Available online at www.pharmacie-globale.info ISSN 0976-8157

Research Article

PHARMACIE GLOBALE

INTERNATIONAL JOURNAL OF COMPREHENSIVE PHARMACY

OPTIMIZATION OF SUPER DISINTEGRANTS AND SUBLIMING AGENT ON DISSOLUTION RATE OF ROSUVASTATIN ORODISPERSIBLE TABLETS BY USING A 3^2 FACTORIAL DESIGN

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Received: 10 October 2010; Revised: 28 December 2010; Accepted: 2 January 2011; Available online: 11 January 2011

ABSTRACT

The aim of this work was to develop Rosuvastatin Orodispersible tablets by exploiting the solubilizing effect of hydroxy propyl β-cyclodextrin (HP-β-CD). Drug–CD complex systems, prepared bydifferent techniques, were characterized by differential scanningCalorimetry (DSC), X-ray diffractometry, and Fourier transforminfra-red (FT-IR) spectroscopy. The inclusion complex containing RST: HP-β-CD (1:1) was formulated into Orodispersible tablets using superdisintegrants like sodium starch glycolate (SSG) and subliming agent such as camphor. Tablets containing RST-HP-β-CD inclusion complex were prepared by direct compression and evaluated for various post compression parameters like hardness, friability, weight variation, thickness, drug content and in-vitro dissolution. 3^2 factorial design was applied to systematically optimize the drug release profile. The proportion of subliming agent Camphor (X_1) and superdisintegrant sodium starch glycolate (X_2) were selected as independent variables. The % friability (Y_3), Disintegration time (Y_2) and drug release in 15 mins (Y_3) was selected as dependent variable. The optimization was carried out using intensive grid and ANOVA. The derived polynomial equations for Y_1, Y_2 and Y_3 were verified by two check point formulations, which showed that factor X_1 and X_2, significantly affects the studied dependent variables.The amount of superdisintegrants didn't show any significant effect on percentage friability, disintegration time and % release but data analysis showed that camphor alone had significant effect on friability.

Keywords: 3^2 factorial design, Rosuvastatin Calcium, hydroxy propyl β-cyclodextrin, superdisintegrant.

INTRODUCTION

Patients often experience inconvenience in swallowing conventional tablets when water is not available. Furthermore, patients who have swallowing problems encounter difficulties in taking tablets[1], particularly pediatric and geriatric patients. Such problems can be resolved by means of mouth disintegrating tablet. This tablet disintegrates instantaneously when put on tongue, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[2].

Rosuvastatin Calcium (RST), a poorly water-soluble 3-hydroxy3-methyl glutaryl CoA (HMG-CoA) Reductase inhibitor, a potent lipid-lowering agent, and used as hypolipidemic agent. It is also used in the treatment of osteoporosis, benign prostatic hyperplasia, and Alzheimer's disease[3]. RST is crystalline in nature so it reduces its aqueous solubility and finally that results in abnormal bioavailability of 20%[4,5]. Cyclodextrins are cyclic oligosaccharides, containing six, seven or eight glucopyranose units (α, β or γ respectively) obtained by the enzymatic degradation of starch. These are torus shaped molecules with a hydrophilic outer surface and lipophilic central cavity, which can accommodate a variety of lipophilic drugs. Cyclodextrins are able to form inclusion complexes with poorly water-soluble drugs and have been shown to improve pharmaceutical properties like solubility, dissolution rate, bioavailability, stability and even palatability without affecting their intrinsic lipophilicity or pharmacological properties. Natural cyclodextrins have limited water solubility. However, a significant increase in water solubility has been obtained by alkylation of the free hydroxyl groups of the cyclodextrins resulting in hydroxyl alkyl, methyl and sulfobutyl derivatives. The ability of cyclodextrins to form inclusion complexes may also be enhanced by substitution on the hydroxyl group[6,7].

A Factorial Design for two factors at three levels each 3^2 is considered identical to a two factor composite design[8,9]. A computer aided optimization process using a 3^2 factorial design was employed to investigate the effect of two independent variable (factors) i.e.; amount of subliming agent: camphor (CAM) and amount of superdisintegrants; Sodium starch glycolate (SSG). The disintegration time,

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release after 15 minutes and percentage friability were taken as the response variables.

MATERIALS AND METHODS

Chemicals

Rosuvastatin Calcium (RST) was gifted from Astron Research limited. Ahmedabad, India. Hydroxyl propyl Beta-cyclodextrin was obtained from Lyka laboratory, Ankleshwar, Gujarat, India. Sodium starch glycolate, Crosspovidone and Crosscarmellose were purchased from S D Fine chemicals ltd. Mumbai. All other chemicals and reagents used were of analytical grade.

Methods

Phase Solubility Studies[10]

Phase solubility studies were carried out according to the method reported by Higuchi and Connors[8]. An excess of Rosuvastatin Calcium RST (5 mg) was added to 10 ml portions of distilled water, each containing variable amount of HP-β-CD such as 0, 2, 4, 6, 8, and 10 milimoles/liter. All the above solutions with variable amount of HP-β-CD were shaken in rotary shaker for 72 hours. After shaking, the solutions were filtered and their absorbance was noted at 248nm. The apparent 1:1 stability constants were calculated from the phase solubility diagrams, according to the following equation:

$$K_c = \frac{slope}{S_o(1 - slope)}$$

Preparation of Cyclodextrin Inclusion Complexes

All the binary mixtures were prepared in a 1:1 molar ratio of drug and HP-β-CD on the basis of the results obtained from the preliminary phase solubility studies.

Physical mixture[11]

The physical mixture of Rosuvastatin-cyclodextrin prepared by mixing RST with HP-β-CD in 1:1 molar ratio in a mortar for about one hour with constant trituration, passed through sieve #100.

Kneading method[12, 13]

RST with HP-β-CD in 1:1 molar ratio was taken. First cyclodextrin is added to the mortar, small quantity of 50% ethanol is added while triturating to get slurry like consistency. Then slowly drug is incorporated into the slurry and trituration is further continued for one hour. Slurry is then air dried at 25 °C for 24 hours, pulverized and passed through sieve #100.

Co-evaporation method[14, 15]

Inclusion complex (1:1) was prepared by dissolving equimolar amount of HP-β-CD and RSTC in required amount of 50% aqueous ethanol. The solution was stirred till a clear solution was observed and the obtained solution was then evaporated under vacuum at a temperature of 45°C and 100 rpm. The solid residues was further dried completely at 45°C for 48h, the dried complex was pulverized into a fine powder and sieved through sieve #100.

Precipitation method[16, 17]

Inclusion complex of RST and hydroxy propyl β-cyclodextrin in 1:1 molar ratio was prepared by drug and CD, which dispersed in water and the solution, was heated to obtain concentrated, viscous and translucent liquid. The solution was left to give a precipitation of inclusion complex. Precipitate obtained was separated and dried to get solid inclusion complex.

In Vitro dissolution studies for RST -CD complexes

In-vitro dissolution of RST inclusion complex was studied in USP XXIV dissolution apparatus (Electrolab) employing a paddle stirrer. 900 ml of phosphate buffer of pH 6.8 was used as dissolution medium at 50 rpm. The temperature of 37 ± 0.5 °C was maintained throughout the experiment. Complex equivalent to 5 mg of RST was used in each test. 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 248 nm after suitable dilution with phosphate buffer. The amount of RST released was calculated and plotted against time and compared with pure drug. The % drug release profile of inclusion complexes shown in Table **2** and Figure **2**.

Characterization of Inclusion Complex

The kneaded inclusion complex of 1:1 (RST: HP-β-CD)shown highest dissolution rate so that complex was further characterized by Fourier Transform infrared (FTIR) Spectroscopy, Differential Scanning Calorimetry (DSC), Powder X-ray Diffractometry (PXRD). Fourier transform IR spectra were recorded on FT/IR-4100 type A. The samples were analyzed by DSC using a Mettler Toledo SR system. The powder X-RD patterns of drug, hydroxy propyl β-Cyclodextrin, and complexe were recorded by using automated Philips Holland -PW 1710 scanner with filter Cu radiation over the interval 5-60°/2θ. The operation data were as follows: voltage 35 kV, current 20 mA, filter Cu and scanning speed 1° / min.

Formulation of Rosuvastatin Orodispersible tablet

The Kneaded complex of RST-HP-β-CD was prepared into Orodispersible tablet by direct compression method containing RST-CD complex equivalent to 5mg of RST. The all excipientswere passed through sieve # 85. All the above ingredients were properly mixed together. Talc and magnesium stearate were mixed. The mixture was then compressed in to tablet by using rotary single punch tablet machine. The formulation of Rosuvastatin Orodispersible tablet is shown in table **1**.

Table 1. Composition of All the Formulation (Batch S1 to S9)

Ingredient (mg/tablet)	S1	S2	S3	S4	S5	S6	S7	S8	S9
	Kneaded Method								
Drug-CD complex equivalent to 5 mg Rosuvastatin Ca	20.6	20.6	20.6	20.6	20.6	20.6	20.6	20.6	20.6
Sodium starch glycolate	10	15	20	10	15	20	10	15	20
Camphor	5	5	5	10	10	10	15	15	15
Mannitol	20	20	20	20	20	20	20	20	20
Aspartame	5	5	5	5	5	5	5	5	5
Mg. Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Avicel PH 102 up to.....	150	150	150	150	150	150	150	150	150
Total Avg. Weight (mg)	150	150	150	150	150	150	150	150	150

Evaluation of Tablet[18]

The prepared tablets were evaluated for weight variation, hardness, thickness, % friability and disintegration time. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in

terms of kg/cm^2. The hardness of 6 tablets was determined using the Monsanto hardness tester. Friability was determined by first weighing 10 tablets after dusting and placing them in a friability tester (Roche friabilator), which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of tablet was recorded and the percent friability was calculated. Disintegration test for all batches was carried out in distilled water at 37 ± 0.5 °C by using USP disintegration test apparatus.

In-vitro dissolution study[18]

In-vitro dissolution of Orodispersible tablet was studied in USP XXIV dissolution apparatus (Electrolab) employing a paddle stirrer. 900 ml of phosphate buffer of pH 6.8 was used as dissolution medium. The stirrer was adjusted rotate at 50 rpm. The temperature of dissolution media was previously warmed to 37 ± 0.5 °C and was maintained throughout the experiment. 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 248 nm after suitable dilution with phosphate buffer pH 6.8. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Percentage amount of Rosuvastatin released was calculated and plotted against time.

3^2 Factorial Design[8, 9]

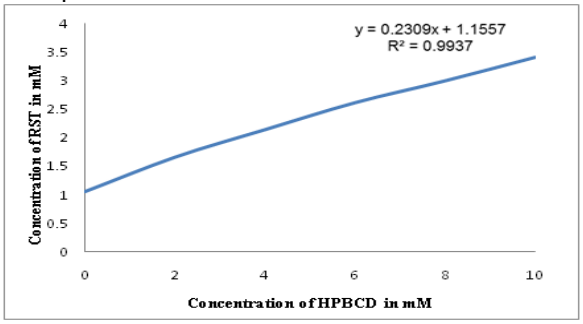
A 3^2 randomized Factorial Design was used, in this design 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations. The proportion of superdisintegrant sodium starch glycolate (X_2) and subliming agent Camphor (X_1) were selected as independent variables. The % friability (Y_1), Disintegration time (Y_2) and drug release in 15 mins (Y_3) was selected as dependent variable. The percentage friability showed no definite relationship with either amount of subliming agent or superdisintegrants. The optimization was carried out using intensive grid and ANOVA.

RESULTS AND DISCUSSION

Phase Solubility Studies

The phase solubility diagrams of RST Ca: HP-β-CD was obtained by plotting the changes in guest solubility as a function of HP-β-CD concentration. The solubility curves were classified as the AL type according to Higuchi and Connors[8]. Figure **1** show that the apparent solubility of RST Ca increases linearly as a function of HP-β-CD over the entire concentration range and was the characteristic of the AL-type of curve, which suggests that water-soluble complex, was formed in solution.

Figure 1. Phase Solubility Diagram for Rosuvastatin Ca with HP-β-CD at 25°C



The slope values obtained were less than 1, which indicates that inclusion complex in the molar ratio of 1:1 between the guest and the host molecule was enough to increase the solubility of poor water soluble Rosuvastatin. The phase solubility profile indicated that the solubility of Rosuvastatin Ca was significantly increased in the presence of HP-β-CD.

Characterization of Inclusion Complex

As shown Figure **3**; it shows that IR characteristic peaks of drug at 564, 1335, 2360 and 2973 cm^{-1} drastically modified or absence due to formation of complex between drug and cyclodextrin. The DSC thermogram Figure **4** of RST-HP-β-CD complex showed endothermic peak at different temperature or absence of sharp endothermic peak by different method of preparation, which is different from the pure drug, which gives clear evidence that there is formation of the complex. Figure **5** shows the X-RD pattern of pure drug presented several diffraction peaks at 11.2, 15.7, 16.6, 19.4, 20.4, 21.8 and 23.4 indicating the crystalline nature of the drug.

Figure 3. FTIR spectra of (A) Rosuvastatin pure (B) Pure HP-β-CD (C) Physical mixture(D) Kneading method

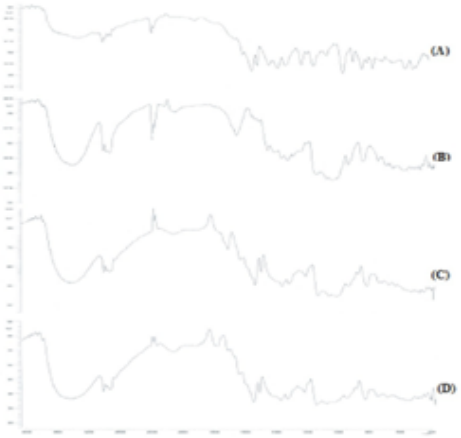


Figure 4. DSC Thermogram of (A) Rosuvastatin pure (B) Pure HP-β-CD (C) Physical mixture(D) Kneading method

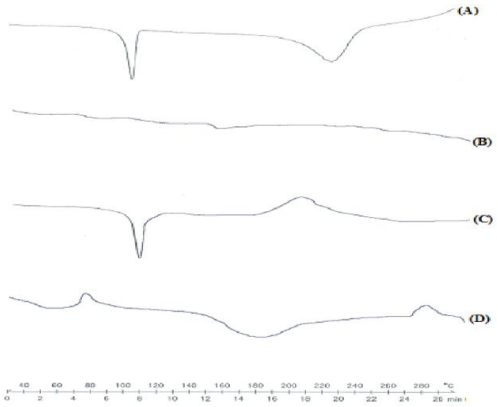
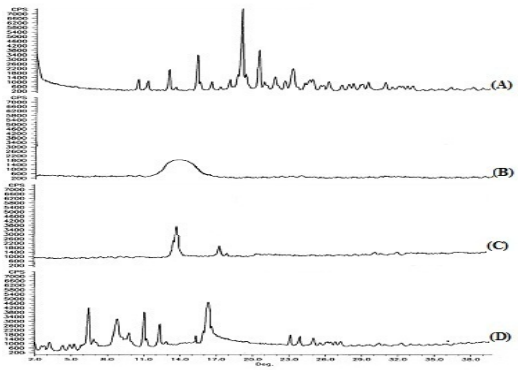


Figure 5. XRD Patterns of (A) Rosuvastatin pure (B) Pure HP-β-CD (C) Physical mixture (D) Kneading method



The PM shows the characteristic peaks of the drug at identical angles, which proves that no interactions take

place during mixing. Almost all drug diffraction peaks were slightly reduced in intensity in the kneaded products with HP-β-CD with respect to the corresponding physical mixture, thus revealing some interaction between the components, as a consequence of their intimate contact obtained during complex preparation.

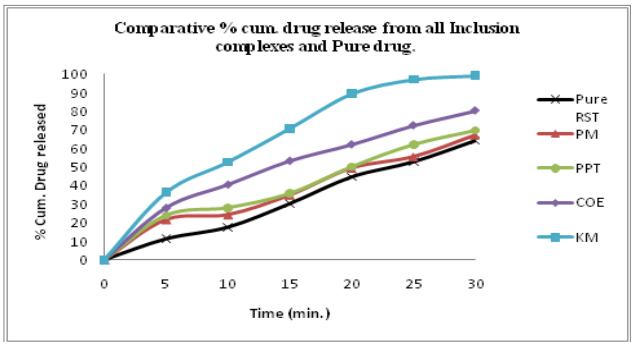
In-vitro dissolution study

Since the presence of cyclodextrin showed that there was decreased in extinction coefficient of the drug, since the hydroxy propyl β-cyclodextrin is highly water soluble it was expected to instantly dissolve in the medium under the condition of dissolution test. Kneaded complex showed highest dissolution profile among all complex 89.46% drug release in 20 min. that shows characteristic improvement in dissolution rate of drug from Kneaded inclusion complex as compared to physical mixture and pure drug. The % drug release profile of inclusion complexes shown in Table **2** and Figure **2**.

Table 2. *In-vitro* % Drug Release Profile of Inclusion complexes and pure drug

Time (min)	Cumulative % drug Release				
	PM	PPT	COE	KM	Pure
5	21.6	24.03	28.08	36.34	11.3
10	24.24	28.12	40.56	52.73	17.58
15	34.81	35.78	53.31	70.81	30.28
20	49.29	50.2	62.1	89.46	44.69
25	55.45	62.15	72.32	97.21	52.87
30	67.04	69.79	80.26	99.26	64.28

Figure 2. Comparative % Cum. drug release from Inclusion complexes and pure drug.



Evaluation of tablet

Hardness, thickness, weight variation and drug content of tablet are given in table **3**. The hardness of tablet was in the range 3.9 - 4.5 kg/cm². The percent weight loss in the friability test was found to be near about 1 %. The tablets were found to contain the Rosuvastatin within 100 ± 2% of the label claim. The dissolution profile of all prepared Orodispersible tablets from complex are shown in table **5** and figure **6**. It shows that there is a maximum drug release from tablets prepared from kneaded product by using sodium starch glycolate as a superdisintegrant. The Dissolution profile of optimized tablet formulation S9 shows higher dissolution (96.54% drug release in 15 min.) than all other formulation.

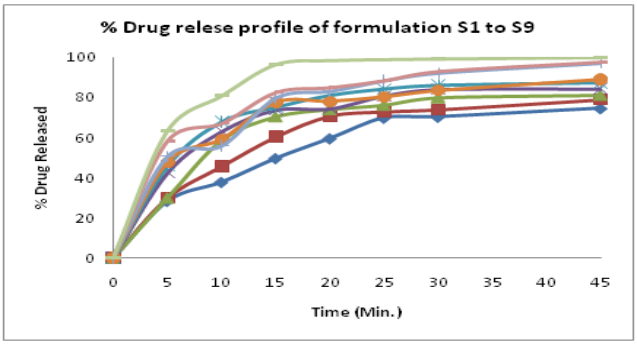
Table 3. Tablet Properties of Rosuvastatin Orodispersible Tablets

Batch	Formulation Composition		Thickness (mm)	Hardness (Kg/cm²)	Weight Variation (mg)	Drug content (%)	Wetting Time
	CAM	SSG					
S1	5	10	4.02 ±0.030	4.2 ± 0.23	148.31 ± 1.61	99.40	142±1.14
S2	5	15	4.17±0.012	4.5 ± 0.52	149.19 ± 1.32	95.50	81±1.673
S3	5	20	4.19±0.01	4.4 ± 0.29	150.42 ± 1.47	96.34	52±2.00
S4	10	10	4.00±0.011	4.1± 0.52	151.92 ± 1.46	97.43	43±1.483
S5	10	15	4.5±0.042	3.9± 0.59	148.89 ± 2.11	99.91	25±1.581
S6	10	20	4.11±0.020	4.3 ± 0.76	147.33 ± 1.68	98.25	19±1.541
S7	15	10	4.43 ±0.032	4.3 ± 0.72	149.06 ± 1.20	99.66	28±2.236
S8	15	15	4.01 ±0.04	4.2 ± 0.53	149.86 ± 1.42	99.44	21±3.050
S9	15	20	4.24 ±0.062	4.1 ± 0.28	150.63 ± 1.63	98.22	9±1.673

Table 5. *In-vitro* Drug Release Profile of Formulation S1 to S9

Time (min)	Cumulative % drug Release								
	S1	S2	S3	S4	S5	S6	S7	S8	S9
5	28.34	29.84	30.02	42.42	45.81	47.82	50.56	58.44	63.44
10	37.78	45.68	58.83	63.09	67.9	59.26	55.88	67.09	80.83
15	49.65	60.45	70.6	73.8	75.23	77.68	79.89	82.67	96.54
20	59.56	70.84	74.24	74.45	81.12	78.1	83.22	85.04	98.46
25	69.85	72.97	76.4	80.89	84.32	80.34	88.45	88.54	98.96
30	70.33	74.03	80.08	84.11	86.13	83.45	92.28	93.13	99.26
45	74.56	78.99	81.34	84.41	87.41	88.99	97.24	97.84	99.98

Figure 6. % Drug Released Profiles of Orodispersible tablets of S1 to S9



Statistical Data Analysis by 3² Factorial Design[8]

Various computations for the current optimization study using RSM were carried out, employing software Design Expert Version 7 and MS EXCEL. Statistical second order models including interaction and polynomial terms were generated for all the response variables. The coefficients of the polynomial equations generated using MLRA for disintegration time (DT), release after 15 minutes (% Rel_{min}) and % friability of the blends containing varying concentration of camphor and sodium starch glycolate studied are listed in Table **6** along with the values of r^2.

The general form of the model is represented as in equation given below.

$$Y = \beta o + \beta 1X1 + \beta 2X2 + \beta 3X1X2 + \beta 4X1^2 + \beta 5X2 + \beta 6\,1X2^2 + \beta 7\,X1^2X2 + \beta 8X1^2X2^2$$

Where Y is the dependent variable, βo is the arithmetic mean response of the nine runs, β1 to β8 are the coefficient computed from the observed experimental values of Y, and X1 and X2 are coded levels of independent variables. The interaction term X1X2 show how response changes when the two factors are simultaneously changed and the polynomial terms Xi^2 (i = 1, 2) are included to investigate nonlinearity. Subsequently, feasibility as well as grid search method was performed to locate the composition of optimum formulation. Also, three

dimensional response surface graphs and contour plots were drawn in MS- Excel using the output files generated by the Design Expert Version 7 software.

Validation of Optimization Model

Nine optimum formulations were selected by intensive search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations. The criterion for selection of formulation was primarily based on the highest possible valuesof disintegration time, drug release after 15 minutes and friability as shown in table **6**. The formulation corresponding to these formulations were prepared and evaluated for various responses. The resultant experimental data of responses were subsequently quantitatively compared with the predicted values. Also, linear regression plots between observed and predicted values of the responses were attempted using MS-Excel, forcing the line through the origin.

Table 6. Values of the coefficients for the polynomial equations and r^2 for various response variables of Orodispersible formulations

Coefficient code	Polynomial coefficient values for response variables		
	% friability	DT (sec)	% Release in 15 mins
B_0	+1.20	+59.56	+76.16
B_1	+0.24	-40.83	+12.77
B_2	-0.24	-24.17	+6.77
B_3	+0.083	+17	-3.13
B_4	+0.0085	+10.28	-0.95
B_5	+0.042	+1.28	+0.18
B_6	-0.053	-5.33	+2.57
B_7	+0.027	-2.17	+1.47
B_8	+0.011	-0.61	+0.15
r^2	0.9954	0.9872	0.9902

Optimization Results

Design of experiment (DOE) has been widely used in pharmaceutical field to study the effect of formulation variables and their interaction on response variable. In the current study, a 3^2 full factorial design was used. All the polynomial equations were found to be highly statistical significant as determined by ANOVA. The response surface plotted for all the three response variables shows that with the increasing amount of camphor and sodium starch glycolate, the disintegration time and percent drug release also increased linearly. Application of two-way ANOVA based factorial analysis indicates that high amount of camphor and sodium starch glycolate has a significant influence on disintegration time and percent drug release. Subsequent application of one-way ANOVA showed a statistically significant difference amongst the observed data for disintegration time and percent release, ratifying the significant positive influence of each factor on both disintegration time and percent release in 15 minutes (table **4**).

It is seen when higher percentage of camphor is used, higher porosity is expected in tablets. Due to increased porosity the water uptake is also increased which further facilitates disintegration. It is obvious that in presence of high concentration of superdisintegrants, sodium starch glycolate faster disintegration is facilitated. However, percentage friability of all the formulation gave nonlinear results but it was observed that with highest level of camphor, the % friability was found to be more than 1% due to increased porosity.

Table 4. Formulation, Physical Properties and Dissolution Characteristics in 3^2 Factorial Design

Batch Code	Coded values		% friability	Disintegration time(sec.)±SD	% Release in 15 min.
	X1	X2			
S1	-1	-1	0.595±0.044	160±2.588	49.65
S2	-1	0	0.630±0.046	105±2.236	60.45
S3	-1	+1	0.583±0.058	67±3.536	70.60
S4	0	-1	0.822±0.029	55±2.303	73.80
S5	0	0	0.782±0.031	34±1.673	75.23
S6	0	+1	0.813±0.023	28±2.881	77.68
S7	+1	-1	1.048±0.019	40±2.775	79.89
S8	+1	0	0.957±0.047	32±2.387	82.67
S9	+1	+1	1.035±0.086	15±3.209	96.54

Translation of coded values to actual values

Coded values	Actual values	
	X1 Amount of camphor	X2 Amount of Sodium starch glycolate
-1	5	10
0	10	15
+1	15	20

The amount of superdisintegrants didn't show any significant effect on percentage friability, disintegration time and % release. Application of one-way ANOVA based analysis showed that camphor alone had significant effect on friability. The response surface plot which shows effect of superdisintegrant and subliming agent on friability, disintegration time and % release as shown in figure **7**, **9**, **11** respectively. Similarly, The Contour plot which shows effect of superdisintegrant and subliming agent on friability, disintegration time and % release as shown in figure **8**, **10**, **12** respectively.

Figure 7. Response surface plot for % Friability

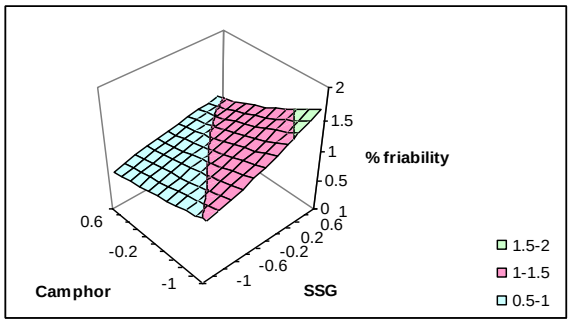


Figure 8. Contour Plot for % Friability

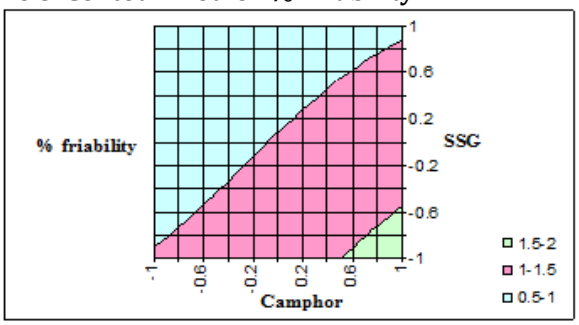


Figure 9. Response Surface Plot for Disintegration time (Sec.)

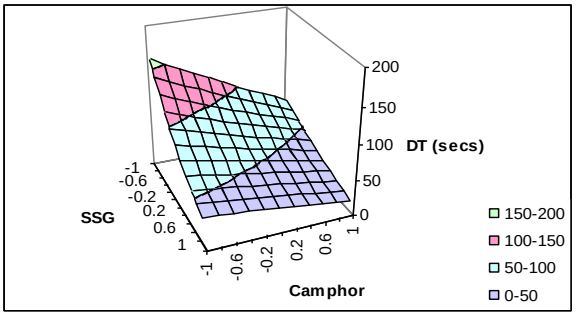


Figure 10. Contour Plot for Disintegration time (Sec.)

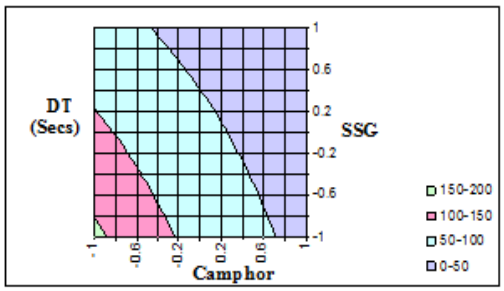


Figure 11. Response Surface Plot for % Drug release in 15 mins.

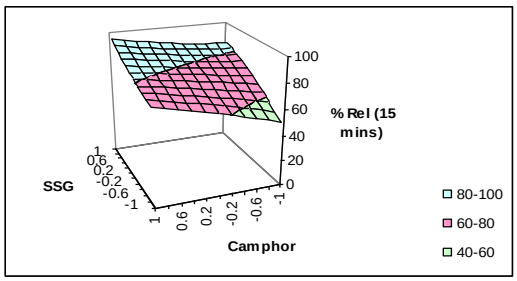
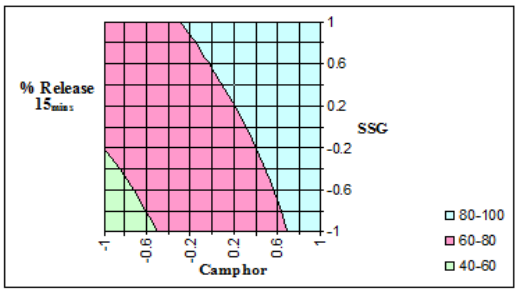


Figure 12. Contour Plot for % Drug release in 15 mins.



CONCLUSION

This study shows that there is formation of a HP-β-CD:Rosuvastatin complex in aqueous solution and this complex, prepared by the various inclusion complexation methods, also exist in the solid state. The inclusion complex prepared with HP-β-CD by kneading method showed highest solubility and fastest dissolution profile (more than 90% drug release in 15 min). 3^2 factorial design was applied to systematically optimize the drug release profile. The amount of superdisintegrants didn't show any significant effect on percentage friability, disintegration time and % release but data analysis showed that camphor alone had significant effect on friability. The improved dissolution rate may be as a result of the increase in solubility, brought about by complexation. From the results we can assume that the aqueous solubility and dissolution rate of Rosuvastatin can be significantly increased by forming an inclusion complex with HP-β-CD and Orodispersible tablets can be developed successfully by using combination of superdisintegrant and subliming agent.

ACKNOWLEDGMENT

We are sincerely thankful to Shree Dhanvantary Pharmacy College, Kim, Surat, for providing us Infrastructure facilities and moral support to carry out this research work. I sincerely express my gratitude to Astron Research limited, Ahmedabad for providing Rosuvastatin Calcium as a gift sample. We are also grateful to Lyka laboratory, Ankleshwar, for providing us Hydroxy Propyl Beta-cyclodextrin.

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