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DEVELOPMENT AND EVALUATION OF ORODISPERSIBLE TABLETS OF ROSUVASTATIN CALCIUM-HP-β-CD INCLUSION COMPLEX BY USING DIFFERENT SUPERDISINTEGRANTS

Akbari B.V[1]*, Valaki B. P[1]., Maradiya V. H[1], Akbari A.K[1], G. Vidyasagar[2]
*Singhania University, Pachari Bari, Jhunjhunu, Rajasthan.
[1]Shree Dhanvantary Pharmacy College, Kim, Surat, Gujarat, India.
[2]Dean, Faculty of Pharmaceutical Sciences, Kachchh University, Bhuj, Kutch, Gujarat.
Email: bhaveshakbari83@gmail.com

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ABSTRACT

Commercial tablets of Rosuvastatin Calcium exhibit unsatisfactory dissolution profiles and, consequently, problems of absorption and poor bioavailability. Rosuvastatin Calcium (RST), a poorly water-soluble 3-hydroxy3-methyl glut aryl CoA (HMG-CoA) Reductase inhibitor through inclusion complexation with hydroxy propyl β-cyclodextrin (HP-β-CD). 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 by different techniques, were characterized by differential scanning Calorimetry (DSC), X-ray diffractometry, and Fourier transform infra-red (FT-IR) spectroscopy. The inclusion complex containing RST: HP-β-CD (1:1) was formulated into tablets using superdisintegrants like sodium starch glycolate, Crosspovidone and Crosscarmellose. 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. A significant improvement of the drug dissolution profile was achieved from tablets containing drug–CD systems (Kneaded products showed the best dissolution profiles, reaching more than 97.46% drug release in 20 min.). The stability of tablets was studied and no significant changes were detected in the dissolution profile of tablets after 1 month.

KEY WORDS: Hydroxy propyl β-cyclodextrin, Rosuvastatin Calcium, Inclusion Complex, Orodispersible tablets.

INTRODUCTION

The rate of absorption and bioavailability of poor water soluble drugs is often controlled by the rate of dissolution of the drug in the gastrointestinal tract. Many technological methods of enhancing the dissolution characteristics of slightly water-soluble drugs are solid dispersions, micronization, solvent deposition, prodrugs, use of surfactants and inclusion complexation etc. Among the various methods, cyclodextrin complexation is an industrially accepted technique[1].

Rosuvastatin Calcium (RST), a poorly water-soluble 3-hydroxy3-methyl glut aryl CoA (HMG-CoA) Reductase inhibitor, a potent lipid-lowering agent, and used as hypo lipidemic agent. It is also used in the treatment of osteoporosis, benign prostatic hyperplasia, and Alzheimer's disease[2]. RST is crystalline nature so it reduces its aqueous solubility and finally that results in an oral bioavailability of 20%. After oral administration of RST, the peak plasma Concentration is reached within 3–5 h, the volume of distribution is 1.1-1.4 liter/Kg, and plasma protein binding is 90%. RST is extensively metabolized by oxidation, lactonisation, and glucuronidation and the metabolites are eliminated by biliary secretion and direct secretion from the blood to the intestine[3, 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 sulfo butyl derivatives. The ability of cyclodextrins to form inclusion complexes may also be enhanced by substitution on the hydroxyl group[6, 7].

The objective of present study is to prepare inclusion complexes of Rosuvastatin Calcium with cyclodextrins by different methods such as physical, kneading and co-evaporation, precipitation method and increase the solubility of Rosuvastatin Calcium (RST) for improvement of dissolution rate and bioavailability of the drug.

EXPERIMENTAL STUDIES

MATERIALS

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 purchase from S. D. Fine chemicals ltd. Mumbai. All other chemicals and reagents used were of analytical grade.

METHODS

Phase Solubility Studies[8]

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 248 nm. The apparent 1:1 stability constants were calculated from the phase solubility diagrams, according to the following equation:

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

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[9, 10]

The physical mixture of Rosuvastatin-cyclodextrin prepared by mixing RST with HP-β-CD in 1:1 molar ratio were in a mortar for about one hour with constant trituration, passed through sieve No. 100.

Kneading method[9, 10]

RST with HP-β-CD in 1:1 molar ratio were 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 No. 100.

Co-evaporation method[10, 11]

Inclusion complex (1:1) was prepared by dissolving equimolar amount of HP-β-CD and RST Ca 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 48 h, the dried complex was pulverized into a fine powder and sieved through sieve No. 100.

Precipitation method[11, 12]

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.

Drug Content Estimation[13]

100 mg of drug HP-β-CD complex was accurately weighed and transferred to 100 ml volumetric flask and volume was made up to the mark with methanol. From this 1ml was taken in 10 ml volumetric flask and the volume is adjusted up to the mark with same solvent. The absorbance of the solution was measured at 248 nm using appropriate blank. The drug content of Rosuvastatin Calcium was calculated using calibration curve.

Fourier Transform infrared (FTIR) Spectroscopy[13, 14]

Fourier transform IR spectra were recorded on FT/IR-4100 type A. The spectra were recorded for Rosuvastatin, hydroxy propyl β-Cyclodextrin physical mixture, kneaded, Co-evaporation and precipitation method. Samples were prepared in KBr disc (2 mg sample in 200 mg KBr).The scanning range was 400-4000 cm^{-1}, resolution was 4 cm

Differential Scanning Calorimetry (DSC) [13, 14]

The samples were analyzed by DSC using a Mettler Toledo SR system. The samples (5 mg each) were placed into pierced aluminum container. The studies were performed under static air atmosphere in the temperature range of

20°C to 400°C at a heating rate of 10° C/min. The peak temperatures were determined after calibration with standard.

Powder X-ray Diffractometry (PXRD) [13, 14]

The powder X-RD patterns of drug, hydroxy propyl β-Cyclodextrin, and complexes 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.

In vitro dissolution studies for RST -CD complexes[15, 16]

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 $\pm$ 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 volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. 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 3 and Figure 2.

Table-3: 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

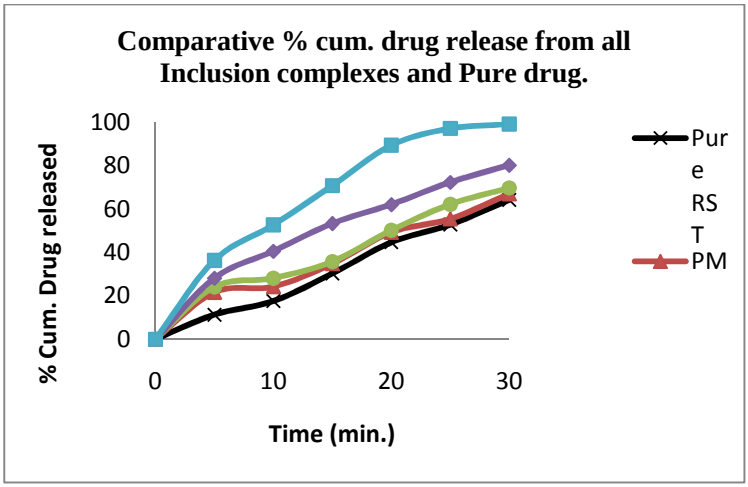

Figure 2: Comparative % Cum. drug release from Inclusion complexes and pure drug.

Preparation of tablet[11]

The complex of RST-HP-β-CD was prepared into tablet by direct compression method containing RST-CD complex equivalent to 5mg of RST. The all excipients were 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 tablet is shown in table 1.

Table 1: Composition of All the Formulation (Batch F1 to F9).

Ingredient (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
	Precipitated			Co-evaporated			Kneaded Method		
Drug-CD complex equivalent 5 mg Rosuvastatin Ca	20.6	20.6	20.6	20.6	20.6	20.6	20.6	20.6	20.6
Crosscarmellose sodium	15	---	---	15	---	---	15	---	---
Crosspovidone	---	15	---	---	15	---	---	15	---
Sodium starch glycolate	---	---	15	---	---	15	---	---	15
Mannitol	20	20	20	20	20	20	20	20	20
Camphor	10	10	10	10	10	10	10	10	10
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[16]

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 ℃ by using USP disintegration test apparatus.

In Vitro dissolution study[16]

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 ℃ 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. For comparison, the dissolution of marketed tablet was studied.

Stability Studies[17, 18]: The tablets of Batch F9 were packed in aluminum pouch and charged for accelerated stability studies at 40^0C in a humidity jar having 75% RH. Samples were withdrawn after 1 month interval. The drug dissolution profile of exposed sample was carried out. The results of accelerated stability studies are shown in Table 5 and Figure 8.

Table 5: Cum % Drug Release of Optimized Batch (F9) After 1 Month.

Time (min.)	Cumulative % Drug release	
	Initial	After 1 month
5	53.44	51.23
10	70.83	68.62
15	86.86	81.18
20	97.46	90.16
25	98.96	92.05
30	99.26	96.77
45	99.98	98.11

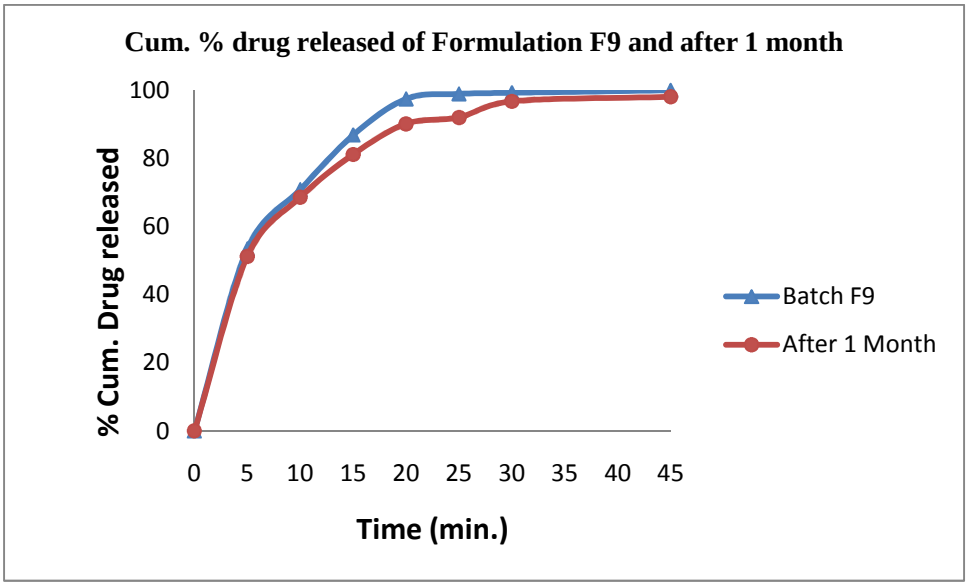

Figure 8: Dissolution Profile of Formulation (F 9) and after one Month.

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 shown 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. 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

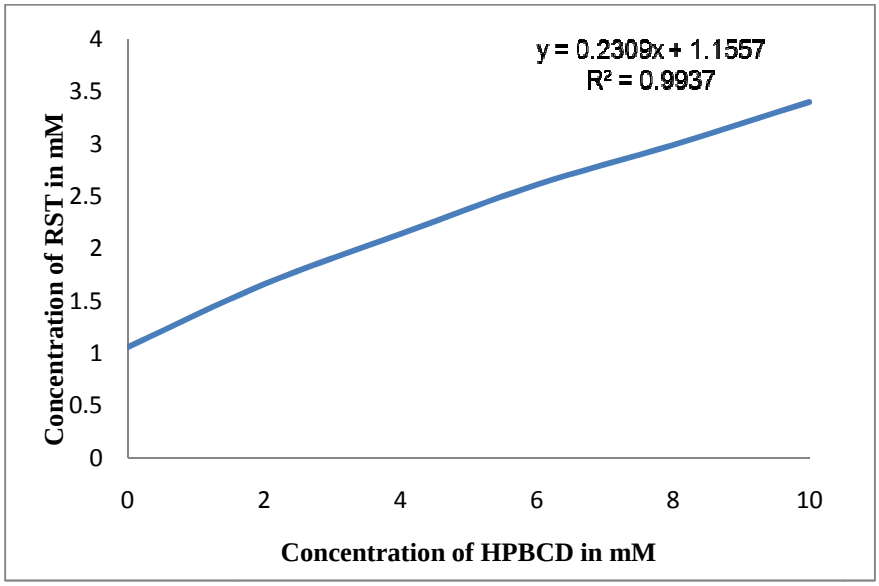

Figure 1: Phase Solubility Diagram for Rosuvastatin Ca with HP-β-CD at 25°C

Drug Content Estimation

UV spectrophotometry was used to determine the drug content of the binary system of the hydroxy propyl β-cyclodextrin: drug molar ratio (1:1). The hydroxy propyl β-cyclodextrin drug ratio would therefore remain 1:1 in the final solution to calculate the drug content. The Drug content in all the system was found to be 49.59 % w/w to 51.15% w/w (99.18 % to 102.31%)

Fourier Transform Infra-Red Spectroscopy

IR Spectra of pure drug and inclusion complexes of Rosuvastatin with HP-β-CD prepared by different methods are given in figure 3. As clearly seen from the spectra, the characteristic peaks of Rosuvastatin Ca at 564, 844, 965, 1335, 2360, 2973 and 3300 cm^{-1}were modified significantly as a result of complex formation. As shown Figure 3C slightly shifting in absorbance of Rosuvastatin it indicates no strong interaction between drug and cyclodextrin.

Figure 3D, 3E and 3F shows that 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.

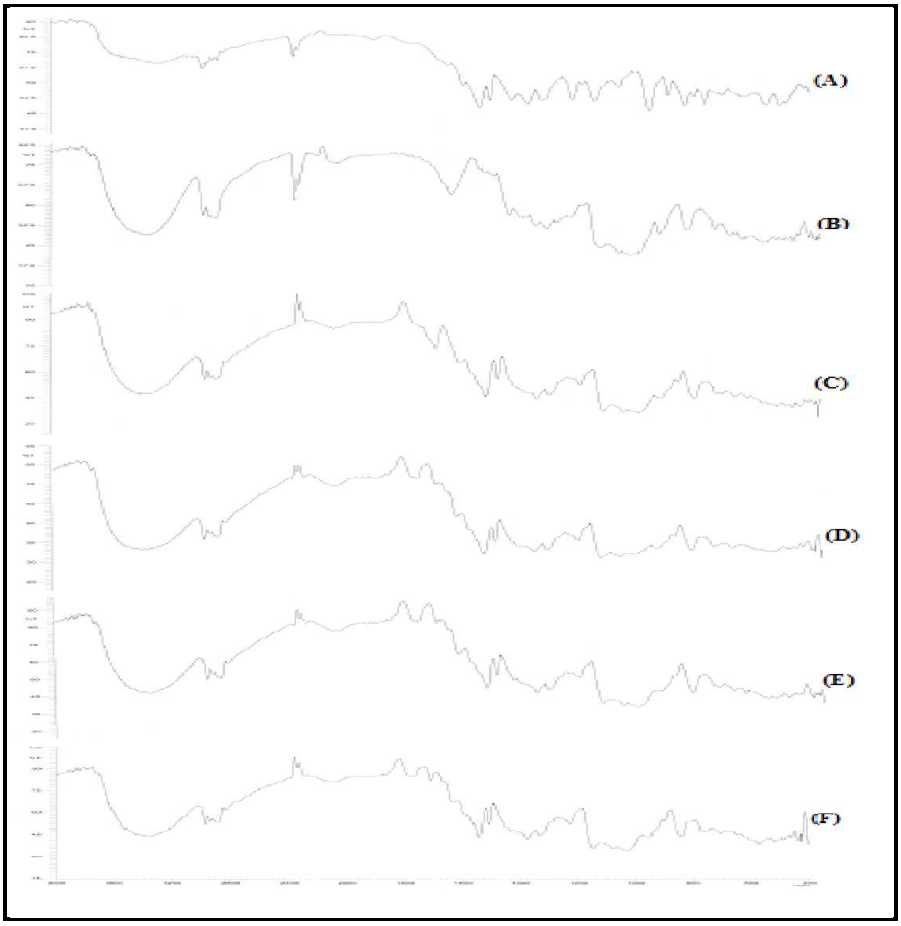

Figure 3: **FTIR spectra of (A) Rosuvastatin pure (B) Pure HP-β-CD (C) Physical mixture (D) Kneading method (E) Co-evaporation method (F) Precipitation method.**

Differential Scanning Calorimetry (DSC)

The thermal behavior RST-HP-β-CD complex was studied using DSC in order to confirm the formation of complex. DSC thermogram of RST, HP-β-CD and all inclusion complexes are shown in figure 4.The DSC thermogram of RST showed an endothermic peak at 105^{o}C corresponding to its melting point. The DSC thermogram 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.

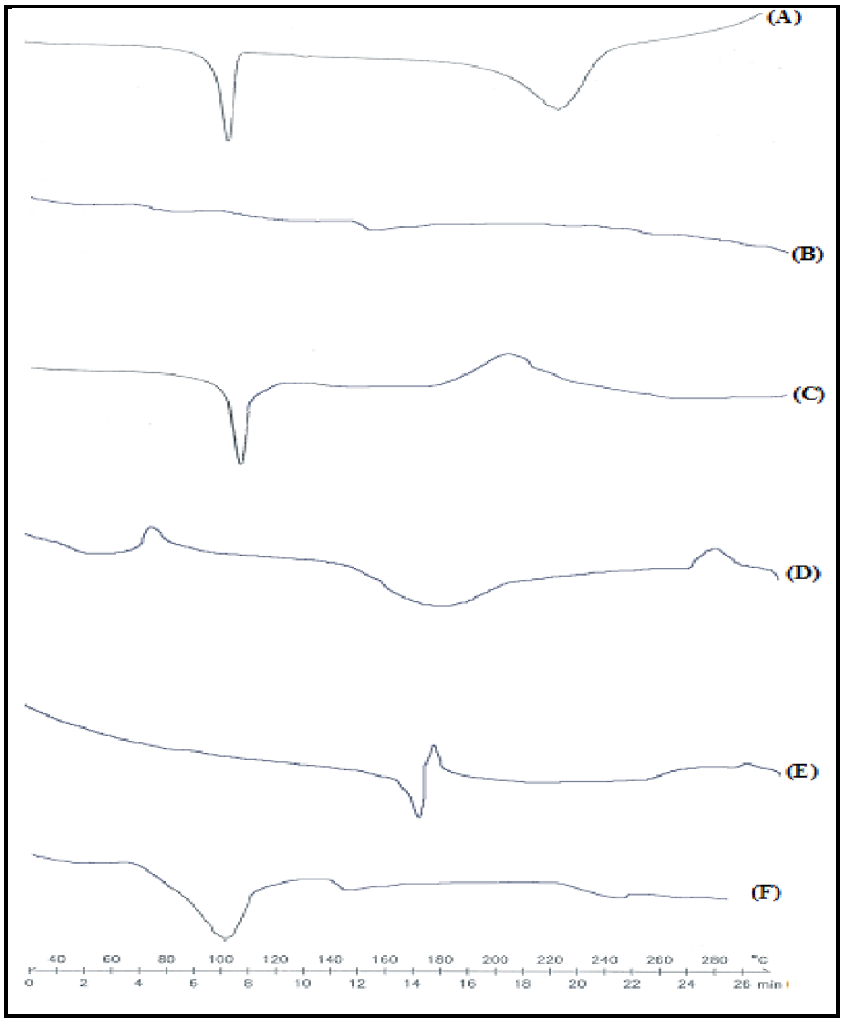

Figure 4: **DSC Thermogram of (A) Rosuvastatin pure (B) Pure HP-β-CD (C) Physical mixture (D) Kneading method (E) Co-evaporation method (F) Precipitation method.**

X-Ray Diffraction Studies (XRD)

The X-RD pattern (Figure 5A) 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. The HP-β-CD is a very amorphous material as there is no any sharp peak present as shown in Figure 5B. The PM shows (Figure 5C) 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 (Figure 5D, 5E & 5F) 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. Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the binary systems with those of a reference. The relation

used for the calculation of the crystallinity was the relative degree of crystallinity (RDC) = I_{SAM}/I_{REF}, where I_{SAM} is the peak height of the sample under investigation and I_{REF} is the peak height of the same angle for the reference with the highest intensity.

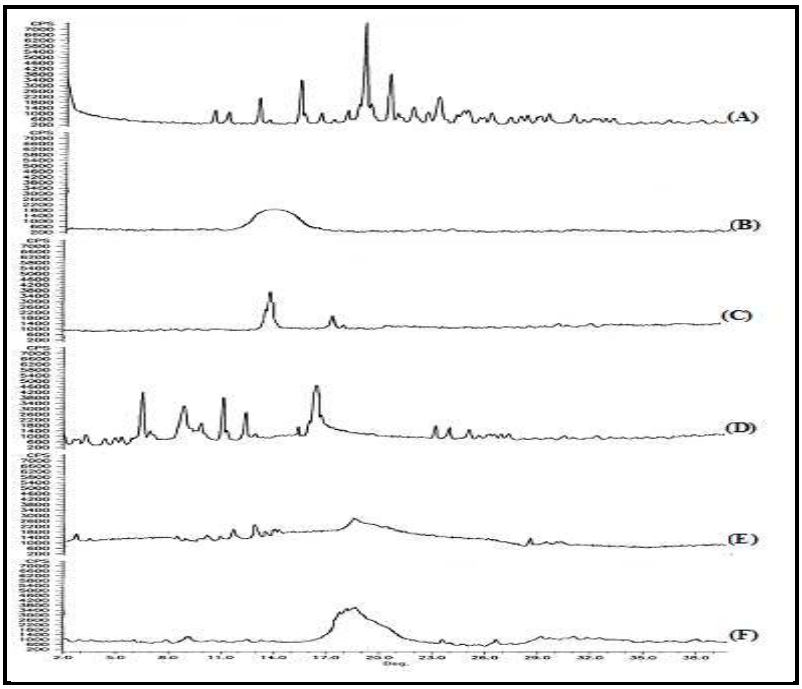

Figure 5: **XRD Patterns of (A) Rosuvastatin pure (B) Pure HP-β-CD (C) Physical mixture (D) Kneading method (E) Co-evaporation method (F) Precipitation method.**

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 .The release rate profile was drawn as the cumulative percent release on y-axis and time on x-axis which showed in figure 2. It showed that 44.69% of the pure Rosuvastatin was released in 20 min, and up to 64.28% after 30 min. Physical mixture shows release up to 49.29% of the drug in 20 min and up to 67.04% after 30 min whereas 69.79% and 80.26% drug release after 30 min from precipitated and co-evaporated respectively. Kneaded products showed highest dissolution profile among all complex 89.46% drug release in 20 min. that shows that there was improvement in dissolution rate of drug from inclusion complex as compared to physical mixture and pure drug.

Evaluation of tablet

Hardness, % friability, weight variation, Disintegration time and drug content of tablet are given in table 2. The hardness of tablet was in the range 4.3 - 4.5 kg/cm^2. The percent weight loss in the friability test was less than 1 %. The tablets were found to contain the Rosuvastatin within 100 ± 2% of the label claim. The dissolution profile of all prepared tablets from complex are shown in table 4 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 F9 shows higher dissolution (97.46% drug release in 20 min.) than the marketed tablet (50.22% drug release in 20 min.) shown in Table 4 and figure 7.

Table 2: Physical Properties of Tablets of Batch F1 to F9

Batch	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug content (%)	Disintegration time (sec.)
F1	4.12 ±0.030	4.5 ±0.17	0.92	149.4 ±1.34	98.41	260±2.588
F2	4.11 ±0.012	4.3 ±0.32	0.82	148.60 ±1.94	98.65	205±2.236
F3	4.12 ±0.01	4.4 ±0.14	0.94	149.95 ±1.68	97.31	97±3.536
F4	4.06 ±0.011	4.2 ±0.02	0.96	151.15 ±1.57	98.44	155±2.303
F5	4.48 ±0.042	4.6 ±0.37	0.99	147.05 ±1.59	99.9	134±1.673
F6	4.10 ±0.020	4.4 ±0.84	0.87	148.4 ±1.74	96.25	88±2.881
F7	4.13 ±0.032	4.5 ±0.34	0.82	150.35 ±1.67	99.65	60±2.775
F8	4.11 ±0.04	4.3 ±0.47	0.97	150.25 ±1.38	96.84	52±2.387
F9	4.14 ±0.062	4.2 ±0.42	0.92	149.59 ±1.39	99.29	25±3.209

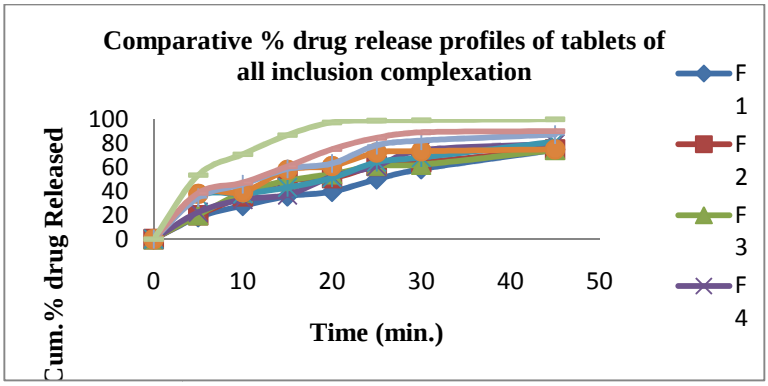

Figure 6: Comparative % Drug Released Profiles of tablets of all inclusion complex products.

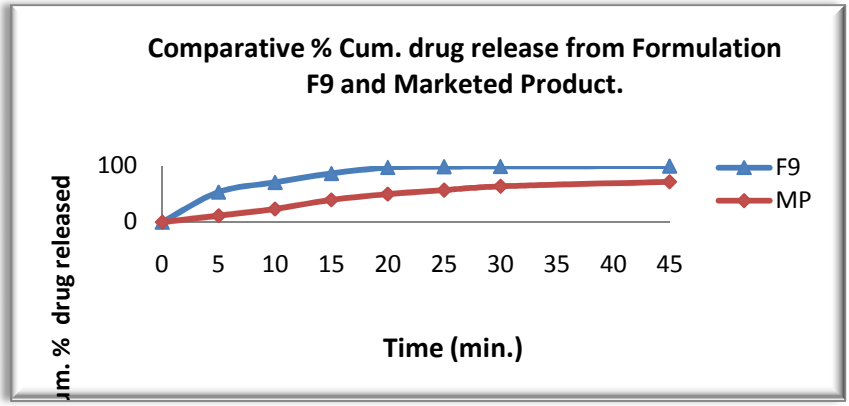

Figure 7: Comparative Dissolution Profile of Formulation (F9) and Market Product (MP)

Table-4: In-vitro Drug Release Profile of Formulation F1 to F9 and Marketed Product.

Time (min)	Cumulative % drug Release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	MP
5	18.34	19.84	20.02	22.42	35.81	37.82	34.56	38.44	53.44	11.34
10	27.78	35.68	38.83	33.09	37.9	39.26	45.88	47.09	70.83	23.67
15	35.67	48.66	48.68	36.88	43.11	57.8	58.56	60.7	86.86	39.9
20	39.56	50.84	54.24	52.05	51.12	61.1	63.22	75.04	97.46	50.22
25	49.85	60.97	61.4	60.89	64.32	72.34	78.45	84.54	98.96	57.56
30	58.33	64.03	62.08	74.11	68.13	73.45	82.28	89.13	99.26	64.23
45	74.56	74.99	74.34	79.41	81.41	74.99	87.24	90.14	99.98	72.4

DISCUSSION

From the result it is observed that the solubility of Rosuvastatin in the presence of hydroxy propyl β-cyclodextrin can be classified as the AL type. This indicated that the complexes at 1:1 ratio are adequately stable. In case of complexes, a diffraction pattern was significantly modified to that of pure drug, hydroxy propyl β-cyclodextrin, with a reduction in peak intensities. This confirms partial complexes formation i.e. some part of Rosuvastatin entrapped in cyclodextrin cavity.

The DSC thermogram for the complexes showed the persistence of the endothermic peak of Rosuvastatin for the physical mixture, solid dispersion, kneaded and precipitation system product. The thermal behavior of physical mixture, solid dispersion, kneaded and precipitation system is similar to the untreated samples, indicating that the physical mixture, solid dispersion, kneaded and precipitation system processes did not affect their solid state properties. For physical mixture, solid dispersion, kneaded and precipitation system complexes, there is reduction in peaks intensity; this can be explained on the basis of major interaction between the drug and cyclodextrin. Furthermore, the characteristic endothermic effect of cyclodextrin and Rosuvastatin is slightly shifted to lower temperature for the Co-evaporated, kneaded and precipitation system complexes, indicating that Rosuvastatin got complex with Cyclodextrin. The enhancement in dissolution profile has been attributed due to the formation of inclusion complexes in the solid state and reduction in the crystallinity of the product, as conformed by powder X-RD study. The dissolution rate increase for the physical mixture, kneaded, co-evaporated and precipitation mixtures is due to the wetting effect of the cyclodextrin, this effect is more evident for the kneaded product, where the mixing process between the two components is more intensive. The effect of complexation with cyclodextrin on the solubility of Rosuvastatin can be explained in terms of the reduction in the crystallinity of the drug caused by the Co-evaporated, kneaded and precipitation process and the inclusion into the hydrophobic cavity of the cyclodextrin. The FTIR spectra of physical mixture, co-evaporated, kneaded and precipitation system shows significant shift of hydroxyl functional group absorption band at 2360 cm^{-1}. This may be indicative that the drug-cyclodextrin complex, as a consequence of the interaction with cyclodextrin through hydrogen bonding, which could result in its inclusion into the hydrophobic cavity of the HP-β-cyclodextrin.

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). The relative efficiency of different superdisintegrants to improve the disintegration and dissolution rate of tablets was in the order, sodium starch glycolate > Crosspovidone > Crosscarmellose. 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.

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Corresponding Author:
Akbari Bhavesh V*,
Shree Dhanvantary Pharmacy College, Nr. Railway Station,
Kudsad road, Kim (E), Surat-394110, Gujarat, India.
Email: *bhaveshakbari83@gmail.com*