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FORMULATION DEVELOPMENT AND SOLUBILITY ENHANCEMENT OF ROSUVASTATIN CALCIUM TABLET PREPARED BY COMPLEXATION WITH β-CYCLODEXTRIN BY KNEADING METHOD

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Keywords:

Rosuvastatin Calcium, B-CD, Kneading Method, Superdisintegrants, Orodispersible Tablets

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ABSTRACT: Rosuvastatin is a Dyslipidaemic agent, which acts by inhibiting HMG-CoA reductase enzyme and used in the treatment of hyperlipidemia. But Rosuvastatin calcium (RST) exhibit unsatisfactory dissolution profiles, problems of absorption and poor bioavailability. Thus objective of the study is to increase the solubility and dissolution rate of Rosuvastatin calcium (RST), a poorly water-soluble 3-hydroxy 3-methyl glutaryl CoA (HMG-CoA) Reductase inhibitor through inclusion Complexation with β-cyclodextrin (β-CD). Therefore the present investigation was to design a formulation of orally disintegrating tablets of Rosuvastatin. Orally disintegrating tablets of Rosuvastatin were formulated by superdisintegrants addition method by direct compression technique. Formulas prepared by direct compression showed good results, the prepared inclusion complex with β-CD by kneading method exhibited greatest enhancement in solubility and fastest dissolution (99.363 % RST release in 45 min, 102.22 % RST release in 50 min.) of RST. The inclusion complex contains RST: β-CD (1:1) was formulated into tablets using super disintegrants like sodium starch glycolate, crosspovidone and crosscarmellose. The prepared tablet were evaluated for various post compression parameters like hardness, friability, weight variation, thickness , drug content and *in vitro* dissolution.

INTRODUCTION: Drug delivery system (DDS) are the strategic tool for expanding markets, extending product life cycles and generating opportunities. The Oral route of administration is the most preferred route due to its many advantages but many patient groups such as elders, children's , and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid – intake, have difficulties of swallowing ordinary tablets i.e dysphasia.

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To solve the above mentioned problems, pharmaceutical technologists have put in their best efforts to develop a Fast dissolving drug delivery tablet i.e Orodispersible tablets.

Rosuvastatin, as rosuvastatin calcium is a HMG-CoA reductase inhibitor used for the treatment of dyslipidaemia, osteoporosis, benign prostatic hyperplasia and Alzheimers disease. RST is crystalline in nature so it reduces its aqueous solubility and results in bioavailability of 20%. Cyclodextrin are cyclic oligosaccharides containing six, seven or eight glucopyranose units (α,β,y respectively) obtained by enzymatic degradation of starch. These are torus shaped molecules with a hydrophilic outer surface and hydrophobic 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.

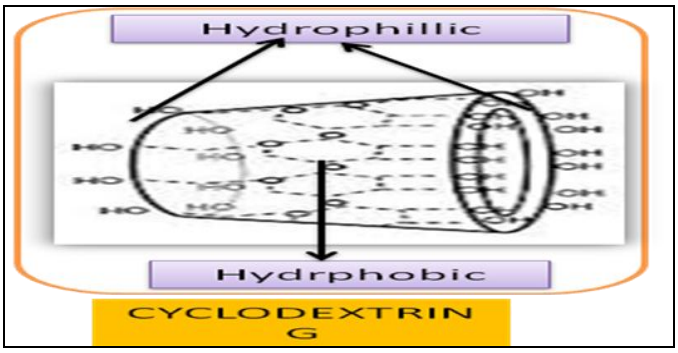

FIG. 1: CYCLODEXTRIN G

The objective of present study is to develop orodispersible tablets of Rosuvastatin calcium with cyclodextrin by using super disintegrants to enhance the disintegration and dissolution of rosuvastatin to improve bioavailability of the drugs.

Thus in this study, Rosuvastatin calcium ODTs were prepared with an aim to improve the dissolution rate and oral bioavailability of drug which will ensure the desired therapeutic efficacy via the more comfortable and convenient oral delivery route and will further preclude the requirement of invasive techniques .

MATERIALS AND METHODS: Rosuvastatin calcium was gifted by Zydus Cadila Ahmedabad. β-cyclodextrin was obtained from Ozone International, Mumbai. Sodium starch glycolate were purchased from S.D Fine Chemicals ltd. Mumbai. All other chemicals and reagents used were of analytical grade.

API- Rosuvastatin calcium: Rosuvastatin is a member of the drug class of statins used in combination with exercise, diet, and weight-loss to treat high cholesterol and related conditions, and to prevent disease. Rosuvastatin belongs to class II drug in BCS classification i.e. low solubility and high permeability. One of the major limitation of the drug is poor bioavailability after oral administration which can be overcome by enhancing its solubility. Complexing of drug with the different types of carriers is feasible to increases the solubility and dissolution rate. By increasing the solubility of Rosuvastatin, its bioavailability can be increased. Rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl - 2- [methyl (methyl sulfonyl) amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt. The empirical formula for rosuvastatin calcium is $(C22H27FN3O6S)_2Ca$. Its molecular weight is 1001.14

Excipients:

Excipients may be selected from:

1. Starches or modified starches such as sodium starch glycolate, corn starch, potato starch and pregelatinized starch.
2. Sweetener such as mannitol , aspertame.
3. Subliming agent such as camphor.
4. Lubricant such as magnesium stearate.
5. Binder such as Avicel Ph 101.
   The selected disintegrates were sodium starch glycolate in the present investigation.

Glidant: mostly used includes talc

Method:

Preparation of Cyclodextrin Inclusion Complexes: Kneading Method: RST with 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 no.100.

Drug Content: The amount of active ingredient(s) is determined by the method described in assay and amount of active ingredient is calculated. New method was used for determination of drug content given below:

Twenty tablets were weighed and powdered. The blend equivalent to 20 mg of Rosuvastatin Calcium was weighed and dissolved in sufficient quantity of simulated gastric fluid 1.2 pH. The solution was filtered through Whatmann filter paper (no.41), suitably diluted with simulated gastric fluid 1.2 pH and assayed at 244 nm, using a UV-Visible double beam spectrophotometer (JASCO V-630)

Differential scanning calorimetry: Thermogram of Rosuvastatin Calcium was recorded on a TA-60 WS Thermal Analyzer (Shimadzu) as shown. The samples were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min over temperature range of 40 to 300°C. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 50 ml/min.

Infrared absorption spectrum: The infrared absorption spectrum of Rosuvastatin Calcium was recorded with a KBr disc over the wave number 4000 to 400 cm^{-1} on a Shimadzu Japan (IR 200) as shown.

***In vitro* Dissolution Study:** Dissolution profiles of Rosuvastatin Calcium tablets were determined using the USP Method II with paddle speed at 50 rpm. Dissolution was performed in 900 ml pH1.2 simulated gastric fluid maintained at 37 ± 0.5°C. Three ml of samples were withdrawn at specified time intervals. The volume of dissolution fluid was adjusted to 900 ml, by replacing each 3 ml aliquot withdrawn with 3 ml of pH 1.2 simulated gastric fluid, pre-warmed at 37±0.5°C. Samples withdrawn were filtered through Whatmann filter paper (no.41), 1 ml is suitably diluted with10 ml of pH1.2 simulated gastric fluid, and analyzed at 234nm, using UV-Visible double beam spectrophotometer (JASCO V-630). The data presented is the average of 3 individual determinations.

Procedure with tabular form given below in table

TABLE 1: PROCEDURE FOR DISSOLUTION STUDY

Dissolution medium	900ml of1.2 simulated gastric fluid
Temperature	$37^0C \pm 1^0C$
RPM	50
Drug Content	Weight of tablet equivalent to 20mg of drug
Volume withdrawn	3ml
Volume made up to	3ml
λ_{max}	244 nm
Beer's range	1-5µg/ml
Dilution factor	10

Preparation of tablet: Accurately weighed quantity of Rosuvastatin Calcium Complex was mixed together with superdisintegrants (Sodium Starch Glycolate), magnesiumsterate, talc and aspertame in mortar and pastel. Mixture was passed through sieve #100. The resulting uniform blends of composition per tablets as mentioned were directly compressed using 6.4 mm, round circular faced tooling to make the tablets of said compression specifications using 8 station Labpress compression machine. The tablet press setting was kept constant across all formulations.

TABLE 2: FORMULATION DESIGN

Ingredients (mg)	T1	T2	T3	T4	T5
Drug-CD complex eq.5mg RosuvastatinCa	7.3	7.3	7.3	7.3	7.3
Sodium starch glycolate	20	25	30	35	40
Mannitol	50	50	50	50	50
Camphor	10	10	10	10	10
Aspertame	5	5	5	5	5
Mg.Stearate (mg)	3	3	3	3	3
Talc	3	3	3	3	3
Avicel PH 102	200.70	195.70	190.70	185.70	180.70
Total Avg.Wt(mg)	300	300	300	300	300

Evaluation of Compressed Tablets: All the tablet formulations were subjected for organoleptic, physical and chemical evaluations as shape, thickness, hardness, friability, weight variation, in vitro disintegration time, drug content and in vitro dissolution studies.

1. Appearance: The size and shape of the tablets can also affect the disintegration time and subsequent dissolution profile. In general, a smaller tablet in terms of mass has a faster disintegration time than larger tablets, all other factors being equal. Similarly, a tablets shape with more surface area generally was a faster disintegration time than a tablets shape having less surface area, all other factors being equal. Randomly picked tablets from each formulation batch examined for shape and in presence of light for color. Tablets showed circular shape and white color

2. Weight Variation Test: The percentage weight variation for all the optimized formulations batches are tabulated in Table "Evaluation of optimized batch". All the tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ±7.5%. The weight of all the tablets was found to be uniform. Uniform weight due to uniform die fill with acceptable variation as per USP standards were obtained since blend of material was free-flowing.

3. Hardness: Tablet crushing strength, the critical parameter was controlled as the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. Hence, hardness for all optimized batches is tabulated in Table "Evaluation of optimized batch".

4. Thickness: The thickness of the tablets was measured by using Vernier caliper by picking the tablets randomly. The values are shown in Table "Evaluation of optimized batch". The values were almost uniform in all formulations.

5. Friability: To achieve percent friability within limits for conventional tablets was challenge to the formulator since all methods of manufacturing of conventional tablets was responsible for increasing the % friability values. The % friability values for all optimized batches are tabulated in Table "Evaluation of optimized batch".

6. Drug Content: The drug content of optimization batch was calculated by using UV-Spectrophotometric method by quantization mode. Drug content for all optimized batches are tabulated in Table "Evaluation of optimized batch".

7. ***In-vitro*** **Disintegration Time:** Disintegration, the first important step for a drug absorption from a solid dosage form after oral administration was preliminarily focused. It was reported that tablets disintegration was affected by the particle size, the degree of substitution, and extent of cross-linkage. An important factor affecting the disintegration is the tablets hardness and/or the compaction force used in making the tablets hardness. The hardness of the tablets has an influence on the disintegration time as it affects the porosity of the matrix and, accordingly, the ability of water to penetrate through the matrix. All tablets disintegrated rapidly without disc in the IP test especially when used at optimum concentrations of selected super disintegrants. In the study, the relatively larger fragments generated by tablets containing sodium starch glycolate were not small enough to pass through the screen of the disintegration vessels.

RESULTS & DISCUSION:

1. Melting Point Determination: Melting point of Rosuvastatin calcium was found to be 122˚C as reported in literature, thus indicating purity of sample.

2. UV Spectroscopic Analysis:

I. Determination of Analytical Wavelength: The pure drug Rosuvastatin Calcium was scanned over a range 200-400 nm to determine its λ_{max}. The UV spectrum of Rosuvastatin Calcium does not show a sharp peak for absorption maxima shown in figure of thermo gram of RST. The maximum absorption was observed at 244 nm in pH 1.2 simulated gastric fluid. This value corresponds to λ_{max} reported in literature.

II. Calibration Curve of Rosuvastatin Calcium: The standard calibration curve of Rosuvastatin Calcium was obtained by plotting Absorbance vs. Concentration. Table "Calibration curve of RST" shows the absorbance values of Rosuvastatin Calcium. The standard curve is shown in figure "IR peak of RST". The standard calibration curve shows the slope of 0.09 and correlation coefficient of 0.998. The curve was found to be linear in the concentration range of 1-5µg/ml (Beer's range) at 244. The calculations of drug content, in vitro dissolution study were based on this calibration curve.

TABLE 3: CALIBRATION CURVE OF ROSUVASTATIN CALCIUM

Sr. No.	Concentration (µg/ml)	Absorbance
1	0.5	0.2241
2	1	0.4395
3	1.5	0.6623
4	2	0.8789
5	2.5	1.18
6	3	1.401
7	3.5	1.61
8	4	1.801
9	4.5	2.013
10	5	2.2012

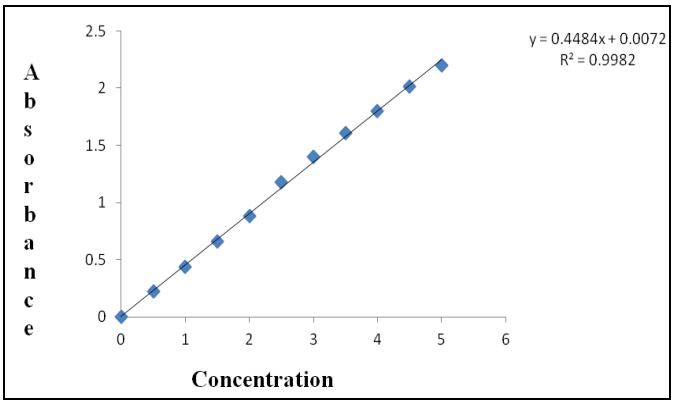

FIG. 2: CALIBRATION CURVE OF ROSUVASTATIN CALCIUM

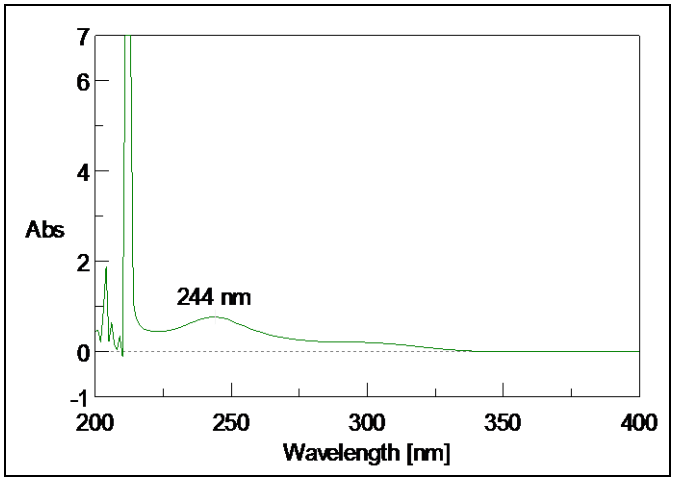

FIG. 3: UV SPECTRUM OF ROSUVASTATIN CALCIUM

TABLE 4: DATA FOR CALIBRATION CURVE IN pH 1.2 SIMULATED GASTRIC FLUID

Sr. No.	Parameters	Values in pH 1.2 simulated gastric fluid
1	Absorbance maximum (λ_{max}) in nm	244nm
2	Slope	0.448
3	Intercept	0.007
4	Correlation coefficient	0.998
5	Equation	Y= 0.448x-0.007

2. IR Spectroscopy Analysis: The IR spectrum of the drug agrees with its chemical structure bis[(E)-7-[4(4-fluorophenyl)-6-isopropyl - 2 [methyl (methylsulfonyl) amino] pyrimidin-5-yl](3R,5S)-3,5 di hydroxylhept-6-enoic acid] calcium salt.

TABLE 5: IR PEAKS OF ROSUVASTATIN CALCIUM

Absorption peak	Attributed to
1500	$-C_6H_5$
400-800	-F
1075-1010	-OH

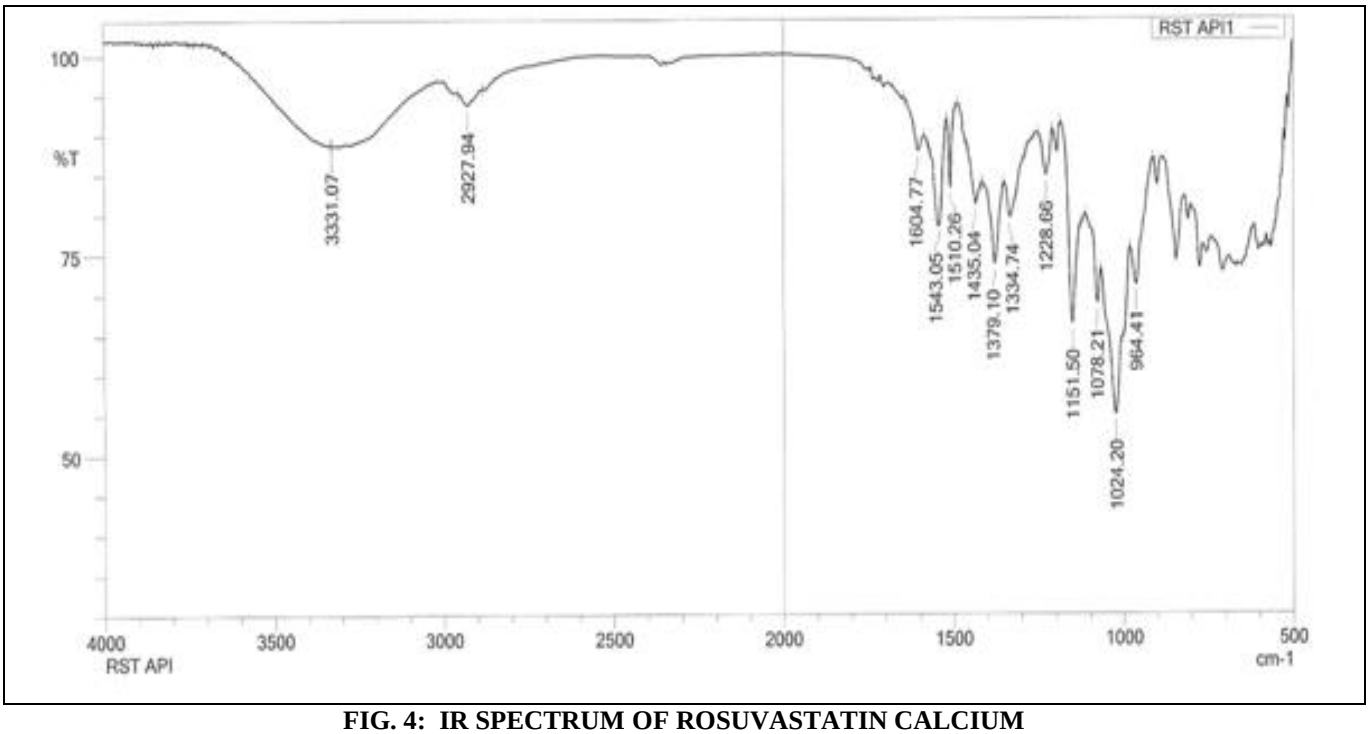

FIG. 4: IR SPECTRUM OF ROSUVASTATIN CALCIUM

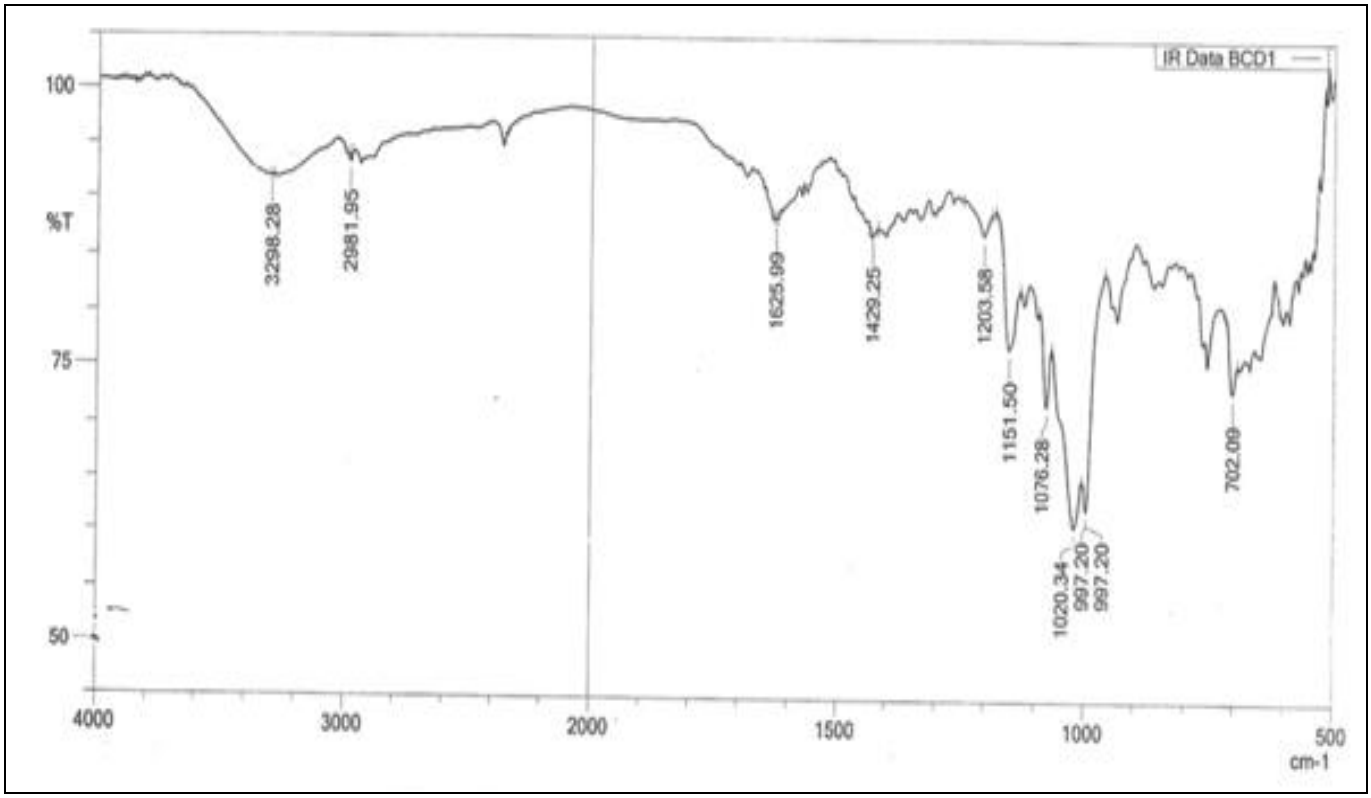

FIG. 5: IR SPECTRUM OF β-CYCLODEXTRIN

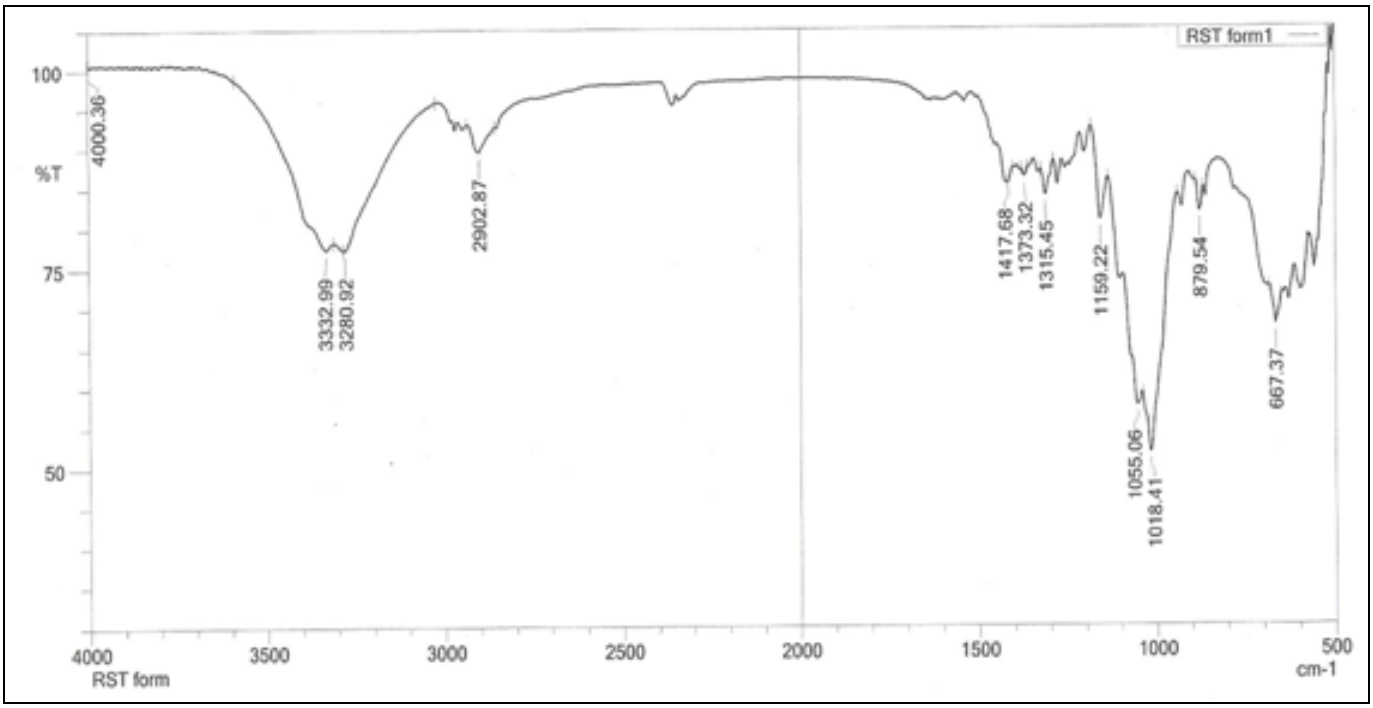

FIG. 6: IR SPECTRUM OF ROSUVASTATIN CALCIUM: β-CYCLODEXTRIN COMPLEX

3. Differential Scanning Calorimetric (DSC) Analysis: The endothermic peak of Rosuvastatin Calcium was seen at 127.72˚C with an onset 121.43˚C. This complies with the reported literature value.

Drug and Excipients Compability Studies: From the spectra of pure drug Rosuvastatin Calcium and the combination of drug with polymers, it was observed that all the characteristic peaks of Rosuvastatin Calcium were present in the combination spectrum, thus indicating compatibility of the drug and polymer.

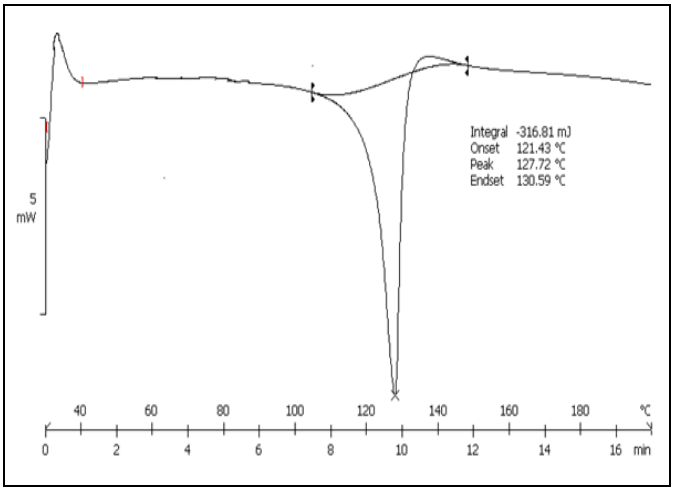

FIG. 7: THERMO GRAM OF ROSUVASTATIN CALCIUM

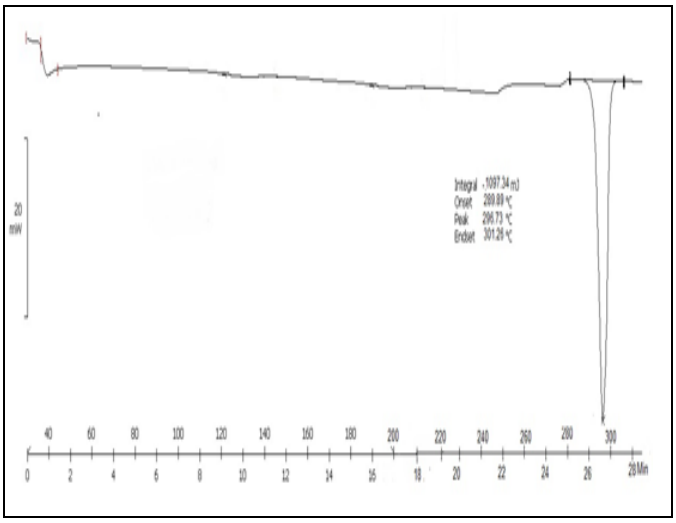

FIG. 8: THERMO GRAM OF β CD

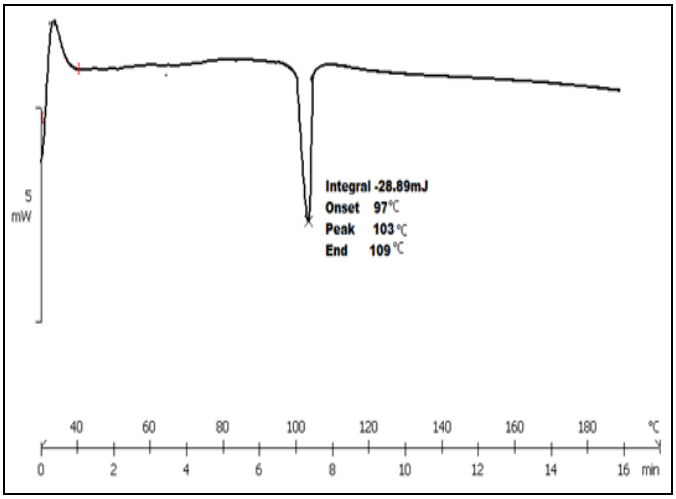

FIG. 9: THERMO GRAM OF ROSUVASTATIN CALCIUM AND β CD COMPLEX

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1. Angle of Repose (ø): Table "characterization of powder blends" shows the results obtained for angle of repose of all the optimized formulations batches. The values were found to be in the range of 28^0.84' to 28^0.90'. All formulations showed the angle of repose within 30^0which indicates a good flow property of the granules.

2. Bulk Density (Db): Bulk density results were shown in Table "characterization of powder blends". The loose bulk density for all the optimized formulations batches varied from 0.5256gm/cm^3 to 0.5646gm/cm^3. The values obtained lies within the acceptable range and not large differences found between loose bulk densities. This result helps in calculating the percent compressibility of the powder.

3 Tapped Density (Dt): Tapped density results were shown in Table" characterization of powder blends". The tapped density for all the preliminary formulations batches varied from 0.6474gm/cm^3 to 0.7050gm/cm^3. The values obtained lies within the acceptable range and not large differences found between tapped densities. This result helps in calculating the % compressibility of the powder.

4. Carrs Index: The percent compressibility of powder mix was determined from Carr's index. Table "characterization of powder blends" shows result obtained for percentage compressibility. The percent compressibility for optimized formulation batches lay within the range of 5.69 to 12.99 %. All formulations were shows good compressibility.

5. Hausners Ratio: Result obtained for Hausner's ratio. The Hausner's ratios for optimized formulation batches lie within the range of 1.2194 to 1.270. The formulation batches of the Hausner's ratios was found between 1.264 and 1.250.

6. Formulation Design: After performing preliminary trials for developing effective formulation, it was been suggested that preferred class of conventional tablets formulation composition had the following generalized formula as shown in table.

TABLE 6: CHARACTERIZATION OF POWDER BLENDS

Formulation batches	Evaluation Parameters				
	Angle of Repose	Bulk Density (g/cm^3) ± S.D.	Tapped Density (g/cm^3) ± S.D.	Carr's index (%)± S.D.	Hausner's Ratio ± S.D.
Rosu 1	28.84	0.5646(±0.024)	0.7050(±0.058)	05.69 (±0.42)	1.250(±0.12)
Rosu 2	28.36	0.5711(±0.042)	0.6948(±0.075)	8.50(±0.65)	1.3422(±0.09)
Rosu 3	28.90	0.5256(±0.047)	0.6427(±0.041)	12.99(±0.66)	1.2164(±0.14)
Rosu 4	28.54	0.5711(±0.042)	0.6948(±0.075)	8.50(±0.65)	1.3422(±0.09)
Rosu 5	28.36	0.5256(±0.047)	0.6427(±0.041)	12.99(±0.66)	1.2164(±0.14)

TABLE 7: GENERALIZED FORMULA

Ingredients	Percentage amount (%)
Active pharmaceutical agent	X
Polymer	95-X
Superdisintegrants (Sodium Starch Glycolate)	2-6%
Lubricant (Magnesium sterate)	0.5%-2%
Glidant (Talc)	0.5%-2%
Binder (AvicelPh 102)	0.5%-2%

The actual formulation design of conventional tablets of Rosuvastatin Calcium along preliminary batches with emphasis on comparative was shown in table "Formulation des.

TABLE 8: FORMULATION DESIGN

Ingredients (mg)	T1	T2	T3	T4	T5
Drug-CD complex eq.5mg Rosuvastatin Ca	7.3	7.3	7.3	7.3	7.3
Sodium starch glycolate	20	25	30	35	40
Mannitol	50	50	50	50	50
Camphor	10	10	10	10	10
Aspertame	5	5	5	5	5
Mg.Stearate (mg)	3	3	3	3	3
Talc	3	3	3	3	3
Avicel PH 102	200.70	195.70	190.70	185.70	180.70
Total Avg.Wt(mg)	300	300	300	300	300

Evaluation of Compressed Tablets: All the tablet formulations were subjected for organoleptic, physical and chemical evaluations as shape, thickness, hardness, friability, weight variation, in vitro disintegration time, drug content and in vitro dissolution studies.

1. Appearance: The size and shape of the tablets can also affect the disintegration time and subsequent dissolution profile. In general, a smaller tablet in terms of mass has a faster disintegration time than larger tablets, all other factors being equal. Similarly, a tablets shape with more surface area generally was a faster disintegration time than a tablets shape having less surface area, all other factors being equal. Randomly picked tablets from each formulation batch examined for shape and in presence of light for color. Tablets showed circular shape and white color.

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7. *In-vitro* Disintegration Time: Disintegration, the first important step for a drug absorption from a solid dosage form after oral administration was preliminarily focused. It was reported that tablets disintegration was affected by the particle size, the degree of substitution, and extent of cross-linkage. An important factor affecting the disintegration is the tablets hardness and/or the compaction force used in making the tablets hardness. The hardness of the tablets has an influence on the disintegration time as it affects the porosity of the matrix and, accordingly, the ability of water to penetrate through the matrix. All tablets disintegrated rapidly without disc in the IP test especially when used at optimum concentrations of selected super disintegrants. In the study, the relatively larger fragments generated by tablets containing sodium starch glycolate were not small enough to pass through the screen of the disintegration vessels.

TABLE 9: EVALUATION OF BATCH

Sr. No.	Formulation Code	Friability (%)	Weight Variation (mg ± SD)	Thickness (mm± SD)	Hardness (kg/cm.sq±SD)
1	ROSU 1	0.35	299.61±1.10	2.15 ± 0.21	4.1 ± 0.16
2	ROSU 2	0.27	298.34 ± 1.74	2.07 ± 0.19	4.2 ± 0.21
3	ROSU 3	0.39	299.54 ± 0.96	2.16 ± 0.14	4.0 ± 0.14
4	ROSU 4	0.35	299.61±1.10	2.15 ± 0.21	4.1 ± 0.16
5	ROSU 5	0.27	298.34 ± 1.74	2.07 ± 0.19	4.2 ± 0.21

8) Comparative Effect of Superdisintegrants:

TABLE 10: COMPARATIVE EFFECT ON DRUG RELEASE BY SUPERDISINEGRANT

Time	Marketed	% Drug Release				
		T1	T2	T3	T4	T5
0	0.000	0.000	0.000	0.000	0.000	0.000
5	34.474	19.528	20.049	31.268	27.791	28.680
10	36.921	21.855	23.779	35.325	34.305	34.634
15	40.231	26.684	27.110	39.439	39.773	41.401
20	43.359	29.183	32.197	41.777	43.882	47.386
25	46.749	35.169	35.172	46.841	49.003	53.342
30	51.527	36.094	38.718	50.697	51.883	59.550
35	56.019	37.616	41.087	55.566	57.682	65.017
40	61.499	42.418	43.602	61.278	62.009	78.083
45	65.853	50.102	50.694	65.848	65.434	99.363
50	70.088	67.279	68.016	70.084	71.929	102.222
55	76.081	76.075	84.121	76.077	75.398	
60	93.449	83.995	88.575	96.409	99.457	

DISCUSION: From the result it is observed that the complex of Rosuvastatin calcium and β-cyclodextrin at 1:1 ratio are adequately stable. In case of pure drug β-CD with a reduction in peak intensities. This confirms partial complexes formation i.e some part of Rosuvastatin calcium entrapped in CD- cavity. The DSC thermogram for the complexes showed the persistence of the endothermic peak of Rosuvastatin calcium for kneading method. The reduction in peak intensity can be explained on the basis of major interaction between the Rosuvastatin calcium and

cyclodextrin. The endothermic effect of cyclodextrin and Rosuvastatin calcium is slightly shifted to lower temperature for kneading complexes, indicating that Rosuvastatin calcium 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. The dissolution rate increases for the kneading method is due to the more intensive mixing process between the two components which leads to wetting effect of the cyclodextrin.

The IR spectra of kneading method shows significant shift of hydroxyl functional group. This may indicate that the Rosuvastatin calcium-β-CD 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- CD.

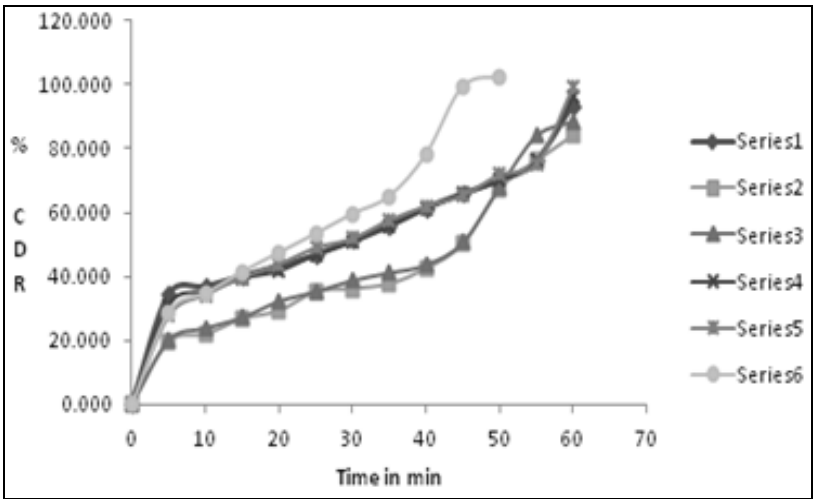

FIG. 10: COMPARATIVE EFFECT ON DRUG RELEASE BY SUPER DISINTEGRANTS

CONCLUSION:

- All the formulations prepared by kneading method have shown satisfactorily better physicochemical properties.
- Complexes prepared of different ratios have shown enhanced drug solubility and dissolution rate.
- Formulation i.e. Rosu-BCD1, Rosu-BCD2, Rosu-BCD3, Rosu-BCD4, Rosu-BCD5 have shown increase in solubility in comparison with marketed preparation respectively.
- The formulation prepared by different concentration of Super disintegrants has shown improved drug release profile.
- The combination of a complex of Drug: Polymer (1:1) and super disintegrants sodium starch glycolate 40mg (Rosu-BCD5) is showing best optimized formulation with respect to onset of action and percentage drug release.

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