



FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF METOPROLOL SUCCINATE

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ABSTRACT

The objective of the current study was to formulate the Metoprolol Succinate sustained release matrix tablets by cost saving and production efficient process. Among various tablet manufacturing process, direct compression is the simplest and cost saving process. Metoprolol Succinate is available in conventional dosage forms, administered four times a day, leading to saw tooth kinetics and resulting in ineffective therapy. The combination of these two drugs in a single dosage form will enhance the patient compliance and prolong bronchodilator. Various polymers, such as hydroxy propyl methylcellulose K4M (HPMC- K4M), hydroxy propyl methylcellulose K100M (HPMC- K100M), xanthan gum, ethyl cellulose and hydroxy propyl methylcellulose phthalate (HPMC-P) were considered. HPMC-P and HPMC- K4M were found to be best in controlling the release. In-vitro dissolution studies were carried out for all the bi-layered tablets developed using USP dissolution apparatus type 2 (paddle). It was bring into being that the tablet FB15-FW3 showed 50% release of salbutamol in first hour and the remaining was released for eight hours. However, Metoprolol Succinate was found to be released as per the USP specifications. This further confirms the integrity of pure drugs and no incompatibility of them with excipients. Also, formulation of FB15-FW3 has shown required release pattern and complies with all the evaluated parameter and comparable to the marketed formulation.

Key words: Sustained release, Metoprolol Succinate, Direct compression, Formulation and Evaluation.

INTRODUCTION

Metoprolol is a selective β_1 receptor blocker used in treatment of several diseases of the cardiovascular system, especially hypertension. The active substance Metoprolol is employed either as Metoprolol Succinate or as Metoprolol tartrate [1-2] but in present study we are using Metoprolol Succinate only. It is freely soluble in water, soluble in methanol, sparingly soluble in ethanol, slightly soluble in dichloromethane and 2 propanol, practically insoluble in ethyl-acetate, acetone, diethyl ether and heptane. Metoprolol is a Beta1-selective (cardio selective) adrenergic receptor blocking agent. This preferential effect is not absolute, however and at higher plasma concentrations, Metoprolol has no intrinsic sympathomimetic activity, and membrane stabilizing activity is detectable only at plasma concentrations much greater than required for beta blockade, Metoprolol crosses the blood brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous 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. The purpose of this study was to design oral sustained release tablet formulations of Metoprolol Succinate using different polymers like grades of HPMC as the release retarding polymer. The tablets were prepared by wet granulation, and their physical parameters and in vitro release characteristics were evaluated. The effect of formulation factors such as polymer proportion and polymer viscosity on the release characteristics was studied in order to optimize these variables.

Metabolism

Metoprolol undergoes a-hydroxylation and O-demethylation as a substrate of the cytochrome liver enzymes CYP2D6 and a small percentage by CYP3A4 [5,6].

Adverse effects

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Adverse effects, especially with higher dosages, include the following: dizziness, drowsiness, fatigue, diarrhoea, ataxia, trouble sleeping, depression, and vision problems. It may also reduce blood flow to the hands and feet, causing them to feel numb and cold; smoking may worsen this effect [3]. Due to the high penetration across the blood brain barrier, lipophilic beta blockers such as propranolol and Metoprolol are more likely than other less lipophilic beta blockers to cause sleep disturbances such as insomnia and vivid dreams and nightmares [4].

Clinical uses

Metoprolol is used for a number of conditions including: hypertension, angina, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, congestive heart failure, and prevention of migraine headaches [7].

- Treatment of heart failure.
- Vasovagal syncope
- Adjunct in treatment of hyperthyroidism
- Long QT syndrome, especially for patients with asthma, as metoprolol's β_1 selectivity tends to interfere less with asthma drugs, which are often β_2 -adrenergic receptor-agonist drugs
- Prevention of relapse into atrial fibrillation (controlled-release/extended-release form) [8]

Due to its selectivity in blocking the β_1 receptors in the heart, Metoprolol is also prescribed for off-label use in performance anxiety, social anxiety disorder, and other anxiety disorders.

Table 1. Brand Names

Brand Name	Manufacturing Company
Lopressor	Novartis
Minax	Alphapharm
Betaloc	AstraZeneca
Bloxan	KrKa
Neobloc	Unipharm

Materials and Methods

Metoprolol Succinate was obtained as a gift sample from Koves India Ltd, Chennai and salbutamol sulphate from Natco chemicals, Hyderabad, India; hydroxy propyl methylcellulose K4M, hydroxy propyl methylcellulose K100M. The immediate sustained release tablets containing Metoprolol Succinate were prepared by wet granulation method using HPMC K4M, HPMC-P, Povidone-K 30 were gifted by Colorcon Asia pvt limited, India.

Formulation

The immediate sustained release tablets containing Metoprolol Succinate were prepared by wet granulation method using HPMC K4M and other ingredients [9,10].

Procedure

Weighed all the ingredients like Metoprolol Succinate and HPMC-K100, Micro crystalline cellulose pH 101 and HPMC K4 M accordingly to the formula.

Dissolve povidone K-30 in Isopropyl alcohol by slow addition. A void lump formation during addition of povidone K-30 stir to dissolve and to form a homogenous clear solution. Mix the ingredients in rotating mixture granulator (RMG) for 25 minutes. Granulate the ingredients with proper addition of binder should be slow to effect granulation. Add extra amount of Binder, if required and recorded the same. Use chopper such that not lumps are formed during granulation. Airs dry the wet mass in fluidized bed dryer for 15 minutes for applying the initial drying. Received the dry granules through the sifter fitted with 20#. Mill the retained granules through a mill fitted with 2 mm screen. Dry the semidried granules in Fluidized Bed Dryer at temperature of 50°C of the outlet temperature gauge to suitably achieve on LOD of 1%. Record the temperature (periodically).Sifted the dried granules through 16#.The ingredients are passed through the sieve no 30 # and Pre- blended the received and a milled granule is double cone blender, along with sifted excipients. Except purified Talc and sodium steryl fumerate. Sift to through 40# and blend it in to the blender and mix it for 8 minutes. Add the sifted lubricant purified Talc magnesium Stearate and sodium steryl fumerate into the previously prepared granules and mix uniformity. Add ponceae 4 R in the in the final stage and mix well. The total weight of the tablet contains 440mg.

In Vitro Dissolution Studies [11,12]

Weigh accurately about 50 mg of Metoprolol Succinate working standard in a 50ml volumetric flask dissolve in a dissolution medium makeup the Dissolution studies were carried out as per the USP 26 specifications, using USP dissolution apparatus type 2 at pH conditions i.e. 6.8 Phosphate Buffer for 1 hr followed by the pH 6.8 for remaining hrs. Analysis Metoprolol Succinate was estimated by U.V.spectrophotometer at 223nm. Best formulation was subjected to HPLC analysis as per the specifications given (Column used - Kromasil C 18 ODS column, Mobile Phase – Buffer : Acetonitrile – 75: 25 , pH of the mobile phase 3.0 (Adjusted with Orthophosphoric acid, Flow Rate - 1ml/min., Injection volume- 100 μ l, Wavelength - 215 nm, HPLC system – Waters). The arranged mobile phase was filtered through 0.45 μ m micro pore filter and degassed by sonication for 10 minutes.

Buffer

50 ml of 1 M monobasic sodium phosphate and 8.0 ml. of 1 M phosphoric acid and dilute with water to 1000ml adjust with 1 M phosphoric acid to pH 3.0.

Standard Preparation

Weigh accurately about 50 mg of Metoprolol Succinate working standard in a 50ml volumetric flask dissolve in a dissolution medium makeup the volume with same. Dilute 5 ml from the above solution to 50 ml with dissolution medium.

Procedure #1

Set dissolution parameters and place 1 tablet into each vessel taking care to exclude air bubbles from the

surface of the tablet and immediately start the apparatus. After 60 minutes withdraw the sample medium 10 ml and replace the pH 6.8 buffer solution and filter through 0.45µ nylon filter and withdraw the sample medium 4th, 8th and 20th hour.

Procedure #2

Inject 20 µl sample preparation (one injection) and standard preparation into the liquid chromatography and record the chromatogram. Measure the responses for the major peaks. Calculate the dissolved quantity of Metoprolol Succinate in percentage form the peak areas of Standard and sample preparation and percentage of potency of working standards used.

Assay

Preparation of Standard Metoprolol Succinate (HPLC method) Weigh accurately about 50 mg of Metoprolol Succinate working standard in a 50ml volumetric flask dissolve in a dissolution medium make up the volume with same. Dilute 5 ml from the above solution to 50 ml with dissolution medium.

Chromatographic condition

Mobile phase used for the analysis consist of Buffer

Acetonitrile aqueous solution in the ratio of 75:25 v/v. They were filtered before use through a 0.45 µm membrane filter and pumped through the column RP C18 (250 x 4.6 i.d) mm, 5µm, in isocratic mode at a flow rate of 1 mL/min. Prior to the injection of the drug solution, the

column was equilibrated for at least 30 min with the mobile phase flowing through the system. The analysis was performed at ambient temperature and the run time was set at 10 min. The eluents were monitored at 223 nm and retention of Metoprolol Succinate was found to be 7.7 min.

Sample preparation

Weighed about 50mg equivalent of Metoprolol Succinate in a 100 ml volumetric flask and 5ml of water, to disperse and 70 ml of methanol warm 10 minutes dilute to volume with methanol. Filter the supernatant liquid with 0.45 micron membrane filter. Dilute 5ml from the solution to the 50 ml with mobile phase.

Fourier transform infrared (FT-IR)

Fourier transform infrared (FT-IR) spectral studies were conducted on FTIR Spectrophotometer (Shimadzu Instrument Corporation Inc., Japan) instrument using KBr pellets to investigate possible interactions between the respective polymers in the release media. All samples were crushed with potassium bromide. The weight ratio of a sample and potassium bromide was 2 mg to 300 mg. Crushed powders were compressed using a hydraulic compactor at approximately 20,000 pounds under vacuum for 3 min. FT-IR measurements were performed under nitrogen atmosphere at a flow rate of 50 standard cubic feet per hour. Spectral scanning was conducted from 4000 to 400 cm⁻¹ at a resolution of 4 cm⁻¹.

Table 2. Composition of various formulations

S. No	Ingredients	F1	F2	F3	F4	F5	F6
1	Metoprolol Succinate	47.5 g	47.5 g	47.5 g	47.5 g	47.5 g	47.5 g
2	HPMC K-100	98 g	112 g	126 g	140 g	77 g	79.5 g
3	HPMC K4M	28 g	28 g	28 g	28 g	15 g	15 g
4	MCC pH 101	112.5 g	94.9 g	78.0 g	64.3 g	46.1 g	25.6g
5	Povidone K 30	5.6 g	79.0 g	4.2 g	9.8 g	9.8 g	9.8 g
6	Isopropyl alcohol Lubrication	150ml	150ml	150ml	150ml	150ml	150ml
7	Magnesium Stearate	2.8 g	4.2 g	5.6 g	-	-	-
8	Sodium stearyl Fumarate	2.8 g	4.2 g	5.6 g	5.6 g	7.2 g	13.5 g
9	Talc	2.8 g	2.8 g	2.8 g	2.8 g	2.8 g	2.8 g
10	Ponceau 4R	2.8 g	2.8 g	2.8 g	2.8 g	2.8 g	2.8 g

Evaluation Studies of Matrix Tablets

Table 3. Friability Test

Formula	F1	F2	F3	F4	F5	F6
Initial	8.8828	9.0776	8.6883	8.6425	8.6130	8.8674
Final	8.7934	8.9982	8.5123	8.5601	8.5924	8.7835
calculate = $\frac{IW - FW}{IW} \times 100$	5.82%	6.11%	5.86%	0.27%	0.24%	0.23%

Table 4. Weight Variation Test

S. No	F1	F2	F3	F4	F5	F6
1	418	442	417.2	445	442.5	443
2	430	442	445.8	442	442.3	440.6
3	438	443	440.4	422.5	424	442.2
4	450	445	440	425	440.3	440.3
5	432	421	456	444.3	453	463.2

6	442	435.6	457.1	444	445	457
7	432	440	445.2	423.4	453	442
8	445	445	428	429	435	440.1
9	428	429.6	441.4	425.4	428.4	4448.1
10	430	429	440	428.6	442	442
11	442	448	446	443	440.4	446
12	450	420	424.8	445.6	448.2	420
13	460	420	430.8	442.4	440.8	448.1
14	441	424.2	426.2	440.5	442.4	462.3
15	440	418.6	440.3	440.7	440.4	428
16	428	420	430	421	442.4	462.8
17	448	428.3	430	420.3	440.9	446.2
18	444	445.1	445	445	456.1	445
19	450	440.6	428	421.9	442.8	446
20	460	443.2	420.8	445.8	444.2	442.8

Table 5. Hardness Test

Hardness test	F1	F2	F3	F4	F5	F6
Limit NLT 5kg	3	2.8	3.5	5.8	5	6
	2.6	3.2	3.2	4.7	4.5	5.4
	2.8	3.5	2.8	5.6	5.5	5.8
Average	2.77 kg/ cm ²	3.22 kg/ cm ²	3.3 kg/ cm ²	5.1 kg/ cm ²	5.12 kg/ cm ²	4.52 kg/ cm ²

Table 6. Thickness Test

Hardness test	F1	F2	F3	F4	F5	F6
Limit NLT ± 0.2mm	4.4	4.2	4.4	4.4	4.1	4.2
	4.3	4.3	4.2	4.1	4.2	4.3
	4.1	4.4	4.0	4.22	4.3	4.2
Average	4.32	4.16	4.22	4.2	4.2	4.22

Table 7. In vitro Analysis of Sustained release formulations

S. No	Formulation Code no	Percentage Drug release (%)
1	F1	41.26
2	F2	63.27
3	F3	74.35
4	F4	81.23
5	F5	97.6
6	F6	95.5

RESULTS AND DISCUSSION

Various formulations are prepared and evaluated with an aim of controlling the release of Metoprolol Succinate. As per the USP specifications (USP 25 NF 2002) 3-15% of drug should be released in the first hour and not less than 80% of the drug should be released in the eight hour for Metoprolol Succinate respectively. The release of Metoprolol Succinate should be completed within 8 hours, so that the Metoprolol Succinate concentration in the body can be maintained for 12 hrs since it has elimination half-life of 6hrs. The granulations were prepared to optimize and control the release of the drugs. Six formulations (F1-F6) containing an immediate release tablets were prepared as described earlier. Preformulation parameters such as Friability, Weight variation, Hardness and Thickness were evaluated (Table 2-5) this gives the basis for the optimization of drug product quality. Parameters of these granulations were also evaluated and found to be satisfactory. The tablets were

subjected for weight variation test, hardness, thickness, assay, content uniformity test and friability test. These were found to be within standard limits and satisfactory. The sustained release tablet was further subjected for in-vitro dissolution studies as described earlier to ascertain the release patterns sustained release tablets. HPMC K100 conc. = 63.00%. In F1 formulation 41.26% of Metoprolol was released at the end of 1st hour. These releases were not within the limit of release profile. In F2 formulation 41.26% of Metoprolol was released was not with the limit. In first hour 34.5% of the drug was released and in second hour the release is 63.27. So the dissolution was discontinued by 4th hour. The polymer concentration was further increased to 5%. In F3 formulation polymer concentration was increased from 40-45%. The release of Metoprolol in first hour is 26.9% which was more than the specified limit. The release of 4th hour was 54.9% which was also over the limit. So further polymer concentration was increased to another 5%. In F4 the release of

Metoprolol was within the limit. In 4th hour the release of Metoprolol exceeds the limit. In 8th hour the release was 72.68% which also exceeds the limit. So further polymer concentration was increased to 5%. In F5 the release of Metoprolol was within the limit. Therefore for the reproducibility of F5 formulation, F6 formulation was developed with 0.7% change in HPMC K100 polymer concentration. In F6 formulation first hour, 2nd hour, 4th hour, 8th hour and 20th hour released was within limit. So we standardize F6 formula for sustained release of Metoprolol. Invitro studies of F1 - F6 formulations are carried out and formulation F5 shows the release within the limit profile. So finally for the Reproducibility F6 formulation was formulated. In the SR formulation F6, using HPMC K100 53.00% and HPMC K4 M 10% gives the drug release of 15.6%, 34.9%, and 54.19%, 80.25%, 95.5% at 1st, 4th, 8th and 20th hour respectively. All the tablet formulations were evaluated for their characteristics such as hardness, thickness, friability, weight variation and content uniformity (assay). From the

investigation it was noted that the drug content were found to fall within the limits. These release profiles of Metoprolol Succinate complied with standards and specifications of USP. The IR spectrum was taken for F1-F6 formulation and it revealed that there is no disturbance in the principle peaks of pure drugs Metoprolol Succinate. This further confirms the integrity of pure drugs and compatibility of them with excipients respectively.

CONCLUSION

The sustained release matrix tablet of Metoprolol Succinate was prepared by wet granulation. Formulation F1-F6 is considered to be the most excellent with the desired drug release. The polymers which have been used in the best formulation F6 containing HPMC K-100 the release can be so well controlled that it almost coincides the theoretical release pattern for the drug by proper adjustment of polymer ratio Hence the mono layer tablet designed possesses all the qualities of a sustained release formulation.

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