CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.579660

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

DESIGN AND CHARACTERIZATION OF PULSATILE DRUG DELIVERY OF METAPROLOL TARTRATE

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Received: 10 April 2017 **Accepted:** 07May 2017

Abstract:
In the present study, an attempt was made to develop the pulsatile drug delivery of Metaprolol tartrate to the colon. Formaldehyde treated Capsule bodies were used for the preparation of pulsincaps. It was sealed with unhardened cap of the capsule. The microspheres were prepared by emulsion solvent evaporation technique. Optimized microsphere formulations were selected based on dissolution studies. Hydrogel plug (HPMCK100 and lactose in 1:1 ratio) having 4.5kg/cm^{2}hardness and 100 mg weight was placed in the capsule opening and found that it was satisfactory to retard the drug release in small intestinal fluid and to eject out the plug in colonic fluid and releasing the microspheres into colonic fluid after a lag time criterion of 5 hours. The sealed capsules were completely coated by dip coating method with 5% cellulose acetate phthalate to prevent variable gastric emptying. Dissolution studies of pulsatile capsule device in media with different pH (1.2, 7.4 and6.8) showed that drug release in colon could be modulated by optimizing the concentration of polymers in the microspheres. Drug–polymer interaction studies indicated no interaction in between the drug and the polymer. Among all the formulations Metaprolol tartrate microspheres prepared with cellulose acetate in 1:2 ratio shown prolonged release for a period of 12 hours. The obtained results showed the capability of the system in delaying drug release for a programmable period of time and to deliver the drug in the early morning hours when the hypertension is more prevalent.

Keywords: *Metaprolol tartrate; Hypertension; Pulsatile; Microspheres; Hydrogel Plug; Solvent evaporation.*

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Please cite this article in press as M.V.Sai Krishna et al, ***Design and Characterization of Pulsatile Drug Delivery of Metaprolol Tartrate****, Indo Am. J. P. Sci, 2017; 4(05).*

INTRODUCTION:

Pulsatile Drug Delivery System is useful in the diseases in which the drug release is timed to match rhythms of the disease so as to optimize the therapeutic effect and minimize the side effects [1]. ·Cardiovascular events occur more frequently in the morning, and ambulatory blood pressure (BP) exhibits a diurnal variation with increase in the morning(morning BP surge). The morning BP surge was reported to be associated with high risk of cardiac death, and ischemic and hemorrhagic stroke [2]. Metaprolol tartrate is a cardio selective β_1 blocker. It is used in the management of hypertension, angina pectoris, cardiac arrhythmias and myocardial infarction[3]. Metaprolol taratrate is rapidly absorbed following an oral dose undergone extensive first pass metabolism, resulting in oral bioavailability of 50% only. The half life of Metoprolol is approximately 3-4 hrs .Usually antihypertensive dose of Metaprolol tartrate range from 25 to 100 mg/day in single doses [4]. Due to its short biological half-life and low bioavailability, it requires frequent administration. Thus chronopharmaceutical drug delivery system will synchronize the drug delivery with the circadian variation in periods of increased risk which is highly desirable for hypertensive patients. The main objective of present work is to formulate and evaluate the chronopharmaceutical drug delivery system containing metaprolol tartrate for the treatment of hypertension which is used to deliver the drug at specific time as per pathophysiological needs of the disease and improvement of therapeutic efficacy and patient compliance.

The pulsatile drug delivery of metaprolol tartrate can be taken before bed time (10 pm) and capable of releasing drug at 3.00 am by proportioning drug concentration in the early morning hours when free cholesterol levels are more prevalent [5]. The intentionally delaying the drug absorption for a specified time period of 5 hours(lag time) was controlled by hydrogel plug which will be taken at bed time with a programmed start of drug release early in morning hours.

MATERIALS AND METHODS:

Metaprolol tartrate was a gratis sample obtained from Apogen Remedies pvt. ltd. (Hyderabad,India).Cellulose acetate(100-140 cps), Ethyl cellulose (48-49.5%) were obtained from Himedia; Mumbai. HPMC K100, carbapol, Na CMC and Methyl Cellulose were purchased from SD fine chemicals, Mumbai. All reagents used were of analytical-reagent grade.

Preparation of Cross-Linked Gelatin Capsules:

The '0' sized hard gelatin capsules (approximately 100 in number) were taken. The bodies of the capsules were then placed on a wire mesh, which was kept in a desicator. An aliquot of 25ml of 15% v/v formaldehyde was taken into a bottom of desiccators and a pinch of potassium permanganate was added to it to generate formalin vapors. The reaction was carried out for 12 hours. After which the bodies were removed and dried at 50^0C for 30 minutes to ensure completion of reaction between gelatin and formaldehyde vapor. The bodies were dried at room temperature to facilitate removal of residual formaldehyde [6]. These capsule bodies were capped with untreated caps and stored in a air tight container.

Preparation of Hydrogel Plug:

Plug for sealing the capsule body was prepared by compressing equal amount of equal amount of HPMC K100: lactose, carbapol: lactose, Na CMC: Lactose and Methyl Cellulose: lactose using 7 mm punches and dies on rotary tablet press keeping varying thickness and hardness values of tablet plug [7].

Preparation of microspheres:

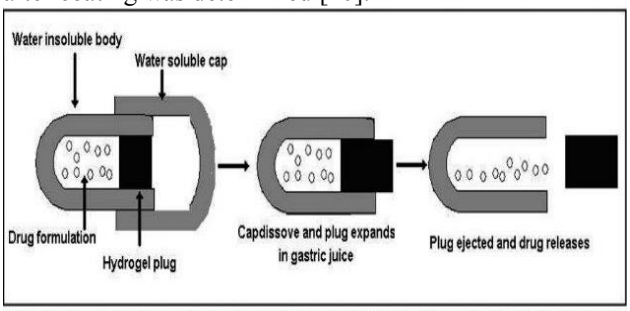
All the microspheres formulations were prepared by emulsion solvent evaporation technique[8] and the composition was shown in table 1.The effect of various formulation and processing factors on microspheres characteristics were investigated by changing polymer: drug ratio. Weighed amount of Metaprolol tartrate and polymer in 1:1 ratio were dissolved in 10ml of chloroform. The homogeneous drug and polymer organic solution was then slowly added in a thin stream to 100ml of liquid paraffin containing 1% surfactant (span 80) with constant stirring for 1h. The resulting microspheres were separated by filtration and washed with petroleum ether. The microspheres finally air dried over a period of 12 hrs and stored in a desiccators. In case of 1:1.5and 1:2 core: coat ratios, the corresponding polymer get varied respectively.

Table.1: Preparation of Metaprolol tartrate microspheres

Polymer employed			
Cellulose acetate		Eudragit RS-PO	
Formulation Code	Core: Coat	Formulation Code	Core: Coat
F-1	1:1	F-4	1:1
F-2	1:1.5	F-5	1:1.5
F-3	1:2	F-6	1:2

Designing of Pulsincap:

The Pulsincap was designed by filling the microspheres equivalent to 50mg of Metaprolol tartrate into the formaldehyde treated bodies by hand filling. The capsules containing the microspheres were then plugged with optimized hydrogel plug. The joint of the capsule body and cap was sealed with a small amount of the 5% ethyl cellulose ethanolic solution [9]. The sealed capsules were completely coated by dip coating method with 5% cellulose acetate pthalate in 5:5 (v/v) mixture of acetone: ethanol plasticized with n-dibutylphthalate (0.75%), to prevent variable gastric emptying. Coating was repeated until an 8–12% increase in weight is obtained. % weight gain of the capsules before and after coating was determined [10].



Physicochemical Characterization of Hydrogel Plug

Hydrogel Plugs were studied for hardness, friability, weight variation and lag time [10].

Drug content uniformity:

Then encapsulated microspheres equivalent to 50mg of Metaprolol tartrate were taken into mortar and grounded with the help of pestle. The grounded power mixture was dissolved in 6.8 pH buffer, filtered and estimated spectrophotometrically at 275nm [11].

***In vitro* release profile of pulsatile capsule:**

Dissolution studies were carried out by using USP XXIII dissolution test apparatus (paddle method). Capsule was tied to paddle with a cotton thread so that the capsule should be immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 hrs (since the average gastric emptying time is 2 hrs), then removed and the fresh pH 7.4phosphate buffer saline (PBS) was added. After 3 hrs (average small intestinal transit time is 3 hrs), the medium was removed and colonic fluid pH 6.8 buffer was added for subsequent hours. Nine hundred milliliters of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at37±0.5°C. Five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 275 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times [12].

IR spectral studies:

The IR Spectra for the formulation, pure drugs and excipients were recorded on JASCO FT-Infra Red Spectrophotometer using KBr pellet technique [13] at the resolution rate of 4 cm^{-1}. Spectrum was integrated in transmittance mode at the wave number range 380 to 4368 cm^{-1}.

RESULTS AND DISCUSSION:

Pulsincap dosage form was a capsule which consists of a water insoluble body and a water soluble cap. The microspheres were sealed within the capsule body by means of a hydrogel plug. When the pulsing

cap was swallowed, the water soluble cap dissolves in the gastric juice and the exposed hydrogel plug begins to swell. At predetermined time after ingestion, the swollen plug was ejected out and the encapsulated drug formulation was then released into the colon, where it is dissolved and then absorbed into blood stream. In the present study, capsule bodies which were hardened with formaldehyde treatment for 12 hrs were used for the preparation of pulsincaps. It was sealed with unhardened cap of the capsule. The microspheres were prepared by emulsion solvent evaporation technique .The method employed gave discrete, spherical, non-sticky and free flowing microspheres. As aggregates these microspheres were also non-sticky and free flowing. The formation of a stable emulsion in the early stages is important if discrete microspheres are to be isolated. An optimal concentration of emulsifier is required to produce the finest stable dispersion. Below optimal concentration the dispersed globules/droplets tend to fuse and produce larger globules because of insufficient lowering in interfacial tension, while above the optimal concentration no significant decrease in particle size is observed, because a high amount of emulsifying agent increases the viscosity of the dispersion medium. The optimal concentration of surfactant was found to be 1.0%. Microscopic examination of the formulations revealed that the microspheres were spherical and appeared as aggregates or discrete particles.

All the formulations offered good flow properties. The particle size of the microspheres ranged between 613.23and 662.53µm. The use of the surfactant permits the remarkable reduction in the size of the microspheres as the result of decrease in the interfacial tension. All formulations had a narrow particle size distribution. The mean particle size of microspheres was influenced by the type of polymer proportion in the formulation. The mean size increased with increasing polymer concentration. It would appear that increasing polymer concentration produced a significant increase in viscosity of the internal phase, thus leading to an increase of emulsion droplet size and finally a higher microspheres size. Microspheres were developed with 1:1, 1:1.5, 1:2 ratios of core: coat to determine the affect of coating material concentration on the release rate of Metaprolol tartrate. These microspheres were characterized for Drug Content and% Encapsulation Efficiency. The results are given in Table 2.The technique also showed good entrapment efficiency.Hydrogel Plugs were evaluated for hardness, friability, weight variation and lag time and the results were shown in Table 3. The formulations fitted with the various hydrogel plugs HP1,HP2, HP3, HP4 shown 0.4% , 7.14% , 15.63 % and 18.21 % of drug release respectively at the end of 5th hour . It was observed that 100 mg hydrogel plug (HPMC K100: lactose in 1:1 ratio) having 4.5kg/cm^2 hardness was satisfactory to retard the drug release in small intestinal fluid and to eject out the plug in colonic fluid and releasing the microspheres into colonic fluid. This suggested that the lag time could also be adjusted and influenced by the plug composition**.**

During dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2 hrs in pH 1.2, but dissolved in intestinal pH, leaving the soluble cap of capsule, which also dissolved in pH 7.4, then the exposed polymer plug absorbed the surrounding swelled and released the drug through the swollen microspheres. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body; releasing the microspheres into simulated colonic fluid (pH 6.8 phosphate buffer). From the *In-vitro* release studies of device, it was observed that with all formulation, there was absolutely no drug release in simulated gastric fluid (acidic pH 1.2) for 2 hours and in simulated intestinal fluid (pH 7.4 phosphate buffer). Burst effect was found in colonic medium (pH 6.8 phosphate buffer).

In-vitro release profiles in colonic medium were found to have very good sustaining efficacy. Pulsin caps loaded with Metaprolol tartrate microspheres prepared with Cellulose acetate

in 1:1,1:1.5 and 1:2 ratios shown sustained drug release for a period of 10 hours (5th hour to 15th hour), 11 hours (5th hour to 16th hour) and 12 hours(5th hour to 17 hour) respectively. respectively and are shown in figure 1.Pulsin caps loaded with Metaprolol tartrate microspheres prepared with ethyl cellulose in 1:1,1:1.5 and 1:2 ratios shown sustained drug release for a period of 9.5 hours (5th hour to 14.5th hour), 10.5 hours (5th hour to 15.5th hour) and 11.5 hours(5th hour to 16.5 hour) respectively and are shown in figure 2.

The correlation coefficient values for dissolution kinetics data was shown in the Table 4. These values clearly indicated that the drug release followed zero order kinetics and the mechanism of drug release was governed by peppas - korsmeyer model. The exponential coefficient (n) values were found to be in between 0.7551 to 0.9730indicating non fickian diffusion mechanism.

The FTIR spectrum of Metaprolol tartrate pure drug (Figure 3) showed characteristic peaks at wave numbers were 3136.49 cm-^{1}, 1555.27 cm-^{1}, 1048.62 cm-^{1}, 1238.64cm-^{1} and 1111.63cm-^{1}

denoting stretching vibration of N-Cstretching, C=C Ring symmetric stretching, carbonyl stretching C-O-

C asymmetric bending and C-O-C symmetric bending respectively. The FTIR spectrum(Figure 4) of optimized formulation (F4) showed The same peaks were also reported in all drug loaded microspheres. There were no change or shifting of the characteristic peaks in drug and excipient mixtures suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in all formulations. From the figures it was observed that similar peaks were also reported in optimized formulation. There was no change or shifting of characteristic peaks in drug loaded microspheres suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in optimized formulation.

Table 2: Evaluationl data of Metaprolol tartrate microspheres

Formulation	Angle of Repose	Bulk Density (g/cm^3)	Carr's Index	Hausner's Ratio	Average Particle Size (µm)	% Drug Content	% Encapsulation Efficiency
F-1	26.94±0.021	0.276±0.014	0.314±0.013	12.10±0.024	612.23	48.91	97.85
F-2	25.6±0.031	0.350±0.012	0.408±0.011	14.21±0.022	622.46	39.86	99.67
F-3	25.42±0.052	0.320±0.020	0.370±0.009	11.89±0.009	653.53	32.89	98.76
F-4	26.85±0.024	0.319±0.005	0.362±0.021	11.87±0.017	579.12	49.13	98.28
F-5	27.01±0.035	0.351±0.009	0.393±0.019	10.68±0.014	602.17	39.67	99.17
F-6	25.76±0.05	0.255±0.025	0.291±0.005	12.37±0.024	633.16	32.58	97.88

Table 3: Evaluation characteristics of hydrogel plugs prepared with various natural polymers

Hydrogel Plug Code	Composition (1:1)	Weight (mg)	Thickness (mm)	Hardness (kg/cm2)	Lag time (hours)
HP1	HPMC K 100 : Lactose	100±1.4	3.16	4.7	5
HP2	Carbopol : Lactose	100±1.1	3.29	4.2	4.5
HP3	Na CMC : Lactose	100±1.5	3.24	3.8	4
HP4	Methyl Cellulose : Lactose	100±1.2	3.54	3.5	3

Table 4: *In-vitro* dissolution kinetics parameters of Metaprolol tartrate microspheres

Formulation	Correlation coefficient				Release kinetics			Diffusion Exponent value(n)
	Zero order	First order	Higuchi	Peppas	K_o (mg/hr)	T_{50} (hr)	T_{90} (hr)	
F1	**0.9916**	**0.8293**	**0.9524**	**0.9963**	**5.11**	**4.9**	**8.8**	**0.7551**
F2	**0.9951**	**0.8058**	**0.9440**	**0.9964**	**4.56**	**5.5**	**9.9**	**0.7976**
F3	**0.9996**	**0.7313**	**0.9269**	**0.9998**	**4.23**	**5.9**	**10.6**	**0.9730**
F4	**0.9917**	**0.8358**	**0.9256**	**0.9966**	**5.43**	**4.6**	**8.4**	**0.7592**
F5	**0.9950**	**0.7892**	**0.9454**	**0.9968**	**4.81**	**5.2**	**9.3**	**0.8018**
F6	**0.9996**	**0.7801**	**0.9264**	**0.9998**	**4.38**	**5.7**	**10.3**	**0.9697**

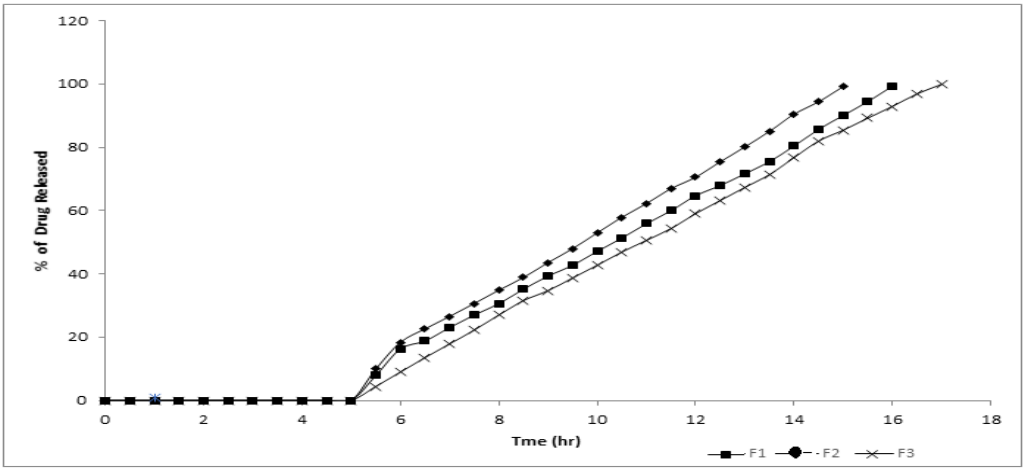


Fig 1: Comparative *In-vitro* drug release profiles plot of Metaprolol tartrate microspheres prepared with cellulose acetate in different ratios

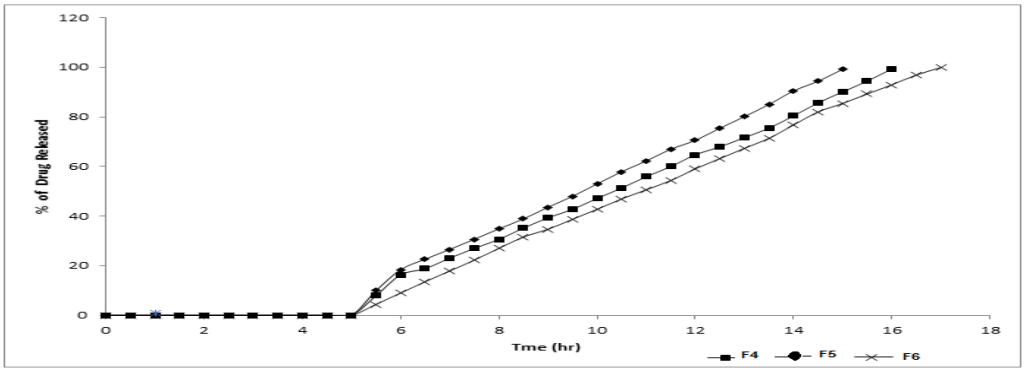


Fig 2: Comparative *In-vitro* drug release profiles plot of Metaprolol tartrate microspheres prepared with Eudragit RS-PO in different ratios

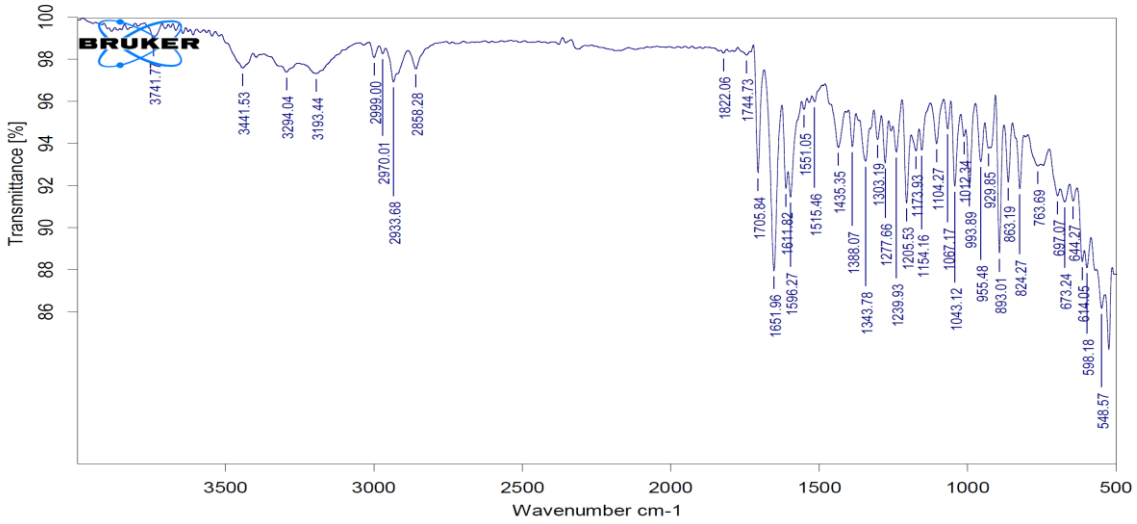


Fig 3: FTIR spectrum of pure Metaprolol tartrate

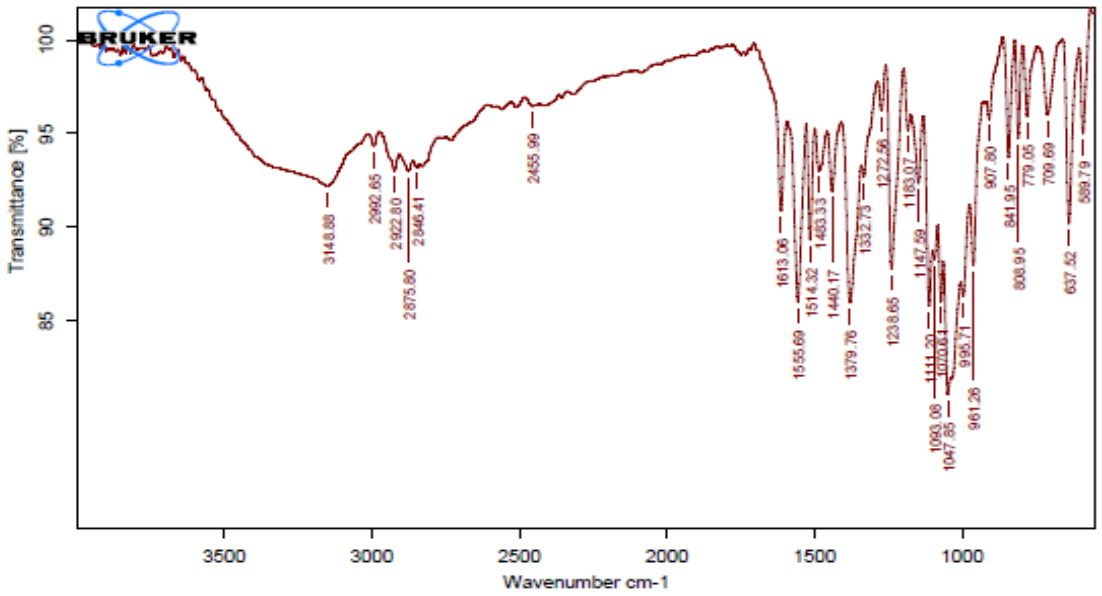


Fig 4: FTIR spectrum of optimized formulation

CONCLUSION:

Among all the formulations Pulsin caps loaded with Metaprolol tartrate microspheres prepared with Cellulose acetate in 1:2 ratio shown prolonged release for a period of 12 hours. The obtained results showed the capability of the system in delaying drug release for a programmable period of time and the possibility of exploiting such delay to attain colon targeting. In accordance with the chronomodulated therapy of hypertension, the lag time criterion of 5 hours and sustained release for a period of 12 hours was satisfied. The dosage form can be taken at bed time and will release the contents in the early morning hours when hypertension is more prevalent.

ACKNOWLEDGEMENTS:

The authors are thankful to Apogen Remedies pvt.ltd (Hyderabad, India) for providing gift samples of Metaprolol tartrate for research work. The authors are also highly thankful to Bapatla Education Society, Bapatla for providing all the facilities to carry out the work.

REFERENCES:

1.Asija Rajesh, Patel Jaimin, Asija Sangeeta, A novel approach: pulsatile drug delivery system, Int Res J of Pharmacy, 2012 ; 3(9): 43-49.

2.Shamima Nasrin Shahi, Ashima Aziz and Mohiuddin Ahmed Bhuiyan. Design, Formulation And In Vitro Evaluation Of Sustained Release Pulsatile Capsule Of Metoprolol Tartrate, International Journal of Pharmaceutical Sciences and Research (2015) ; Vol. 6, Issue 7.

3.D. Pavani, E. Hari Krishna1, Ramesh S.[2]. Development and Evaluation of Metoprolol Tartrate Chronotherapeutic Drug Delivery System, Journal of Innovations in Pharmaceuticals and Biological Sciences, 2015; 2 (1): 53-63.

4.Rose marie,R and Dadiv,R. Drugs used for the treatment of myocardial ischemia.In, Joel, G H(ed), Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th edition. New York, McGraw-Hill medical Publishing Division, 2005; 1786-1787.

5.Halsas M, Ervasti P, Veski P, Jürjenson H, Marvola M. Biopharmaceutical evaluation of time controlled press-coated tablets containing polymers to adjust drug release. Eur J Drug Metabol Pharmacokinet., 1998; 23:190-196 .

6. Kro gel, Bodmeier R. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug, Pharm. Res., 1998; 15 (3): 474-481.

7.Sandeep M, Sai Kishore V, Sudheer B, Ershad S, Adithya K, Phanil kumar DS, Design and development of chronopharmaceutical drug delivery of lansoprazole Asian Journal of Pharmaceutical Research and Development , 2013;1(5) : 1-9.

8.S.Lakshmi Sravani, V. Saikishore , M.V.Saikrishna, Design And Characterization Of Pulsatile Drug Delivery Of Losartan Potassium, Indo American Journal Of Pharmaceutical Sciences, 2017; 4 (03): 706-712.

9.Dasharath M Patel, Rushiraj H Jani,Chhagan N Patel. Design and evaluation of colon targeted modified pulsincap delivery of 5-fluorouracil according to circadian rhythm, Int J Pharm Investig , 2011; 1(3):172–181.

10.Geest S, Koker J, Demeester J, De Smedt S, Hennink WE. Pulsed in vitro release and in vivo behavior of exploding microcapsules. J. Control. Release., 2009; 135: 268-73.
11.Kumar S, Nagpal K, Singh SK, MishraDN**.** **I**mproved bioavailability through floating microspheres of lovastatin. Daru., 2011;19(1):57–64.
12.Kaur Dupinder , Saini Seema. Development and characterization of lovastatin loaded microspheres**.** Int. Res J Pharm. App Sci., 2013:3(5): 197-205.
13.Yamada.T, Onishi H, Machida Y, Sustained release ketoprofen microparticles withethylcellulose and carboxymethylethylcellulose Journal of Controlled Release., 2001;75:271–282.
14.Sarfaraz Md , Venubabu. P, Hiremath Doddayya,**.**Prakash S.G. Mucoadhesive Dosage Form Of Glibenclamide: Design And Characterisation**.**Int J Pharm and Biological Sci , 2012;2(2):162-172.
15.Saraf S, Dashora K, Effect of processing variables on microparticulate system of aceclofenac. Pak. J. Pharm. Sci., 2006;19 (1): 1-6.