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Research Article

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF ROSUVASTATIN BY USING SOLID DISPERSION TECHNIQUE

Swathi T[1]*, Vamshi Krishna M[1], Sudheer kumar D[1], Krishnaveni J[2]
[1]Department of pharmaceutics, Care College of Pharmacy, Warangal, India
[2]Department of pharmaceutics, University College of Pharmaceutical Sciences, Warangal, India
*Corresponding Author Email: swathi.trao@gmail.com
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ABSTRACT
The objective of the study was to increase the solubility, and dissolution rate of Rosuvastatin (RST), a poorly water-soluble 3-hydroxy3-methyl glut aryl CoA (HMG-CoA) Reductase inhibitor through solid dispersion technique. The solid dispersions were prepared by three different methods viz. melting, co grinding, surface solid dispersions and spray drying method using carriers like PEG 4000, β-cyclodextrin, microcrystalline cellulose and PVP K30. The prepared dispersions were characterized using FTIR and Differential Scanning Calorimetry. The solid dispersion prepared with PVP K30 by spray drying method exhibited greatest enhancement in solubility and fastest dissolution (98.96 % RST release in 60 minutes) of Rosuvastatin. It was observed that the solubility increased with the increase in the concentration of carrier and amongst the various methods and carriers used the solubility was Rosuvastatin was enhanced greatest with PVP K30 by spray drying method. The stability of tablets was studied and no significant changes were detected in the dissolution profile of tablets after 1 month.
Keywords: solid dispersion, complexation, spray drying

INTRODUCTION

It is well established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. Poor drug dissolution and solubility rather than limited permeation through the epithelia of the gastro intestinal tract are responsible for low bioavailability of orally taken drugs. Together with permeability, the solubility and dissolution behavior of a drug are key determinants of its bioavailability when administered orally.[1] Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased oral bioavailability and subsequently to clinically relevant dose reduction.[2] Solid dispersions is a useful method to disperse drugs in the molecular state in a carrier matrix. The interaction between the drug and carrier is responsible for drug dispersion, and may depress the crystallization of drug in the prepared system. Solid dispersions are prepared mainly by a melting method or a solvent method, which are usually consisted of two components, a poorly water soluble drug and a water soluble polymer like polyvinyl pyrrolidone, polyethylene glycol, hydroxyl propyl cellulose, hydroxyl propyl methyl cellulose, methyl cellulose, micro crystalline cellulose, polyvinyl alcohol and so on.[3] Now a day's spray drying technology occupies a wide range in the production of various drug delivery systems, co-processed excipients and a solution for poor aqueous solubility of drugs[9]. Rosuvastatin (RST), is a crystalline, poorly water-soluble drug and therapeutically HMG-CoA Reductase inhibitor. Currently, using as a potent lipid-lowering agent and hypolipidemic agent. In some cases, clinically it is useful in the treatment of osteoporosis, benign prostatic hyperplasia and Alzheimer's disease. It is have bioavailability of 20 %.[4,5] The aim of the present study was to increase the extent of bioavailability of Rosuvastatin by increasing its aqueous solubility. Solid dispersion is the technique chosen to increase the solubility of Rosuvastatin by using different methods with different carriers like polyethylene glycol 4000, Microcrystalline cellulose, β-cyclodextrin and Polyvinyl pyrrolidine k30.

Experimental Studies

Materials

Rosuvastatin was a kind gift sample from Aurobindo Pharma Ltd, Hyderabad, India. PEG4000 and MCC are purchased from SD fine chemicals. PVP K30 is purchased from Hi Media labs. β-cyclodextrin is purchased from Sri SJS Pharma and all other materials used in this study were of analytical and pharmaceutical grade.

Methods

Solubility Studies

Solubility studies were carried out according to the method reported by Higuchi and Connors. An excess of Rosuvastatin was added to 10 ml portions of distilled water and was shaken in rotary shaker for 24 hours. After shaking, the solution was filtered and their absorbance was noted at 241 nm.

Preparation of solid dispersions

Solid dispersions were prepared by various polymers and different methods as shown in the table 1.

Melting

Drug and carrier are taken in different ratios in a china dish and melted on water bath. Then the mixture is set to cool on ice bath and air dried. The obtained solid is sieved through 60#.

Surface solid dispersion

The drug is dissolved in a solvent (methanol). The carrier (MCC) is taken in china dish. The drug solution is poured

onto the carrier and mixed thoroughly. Then the solvent is made air-dried and obtained SDs is sieved through 60#.[10]

Co grinding

The carrier or complexing agent (β-cyclodextrin) and drug of different proportions are taken in a motor and triturated for about one hour. The obtained Solid Dispersion powders were sieved through 60#.[7]

Spray drying

The drug and carrier of different ratios are dissolved in a common solvent (methanol: acetone 1:1 ratio). Then the solution is spray dried with a flow rate of 4ml/min, vacuum of 20 Nm^3/hr, pressure 20 kg and temperature of 65^0C. the SDs are collected and sieved through 60#.

Drug Content Estimation

100 mg of drug: carrier was accurately weighed and transferred to 100 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer. From this 1 ml 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 241 nm using appropriate blank. The drug content of Rosuvastatin was calculated using calibration curve[4].

***In vitro* dissolution studies for RST solid dispersions:**

In-vitro dissolution of Rosuvastatin solid dispersions were studied in USP dissolution apparatus (Electro lab) employing a basket stirrer. 900 ml of phosphate buffer of pH 6.8 was used as dissolution medium at 50 rpm. The temperature of 37 + 0.5°C was maintained throughout the experiment. Solid dispersions equivalent to 10 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 241 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[4].

Fourier Transform infrared (FTIR) Spectroscopy

Fourier transform IR spectra were recorded on FT/IR-Alpha type A. The spectra were recorded for Rosuvastatin, melting, co grinding, surface solid dispersion and spray drying method. Samples were prepared in KBr disc (2 mg sample in 200 mg KBr). The scanning range was 400-4000cm^{-1}.

Differential Scanning Calorimetry (DSC)

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.

Table 1: Composition of Solid Dispersions

Batch no.	Composition	Method	Drug: carrier ratio
SD1	Drug + PVP K 30		1:2
SD2		Spray drying	1:4
SD3			1:6
SD4	Drug + MCC		1:2
SD5		Surface solid dispersion	1:4
SD6			1:6
SD7	Drug + PEG4000		1:2
SD8		Melting	1:4
SD9			1:6
SD10	Drug + β- cyclodextrin		1:2
SD11		Co grinding	1:4
SD12			1:6

Table 2: Drug Content Estimation

S. No.	Solid Dispersion	Method	Drug Content (mg)
1	SD1	Spray drying	9.55
2	SD2		10.29
3	SD3		9.88
4	SD4	Surface solid dispersion	9.55
5	SD5		9.63
6	SD6		9.55
7	SD7	Melting	9.34
8	SD8		9.23
9	SD9		9.13
10	SD10	Cogrinding	9.15
11	SD11		9.01
12	SD12		9.01

Table 3: Dissolution profile of Rosuvastatin pure drug and solid dispersions prepared by spray drying method in carrier PVP K30

Time (minutes)	Pure drug	SD1	SD2	SD3
10	3.294 ± 0.4	18.31 ± 1.135	22.086 ± 1.01	24.923 ± 1.61
20	5.374 ± .053	35.06 ± 1.00	46.14 ± 1.03	51.90 ± 1.25
30	7.970 ± 0.98	57.76 ± 1.45	64.32 ± 1.01	67.35 ± 1.24
40	9.168 ± 0.90	69.64 ± 1.50	72.74 ± 1.18	74.26 ± 1.53
50	17.288 ± 0.89	77.51 ± 1.04	83.80 ± 0.90	87.30 ± 0.89
60	20.271 ± 0.88	81.66 ± 1.52	89.41 ± 0.57	96.18 ± 0.96

Table 4: Dissolution profile of Rosuvastatin pure drug and solid dispersions in carrier MCC by surface solid dispersion method

Time (minutes)	Pure drug	SD4	SD5	SD6
10	3.294 ± 0.407	19.1 ± 1.01	20.23 ± 1.66	21.02 ± 1.00
20	5.374 ± .0532	35.16 ± 0.88	44.81 ± 2.45	58.54 ± 1.49
30	7.970 ± 0.98	51.46 ± 1.12	54.71 ± 1.55	63.28 ± 1.11
40	9.168 ± 0.90	58.07 ± 1.50	69.51 ± 1.4	73.69 ± 1.538
50	17.288 ± 0.89	65.35 ± 1.43	73.62 ± 1.645	81.95 ± 1.69
60	20.271 ± 0.88	78.49 ± 1.36	87.08 ± 1.28	91.44 ± 1.50

Results were expressed as Mean ± S.D (n = 6)

Table 5: Dissolution profile of Rosuvastatin pure drug and solid dispersion in carrier PEG4000 by melting method

Time (minutes)	Pure drug	SD7	SD8	SD9
10	3.294 ± 0.407	21.32 ± 0.59	22.35 ± 0.81	23.54 ± 0.90
20	5.374 ± .0532	51.39 ± 0.99	53.12 ± 0.45	58.14 ± 1.01
30	7.970 ± 0.98	64.87 ± 1.30	69.34 ± 1.06	73.00 ± 0.56
40	9.168 ± 0.90	67.64 ± 0.715	73.40 ± 0.97	78.16 ± 0.99
50	17.288 ± 0.89	76.12 ± 0.50	79.07 ± 1.06	82.08 ± 1.09
60	20.271 ± 0.88	80.53 ± 0.84	81.55 ± 0.80	88.35 ± 1.05

Results were expressed as Mean ± S.D (n = 6)

Table 6: Dissolution profile of Rosuvastatin pure drug and solid dispersion in carrier β-cyclodextrin by Cogrinding method

Time (minutes)	Pure drug	SD10	SD11	SD12
10	3.294 ± 0.407	1.27 ± 0.19	4.72 ± 0.67	15.66 ± 0.69
20	5.374 ± .0532	11.53 ± 0.85	20.52 ± 0.86	20.48 ± 0.88
30	7.970 ± 0.98	19.17 ± 0.48	35.8 ± 1.18	38.04 ± 1.11
40	9.168 ± 0.90	27.33 ± 0.88	41.98 ± 1.17	42.24 ± 0.90
50	17.288 ± 0.89	31.78 ± 1.17	45.18 ± 0.96	45.08 ± 0.48
60	20.271 ± 0.88	33.39 ± 0.64	50.08 ± 1.06	56.15 ± 0.98

Results were expressed as Mean ± S.D (n = 6)

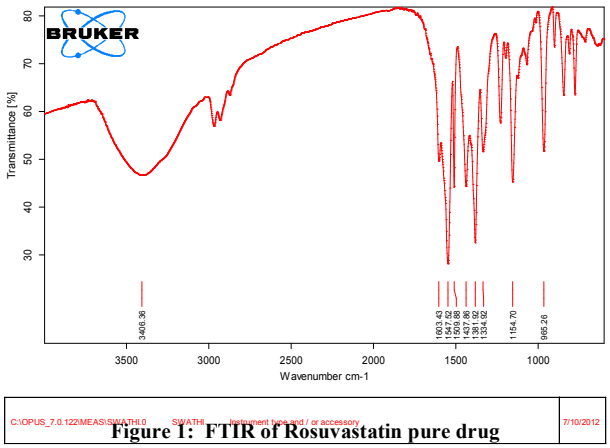

Figure 1: FTIR of Rosuvastatin pure drug

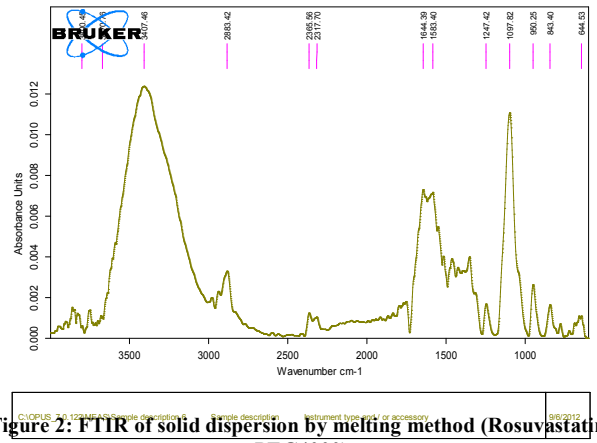

Figure 2: FTIR of solid dispersion by melting method (Rosuvastatin: PEG4000)

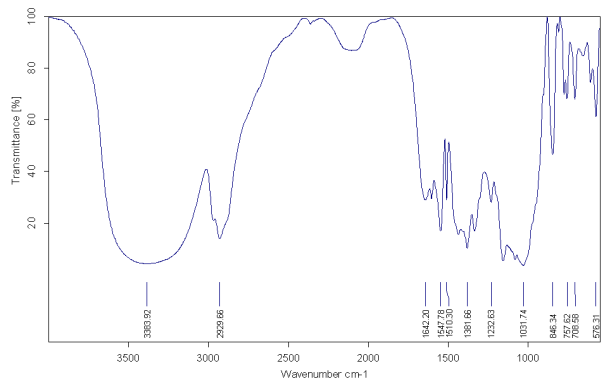

Figure 3: FTIR of solid dispersion by Co grinding method (Rosuvastatin : β-cyclodextrin)

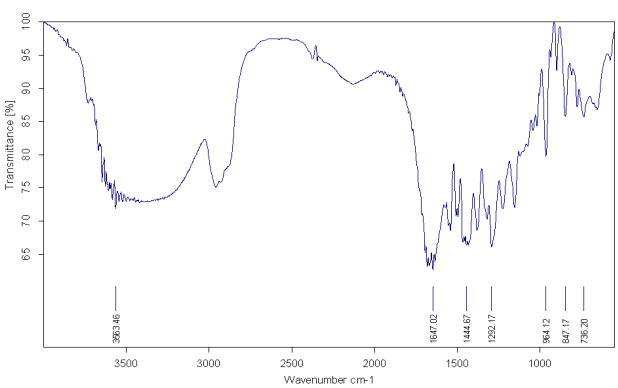

Figure 4: FTIR of solid dispersion by Spray drying method (Rosuvastatin : PVP K 30)

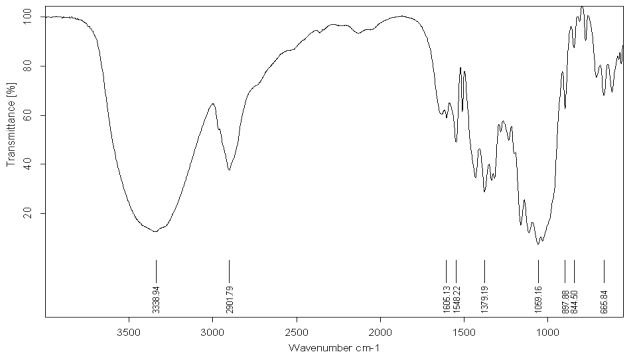

Figure 5: FTIR of solid dispersion by surface solid dispersion method (Rosuvastatin: MCC)

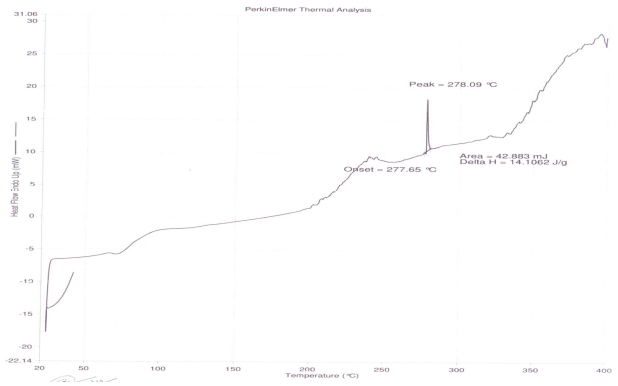

Figure 6: DSC graph of Rosuvastatin

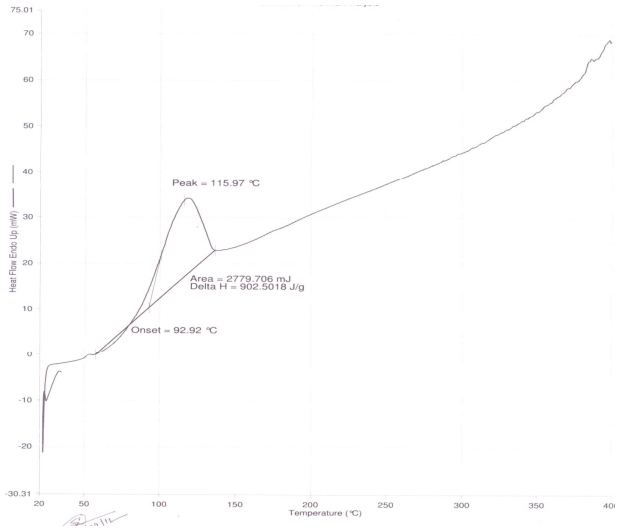

Figure 7: DSC graph of PVP K30

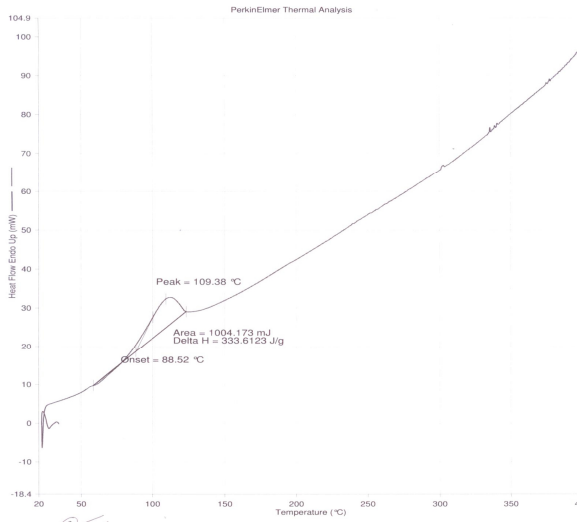

Figure 8: DSC graph of solid dispersion by PVP K 30

RESULTS AND DISCUSSION

Solubility Studies

Solubility studies were carried out according to the method reported by Higuchi and Connors. The solubility of rosuvastatin in 6.8 pH phosphate buffer was found to be 0.008108 mg/ml.

Drug content analysis

Drug content of the solid dispersions was found to be between 9.01 mg and 10.29 mg. It indicates that the drug is uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for preparation of solid dispersion. The results were shown in Table 2. The occurrence of any interaction between a drug and polymers in the formulation can be predicted by conducting the differential scanning calorimetry studies. The thermo grams of solid dispersions display the characteristic features of the drug. This indicates no possible interaction between the polymers and Rosuvastatin. The results are shown in Figure 6-8. Infra red spectral analysis showed that there were no interactions between pure drug and solid dispersion. The results are shown in Figure 1-5.

In vitro Dissolution Studies

In vitro dissolution studies indicated that as concentration of carrier increases, dissolution of drug improved. The results of drug release from solid dispersion of PVP K30, MCC, β-cyclodextrin and PEG 4000 are shown in Table 3-6. The dissolution profile graphs are shown in Figure 1-4. The formulation code SD3 (Rosuvastatin: PVP K30 1:6) showed 95.7 % release in 60 minutes than other solid dispersions whereas the pure drug showed 20 % release in 60 minutes. This may be due to the presence of polymer, which increases wetting, and dissolution of the drug. This increase in dissolution rate of solid dispersion was attributed to molecular/colloidal dispersion of drug in mixture. Higher the proportion of carrier there was a steep increase in dissolution rate of drug. The fast and rapid dissolution of drug observed in solid dispersions due to the presence of drug in amorphous form. The amorphous form is the highest energy of pure compound and produces faster dissolution. The other factors like absence of aggregation, good wettability and dispersability might have also contributed to the increase in dissolution rate.[8,6]

CONCLUSION

An increased solubility and dissolution rate of Rosuvastatin were achieved by forming solid dispersion using various carriers with different techniques like melt method, co grinding, surface solid dispersion and spray drying. New techniques like Spray drying technique is found highly useful for preparation of solid dispersions and solubility enhancement as compared to other methods. The dissolution rate of the solid dispersion was found highest as compared to the plain Rosuvastatin.

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