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Design, Development and Evaluation of Metoprolol Succinate and Hydrochlorothiazide Bilayer Tablets

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Abstract-Lowering elevated blood pressure (BP) with drug therapy reduces the risk for catastrophic fatal and nonfatal cardiovascular events. Due to the marked variability in an individual patient's BP response and low response rates with monotherapy, expert groups such as Joint National Committee (JNC) emphasize the value of combination antihypertensive regimen, usually of different classes, having additive antihypertensive effects. Metoprolol succinate is a Beta – 1- selective (cardio selective) adrenoceptor blocking agent formulated to provide sustained release of Metoprolol. Hydrochlorothiazide (HCT) is a well established diuretic and antihypertensive agent, which promotes natruresis by acting on the distal renal tubules. The objective of the current research work is to design and evaluate an oral bilayer tablet containing Metoprolol succinate as sustained release and hydrochlorothiazide as immediate release layer. Sustained layer were prepared by wet granulation method using different grades of HPMC (HPMCK4M and HPMC K100M) as hydrophilic polymers and immediate release layer prepared by direct compression. The tablets were evaluated for physicochemical parameters. *In vitro* release studies were carried out using USP (type II) paddle apparatus. Combination of polymers namely HPMCK4M and HPMC K100M showed a controlled release of drug from sustained layer. The *in vitro* release profiles of drug from sustained release layer could be best expressed by Korsmeyer - peppas equation as the plots showed high linearity ($R^2 = 0.999$). The present study concluded that bilayer tablets of Metoprolol succinate and Hydrochlorothiazide as an alternative to the conventional dosage form.

Keywords: Metoprolol succinate, Hydrochlorothiazide, Sustained release, Immediate release, Bilayer tablets

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration [1]. Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Among various dosage forms administered orally, the tablet is one of the most preferred dosage form, because of its patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and stability when compared to other dosage forms [2, 3].

Combination therapy has various advantages over monotherapy. A low dose combination of two different agents reduced the dose-related risk minimize the clinical and metabolic effects that occur with maximal dosage of individual components [4, 5].

The term bilayered tablets refer to tablet containing two subunits that may contain same or two different drugs. Bilayered tablet allows for designing and modulating the dissolution and release characteristics and they are prepared with one layer of drug for immediate release while second layer of drugs as an sustained release manner [1, 6-9].

Metoprolol succinate is a Beta 1- selective (cardio selective) adrenoceptor blocking agent its chemical name is (±) 1-(isopropylamino)-3- [p-(2-methoxyethyl) phenoxy] -2-propanol succinate [10, 11] and its structural formula given in figure 1.

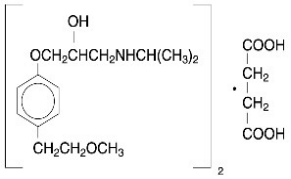

Figure 1: Structure of Metoprolol Succinate

It is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water, soluble in methanol, sparingly soluble in ethanol, slightly soluble in dichloromethane and 2-propanol, practically insoluble in ethyl-acetate, acetone, diethylether and heptane.

Hydrochlorothiazide is a diuretics of benzothiadiaze group and has proved very important in the management of mild to moderate hypertension and its chemical name is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide [12, 13] and its structural formula given in figure 2.

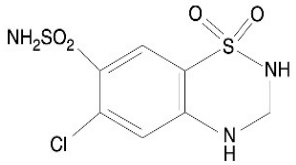

Figure 2: Structure of Hydrochlorothiazide

Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Hence, to reduce the frequency of administration and to improve patient compliance, bilayer tablets formulation having a sustained release layer (Metoprolol succinate) and an immediate releasing layer (Hydrochlorothiazide) was attempted [5, 14].

The objective of the current research work is to design and evaluate an oral bilayer tablet containing Metoprolol succinate and hydrochlorothiazide with Metoprolol succinate as a sustained release layer using HPMC as hydrophilic polymer and hydrochlorothiazide as an immediate release layer.

MATERIALS AND METHODS

Metoprolol succinate (Koves India Ltd) and Hydrochlorothiazide (Unichem laboratories Ltd.,) were obtained as a gift sample. Hydroxy propyl methyl cellulose (HPMC-K100M and HPMC K4M) (Colorcon Asia Pvt. Ltd., India), Lactose DCL 11 (DMV Holland), Maize Starch (Maize product), Povidone (PVP-K30) (Basf, India), Hydroxy propyl cellulose (Corel Pharma, India), Microcrystalline cellulose IP – Avicel pH 101 & 102 (RanQ Remedies, India), Colloidal silicon dioxide (Cobot sanmar, India), Purified Talc (Aravelli Pvt. Ltd, India), Magnesium sterate (Amshi Drug and Chemicals, India), Brillant blue lake (Roha Dye Chem, India) and Iso propyl alcohol (Taiwan) were procured and used for this study.

METHODS

Drug-Excipients compatibility studies

In tablet dosage form the drug is in intimate contact with one or more excipients, the latter could affect the stability of drug. Knowledge of drug-excipients interactions is therefore very useful to the formulator for selecting the excipients.

Active ingredients were mixed with all excipients in binary ratio and small portion of this mixed powder was placed in clean and dry vial in stability chamber at 40°C ± 2°C / 75% ± 5% RH and 25°C ± 2°C / 60% ± 5% RH. Physical observation has been carried out visually in the 14^{th} day and 28^{th} day.

Manufacturing process of bilayer tablets

Based on the inference from excipients compatibility studies, the non-compatible excipients were used for formulation and developed using suitable process. Development trials were made and their evaluation of physical parameters for both blend and compressed tablets was done.

Manufacturing process of Metoprolol succinate sustained release granules

Metoprolol succinate sustained release granules were prepared by Wet granulation method employing various excipients as mentioned in the Table 1. Weighed quantity of Metoprolol succinate, Microcrystalline cellulose pH 101, Hydroxy propyl methyl cellulose K100M and Hydroxy propyl methyl cellulose K4M were shifted through #30 mesh and mixed for 10 mins in rapid mixer granulator. The binding solution containing PVP K-30 in IPA was added slowly to the above ingredients and mixed at slow speed and mixed well till granules are obtained. The wet granules were loaded in fluidized bed drier and dried till the moisture content of granules are between 2 to 3. The dried granules were sifted through #20 mesh. Weighed amount of Hydroxy propyl methyl cellulose K100M and Hydroxy propyl methyl cellulose K4M along with Hydroxyl propyl cellulose and purified talc were sifted through #30 mesh and loaded to the planetary mixer along with dried granules and mixed well for 3 mins at slow speed.

Manufacturing process of Hydrochlorothiazide immediate release granules

Hydrochlorothiazide immediate release granules were prepared by employing various excipients as mentioned in the Table 2. Weighed quantity of Hydrochlorothiazide, Microcrystalline cellulose pH 102, Lactose DCL 11 and Maize starch were sifted through #30 mesh sieve and mixed for 10 mins in hexagonal blender. Colloidal silicon dioxide and magnesium stearate sifted through #30 mesh and brilliant blue lake sifted through #100 mesh were loaded in blender along with the above sifted materials and mixed well for 2 mins in slow speed.

Compression of Bilayer tablets

The required quantity of granules for the immediate release layer was compressed lightly using 27 stationary double rotator compression machine (Cad Mach, India) using 13/32 inch circular shape plain punches. Over this compressed layer, required quantity of sustained release layer was placed and compressed to obtain hardness in the range of 6-8 kg/cm^2 to form a bilayer tablet of sustained release of Metoprolol succinate and immediate release of Hydrochlorothiazide.

Characterization of Blend [15 - 17]

Prior to compression, the blend was evaluated for their characteristics parameters such as Bulk density, Tapped density, Compressibility index, Hausner's ratio, Angle of repose and Moisture content.

Bulk Density

Weighed quantity of granules was transferred into a 50ml measuring cylinder without tapping and the volume occupied by granules was measured. Bulk density was measured using the following formula

$$\mathbf{P_b = M/V_o}$$

Where, P_b = Bulk density

M = Mass of blend

V_o = Untapped volume

Tapped Density

Weighed quantity of granules was taken into graduated measuring cylinder volume occupied by granules was noted down. The measuring cylinder was subjected to 500 taps in tapped density tester (Electro Lab USP II), the change in volume is noted down. Tapped density was measured using the following formula

$$\mathbf{Pt = M/V_t}$$

Where, P_t = Tapped density

M = Mass of blend

V_t = Tapped volume

Compressibility Index

Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density. Table 3 shows the percentage compressibility index and its flow characteristics. The percentage compressibility of granules were determined using the following formula

$$\mathbf{CI = P_t - P_b / P_t \times 100.}$$

Where, CI = Compressibility Index.

P_b = Bulk density,P_t = Tapped density ,P_t = Tapped density

Sl. no	*Ingredients*	*Quantity per Tablets (mg)*								
		F-1	*F-2*	*F-3*	*F-4*	*F-5*	*F-6*	*F-7*	*F-8*	*F-9*
Dry Mixing										
01	Metoprolol succinate	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75	23.75
02	MCC PH 101	95	85	85	85	89	88	86	86	86
03	HPMC K100M	55	35	45	48	57	45	57	57	57
04	HPMC K4M	-	15	20	17	-	20	15	15	15
Binding Solution										
05	PVP K-30	8	15	16	15	17	16	13	12	12
06	IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Blending										
07	HPMC K100M	60	63	40	45	46	45	43	45	45
08	HPMC K4M	-	-	18	14	15	12	9	7.7	7.7
09	HPC	1.50	1.75	1.25	1.25	1.25	1.25	1.25	1.55	1.55
10	Purified Talc	1.75	1.50	1.00	1.00	1.00	1.00	1.00	2.00	2.00

Table 1: The formulation composition of Metoprolol succinate sustained release granules

Sl. no	*Ingredients*	*Quantity per Tablet (mg)*					
		F-1	*F-2*	*F-3*	*F-4*	*F-5*	*F-6*
01	Hydrochlorothiazide	12.50	12.50	12.50	12.50	12.50	12.50
02	Lactose DCL 11	45.60	41.50	34.00	34.00	19.00	19.00
03	MCC PH 102	65.90	65.00	71.25	71.12	74.00	74.00
04	Maize Starch	-	5.00	4.00	4.00	13.00	13.00
05	Colloidal Silicon dioxide	-	-	2.25	2.25	5.00	5.00
06	Magnesium Stearate	0.50	0.50	0.50	0.625	1.00	1.00
07	Brilliant blue lake	0.50	0.50	0.50	0.50	0.50	0.50

Table 2: The formulation composition of Hydrochlorothiazide immediate release granules

Hausner's ratio

It is measurement of frictional resistance of the drug. Table 3 shows the Hausner's ratio and its flow characteristics. It was determined by ratio of tapped density and bulk density.

Hausner's ratio = P_t / P_b

Where, P_b = Bulk density

Angle of Repose

Weighed quantity of granules was passed through a funnel kept at a height of 2cm from the base. The powder is passed till it forms heap and touches the tip of funnel. Table 3 shows the Angle of repose and its flow characteristics. The radius was measured and angle of repose was calculated using the following formula

Type of Flow	*Compressibility Index*	*Hausner's ratio*	*Angle of repose (θ)*
Excellent	1-10	1-1.1	25 – 30
Good	11-15	1.12 – 1.18	31 – 35
Fair	16-20	1.19 – 1.25	36 – 40
Passable	21-25	1.26 – 1.34	41 – 45
Poor	26-31	1.35 – 1.45	46 – 55
Very Poor	32-37	1.46 – 1.59	56 – 65
Extremely Poor	>38	>1.6	>66

Table 3: Compressibility Index, Hausner's Ratio, Angle of repose with corresponding Flow characters.

EVALUATION OF TABLETS [15, 16, 18]

The formulated tablets were evaluated for the following physicochemical parameters

$\theta = Tan^{-1}(h/r)$

Where, θ = Angle of repose

h = height of heap of pile

r = radius of base of pile

Moisture content

Initially, 5g of weighed granules were taken and kept for drying at 105ºC for a required time in oven, then it was removed and again reweighed and noted as final weight. The moisture content is calculated using the following formula

Moisture content = Initial weight – Final weight / Initial weight × 100.

Micromeritic Properties

Thickness

Thickness mainly depends on die filling, physical properties of materials to be compressed under compression force. There may be a small variation in the thickness of individual tablets in a batch. The thickness was measured by using vernier calipers (Mitutoyo corps, Japan).

Hardness

Tablet required certain amount of strength or hardness and is measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and evaluated for hardness during manufacturing and were expressed in Kg/cm^2.

Friability

Friability was performed by using Roche friabilator. Normally, pre weighed ten tablets were placed in plastic chamber of friabilator. This was then operated for 100 revolutions dropping from a distance of 6 inches in each revolution. Tablets are then dusted and reweighed.

Friability (%) = Initial weight – Final weight / Initial weight × 100.

Weight variation test

Twenty tablets were selected randomly and weighed individually. The average weight was calculated and compared with the individual tablet weight. Not more than two of the individual tablet weight should deviates from the average weight by more than the percentage.

Assay

Assay for Metoprolol succinate and Hydrochlorothiazide

Chromatographic parameters

Apparatus	:	HPLC, PDA detector
Column	:	Inertsil ODS C18
Flow rate	:	1.0 ml/min
Wavelength	:	222nm
Injection volume	:	20µl
Column temperature	:	Ambient
Mobile phase	:	Mix 85 part of buffer and 15 part of Acetonitrile.

Preparation of standard solution

95mg of Metoprolol succinate and 50mg Hydrochlorothiazide working standards were weighed accurately and transferred separately into 100ml and 50ml volumetric flask, then methanol was added, the flask was shaken and sonicated for 15 mins. Finally, the volume was made upto the mark with methanol. Pipette out 5ml of above solution to 50ml volumetric flask and made up to the volume with mobile phase.

Preparation of sample solution

Twenty tablets were finely powdered and an amount equivalent to 47.5mg of Metoprolol succinate and 55mg of Hydrochlorothiazide was weighed accurately and transferred separately into 100ml and 50ml volumetric flask, then methanol was added, the flask was shaken and sonicated for 15 mins. Finally, the volume was made upto the mark with methanol. Pipette out 10ml of above solution to 50ml volumetric flask and make up to the volume with mobile phase.

Procedure

20 µl of filtered portion of the standard solution and sample solution prepared was injected into the HPLC system. The chromatogram was recorded and the responses were measured for the major peaks. The content of Metoprolol succinate and Hydrochlorothiazide per tablet was calculated using the following expressions.

Calculation

For Metoprolol succinate

$$\frac{\text{Spl Area}}{\text{Std Area}} \times \frac{\text{Std. Wt}}{100} \times \frac{5}{50} \times \frac{100}{\text{LC}} \times \frac{50}{10} \times \frac{\text{Purity (as in)}}{100} \times 100$$

For Hydrochlorothiazide

$$\frac{\text{Spl Area}}{\text{Std Area}} \times \frac{\text{Std. Wt}}{100} \times \frac{5}{50} \times \frac{100}{\text{LC}} \times \frac{50}{10} \times \frac{\text{Purity (as in)}}{100} \times 100$$

***In vitro* dissolution studies** [19]

Chromatographic parameters

Apparatus	:HPLC, PDA detector
Column	:Inertsil ODS C18, 250×4.6 mm, 5µ
Flow rate	:1.0 ml/min
Wavelength	:222nm
Injection volume	:20µl
Column temperature	:Ambient
Mobile phase	:Mix 85 part of buffer and 15 part of Acetonitrile.

Release of Metoprolol succinate was determined using a dissolution apparatus of USP II (Paddle) at 50 rpm. 500ml of pH 6.8 phosphate buffer was used as the dissolution medium and were maintained at the temperature of 37.5±0.5°C. The sample (5 ml) was withdrawn at different time intervals, i.e., 1st, 4th, 8th and 20th hours, filtered through Whatmann filter paper (Sartourious 292A) and replaced by equal volume of dissolution medium. The samples were diluted and analyzed for Metoprolol succinate content using Chromatography. The samples were analyzed by using same procedure as that of determination of drug content. The percentage release of Metoprolol succinate was calculated.

Release of Hydrochlorothiazide was determined using a dissolution apparatus of USP I (Basket) at 100 rpm. 900ml of 0.1N hydrochloric solution acid was used as the dissolution medium and were maintained at the temperature of 37.5±0.5°C. The sample (5 ml) was withdrawn at different time intervals, i.e., 1 hours (60 mins), filtered through Whatmann filter paper (Sartourious 292A) and replaced by equal volume of dissolution medium. The samples were diluted and analyzed for Hydrochlorothiazide content using Chromatography. The samples were analyzed by using same procedure as that of determination of drug content. The percentage release of Hydrochlorothiazide was calculated.

KINETICS OF DRUGS RELEASE [20, 21]

Kinetics of drug release is studied by plotting the data obtained from *in vitro* release in various kinetics models.

Zero Order Kinetics

The graph was plotted as cumulative % drug release Vs Time where the drug release rate is independent of its concentration [22].

$$C = K_0 t$$

Where, Kθ = Zero order rate constant expressed in units of concentration/time

t = Time in hours.

First order Kinetic model

The graph was plotted as log cumulative % of drug remaining Vs Time, where release rate is concentration dependent [23].

$$\text{Log } C = \log C_0 - Kt / 2.3030$$

Where, C0 = Initial concentration of drug

K = First order constant

t = Time in hours.

Higuchi kinetics

Higuchi describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The graph was plotted as cumulative % drug released Vs square root of time [24].

$$Q = Kt^{1/2}$$

Where, K = Constant reflection design variable system

$t^{1/2}$ = Time in hours.

Hence, drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line, and the slope is one then the particular dosage form is considered to follow Higuchi kinetics of drug release.

Hixson-crowell erosion equation

It describes the drug release with changes in the surface area and the diameter of particles the data were plotted using the Hixson and crowell rate equation. The graph was plotted by cube root of % drug remaining in matrix Vs time.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t.$$

Where, Q_t = Amount of drug released in time t

Q_0 = Initial amount of drug in tablet.

K_{HC} = Rate constant for Hixon crowell rate equation

Korsmeyer-Peppas equation

To find out the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released Vs log time.

$$Mt / M\alpha = Kt\, n,$$

$$\text{Log } Mt / M\alpha = \log K + n \log t$$

Where, Mt / Mα = Fraction of drug released at time t

K = Kinetic rate constant

t = Release time

n = Diffusion exponent indicative of the mechanism drug release.

This model is used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The n value could be obtained from slope of the plot of log cumulative % of drug released Vs log Time.

Diffusion exponent (n)	*Overall solute diffusion mechanism*
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

Table 4

STABLITY STUDIES [28 – 31]

Stability of the drug has been defined as the ability of particular formulations, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. The selected batches were charged on accelerated stability as per ICH guidelines.

The storage conditions used for stability studies were accelerated conditions (40±2°C / 75±5%RH) and ambient temperature (30±2°C / 65±5%RH). Tablets were analyzed after 1st and 2nd month for physical parameters (Description, Weight variation, Friability), followed by assay and *in vitro* dissolution test.

RESULTS AND DISCUSSION

Drug – excipients compatibility studies

The physical compatibility test and assay test between the drug and tablet components was carried out at 40°C ± 2°C / 75% ± 5% RH and 25°C ± 2°C / 60% ± 5% RH for 14 and 24 days. The mixture does not show any visible change, thus indicating drug and other tablet components do not have any physical compatibility. Hence, there are no interactions between the drug, polymers and other excipients used in the tablets.

Evaluation of Tablets

The formulation consists of two layers sustained release layer of Metoprolol succinate and immediate release layer of Hydrochlorothiazide. Developed trials were taken and evaluated for pre compression and post compression parameters of bilayer tablets.

Drugs	*Formulation*	*Bulk Density (gm/ml)*	*Tapped Density (gm/ml)*	*Carr's Index (%)*	*Hausner's Ratio*	*Angle of Repose (θ)*
Metoprolol succinate	F – 1	0.645	0.764	15.57	1.18	26.22
	F – 2	0.646	0.785	17.70	1.12	26.29
	F – 3	0.687	0.789	12.92	1.14	25.73
	F – 4	0.695	0.797	12.79	1.14	26.48
	F – 5	0.688	0.779	11.68	1.13	26.94
	F – 6	0.618	0.787	12.15	1.13	25.93
	F – 7	0.657	0.739	11.09	1.12	25.28
	F – 8	0.669	0.755	11.39	1.12	24.32
	F – 9	0.657	0.735	10.61	1.12	24.42
Hydrochlorothiazide	F – 1	0.583	0.740	21.21	1.26	32.02
	F – 2	0.629	0.769	18.20	1.22	34.10
	F – 3	0.640	0.738	13.27	1.15	26.87
	F – 4	0.639	0.728	12.22	1.13	24.79
	F – 5	0.646	0.727	11.14	1.12	26.43
	F – 6	0.649	0.724	10.35	1.11	25.12

Table 5: Micromeritic Properties of powder blend

Sustained release layer of Metoprolol succinate

In the present study, the sustained release layer of Metoprolol succinate was designed with the dose of 23.75mg. The granules were prepared by wet granulation technique using PVP K30 as binder. HPMC K100M and HPMC K4M were used as drug release retardants for sustained release layer of Metoprolol succinate, Microcrystalline cellulose pH 101 was used to balance the weight of the tablet. The weight of Metoprolol succinate layer for all formulations was kept constant at 250mg.

Bulk Density and tapped density for Metoprolol succinate sustained release granules were found to be between 0.648 to 0.668 and 0.728 to 0.778 respectively. Compressibility index and Hausner's ratio were obtained in the range of 11.82 to 14.51 and 1.13 to 1.17 respectively. Angle of repose was observed in the range of 25°11′ to 27°84′. Moisture content was found to be between 2.0 to 2.5. The results showed in the table 5 indicate that the granules posses good flow property and compressibility.

In vitro dissolution study of the formulation containing polymer in different concentration were compared. In formulation, F – 1 to F – 6 the sustained release layer consist of HPMC K100M and HPMC K4M in the concentration of 20 to 50% and 2 to 5% with respect to the average weight and the weight of the tablet was balanced with Microcrystalline cellulose pH 101. The release of drug in F – 1 to F – 6 was not found to be within the internal specification limit. Therefore, the release of the drug was more than the limit.

In order to retard the release of drug, the polymer HPMC K100 concentration was increased to 51.67% (26.67% in intra granulation and 25% in extra granulation) and HPMC K4M concentration was increased to 3.34% (1.67% in intra granulation and 1.67% in extra granulation) in formulation F – 6. But the release of the drug at 4^{th} and 8^{th} hour was 42.45% and 62.8% higher to the desired release pattern.

To meet the required release profile of the drug, HPMC K100M concentration was made to 50% (25% in intra granulation and 25% in extra granulation) and HPMC K4M concentration was increased to 6.66% (3.33% in intra granulation and 3.33% in extra granulation) to release the drug from the matrix in formulation F – 7. It was found that the drug release profile of formulation F – 7 was less than the limit i.e., 55.7% of drug was released in 8^{th} hour which was not satisfactory.

To increase the release of drug the concentration of HPMC K100 was increased by 1.5% in formulation F – 8 and the release was found to be satisfactory where the release of the drug at 1^{st}, 4^{th}, 8^{th} and 20^{th} hour was 13.32%, 33.59%, 54.75% and 97.98% and it matches with the internal specified limit.

Immediate release layer of Hydrochlorothiazide

The immediate release layer of Hydrochlorothiazide was designed with the dose of 12.5mg. The weight of hydrochlorothiazide layer for all the formulations were kept constant at 125mg. Bulk density and tapped density for Hydrochlorothiazide immediate release granules were found to be between 0.593 to 0.640 and 0.720 to 0.771 respectively. Compressibility index and Hausner's ratio were obtained in the range of 11.11 to 19.32 and 1.13 to 1.24 respectively. Angle of repose was observed between 27°69′ to 33°70′. The results showed in the table 5 indicate that the granules possessed good flow property and compressibility.

In the formulation F – 2 to F – 5, Starch was used in the concentration of 4 to 12% and lubricant at 0.4 to 0.8% respectively to meet the compression and dissolution profile of Hydrochlorothiazide within the specified limit. At the end of 60 min, the release profile of Hydrochlorothiazide in the formulation F – 2, F – 3, F – 4 and F – 5 was found to be 82.33%, 85.72%, 89.50% and 94.5% respectively. Among these four trials, F – 5 was found to be satisfactory and it was selected as an immediate release layer to formulate with the sustained release layer of Metoprolol succinate as a bilayer tablet.

All the batches of bilayer tablets fulfilled the official requirements of uniformity of dosage unit. The average percentage deviation of 20 tablets of each formula was less than ±4%. The thickness and hardness of tablet ranged from 4.5 – 4.7 mm and 6.8 – 7.6 kg/cm^2 respectively. The percentage friability of all batches ranged from 0.11 to 0.34% w/w. The drug content was found to be ranged from 95.2% to 97.1% for Metoprolol succinate and 96% to 98.2% for hydrochlorothiazide as shown in the table 6 &7

Tests	***F – 1***	***F – 2***	***F – 3***	***F – 4***	***F – 5***
Average Weight (mg)	377.5	377.8	377.2	377.2	377.8
Thickness (mm)	4.6 ± 0.2	4.7 ± 0.2	4.6 ± 0.2	4.7± 0.2	4.8 ± 0.2
Hardness (Kg/cm^2)	6.6 ± 0.2	6.9 ± 0.2	6.7 ± 0.2	6.8 ± 0.2	6.7 ± 0.2
Friability (%)	0.04 ± 0.01	0.14 ± 0.01	0.19 ± 0.01	0.17 ± 0.01	0.18 ± 0.01
Weight Variation	+2.2 to - 2.4	+2.4 to -2.6	+2.9 to -2.8	+3.5 to -2.6	+2.2 to -2.4
Assay					
a) Metoprolol succinate	94.2	95.7	96.2	96.4	96.6
b) Hydrochlorothiazide	95.2	95.9	96.9	97.2	97.4

Table 6: Evaluation of bilayer tablets of Metoprolol succinate SR and Hydrochlorothiazide IR (F-1 – F-5)

Tests	F – 6	F – 7	F – 8	F – 9
Average Weight (mg)	377.2	376.8	377.2	376.2
Thickness (mm)	4.7 ± 0.2	4.8 ± 0.2	4.7 ± 0.2	4.8 ± 0.2
Hardness (Kg/cm^2)	6.9 ± 0.2	6.8 ± 0.2	6.8 ± 0.2	7.0 ± 0.2
Friability (%)	0.14 ± 0.01	0.19 ± 0.01	0.20 ± 0.01	0.19 ± 0.01
Weight Variation	+3.3 to - 2.9	+3.6 to -3.2	+3.2 to -2.2	+3.6 to -3.0
Assay				
c) Metoprolol succinate	96.4	97.3	97.9	99.6
d) Hydrochlorothiazide	97.7	97.9	98.1	99.4

Table 7: Evaluation of Bilayer tablets of Metoprolol succinate SR and Hydrochlorothiazide IR (F-6 – F-9)

Sl. no	Time (Hrs)	Limit (%)	F – 1	F – 2	F – 3	F – 4	F – 5	F – 6	F - 7	F – 8	F - 9
Sustained release layer of Metoprolol succinate											
01	1	NMT 25	47.46 ± 1.79	15.26 ± 1.82	13.54 ± 1.95	13.56 ± 1.62	14.46 ± 1.92	10.86 ± 1.73	9.65 ± 1.71	12.75 ± 1.45	13.73 ± 1.30
02	4	20 – 40	73.98 ± 1.86	68.92 ± 1.59	35.25 ± 1.67	34.23 ± 1.48	45.27 ± 1.29	43.02 ± 1.71	34.29 ± 1.46	33.09 ± 1.04	33.59 ± 1.74
03	8	40 – 60	93.79 ± 1.45	87.94 ± 1.71	67.68 ± 1.45	73.01 ± 1.30	80.87 ± 1.65	63.02 ± 1.49	55.34 ± 1.84	54.27 ± 1.83	54.72 ± 1.69
04	20	NLT 80	95.05 ± 1.89	97.34 ± 1.75	94.49 ± 1.60	97.38 ± 1.93	95.89 ± 1.84	93.23 ± 1.82	94.89 ± 1.80	96.99 ± 1.49	97.96 ± 1. 70
Immediate release layer of Hydrochlorothiazide											
01	1	NLT 60	95.05 ± 1.89	81.79 ± 1.50	86.69 ± 1.89	89.49 ± 1.83	94.70 ± 1.70	95.36 ± 1.83	95.86 ± 1.96	95.99 ± 1.49	96.73 ± 1.92

Table 8: *In vitro* dissolution profile of bilayer tablets (F – 1 to F – 9)

Reproducibility batch

To check the reproducibility of the batch, another batch (F – 9) was prepared with the same formula of F – 8. The drug release of 1st, 4th, 8th and 20th hour was found to be 13.29%, 33.62%, 54.71% and 97.92% for Metoprolol succinate and 95.4% for hydrochlorothiazide at 1 hour. The drug release of reproducibility batch was observed similar to the optimized batch.

Release kinetics study for optimized bilayer tablet

The kinetics of drug release was determined based on korsmeyer - peppas equation obtained by *in vitro* dissolution data to various kinetics models. Accordingly the R^2 value was found to be 0.981 for Zero order, 0.962 for first order, 0.996 for Higuchi, 0.999 for korsmeyer-peppas and 0.845 for Hixson-crowell cube root plot. The R^2 value of korsmeyer-peppas was close to 1 and n value was found to be 0.669.

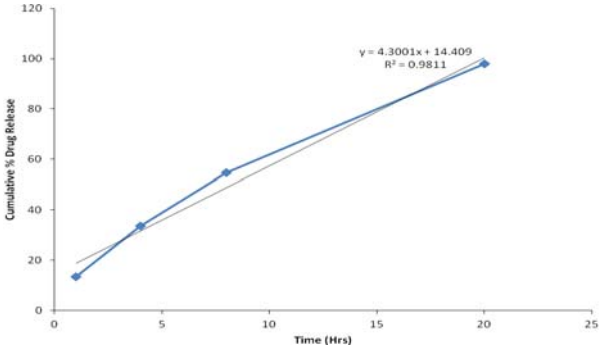

Figure 3: Zero order release model of Metoprolol succinate sustained release formulation (F – 9).

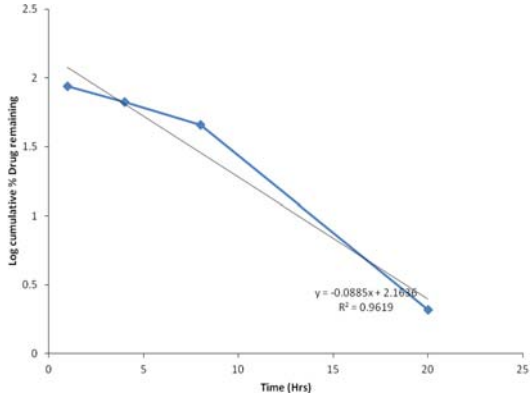

Figure 4: First order release model of Metoprolol succinate sustained release formulation (F – 9).

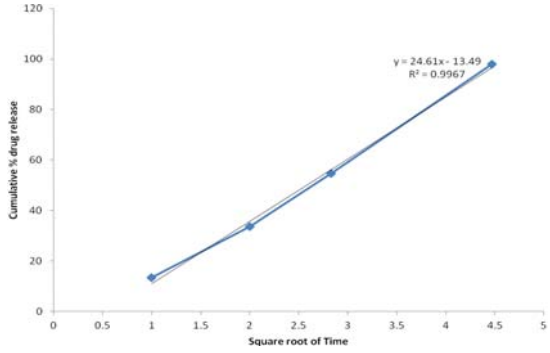

Figure 5: Higuchi release model of Metoprolol succinate sustained release Formulation (F – 9).

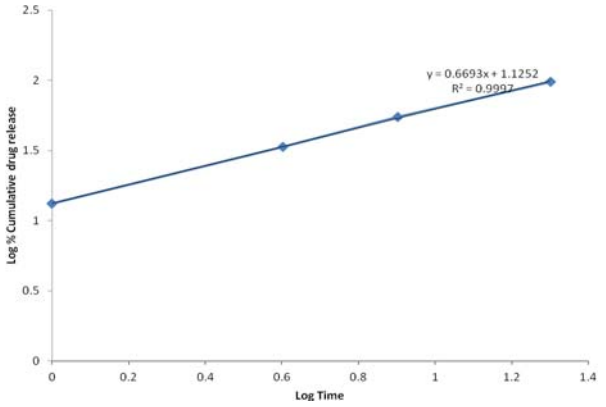

Figure 6: Korsmeyer – Peppas Model of Metoprolol succinate sustained release formulation (F – 9).

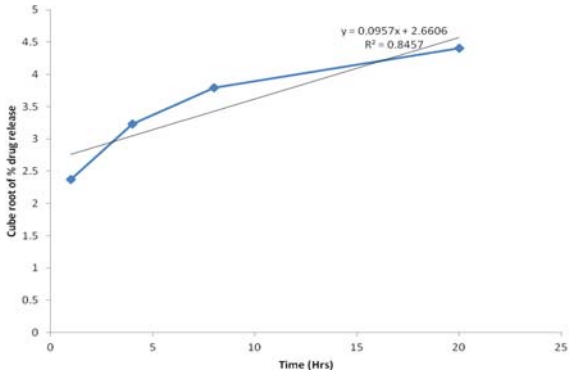

Figure 7: Hixson-Crowell cube root plots of Metoprolol succinate sustained release formulation (F – 9).

Tests	Optimized Formulation	Marketed Product
Description	Blue/White colored circular shaped uncoated bilayer tablet	Yellow/white colored uncoated oval shaped bilayer tabet
Average Weight (mg)	375.9	376.0
Thickness (mm)	4.86 ± 0.25	4.89 ± 0.20
Hardness (Kg/cm^2)	6.7 ± 0.02	6.8 ± 0.5
Friability (%)	0.19 ± 0.01	0.20 ± 0.01
Weight Variation	+3.6 to - 3.0	+4.90 to -3.0
Assay		
e) Metoprolol succinate	99.4	101.3
f) Hydrochlorothiazide	98.7	98.3

Table 9: Optimized formulation (F-9) comparison with the marketed product (Supermet XL)

Comparison of the optimized batch and marketed bilayer tablet

The optimized batch (F – 9) was compared with the marketed product. The drug release of optimized batch and optimized batch was found to be 97.88% and 96.80% for Metoprolol succinate at the end of 20th hour and 95.65% and 96.3% for hydrochlorothiazide at the end of 1st hour. Hence, Metoprolol succinate is sustained till 20th hour and hydrochlorothiazide release in within 1hr. The results were shown in table 9

Stability studies

Stability studies were conducted for the formulation F – 9. The stability study was performed at 40±2°C / 75±5%RH and 30±2°C / 65±5%RH for a specific time period. The tablets were analyzed for appearance, weight variation, drug content and *in vitro* drug release. The overall results showed that the formulation is stable at above mentioned storage conditions shown in table 10.

Test	Specification	Stability Results 40°C / 75% RH 30°C / 60% RH	
		1 Month	2 Months
Description	*	*	*
Average Weight (gm)	376.3 ± 3	376 ± 3	375 ± 2
Thickness (mm)	4.9 ± 0.2	4.9 ± 0.24	4.8 ± 0.42
Hardness (Kg/cm^2)	NLT 3.0	6.6 ± 0.02	6.5 ± 0.05
Friability (%)	NMT 1%	0.23 ± 0.01	0.27 ± 0.01
Weight Variation	± 5%	± 3.2	± 3.9
Assay			
g) Metoprolol succinate	90 – 110%	96.2	95.7
h) Hydrochlorothiazide	90 – 110%	95.4	94.2

*Blue/White colored circular shaped uncoated bilayer tablets.

Table 10: Stability data for F- 9 Metoprolol succinate and Hydrochlorothiazide bilayer tablets

CONCLUSION

The present research work was carried out to develop a bilayer tablet of Metoprolol succinate as sustained release layer was prepared by using hydrophilic matrix polymers such as HPMC K100M and HPMC K4M and hydrochlorothiazide as immediate release layer was prepared in order to match release profile with the innovator product.

Combination of Metoprolol succinate and hydrochlorothiazide are indicated for the treatment and relief as an antihypertensive agent. Tablet formulation (F – 9) complied with the internal specification for weight variation, thickness, hardness, friability, drug content and in vitro drug release. Drug release from the matrix was found to decrease with increase in polymer concentration in intra and extra granulation, where the polymer concentration was employed from 20 – 50% W/W of the average tablet weight. However, HPMC 4M required to channelize the drug release was optimized with 2 – 5%.

The optimized formulation was compared with market product and showed no much difference. Reproducibility was checked by intra batch variability study and found no pronounced variation was observed. The drug release kinetics

of the optimized bilayered tablets correspond best to Korsmeyer- peppas model and the drug release mechanism as per n value of Korsmeyer – peppas is anomalous (non-fickian) diffusion and the tablets showed no significant change in physical appearance, drug content or *in vitro* dissolution pattern after storage at 40±2°C / 75±5%RH and 30±2°C / 65±5%RH for 2 months. Hence, it is finally concluded that, the bilayer tablet technology can be successfully applied for sustained release of Metoprolol succinate and immediate release of hydrochlorothiazide.

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