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Once-Daily Sustained-Release Matrix Tablets of Metoprolol Tartrate : Formulation and *In-vitro* Evaluation

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Abstract

The purpose of the present work was to design and evaluate the once daily sustained release matrix tablets of metoprolol tartrate based on hydrophilic matrices of hydroxypropyl methyl cellulose (HPMC) of different viscosity grades (Methocel K4M, K15M and K100M) and Carbopol-940. The compressed matrix tablets were evaluated for various parameters like hardness, friability, weight variation, drug content uniformity, drug-polymer interaction and in-vitro drug release studies. In-vitro drug release studies were performed in pH 6.8 phosphate buffer using USP apparatus-II (paddle) at 50 rpm. The drug release rate from higher viscosity grade matrices was slower when compared to lower viscosity grades. Increase in drug-polymer ratio from 1:1 to 1:3 resulted in decreased release of metoprolol tartrate. Inclusion of Carbopol-940 in tablets along with HPMC resulted in a further reduction in the drug release rate. Formulation containing drug-polymer ratio (1:3) with the combination of HPMC and Carbopol as matrix material showed promising results and release approximately 90% of metoprolol tartrate in 20 hours. The drug release mechanism was predominantly found to be non-Fickian (anomalous) diffusion controlled. Release profile also showed a tendency to follow near zero-order kinetics. The results of this study provided the framework for further work involving both in-vivo studies and scale-up .

Key word: *Metoprolol Tartrate; HPMC; Matrix; Sustained release*

INTRODUCTION

The purpose of this study was to design and evaluate once daily sustained release matrix tablets of metoprolol tartrate using various grades of HPMC as matrix material. Metoprolol tartrate is selective $_1$-adrenoreceptor blocking agent used in the treatment of various cardiovascular disorders and prophylaxis of migraine[1-2]. It has been classified as a class I substance according to the Biopharmaceutics Classification Scheme (BCS), meaning that it is highly soluble and highly permeable. The drug is readily and completely absorbed throughout the whole intestinal tract but is subject to extensive first pass metabolism resulting in incomplete bioavailability (about 50%). After a single oral dose, peak plasma concentrations occur after about 1-2 hours. The drug is eliminated within 3 to 4 hours, which, depending on therapeutic intention, makes it necessary to administer simple formulations of Metoprolol tartrate up to 4 times daily. Based on these properties and the well-defined relationship between the beta blocking effect and plasma drug concentration, Metoprolol tartrate lends itself to an sustained-release (SR) formulation. Metoprolol tartrate SR formulations smooth out peaks and valleys in theplasma levels and enable less frequent dosing. Dosing intervals are typically reduced to once or twice a day[3].

In the present work hydrophilic polymers such as carbomers (carbopol-940) and cellulose derivatives such as HPMC of various grades have been used as release retarding agents. Cellulose derivatives have been widely used in the formulation of hydrogel matrices for controlled drug delivery. Among them, HPMC is the most extensively utilized because of its ease of use, availability and very low toxicity. Carbomers and HPMC are hydrophilic polymers with high gelling capacities. When these polymers comes in contact with water it undergoes rapid hydration of the macromolecules in the

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solid-liquid interface followed by formation of a viscous layer. The matrix system produced as a result of this process can pass along the gastrointestinal tract without breaking up and releasing the active ingredient progressively[4].

MATERIALS AND METHODS

Metoprolol tartrate and Cellactose were gift samples from Astra-Zeneca Pharma India Limited., Bangalore and Anglo-French, Bangalore respectively. HPMC (Methocel K4M, K15M and K100M) procured commercially from Colorcon India Private Limited, Goa. Carbopol-940, magnesium stearate and talc are obtained from S.d Fine Chemicals Limited, Mumbai.

Preparation of Matrix Tablets

The sustained release matrix tablet formulation consisted of a drug, polymer and diluent. The ratios of the drug and polymer were maintained at 1:1, 1:2 and 1:3 levels, while diluent content was varied. The composition of various tablet formulations are given in Table-1. The drug, polymer and diluents were passed through a 100-mesh sieve and thoroughly mixed in a glass mortar for 15 minutes. The lubricant and glidants were added to the previous mixture and again mixed for 5 minutes. Then the tablets were directly compressed using a Cadmach Single Punch Tablet Machine. The compressed tablets were evaluated for physical parameters such as weight uniformity, hardness, friability, drug content uniformity and *in vitro* release pattern.

Drug Content Uniformity

Five tablets were powdered in a mortar, from this powder equivalent to 50 mg of drug was taken in a 100 ml round bottom flask. It was extracted by shaking with two successive 10 ml portions of methanol for 15 min each, filtered in a 25 ml volumetric flask and the filtrate was made up to the mark with methanol. Further appropriate dilutions were made and the absorbance was measured at 276 nm using a Shimadzu 1700 UV/Vis spectrophotometer against methanol blank.

In-vitro Drug Release Studies [5,6]

In vitro dissolution studies of metoprolol tartrate tablets were carried out in USP XXIII tablet dissolution test apparatus-II (Electrolab) employing a paddle stirrer rotating at 50 rpm, 900 ml of pH 6.8 phosphate buffer was used as a dissolution medium. The temperature of the dissolution medium was maintained at 37±0.5 ºC throughout the experiment. One tablet was used in each test, 5 ml sample of dissolution medium was withdrawn by means of a syringe fitted with a prefilter at specified intervals of time and was immediately replaced with fresh medium. The sample was analyzed for drug release by measuring the absorbance at 274.2 nm using UV-Visible spectrophotometer after suitable dilution.

Drug-Excipient Interaction study

There is always possibility of drug-excipient interaction in any formulation due to there intimate contact. The drug-excipient interaction studies were carried out by employing IR spectrocopic technique, which is one of the most powerful analytical techniques that offers possibility of chemical identification. The IR spectrum of metoprolol tartrate, cellactose, HPMC (K100 M), carbopol 940 and formulation F10 were obtained by KBr pellet method .

RESULTS AND DISCUSSION

The prepared matrix tablets were evaluated for parameters such as hardness, weight variation, friability, drug content uniformity and were found to be in the range of 5.60±0.59 to 5.90±0.37, 199±0.87 to 254±1.46,0.59 to 0.67, 96.32±1.41 to 99.72±.052 respectively (Table-2).

IR spectroscopy was used as a means of studying drug-excipient interaction. The IR spectrum of metoprolol tartrate exhibits peak at 1162.7 cm^{-1} is due to ether linkage, peak at 3693.9 cm^{-1} is due to (-OH-) linkage and peak at 2981.1 cm^{-1} is due to secondary amine (-NH-) confirm the structure of the drug. The IR spectrum of F10 formulation exhibited peak at 1167.7 cm^{-1} is due to ether linkage, peak at 3694.8 cm^{-1} is due to (-OH-) linkage and peak at 2926.5 cm^{-1} is due to secondary amine (-NH-). The presence of all the above peaks in the formulation confirms undisturbed structure of metoprolol tartrate and there was no drug-excipient interaction.

From the *in vitro* dissolution studies, it was observed that among the three different drug-polymer ratios used, formulations with drug-polymer ratio 1:1 showed higher drug release rates, when compared to 1:2 and 1:3. As the polymer concentration is increased, the drug release rates were found to be decreasing. Higher drug release rates were observed for formulations with lower polymer ratio. An increase in polymer concentration causes increase in the viscosity of the gel as well as the formation of the gel layer with longer diffusional path. This could cause a

decrease in effective diffusion coefficient of drug and therefore a reduction in drug release rate. Among the three grades of polymers used, the tablets prepared with lower viscosity grade polymer i.e., HPMC K4M have shown greater drug release rates when compared to drug release rates of higher viscosity grade polymers HPMC K15M and K100M.

In all the formulations studied from F1 to F10 (Fig. 1), formulations containing HPMC K15M (F7) and K100M (F8) with drug-polymer ratio 1:3 containing cellactose as a diluent have shown sustained release of metoprolol tartrate up to 15 h. Further to prolong the drug release up to 20 h, an attempt was made by incorporating Carbopol-940 (release-modifying agent) in the formulations.

Formulations F9 and F10 containing drug-polymer ratio (1:3) with polymers composition of HPMC K15M:Carbopol-940 (2:1) in F9 and with polymers composition of HPMC K100M: Carbopol-940 (2:1) in F10 were prepared. The dissolution profiles of formulations shows that F9 and F10 have sustained the release of drug for more than 20 h. The dissolution profiles of formulations containing HPMC and Carbopol-940 i.e., F9 and F10 have shown much slower release rates when compared to formulations containing HPMC alone i.e., F1 to F8.

The mechanism of drug release was studied using Peppas equation, $M_t/M = kt^n$, where, M_t/M is fractional release of the drug, 't' denotes the release time, K represents a constant incorporating structural and geometrical characteristics of the device, and *n* is the diffusional exponent and characterizes the type of release mechanism during the dissolution process. For non–Fickian release, the *n* value falls between 0.45 and 0.89, while in case of Fickian diffusion, n=0.45; for zero order release (case II transport), n=1, and for super case II transport, $n>1$[7].

The values of *n* were estimated by linear regression of log (M_t/M) versus log (t) for different formulations and was found to be in between 0.45 to 0.89 indicating that diffusion is the predominant mechanism limiting the drug release. The formulations prepared were found to release the drug by non-Fickian transport (anomalous) since the slope values for Peppas plot were found to be in the range of 0.45 to 0.89 and also follows a near zero order release profile ('r' values for F9 and F10 formulations were found to be 0.984 and 0.994 respectively). From the above discussion, it may be concluded that HPMC along with Carbopol-940 can be used as an aid to control the delivery of water soluble drug from matrix tablets. Among the various formulations of metoprolol tartrate developed, the formulations F9 and F10 appear suitable for further pharmacodynamic and pharmacokinetic evaluation in a suitable animal model.

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Table 1. Composition of various tablet formulations

FC	Ingredients (mg/tablet)								
	MT	Methocel			C-940	Cellactose	Talc	MS	Drug Polymer:
		K4M	K15M	K100M					
F1	50	50	--	--	--	100	2	2	1:1
F2	50	100	--	--	--	50	2	2	1:2
F3	50	--	50	--		100	2	2	1:1
F4	50	--	100	--	--	50	2	2	1:2
F5	50	--	--	50	--	100	2	2	1:1
F6	50	--	--	100	--	50	2	2	1:2
F7	50	--	150	--	--	50	2	2	1:3
F8	50	--	--	150	--	50	2	2	1:3
F9	50	--	100	--	50	50	2	2	1:2:1
F10	50	--	--	100	50	50	2	2	1:2:1

FC: Formulation Code, MT: Metoprolol Tartrate, C-940: Carbopol-940,
MS: Magnesium Stearate.

Table 2. Physicochemical evaluation of matrix tablets of metoprolol tartrate

FC	**Hardness**[a] (kg/cm^2)	**Friability**[b] (%)	**Weight Variation**[c] (mg)	**Drug Content**[d] (%)
F1	5.80±0.76	0.64	202±0.42	99.72±0.52
F2	5.90±0.51	0.62	200±0.25	98.10±3.00
F3	5.60±0.59	0.63	199±0.87	97.10±1.53
F4	5.90±0.49	0.59	202±0.92	97.50±2.51
F5	5.80±0.34	0.62	200±0.32	96.78±2.08
F6	5.80±0.51	0.64	201±0.60	96.32±1.41
F7	5.60±0.42	0.66	243±2.55	98.62±0.60
F8	5.80±0.67	0.63	249±0.08	99.36±0.28
F9	5.90±0.37	0.61	254±1.46	99.60±0.20
F10	5.70±0.49	0.67	249±0.66	99.60±0.76

FC: Formulation code, a Mean ± S.D., n= 6 tablets, b n= 10 tablets, c Mean ± S.D.,
n = 20 tablets and d Mean ± S.D., n=5 tablets, SD: Standard Deviation.

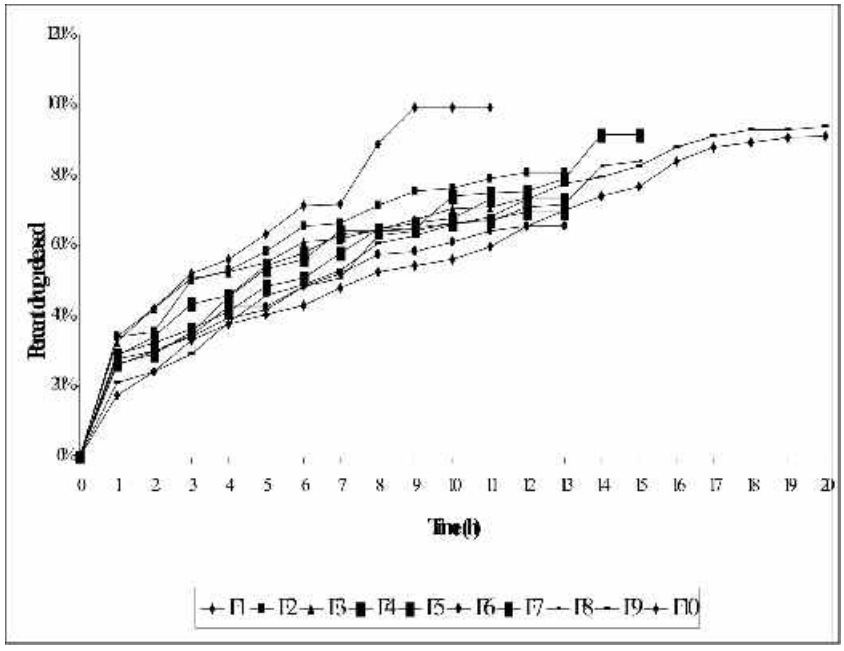

Fig. 1 : Drug release profiles of sustained release matrix tablets of Metoprolol Tartrate (F 1 to F 10) formulations.

Fl & F2: Drug -polymer ratio 1:1 & 1:2 using HPMC K4M Polymer

F3 &F4: Drug -polymer ratio 1:1 & 1:2 using HPMC K15M Polymer

F5 & F6: Drug -polymer ratio 1:1 & 1:2 using HPMC KI00M Polymer

F7 & F8: Drug -polymer ratio 1:3 using HPMC K15M & KI00M Polymer

F9&FI0: Drug -polymer ratio 1:3 with polymers composition of HPMC K15M : Carbopol-940 (2: 1) in F9 and with polymers composition of HPMC KI00M: Carbopol-940 (2:1) in F10

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