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Original Research

Formulation and Evaluation of Metoprolol Succinate Sustained Release Matrix Tablets

Pavani Uppu* and Rajendra Prassad Ramshetti

Chaitanya College of Pharmacy Education and Research, Kishanpura, Hanamkonda-506001, Warangal, Telangana, India

Abstract

Present study is intended to formulate and evaluate the metoprolol succinate sustained release matrix tablets to give efficient treatment of angina pectoris and to improve the patient compliance by reducing the frequency of dosage administration. Wet granulation method was used to prepare the metoprolol succinate sustained release matrix tablets using different ratios of Ethocel and HPMC K4M. Tablets were characterized for physical parameters, drug release behavior and optimized formulation was subjected to stability studies. *In vitro* drug release behavior was studied in 6.8 pH phosphate buffer USP type-II dissolution apparatus. The optimized formulation showed 99.24±1.32 % drug release in 24 hrs that clearly indicates the sustained drug release and the formulation F10 was showed good stability after three months. The drug release from above formulation followed zero order profile and the mechanism of drug release from matrix tablets followed non-Fickian release (diffusion and polymer relaxation). The results of this study suggest that combination of hydrophilic and hydrophobic polymers is a good approach to give sustained release profile when compared to that of individual polymers.

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***Corresponding Author:**
Pavani Uppu

E-mail:
pavaniramshetti@gmail.com

INTRODUCTION

Oral route of administration is the preferred one when compared to the other routes of administration due to high patient compliance, flexibility and low cost (Belgamwar *et al*., 2009). In these, development of oral controlled release dosage forms has attracted much attention in the recent years so that an optimal amount of drug is used to cure or control the condition for prolonged time (Vemula, 2015a). Among the numerous controlled releases dosage forms currently available matrix systems have gained widespread importance in controlled drug delivery due to cost-effective manufacturing technology (Radhika *et al*., 2009). Matrix drug delivery systems are of two types: diffusion/swellable systems and dissolution systems. In diffusion systems, drug release is mainly governed by the hydration of matrices followed by diffusion of the drug molecules from the hydrated layer to the surrounding bulk solution, and sometimes, partially by erosion/dissolution. With dissolution systems, drug release is mainly due to dissolution/erosion of the matrix and hence, achievement of constant drug delivery rate is easier by these systems (Goyal *et al*., 2009).

In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery system because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance (Tiwari *et al*., 2003). Among the hydrophilic polymers cellulose derivatives are generally considered to be stable and safe as release retardant excipient in the development of oral controlled release dosage forms (Bhupendra *et al*., 2010). The drug release properties of matrix device may be dependent upon the solubility of the drug in the polymer matrix, the solubility in the sink solution within the particles pore network (Tajarobi *et al*., 2011).

Metoprolol succinate is a selective Beta adrenoceptor blocking agent, for oral administration in the treatment of hypertension, angina pectoris and heart failure. It has short half-life of 3 to 7 h (Bharkatiya *et al*., 2010). When dose is missing it may causes nocturnal attack, so attention was made to develop the sustained release tablets of Metoprolol succinate by utilizing HPMC K4M, and Ethocel. The purpose of sustained release systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible and also decreases the side effects. In other words, they are able to exert a control on the drug release rate and duration. In the present study Metoprolol succinate sustained release matrix tablets were developed using combination of hydrophilic and hydrophobic polymer to achieve the better control in drug release and elucidate the effect of hydrophobic polymer on hydrophilic polymers as release modifying matrices.

MATERIALS AND METHODS

Materials

Metoprolol succinate, Ethocel (Ethyl cellulose) and HPMC K4M (Hydroxypropyl methylcellulose), were obtained from KP Labs, Hyderabad as gift samples. All reagents and solvents used were of analytical grade satisfying pharmacopoeial standards.

Preparation of Sustained Release Matrix Tablets

Sustained release matrix tablets, each containing 200mg of metoprolol succinate were prepared by wet granulation method using hydrophilic and hydrophobic polymers in different proportions. Granules were prepared using standard procedure given in Vemula, 2015b. Finally the material is to be compressed at desired compression force as to achieve perfect matrix tablets with 12 mm punches using 8-station rotary tabletting machine (Ridhhi, India). The final weight of the tablet was adjusted to 600 mg. The compositions of the matrix tablets are given in Table 1.

Table 1: Composition of metoprolol succinate sustained release matrix tablets

Formulation	Metoprolol Succinate	Ethocel	HPMC K4M
F1	200	50	-
F2	200	100	-
F3	200	150	-
F4	200	200	-
F5	200	-	50
F6	200	-	100
F7	200	-	150
F8	200	-	200
F9	200	50	50
F10	200	75	75

Note: Each tablet weight is adjusted to 600 mg using Avicel PH101 and consists of 1% magnesium stearate and 1% Aerosil.

Powder Characterization

The powder mixtures of different formulations were evaluated for bulk and tapped densities, Hausner ratio and compressibility index. The compressibility index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities and is calculated using the following formulas:

$$\text{Carr's Index} = [(\rho_{tap} - \rho_b) / \rho_{tap}] / \times 100$$

In which, ρ_b is bulk density and ρ_{tap} is tapped density. Hausner Ratio is the ratio of taped density to bulk density (Staniforth and Aulton, 2007).

Evaluation of Physical Parameters

The designed formulations were studied for their physical properties like weight variation, hardness and friability. For estimating weight variation, 20 tablets of each formulation were weighed using an Electronic weighing balance. The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability was determined on ten tablets in a Roche friabilator (Electrolab, Mumbai, India) for 4 min at 25 rpm. Accurately weigh twenty tablets and crushed in a motor; a quantity of powder equivalent powder to label claim in to 500ml volumetric flask and then add 250ml of water bath for 30 minutes with occasional stirring and remove from water bath after 30 minutes and kept sonication for 10 minutes then make up to the volume with distilled water, mix well then 1ml of solution into 10ml volumetric flask, make up the volume with water and mix well. The drug content was analyzed spectrophotometrically at 275 nm using a UV-Visible spectrophotometer.

In Vitro Dissolution Study

The *in vitro* dissolution studies were carried out using USP dissolution apparatus type-II at 50 rpm. Dissolution test was carried out for a total period of 24 hrs and the time interval was 1, 4, 8, 20, 24 hrs using 500ml phosphate buffer of pH 6.8. Samples were analyzed spectrophotometrically at 275 nm using a UV-Visible spectrophotometer.

In Vitro Release Kinetics

Cumulative percentage drug release was plotted as a function of time. The data was fitted to zero order, first order and Higuchi models to explain the pattern and the release mechanism. Koresmeyer–Peppas model is one of the mathematical expressions, used to understand the mechanism of drug release from these formulations (Talukder and Fassihi, 2008). The Koresmeyer–Peppas equation is as follows;

$$M_t / M_\alpha = Kt^n$$

In which, M_t / M_α is the fractional amount of drug released at time t, K is a kinetic rate constant, and n is the diffusional exponent that characterizes the mechanism of drug release. The values of the coefficient were calculated using linear regression analysis between log M_t / M_α and log t data obtained from drug release studies. The value of n was obtained as slope of the regression equation, and K was calculated as antilog of the intercept value (Veerareddy and Vemula 2012).

The mean dissolution time (MDT) is defined as the sum of different release fraction periods (release areas) during dissolution studies divided by the initial loading dose and is calculated by the following equation (Vemula and Veerareddy, 2013).

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M}$$

Where i is the dissolution sample number, n is the number of dissolution sample time, t_{mid} is the time at the midpoint between i and i-1, ΔM is the amount of drug dissolved between i and i-1.

Stability Studies

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions. Stability studies were done according to ICH and WHO guidelines (Mathews, 1999). The selected batch (F10) was subjected to short term stability studies which are kept at 30^0C with 60% RH and the sample were withdrawn after 90 days and evaluated for physical appearance, drug content and *in vitro* drug release.

RESULTS AND DISCUSSION

Powder Characterization

The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped), compressibility index and their values were showed in the Table 2. The results of % Carrs index and Hausner's ratio indicate the fair to passable flow properties of the powder mixture.

Table 2: Characterization of metoprolol succinate sustained release granules

Formulation	Bulk density (gm/cc^3)	Tapped density (gm/cc^3)	% Carr's Index	Hausner's Ratio
F1	0.344	0.436	21.100	1.245
F2	0.362	0.448	25.450	1.365
F3	0.368	0.518	26.103	1.397
F4	0.312	0.386	19.170	1.066
F5	0.362	0.483	25.112	1.435
F6	0.365	0.469	22.174	1.301
F7	0.344	0.436	21.100	1.245
F8	0.362	0.448	25.450	1.365
F9	0.315	0.402	21.341	1.322
F10	0.353	0.512	26.023	1.481

Evaluation of Physical Parameters

The physical properties of Metoprolol succinate sustained release matrix tablets are given in Table 3. In weight variation test, the pharmacopoeial limit for the tablets of not more than 5% of the average weight. The average percentage deviation of all tablet formulations was found to be within the Pharmacopoeial limits (Indian Pharmacopoeia, 1996). The hardness of the tablets was found to be in the range of 5.0-5.8 kg/cm^2. Conventional compressed tablets that loss less than 1% of their weight are generally considered acceptable. The percentage friability for all formulations was below 1%, indicating that the friability is within the prescribed limits. The tablets were found to contain 97.6±0.28 to 102.4±0.42 % of the labeled amount indicating uniformity of drug content. The physical properties like weight variation, thickness, hardness and friability of all formulations were complied with pharmacopoeial standards, so all the tablets were with acceptable physical characteristics.

Table 3: Physical characterization of metoprolol succinate sustained release tablets

Formulation	* Weight variation (mg)	‡ Hardness (Kg/cm^2)	† Friability (%)	‡ Drug content (%)
F1	604.57±1.56	5.0±0.25	0.38	97.8±1.74
F2	597.22±1.05	5.4±0.64	0.54	98.2±0.35
F3	601.02±1.10	5.8±0.69	0.54	101.5±0.54
F4	607.09±2.43	5.8±0.54	0.62	100.7±0.72
F5	593.05±2.51	5.4±0.44	0.43	102.4±0.42
F6	602.37±2.89	5.6±0.22	0.55	101.1±0.36
F7	592.01±2.12	5.1±0.43	0.45	97.6±0.28
F8	595.09±2.43	5.8±0.54	0.62	101.7±0.72
F9	604.05±2.53	5.3±0.42	0.44	101.5±0.23
F10	603.47±2.67	5.6±0.22	0.55	101.1±0.36

* All values represent mean ± standard deviation, n=20; † All values represent mean ± standard deviation, n=6; ‡ All values represent mean ± standard deviation, n=3

In Vitro Dissolution Study

Drug release profile of all the above formulations was determined by conducting dissolution study in 500ml of pH 6.8 phosphate buffer using USP-II (paddle) apparatus. Dissolution of Metoprolol succinate from all the formulations developed in slow and spread over 24hrs. In the present study combination of hydrophilic polymer with hydrophobic polymer were found to play a great role in controlling the release of drug from the matrix system. The cumulative percentage drug release from all the formulations were calculated and showed in Figure 1. From the *in vitro* dissolution studies, tablets containing combination of Ethocel and HPMC K4M showed better sustained release than single polymers in low concentrations. Among all the formulations, F10 tablets showed complete drug release in a sustained manner for 24 h when compared to other formulations i.e., 99.24±1.32%.

In Vitro Release Kinetics

The drug release kinetics studies revealed high correlation coefficient values for zero order than first order indicating that the drug release from matrix tablets followed zero order profile. The high regression value of Higuchi model ensured that the release of drug from matrix tablets followed diffusion mechanism. The values of K, and r^2 (correlation coefficient of the regression analysis) of zero order, first order and Higuchi models of designed formulations are given in Table 4. The n values calculated for different formulations were found in the range of 0.447 to 0.836, indicating non-Fickian release (diffusion and polymer relaxation). The MDT was higher for formulations with single hydrophobic polymer compared to single hydrophilic polymers and combination formulations, indicating more prolonged release. The values of K, n, r^2, and MDT from the dissolution data of designed formulations are given in Table 5.

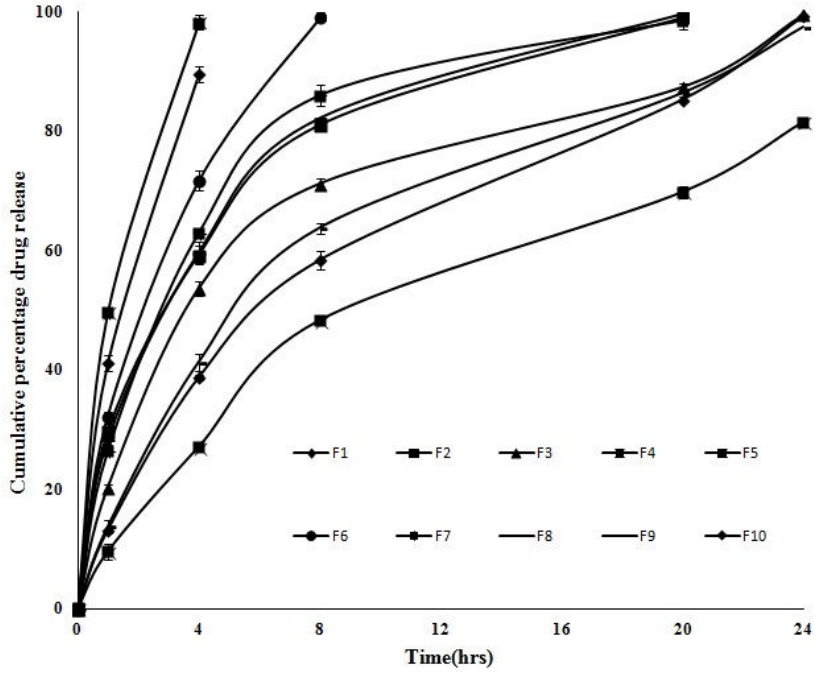

Figure 1: Release profile of Metoprolol succinate from sustained release matrix tablets

Table 4: Release kinetics of metoprolol succinate sustained release tablets

Formulation	Zero order		First order		Higuchi model	
	K_0 (mg/hr)	r^2	K_1 (hr^{-1})	r^2	K ($mg/hr^{-1/2}$)	r^2
F1	20.954	0.945	0.401	0.641	44.8	0.997
F2	4.261	0.757	0.062	0.383	22.62	0.954
F3	4.164	0.792	0.065	0.430	21.707	0.963
F4	3.542	0.927	0.069	0.564	17.25	0.985
F5	22.588	0.898	0.404	0.605	49.55	0.998
F6	11.246	0.887	0.187	0.528	34.92	0.995
F7	4.336	0.732	0.063	0.383	23.16	0.935
F8	4.243	0.829	0.067	0.465	21.69	0.969
F9	4.319	0.756	0.063	0.389	22.91	0.953
F10	4.011	0.869	0.068	0.502	20.15	0.981

K_0- Zero order rate constant, K_1- First order rate constant,
K- Higuchi model rate constant and r^2 -Correlation coefficient

Table 5: Release kinetics and MDT of metoprolol succinate sustained release tablets

Formulation	n	K	r^2	MDT (h)
F1	0.836	0.602	0.998	1.58
F2	0.451	1.502	0.972	4.46
F3	0.517	1.352	0.958	5.19
F4	0.695	1.003	0.988	7.22
F5	0.807	0.602	0.998	1.42
F6	0.453	1.612	0.991	2.63
F7	0.447	1.503	0.956	4.29
F8	0.575	1.271	0.967	5.61
F9	0.454	1.484	0.966	4.74
F10	0.637	1.161	0.975	6.25

n- diffusional exponent, K- Kinetic rate constant,
r^2 -Correlation coefficient and MDT- Mean dissolution time

Stability Studies

In view of the potential utility of the formulation, stability studies were carried out at 30^0C with 60% RH and the sample were withdrawn after 90 days. After storage, the formulation was subjected to drug assay and *in vitro* dissolution studies and there was no significant changes (Similarity factor f_2=87.96) were observed when compared with optimized formulation at normal conditions. The dissolution and assay date after stability are given in Table 6.

Table 6: Cumulative % drug release of optimized formulation after stability studies

Time (h)	* Cumulative % drug Release Initial	* Cumulative % drug release after 90 days	Similarity factor (f_2)
0	0	0	
1	13.26±0.51	12.41±1.32	
4	38.71±0.34	37.56±1.76	87.96
8	58.43±1.71	56.92±1.48	
20	85.36±1.56	83.74±0.81	
24	99.24±1.32	98.16±1.23	
*** Assay (%)**	101.1±0.36	99.24±0.63	--

* All values represent mean ± standard deviation, n=3

CONCLUSIONS

In the present investigation Metoprolol succinate sustained release tablets were developed by wet granulation method and all the formulations were showed acceptable physical characteristics. The combination of hydrophilic polymer with hydrophobic polymer in proper proportions will give a good drug release profile while compared to that of single polymers. Based on *in vitro* drug release studies, F10 formulation showed the significant level of drug release for prolong period as per USP specifications. The drug release from above formulation followed zero order profile and the mechanism of drug release from matrix tablets followed non-Fickian release (diffusion and polymer relaxation). Further the efficacy of the developed formulations has to be assessed by pharmacokinetic studies in humans.

Conflict of Interest

None Declared.

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