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Formulation and optimization of Metoprolol succinate extended release matrix tablet

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ABSTRACT

The aim of study was to formulate and characterize extended release matrix tablets of metoprolol succinate using hydrophilic polymers like Hydroxy Propyl Methyl Cellulose (HPMC K100M), Hydroxy Propyl Cellulose (HPC), Ethyl Cellulose, Carbopol 934 and Megnesium Stearate, and these selected matrices were directly compressed into tablet. Undesirable effects with ß blocker mainly derived from blockade of $ß_2$ receptors. The potential advantages of extended release or controlled release formulation are its ability to maintain $ß_1$ selectivity over 24hours, but with relative lack of peak plasma concentration, thus avoiding decreased clinical $ß_1$ selectivity as seen at high plasma concentration. Release kinetics evaluated by using USP-22 (Paddle) dissolution apparatus. In-vitro release study showed that ERT10 for 25mg label claimed were well suited to extend release for 20 hours with zero order release. In-vitro swelling studies revealed by Korsmeyer-Peppa's model that, the drug release governed by swelling of polymer and it is anomalous diffusion or non-fickian transport.

Key words: Metoprolol Succinate, Hydroxy Propyl Methyl Cellulose, Hydroxy Propyl Cellulose, Carbopol 934, Matrix tablet.

INTRODUCTION

Hypertension, a diseases of circulatory system, is characterized by persistently elevated systolic or diastolic pressure or both, is a major common risk factor for coronary heart disease and both varieties of stroke[1&2].

Hydrophilic polymer systems are widely used in oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance[3]. Hydroxypropylmethylcellulose (HPMC), Hydroxy propylcellulose,Sodiumcarboxymethylcellulose and Carbopols are a few representative examples of hydrophilic polymers that have been extensively used in formulation of oral controlled release system. Drug release from hydrophilic systems is known to be a complex interaction between dissolution, diffusion and erosion mechanisms. This dissolution can be depending on polymer molecular weight and thickness of different boundary layer[4]. HPMC is first choice for formulation of hydrophilic systems, providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles and utilization of existing conventional equipment and methods.

Metoprolol succinate is a selective â$_1$ adreno receptor blocking agent[5&6], used in the treatment of hypertension and angina-pectoris. As hypertension is not cured by any antihypertensive agents, the patient is likely to the under treatment for the reminder of his or her life in this point of view, extended release formulation is better choice than conventional formulation to get the rational drug therapy. Hence to improve its therapeutic efficacy and patient compliance, extended release dosage forms are needed for metaprolol succinate.

In present study, attempts were made to formulate and evaluate 25mg ER tablet of metoprolol succinate, in order to minimize the extensive metabolism of metoprolol, which results in only about 50% bioavailability.

MATERIALS AND METHODS

Metoprolol succinate was obtained from sun pharmaceuticals Ind. Ltd., as gift sample, other chemicals such as HPMC-K100, HPC (L.F&H.F), Carbopol 934, Magnesium Sterate, were of analytical grade, purchased locally and used s received.

Preparation of tablets by Dry granulation technique

All sifted ingredients mentioned as per table-I were mixed thoroughly, not less than 5 min and until to get the uniform mixed powder. Aerosil (50%) passed through the 30 mesh and mixed with that blended powder .Magnesium Sterate sifted through he 30 mesh and mix with that blended powder. Above blended powder was then slugged by tablet punching machine, keeping moderate hardness to get slugs[7&8].These slugs were then milled and passed through the 20 meshes. Sifted remaining aerosil passed through 30 mesh and mixed well with that milled granules, magnesium Stearate sifted remaining portion passed through 30 mesh and mixed thoroughly with these granules. The granules are compressed with 9x6 mm punch size by keeping average weight 150mg. After compression weight variation, thickness, friability, dissolution and assay test were carried out.

Film coating

Preparation of film coating solution was performed in laboratory coating machine. In colloidal mill, Indigo caramine and isopropyl alcohol were mixed, the added opadry white to that ongoing mixing solution and continue to mix. Finally added methylene chloride and mixed well until to get the homogenized solution. Metoprolol succinate tablet were placed in the laboratory coating pan (Kalweka series – CPS) whilst the tablet were rotating in pan and the coating fluid was applied in 3 aliquots of 5 ml each allowing 5 minutes drying at 60^0C between in each application and drying finally for 1 hour at

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Table 1: Formulation of metoprolol succinate ER matrix tablets

Ingredients	Quantity in each tablet (gms)									
	ERT1	**ERT2**	**ERT3**	**ERT4**	**ERT5**	**ERT6**	**ERT7**	**ERT8**	**ERT9**	**ERT10**
Metoprolol succinate	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75
HPMC K 100	50.0	50.0	50.0	50.0	60.0	50.0	70.0	73.0	70.0	70.0
HPC	12.0	15.0	20.0	12.0	12.0	12.0	15.0	15.0	20.0	20.0
Ethyl cellulose	20.0	30.0	30.0	20.0	20.0	20.0	25.0	28.0	25.0	25.0
PVA	-	-	-	-	-	10.0	10.0	-	-	-
Campritol	-	-	-	1.5	-	-	-	-	4.5	-
Carbopol 934	-	-	-	-	-	-	-	-	-	4.5
Avicel 102	42.6	24.6	24.6	41.0	31.6	62.6	5.1	8.6	5.1	5.1
Aerosol	0.825	0.825	0.825	0.825	0.825	0.825	0.825	0.825	0.825	0.825
Mg.stearate	0.825	0.825	0.825	0.825	0.825	0.825	0.825	0.825	0.825	0.825

HPMC K100 – Hydroxy Propyl Methyl Cellulose K100; HPC – Hydroxy Propyl Cellulose
PVA – Polyvinylalcohol ;Mg.stearate – Megnesium Stearate

Table 2: Physical parameters of granules and tablets

F. Code	B.D	Angle of repose	Hardness	Friability	Drug content	Wt. variation	LBD	TBD	Carr's index
ERT1	0.476	29.23	4-5	0.26	98.25	4	0.277	0.476	41.66
ERT2	0.474	25.08	4-5	0.26	99.16	4	0.270	0.454	40.48
ERT3	0.476	28.93	5-6	0.26	97.74	3	0.277	0.500	44.46
ERT4	0.474	24.41	4-5	0.26	99.11	2	0.271	0.458	40.85
ERT5	0.474	30.73	4-5	0.26	98.10	4	0.272	0.468	41.86
ERT6	0.475	23.59	4-5	0.27	100.60	2	0.269	0.421	35.91
ERT7	0.475	26.41	4-5	0.27	99.87	3	0.275	0.474	41.96
ERT8	0.473	27.69	5-6	0.26	98.12	3	0.269	0.469	42.54
ERT9	0.477	29.78	4-5	0.26	102.25	4	0.278	0.502	44.36
ERT10	0.476	27.13	4-5	0.26	99.85	3	0.276	0.498	44.48

F.Code- Formulation code;B.D – Bulk Density;Wt.variation -Weight variation
LBD -Loose Bulk Density;TBD -Tapped Bulk Density

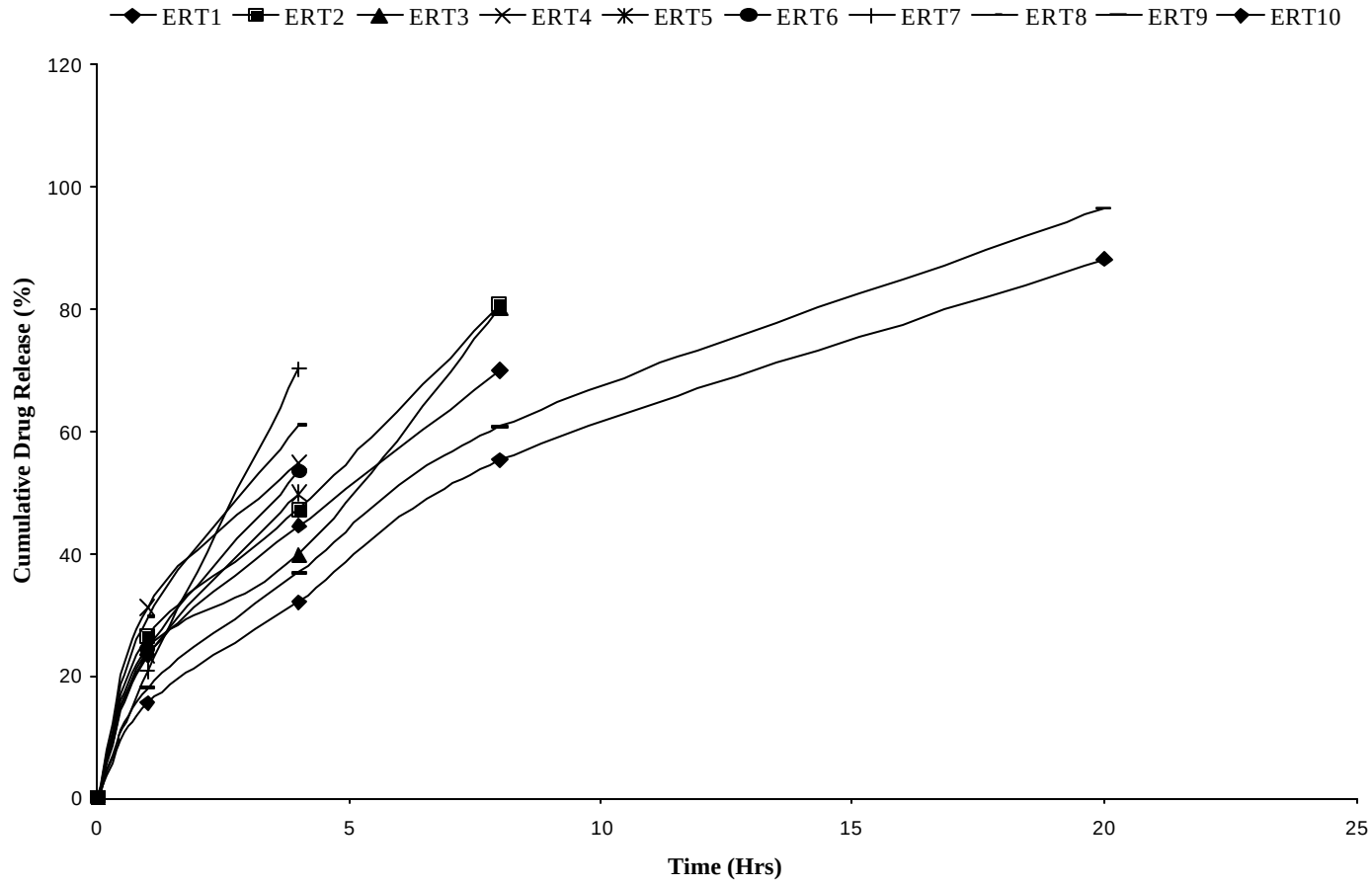

Fig 1:In-vitro release rates of metoprolol succinate ER matrix tablets

60^{0}C.

Characterization of granules

Prior to compression, granules were evaluated for their characteristic parameters. Moisture content was determined using moisture balance equipped with an IR unit (IEC, Mumbai). Angle of repose, Bulk density, Tapped density and Carr's index were also determined[9]. The drug content in the granules was determined by extracting an accurately weighed amount of powdered granules with pH 6.8 phosphate buffer. The solution was filtered through 0.45ìm membrane and absorbance was measured at 274nm after suitable dilution.

Characterization of tablets

The properties of compressed ER tablets, such as hardness, friability, weight variation and content uniformity were determined using reported procedure. Briefly, hardness and friability were determined by using Monsanto hardness tester, Roche Friability apparatus respectively. Weight variation and uniformity of drug content were performed according to the IP procedure[10]. Content uniformity was determined by weighing 10 tablets individually, and the drug was extracted in pH 6.8 phosphate buffer. The drug content was determined as described for granules.

In-vitro dissolution studies

The in-vitro dissolution studies were performed using the USP-II (Paddle) dissolution apparatus at 50 rpm. The dissolution medium consisted of 900ml of phosphate buffer pH 6.8, maintained at 37±0.5^{0}C. An aliquot (5ml) was with drawn at specific time intervals and drug content was determined by UV-visible spectrometer (DU640B, Backman, Fullerton, CA) at 274nm. The study was performed in triplicate[11].

Stability study

Any ideal dosage form apart from other dosage requirement should provide consistency of drug content and release throughout its shelf life. The ER metaprolol succinate tablets (25mg) were placed in blister packing and stored at temperature of 40^{0}C ± 2^{0}C / 75% RH ± 5% RH and room temperature. After 30 days storage period the formulation were evaluated for drug content and drug release profile in 6.8 pH phosphate buffer and physiological parameter by method described.

RESULT AND DISCUSSION

Tablets were compressed without any problem and do not require any change in ratio of excipient in formulation. Polymer coating was performed for patient compliance and palatability. The granules for matrix tablet were prepared according to the formula given in Table.1 and characterized with respect to angle of repose, bulk density and total drug content (Table.2). Angle of repose was less than 30^0 for all batches of granules indicating satisfactory flow behavior. Other parameters for granules were also determined and found to be in acceptable range. The tablets of different formulations were subjected to various evaluation tests such as weight variation, friability, hardness and content uniformity according to procedure specified in Indian Pharmacopoeia. The weight variation and friability was less than 4% and 0.3%, respectively. Good uniformity in drug content was found among different batches of tablets and drug content was more than 97%. The hardness of tablets was varied between 4-6 kg / sq.cm.

The mechanism of drug release for matrix tablets were combination of swelling, diffusion and erosion in all cases. Two formulations ERT9 and ERT10 were able to release drug according to USP specifications. But ERT10 complied with the USP specifications. The release rate of metoprolol succinate from matrix tablet followed zero order kinetics, which was obtained by plotting the graph of cumulative percentage drug release vs. time (Fig: 1).

In-vitro swelling studies revealed by Korsmeyer-Peppa's model that, the drug release governed by swelling of polymer and it is anomalous diffusion or non-fickian transport as the n values is in the range of 0.45-0.89.

Formulations were stable at 37^{0}C – 45^{0}C for a period of 1 month. There was no appreciable change in physical properties and drug content during the testing period.

CONCLUSION

In present study attempt were made to formulate 25mg extended release once daily formulation, which can provide effective drug release for 20 hours. Metaprolol succinate ER matrix tablets were prepared by Dry formulation. In vitro study showed ERT 10 for 25mg label claimed were well suited to extended release formulation. All of the batches were found to be nearly zero-zero order drug release governed by diffusion through swollen matrix and erosion of the matrix, showing the anomalous diffusion or non-fickian transports.

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