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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF METOPROLOL SUCCINATE

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ABSTRACT

Metoprolol succinate, β1- selective adrenergic receptor- blocking agent used in the management of hypertension, angina pectoris, cardiac arrthymias, myocardial infarction, heart failure, hyperthyroidism. In present investigation an attempt was made to reduce the frequency of dose administration to prevent nocturnal attack and to improve the patient compliance by developing to a sustained release formulation of Metoprolol succinate, the tablet was prepared by the direct compression method using different polymer with different concentration Ethyl Cellulose, HPMCK4M. Metoprolol Succinate and polymer compatibility interaction was investigated by using FTIR spectroscopy and DSC. The powder blends evaluated for precompression parameter, and tablet were subjected to post compression parameter. Also *in vitro* release studies upto the 12 hrs. Mathematical model in which Zero order, Higuchi model, First Order, Korsmeyer-peppas model. Formulation was optimized on the basis of acceptable tablet properties and in vitro drug release. The release kinetic of the optimized formulation F5 followed by Higuchi model and non fickian transport. Design the sustained release matrix tablet formulation of Metoprolol succinate and elucidate the release behaviour was most successful formulation of the study using direct compression process.

KEYWORD: Sustained Release Metoprolol Succinate, Ethyl Cellulose HPMCK4M, Direct Compression and Mathematical model.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. The sustained release oral

dosage forms have been demonstrated to improve therapeutic efficacy by maintaining steady state drug plasma concentration. Various types of modified release formulations have been developed to improve the patient compliance and also clinical efficacy of the drug.

Hydroxypropyl methyl cellulose (Hypromellose, HPMC) polymers have been widely studied for their application in oral sustained release formulations. Such hydrophilic polymers are most popular because of their flexibility to get a desirable drug release profile, cost effectiveness and broad regulatory acceptance.[1] HPMC has always been a first choice for formulation of hydrophilic matrix systems, because of providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles, and cost effectiveness.

Also used in the formulation ethyl cellulose [ec-22]. It has hydrophobic polymer ethyl cellulose is stable highly hygroscopic material. it is inert to attack by aqoues alkali even when hot and highly conc. is often used for controlled release, taste masking and moisture barrier applications. It is non-toxic, non-allergenic, non-irritant and widely used in oral drug delivery system.

Metoprolol succinate, β1- selective adrenergic receptor- blocking agent used in the management of hypertension, angina pectoris, cardiac arrthymias, myocardial infarction, heart failure, hyperthyroidism . The half-life of drug is relatively short approximately 4-6 hrs, thus warrants the use of sustain release formulation for prolong action and to improve patient compliance common cardiovascular diseases, require constant monitoring.

MATERIALS AND METHODS

Materials: Metoprolol succinate was obtained from Gen. International Pharma. Pune. HPMC and Ethyl cellulose grades were received from Fine chemical industries, Mumbai. Other materials were purchased from Signet Chem, Mumbai, India.

Methodology

Standardization of Metoprolol succinate by UV-Visible spectrophotometry in 0.1 N HCl Solution

Preparation of stock solution

Stock solution 100µg/ml of Metoprolol succinate was prepared in 0.1N Hcl solution. This solution was approximately diluted with 0.1N Hcl to obtain a concentration of 10µg/ml. The

resultant solution was scanned in range of 200-400nm using UV double beam spectrophotometer (Lab India UV-3000+).

Standard calibration of Metoprolol succinate in 0.1N Hcl [pH 1.2]

100mg of Metoprolol succinate was accurately weighed and dissolved in100ml of 0.1N Hcl to obtain a concentration of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 2ml, 4ml, 6ml, 8ml, 10ml were diluted in 10ml volumetric flask with phosphate buffer to give concentrations in range of 2µg/ml to 10µg/ml respectively, absorbance was measured at 221nm.

In pH 6.8 Buffer

Preparation of stock solution

Stock solution 100µg/ml of Metoprolol succinate was prepared in phosphate buffer of pH 6.8. This solution was approximately diluted with phosphate buffer of pH 6.8 to obtain a concentration of 10µg/ml. The resultant solution was scanned in range of 200- 400nm using UV double beam spectrophotometer (Lab India UV-3000+).

Standard calibration of Metoprolol succinate in phosphate buffer of pH 6.8

100mg of Metoprolol succinate was accurately weighed and dissolved in100ml of pH 6.8 phosphate buffer to obtain a concentration of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 2ml, 4ml, 6ml, 8ml, 10ml were diluted in 10ml volumetric flask with phosphate buffer to give concentrations in range of 2µg/ml to 10µg/ml respectively, absorbance was measured at 221.8nm.

DRUG- EXCIPIENT COMPATIBILITY BY FTIR STUDIES

In the preparation of SR tablet, drug and polymer may interact as they are in close contact with each other, which could lead to instability of drug. Preformulation studies regarding drug-polymer interactions are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy (Agilent Technologies) was employed to ascertain the compatibility between Metoprolol succinate and selected polymers. The individual drug and drug with excipients were scanned separately.

Procedure: Potassium bromide was mixed with drug and polymer in the ratio of 100:1 and pellet was prepared using KBr pellet press and spectrum was taken using FTIR (Agilent Technologies). FT-IR spectrum of Metoprolol succinate was compared with spectrum of Metoprolol succinate and polymer. Disappearance of Metoprolol succinate peaks or shifting of peak in any of the spectra was studied.

Angle of repose: The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated using the following equation.

Tan Θ= h/r Where 'h' and 'r' are the height and radius respectively of the powder cone.

Carr's compressibility index: The Carr's compressibility Index was calculated from Bulk density and tapped density of the blend. A quantity of 2g of blend from each formulation, filled into a 10mL of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5cm. The tapped frequency was 25±2 per min to measure the tapped volume of the blend. The bulk density and tapped density were calculated by using the bulk volume and tapped volume. Carr's compressibility index was calculated by using following formula:

Carr's compressibility index (%) = [(Tapped density-Bulk density) X100]/Tapped density

Bulk Density (BD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The bulk densities (BD) of powder blends were determined using the following formula.

Bulk density = Total weight of powder / Total volume of powder

Tapped bulk density (TBD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped

volume. The tapped bulk densities (TBD) of powder blends were determined using the following formula.

TBD= Total weight of powder / Total volume of tapped powder

PREPARATION OF TABLETS

Different tablets formulations were prepared by direct compression and wet granulation technique. Direct compression method: All powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Talc was used as Glidant. Micro crystalline cellulose was used as diluent. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests. In all formulations, the amount of the active ingredient is equivalent to 50mg of Metoprolol succinate.

EVALUATION OF TABLETS

The weight of tablets was evaluated on 20 tablets using an electronic balance. Friability was determined using 6 tablets in Roche friability tester at 25rpm. Hardness of the tablets was evaluated using an Monsanto hardness tester. The hardness of all the formulation was between 5.45 -6.20 kg/cm^2

IN VITRO DISSOLUTION STUDIE[4]

In vitro drug release studies from the prepared matrix tablets were conducted using USP type II apparatus at 37°C at 50rpm. Dissolution mediums used were 900mL of 0.1N Hcl and phosphate buffer of pH 6.8. The release rates from matrix tablets were conducted in Hcl solution (pH 1.2) for 2h and changed to phosphate buffer (pH 6.8) for further time periods. The samples were withdrawn at desired time periods from dissolution media and the same were replaced with fresh dissolution media of respective pH. The samples were analyzed by UV-Visible Spectrophotometer (Lab India 3000+). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time curve.[4]

Table 1: Formulations Containing Ethyl Cellulose [EC22], HPMC K4M [Direct Compression]

Ingredients (mg/tab)	Formulation code (qty: mg/tab)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoprolol Succinate	50	50	50	50	50	50	50	50	50
Ethyl Cellulose[EC22]	25	50	100	_	_	_	_	_	_
HPMC K4M	__	__	__	25	50	100	__	__	__
MCC 102	121	96	46	121	96	46	121	96	46
Magneshium Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total Weight (Mg)	200	200	200	200	200	200	200	200	200

DATA ANALYSIS (CURVE FITTING ANALYSIS)

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as:

Cumulative percentage drug released Vs Time (*In-vitro* drug release plots).

Cumulative percentage drug released Vs Square root of time (Higuchi's plots).

Log cumulative percentage drug remaining Vs Time (First order plots).

Log percentage drug released Vs Log time (Peppas plots).

Zero order

Where K_{0} - is the zero-order rate constant expressed in units of concentration/time

- t - is the time in hrs.

Where K_{0} - is the zero-order rate constant expressed in units of concentration/time

- t - is the time in hrs.

First order

Where C_{0} - is the initial concentration of drug,

K - is the first order constant.

t - is the time in hrs.

Higuchi

Where Q_{t} - is the amount of the release drug in time t,

K- is the kinetic constant and

- t- is time in hrs.

Korsmeyer Peppas

Where M_t- represents amount of the released drug at time t,

M_∞ is the overall amount of the drug (whole dose) released after 12 hrs.

K- is the diffusional characteristic of drug/ polymer system constant.

n- is a diffusion exponent that characterizes the mechanism of release of drug.

The value of n indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent n = 0.5, then the drug release mechanism is Fickian diffusion.

If n < 0.5 the mechanism is quasi-Fickian diffusion, and 0.5 < n < 1.0, then it is non-Fickian or anomalous diffusion and when n = 1.0 mechanism is non Fickian case II diffusion, n> 1.0 mechanism is non Fickian super case II.[3]

RESULTS AND DISCUSSION

Preformulation characteristics

The drug Metoprolol succinate was standardized by UV method in 0.1N Hcl and pH 6.8 Buffer separately. The λ_{max} were 221nm and 221.8 nm in 0.1N Hcl and pH 6.8 buffers respectively and the linearity range was 2-10 mcg/ml in both the media.

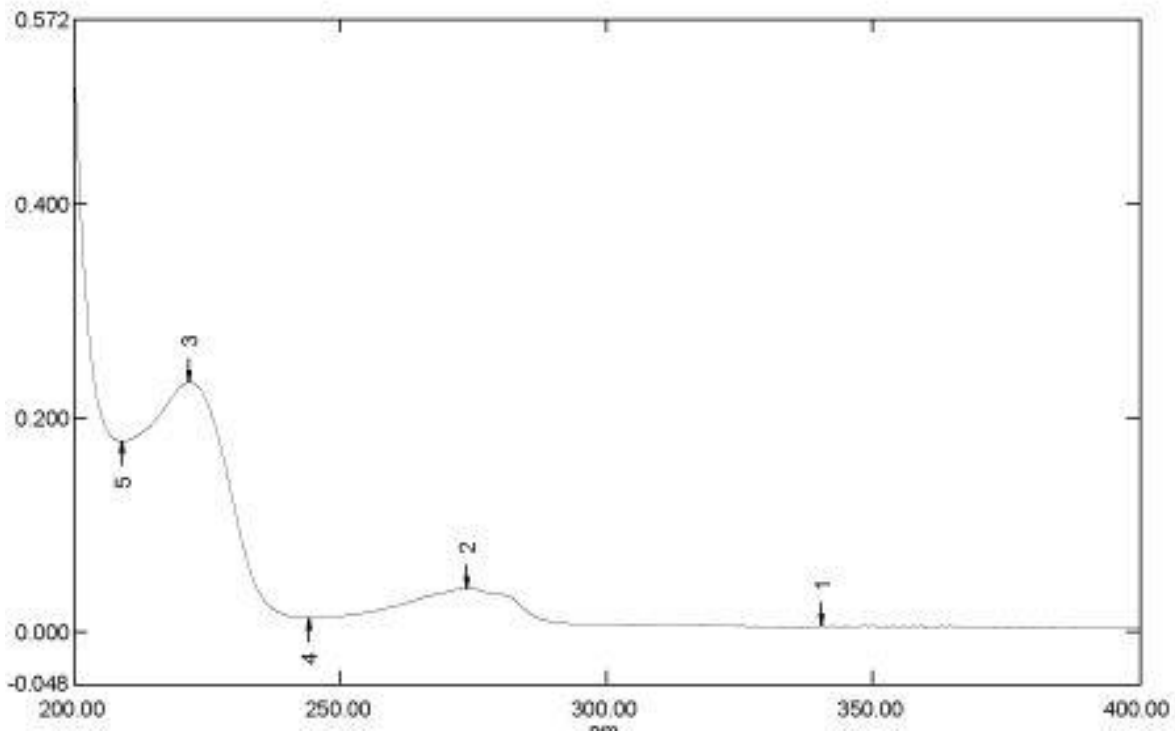


Fig. 1: λ_{max} of Metoprolol succinate in 0.1 N Hcl (221nm)

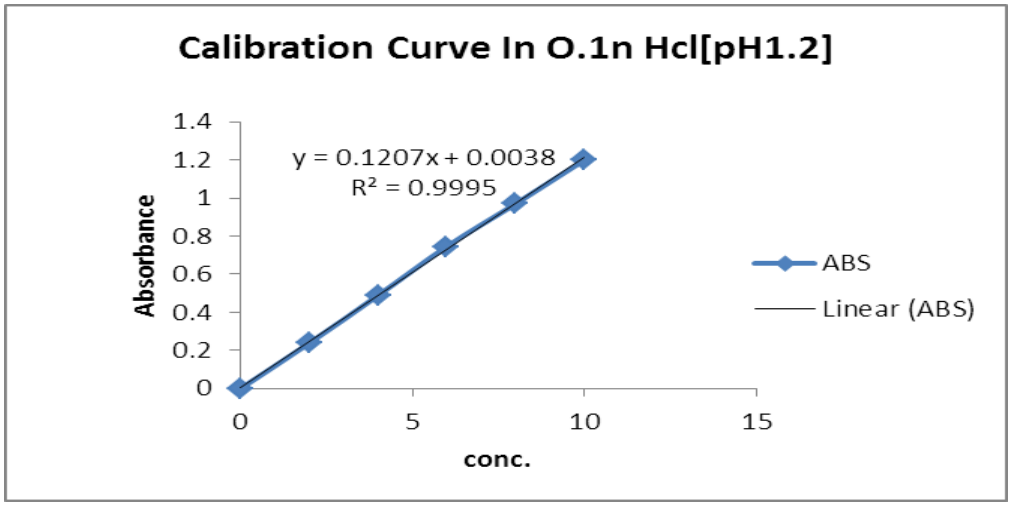


Fig. 2: Calibration curve of Metoprolol Succinate in 0.1N Hcl

Table 3: Absorbance's of Metoprolol Succinate in 0.1N Hcl

Sr. no	Conc.	Absorbance [Nm]
1.	0	0
2.	2	0.239
3.	4	0.489
4.	6	0.746
5.	8	0.97
6.	10	1.2

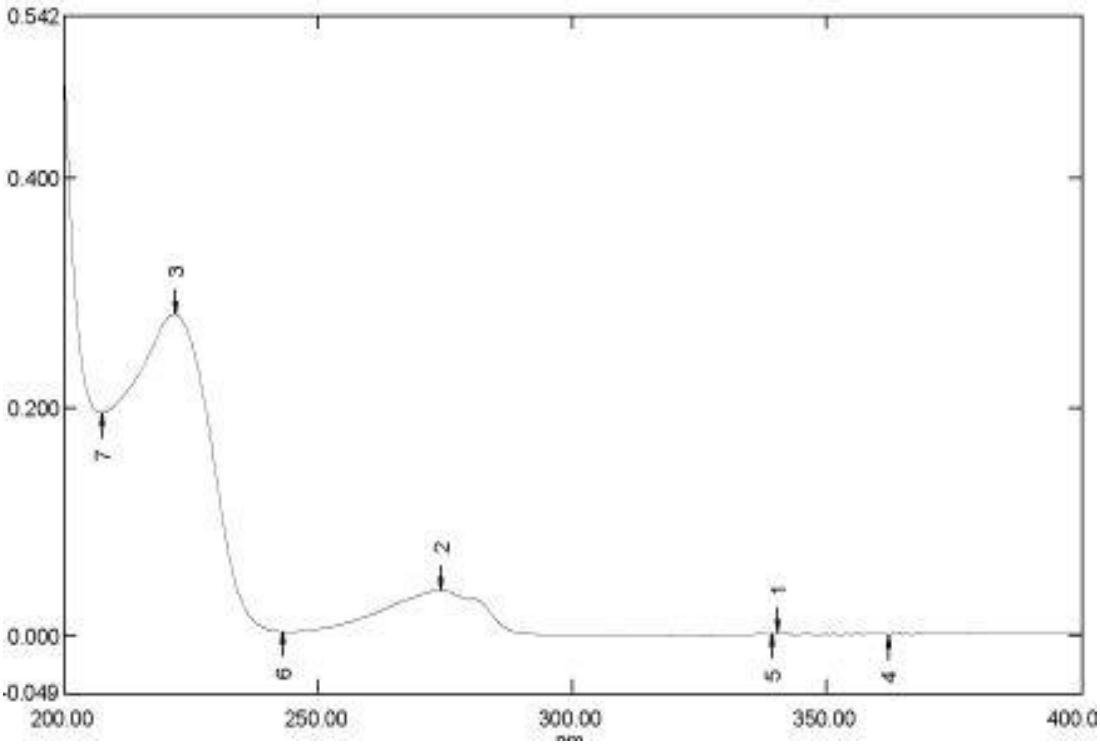
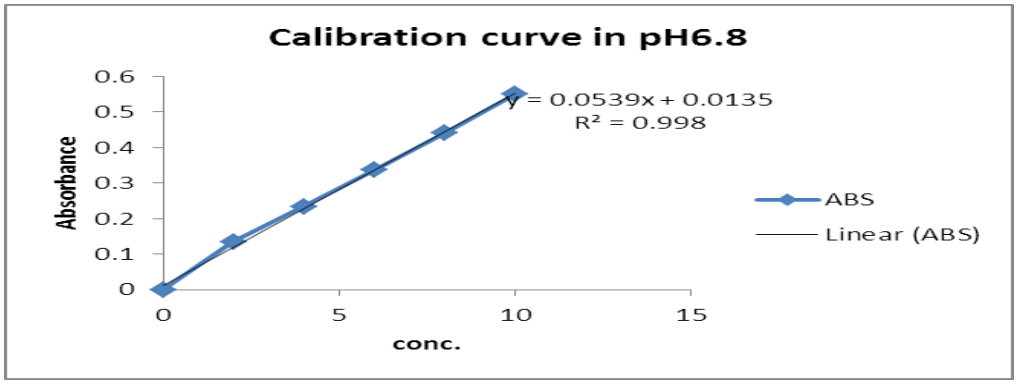


Fig. 3: λ_{max} of Metoprolol succinate in pH 6.8 buffer (228nm)



Calibration curve of Metoprolol Succinate in 6.8 pH Phosphate buffer

Table 4: Absorbences of Metoprolol succinate in 6.8 pH phosphate buffer

Sr. no.	Conc.	Absorbance
S1	00	00
2	2	0.135
4	4	0.234
6	6	0.337
8	8	0.441
10	10	0.550

Physical characteristics of blends and tablets

The blends of different formulations were evaluated for angle of repose, Carr's compressibility index etc., The results of Angle of repose and Carr's compressibility Index (%) ranged from 19-26 and 10-14, respectively which showed that blends from all the formulations having good flow property. The hardness and percentage friability ranged from 5-7kg/cm2 and 0.3-0.8% respectively.

DRUG: EXCIPIENT COMPATIBILITY STUDIES- FTIR:

Drug-Excipient compatibility studies by FTIR revealed no interaction between drug and the polymers used in the formulation thus showing compatibility.

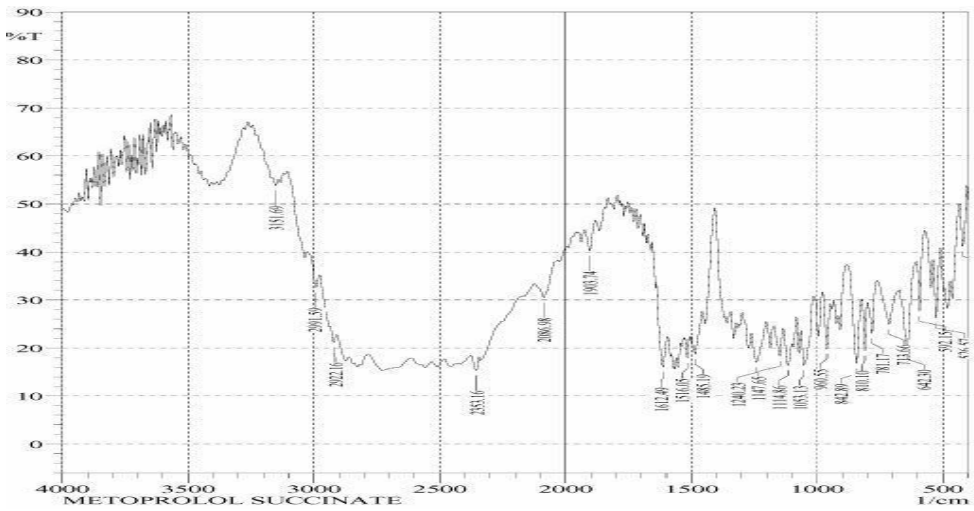


Fig. 5: FTIR spectra of pure Drug

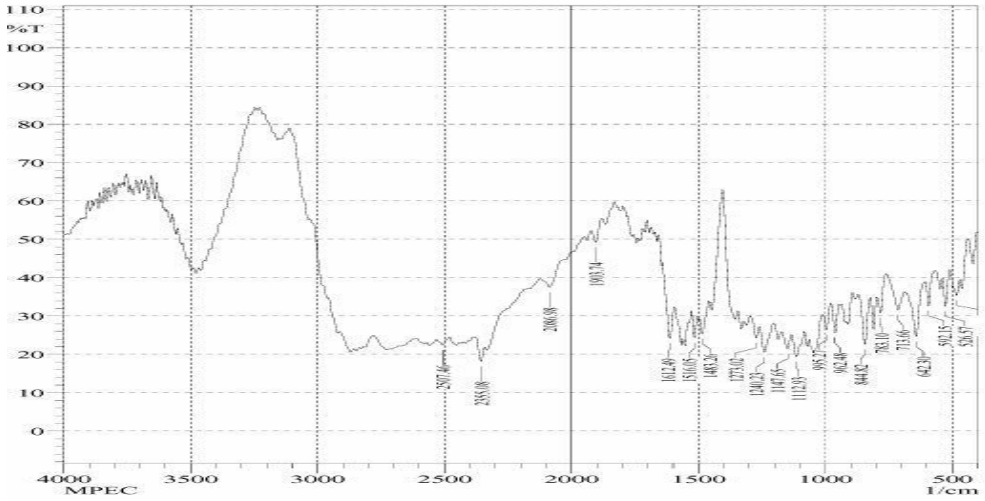


Figure No7: IR spectra of Metoprolol Succinate + [Ethyl cellulose22cps]

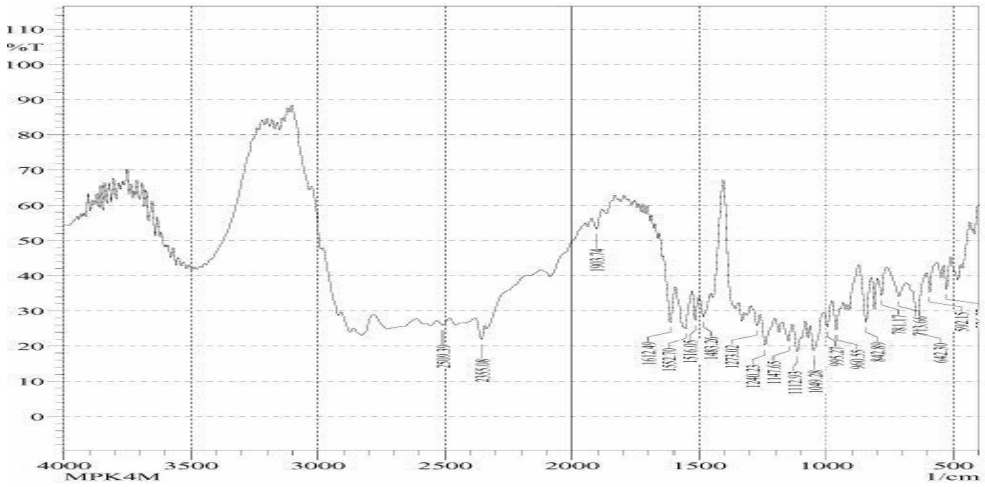


Figure No 8: IR spectra of Metoprolol Succinate + HPMC K4M

IN- VITRO DISSOLUTION STUDIES

In-vitro release studies were carried out for all the formulations as per USP XXII tablet dissolution tester employing basket at 50rpm using 900ml of phosphate buffer pH 6.8 & pH 1.2 as dissolution medium. The results were evaluated for 12 hours. The various concentration of polymer HPMCK4M, Ethyl cellulose combination on release profile of the drug studied of Metoprolol succinate in pH 6.8 buffer (228nm) the release rate of Metoprolol succinate mainly controlled by the hydration and swelling properties of HPMC which forms a gel layer that controls the water penetration and drug diffusion. The effect of polymer concentration on drug release could be clearly seen from the variation of the dissolution profiles. The drug release data of dissolution studies of formulation (F1 to F3) containing Ethyl cellulose, F4 to F6 containing HPMC K4M), When cumulative % drug release plotted versus time was observed that, for two polymers used, an increase in polymer concentration

induce a decrease in the release rate. Formulation F5 containing HPMC K4M (1:1) met the needed theoretical drug release profile and has the sustain action i.e., retarding the drug release so the release is for a long time and thus more bioavailability; for these reasons, it was considered the best formulation among all the formulations of this series. Hence F5 Optimized Formulation.

Table 5: Pre compression parameters

Formulation code	Bulk density (g/cm3) [n=3]	Tapped Density (g/cm3)[n=3]	Compressibility Index (%) [n=3]	Hausner Ratio [n=3]	Angle of Repose
F1	0.458±0.05	0.525±0.08	10.78 ± 0.5	1.059±0.05	19.093±0.020
F2	0.465±0.08	0.592±0.12	11.92 ± 0.7	1.058±0.02	23.734±0.214
F3	0.442±0.06	0.567±0.08	12.54±0.01	1.056±0.10	24.764±0.210
F4	0.434±0.08	0.558±0.02	14.53±0.02	1.055±0.03	26.552±0.013
F5	0.497±0.05	0.531±0.07	11.67±0.06	1.068±0.08	23.699±0.113
F6	0.477±0.08	0.508±0.08	12.50±0.35	1.061±0.12	24.139±0.022

Table 6: Post compression parameters

Formulation code	Hardness [kg/cm2] n=3	Weight Variation[mg] n=20	Thickness[mm] n=3	Friability [%]n=10	Drug Content[%] Mean±S.D n=3
F1	6.20±0.01	200 ± 0.02	3.1±0.01	0.5±0.02	99.75±0.173
F2	6.01±0.03	198 ± 0.04	3.0±0.02	0.6±0.01	98.74±1.05
F3	6.20±0.01	199 ± 0.02	3.2±0.04	0.3±0.03	97.92±2.10
F4	6.70±0.01	196 ± 0.05	3.2±0.03	0.4±0.05	97.35±0.95
F5	6.03±0.05	199 ± 0.05	3.0±0.02	0.5±0.02	99.55±0.90
F6	5.45±0.08	197 ± 0.04	3.3±0.2	0.8±0.04	98.83±1.25

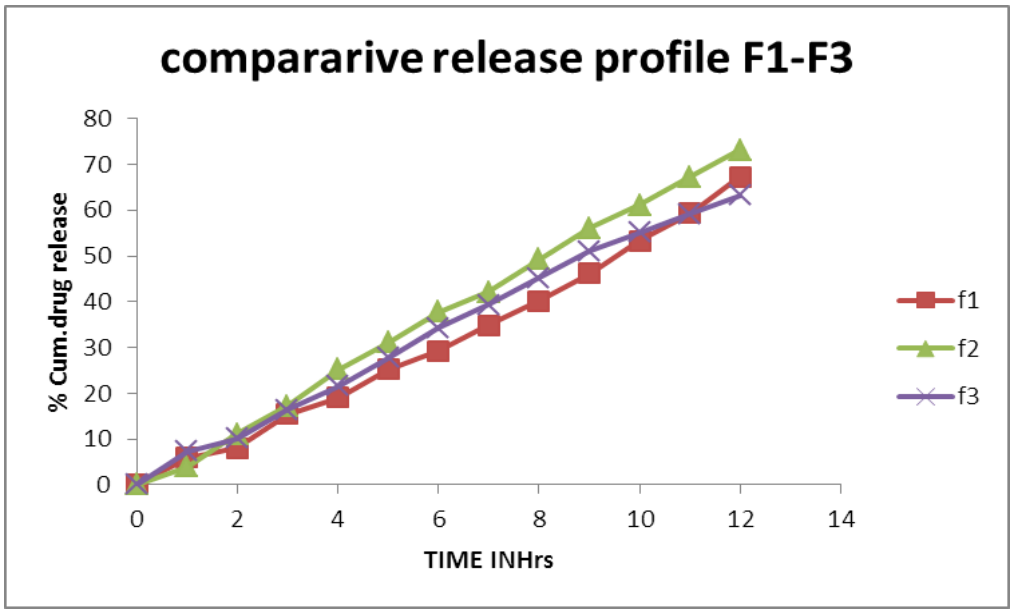


Fig. 7: Dissolution graphs of F1, F2, F3, F4 Formulations

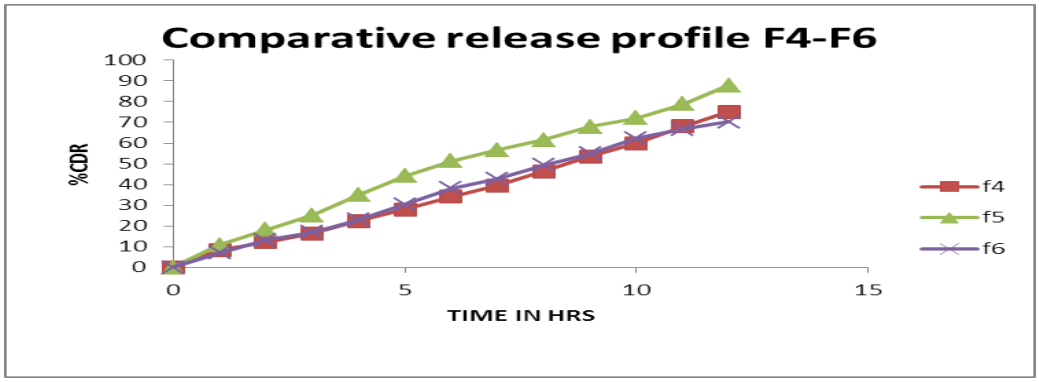


Fig. 8: Dissolution graphs of F4, F5, F6, Formulations

RELEASE KINETICS OF OPTIMIZED FORMULATION F5

Table 7: Evaluation of drug release kinetics

Batch no.	R^2 values(Correlation coefficient)				
	Zero order	First order	Higuchi	Korsmeyer- Peppas	
				R^2 value	n value
F5	0.988	0.943	0.990	0.783	0.810

Zero order

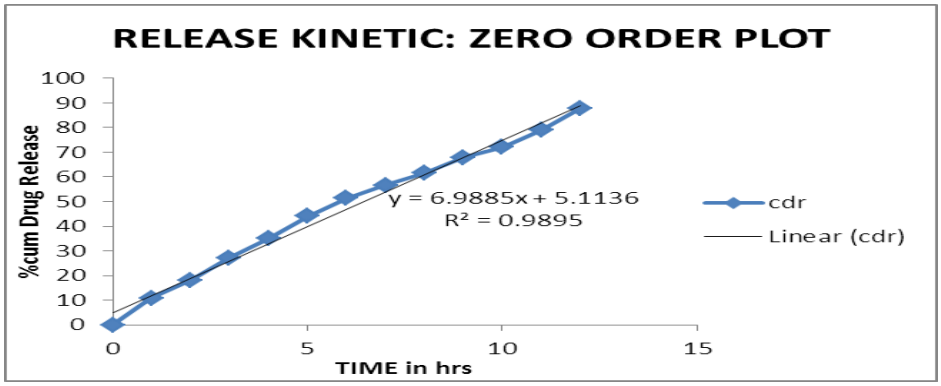


Figure 9: Zero order plots for F5 formulation

First order

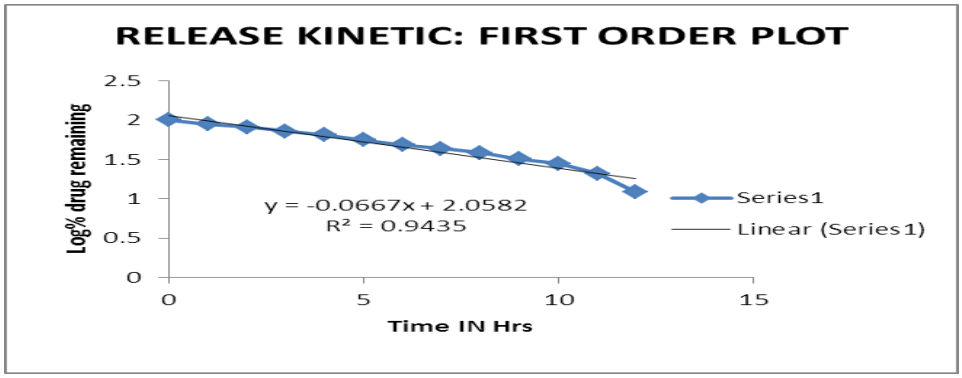


Figure 10: First order plots for F5 formulation.

Higuchi plot

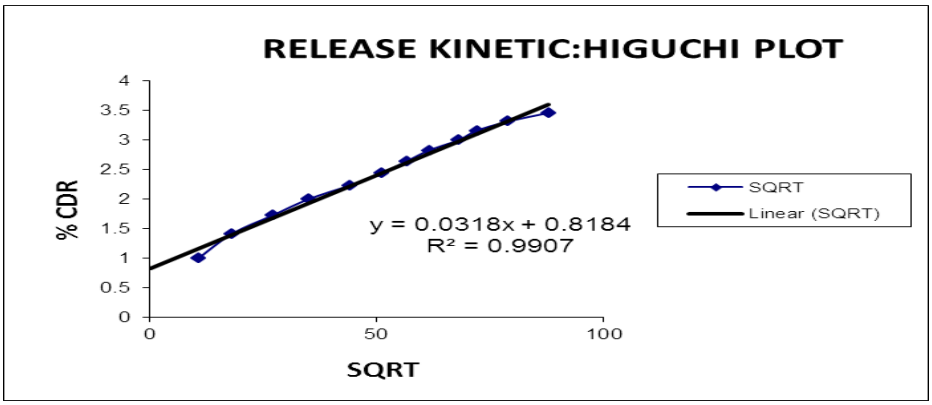


Figure 11: Higuchi plot for F5 Optimized batch

Korsemeyer-peppas model

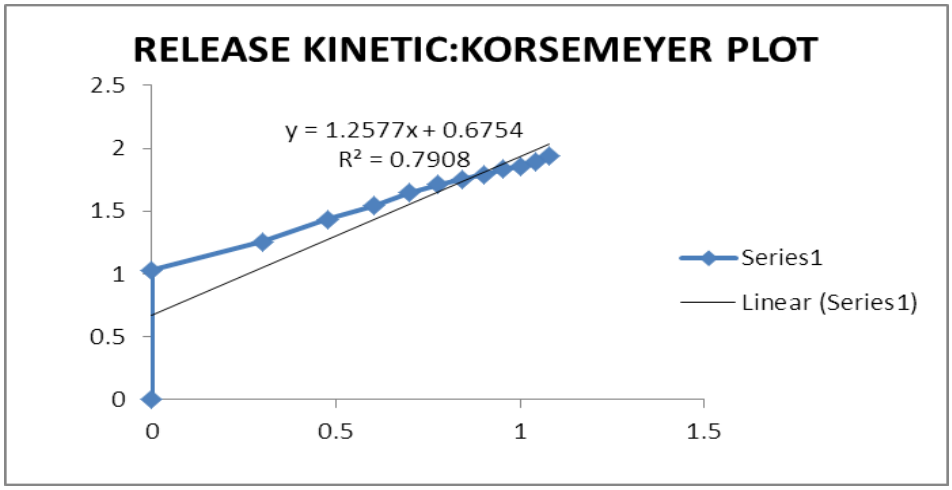


Figure 12: Korsmeyer-peppas plot for F5 Optimized batch

Stability studies: Stability studies were conducted on Metoprolol succinate sustained release matrix tablets to assess drug stability with respect to drug content and drug release characteristics. stored in the drug stability testing chamber for up to 3 months. Typical stress condition of 40 ± 2°C at 75 ± 5% RH to represent accelerated stability condition.[18]

Table 8: Tests for stability studies of the optimized formulation

Sr No	Test	Initial	Month 1		Month 3	
		25 ^{0} C, 60 % RH	25 ^{0} C, 60 %RH	40^{0}C, 75 %RH	25 ^{0}C, 60 % RH	40 ^{0}C, 75 %RH
1	**Hardness**	6.03±0.05	5.80±0.04	5.60±0.06	5.30±0.05	5.05±0.02
2	**Weight variation**	199 ± 0.05	198.80±0.02	198.50±0.06	198.20±0.4	197±0.04
4	**Friability**	0.5±0.02	0.490±0.04	0.481±0.02	0.465±0.05	0.452±0.04

Stability studies were carried out at 60 ± 2 ºC and relative humidity 75 ± 5% for these formulations are able to remain their stability for 3 month in a stability chamber. The optimized F5 were stable for one month and no significant changes were observed in Hardness, Weight variation, Friability, % drug content from after stability study

CONCLUSION

Metoprolol succinate sustained release matrix tablets were prepared successfully using HPMCK4M, Ethyl Cellulose polymer of different viscosity. According to *in vitro* release studies, the release rate was decreased with increasing viscosity and amount of polymer. The results of the study clearly demonstrated that HPMCK4M matrix tablet formulation is an effective and promising drug delivery system for once daily administration of Metoprolol succinate. The analysis of the release profiles in the light of distinct kinetic models (zero order, first order, Higuchi, Korsmeyer Peppas) led to the conclusion that, the drug release characteristics from HPMC polymer matrices follows Korsmeyer-peppas kinetics and the mechanism of drug release was diffusion by non fickian diffusion mechanism.

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