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Research Article

FORMULATION AND EVALUATION OF BILAYER TABLET OF METOPROLOL SUCCINATE AND RAMIPRIL

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ABSTRACT

In the present investigation an attempt was made to reduce the frequency and units of dose administration, to prevent nocturnal heart attack and to improve the patient compliance by developing a Bilayer tablet having extended release (ER) layer of Metoprolol succinate and immediate release(IR) layer of Ramipril. Ten batches of ER/IR Bilayer tablets of Metoprolol succinate and Ramipril were developed by using wet granulation and dry granulation technique, respectively. Hydroxylpropylmethylcellulose K100M and Sodium Carboxymethylcellulose was used for extended release of Metoprolol succinate. Preformulation studies of Metoprolol succinate and Ramipril like compatibility studies with polymers, using FTIR and DSC were carried out. The drugs and Excipients was found to be compatible with each other. Compressed tablets were evaluated for weight variation, hardness, and in vitro dissolution using paddle (USP type II) method. Among the Ten formulations, F_{10} showed compliance with US pharmacopoeial standards, extend the release of drug for 20 hours with 99.6% drug release and subjected to stability studies for 1 month at 40 ^{0}C/75% RH.

Keywords: Bilayer tablet, Metoprolol Succinate, Ramipril

INTRODUCTION

The oral route of drug administration is the most convenient and commonly used method of drug delivery. Layer tablets are composed of two or three layers of granulation compressed together. It makes possible to formulate sustained release preparation as one layer with the immediate release preparation as the second layer.[1,2]

Hypertension is the most common cardiovascular disease; its prevalence increases with advancing age. Hypertension is the principal cause of stroke, is a major risk factor for coronary artery disease and its complications, and is a major contributor to cardiac failure, renal insufficiency, and dissecting aortic aneurysm. Hypertension is defined as a sustained increase in blood pressure ≥140/90 mm Hg.[3]

Literature survey shows that, a combination of ACE inhibitors and beta blockers helps for the improvement in cardiac function after myocardial infarction. Metoprolol reduces blood pressure (BP) by competitive antagonism of catecholamine peripherally and through suppression of renin activity. Ramipril reduces BP by inhibition of the angiotensin converting enzyme. This combination does not have any pharmacokinetic interaction. A combination of ACE inhibitors and beta blockers helps for the improvement in cardiac function after myocardial infarction.

Metoprolol succinate is Class-I drug and has very short half life i.e. 3-4hrs. So, to Reduce frequency of administration of drug in a day Extended release tablet of Metoprolol Succinate is formulated.[4] 444bjk44

Ramipril is Class-I drug and has a longer half life 9-18hrs. As it is moisture and light sensitive Direct compression was done to avoid the instability due to moisture. Coating was also done to avoid direct contact of Ramipril with light.

The present work aims to develop a stable and optimized Bilayer dosage form containing one immediate release drug Ramipril and another extended release drug metoprolol succinate.

MATERIALS AND METHODS

Metoprolol succinate was supplied by CTX Life sciences Pvt. Ltd, Ramipril was supplied by Neuland Lab. Ltd, Hyderabad, (A.P., India). HPMC K100M, Metalose 90 SH, Sodium CMC, Ethyl Cellulose E 50 were supplied by Colorcon Asia Private Limited, (Goa, India). Povidone K-30 (PVP K-30) was supplied by Boai Nky pharma Ltd. Lactose, Pregelatinised Starch (Lycatab PGS) were supplied by Roquette Signet Chemical Corp. Calcium Sulphate Dihydrate, Cross carmellose sodium, Polyethylene glycol-6000 were supplied by Ascot Pharmachem PVT. Ltd, Vadodara. All solvents used were of analytical grade.

Fourier transforms infrared (FT-IR) spectroscopy

Compatibility studies were carried out to know the possible interactions between Metoprolol Succinate, Ramipril and excipients used in the formulation. Physical mixtures of drug and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using FT-IR spectroscopy3. IR spectrum of pure drug and polymers was seen in between 600-4000 cm^{-1}.

Differential scanning calorimetry (DSC)

To study the compatibility pure drug, physical mixtures of drug and excipients the DSC studies were carried out. The analysis were performed at a standard heating rate of 10 ºC/min over a temperature range of 50 ºC – 200 ºC using a DSC 822 mettler instrument[5].

Preparation of Bilayer Tablets

Bilayer tablets were prepared involving 2 steps by both wet granulation and direct compression method procedure. Various batches were prepared by by varying the ratio of HPMC K100 M, Metalose 90 SH, Sodium CMC, Ethyl Cellulose E 50 to identify the most effective formulation. The antihypertensive drug/ polymer mixture was prepared by homogeneously mixing the drug with HPMC K100 M, Metalose 90 SH, Sodium CMC, Ethyl Cellulose E 50 for 15 minutes. The mixture (390 mg) was then compressed using an 9.5-mm diameter die in a bilayer multistation tablet machine (General Mechanical Industries, Mumbai). The first-layer granulation (also thought of as the bottom layer) was fed into the die (9.5 mm diameter) as the cavity passes under the first feed frame. This cavity then continued through an initial compression stage, where with a double-layer tablet it was often simply "tamped". The dies then pass under the second feed frame and were filled with an amount of the second layer granulation, which when combined with the first layer, was appropriate for the desired total tablet weight. The coating was done by using HPMC E5M Premium as well as Instacoat ICS-3104 orange. Each tablet weighed ~400 mg with a thickness of 5.6 ±0.2 mm.(table No.1)

Weight variation

Ten bilayer tablets of each formulation were weighed using an electronic balance and average weight of ten tablets and standard deviation were calculated.

Thickness

Thickness of each formulation was measured using vernier calipers. Ten bilayer buccal tablets from batch were used and average values were calculated.

Hardness

The hardness of the tablets was determined using electrolab hardness tester. It was expressed in kilogram (kg).

Friability

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). About 20 tablets ($W_{initial}$) were transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were dedusted and weighed again (W_{final}).[6]

Disintegration test

It is determined by using USP device which consist of 6 glass tubes that are 3 inches long, open at one end and held against 10 mesh screen at the bottom end of basket rack assembly. To test for disintegration time, one tablet is placed in each tube and the basket arch is positioned in a1 liter beaker of water at 37^{0}C ± 2^{0}C.A standard motor driven device is used to move the basket assembly up and down. To be incompliance with the USP standard, all tablets must disintegrate and all particles must pass through the 10 mesh in the time specified.[7]

In vitro dissolution study of Bilayered Tablet

The US Pharmacopeia rotating paddle method was used to study the drug release from the Bilayer tablet. The dissolution medium consisted of 500 ml of phosphate buffer pH 6.8 for Metoprolol Succinate and 0.1N Hydrochloric acid for Ramipril. The release study was performed at 37 ^{0}C ± 0.5 ^{0}C, with a rotation speed of 50 rpm. The Ramipril layer releases its content within 45 min, as it is immediate release layer. Metoprolol succinate is extended release layer for 20 Hrs, so it releases its content within 20 Hrs. Samples of 5 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.2-µm Whatman filter paper and analyzed after appropriate dilution by HPLC (Merck Hitachi).

Kinetic analysis of Bilayer Tablet in vitro release data[8, 9, 10]

Release data was fitted to various mathematical models for describing the release mechanism from bilayered tablets; Korsmeyer- Peppa's, zero order, Higuchi release models, Hixon Crowel , First order.

Stability Study

The optimized formulation was tested for stability of period of 1 Month accelerated study at 40 ^{0}C ± 75% RH, for their drug content and other parameters.

RESULTS

The main aim of this work was to prepare bilayered tablets of Metoprolol Succinate and Ramipril, to release the drug at predetermined interval of time i.e. Metoprolol Succinate within 20hrs and Ramipril within 45 minutes. HPMC K100M, Sodium CMC, Ethyl cellulose and Metallose 90 SH were selected as Release retarding polymers on the basis of their matrix forming properties.

Drug polymer compatibility studies using FTIR

All the characteristic IR peaks related to pure drug, Metoprolol Succinate and Ramipril were also appear in the IR spectrum of mixture of Drug-excipients so there was no any chemical incompatibility between drug, polymer and excipients (Fig 1).

Drug polymer compatibility studies using DSC

In order to investigate the possible physical interaction between drug and excipients, DSC studies were carried out. The drug exhibited a sharp melting endotherm at 236^{0}C and 110^{0}Cwhich is the melting point of the Metoprolol succinate and Ramipril, respectively. Similarly the thermograms of the physical mixture of Metoprolol succinate and Ramipril with excipients under study exhibited endothermic peak in the vicinity of its melting point range indicating absence of any drug polymer interactions (Fig 2).

Preparation of Bilayer Tablets

Bilayered tablets of Metoprolol Succinate and Ramipril were formulated using Wet granulation and direct compression technique, respectively, which involved compressing the tablets in two layers. The formulations with various polymers alone and in different combinations were prepared. The various combinations used were HPMC K100 M with Ethyl cellulose, HPMC K 100M with sodium CMC, HPMC K 100M with Metallose 90 SH. (Table 1 and Table 2).

Weight variation and thickness

The maximum average weight of the tablets was found to be 405.75 ± 5mg. As none of the formulation shows a deviation (I.P. limit, ± 7.5%) for any of the tablets tested, the prepared formulations comply with the weight variation test (Table 2). The average thickness from all the formulations was found to be 5.6 ± 0.2mm. (Table No.3)

Hardness and Friability

Hardness bilayered buccal tablets ranged from 6 to 10kg/ cm^2.Friability of bilayered buccal tablets was found to be within the limits of conventional oral tablets stated in the Indian Pharmacopoeia. (Table 3)

Disintegration test

Ramipril layer of 6 Tablets disintegrates within 4-5 minutes (Table No.3)

***In vitro* dissolution studies**

Release of drug from the bilayered tablets varied according to the type and ratio of matrix forming polymer. HPMC K 100M has excellent release retarding, gelling properties and also helps in sustaining effect. The *in vitro* drug release profile of tablets containing HPMC K100M with sodium CMC show cumulative percent drug release for formulation MSRP/7- MSRP/10 were ranging from15.8% - 20.6 % during first hour. Also at the end of 4 h, the cumulative percent drug releases were found to vary from 35.47% - 58.9%. At the end of 8 Hr the cumulative percent drug releases were found to vary from 59.8% - 80.7%. At the End of 20 Hr the cumulative percent drug releases were found to vary from 97.89% - 99.6%.On physical examination of tablets during dissolution study, it was found that tablets were initially swell and slowly eroded over the period of time (Fig.No.3) (Table No. 4).

Release mechanism

For non-Fickian release, the value of n falls between 0.5 and 1.0, while in case of Fickian diffusion, n=0.5; for zero order release (case II transport), n=1; and for supercase II transport, n is greater than 1. Observation of all the R2 values indicated the values for Zero order, First order, Higuchi, Peppas. Hixon crowel. It was found that the in vitro drug release of Metoprolol succinate ER was best explain by Higuchi equation (r^2 = 0.9898) and n value of formulation MSRP/10 was 0.6218. (Table No.5)

Table 1: Brief summary of formulation of Metoprolol succinate

Name of Ingredients	MS/1	MS/2	MS/3	MS/4	MS/5	MS/6	MS/7	MS/8	MS/9	MS/10
Metoprolol succinate	23.7	23.7	23.7	23.7	23.7	23.7	23.7	23.7	23.7	23.75
Lactose	20	20	-	-	20	5	17.2	8.75	8.75	8.75
HPMC K 100M	164	164	164	164	164	164	169	176	176	176
Povidone (pvpk-30)	5.75	5.75	5.75	5.75	5.75	5.75	6	2.5	2.5	2.5
Isopropyl Alcohol(ml)	175	175	150	150	175	100	QS	QS	QS	QS
EthylCellulose N 50P	-	-	20	45	-	-	-	-	-	-
Metalose -90SH	15	25	25	-	25	25	-	-	-	-
Lycatab PGS	10	-	-	-	-	-	-	-	-	-
SodiumCMC	-	-	-	-	-	-	19.7	24	24	24
PEG- 6000	-	-	-	-	-	15	-	-	-	-
Talc	5.2	5.2	5.2	5.2	5.2	5.2	2.6	2.4	2.4	2.4
Magnesium Stearate	1.3	1.3	1.3	1.3	1.3	1.3	1.4	1.75	1.75	1.75
Water	-	-	-	-	-	25	-	-	-	-

Table 2: Brief summary of formulation of Ramipril

Name of Ingeredients	RP/1	RP/2	RP/3	RP/4	RP/5	RP/6	RP/7	RP/8	RP/9	RP/10
Ramipril	5	5	5	5	5	5	5	5	5	5
Lactose(DCL-21)	93	93	93.75	93.75	94.8	-	94.8	94.8	94.8	94.8
Calcium Sulfate Dihydate	-	-	-	-	-	121.8	-	-	-	-
Sodium Bicarbonate	10	10	10	10	10	-	10	10	10	10
Cross Carmellose Sodium	5	5	5	5	5	-	5	5	5	5
Lycatab PGS	30.5	30.5	30.5	30.5	30	10	30	30	30	30
Lycatab-c	-	-	-	-	-	12	-	-	-	-
Sodium Stearyl Fumarate	5	5	5	5	5	1.5	5	5	5	5
Sodium Carbonate Anhydrous	-	-	-	-	-	2	-	-	-	-
Lake of sunset yellow	1.5	1.5	0.75	0.75	0.2	0.2	0.2	0.2	0.2	0.2
Water	-	-	-	-	-	q.s	-	-	-	-

Table 3: Post Physicochemical Properties Bilayer tablet

Batch No	Av. Wt (mg)	Thickness	Hardness (kg/cm²)	DT	
				MS	RM
01	405.15	5.76	9.3	-	4’40”
02	405.25	5.79	8.8	-	5’
03	405.20	5.65	7.3	-	4’45”
04	405.30	5.87	8.5	-	4’40”
05	405.45	5.76	6.3	-	3’55”
06	398.35	5.63	5.7	-	12’
07	400.10	5.72	6.20	-	3’47”
08	400.95	5.92	6	-	3’10”
09	387.10	5.09	7.4	-	4’34”
10	400.6	5.69	8.8	-	5’10”

Table 4: Comparative dissolution profile of Bilayer tablets containing Metoprolol succinate

Batches	Time in Hours			
	1	4	8	20
01	22.2	53.6	76.2	99.4
02	20.8	50.6	72.7	98.00
03	22.4	57.8	81.4	99.60
04	21.9	54.7	79.5	98.79
05	21.5	52.4	72.1	97.80
06	20.8	51.7	75.4	99.20
07	20.6	58.9	80.7	97.89
08	15.25	43.05	61.25	94.4
09	-	-	-	-
10	15.8	35.47	59.8	99.6

Table 4: Comparative dissolution profile of Bilayer tablets containing Ramipril

Batches	Time 45 min
01	83.8
02	92.2
03	91.6
04	81.9
05	85.0
06	69.6
07	97.9
08	97.8
09	NA
10	96.05

Table 5: Drug release Kinetic studies of all Batches

Formulation	Square of regression coefficient Value (R^2)					
	Zero order	First order	Higuchi	Peppas	Hixon Crowell	n value
MSRP/01	0.8179	0.9835	0.9762	0.9895	0.9926	0.5101
MSRP/02	0.8399	0.9940	0.9835	0.9895	0.9893	0.5262
MSRP/03	0.7884	0.9889	0.9608	0.9895	0.9859	0.5130
MSRP/04	0.8283	0.9940	0.9672	0.9895	0.9818	0.5257
MSRP/05	0.8328	0.9941	0.9825	0.9895	0.9868	0.5119
MSRP/06	0.8295	0.9860	0.9786	0.9895	0.9931	0.5322
MSRP/07	0.7618	0.9987	0.9472	0.9895	0.9549	0.5320
MSRP/08	0.9035	0.9936	0.9945	0.9895	0.9941	0.6113
MSRP/09	NA	NA	NA	NA	NA	NA
MSRP/10	0.9497	0.9407	0.9898	0.9895	0.9815	0.6218

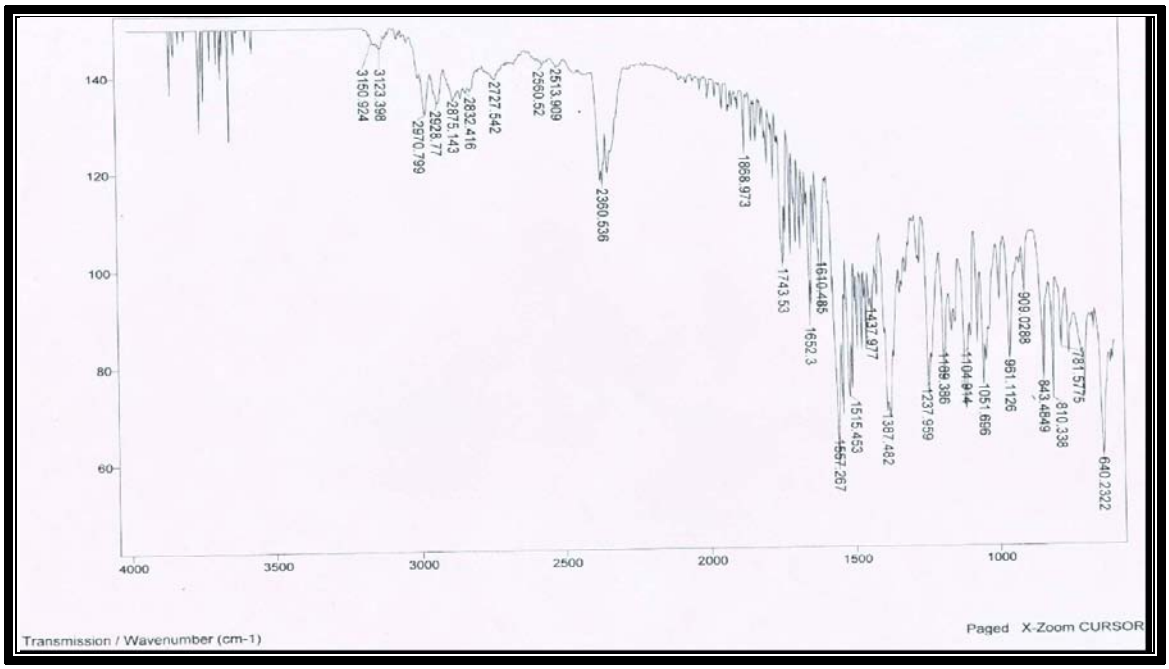

Fig. 1: FT-IR of Metoprolol succinate blend and Ramipril Blend

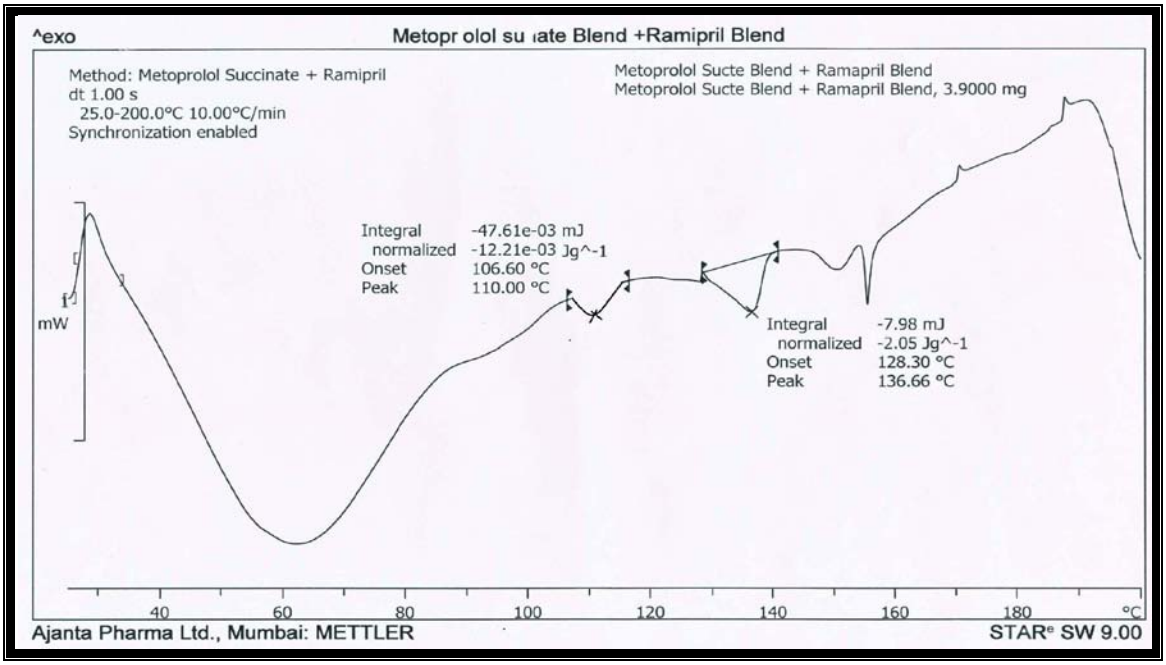

Fig. 2: DSC of Metoprolol Succinate blend + Ramipril

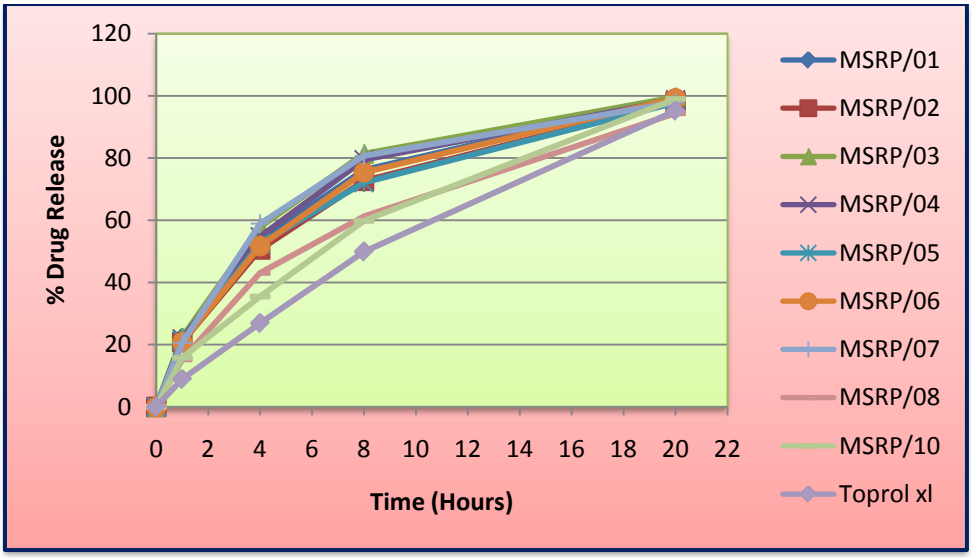

Fig. 3: Comparitive dissolution Profile trial batches of Bilayer tablets containing Metoprolol succinate with Innovator product

DISCUSSION

The Physically robust Bilayer tablets of Metoprolol succinate and Ramipril can be formulated by using combination of polymers like HPMC K100M and Sodium CMC for metoprolol succinate ER layer. Metoprolol succinate showed released upto 20hrs. It was found that the in vitro drug release of Metoprolol succinate ER is by erosion and diffusion mechanism.

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