Formulation Development and Solubility Enhancement of Rosuvastatin Calcium by Using different Polymers and Solid Dispersion Method

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Abstract

Lipid and lipoprotein abnormalities are extremely common in general population and are regarded as a highly modifiable risk factor for cardiovascular diseases. Hypertension and hypercholesterolemia are the two leading risk factors for heart diseases and causes an increase in coronary heart disease related events and more common in elderly patients. Rosuvastatin calcium is a BCS class II drug (low solubility and high permeability), used as a lipid lowering agent by acting as HMG CoA reductase inhibitor and it is used for the management of hyperlipidemia. BCS class 2 having low solubility & therefore low oral bioavailability. Solid dispersion of Rosuvastatin calcium loaded with combination of HPMC and Acacia Gum for the beneficial of cholesterol patients, to provide sustained release effects. Increase in the solubility of poorly water soluble drug is the most challenging aspect for various new chemical entities which leads to the unsatisfactory dissolution profile, consequently, the bioavailability. Solid dispersions in water-soluble carriers have attracted considerable interest as a means of improving the dissolution rate and hence possibly bioavailability, of a range of hydrophobic drugs The solid dispersions were prepared by Melt method and Solvent evaporation method using carriers at different drug carriers' ratio (HPMC and Acacia Gum). Solid dispersions were prepared in which the dispersion of one or more active ingredient in a carrier or matrix at the solid state that increases the solubility and dissolution of drug.

Keywords: Solid dispersions, Rosuvastatin calcium, HPMC, Acacia Gum, Hyperlipidemia, Melt Method, Solvent Evaporation Method, Capsule dosage form.

INTRODUCTION

Solubility is defined as the maximum amount of solute dissolve in the given amount of solvent or the concentration of solute in saturated solution at a certain temperature, pressure or presence of certain chemical [1,9]. The solubility of a substance depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution [8,2].

Solute: It is a substance which is present in small quantity and dissolves in the solvent. [2]

Solvent: It is the component which forms the main constituent of a solution and it is also capable of dissolving another substance to form a consistently disperse mixture at a molecular level.**[10]**

Solubility Expression:[5,6,7]

Conditions	**Parts of Solvent required for Part of Solute**
Very soluble	≤ 1
Freely soluble	1 to 10
Soluble	10 to 30
Sparingly soluble	30 to 100
Slightly soluble	100 to 1000
Very slightly soluble	1000 to 10,000
Practically insoluble, or soluble	10,000 or more

IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent.[11] Solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units [4].

Possible Causes for Poor Oral Absorption [3]

Any drug is said to be poorly soluble when:

1. Aqueous solubility 500),
2. Poor dissolution: Intrinsic dissolution rate <0.1g/cm^2/min

3.High molecular weight (>500), .Self association and aggregation.

4. High crystal energy.

Factors affecting solubility:[12,13]

1. Particle size
2. Temperature
3. Molecule size
4. Nature of solute and solvent:

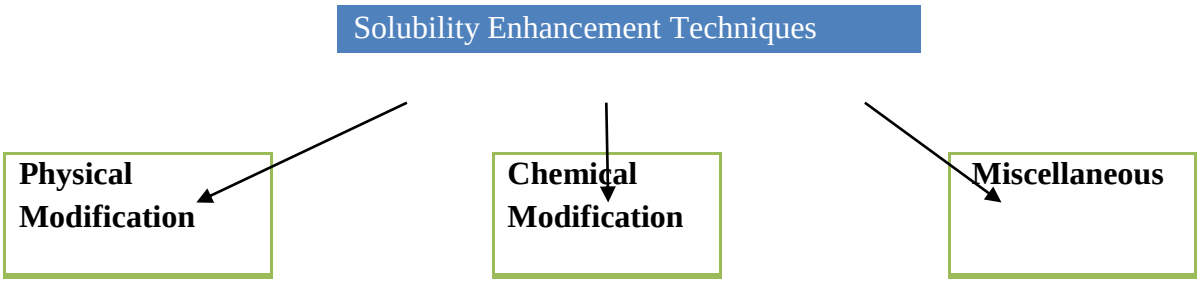
5. Pressure:
6. Polarity:
7. Polymorphs
8. pH
9. Dielectric Constant
10. Rate of solution

The drugs can be classified in to four basic groups on the bases of their solubility and permeability GIT mucosa. This system of classification is called as Biopharmaceutical classification system (BCS).[14,15,16]

Class	Solubility	Permeability	Characteristics features
I	High	High	well absorption orally
II	Low	High	variable absorption due to solubility limitation
III	High	Low	variable absorption due to permeability limitation
IV	Low	Low	poorly absorbed due to both solubility and permeability limitation

Class I: Drugs belonging to this class have high solubility & High permeability.
e.g. Metoprolol, Diltiazem, Verapamil, Propranolol.
Class II Drugs belonging to this class have low solubility & high permeability
e.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine.
Class III Drugs belonging to this class have high solubility & low permeability.
e.g. Cimetidine, Acyclovir, Neomycin B, Captopril.
Class IV Drugs belonging to this class have low solubility & low permeability.
Taxol, Griseofulvin.

Methods of solubility enhancement:[9,12,13,17]



1 Physical Modification:

i. Particle Size Reduction
ii. Modification of Crystal Habit
iii. Solid Dispersions
iv. Complexation
v. Microemulsions

2 Chemical Modification

i. Change In pH
ii. Salt Formation
iii. Use of Buffer
iv. Nanotechnology

3 Miscellaneous

i. Supercritical Fluid Process
ii. Addition of Surfactants
iii. Co-solvency
iv. Hydrotrophy

Material & Methods

Materials:

Drug	Synonyms	State	BCS Class	Polymers
Rosuvastatin Calcium	Crestor,Rosuvas, Razel	Solid	Class II	HPMC, Gum Acacia

Method:

Solid Dispersion

PREPARATION OF SOLID DISPERSIONS OF ROSUVASTATIN

Melt Method

The polymer HPMC was melted at 60°C and then the drug was added, mixed well and cooled in an ice bath to obtain a solidify mass. The solidified mass was crushed and then passed through a sieve no. 60. The resulting solid dispersion was stored in a desiccator until further evalution.

Formulation code	Drug : Carrier weight ratio
ROS 1	1:1
ROS 2	1:3
ROS 3	1:5

Table :Composition Rosuvastatin calcium -HPMC Solid dispersions

Solvent Evaporation Method

Accurately weighed amount of drug and carriers in various ratios dissolved in ethanol in a round bottom flask and the solvent was evaporated at 45 °C temperature. Solid dispersions were subsequently stored in a vacuum oven at room temperature for 48 hours to remove the residual solvent. The dried solid dispersions were grinded in a mortar and pestle and passed through sieve no. 60 and were stored in desiccators until further evalution.

Formulation code	Drug : Carrier weight ratio
ROS 4	1:1
ROS 5	1:3
ROS 6	1:5

Table :Composition Rosuvastatin calcium -HPMC and Acacia Gum Solid dispersions

Results & Discussuion

1. Physical appearance and Melting point

Physical appearance of drug was examined by its various organoleptic properties. The sample of Rosuvastatin possesses similar colour, odour, texture and taste as given in the literature values. The drug was white in color and crystalline in nature. The Melting point was of the drug sample was found to be 135° to 138°C by Capillary method which is accordance literature value.

2. DSC

The DSC of the drug sample Rosuvastatin shows a sharp endothermic peak at 152.67ºC that supports the purity and authenticity of the sample as shown in given Figure.

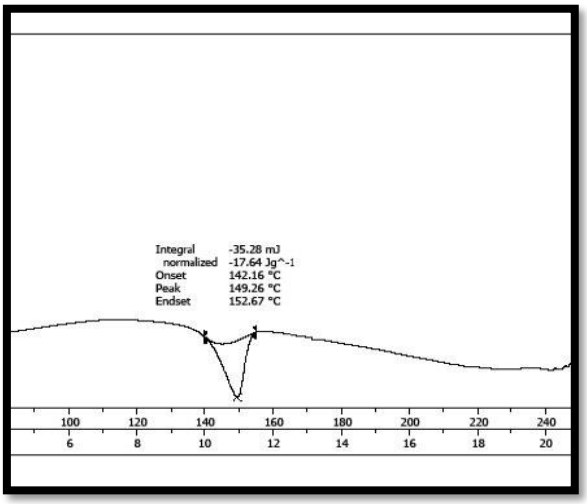


Figure : DSC thermo gram of Rosuvastatin

Solubility

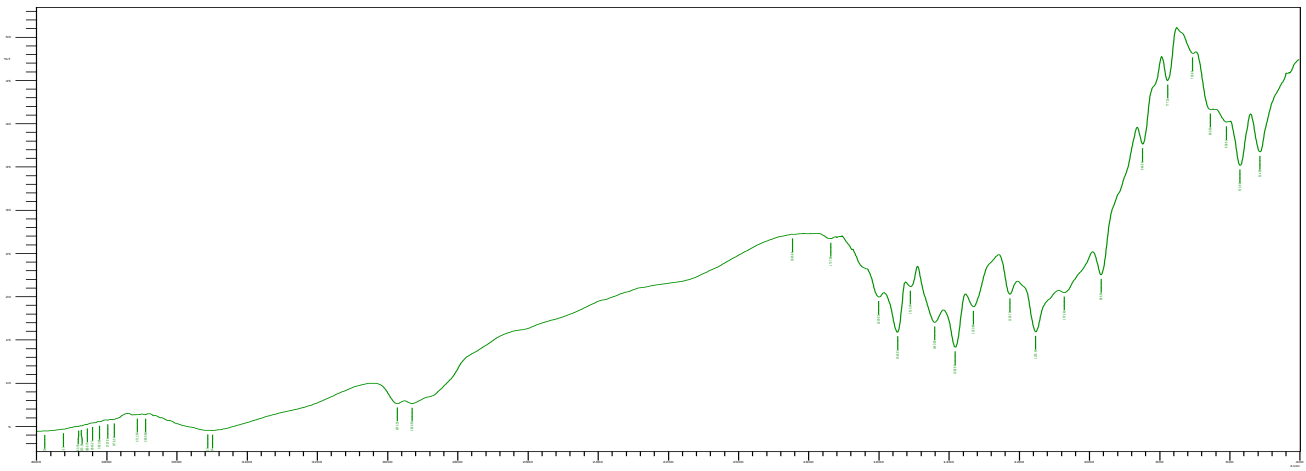
The solubility studies of Rosuvastatin Calcium were determined in different solvents.

Table : Solubility of Rosuvastatin Calcium in different solvents

Solvent	Solubility
Phosphate buffer	4.028±0.556
Water	1.648±0.328
Methanol	2.668±0.124

Data Expressed as mean ± S.D (n=3)

Drug Excipients compatibility studies: Drug excipients studies showed that there was no discoloration, liquefaction between drug and polymer. FTIR spectra of the physical mixture of drug and polymer showed no physical interaction between drug and the polymer used. No significant shift in the peak was observed which revealed that both the drug and polymer are compatible with each other. Physical mixtures of both Rosuvastatin Calcium and excipients HPMC and Gum acacia are prepared and Drug-Exciepient studies were carried out. No major changes were observed in the drug like there was no discoloration of the drug, No liquefaction between drug and polymer, No odour changes in the pure form of the drug was noticed which confirms the compatibility between the drug and excipients. The FTIR spectra of Rosuvastatin Calcium and HPMC /GA physical mixture are shown below which indicate that Rosuvastatin compatible with the HPMC and GA.



FTIR spectra of Rosuvastatin Calcium and HPMC /GA

	Week 1	Week 2	Week 3	Week 4
Drug + Polymer	-	-	-	3629.51, 1800.08, 1343.03, 1200.53, 1058.12
Drug, Polymer and Gum	-	-	-	3619.57, 2992.96, 1783.87, 1367.10, 869.27

Standard curves/ plot:

The standard curve of Rosuvastatin Calcium was found to be linear in the concentration range of 2-12 µg/ml in Phosphate buffer (pH 6.8), methanol, 0.1N HCl and water and obey Beer' s Lambert Law. The absorbance at different concentrations is shown in table 6.1-6.4 and graph is represented in figure 6.2-6.5 respectively.

The calibration curve of Rosuvastatin Calcium was found to be linear in the concentration range of 2.5-15 µg/ml at 241 nm in Phosphare buffer buffer (pH 6.8), methanol and water. The absorbance at different concentrations is shown in table 6.5-6.7 and graph is represented in figure 6.4-6.6 respectively.

Table : Standard plot data of Rosuvastatin in Phosphate Buffer(pH6.8) at 239.5nm

S.No.	Concentration (µg/ml)	Absorbance (nm)
1.	2	0.128±0.022
2.	4	0.248±0.186
3.	6	0.357±0.012
4.	8	0.466±0.014
5.	10	0.571±0.022
6.	12	0.689±0.014

Data are expressed as mean ± S.D. (n=3)

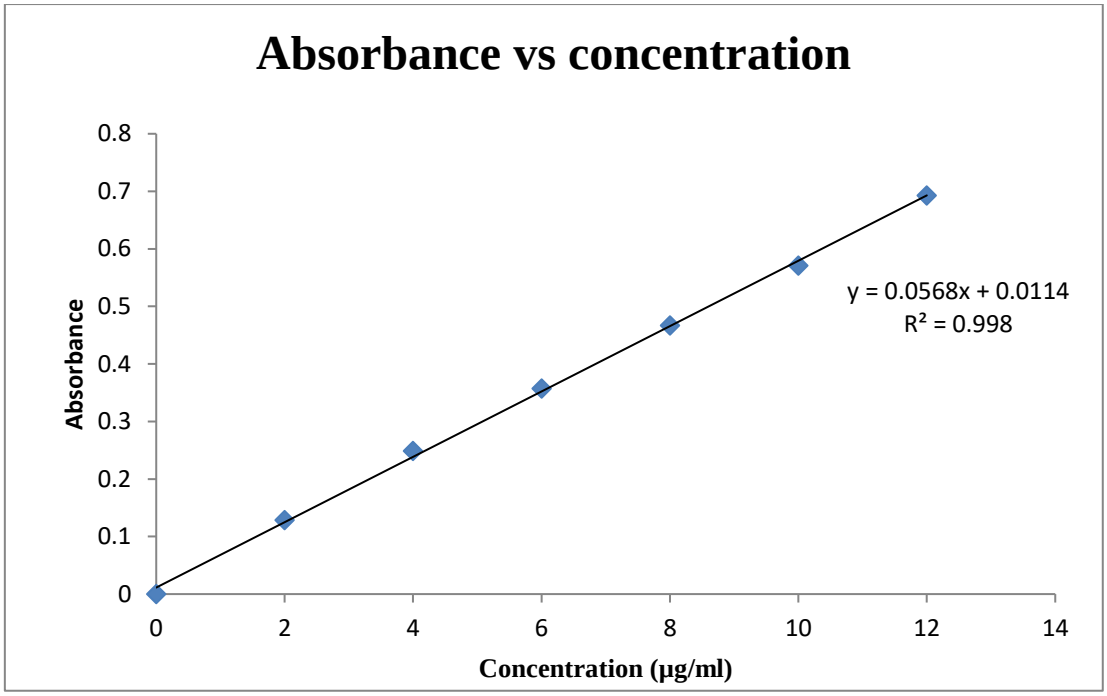


Figure : Standard plot of Rosuvastatin in Phosphate Buffer (pH6.8)

Table : Standard plot data of Rosuvastatin in Methanol at 238nm

S.No.	Concentration (µg/ml)	Absorbance (nm)
1.	2	0.116±0.006
2.	4	0.221±0.004
3.	6	0.305±0.016
4.	8	0.389±0.038
5.	10	0.476±0.018
6.	12	0.561±0.056

Data are expressed as mean ± S.D. (n=3)

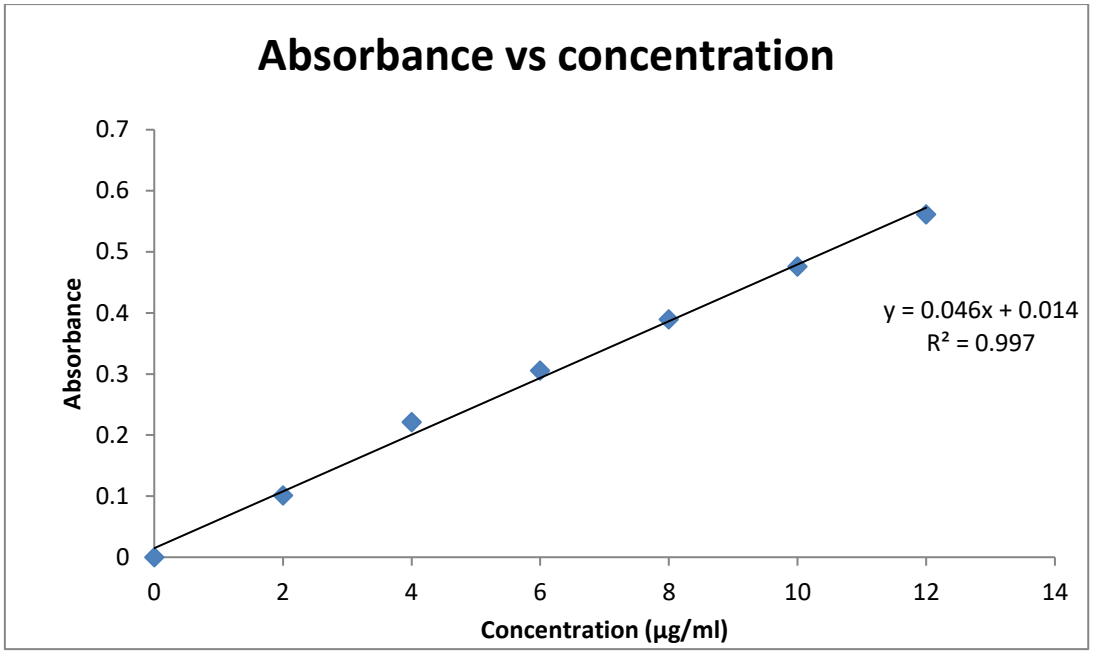


Figure : Standard plot of Rosuvastatin in Methanol

Table: Standard plot Data of Rosuvastatin in 0.1N HCL at 238nm

S.No.	Concentration (µg/ml)	Absorbance (nm)
1.	2	0.153±0.012
2.	4	0.304±0.012
3.	6	0.453±0.014
4.	8	0.586±0.016
5.	10	0.752±0.022
6.	12	0.887±0.058

Data are expressed as mean ± S.D. (n=3)

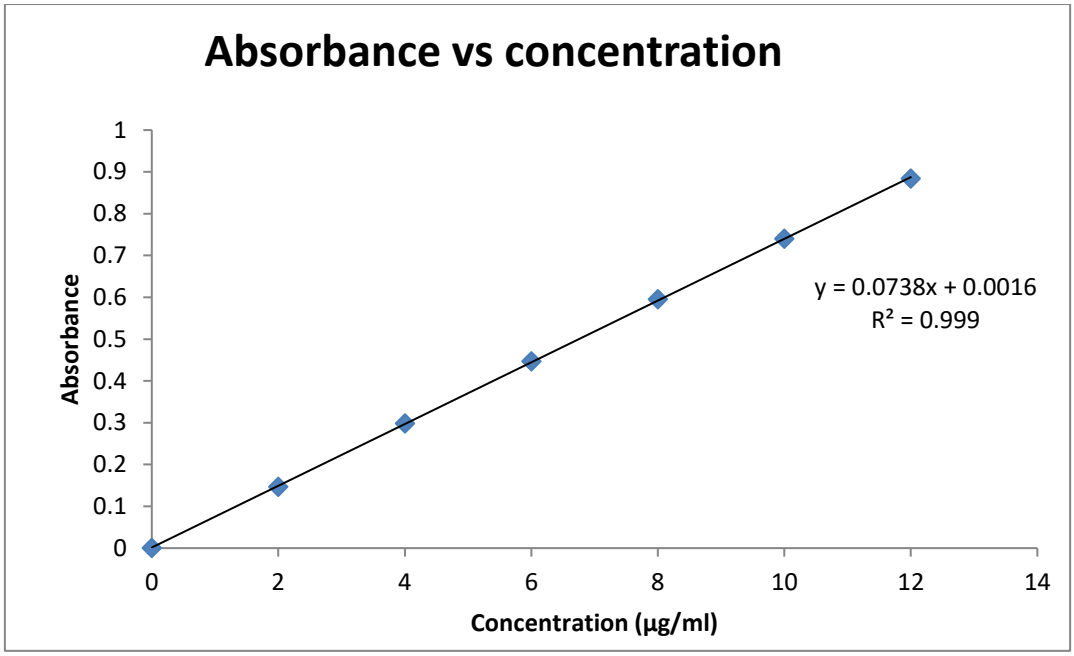


Figure : Standard Plot of Rosuvastatin in 0.1N HCL

Table : Standard plot Data of Rosuvastatin in Water at 239nm

S.No.	Concentration (µg/ml)	Absorbance (nm)
1.	2	0.084±0.056
2.	4	0.146±0.098
3.	6	0.204±0.152
4.	8	0.278±0.112
5.	10	0.332±0.092
6.	12	0.446±0.068

Data are expressed as mean ± S.D. (n=3)

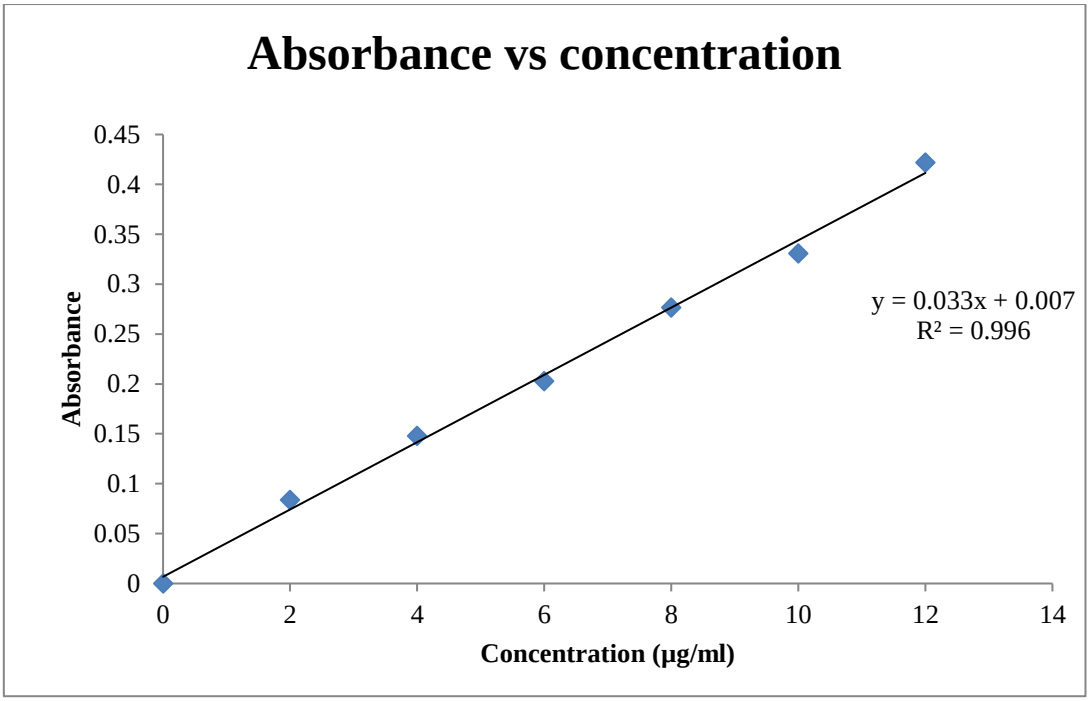


Figure: Standard plot of Rosuvastatin in Water

Table : Characteristics of Gum Acacia and HPMC

Parameter	HPMC	GUM ACACIA
Loss on drying	≥10.0%	≥15%
Apparent viscosity	75 to 140%	-
Swelling index	-	5.68±0.05
pH	5.0-8.0	4.5-5.0
Apparent density	0.25~0.70g/cm^3	-
Surface tension	42 to 56 mN/m	42.8 mN/m

Percent yield and drug content

The percent yield and drug content of pure drug and different solid dispersions which are prepared with polymers were determined. The % yields decreased at the higher concentrations due to the difficulty in sieving at higher polymer and surfactants concentration. The percent yield and drug content of pure drug and different solid dispersions were determined. The results of percentage yield and drug content of different solid dispersions as shown in Tables respectively. The % yields decreased at the higher concentrations due to the difficulty in sieving at higher polymer and surfactants concentration. Low values of standard deviation in percent yield and drug content indicated that drug was uniformly distributed in all solid dispersions and all the formulations showed uniformity and reproducibility of the results obtained.

Table : Percentage yield and drug content of Solid dispersion of Rosuvastatin and HPMC

Formulation code	Percentage yield	Drug content
ROS 1	93.18±0.766	91.36±0.006
ROS 2	92.84±0.186	90.24±0.008
ROS 3	90.32±0.546	92.24±0.004

Data are expressed as mean ± S.D. (n=3)

Table : Percentage yield and drug content of Solid dispersion of Rosuvastatin, HPMC and Gum Acacia

Formulation code	Percentage yield	Drug content
ROS 4	90.48±0.592	92.46±0.004
ROS 5	87.16±0.252	96.23±0.058
ROS 6	88.64±0.578	93.56±0.014

Data are expressed as mean ± S.D. (n=3)

9. Solubility study

Solubility data of pure drug and different solid dispersions as shown in given Tables respectively. Solubility of drug increased with increased in the ratio of polymer.

Table : Solubility of pure drug and solid dispersion (Drug: HPMC)

Formulation code	Solubility(mg/ml)
Pure drug	3.954±0.586
ROS 1	4.484±0.644
ROS 2	6.458±0.012
ROS 3	8.708±0.746

Data are expressed as mean ± S.D. (n=3)

Table : Solubility of pure drug and solid dispersion (Drug: Gum+HPMC)

Formulation code	Solubility(mg/ml)
Pure drug	3.958±0.586
ROS 4	5.768±0.566
ROS 5	6.733±0.584
ROS 6	9.264±0.702

Data are expressed as mean ± S.D. (n=3)

Dissolution studies

The In vitro release of pure drug and different solid dispersions were determined as shown in Tables and plotted the graph between % drug released vs time as shown below in Figures.
The dissolution profile of pure drug and solid dispersion were carried out in Phosphate buffer (pH 6.8). The presence of HPMC:GA increases the dissolution of Rosuvastatin Calcium from the solid dispersion, which increases the dissolution rate as shown in figure . The figure indicates that the solid dispersion (1:5) of Rosuvastatin Calcium: HPMC: GA gives fastest dissolution of drug as compared to other formulation. The In vitro release of pure drug and different solid dispersions were determined and plotted the graph between % drug released vs time.

Table : Drug release of Solid dispersion of Rosuvastatin and HPMC

Mean Percent drug Released ± Standard Deviation				
Time (min)	**Pure drug**	**ROS 1**	**ROS 2**	**ROS 3**
10	12.48±0.22	32.27±0.12	53.92±0.16	68.22±0.14
20	16.38±0.82	37.23±0.08	58.68±0.06	72.55±0.04
30	19.36±0.92	42.57±0.12	64.59±0.26	73.79±0.04
40	22.88±0.02	44.14±0.32	66.98±0.02	74.61±0.06
50	24.14±0.01	48.67±0.18	69.46±0.04	78.75±0.29
60	25.24±0.01	52.67±0.14	70.46±0.18	80.85±0.32

Data are expressed as mean ± S.D. (n=3)

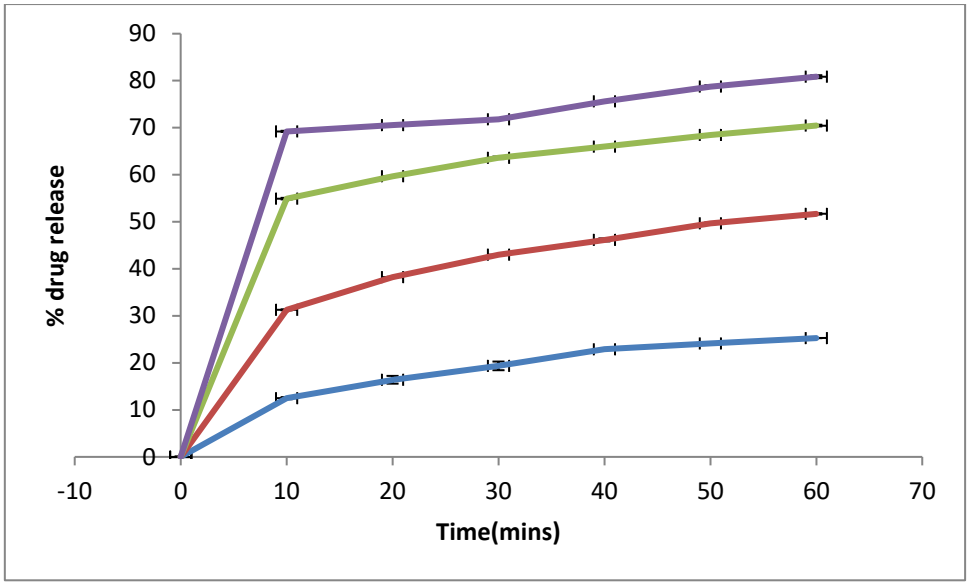


Figure : In vitro dissolution profile of %pure drug released vs time solid dispersions with HPMC

---------- **Pure Drug**
---------- **ROS 1**
---------- **ROS2**
---------- **ROS 3**

Table : Drug release of Solid dispersion of Rosuvastatin, HPMC and Acacia Gum

Mean Percent drug Released ± Standard Deviation				
Time (min)	**Pure drug**	**ROS 4**	**ROS 5**	**ROS 6**
10	12.48±0.92	58.11±0.20	69.14±0.18	73.51±0.09
20	16.40±0.82	62.26±0.38	72.46±0.04	77.51±0.18
30	19.36±0.92	65.21±0.06	77.24±0.14	88.29±0.12
40	22.88±0.02	68.22±0.12	80.56±0.08	92.58±0.12
50	24.14±0.01	70.65±0.32	86.18±0.42	93.15±0.14
60	25.28±0.01	71.89±0.32	87.64±0.26	93.44±0.18

Data are expressed as mean ± S.D. (n=3)

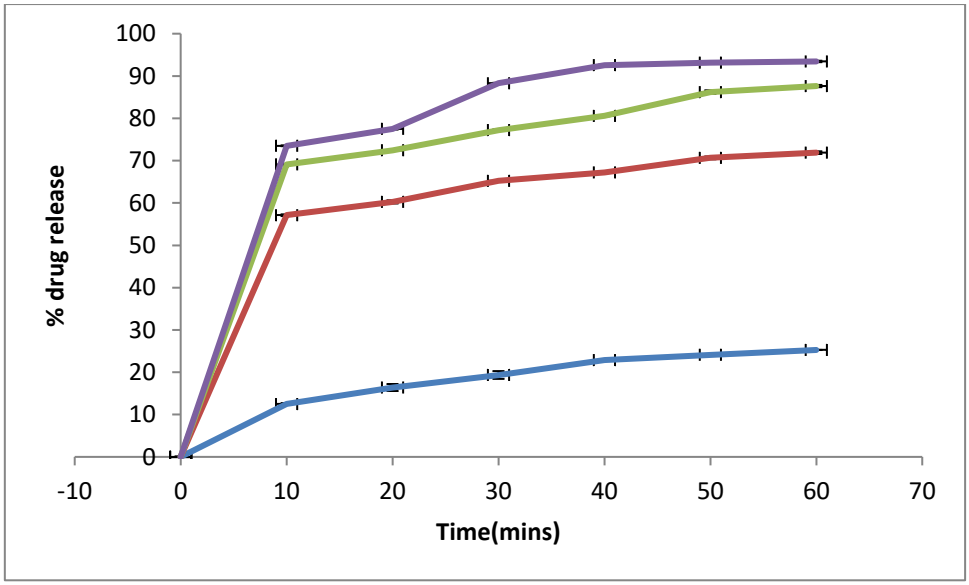


Figure : In vitro dissolution profile of %pure drug released vs time solid dispersions with HPMC and Acacia Gum

---------- **Pure Drug**

---------- **ROS 4**

---------- **ROS5**

---------- **ROS 6**

Table : Dissolution efficiency of Solid dispersion of Rosuvastatin and HPMC

Formulation code	Dissolution efficiency (%DE 60)
Pure drug	17.98±2.96
ROS 1	39.12±1.36
ROS 2	57.98±0.96
ROS 3	67.74±1.08

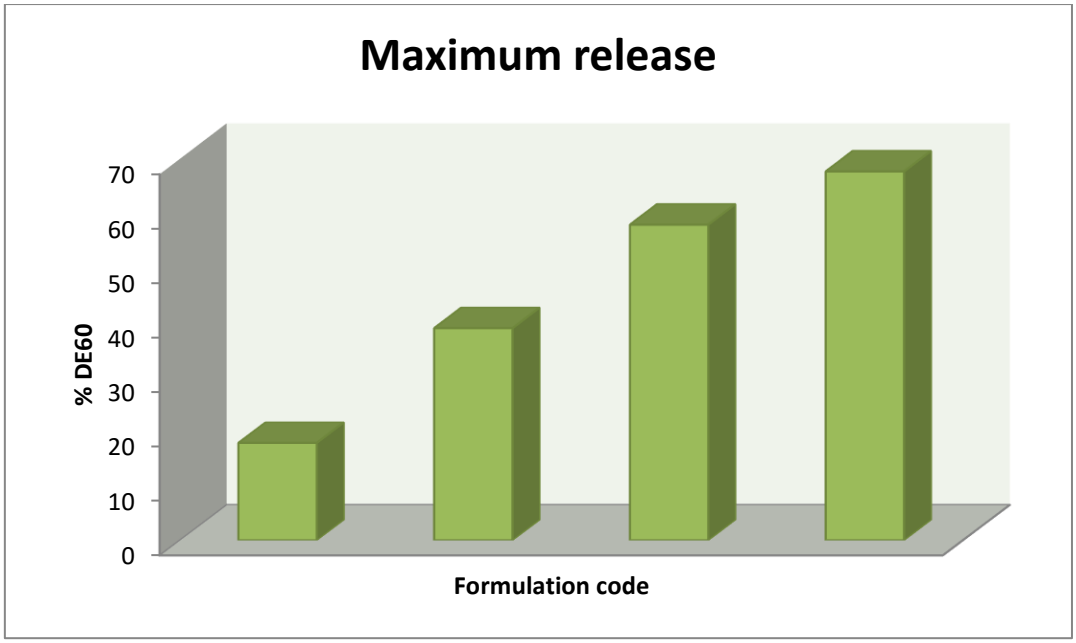
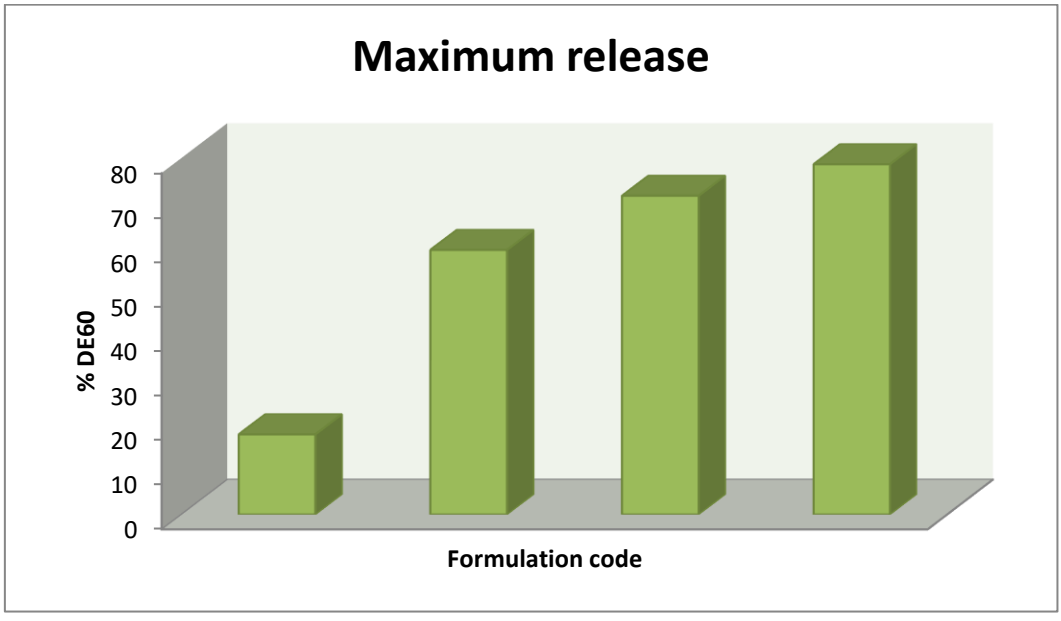


Figure: Comparison of %DE60 of pure drug and different formulations with HPMC (Pure Drug Vs. ROS 1,ROS 2,ROS 3)

Table : Dissolution efficiency of Solid dispersion of Rosuvastatin, HPMC and Acacia Gum

Formulation code	Dissolution efficiency (%DE 60)
Pure drug	18.98±2.96
ROS 4	59.42±1.28
ROS 5	72.56±1.44
ROS 6	78.64±1.28



Comparison of %DE60 of pure drug and different formulations with HPMC and Acacia gum

(Pure Drug Vs. ROS 4,ROS 5,ROS 6)

Table : Dissolution efficiency and percentage yield of optimized formulations

Optimized formulations	%DE 60	%Yield
ROS 6	78.64±1.28	88.68±0.57

Differential scanning calorimetry

DSC of Rosuvastatin and optimized solid dispersions as shown in Figure. The DSC curve for Rosuvastatin showed a sharp melting peak at 142.8^{o}C corresponding to its melting indicates its crystalline nature. However, the characteristic endothermic peak, corresponding to drug melting was broadened and shifted toward lower temperature, with reduced intensity, in the optimized prepared solid dispersions (i.e. HPMC and Acacia Gum). This might be due to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer. Absence of peak for the drug indicates that the drug is distributed homogenously in an amorphous nature state within the solid dispersions without any interaction.

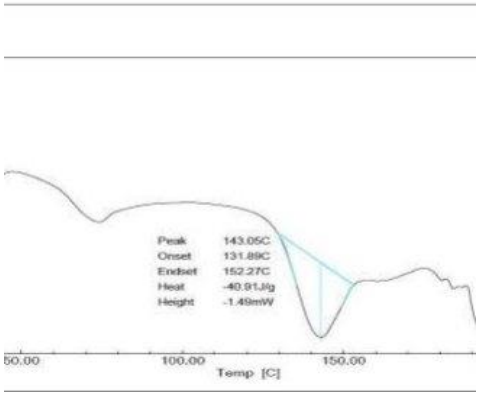
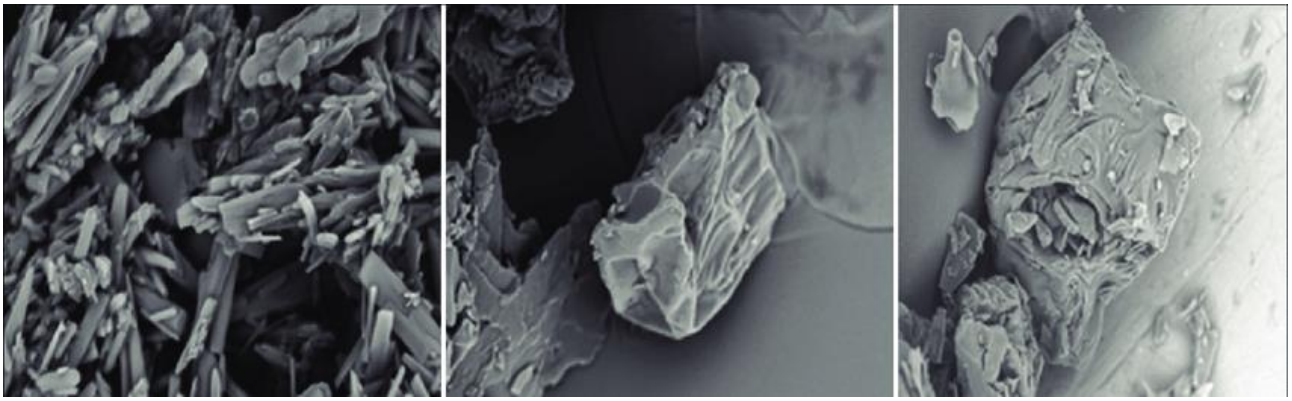


Figure : DSC Thermogram of optimized batch

Scanning electron microscopy (SEM)

The Scanning electron microscopy (SEM) photographs of Rosuvastatin, and optimized solid dispersions as shown in Figures respectively. It was observed that Rosuvastatin was highly crystalline material and characterized by its needle shaped crystals as shown in the given Figure. It was found that the crystals of solid dispersions of drug did not show any needle shaped crystals and shows uniform dispersion of the drug in the polymeric matrix of the polymer and surfactant was observed in the solid dispersions and that shows reduces the crystallinality nature of the drug and changes into an amorphous form as shown in the given Figures.



Scanning electron photomicrographs of Rosuvastatin optimized solid dispersion at 250 X, 350 X & 500 X

Evaluation parameters

The optimized solid dispersion was filled into the "0" hard gelatin capsule shell and the final capsule dosage forms were prepared and designated as ROSCAP

Table :Evaluation parameters of Capsule dosage form ROSCAP with HPMC and Acacia Gum

Formulation code **ROSCAP**	Weight variation (mg)	Disintegration time (min)	Content uniformity
1	0.112±0.002	28	96.98 ± 0.06
2	0.108±0.004	26	98.22±0.06
3	0.107±0.004	25	99.68±0.08
4	0.107±0.006	31	99.96 ± 0.04
5	0.111±0.002	26	95.52±0.24
6	0.106±0.004	29	98.98±0.08
7	0.108±0.002	28	97.26±0.52
8	0.108±0.002	31	96.34±0.03
9	0.109±0.004	25	97.58 ± 0.02
10	0.103±0.002	28	96.92 ± 0.06

Data are expressed as mean ±S.D (n = 3)

Table :Dissolution profile of pure drug and Capsules dosage forms

Time (min)	Pure drug	ROSCAP
10	13.68±0.92	90.86±0.02
20	16.38±0.82	93.92±0.12
30	19.36±0.92	96.68±0.18
40	22.14±0.92	98.49±0.02
50	24.21±0.98	99.48±0.16
60	25.15±1.04	99.66±0.12

Data are expressed as mean ± S.D. (n=3)

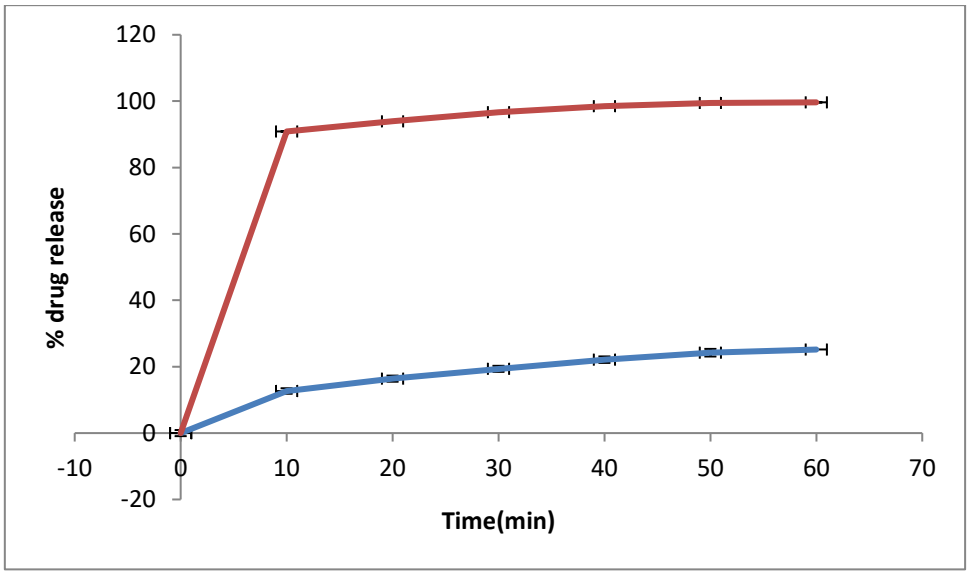


Figure : In vitro dissolution profile of %drug released vs time of pure drug and Capsule dosage form

---------- **Pure Drug**

---------- **ROSCAP**

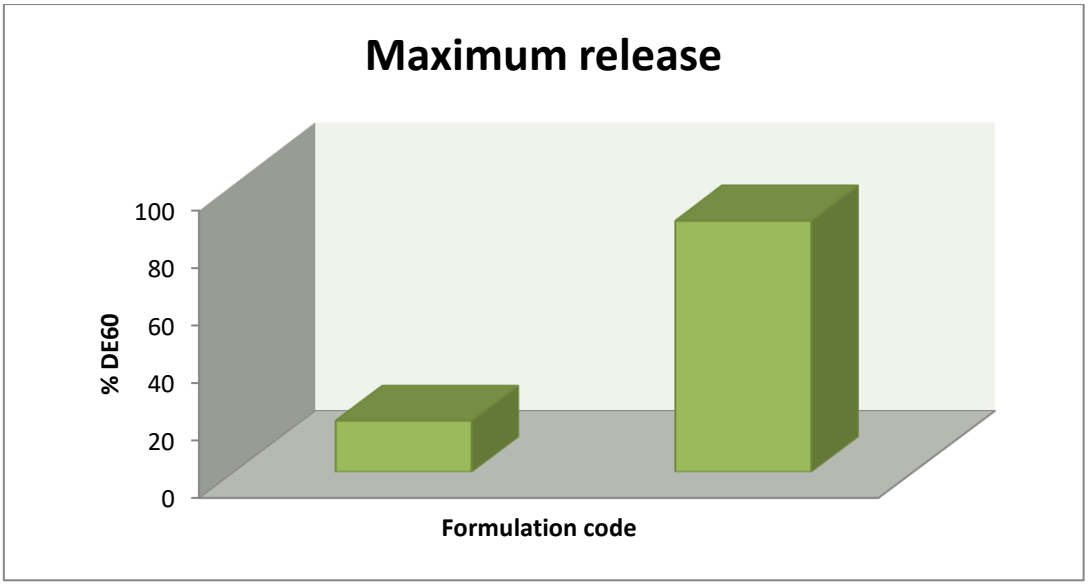


Figure : Comparison of % DE60 with pure drug and capsules dosage formulations (Pure Drug vs. ROSCAP)

Table : Dissolution efficiency of pure drug and Capsules dosage formulations

Formulation codes	Dissolution efficiency (% DE60)
Pure drug	18.98±2.98
ROSCAP	87.38±1.36

Stability studies

All the three prepared capsule dosage formulations kept for stability studies showed no significant variation in all the parameters under the test period at different conditions i.e.40±2ºC and75±5 %RH. The results are shown in Table .

Table :Evaluation of Capsule formulation after stability studies

Time period (days)	0	7	14	21	30
Color appearance	No change in colour	No change in colour	No change in colour	No change in colour	No change in colour
Content uniformity	97.22	99.28	91.64	93.36	94.52

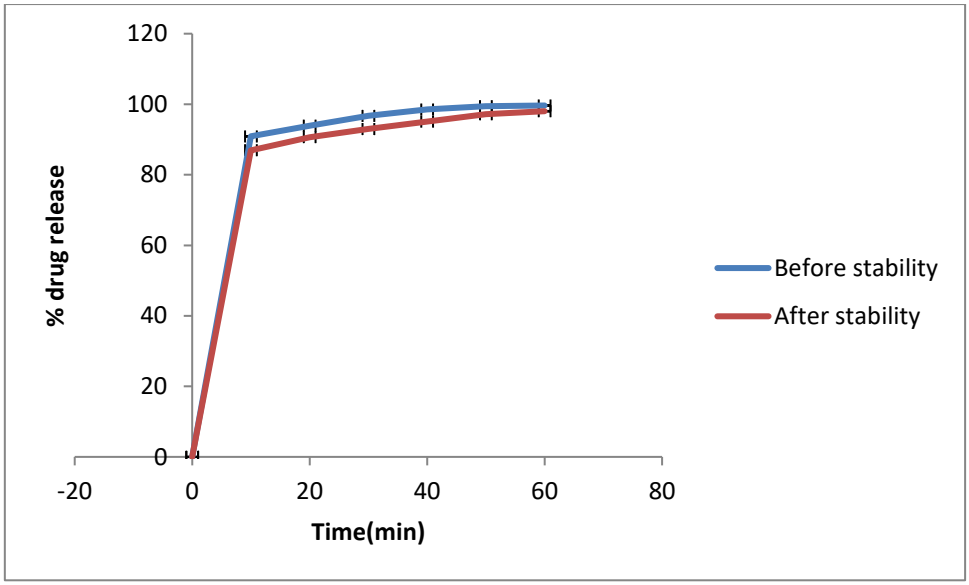


Figure : In vitro dissolution profile of %drug released vs time of pure drug and Capsule dosage forms ROSCAP

The similarity factor was calculated for the comparison of the dissolution profiles of capsule formulations before and after stability studies. The f2 value was found to be for ROSCAP , 72.01. Hence, it was confirmed from the results of stability studies that the developed capsule formulations were stable.

Conclusion

Solid dispersions of rosuvastatin were prepared to enhance aqueous solubility and dissolution rate. Two types of solid dispersions were prepared. First was prepared by melt method using HPMC at different concentrations in the ratio 1:1, 1:3, 1:5 & Second was prepared by solvent evaporation method using gum acacia in the ratio of 1:1, 1:3; 1:5. Total six formulations were prepared. Solid dispersion of Rosuvastatin by the above mentioned method increased the solubility & dissolution rate of Rosuvastatin. The solubility & Dissolution was increased when the drug: carrier ratio was increased. ROS 6 formulation found to have highest solubility,& dissolution efficiency. The optimised solid dispersions (ROS 6**)** are filled into the hard gelatin capsule shells in lactose, magnesium sterate and talc and prepared final capsule dosage form which were characterised 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 prepared capsule dosage form was found to be having better dissolution efficiency at 60 min.

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