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Research Article

FORMULATION AND EVALUATION OF EXTENDED RELEASE MONOLITHIC MATRIX TABLETS OF METOPROLOL SUCCINATE

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Abstract: The present investigation was undertaken to fabricate once- daily extended release monolithic matrix tablets of Metoprolol succinate by direct compression method to overcome its side effects, to increase bioavailability, to reduce the dosing frequency and to improve the patient compliance. The tablets were prepared using xanthan gum. Prepared matrix tablets were evaluated for various parameters like hardness, friability, weight variation, percentage of drug content. Tablet formulations were subjected to in vitro drug release studies as per USP guidelines. The formulation containing drug: Xanthan gum ratio 1:1.5 offered the required *in - vitro* drug release according to the official limits of drug release as per USP. The economy of Xanthan gum & faster hydration rate favors its use in modified release tablets. Xanthan gum can effectively control the drug release for freely soluble drug in case of extended release formulations which are upcoming dosage forms for patient compliance in all aspects.

Key**words:** Extended release tablets, Metoprolol succcinate, Matrix tablets and Xanthan gum

INTRODUCTION

Oral administration is the most popular route for drug delivery and the concept of regulated drug delivery in the human body has been in existence for many years because of major benefits such as improved patient compliance and decreased side effects. Hydrophillic matrix formulates is one of the least approach for developing extended release dosage forms to allow at least a twofold reduction in dosing frequency or patient compliance when compared to conventional immediate release dosage form . Extended drug delivery systems are used in the treatment of chronic rather than the acute condition, and they process a good margin of safety. [1, 2 & 3]

Metoprolol ((+)-1- (isopropyl amino) – 3- [p- (2-methoxy ethyl)] - 2- propanol succinate) is a selective β adrenergic receptor blocker useful in the treatment of hypertension, angina pectoris and heart failure. Metoprolol Succinate is a white powder with high aqueous solubility and high permeability throughout the gastro intestinal tract. Half life of metoprolol succinate ranges from 3 – 7 hrs. Its bioavailability is 50 % following oral administration. It has been reported that conventional dosage forms increase the plasma concentration of metoprolol above that achieving the mximum β_1 blockage (> 300 nM). A therapeutic level of β_2 blockage but little additional β1 blockage is achieved when plasma concentration is in the range of 80 – 300 nM. Higher concentration produces more β_2 blockage but little additional 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 avoid the extreme peaks and troughs characteristics of metoprolol immediate release formulation. [4]

Metoprolol is a recemic mixture of R and S enantiomers and is primarily metabolized by CYP2D6. When administered orally it exhibits stereo selective metabolism that is dependent on oxidation phenotype.[5] When dose is missing it may cause nocturnal attack so attention was paid to develop the extended release tablets of metoprolol succinate by utilizing different concentrations of xanthan gum. Xanthan gum is a high molecular weight extracellular polysaccharide produced by fermentation process from microorganism, *Xanthomonas campestris.* Xanthan gum is biodegradable, biocompatible and form gel in water. It is readily available, cheap and has good flow properties.[6]

MATERIALS AND METHODS

Metoprolol succinate was obtained from Aman scientific Ltd. Xanthan gum, di calcium phosphate, magnesium stearate and talc (SD Fine Chemicals Ltd., Mumbai). All other materials were of analytical grade.

Micromeritics of formulation powder blend:

Bulk density & tapped density of the powder blend was determined. Carr's index and Hausner ratio was determined to assess the flow properties of the formulation blend.[5] The flow properties of powder blends are presented in table-1.

Table – 1: Micromeritics of formulation powder blend

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (1-BD/TD)*100 (%)	Hausner ratio (TD/BD)
F1	0.73	0.86	14.7	1.17
F2	0.75	0.87	13.63	1.15
F3	0.74	0.86	13.43	1.15

Preparation of tablets:

Matrix tablets containing metoprolol succinate (47.5 mg) were prepared by direct compression method.[7, 8] Xanthan gum was used as matrix forming material, dicalcium phosphate (DCP) was used as diluents. Magnesium stearate was incorporated as lubricant and talc was used as glidant. All the ingredients were passed through a # 80 sieve, weighed & blended to ensure thorough mixing and homogenization. The lubricated formulations were compressed using 12 station rotary tablet punching machine (Cadmach, Ahmedabad) using 10 mm flat faced punches punching machine. The composition of formulations is presented in table - 2

Evaluation of prepared matrix tablets

Hardness

The hardness of the tablets was determined using monsanto hardness tester. It is expressed in kg/cm^2. Ten tablets were randomly picked and hardness of the same tablets from each formulation was deter-mined. The mean and standard deviation values were also calculated.[9]

Friability test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The friability was then calculated by following equation. [9]

Friability (%) = $(W_o\text{-}W) / WX100$

Where, W_o = initial weight of tablets

W = Final weight of tablets

Weight variation test

Ten tablets were selected randomly from each formulation and individually weighed accurately on electronic balance (Shimadzu, Japan) and their average weight and deviations from average weight were calculated.[9]

Content uniformity test

Five tablets were selected randomly from each formulation and powdered in a mortar and the powder equivalent to 50 mg of drug was placed into 100 ml volumetric flask containing 20 ml of pH 6.8 phosphate buffer. The contents of the flask were filtered through a filter and the residue was washed with another 20 ml of pH 6.8 phosphate buffer and the volume was made up to the mark. The sample was suitably diluted and analyzed spectrophotometrically against blank (pH 6.8 phosphate buffer) at 274.0 nm using double-beam UV-visible spectrophotometer.[10]

In-vitro drug release studies

The *in - vitro* dissolution studies of sustained release matrix tablets of metoprolol succinate were carried out using USP dissolution test apparatus, employing a paddle stirrer at 50 rpm in 500 ml of pH 6.8 phosphate buffer at 37.0°C ± 0.5°C. Then 5 ml of samples were collected and replaced with the same amount of dissolution medium at 1, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 h. The samples withdrawn were analyzed spectrophotometrically at 274.0 nm using UV-visible spectrophotometer (Shimadzu UV-1800 spectrophotometer).[11, 12]

Kinetic release studies

In order to investigate the mode of release from tablets, the release data was analysed with the following mathematical models. [13]

Zero order equation ($Q = K_o t$),

First order equation {$In (100\text{-}Q) = In\ Q\text{-}K_1 t$},

Higuchi equation ($Q == kt^{1/2}$),

Korsmeyer and peppas equation ($Q= k_p t^n$),

Where Q is the percent of the drug release at time t and

k_o and k_t are the coefficients of equation.

K_p is constant incorporating structural and geometric characteristics of the release device

n is the release exponent indicate the release mechanism.

The values of mathematical modeling and drug release kinetics are given in Table 3

Drug-excipients interaction study

(FT-IR spectroscopy)This study was conducted to find out the compatibility between the drug metoprolol succinate, xantham gum and other excipients. First of all, 10 mg of the sample and 400 mg of KBr were taken in a mortar and triturated. A small amount of the triturated sample was taken into a pellet maker and was compressed at 10 kg/cm^2 pressure using a hydraulic press. The pellet was kept onto the sample holder and scanned from 4000 cm^{-1} to 400 cm^{-1} in Shimadzu FT - IR spectrophotometer.

RESULTS AND DISCUSSION

As the formulation powder blends showed satisfied flow properties because of directly compressible excipients. The matrix tablets of metoprolol succinate were prepared by direct compression method using different drug: polymer ratios (1:0.5, 1:1 and 1:1.5) as given is Table 2.

Table 2: Composition of matrix tablets of metoprolol succinate

Ingredients mg / tablet	Formulation code		
	F1 (1:0.5)	F2 (1:1)	F3 (1:1.5)
Metoprolol succinate	47.5	47.5	47.5
Xanthan gum	23.75	47.5	71.25
Di calcium phosphate	320.75	297	273.25
Magnesium stearate	4	4	4
Talc	4	4	4
Total weight	400	400	400

All the prepared matrix tablets were evaluated for physical parameters like hardness, thickness, weight variation, friability, drug content uniformity, swelling index, *in - vitro* drug release studies and drug-excipients interaction study (FT-IR spectroscopy).The results of all physical parameters of the prepared tablets are presented in Table 3. The hardness of all the prepared matrix tablets was found to be in the range of 5 to 6 kg/cm^2. The weight of all the 4 tablet formulations were found to be uniform as indicated by the low values of standard deviation, which are in the range of 399 to 399.3 mg. The friability of all the prepared tablet formulations was found to be in the range of 0.5 to 0.8%. The average drug content of matrix tablets was found to be within the range of 98.5 to 99.4% and low values of standard deviation indicate uniform distribution of the drug in all the prepared matrix tablets. All data revealed that all the tablet formulations complied with the pharmacopoeial limits.

Table – 3: Evaluation of physical parameters of matrix tablets

Formulation	Average weight(mg) Mean ± SD (n=10)	Hardness (kg/cm^2) Mean ± SD (n=3)	Friability (%)	Drug content (%) Mean ± SD (n=3)
F1	399.2 ± 1.22	5.6 ± 0.55	0.5	99 ± 0.88
F2	399± 1.24	5.2 ± 0.45	0.4	98.3 ± 0.5
F3	399.3 ± 0.948	5.0 ± 1.25	0.6	98.23 ± 1.12

The inverse relationship was noted between amount of xanthan gum and release rate of metoprolol succinate. Increasing the amount of gum in the formulation resulted in slower rate and decreased amount of drug release from the tablet. This slow release is because of the formation of a thick gel structure that delays drug release from the tablet matrix, results in extensive swelling. As a result of rheology of hydrated products, the swollen particles coalesce. This results in a continuous viscoelastic matrix that fills the interstices, maintaining the integrity of the tablet and retarding further penetration of the dissolution medium. Figure – 1 shows the dissolution profile of the three formulations of matoprolol succinate

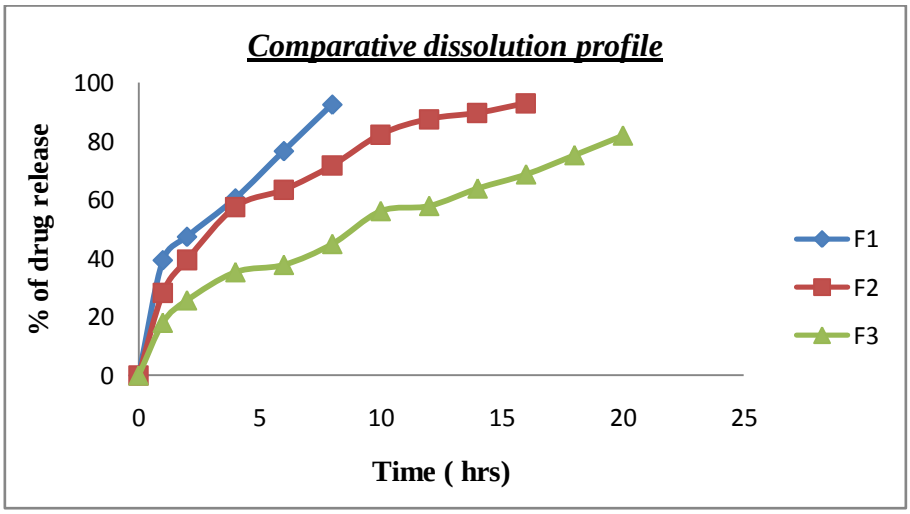

Figure 1: cumulative % drug release for the formulations F1, F2 and F3

Table 4: release profile of formulationF3 in comparison with USP Pharmacopoeial guidelines

Time (hours)	% Drug releases as specified in USP Pharmacopoeia	% Drug released
1	Not more than 25 %	18
4	Between 20 % and 40 %	35.25
8	Between 40 % and 60 %	44
20	Not less than 8 0 %	81.9

The formulation F3 (1:1.5) showed the best release rate and fulfilled the USP compendia requirements for release rate of extended release tablets as shown in table 4.

The in – vitro drug release data of all the prepared tablet formulations of metoprolol succinate were subjected to goodness of fit test by linear regression analysis according to zero and first order kinetics, whereas Higuchi's and Peppas equations to ascertain mechanisms of drug release. The drug release from all the prepared formulations were found to be following first order kinetics, non - Fickian diffusion mechanism because the release exponent in Peppas equation is > 0.5. The release kinetics of all formulations are presented in table – 5

Table- 5: Release kinetics of metoprolol succinate extended release tablets

Formulation code	Zero order R^2	First order R^2	Higuch R^2	Koremeyer-Peppas R^2	n	Hixon-Crowel R^2
F1	0.889	0.934	0.975	0.981	1.5	0.960
F2	0.885	0.991	0.983	0.984	1.4	0.973
F3	0.948	0.971	0.984	0.986	1.2	0.980

CONCLUSION

The results of the study demonstrate that hydrophilic natural polymer xanthangum can effectively control the extended release of Metoprolol succinate for 24 hrs. Direct compression is feasible for development once – daily extended release tablets of metoprolol succinate using xanthan gum at 1:1.5 ratio. It can be concluded that the development of extended release formulation of hydrophilic drugs does not necessitate the inclusion of hydrophobic polymers to hydrophilic polymers and the desired extended release of hydrophilic drugs is also viable with hydrophilic polymer alone

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