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Original Article

METOPROLOL SUCCINATE SUSTAINED RELEASE MATRIX TABLETS- FORMULATION DEVELOPMENT AND INVITRO EVALUATION

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ABSTRACT

Objective: Metoprolol succinate is a Beta 1 selective antagonist used as an Anti hypertensive, Anti angina, Anti arrhythmic. The aim of present investigation was to develop matrix tablets of Metoprolol succinate using different polymers.

Methods: Metoprolol succinate matrix tablets were prepared by direct compression and wet granulation method using different polymers. All the formulations were evaluated for weight variation, thickness, hardness, friability and dissolution.

Results: It has been studied that a matrix tablet containing hydroxyl propyl methyl cellulose polymers for oral controlled delivery of Metoprolol succinate has been formulated with greater significance; hence it was decided to check the *in-vitro* drug-polymer study in formulating a sustained release tablet for Metoprolol succinate. All the formulations are prepared by using polymers include HPMC K15M, HPMC K100M, Ghatti gum, Sodium CMC, Pectin. All the formulation is subjected to invitro dissolution studies.

Conclusion: Among all these formulations F-11 is optimized. This formulation containing 50mg of drug, 150mg of HPMC K15M, 3mg of Mg stearate, 3mg of talc, and 69mg of MCC. As the result of this study it may conclude that the formulation meet 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 bio availability.

Keywords: Metoprolol succinate, Sustained release Matrix tablets, Direct compression, Wet granulation method.

INTRODUCTION

Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drug via 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, cost effectiveness and utilization of existing conventional equipment and methods. HPMC most widely used as the gel forming agent in the formulations of solid, liquid, semisolid and controlled release dosage forms. The adjustment of the polymer concentration, the viscosity grades and the addition of different types and levels of excipients to the HPMC matrix can modify the drug release rates. The other advantages of sustained release dosage forms are patient compliance, reduction of local and systemic side effects, minimization of peaks and valleys in drug blood levels [2].

Metoprolol is a β_1 selective antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 38% and a plasma elimination half-life ranging from 1.5 to 2 hours. Administration of Metoprolol succinate in a sustained release dosage form would be more desirable by maintaining the plasma concentrations of the drug well above the therapeutic concentration.

MATERIALS AND METHODS

Materials

Metoprolol succinate was obtained from Dr.Reddy's Laboratories Ltd, Hyderabad. HPMC grades were received from yarrow chem products, Mumbai. Other materials were purchased from Signet Chem, Mumbai, India.

Methodology

Preformulation Studies

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

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 0.5ml, 1ml, 1.5ml, 2ml, 2.5ml and 3.0ml were diluted in 10ml volumetric flask with phosphate buffer to give concentrations in range of 5µg/ml to 30µg/ml respectively, absorbance was measured at 224nm.

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 0.5ml, 1ml, 1.5ml, 2ml, 2.5ml and 3.0ml were diluted in 10ml volumetric flask with phosphate buffer to give concentrations in range of 5µg/ml to 30µg/ml respectively, absorbance was measured at 228nm.

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.

$$\text{Tan } \theta = h/r$$

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 ..... Eqn. (2)

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.

Wet granulation method: All the powders were passed through 80 mesh. Required quantities of all ingredients were mixed thoroughly and a sufficient volume of granulating agent was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at 40 C for 12hrs. Once, dry the granules retained on 44 mesh were mixed with 10% of fine granules that passed through 44 mesh. Talc and magnesium stearate were added as glidant and lubricant.

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 4-6kg/cm^2.

In vitro dissolution studies

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 HPMC K100M, HPMC K15M (Wet granulation)

Ingredients	F1	F2	F3	F4
Metoprolol succinate	50	50	50	50
HPMCK100M	100	150	-	-
HPMCK15M	-	-	100	150
PVP K30	10	10	10	10
Mg Stearate	3	3	3	3
Talc	3	3	3	3
MCC	109	59	109	59
Total	275	275	275	275

Table 2: Formulations Containing HPMC K100M, HPMC K15M, Sodium CMC, Ghatti gum (Direct compression)

Ingredients	F5	F6	F7	F8	F9	F10	F11
Drug	50	50	50	50	50	50	50
HPMCK100M	100	150	-	-	-	-	-
HPMC K15M	-	-	-	-	-	100	150
Sodium CMC	-	-	100	150	-	-	-
Ghattigum	-	-	-	-	100	-	-
Mg Stearate	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3
MCC	119	69	119	69	119	119	69
Total	275	275	275	275	275	275	275

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:

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

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

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

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

Zero order

$$C = K_0 t$$

Where K_0 . is the zero-order rate constant expressed in units of concentration/time

t - is the time in hrs.

First order

$$LogC = LogC_0 - Kt / 2.303$$

Where C_0 - is the initial concentration of drug,

K - is the first order constant

t - is the time in hrs.

Higuchi

$$Qt = Kt^{1/2}$$

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

$$Mt / M\infty = Kt\, n$$

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 diffusional 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 lambda max were 224nm and 228 nm in 0.1N HCl and pH 6.8 buffer respectively and the linearity range was 5-30 mcg/ml in both the media.

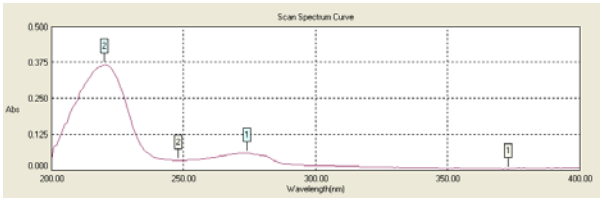


Fig. 1: λ_{max} of Metoprolol succinate in 0.1 N HCl (224nm)

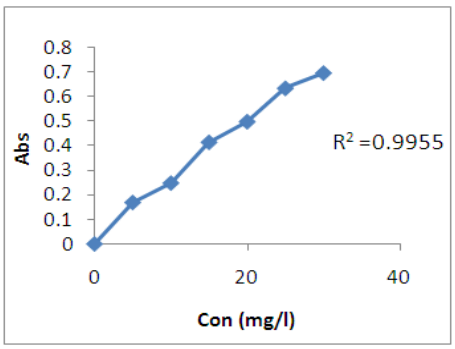


Fig. 2: Calibration curve of Metoprolol Succinate in 0.1N HCL

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 16-28 and 14-16, respectively which showed that blends from all the formulations having good flow property. The hardness and percentage friability ranged from 4-5kg/cm2 and 0.18-0.35% respectively.

Table 3: Absorbences of Metoprolol Succinate in 0.1N HCL

S. No.	Concentration	Absorbance
1	5	0.212
2	10	0.340
3	15	0.431
4	20	0.576
5	25	0.694
6	30	0.795
7	35	0.853

Table 4: Absorbences of metoprolol succinate in 6.8 ph phosphate buffer

S. No.	Concentration	Absorbance (nm)
1	5	0.169
2	10	0.248
3	15	0.414
4	20	0.498
5	25	0.634
6	30	0.696

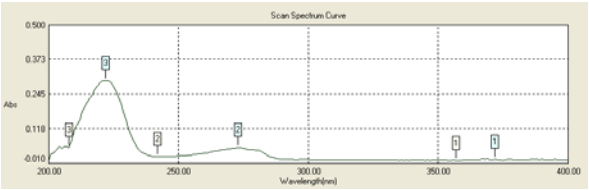


Fig. 3: λ_{max} of metoprolol succinate in pH 6.8 buffer (228nm)

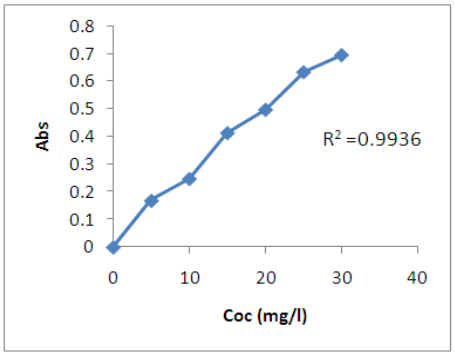


Fig. 4: Calibration curve of Metoprolol Succinate in 6.8 pH Phosphate buffer

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.

In vitro dissolution studies

Sustained release tablets of Metoprolol succinate were prepared by using HPMC polymers. 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 F4) containing HPMC K100M & HPMC K15M (wet granulation method), F5 to F6 containing HPMC K100M (By direct compression method), F7 to F8 containing Sodium CMC, F9 containing ghatti gum and F10 to F11 containing HPMC. When cumulative % drug release plotted versus time was observed that, for three of the polymers used, an increase in polymer concentration induce a decrease in the release rate. Formulation F11 containing HPMC K100 (1:3) 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.

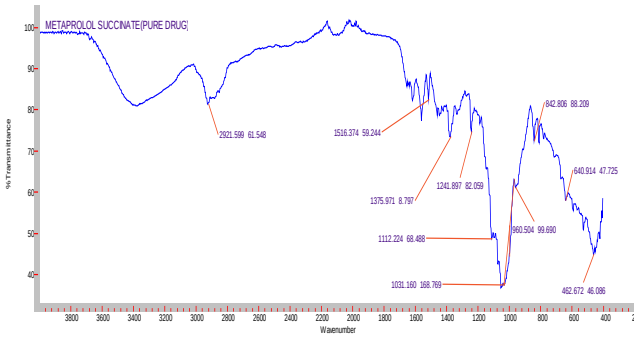


Fig. 5: FTIR spectra of pure Drug

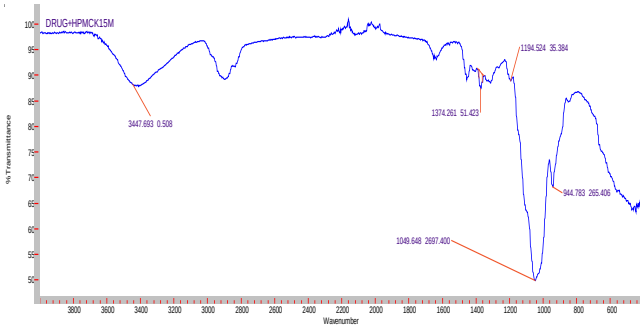


Fig. 6: FTIR spectra of pure Drug, polyme

Table 5: Pre compression parameters

Formulations	Bulk density	Tapped density	Hausners ratio	Compressibility index%	Angle of repose
F1	0.427±0.003	0.577±0.06	1.35	30.7	31.2±1.001
F2	0.43±0.036	0.663±0.04	1.54	35.6	31.6±0.5
F3	0.412±0.003	0.646±0.03	1.56	32.75	35.8±0.95
F4	0.423±0.006	0.623±0.04	1.47	33.8	32.6±0.5
F5	0.435±0.001	0.634±0.06	1.45	32.4	33.4±0.4
F6	0.421±0.001	0.652±0.05	1.54	33.4	35.9±0.458
F7	0.423±0.003	0.632±0.09	1.49	33.9	32.3±0.3
F8	0.462±0.004	0.648±0.04	1.40	34.7	34.2±0.34
F9	0.453±0.003	0.655±0.03	1.44	29.4	32.5±0.5
F10	0.441±0.002	0.648±0.06	1.46	21.4	36.8±0.529
F11	0.437±0.002	0.638±0.05	1.45	32.1	33.1±0.624

Table 6: Post compression parameters

Formulation code	Hardness	Friability	Weight variation	Thickness
F1	5.3	0.09	275	2.5
F2	5.0	0.06	275	3.0
F3	4.8	0.06	274	2.8
F4	5.1	0.11	274	2.0
F5	5.0	0.07	275	2.5
F6	4.9	0.04	275	2.5
F7	5.0	0.08	275	2.5
F8	5.0	0.02	276	3
F9	4.7	0.05	275	2.5
F10	4.7	0.04	275	2.5
F11	4.8	0.06	274	2.5

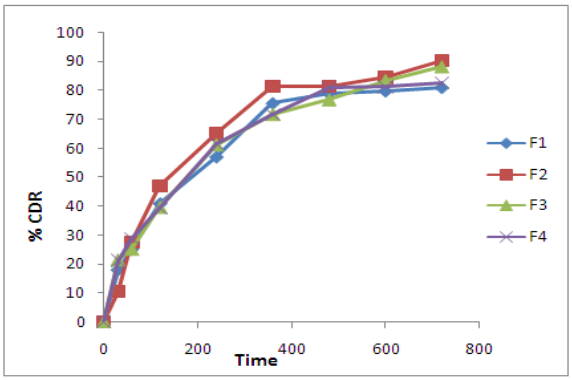


Fig. 7: Dissolution graphs of F1, F2, F3, F4 Formulations

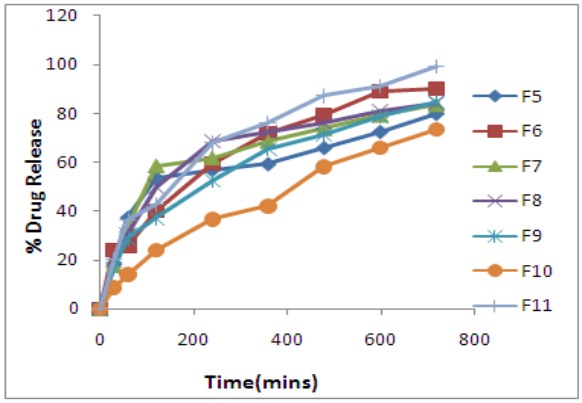
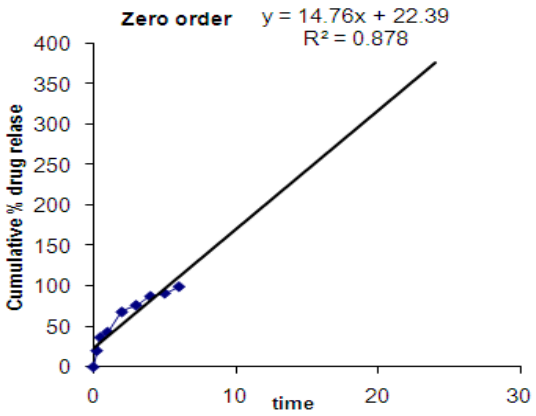
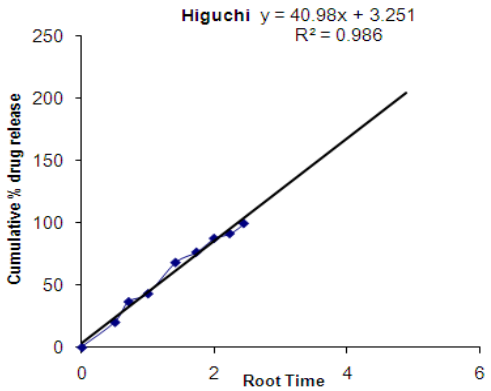
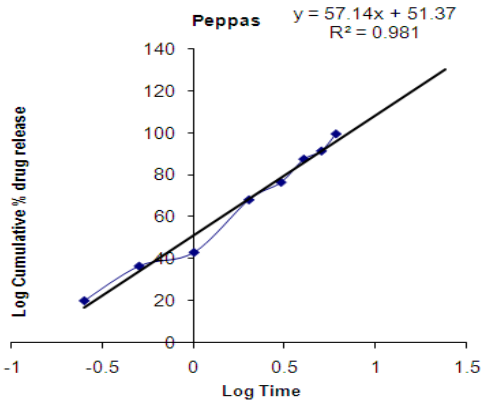


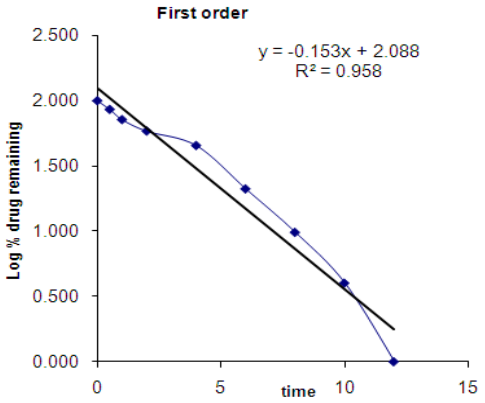
Fig. 8: Dissolution graphs of F5, F6, F7, F8, F9, F10, F11 Formulations

Release Kinetics of optimized formulation F11:









CONCLUSION

Metoprolol succinate sustained release matrix tablets were prepared successfully using HPMC 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 HPMC 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 both diffusion and erosion.

CONFLICT OF INTERESTS

Declared None

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