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ORIGINAL ARTICLE

Formulation and Evaluation of Sustained Release Tablets of Metoprolol Succinate

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ABSTRACT
Sustained release matrix tablets reduce the frequency of the dosing and increase the effectiveness of the drug by localization at the site of action, providing uniform drug delivery. The work aims to formulate Metoprolol Succinate sustained release matrix tablet using combination of HPMC K100M, Carbopol 934P and PVP K30. Metoprolol Succinate is a beta 1-selective (cardioselective) adrenergic receptor blocking agent, antihypertensive agent. It is having half-life of 3-7 hours with the usual oral dose of 25 to 100 mg once daily. An attempt was made to sustain the release of Metoprolol Succinate up-to 24 hrs using minimum amount of polymers. The Eight formulations were prepared using 2^3 factorial design. The tablets produced were evaluated for thickness, hardness, friability, weight variation, content uniformity and in vitro dissolution studies. The dissolution data obtained were fitted to the various kinetic models of dissolution. Model fitting depicted that the formulations followed Korsmeyer Peppas Equation. The similarity factor (f2) was found to be 51.69 for the developed formulation indicating the release was similar to that of the marketed formulation. Thus, a combination of HPMC K100M and Carbopol 934P sustained the release of Metoprolol Succinate for a period of 24 hrs.
From this study it conclude that using the combination of HPMC K100M, Carbopol 934P and PVP K30 the Metoprolol Succinate SR tablet shows 85.010±0.784% of the cumulative drug release within 20 hours without burst release and followed Korsmeyer peppas model.
Keywords: *Metoprolol Succinate (MS), Matrix Tablet(MT), Sustained Release (SR), HPMC(Hydroxypropyl methyl cellulose).*

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INTRODUCTION

Metoprolol Succinate is a beta 1-selective adrenergic receptor blocking agent, antihypertensive agent [1]. The elimination half-life of Metoprolol Succinate is 3 to 7 hour. So frequent dosing of drug is necessary. A sustained-release formulation that would maintain plasma levels of the drug for 10 to16 hours might be sufficient for once-daily dosing of Metoprolol Succinate [2, 3]. The objective of study is to develop suitable formulae and procedure for the manufacture of sustained release Metoprolol Succinate tablets in a relatively economical way. To decrease the number of polymers used for Sustaining the release as compared to marketed product and to Study the effect of excipients (polymers) on Mechanism of Drug Release System. Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time [4, 5, 6]. Possible therapeutic benefits of a properly designed sustain release dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable and patient compliance [7,8].

So the Sustained Release tablet is suitable dosage form for Metoprolol Succinate. Many innovative methods have been developed for obtaining modified drug release. From the practical view point, hydrophilic matrix tablet is one of the least complicated approaches for developing modified release

dosage form [9, 10]. Hence, the use of these dosage forms is increasing in treatment of an angina, heart failure, and high blood pressure. Hypertension is the most common cardiovascular diseases. For hypertension β-blockers are presently most important class of drug [11]. Hence in the present study work an attempt has been made to develop sustained release matrix tablet of Metoprolol Succinate by using combination of HPMC K100M, Carbopol 934P and PVP K30.

MATERIAL AND METHODS

Materials

Metoprolol Succinate was obtained from Wochardt Limited, (Aurangabad, India.) Microcrystalline cellulose and Carbopol 934 P was purchased from S. D. Fine Chem. Labs, (Mumbai, India). Hydroxypropyl methylcellulose K100M were obtained as a gift sample from colorcon,(Mumbai.), PVP K30, magnesium stearate and Talc was obtained as gift samples from Zydus Healthcare Pvt. Ltd. (Ahmedabad).

Preparation of Metformin hydrochloride matrix tablets

Eight formulations were prepared using 2^3 factorial design. The direct compression method was utilized for the preparation of tablets. The ingredients were passed through the sieve no. 100 the drug metoprolol succinate. Carbapol 934 P, HPMC K100M, PVP K-30 and MCC PH101, were mixed thoroughly in mortar and pestle for 5 min. The blends of the prepared powder were lubricated with Magnesium Streate and mixed with Talc. The tablets were compressed using 12 mm concave faced punches using Rimek mini tablet compression machine**.** The formulae of all factorial batches of Metoprolol succinate sustain release matrix tablet are shown in the Table 1.

Table 1: Composition of factorial batches

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
M.S	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5
HPMC K100M	120	120	120	80	80	80	80	120
CP 934P	90	90	60	60	60	90	90	60
PVP K30	25	20	20	20	25	25	20	25
MCC p101H	27.5	32.5	62.5	102.5	97.5	67.5	72.5	57.5
Mg.st.	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10
Total	325	325	325	325	325	325	325	325

Evaluation of Metoprolol Succinate (SR) matrix tablets

Hardness

Tablet hardness is defined as force required for crushing the tablet in diametric compression test. The hardness was measured with Pfizer hardness tester. The tablets were placed diametrically between two plungers and the lower plunger is kept in contact of tablet and the upper plunger is forced against tablet until tablet fractures. Results shown in Table 2.

Friability

Ten tablets were weighed and subjected to friability test in Roche friabilator. The pre-weighed sample was placed in friabilator which revolves at 25 rpm for 4 minutes dropping the tablets through a distance of 6 inch with each revolution. This process was repeated for all formulations and the percentage friability was calculated by using the formula.

$$\% F = Wo\text{-}W/Wo \times 100$$

Where, F - friability

Wo - Weight of tablets before test

W- Weight of tablets after test

Weight variation

All prepared matrix tablets were evaluated for weight variation as per USP XXIV monograph. Twenty tablets of each batch were used to evaluate weight variation among tablets and standard deviation was calculated.

Drug content

Randomly selected 3 tablet from each batch was crushed in a mortar and pestle. The crushed powder equivalent to 47.5 mg of Metoprolol succinate was taken and dissolved in 47.5 ml of distilled water (1000µg). Then filtered through Whattman filter paper. The concentration of Metoprolol succinate was determined by measuring the absorbance at 274.00 nm by using double beam UV-Visible Spectrophotometer (UV-2450 SHIMADZU).

In vitro drug release study

The drug release rate from Metoprolol succinate SR matrix tablets (n=3) was determined using USP apparatus type II (DS 8000, Labindia, India). The dissolution test was performed using 500 ml of pH 6.8 buffer, for 20 hrs at 37 ⍰ 0.5⍰C and 50 rpm. A sample (10 ml) was withdrawn at a specific interval and replaced with fresh dissolution medium of same quantity. The samples were filtered through a Whatman filter paper. Absorbance of the solutions was measured at 274.00 nm by using double beam UV-Visible Spectrophotometer (UV-2450 SHIMADZU).

Kinetics analysis of drug release

To analyze the mechanism of drug release from the tablet the *in vitro* dissolution data were fitted to zero order, first order, Higuchi release model, Hixson and Crowell powder dissolution method and Korsmeyer and Peppas model, and the model with the higher correlation coefficient was considered.

Comparison with marketed formulation

The developed product was quantitatively evaluated. The quality control tests were carried out on marketed tablets for comparative evaluation of developed and marketed product.

RESULT AND DISCUSSION

The tablets from the factorial batches were evaluated for different evaluation parameters of tablets as listed Table 2.

Table 2: Evaluation of Metoprolol succinate SR matrix tablets

Formulation	Weight variation mg	Hardness (Kg/cm2)	Friability %	Thickness (mm)	Drug Content (%)
F1	326±1.251	6.55±0.173	0.22	4.2±0.10	101.274±0.002
F2	324±1.229	7.025±0.221	0.15	4.22±0.08	99.805±0.002
F3	324±1.100	6.725±0.236	0.31	4.3±0.07	101.365±0.002
F4	325±0.994	6.5±0.282	0.31	4.44±0.09	101.624±0.003
F5	326±1.197	6.425±0.262	0.15	4.24±0.11	101.494±0.002
F6	324±1.663	6.35±0.264	0.31	4.18±0.08	101.429±0.003
F7	323±1.074	6.4±0.258	0.28	4.36±0.11	101.105±0.002
F8	325±1.595	6.925±0.206	0.25	4.2±0.10	99.415±0.002

The hardness of tablets was found to be 6.3 to 7.0 Kg/cm^2. The friability of tablets was less than 0.5% and the weight variation within limits indicates uniformity in tablet compression. The drug content of all the 8 formulations was found to be between 99.4 to 101.2 %. The value ensures good uniformity of the drug content in the tablet.

***In vitro* drug release studies**

The formulations F1, F5 and F6 comprising of HPMC K100M 120 mg, 80 mg, 80 mg and CP 934 P 90 mg, 60 mg, 90 mg and PVP K30 25 mg, showed improved drug release up to 8 hour and minimum burst release in 1 hour with more than 80% release in 20 hour. Hence formulation with comparatively higher drug release F1, which fits best the pharmacopoeia criteria for drug release in 20 hour. Results shown in Table 3.

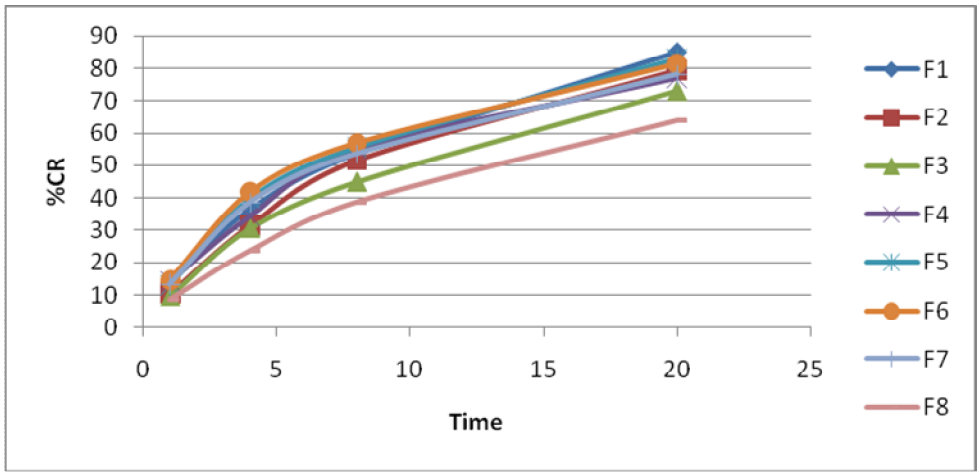

Figure 1: Percent cumulative drug release of formulation F 1 to F 8

Table 3: Percent cumulative drug release of F1 to F8

Time (Hrs)	Cumulative Drug Release (%)							
	F1	F2	F3	F4	F5	F6	F7	F8
1	13.642±0.386	10.309±0.466	9.568±0.466	14.074±1.335	12.839±1.301	14.630±0.926	13.272±0.748	8.580±0.950
4	36.384±0.008	31.070±0.605	30.623±0.645	34.294±0.994	39.701±0.324	41.836±0.756	38.537±1.068	23.567±0.744
8	53.587±0.008	51.441±0.122	44.936±0.834	54.974±1.309	55.614±0.577	57.049±0.824	53.500±0.769	38.726±0.890
20	85.010±0.748	79.305±0.664	73.164±1.173	77.104±1.225	83.125±0.952	81.501±1.138	78.006±0.825	63.932±0.870

Kinetics of drug release

In the present study, the drug release was analyzed to study the kinetics of drug release mechanism. The results showed that the factorial design batches followed korsmeyer peppas models. The R value of korsmeyer peppas was found close to one as shown in Table 4.

Table 4: Model fitting data of SR matrix tablet of Metoprolol succinate of F1

Sr. no.	Formulation	Models	r
1	F1	Zero Order	0.9506
		First Order	0.7641
		Higuchi	0.9889
		Korsmeyer Peppas	**0.9943**
		Hixon Crowell	0.9916

The rate of drug release from the matrix tablet is rapid initially followed by progressively slow drug release through the matrix. The initial burst release can be accounted for the high concentration of highly soluble Metoprolol succinate at the surface that dissolves immediately. The slow release of the drug from the matrix may be due to the formation of viscous gel of HPMC K100 M.

The optimized formulation F1 has compared with marketed product according to USP sampling interval. All parameters were found to have good similarity. The conclusion was drawn on comparison of dissolution profile and determination of similarity factor (*f2*) which was 51.69 Results shown in table 5.

Table 5: Comparative dissolution profile of developed and marketed formulation

Time (hrs)	Cumulative Drug Release (%)	
	Developed formulation	Marketed formulation
1	13.642	4.814667
4	36.384	23.67667
8	53.587	45.38267
20	85.01	83.25433
	Similarity Factor (50-100)	51.69

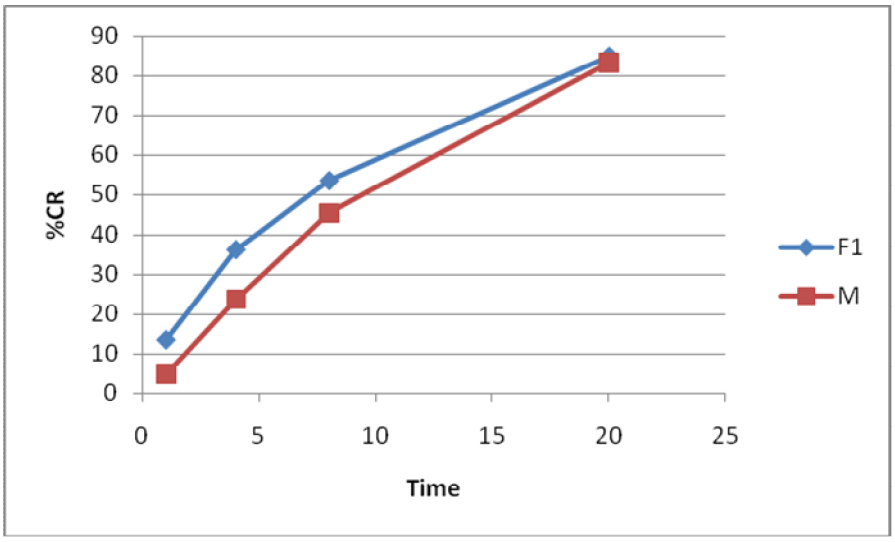

Figure 2: Dissolution profile of developed and marketed formulation

CONCLUSION

The 2^3 factorial design was applied for the optimization of the batches. It was observed that F1 showed 85.010±0.784% of the cumulative drug release within 20 hours without burst release and followed Korsmeyer peppas model. The comparison of dissolution profile and determination of similarity factor (*f2*) which was 51.69**.**

The future scope is to designed drug system holds promise for further study such as Stability studies as per ICH guideline and in vivo studies leading to IVIVC.

ABBREVIATIONS

ABS: Absorbance; **Conc.:** Concentration; **Hrs.:** Hours; **SD:** Standard deviation; **MCC:** Microcrystalline Cellulose; **PVP:** Polyvinyl pyrrolidone; **HPMC:** Hydroxy Propyl Methyl Cellulose; **Mg. St.:** Magnesium stearate; **CP 934 P:** Carbopol 934 P; **IPA:** Isopropyl Alcohol; **r**: Regression coefficient.

CONFLICT OF INTEREST

Authors have no conflicts of interest to declare.

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