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DISSOLUTION ENHANCEMENT OF ROSUVASTATIN CALCIUM BY USING VARIOUS GENERATIONS OF HYDROPHILIC POLYMERS: A COMPARATIVE STUDY

K. Sibi *, K. P. Mohanraj, S. Satheesh Kumar, C. Gowrishankar and P. Karthick

Department of Pharmaceutics, Nandha College of Pharmacy, Erode - 638052, Tamil Nadu, India.

Keywords:

Solid dispersion, Dissolution enhancement, RST, Hydrophilic carriers, Solubility and bioavailability

Correspondence to Author:
K. Sibi

Research Scholar,
Department of Pharmaceutics,
Nandha College of Pharmacy,
Erode - 638052, Tamil Nadu, India.

E-mail: sibi3004@gmail.com

ABSTRACT: Oral administration is the preferred route of drug administration owing to its convenience, patient compliance, and cost-effectiveness. The study aspired to augment the solubility and dissolution rate of Rosuvastatin calcium (RST) by using the solid dispersion (SD) technique with various generations of hydrophilic polymers. Hot melt and solvent evaporation methods were employed to prepare SD using various hydrophilic carriers such as Urea, PEG-6000, Poloxamer-F127 and β-cyclodextrin (β-CD). The prepared SD was evaluated and the optimized formulation was subjected to tablet formulation by direct compression method and a quality control test was performed. After screening all the hydrophilic polymers, SD was prepared by using β-CD shows a remarkable increase in solubility and dissolution. Among the ratios 1:1, 1:5 and 1:7, SD with 1:5 showed increased solubility and maximum drug release and shows good surface characteristics were identified by SEM analysis. Finally, the prepared core tablet CF2 was found to have better dissolution efficiency of 96.34% drug release at 60mins, when compared with CF1 (81.46%) and the Marketed tablet (85.44%). The result suggested that the optimized formulation of SD with the hydrophilic carrier is an effective tool in the predominant increase in solubility and dissolution rate, thereby enhancing the solubility and bioavailability.

INTRODUCTION: The oral route of drug administration has several advantages owing to its ease of drug administration, cost-effectiveness and patient compliance. From the research and development perspective, the strengths are formulation stability, dose precision, storage, the choice of sterile facilities, and a decreased risk of acute drug response. As a consequence, when considering a dosage form, pharmaceutical researchers invariably proceed with the invention of a solid oral dosage form [1].

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The aqueous solubility of drugs controls the rate of dissolution and bioavailability of drugs. As a result, poorly water-soluble drugs show erratic and incomplete absorption from the GIT, leading to therapeutic failure. Solubility is the dominant factor regulating the efficacy of oral drug administration. Because of their limited solubility in GIT fluids, poorly water-soluble biologically active drugs typically have lower oral bioavailability.

In attempts to enhance the solubility of chemically active biological elements, a multitude of strategies have been employed, notably micronation, salt preparation, nanonization, the fabrication of dispersion, pH regulation, complexation, *etc*. The most challenging aspect of pharmaceutical drug development continues to be enhancing the oral solubility of poorly water-soluble drugs. Despite

salt formation solubilization and particle size reduction being extensively employed to fast-track drug dissolution and eventually oral drug absorption and bioavailability, these methods have several limitations, like the fact that higher salt dissolution in the digestive tract may not always be feasible, even when salts of the respective drug can be developed, because salts often convert back to clusters of their respective acid and base forms. Surfactants and cosolvents are typically used to solubilize pharmaceuticals in organic solvents or aqueous media, resulting in liquid formulations that are typically undesirable from the perspectives of patient acceptability and economic viability. Although increasing the dissolution rate by reducing particle size is a typical practice, there is a practical limit to the amount of size reduction that can be accomplished using common techniques such as controlled crystallization, grinding, pearl milling, etc. Because of handling issues and poorly wettable and water-soluble medicines, using very fine powders in dosage forms may also pose challenges [2].

Rosuvastatin is a statin derivative that suppresses cholesterol levels by inhibiting the enzyme HMG-CoA reductase (3-hydroxy-3-methyl glutaryl CoA), which is accountable for converting mevalonate to cholesterol, the first and earliest stage in the biosynthesis of cholesterol. It is a potent lipid-lowering agent used to treat hyperlipidemic individuals. It is also employed in the management of Alzheimer's, benign prostate hyperplasia, and osteoporosis. Despite being a BCS class II medication, RST has limited bioavailability (20%) and poor water solubility (0.33 mg/ml) since it is crystalline in form [3].

If a solid dispersion is employed, a portion of the drug dissolves right away to saturate the gastrointestinal fluid, and the extra drug precipitates out as tiny, submicron-sized colloidal particles or greasy globules. Therefore, solid dispersion has emerged as one of the most active areas of research in the pharmaceutical industry due to the promising increase in the bioavailability of drugs that seem to be poorly water-soluble. Solid dispersions have garnered a great deal of attention as a promising method for increasing the rate of dissolution and, consequently, the bioavailability of a variety of hydrophobic medicines [4].

A class of solid products with at least two distinct components, often a hydrophilic matrix and a hydrophobic medication, are referred to as solid dispersions. Either the matrix is crystalline or amorphous. The medication can be spread molecularly in crystalline or amorphous particles (clusters) by reducing particle size, improving wettability and dispersibility, transforming the drug's crystalline form to amorphous, and reducing drug particle aggregation and agglomeration, solid dispersions speed up the dissolution of pharmaceuticals that are weakly water-soluble. Solid dispersion is mostly preferred due to its advantages, like particles with reduced particle size [5], particles with improved wettability [6], particles with higher porosity, and drugs in an amorphous state. The study intended to employ the solid dispersion (SD) methodology with a variety of hydrophilic carriers to enhance the solubility and dissolution rate of rosuvastatin calcium (RST).

Various preparation methods for solid dispersions have been reported, such as the kneading technique, solvent evaporation method, co-perception method, holt melt method, co-grinding method, gel entrapment technique, spray dry method, lyophilization technique, electrospinning method, drop solution method, melt extrusion method, and melt agglomeration process [7]. To formulate SD from RST, hot melt, and solvent evaporation techniques are used, and the choice of the method is based on the melting points of the carriers like urea, PEG-600, poloxamer-F127 and β-cyclodextrin that are used in the formulation of solid dispersions of RST.

The selection of carriers is based on the use of carriers in the formulation of solid dispersion, which is classified into four generations. In the first generation, crystalline carriers are used in the preparation of solid dispersion; in the second generation, amorphous carriers are used instead of crystalline carriers, in which most drugs are dispersed in the polymer matrix; in the third generation, surfactants or a mixture of surfactants and amorphous carriers are used; and in the fourth generation, complexing agents or carriers control drug release [8]. The optimized formulation of carriers containing RST is subjected to tablet formulation by the direct compression method.

MATERIALS AND METHODS:

Materials: RST was kindly donated by NTK Pharma Pvt. Ltd. (Maharashtra, India). Following chemicals were purchased: PEG 4000 (Merck Specialties Private Ltd., Mumbai, India), urea (SD fine chem), PEG 600(SD fine chem), Poloxamer F127(Spectrum chemicals), β-cyclodextrins (Nice chemicals) and chemicals received as gift samples were Sodium Hydroxide (Nice chemicals), Magnesium stearate (Phoenix Biologicals Pvt. Ltd.), Microcrystalline cellulose (Nice chemicals), Crospovidone (Phoenix Biologicals Pvt. Ltd.), PVP K30 (Loba Chemie), Aerosil (Phoenix Biologicals Pvt. Ltd.), Methanol (Changshu Hongsheng Fine Chemical Co., Ltd) and Ethanol (Changshu Hongsheng Fine Chemical Co., Ltd). All other chemicals and reagents were of analytical grade.

Methods:

Pre-formulation Studies: Evaluating the physiochemical properties of the drug molecule is crucial for creating a pharmaceutical dosage form. The first step in developing a dosage form is pre-formulation research. Studying the physical and chemical characteristics of pharmacologically active compounds on their own and when coupled with excipients is crucial. The pre-formulation research is done to gather data on the drug ingredients so that this data may be used to create a formulation [9].

The goal of pre-formulation research is to determine the physiochemical characteristics of pharmaceuticals and excipients that may affect the formulation process, formulation design and pharmacokinetic and biopharmaceutical aspects of the finished product. The investigations for the pre-formulation are done as follows: The fundamental purpose of pre-formulation studies is to produce data that will aid the environment and enhance the creation of stable and bioavailable dosage forms [10].

Organoleptic Properties: The color, odor and taste of the drug were recorded using descriptive terminology [9-10].

Melting Point: The melting point of the pure drug sample is determined by placing the drug powder in a capillary tube and sealing one end. The capillary tube should be 6-7 cm and 1 mm in diameter. The substance should be standing in the capillary 3–4 mm from the bottom of the packed capillary tube. The capillary tube is wetted with the liquid in the bath and placed in an iron stand fixed in the thermometer. The capillary remains stuck to the thermometer by itself and is so adjusted that the solids in it stand opposite the middle of the mercury bulb. The thermometer is lowered into a beaker containing paraffin oil, and the beaker is heated slowly to a uniform temperature with constant stirring. When the substance in the capillary shows signs of liquefaction, the burner is removed with constant stirring. The temperature at which the substance just melts and becomes transparent is noted [11].

λ_{max} Determination: The standard stock solution of RST is prepared by dissolving 10 mg of the drug in a 100 ml volumetric flask using a phosphate buffer at pH 6.8, which contains 100 µg/ml. Working standard solutions of 10 µg/ml were scanned in the UV range of 200–400 nm to obtain the absorbance [12].

Solubility Study: To determine drug solubility, it is dissolved in acid buffer (pH 1.2), phosphate buffer (pH 6.8) and distilled water. The sample was shaken for 8 h at 37 °C in a mechanical shaker. The supernatant was filtered using Whatman filter paper, and the filtrate was analyzed by a UV-visible spectrophotometer [13, 14].

FT-IR Studies: The possibility of drug-carrier interaction is investigated by FT-IR. Pure RST, excipients, polymers, and drug and polymer mixtures (PM1, PM2, PM3 and PM4) and optimized formulations are subjected to FTIR studies to investigate the drug, polymer, and excipient interactions. The analysis is performed by using an FT-IR Spectrophotometer (SHIMADZU, Japan), and the IR spectra of the test samples are obtained by the KBr Pellet Technique. The scanning range is 450–4000 cm^{-1} and the resolution is 4 cm^{-1} [4, 15].

Preparation of Standard Curve:

Preparation of 0.1M Hydrochloric Acid: 8.5 ml of hydrochloric acid is transferred into 1000 ml of volumetric flask and made up the volume with distilled water [16].

Preparation of Phosphate Buffer (pH-6.8): 6.80 g of potassium Dihydrogen orthophosphate and

0.90 g of sodium hydroxide are weighed accurately and dissolved in 1000 ml of distilled water [16].

Standard Curve of Rosuvastatin Calcium in 0.1N HCl: In a 100 ml volumetric flask, 10 mg of calcium rosuvastatin is accurately measured, and dissolved in a pH 1.2 acid buffer, and the primary stock solution, containing 100 g/ml, is prepared. 10 ml of this main stock solution is pipetted into a 100 ml volumetric flask and 100 ml of acid buffer pH 1.2, containing the drug at a concentration of 10 µg/ml, is used to make up the volume with acid buffer.

Pipette 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 8 ml, and 10 ml (1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml, 5 µg/ml, 6 µg/ml, 8 µg/ml and 10 g/ml from the aforementioned secondary stock solution into a 10 ml volumetric flask and then adjust the volume with a pH 1.2 acid buffer. The drug's absorbance was determined using a UV spectrophotometer at 241 nm. The concentration (X-axis) and absorbance (Y-axis) data are used to plot the calibration curve [12].

Standard Curve of Rosuvastatin Calcium using Phosphate Buffer pH 6.8: In a 100 ml volumetric flask, 10 mg of RST is accurately measured, dissolved in a pH 6.8 acid buffer, and the primary stock solution, containing 100 g/ml, is prepared. 10 ml of this main stock solution is pipetted into a 100 ml volumetric flask and 100 ml of phosphate buffer pH 6.8 containing the drug at a concentration of 10 µg/ml is used to make up the volume with acid buffer. Pipette 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 8 ml and 10 ml (1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml, 5 µg/ml, 6 µg/ml, 8 µg/ml and 10 g/ml from the aforementioned secondary stock solution into a 10 ml volumetric flask and then adjust the volume with a pH 6.8 phosphate buffer. The drug's absorbance was determined using a UV spectrophotometer at 241 nm. The concentration (X-axis and absorbance (Y-axis) data are used to plot the calibration curve [12].

Phase Solubility Study of Drugs with Different Percentages of Carriers: An excess amount of RSC is added to a volumetric flask containing 10 ml of aqueous carrier solutions (pH 1.2 and 6.8 buffers) of Urea, PEG 6000, Poloxamer F 127 and Beta-cyclodextrin at 3, & 6% w/v [13, 17] concentrations and placed in a Mechanical shaker and agitated at room temperature for 8 h. The solutions are filtered and analyzed at 241 nm using a UV-visible spectrophotometer. The study was performed in triplicates [4]. An excess amount of RST is added to a volumetric flask containing 10 ml of aqueous carrier solutions (pH 1.2 and 6.8 buffers) of Urea, PEG 6000, Poloxamer F 127 and Beta-cyclodextrin at 3, & 6% w/v [13,17] concentrations and placed in a Mechanical shaker and agitated at room temperature for 8 h.

The solutions are filtered and analyzed at 241 nm using a UV-visible spectrophotometer. The study was performed in triplicates [4]. An excess amount of RST is added to a volumetric flask containing 10 ml of aqueous carrier solutions (pH 1.2 and 6.8 buffers) of Urea, PEG 6000, Poloxamer F 127 and Beta-cyclodextrin at 3, & 6% w/v [13, 17] concentrations and placed in a Mechanical shaker and agitated at room temperature for 8h. The solutions are filtered and analyzed at 241 nm using a UV-visible spectrophotometer. The study was performed in triplicates [4].

Preparation of Solid Dispersion:

Preparation of Solid Dispersion by Melting Method: The carrier (urea and PEG 6000) is added to a clean China dish with different ratios as shown in **Table 1** and heated in the electric heating mantle until the carriers are melted. Then the drug is dispersed into the melted carrier by being stirred with a glass rod and finally cooled to room temperature. The resulting mass was transferred to desiccators containing $CaCl_2$ and stored until completely dry. The solid mass that results is then pulverized in a mortar to produce a dry, free-flowing powder. The powder is made to pass through a sieve no. 60 [18, 21].

Preparation of Solid Dispersion by Solvent Evaporation Method: The carrier (Poloxamer F127 and β- cyclodextrin) is dissolved in different ratios as shown in **Table 1** in 10 ml of distilled water, to which the drug is added and stirred well to dissolve the drug 5 ml of ethanol is added to it, and tried to get clear a solution. The substance is heated to evaporate the solvents. The resulting mass is transferred to desiccators containing $CaCl_2$ and stored until completely dry.

The solid mass that resulted was then pulverized in a mortar to produce a dry, free-flowing powder. The powder is made to pass through a sieve no. 60 [19, 21].

TABLE 1: FORMULATION CHART OF SOLID DISPERSION

S. no.	Method used	Formulations	Composition (Drug: Carrier)	Ratio (Drug: Carrier) (mg)
1	Melting method	SD F1	Rosuvastatin Calcium + Urea	200:200
2		SD F2	Rosuvastatin Calcium + Urea	200:1000
3		SD F3	Rosuvastatin Calcium + Urea	200:1400
4		SD F4	Rosuvastatin Calcium + PEG6000	200:200
5		SD F5	Rosuvastatin Calcium + PEG6000	200:1000
6		SD F6	Rosuvastatin Calcium + PEG6000	200:1400
7	Solvent	SD F7	Rosuvastatin Calcium +Poloxamer F127	200:200
8	evaporation	SD F8	Rosuvastatin Calcium +Poloxamer F127	200:1000
9	method	SD F9	Rosuvastatin Calcium +Poloxamer F127	200:1400
10		SD F10	Rosuvastatin Calcium + β-cyclodextrin	200:200
11		SD F11	Rosuvastatin Calcium + β- cyclodextrin	200:1000
12		SD F12	Rosuvastatin Calcium + β -cyclodextrin	200:1400

Evaluation of Solid Dispersion:

Drug Content: A solid dispersion containing 50 mg is weighed accurately and dissolved in 50 ml of phosphate buffer at pH 6.8. The solution was filtered, and the RST content was analyzed by observing absorbance in a UV spectrometer at 241 nm [12].

Saturation Solubility: RST and solid dispersions in exorbitant quantities are placed in volumetric flasks containing 10 ml of pH 6.8 phosphate buffer. The samples are placed in a mechanical shaker at 37 °C and 50 rpm for 8 h. A UV spectrophotometer is used to analyze the solutions [12].

FTIR Spectroscopy: The FTIR spectra of the drug and its formulations are carried out using an FT-IR spectrophotometer (SHIMADZU, Japan). Each formula (5 mg) is mixed with about 100 mg. Potassium bromide was compressed into discs under a pressure of 10,000 to 15,000 pounds per square inch. The IR spectra were recorded using an infrared spectrometer [13, 17].

Formulation Chart of Core Tablet: The composition of RST core tablets is depicted in **Table 2**. All of the powders used are passed through Sieve No. 45 separately. Rosuvastatin calcium, PVP K30, crospovidone, and microcrystalline cellulose are mixed by the geometric addition technique. Aerosil and magnesium stearate are then added to the mixed powders. Finally, the direct compression of 300 mg of the blend was weighed and compressed by a tablet punching machine equipped with 10 mm flat-faced punches [20].

TABLE 2: FORMULATION CHART OF CORE TABLET

Ingredients	C F1	C F2
Rosuvastatin calcium & β-cyclodextrin carrier	10	10
PVP K30	10	10
Crospovidone	15	15
Microcrystalline cellulose	261	261
Aerosil	2	2
Magnesium stearate	2	2
Total weight	300	300

* All weights are expressed in milligrams.

Pre-compression Parameters:

Bulk Density: The weight of the powder divided by the bulk volume it takes up is termed the bulk density. It is expressed as gm/ml. The finely weighed amount of powder mixture that had earlier been agitated to break up any agglomerates that had formed was introduced into the measuring cylinder, and the volume was recorded [22, 23]. The following equation is employed to estimate bulk density:

Bulk Density = (mass of the powder) / (Bulk volume)

Tapped Density: The weight-to-tapped-volume ratio of a powder is referred to as the tapped density. With the use of a funnel, the powder is poured into the measuring cylinder. At 2 sec increments, the measuring cylinder was tapped on a wooden surface and the volume gained is the tapped volume [22, 23]. It is expressed as g/ml.

Tapped Density = (mass of the powder) / (Tapped volume)

Angle of Repose: The angle of repose of the powder blend is determined by the funnel method. The accurately weighed powder blend is taken in the funnel. Allow the powder mixture to freely

flow through the funnel and onto the surface the following equation is used to figure out the angle of repose and evaluate the diameter of the powder cone [22].

$$\text{Tan } \theta = \text{height} / \text{radius}$$

Compressibility Index (CI): The compressibility index is measured using the values of bulk density and tapped density. The following equation is used to find the compressibility index [22].

$$\text{Compressibility index} = (\text{Tapped density} - \text{Bulk density}) / (\text{Tapped density}) \times 100$$

Hausner's Ratio: Hausner's ratio is an important character to determine the flow property of powders and granules and is measured by the ratio of the tapped density to the bulk density. This can be calculated by using the following formula [22].

$$\text{Hausner's ratio} = (\text{Tapped density}) / (\text{Bulk density})$$

Post-compression Parameters:

Thickness: The thickness of the tablets is determined by using the Vernier caliper scale. Five tablets are taken and average values are calculated [10, 12].

General Appearance: The general appearance of tablets is observed. The general appearance parameters are shape, color and the presence or absence of odor and taste. They were evaluated visually [10, 12].

Hardness: The tablet must possess sufficient strength, and the hardness of five tablets is determined by using the Pfizer hardness tester. The average values are calculated and can be expressed in kg/cm^2 [10, 12].

Friability: Friability can be performed in the Roche friabilator by introducing ten pre-weighed tablets into the friabilator. The machine is then set to rotate at 25 rpm for 4 min. dropping from a distance of six inches with each revolution [12]. The tablets were then reweighed. The difference in weight is noted and expressed as a percentage. Weight loss of less than 1% is deemed acceptable and within the standards10.

$$\% \text{ Friability} = (W1 - W2) / W1 \times 100$$

Where, W1= weight of tablets before the test. W2= weight of tablets after test.

Disintegration Time: A disintegration test apparatus is used to determine the *in-vitro* disintegration time. One tablet and one disc were inserted into each of the six test tubes of the apparatus. The time in min or sec required for the pill to completely disintegrate in distilled water without any discernible bulk remaining in the disintegration apparatus [10, 20].

Weight Variation Test: The individual weight of erratically selected twenty tablets is recorded. Calculate the average weight and contrast the individual tablet weight to the average weight and 20 the average weight was calculated by

$$\text{Average weight} = (\text{Weight of 20 tablets}) / 20$$

Uniformity of Drug Content: 20 tablets are erratically selected from each formulation and weighed then crushed. The powder selfsame to 300 mg of RST is weighed and diluted to 100 ml with a sufficient amount of buffer. Then aliquot filtrate is diluted suitably. The absorbance of the resulting solution is measured at 241 nm against a blank solution using a UV visible spectrophotometer (LABMAN; PLMSP UV 1900) [22].

Scanning Electron Microscopy: Morphological evaluation of the coarse drug and prepared formulation was performed and comparisons were made with a scanning electron microscope. All samples were evaluated on a brass stub using carbon double-sided tape. The samples were gold coated (thickness ≈ 15–20 nm) with a sputter coater using an electrical potential of 2.0 kV at 25 mA for 10 minutes. An excitation voltage of 20 kV was used in experiment [23].

***In-vitro* Dissolution Studies:** *In-vitro* dissolution studies for the pure drug, the core tablet without solid dispersion, the formulation SD F11 and the marketed tablet are carried out in a pH 6.8 phosphate buffer using the dissolution apparatus USP type 2 (paddle) method [4]. The test is performed at a stirring speed of 75 rpm with a temperature maintained at 37±0.5 °C in 900 ml of pH 6.8 buffer for 60 min. The dissolution samples of 5 ml are withdrawn at sampling intervals and the dissolution medium is replaced with 5 ml of pH 6.8 phosphate buffer after each sample withdrawal [10]. The concentration of the drug was estimated in the aliquots withdrawn by measuring the absorbance at

241 nm using a UV spectrophotometer after filtering the solution through the Whatman filter paper. The concentration was determined from the standard plot and finally, the results are plotted as cumulative % drug release versus time [17, 20].

RESULT AND DISCUSSION:

Pre-formulation Studies of the Drug:

Organoleptic Properties: Physical observation of the drug revealed that RST is a white solid powder.

Melting Point: The melting point of RST is seen to be in the range of 121 ^{o}C. The reported melting point of the drug was found at 122 ^{o}C, hence experimental values were in good agreement with official values.

λ_{max} Determination: The maximum absorption of RST was found to be 241 nm represented in the **Fig. 1.**

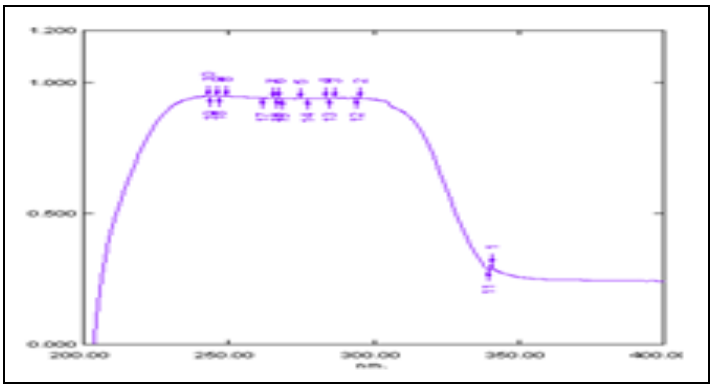

FIG. 1: ABSORPTION MAXIMA OF ROSUVASTATIN CALCIUM

Solubility Study: The solubility of RST in different physiological solvents was represented the **Table 3**. The drug has higher solubility in a pH 6.8 buffer (699.0 mg/ml).

TABLE 3: SOLUBILITY DATA OF RST IN DIFFERENT PHYSIOLOGICAL SOLVENTS

Physiological solvents	Solubility in mg/ml
pH 1.2 buffer	250.3
pH 6.8 buffer	699.0
Distilled water	359.4

Incompatibility Study:

RST Pure Drug: The IR spectrum was measured in the solid state as KBr dispersion. The IR spectrum of RST is represented in **Fig. 2** observed peaks are shown in **Table 4**. For these peaks are similar to the reported peaks of RST.

Drug-Carrier Interaction Study: The major peaks obtained in the pure drug were in the same characteristic bands without any significant spectral changes.

The FT-IR peak of spectra for β -CD solid dispersion showed No shift and No Disappearance of the characteristic peaks suggesting that there is No Interaction between the drug and indicating that they were chemically compatible. The results are shown in **Table 4** and **Fig. 3.**

TABLE 4: FT-IR INTERPRETATION OF PURE DRUG, CARRIERS AND RST-SD

Samples	C-F	COOH	S=O	OH	C-O	C=O
Pure drug	1150.46	1549.7	1338.51	-	-	-
Urea	-	-	-	-	-	1339.47
PEG 6000	-	-	-	3291.5	-	-
Poloxamer F127	-	-	-	3384.84	1280.65	-
β-cyclodextrin	-	-	-	3373.21	1339.47	-
PM 1	1058.55	1600.81	-	3604.71	-	1626.84
PM 2	1068.78	1549.7	1342.36	3501.52	-	-
PM 3	1112.85	1549.7	1343.33	3566.14	1280.5	-
PM 4	1028.95	1546.8	1335.61	3347.23	1335.61	-
SD F2	1068.49	1605.63	1334.65	-	-	1622.02
SD F5	1108.99	1547.77	1330.23	3552.63	-	-
SD F8	1112.85	1552.59	1342.36	3507.31	1342.36	-
SD F11	1028.95	1552.59	1335.63	3331.3	1335.61	-

Determination of Standard Calibration Curve:

A Standard Curve in 0.1N HCL: Beer's law is obeyed when a graph of absorbance (Y-axis) versus concentration (X-axis) is generated due to the linearity over the concentration range of 1 to 10 mcg/ml. Results are shown in **Fig. 2.**

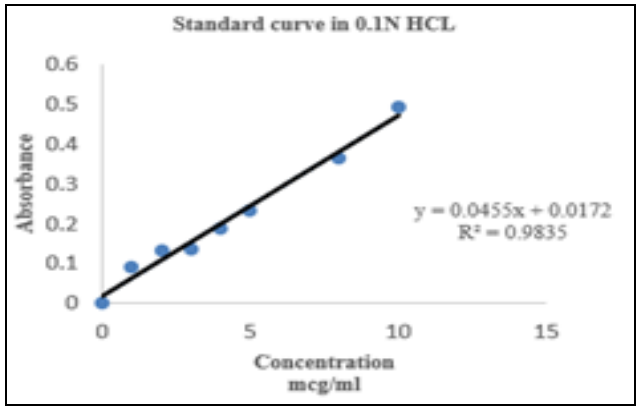

FIG. 2: STANDARD CURVE IN 0.1N HCL

A Standard Curve in Phosphate Buffer: Beer's law is obeyed when a graph of absorbance (Y-axis) versus concentration (X-axis) is generated due to the linearity over the concentration range of 1 to 10 mcg/ml. Results are shown in **Fig. 3.**

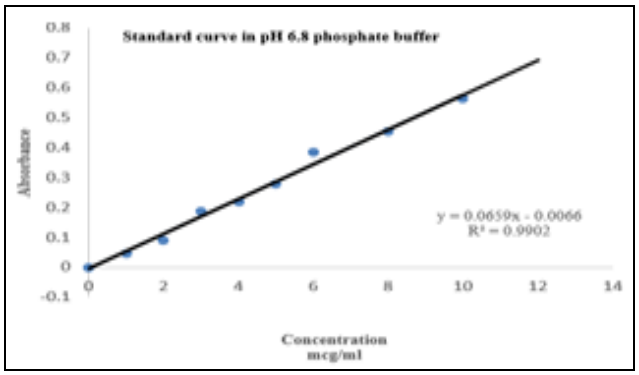

FIG. 3: STANDARD CURVE IN PH 6.8 PHOSPHATE BUFFER

Phase Solubility Study: The phase solubility results of RST with different carriers were found in below **Fig. 4**. It shows that β-CD has a more soluble drug than other carriers. So -CD was used for the final formulations SD F10, SD F11 and SD F12 in the ratios of 1:1, 1:5, and 1:7 (Drug: Carriers).

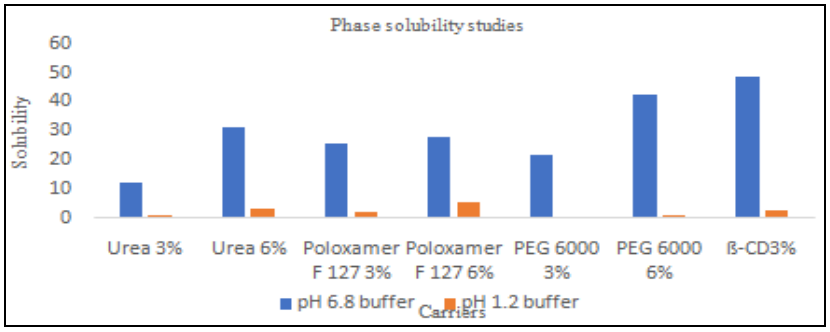

FIG. 4: PHASE SOLUBILITY STUDIES

Drug Content: The drug content of the Solid dispersions SD F10, SD F11 & SD F12 was found to be 98.2, 98.9 & 98.3%. The carrier concentration increased the drug dispersed to the carriers shows optimized results.

Saturation Solubility: The saturation solubility increased with an increase in carrier concentration. This might be due to the better wetting ability associated with carriers.

Formulation SD F11 shows a higher concentration of drug solubility. The saturation solubility of the prepared solid dispersion is represented in **Fig. 5.**

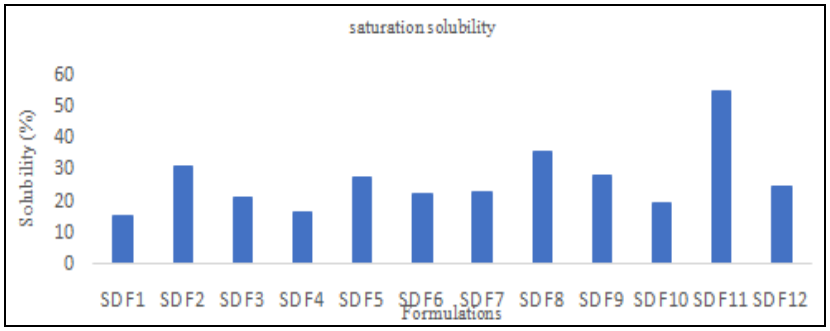

FIG. 5: SATURATION SOLUBILITY

Evaluations for Core Tablet Preparation:

Pre-formulation Studies of Drug, Polymer & Excipients: Physical characteristics including the angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio were used to characterize drugs, polymers and excipients. The physical properties of all the materials are within an acceptable range, as shown in **Table 5.**

TABLE 5: PRE-COMPRESSION PARAMETERS OF DRUG, POLYMERS & EXCIPIENTS

Ingredients	Angle of repose(Θ)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index	Hausner's ratio
RSC	25°87	0.556±0.014	0.631±0.007	11.88	1.134
PVP K 30	23°57	0.690±00.018	0.813±0.015	15.129	1.178
Crospovidone	24°62	0.570±0.022	0.656±0.006	13.109	1.150
MCC	30°58	0.456±0.005	0.506±0.002	9.881	1.109
Aerosil	28°23	0.733±0.007	0.833±0.001	10.914	1.122
Mag. Stearate	33°73	0.275±0.004	0.310±0.002	11.29	1.127

Mean ±SD (n=3).

Pre-compression Parameters of Core Tablet Granules:

Angle of Repose: The prepared powder blends are evaluated for their flow properties **Table 6**. The resistance offered to the movement of particles can be judged by the angle of repose. It provides a qualitative and quantitative assessment of internal cohesive and frictional forces under a low level of external load applied during mixing and table ting. The angles of repose of all three samples were within the range of 19–21°. These values indicate that the powder blend had good flow properties.

Bulk Density & Tapped Density: The powdered blends are evaluated for bulk density and tapped density by using bulk density apparatus, and the results were shown in **Table 6**. The bulk density was found in the range of 0.460±0.33 - 0.514±0.39 gm/cc. The tapped density ranged between 0.563±0.39 -0.672±0.34 gm/cc. Which indicates that powder is loosely packed. These values were then used to calculate Carr's index and Hausner's ratio to check the flow ability of powder.

Carr's Index & Hausner's Ratio: The Compressibility index exists in the range between 12.39±0.27 &13.54±0.29. The Hausner's ratio of all samples between 1.116±0.25 & 1.054±0.16 are shown the table no.6.These values indicate that the prepared blends possessed minimum interparticulate interactions and good flow properties which is a preliminary requirement for formulating the tablets.

TABLE 6: PRE-COMPRESSION PARAMETERS OF CORE GRANULES

Sample	Angle of repose(Θ)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index	Hausner's ratio
C F1	20° 80	0.514±0.29	0.672±0.34	12.39±0.27	1.116±0.25
C F2	19° 61	0.460±0.33	0.563±0.39	13.54±0.29	1.054±0.16

Mean ±SD (n=3).

Post-compression Parameters of Core Tablets: The tablets were white in color, flat in shape and had a smooth surface. The hardness of all sample tablets was adjusted to 3 kg/cm^2. The friability of all three samples of tablets was within 1%, which was an indication of the good mechanical resistance of the tablet.

The drug content of the formulations C F1 and C F2 is 98.23 to 97.01%. The thickness is measured for all tablets and found to be within the acceptable range. The weight of the tablet varied between 300.1±0.62 to 302.2±0.98 mg, as represented in **Table 7**. The variation in weight was within the range of ± 5% complying with pharmaceutical specifications. Disintegration time is essential for drug delivery from tablets, which are designed for the rapid bursting of granules.

The *in-vitro* disintegration times of prepared tablets range between 24 and 26 sec. This due to the preparation of the tablets using Crospovidone showed rapid disintegration in 26 sec.

TABLE 7: POST-COMPRESSION PARAMETERS OF CORE TABLETS

Sample	**Average weight	*Hardness	*Thickness	**Friability	DT (seconds)	Drug content
C F1	300.1±0.62	3.5±0.14	3.9±0.001	0.600±0.008	26	98.23
C F2	302.2±0.98	3.1±0.15	3.7±0.004	0.398±0.008	24	97.01

Mean SD*(n=6), Mean SD** (n=20)

Scanning Electron Microscopy: Scanning electron microscopy was carried out to study the surface morphology of particles. It was found that the CF2 (SD F11 of RST) revealed a smooth texture as shown in **Fig. 6**. The SEM picture of pure drug particles was found abundantly with larger particle sizes when compared to the SD formulation. Thus, the optimized formulation of RST- produced better surface characteristics. The surface structure of optimized SD in the SEM appeared good in shape. This micrograph agreed with those measured by particle size distribution.

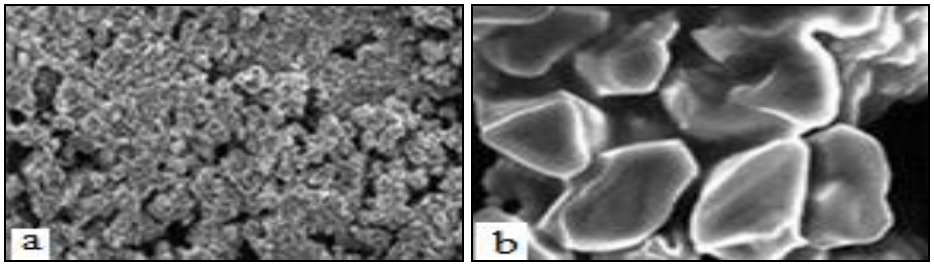

FIG. 6: (A): SEM OF RSC, (B) SEM OF OPTIMIZED FORMULATION CF2

***In-vitro* Release Studies:** The release profiles of the formulations were determined using USP dissolution apparatus type II. The core tablets that were placed in the dissolution flask contained a pH 6.8 phosphate buffer solution. Then the paddle was rotated at 75 rpm and immediately aliquots of a 5 ml sample were withdrawn at every interval up to 60 min. The drug content was determined at 241 nm by using a UV spectrophotometer. The *in-vitro* drug release studies were performed to evaluate the release of core tablets. The cumulative percentage release in pH 6.8 buffer for the marketed drug, C F1, and C F2 was recorded, and the SD C F2 showed higher drug release, 85.44%, 81.46% and 96.34% within 60 minutes, respectively. The cumulative amounts of drug released from the marketed drug, C F1 and C F2, are shown in **Fig. 7**. The dissolution rate of tablets formulated with -beta-cyclodextrin solid dispersion was faster.

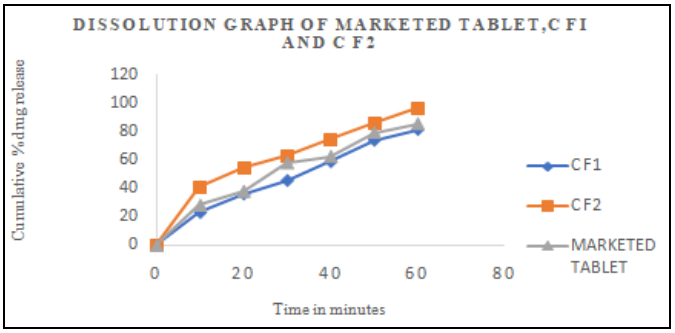

FIG. 7: DISSOLUTION STUDY OF MARKETED DRUG, PURE DRUG(C F1) AND SD(C F2)

CONCLUSION: The current study aims to improve the solubility and dissolution of poorly soluble drugs through the use of various solid dispersion formulation methods. The solid dispersion was prepared by adding the carriers, i.e., urea, PEG6000, Poloxamer F127 and β-cyclodextrin at different concentrations in the ratios of 1:1, 1:5, and 1:7, by using the solvent evaporation method and the hot melt method. The saturation solubility demonstrates that the cyclodextrin formulation SD F11 was chosen as the best formulation to improve the dissolution rate of RST. The surface characteristic study was performed which appears good in shape.

The optimized solid dispersion SD F11 was made into a tablet by the direct compression method and it was characterized by its evaluation, such as weight variation, thickness, content uniformity, disintegration time and *in-vitro* dissolution studies. It was then compared to the pure drug, C-F1, as well as the marketed drug. Finally, the prepared core tablet C F2 was found to have a better dissolution efficiency of 96.34% drug release at 60mins, when compared with C F1's 81.46% and the market tablet's 85.44%. According to the results of the in vitro dissolution study, the tablet prepared from optimized solid dispersion CF2 containing Rosuvastatin calcium had better dissolution capability than marketed and pure drug

formulations and the hydrophilic carrier beta-cyclodextrin increased the solubility of Rosuvastatin calcium at a specific concentration.

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