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COMPARATIVE STUDY OF MARKETED METOPROLOL SUCCINATE EXTENDED RELEASE TABLETS

Marturi Ram Murthi*, Bangaruthalli J., K. Sandheep Kumar Reddy, L. Ramanamma, S. Asha and R. Urmila

A. U. College of Pharmaceutical Sciences, Andhra University, India.

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***Corresponding Author**
Marturi Ram Murthi
A. U. College of Pharmaceutical Sciences, Andhra University, India.

ABSTRACT

The Objective of The Present Study was for improving bioavailability and reducing the dosage frequency of Metoprolol Succinate in the form of extended release tablets by pan coating technology. Initially drug solution coated on different cores i.e. water soluble, insoluble and swellable cores and layered by different combinations of extended release polymers as ethyl cellulose 10 tab + HPMC (Hydroxy Propyl Methyl Cellulose), ethyl cellulose 10 tab + di ethyl phthalate and ethyl cellulose 10 tab + HPMC+ diethyl phthalate. Formulated tablets were evaluated for flow properties, surface morphology, size analysis and *in vitro* dissolution studies. Studies were done on the effect of core nature and coating composition and effect of plasticizer. *In vitro* dissolution studies revealed that higher release observed from water-soluble core compared to insoluble and swellable cores. Controlled drug release observed from coating composition containing combination of EC + diethyl phthalate. Moderate drug release observed from combination of HPMC + EC+ diethyl phthalate. The mechanism of drug release follows Higuchi diffusion model. In conclusion the resulting formulations F6 (Water soluble core and coat was EC 10 cps + HPMC+ Di ethyl phthalate) can reducing frequency of the Metoprolol succinate to once day.

KEYWORDS: Metoprolol succinate, Pellets, HPMC, Di ethyl phthalate, Plasticizer, Sustained release tablets, Non Fickian Mechanism.

INTRODUCTION

Several approaches existed for administration of drugs to the patients. In all those approaches oral administration has been received more attention due to more flexibility in designing of dosage forms. From the years onwards tremendous work had done for designing of controlled

delivery systems to reduce the fluctuations in plasma concentrations which is observed in conventional delivery. The main aim in designing of controlled delivery is to reduce fluctuations in plasma concentrations and increasing the patient compliance. Now a days in pharmaceutical market per oral multi-unit controlled release dosage forms (pellets, granules, Nano particles, micro particles, mini tablets) are more important than single unit dosage forms (tablets and capsules) due to low risk of dose dumping, increasing the bioavailability of drugs, flexibility to produce different release patterns and targeted drug delivery.

Palletisation technology is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small free flowing spherical units, (0.5 to 1.5 mm) known as pellets. Pellets not only have technological advancements but also show better flow properties, uniform and reproducible fill weights of capsules and tablets, disperse freely in GI tract leads to maximum drug absorption and pack easily without significant difficulties. Coating of multi-particulates is used for modifying the drug release such as targeted or extended release.

Metoprolol succinate is cardio selective β1 blocker used for the treatment of angina pectoris, hypertension and heart failure. According to the Biopharmaceutical classification system (BCS) Metoprolol succinate comes under class I drug means that highly soluble and highly permeable. It is rapidly and completely absorbed but due to extensive first pass effect, it is bioavailable only 50% after oral administration. Due to its short half-life (3-7 Hrs.) drug should be administer 4 times daily. Whenever dose is missing leads to nocturnal attack. Therapeutic level of β1 (beta 1) blockage occurs when plasma concentration is 80-300 nm. Immediate release dosage forms increase the plasma concentration above 300nM leads to more β2 (beta 2) blockage and little β1 blockade. For maintaining the therapeutic concentration and eliminating the fluctuation in plasma concentration Metoprolol succinate is suitable agent for controlled drug delivery.

It is a challenge to pharmaceutical technologist to design a sustained release dosage form for class I drugs having extensive hepatic metabolism like Metoprolol succinate. Poor formulation leads to high rate of drug release and produce toxic concentrations in the body. Polymeric film coatings used for achieving sustained release because coated dosage forms enable précised drug release with good reproducibility.

Main objective of the present study is to prepare extended release pellets of Metoprolol succinate by using three different inert cores i.e. water soluble, water insoluble and water swellable and to study the effect of coating composition and the effect of water insoluble plasticizer in drug release. In the present study Hydroxy propyl methyl cellulose (HPMC) confers more hydrophilic nature to the film and alters its structure by virtue of pores and channels through which the substance can diffuse more easily to control the release pattern. Ethyl cellulose (EC) 10 tablets are used as water insoluble polymer and di ethyl phthalate is used as water insoluble plasticizer.

MATERIALS AND METHODS

Materials: Metoprolol Succinate, water swellable core, insoluble core and soluble cores was obtained from Hetero drugs limited, Hyderabad, India. Hydroxy propyl methyl cellulose (HPMC), ethyl cellulose 10 tablets (PVP) were obtained from Desai chemical company, Visakhapatnam, India. Remaining all chemicals used were analytical grade.

Water soluble, water in soluble and swellable) were sieved through 80# and drug loaded tablets were prepared by layering the aqueous solution of Metoprolol succinate on inert cores using fluid bed processor (Wurster technique).

Drug solution was prepared by heating the purified water up to 60°C and Metoprolol succinate was Formulation of Extended release tablets:

A) Coating of the core tablets with drug solution

Inert cores (slowly added while heating with continuous stirring by pneumatic stirrer to get clear solution.

Sprayed the drug solution on the pre-warmed the inert core beads by using Wurster technique. Continued the drug-loading till desired weight gain occurs to yield the unit dose as per the formula. After coating pellets were dried with an inlet air temperature maintained at 40 ± 3°C for 1 hour.

B) Extended release coating of drug tablets

Ethyl cellulose was dissolved in required quantity of isopropyl alcohol with continuous stirring To prevent formation of lumps and foam. To this 5% methylene chloride solution was added to Get clear solution. This is to evaluate the effect of plasticizer and polymer on dissolution behaviour.

Characterization of tablets

Prepared Metoprolol succinate extended release tablets were evaluated for particle size, size distribution surface morphology, density, porosity, flow properties, friability drug content and in vitro dissolution studies.

Surface Morphology

Surface morphology of extended release coated pellets was observed before and after dissolution by Trinocular Microscope (with DE winter pharmapro 4.0 software) which was attached with a camera (Nikon).

Particle Size distribution

Mechanical sieve shaker was used to evaluate the particle size distribution of tablets of each core.

Drug content

Tablets of weight equivalent to unit dosage form were transferred in to 100ml volumetric flask. To this 10ml of methanol and 10 ml of 6.8 pH phosphate buffer was added and sonicated for 20 min for complete solubilisation. Then make up the volume with phosphate buffer and dilutions were made to get the absorbance in linearity range and measured at 274 nm by using UV-Visible double beam spectrophotometer.

***In vitro* Dissolution study & Kinetics**

Dissolution study of formulations M1, M2 & M3 was performed using USP 23 Dissolution procedure over a 24-hour period, using an automated Electro lab paddle dissolution system tester coupled to an automated sample collector. Capsule containing pellets equivalent to 50 mg were taken and release study performed in 900ml of pH 6.8 phosphate buffer with USP Type-II apparatus at 100 rpm with temperature of 37 ± 0.5°C. At the predetermined sampling points (1, 2, 4, 8, 12 and 24 hours) 5 ml of aliquot sample was withdrawn and replaced with fresh dissolution medium. Tablets release of corresponding core was determined by UV-Visible Spectrophotometer at 274 nm.

In vitro drug release data was fitted into various mathematical models, zero-order, first – order, Higuchi for determination of rate and drug release mechanism.

Comparative dissolution profile of optimized formulation and marketed formulation

In vitro dissolution profile of optimized formulation was compared with the similarity factor using marketed drug release profile (METOPOLE XL 50) as a reference. Similarity factor is a logarithmic reciprocal square root transformation to the sum of squared errors. If f2 value in between 50-100 two dissolution profiles considered to be similar.

Stability studies

Stability studies were performed according to ICH guidelines for the optimized formulation. Optimized formulation was kept at humidity chamber maintained at 40^{o}C and 75% relative humidity (RH) for 3 months. The sample was analysed for the physical changes and percent drug content at interval of 7, 15, 30, 60 and 90 days.

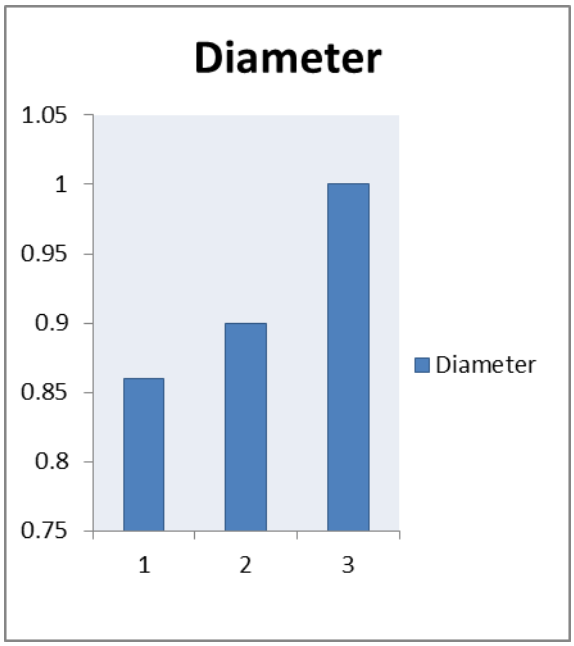
RESULTS AND DISCUSSION

Three commercially available marketed metoprolol succinate extended release tablets were selected and evaluated the details of the tablets is given in the table below.

Code:	**M1**	**M2**	**M3**
Brand name:	METOPOLE XL 50	METODER XL50	MET XL 50
Manufactured by:	KNOLL	ELDER	AJANTA

Tablet size and thickness.

Tablet code	**Thickness (mm)**	**Diameter (mm)**	**Hardness (kg/cm^3)**
M 1	0.8	0.86	2.16
M2	0.8	0.9	2
M3	0.9	1.0	2.5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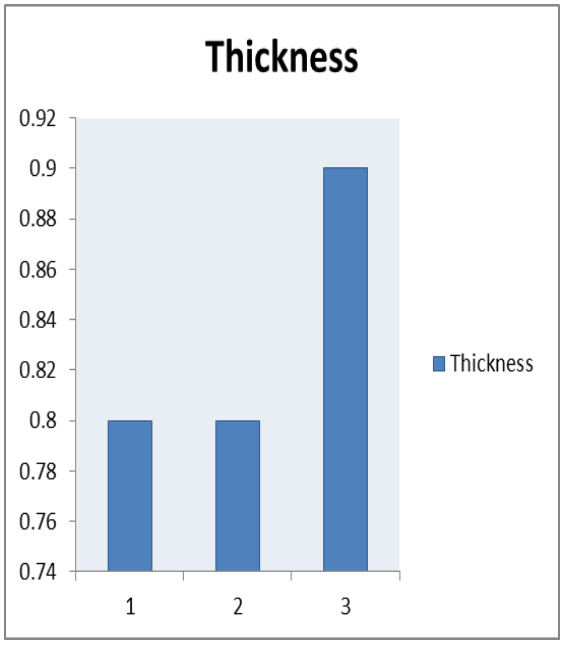
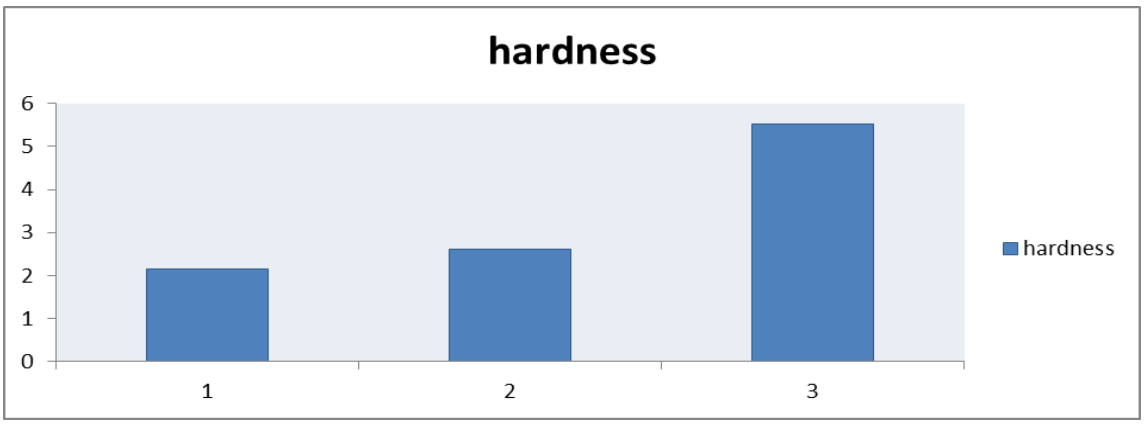
1
0.95
0.9
0.85
0.8
0.75
1
2
3
Diameter


Thickness
0.92
0.9
0.88
0.86
0.84
0.82
0.8
0.78
0.76
0.74
1
2
3
Thickness

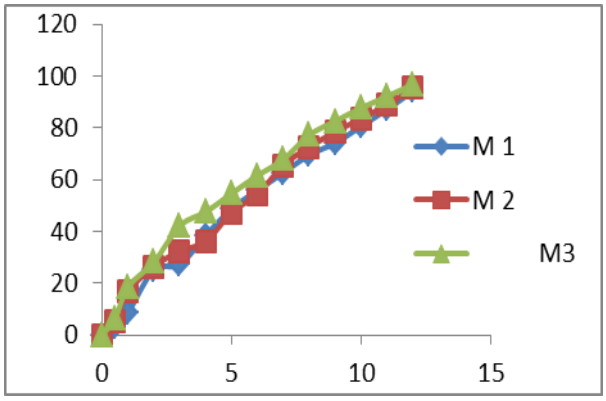

hardness
6
5
4
3
2
1
0
1
2
3
hardness

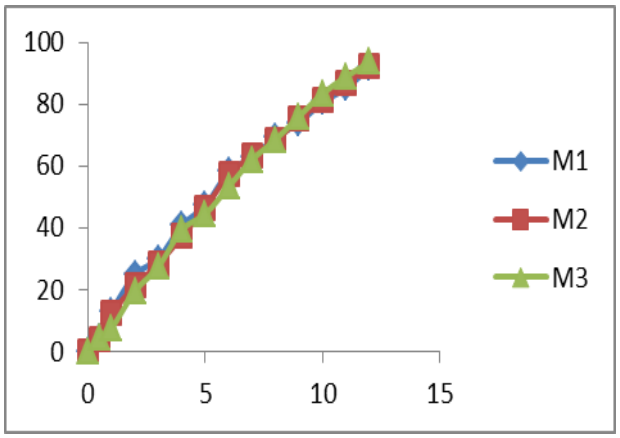
***Invitro* Dissolution Studies**

Three different brands of metoprolol succinate ER tablets M1, M2 and M3 were selected to compare the dissolution profiles.

***In-vitro* drug release profiles of different brands of Metoprolol succinate tablets in pH 1.2 HCl buffer and pH 6.8 phosphate buffer.**

Time (hrs.)	HCl buffer (pH 1.2)			phosphate buffer (pH 6.8)		
	M1	M2	M3	M1	M2	M3
0	**0**	**0**	**0**	**0**	**0**	**0**
0.5	3.2	5.5	6.2	4.6	3.8	4.5
1	8.6	16.7	18.5	13.1	12.3	7.6
2	25.1	26.4	28.1	24.8	21.2	19.5
3	27.2	32.3	42.1	30.1	28.4	27.5
4	38.5	36.1	47.5	40.8	37.3	39.4
5	48.6	47.3	54.6	47.3	46.5	44.5
6	55.9	54.4	61.5	58.2	57.3	53.4
7	62.6	65.5	67.8	62.8	63.2	62.1
8	69.5	72.6	77.2	69.3	68.3	38.6
9	74.1	78.4	82.4	74.1	75.2	76.1
10	80.6	83.6	87.6	80.6	81.3	83.4
11	87.1	88.8	92.1	85.2	86.7	88.9
12	94.2	95.4	96.7	91.8	92.5	93.6





***In Vitro* Dissolution Parameters of Metoprolol succinate ER Marketed Tablets**

In pH 1.2 HCl buffer and 6.8 phosphate buffer

Brands	Zero order plot		First order plot			Higuchi plot	Korsmeyer peppas plot		Release rate (Mg/hr.)	Possible mechanism of drug release
	R	Zero order Rate constant K0	R	n	First order Rate constant K1 (h-1)	R	R^2	n		
M1	0.91	110.699	0.96	0.24	0.4563	0.956	0.996	0.636	2.12	First order non-fickian diffusion
M2	0.925	9.8095	0.976	0.181	0.4226	0.9756	0.998	0.543	2.36	First order non-fickian diffusion
M3	0.886	8.997	0.948	0.155	0.389	0.936	0.922	0.517	2.40	First order non-fickian diffusion
Brands	**Zero order plot**		**First order plot**			**Higuchi plot**	**Korsmeyer peppas plot**		**Release rate (mg/hr)**	**Possible mechanism of drug release**
	R	**Zeroorder Rate constant K0**	**R**	**n**	**Firstorder Rate constant K1(h-1)**	**R**	**R^2**	**n**		
M1	0.95	110.699	0.96	0.24	0.4563	0.956	0.996	0.636	2.12	First order non-fickian diffusion
M2	0.92	9.8095	0.976	0.181	0.4226	0.9756	0.998	0.543	2.36	First order non-fickian diffusion
M3	0.86	8.997	0.948	0.155	0.389	0.936	0.922	0.517	2.40	First order non-fickian diffusion

CONCULSION

The rate of dissolution was dependent on the composition of dissolution medium. pH 1.2 Hcl buffer is equally suitable to pH 6.8 phosphate buffer for dissolution studies of Metaprolol succinate ER formulations and all the tablets follow nonfickian diffusion all the tablets are good.

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