.93	66.82	80.11	78.62	81.48	89.22	80.47	88.63	99.39
8	64.24	70.96	85.69	84.23	90.23	98.73	91.24	99.18	
9	73.82	78.21	90.67	91.45	99.69		98.93		
10	84.76	89.47	99.22	98.31					
11	92.04	98.26							
12	99.67								



FigureNo.2. Graph - Cumulative % Release of C or Formulation C1-C9



Press coating material dry blend

The flow properties of different outer coating material formulation are shown in the TableNo.8. The results for angle of repose for Press coating material blend was found to vary from23°04' to 28°94' which indicated a good flow property. Carr's index and Hausner's ratio ranges representing a good flow.

TableNo.8. Evaluation of Precompression parameters of Pulsatile coat powder blend

Batch No.	Angle of Repose(^{0})	Bulk Density(g/ml)	Tapped-bulk density(g/ml)	Carr's index (%)	Hausner's Ratio
F1	24°57'	0.45	0.56	9.2	1.10
F2	23°09'	0.46	0.57	9.3	1.11
F3	24°54'	0.44	0.55	9.2	1.10
F4	23°49'	0.46	0.57	9.8	1.11
F5	25°95'	0.45	0.59	9.9	1.11
F6	24°74'	0.45	0.56	9.8	1.12
F7	23°21'	0.44	0.53	10.5	1.13
F8	25°56'	0.45	0.56	10.4	.1.13
F9	25°77'	0.49	0.58	10.8	1.14
F10	24°65'	0.46	0.57	9.2	1.11
F11	25°79'	0.47	0.58	9.3	1.10
F12	23°04'	0.46	0.57	9.1	1.11
F13	26°62'	0.46	0.57	9.9	1.12
F14	23°75'	0.47	0.58	9.8	1.11
F15	24°94'	0.48	0.57	9.7	1.12
F16	26°52'	0.49	0.61	10.6	1.13
F17	26°73'	0.47	0.59	10.6	1.15

F18	23°31'	0.48	0.58	10.4	1.14
F19	28°82'	0.49	0.60	8.9	1.11
F20	27°53'	0.49	0.61	9.3	1.10
F21	27°26'	0.48	0.59	9.1	1.10
F22	28°94'	0.47	0.62	9.8	1.12
F23	27°49'	0.48	0.59	9.7	1.12
F24	27°51'	0.49	0.57	9.9	1.11
F25	28°63'	0.48	0.58	10.5	1.14
F26	28°94'	0.47	0.59	10.7	1.13
F27	28°04'	0.48	0.58	10.4	1.14

Evaluation of press coated tablets

All the evaluated parameters for core tablets are shown in the Table No.7. The individual weight of different batch tablets was within the official limits (±7.5%) of % deviation and passes the uniformity of weigh test. The hardness of core tablets in each formulation batch ranges from 8.0-14.8kg/cm^2, therefore ensuring appropriate strength. The thickness observed was 3.5-4.1 mm and is even for all batches.

The % drug content of all the core tablet formulation ranged from 97.8 ± 1.2% to 99.9 ± 1.5% all within the acceptable limits.

Table. No.: 9. Physical parameters of Pulsatile coat tablets

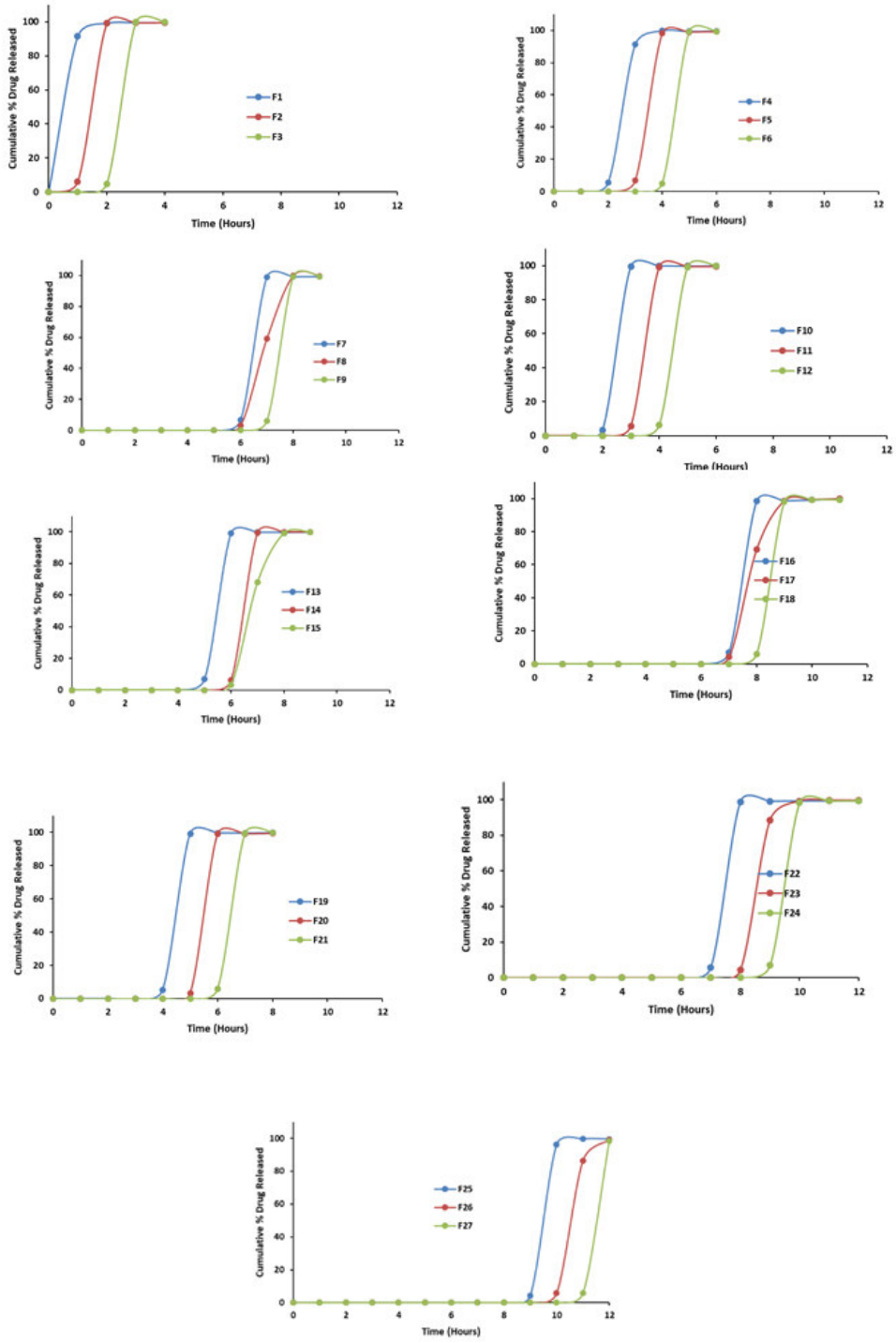
Batch. N0.	Weight Variation (%)	Friability (%)	Thickness (mm)	Hardness (Kg/cm^2)
F1	309±1.2	0.21	4.1	8.1
F2	311±1.3	0.19	4.1	8
F3	309±1	0.23	4.1	8.2
F4	312±1.4	0.18	4	8.2
F5	310±1.2	0.20	4.1	8.1
F6	311±1.3	0.21	4	8
F7	311±1.1	0.21	4.1	8.3
F8	310±1.3	0.23	4.1	8.2
F9	310±1.4	0.19	4	8.2
F10	311±1.5	0.21	3.9	10.4
F11	309±1.5	0.19	3.8	10.3
F12	311±1.4	0.19	3.8	10.4
F13	309±1.5	0.18	3.9	10.2
F14	312±1.4	0.21	3.9	10.3
F15	310±1.5	0.23	3.8	10.5
F16	311±1.4	0.21	3.9	10.4
F17	312±1.4	0.19	3.9	10.3
F18	311±1.4	0.19	3.8	10.4
F19	309±1.4	0.18	3.6	14.8
F20	309±1.4	0.19	3.5	14.6
F21	309±1.3	0.21	3.5	14.6
F22	311±1.2	0.21	3.6	14.6
F23	311±1.1	0.23	3.5	14.8
F24	312±1.2	0.22	3.5	14.7
F25	310±1.3	0.19	3.5	14.8
F26	311±1	0.18	3.5	14.7
F27	312±1.2	0.18	3.5	14.8

Dissolution study of press coated tablets

The dissolution study of press coated tablets were performed in 0.1 N HCl for 2 hours and remaining time in phosphate buffer (pH 6.8) shown in shown in Table.No.:10, and FigureNo.2., the coat tablet formulation F9, F14 & F19 were selected as the optimized formulation based on their lag time of 6 hours and maximum of drug release within 7 hours expected release. The % drug content of all the core tablet formulation ranged from 97.3 ± 3.8% to 100.2 ± 1.6% all within the acceptable limits.

Table. No.: 10. Cumulative % Release of Press coated Pulsatile Formulation F1-F27

Time (hours)	0	1	2	3	4	5	6	7	8	9	10	11	12
F1	0	91.44	99.05	99.43	99.38								
F2	0	6.25	99.12	99.38	99.49								
F3	0	0	4.91	99.73	99.81								
F4	0	0	5.49	91.32	99.86	99.53	99.72						
F5	0	0	0	6.82	98.21	99.09	99.33						
F6	0	0	0	0	5.09	99.26	99.24						
F7	0	0	0	0	0	0	6.73	98.99	99.07	99.12			
F8	0	0	0	0	0	0	3.14	59.21	99.79	99.54			
F9	0	0	0	0	0	0	0	6.18	99.32	99.27			
F10	0	0	3.38	99.57	99.85	99.79	99.88						
F11	0	0	0	5.65	99.23	99.44	99.58						
F12	0	0	0	0	6.32	99.12	99.79						
F13	0	0	0	0	0	6.92	99.03	99.71	99.58	99.75			
F14	0	0	0	0	0	0	6.21	99.34	99.82	99.88			
F15	0	0	0	0	0	0	3.27	68.23	99.15	99.66			
F16	0	0	0	0	0	0	0	7.02	98.47	98.52	99.03	99.71	
F17	0	0	0	0	0	0	0	4.21	69.35	98.67	99.34	99.89	
F18	0	0	0	0	0	0	0	0	6.04	98.21	99.32	99.24	
F19	0	0	0	0	5.32	99.25	99.58	99.46	99.62				
F20	0	0	0	0	0	3.33	99.08	99.18	99.45				
F21	0	0	0	0	0	0	5.98	99.3	99.81				
F22	0	0	0	0	0	0	0	5.62	98.82	99.04	99.15	99.21	
F23	0	0	0	0	0	0	0	0	4.28	88.38	99.12	99.52	99.49
F24	0	0	0	0	0	0	0	0	0	6.91	98.34	99.24	99.38
F25	0	0	0	0	0	0	0	0	0	4.24	96.14	99.61	99.53
F26	0	0	0	0	0	0	0	0	0	0	5.91	86.46	99.08
F27	0	0	0	0	0	0	0	0	0	0	0	5.83	98.46



FigureNo.3.Graph - Cumulative % Release of Press coated Pulsatile Formulation F1-F27

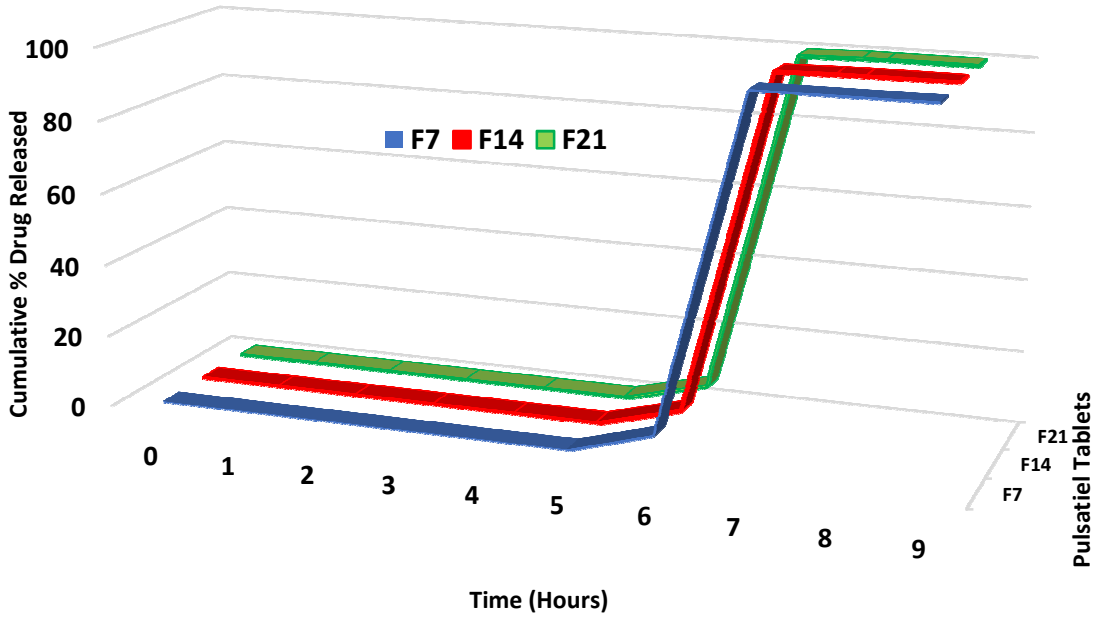


Figure No.4. *Invitro* Drug Release for Captopril Pulsatile tablets of F7, F18, and F21 Formulation

Effect of HPMC K4m, K15M and K 100M on release of the Drug

The prime objective of formulation research is to develop drug delivery systems which fulfil the therapeutic needs related to specific pathological conditions and chronobiology. In short, pulsatile release behaviour of dosage form is desirable in such cases involving circadian rhythm of body or food intake timings associated in managing such disorders. Therefore, a drug with concentration in therapeutic range should be delivered in target site with respect to time for getting the required activity.

Numerous variables are known to affect drug release from time-controlled compression coated tablet formulations. They include the viscosity grade of polymer, the amount of polymer, the drug-polymer ratio, and the nature of the drug used in the tablet system. The research summarized in this article set out to investigate the influence of the type, amount of polymer and compression force on the time-controlled swelling or rupturing of compression coated tablets.

The system described in this work delivers the drug from the core tablet after swelling or eroding of the hydrophilic or hydrophobic barrier of the coating shell to exhibit a pulsatile manner of drug release. The function of this outer shell is to protect the core layer and delay the drug release by prolonging the lag time prior to the start of drug release and control the fluid penetration into the core. Due to interaction with biological fluids, the polymer coat goes on swelling leading to increment in permeability and erosion-dissolution phenomena over a period of time which further contributes to the delay in release of drug from developed dosage form.

In this study, the effects of different viscosity grade of HPMC and compression force on lag time of captopril pulsatile drug delivery system were studied. Core tablet consisting of super disintegrantcrospovidone was used for press coating. Concentration of the polymer in outer coat is an important factor which control the lag time in pulsatile drug delivery systems. When the concentration of polymer increases the thickness of outer coat increases which ultimately increase the gel thickness upon contact with water. Gel thickness alters the lagtime/drug release from the core. In addition to concentration of polymer the compression force plays important role in drug release from drug delivery systems. When the Compression force

increases, the hardness of the tablet increases due to high compact arrangement of the polymer particles in the tablet, so the tablet requires more time and effort to get swelling in the dissolution medium. Similarly, the compression force increases, surface area of the tablet that is exposed to the dissolution medium will be decreased/reduced, so the dissolution rate will be minimized. In addition, if compression force increases, the wettability of the tablet decreases in the dissolution medium making the penetrability of the dissolution medium into the tablet core at slow pace, so it will slows down the dissolution of the tablet.

Hypromellose, also known as HPMC, is the most commonly used cellulose derivative for oral pulsatile formulations. HPMC has a number of advantages, such as low cost, safety (generally regarded as safe) and existing tablet technology can be used in the formulation process[22]. This polymer is resistant to enzymes, stable over the pH range of 3–11, non-ionic and swells to form a gel that controls drug release[22].

HPMC is available in a wide range of viscosity/ molecular weight (MW) grades which possess different functional properties and thereby employed for different applications such as tablet binder, coating agent, control release matrix, bio adhesive, rheology controller, and so on [18, 19]. Normally, low MW HPMCs are useful as tablet binder, whereas higher MW HPMCs are helpful as controlled release agents.

Developing press-coated pulsatile formulations, which HPMC grades at which compression force would be more efficient was a question and no available literature, had an answer to the same. Hence, it was of common interest to carry out a comprehensive comparative assessment of various molecular weights HPMCs K4M, K15M and K100M with different compression force in formulation of press- coated pulsatile formulations and thus the present study was a desideratum to solve selection perplexity.

Lag period plays an important role in determining drug release from the pulsatile drug delivery system at specific period. The effect of compression force and concentration of HPMC on lag time are shown in figureNo.3. It was observed that Increase in HPMC polymer concentration and compression force increases the lag time. It may be due to an increase in polymer concentration causes an increase in the viscosity of the gel as well as the formation of a gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion solvent into the core of the drug and therefore a reduction in the drug release rate.

When a system containing HPMC is in contact with aqueous media, water uptake occurs quickly. The water enters in the polymer spaces and the polymer chains unwind and extend but do not become straight. Consequently, hydrogen bonds holding the polymer break allowing hydrogen bonding formation with water molecules. The more water taken by the dosage form initially, the thicker the gel formed, which controls water uptake by the tablet. Drug is then released by diffusion through the gel or erosion of the gel.

It was observed that HPMC concentration and compression force was a significant factor in increasing drug release rate/lag time in pulsatile drug delivery system. Best formation was selected from each type polymer.

It was aimed to have a lag time of six hours i.e., the system is taken at the bed time and expected to release the drug after a period of 6 h i.e., at 4.00 am when the blood pressure related health risks are more prevalent. In our study it was observed the HPMC K4M coated tablets consisting of 225mg HPMC K4M with 3 ton compression force (Formulation F21) showed better lag time. Similarly, HPMC K15M coated tables consisting of 150mg of HPMC K15M with 2 ton compression force (Formulation F14) showed better lag time.

In case of HPMC K100M coated tablets, the tablets consisting of 75mg HPMC K100M with 1 ton compression force (Formulation F7) formulation showed better lag time.

It was observed that when increasing the polymer concentration and compression force, the lag time increases significantly ($P < 0.05$). Concentration of HPMC was a significant factor in increasing drug release rate. When a dosage form is placed in the dissolution media, wetting of the surface occurs first, followed by hydration of the inner part of the matrix by the passage of the liquid through the microscopic pores, causing the formation of more pores due to the dissolving of the excipients present in the microscopic pores. At higher polymer content, these microscopic pores block up quickly, preventing further water uptake, leading to reduced drug release rate, due to the formation of a thick and turbid gel, which is resistant to erosion and diffusion. Lower

HPMC concentration in the formulation can result in a slower formation of a weaker gel. Erosion of the tablets was dependent on the HPMC levels. At low HPMC concentrations, tablets eroded and dissolved in the test media quickly, whereas the gel formed by larger tablets remained intact for longer periods of time, more than 6 h. Thus, larger tablets are more likely to form stronger gels that are resistant to erosion and diffusion and the drug takes longer to be released, due to the longer diffusion pathway.

Several authors [23-28], have stated that compression force had very little effect on drug release from HPMC tablets. It also depends upon type of fillers used with HPMC[29]. In our study it was found that the applied compression force influenced drug release rate ($P < 0.05$). The time taken for burst drug release from formulations manufactured at different compression forces indicates that drug release become slower with increasing applied force. Depending on the compressibility behaviour of the fillers, the porosity of the matrices may be reduced with increasing compression force, leading to slower water uptake and waterfront movement into the matrix, which in turn, may lead to slower drug release.

Stability Studies

There were no significant changes for the core and press coated formulations in drug content, physical stability, hardness, and drug release for the selected formulation C9, F7, F14 and F21, after 90 days at $25^{o}C\pm 2^{0}C$ / 60% ± 5% RH, $30^{0}C \pm 2^{0}C$ / 65% ±5% RH and $40^{0}C \pm 2^{0}$ / 75% ± 5% RH were show in table.No.:11.

Table No. 11. Stability studies of optimized formulation C9, F7, F14, and F21

Core tablet Formulation C9			
Time(days)	**Hardness(kg/cm^2)**	**Drug content (%)**	**% Drug release**
0	**2.27**	**99.21**	**99.39**
30	**2.27**	**99.19**	**99.31**
60	**2.27**	**99.15**	**99.35**
90	**2.27**	**99.19**	**99.28**
Press coated formulation F7			
0	**8.2**	**99.11**	**99.27**
30	**8.2**	**99.09**	**99.25**
60	**8.2**	**99.03**	**99.29**
90	**8.2**	**99.02**	**99.21**
Press coated formulation F14			
0	**10.3**	**99.51**	**99.88**
30	**10.3**	**99.39**	**99.59**
60	**10.3**	**99.05**	**99.89**
90	**10.3**	**99.02**	**99.75**
Press coated formulation F21			
0	**14.8**	**99.63**	**99.62**
30	**14.8**	**99.50**	**9.59**
60	**14.8**	**99.52**	**99.65**
90	**14.8**	**99.34**	**99.61**

CONCLUSION

The aim of the study was to design pulsatile release capsule of Captopril. The rapid release of the drug after a lag time consistent with requirement for chronotherapeutics was achieved with developed formulation. The chronotherapeutics formulations of captopril were developed as press coated tablets using different viscosity grades of semisynthetic Polymers (HPMC polymers) different concentrations at different compression force. The research undertaken explicates the crucial effects of different viscosity grades/molecular weight of HPMC,

concentration of HPMC and influence of compression force on lag time of captopril chrono modulated drug delivery system. It was observed that increasing concentrations different viscosity grades/molecular weight of HPMC, concentration of HPMC and compression in the formulations caused a decrease in drug release rates. Increasing the molecular weight of HPMC, concentration of HPMC and compression force significantly increased the lag time. Because of the erosion-based release mechanism and the stronger gel and slower erosion with the higher molecular weight HPMC grades and compression forces. By varying the concentration of HPMC, molecular weight of HPMC used in the outer barrier layer with suitable compression force the lag time of drug release from the HPMC based formulation could be readily modulated.

REFERENCES

[1]. U. Conte, L. Maggi, ML. Torre, P. Giunchedi and A. La Manna, Press-coated tablets for time- programmed release of drugs, Biomaterials, 14 13, 1993, 1017-1023.

[2]. RiddhishPatadia, Chintan Vora, Karan Mittal, and RajashreeMashru, Investigating effects of hydroxypropyl methylcellulose (HPMC) molecular weight grades on lag time of press-coated ethyl cellulose tablets, Pharmaceutical Development and Technology, 21:7, 2015, 794-802. DOI: 10.3109/10837450.2015.1055767.

[3]. Robson da Silva Lopes, Nathalia Maria Resende, Adenilda Cristina Honorio-França and Eduardo LuzíaFrança, Application of Bioinformatics in Chronobiology Research, Article ID 153839, 2013, 1-8. http://dx.doi.org/10.1155/2013/153839.

[4]. J. Aschoff, Circadian rhythms in man, Science, 148(3676), 1965, 1427–1432.

[5]. B. Lemmer, Discoveries of rhythms in human biological functions: a historical review, Chronobiology International, 26(6), 2009 , 1019–1068.

[6]. RohitBisht, Chronomodulated drug delivery system: A comprehensive review on the recent advances in a new sub-discipline of chronopharmaceutics, Asian J Pharm 2011, 5:1-8.

[7]. C. E. D. S. Ferreira and A.Andriolo, "Reference ranges in clinical laboratory," JornalBrasileiro de Patologia e Medicina Laboratorial, 44(1), 2008, 11–16.

[8]. Sajan, TA Cinu, AJ Chacko, J Litty and T Jaseeda, Chronotherapeutics and Chronotherapeutic Drug Delivery Systems, Tropical Journal of Pharmaceutical Research, 8 (5), 2009, 467-475.

[9]. Natesh R, Schwager SL, Evans HR, Sturrock ED, Acharya KR: Structural details on the binding of antihypertensive drugs captopril and enalaprilat to human testicular angiotensin I-converting enzyme. Biochemistry, 43(27), 2004, 8718-24.

[10]. Song JC, White CM: Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: an update. Clin Pharmacokinetic. 41(3), 2002, 207-24.

[11]. Hasan MD &Someshwar, Komuravelly&Patha, Chaitanya &Mohd, AbdulBari&Pratyusha, Ande&Rao, Vattikuti. Formulation and evaluation of press coated tablets of salbutamol sulphate for time controlled release. Asian Journal of Pharmaceutics. 8, 2014, 161-170. DOI: 10.4103/0973-8398.139179.

[12]. AshishBabulalRane, SurendraGaneshlalGattani, Vinayak DinkarKadam, AvinashRamraoTekade, Formulation and Evaluation of Press Coated Tablets for Pulsatile Drug Delivery Using Hydrophilic and Hydrophobic Polymers, Chemical and Pharmaceutical Bulletin, 57(11), 2009, 1213-1217.

[13]. doi: 10.1248/cpb.57.1213.

[14]. Ashok Ch, Bhaskar NV and Prakash PR: Design and Characterization of Press Coated Tablets of Aceclofenac for Pulsatile Delivery. Int J Pharm Sci Res, 6(7), 2015, 2902-12.

a. doi: http://dx.doi.org/10.13040/IJPSR.0975-8232

[15]. Patil AS, Dandagi PM, Masthiholimath VS, Gadad AP, Najwade BK. Development and characterization of chronomodulated drug delivery system of captopril. Int J Pharm Investig. 1(4), 2011, 227-233. doi:10.4103/2230-973X.93010.

[16]. Gangane, P S., N M. Mahajan, K. R. Danao, and G. N. Pawde. "Formulation and Evaluation of Chronomodulated Pulsatile Therapeutic System for Early Morning Surge in Blood Pressure". International Journal of Pharmacy and Pharmaceutical Sciences, 7 (6), 2015, 337-41.

[17]. Haribansh Narayan Singh, ShivangiSaxena, Sunil Singh, Ajit Kumar Yadav, Pulsatile Drug Delivery System: Drugs used in the Pulsatile Formulations, Research J. Pharma. Dosage Forms and Tech. 5(3), 2013, 115-121. DOI: 10.13040/IJPSR.0975-8232. 6(9).

[18]. HemaJaiswal, VaseemAhamad Ansari, J. N. Pandit, FaroghAhsan. Pulsatile Drug Delivery System: An Overview with Special Emphasis on Losartan and Captopril. Research J. Pharm. and Tech. 12(7), 2019, 3175-3188. doi: 10.5958/0974-360X.2019.00535.3.

[19]. Jagdale SC, Suryawanshi VM, Pandya SV, Kuchekar BS, Chabukswar AR. Development of press-coated, floating-pulsatile drug delivery of lisinopril. Sci Pharm, 82(2), 2014, 423-440. doi:10.3797/scipharm.1301-27.

[20]. Abbas, Ali &Maraie, Nidhal, Optimization and Evaluation of Time Programmed Press Coated Tablets for Atenolol. World J Pharm Sci, 1(4), 2013, 130-137.

[21]. Patel SR, Patel AK, Modasiya MK, Patel VM, Floating pulsatile drug delivery system for chronotherapy, Journal of Pharmacy Research, 5(4), 2012, 2264-2271.

[22]. Li CL, Martini LG, Ford JL, Roberts M, The use of hypromellose in oral drug delivery. J Pharm Pharmacol, 57, 2005, 533–546.

[23]. Wan LSC, Heng PWS, Wong LF, The effect of hydroxypropyl ethyl cellulose on water penetration into a matrix system. Int J Pharm, 73, 1991, 111–116.

[24]. Ford JL, Rubinstein MH, Hogan JE. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl methylcellulosematrices. Int J Pharm 24, 2005, 327–338.

[25]. Ford JL, Rubinstein MH, Hogan JE, Propranolol, hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose.Int J Pharm, 24, 1985, 339–350.

[26]. Ford JL, Rubinstein MH, Hogan JE, Dissolution of a poorly water soluble drug, indomethacin, from hydroxypropyl methyl cellulose controlled release tablets. J Pharm Pharmacol, 1985; 37:33.

[27]. Dahl TC, Calderwood T, Bormeth A, Trimble K, PiepmeirE, Influence of physico-chemical properties of hydroxypropylmethylcellulose on naproxen release from sustained release matrix tablets. J Controlled Release, 14, 1990, 1–10.

[28]. Liu C, Kao Y, Chen S, Sokoloski TD, Sheu MT, In-vitro and in-vivo studies of the diclofenac sodium controlled-release matrix tablets. J Pharm Pharmacol, 47, 1995, 360–364.

[29]. Velasco MV, Ford JL, Rowe P, Rajabi- Siahboomi AR, and Influence of drug: hydroxypropyl methylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. J Controlled Release, 57, 1999, 57, 75–85.

[30]. Marina Levina, Ali R. Rajabi-Siahboomi. The influence of excipients on drug release from hydroxypropyl methylcellulose matrices. Journal of Pharmaceutical Sciences, 93(11), 2004, 2746-2754. DOI: 10.1002/jps.20181.