Research Article

Formulation and Evaluation of Dual Component Tablets of Metoprolol tartrate

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ABSTRACT

The aim of this study was to prepare bilayer tablet of Metoprolol Tartrate (MTP) for the effective treatment of hypertension. MTP were formulated as immediate and sustained release layer. MTP was formulated as immediate release layer by using various super disintegrants like sodium starch glycolate (SSG), cross carmellose sodium (Ac-Di-Sol) and kyron T 314. They are compared for their disintegrant efficiency. MTP was formulated as sustained release layer using hydrophilic matrix (hydroxypropylmethylcellulose [HPMC K15 M]) and Polyoxy ethylene (PEO) WSR 303. The effect of combination of hydrophilic matrix (HPMC K15M) and Polyoxy ethylene (PEO) WSR 303 on MTP release was studied. More than 90% of Diltiazem drug was released within 1 hour. HPMC K15M and PEO WSR 303 sustained the release of Diltiazem hydrochloride from the sustained release layer for 12 hrs. Diffusion exponents (n) were determined for optimized formulation (<0.5).So, predominant drug release mechanism is Fickian diffusion mechanism. The stability study showed no significant change in appearance of tablets, drug content and dissolution profile. Therefore, biphasic drug release pattern was successfully achieved through the formulation of bilayer sustained release tablets.

Keywords: Bilayer tablet, Hydrophilic polymers, Superdisintegrants, Wet granulation Method.

INTRODUCTION

Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release Drug, later, either as second dose or in an extended release Manner. Bilayer tablet is suitable for sequential release of one drug as immediate release and sustained release from Bilayer tablet in which one layer is immediate release as initial dose and second layer is maintenance dose.[1] Metoprolol tartrate, a nonselective beta adrenergic blocking agent, is widely used in the treatment of hypertension, angina pectoris and many other cardiovascular disorders. The bioavailability[2] of Metoprolol tartrate is low (20%-50%). Metoprolol tartrate is highly water soluble drug with relatively short biological half-life of 4-5 hrs and usual dose is 25 mg thrice daily. This demands high frequency of administration resulting in oscillation of plasma drug concentration, it is necessary to develop sustained release dosage form with extended clinical effect. The strong need for the development of sustained release bilayer is recognized to deliver loading does of drug in the stomach, to reduce frequency of administration and to increase the efficacy and bioavaibility of the drug, providing sustained action.

In formulation of immediate release layer of MTP, various disintegrants likes SSG, Ac-Di-Sol and kyron T 314 were used. Formulation of sustained release layer of MTP, hydrophilic matrix (HPMC K4M) was used. The effect of combination of hydrophilic matrix (HPMC K15M) and Polyoxy ethylene (PEO) WSR 303 were studied on in-vitro release of MTP from hydrophilic matrix. The aim of the present study was to design and evaluate bilayer tablet in which the immediate release layer was fabricated to release the MTP within 1 hour in stomach, then sequential release of sustained release of second layer of MTP in small intestinal for sustained action. The study was also extended to investigate the disintegrant efficiency of likes SSG, Ac-Di-Sol and kyron T 314.

EXPERIEMENTAL MATERIAL AND METHOD

Materials

Metoprolol Tartrate was kindly gifted by Lincoln Pharmaceutical Ltd. (Ahmedabad, India). Kyron T- 314 was gifted by Corel Pharma chem. (Ahmedabad, India). PEO WSR 303 and HPMC K15 M were gifted from Colorcon Asia Private Ltd (Goa, India). Starch, sodium starch glycolate, cross carmellose sodium and Polyvinylpyrrolidone (PVP) K-30 was purchased from S.D. Fine Chemicals (Mumbai, India). All other ingredients were of laboratory grades.

Preparation of Immediate Release Tablets of MTP

The immediate release tablets of Metoprolol tartrate were prepared by wet granulation method[7]. Various formulations were prepared by taking appropriate quantities of the ingredients as mentioned in the Table 1. All ingredients were screened through sieve no. 40. All the ingredients except talc and magnesium stearate were mixed in a polybag for 10 minutes. To this blend, PVP K-30 in isopropyl alcohol was added gradually and mixed thoroughly. The obtained mass was passed through sieve no.16. The granules thus obtained were air dried and passed through sieve no.20. To the dried granules, appropriate quantities of glidant were added and mixed well in polybag for 10 minutes, just before punching and processed for compression by using Round flat-faced punch of rotary tablet machine (Karnavati, India).

Calculation of dose for Metoprolol Bilayer Tablets

The immediate release part of Metoprolol bilayer tablet was calculated using following equation[5];

$$D_{IR}=\frac{C_p \times V_d}{F} \quad \text{..... (1)}$$

Where C_p is target serum level, V_d is volume of distribution and F is bioavailability factor.

The total dose of Metoprolol for a once-daily SR formulation was calculated by the following equation using available pharmacokinetic data[6]:

$$D_{Total}=Dose(1+0.693\times t/t_{1/2}) \text{ ..... (2)}$$

Where, D_t = Total dose of drug; Dose = dose of the immediate release part; t = time (hrs) during which the SR is desired and $t_{1/2}$ =half-life of the drug.

Evaluation of MTP Blend

Prior to the compression, the blends of all batches were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio[8]. The results are shown in Table 2.

Evaluation of MTP Tablet

Tablets were evaluated for weight variation, friability, hardness, drug content and disintegration test performed according to the IP '96 [9, 10]. The results are shown in Table 3.

Dissolution Test[11]

Dissolution test of MTP tablet was performed using simulated gastric fluid with USP dissolution apparatus II at 75 rpm and 37±0.5 °C temperature. Test sample (5 mL) was withdrawn at particular time interval (5, 10, 20, 30, 40, 50 and 60 mins) and replaced with fresh dissolution media maintained at 37±0.5 °C. The test sample was filtered (membrane filter, 0.45 µm) and the concentration of dissolved drug was determined using ultraviolet (UV) spectrophotometer at λmax 222 nm. This test was performed on six tablets and mean± SD calculated.

Preparation of Sustained Release Tablets of MTP

The sustained release tablets of Metoprolol tartrate were prepared by wet granulation method[12].MTP, PEO WSR-303 and HPMC K15M were mixed with other excipients for 15 min in porcelain mortar except talc, magnesium stearate and the mass was prepared using PVP K-30 as binder and isopropyl alcohol as a granulating fluid. Then passed the mass through 20 # sieve and granules were allowed to dry in oven at 40 °C for 30 min. Dried granules passed through 16 # sieve.

Then 15% fine was added in the granules and mixed with magnesium stearate and talc for 5 min and processed for compression by using round flat faced punches of rotary tablet machine (Karnavati, India).Composition of all batches was represented in Table 4. Prior to the compression, granules were evaluated for several tests.

Precompression Parameter of MTP Tablet

Angle of Repose, Bulk Density, Tapped density, Compressibility Index and Hausner's Ratio

Granules were evaluated by various parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio as per the reported methods described in previous section. The results are shown in Table 5.

Evaluation of MTP Tablets

Weight Variation, Drug Content, Friability and Hardness

Tablet weight variation, hardness, drug content and friability were measured using the I.P. method[13]. The results are shown in Table 6.

Dissolution Test[14]

The in vitro dissolution studies were carried out using USP apparatus type II at 75 rpm. The dissolution medium(900 mL) consisted of simulated gastric fluid (pH 1.2 HCl buffer) was used for the first 2 hrs and then replaced with phosphate buffer (pH 6.8) for 3 to 10 h (900 mL), maintained at 37±0.5 °C. The drug release at different time interval was measured by UV–visible spectrophotometer at 222 nm. The release studies were conducted on (six tablets in each batch).

Mechanism of Drug Release[15]

To evaluate the mechanism of drug release from MTP sustained release tablet, data for the drug release were plotted in Korsmeyer log cumulative percentage of drug released vs log time, and the exponent n was calculated through the slope of the straight line

$Mt/M1 = Kt^{n}$

Where $Mt/M\infty$ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of drug. For cylindrical matrix tablets, if the exponent $n<0.5$, then the drug release mechanism is quasi-Fickian diffusion, if $n=0.5$ then Fickian diffusion, $0.5<n<1$, then it is anomalous diffusion. An exponent value of 1 is indicative of Case-II Transport or typical zero-order and $n>1$ non-Fickian super case II. The diffusion exponent is based on Korsmeyer–Peppas equation. The results are shown in Table 7.

Preparation of Bilayer Tablets of MTP[16]

Optimized batch of MTP immediate release layer (batch MI3) and MTP sustained release layer (batch MF2) was selected for formulation of Bilayer tablet. As previously reported procedure granules of MTP layer and powder blend of MTP layer were prepared separately. One by one both layer were filled in rotary tablet machine and compressed.Composition is shown in Table 8.

Evaluation of Bilayer Tablet

Weight Variation, Friability, Hardness, Disintegration Time and Drug Content[17]

Bilayer tablets were evaluated for weight variation, friability, disintegration time, hardness and drug content. The results are shown in Table 9.

Dissolution Test[18]

The in-vitro dissolution studies were carried out using USP apparatus type II at 75 rpm. The dissolution medium (900 mL) consisted of simulated gastric fluid was used for the first 2 hrs and then replaced with phosphate buffer (pH 6.8) for 3 to 12 hrs (900 mL), maintained at 37±0.5 °C. The drug release at different time intervals was measured by U.V. spectrophotometer at 222 nm for MTP respectively. The release studies were conducted on (six tablets). In vitro drug release profile of prepared bilayer tablet was compared with theoretical drug release profile. The similarity factor was calculated for

comparison of dissolution profile of bilayer tablet with theoretical drug release profile.

Accelerated stability study of Bilayer tablet[19]

The similarity factor was calculated for comparison of dissolution profile before and after stability studies. The *f2* value should be more than 50 indicate a good similarity between both the dissolution profiles. There should be no significant difference was observed in the dissolution profile after stability studies.

RESULTS AND DISCUSSION

Precompression parameters of MTP granules

Angle of Repose, Bulk Density, Tapped density, Compressibility Index and Hausner's Ratio

Precompression parameter like angle of repose, lose bulk density, tapped bulk density, compressibility index and Hausner's ratio of all batches of MTH was evaluated. The results of physical parameters for all batches complied all specifications (Hausner's ratio < 1.25, Carr's index between 5-15, Angle of repose between 20-30) which indicate good flow properties.

Characterization of MTP tablet

Weight Variation, Friability, Hardness, Drug Content and Disintegration Time

All batches passed weight variation (between 92.5–107.5%) Friability of all batches were found <1%. Tablet of batch DI3was disintegrate faster than all other batches. Drug content of all batches was found within limit (90–110%). Disintegration and dissolution test of all batches were performed in simulated gastric fluid, represent that Kyron T-314 was found to be best among all disintegrates.

Dissolution Test

The both batch MI2 (2% of Kyron T-314) and MI3 (3% of Kyron T-314) released drug 97.54% & 100% within 60 minutes which are higher drug release than that of other batches. So, Batch MI2 was selected as best batch for preparation of immediate release layer in bilayer tablet. The results are shown in Figure 1.

Precompression parameters of MTP granules

Angle of Repose, Bulk Density, Tapped density, Compressibility Index and Hausner's Ratio

Precompression parameters like angle of repose, loose bulk density, tapped bulk density; compressibility index and Hausner's ratio of all batches of MTP were evaluated. The results of physical parameters for all batches complied all specifications (Hausner's ratio < 1.25, Carr's index between 5-15, Angle of repose between 20-30) which indicate good flow properties.

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Dissolution Test

The both batch MF1 and MF2 released drug 99.99% and 100% within 12hours which are higher drug release than that of other batches. So, Batch MF2 was selected as best batch for preparation of sustained release layer in bilayer tablet. The results are shown in Figure 2.

Evaluation of Bilayer Tablet of MTP

The average weight (n=20), drug content (n=10), friability (n=10) and hardness (n=6) of prepared bilayer tablets were found to be 499.81±1.1 mg, 101 ± 1.02%, 0.41% and 5.5 ± 0.02 kg/cm^2 respectively. The disintegration time for immediate release layer (n=6) was found to be 32 ± 0.99 secs.

Dissolution Test

Dissolution profile of prepared bilayer tablet of MTP is shown in Figure 3.In

vitro drug release profile of prepared bilayer tablet was compared with theoretical drug release profile. The similarity factor was calculated for comparison of dissolution profile of bilayer tablet with theoretical drug release profile. The f_2 value was found more than 50 (~ 73.64) that indicate a good similarity between both the dissolution profiles. Similarly, no significant difference was observed between dissolution profile of Bilayer tablet and theoretical drug release profile.

Accelerated stability study of Bilayer tablet

The similarity factor was calculated for comparison of dissolution profile before and after stability studies. The *f2* value was found more than 50 (~ 95.28) indicate a good similarity between both the dissolution profiles. Similarly, no significant difference was observed in the dissolution profile after stability studies. Hence, the results of stability studies reveal that the developed formulation has good stability. The results of accelerated stability studies are shown in Figure 4.

CONCLUSIONS

In the present investigation, bilayer sustained release tablet of Metoprolol tartrate was made. Both layers, immediate release layer as well as sustained release were optimized separately. Loading dose of Metoprolol was released within 60 minutes. This is due to the very fast disintegration of tablet (31 second), which is sufficient to relieve the symptoms of high blood pressure, immediately. Than after, maintenance dose of Metoprolol was released till 12 hours. A sustain release layer release drug, slowly till 12 hours. This is due to the good sustained release properties of HPMC and Polyoxyethylene polymer.

The release pattern of Bilayer tablet was best fitted to Higuchi kinetic model (sustained release phase) with R^2 values of 0.9975. The value of n = 0.0015 suggested that the drug is released from Bilayer sustain dosage form by Fickian diffusion mechanism. A prepared bilayer tablet passed all the Pharmacopeial specifications.

Finally, it is concluded that by adopting biphasic drug release pattern in a single dosage form can be obtained which could improve patient compliance and give better disease management.

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Table 1: Optimization of immediate release tablets of metoprolol tartrate

Batches	Angle of repose	Bulk density	Tapped density	Carr's index (%)	Hausner's ratio
MI1	24.02	0.39	0.43	9.30	1.10
MI2	**21.90**	**0.40**	**0.43**	**6.97**	**1.075**
MI3	**21.12**	**0.42**	**0.45**	**6.66**	**1.071**
MI4	**25.96**	**0.41**	**0.46**	**10.86**	**1.12**
MI5	**23.55**	**0.42**	**0.46**	**8.69**	**1.09**
MI6	25.23	0.43	0.48	10.41	1.11

Table 2: Precompression Parameter of Immediate Release Formulations

Formulations	MI1	MI2	MI3	MI4	MI5	MI6
Drug	25	25	25	25	25	25
Kyron T-314	2	4	6	-	-	-
Ac-di-sol	-	-	-	2	4	6
Lactose	157	155	153	157	155	153
PVP K-30	10	10	10	10	10	10
Mg-stearate	4	4	4	4	4	4
Talc	2	2	2	2	2	2
Total Wt.	200	200	200	200	200	200

Table 3: Physical Parameters of Tablets Containing Metoprolol Tartrate

Batches	Disintegration time (seconds)	Hardness (kg/cm^2)	Weight variation (mg)	Drug Content (%)	Friability (%)
MI1	76 ± 3.65	5.5± 0.15	202± 0.98	98 ±1.99	0.43
MI2	68± 5.53	5 ± 0.52	204 ±1.88	96 ±4.01	0.50
MI3	58± 3.96	6 ± 0.49	201± 0.49	101±0.98	0.36
MI4	100± 3.26	5.5 ± 0.1	197 ± 1.51	103±3.02	0.44
MI5	89 ± 4.58	5 ± 0.48	202 ± 1.02	101 ±1.0	0.51
MI6	70± 4.12	6 ± 0.6	199 ± 0.51	98 ±2.04	0.35

Table 4: Composition of Sustained Release Formulations

Formulations	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
Drug	50	50	50	50	50	50	50	50	50
HPMC K-15M	45	60	75	45	60	75	45	60	75
PEO WSR-303	30	30	30	45	45	45	60	60	60
Lactose	151	136	121	136	121	106	121	106	91
PVP K-30	15	15	15	15	15	15	15	15	15
Talc	6	6	6	6	6	6	6	6	6
Mg-stearate	3	3	3	3	3	3	3	3	3
Total Wt.	300	300	300	300	300	300	300	300	300

Table 5: Precompression Parameter of Factorial Design Formulations

Batch	Angle of repose	Bulk density	Tapped density	Carr's index (%)	Hausner's ratio
MF1	23.54	0.34	0.37	8.10	1.08
MF2	20.96	0.35	0.37	5.40	1.057
MF3	21.10	0.34	0.36	5.55	1.058
MF4	25.78	0.36	0.40	10.0	1.11
MF5	23.13	0.35	0.38	7.89	1.085
MF6	26.12	0.33	0.37	10.81	1.12
MF7	22.02	0.37	0.40	7.50	1.081
MF8	22.73	0.36	0.39	7.69	1.083
MF9	24.78	0.33	0.36	8.33	1.09

Table 6: Physical Parameters of Factorial Design Formulations

Batches	Weight variation (mg) (n=20)	Hardness (kg/cm^2) (n=6)	%Friability (n=10)	Drug content (%)(n=10)
MF1	198 ± 1.04	5.5 ± 0.1	0.40	99 ± 1.2
MF2	201 ± 0.51	6 ± 0.51	0.32	101± 0.01
MF3	202 ± 1.05	5.5 ± 0.2	0.40	99 ± 1.1
MF4	201 ± 0.49	6 ± 0.51	0.34	101 ± 0.01
MF5	198 ± 1.1	5 ± 0.49	0.47	98± 2.05
MF6	202 ± 1.05	6 ± 0.48	0.33	103± 3.1
MF7	199 ± 0.52	5± 0.5	0.46	101 ± 0.02
MF8	197 ± 1.52	6 ± 0.48	0.33	97 ± 2.98
MF9	203 ± 1.48	5.5 ± 0.1	0.39	102± 0.57

Table 7: Kinetic Modeling Data of Batch MF2

Composition	Immediate release formulation Batch (MI3)	Sustained release formulation Batch (MF2)	Bilayer sustained release formulation(MBT)
Drug	25	50	75
Kyron T-314	6	-	6
HPMC K-15M	-	60	60
PEO WSR-303	-	30	30
Lactose	153	136	289
Starch paste	10	-	10
PVP K-30	-	15	15
Mg-stearate	4	6	10
Talc	2	3	5
Total wt.	200	300	500

Table 8: Composition of Bilayer Sustained Release Tablets of Metoprolol Tartrate

Model	Zero-order	First-order	Higuchi	Hixon- crowell	Korsmeyer-peppas
R^2	0.9945	0.8993	0.9826	0.9945	0.9971

Table 9: Physical Properties of Bilayer Tablet of Metoprolol Tartrate

Formulation	Weight variation (mg) (n=20)	Disintegration time (sec) (n=6)	Hardness (kg/cm^2) (n=6)	%Friability (n=10)	Drug content (%) (n=10)
MBT	499 ± 1.1	32 ± 0.99	5.5 ± 0.02	0.41	101± 1.02

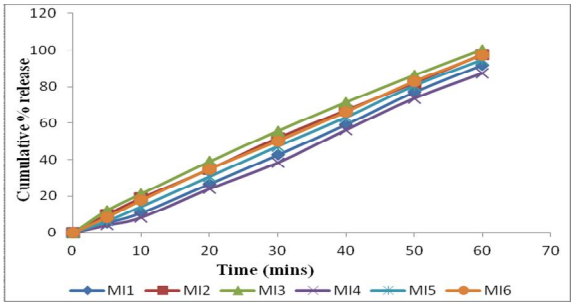

Fig. 1: In vitro release profile of different immediate release formulations of Metoprolol tartrate

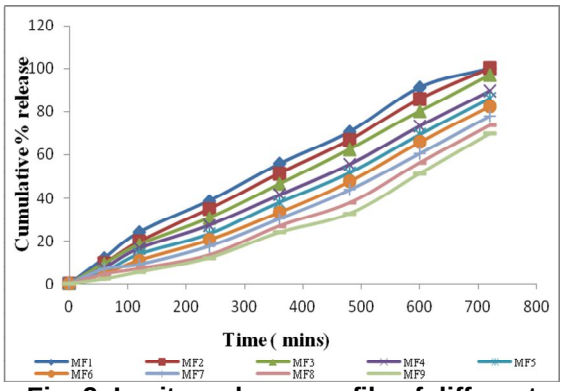

Fig. 2: In vitro release profile of different sustained release formulations of Metoprolol tartrate

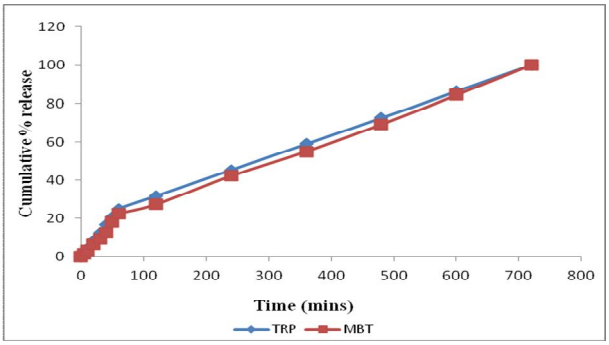

Fig. 3: Comparison of Theoretical release profile (T.R.P) with Metoprolol bilayer tablet (MBT)

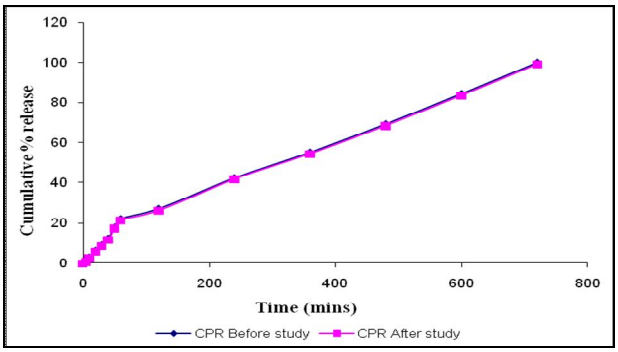

Fig. 4: Results of Stability study of Metoprolol tartrate bilayer formulation

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