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Formulation and Evaluation of Metoprolol Succinate Er and Atorvastatin Calcium Ir Using Natural Gum

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ABSTRACT

The aim of present investigation was to develop and evaluate Atorvastatin calcium IR and Metoprolol succinate ER in same dosage form so, there is no need to take individual dosage form. Atorvastatin calcium immediate release for controlling the lipid profile after meal and Metoprolol succinate release after 6 hrs lag time at bedtime for prevention of early morning hypertension. Xanthan gum and HPMC K4M sustained the release of Metoprolol succinate from the extended release layer. Metoprolol succinate ER layer was coated by Eudragit S 100 polymer for providing sufficient the lag time and atorvastatin calcium IR layer again coated on ER layer by direct compression coated method. Preformulation studies were carried out for atorvastatin calcium and metoprolol succinate drugs. In vitro release profile and in process parameters were determined for all preliminary trial batches and 32 full factorial batches. Eudragit S 100 5% was optimized for retain 5-6 hrs lag time. From the preliminary trial batches of sustained tablets and dissolution profile it was found that amount of Xanthan Gum increases from 38 mg to 62 mg, the drug release decreases. HPMC K4M was found to be not sufficient to provide sustain release. Thus, HPMC K4M was removed for optimization of drug release profile. The results of 32 full factorial designs revealed that concentration of xanthan gum and type of filler significantly affect the responses, Q6, Q24 and T80%. Based on result of multiple linear regression analysis, it was concluded that satisfactory release lag time and good drug release profile of tablet could be obtained when X1 kept high level and X2 kept at high level. Finally it is concluded that by adopting a systematic formulation approach, delivery of two drugs from, a single dosage form can be obtained which could improve patient compliance and give better disease management.

Keywords: Extended release, immediate release, Xanthan gum, Chronomodulated drug delivery system.

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INTRODUCTION

Cardiovascular functions such as heart rate (HR) and blood pressure (BP) show 24 h variation. The incidence of cardiovascular diseases such as acute myocardial infarction, strokes and arrhythmia also exhibits clear diurnal oscillation. Since most of these disorders can induce fatal or severe outcomes, it is important to elucidate the precise mechanism of the onset of these diseases. This circadian occurrence is believed to be tightly associated with an internal clock.

MATERIALS AND METHODS

MATERIALS

Metoprolol Succinate, Atorvastatin Calcium, Xanthan Gum, Eudragit S 100, Micro crystalline cellulose, Dicalcium Phosphate Calcium, Lactose, Talc, Magnesium stearate, Sodium Starch Glycolate, Starch. All the ingredients are laboratory grade and procured from yarrow chemical Products, Mumbai.

METHODOLOGY

Preliminary Trails Batches of Sustained Release Layer of Metoprolol Succinate

The sustained release layer composed of Metoprolol succinate, Various Hydrophilic Polymers such as HPMC K_4M, Xanthan Gum and Diluents such as microcrystalline cellulose, dicalcium phosphate, spray dried lactose. Each 150mg tablet contains Mg. Stearate (2%), Talc (1%) q.s. All components were uniformly mixed and the sustained release layer was prepared by direct compression.

Study of the effect of HPMC K_4M and xanthan gum on drug release

Sustained release layer containing metoprolol succinate was prepared by direct compression technique using varying concentrations of HPMC $_{K4M}$ with Xanthan Gum. The HPMC $_{K4M}$ and Xanthan Gum were taken in a ratio ranging 10:62, 15:50 and 20:38 (referred by review of literature). This was done to select the optimum ratio in the sustained drug delivery. The other excipients used were microcrystalline cellulose, talc and Magnesium stearate. The hydrocolloids along with the excipients were blended homogenously with the drug. The blended mixture was compressed to prepared sustained tablet using direct compression method. The prepared tablets were coated with 5% Eudragit S 100. The composition of batches B1 to B3 shown in Table 1.

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Table 1: Compositions of Preliminary Trial Batches (B1 to B3) of Metoprolol succinate.

INGREDIENTS	BATCH CODE		
	B1	B2	B3
Metoprolol Succinate	56.33	56.33	56.33
HPMC $_{K4M}$	15	10	20
Xanthan Gum	50	62	38
Talc	1%	1%	1%
Mg. Stearate	2%	2%	2%
Microcrystalline cellulose	q.s. to 160	q.s. to 160	q.s. to 160

* Each quantity given in mg

Study of the effect of xanthan gum on drug release

Sustained release layer containing metoprolol succinate was prepared by direct compression technique using varying concentrations of Xanthan Gum. The Xanthan Gum and diluents like microcrystalline cellulose were taken in a ratio ranging 60:40, 70:30 and 80:20. This was done to select the optimum ratio in the sustained drug delivery. The other excipients used were talc and Magnesium stearate. The hydrocolloids along with the excipients were blended homogenously with the drug. The blended mixture was compressed to prepared sustained tablet using direct compression method. The prepared tablets were coated with 5% Eudragit S 100. The composition of batches B4 to B6 shown in Table 2.

Table 2: Compositions of preliminary trial batches (B3 to B6) of metoprolol succinate.

INGREDIENTS	BATCHES CODE		
	B4	B5	B6
Metoprolol Succinate	50	50	50
Xanthan Gum	60	70	80
Microcrystalline cellulose	40	30	20
Mg. Stearate	2%	2%	2%
Talc	1%	1%	1%

Optimization of Sustain Release Layer of MP Using 3^2 Full Factorial Design [1-3]

It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man-hrs and raw materials. Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to evolve an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design.

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In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions. The number of experiments required for these studies is dependent on the number of independent variables selected. The responses (Yi) is/are measured for each trial and then either

A statistical model incorporating interactive and polynomial term was used to evaluate the response:

$$Y = B0 + B_1X_1 + B_2X_2 + B_{12}X_1X_2 + B_{11}X_1^2 + B_{22}X_2^2 \qquad (1)$$

Where, Y is the dependent variables, B0 is the arithmetic mean response of the nine runs, and B1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity.

In the present study, a 3^2 full factorial design was employed containing 2 factors evaluated at 3 levels and experimental trials were performed at all 9 possible combinations. The formulation variables and their ranges were chosen from the knowledge acquired from the preliminary studies and from the experiments previously reported. The two independent variables selected were ratio of Xanthan gum: Filler (X_1) and Type of filler (X_2) as per Table 3 and the nine formulations were formulated as per the experimental design (Table 4) for the study of effect of polymer ratio and different filler on release rate of drug. All the nine formulations were prepared using factorial design and described in Table 5.

Table 3: Variables in 3^2 full factorial design batches

Coded values	Actual Value (%)	
	X_1	X_2
	Amount of Xanthan Gum (mg)	Type of Filler
-1	75	MCC
0	80	S.D. Lactose
1	85	DCP

MCC = Microcrystalline Cellulose, S.D. Lactose = Spray Dried Lactose, DCP = DiCalcium phosphate

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Table 4: Experimental design by using 3^2 full factorial design

Formulation Code	Coded values		Actual Value	
	X_1	X_2	X_1 Amount of Xanthan Gum (mg)	X_2 Type of Filler
F1	-1	-1	75	MCC
F2	0	-1	80	MCC
F3	+1	-1	85	MCC
F4	-1	0	75	S.D. Lactose
F5	0	0	80	S.D. Lactose
F6	+1	0	85	S.D. Lactose
F7	-1	+1	75	DCP
F8	0	+1	80	DCP
F9	+1	+1	85	DCP

Table 5: Formulations of 3^2 full factorial design batches

Ingredients	Formulation Code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Metoprolol Succinate	50	50	50	50	50	50	50	50	50
Xanthan Gum	75	80	85	75	80	85	75	80	85
Microcrystalline cellulose	24	19	14	-	-	-	-	-	-
Spray Dried Lactose	-	-	-	24	19	14	-	-	-
Di-Calcium Phosphate	-	-	-	-	-	-	24	19	14
Talc	1%	1%	1%	1%	1%	1%	1%	1%	1%
Mg. stearate	1%	1%	1%	1%	1%	1%	1%	1%	1%
Total Weight	150	150	150	150	150	150	150	150	150

* Each quantity given in mg

Optimization of Eudragit S 100 Coating on Sustain Release Tablet of Metoprolol Succinate

Eudragit S100 was used to coat metoprolol sustain release tablet. For Optimization of Eudragit S100 concentration purpose, basic mixture of drug, hydrophilic polymer like HPMC $_{K4M}$, Xanthan Gum & filler like microcrystalline cellulose was compressed to prepared tablet & different concentration on Eudragit S100 in acetone was taken as coating solution.

Formulation of Compression Coated Tablet

For the preparation of the compression coated tablet formulation, the die of the tablet machine was filled manually with the weighed amounts of the sustain release component (MP). The sustain release component is compressed lightly and enteric coated with the Eudragit S 100 using pan coater. The prepared enteric coated tablet was again with the fast release powder

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(ATC) by compression coated method. The dual component compressed tablet systems were prepared by direct compression, Rimek Mini Press II MT (Karnavati Engineering Private Ltd., Kadi). The formulation of dual component system is shown in Table 7.

Table 6: Formula of basic mixture for optimization of Eudragit S100

Ingredients	Quantity (mg)
Metoprolol Succinate	50
HPMC $_{K4M}$	10
Xanthan Gum	50
Talc	1 %
Mg. Stearate	2 %
Microcrystalline cellulose	q.s. to 150

Table 7: Composition of compression coated tablet

COMPOSITION	QUANTITY (mg)
IMMEDIATE RELEASE LAYER	
Atorvastatin Calcium	20
SSG (5%)	17.5
Starch (3%)	10.5
Mg. Stearate (1%)	3.5
Talc (1%)	3.5
MCC: Spray Dry Lactose(1:1) (q.s. to 350 mg)	295
EXTENDED RELEASE LAYER	
Metoprolol Succinate	50
Xanthan Gum	85
Talc (1%)	0.5
Mg. Stearate (1%)	0.5
Di-Calcium Phosphate (q.s. to 150 mg)	14
Total Weight	**500**

RESULTS AND DISCUSSION

Preformulation Study of Drugs

Evaluation parameters of preformulation study are shown in Table 8.

Table 8: Result of preformulation study of metoprolol succinate

Drug	Angle of Repose (^{0})	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Carr's Index (%)	Hausner's Ratio
Metoprolol Succinate	27.85^o	1.28 g/ml	1.46 g/ml	12.32 %	1.14
Atorvastatin Calcium	31.35^o	1.33 g/ml	1.54 g/ml	13.63%	1.15

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Optimization of Eudragit S 100 Coating on Sustained Release Layer

Evaluation parameters of optimization of Eudragit S 100 coating is shown in Table 9.

Table 9: Effect of Eudragit S 100 concentration on lag time of drug release

% Eudragit S 100 concentration in acetone*	Lag time for drug release (hr& min)
2	4.0 hr ±10 min
3	4.5 hr ±10 min
4	5.0 hr ±10 min
5	**5.5 hr ±20 min**
6	6.5 hr ±20 min
7	8.0 hr ±10 min

* means number of coat are fixed (3).

Preliminary Trial Batches of Sustain Release Tablet of Metoprolol Succinate

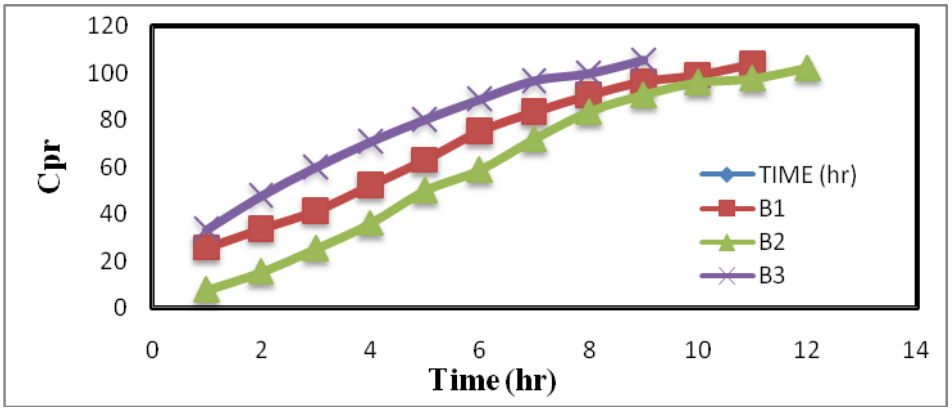
To Study the Effect of Hpmc K4m and Xanthan Gum on Sustained Release Layer (B1 to B3)

From the preliminary trial batches (B1 to B3) of sustained tablets and dissolution profile it was found that amount of Xanthan Gum increases from 38 mg to 62 mg, the drug release decreases which is shown in Table 10 and Figure 1. HPMC K_4M was found to be not sufficient to provide sustain release. Thus, HPMC K_4M was removed for optimization of drug release profile.

Table 10: Result of evaluation of tablets of trial batches (B1 to B3)

Trial batches	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Avg. Wt. (mg)	Assay (%)
B1	3.5 ± 0.3	0.9 ± 0.2	0.6 ± 0.07	158 ± 2.3	97.85 %
B2	3.9 ± 0.6	1.1 ± 0.1	0.4 ± 0.08	162 ± 4.1	102.63%
B3	3.8 ± 0.4	1.0 ± 0.1	0.4.5 ± 0.06	161 ± 1.2	98.21%

Figure 1: CPR Profile of tablets of trial batches (B1 to B3)



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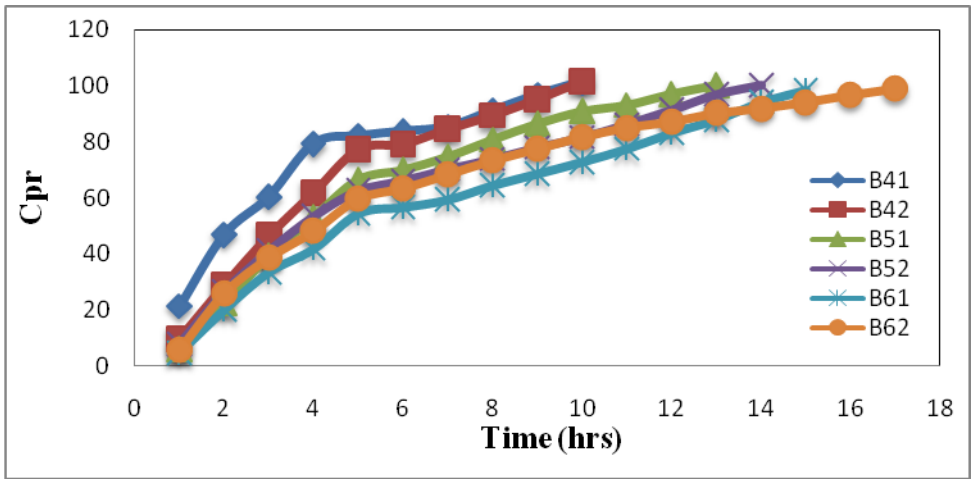
To Study the Effect of Xanthan Gum on Sustained Release Layer

From the preliminary trial batches (B4 to B6) of sustained tablets and subsequent dissolution it was found that amount of Xanthan Gum increases from 60 to 80 mg, drug release decreases which is shown in Table 11 and Figure 2. Batch B6 (80 mg Xanthan Gum) was optimized for once a day therapy of metoprolol succinate. Full factorial design will be required for fine tuning of optimizing concentration of Xanthan gum.

Table 11: Result of evaluation of tablets of trial batches (B4 to B6)

Trial batches	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Avg. Wt. (mg)	Assay (%)
B4	3.6 ± 0.3	0.8 ± 0.2	0.7 ± 0.07	157 ± 2.3	99.85 %
B5	4.2 ± 0.6	1.1 ± 0.1	0.5 ± 0.08	160 ± 4.1	102.63%
B6	3.9 ± 0.4	0.9 ± 0.1	0.6 ± 0.06	159 ± 1.2	98.21%

Figure 2: CPR Profile of tablets of trial batches (B4 to B6)



Result of Sustain Release Layer of Metoprolol Succinate Using 3^2 Full Factorial Design [1-3]
Physicochemical Characterization

The results of weight variation, hardness, thickness, drug content and diameter of factorial batches are presented in Table 12.

In Vitro Dissolution Study

Based on the data obtained from release profile of Metoprolol from preliminary trial batches, the factorial design was applied to screen the optimum batch. All the factorial batches showed drug release up to 15-24 hrs depending on concentration of Xanthan gum and type of filler (Figure 3). The results shown that there is little effect of type of filler as compared to concentration of Xanthan gum on the release of MP. At the initial stage, retain the tablet shape due to Eudragit s 100 enteric coating. After 5 to 6 hrs, show that rapid release profile due to

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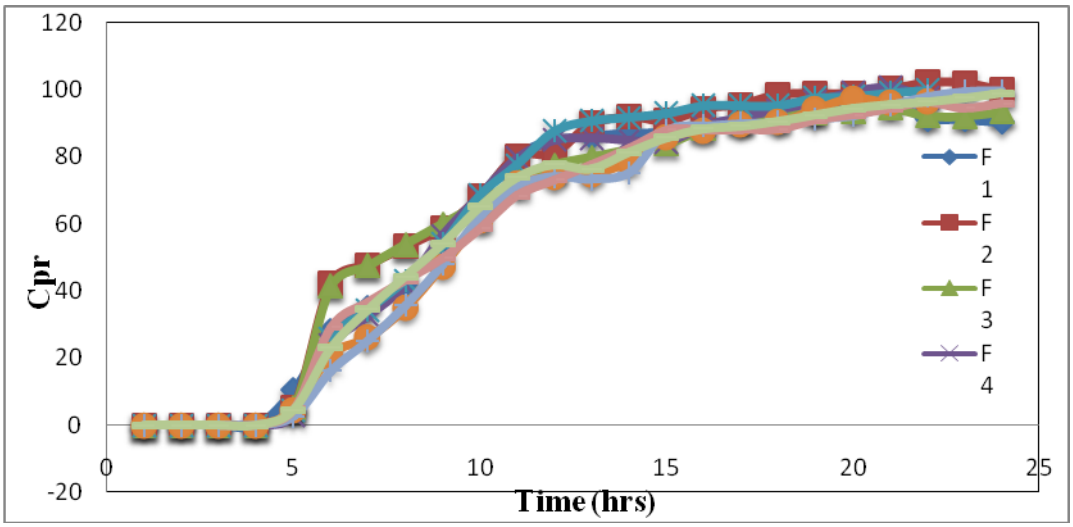
burst the enteric coating in PH 7.4 buffer and water via metastable pores in the tablet containing xanthan gum. So, more sustain release effect was observed. Formulations F1-F6 shows rapid release profile and complete drug release within 18-20 hrs. Here, drug release was observed faster than the required release for once a day formulation. Formulations F7-F9 shows drug release in a controlled manner for more than 24 hrs. The percentage drug release after 24 hrs was 99.64%, 95.89% and 98.98 for Formulations F7, F8 and F9 respectively which shows good release profile compare to other formulations and exactly fit in the criteria for drug release. (More than 95% drug release within 21 hrs. for once a day formulation). Among all the factorial batches, the Formulation F9 containing 85 mg of Xanthan gum and Di-Calcium Phosphate filler was considered as the optimum formulation according to in vitro dissolution study.

Table 12: Evaluation parameters of physicochemical characterization

Batch Code	Weight mg (n=20)	Hardness kg/cm^2	Thickness mm (n=3)	Drug Content % (n=10)
F1	147.33±3.51	2.5±0.40	1.59±0.034	97.5±0.65
F2	148.1±2.62	3.1±0.45	1.62±0.033	98.4±0.58
F3	146.5±3.81	3.8±0.40	1.58±0.034	97.6±0.38
F4	149.1±1.08	2.7±0.50	1.57±0.034	99.5±0.29
F5	147.67±2.78	2.3±0.45	1.63±0.034	98.8±0.61
F6	146.9±3.42	2.9±0.45	1.59±0.033	99.6±0.54
F7	148.4±2.21	3.5±0.50	1.56±0.034	97.9±0.55
F8	147.43±3.45	3.4±0.40	1.61±0.034	98.4±0.37
F9	148.9±1.15	2.7±0.45	1.64±0.034	99.3±0.46

Figure 3: CPR Profile of tablets of F1 to F9 batches



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Statistical Analysis of Factorial Design Batches

The Q6, Q24 and T80% of the nine batches showed wide variation. The results depicted in Table 13 clearly indicate that all the dependent variables are strongly dependent on the selected independent variables.

Table 13: Characterization of factorial design batches

Batch Code	Q6 (%)	Q24 (%)	T80% (hrs)
F1	27.35	90.33	11
F2	42.27	99.99	12
F3	41.32	93.48	13
F4	23.75	96.36	11
F5	25.67	100.37	12
F6	20.86	94.86	14
F7	16.15	90.73	14
F8	29.1	91.77	14
F9	21.37	88.48	15

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis carried out in Microsoft Excel 2007. The results are shown in Table 5.8. The data clearly indicate that the values of Q6, Q24 and T80% are strongly dependent on the independent variables. The fitted equations (full and reduced) relating the responses Q6, Q24 and T80% to the transformed factors are shown in Table 14.

Table 14: Summary of regression analysis

Response	B0	B1	B2	B12	B11	B22
Coefficients for Q6						
FM	28.23	2.71	-7.38	-2.18	-7.21	6.16
RM	28.23	-	*-7.38*	-	-	-
Coefficients for Q24						
FM	100.53	-0.1	-2.13	-1.35	-5	-4.73
RM	100.53	-	-	-	*-5*	*-4.73*
Coefficients for T80%						
FM	12.11	1	1.16	-0.25	0.33	0.83
RM	12.11	1	*1.16*	-	-	-

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and mathematical sign it carries (i.e. positive or negative) Table 15 shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors.

The high value of correlation coefficient for Q6, Q24 and T80% good fit i.e., good agreement between dependent and independent variables. The equations may be used to obtain estimates of the responses as small error of variance was noticed in the replicates. The

significant test for regression coefficients was performed by applying student F test. A coefficient is significant if the calculated F value is greater than the critical value of F.

Table 15: Calculation for testing the model in portion (ANOVA)

FOR Q6							
Regression	**DF**	**SS**	**MS**	**F**	**R^2**		
FM	5	570.9193	114.1839	4.986479	0.892598	**F CAL**	2.659895
RM	1	327.3771	327.3771	7.339393	0.511834	**F TAB**	9.117182
Error							DF(4,3)
FM	3	68.69	22.8987	-	-		
RM	7	312.2383	44.60547	-	-		
FOR Q24							
Regression	**DF**	**SS**	**MS**	**F**	**R^2**		
FM	5	129.62	25.924	5.9783	0.9087	**F CAL**	3.028099
RM	4	235.83	58.95	4.5054	0.8184	**FTAB**	10.12796
Error							DF(1,3)
FM	3	13.009	4.33	-	-		
RM	4	52.344	13.086	-	-		
FOR T80%							
Regression	**DF**	**SS**	**MS**	**F**	**R^2**		
FM	5	16.028	3.2058	11.168	0.949	**F CAL**	2.161324
RM	2	14.16	7.0833	15.612	0.8388	**FTAB**	9.276628
Error							DF (3,3)
FM	3	0.8611	0.287	-	-		
RM	6	2.722	0.4537	-	-		

Full and Reduced Model for Q_6

The significant level of coefficient b1, b12, b11 and b22 found to be p= 0.258, p= 0.427, p= 0.122 and p= 0.165 respectively hence it was omitted from full model to generate reduced model. The results of statistical analysis are shown in Figure 4. The coefficients b2 was found to be significant at p (0.032) < 0.05; hence they were retained in reduced model. The results for testing the model in portion are shown in Figure 4. The critical value of F for $\alpha = 0.03$ is equal to 9.11 (DF = 4, 3). Since the calculated value (F = 2.65) is less than critical value (F = 9.11), it may be concluded that the polynomial term b1, b12, b11 and b22 do not contribute significantly to the prediction of Q6 and therefore can be omitted from the full model. The fitted equation for full and reduced model relating the response was given below.

Full model

$$Q_6 = 28.23 + 2.71X_1 - 7.38X_2 - 2.18X_1X_2 - 7.21X_1^2 + 6.16X_2^2$$

Reduced model

$$Q_6 = 28.23 - 7.38X_2$$

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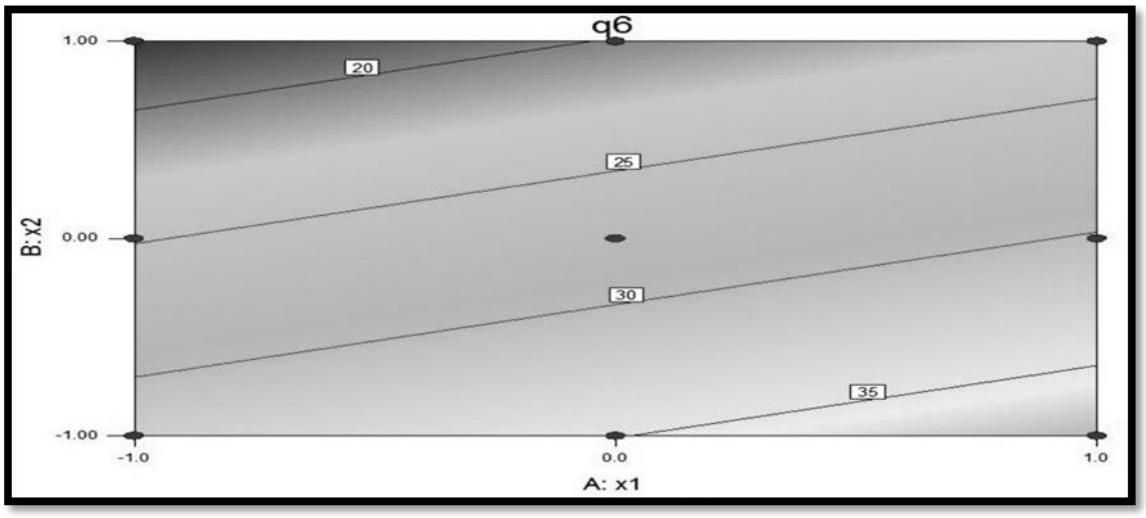
Figure 4: Contour plot showing effect of concentration of xanthan gum and type of filler on Q_6



Full and Reduced Model for Q_{24}

The significant level of coefficient b1, b2 and b12 found to be p= 0.913, p= 0.086 and p= 0.285 respectively hence it was omitted from full model to generate reduced model. The results of statistical analysis are shown in Figure 5. The coefficients b11 and b22 were found to be significant at $p < 0.05$; hence they were retained in reduced model. The results for testing the model in portion are shown in Figure 5. The critical value of F for $\alpha = 0.08$ is equal to 10.12 (DF = 1, 3). Since the calculated value (F = 3.02) is less than critical value (F = 10.12), it may be concluded that the polynomial term b1, b2 and b12 do not contribute significantly to the prediction of Q24 and therefore can be omitted from the full model. The fitted equation for full and reduced model relating the response was given below.

Full model

$$Q_{24} = 100.53 - 0.1X_1 - 2.13X_2 - 1.35X_1X_2 - 5.0X_1^2 - 4.73X_2^2$$

Reduced model

$$Q_{24} = 100.53 - 5.0X_1^2 - 4.73X_2^2$$

Full and Reduced Model for $T_{80\%}$

The significant level of coefficient b12, b11 and b22 found to be p= 0.419, p= 0.443 and p= 0.115 respectively hence it was omitted from full model to generate reduced model. The results of statistical analysis are shown in Figure 6. The coefficients b1 and b2 were found to be significant at $p < 0.05$; hence they were retained in reduced model. The results for testing the model in portion are shown in Figure 6. The critical value of F for $\alpha = 0.04$ is equal to 9.27 (DF = 3, 3). Since the calculated value (F = 2.16) is less than critical value (F = .27), it may be concluded that the polynomial term b12, b11 and b22 do not contribute significantly to the prediction of

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T80% and therefore can be omitted from the full model. The fitted equation for full and reduced model relating the response was given below.

Full model

$$T_{80\%} = 12.11 + 1.0X_1 + 1.16X_2 - 0.25X_1X_2 + 0.33X_1^2 + 0.83X_2^2$$

Reduced model

$$T_{80\%} = 12.11 + 1.0X_1 + 1.16X_2$$

Figure 5: Contour plot showing effect of concentration of xanthan gum and type of filler on Q_{24}

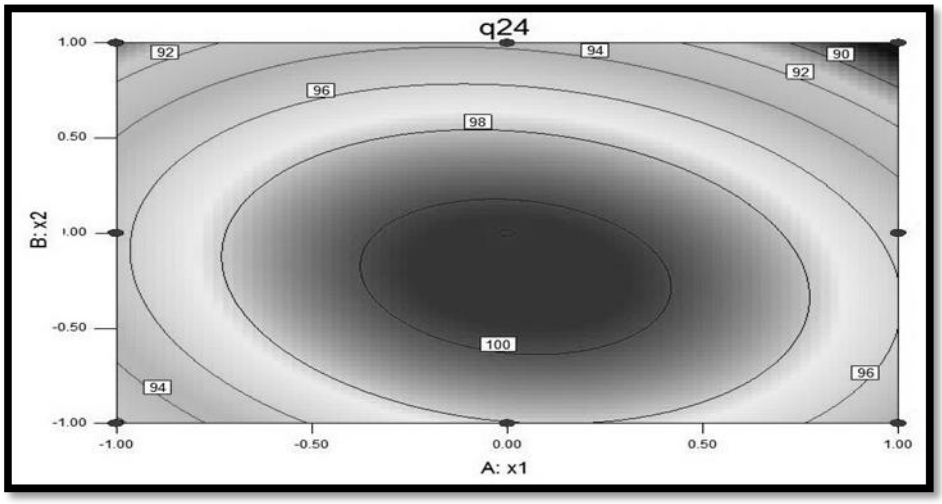
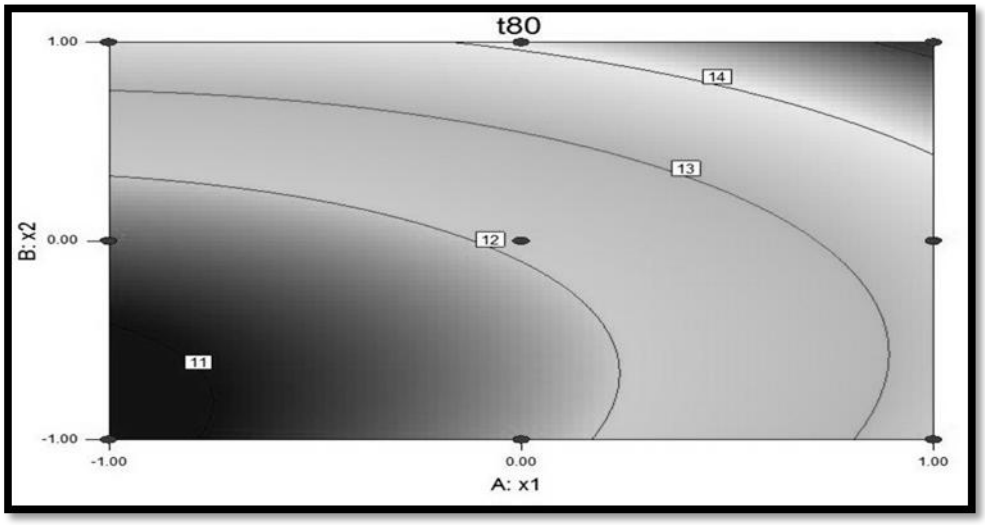


Figure 6: Contour plot showing effect of concentration of xanthan gum and type of filler on $T_{80\%}$



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Validation of Evolved Model

To validate evolved model batch FCP (check point batch) was prepared from X_1= 0.5 (82.5mg of Xanthan gum) & X_2= +1 (Di-Calcium Phosphate) along with all other excipients in same amount as used in factorial design. Dependent parameters were determined and compared with predicted values as shown in Table. The results obtained with check point batch are very close to predicted values (Table 16). Thus, we can conclude that the statistical model is mathematically valid.

Table 16: Comparison of observed and predicted value

Parameter	Observed value	Predicted value	% Relative Error
Q_6	25.45%	26.08%	2.41
Q_{24}	96.28%	97.43%	1.18
$T_{80\%}$	14.00h	13.55h	3.2
K	0.02232	0.02253	0.93
N	1.2922	1.2893	0.22

Kinetic analysis of dissolution data

The in vitro release data obtained were fitted in to various kinetic equations (i.e. zero, first, higuchi, Hixon and korsmeyer peppas kinetic model). Table 17 indicates correlation coefficients of individual batches which clearly indicate that release profile of metoprolol followed Higuchi and Zero Order kinetics in different formulations.

Table 17: Results of model fitting

Batch Code	Higuchi	Zero Order	Korsmeyer	Hixon	First Order
F1	0.8944	0.8471	0.8692	-0.7968	0.7577
F2	0.9201	0.8797	0.7833	-0.7636	0.6765
F3	0.9126	0.8710	0.7656	-0.7457	0.6580
F4	0.9169	0.8744	0.8077	-0.7783	0.6938
F5	0.9145	0.8709	0.8279	-0.7878	0.7149
F6	0.9484	0.9134	0.8748	-0.8371	0.7704
F7	0.9424	0.9061	0.8472	-0.8183	0.7371
F8	0.9418	0.9047	0.8343	-0.8100	0.7290
F9	0.9099	0.9309	0.9574	-0.9606	0.9692

Batches F2, F3, F4, F5, F6, F7, F8 and F9 showed sufficient correlation with Higuchi kinetic and Batches F6, F7, F8 and F9 showed sufficient correlation with zero order kinetics. The correlation coefficient of the optimized formulation F9 is follows the all kinetic models and shows the higher correlation (0.9692) with First order kinetic. In the entire batches exponent 'n' was in between 1.05 and 1.59, so predominant drug release mechanism is Zero order (dissolution control release).

Selection of Best Batch

It was arbitrarily decided to select a batch of tablets that gives good chrono release behavior. The final selection was done after considering some aspects such as Q_6, Q_{24} and $T_{80\%}$. On the basis of chrono release behavior and dissolution release studies F9 comprising Xanthan Gum (85 mg) and Di-Calcium Phosphate as a filler was considered a good candidate. The aim of study was, tablet should release more than 90% drug within 20-24 hrs and tablet should have satisfactory chrono release lag time and release profile in controlled manner as well. Batch F9 shows good release profile which exactly fit in our objective.

Results of Compression Coated Tablet

Physicochemical Characterization

The average weight (n=20), diameter (n=3), thickness (n=3) and hardness (n=3) of prepared compression coated tablets were found to be 497.81±2.92 mg, 11.34±0.06 mm, 3.25±0.025 mm and 4.1±0.35 kg/cm2 respectively.

The drug content of prepared compression coated tablets (n=3) was found to be 98.91 ± 1.07 (MP) and 99.9 ± 1.62 (ATC).

In vitro dissolution study

The compression coated tablet formulated as per the formula of optimized batches of ATC and MP was subjected for in vitro dissolution study. The dissolution (n=3) was carried out using a USP XXIII dissolution rate test apparatus (Apparatus 2, 50 rpm, 37±1°C) in 0.1 N HCl (900 ml) for 2 hr as the average gastric emptying time is about 2 hr. The tablet is taken outside carefully & then the dissolution medium is replaced with pH-6.8 phosphate buffer (900 ml) and tested for drug release for 3 hr as the average small intestinal transit time is about 3 hr. After 5 hr, the dissolution medium was replaced with pH 7.4 Phosphate buffer (900 ml) and tested for drug release up to 18 hr. At the end of the time period 5ml of the samples are taken and analyzed for content as described previously. A 5 ml volume of fresh and filtered dissolution medium is added to make the volume after each sample withdrawal. The samples were filtered through a 0.45 m membrane filter. Absorbance of these solutions was measured at 245 nm and 275 nm for ATC and MP respectively using a Shimadzu UV-1800 UV/Vis double beam spectrophotometer.

The release of ATC and MP from compression coated tablet was detected by applying simultaneous spectrophotometric estimation method developed and validated for estimation of ATC and MP in single dosage form. All dissolution tests were performed in triplicate. The release rate of ATC and MP from prepared compression coated tablet was described as a function of time as shown in Figure 7 & 8. More than 99% ATC released within 1 hr whereas MP releases in a sequential manner up to 24 hours.

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Figure 7: Release profile of ATC (Test and Market) from compression coated tablet

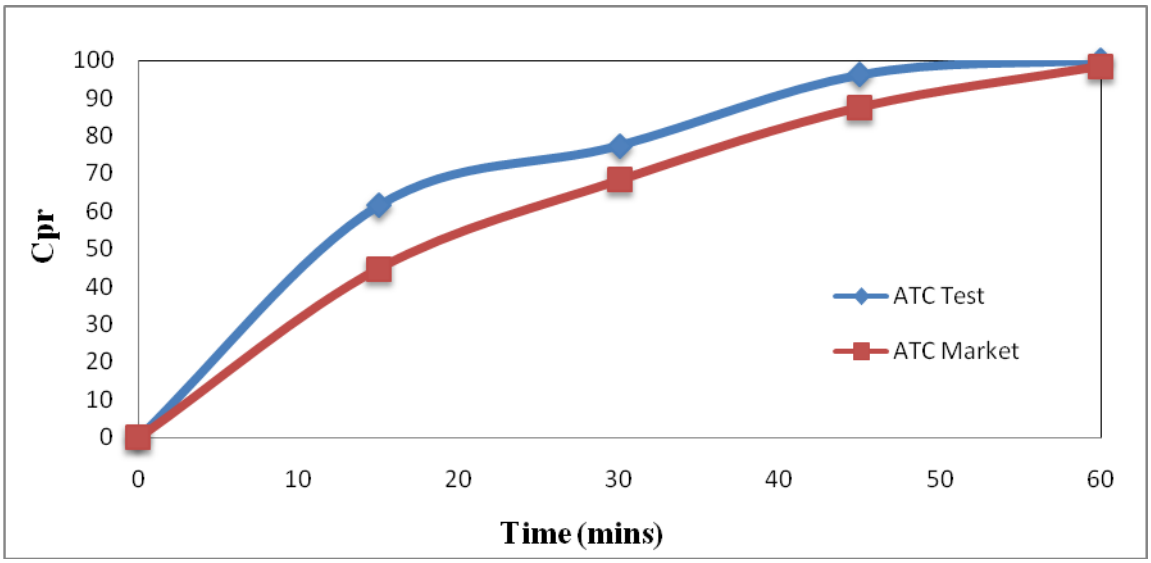
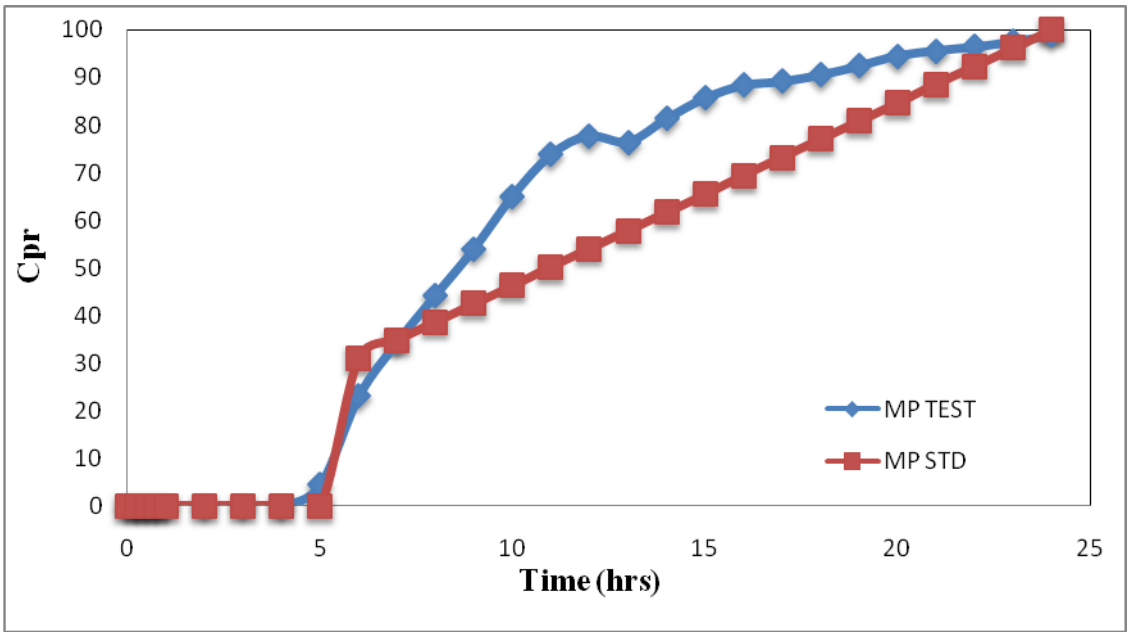


Figure 8: Release profile of MP (Test and Std) from compression coated tablet



Comparison of dissolution profile

The similarity factor, f_2, given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profiles [4]. The dissolution profiles are considered to be similar when f_2 is between 50 and 100.

The dissolution profiles of products were compared using a similarity factor (f_2). This similarity factor is a logarithmic reciprocal square root transformation of one plus the average mean squared (the average sum of squares) differences of drug percent dissolved between the test and reference products over all time points.

In vitro drug release profile of ATC of prepared compression coated tablets was compared with marketed product (ZIVAST) as well as MP compared with theoretical drug release profile. The f_2 value, for ATC is 75.18 and for MP is 68.79 which indicate that the prepared compression coated tablet have good similarity to marketed product and theoretical release profile for ATC and MP respectively.

Accelerated Stability Study

The compression coated tablet containing ATC as immediate release and MP as extended release, formulated as per formula of optimized batch were subjected to accelerated stability studies. Aluminum pack as aluminum strip is considered the best protecting packaging material but in the present study simulation was made using aluminum foil pouch. As the dosage form is formulated for chronomodulated drug delivery, no change should occur in its release lag time and drug dissolution profile.

The prepared compression coated tablet was packed in aluminium pouch and charged for accelerated stability studies at 40 °C and 75% RH for 3 months in a humidity chamber. Samples withdrawn after 3 month showed no significant change in appearance of tablets, release lag time and drug dissolution profile. The results of accelerated stability studies are shown in Figure 9 & 10. The result of accelerated stability studies indicates that the formulation was stable on the required storage condition.

Figure 9: Drug release profile of ATC before and after accelerated stability study of dual component tablet

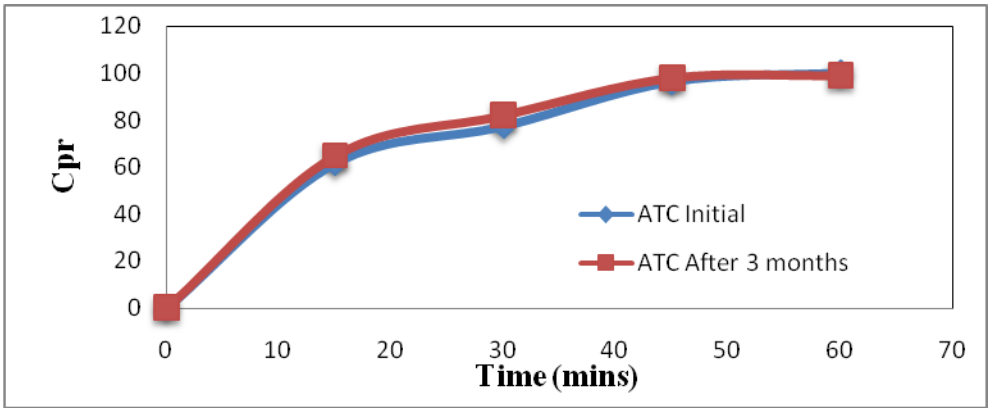


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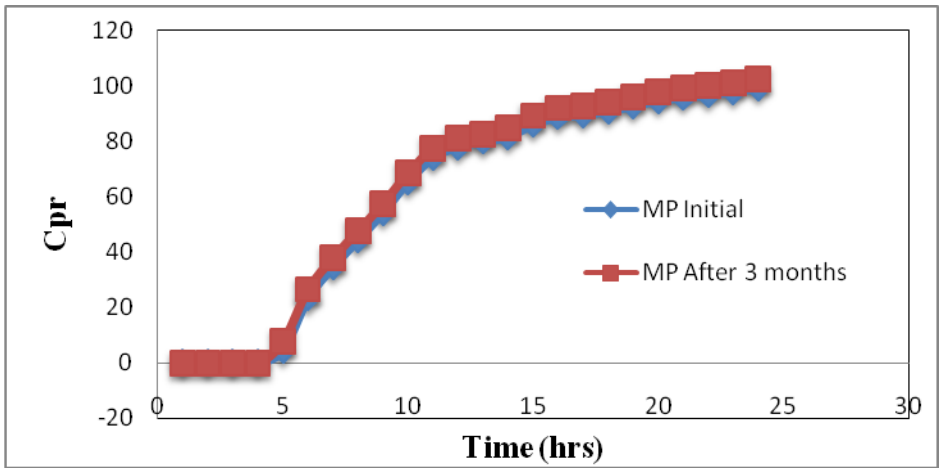
Figure 10: Drug release profile of MP before and after accelerated stability study of dual component tablet



CONCLUSION

The design of two different release phases can be easily adjusted in both delivery rate and ratio of the dose fractions, according to the pharmacokinetics and therapeutic needs.

The results obtained with the dissolution test show that the release profile is dependent on both concentration of Xanthan gum and type of filler.

The results of 3^2 full factorial designs revealed that concentration of Xanthan gum and type of filler significantly affect the responses, Q_6, Q_{24} and $T_{80\%}$. Full and reduced models were derived for the prediction of the response variable, Y. Based on result of multiple linear regression analysis, it was concluded that satisfactory release lag time and good drug release profile of tablet could be obtained when X1 kept high level and X2 kept at high level. Finally it is concluded that by adopting a systematic formulation approach, delivery of two drugs from, a single dosage form can be obtained which could improve patient compliance and give better disease management.

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