Journal of Pharmaceutical Research Vol. 12, No. 2, April-June 2013 : 86-93.

FORMULATION DEVELOPMENT AND IN VITRO EVALUATION OF METOPROLOL SUCCINATE EXTENDED RELEASE MATRIX TABLETS BY OPTIMIZING HYDROPHILIC POLYMERS

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Received on : 04.04.2013 Revised : 29.05.13 Accepted : 01.06.13

ABSTRACT
Metoprolol Succinate extended release matrix tablet was formulated for the treatment of hypertension by direct compression method using hydrophilic polymers. Formulations F1-F6 were developed using HPMC K4M & K15M; F7-F12 were developed using HPMC K15M & K100M and F12 (A-D) for optimization. The physicochemical and *in-vitro* release characteristics of all the formulations were investigated and compared. In Preformulation studies physicochemical interaction between the drug and excipients were determined by using FTIR. Pre-compression properties of all formulations indicated good flow and compression properties (angle of repose<30°, Compressibility index<17% and Hausner ratio <1.25). Post-compression properties like weight variation, friability, Drug content (between 90-110%) for all batches was within USP limits. Among all batches, F12B release pattern conform to USP specification for extended release drug delivery systems and when compared with innovator product, its similarity factor (f_2=95.23) indicates the best optimized formulation. It can be concluded that desired extended release of hydrophilic drug is also viable with hydrophilic polymer alone. F12B dissolution data was applied to various model fitting kinetic equations like Zero-order, First order, Higuchi and Korsmeyer-Peppas. Correlation coefficent (r^2 =0.9989) and diffusion release exponent (n=0.5865) confirmed that anomolous (non-fickian) diffusion was the main drug release mechanism.

Keywords: *Metoprolol Succinate; Direct compression; Preformulation; Precompression; Postcompression.*

INTRODUCTION

Conventional oral drug delivery systems are slowly fading away in the market owing to various disadvantages. These delivery systems produce fluctuation of drug plasma level that either exist at safe therapeutic level or quickly falls below the minimum effective level. This effect is usually dependent on the biological half life, frequency of administration and release rate. It is recognized that many patients can benefit from drugs intended for chronic administration by maintaining the plasma level within the safe effective range[1]. Extended oral drug delivery systems are highly recognized today for their benefits, as they overcome the disadvantages of conventional drug delivery system[2].

To be a successful, extended-release product the drug must be released from the dosage form at a predetermined rate in gastrointestinal fluids, to maintain sufficient gastrointestinal residence time and be absorbed at a rate that will replace the amount of drug being metabolized and excreted. Extended drug delivery systems are used in the treatment of chronic rather than the acute condition and they possess a good margin of safety[3].

Metoprolol succinate is a cardio selective â$_1$- blocker used in the treatment of hypertension, angina pectoris and heart failure. It is available commercially in 25mg, 50 mg strength as immediate release tablets. Its half life is about 3-7 hours. Its bioavailability is 50% following oral administration. It has been reported that conventional dosage forms increase the plasma concentration of Metoprolol above the level required for maximum â$_1$ blockage (>300 nM). A therapeutic level β blockage is achieved when plasma concentration is in the range of 80-300 nM. Higher concentration produces more β2-blockage but little additional β_1-blockage. Lower concentration may result in suboptimal β_1-blockage. To meet the need for effective and well tolerated β_1-blockage, an extended release formulation of Metoprolol Succinate is beneficial to meet the objective of providing once daily dosing that maintains therapeutic plasma concentration and avoids the extreme peak and trough characteristic of Metoprolol immediate release formulation[4].

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Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because it is easy to achieve a desirable drug-release profile; cost-effective and they have broad US Food and Drug Administration acceptance[5]. Among the hydrophilic polymers, cellulose derivatives such as methylcellulose, hydroxylpropyl methylcellulose are generally considered to be stable and safe as release retardant excipient in the development of oral extended release dosage forms. HPMC is widely used in oral and topical formulations. In oral product, HPMC is primarily used as a tablet binder and in film-coating solution.

The main objective of the present study was to develop Metoprolol Succinate ER matrix tablets using HPMC in different viscosities. The formulations were prepared by direct compression and investigated for physicochemical and release characteristics.

Direct compression is a process by which tablets are compressed directly from the mixture of drug and excipients, without any preliminary treatment[6]. A simple formula is considered to be composed of an active ingredient, a diluents and lubricant[7].

Tablet manufacturing by direct compression process increased steadily over the years. It offers advantages over the other manufacturing processes for tablets, such as wet granulation and provides high efficiency[8]. Direct compression is more economic, as it reduces the cycle time and is more adaptable for the GMP requirements. On the other hand wet granulation, not only increases the cycle time, but also has certain limits imposed for thermo labile and moisture sensitive active ingredients. So pharmaceutical industry is now focusing increasingly on direct compression process [9-10]. The unnecessary exposure of any drug to moisture and heat can never be justified[11]. Tablets produced by direct compression method give lower microbial levels than those prepared by the wet granulation method. The compaction process exerts lethal effect on the survival of microorganisms[12].

MATERIALS AND METHODS

Materials

Metoprolol succinate USP obtained as a gift samples from Sania Humancure Pvt. Ltd., Gadarpur (Udham Singh Nagar), Uttarakhand, India. HPMC K4M, HPMC K15M, HPMC K100M were obtained from Colorcon Asia Pvt. Ltd. (Goa, India). Sodium Stearyl Fumarate and Colloidal Anhydrous Silica and Microcrystalline Cellulose (Avicel pH 102) were purchased from SD Fine Chemicals (Mumbai, India). PEG 6000 purchased from Dow Chemicals (Mumbai, India). Ethylcellulose, Isopropyl Alcohol, Talc and Titanium dioxide were purchased from G.R.Traders, (Hyderabad, India). All other chemical were of high analytical grade obtained from Venkateswara Scientific Traders (Hyderabad, India). Double distilled water was used throughout the study.

Methods

Calibration curve

The UV spectral analysis [13] of drug sample was carried out; the $\ddot{e}_{max}$ was observed at 222nm as shown in Figure 1. The calibration curve was prepared by taking accurately 100 mg of Metoprolol Succinate in 100 ml volumetric flask and the volume was made up with water and ultra sonicated for 10 min to ensure complete solubilization of drug, which gave a concentration of 1000 µg/ml, this was stock I. From this 10 ml was taken and diluted to 100 ml which gives a concentration of 100 µg/ml solution, this is stock II. From the above stock II solution 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 ml were withdrawn into 10 ml volumetric flasks and diluted up to the volume with 6.8 pH phosphate buffer solution. Absorbance of these solutions was measured at 222nm using (UV-3000+, Lab India) U.V-Visible Spectrophotometer. Drug content was calculated using the equation (y = 0.0323x + 0.0136) generated from Beer Lambert's Calibration curve in the linearity range of 5-30 µg/ml (r^2 = 0.999). The calibration curve is shown in Figure 2.

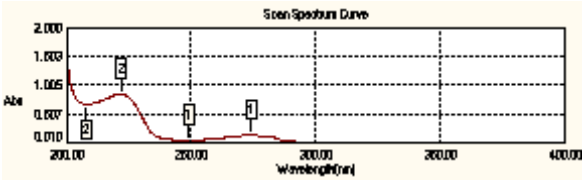

Fig. 1: *Spectrum of Metoprolol Succinate*

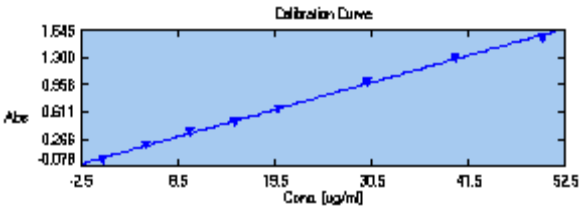

Fig. 2: *Calibration curve of Metoprolol succinate USP.*

Drug-Excipient Interaction

The physicochemical incompatibilities of the drug and the excipients were tested by FTIR (Model 8400, Shimadzu). The samples such as Metoprolol Succinate and excipients were mixed in definite ratios, triturated in mortar and subjected to IR spectral analysis to obtain IR spectra for analysis and interpretation[14]. IR spectra are shown in Figure 3.

Tablet Prep aration

The tablets were prepared by direct compression method[15]. #40 ASTM sieve was used throughout the process. Firstly the Drug, HPMC K4M, HPMC K15M, HPMC K100M, Avicel pH 102 and Colloidal anhydrous silica were sifted through sieve #40. The sifted material was put in large size polybag and blended for 25

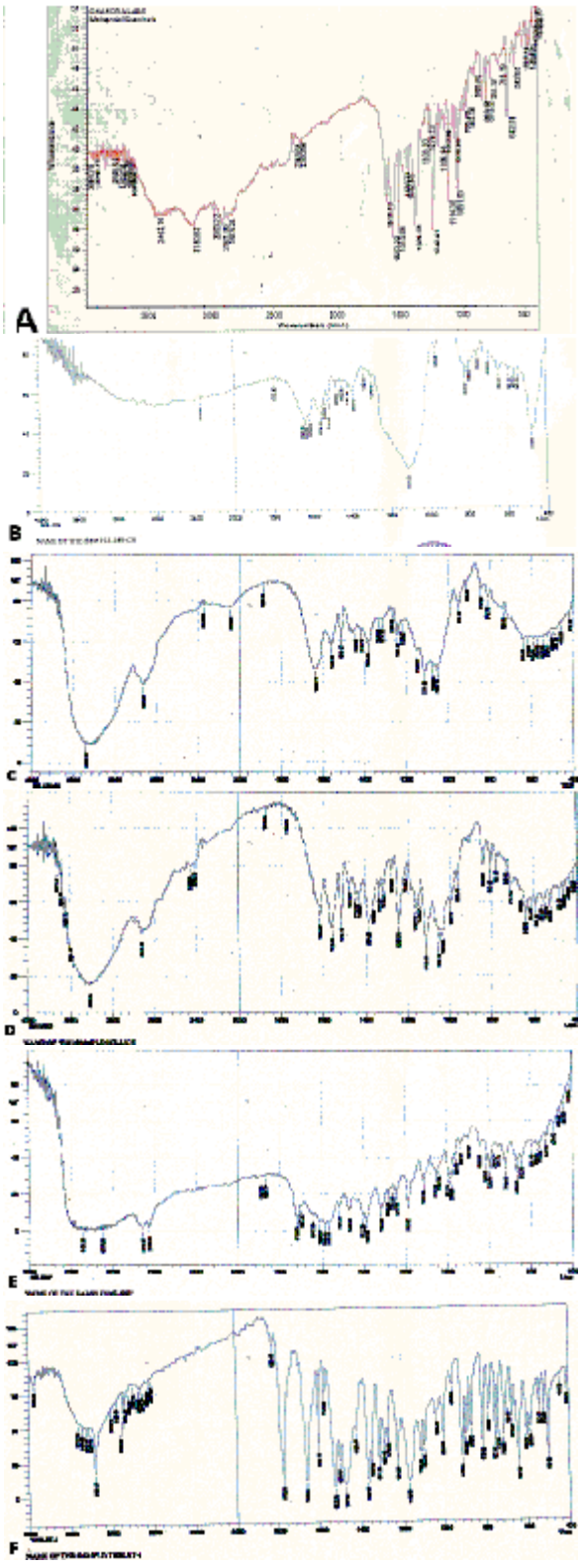

Fig. 3: FTIR Spectrum of pure drug Metoprolol Succinate(A), Drug+Colloidal anhydrous mixture(B), Drug+HPMC mixture(C), Drug+MCC mixture(D), Drug+Sodium Stearyl Fumarate mixture(E), F12B tablet mixture(F)

minutes and then Sodium Stearyl Fumarate was added to the materials in the polybag for lubrication and blended for 5 minutes. The lubricated blend was then compressed on single station tablet press (Cadmach Machinery, Ahmadabad, India). The total weight of uncoated tablet was 250 mg. Target weight of coat per tablet was 5mg. The composition of various formulations is given in Table 1, 2 & 3.

Table 1: *Composition of Metoprolol Succinate tablets (using HPMC K4M & K15M)*

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6
Metoprolol Succinate USP	23.75	23.75	23.75	23.75	23.75	23.75
Ethyl Cellulose	75	50	50	50	25	-
HPMC K4M	150	150	125	100	100	100
HPMC K15M	-	25	50	75	100	125
Sodium Stearyl Fumarate	1.25	1.25	1.25	1.25	1.25	1.25
Total wt of tablet	250	250	250	250	250	250
Film coating target wt	5	5	5	5	5	5

Table 2: *Composition of Metoprolol Succinate tablets (using HPMC K15M & K100M)*

Ingredients (mg/tab)	F7	F8	F9	F10	F11	F12
Metoprolol Succinate USP	23.75	23.75	23.75	23.75	23.75	23.75
HPMC K15M	125	100	75	50	10	-
HPMC K100M	100	125	150	175	175	175
Colloidal Anhydrous Silica	-	-	-	-	15	25
MCC (Avicel pH 102)	-	-	-	-	25	25
Sodium Stearyl Fumarate	1.25	1.25	1.25	1.25	1.25	1.25
Total wt of tablet	250	250	250	250	250	250
Film coating target wt	5	5	5	5	5	5

Table 3: *Composition of Metoprolol Succinate tablets (optimization of F12)*

Ingredients (mg/tab)	F12A	F12B	F12C	F12D
Metoprolol Succinate USP	23.75	23.75	23.75	23.75
HPMC K100M	175	175	175	175
Colloidal Anhydrous Silica	27	28	28.25	28
MCC (Avicel pH 102)	23	22	22	22.25
Sodium Stearyl Fumarate	1.25	1.25	1	1
Total wt of tablet	250	250	250	250
Film coating target wt	5	5	5	5

Coating of t ablets

The compressed tablets obtained by direct compression method were coated using coating solution in R&D coater by pan coating process[16].

Preparation of film coating solution

HPMC 15 cps was added to Isopropyl Alcohol, constantly stirred for 10 minutes in a vessel until it dissolved completely. The solution was then filtered through 200-mesh nylon cloth. Talc and Titanium dioxide were sifted through 100 mesh sieve and added to above solution, and mixed by constant stirring for 5 minutes. Polyethylene Glycol was added to the above solution with constant stirring for 5 minutes. Finally Methylene chloride was added to the above solution

with constant stirring being continued for 15 minutes. The above solution was filtered through nylon cloth (200-mesh) and collected in a suitable container.

Evaluation of Powder blend

Angle of Repose

The angle of repose of powder blend was determined by the funnel method[17]. The accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the blend. The accurately weighed blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

Tan è = h/r —— eq (1)

Where h and r are the height and radius of the powder cone respectively. The values are given in Table 4.

Table 4: *Properties of Metoprolol Succinate Powder Blend**

Batch code	Angle of repose( )	LBD(g/ml)	TBD(g/ml)	Carr's Index (%)	Hausner Ratio	Drug content
F1	26.51±0.01	0.478±0.89	0.576±0.88	17.01±0.38	1.21	95.60±0.08
F2	27.11±0.02	0.435±0.23	0.526±0.80	17.30±0.03	1.21	98.83±0.07
F3	28.45±0.04	0.441±0.46	0.531±0.76	17.13±0.74	1.20	97.44±0.03
F4	29.72±0.07	0.432±0.77	0.523±0.26	17.78±0.20	1.21	104.61±0.02
F5	25.85±0.04	0.431±0.16	0.524±0.09	17.74±0.80	1.22	102.92±0.06
F6	26.40±0.02	0.429±0.98	0.514±0.64	16.53±0.69	1.20	98.86±0.05
F7	24.85±0.08	0.435±0.02	0.518±0.66	16.02±0.31	1.19	102.20±0.03
F8	25.42±0.02	0.44±0.66	0.529±0.19	16.82±0.41	1.20	100.24±0.07
F9	28.51±0.01	0.559±0.13	0.479±0.70	14.31±0.12	0.86	99.34±0.07
F10	27.11±0.02	0.549±0.27	0.471±0.50	14.20±0.76	0.86	105.71±0.09
F11	24.45±0.04	0.545±0.65	0.471±0.81	13.57±0.79	0.86	102.92±0.02
F12	25.72±0.07	0.552±0.68	0.479±0.37	13.22±0.46	0.87	97.86±0.03
F12A	25.85±0.04	0.561±0.02	0.484±0.49	13.72±0.54	0.86	102.93±0.06
F12B	24.42±0.02	0.549±0.74	0.478±0.60	12.93±0.26	0.87	96.87±0.05
F12C	27.85±0.08	0.559±0.24	0.488±0.52	12.70±0.12	0.87	97.91±0.03
F12D	26.72±0.02	0.553±0.85	0.483±0.27	12.65±0.82	0.87	98.64±0.08

**All values are expressed as mean ± SE, n = 5*

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2g of powder from each formula, was taken and sieved lightly to break any agglomerate formed, then it was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from a height of 2.5cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula.[17]

LBD = Weight of the powder/ Volume of packing

TBD = Weight of the powder/ Tapped volume of packing.

The values are given in Table 4.

Compressibility index

The Compressibility index of the blend was determined by Carr's compressibility index.[17]

Carr's index (%) = {(TBD – LBD) x 100/TBD} — eq (2)

The values are given in Table 4.

Hausner ratio

Hausner found that the ratio $\tilde{n}_{T} / \tilde{n}_{B}$ was related to interparticle friction and, as such, could be used to predict powder flow properties[17] and its values are given in Table 4.

Drug content

An accurately weighed amount of powdered blend Metoprolol Succinate (100 mg) was extracted with water and the solution was filtered through 0.45-µ membrane (Nunc, New Delhi, India). The absorbance was measured at 222 nm after suitable dilution and values are given in Table 4.

Evaluation of Tablets

Thickness & Diameter [18]

The thickness and diameter of the tablet was determined using a vernier caliper for six tablets from each batch and its values are given in Table 5.

Table 5: *Properties of Metoprolol Succinate Compressed Tablets*

Batch code	Thickness* (mm)	Diameter* (mm)	weight variation† mg)	Drug content* (%)	Hardness* (Kg/cm2)	Friability‡ (%)
F1	4.52±0.2	9.16±0.4	249.49±2.561	95.10±0.06	7.3±0.23	0.45±0.04
F2	4.56±0.1	9.10±0.4	249.28±2.984	98.23±0.08	7.3±0.16	0.42±0.02
F3	4.58±0.2	9.21±0.2	250.49±2.552	96.84±0.01	7.5±0.14	0.46±0.01
F4	4.61±0.3	9.11±0.3	251.82±1.675	104.21±0.01	7.2±0.24	0.38±0.08
F5	4.58±0.2	9.12±0.4	249.35±1.982	102.42±0.05	7.3±0.23	0.41±0.09
F6	4.62±0.1	9.22±0.4	249.99±1.868	98.46±0.04	8.6±0.20	0.36±0.18
F7	4.56±0.2	9.23±0.2	250.23±2.251	101.50±0.02	8.2±0.21	0.38±0.10
F8	4.55±0.1	9.25±0.3	251.04±1.991	99.74±0.06	8.3±0.20	0.43±0.08
F9	4.59±0.2	9.16±0.4	249.59±2.894	98.84±0.06	8.5±0.22	0.29±0.04
F10	4.62±0.1	9.28±0.1	250.24±1.986	105.21±0.08	8.4±0.26	0.32±0.12
F11	4.53±0.3	9.27±0.2	251.05±2.543	102.52±0.01	8.8±0.18	0.23±0.16
F12	4.55±0.2	9.18±0.2	250.36±1.762	97.16±0.01	9.1±0.25	0.31±0.09
F12A	4.57±0.1	9.15±0.4	251.15±2.998	102.43±0.05	8.9±0.14	0.36±0.15
F12B	4.54±0.2	9.13±0.4	251.46±1.563	96.27±0.04	9.4±0.29	0.31±0.09
F12C	4.56±0.2	9.14±0.2	249.89±1.348	97.21±0.02	9.5±0.21	0.28±0.17
F12D	4.58±0.1	9.24±0.3	250.56±2.050	98.14±0.06	9.4±0.24	0.29±0.04

** All values are expressed as mean ± SE, n = 6.*

† All values are expressed as mean ± SD, n = 20

‡ All values are expressed as mean ± SE, n =20

Weight Variation [18]

To study weight variation, 20 tablets of each batch were weighed using an electronic digital balance (AX 200 Shimadzu) and the test was performed according to the official method and its values are given in Table 5.

Hardness Test [18]

For each formulation, the hardness of six tablets was determined using a hardness tester (Strongcobb hardness tester). Hardness values were reported in (kg/cm^2) as given in Table 5.

Friability Test [18]

For each formulation, 20 tablets were weighed and placed in a friabilator (Roche Friabilator) and subjected to 100 rotations for 4 minutes. The tablets were then dedusted and reweighed. The friability was calculated as the %weight loss as given in Table 5.

Drug content [19]

Six tablets were weighed individually and all tablets were grinded in a mortar until no large particle was seen and from that weight of powder equivalent to one tablet weight was taken. The drug was extracted with distill water and the solution filtered through 0.45µ membrane (Nunc, New Delhi, India). The absorbance was measured at 222 nm after suitable dilution, using U.V-Visible Spectrophotometer(UV-3000+, Lab India) and the quantity in mg of $[(C_{15}H_{25}NO_3)_2{\cdot}C_4H_6O_4]$ in the tablet taken was calculated. The amount of drug in the tablet was determined. The tablets pass the test if the amount of the active ingredient in each tablet lies within the range of 90% to 110% of the stated amount in the USP monograph and test values are given in Table 5.

In Vitro Drug Release S tudies

The release rate of Metoprolol Succinate from directly compressed tablets was determined using USP Type 2 dissolution Apparatus (DS 8000, Lab India). The dissolution test was performed for 6 tablets from each batch in triplicate, using 500ml of pH 6.8 phosphate buffer, at 37±0.5°C at 50 rpm for 20 hrs. 5ml sample was withdrawn from the dissolution apparatus at specified time points and replaced with fresh dissolution medium. The samples were filtered through a 0.45-µm membrane filter and diluted if necessary. Absorbance of these solutions was measured at 222nm using (UV-3000+, Lab India) UV-Visible Spectrophotometer. Drug release was calculated using the standard calibration curve as shown in Figure 4.

Analysis of Release Dat a

The description of dissolution profiles has been attempted using different release models[20]. The data were evaluated according to the following equations.

Zero order: $M_t = M_o + K_o t$ —— eq (3)

First order: $\ln M_t = \ln M_o + K_1 t$ —— eq (4)

Higuchi model: $M_t = K_H$ “t —— eq (5)

Korsmeyer –Peppas model: $M_t/M_o = K_k t^n$ —— eq (6)

Where M_t is the amount of drug dissolved in time t, M_o the initial amount of drug, $K_1$is the first order release constant, K_0 the zero order release constant, K_H the Higuchi rate constant, K_k the release constant and *n* is the diffusion release exponent indicative of the operating release mechanism. The correlation coefficient (r^2) was used as an indicator of the best fitting, for each models considered and values are given in Table 6.

Similarity factor

The similarity factor[21] (f_2) was calculated from the mean dissolution data according to the following equation:

$f2=50\log\{[1+1/n\text{”}_{t=1}^{n}(Rt-Tt)^2]^{-0.5}]*100$ —— eq (7)

Where n, the number of pull points; R_t, the reference profile at time point t and T_t, the test profile at the same time point. The value of f_2 should be between 50 and 100. The f_2 value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between release profiles increases. Similarity factor determined for all formulations from F1 to F12 (A-D) and values are given in Table 7.

Table 6: *Model Fitting Analysis for Formulation F12B*

Model	R^2	n value	conclusion
Zero order	0.9566		Anomalous (non-Fickian) diffusion
First order	0.9884		
Higuchi	0.9907		
Korsmeyar Peppas	0.9989	0.5865	

Table 7: *Similarity Factor (f_2) for Formulations F1-F12D*

Batch code	f_2
F1	33.17
F2	31.72
F3	32.22
F4	29.04
F5	30.34
F6	32.63
F7	37.13
F8	39.72
F9	40.57
F10	42.28
F11	55.48
F12	70.93
F12A	73.91
F12B	95.23
F12C	72.81
F12D	71.77

Stability study

Stability study[22] was conducted for the selected and optimized formulation F12B to assess its stability with respect to its physical appearance, drug content and drug release characteristics. The sample was subjected to accelerated stability testing at 40°C/75% RH for 6 months and the drug release pattern is as shown in Figure 5.

Statistical analysis [23, 24]

In-vitro release data of Metoprolol Succinate from the marketed tablets (Seloken XL 25) and optimized formulations (F12B) were subjected to the one-way analysis of variance (ANOVA) at different time intervals of drug release up to 20hrs as given in Table 8.

Table 8: *Statistical Analysis for F12B vs. Reference Product*

Anova: Single Factor						
SUMMARY						
Groups	*Count*	*Sum*	*Average*	*Variance*		
F12B	5	188.85	37.77	1201.911		
Seloken XL 25	5	185.88	37.176	1334.238		
ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	0.88209	1	0.88209	0.000696	0.979605	5.317655
Within Groups	10144.6	8	1268.075			
Total	10145.5	9				

RESULTS AND DISCUSSION

Tablet characteristics

The extended release matrix tablets of Metoprolol Succinate were prepared by direct compression method in order to assess the performance of physicochemical and drug release characteristics. The selected FT-IR spectrums of Metoprolol Succinate and samples of physical powder mixure are shown in Figure 3. The following characteristic streching bands were observed at 3443.14 cm^{-1}(N-H str, 2°-amines), 3150.83 cm^{-1} (C-H str, aromatic), twin peaks at 1515.86 cm^{-1} and 1562.22 cm^{-1}(C=C, aromatic), 1114.36 cm^{-1} (C-O str, C-O-C) for pure Metoprolol Succinate. When IR spectrum of pure Metoprolol Succinate was compared to the spectrum of Metoprolol Succinate in powder mixtures, no difference was observed between the spectra. Furthermore, neither any missing in the bands nor appearance of new bands in the IR spectra of powder mixtures was noted. Angle of repose, bulk densities, tapped density, compressibility index, Hausner ratio of the powder blend were all within acceptable limits as per USP (Table 4). The results indicated that all the formulations from F1-F12D met the requirement of physicochemical characteristics. All the formulation passed the test for weight variation; friability and drug content. The values were within the acceptable limits of Pharmacopoeia as given in Table 5.

In-vitro Release Studies

The *in vitro* release profiles of Metoprolol Succinate formulations from F1 - F12D are shown in (Fig. 4) Each experiment was done in triplicate and the mean values recorded as cumulative percentage release at 1st, 4th, 8th and 20th hr according to USP specification. Hydrophilic polymers are the most widely employed in the preparation of extended release tablets because of their flexibility to obtain a desirable drug delivery profile, cost effectiveness and broad regulatory acceptance. HPMC is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery systems.

Formulations F1-F6 was prepared as mentioned in Table 1 but the desired dissolution criterion as per USP was not achieved as shown in Figure 4. Target weight of the tablet for all batches was kept constant at 250mg and target weight of the film coating was 5 mg. In formulations F1 to F6, quantity of HPMC K4M was geometrically decreased and HPMC K15M was increased, burst release of drug was seen at 4thhr and 8th hr. Trials from F7-F12 was prepared as per Table 2, here quantity of HPMC K15M was geometrically decreased and HPMC K100M was increased to get desired dissolution profile. Addition of HPMC K100M in increasing concentration retarded the release rate from 23.24% to 19.22% in the 1st hr but drug release was not within the limits at 4th hr and 8th hr. Formulations F7-F10 showed erosion of the drug ranging between (55.41% to 42.24%) in the 4th hour and burst release of the drug ranging between (84.25% to 77.58%) in the 8th hour. In formulation F11, addition of colloidal anhydrous silica and Avicel pH 102 gave good sign of drug release at predetermined intervals. Formulation F12 gave drug release at the predetermined intervals as per USP. Now optimization of F12 was further continued and new trials were taken from F12A to F12D as shown in table5. Here HPMC K100M was kept constant and Avicel pH 102 was reduced little by little and colloidal anhydrous silica was increased little by little. In these batches drug released at 1st hr was below 20% and at 4th hr was seen between 33.17% and 36.39%, and at 8th hr between 53.41% and 56.71%, and at 20th hr all above 80% as per USP specification as shown in Figure 4.

F-12B dissolution data was applied to various models fitting kinetic equations like Zero-order, First order, Higuchi and Korsmeyer-Peppas. Correlation coefficient (r^2 =0.9989) and diffusion release exponent (n=0.5865) results confirmed that the Anomolous (non-fickian) diffusion was the main drug release mechanism as given in Table 6.

These findings indicate that decreasing low viscosity HPMC Polymer and increasing high viscosity HPMC Polymer concentration retards the release rate of the drug. As the polymer level was increased, the polymer gel formed is more likely to be resistant to drug diffusion and gel erosion. As the release rate limiting polymer changes from a glassy state to rubbery state, a gel structure was formed around the tablet matrix, which considerably decreases the release of drug since it has to diffuse through this gel barrier in to the bulk phase. The strength of gel depends on the chemical structure and molecular size of polymer. The faster drug release in case of formulation containing low amount of HPMC K100M may be due to less tortuous diffusion path. It is known that higher viscosity grade polymer (HPMC K100M) hydrates faster and therefore is capable of forming a gel structure faster than medium viscosity grade (HPMC K15M) and low viscosity grade (HPMC K4M) polymer. The release rate was significantly dependent on the proportion and type of the polymer used. Similarity factor (f_2) was employed for all batches with respect to reference product; values are given in Table 7. Batch F12B showed highest *f*2 value of 95.23 and hence, considered as best optimized batch.

Statastical analysis justified that the observed F value (0.00069) is less than the critical F value (5.31) at 5% level of significance, it can be concluded that there is no significant difference between the rate of release of F12B and Reference product as given in Table 8.

Accelerated stability study of the optimized batch F-12B was carried out for six months at 40°C±2°C and 75%RH±5%RH as shown in Figure 5. The crushing strength, friability, drug content and *in vitro* drug release profile of batch F-12B was not significantly changed during the study and was found to be within the limits of USP. The similarity factor (*f*2) of batch F-12B at the end of stability study was 83.27, indicating that the Metoprolol Succinate was stable during processing and storage.

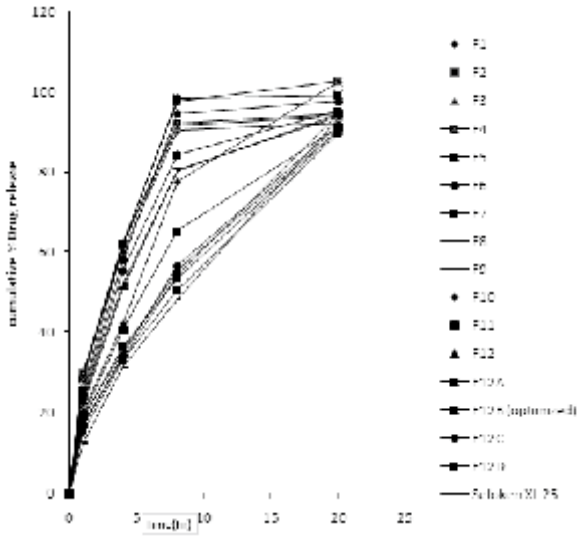

Fig. 4: *In vitro release profile of Metoprolol Succinate from matrix tablets*

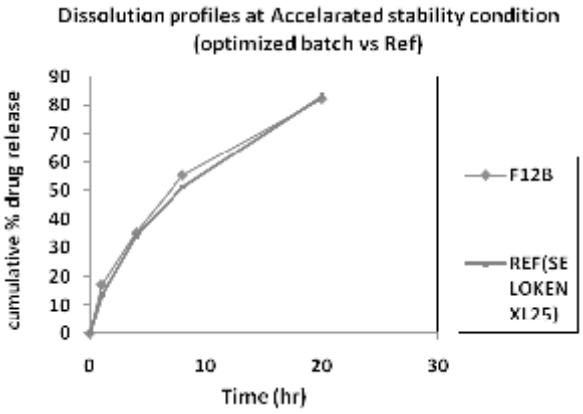

Fig. 5: *In vitro release profile of F12B and Reference Product at Accelerated Stability*

CONCLUSION

The results of the study demonstrate that hydrophilic polymer can effectively control the extended release of Metoprolol Succinate for 20 hrs. Direct compression process is easy and inexpensive and does not require special production equipment and the matrices had high mechanical strength and is feasible for development of once a day extended release tablet of Metoprolol Succinate provided careful selection of optimum concentration of HPMC K100M is followed. This investigation enables us to conclude that the drug release profile from optimized formulation F12B containing 70% of Methocel K100M satisfies dissolution criteria of USP and it passed accelerated stability study. It can also be stated that desired extended release of hydrophilic drug is also viable with hydrophilic polymer alone.

ACKNOWLEDGEMENT

Authors are thankful to Sania Humancure Pvt. Ltd for providing drug as gift samples and Vision College of Pharmaceutical Sciences & Research for giving few excipients and facilities.

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