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Formulation of bilayer tablet containing metoprolol succinate and amlodipine besylate as a model drug for antihypertensive therapy

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ABSTRACT

The purpose of the present work was to develop an optimized bilayer tablet for antihypertension patients using Metoprolol succinate and Amlodipine besylate as a model drug candidate by optimization technique. A 3^2 factorial design was employed in formulating bilayer tablet with individual release layer i.e. sustained release layer and immediate release layer. The independent variables selected both cases HPMC(X_1), Starch 1500 (X_2) and SSG (X_1), MCC (X_2), respectively. Two dependent variables were considered: t_{50} (Y_1), Q_{12} (Y_2) and t_{50} (Y_1), Q_2 (Y_2), respectively. The main effect and interaction terms were quantitatively evaluated using mathematical model. Bilayer tablets were evaluated for thickness, hardness, friability, drug content and in vitro dissolution studies. The drug release of Amlodipine besylate and Metoprolol succinate depicted non-fickian diffusion and Super Case II transport mechanism, respectively.

Keywords: Bilayer tablets, factorial design, non-fickian diffusion, super case II transport

INTRODUCTION

Combination drug therapy is recommended for treatment of hypertension to allow medications of different mechanism of action to complement each other and together effectively lower blood pressure at lower than maximum doses of each.

The rational for combination therapy is to encourage the use of lower doses of drug to reduce the patient's blood pressure to goal to minimize dose dependent side effects and adverse reactions. When smaller doses of medication with different mechanism of action are combined synergistic or additive effects on blood pressure are achieved and dose dependent side effects are minimized.

JNC VI recognized the value of combination therapy and suggested that combining drug with different modes of action will often allow smaller doses of drugs to be used to achieve control and minimize the potential for dose dependent side effects. JNC VI recommended that the combination of a low dose of two drugs in fixed dose combination is an appropriate choice for initial treatment.[1]

Amlodipine is a prototype second generation dihydropyridine calcium channel blocker. They have a longer duration of action and can be given once daily.[2]

Amlodipine is used in the treatment of mild to moderate hypertension, chronic stable angina pectoris or vasopastic angina (prinzmetal's or variant). In these conditions it may be employed as monotherapy or in combination with other antihypertensives or antianginals. Amlodipine can be safely combined with ß blockers, ACE inhibitors, thiazides and nitrates. It has a half life of 40 hours and the initial effects are cumulative over many days.

Metoprolol is selective ß1 receptor blocker devoid of ISA. It effectively inhibits the inotropic and chronotropic responses of isoprenaline and it's potency in this regard is equal to propanolol. It reduces plasma rennin activity in hypertensives. It also reduces mortality in postinfract patients.[3] It has half life of 3 to 4 hours in fast hydroxylator and about 7 hour in slow hydroxylators.

The bilayer tablets were prepared by wet granulation method. The Metoprolol succinate matrix layer were prepared by wet granulation method using HPMC K4M, Starch 1500 as an active ingredients[4], also the Amlodipine besylate immediate release layer were prepared by wet granulation method by an active ingredients such as sodium starch glycolate and microcrystalline cellulose[5].

The 3^2 factorial designs were applied to sustained release matrix layer and immediate release layer. The effect of independent variables on the dependent variable shows the significant effect on the response such as t_{50}, Q_{12} and t_{50}, $Q_{2,}$ for Metoprolol succinate sustained release layer and Amlodipine besylate immediate release layer, respectively.

MATERIAL AND METHOD

Materials

Amlodipine besylate, Metoprolol succinate was received gift sample from Concept Pharmaceutical, Aurangabad. HPMC K4M, Microcrysatalline cellulose was received gift sample from Colorcorn Asia Pvt. Ltd. Goa. Starch 1500, Sodium starch glygolate, Sunset yellow was received gift sample from Concept pharmaceutical, Aurangabad. All other chemicals are of analytical grades.

Methods

Simultaneous estimation of Metoprolol succinate and Amlodipine besylate by UV spectroscopy[6,7]

Preparation of stock solution of Metoprolol succinate

Metoprolol succinate equivalent to 20 mg of metoprolol was accurately weighed and transfer to 100 ml volumetric flask. About 90 ml of 0.1 N HCl was added and sonicated to dissolve. The volume was made up to the mark with 0.1 N HCl. The final dilution contained 200 µg/ml of metoprolol.

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Preparation of stock solution of Amlodipine besylate

Amlodipine besylate equivalent to 10 mg of amlodipine was accurately weighed and transfer to 100 ml volumetric flask. About 90 ml of 0.1 N HCl was added and sonicated to dissolve. The volume was made up to the mark with 0.1 N HCl. The final dilution contained 100 µg/ml of amlodipine.

Preparation of synthetic mixture of Metoprolol and Amlodipine

10 ml of each of the stock solutions of metoprolol and amlodipine were transferred to 10 ml volumetric flask. The volume was made up to mark with 0.1 N HCl. The resultant solution contained 20 µg/ml of metoprolol and 10 µg/ml of amlodipine.

Linearity and calibration

0.5-5.0 ml of each of stock solution of metoprolol and amlodipine 200 µg/ml and 100 µg/ml respectively, were transferred to a series of 10 ml volumetric flasks. The volume in each flask adjusted to 10 ml with 0.1 N HCl and mixed so as to obtained solution of final concentration in the range of 5 to 50 µg/ml for amlodipine and 10 to 100 µg/ml for metoprolol. These solutions were analyzed using multi component mode of analysis. The method was found to be linear in the range of 70 to 130% of the test concentration. In the linearity study, regression equation and correlation coefficient for metoprolol and amlodipine were found to be r^2= 0.99453, y = 0.03184x + 0.00023 and r^2 = 0.99853, y = 0.00460x + 0.00818 respectively. (Figure 1, 2)

Formulation of Bilayer Tablets

The literature survey reveals that the concentration of HPMC K4M used for matrix tablet is in the range of 50-60%, and results in maximum matrix integrity and average drug release from matrix tablet. Therefore, for matrix tablets were formulated using 50%, 55% and 60% of HPMC K4M. Also, the literature survey reveals that the concentration of superdisintegrant for immediate release tablet is upto 10%. Therefore, for immediate release tablet were formulated using 4%, 6% and 8% of superdisintegrant.

Factorial Design

For the present work 3^2 factorial design was selected for two different release layer i.e. Metoprolol succinate sustained release matrix layer tablet and Amlodipine besylate immediate release layer tablet. The two independent variables selected were for Metoprolol succinate sustained release matrix layer tablet, HPMC K4M (X_1) and Starch 1500 (X_2), and the nine formulations formulated as per the experimental design. Also the two independent variables selected for Amlodipine besylate immediate release layer tablet, Sodium Starch Glycolate (X_1) and Microcrystalline Cellulose (X_2) and the nine formulations formulated as per the experimental design.

Preparation of Metoprolol succinate sustained release matrix layer tablets

The nine formulations bearing 50 mg of drug Metoprolol succinate were prepared by wet granulation method. Metoprolol succinate, HPMC K4M, Starch 1500, MCC PH102, Eudragit L100[8] were mixed thoroughly in mortar and pestle for 10 minutes to obtain a homogeneous blend. The wet mass was then passed through sieve # 16 to obtain the granules. The granules were dried at 50ºC for 1hr. The dried granules were lubricated with magnesium stearate, talc and aerosil passed through sieve # 22. The granules compressed using Labpress rotary tablet machine using 10mm flat faced punches.

Preparation of Amlodipine besylate immediate release layer tablets

The nine formulations bearing 5 mg of drug Amlodipine besylate were prepared by wet granulation method. Amlodipine besylate, MCC PH102, sodium starch glycolate, Starch 1500 were mixed thoroughly in mortar and pestle for 10 minutes to obtain a homogeneous blend. The wet mass was then passed through sieve # 16 to obtain the granules. The granules were dried at 50ºC for 1hr. The dried granules were lubricated with magnesium stearate, aerosil and passed through sieve # 22. The granules compressed using Labpress rotary tablet machine using 10mm flat faced punches.

Evaluation of Granules Flow Properties

The prepared granules were evaluated for parameters like bulk density, tap density, Carr index, Angle of repose, and Hausner's ratio.

Bulk density

The bulk density was calculated using the equation,

Bulk density = Weight of sample/Bulk volume

Tap density

The tap density was calculated by the following equation,

Tap density = Weight of drug sample / Tapped volume

Carr index

It is calculated by the formula,

$C = V_T - V_B / V_T$

Where V_B is the freely settled volume of a given mass of powder, and V_T is the tapped density of the same mass of powder.

Angle of repose

The angle of repose is calculated by,

$\tan \theta = h/r$

Where, h is height of the pile

r is the radius of the pile.

Hausner's ratio

It is calculated by the formula,

$$H = \frac{r_T}{r_B}$$

Where, ρ_B is the freely settled bulk density of the powder, and ρ_T is the tapped density of the powder.

In vitro dissolution study of Metoprolol succinate sustained release matrix layer tablet

Drug release studies were carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C, and pH 1.2 buffer (900ml) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and experiment continued for another 10 hours. At the different time intervals, 5ml of the sample was withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer at 274.20nm.

In vitro dissolution study of amlodipine besylate immediate release layer tablet

Amlodipine besylate immediate release tablets drug release studies carried out using USP dissolution rate test apparatus (apparatus 2, 50 rpm, 37±0.5°C) for 2 hours in 0.1 N HCl (900ml). at the different time interval, 5ml of the sample was withdrawn and replaced with 5ml of the 0.1 N HCl. The dissolution samples were obtained at different time interval replacing with drug-free dissolution medium. The samples withdrawn were analyzed by a UV spectrophotometer at 240.80nm.

Preparation of Bilayer Tablets

Out of the nine formulations of Metoprolol succinate matrix tablet and Amlodipine besylate immediate release tablet, three formulations were selected on the basis of in vitro drug release studies.

The different combination of Metoprolol succinate matrix and Amlodipine besylate immediate release granules were used for formulation of bilayer tablet. The granules compressed using Labpress rotary tablet machine using 10 mm flat faced punches. The formulated nine bilayer formulations are shown in table.

Evaluation of Tablets

The tablets were evaluated for various parameters such as appearance, shape, hardness, weight variation, friability, drug content, etc.

Dissolution Studies

Bilayer tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to asses their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis.

Dissolution Efficiency

The dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain limit, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. It is calculated by the following equation

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100$$

Where y is drug percent dissolved at time t.

Kinetics of Drug Release

The dissolution profile of all the batches were fitted to zero order kinetics, first order kinetics, Higuchi, Hixon-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model.

Analysis of data by Design Expert software

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, for Metoprolol succinate and Amlodipine besylate respectively. For Metoprolol succinate sustained release layer matrix tablet, the percentage of HPMC K4M (X_1) and Starch 1500 (X_2) were selected as independent variables and the dependent variables were t_{50} and $Q_{(12h)}$. For Amlodipine besylate immediate release layer tablet, the percentage of SSG (X_1) and MCC (X_2) were selected as independent variables and the dependent variables were t_{50} and $Q_{(2h)}$. The data obtained were treated using Stat Ease Design Expert 7.1.4 software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to study the interaction of HPMC K4M (X_1) and Starch 1500 (X_2) on dependent variables and also the study of interaction of SSG (X_1) and MCC (X_2) respectively.

RESULT AND DISCUSSION

Formulation Studies

Formulation studies of tablet

In the present study, an attempt had been made to design a controlled release matrix tablet with minimum dose of drug Metoprolol succinate (50 mg).

The literature survey revealed the maximum concentration of HPMC K4M for matrix tablet containing 60% is able to withstand good tablet integrity and drug release profile for a period of 12 hours. The formulations bearing polymer concentration 50%, 55% and 60% were selected for further studies.

The highly water soluble drug shows exuberated drug release in the simulated gastric fluid. Hence, to over come this problem Eudragit L100 was used as an enteric coating polymer[1] . Metoprolol succinate was used as a model drug.

The preliminary trails were conducted with 5% and 10% of Eudragit L100. The trial conducted with 10% of Eudragit L100 shows the prominent result on controlling the in vitro drug release in gastric condition and selected for further investigation.

In order to evaluate the effect of HPMC and Starch 1500 combination, the 3^2 factorial design was used to prepare model formulations with two independent variables: HPMC K4M (X_1) and Starch 1500 (X_2). The dependant variables examined were: t_{50} (Y_1) and Q_{12} (Y_2). According to 3^2 factorial design approach 9 model formulations were randomly arranged by Design-Expert software. (Table 1, 2, 3) The response t_{50} and Q_{12} for the formulations M7, M10 and M13 containing polymer concentration 50%, 55% and 60% respectively showed significant results.

The response t_{50} for formulation M7, M10 and M13 were 7.80, 7.66 and 7.82 hour respectively. The Q_{12} i.e. drug release after 12 hours for formulation M7, M10 and M13 were 74.3±0.52, 69.84±0.17 and 110.2±0.98% respectively. (Table 9) (Figure 3, 4)

Hence, it was evidence that increase in concentration of polymer and starch increases the drug release but again reduces the drug release after increasing the concentration of starch.

An attempt was made to formulate immediate release tablet of the drug amlodipine besylate (5 mg). The literature survey revealed that the maximum effect of superdisintegrant was obtained in the range of 1 to 10% by weight, which enhanced the dissolution rate in the oral cavity of the tablet. The preliminary formulation batches formulated containing sodium starch glycolate (SSG) as a superdisintegrant in the concentration 5 and 10% respectively. The formulations showed poor tablet integrity. Therefore, for further studies superdisintegrant in concentration 4%, 6% and 8% were selected.

In order to easily optimize the formulation and evaluation of the influence of each additive the 3^2 factorial design was used to prepare systematic model formulations which were composed of two independent variable: SSG (X_1) and MCC (X_2). The dependant variables examined were t_{50} and Q_2. According to 3^2 factorial design approach 9 model formulations were randomly arranged by Design-Ex-

Table 1: Amount of variables in 3^2factorial design batches for Metoprolol succinate succinate

Coded Values	Actual Values (%)	
	X_1	X_2
-1	50	5
0	55	10
+1	60	15

Table 2: Experimental design of Metoprolol succinate sustained release matrix layer tablet

Formulation code	Coded values		Total Weight of Tablet(mg)
	X_1	X_2	
M6	-1	-1	188
M7	-1	0	199
M8	-1	+1	210
M9	0	-1	199
M10	0	0	210
M11	0	+1	221
M12	+1	-1	210
M13	+1	0	221
M14	+1	+1	232

Table 3: Formulation Design of Metoprolol succinate sustained release matrix layer tablet per Full Factorial Design (3^2) Layout

Tablet Ingredients (mg) /Formulation Code	M6	M7	M8	M9	M10	M11	M12	M13	M14
Metoprolol succinate	50	50	50	50	50	50	50	50	50
HPMC K4M	110	110	110	121	121	121	131	131	131
Starch 1500	11	22	33	11	22	33	11	22	33
MCC PH 102	13.75	13.75	13.75	13.75	13.75	13.75	13.75	13.75	13.75
Aerosil	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Talc	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2

Table 4: Amount of variables in 3^2factorial design batches for Amlodipine besylate

Coded Values	Actual Values (%)	
	X_1	X_2
-1	4	40
0	6	45
+1	8	50

Table 5: Experimental design of Amlodipine besylate immediate release layer tablet

Formulation code	Coded values		Total Weight of Tablet(mg)
	X_1	X_2	
A6	-1	-1	89
A7	-1	0	94
A8	-1	+1	99
A9	0	-1	91
A10	0	0	96
A11	0	+1	101
A12	+1	-1	93
A13	+1	0	98
A14	+1	+1	103

Table 6: Formulation Design of Amlodipine besylate immediate release layer tablet per Design (3^2) Layout

Tablet Ingredients (mg) /Formulation Code	A6	A7	A8	A9	A0	A11	A12	A13	A14
Amlodipine besylate	5	5	5	5	5	5	5	5	5
SSG	4	4	4	6	6	6	8	8	8
MCC PH 102	40	45	50	40	45	50	40	45	50
Starch 1500	35	35	35	35	35	35	35	35	35
PVP K30	2	2	2	2	2	2	2	2	2
Aerosil	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Magnesium stearate	1	1	1	1	1	1	1	1	1

Table 7: Evaluation parameters of Metoprolol succinate granules

Formulation code	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's index (%)	Angle of repose	Hausner ratio
M6	0.3076±0.005	0.3333±0.012	7.7107±0.55	28.95±1.34	1.0835±0.04
M7	0.3571±0.003	0.4166±0.010	14.28±0.76	32.38±1.20	1.1666±0.02
M8	0.2272±0.010	0.250±0.032	9.12±1.05	32.55±1.08	1.1003±0.07
M9	0.2777±0.006	0.2941±0.005	5.57±0.30	32.23±1.44	1.0590±0.09
M10	0.3030±0.021	0.40±0.016	24.25±0.90	34.90±1.32	1.3201±0.02
M11	0.3030±0.004	0.3571±0.011	15.14±0.78	29.16±1.26	1.1785±0.05
M12	0.2777±0.007	0.2127±0.013	22.23±0.44	34.65±1.08	1.2859±0.03
M13	0.1785±0.015	0.2127±0.023	16.07±1.03	36.32±1.10	1.1915±0.05
M14	0.3125±0.020	0.4166±0.021	24.98±1.42	36.19±1.22	1.331±0.07

Table 8: Evaluation parameter of Amlodipine besylate granules

Formulation code	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's index (%)	Angle of repose	Hausner ratio
A6	0.3846±0.012	0.4166±0.005	7.6812±0.04	33.69±1.34	1.0832±0.55
A7	0.3703±0.010	0.4347±0.003	14.81±0.02	32.38±1.20	1.1739±0.76
A8	0.3571±0.032	0.4347±0.010	17.85±0.07	34.99±1.08	1.2173±1.05
A9	0.3333±0.005	0.40±0.006	16.67±0.09	44.16±1.44	1.2001±0.30
A10	0.3225±0.016	0.40±0.021	19.37±0.021	36.59±1.32	1.2547±0.90
A11	0.3125±0.011	0.3921±0.004	20.30±0.05	32.38±1.26	1.2547±0.78
A12	0.2941±0.013	0.3773±0.007	22.05±0.03	31.75±1.08	1.2828±0.44
A13	0.3571±0.023	0.4347±0.015	17.85±0.05	35.39±1.10	1.2173±1.03
A14	0.3571±0.021	0.4347±0.020	17.85±0.07	26.88±1.22	1.2173±1.42

Table 9. % Cumulative release formulation of Metoprolol succinate sustained release matrix layer

Time (hours)	% Cumulative Release								
	M6	M7	M8	M9	M10	M11	M12	M13	M14
1	14.71	9.82	12.07	22.51	9.82	12.11	20.89	22.12	20.44
2	27.68	24.55	21.06	35.67	17.27	20.67	34.72	38.08	34.07
4	34.93	30.90	27.98	48.84	22.47	33.52	48.81	52.51	43.3
6	36.77	45.92	39.23	51.82	36.49	41.77	61.94	61.86	66.71
8	46.66	55.99	49.64	66.96	59.22	54.3	70.52	77.42	71.74
10	50.05	66.83	51.12	78.29	70.00	69.65	76.89	85.83	79.53
12	81.2	74.30	90.50	87.68	90.89	79.65	89.65	102.31	85.4

Table 10. % Cumulative release formulation of Amlodipine besylate immediate release layer

Time (hours)	% Cumulative release								
	A6	A7	A8	A9	A10	A11	A12	A13	A14
0.5	59.03	68.23	46.3	52.30	75.04	71.06	59.03	36.02	73.15
1	72.8	69.23	57.87	56.61	79.54	72.49	66.62	46.27	75.71
1.5	75.32	75.35	63.14	67.85	81.84	76.11	76.12	59.36	77.54
2	82.21	81.91	81.82	98.75	95.71	93.71	81.17	84	82.21

Table 11: Combination batches for bilayer tablet

Tablet Ingredients (mg) /Formulation Code	Metoprolol succinate sustained release layer		Amlodipine besylate immediate release layer	
	HPMC K4M (mg)	Starch 1500 (mg)	SSG (mg)	MCC PH102 (mg)
MA1: (M11+ A9)	121	33	6	40
MA2: (M11+ A10)	121	33	6	45
MA3: (M11+ A11)	121	33	6	50
MA4: (M12+ A9)	132	11	6	40
MA5: (M12+ A10)	132	11	6	45
MA6: (M12+ A11)	132	11	6	50
MA7: (M13+ A9)	132	22	6	40
MA8: (M13 + A10)	132	22	6	45
MA9: (M13 +A11)	132	22	6	50

Table 12: Evaluation of Bilayer Tablets for Formulation Batches

Evaluation Parameters* Formulation Code	Appearance	Weight Variation (mg)** (± %)	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Drug Content A (%)	Drug Content M (%)
MA1	Off-white and Orange colored, 10 mm, round flat faced.	312.25 ±2.55	7.56 ±0.057	3.23 ±0.065	0.556 ±0.030	100.25 ±0.0905	98.25 ±1.12
MA2	Off-white and Orange colored, 10 mm, round flat faced.	317.25 ±2.78	7.5±0.1	3.25 ±0.025	0.57 ±0.026	101.69 ±0.987	99.0 1±1.10
MA3	Off-white and Orange colored, 10 mm, round flat faced.	322.25 ±2.75	7.46 ±0.057	3.21 ±0.030	0.596 ±0.015	101.15 ±1.924	98.97 ±1.23
MA4	Off-white and Orange colored, 10 mm, round flat faced.	301.25 ±3.068	7.4 ±0.1	3.35 ±0.032	0.663 ±0.037	101.34 ±1.527	99.19 ±0.90
MA5	Off-white and Orange colored, 10 mm, round flat faced.	306.25 ±3.105	7.43 ±0.115	3.33 ±0.043	0.696 ±0.020	101.58 ±1.527	98.26 ±0.78
MA6	Off-white and Orange colored, 10 mm, round flat faced.	311.25 ±3.31	7.53 ±0.057	3.43 ±0.032	0.703 ±0.015	100.52 ±1.415	98.78 ±0.86
MA7	Off-white and Orange colored, 10 mm, round flat faced.	312.25 ±3.30	7.43 ±0.057	3.46 ±0.05	0.713 ±0.025	101.99 ±0.614	98.69 ±1.13
MA8	Off-white and Orange colored, 10 mm, round flat faced	317.25 ±2.75	7.56 ±0.057	3.45 ±0.040	0.71 ±0.020	101.10 ±1.546	99.26 ±0.95
MA9	Off-white and Orange colored, 10 mm, round flat faced	322.25 ±2.93	7.43 ±0.057	3.46 ±0.032	0.716 ±0.040	101.24 ±1.453	98.36 ±1.19

All values are mean ± SD, n=5 and **Values are mean± SD, n=20, ***Values are mean± SD, n=5, M= Metoprolol succinate succinate, A= Amlodipine besylate besylate .

pert software Table (4, 5, 6). The response t_{50} and Q_2 for the formulations A9, A10 and A11 containing polymer concentration 6% by weight showed significant results.

The response t_{50} for formulation A9, A10 and A11 were 1.01, 1.04 and 1.06 hour respectively. The Q_2 i.e. drug release after 2 hours for formulation A9, A10 and A11 were 76.81%, 83.71% and 84.01% respectively. (Table10) (Figure 5, 6)

Hence, it was evident that drug release increases with increase in concentration of microcrystalline cellulose and concentration of sodium starch glycolate but decreases when increases the concentration of sodium starch glycolate.

Evaluation of granules flow properties

The granule characteristics are the most important parameter for consideration for formulation of successful pharmaceutical dosage forms. (Table 7, 8) depicts the granule properties of Metoprolol succinate matrix sustained release layer tablet and Amlodipine besylate immediate release layer tablet respectively.

Many different types of angular properties have been employed to assess flowability, of these; angle of repose is the most relevant. Repose angle of the granules was investigated. The value of Angle of repose (θ) decreased after the addition of lubricant. Angle of repose (θ) is an indicative parameter of powder flowability from hopper to die cavity. A repose angle between 20° to 30° indicates excellent flowability of granules. The angles of repose of all the formulations were within the range of 25° – 35°, indicative of good flowability. Bulk density may influence compressibility, tablet porosity, dissolution and other properties and depends on the particle size, shape and tendency of particles to adhere together. The bulk density of granules was found to be between 0.30-0.35 gm/cm^3. The value indicates good packing capacity of granules. The tap density of the granules of factorial design batches were found in the range of 0.35-0.45 gm/cm^3. The bulk density and tap density was used to calculate the percent compressibility of the granules.

The Carr's index of the granules was observed between 10 to 25, indicating good compressibility of the granules. The values of the Hausner ratio were found to be in the range of 1.03 to 1.21, indicating good flowability.

Tablet Evaluation Parameters

All formulated bilayer tablet batches were off white and orange coloured with smooth surface, circular flat faced with good texture.

The thickness of the formulated bilayer tablet batches were found in range of 3.26 and 3.46 mm, due to constant tablet press setting across all batches irrespective of weight variation.

The hardness of the tablet was found to be in the range of 7.40 to 7.60 kg/cm^2. This ensures good mechanical strength.

The friability of the factorial design batches were in the range of 0.556 to 0.716, which was within the specified limits. Tablets with friability less than 1% of their weight are acceptable.

The average weight of tablets within each formulation was found to be uniform. This indicates uniform feeling of the die cavity during tablet compression. According to I.P., for tablets weighing 250 mg or more, not more than two tablets differ from the average weight by not more than 5% and no tablet differs by more than double the relevant percentage. The percent deviation in weight variation from average value for all formulation of factorial design batches were within limit (Table 12).

The drug content of the nine formulations was found to be in the range of 98 and 102 % (i.e. variation of ±3%) for both Amlodipine besylate and Metoprolol succinate. The value ensures good uniformity of the drug content in the tablets.

In vitro dissolution study

The in vitro drug release profile of Metoprolol succinate from bilayer tablet containing different proportions of HPMC 4M and Starch 1500 are shown in figure 8. After 2 hours, the initial pH 1.2 was changed to 6.8 continue the dissolution upto 12 hours. It was shown that, the matrix corresponding to lengthening of drug diffusion pathway and drug release rate.

The in vitro drug release profile of Amlodipine besylate from bilayer tablet containing different proportion of sodium starch glycolate and microcrystalline cellulose are shown in figure 7 . It was shown that as the amount of sodium starch glycolate increases in formulation the drug release increase up a certain level and decreases with higher concentration.

Dissolution efficiency (%)

The dissolution efficiency of the all formulated bilayer tablet batches were found between 59.25- 69.25% of amlodipine besylate and 6.38-18.38% and 43.94-57.54% of metoprolol succinate for 0.1 N HCl and Phosphate buffer pH 6.8 respectively. (Figure 9, 10)

Kinetic of drug release

Several theories or a kinetic model describes drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where f_t is a function of t (time) related to the amount of the drug dissolved from the pharmaceutical dosage system.

Korsmeyer et.al., is used to describe drug release from polymeric systems:

$M_t/M_x = kt^n$

Where, M_t/M_x is the fractional release of drug, t is the release time (expressed in hours), k is a constant that incorporates structural and geometric characteristics of the release device and n is the release exponent which indicates the kinetics of the release.

Peppas and Sahlin proposed a heuristic model and derived an equation which is very useful for quantifying the approximate amount of drug released by Fickian and polymer relaxation.

$M_t/M_x = k_1 t^{1/2} + k_2 t$

Where, the first term of the right hand side represents the fickian contribution, and the second term is the case II relaxational contribution, k_1 and k_2 corresponding to the release rates of case I and case II mechanism respectively.[2]

In the present study the dissolution data were analyzed by PCP Disso Version V3 software to study the kinetics of drug release mechanism for individual drug release layer.

Drug release data of Amlodipine besylate immediate release layer and Metoprolol succinate matrix layer revealed Korsmeyer Peppas equation as the best fit model and the value of n i.e. release exponent was >0.5. The n value is used to interpret the release mechanism. (Table 15, 16) Thus, the drug release of Amlodipine besylate and Metoprolol succinate depicted non-fickian diffusion and Super Case II transport

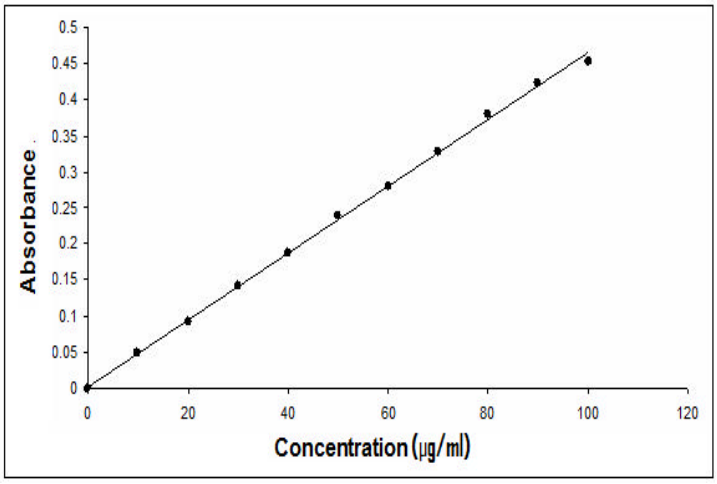

Figure 1 Standard Calibration Curve of Metoprolol succinate in 0.1N HCl

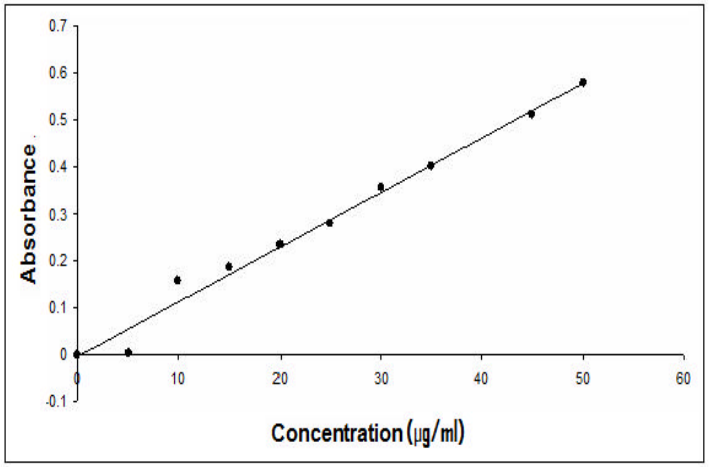

Figure 2 Standard Calibration Curve of Amlodipine besylate in 0.1N HCl

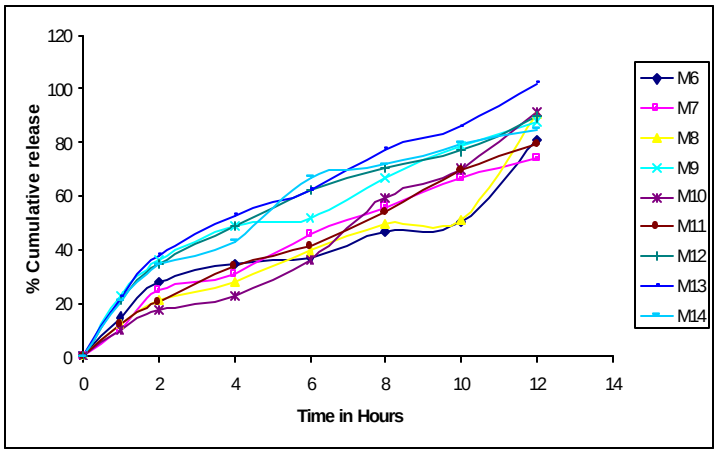

Figure 3 Comparative % release profile of Metoprolol succinate in PBS 6.8

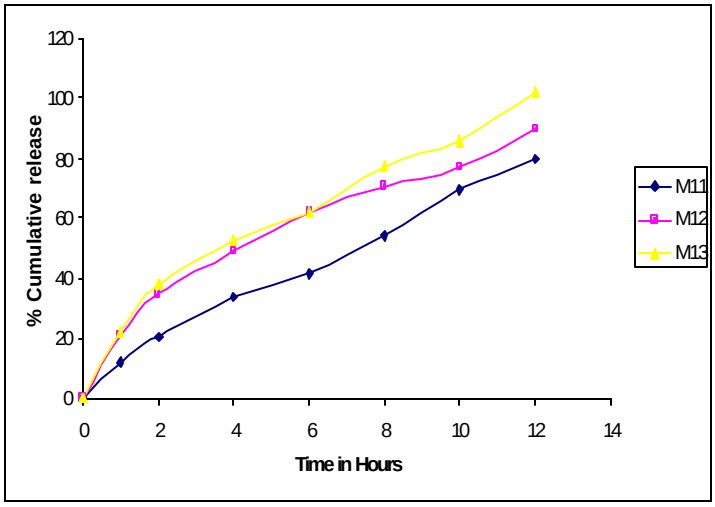

Figure 4 Comparative % release of selected Metoprolol succinate formulation

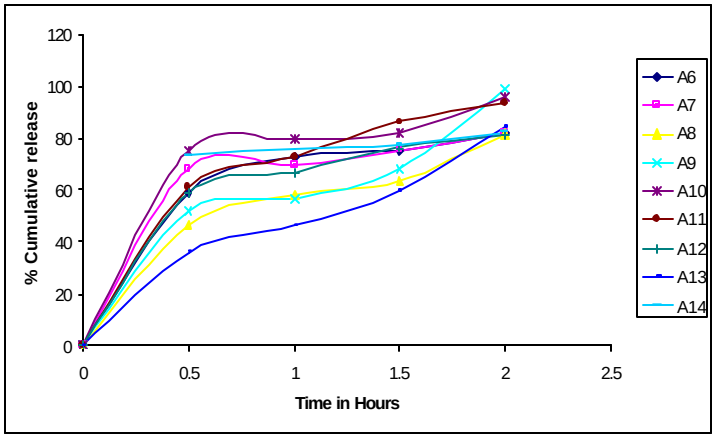

Figure 5 Comparative % release profile of Amlodipine in 0.1 N HCl

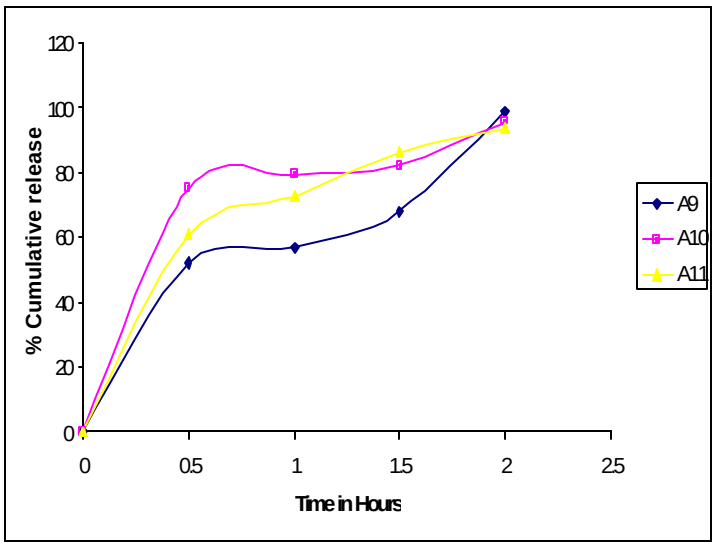

Figure 6 Comparative % release of selected Amlodipine besylate formulation

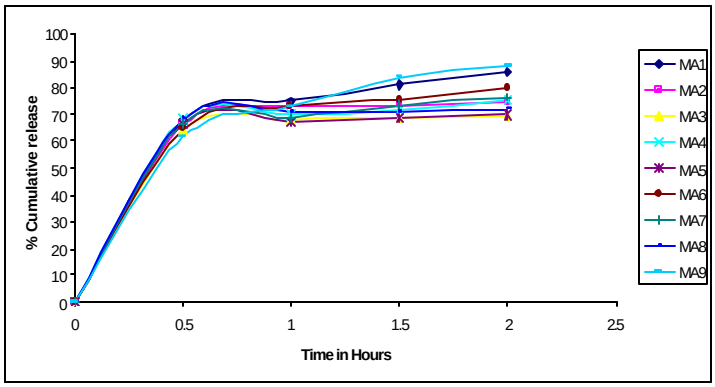

Figure 7 Comparative % release profile of overall Amlodipine besylate bilayer tablet (0.1 N HCl)

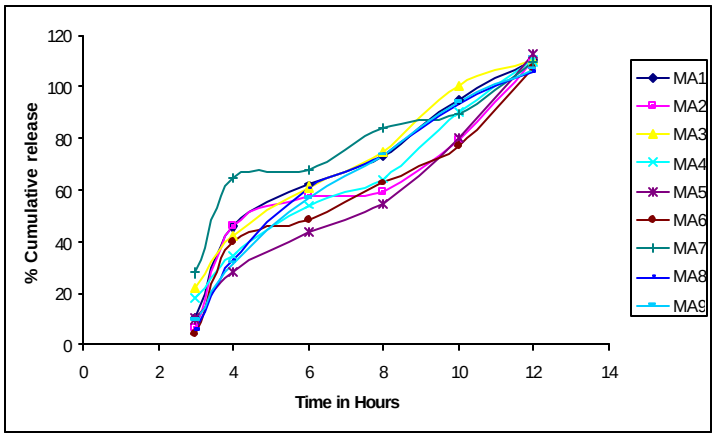

Figure 8 Comparative % release profile of Metoprolol succinate bilayer tablet (PBS 6.8)

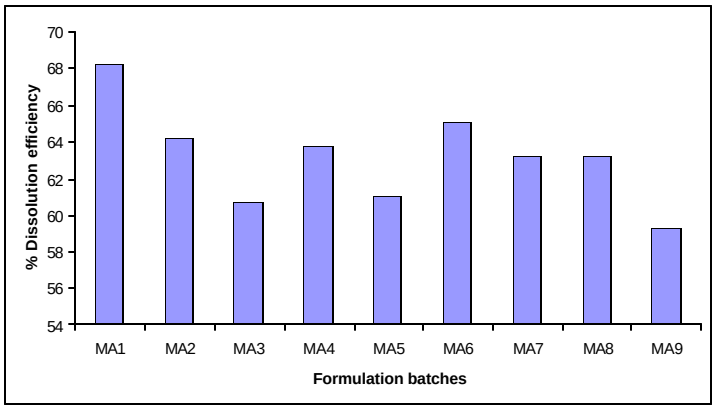

Figure 9 Dissolution Efficiency of Formulation Batches of Amlodipine besylate in 0.1 N HCl after 2 hour

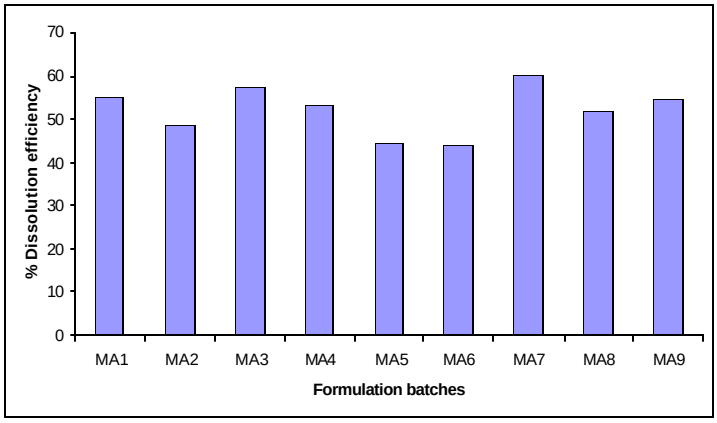

Figure 10 Dissolution Efficiency of Formulation Batches of Metoprolol succinate in Phosphate buffer ph 6.8 after 12 hours

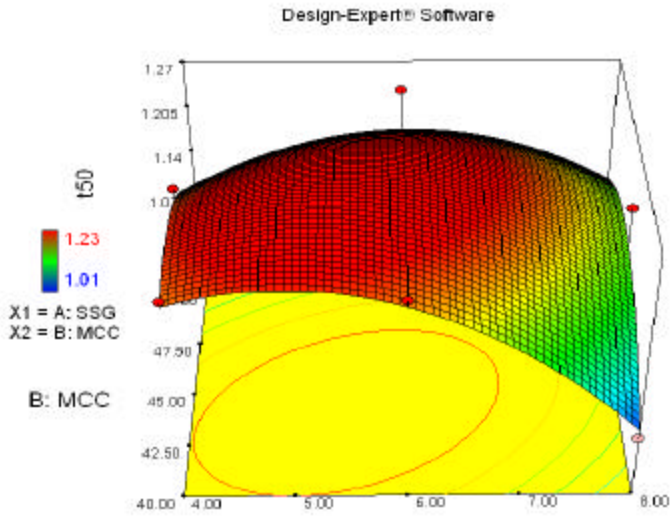

Figure 11 Response surface plot of t_{50} (Amlodipine besylate)

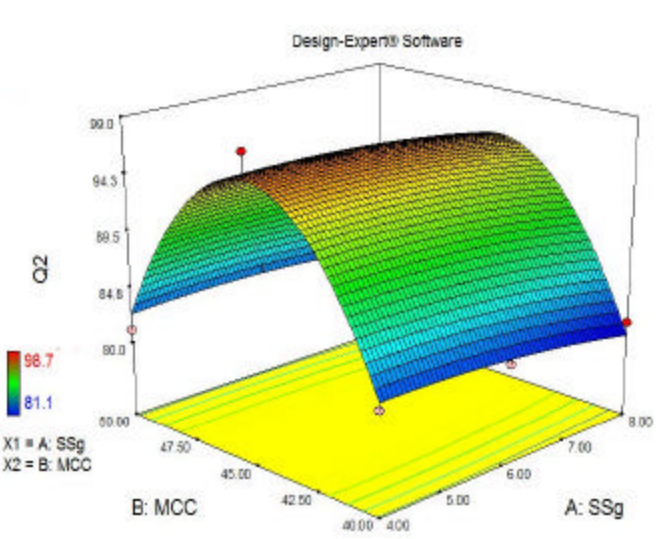

Figure 12 Response surface plot of Q_2 (Amlodipine besylate)

mechanism, respectively. The n values were found to be between 0.5-1, indicating non-fickian diffusion or anomalous transport. The n ($0.5<n<1$) value also revealed the drug release mechanism via diffusion coupled with erosion.

Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case II relaxational release is the drug transport mechanism associated with stress and state transition hydrophilic glassy polymers, which swells in water or biological fluids. This term also includes polymer disentanglement and erosion.

Data Analysis by Design Expert Software

The 3^2 factorial design was selected for the present study. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1^2+b_{22}X_2^2 \quad (1)$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_i(b_1,b_2,,b_{12},b_{11} and b_{22}) is the estimated coefficient for the corresponding factor X_i(X_1,X_2,X_{12},X_{11},and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The t_{50} and Q_2 for the nine batches (Amlodipine besylate) (A6-A14) showed a wide variation (i.e., 1.01-1.22 hours and 81.17-95.71%, respectively). Apart from this the response t_{50} and Q_{12} for nine batches (Metoprolol succinate) (M6-M14) showed (i.e. 7.49-7.82 hours and 74.30-12.31%). The responses of the formulations prepared by 3^2 factorial design batches are indicated in the table 17-20. The fitted regression equations relating the responses t_{50}, Q_2 and Q_{12} are shown in the following equations, respectively.

Final Equations in Terms of Coded Factors (amlodipine):

$t_{50} = 1.0344+0.0083X_1-0.0033X_2-0.0075X_1X_2-0.0083\ X_1^2+0.1733\ X_2^2$

(2)*Final equations in Terms of Actual Factors (amlodipine):*

t_{50} = 14.95+0.0129 SSG-0.6201 MCC-0.0007 SSG MCC -0.0020 SSG^2+0.0069 MCC^2 (r^2=0.9699)

(3) *Final Equations in Terms of Coded Factors (amlodipine):*

$Q_2 = 96.42-0.7166X_1+0.235X_2+0.375X_1X_2-0.5866X_1^2-13.8317\ X_2^2$

(4)*Final equations in Terms of Actual Factors (amlodipine):*

Q_2 = -1019.06-0.2858 SSG+49.61 MCC+0.0375 SSG MCC -0.1466 SSG^2-0.5532MCC^2 (r^2=0.9681)

(5)*Final Equations in Terms of Coded Factors (metoprolol):*

$Q_{12} = 93.76+5.272X_1-3.2483X_2+0.5875X_1X_2+0.805\ X_1^2-11.435\ X_2^2$

(6)*Final equations in Terms of Actual Factors (metoprolol):*

Q_{12} = -106.8217-2.722 HPMC K4M+7.2058 Starch 1500+0.0235 HPMC K4M Starch 1500+0.0322 HPMC $K4M^2$-0.4574 $Starch\ 1500^2$ (r^2=0.9530)

(7)*Final Equations in Terms of Coded Factors (metoprolol):*

$t_{50} = 7.8611+0.1183X_1-0.105X_2-0.0075X_1X_2-0.1516\ X_1^2-0.2316\ X_2^2$

(8)*Final equations in Terms of Actual Factors (metoprolol):*

t_{50}= -12.6739+0.694 HPMCK4M+0.1808Starch 1500-0.0003 HPMCK4M Starch1500-0.0060 $HPMCK4M^2$-0.0092 $Starch\ 1500^2$ (9)(r^2 =0.9414)

The above equation revealed the effect of independent variables on the desired response. The regression coefficient values are the estimates of the model fitting. The r^2 was high indicating the adequate fitting of the quadratic model. The polynomial equations can also be used to draw conclusions considering the magnitude of co-efficient and the mathematical sign it carries; i.e. positive or negative.

The positive coefficient of variable X_1 i.e. HPMC K4M in the case of Metoprolol succinate and SSG in the case of Amlodipine besylate. The response of metoprolol succinate showed an increase in the t_{50} and Q_{12} value with the increase in the HPMC concentration. The response of amlodipine besylate depicted an increase in the t_{50} but decrease in Q_2 with the increase SSG concentration.

The second variable X_2 i.e. Starch 1500 in case of Metoprolol succinate and MCC in case of Amlodipine besylate responses showed positive coefficient for response Q_{12} and Q_2, respectively.

ANOVA for the dependent variables t_{50}, Q_{12} and t_{50}, Q_2 for both Metoprolol succinate and Amlodipine besylate, respectively are shown in table 21-24. ANOVA and Multiple regression analysis were done using Stat-Ease Design Expert 7.1.4 software. The response surface plot of the Metoprolol succinate and Amlodipine besylate are shown in figure 11-14.

The main effect of A and B represents the average result of changing variables at a time from its low level to high level. The interaction terms (AB, A^2,B^2) reveal the Q_{12} and t_{50} changes when the two variable are simultaneously changed. The negative coefficient for the independent variable (B, B^2), (B, AB, A^2,B^2) and (B, B^2), (B, AB) indicate unfavorable effects on the Metoprolol succinate matrix tablet (Q_{12} and t_{50}) and Amlodipine besylate (Q_2 and t_{50}), respectively. The independent variables exhibit positive interaction which indicates the favorable effect on the Metoprolol succinate matrix tablet (Q_{12} and t_{50}) and Amlodipine besylate (Q_2 and t_{50}), respectively.

The variance Inflation Factor (VIF) measures how much the variance of that model coefficient is inflated by the lack of orthogonality in the design and calculated for Metoprolol succinate matrix tablet (Q_{12} and t_{50}) and Amlodipine besylate (Q_2 and t_{50}), respectively, which is found to be 1 indicating good estimation of coefficients. Similarly, Ri-squared is near to zero which is leading to good model. The model F value calculated for Metoprolol succinate matrix tablet (Q12 and t50) and Amlodipine besylate (Q_2 and t_{50}) respectively, are found to be (13.82 and 9.56) and (18.24 and 20.58) respectively, and there are only 5-10% chance of large lack of fit F value which could be due to noise and non significant lack of fit F value is good fit of model. In all cases "Pred R-squared" values are in reasonable agreement with the "Adj R-squared" values. The Adeq-Precision is the measures of the signal to noise ratio. A ratio> 4 is desirable. In the case of Metoprolol succinate matrix layer and Amlodipine besylate immediate layer, the Adeq-Precision value is in range of 9-12 which indicates an adequate signal.

CONCLUSION

The Seventh Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) offers combination drugs an advantage to clinicians designing complex drug regimen needed to improve outcomes in older persons with chronic conditions. Combination drugs offer the additional benefits of fewer pills for older adults who may have swallowing difficulties. The increased use of fixed dose combination therapy may make it easier for patients to remember to take pills and get them to goal quicker and with less trouble. This should improve the rates of blood pressure control and ultimately accelerate the reduction in cardiovas-

Table 13. Comparative Dissolution Profile of Bilayer Tablets of Amlodipine besylate in 0.1N HCl for Formulation Batches

Time(Hr)	Cumulative % Drug Release								
	MA1	MA2	MA 3	MA 4	MA 5	MA 6	MA 7	MA 8	MA 9
0.5	68.01 ±0.218	66.40 ±0.102	64.47 ±0.433	68.14 ±0.499	66.72 ±0.343	64.67 ±0.302	66.75 ±0.413	68.81 ±0.904	61.94 ±0.384
1	75.02 ±0.978	73.12 ±0.450	68.50 ±0.345	69.94 ±0.260	67.52 ±0.375	72.80 ±0.377	68.76 ±0.312	70.69 ±2.584	72.89 ±0.130
1.5	80.92 ±1.234	73.59 ±1.145	68.87 ±0.555	71.32 ±0.614	68.65 ±0.996	75.46 ±0.343	73.52 ±0.303	71.03 ±0.237	83.64 ±0.241
2	85.61 ±0.957	74.32 ±0.434	69.27 ±1.791	75.73 ±0.044	69.93 ±0.531	79.90 ±0.801	76.74 ±0.370	71.79 ±0.823	88.09 ±0.044

All values are mean ± SD, n=3

Table 14 Comparative Dissolution Profile of Bilayer Tablets of Metoprolol succinate in Phosphate buffer pH 6.8 for Formulation Batches

Time (Hr)	Cumulative % Drug Release								
	MA1	MA2	MA 3	MA 4	MA 5	MA 6	MA 7	MA 8	MA 9
3	10.68 ±1.031	6.89 ±0.075	22.05 ±0.114	18.06 ±0.384	10.08 ±0.433	4.12 ±0.481	27.71 ±0.565	6.01 ±0.377	9.57 ±0.342
4	46.03 ±0.157	45.66 ±0.042	42.11 ±0.114	34.55 ±0.130	28.49 ±1.313	39.82 ±0.413	64.87 ±0.173	32.77 ±0.344	31.71 ±0.156
6	62.24 ±0.821	57.63 ±0.327	61.09 ±0.043	54.28 ±0.241	43.48 ±0.498	48.33 ±0.312	67.67 ±0.302	60.55 ±0.377	56.61 ±0.342
8	73.03 ±0.300	59.31 ±0.043	74.98 ±0.270	64.12 ±0.044	54.81 ±0.907	62.44 ±0.303	83.99 ±0.377	73.49 ±0.344	73.71 ±0.156
10	95.33 ±0.002	79.22 ±0.283	100.28 ±0.197	89.99 ±0.338	79.95 ±0.904	76.74 ±0.370	89.28 ±0.343	93.79 ±0.172	94.14 ±0.338
12	110.57 ±0.414	109.81 ±0.129	110.48 ±0.413	110.15±0.043	112.58 ±2.584	107.47 ±0.432	109.51 ±0.801	105.95 ±0.225	106.82±0.043

***All values are mean ± SD, n=3**

Table 15: Model Fitting Data of Metoprolol succinate matrix tablet

Model / For. code	r					n	k
	Zero order	First order	Matrix	Korsmeyer Peppas	Hixson crowell		
MA1	0.9780	#	0.9063	0.9021	0.8356	1.4612	3.5163
MA2	0.9603	#	0.8815	0.8660	0.7620	1.5736	2.4702
MA3	0.9941	#	0.9322	0.9805	0.8704	1.0991	7.8043
MA4	0.9859	#	0.8958	0.9845	0.8392	1.2151	5.2473
MA5	0.9684	#	0.8503	0.9716	0.7403	1.5428	2.4378
MA6	0.9602	#	0.8693	0.8687	0.7580	1.8888	1.1995
MA7	0.9719	#	0.9504	0.9173	0.8357	1.0519	14.0148
MA8	0.9751	#	0.8837	0.9137	0.8365	1.3149	1.5628
MA9	0.9973	#	0.9270	0.9961	0.8370	1.3111	7.5554

Table 16: Model Fitting Data of Amlodipine besylate immediate release tablet

Model / Formulation Code	r					n	k
	Zero order	First order	Matrix	Korsmeyer Peppas	Hixson crowell		
MA1	0.6457	0.8810	0.9370	0.9964	0.8059	0.1651	77.8327
MA2	0.4958	0.6132	0.8908	0.9249	0.5715	0.0806	73.0652
MA3	0.4432	0.5197	0.8746	0.9246	0.4920	0.0506	69.1559
MA4	0.5099	0.6501	0.8928	0.9598	0.5995	0.0756	73.0671
MA5	0.4133	0.4766	0.8645	0.9695	0.4532	0.007	69.7598
MA6	0.6183	0.8081	0.9291	0.9977	0.7443	0.1516	74.0780
MA7	0.5564	0.7021	0.9070	0.9496	0.6625	0.1002	72.4666
MA8	0.4110	0.4774	0.8646	0.9837	0.4527	0.0325	75.2074
MA9	0.4492	0.5195	0.8769	0.8141	0.4945	0.0583	67.3430

Table 17 Design Summary for Metoprolol succinate matrix tablet

Factor	Name	Units	Type	Low Actual	High Actual	Low Coded	High Coded
A	HPMC K4M	%	Numerical	50	60	-1	+1
B	Starch 1500	%	Numerical	5	15	-1	+1

Table 18 Design Summary for Amlodipine besylate immediate release tablet

Factor	Name	Units	Type	Low Actual	High Actual	Low Coded	High Coded
A	SSG	%	Numerical	4	8	-1	+1
B	MCC	%	Numerical	40	50	-1	+1

Table 19 Response Summary for Metoprolol succinate matrix tablet

Response	Name	Units	Observations	Analysis	Minimum	Maximum	Mean
Y1	Q_{12}	%	9	Polynomial	74	102	86.67
Y2	t_{50}	Hours	9	Polynomial	7.18	7.82	7.53

Table 20 Response Summary for Amlodipine besylate immediate release tablet

Response	Name	Units	Observations	Analysis	Minimum	Maximum	Mean
Y1	Q_2	%	9	Polynomial	81.1	98.7	86.81
Y2	t_{50}	Hours	9	Polynomial	1.01	1.23	1.15

Table 21 Analysis of Variance for Q12 for metoprolol succinate matrix tablet

Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	P Value	Model Significant/Non significant
Model	494.4589	5	98.8917	13.8224	0.0277	Significant
X_1	166.9538	1	166.9538	23.3357	0.0169	Significant
X_2	63.3100	1	63.3100	8.8490	0.0588	Significant
X_1X_2	1.3806	1	1.3806	0.1929	0.6902	Nonsignificant
$(X_1)^2$	1.2960	1	1.2960	0.1811	0.6991	Nonsignificant
$(X_2)^2$	261.5185	1	261.5185	36.5533	0.0091	Significant
Residual	21.4633	3	7.1544		-	-
Core Total	515.9222	8	-	-	-	-
R - Squared	0.9583		Pred- R-Squared	0.6635		
Adj – R-Squared	0.8890		Adeq Precision	11.8230		

Table 22 Analysis of Variance for t50 for metoprolol succinate matrix tablet

Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	P Value	ModelSignificant/ Non significant
Model	0.3037	5	0.0607	9.6495	0.0456	Significant
X_1	0.0840	1	0.0840	13.3457	0.0354	Significant
X_2	0.0661	1	0.0661	10.5077	0.04878	Significant
X_1X_2	0.00022	1	0.00022	0.0357	0.8621	Nonsignificant
$(X_1)^2$	0.0460	1	0.0460	7.3078	0.0736	Nonsignificant
$(X_2)^2$	0.1073	1	0.1073	17.0504	0.0258	Significant
Residual	0.0188	3	0.0062		-	-
Core Total	0.3226	8	-	-	-	-
R - Squared	0.9414		Pred- R-Squared	0.4101		
Adj – R-Squared	0.8438		Adeq Precision	9.2487		

Table 23 Analysis of Variance for Q2 for Amlodipine besylate immediate release tablet

Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	P Value	Model Significant /Non significant
Model	387.2939	5	77.4587	18.2415	0.0187	Significant
X_1	3.0816	1	3.0816	0.7257	0.4569	Nonsignificant
X_2	0.3313	1	0.3313	0.0780	0.7981	Nonsignificant
X_1X_2	0.5625	1	0.5625	0.1324	0.7400	Nonsignificant
$(X_1)^2$	0.6883	1	0.6883	0.1621	0.7142	Nonsignificant
$(X_2)^2$	382.63	1	382.63	90.1091	0.0025	Significant
Residual	12.7388	3	4.2462	-	-	-
Core Total	400.0328	8	-	-	-	-
R - Squared	0.9681		Pred- R-Squared	0.6258		
Adj – R-Squared	0.9150		Adeq Precision	9.4352		

Table 24 Analysis of Variance for t50 for Amlodipine besylate immediate release tablet

Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	P Value	Model Significant /Non significant
Model	222.6703	5	44.5340	20.5828	0.0158	Significant
X_1	1.1266	1	1.1266	0.5207	0.5227	Nonsignificant
X_2	0.24	1	0.24	0.1109	0.7610	Nonsignificant
X_1X_2	0.4489	1	0.4489	0.2074	0.6797	Nonsignificant
$(X_1)^2$	0.6346	1	0.6346	0.2933	0.6257	Nonsignificant
$(X_2)^2$	220.2201	1	220.2201	101.7818	0.0021	Significant
Residual	6.4909	3	-	-	-	-
Core Total	229.1613	8	-	-	-	-
R - Squared	0.9699		Pred- R-Squared	0.6392		
Adj – R-Squared	0.9199		Adeq Precision	9.8097		

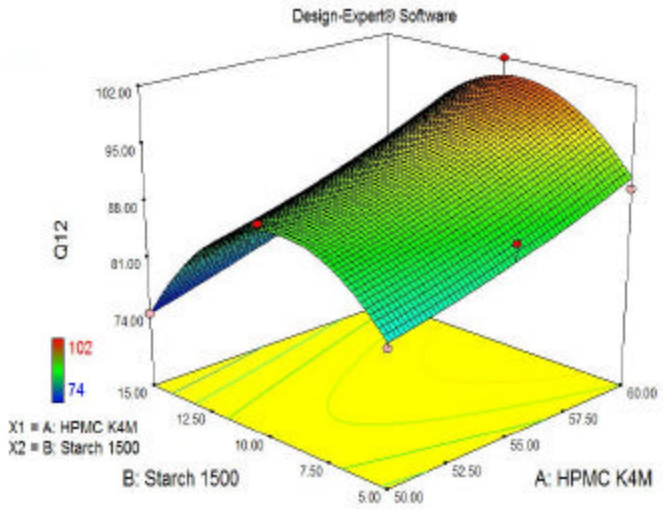

Figure 13 Response surface plot of Q_{12} (Metoprolol succinate)

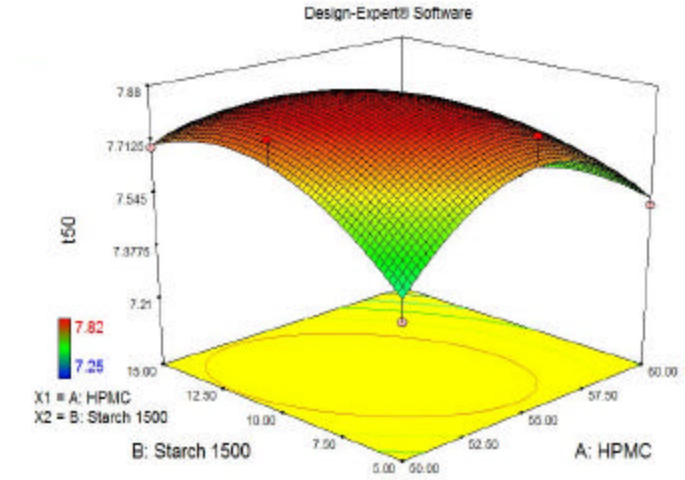

Figure 14 Response surface plot of t50 (Metoprolol succinate)

cular disease to hypertension.

The present work an attempt to develop bilayer tablet for antihypertensive patients using Metoprolol succinate and Amlodipine besylate as a model drug candidate by application of factorial design method.

The study reveals that the Metoprolol succinate and Amlodipine besylate are a good candidate for lowering the blood pressure when given in combination with minimum amount of dose. The HPMC K4M has the ability to maintained the matrix integrity and sustained the release up to the 12 hours when the there are positive interaction of Starch 1500 which helps the drug release for sustained action. Also the sodium starch glycolate has the superdisintegrant properties but when in combination with Microcrystalline cellulose the release of drug up to 2 hours.

The significant effects of the interaction and polynomial variables on the investigated characteristics for both Metoprolol succinate matrix sustained release and Amlodipine besylate immediate release were verified using 3^2 factorial design. The ANNOVA shows the predetermined effect of both the dependant and independent variable in both the cases.

Thus, an attempt was made to design an effective, rugged formulation technology was feasible with the advantages of sustained release and immediate release action with a minimum amount of dose for antihypertensive patients.

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