

Original Article

“FORMULATION DEVELOPMENT AND SOLUBILITY ENHANCEMENT OF ROSUVASTATIN CALCIUM BY USING HYDROPHILIC POLYMERS AND SOLID DISPERSION METHOD”

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ABSTRACT

Objective: Preparation of Rosuvastatin Calcium by Using Hydrophilic Polymers and Solid Dispersion Method, Rosuvastatin calcium is a Dyslipidaemic agent, which act as a selective competitive inhibitor of HMG CoA educates enzyme and is used in the treatment of hyperlipidemia.

Methods: In the present work, Solid Dispersion was prepared by kneading method to increase the solubility of Rosuvastatin Calcium.

Results: Solid dispersions were evaluated by determining percentage yield, drug content, solubility, Scanning electron microscopy (SEM), powder X-ray diffraction (PXRD), DSC and *in vitro* dissolution profile. The prepared solid dispersion are formulated into capsule dosage form and characterized by various parameters i.e. weight variation, content uniformity, disintegration and dissolution. The evaluated parameters of capsule dosage form increase in solubility and dissolution rate of the pure drug.

Conclusion: These are various techniques to enhance the solubility of the drug, such as particle size reduction, use of surfactants, solid dispersion etc. Carriers are the major players in these formulations, e. g. Hydroxypropylmethylcellulose, ethylcellulose, Carbopol, Acacia Gum etc. Carbopol and Acacia Gum is one of the most efficient polymers work as a carrier for these drugs to enhance solubility.

Keywords: Solid dispersions, Rosuvastatin calcium, Carbopol, Acacia gum, Kneading method

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INTRODUCTION

The solubility and dissolution rate of medication determine its oral bioavailability, and dissolution rate may be a rate-determining step for the emergence of medicinal action. As a result, increasing the dissolution of drugs with low water solubility is often required. As a result, regardless of the chemical structure or molecular space dimension, certain methods may be employed to enhance the solubility of medicines. Solid dispersion has become one of the most active areas of study in the pharmaceutical industry because it improves medication solubility [1, 2].

Solid dispersion is a suitable technique in which one or more active substances are dispersed in a solid form in an inner carrier or matrix produced by melting, dissolving in the solvent, or melting solvent method. Solubility and dissolution are essential phenomena in pharmaceutical formulations, and they play a crucial and major role in the pharmaceutical dosage form. Dissolution is defined as the process by which a solid material is solubilized in a given solvent, i.e., mass transfer from the solid surface to the liquid phase, while solubility is defined as the greatest quantity of solute that can be dissolved in a given amount of solvent [3-5].

Rosuvastatin is a white crystalline powder that is poorly soluble in water (E,3R,5S)-7-[4-(4-fluorophenyl)-2-[methyl(methylsulfonyl)amino]-6-propan-2-ylpyrimidin-5-yl]-3,5-dihydroxyhept-6-enoate. Rosuvastatin belongs to the phenylpyrimidines family of chemical substances. A benzene ring is connected to a pyrimidine ring by a CC or CN bond in these polycyclic aromatic compounds. Pyrimidine is a 6-membered ring with four carbon atoms at the 1- and 3-ring locations and two nitrogen centres. HMG-CA reductase inhibitor is a drug that is used to treat HMG-CA reductase. It's now being used as a lipid-lowering and hypolipidemic drug. It is also utilised in the treatment of osteoporosis, benign prostatic hyperplasia, and Alziemer's disease in certain instances. It has a 20 percent oral bioavailability and a 19-hour half-life. As a result, the present study's goal is to improve the solubility and dissolution of a pure medication utilising a solid dispersion method and a capsule dosage form [6-8].

MATERIALS AND METHODS

Materials

Rosuvastatin Calcium is a lipid-lowering agent provided by (Vadsp Pharmaceuticals pvt. Ltd. Baddi, India). Carbopol and Acacia Gum are used as a polymer by (Vadsp Pharmaceuticals pvt. Ltd. Baddi, India) (Balaji Pvt. Ltd. Baddi and Loba ChemPvt. Ltd.,). Ethanol, methanol, magnesium stearate, talc, and lactose were bought from Loba Chemicals in Mumbai, India, as were disodium hydrogen orthophosphate and potassium dihydrogen orthophosphate. All of the compounds were analytical or technical grade, and they were utilised as is.

Methods

Physiochemical characterization of pure drug

The drug sample (Rosuvastatin) was analysed by different means such as color, odor and texture in order to prove the authenticity of the sample.

Determine the solubility of the pure drug by using UV spectroscopic method

Determination of absorption maxima (λ max)

A UV absorption maxima of the drug was determined by scanning (10 μ g/ml) solution of the drug in methanol between 200-400 nm.

Preparation of calibration curve in phosphate buffer (pH 6.8)

10 mg of rosuvastatin calcium were dissolved in a tiny quantity of methanol (used as a co-solvent) and diluted in 100 ml of phosphate buffer. pH6.8. A stock solution of 250g/ml was prepared by diluting 50 ml of this solution to 100 ml with phosphate buffer pH6.8 to make a stock solution. Take 0.1, 0.2, 0.3, 0.4, 0.6, and 0.8 ml of this stock solution and transfer it to a 10 ml volumetric flask with phosphate buffer to make it up to 10 ml. Using phosphate buffer as a blank, the absorbance of these solutions was measured at 241 nm [9].

Preparation of calibration curve in methanol

10 mg of Rosuvastatin Calcium was dissolved in 100 ml methanol; 50 ml of this solution was taken and diluted to 100 ml again with

methanol to prepare a stock solution of 250µg/ml as a stock solution. From this stock solution, aliquots of 0.1, 0.2, 0.3, 0.4, 0.6, and 0.8, and transferred to 10 ml volumetric flask and volume was made up to 10 ml with methanol. The absorbance of these solutions was measured at 238 nm using methanol as blank [10].

Preparation of solid dispersions of rosuvastatin calcium

Kneading method

Rosuvastatin Calcium and several water-soluble carriers (Carbopol and Acacia Gum) were weighed in varied ratios of 1:1, 1:3, and 1:5 and transported to a mortar for 45 min of kneading with hot water. Enough methanol was added to maintain the paste-like consistency. The paste was then dried for 24 h in a hot air oven at 45 °C. The dry dispersions were milled and sieved using No. 18 sieve. The produced dispersions were kept in glass vials and utilised in further research.

Characterization of solid dispersions

The prepared physical mixtures and solid dispersions were evaluated for percentage yield, drug content, solubility studies, Differential scanning calorimetry (DSC), X-ray diffraction (XRD), and *in vitro* drug release and dissolution efficiency [11].

Percentage of practical yield

The percent yield of Rosuvastatin solid dispersions was determined by using the following formula:

$$[PY (\%) = [\text{Practical mass (Solid dispersion)}/\text{Theoretical mass (Drug+Carrier)}] \times 100]$$

Determination of drug content

Solid dispersions equivalent to 10 mg of Rosuvastatin were weighed accurately and dissolved in 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 241 nm by UV Spectrophotometer.

Powder X-Ray diffraction (XRD) analysis

Using an X-ray diffractometer, researchers studied the solid dispersion of pure drugs, Carbopol, and Acacia Gum. Data was obtained using scan mode with a step size of 0.010 at 20/s with target CuKa monochromatized radiation, voltage 40KV, and current 40mA at ambient temperature.

In vitro drug release

The *in vitro* dissolution of Rosuvastatin solid dispersions was investigated using a basket stirrer in a USP dissolution device (Electro lab). At 50 rpm, 900 ml of pH 6.8 phosphate buffer was utilized as the dissolving media. Throughout the experiment, a temperature of 37±0.5 °C was maintained. Each test utilised solid dispersions containing 10 mg of RST. After appropriate dilution with phosphate buffer, 5 ml of dissolution media sample was taken at known intervals using a pipette equipped with a pre-filter and tested for drug release by detecting the absorbance at 241 nm. At each time interval, the volume removed was replaced with a new batch of dissolving media. The quantity of RST released was quantified and displayed versus time, with the pure drug being compared [12, 13].

Differential scanning calorimetry (DSC) analysis

The samples (5 mg each) were placed into the 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.

Preparation of capsule

Capsules are tiny receptacles (shells) composed of gelatin that include precisely calibrated medicinal ingredients and are offered as a unit solid dose form of medicaments. Capsule comes from the Latin word capsula, which means "little container." Capsules are divided into two categories: "hard" and "soft." The hard capsule is also known as a "two-piece" capsule because it is made up of two pieces in the shape of small cylinders, one of which is called the "cap" and the other is called the "body." The shorter piece is called the "cap," and it fits over the open end of the longer piece, which is called the "body." The soft gelatin capsule is sometimes referred to as a "one-

piece" capsule. The bland gelatin casing may conceal unpleasant medication tastes and smells. One of the most often used dose forms is the delivery of liquid and solid medicines in hard gelatin capsules.

Evaluation of capsule dosage form

General appearance

The general appearance of a capsule shell, its visual identification and 'elegance' should be determined.

Weight variation

The weight variation test was carried out by weighing the intact capsules individually and calculating the average weight. If none of the individuals weighed less than 90% or more than 110 percent of the average, the test criteria were satisfied. Individual net weights are calculated if the initial 20 do not satisfy these requirements. These were averaged, and discrepancies between each individual net content and the average were calculated. The criteria of the exam were met:

1. If two or more than two of the individual differences are greater than 10% of the average or
2. If in no case any difference is greater than 25%.

Content uniformity

The content uniformity was performed by specified individual monographs. The requirements are met for the capsule if 9 of the 10 are specified potency range of 85 to 115% and tenth not outside 75 to 125%.

In vitro dissolution test

The dissolution test was used to study the dissolution of the capsule dosage form in phosphate buffer pH 6.8. 10 mg of simvastatin was added to 900 cc of phosphate buffer pH 6.8 (100rpm at 37.0 ± 0.5 °C) in capsules. At various time intervals, 10 ml of aliquots were removed, filtered, and replaced with 10 ml of newly produced dissolving medium. Simvastatin concentration was evaluated spectrophotometrically at 239.5 nm, and (percent DE60) and percent drug released of the capsules were calculated and compared to the pure drug.

Disintegration test

The disintegration test equipment was used to measure the *in vitro* disintegration time. A disc may be added if the capsule floats on the surface of the medium. If the capsules stick to the discs, replace the discs with a detachable piece of stainless steel woven gauze with a mesh size of 2.00 mm and repeat the test. In this instance, each capsule was put in one of six tubes of equipment, and a three-inch-long disc was added to each tube, which was open at the top and held against a 10-mesh screen at the basket rack assembly's bottom end. At 37 °C±0.2 °C, the basket rack assembly was submerged in one litre of distilled water. The time it took for the capsule to fully disintegrate and pass through the screen was calculated. Unless otherwise instructed, use the device for 30 min.

Stability studies

Accelerated stability tests were conducted on produced solid dispersion in amber coloured screw sealed bottles for one month at 40 ± 2 °C and 75 percent RH, as per ICH standards. In a stability chamber, solid dispersions were maintained. Physical characterization, content uniformity, and *in vitro* dissolution tests were performed on samples taken at regular intervals of 7 d, 14 d, 21 d, and 30 d. To compare dissolution profiles, the similarity factor (f_2) was employed. The profiles of disintegration when f_2 is between 50 and 100, dissolution profiles are thought to be comparable. A similarity factor (f_2) was derived using the following formula to compare the dissolution profiles of C1 formulation before and after stability testing [14].

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

RESULTS AND DISCUSSION

Physical appearance and melting point

The Physical appearance of the pure drug was studied by its various organoleptic properties. The sample of rosuvastatin calcium was found to be white, non-hygroscopic, crystalline solid powder. The

melting point of rosvastatin calcium was found to be in the range of 173-185 °C by Capillary method.

Absorption maxima

Absorption maxima (λ_{max}) of rosvastatin calcium were observed in different solvents.

Table 1: Absorption maxima (λ_{max}) of the rosvastatin calcium in different solvent

Solvent	(λ_{max})nm
Phosphate buffer	241 nm
Methanol	238 nm

Solubility

The solubility studies of Rosuvastatin Calcium were determined in different solvents.

Table 2: Solubility of rosvastatin calcium in different solvents

Solvent	Solubility
Phosphate buffer	3.321±0.432
Methanol	2.476±0.251

Data expressed as mean±SD (n=3)

Standard curves

The calibration curve of Rosuvastatin Calcium was found to be linear at 241 nm in phosphate buffer (pH6.8) in the concentration range of 2-12($\mu\text{g/ml}$), which obeys Lambert-Beer Law. The absorbance at different concentrations is represented in fig. respectively.

Percent yield and drug content

The parameters such as percent yield and drug content of pure drug with different ratios of solid dispersions and polymers were determined. The % yields decreased at the higher concentrations due to the difficulty in sieving at higher polymer and surfactants concentrations.

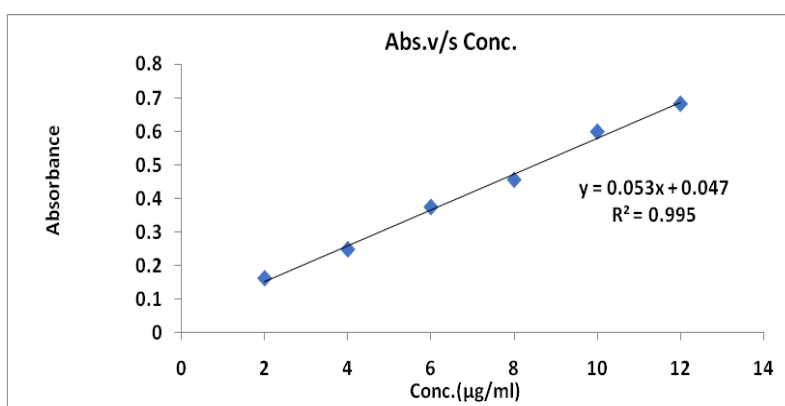


Fig. 1: Standard curve of rosvastatin calcium in phosphate buffer (pH6.8)

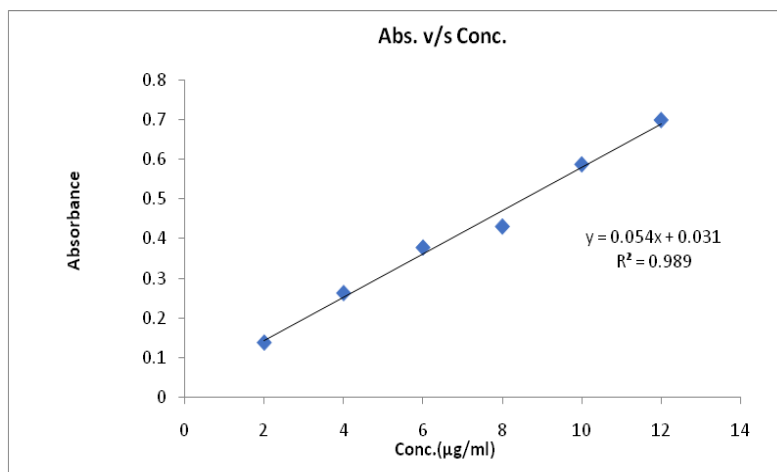


Fig. 2: Standard curve of rosvastatin calcium in methanol

Table 3: Percentage yield and drug content of solid dispersion rosvastatin, carbopol, acacia gum

Formulation code	Percentage yield	Drug content
ROCG 1:1	82.49±0.741	95.56±0.019
ROCG 1:3	81.89±0.512	85.41±0.026
ROCG 1:5	89.92±0.568	92.11±0.124

Data expressed as mean±SD (n=3)

Dissolution studies

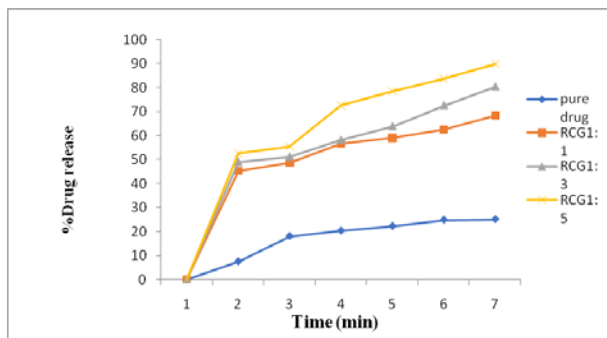


Fig. 3: In vitro dissolution profile of % pure drug released vs time solid dispersions with carbopol and acacia gum

Optimized formulation

On the basis of dissolution, the data-optimized formulation is detected and the formula was prepared, which was shown below the table

Table 4: Dissolution efficiency and yield of optimized formulations

Optimized formulation	%DE60	% Yield
100:500	86.65	92.17
100:500	73.41	89.65
100:250:250	80.93	94.52

Table 5: Evaluation parameters of capsule dosage form ROSU with carbopol and acacia gum

Formulation code rosu	Weight variation (mg)	Disintegration time (min)	Content uniformity
1	0.149±0.051	28	95.58±0.14
2	0.103±0.012	25	97.41±0.02
3	0.117±0.001	27	94.27±0.03
4	0.108±0.005	23	96.12±0.51
5	0.102±0.010	30	93.87±0.07
6	0.109±0.004	26	97.65±0.05
7	0.123±0.007	29	93.25±0.03
8	0.108±0.003	24	95.23±0.06
9	0.110±0.004	26	96.85±0.21
10	0.112±0.035	27	94.51±0.04

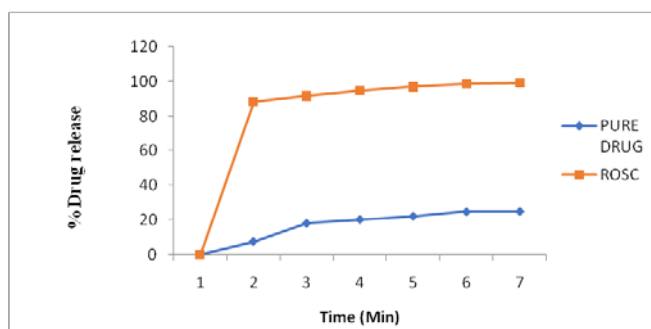


Fig. 4: In vitro dissolution profile of % drug released vs time of pure drug and capsule dosage form

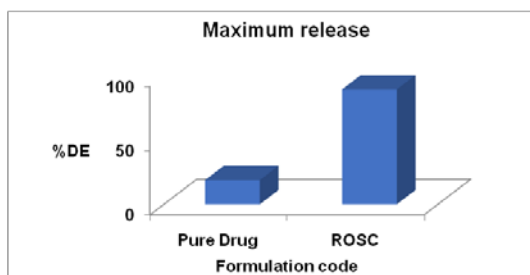


Fig. 5: Comparison of % DE60 with pure drug and capsules dosage formulations stability testing of the capsule dosage form

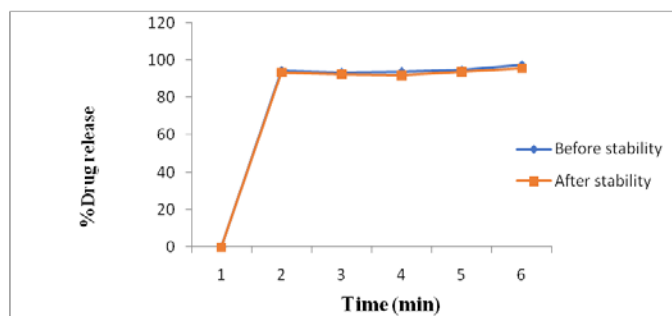


Fig. 6: *In vitro* dissolution profile of % drug released vs time of pure drug and Capsule dosage forms ROSC

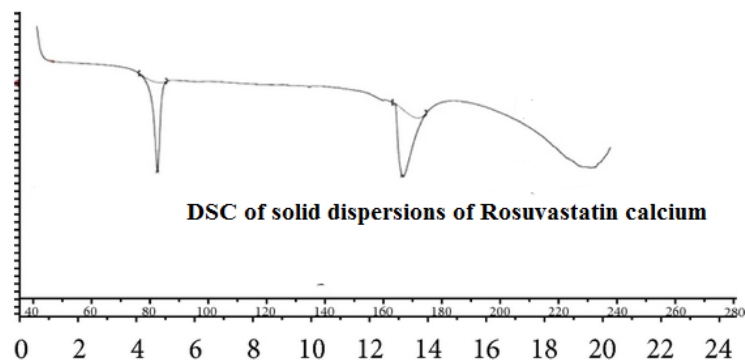


Fig. 7: DSC of solid dispersions of rosuvastatin calcium

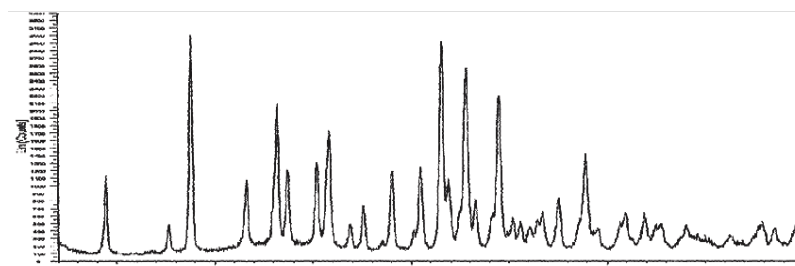


Fig. 8: XRD of solid dispersions of rosuvastatin calcium

Dissolution data after stability

The similarity factor was calculated for the comparison of the dissolution profiles of capsule formulations before and after stability studies. The f_2 value was found to be for ROSC 75.02. Hence, it was confirmed from the results of stability studies that the developed capsule formulations were stable.

CONCLUSION

The present study was designed to increase the solubility and dissolution enhancement of poorly soluble drugs by the formulation of solid dispersions and different methods to prepare the solid dispersions. Kneading method was used for the preparation of solid dispersions. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

The solid dispersions were prepared by adding the polymer i.e. Carbopol at different concentrations in the ratio 1:1, 1:3, 1:5 by using kneading method. Acacia gum was selected as the carrier to improve the dissolution rate and the solid dispersions were prepared of Rosuvastatin Calcium with polymer (Carbopol) and Acacia gum in the ratio 1:1, 1:3; 1:5 by using Kneading method for

30 min respectively and total Six formulations were prepared and characterized the percentage yield, drug content, solubility of solid dispersions in phosphate buffer pH 6.8., and *in vitro* drug release studies. The optimised solid dispersions are filled into the hard gelatin capsule shells in lactose, magnesium stearate and talc and prepared final capsule dosage form which was characterized by its evaluation parameters such as weight variation, content uniformity, Disintegration test and *in vitro* dissolution studies. Then it was compared with the pure drug and finally, the prepared capsule dosage form was found to be having better dissolution efficiency at 60 min. There is no remarkable change that occurs in the capsule dosage form before and after stability studies.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

There are no conflicts of interest.

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