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ORIGINAL RESEARCH ARTICLE

Enhancement of Solubilityand Dissolution Rate OfRosuvastatin Calcium By Complexation With B-Cyclodextrin

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ABSTRACT

The objective of the study was to increase the solubility, and dissolution rate of Rosuvastatin Calcium (RST), a poorly water-soluble 3-hydroxy3-methyl glut aryl CoA (HMG-CoA) Reductase inhibitor through inclusion complexation with β-cyclodextrin (β-CD).The phase solubility profile indicated that the solubility of RosuvastatinCa was significantly increased in the p resence of β-CD and Apparent stability constant (K_C) wasfound to be 42.003M^{-1}. The inclusion complexes were prepared by three different methods viz. physical, kneading, Co-evaporation and precipitation method. The prepared complexes were characterized using FTIR, Differential scanning Calorimetry and Powder X-ray diffractometry. The inclusion complex prepared with β-CD by kneading method exhibited greatest enhancement in solubility and fastest dissolution (98.96% RST release in 30 min) of RST. The inclusion complex containing RST: β-CD (1:1) was formulated into tablets using superdisintegrants like sodium starch glycolate, Crosspovidoneand Crosscarmellose. The prepared tablet were evaluated for various post compression parameters like hardness, friability, weight variation, thickness, drug content and in-vitro dissolution. The stability of tablets was studied and no significant changes were detected in the dissolution profile of tablets after 1 month.

KEY WORDS: Rosuvastatin Calcium, β-CD, Physical method, Kneading method, Co-evaporation and precipitation method.

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, pro-drugs, 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-lower ingredient, and used as hypolipidemic agent. It is used in the treatment of osteoporosis, benignprostatichyperplasia, and Alzheimer's disease2.RSTiscrystalline nature so it reduces its aqueous solubility and finally that results in a normal bioavailability of 20%.After oral administration of RST, the peak plasma concentration is reached within 3–5h,thevolumeof distributionis1.1-1.4 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

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inclusion complexes with poorly water-soluble drugs and have been shown to improve pharmaceutical properties like solubility, dissolution rate, bioavailability, stability and even palatability with out 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].

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.Beta-cyclodextrin was gifted from Apex laboratory, Ankleshwar, Gujarat, India. Sodium starch glycolate, Cross povidone and Cross carmellose 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 β-CD such as 0, 2, 4, 6, 8, and 10 milli moles/liter. All the above solutions with variable amount of 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:

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

PREPARATION OF CYCLODEXTRIN INCLUSION COMPLEXES

Allthebinarymixtureswerepreparedina1:1molar ratio of drug and 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 β-CD in1:1 molar ratio was in a mortar for about one hour with constant trituration, passed through sieve No. 100.

Kneading method [9, 10]

RST with β-CD in1:1 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 No. 100.

Co-evaporation method [10, 11]

Inclusion complex (1:1) was prepared by dissolving equimolar amount of β-CD and RSTCain required amount of 50% aqueous ethanol. The solution was stirred till a clear solution was observed and the obtained solution was evaporated under vacuum at a temperature of 45°C and 100rpm.The solid residues was further dried completely at 45°C for 48h, the dried complex was pulverized in to a fine powder and sieved through sieve No. 100.

Precipitation method[11, 12]

Inclusion complex of RST and 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 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, β-Cyclodextrin physical mixture, kneaded, and 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

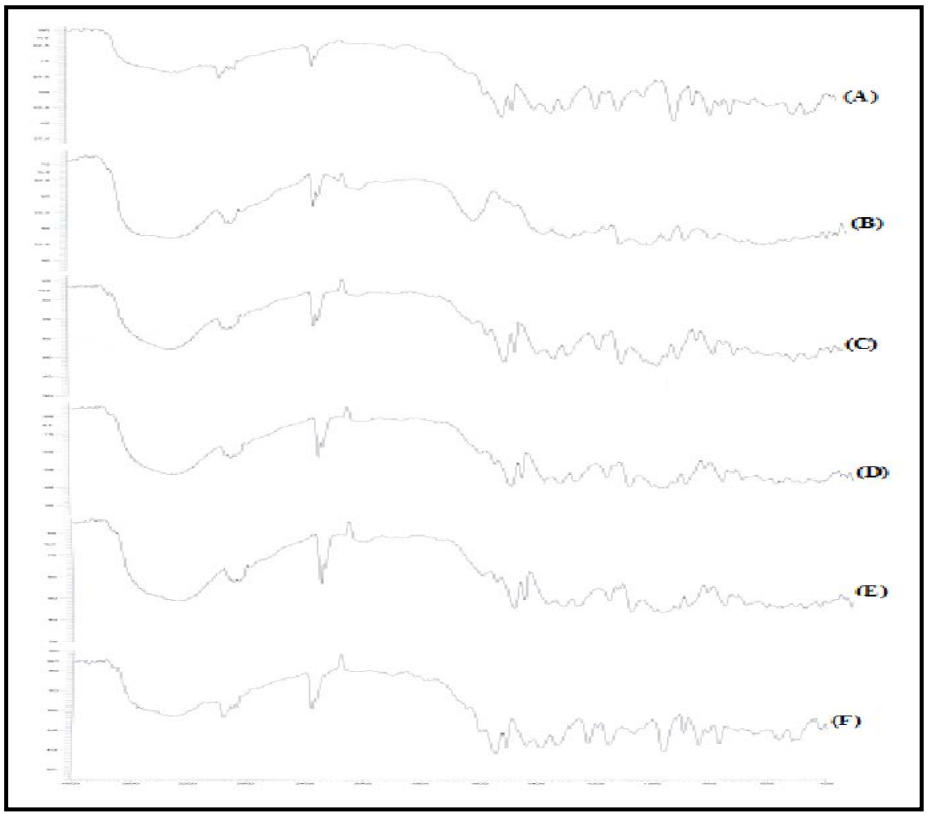

Figure 3: **FTIR spectra of (A) Rosuvastatin pure (B) Pure β-CD (C) Physical mixture(D) Kneading method (E) Co-evaporation method (F) Precipitation method.**

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, 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 (Electro lab) 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 through out 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**).

Time (min)	Cumulative % drug Release				
	PM	COE	PPT	KM	Pure
5	18.4	27.88	20.03	31.34	11.3
10	22.24	34.66	28.23	44.23	17.58
15	41.88	47.3	43.78	59.68	30.28
20	54.89	60.1	56.29	73.66	44.69
25	67.45	70.23	69.45	82.65	52.87
30	80.04	87.23	84.99	98.96	64.28

Table 3: In-vitro % Drug Release Profile of Inclusion complexes and pure drug

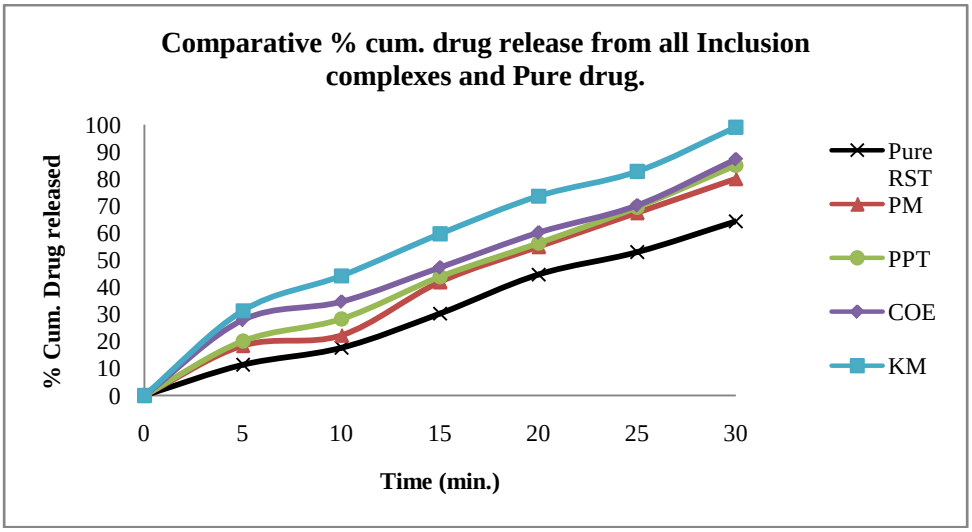

Figure 2: Comparative % Cum. drug release from Inclusion complexes and pure drug.

Preparation of tablet[11]

The complex of RST-β-CD was prepared into tablet by direct compression method containing RST-β-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**).

Ingredient (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug-β-CD complex equivalent RosuvastatinCa	5	5	5	5	5	5	5	5	5
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
Aspartame	2	2	2	2	2	2	2	2	2
Mg. Steerage	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

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

Evaluation of Tablet [16]

The prepared tablets were evaluated for weight variation, hardness and friability. 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.

***In Vitro* dissolution study [16]**

In-vitro dissolution of 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. For comparison, the dissolution of marketed tablet was studied.

Stability Studies [17, 18]: The tablets of Batch F10 were packed in aluminum pouch and charged for accelerated stability studies at 40^{0}C 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**).

Time (min.)	Cumulative % Drug release	
	Initial	After 1 month
5	19.44	16.42
10	36.13	32.2
15	49.99	46.8
20	64.18	60.46
25	78.62	76.55
30	91.67	87.67
45	97.9	96.91

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

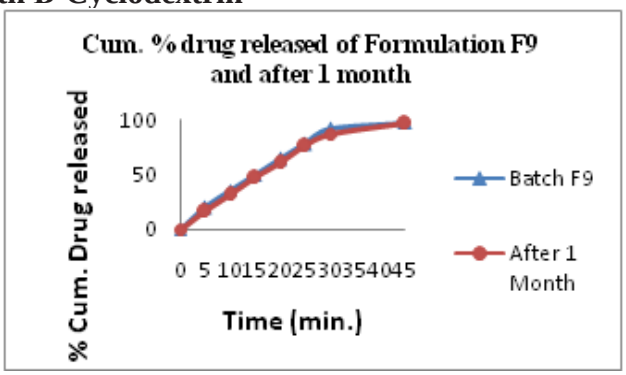

Figure 8: Dissolution Profile of Optimized Formulation (F 9) and after one Month.

RESULTS AND DISCUSSION

Phase Solubility Studies

The phase solubility diagrams of RST Ca: β-CD was obtained by plotting the changes in guest solubility as a function of 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 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 than1, which indicates that inclusion complex in the molar ratio of 1:1between the guest and the host molecule were obtained irrespective of the pH. The phase solubility profile indicated that the solubility of RosuvastatinCa was significantly increased in the presence of β-CD and Apparent stability constant (K_C) was found to be 42.003M^{-1}.

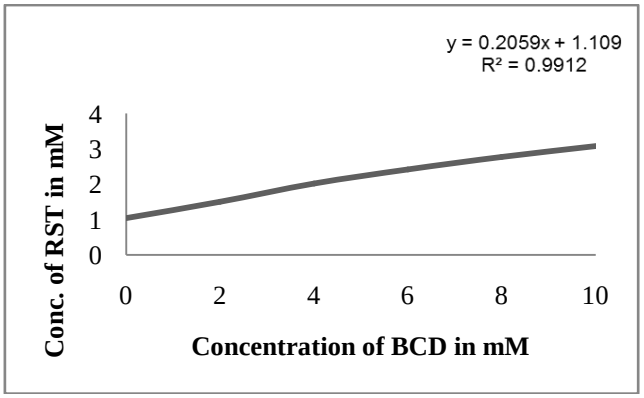

Figure 1: Phase Solubility Diagram for RosuvastatinCa with BCD at 25°C

Drug Content Estimation

UV spectrophotometry was used to determine the drug content of the binary system of the β-cyclodextrin: drug molar ratio (1:1).The β-

cyclodextrin drug ratio would therefore remain1:1 in the final solution to calculate the drug content. The Drug content in all the system was found to be 49.86 % w/w to 52.5% w/w (99.77 % to 105.01%)

IR Spectroscopy

IR Spectra of pure drug and inclusion complexes of Rosuvastatin with β-CD prepared by different methods are given in figure 3. As clearly seen from the spectra, the characteristic peaks of RosuvastatinCa at 564, 844, 965, 1335, 2973 and 3300cm^{-1} were modified significantly as a result of complex formation.

Differential Scanning Calorimetry (DSC)

The thermal behavior RST-β-CD complex was studied using DSC in order to confirm the formation of complex. DSC thermogram of RST, 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-β-CD complex showed endothermic peak at different temperature by different method of preparation, which is different from the pure drug, which gives clear evidence that there is formation of the complex.

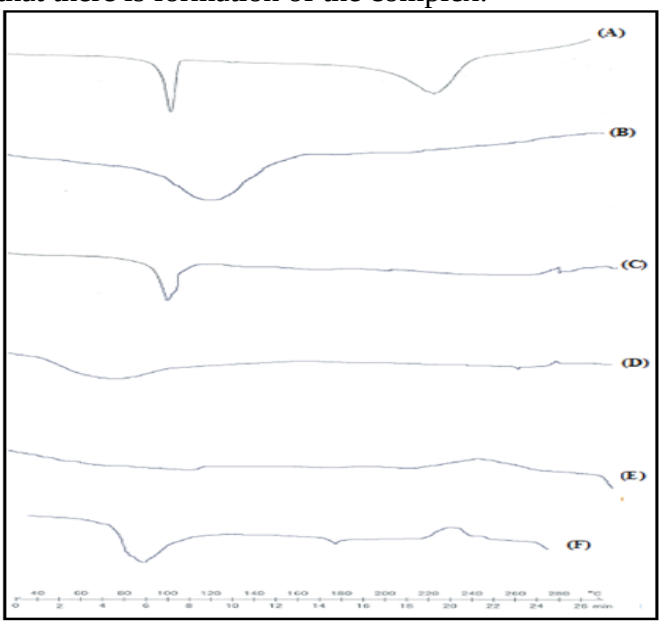

Figure 4: **DSC Thermogram of (A) Rosuvastatin pure (B) Pure β-CD (C) Physical mixture(D) Kneading method (E) Co-evaporation method (F) Precipitation method.**

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 β-CD was a very crystalline molecule with major peaks at 2θ values of 11.6, 19.1, 21.1, 23.5, 26.0 and 30.0 as shown in (**Figure 5B**). The XRD pattern of Rosuvastatin showed (**Figure 5A**) intense and sharp peaks, indicating its crystalline nature. 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. The diffraction patterns of physical mixture (**Figure 5C**), Co-evaporated product (**Figure 5E**) and precipitated products (**Figure 5F**) showed peaks of Rosuvastatin and β-CD with little decrease in the peak intensity of Rosuvastatin indicating reduction in crystallinity. The kneaded system presented a diffraction pattern (**Figure 5D**) showed modified diffraction pattern of Rosuvastatin. However the crystallinity of Rosuvastatin was reduced to a greater extent as compared to physical mixture as almost all peaks of Rosuvastatin except peak at 11.2 were disappeared in diffraction pattern of kneaded product.

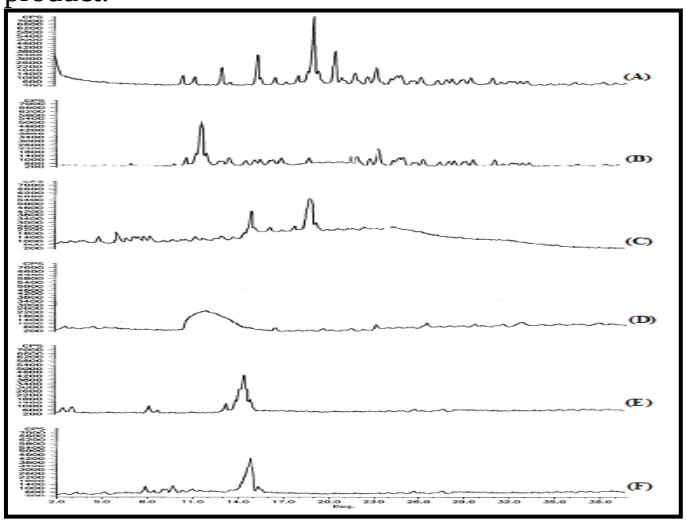

Figure 5: **XRDPatterns of (A) Rosuvastatin pure (B) Pure β-CD (C) Physical mixture(D) Kneading method (E) Co-evaporation method (F) Precipitation method.**

In Vitro dissolution study

Since the presence of β-cyclodextrin showed that there was decreased in extinction coefficient of the drug, since the 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 (**figure2)**. 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 54.89% of the drug in 20 min and up to 80.04% after 60 min whereas 84.99%, 87.23% and 98.96% drug release after 30 min from precipitated, co-evaporated and kneaded complex respectively that shows that there was improvement in dissolution rate of drug from inclusion complex as compared to physical mixture and pure drug.(**Table 4**)

Time (min)	**Cumulative % drug Release**									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**MP**
5	13.45	17.34	20.03	24.34	25.87	27.88	14.56	18.44	19.44	11.34
10	17.88	25.88	28.23	30.89	31.9	34.66	25.88	27.09	36.13	23.67
15	25.67	38.77	43.78	36.88	44.11	47.3	38.56	40.7	49.99	39.9
20	32.34	47.89	56.29	52.45	58	60.1	41.34	48.04	64.18	50.22
25	43.45	56.37	60.45	58.89	66.34	70.23	58.67	65.45	78.62	57.56
30	48.89	61.23	64.88	64.11	68.23	78.65	71.22	75.43	91.67	64.23
45	68.56	74.89	78.99	74.11	81.45	83.23	88.34	80.54	97.9	72.4

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

Evaluation of tablet

Hardness, % friability, weight variation 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 super disintegrate. The Dissolution profile of optimized tablet formulation F9 shows higher dissolution (98.96) than the marketed tablet (72.4) shown in Table 4 and (**figure7**).

Batch	**Diameter (mm)**	**Thickness (mm)**	**Hardness (Kg/cm^2)**	**Friability (%)**	**Weight Variation (mg)**	**Drug content (%)**
F1	8	4.16 ±0.010	4.5 ±0.47	0.96	148.65 ±1.29	97.01
F2	8	4.14 ±0.012	4.4 ±0.32	0.72	146.50 ±1.74	99.5
F3	8	4.12 ±0.06	4.4 ±0.54	0.91	149.55 ±1.18	98.01
F4	8	4.16 ±0.011	4.3 ±0.42	0.86	150.05 ±1.37	97.4
F5	8	4.18 ±0.012	4.5 ±0.35	0.79	149.65 ±1.49	98.4
F6	8	4.16 ±0.010	4.5 ±0.54	0.97	147.5 ±1.19	99.05
F7	8	4.14 ±0.012	4.5 ±0.54	0.82	151.55 ±1.19	99.05
F8	8	4.12 ±0.06	4.3 ±0.42	0.87	150.55 ±1.19	98.4
F9	8	4.18 ±0.012	4.4 ±0.32	0.72	149.55 ±1.19	98.2

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

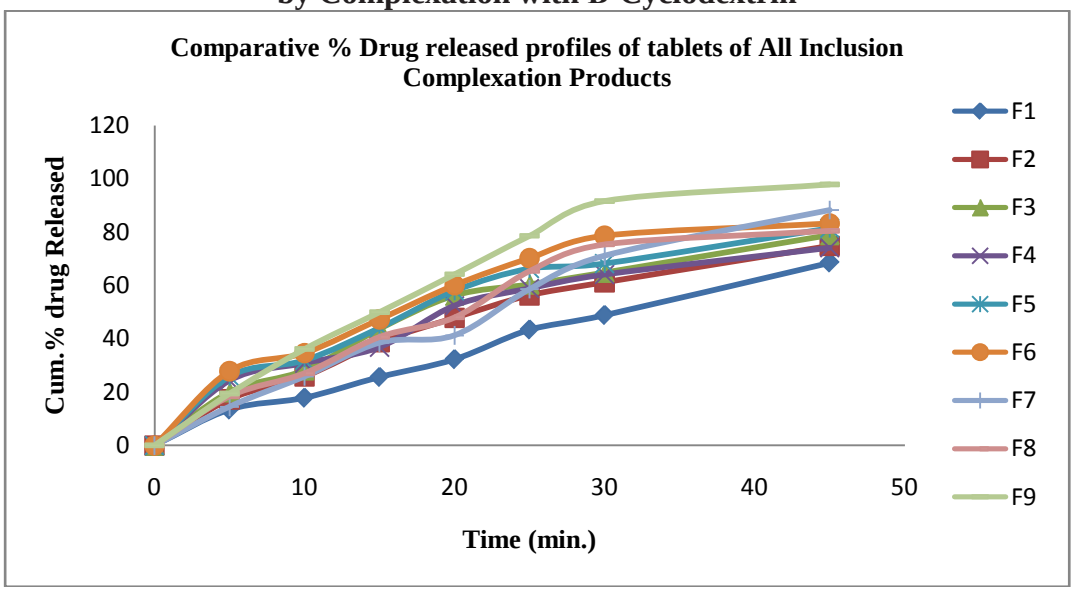

Figure 6: Comparative % Drug Released Profiles of tablets of all inclusion complex products.

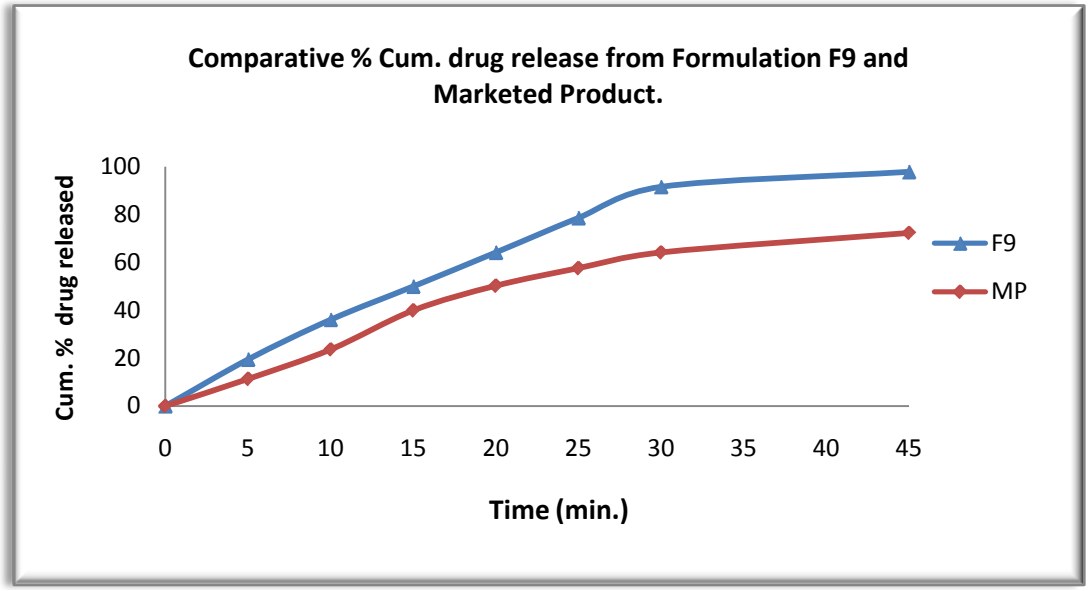

Figure 7: Comparative Dissolution Profile of Optimized Formulation (F9) and Market Product (MP)

DISCUSSION

From the result it is observed that the solubility of Rosuvastatin in the presence of 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 similar to that of pure drug, β-cyclodextrin, but with a reduction in peak intensities. This confirms partial complexes formation i.e. some part of Rosuvastatin entrapped in β-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 β-cyclodextrin. Furthermore, the characteristic endothermic effect of β-cyclodextrinand Rosuvastatin is slightly shifted to lower temperature for the Co-evaporated, kneaded

and precipitation system complexes, indicating that Rosuvastatin got complex with β-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 β-cyclodextrin, this effect is more evident for the kneaded product, wherethe mixing process between the two components is more intensive. The effect of complexation with β-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 β-cyclodextrin. The FTIR spectra of physical mixture, co-evaporated, kneaded and precipitation system shows significant shift of hydroxyl functional group absorption band at 965cm^{-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 β-cyclodextrin.

CONCLUSION

This study shows that there is formation of a β -CD:Rosuvastatin complex in aqueous solution and this complex prepared by the various inclusion complex at ion methods ,also exist in the solid state. Association constant and stoichiometric ratio has been calculated by phase solubility study and from the results we can assume that the formation of the complex association of both Rosuvastatin and CD can increase the aqueous solubility of Rosuvastatin. 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 β-CD.

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