RESEARCH ARTICLE

Effect of hydrophilic and hydrophobic polymers on release kinetics of metoprolol succinate extended release tablets

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The purpose of the present work is to design and evaluate extended release matrix tablets of metoprolol succinate to reduce the dosing frequency and to improve patient compliance. The matrix tablets were prepared by the combination of hydrophilic and hydrophobic polymers, using methocel 10000 Cps in combination with ethyl cellulose 7 Cps, Eudragit® RS100, Eudragit® S100, and Eudragit® L100. The tablets were prepared by direct compression technique. Prepared formulations were evaluated for various parameters like weight variation, thickness, hardness, friability, and % drug content. Tablets were subjected to *in vitro* drug release studies. The formulations containing methocel 10000 Cps, Eudragit® L100 showed good release retardation. All the prepared formulations showed first-order release kinetics with matrix diffusion mechanism of release. The formulation containing 52.06% w/w of methocel 10000 Cps, 8.75% Eudragit® L100 offered the required release rate according to USP Pharmacopoeial guidelines. The combination of hydrophilic and hydrophobic polymers can effectively control the drug release for freely water-soluble drugs in case of extended release formulations which are the upcoming dosage forms for patient compliance in all aspects.

Key words: *Extended release tablets, hydrophilic and hydrophobic polymers, matrix tablets, metoprolol succinate*

INTRODUCTION

Oral administration is the most popular route for drug delivery and tablets are the preferred dosage forms. Tablets offer a safe and convenient method for administration of active pharmaceutical ingredients with excellent physico-chemical stability and accurate dosing. Extended release formulations are designed to allow at least a twofold reduction in dosing frequency or patient compliance or therapeutic performance when compared to a conventional immediate release dosage form.[1,2]

Metoprolol succinate is a beta selective adrenoceptor blocking agent, for oral administration in the treatment of hypertension, angina pectoris and heart failure. It has a half life of 3–7 h.

Metoprolol crosses the blood-brain barrier and has been reported in the Ceribrospinal fluid in a concentration 78% of the simultaneous plasma concentration. Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S- enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereo-selective metabolism that is dependent on oxidation phenotype.[3]

When dose is missing it may cause nocturnal attack, so attention was paid(made) to develop the extended release tablets of metoprolol succinate by utilizing various polymers like methocel 10000 Cps in combination with ethyl cellulose 7 Cps, Eudragit® RS100, Eudragit® L100, Eudragit® S100.

The drug is freely soluble in water and hence selection of release-retarding excipients is necessary to achieve the desired therapeutic efficacy. The most commonly used method of modulating the drug release is to include it in a matrix system. Matrix systems are

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widely used in oral controlled drug delivery because of their flexibility in obtaining a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.

The purpose of controlled release systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible.

Roni, Kibria *et al*., formulated alfuzosin extended release tablets using binary mixer of one hydrophilic polymer (hydroxypropylmethylcellulose) and one directly compressible Eudragit® (RSPO) by direct compression technique.[4]

Low-viscosity hydroxypropylmethylcellulose (HPMC) was used by Nair *et al.,* to prepare controlled release alfuzosin tablet (10 mg) that sustained drug release only for 12 h.[5] To obtain once daily dosage form, high viscosity HPMC (such as methocel 10000 Cps) should be used which (methocel 10000 Cps) can sustain the drug release for longer period. (Metoprolol Succinate is a freely soluble drug so that a large quantity of HPMC is required to control the release that ultimately results in tablets which are difficult to swallow. This problem can be resolved by using water-insoluble polymer in the formulation. Therefore, directly compressible Eudragit® L100, Eudragit® S100 were used in the present study along with methocel (10000 Cps). Similar binary mixer was reported by several workers who used different grades of HPMC and Eudragit® for preparing matrix tablets.[5-7]

The objective of the present study was to investigate how high-viscosity HPMC and directly compressible Eudragit® combination affect the dissolution rate of metoprolol succinate from matrices on drug dissolution.

MATERIALS AND METHODS

The following materials were used in the experiment

Metoprolol succinate, methocel 10000 Cps, Eudragit® (Eudragit® L 100) L100, and Eudragit® S100 were obtained from Natco Pharma Pvt. Ltd, Hyderabad, directly compressible lactose, talc, Mg. stearate were obtained from S.D. Fine Chemicals, Mumbai. Other chemicals used were reagent grade.

Micromeritics of formulation powder blends

Bulk density and tapped density of the powder blend was determined with bulk density apparatus. Hausner ratio and Carr's index was determined to assess the flow property and compressibility of the powder blend.[8] The flow properties of the formulation blends are presented in Table 1.

Preparation of tablets

Tablets containing Metoprolol succinate (47.5 mg) equivalent to Metoprolol tart rate (50 mg) were prepared by direct compression technique.[8,9] Drug, polymer, talc and mg. stearate were sieved through Sieve no. 80. First of all, drug, polymers and talc were mixed for 10 mins. Lubricant was added during blending. During blending total mass was taken in a laboratory-designed blender and mixed for 30 mins. Attention was given to ensure thorough mixing and phase homogenization. The appropriate amounts of the mixtures were accurately weighed in an electronic balance for the preparation of tablets and finally compressed using 16-station rotary tablet punching machine. The composition of formulations is presented in Table 2.

Physical evaluation of tablets

The prepared matrix tablets were evaluated for various parameters. Weight variation according to the USP pharmacopoeia, thickness by vernier calipers. Hardness was determined using Monsanto hardness tester, while friability was determined with a Roche friabilator (Erweka, Germany).[8,9] The physical parameters of prepared tablets are presented in Table 3.

Drug content

The prepared tablet was weighed, triturated in a mortar and the powder transferred into a 100-ml volumetric flask containing 50 ml of pH 6.8 phosphate buffer for the estimation of drug content. The contents of the flask were filtered through a filter, kept in a 100-ml volumetric flask. The residue was washed with another 40 ml of pH 6.8 phosphate buffer and the volume was made up to the mark. The sample was suitably diluted and analyzed spectrophotometrically against blank (pH 6.8 phosphate buffer) at 275 nm using double-beam UV-visible spectrophotometer.[10]

Table 1: Micromeritics of formulation powder blends

Formulation code	Bulk density g/cm³ B.D	Tapped density g/cm³ T.D	Carr's index (1-B.D/T.D)×100	Hausner ratio (T.D/B.D)
F1	0.66	0.75	13.84	1.16
F2	0.64	0.73	14.28	1.16
F3	0.63	0.72	14.51	1.15
F4	0.62	0.70	13.5	1.15
F5	0.63	0.71	13.1	1.15
F6	0.69	0.79	13.67	1.14
F7	0.61	0.70	13.55	1.15
F8	0.60	0.75	14.4	1.14
F9	0.64	0.79	13.98	1.16
F10	0.68	0.73	14.6	1.14

In vitro drug release studies

The *in vitro* dissolution studies were carried out using USP dissolution apparatus-II at 50 rpm. Dissolution test was carried out in 500 ml of pH 6.8 phosphate buffer at 37±0.5°C.[10,11] Sampling was done every hour. Then at each interval of time, 5 ml of samples were collected and replaced with the same amount of dissolution medium. The samples withdrawn were analyzed spectrophotometrically at 275 nm using *UV*-visible double-beam spectrophotometer. This drug release profile was fitted into several mathematical models to get an insight into the release mechanism of the drug from the dosage form.

Swelling behavior of matrix tablets

The extent of swelling was measured in terms of percentage weight gain by the tablets.[12,13] The swelling behavior of all the formulations was studied. One tablet from each formulation was kept in a Petri dish containing 20 ml phosphate buffer pH 6.8. At the end of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 h, the tablets were withdrawn, soaked on tissue paper and weighed, and then percentage weight gain by the tablet was calculated using formula

$$SI = \frac{Mt - Mo}{Mo} \times 100$$

Where, SI=Swelling index, Mt=Weight of tablet at Time '*t*' and Mo=Weight of tablet at time '0'

Study of release kinetics

In order to investigate the mode of release from tablets, the release data was analyzed with the following mathematical models:

Zero order equation (Q=Kot),
First-order equation {In (100-Q)=In Q-K1t},
Higuchi equation (Q=kt1/2),
Korsmeyer and peppas equation (Q=kptn),

Where Q is the percent of the drug released at time t and ko and kt are the coefficients of equation. Kp is constant, incorporating structural and geometric characteristics of the release device and n is the release exponent indicating the release mechanism.[14,15] The values of mathematical modeling and drug release kinetics (data release kinetics represented after the cumulative % release data and comparative % release profiles).

RESULTS AND DISCUSSION

As the formulation powder blends showed satisfied flow properties because of directly compressible excipients, the tablets were prepared by direct compression technique and the data is presented in Table 2.

The formulated tablets had an average weight range of 300±0.05 to 800±0.06, hardness 4±0.01 to 4±0.05kg/cm2, %drug content 99.12 to 101.20 as shown in Table 3. Percentage friability (0.01 to 0.05) and weight variation passes the test as per the USP pharmacopoeia limit.

Table 2: Composition of metoprolol succinate extended release tablets

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Metoprolol succinate	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5
Methocel 10000 Cps	126.5	242.5	416.5	416.5	416.5	416.5	416.5	416.5	416.5	416.5
Ethylcellulose 7Cps	-	-	-	40	80	-	-	-	-	-
Eudragit® RS100	-	-	-	-	-	40	-	-	-	-
Eutraged (Eudragit® S100) S100	-	-	-	-	-	-	40	-	-	-
Eudragit® L100	-	-	-	-	-	-	-	40	50	60
Directly compressible lactose	120	200	320	280	200	280	280	280	270	260
Talc	3	5	8	8	8	8	8	8	8	8
Mg. stearate	3	5	8	8	8	8	8	8	8	8
Total weight (mg)	300	500	800	800	800	800	800	800	800	800

Table 3: Physical characteristics of prepared metoprolol succinate extended release tablets

Formulation code	Average weight (mg)	Thickness (mm)	Hardness (kg/cm²)	%Friability	%Drug content
F1	300±0.05	4.01±0.010	4±0.02	0.03	100.12
F2	500±0.05	4.07±0.010	5±0.03	0.01	99.97
F3	800±0.05	3.98±0.010	5±0.01	0.04	99.24
F4	800±0.01	4.01±0.020	5±0.01	0.01	99.12
F5	800±0.02	3.99±0.030	5±0.01	0.05	99.08
F6	800±0.01	4.01±0.030	5±0.05	0.02	99.93
F7	800±0.06	4.04±0.010	5±0.02	0.04	98.98
F8	800±0.02	4.06±0.020	5±0.01	0.02	99.93
F9	800±0.04	4.01±0.040	5±0.04	0.01	99.73
F10	800±0.02	4.01±0.010	5±0.01	0.01	101.2

Mean±S.D values of all physical properties tested are shown in the table

Usually, high viscosity grades of HPMC form a strong viscous gel when they come in contact with aqueous media, and are very useful in drug delivery of highly water-soluble drugs. During dissolution study, such HPMC-based matrix tablets do not disintegrate and remain intact in the media. Hence in the present study, methocel 10000 Cps-based tablets were prepared to extend the release of metoprolol succinate.

Figure 1 shows the dissolution profiles of the F1 to F3 formulations of metoprolol succinate hydrophilic matrix tablets containing 42.16%, 48.5%, and 52.06% methocel 10000 Cps respectively. As evident in Figure 1, an increasing the amount of methocel 10000 Cps decreased the release rate of metoprolol succinate. Among F1 to F3 formulations, F3 released about 64% of the drug in about 12 h and the rate of drug release could not be extended for more than 16 h even by incorporating 52.06% of methocel 10000 Cps in the formulation. This was due to the faster swelling characteristics of the matrix tablets.

To increase the release retardation of the drug, the formulations were prepared by a combination of both hydrophilic and hydrophobic polymers.

Matrix formulations containing both hydrophilic and hydrophobic polymers (methocel 10000 Cps and EC7 Cps) were also investigated due to undesirable release profiles obtained from methocel 10000 Cps matrix tablets. Increasing amounts of EC 7 Cps (5%, 10%) were mixed separately into the fixed amount of methocel 10000 Cps (52.06%). Figure 2 shows the release profiles of metoprolol succinate from the matrices of formulations F4 and F5. The release rate of metoprolol succinate in the 12th hour was 73.01%, 96.63% from the formulations containing (5% and 10% of EC 7 Cps) respectively. The increased concentration of insoluble ethyl cellulose in the formulation F5 showed faster release rate of the drug due to erosion of the matrix. However, the required release rate was not obtained from the formulations F4 and F5.

For further investigation, matrices of formulations F6, F7, F8 were prepared using different grades of Eudragit® (Eudragit® RS 100, Eudragit® L100 and Eudragit® S 100). Among them, the formulation F8 showed better release retardation. When a drug is formulated with gel-forming hydrocolloids such as HPMC (methocel 10000 Cps), it swells in the gastric fluid affording a prolonged gastric residence time. On the other hand, Eudragit® L100 is the anionic copolymer of methacrylic acid and methyl methacrylate. The ratio of the free carboxyl group to ester is approximately 1:1. It has pH-dependent solubility (pH>6) and is readily soluble in neutral to weakly alkaline conditions and forms salts with alkalies. Eudragit® S100 is the anionic copolymer of methacrylic acid and methyl

Table 4: Release profile of formulation F10 in comparison with USP pharmacopoeial guidelines

Time (hours)	%Drug released as specified in USP Pharmacopoeia	%Drug released
1	Not more than 25%	19.418
4	Between 20% to 40%	36.028
8	Between 40% to 60%	54.803
20	Not less than 80%	88.755

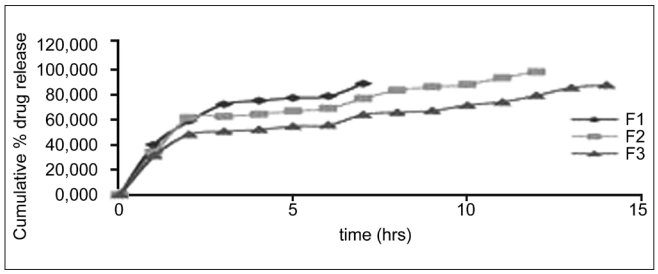

Figure 1: Cumulative % drug release for the formulations F1 to F3

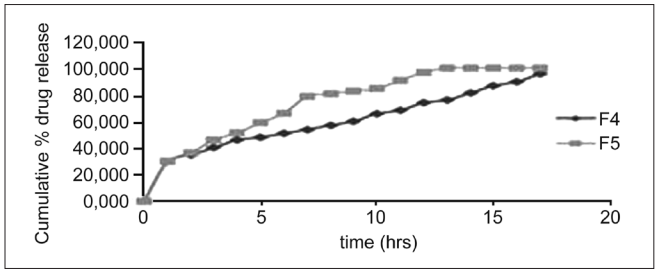

Figure 2: Cumulative % drug release for the formulations F4 and F5

Table 5: Release kinetics of metoprolol succinate extended release tablets

Formulation code	Correlation coefficient (r^2)				Peppas release exponent value (n)	First-order rate constant (k)h^{-}	T_{50} (hours)	T_{90} (hours)
	Zero order	First order	Higuchi	Peppas				
F1	0.7175	0.9436	0.9709	0.9692	0.3769	0.7325	2.2	7.2
F2	0.6178	0.9091	0.9610	0.9562	0.3600	0.6206	2.6	8.5
F3	0.6421	0.9492	0.9677	0.9544	0.3464	0.3297	4.8	16.1
F4	0.8391	0.9292	0.9878	0.9785	0.4172	0.3030	5.3	17.5
F5	0.8786	0.9580	0.9955	0.9914	0.4998	0.6897	3.2	10.5
F6	0.8766	0.9350	0.9927	0.9781	0.4736	0.6943	2.3	7.6
F7	0.8107	0.9037	0.9839	0.9674	0.3838	0.4382	3.6	12.1
F8	0.8637	0.9226	0.9951	0.9948	0.4794	0.2662	6.0	19.9
F9	0.8740	0.9571	0.9971	0.9966	0.5015	0.2639	6.0	20.1
F10	0.8983	0.9189	0.9949	0.9944	0.5462	0.2517	6.3	21.1

methacrylate. The ratio of the free carboxyl group to ester is approximately 1:2. It has pH-dependent solubility (pH>7) and is readily soluble in neutral to weakly alkaline conditions.

The water-insoluble Eudragit® RS 100 is the ammoniomethacrylate copolymer (Type B) made with copolymers of acrylate and methacrylates with quarter nary ammonium group. The ammonium groups are present as salts and make the polymers permeable.

The release profiles of formulations F6, F7 and F8 are shown in Figure 3.

The formulation F6 releases the drug at a faster rate due to the high swellability and permeability of Eudragit® RS100. In case of formulations F7 and F8 the early release rate of the drug was slow in F8 when compared to F7 and the release rate increased slowly as time proceeded because of slow swelling behavior. The swelling behavior of the formulations F6, F7, F8 was in the following order F6>F7>F8. The swelling behavior of the formulations is shown in Figure 4.

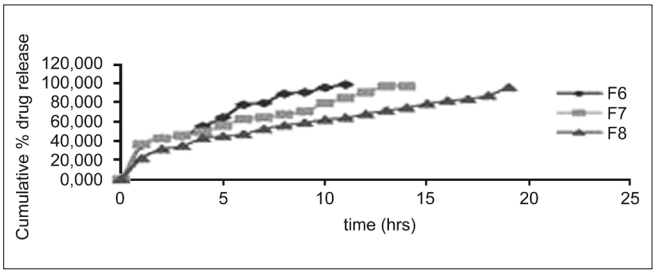

Figure 3: Cumulative % drug release for the formulations F6 to F8

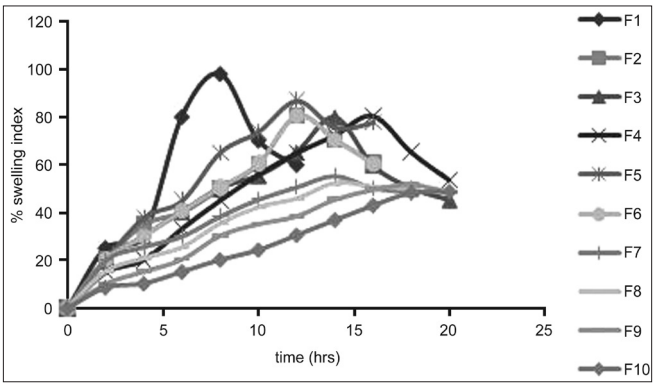

Figure 4: % Swelling index for the formulations F1 to F10

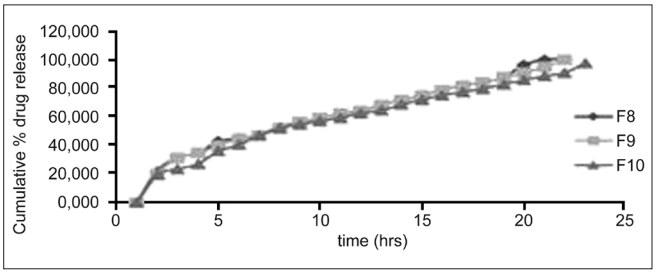

Figure 5: Cumulative % drug release for the formulations F8 to F10

So further investigation was preceded(proceeded)with the polymer Eudragit® L100. The formulations F9 and F10 were prepared with 7.5% and 8.75% of the polymer respectively. Comparative release profiles of the formulations F8, F9 and F10 are shown in Figure 5. The formulation F10 showed the best release rate and fulfilled the USP compendial requirements for release rate of extended release tablets as shown in Table 4.

The release kinetics of all the formulations are presented in Table 5. The formulations showed first-order release kinetics with Higuchi mechanism of release. F10 formulation prepared with 52.06% of methocel 10000 Cps and 8.75% of Eudragit® L100 showed good retardation.

CONCLUSION

The drug release rate was found to be dependent on the release-retarding polymer and concentration of polymer. Thus by changing (the nature i.e hydrophilic or hydrophobic and concentration of polymer), the required release rate can be attributed. This investigation concludes that the matrix tablet containing F10 formulation prepared with 52.06% of methocel 10000 Cps and 8.75% of Eudragit® L100 showed good retardation.

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