



Statistical Design and Optimization of Sustained Release Formulations of Pravastatin

Pravastatinin Uzatılmış Salım Formülasyonlarının İstatistiksel Tasarım Kullanılarak Geliştirilmesi ve Optimizasyonu

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ABSTRACT

Objectives: The objective of the current study was to formulate a sustained release (SR) formulation for pravastatin. Pravastatin is a lipid lowering, biopharmaceutical classification class-III agent.

Materials and Methods: SR tablets of pravastatin were prepared using variable amounts of hydroxy methyl propyl cellulose (HPMC) K4M and sodium carboxy methyl cellulose in various proportions by direct compression in a 3² factorial design. The amounts of the polymers HPMC K4M and sodium carboxy methyl cellulose required to obtain prolonged release of drug were chosen as independent variables, X₁ and X₂, respectively, whereas times taken for 10%, 50%, 75%, and 90% drug release were chosen as dependent variables.

Results: Nine formulations were developed and were checked using pharmacopoeial tests. The results showed that all the factorial batches were within the standard limits. The dissolution parameters of all formulations were subjected to kinetic fitting and various statistical parameters were determined. Polynomial equations were developed and verified for dependent variables. Formulation F₅, containing 25 mg of HPMC K4M and 25 mg of sodium carboxy methyl cellulose, was the formulation most similar (similarity factor f₂=89.559, difference factor f₁=1.546) to the marketed product (Pravachol).

Conclusion: The best formulation (F₅) follows Higuchi's kinetics and non-Fickian diffusion zero order kinetics (n=1.083).

Key words: Pravastatin, sustained release tablet, HPMC K4M, 3² factorial design, zero order kinetics, non-Fickian diffusion mechanism

ÖZ

Amaç: Bu çalışmanın amacı, biyofarmasötik sınıflandırma sistemi III grubunda yer alan lipit düşürücü etkili pravastatinin sürekli salım yapan formülasyonunun geliştirilmesidir.

Gereç ve Yöntemler: Pravastatin'in sürekli salım tabletleri, direkt kompresyonla 3² faktöryel tasarıma göre çeşitli oranlarda hidroksi metil propil selüloz (HPMC) K4M ve sodyum karboksil metil selüloz kullanılarak hazırlanmıştır. Pravastatin'in uzun süreli salınımını elde etmek için bağımsız değişkenler olarak HPMC K4M (X₁) ve sodyum karboksil metil selüloz (X₂) miktarları; %10, %50, %75 ve %90 ilaç salımı için geçen süreler ise bağımlı değişkenler olarak seçilmiştir.

Bulgular: Dokuz formülasyon geliştirilmiş ve bu formülasyonlara farmakopede belirtilen kontrol testleri uygulanmıştır. Sonuçlar geliştirilen tüm formülasyonların standart limit değerler arasında olduğunu göstermiştir. Tüm formülasyonların disolüsyon parametreleri kinetik modellere uygulanarak çeşitli istatistiksel parametreler belirlenmiştir.

Polinomial denklemler bağımlı değişkenler için geliştirilmiş ve doğrulanmıştır. 25 mg HPMC K4M ve 25 mg sodyum karboksil metil selüloz içeren formülasyondan (F₅) pravastatin salımı, ticari preparatı (Pravachol) ile benzer bulunmuştur (benzerlik faktörü f₂=89,559; fark faktörü f₁=1,546).

Sonuç: En iyi formülasyonunun (F₅), Higuchi kinetiği, Fick kanununa uymayan difüzyonun sıfırıncı derece kinetiğine (n=0,864) uygun davranış gösterdiği bulunmuştur.

Anahtar kelimeler: Pravastatinin, sürekli salım tableti, HPMC K4M, 3² faktöryel tasarım, sıfırıncı derece kinetik, Fick kanununa uymayan difüzyon mekanizması

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INTRODUCTION

Enteral delivery is an effective, popularly used mode of administration for both immediate and new drug delivery systems. In the case of chronic therapy, immediate release dosage forms are administered in a repetitive manner, resulting in more problems. The majority of these drugs undergo the first pass effect or presystemic elimination, which results in poor bioavailability and shorter activity.

Sustained release (SR) formulations show constant C_{ss} levels for a prolonged period, decreased dosing frequency, and patient compliance.² Zero-order drug release from the formulation will aid the C_{ss} constantly for a longer period. Zero-order kinetics is one of the aims of SR forms.^{2,3}

Polymers were utilized for achieving sustained drug release. The literature reveals that utilization of polymers plays a key role in pharmaceutical product development.⁴

Natural polymers remain preferred due to their numerous advantages. Extensively used natural gums include xanthan gum, guar gum, tragacanth gum, and alginates. Cellulosics like hydroxy methyl propyl cellulose (HPMC), hydroxy propyl cellulose, carboxy methyl cellulose (CMC), and sodium (S) CMC belong to the semisynthetic category and have been extensively studied in SR tablet formulations.⁵

Direct compression is a widely used manufacturing method for the preparation of tablets.⁶ The current research experimentation focuses on the design of a SR formulation for pravastatin.

Pravastatin, a potent hypolipidemic agent, belongs to biopharmaceutical classification class-III. It is a specific inhibitor (competitive) of HMG CoA. Pravastatin is useful for the effective management of atherosclerotic vascular disease. It undergoes an extensive first pass effect in the liver. Its bioavailable fraction is 0.17, about 50% of protein binding (plasma proteins). The elimination half-life for pravastatin is 1.5-2 h and it is eliminated from the body via feces and urine. Hence, research work was planned to formulate and evaluate SR tablets for pravastatin as a model drug and had the objective that the optimized formulation trial should show desired SR of the drug by means of an enhanced dissolution rate.⁷⁻¹⁴

Response surface methodology (RSM) with a polynomial equation has been extensively applied in the design and development of pharmaceutical products. Variations of RSM include 3^2 factorial design, central composite design, and Box-Behnken design. RSM is applied when only a few significant factors are involved in the optimization procedure. The advantage of this method is less experimentation and time, the results are more effective, and it is more cost effective than tradition experimentation models.¹⁵⁻¹⁸

Hence an attempt was made in the present research work to formulate SR tablets of pravastatin using HPMC K4M and SCMC. Instead of a heuristic method, a standard statistical tool design of experiments was used to study the effect of formulation variables on the release properties.

A 3^2 factorial design was used to study the effect of polymers on the drug release profile (effect of independent variables

or factors), i.e. the quantity of HPMC K4M and SCMC, on the dependent variables ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$).¹⁹

MATERIALS AND METHODS

The materials used in the research were procured from various sources. Pravastatin was a gift sample from Konis Pharma Ltd, Baddi, India. HPMC K4M, SCMC, and lactose were obtained from Meditech Pharma Ltd, Solan. Magnesium stearate, talc, and lactose obtained from Loba Chemie Pvt. Ltd, Bombay.

Formulation and development of SR pravastatin tablets

Quantities required for the HPMC K4M and SCMC for the preparation of SR pravastatin tablets were selected as independent variables. $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ were selected as dependent variables. Polynomial equations were developed for dependent variables as per backward stepwise linear regression analysis.^{20,21}

The 3 levels of X_1 (HPMC K4M) were 7.5%, 12.5%, and 17.5%. The 3 levels of X_2 (SCMC) were 7.5%, 12.5%, and 17.5% (% with respect to average weight of tablet). Nine SR pravastatin tablet formulations were designed using selected combinations of X_1 and X_2 and checked for the selection of the optimum composition required to meet the primary objective of the study.

Preparation of SR pravastatin tablets

All the ingredients were procured and weighed accurately. They were mixed uniformly in a poly bag for 10-15 min. The resulting mix was subjected to screening (#44). Lubricant was added, followed by mixing well and then compression using a tablet compressor. The resulting tablets were checked in terms of pharmacopoeial limits. The tablets were packed in well-closed air-tight containers.

Experimental design

The experimental design used in the current research was a 3^2 factorial design; the quantity of HPMC K4M was labeled X_1 and the quantity of SCMC was labeled X_2 and they are presented in Table 1. The 3 levels chosen for both X_1 and X_2 were coded as -1=7.5%, 0=12.5%, and +1=17.5%. The formulations for the factorial trials are presented in Table 2.

Evaluation of SR pravastatin tablets

Hardness

This test was performed with the help of a Monsanto hardness tester.

Friability

This test was carried out in a Roche friabilator. The initial weight (W_0) of 20 tablets was noted and then they were dedusted in a drum with a speed of 25 rpm for 4 min and weighed (W) again. Percentage friability was calculated using the following equation. The weight loss should not be more than 0.8%.

$$\text{Friability (\%)} = \frac{(w_0 - w)}{w} \times 100$$

Assay

This test was carried out by taking a fixed number of samples (20) and subjecting them to pulverization. From that above resultant

mixture powder equivalent to 100 mg was dissolved in 100 mL of solvent (6.8 buffer) and sonicated if necessary followed by filtration. The absorbance of the resultant solution was measured using a ultraviolet (UV)-Visible spectrophotometer at 239 nm.¹⁵

Thickness

This test was performed with the help of vernier calipers.

In vitro dissolution study

Dissolution tests were performed using the USP Apparatus 2. The specifications were followed as per official methods such as dissolution medium for initial 2 h is 900 mL of pH 1.2 buffer followed by pH 6.8, at 50 rpm and 37±0.5°C. Samples were collected at fixed time intervals by a pre-filter connected syringe and replacement of fresh fluid was done simultaneously. The absorbance of samples was measured at 239 nm using a Labindia UV-3200 UV-Visible spectrophotometer (n=3).^{9,12,14}

Kinetic modeling of drug release

The kinetic data were subjected to statistical modeling, i.e. zero order, first order, Higuchi, and Korsmeyer-Peppas kinetics.^{22,23}

The study did not require ethics committee approval or patient informed consent because it did not focus on any clinical parameter and did not utilize any humans/animals for the processing of work.

RESULTS AND DISCUSSION

SR tablets of pravastatin were formulated with the help of a 3² factorial design for identifying the optimized composition of polymers (HPMC K4M and SCMC) and to obtain prolonged/sustained drug release from the formulation. The experimental design is presented in Table 1. The 2 factors involved in the design of formulations are quantity of HPMC K4M and SCMC, which were labeled as independent variables (X_1 , X_2), while kinetic parameters were labeled as dependent variables ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$). Nine factorial batches were designed and all trials had 40 mg of pravastatin as a SR tablet dosage form by direct compression technique as per the formulae given in Table 2.

All final batches were subjected to various final product quality assurance tests like mean hardness, mean thickness, friability, weight variation, and drug content, and the results are summarized in Table 3. Hardness for finished batches was in the range of 3.47±0.3-4.10±0.5 kg/cm². Thickness for finished batches was in the range of 2.45±0.15-2.86±0.14 mm. Results for the friability test were less than 0.51%. Drug content for finished batches met the acceptance criterion. Drug release studies were performed for finished batches using pH 1.2 buffer for an initial 2 hour followed by phosphate buffer pH 6.8 as operated under a standard set of conditions at 50 rpm (paddle), 37±0.5°C. Dissolution plots are presented in Figures 1-4 (kinetic plots) and the statistical parameters are summarized in Table 4. % percentage cumulative drug release for finished batches F_1 - F_9 at 12 hour was 88.88-99.61%. The result revealed that the release rate of drug was inversely proportional to the quantity of polymers. Hence the desired drug release was achieved by

manipulating values of independent variables. A difference was seen in dependent variables due to change in proportions of X_1 and X_2 . Formulation coded F_5 containing 25 mg of HPMC K4M and 25 mg of SCMC produced desirable release characteristics ($t_{10\%}$ =0.459 h, $t_{50\%}$ =3.025 h, $t_{75\%}$ =6.040 h, $t_{90\%}$ =10.045 h), which was probably due to variation in the viscosity of the polymer matrix. An increase in the viscosity of the stagnant layer results in a corresponding decrease in drug release (due to thicker gel layer formation).²⁴ The dissolution profiles of SR pravastatin tablets were subjected to kinetic modeling. The results are presented in Table 4 and Figures 1-4. The results reveal that all formulation batches best fitted zero order kinetics and r^2 was in the range of 0.995-0.999. They also fitted Higuchi's kinetics; r^2 was in the range of 0.941-0.968. The Peppas treatment revealed that all batches follow a non-Fickian diffusion path (n values 1.046-1.397). Polynomial equations were developed for all dependent variables by linear stepwise backward regression analysis with the help of PCP Disso software and response morphological plots were constructed using SigmaPlot V13. The response morphological plots are presented in Figures 5-8 for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ using X_1 and X_2 on both axes to show the effects of independent variables on the dependent variables. Kinetic parameters for the trials (F_1 - F_9) are presented in Table 5.

The polynomial equation for the 3² full factorial design was as follows:

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2 \dots$$

Y- dependent variable, b_0 - mean response of 9 trials, b_1 - estimated coefficient for X_1 , b_2 - estimated coefficient for X_2 , b_{12} - interaction term, X_1^2 and X_2^2 - coefficients for nonlinearity. Validity of the derived equations was evaluated by formulating 2 counter check batches of intermediate quantities (C_1 , C_2).

Table 1. Experimental design layout

Name of ingredients	Experimental design										
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	C_1	C_2
X_1	1	1	1	0	0	0	-1	-1	-1	-0.5	+0.5
X_2	1	0	-1	1	0	-1	1	0	-1	-0.5	+0.5

Table 2. Formulation of SR pravastatin tablets

Name of ingredients	Quantity of ingredients per tablet (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Pravastatin	40	40	40	40	40	40	40	40	40
HPMC K4M	35	35	35	25	25	25	15	15	15
SCMC	35	25	15	35	25	15	35	25	15
Lactose	82	92	102	92	102	112	102	112	122
Talc	4	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200	200	200

SR: Sustained release, HPMC: Hydroxy methyl propyl cellulose, SCMC: Sodium carboxy methyl cellulose

The equations for dependant variables developed as mentioned below,

$$Y_1 = 0.514 - 0.012 X_1 - 0.094 X_2 - 0.038 X_1 X_2 + 0.055 X_1^2 + 0.0171 X_2^2 \text{ (for } t_{10\%})$$

$$Y_2 = 3.393 - 0.078 X_1 - 0.612 X_2 - 0.250 X_1 X_2 + 0.363 X_1^2 + 0.112 X_2^2 \text{ (for } t_{50\%})$$

$$Y_3 = 6.79 - 0.155 X_1 - 1.222 X_2 - 0.507 X_1 X_2 + 0.722 X_1^2 - 0.225 X_2^2 \text{ (for } t_{75\%})$$

$$Y_4 = 11.280 - 0.260 X_1 - 2.01 X_2 - 0.840 X_1 X_2 + 1.21 X_1^2 + 0.371 X_2^2 \text{ (for } t_{90\%})$$

Batch (F₅) is the identical product

The +ve sign for the coefficient of X₁ in Y₁, Y₂, Y₃, and Y₄ signifies that as the amount of X₁ increases all independent variable values also increase. In other words the data demonstrate that both X₁ and X₂ affect t_{10%}, t_{50%}, t_{75%}, and t_{90%}. From the results it can be concluded that an increase in the amount of polymer leads to a decrease in release rate of the drug and the drug release pattern may be altered by changing the quantities of X₁ and X₂ to appropriate levels. The dissolution parameters predicted from the polynomial equations and those actually observed from the experimental results are summarized in Table 6. Closeness of results was seen between actual values and predicted values. This proves that the polynomial equation developed was valid and confirms the validity of the derived

equations. The response surface/surface morphological plots were presented to show the effects of X₁ and X₂ on dependent variables. The final best (optimized, based on desirability factor above 0.999) formulation (F₅) is an identical product showing a similarity factor (f₂) of 89.559, difference factor (f₁) of 1.546, and t_{cal} is <0.05 when compared with the marketed product (Pravachol).

CONCLUSION

The current research work focused on the utility of macromolecules (polymers) such as HPMC K4M and SCMC in the formulation of SR tablets for pravastatin using a 3² factorial design. The results revealed that the amount of polymers was inversely proportional to the rate of drug release from the formulation. Utilization of polymers in the formulation was beneficial for obtaining prolonged release of the active moiety. Formulation F₅ follows zero order release and a non-Fickian diffusion mechanism. F₅ may be administered for the effective management of hypercholesterolemia and atherosclerotic vascular disease and to reduce the risk of cardiovascular disease. The best formulation shows good retaining

Table 3. Final product quality assurance parameters

S.no.	Formulation code	Hardness (kg/cm ²)	Thickness (mm)	Friability (%)	% Weight variation	Drug content (%)
1	F ₁	3.52±0.1	2.76±0.12	0.28±0.02	200.3±0.12	99.23±0.27
2	F ₂	3.47±0.3	2.86±0.14	0.25±0.022	199.72±0.28	98.36±0.64
3	F ₃	4.10±0.5	2.76±0.12	0.41±0.04	199.2±0.31	98.53±0.37
4	F ₄	3.79±0.2	2.64±0.16	0.38±0.022	199.51±0.45	99.46±0.44
5	F ₅	4.05±0.5	2.68±0.12	0.35±0.05	201.0±0.19	99.40±0.300
6	F ₆	3.88±0.20	2.54±0.26	0.22±0.027	202.1±0.14	99.65±0.35
7	F ₇	3.50±0.40	2.56±0.14	0.51±0.04	200.6±0.14	99.23±0.32
8	F ₈	4.05±0.20	2.54±0.16	0.48±0.02	201.1±0.19	99.59±0.31
9	F ₉	3.85±0.5	2.45±0.15	0.23±0.027	199.6±0.28	98.47±0.43

Table 4. Regression analysis for factorial trials

S.no.	Formulation code	Kinetic parameters											
		Zero order			First order			Higuchi			Korsmeyer-Peppas		
		a	b	r	a	b	r	a	b	r	a	b	r
1	F ₁	5.626	8.461	0.998	2.231	0.106	0.878	24.13	30.78	0.941	0.566	1.352	0.995
2	F ₂	3.711	8.25	0.999	2.175	0.093	0.929	22.35	30.260	0.953	0.659	1.258	0.999
3	F ₃	1.123	7.550	0.999	2.103	0.071	0.972	18.85	28.020	0.964	0.739	1.147	0.997
4	F ₄	1.384	8.337	0.999	2.278	0.133	0.892	18.58	31.11	0.968	0.961	0.966	0.999
5	F ₅	2.222	8.354	0.997	2.185	0.100	0.932	21.36	30.76	0.951	0.830	1.083	0.996
6	F ₆	2.571	7.513	0.999	2.078	0.072	0.991	16.32	28.42	0.974	0.864	1.046	0.992
7	F ₇	3.976	8.231	0.997	2.164	0.090	0.925	22.57	30.21	0.952	0.631	1.282	0.999
8	F ₈	1.165	7.850	0.999	2.130	0.082	0.949	19.71	29.17	0.961	0.618	1.317	0.974
9	F ₉	4.121	8.125	0.995	2.137	0.081	0.968	22.66	29.91	0.957	0.525	1.397	0.992

a: Intercept, b: Slope, r: Correlation coefficient

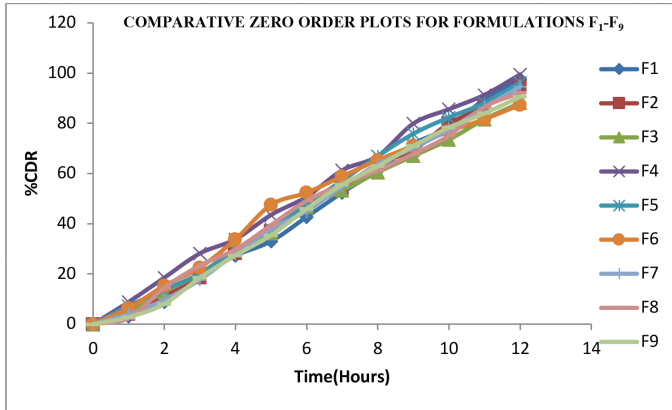


Figure 1. Comparative zero order plots

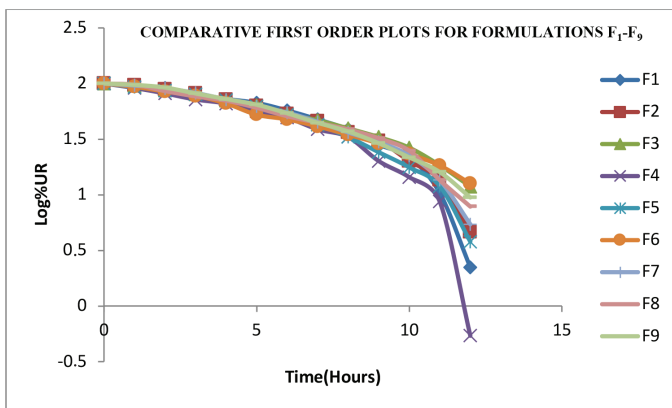


Figure 2. Comparative first order plots

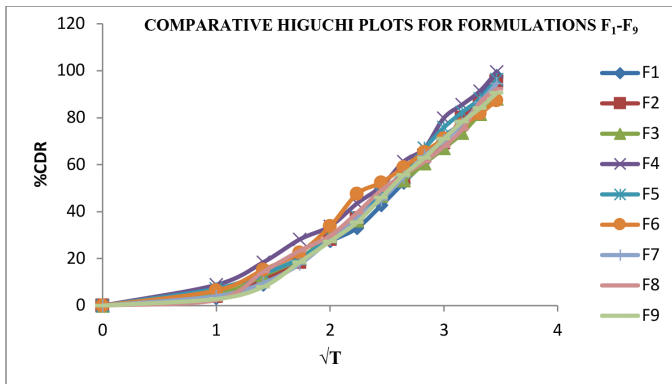


Figure 3. Comparative Higuchi plots

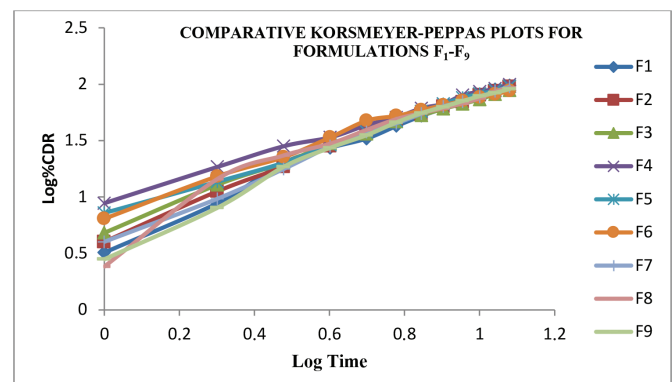


Figure 4. Comparative Korsmeyer-Peppas plots

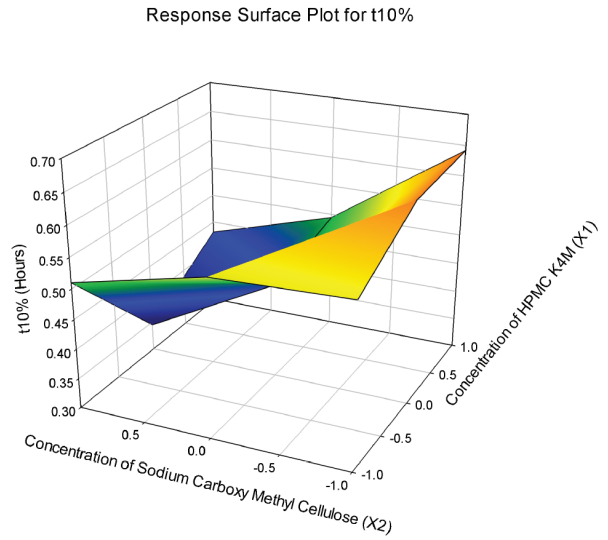


Figure 5. Response surface plots for t10%

t: Time taken to release

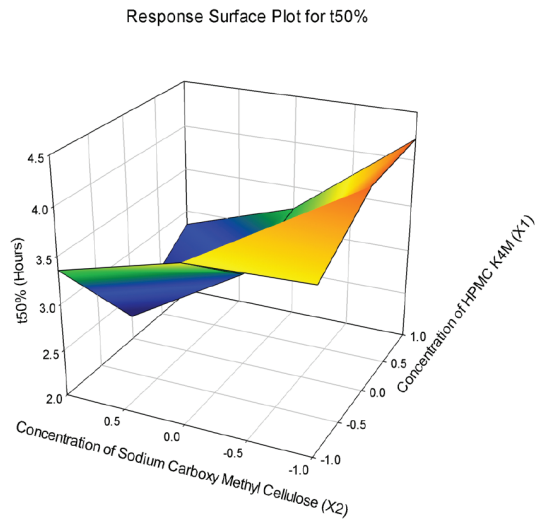


Figure 6. Response surface plots for t50%

HPMC: Hydroxy methyl propyl cellulose

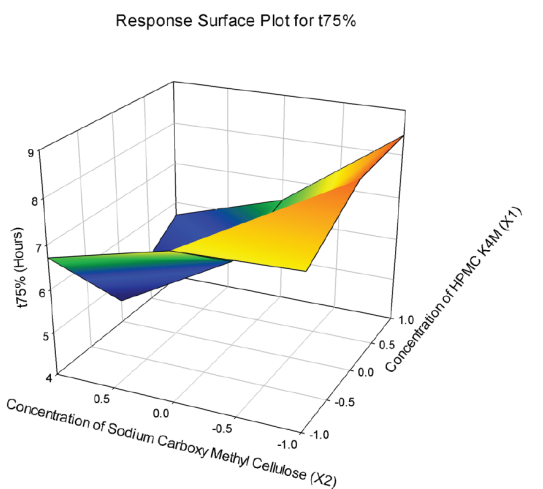


Figure 7. Response surface plots for t75%

t: Time taken to release

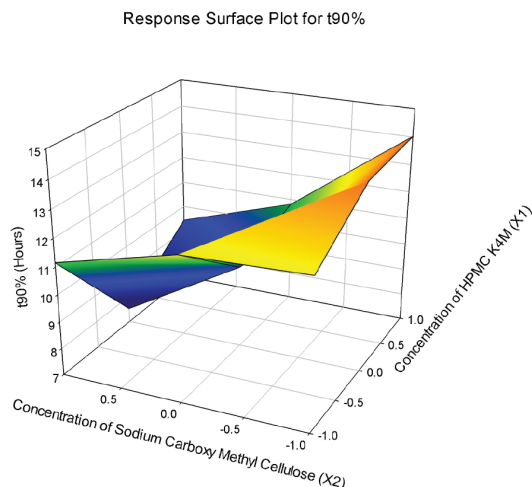


Figure 8. Response surface plots for $t_{90\%}$

Table 5. Dissolution parameters of SR pravastatin tablets

S.no.	Formulation code	Kinetic parameters			
		$t_{10\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)
1	F ₁	0.431	2.837	5.671	9.423
2	F ₂	0.493	3.253	6.521	10.81
3	F ₃	0.646	4.225	8.449	14.01
4	F ₄	0.352	2.267	4.539	7.529
5	F ₅	0.459	3.025	6.040	10.045
6	F ₆	0.637	4.181	8.341	13.859
7	F ₇	0.511	3.361	6.718	11.120
8	F ₈	0.564	3.694	7.383	12.252
9	F ₉	0.561	3.735	7.469	12.411

t: Time taken to release, SR: Sustained release

Table 6. Kinetic parameters for counter check formulations

Formulation code	Predicted value				Actual observed value			
	$t_{10\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)	$t_{10\%}$ (h)	$t_{50\%}$ (h)	$t_{75\%}$ (h)	$t_{90\%}$ (h)
C ₁	0.579	3.790	7.591	12.610	0.582	3.785	7.597	12.585
C ₂	0.473	3.101	6.212	10.317	0.477	3.107	6.215	10.313

characteristics. It also avoids the first pass effect, which will ultimately improve the clinical response.

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