Research Article

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Formulation Development and Evaluation of Rosuvastatin Sustained Release Tablets

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Abstract

Purpose: The main objective of present research investigation is to formulate the sustained release formulation of Rosuvastatin. Rosuvastatin, an antihyperlipidemic agent, belongs BCS class-II agent.

Methods: The SR tablets of Rosuvastatin were prepared employing different concentrations of HPMCK4M and SCMC in different combinations by Direct Compression using 32 factorial design. The concentration of Polymers, HPMCK4M and SCMC required to achieve the desired drug release was selected as independent variables, X1 and X2 respectively whereas, time required for 10% of drug dissolution ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) were selected as dependent variables.

Results and Discussion: Totally nine formulations were designed and are evaluated for hardness, friability, thickness, % drug content, In-vitro drug release. From the Results it was concluded that all the formulation were found to be within the Pharmacopoeial limits and the In-vitro dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept, slope & regression coefficient were calculated. Polynomial equations were developed for dependent variables. Validity of developed polynomial equations were verified by designing 2 check point formulations (C1,C2). According to SUPAC guidelines the formulation (F4) containing 30 mg of HPMCK4M and 40 mg of SCMC, is the most similar formulation (similarity factor $f_2 = 89.561$, dissimilarity factor $f_1 = 1.543$ & No significant difference, $t = 0.0056$) to marketed product (CRESTOR).

Conclusion: The selected formulation (F4) follows Zero order, Higuchi's kinetics, and the mechanism of drug release was found to be Non-Fickian Diffusion ($n = 0.963$).

Keywords: Rosuvastatin, 3^2 Factorial design, Sustained release tablet, HPMCK4M, SCMC, SUPAC, Non-fickian diffusion mechanism, Zero order kinetics

Abbreviations: SR: Sustained Release; HPMC: Hydroxy Methyl Propyl Cellulose; SCMC: Sodium Carboxy Methyl Cellulose; BCSs: Biopharmaceutical Classification; V_d : Apparent Volume of Distribution; L: Litre; kg: Kilogram; cm: Centimetre; %: Percentage; mg: Milligram; ml: Millilitre; %CDR: Percentage Cumulative Drug Release; UR: Un Released; H: Hour; °C: Degree Centigrade; mm: Millimeter; $t_{1/2}$: Half Life; $t_{10\%}$: Time Taken to Release 10% Drug from Dosage Form; $t_{50\%}$: Time Taken to Release 50% Drug from Dosage Form; $t_{75\%}$: Time Taken to Release 75% Drug from Dosage Form; $t_{90\%}$: Time Taken to Release 90% Drug from Dosage Form

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 presystemic 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 sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting 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). Sustained release 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 sustained release delivery [4,5,6,7].

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

Among the different Sustained release 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, alginates. Semisynthetic polymers (cellulose derivatives) like carboxymethyl cellulose (CMC), sodium carboxy methyl cellulose (SCMC), hydroxypropyl cellulose (HPC), and hydroxypropyl methyl cellulose (HPMC) have been extensively studied as polymer in the sustained release tablet formulations [9]. These polymers are most preferred because of its cost effectiveness, broad regulatory acceptance, non-toxic and easy of compression. Some factors like 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 sustained release formulation.

Oral sustained release 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 sustained release system needs consideration of several biopharmaceutical, pharmacokinetic and pharmacodynamic properties of drug molecule [12].

In the present study, a sustained release dosage form of Rosuvastatin has been developed that makes less frequent administering of drug.

Rosuvastatin, a potent hypolipidemic agent, belongs BCS 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. 90% of protein binding. V_d was found to be 134 L in steady state. primarily eliminated in the faeces (90%) compared with 10% renal excretion. 72% of absorbed rosuvastatin is eliminated in bile and 28% via renal excretion. Thus, there is a need to increase rate of dissolution. Hence, the study was carried out to formulate and evaluate sustained release dosage form of Rosuvastatin as a model drug and had an aim that final batch formulation parameters should shows prolong drug release [13,14,15,16,17,18,19].

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

It is an important issue is 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 (CCD), Box-Behnken design and D-optimal design. Response surface methodology (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 sustained release dosage forms [20].

Hence an attempt is made in this research work to formulate sustained release (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. $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$ (Time taken to release 10%,50%,75%,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, Lactose were procured from Amna Pharmaceuticals, Surath. Other excipient such as magnesium stearate was procured from Loba Chemie Pvt.Ltd, Mumbai.

Formulation development of rosuvastatin sustained release 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) describe the proportion in which the independent variables HPMCK4M and SCMC were used in formulation of Rosuvastatin sustained release (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 $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (step-wise backward Linear Regression Analysis) [22].

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

Preparation of rosuvastatin sustained release 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 minutes and subjected compression by 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 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 was given in the table 1. Three levels for the Concentration of HPMCK4M were selected and coded as -1 = 10%, 0 = 15%, +1 = 20%. Three levels for the Concentration of SCMC were selected and coded as -1 =

10%, 0 = 15%, +1 = 20%. Formulae for all the experimental batches were given in table 2.

Table 1: Experimental design layout.

Formulation Code	X1	X2
F1	1	1
F2	1	0
F3	1	
F4	0	1
F5	0	0
F6	0	
F7		1
F8		0
F9		
C1	-0.5	-0.5
C2	0.5	0.5

Evaluation of rosvastatin sustained release 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.

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 dedusted 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 more than 1 %

Friability (%) = $[(\text{Initial weight} - \text{Final weight}) / (\text{Initial weight})] \times 100$

Content uniformity

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or more than 115% of the labelled 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, 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 sustained release tablets were 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 two hours followed by phosphate buffer pH 7.4 at 50 rpm and temperature $37 \pm 0.5^\circ\text{C}$. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with 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 UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate ($n = 3$).

Table 2: Formula for the preparation of rosvastatin sustained release tablets.

Name of Ingredients	Quantity of Ingredients per each Tablet (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
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

Kinetic modeling of drug release:

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

Results and Discussion

Sustained release tablets of Rosuvastatin were prepared and optimized by 32 factorial design in order to select the best combination of different Polymers, HPMCK4M, SCMC and also to achieve the desired prolong/sustained release of drug from the dosage form/ Formulation. The two factorial parameters involved in the development of formulations are, quantity of HPMCK4M & SCMC polymers as independent variables (X1, X2), and In vitro dissolution parameters such as $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ & $t_{90\%}$ as dependent variables. Totally nine formulations were prepared using 3 levels of 2 factors and all the formulations containing 20 mg of Rosuvastatin were prepared as a sustained release 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, mean thickness as per official methods and 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/cm². 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 less than 0.51%. Drug content of prepared tablets was within acceptance range only. Results for all Post-compression parameters were tabulated or summarised in table 3. In-vitro Dissolution studies were performed for prepared tables using 0.1 N HCl for first two hours followed by phosphate buffer pH 7.4 as a dissolution media at 50 rpm and temperature $37 \pm 0.5^\circ\text{C}$. The In-vitro dissolution profiles of tablets were shown in figure 1-4 (Kinetic Plots) and the dissolution parameters were summarised in table 4. Cumulative % drug release of factorial design formulations F1-F9 at 12 h were 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 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.

Figure 1: Comparative zero order plots for F1-F9.

Figure 2: Comparative first order plots for F1-F9.

Figure 3: Comparative Higuchi plots for F1-F9.

Much variation was observed in the $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ due to formulation variables. Formulation F4 containing 35 mg of HPMCK4M, 60 mg of SCMC showed promising dissolution parameter ($t_{10\%} = 0.350$ h, $t_{50\%} = 2.268$ h, $t_{75\%} = 4.537$ h, $t_{90\%} = 7.530$ h). The difference in burst effect of the initial time is a result of the difference in the viscosity of the polymeric mixtures. As the increase in viscosity results in a corresponding decrease in the drug release, which might be due to the result of thicker gel layer formulation [25].

Table 3: Post-compression parameters for the formulations.

S.No	Formulation Code	Hardness (kg/cm ²)	Thickness (mm)	Friability (%)	% Weight Variation	Drug Content (%)
1	F1	3.51±0.1	2.76±0.12	0.28±0.02	200.3±0.12	99.13±0.47
2	F2	3.50±0.5	2.86±0.14	0.25±0.022	199.72±0.28	98.47±0.53
3	F3	4.01±0.5	2.76±0.12	0.41±0.04	199.2±0.31	98.53±0.37
4	F4	3.78±0.2	2.64±0.16	0.38±0.022	199.51±0.45	99.46±0.44
5	F5	4.04±0.5	2.68±0.12	0.35±0.05	201.0±0.19	99.40±0.300
6	F6	3.82±0.20	2.54±0.26	0.22±0.027	202.1±0.14	98.64±0.35
7	F7	3.51±0.40	2.56±0.14	0.51±0.04	200.6±0.14	99.23±0.32
8	F8	4.07±0.20	2.54±0.16	0.48±0.02	201.1±0.19	99.59±0.31
9	F9	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.

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	F1	5.625	8.455	0.998	2.23	0.106	0.872	24.131	30.775	0.942	0.567	1.352	0.995
2	F2	3.71	8.24	0.999	2.173	0.093	0.921	22.354	30.263	0.95	0.658	1.258	0.999
3	F3	1.12	7.551	0.999	2.101	0.071	0.967	18.858	28.019	0.963	0.74	1.147	0.997
4	F4	1.382	8.335	0.999	2.276	0.133	0.841	18.584	31.103	0.967	0.962	0.966	0.999
5	F5	2.221	8.345	0.997	2.183	0.1	0.927	21.355	30.759	0.95	0.829	1.083	0.996
6	F6	2.57	7.507	0.993	2.075	0.072	0.988	16.332	28.42	0.975	0.865	1.046	0.992
7	F7	3.977	8.223	0.997	2.165	0.09	0.92	22.572	30.195	0.951	0.632	1.282	0.999
8	F8	1.164	7.849	0.999	2.129	0.082	0.94	19.7	29.169	0.958	0.617	1.317	0.974
9	F9	4.119	8.127	0.995	2.134	0.081	0.964	22.659	29.911	0.959	0.524	1.397	0.992

F1 to F9 are factorial formulations, r-correlation coefficient, a-Intercept, b-Slope.

Table 5: Dissolution parameters of rosuvastatin sustained release tablets 32 full factorial design batches.

S.no	Formulation code	Kinetic parameters			
		t10% (h)	t50% (h)	t75% (h)	t90% (h)
1	F1	0.432	2.838	5.672	9.425
2	F2	0.49	3.252	6.503	10.81
3	F3	0.645	4.224	8.444	14.03
4	F4	0.35	2.268	4.537	7.53
5	F5	0.46	3.024	6.041	10.044
6	F6	0.635	4.172	8.342	13.86
7	F7	0.512	3.358	6.717	11.121
8	F8	0.562	3.687	7.382	12.25
9	F9	0.56	3.733	7.468	12.41

Figure 4: Comparative Korsmeyer-peppas plots for F1-F9.

The In -vitro dissolution data of Rosuvastatin SR tablet formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's 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 shown in figure 1,2,3 and 4. It was observed from the above that dissolution of all the tablets followed zero order kinetics with co-efficient 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's square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation, the slope (n) values ranges from 0.524-0.962 that shows Non-Fickian diffusion mechanism. 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 were shown in figure 5-8 for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ using X_1 and X_2 on both the axes respectively. The dissolution data (Kinetic parameters) of factorial formulations F1 to F9 were shown in table 5.

Polynomial equation for 3^2 full factorial designs is given in Equation

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

Where, Y is dependent variable, b_0 arithmetic mean response of nine batches, and b_1 estimated co-efficient 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 ($X_1 X_2$) 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 , C_2).

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

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

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

$$Y_1 = 0.515 - 0.011X_1 - 0.095X_2 - 0.037X_1X_2 + 0.055X_1^2 + 0.0172X_2^2 \text{ (for } t_{10\%})$$

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

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

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

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

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

The positive sign for co-efficient 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, and

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 summarised 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 (Optimised) formulation (F_4) is compared with marketed product (CRESTOR) shows similarity factor (f_2) 89.561, 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 sustained release tablet formulations of Rosuvastatin utilizing the 3^2 factorial design. 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 sustained release 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, 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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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)
C1	0.578	3.792	7.588	12.605	0.589	3.789	7.595	12.597
C2	0.474	3.102	6.21	10.315	0.481	3.117	6.218	10.333

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References

1. Jain S, Mehra NK, Singhai AK, Saraogi GK. Development and evaluation of sustained release matrix tablet of lamivudine. *Int J Pharm Sci Res.* 2011; 2(1): 454-461. DOI: [http://dx.doi.org/10.13040/IJPSR.0975-8232.2\(2\).454-61](http://dx.doi.org/10.13040/IJPSR.0975-8232.2(2).454-61)
2. Singh RR. Design, formulation and *In vitro* evaluation of lamivudine Hcl sustained release tablets. *Int J Res Pharm Nano Sci.* 2014; 3(2): 113-121. Available form: <http://www.ijrpn.com/article/DESIGN-%20FORMULATION%20AND%20IN%20VITRO%20EVALUATION%20OF%20LAMIVUDINE%20HYDROCHLORIDE%20SUSTAINED%20RELEASE%20TABLETS.pdf>
3. Gunda RK, Kumar JNS, Babu CH, Anjaneyulu MV. Formulation development and evaluation of lamotrigine sustained release tablets using 3^2 factorial design. *Int J Pharm Sci Res.* 2015; 6(4): 1746-1752. DOI: [https://doi.org/10.13040/IJPSR.0975-8232.6\(4\).1746-52](https://doi.org/10.13040/IJPSR.0975-8232.6(4).1746-52)
4. Bankar GS, Rhodes CT. Eds. Modern pharmaceuticals. 3rd edn. *Marcel Dekker, Inc. New York*; 1996. p. 668-9.
5. Lachmann L, Lieberman HA, Kanig JL. The theory & practice of industrial pharmacy. *Varghese Publishing House, Bombay, 3rd Edition.* 1991; p. 430. Available form: <https://www.worldcat.org/title/theory-and-practice-of-industrial-pharmacy/oclc/148231775?referer=di&ht=edition>
6. Gunda RK, Kumar JNS. Formulation development and evaluation of zidovudine sustained release tablets using 3^2 factorial design. *Der Pharm Sin.* 2015; 6(6):59-67. DOI: <https://doi.org/10.18579/jpcrk/2017/16/4/115881>
7. Kumar JNS, Satyaprasad B, Venkateswarlu G, Brahma CH, Gunda RK. Formulation development and evaluation of metoprolol succinate sustained release tablets using 3^2 factorial design. *Der Pharm Let.* 2015; 7(7):148-157. Available from: <https://pdfs.semanticscholar.org/37d0/45b5df404c230c26230f633912e4927e8cfb.pdf>
8. Gunda RK. Formulation development and evaluation of rosiglitazone maleate sustained release tablets using 3^2 factorial design. *Int J Pharm Tech Res.* 2015; 8(4):713-724. Available from: https://www.researchgate.net/publication/281460230_Formulation_Development_and_Evaluation_of_Rosiglitazone_Maleate_Sustained_Release_Tablets_using_3_2_Factorial_Design
9. Gunda RK, Kumar JNS, Brahma CH, Viragandham S. Design, formulation and evaluation of lamivudine controlled release tablets. *Pharm Bio Eva.* 2015; 2(4): 110-121. Available from: <http://www.onlinepbe.com/index.php/PBE/article/view/30>
10. Prakash P, Porwal M, Saxena A. Role of natural polymers in sustained release drug delivery system: application and recent approaches. *Int Res J of Pharmacy.* 2011; 2(9):6-11. Available from: <https://irjponline.com/admin/php/uploads/vol2-issue9/2.pdf>
11. Gunda RK, Kumar JNS, Brahma CH, Viragandham S, Naga Prashant K. Design, formulation and evaluation of atenolol gastro retentive floating tablets. *Asian J Pharm.* 2015; 9(4):S34-S42. DOI: <http://dx.doi.org/10.22377/ajp.v9i4.484>
12. Rhodes CT, Robinson JR. Sustained and controlled drug delivery system; In Banker GS, editor, *Modern Pharmaceutics*, 4th ed., *USA: Marcel Dekker.* 2003; pp 503-505.
13. Kapse Vidya N, Chemate SZ, Dharashive VM. Formulation development and solubility enhancement of rosuvastatin calcium tablet prepared by complexation with β -cyclodextrin by kneading method. *Int J Pharm Sci Res.* 2016; 7(12): 4882-4892. DOI: [https://doi.org/10.13040/IJPSR.0975-8232.7\(12\).4882-92](https://doi.org/10.13040/IJPSR.0975-8232.7(12).4882-92)
14. Gupta MM, Pandey S, Chauhan BS, Gupta N. Design, development and evaluation of rosuvastatin calcium and diltiazem hydrochloride bilayer tablet using combination concept of sustained layer with conventional layer. *Turk J Pharm Sci.* 2014; 11(3): 269-284. Available from: <http://turkjps.org/archives/archive-detail/article-preview/design-development-and-evaluation-of-rosuvastatin-/12333>
15. Sanjana, Ahmed MG. Development and in vitro evaluation of rosuvastatin tablets by floating drug delivery system. *Asian J Pharm.* 2017; 11(2): S260- 64. DOI: <http://dx.doi.org/10.22377/ajp.v11i02.1262>
16. Sreelatha P, Manohar Babu S, Raja Jaya Rao Y. Formulation and evaluation of matrix type rosuvastatin sustained release tablets. *Int J Pharm Ana Res.* 2014; 3(4):370-383. Available from: http://www.ijpar.com/sites/default/files/articles/IJPAR_14_903%20Sreelatha.pdf
17. Sarfraz RM, Ahmad M, Mahmood A, Minhas MU,

- Yaqoob A. Fabrication and evaluation of rosuvastatin calcium fast disintegrating tablets using β -cyclodextrin and superdisintegrants. *Trop J Pharm Res.* 2015; 14(11): 1961-68. DOI: <https://doi.org/10.4314/tjpr.v14i11.2>
18. Quasim SZU, Naveed A, Abbas SA, Irfan MA. Formulation and evaluation of rosuvastatin calcium oral floating tablets. *Research J Pharm Tech.* 2012; 5(11): 1389 -1392. Available from: <https://search.proquest.com/openview/e7e8addbaa088a61ea2b3e58be4bb61a/1?pq-origsite=gscholar&cbl=1096441>
  19. Sarfraz RM, Ahmad M, Mahmood A, UsmanMinhas M, Yaqoob A. Development and evaluation of rosuvastatin calcium based microparticles for solubility enhancement: an in vitro study. *Advances in Poly Tech.* 2017; 36(4):433-441. DOI: <https://doi.org/10.1002/adv.21625>
  20. Gunda RK, Kumar JNS, Satyanarayana V, Satyprasad B. Formulation development and evaluation of carvedilol phospophate gastro retentive floating tablets. *Int Res J Pharm.* 2016; 7(1):44-51. DOI: <https://doi.org/10.7897/2230-8407.0718>
  21. Kharia, Hiremath SN, Singhai K, Omray K, Jain K. Design and optimization of floating drug delivery system of acyclovir. *Indian J Pharm Sci.* 2010; 72(5): 599-606. DOI: <https://doi.org/10.4103/0250-474X.78527>
  22. Gunda RK, Manchineni PR, Dhachinamoorthi D. Design, development, and in vitro evaluation of sustained release tablet formulations of olmesartan medoxomil. *MOJ Drug Des Develop Ther.* 2018; 2(3):164-169. DOI: <https://doi.org/10.15406/mojddt.2018.02.00043>
  23. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci.* 1963; 51:1145-9. DOI: <https://doi.org/10.1002/jps.2600521210>
  24. Peppas NA. Analysis of fickian and non-fickian drug release from polymers. *Pharm Acta Helv.* 1985; 60:110-1. PMID:<https://www.ncbi.nlm.nih.gov/pubmed/4011621>
  25. Dortunc B, Gunal N. Release of acetazolamide from swellable HPMC matrix tablets. *Drug Dev Ind Pharm.* 1997; 23:1245-9. DOI: <https://doi.org/10.3109/03639049709146165>

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