ORIGINAL ARTICLE

Design, Formulation, and Evaluation of Sustained Release Tablets for Antihyperlipidemic Agent

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Abstract

Aim and Objective: The main objective of the present research investigation is to formulate the sustained release (SR) formulation of rosuvastatin. Rosuvastatin, an antihyperlipidemic agent, belongs to Biopharmaceutical Classification System class-II agent. **Materials and Methods:** The SR tablets of rosuvastatin were prepared by employing different concentrations of hydroxy methyl propyl cellulose (HPMCK4M) and sodium carboxymethyl cellulose (SCMC) in different combinations by direct compression using 3^2 factorial designs. The concentration of polymers, HPMCK4M, and SCMC required to achieve the desired drug release was selected as independent variables, X_1 and X_2, respectively, whereas time required for 10% of drug dissolution ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$), and 90% ($t_{90\%}$) was selected as dependent variables. **Results and Discussion:** A total of nine formulations were designed and are evaluated for hardness, friability, thickness, % drug content, and *in vitro* drug release. From the results, it was concluded that all the formulations were found to be within the pharmacopeial limits and the *in vitro* dissolution profiles of all formulations were fitted into different kinetic models; the statistical parameters such as intercept, slope, and regression coefficient were calculated. Polynomial equations were developed for dependent variables. The validity of developed polynomial equations was verified by designing 2 check point formulations (C_1 and C_2). According to SUPAC guidelines, the formulation (F_4) containing 30 mg of HPMCK4M and 40 mg of SCMC is the most similar formulation (similarity factor f_2= 89.561, dissimilarity factor f_1 = 1.543, and no significant difference, t = 0.0056) to marketed product (CRESTOR). **Conclusion:** The selected formulation (F_4) follows zero-order and Higuchi kinetics, and the mechanism of drug release was found to be non-Fickian Diffusion (n = 0.963).

Key words: 3^2 factorial design, Hydroxy methyl propyl cellulose K4M, non-Fickian diffusion mechanism, rosuvastatin, sodium carboxymethyl cellulose, SUPAC, sustained release tablet, zero-order kinetics

INTRODUCTION

Oral administration is the most convenient, popularly used route of administration for both conventional and novel drug delivery systems. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages.[1] Major problem associated with oral administration of formulations is extensive pre-systemic elimination by gastrointestinal degradation and/or first-pass hepatic metabolism which results low systemic bioavailability and shorter duration of therapeutic activity and formation of inactive or toxic metabolites.[2]

Sustained release (SR) tablet formulations offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs.[3] The goal of a SR dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting

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to obtain zero-order release from the dosage form. Zero-order release constitutes the drug release from the dosage form that is independent of the amount of drug in the delivery system (i.e., constant release rate). SR systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow first-order fashion (i.e., concentration dependent). Systems that are designated as prolonged release can also be considered as attempts at achieving SR delivery.[4-7]

SR products provide advantage over immediate release dosage form by optimizing biopharmaceutical, pharmacokinetic, and pharmacodynamic properties of drug. SR dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration.

Among the different SR drug delivery systems, matrix-based SR tablet formulations are the most popularly preferred for its convenience to formulate a cost-effective manufacturing technology in commercial scale. The use of polymers in controlling the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. Over many years, numerous studies have been reported in the literature on the application of hydrophilic polymers in the development of SR matrix systems for various drugs.[8,9]

Natural polymers remain preferred due to numerous advantages such as they are readily available, economic, non-carcinogenicity, be capable of chemical modifications, mucoadhesivity, biodegradable, biocompatible, high drug holding capacity and high thermal stability, and easy of compression.[10] Various natural gums and mucilages have been examined as polymers for sustained drug release in the last few decades, for example, guar gum, tragacanth gum, xanthan gum, pectin, and alginates. Semisynthetic polymers (cellulose derivatives) such as carboxymethyl cellulose (CMC), sodium (SCMC), hydroxyproyl cellulose, and hydroxypropyl methyl cellulose (HPMC) have been extensively studied as polymer in the SR tablet formulations.[9] These polymers are most preferred due to its cost effectiveness, broad regulatory acceptance, non-toxic, and easy of compression. Some factors such as molecular size, diffusivity, pKa-ionization constant, release rate, dose and stability, duration of action, absorption window, therapeutic index, protein binding, and metabolism affect the design of SR formulation.

Oral SR dosage form by direct compression is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms.[11] The selection of the drug candidates for SR system needs consideration of several biopharmaceutical, pharmacokinetic, and pharmacodynamic properties of drug molecule.[12]

In the present study, a SR dosage form of rosuvastatin has been developed which makes less frequent administering of drug.

Rosuvastatin, a potent hypolipidemic agent, belongs to Biopharmaceutical Classification System Class-II agent. It is a specific inhibitor (competitive) of HMG CoA. It has low extrahepatic tissue penetration (the drug acts primarily in liver). It is sparingly soluble in water. Its bio available fraction is 0.20. Rosuvastatin shows around 90% protein binding. Apparent volume of distribution was found to be 134 L in steady state. 90% of rosuvastatin is eliminated in feces whereas 10% is eliminated via renal excretion. 72% of absorbed rosuvastatin is eliminated in bile and 28% through renal excretion. Thus, there is a need to increase the rate of dissolution. Hence, the study was carried out to formulate and evaluate SR dosage form of rosuvastatin as a model drug and had an aim that final batch formulation parameters should show prolonged drug release.[13-19]

Development of dosage form depends on the chemical nature of the drug/polymers, matrix structure, swelling, diffusion, erosion, release mechanism, and *in vivo* environment.

It is an important issue to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. For this purpose, response surface methodology (RSM) utilizing a polynomial equation has been widely used. Different types of RSM designs include 3-level factorial design, central composite design, Box–Behnken design, and D-optimal design. RSM is used when only a few significant factors are involved in experimental optimization. The technique requires less experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating SR dosage forms.[20]

Hence, an attempt is made in this research work to formulate SR tablets of rosuvastatin using HPMCK4M and SCMC. Instead of normal and trial method, a standard statistical tool design of experiments is employed to study the effect of formulation variables on the release properties.

Large-scale production needs more simplicity in the formulation with economic and cheapest dosage form.

A 3^2 full factorial design was employed to systematically study the drug release profile. A 3^2 full factorial design was employed to investigate the effect of two independent variables (factors), i.e., the amounts of HPMCK4M and SCMC on the dependent variables, i.e., $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$, (time taken to release 10%, 50%, 75%, and 90%, respectively).

MATERIALS AND METHODS

Materials used in this study were obtained from the different sources. Rosuvastatin was a gift sample from Konis Pharma Ltd., Baddi, India. HPMCK4M, SCMC, and lactose were

procured from Amna Pharmaceuticals, Surat. Other excipient such as magnesium stearate was procured from Loba Chemie Pvt. Ltd., Mumbai.

Formulation development of rosuvastatin SR tablets

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses.[21]

A selected three level, two factor experimental design (3^2 factorial design) describes the proportion in which the independent variables such as HPMCK4M and SCMC were used in formulation of rosuvastatin SR tablets. The time required for 10% ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$), and 90% ($t_{90\%}$) drug dissolution were selected as dependent variables. Significance terms were chosen at 95% confidence interval ($P < 0.05$) for final equations. Polynomial equations were developed for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ (step-wise backward linear regression analysis).[22]

The three levels of factor X_1 (HPMCK4M) at a concentration of 10%, 15%, and 20% and three levels of factor X_2 (SCMC) at a concentration of 10%, 15%, and 20% (percentage with respect to total tablet weight) were taken as the rationale for the design of the rosuvastatin SR tablet formulation. Nine rosuvastatin SR tablet formulations were prepared employing selected combinations of the two factors, i.e., X_1 and X_2 as per 3^2 factorial and evaluated to find the significance of combined effects of X_1 and X_2 to select the best combination and the concentration required to achieve the desired prolonged/SR of drug from the dosage form.

Table 1: Experimental design layout

Formulation code	X_1	X_2
F_1	1	1
F_2	1	0
F_3	1	−1
F_4	0	1
F_5	0	0
F_6	0	−1
F_7	−1	1
F_8	−1	0
F_9	−1	−1
C_1	−0.5	−0.5
C_2	+0.5	+0.5

Preparation of rosuvastatin SR tablets

All ingredients were collected and weighed accurately. They were mixed uniformly in poly bag for 10–15 min. The powder blend was passed through sieve no 44. Add magnesium stearate and then again blend for 5–6 min and subjected compression using rotary tablet punching machine. Compressed tablets were examined as per official standards and unofficial tests. Tablets were packaged in well-closed light resistance and moisture proof containers.

Experimental design

Experimental design utilized in the present investigation for the optimization of polymer concentration such as concentration of HPMCK4M was taken as X_1 and concentration of SCMC was taken as X_2. Experimental design is given in Table 1. Three levels for the concentration of HPMCK4M were selected and coded as −1 = 10%, 0 = 15%, and +1 = 20%. Three levels for the concentration of SCMC were selected and coded as −1 = 10%, 0 = 15%, and +1 = 20%. Formulae for all the experimental batches are given in Table 2.

Evaluation of rosuvastatin SR tablets

Hardness

The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2–4 kg/cm² is considered adequate for mechanical stability.

Table 2: Formulae for the preparation of rosuvastatin sustained release tablets

Name of ingredients	Quantity of ingredients per each tablet (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Rosuvastatin	20	20	20	20	20	20	20	20	20
HPMC K4M	40	40	40	30	30	30	20	20	20
SCMC	40	30	20	40	30	20	40	30	20
Lactose	92	102	112	102	112	122	112	122	132
Magnesium stearate	4	4	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200	200	200

SCMC: Sodium carboxy methyl cellulose, HPMC: Hydroxy methyl propyl cellulose

Friability

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W_0) or a sample of 20 tablets are degusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be >1%.

Friability (%) = ([initial weight - final weight]/[initial weight]) ×100

Content uniformity

In this test, 20 tablets were randomly selected and the percentage drug content was determined, and the tablets contained not <85% or >115% of the labeled drug content can be considered as the test was passed.

Assay

The drug content in each formulation was determined by triturating 20 tablets, and powder equivalent to 40 mg was dissolved in 100 ml of phosphate buffer pH 7.4, followed by stirring. The solution was filtered through a 0.45 µ membrane filter and diluted suitably, and the absorbance of resultant solution was measured spectrophotometrically at 245 nm using phosphate buffer pH 7.4 as blank.

Thickness

Thickness of the all tablet formulations were measured using Vernier calipers by placing tablet between two arms of the Vernier calipers.

In vitro dissolution study

The *in vitro* dissolution study for the rosuvastatin SR tablets was carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium for first 2 h followed by phosphate buffer pH 7.4 at 50 rpm and temperature 37 ± 0.5°C. At pre-determined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, and the volume withdrawn at each interval was replaced with the same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 245 nm using

Table 3: Post-compression parameters for the formulations

Formulation code	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	% Weight variation	Drug content (%)
F_1	3.51±0.1	2.76±0.12	0.28±0.02	200.3±0.12	99.13±0.47
F_2	3.50±0.5	2.86±0.14	0.25±0.022	199.72±0.28	98.47±0.53
F_3	4.01±0.5	2.76±0.12	0.41±0.04	199.2±0.31	98.53±0.37
F_4	3.78±0.2	2.64±0.16	0.38±0.022	199.51±0.45	99.46±0.44
F_5	4.04±0.5	2.68±0.12	0.35±0.05	201.0±0.19	99.40±0.300
F_6	3.82±0.20	2.54±0.26	0.22±0.027	202.1±0.14	98.64±0.35
F_7	3.51±0.40	2.56±0.14	0.51±0.04	200.6±0.14	99.23±0.32
F_8	4.07±0.20	2.54±0.16	0.48±0.02	201.1±0.19	99.59±0.31
F_9	3.81±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

Formulation code	Kinetic parameters											
	Zero order			First order			Higuchi			Korsmeyer-peppas		
	a	b	r	a	b	r	a	b	r	a	b	r
F_1	5.625	8.455	0.998	2.230	0.106	0.872	24.131	30.775	0.942	0.567	1.352	0.995
F_2	3.710	8.240	0.999	2.173	0.093	0.921	22.354	30.263	0.950	0.658	1.258	0.999
F_3	1.120	7.551	0.999	2.101	0.071	0.967	18.858	28.019	0.963	0.740	1.147	0.997
F_4	1.382	8.335	0.999	2.276	0.133	0.841	18.584	31.103	0.967	0.962	0.966	0.999
F_5	2.221	8.345	0.997	2.183	0.100	0.927	21.355	30.759	0.950	0.829	1.083	0.996
F_6	2.570	7.507	0.993	2.075	0.072	0.988	16.332	28.420	0.975	0.865	1.046	0.992
F_7	3.977	8.223	0.997	2.165	0.090	0.920	22.572	30.195	0.951	0.632	1.282	0.999
F_8	1.164	7.849	0.999	2.129	0.082	0.940	19.700	29.169	0.958	0.617	1.317	0.974
F_9	4.119	8.127	0.995	2.134	0.081	0.964	22.659	29.911	0.959	0.524	1.397	0.992

F_1 to F_9 are factorial formulations, r - correlation coefficient, a - intercept, b - slope

UV visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate ($n = 3$).

Kinetic modeling of drug release

The dissolution profile of all the formulations was fitted in to zero-order, first-order, and Higuchi and Korsmeyer-Peppas models to ascertain the kinetic modeling of drug release.[8,23,24]

RESULTS AND DISCUSSION

SR tablets of rosuvastatin were prepared and optimized by 3^2 factorial design to select the best combination of different polymers, HPMCK4M and SCMC, and also to achieve the desired prolong/SR of drug from the dosage form/ formulation. The two factorial parameters involved in the development of formulations are quantity of HPMCK4M and SCMC polymers as independent variables (X_1 and X_2) and *in vitro* dissolution parameters such as $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ as dependent variables. A total of nine formulations were prepared using 3 levels of 2 factors, and all the formulations containing 20 mg of rosuvastatin were prepared as a SR tablet dosage form by direct compression technique as per the formulae given in Table 2.

All the prepared tablets were evaluated for different post compression parameters, drug content, mean hardness, friability, and mean thickness as per official methods, and the results are given in Table 3. The mean hardness of tablets was in the range of 3.5 ± 0.5–4.07 ± 0.21 kg/cm^2. The mean thickness of all formulations was founded to be in the range of 2.45 ± 0.15–2.86 ± 0.14 mm. Weight loss in the friability test was <0.51%. Drug content of prepared tablets was within acceptance range only. Results for all post-compression parameters were tabulated or summarized in Table 3. *In vitro* dissolution studies were performed for prepared tables using 0.1 N HCl for first 2 h followed by phosphate buffer pH 7.4 as a dissolution media at 50 rpm and temperature 37 ± 0.5°C. The *in vitro* dissolution profiles of tablets are shown in Figures 1-4 (kinetic plots) and the dissolution parameters were summarized in Table 4. Cumulative percentage drug release of factorial design formulations F_1–F_9 at 12 h was found to be in the range of 86.87–99.61%. From the result, it reveals that the release rate was higher for formulations containing low level of HPMCK4M compared with other formulations containing higher level, due to high concentration of polymer drug which may have entrapped within a polymer matrix causing a decrease in rate of drug release. Therefore, required release of drug can be obtained by manipulating the composition of HPMCK4M and SCMC.

Much variation was observed in the $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ due to formulation variables. Formulation F_4 containing 35 mg of HPMCK4M and 60 mg of SCMC showed promising dissolution parameter ($t_{10\%}$ = 0.350 h, $t_{50\%}$ = 2.268 h, $t_{75\%}$ = 4.537 h, and $t_{90\%}$ = 7.530 h). The difference in burst effect of the initial time is a result of the difference in the viscosity of the polymeric mixtures. The decrease in drug release with corresponding increase in polymer concentration might be due to the resulting thick gel layer in formulation.[25]

The *in vitro* dissolution data of rosuvastatin SR tablet formulations were subjected to goodness of fit test by linear regression analysis according to zero-order and first-order kinetic equations, Higuchi, and Korsmeyer–Peppas models to assess the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4 and plots are shown in Figures 1-4. It was observed from the above that dissolution of all the tablets

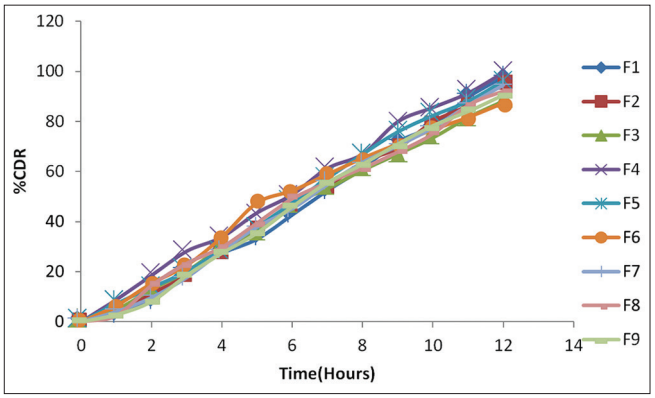

Figure 1: Comparative zero-order plots for F_1–F_9

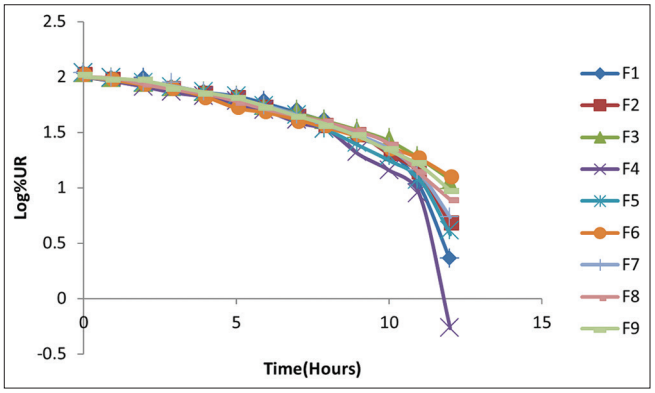

Figure 2: Comparative first-order plots for F_1–F_9

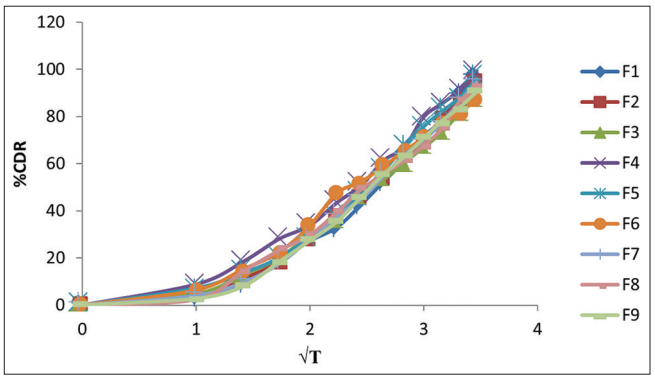

Figure 3: Comparative Higuchi plots for F_1–F_9

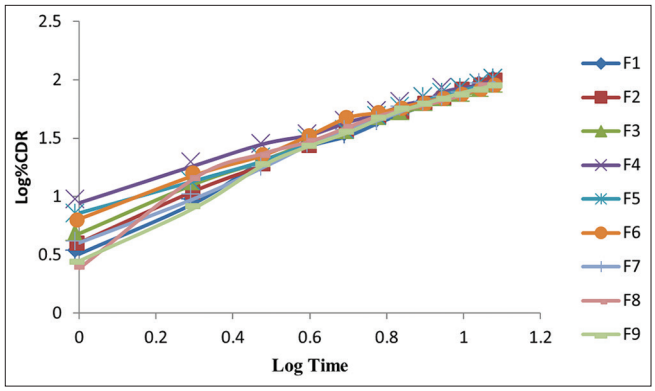

Figure 4: Comparative Korsmeyer–Peppas plots for F_1–F_9

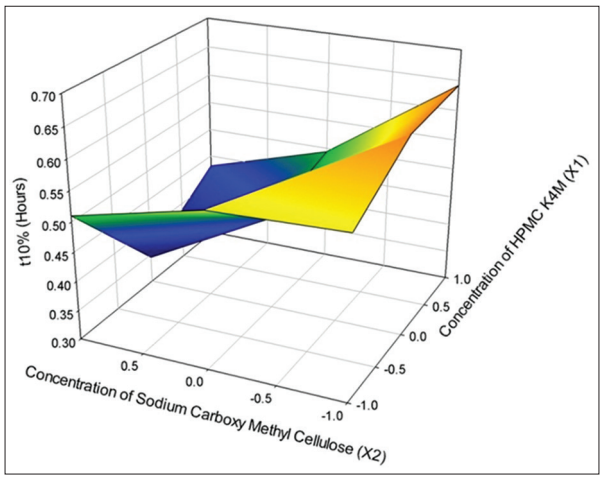

Figure 5: Response surface plots for $t_{10\%}$

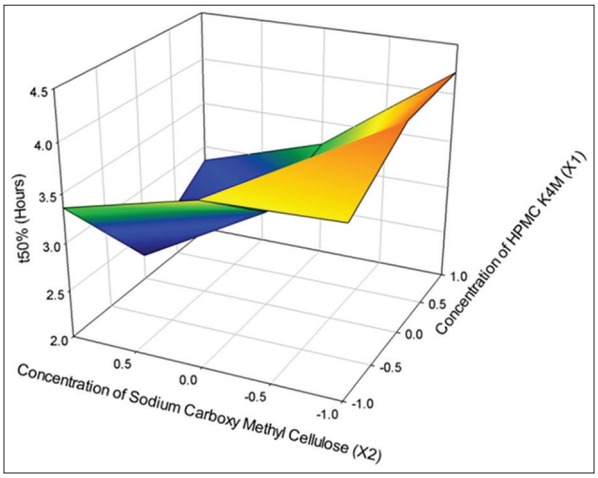

Figure 6: Response surface plots for $t_{50\%}$

followed zero-order kinetics with coefficient of determination (R^2) values above 0.993 (0.993–0.999). The values of r of factorial formulations for Higuchi's equation was found to be in the range of 0.942–0.975, which shows that the data fitted well to Higuchi square root of time equation confirming the release followed diffusion mechanism. Kinetic data was also fitted to Peppas model and it is found to follow non-Fickian diffusion mechanism as the slope (n) values are in the range

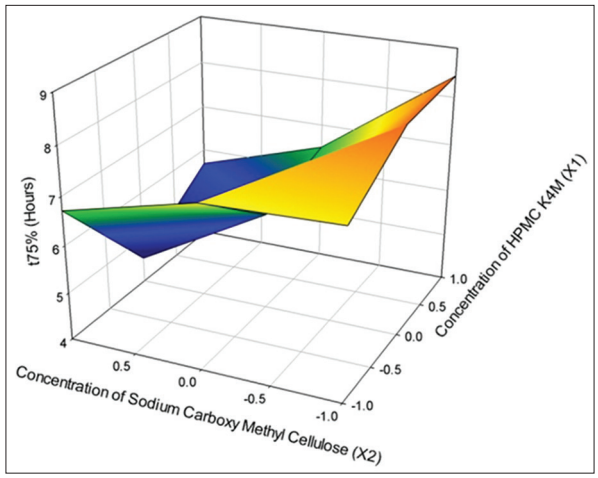

Figure 7: Response surface plots for $t_{75\%}$

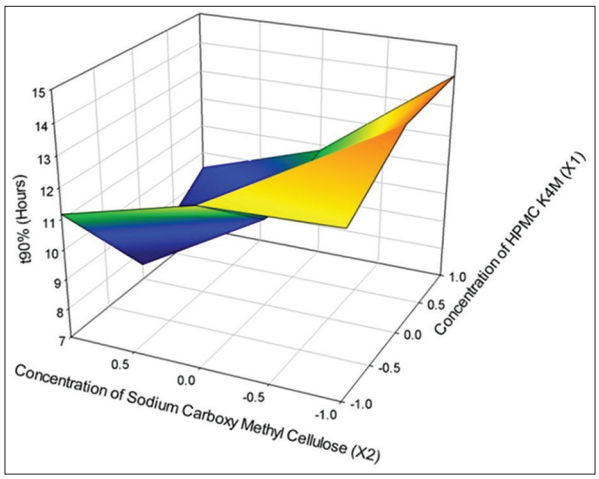

Figure 8: Response surface plots for $t_{90\%}$

Table 5: Dissolution parameters of rosuvastatin sustained release tablets 3^2 full factorial design batches

Formulation code	Kinetic parameters			
	$t_{10\%\ (h)}$	$t_{50\%\ (h)}$	$t_{75\%\ (h)}$	$t_{90\%\ (h)}$
F_1	0.432	2.838	5.672	9.425
F_2	0.490	3.252	6.503	10.810
F_3	0.645	4.224	8.444	14.03
F_4	0.350	2.268	4.537	7.530
F_5	0.460	3.024	6.041	10.044
F_6	0.635	4.172	8.342	13.860
F_7	0.512	3.358	6.717	11.121
F_8	0.562	3.687	7.382	12.250
F_9	0.560	3.733	7.468	12.410

0.524–0.962. Polynomial equations were derived for all dependent variables by backward stepwise linear regression analysis using PCP Disso software, and response surface plots were constructed using SIGMAPLOT V13 software. The response surface plots are shown in Figures 5-8 for

Table 6: Dissolution parameters for predicted and observed values for check point 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	0.578	3.792	7.588	12.605	0.589	3.789	7.595	12.597
C_2	0.474	3.102	6.210	10.315	0.481	3.117	6.218	10.333

$t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ using X_1 and X_2 on both the axes, respectively. The dissolution data (Kinetic parameters) of factorial formulations F_1–F_9 are shown in Table 5.

Polynomial equation for 3^2 full factorial designs is given in the following equation:

$$Y = b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1^2+b_{22}X_2^2$$

Where Y is dependent variable, b_0 arithmetic mean response of nine batches, and b_1 estimated coefficient for 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 term (X_1X_2) shows 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. Validity of derived equations was verified by preparing two check point formulations of intermediate concentration (C_1 and C_2).

The equations for $t_{10\%}$, $t_{50\%}$ $t_{75\%}$, and $t_{90\%}$ developed as follows:

$Y_1 = 00.515–0.011\ X_1–0.095\ X_2–0.037\ X_1X_2+0.055\ X_1^2+0.0172\ X_2^2$ (for $t_{10\%}$)

$Y_2 = 3.395–0.077\ X_1–0.611\ X_2–0.251\ X_1X_2+0.362\ X_1^2+0.114\ X_2^2$ (for $t_{50\%}$)

$Y_3 = 6.789–0.156\ X_1–1.223\ X_2–0.505\ X_1X_2+0.721\ X_1^2–0.224\ X_2^2$ (for $t_{75\%}$)

$Y_4 = 11.280–0.259\ X_1–2.01\ X_2–0.840\ X_1X_2+1.21\ X_1^2+0.370\ X_2^2$ (for $t_{90\%}$)

The positive sign for coefficient of X_1 in Y_1, Y_2, Y_3, and Y_4 equations indicates that, as the concentration of HPMCK4M increases, $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ value increases. In other words, the data demonstrate that both X_1 (amount of HPMCK4M) and X_2 (amount of SCMC) affect the time required for drug release ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$). From the results, it can be concluded that an increase in the amount of the polymer leads to decrease in release rate of the drug and drug release pattern may be changed by appropriate selection of the X_1 and X_2 levels. The dissolution parameters for predicted from the polynomial equations derived and those actual observed from experimental results are summarized in Table 6. The closeness of predicted and observed values for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ indicates validity of derived equations for dependent variables. The response surface plots were presented to show the effects of X_1 and X_2 on $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$. The final best (optimized) formulation (F_4) is compared with marketed product (CRESTOR) which shows similarity factor (f_2) 89.561 and difference factor (f_1) 1.543 (there is no significant difference in drug release because t_{cal} is<0.05).

CONCLUSION

The present research work envisages the applicability of polymers such as HPMCK4M and SCMC in the design and development of SR tablet formulations of rosuvastatin utilizing the 3^2 factorial designs. From the results, it was clearly understand that as the retardant (HPMC) concentration increases, the release rate of drug was retarded and both of these polymers can be used in combination since do not interact with the drug which may be more helpful in achieving the desired SR of the drug for longer periods. The optimized formulation followed Higuchi's kinetics while the drug release mechanism was found to be non-Fickian diffusion and zero-order release type, controlled by diffusion through the swollen matrix. On the basis of evaluation parameters, the optimized formulation F_4 may be used once a day administration in the management of hypercholesterolemia and to reduce the risk of cardiovascular disease. This may improve the patient compliance by reducing the dosing frequency. Which will ultimately improve the therapeutic outcome? We could be able to minimize the per oral cost of the formulation.

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