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Formulation and Evaluation of Controlled Release Tablet of Metoprolol Tartarate

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ABSTRACT:

The aim of this research work is to formulate an oral controlled drug delivery system for Metoprolol tartrate. Instead of normal trial & error method, a standard experimental design was adapted to study the effect of formulation variables in the development of the oral controlled drug delivery system of Metoprolol tartrate. A CCD was adapted to study the effect of formulation variables on the release properties with amount of HPMCK100M & CAP as two independent variables. Tablets were prepared following wet granulation technique by using IPA as granulating agent. The formulated dosage forms were evaluated for both pre-compression & post- compression parameters. Further, the results of the pre compression parameters were found to be within the permissible limits of the Pharmacopoeia. The release mechanism of Metoprolol tartrate from the matrix tablets were evaluated on the basis of Korsmeyer and Peppas model which indicate the mechanism of drug release from the optimized dosage form as non fickian transport. Validation of optimization was carried out and the results obtained from optimized formula were close to the predicted values which indicate a good reproducibility. A short term stability studies were conducted as per ICH guidelines for the Optimized formula and it was found to be stable for long period of time.

KEY WORDS: Controlled drug delivery systems, Cellulose Acetate Phthalate, Matrix tablet, Hydroxypropylmethylcellulose(HPMC) K100M, Central Composite Deign.

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INTRODUCTION:

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages.¹ Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs.¹

Developing oral-controlled release tablets for highly water-soluble drugs with constant release rates has always been a challenge to pharmaceutical technologists. Most of these highly water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate and are likely to produce toxic concentrations when administered orally.² In recent years, multilayered matrix tablets containing one or two layers of release-retardant polymers have been attracting more attention in the design of oral-controlled drug-delivery systems.^{3,4} Metoprolol tartrate (MT), 1-(isopropylamino)-3-*p*-(2-methoxyethyl)phenoxy-2-propanol (2:1) dextro-tartrate, is a selective β_1 -adrenergic antagonist agent and is widely used in the treatment of angina pectoris, arrhythmias, and hypertension in

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doses of 100 to 450 mg daily⁵. In the literature, different types of controlled-release formulations such as matrix tablets,⁶ porous tablets⁷, mini-matrices produced by hot-melt extrusion⁸, sustained-release granules⁹, buccal and transdermal applications^{10, 11}, multiple emulsions¹², iontophoretic application¹³, and electrolyte-induced peripheral stiffening matrix systems¹⁴ have been developed to improve the clinical efficacy of metoprolol tartrate.

MATERIALS AND METHOD

Materials and reagents

Metoprolol tartrate was obtained as gift sample from Torrent pharma Ltd. HPMC and CAP was gift sample from Eros pharma Pvt Ltd. All other chemicals and reagents used were of pharmaceutical or analytical grade.

Method

Matrix tablets were prepared by wet granulation method. The composition of various formulations is given in Table 1. CAP, Lactose, and HPMC K100M were mixed in a polybag, and the mixture was passed through mesh (No. 40). Granulation was done using a solution of PVP K90 in sufficient isopropyl alcohol. The wet mass was passed through mesh No 8. The wet granules were air dried. The granules were then sized by mesh No. 16 and mixed with aerosil and talc. Tablets were compressed at 500 mg weight on rotary tableting machine with oval-shaped punches.

Table 1 Formulation Batch(F1-F6)

Formulation Code	F1	F2	F3	F4	F5	F6
Metoprolol tartrate	200	200	200	200	200	200
HPMC K 100M	75	150	75	150	59.47	165.53
CAP	75	75	100	100	87.50	87.50
PVP	25	25	25	25	25	25
Aerosil	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Lactose	107.5	32.5	82.5	7.5	110.53	4.47
Total Weight	500	500	500	500	500	500

Physical Tests of Tablets

All of the formulations were evaluated for hardness, diameter/thickness ratio, drug content uniformity, friability, and weight variation^{15,16}. Tablet diameter and thickness were measured by a micrometer, whereas hardness was evaluated by a hardness tester (Monsanto Type). Diameter/thickness ratio was also calculated.

Table 2 Formulation Batch (F7-F11)

Formulation Code	F7	F8	F9	F10	F11
Metoprolol tartrate	200	200	200	200	200
HPMC K 100M	112.50	112.50	112.50	87.50	68.85
CAP	69.82	105.18	87.50	112.50	110.47
PVP	25	25	25	25	25
Aerosil	10	10	10	10	10
Mg stearate	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5
Lactose	75.18	39.82	57.5	57.5	75.18
Total Weight	500	500	500	500	500

* HPMC indicates hydroxypropylmethylcellulose ;quantity Sufficient; PVP, polyvinylpyrrolidone.

CAP, cellulose acetate phthalate.

The friability was determined as the percent weight loss of 10 tablets. Ten tablets were weighed (W_1) and rotated for 100 revolutions in 4 min in a Roche friabilator. The tablets were then weighed (W_2) again and percentage friability (%F) calculated with the following equation:

$$\%F = (W_1 - W_2) \times 100 / W_1 \dots\dots\dots 1$$

Analytical Methods: Drug Content Uniformity Testing

In the case of drug content uniformity test, tablets were pulverized and then transferred into a 250-ml volumetric flask. The volume was adjusted with pH 7.4 phosphate buffer and then extracted by shaking for 24 h. The mixture was filtered, and the drug was assayed spectrophotometrically at 222 nm (Shimadzu UV-1208)

Dissolution Testing of Tablets

In vitro drug-release studies were performed by using a USP dissolution rate apparatus (apparatus 1, 100 rpm, $37 \pm 0.5^\circ\text{C}$) in pH 0.1N hydrochloric acid buffer (900 ml) for 2 h as the average gastric emptying time. Then, the dissolution medium was replaced with a pH 7.4 phosphate buffer (900 ml), and the experiment continued for another 10 h. The amount of MT released from the tablets at different time intervals was determined spectrophotometrically at 222 nm (Shimadzu UV-1208). Commercial MT SR tablets were also studied for comparison purpose. During the drug-release studies, all formulations were observed for physical integrity. All experiments were done in triplicate.

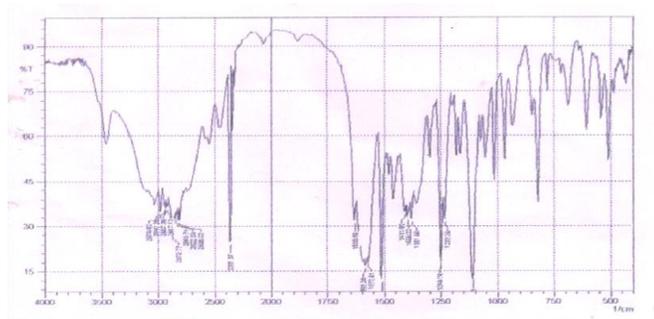


Figure 1: IR Spectra of Metoprolol tartrate

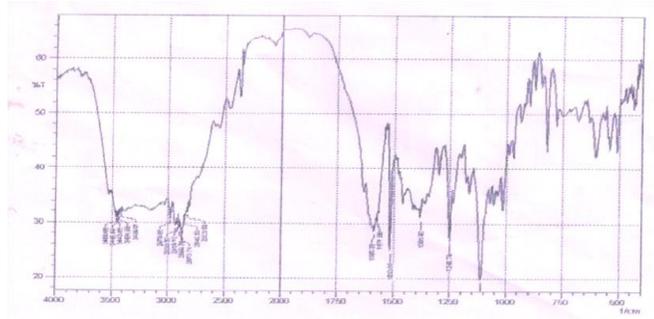


Figure 2: IR Spectra of drug and excipients mixture (CAP, HPMC, DRUG, Lactose)

Target-Release Profile Generation

In order to select the ideal dissolution profile obtained from formulations, the appropriate target profile of MT was needed for twice-daily administration. The target release profile of MT was plotted according to drug release by zero-order process using Eqs. 2-4 ^{17,18}.

$$kr_o = k_d \times C_{max} \times V_d \dots\dots\dots 2$$

$$k_d \times t_{1/2} = 0.693 \dots\dots\dots 3$$

$$D = kr_o \times h \dots\dots\dots 4$$

Where,

kr_o : zero-order release rate constant,

k_d : drug elimination rate constant,

C_{max} : peak concentration of drug released,

V_d : apparent volume of distribution,

$t_{1/2}$: plasma half life,

D : maintenance dose;

h is the total desired time for sustained action in hours.

$$t_{1/2} = 3.2 \pm 0.2 \text{ h}$$

$$V_d = 4.2 \pm 0.7 \text{ l/kg}$$

$$C_{max1} = 99 \pm 53 \text{ ng/ml (extensive metabolism)}$$

$$C_{max2} = 262 \pm 29 \text{ ng/ml (poor metabolism)}$$

Determination of Release Mechanism

The dissolution data, obtained up to 12 h, were fitted to Peppas equation, and best-fit parameters were calculated in order to determine the release mechanism.

STABILITY STUDY

Stability is most important aspects for the formulation development. It is important that a person produces the stable product. Stability is also important for the regulatory purpose. As the regulatory agencies around the world have their own product stability guidelines. The stability study is performed to check the physical chemical integrity of the product. For performing the stability study storage condition was determined based on ICH Guidelines.

The selected F9 batch was subjected to stability study. All the tablets were packed in aluminum foil, at the end of every week; the tablets were visually examined for any physical changes and changes in drug content for 2 month.

Storage conditions:

1. 40°C/75 % RH
2. 30°C/65 % RH
3. 25°C/60 % RH

Statistical Study

Physical tests of tablets, drug content uniformity testing and dissolution testing. Comparisons among the multiple means of dissolution data were made by analysis of variance. Tukey HSD or Dunnet C/one-way ANOVA test was used according to the variance homogeneity. $p < 0.05$ was considered to be statistically significant.

RESULTS

Physical Tests of Table

The characteristics of MT tablets which were found good for controlled release tablets. Hardness of tablet(optimized) is $14.16 \pm 0.16 \text{ kg/cm}^2$, thickness $5.13 \pm 0.01 \text{ mm}$, friability 0.22% . In this formulation CAP 100mg, HPMC K 100M 75mg, Lactose 82.5mg and other exipients.

Validation of UV-Spectroscopic Method

Calculated regression variations of plotted standard curves were $Y = 0.0245X + 0.0184$ and $Y = 0.0252X + 0.0459$ in pH 0.1N hydrochloric acid buffer and pH 7.4 phosphate buffer, respectively. Y corresponds to the concentration ($\mu\text{g/ml}$) and X corresponds to the absorbance. The sensitivity of the standard calibration curve in both media is 5–40 $\mu\text{g/ml}$. The standard curves and equations of MT in both pH 0.1N hydrochloric acid buffer and pH 7.4 phosphate buffer.

$$Y = 0.004x + 0.007$$

$$R^2 = 0.997$$

In Vitro Drug Release Studies:

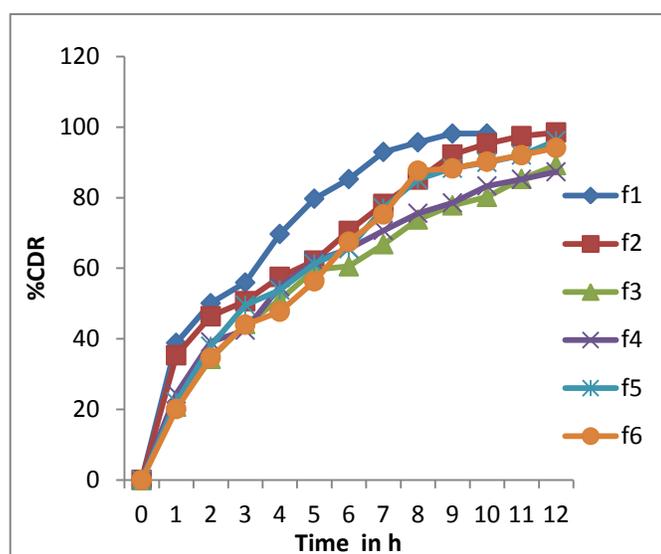


Figure 3 Dissolution Profile of Formulations F1-F6

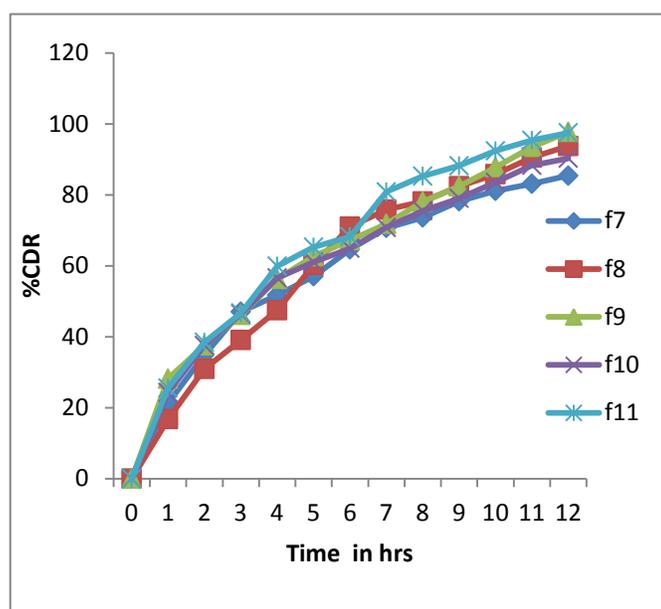


Figure 4: Dissolution Profile of Formulations F7- F11

CONCLUSIONS

CR matrix tablets of Metoprolol tartrate conforming to good quality were prepared using HPMC and CAP by the wet granulation method. Release rate of the drug from the matrix tablets was dependon CAP and proportion as well as viscosity of HPMC used. The effect of compression force on the drug release was more pronounced at lower compression forces than at higher compression forces. Drug release was found to follow a non-Fickian or anomalous release mechanism. The designed CR matrix tablets of Metoprolol tartrate, which release 20% to 30% of drug in the first hour and extend the release up to 16 to 20 hours, can overcome the disadvantages associated with conventional tablet formulations of Metoprolol tartrate.

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