INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN:2320-2831

IJPAR |Vol.5 | Issue 4 | Oct - Dec -2016

Journal Home page: www.ijpar.com

Research article *Open Access*

Formulation and evaluation of chronomodulated drug delivery system by using metaprolol succinate

[1]K.Narendra Naidu*, Dr.V.Kiran Kumar[2], S.Revathi[1], A.Gopi Reddy[1]

[1]Sana College of Pharmacy, JNTUH, Kodad, Nalgonda,Telangana,India.

[2]Unity College of Pharmacy, Bhongiri, Nalgonda, Telangana,India.

***Corresponding Author: K.Narendra Naidu**

Email: narendranaidukundavarapu@gmail.com

ABSTRACT

There is an impact of circadian rhythms in the symptoms of certain diseases like cardiac diseases, arthritis, depression, ulcer, allergic rhinitis, sleep disorders etc. The human body follows the solar/ lunar adaptations known as biological clock. The biological clock follows the main rhythm known as circadian rhythm. If the circadian rhythms dysfunctions it can greatly affect the function of the brain and behavior cognition. This can be improved by the chronotherapeutics approach. The objective of the present study was to develop chronomodulated tablets of metoprolol succinate, β1- selective adrenergic receptor blocking agent. The recent interest is occur in the field of chronotherapeutics is to match the circadian rhythms of the disease for the successful treatment of disease.The impact of chronotherapeutics in the optimal treatment of diseased patients is evaluated because in this method the treatment is done at right time with right medication at right targeted site and in the right concentration. The optimized formulation is F_9 and the percentage drug release of the optimized formulation is 98.77%.The tablets were prepared by the wet granulation method.

Keywords: Chronotherapeutics, Circadian rhythms, Chronotherapeutics drug delivery, Metaprolol succinate.

INTRODUCTION

Chronotherapy refers to the use of circadian or other rhythmic cycles in the application of therapy [1-17]. Examples of this are treatments of psychiatric and somatic diseases that are administered according to a schedule that corresponds to a person's rhythms in order to maximize effectiveness and minimize side effects of the therapy [2-16]. Chronotherapy is used in different fields, examples of this are the treatment of asthma, cancer, hypertension [3-15], and multiple types of depression, among others seasonal affective disorder and bipolar disorder [4]. Apart from the clinical applications, chronotherapy is becoming increasingly popular in non-clinical settings [5], for example on the work floor [18], where it is used to increase productivity and performance [6]. Blood pressure and heart rate

are highest during hours of 6.00 a.m. to 12.00 noon. Many diseased the chronotherapeutics approach is based on the re- symptoms occurred during the morning hours because most of the hormones and cytokines are released during this time period [7].

The pulsatile effect i.e the release of drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time such systems are also called time controlled as the drug released is independent of the environment [8]. Pulsatile drug delivery systems are gaining a lot of interest and attention these days [9]. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time i.e a period of no drug release though most delivery systems designed for constant drug release over a prolonged period of time [10], pulsatile delivery systems are characterized by a prepared drug release [11-16], as constant blood levels of a drug may not always be desirable [12-14]. Pulsatile systems are designed in a manner that the drug is available at the site of action at the night time in the light amount. These systems are beneficial for drugs having high first pass effect [13].

MATERIALS

The materials Metaprolol succinate drug is obtained as a sample from Hetero labs Hyderabad, Polymers and excipients are obtained from NR chemicals Hyderabad.

Methods

Wet granulation

Wet granulation is the most widely used process of granulation in the pharmaceutical industry. It involves addition of a liquid solution (with or without binder) to powders, to form a wet mass or it forms granules by adding the powder together with an adhesive, instead of by compaction. The wet mass is dried and then sized to obtained granules. The liquid added binds the moist powder particles by a combination of capillary and viscous forces in the wet state. More permanent bonds are formed during subsequent drying which leads to the formation of agglomerates.

Preparation of Metraprolol succinate sustained release tablets

The Metaprolol succinate sustained release tablets are prepared by taking the drug metaprolol succinate. By using various polymers sustained release core tablet of metaprolol succinate is prepared through wet granulation method. Then by using coating polymers. The coating of metaprolol succinate core tablet is carried out for achiving chronomodulated drug delivery.

Coating of metaprolol succinate core tablets

Different concentrations of the coating solutions were prepared by dissolving required quantities of Eudragit S and Eudragit L 100 in a mixture of Isopropyl alcohol and acetone in the ratio 1:1. Plasticizer and talc are added to the mixture. The compressed tablet formulations are coated with the coating solutions by spray coating. The tablets are first coated with Eudragit L 100 till the coating solution id distributed uniformly on the tablet. The tablets are dried and are then coated with Eudragit S 100 uniformly. Finally these coated tablets are dried completely.

Formulation table

INGREDIENTS	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)	F_7 (mg)	F_8 (mg)	*F_9 (mg)
METAPROLOL SUCCINATE	50	20	50	50	50	50	50	40	55
HPMC K4	40	20	20	37	45	30	50	20	25
ETHYL CELLULOSE	4	6	12	17	25			14	20
MCCP	48	90	50	30	12	14	34	60	33
SSG	4		4	4	4	4	4	4	5
MAGNESIUM STEREATE	3	3	3	2	3	2	2	2	2
TALC	3	3	3	2	3	2	2	2	2

HPMC E15						40			
POVIDONE	8	8	8	8	8	8	8	8	8
total	150	150	150	150	150	150	150	150	150

EVALUATION

Thickness

Control of physical dimension of the tablets such as size and thickness is essential for consumer acceptance and to maintain tablet-to-tablet uniformity. The dimensional specifications were measured using digital micrometer calipers. The thickness of the tablet is mostly related to the tablet hardness it can be used as initial control parameter.

Weight variation test

Twenty tablets were randomly selected an weighed to determine the average weight and was compared with individual tablet weight. The percentage weight variation was calculated. As per pharmacopoeia specification.

Hardness test

The hardness of the tablet was carried out by using Monsanto hardness tester. The hardness of the tablet kg/cm^2 was measured.

Friability test

Weighed amount of 20 dedusted tablets were subjected to rotating chamber of "Roche type friability". The chamber that revolves at 25rpm. This is then operated for 100 revolutions. The tablets are then dusted and reweighed.

$$F = \frac{W_o - W}{W_o} x100$$

Where W_o = Initial weight

W = Final weight

Limit for compressed tablets that lose less than 0.5 to 1.0% of their weight.

Dissolution test

The in vitro dissolution study was carried out using USP Type II dissolution apparatus. The study was carried out of 0.1N HCl for first 2 hours and then phosphate buffer (pH 6.8) from 3 to 12 hr. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37±0.5^{o}C. The paddle was lowered so that the lower end of the stirrer was 25 mm above from the base of the beaker. The tablet was then introduced into the dissolution jar and the paddle was rotated at 75 rpm. At different time intervals, 5 mL sample was withdrawn and analyzed by using spectrophoto-metrically at 275 nm. At each time of withdrawal, 5 mL of fresh dissolution medium was replaced into the dissolution flask.

Stability study

In order to assess the stability of drug that may vary with time under the influence of humidity and temperature the optimized formulation of metronidazole tablets was kept at 25°C±2 60% RH, 30°C±2 65%RH and 40°C±2 75% RH for three months. The samples are withdrawn and evaluated for their thickness, hardness, content, weight variation, friability and in-vitro drug release.

RESULTS

Solubility study

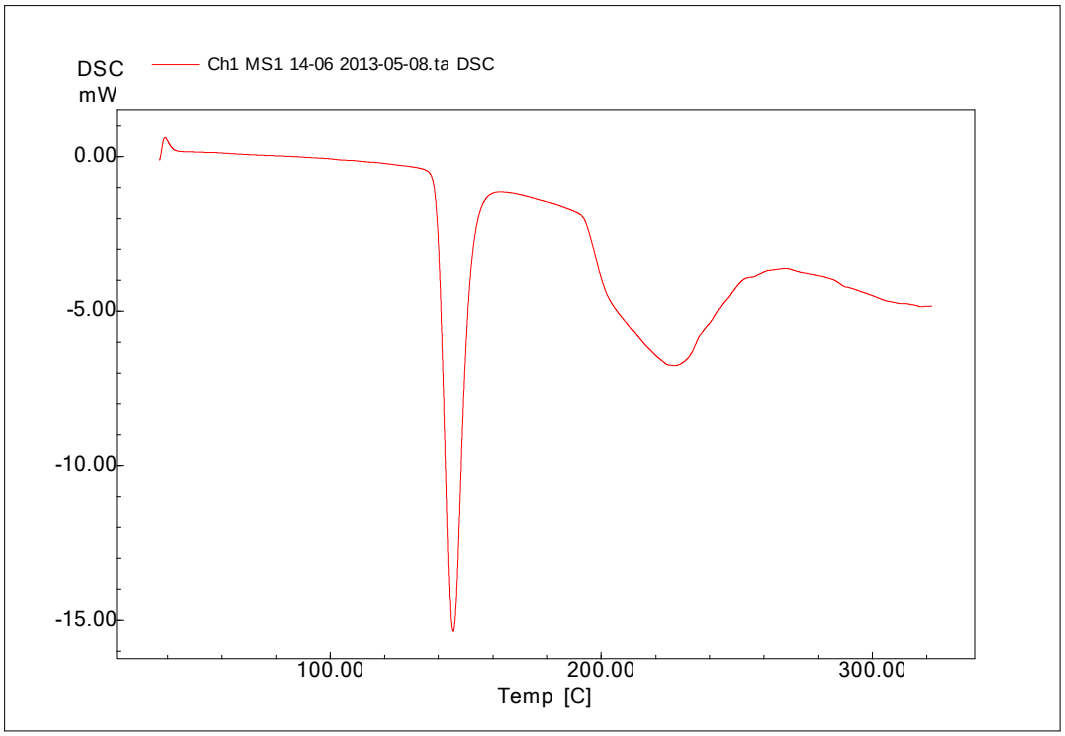
S.no	Solvent medium	Solubility
1	0.1N HCL	0.513±0.004
2	Phosphate buffer 6.8	4.12±0.01
3	Phosphate buffer 7.2	0.921±0.068
4	Phosphate buffer 7.4	0.824±0.033
5	1% Sodium lauryl sulphate	3.43±0.003
6	2% Sodium lauryl sulphate	2.21±0.048

Preformulation study of API

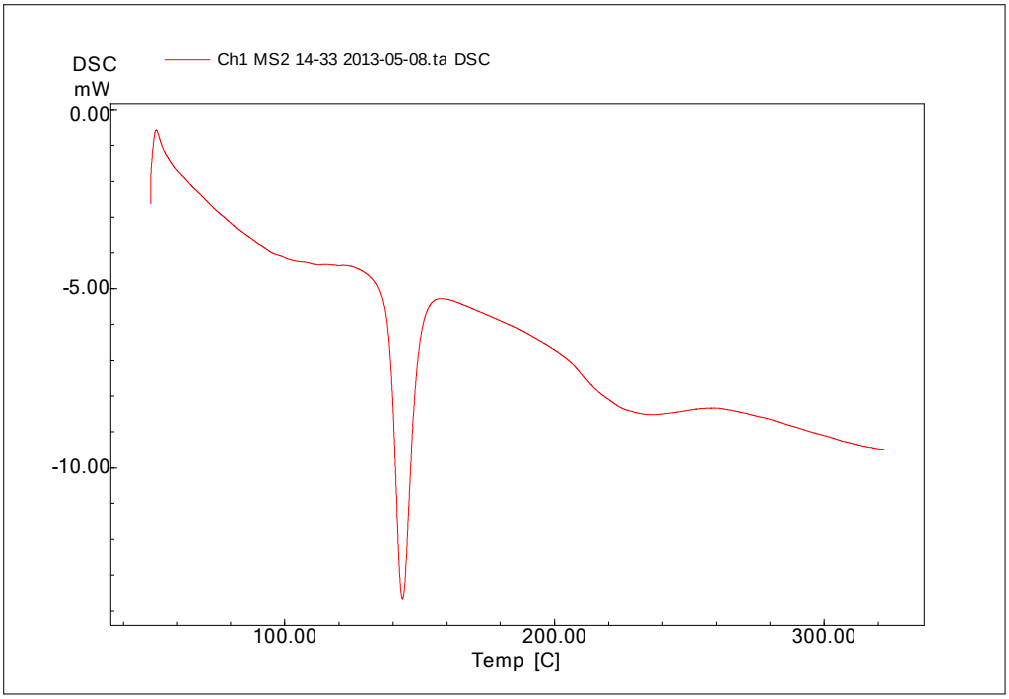
Formulation	Angle of repose	Bulk density	Tapped density	Compressibility index	Hausners ratio
F_1±sd	26.05±0.3	O.456±0.3	0.568±0.3	19.64±0.4	1.24±0.02
F_2±sd	24.32±0.2	0.461±0.2	0.548±0.4	14.815±0.3	1.17±0.03
F_3±sd	23.15±0.4	0.472±0.1	0.561±0.2	16.071±0.2	1.19±0.02
F_4±sd	24.24±0.1	0.598±0.5	0.641±0.3	7.812±0.3	1.08±0.04
F_5±sd	26.19±0.5	0.463±0.7	0.583±0.3	26.08±0.4	1.26±0.07
F_6±sd	22.13±0.1	0.475±0.8	0.536±0.4	11.32±0.2	1.12±0.06
F_7±sd	24.15±0.3	0.513±0.3	0.658±0.2	21.58±0.1	1.27±0.02
F_8±sd	23.12±0.2	0.479±0.2	0.561±0.5	16.07±0.6	1.19±0.04
*F_9±sd	20.11±0.4	0.452±0.3	0.483±0.3	6.418±0.6	1.06±0.01

Compatibility study

Differential scanning calorimetry



Pure drug DSC graph

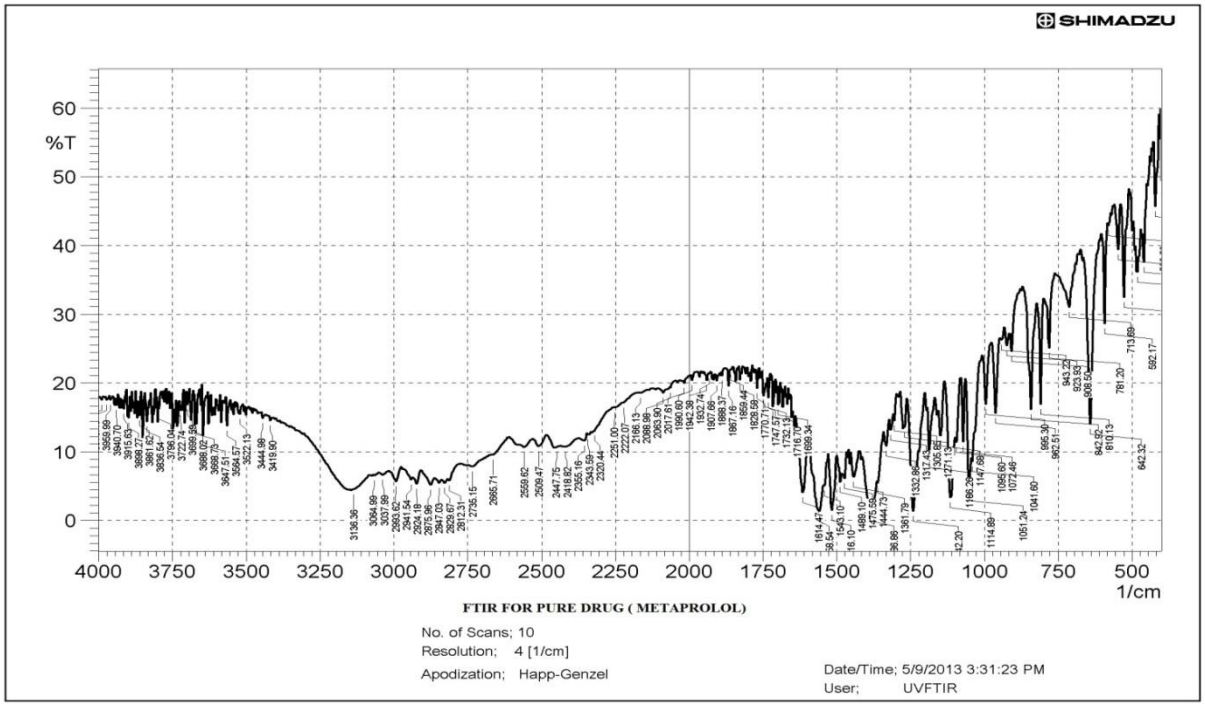


DSC graph of drug with excipients

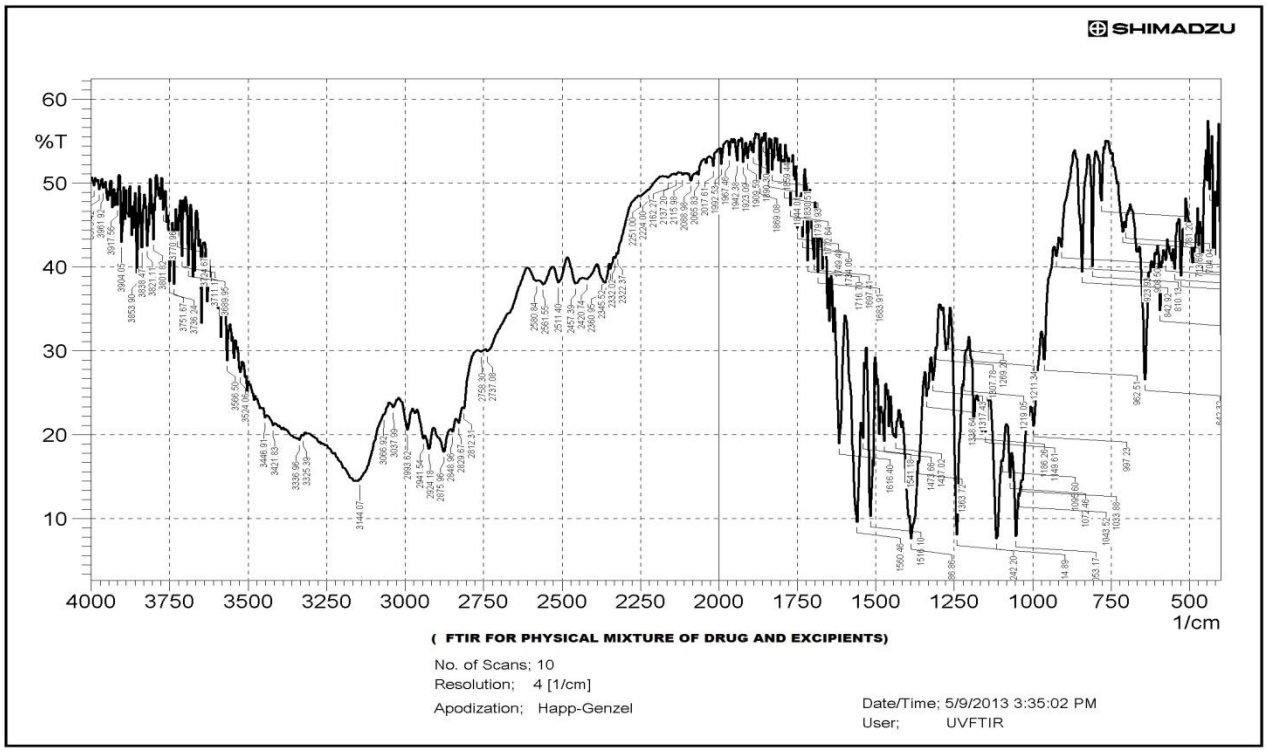
Differential scanning calorimetry studies

S.no	Formulation	Dsc melting point
1	Pure drug	145.2 degrees
2	Drug with polymers	144.6 degrees

Fourier transform infrared spectroscopy



FTIR graph of pure drug



FTIR graph of drug with polymers

FTIR studies

S.no	Functional group	Pure drug	Physical mixture
1	C-H	2924.18	2924.18
2	Aromatic ether	1242.2	1242.2
3	Isopropyl group	1186.26	1186.26
4	Ether	1614.89	1616.40
5	1,4 disubstituted benzene	842.92	842.92

Evaluation of core tablet

Formulation code	Shape	Diameter (mm)	weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Content uniformity (%)
F_1±sd	Round biconvex	8.3	138± 1.3	3.3±0.36	5.5±0.46	0.35±0.12	97.13±0.02
F_2±sd	Round biconvex	7.8	148±1.1	4.1±0.32	4.9±0.61	0.49±0.09	96.21±0.01
F_3±sd	Round biconvex	7.9	153±1.5	3.6±0.31	6.1±0.35	0.42±0.08	97.19±0.05
F_4±sd	Round biconvex	8.1	146±1.8	4.2±0.38	5.9±0.54	0.38±0.02	96.23±0.03
F_5±sd	Round biconvex	9.3	145±2.1	3.1±0.11	5.3±0.32	0.62±0.03	97.17±0.01

F_6±sd	Round biconvex	8.2	142±1.2	4.6±0.16	5.7±0.24	0.56±0.05	97.16±0.06
F_7±sd	Round biconvex	9.1	151±1.1	3.5±0.19	5.9±0.31	0.41±0.02	96.25±0.03
F_8±sd	Round biconvex	7.9	146±1.5	4.5±0.23	5.3±0.23	0.38±0.03	97.27±0.02
*F_9±sd	Round biconvex	9.1	150±1.1	4.4±0.13	5.8±0.13	0.43±0.01	98.13±0.01

*All values are expressed as mean ± SE, n=5

Evaluation of coating tablet

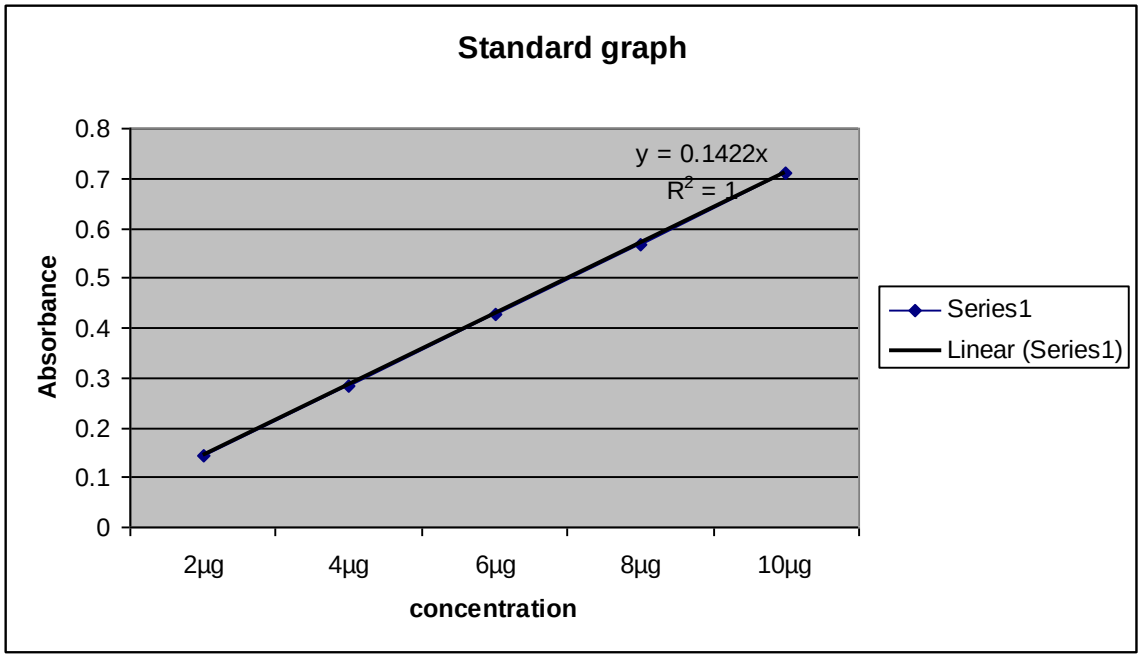
Formulation code	shape	Diameter (mm)	Thickness (mm)	weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Content uniformity (%)
F_1±sd	biconvex	11.11	4.9±0.31	241±2.5	5.2±0.46	0.45±0.12	96.50±0.03
F_2±sd	biconvex	10.14	5.2±0.52	246±3.2	5.6±0.61	0.59±0.09	95.21±0.02
F_3±sd	biconvex	10.16	4.8±0.33	251±2.7	5.1±0.35	0.32±0.08	97.12±0.04
F_4±sd	biconvex	11.21	5.2±0.58	244±3.1	5.8±0.54	0.58±0.02	95.21±0.01
F_5±sd	biconvex	10.25	5.1±0.31	249±2.6	5.3±0.32	0.42±0.03	97.15±0.03
F_6±sd	biconvex	11.18	4.6±0.26	247±3.2	5.5±0.24	0.36±0.05	96.13±0.02
F_7±sd	biconvex	10.12	5.5±0.29	253±3.1	5.1±0.31	0.41±0.02	96.21±0.04
F_8±sd	biconvex	10.17	4.7±0.27	242±2.8	4.9±0.23	0.58±0.03	97.23±0.06
*F_9±sd	biconvex	11.10	5.1±0.16	250±2.9	5.3±0.13	0.33±0.01	98.11±0.02

*All values are expressed as mean ± SE, n=5

DISSOLUTION STUDY

Standard curve

Concentration	Absorbance
2µg	0.142
4µg	0.284
6µg	0.426
8µg	0.568
10µg	0.712



Dissolution table of core tablet: (Sustained release)

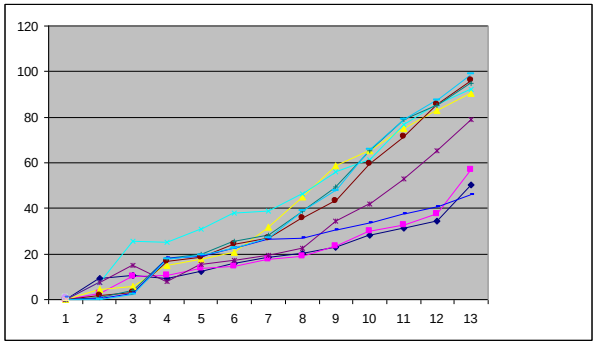
time	F_1±sd	F_2±sd	F_3±sd	F_4±sd	F_5±sd	F_6±sd	F_7±sd	F_8±sd	*F_9±sd
1hr	8.15±0.1	9.75±0.1	11.55±0.1	11.05±0.2	11.35±0.2	12.56±0.2	14.45±0.4	10.55±0.2	15.16±0.3
2hr	12.64±0.3	12.71±0.1	20.55±0.1	27.55±0.2	14.16±0.4	18.07±0.4	20.47±0.3	16.39±0.1	20.45±0.1
3hr	16.65±0.2	16.85±0.2	37.71±0.3	36.83±0.4	18.55±0.3	25.03±0.1	35.05±0.2	19.25±0.3	35.13±0.2
4hr	20.35±0.1	18.91±0.3	42.13±0.5	45.33±0.3	20.31±0.1	35.62±0.2	40.63±0.1	20.01±0.1	40.62±0.3
5hr	23.10±0.2	23.42±0.4	58.61±0.4	57.12±0.5	36.51±0.2	48.14±0.3	50.61±0.3	28.23±0.3	50.39±0.4
6hr	28.15±0.3	29.15±0.3	63.24±0.2	61.52±0.1	41.12±0.3	55.32±0.1	58.21±0.4	39.45±0.1	63.52±0.1
7hr	29.14±0.1	30.56±0.3	70.11±0.4	66.69±0.5	59.12±0.1	68.31±0.4	68.91±0.3	43.52±0.3	72.82±0.2
8hr	34.36±0.2	32.61±0.2	73.12±0.1	75.71±0.2	68.21±0.2	65.39±0.1	70.13±0.3	50.45±0.1	79.67±0.3
9hr	40.31±0.1	36.68±0.1	74.56±0.2	78.43±0.1	75.91±0.3	78.12±0.2	76.62±0.1	55.35±0.2	80.16±0.1

Dissolution table of coated tablet

time	**F_1(%)**	**F_2(%)**	**F_3(%)**	**F_4(%)**	**F_5(%)**	**F_6(%)**	**F_7(%)**	**F_8(%)**	***F_9(%)**
0.1NHCL									
1hr	9.27	2.79	4.51	7.38	7.42	1.845	1.035	0.495	0.207
2hr	10.62	10.215	5.67	25.52	14.98	2.92	3.76	2.7	2.403
6.8PHOSPHATE BUFFER									
3hr	9.135	10.62	15.03	25.2	7.92	16.677	18.17	18.225	17.595
4hr	12.15	13.725	17.55	31.05	15.35	18.54	19.845	18.855	19.416
5hr	15.84	14.71	20.565	37.755	17.17	24.08	25.45	22.69	22.48

6hr	18.67	17.865	31.77	38.83	19.52	27.02	28.056	26.28	27.13
7hr	20.385	18.99	45.12	46.31	22.34	35.63	38.65	27.03	38.92
8hr	23.13	23.44	58.63	56.12	34.56	43.14	49.63	30.25	47.59
9hr	28.17	30.15	65.34	61.54	42.13	59.34	65.12	33.48	65.63
10hr	31.14	32.76	75.14	76.67	53.14	71.35	78.94	37.58	78.82
11hr	34.38	37.71	83.13	85.76	65.27	85.65	85.16	40.65	87.16
12hr	50.35	56.78	90.56	92.34	78.93	96.12	94.65	45.85	98.77

Dissolution graph of formulations



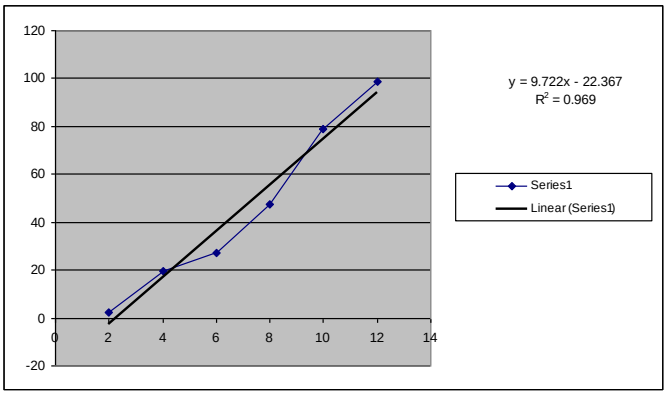
The graph of dissolution profile is drawn for formulations. The graph is drawn by taking time on x-axis and dissolution rate on y-axis.

Drug release kinetics

Formulation	Zeroorder regression coefficient(R^2)	First order regression coefficient(R^2)	Higuchi regression coefficient(R^2)	Korsmeyor regression coefficient(R^2)
F_1	0.88	0.82	0.99	0.97
F_2	0.85	0.77	0.99	0.97
F_3	0.98	0.90	0.99	0.91
F_4	0.95	0.82	0.91	0.98
F_5	0.87	0.77	0.97	0.94
F_6	0.96	0.73	0.99	0.87
F_7	0.97	0.82	0.99	0.88
F_8	0.95	0.97	0.98	0.71
*F_9	0.96	0.71	0.99	0.85

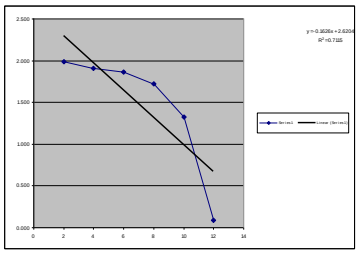
The kinetic release studys are performed by taking time and dissolution rates and the graphs of zero order, first order, higuchi and peppas graphs are plotted.

Zero order release graph of optimized formulation



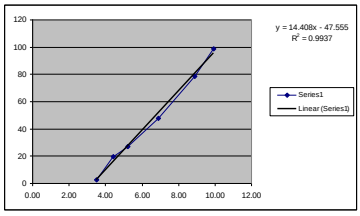
The zero order release graph was plotted by taking time on x-axis and cumulative drug release on y-axis.

First order release graph of optimized formulation:



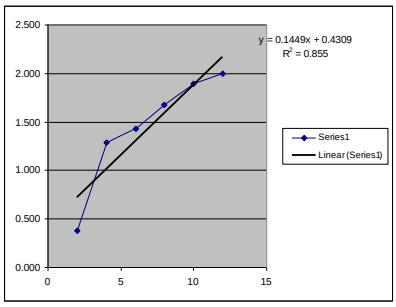
The first order graph was plotted by taking time on x-axis and log ADR on y-axis.

Higuchi graph for optimized formulation



The higuchi graph was plotted by taking √t on x-axis and cumulative drug release on y-axis.

Korsmeyer-peppas graph for optimized formulation



The peppas graph was plotted by taking log t on x-axis and log cumulative drug release on y-axis.

Stability studies

Parameters	25degrees&60%RH				30degrees&70%RH			40degrees&80%RH		
	initial	1st month	2nd month	3rd month	1st month	2nd month	3rd month	1st month	2nd month	3rd month
Appearance	White coloured	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Shape	biconvex	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Weight variation	250mg	250mg	250mg	250mg	250mg	250mg	250mg	250mg	250mg	250mg
Thickness	5.1±0.16	5.1±0.16	5.1±0.16	5.1±0.16	5.1±0.16	5.1±0.16	5.0±0.16	5.1±0.16	5.1±0.16	4.9±0.16
Hardness	5.3±0.13	5.3±0.13	5.3±0.13	5.2±0.13	5.3±0.13	5.3±0.13	5.2±0.13	5.3±0.13	5.1±0.13	4.8±0.13
Friability	0.33±0.01	0.33±0.01	0.31±0.01	0.29±0.01	0.33±0.01	0.31±0.01	0.28±0.01	0.33±0.01	0.30±0.01	0.27±0.01
Drug content	98±0.01	98±0.01	96±0.01	95±0.01	98±0.01	95±0.01	93±0.01	98±0.01	92±0.01	90±0.01
Dissolution	98.77	98.77	97.77	96.57	98.77	96.65	95.14	98.77	95.76	90.19

DISCUSSIONS

The solubility study is performed by taking different solvent media. It has shown good solubility in different media. The optimum solubility is achieved in phosphate buffer 6.8. The lowest solubility is achieved in 0.1N hydrochloric acid. The drug is suitable for 0.1N HCL as well as 6.8 Phosphate Buffer. The preformulation study was performed for the active pharmaceutical ingredient. All the formulations have shown acceptable values within the limits of I.P. The optimized formulation F_9 have shown excellent angle of repose. Bulk density and tapped density are within the limits. The compressibility index and hausners ratio is excellent according to the limits of I.P. The FTIR studies are performed on the drug and physical mixture and granules. All the functional groups in all the graphs have shown similar wave numbers it indicates there are no interaction of drug with polymers. The ether has the minute variations it may be due to the improper maintenance of environmental conditions. So, the FTIR studies confirmed that there are no interactions of drug. The post formulation study or evaluation of core tablet is carried out. The Shape of the tablet is found to be round convex, the diameter of the tablet is found to be 7.8 to 9.1 mm. The weight variation of the tablet is found to be 150±7.5%. The thickness of the tablet is found to be 3.1 to 4.6 mm. The hardness of the tablet is found to be 4.9 to 6.1 kg/cm^2. The friability is less than 1%. The content uniformity of the tablet is found to be 96.21 to 98.13%.

The evaluation study is carried out after coating of the tablet. The Shape of the tablet is found to be round convex, the diameter of the tablet is found to be 10.12 to 11.21 mm. The weight variation of the tablet is found to be 250±7.5%. The thickness of the tablet is found to be 4.6 to 5.5 mm. The hardness of the tablet is found to be 4.9 to 5.6 kg/cm^2. The friability is less than 1%. The content uniformity of the tablet is found to be 96.50 to 98.11%. Determination of λmax was done in different Medias. Then that was found to be 272nm. Standard curve was plotted by taking concentration on x-axis and absorbance on y-axis. The graph is linear. According to the graph the slope value is 0.1422x and Regression coefficient value is 1. Dissolution studies are performed on core tablet with dissolution apparatus. The F_9 formulation shown good dissolution pattern. F_1, F_3, F_8 have shown poor dissolution pattern. The F_9 is taken as optimized formulations as it have shown the good dissolution pattern. The dissolution study for all the formulations is carried out after coating. The formulations F_1, F_2, F_5, F_8 have shown some poor dissolution. The F_9 formulation shown optimum dissolution compared to all the formulations.

The kinetic release studies are performed. It was concluded that the kinetic release follows Higuchi

model. As the plot showed the highest linearity of 0.9937. The drug release was best fitted for Higuchi release pattern The stability study is performed on the metaprolol succinate chronomodulated tablets and stability study shown there is only slight variation of parameters in third month due to extreme temperature conditions.

CONCLUSION

There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place, and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension etc.

BIBILOGRAPHY

[1]. Yeole P.G. and Galgatte U.C., Design & evaluation of xanthan gum based sustained release matrix tablets of diclofenac sodium, Indian journal of pharmaceutical science, 2006, 185 -189.

[2]. Varshosaz J. and Tavakoli N., Use of hydrophilic natural gums in formulation of SR matrix tablets of tramadol, AAPS Pharmascitech United State Pharmacopoeia 30 NF 25, 2648. 7(1), 2006, 24, E1-E6. 6.

[3]. Elizabeth B., Gennaro A. R., Eds., Reimington: The Science and Practice of Pharmacy, Mack Publishing Company, Easton, PA, 1(20), 2000, 986-987.

[4]. Kanvinde S.A. and Kulkarni M. S., Stability of oral solid dosage forms – A global perspective. Pharma Times. 37 (5), 2005, 9-16.

[5]. Chowdary K.P. and Monhapatra P., Evaluation of olibanum and its resin as rate controlling matrix for controlled release of diclofenac, Indian journal of pharmaceutical sciences, 2006, 497- 500.

[6]. Sahel, M.A., Yellela, S. R. K., Srinivas S. P. and Vemulapalli, S. In Vitro and In Vivo Evaluation of Guar Gum Matrix Tablets for Oral Controlled Release of Water-soluble Diltiazem Hydrochloride. AAPS PharmSciTech 6(1), 2005. Article 5.

[7]. Deshmukh, V. N., Singh,S. P. & Sakarkar, D. M. Formulation and Evaluation of Sustained Release Metoprolol Succinate Tablet using Hydrophilic gums as Release modifiers. International Journal of PharmTech Research, 1(2), 159-163.

[8]. Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, eds. Tutorial Pharmacy. New Delhi, India: CBS Publishers and Distributors; 1986, 211-233.

[9]. Aulton ME, Wells TI. Pharmaceutics: The Science of Dosage Form Design. London, England: Churchill Livingstone; 1988.

[10]. Martin A. Micromeritics. In: Martin A, ed. Physical Pharmacy. Balti-more, MD: Lippincott Williams & Wilkins; 2001, 423- 454.

[11]. Pharmacopoeia of India. New Delhi: Ministry of Health and Family Welfare, Government of India, Controller of Publications; 1996.

[12]. Cacovean Ioana, Ilie Mihaela, Bădulescu Magdalena, Bălălău Dan, Gubandru Miriana – UV-VIS Spectrophotometric Assay of Metoprolol. Note 1. Comparison between the Direct and the Oxydative Methods – Farmacia, 2007, 540-544.

[13]. Shah D, Shah Y, Rampradhan M. Development and evaluation of con-trolled release diltiazem hydrochloride microparticles using cross-linked poly (vinyl alcohol) drug Dev Ind Pharm. 23(6), 1997, 567-574.

[14]. Banker GS, Anderson LR. Tablets. In: Lachman L, Liberman HA, Kanig JL, eds. The Theory and Practice of Industrial Pharmacy. Mumbai, India: Varghese Publishing House; 1987, 293-345.

[15]. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate release of solid drugs dispersed in solid matrices. J Pharm Sci. 52, 1963, 1145-1149.

[16]. Korsmeyer RW, Gurny R, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers int j pharm, 15, 1983, 25-35.

[17]. Derle D. V. and Kasliwal N. H., Development & comparative evaluation of xanthan gum & guar gum based sustained release matrix tablets of tizanidine HCL, Int. Journal of Excipients, 2006, 116- 119.

[18]. Salsa T., Veiga F. and Pina M.E., Oral controlled- release dosage form- Cellulose ether polymers in hydrophilic matrices, Drug Development and Industrial pharmacy, 23(9), 1997, 929-938.