SUSTAINED RELEASE MATRIX METOPROLOL TARTRATE WITH INLAY HYDROCHLOROTHIAZIDE TABLET

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ABSTRACT

The objective of the present study was to develop once-daily sustained release matrix tablets of metoprolol tartrate with inlay hydrochlorothiazide tablet as an immediate release formulation. The inlay tablets were prepared by wet granulation method using hydroxy propyl methylcellulose in various percentages. The drug-excipient incompatibility studies were performed by Differential Scanning Calorimetry(DSC).The granules showed satisfactory flow properties and compressibility. Five trial batches were prepared using various excipients. The trial batch M4(35% hydroxy propyl methyl cellulose) could extend the release of metoprolol tartrate for 24h and that of hydrochlorothiazide for 2h, which matched with the USP drug profile. The *in vitro* and the *in vivo* release studies in rabbit were performed. The mechanism of drug release was diffusion coupled with erosion. The stability studies were performed on trial batch M4 which were kept at 40°C and 75%Relative humidity for 90days and the product was evaluated every 30 days.

KEYWORDS

Metoprolol tartrate, hydroxy propyl methylcellulose, once-daily sustained release, Hypertension and soft X-ray

INTRODUCTION

Hypertension and angina pectoris, the most common cardiovascular diseases, require constant monitoring. Hypertension means high pressure in the arteries. High blood pressure does not mean excessive emotional tension, although emotional tension and stress can temporarily increase the blood pressure. Normal blood pressure is below 120/80; blood pressure between120/80 and 139/89 is called 'pre-hypertension' and a blood pressure of 140/90 or above is considered high blood pressure. High blood pressure is one of the most important modifiable risk factors for cardiovascular disease. Hypertension is designated as either primary hypertension or secondary hypertension.

Anti-hypertensive medications can be used alone or in combination. The goal of therapy for hypertension is to bring the blood pressure down to 140/85 in the general population and to even lower levels in diabetics, blacks and people with certain chronic kidney diseases. Beta-adrenergic blocking

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agents or beta blockers are used to treat cardiac arrhythmias[1] and angina pectoris. Diuretics can also be combined with other medication to treat hypertension[2].

Beta-blockers cause retention of sodium and water. Diuretics can cause mild volume reduction that leads to an increase in rennin secretion by the kidney. The rationale for combining beta blockers with diuretics is two fold: beta blockers blunt the increase in the plasma renin level that is induced by diuretics and diuretics decrease the sodium and water retention that is caused by beta blockers. The combination of a beta-blocker and a diuretic produces additive effects compared with monotherapy using either agent alone. A recent study assessed the safety and efficacy of anti-hypertensive therapy using the cardio selective beta-blocker metoprolol alone and in combination with low dosages of hydrochlorothiazide[2].

Sustained release dosage forms are designed to reduce the frequency of dosing and thus to improve the compliance. They also reduce variations in plasma/blood levels for more consistent results[3].

Present study is undertaken to combine the additive effect of metoprolol tartrate and hydrochlorothiazide as inlay tablets for sustained release combined dosage form, which will prolong the drug release leading to reduced frequency of dosing and for better control of hypertension by maintaining the plasma/blood level of the drug consistently.

MATERIALS AND METHODS

Materials

Metoprolol tartrate was purchased from Sun Pharmaceuticals. Hydrochlorothiazide was purchased from Unichem Laboratories Ltd. Hydroxy propyl methylcellulose (HPMC) K100 MCR was purchased from Colorcon Asia Pvt.Ltd. India . Avicel pH 102 was purchased from Pioma Chemicals. India. Starch was purchased from Colorcon Asia Pvt. Ltd. India. The other chemicals used were of analytical grade obtained from commercial sources. All materials were used as received.

Compatibility studies

Compatibility studies were performed by using differential scanning calorimetry (DSC S-650)[4] technique on the drug, excipients and polymers to determine any incompatibility between the ingredients.

Preparation of inlay tablets[5]

Different tablet formulations were prepared by wet granulation technique (formulations M1-M5). The formulations were composed of polymer HPMC K100 MCR in various percentages for the sustained release matrix. The hydrochlorothiazide immediate release[5] core for the inlay tablets were formulated using crospovidone by wet granulation method. All the powders were passed through 60 mesh sieve. Required quantity of drugs, polymers and diluents were mixed thoroughly and a sufficient quantity of granulating agent (isopropanol and water in the ratio 1:1) were added slowly to get a dough mass. The mass was sieved through 22/40 mesh and dried at 50° for 2h.The dried granules retained on 40 mesh were mixed with 2% talc and 1% magnesium stearate. The granules of hydrochlorothiazide were precompressed and then placed along with the granules of metoprolol tartrate for final compression for inlay tablets using punches of 23-station compression machine(Remik).

Evaluation of granules

The angle of repose was measured by a reposograph[6], whereby the cone formed on the base of reposograph was examined to observe the zone, which indicates the flowability of the granules. Bulk density

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(BD) (ρ_{bulk}) and tapped density (TD)(ρ_{tapped}) were measured using the formula: BD=weight of powder/volume of packing; TD=weight of powder/ tapped volume of packing. Compressibility index (CI) of the granules was determined by using the formula: CI (%) =100(ρ_{tapped} - ρ_{bulk}/ ρ_{tapped}) and Hausner ratio= (ρ_{tapped}/ ρ_{bulk}). Particle size distribution[7] was also determined by sieving method.

Physical characteristics of inlay tablets

The thickness and diameter were measured using a digital caliper. Hardness test was performed using a Monsanto hardness tester. Friability test was performed using Roche friability testing machine. Weight variation test was conducted as per specifications. Drug content uniformity [8]was also performed.

In vitro dissolution studies

The formulations M1-M5 were subjected to *in vitro* dissolution studies. The *in vitro* drug release studies were carried out using USP type II apparatus. The dissolution medium consisted of 900ml of 0.1N HCl and the paddle was rotated at 50 rpm for the first 2h.500ml of phosphate buffer pH 6.8 was used from the 3h to 24h.The paddle was rotated at 100 rpm for the first 2h of phosphate buffer pH 6.8.Aliquots were collected at pre determined time intervals and the samples were analyzed by HPLC. The formulation M4 was found to adhere USP limits .The *in vitro* release profile of M4 was tabulated and further studies were carried on.

Stability studies[9]

The formulated inlay tablets of metoprolol tartrate and hydrochlorothiazide of trial batch M4 was subjected to stability studies at 40°/75%RH for 90d.The product was evaluated for appearance and hardness every 30d.

In vivo studies

In vivo studies were conducted by X-ray analysis[10] to study the adherence activity of the inlay tablet in comparison with the dummy tablet in rabbits. The inlay tablets were incorporated with barium sulphate in the place of drug and X-ray analysis was carried out in comparison with the dummy tablet incorporated with barium sulphate. The tablets were administered by oral route through a stomach tube and flushing 5ml of water from the syringe through the tube and the X-ray analysis were carried out at regular intervals of time.

RESULTS AND DISCUSSION

The present investigation was undertaken to design ,formulate (Table 1) and evaluate metoprolol tartrate sustained release and hydrochlorothiazide immediate release inlay tablet for combined dosage form. DSC studies indicate good compatibility between drugs, polymers and excipients (Fig.1).

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Table 1.
Composition of tablet formulations
(a) For metoprolol tartrate (sustained release granules)

Ingredients (mg/tablet)	**M1**	**M2**	**M3**	**M4**	**M5**
Metoprolol Tartrate	50	50	50	50	50
HPMC K100MCR	10	20	25	30	50
Avicel pH-102	159	149	144	139	119
HPMC K 100 MCR (Lubrication)	75	75	75	75	75
Magnesium Stearate	3	3	3	3	3
Aerosil	3	3	3	3	3
Total	300	300	300	300	300

Quantities are in milligrams per tablet.

(b) For hydrochlorothiazide (Immediate release granules)

Ingredients (mg/tablet)	**H1**
Hydrochlorothiazide	6.25
Micro Crystalline Cellulose	11.25
Lactose	11.25
Starch	15.9
Starch (Paste)	1.6
Starch (Lubrication)	0.25

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Magnesium Stearate	1
Crospovidone	2.5
Total	50

Quantities are in milligrams per tablet.

Table 2.
Evaluation data of granules

Formulation code	Bulk density(g/ml)	Compressibility Index (%)	Angle of repose	Hausner's ratio	Particle size
M4	0.38±0.02	13.72±0.03	$24^0$12'±0.04	1.372±0.01	412±0.01
H1	0.47±0.01	20.07±0.01	$28^0$37'±0.03	1.2104±0.02	147±0.03

All the values are Mean ±S.D. of n=5

Table3
In vitro cummulative percentage drug release profile of formulation M4 for 24 h

S.No	Time (hour)	pH of the medium	Mean area of the peak	In *vitro* percentage drug release*		USP Limits
				Hydrochlorothiazide	Metoprolol Tartrate	
1	1	1.2	48231.5 1173566.5#	79.2	16.225	Not more than 10% - 25%
2	2	1.2	57907.8 1489822.8#	100.54	19.48	-----
3	4	6.8	161306.8	-	29.23	Between 25% - 40%
4	8	6.8	29440.3	-	53.35	Between 40% - 60%
5	12	6.8	399984.3	-	72.48	----
6	16	6.8	461889.1	-	83.7	-----
7	20	6.8	520102.3	-	94.25	Not less than 80%
8	24	6.8	566836.3	-	102.72	------

*Values expressed as mean of triplicates.

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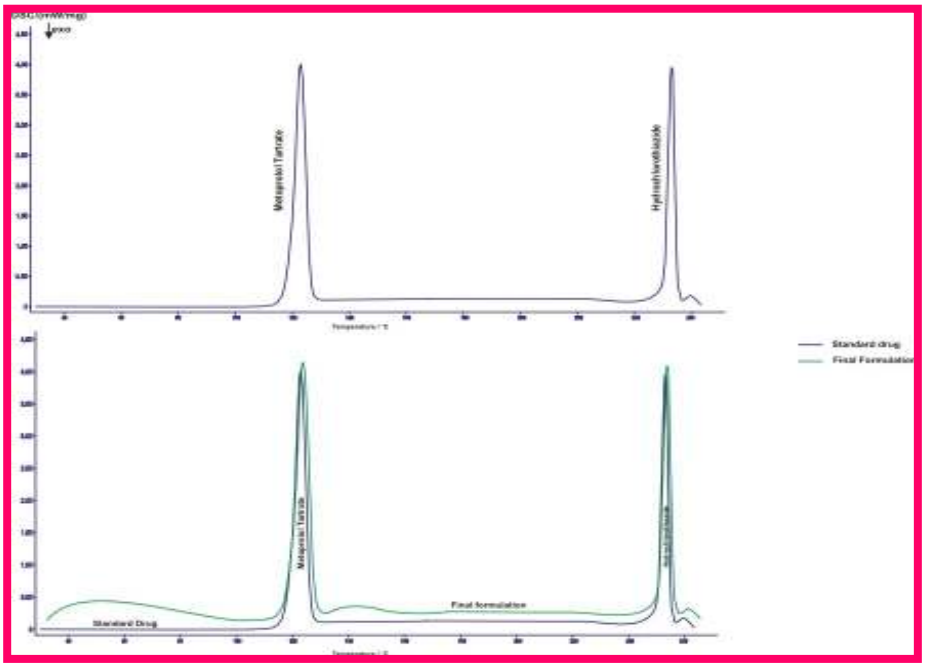
Fig.1.

DSC thermograms showing compatibility of metoprolol tartrate and hydrochlorothiazide with the excipients and polymers in the inlay tablets



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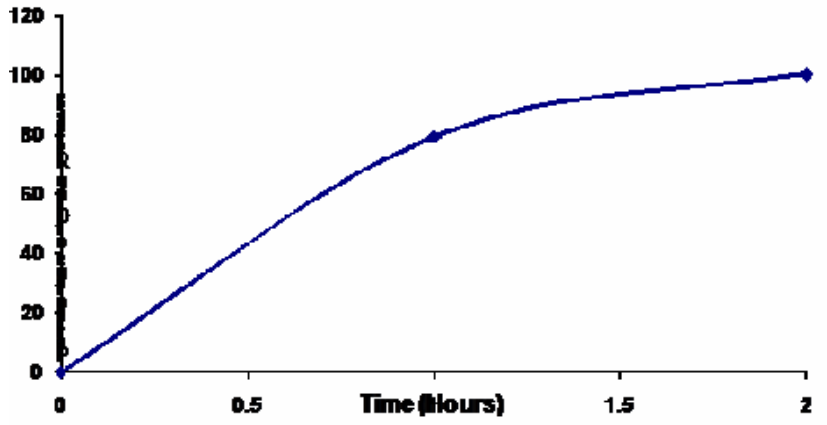

Fig.2. *In vitro* cumulative percent drug release Vs time (h) profile of metoprolol tartrate M4

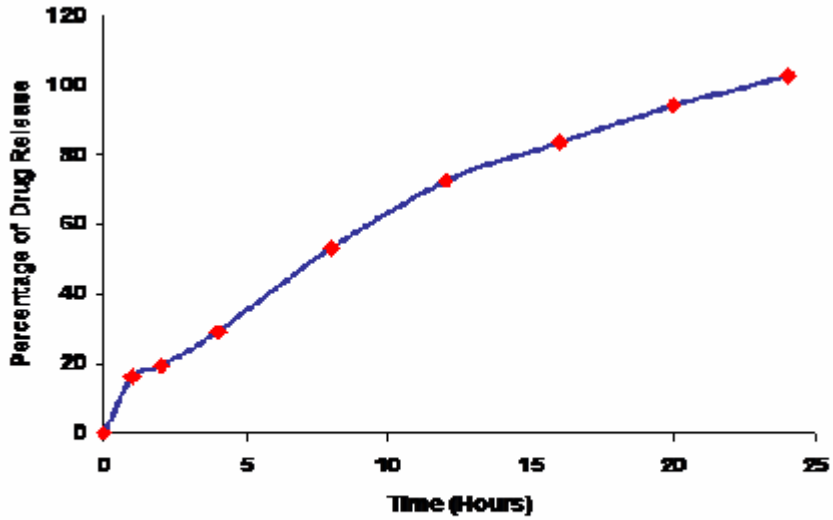

Fig.3: *In vitro* cumulative percent drug release Vs time (h) profile of Hydrochlorothizide (H1).

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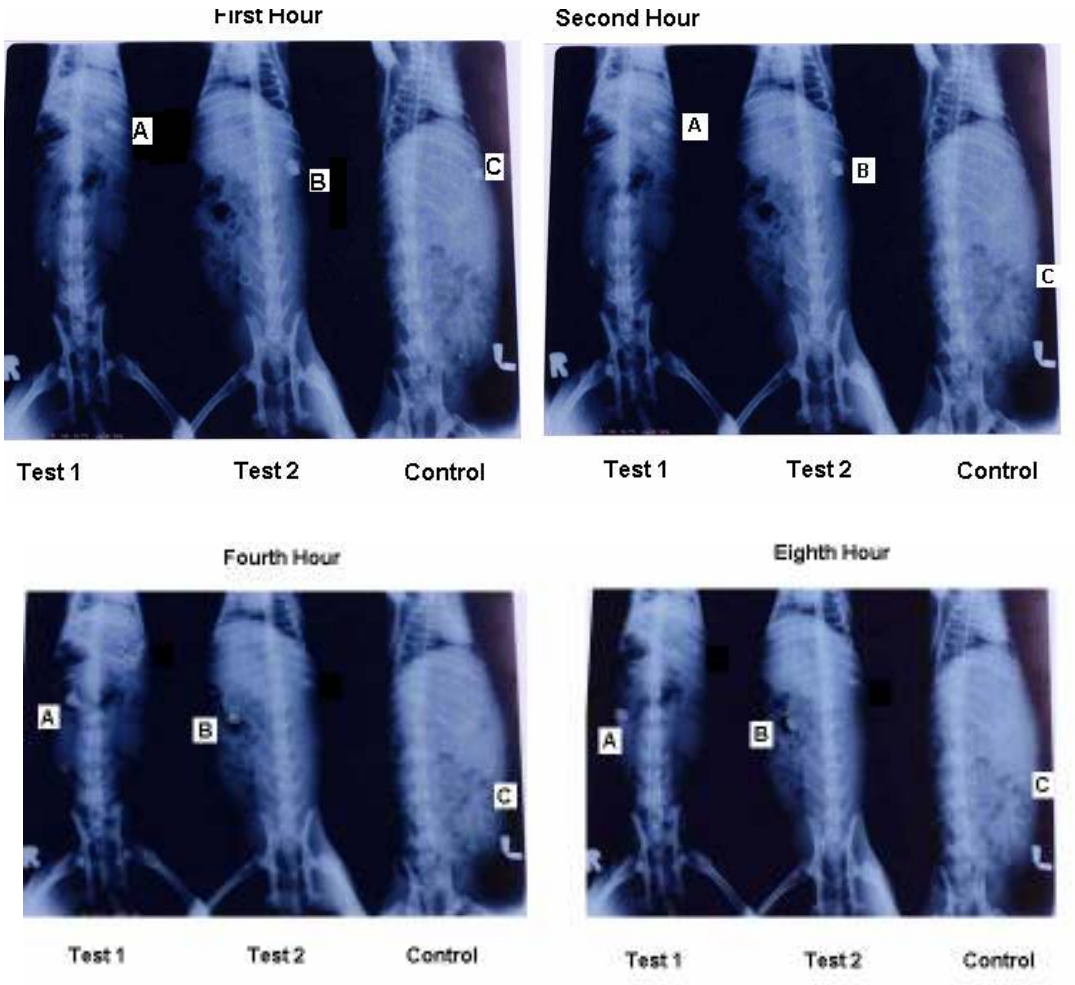

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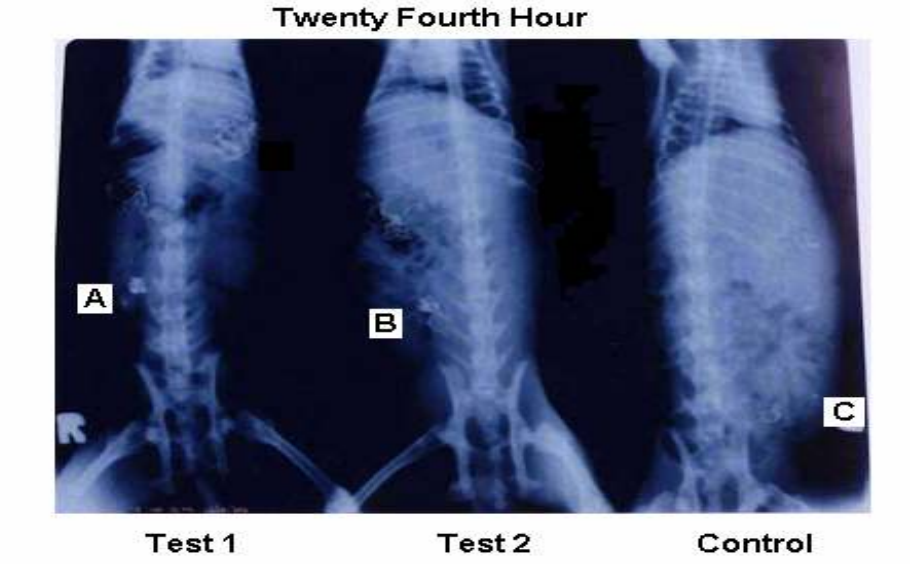

Fig.4.Soft X-ray photographs showing the sustaining effect of inlay tablets of metoprolol tartrate and hydrochlorothiazide

The granules of formulations were evaluated for angle of repose, bulk density, compressibility index, particle size. The granules indicated excellent flowability with the angle of repose value ranging from 25-30% according to reposograph readings. The results of bulk density, compressibility index are mentioned in Table 2.The results of compressibility index lies between 13.72±0.03 and 20.07±0.01 which is below20% indicating fair to good flow properties. All tablet formulations were subjected to various evalution parameters and the results obtained were within the range. The weight variation test indicates that all the tablets were uniform with low standard deviation values. The tablets mean thickness and mean diameter values ranged from 5.07±0.03mm to 5.64±0.02mm and 8.52± 0.02mm to 8.94±0.03mm respectively. The hardness of all the tablets were within a range of 8.4±0.03 to 10±0.02 kg/cm^2.The loss in total weight in friability test was in a range of 0.0972 to 0.0982%.The percentage drug content for different tablet formulations (Table 3) varied from 99.41 to 102.56 % for metoprolol tartrate and 98.67 to 100.04 % for hydrochlorothiazide, were found to be within range.

F4 was selected as the optimum formulation on the basis of results of *in vitro* dissolution studies, which indicates maximum sustained release till 24 h for metoprolol tartrate and immediate release of hydrochlorothiazide extending up to 2h from a single sustained release matrix metoprolol tartrate with inlay hydrochlorothiazide tablets. F4 (35% HPMC K 100 MCR) showed 102.72% metaprolol tartrate release at the end of 24h and hydrochlorothiazide showed 100.54% release at the of 2h.

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The *in vivo* studies were carried out in rabbit using soft X-ray analysis. The polymer utilized for the optimization of the formulation showed the sustaining activity *in vivo* in rabbit by adhering to various sites in the gastrointestinal tract. The inlay tablets showed sustaining effect for 24 h as shown in (Fig.4).

From the above results it can be concluded that formulation F4 has achieved the objectives of sustained release for metoprolol tartrate and immediate release for hydrochlorothiazide, patient convenience and cost effectiveness as a combined dosage form and appears to be assessed further by conducting bioavailability studies in human volunteers and long term stability testing.

ACKNOWLEDGEMENT

Authors are thankful to Vel's College of Pharmacy, Pallavaram, Chennai for providing necessary facilities to conduct the work.

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