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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF SIMVASTATIN BY USING SOLID DISPERSION TECHNIQUE ALONG WITH DIFFERENT COMBINATION OF POLYMERS

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ABSTRACT

The solubility and dissolution rate of simvastatin, a drug used for the treatment of hyperlipidaemia. Simvastatin is a selective competitive inhibitor of HMG Co A reductase. However its absolute bioavailability is 5%. To increase the solubility of drug solid dispersion was prepared. Solid dispersion preliminary solubility analysis was carried out for the selection of the carrier and solid dispersion was prepared with Hydroxy Propyl Methyl Cellulose (HPMC) and Methyl Cellulose (MC). These solid dispersions were analyzed for the solubility and in-vitro dissolution profile solid dispersion of drug with polymer has shown enhanced solubility with improved dissolution rate. Further FTIR, X-Ray studies were carried out. Solid dispersion prepared with polymer in 1:5 ratios shows the presence of amorphous form confirmed by the characterization study. The study also shows that dissolution rate of simvastatin can be enhanced to considerable extent by solid dispersion technique with Polymer.

Keywords: Solubility enhancement, Solid dispersion, Low aqueous solubility

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INTRODUCTION

In recent years, many drug delivery systems like soild dispersion[1], liposome[2, 3], nanoemulsion etc used in order to model the kinetics release, improve the absorption and increase stability drugs. From this arose the main difficulties with regard to the development and the therapeutic activity of many drugs, which results in large part to the low aqueous solubility of drugs[1].

Thus, some techniques can be used to increase the solubility of drugs, independent of their chemical structure and dimension Molecular space[4, 5]. Since solid dispersion increases the solubility of the drugs, it has become one of the most active areas of research in the pharmaceutical field. This technique produces a significant reduction in particle size drug with increased uniformity and surface contact, allowing dissolution and faster absorption[6].

The production of solid dispersions (SDs) is one of the acknowledged methods and used to enhance the aqueous solubility, thereby increasing the oral bioavailability and dissolution rate of drugs with aqueous low solubility[1, 7].

Because of the toxicity and environmental problems associated with the use of organic solvents, the use the fusion method represents an advantageous means in Preparation of SD when the drug is stable Thermal. However, its use is inappropriate when there

polymorphism due to transition that may occur during fusion between the polymorphic forms [8, 9].

Simvastatin (BCS II drug) is a white crystalline powder form and (1*S*,3*R*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a–hexahydro–3,7–dimethyl–8-[2-[(2*R*,4*R*)-tetrahydro–4–hydroxy–6–oxo–2*H*-pyran–2yl]ethyl]-1–naphthalenyl ester. After oral ingestion, SMS, an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG Co-A) reductase, the enzyme that catalyses an early and rate-limiting step in the biosynthesis of cholesterol. It is a Hypolipidemic drug having a potent inhibitor of HMG-CoA reductase inhibitor and used to treat the Hypercholestremia, Dyslipidemia and coronary heart diseases.[10, 11, 12] Hdroxy Propyl Methyl Cellulose (HPMC) is a 2-hydroxy propyl methyl ether and soluble in ethanol, methanol and propanol. Methyl Cellulose (MC) is a Methyl Ether of Cellulose and soluble in water, glacial acetic acid and both these polymers used as a soluility enhancer and improving the dissolution rate of water insoluble drug.

MATERIAL AND METHODS

Materials

The Simvastatin gift sample was received from Dr. Reddys' Pharmaceuticals' Ltd. Hyderabad. The Hydroxy propyl methyl cellulose (HPMC) and Methyl cellulose (MC) polymers were gifted from Signet Chemicals Pvt. Ltd and Loba Chem Pvt. Ltd Mumbai. The other chemicals are ethanol, methanol, magnesium state, talc, lactose; disodium hydrogen orthophosphate and potassium dihydrogen orthophosphate were purchased from Loba Chemicals Mumbai, India.

Methods[9]

Physiochemical Characterisation of Pure Drug

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

Determine the Solubility of Pure Drug by using UV Spectroscopic Method

A. Determination Absorption Maxima of the Drug (λ_{max})

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

B. Preparation of Calibration Curve in phosphate buffer (pH 6.8)

10mg of Simvastatin was dissolved in small amount of methanol (used as co solvent) and diluted to 100ml of phosphate buffer pH6.8. 50ml of this solution was taken and diluted to 100ml with phosphate buffer pH6.8 to prepare a stock solution of 250µg/ml as a stock solution. From this stock solution, aliquots of 2, 4, 6, 8, 10 and 12were transferred to 10ml volumetric flask and volume was made up to 10ml with phosphate buffer. The absorbance of these solutions was measured at 239.5nm using phosphate buffer as blank.

C. Preparation of Calibration Curve in Methanol

10mg of Simvastatin was dissolved in 100ml methanol; 50ml of this solution was taken and diluted to 100ml again with methanol to prepare a stock solution of 250µg/ml as a stock solution. From this stock solution, aliquots of 2, 4, 6, 8, 10 and 12 were transferred to 10ml volumetric flask and volume was made up to 10ml with methanol. The absorbance of these solutions was measured at 238nm using methanol as blank.

Preparation of solid dispersions of simvastatin

Melt Method[7]

The fusion method is sometimes referred to as the 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 solid mass. The solidified mass was crushed and passed through a sieve No. 60. The resulting solid dispersion was stored in a desiccator until further evalution.Same procedure carry out with methyl cellulose.

Characterization of solid dispersions[9, 13, 14]

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

Percentage of Practical Yield

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

[PY (%) = [Practical Mass (Solid dispersion)/ Theoretical Mass (Drug+ Carrier) ×100] eq 1

Determination of Drug Content

Solid dispersions equivalent to 10mg of Simvastatin were weighed accurately and dissolved in 10ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 238 nm by UV Spectrophotometer.

In vitro Drug Release

Accurately weighed preparations equivalent to 10 mg of Simvastatin were added to 900 ml of dissolution media (6.8 phosphate buffer) contained in USP dissolution apparatus II and stirred at a speed of 50 rpm at 37±0.5˚C. 5ml aliquots were withdrawn at 10, 20, 30, 40, 50 60 minute and replaced by 5 ml of fresh dissolution media (37˚C). The collected samples were analyzed after suitable dilution at 239.5 nm using UV-visible spectrophotometer against the blank. The dissolution of pure Simvastatin was done similarly.

Saturation solubility studies

Saturation solubility was determined by adding excess amounts of solid dispersions to water and bio relevant media at 37 ± 0.5°C, respectively. The solutions were

equilibrated under continuous agitation for 24 h and filtered through Whatman filter paper to obtain a clear solution. The absorbance of the samples was measured by UV spectrophotometer (WFZ 800-D2, Beijing Second Telescope Factory) at 238 nm and the concentrations in µg/ml were determined. Each sample was determined in triplicate.

Powder X-Ray Diffraction (XRD) Analysis

The crystallinity of samples was investigated by XRPD using Bruker diffractometer (WI 1140, Japan) and Cu-Kα radiation. The diffractograms were run at 2.5 °C min-1 and chart speed of 2°/2 cm per 2θ angle.

Fourier Transform Infrared (FTIR) Spectroscopy

Simvastatin and solid dispersions were further characterized by FT-IR. Samples prepared in KBr discs were subjected to FTIR recording on FTIR- 8400S, CE (Shimadzu, Japan) instrument (SEM). Data was collected over a spectral range of 4000 to 400 cm^{-1}.

After the characterisation of the prepared solid dispersions on the basis of dissolution studies and optimise the formulation from the drug release studies and select the highest drug:polymer ratio which shows maximum release in the phosphate buffer pH6.8. and its calculative parameters as shown respectively.

Stability studies

Accelerated stability studies were performed on prepared solid dispersion in amber coloured screw capped bottles and was checked as per ICH guidelines at 40±2°C and 75±5% RH up to one month. The solid dispersions were kept in stability chamber. Samples were removed at regular intervals as initial, 7 days, 14 days, 21days and 30 days and were analysed for physical characterization, content uniformity and in vitro dissolution studies. The similarity factor (f2) was used as a basis to compare dissolution profiles. The dissolution profiles. The dissolution profiles are considered to be similar when f2 is between 50 and 100. The dissolution profiles of C1 formulation before and after stability testing were compared using a similarity factor (f2) which is a calculated from the following formula.

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

.....eq 2

Where, n is the dissolution time and R_j and T_j are the reference and test dissolution values at time t. (Morre Flamer equation).

A model independent method for comparison of two dissolution profiles is based upon similarity factor f_2 and difference factor f_1.similarity factor as discussed above, the equation of difference factor discussed below.

$$f_2 = \sum_{t=1}^{n}(R_t - T_t) / \sum_{t=1}^{n} R_t$$

.....eq 3

RESULT AND DISCUSSION

Physical Appearance

Physical appearance of drug was studied by its various organoleptic properties. The sample of simvastatin was found to be white, non hygroscopic, crystalline solid powder. The melting point of simvastatin was found to be in the range of 135 -140^{0}C by Capillary method.

Absorption Maxima

Absorption maxima (λ max) of simvastatin were observed in different solvents.

Table 1: Absorption maxima (λmax) of the Simvastatin

Solvent	(λmax)nm
Phosphate buffer	239nm
Methanol	238nm

Solubility

The solubility studies of Simvastatin were determined in different solvents.

Table 2 Solubility of Simvastatin in different solvents

Solvent	Solubility
Phosphate buffer	4.036±0.549
Methanol	2.516±0.166

Data Expressed as mean ± S.D (n=3)

Standard curves

The standard curve of simvastatin was found to be linear at 237nm in phosphate buffer (pH6.8) in the concentration range of 2-12(µg/ml), which obeys Lambart Beer Law. The absorbance at different concentrations is shown in tables and graph is represented in figure respectively.

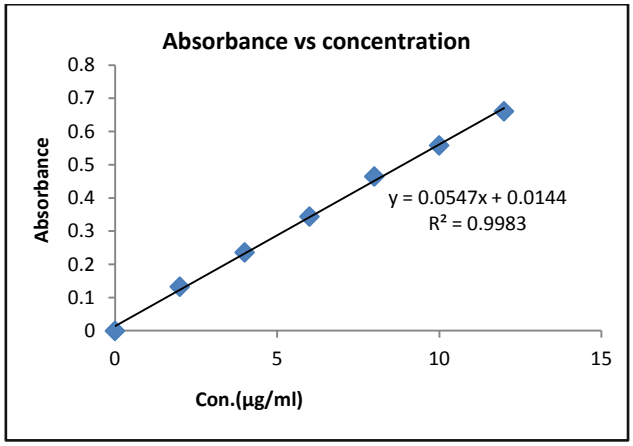

Figure 1: Standard Curve of Simvastatin in Phosphate Buffer (pH6.8)

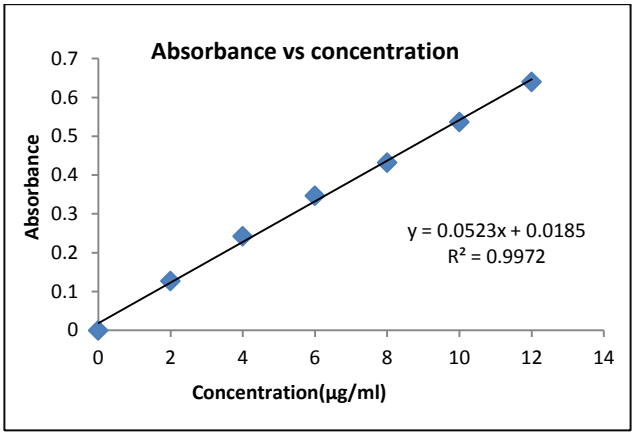

Figure 2: Standard Curve of Simvastatin in Methanol

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.

Table 3: Percent yield or drug content of solid dispersions Sim/HPMC

Formulation Code	Percentage yield	Drug content
SIH1:1	95.52±0.804	84.42±0.020
SIH1:3	94.81±0.635	91.73±0.006
SIH1:5	90.27±0.245	95.96±0.009

Data Expressed as mean ± S.D (n=3)

Table 4: Percent yield or drug content of solid dispersions Sim/MC

Formulation Code	Percentage yield	Drug content
SM1:1	90.14±0.759	77.69±0.018
SM1:3	89.63±0.514	87.88±0.007
SM1:5	89.26±0.865	84.23±0.016

Data Expressed as mean ± S.D (n=3)

Table 5: Percentage yield and drug content of solid dispersion Simvastatin MC: HPMC

Formulation Code	Percentage yield	Drug content
SHM1:1	92.29±0.935	85.76±0.015
SHM1:3	91.99±0.404	89.61±0.016
SHM1:5	92.54±0.402	92.11±0.007

Data Expressed as mean ± S.D (n=3)

Solubility studies

Solubility data of pure drug and different solid dispersions as shown in given Table 6 to 8 respectively. Solubility of drug increased with increased in the ratio of polymer.

Table 6: Solubility of Pure Drug Simvastatin and HPMC

Formulation Code	Solubility
Pure drug	4.036±0.549
SIH 1	6.156±0.645
SIH2	7.043±0.422
SIH3	8.273±0.159

Table 7: Solubility of Pure Drug Simvastatin and MC

Formulation Code	Solubility
Pure drug	4.036±0.549
SM1	5.356±0.285
SM2	6.066±0.351
SM3	7.676±0.442

Data Expressed as mean ± S.D (n=3)

Table 8: Solubility of Pure Drug Simvastatin and HPMC: MC

Formulation Code	Solubility
Pure drug	4.036±0.549
SHM1	9.516±0.232
SHM2	11.186±0.178
SHM3	12.516±0.232

Data Expressed as mean ± S.D (n=3)

In Vitro Dissolution studies

The *In vitro* release of pure drug and different solid dispersions were determined and plotted the graph between % drug released vs time.

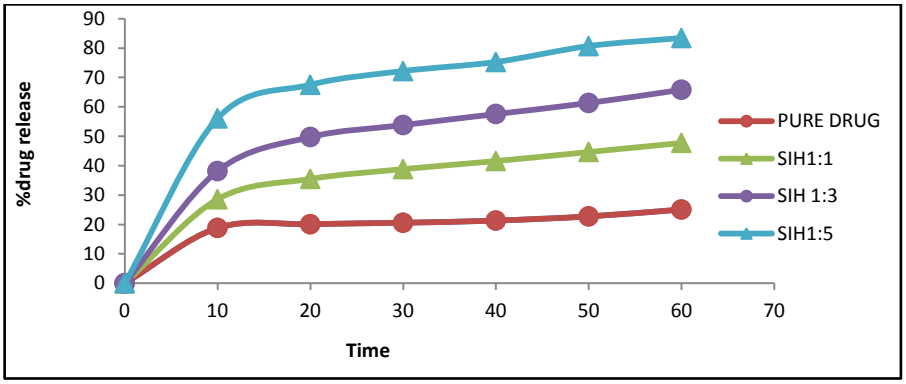

Figure 3: In vitro dissolution profile of %drug released vs time pure drug and Solid dispersions (Sim/HPMC)

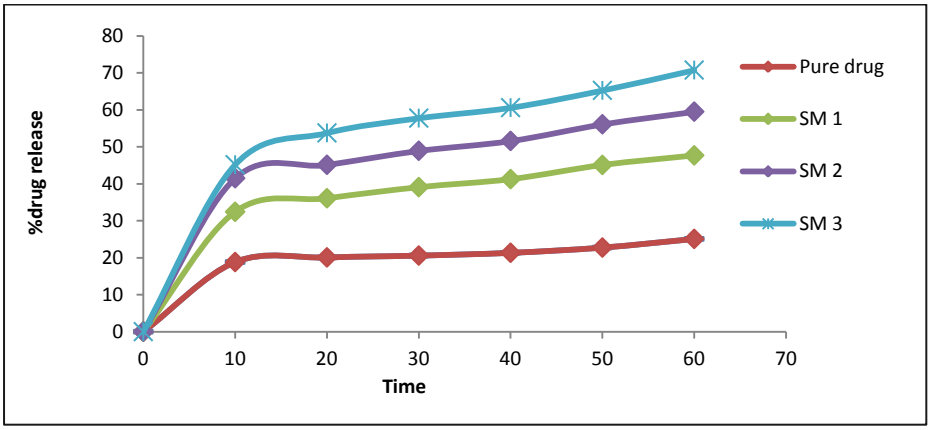

Figure 4: In vitro dissolution profile of %drug released vs time pure drug and Solid dispersions (Sim/MC)

X-ray diffraction studies

The X-ray diffraction studies of pure simvastatin and optimized solid dispersions of both polymers HPMC and Methyl Cellulose. The characteristics diffraction peaks of simvastatin present peaks at (2θ) 9.63o, 11.24o, 15.90o, 16.889o, 17.56o, 18.04o, 19.74o, 22.84o, 28.68o, 33.51o, 35.17o, and 38.73o indicate the pr crystalline nature of the drug. Peaks of optimized solid dispersion shows the reduction in peak height area which indicates the reduction in the crystallinity nature of the simvastatin as some of the drug converted into the amorphous form in the solid dispersions.

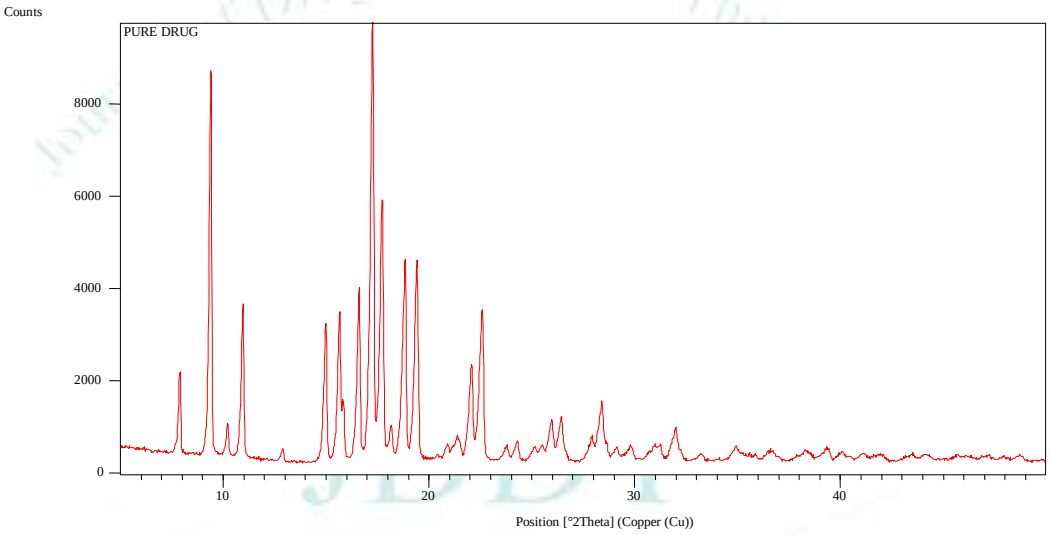

Figure 5: X-ray diffraction of Simvastatin

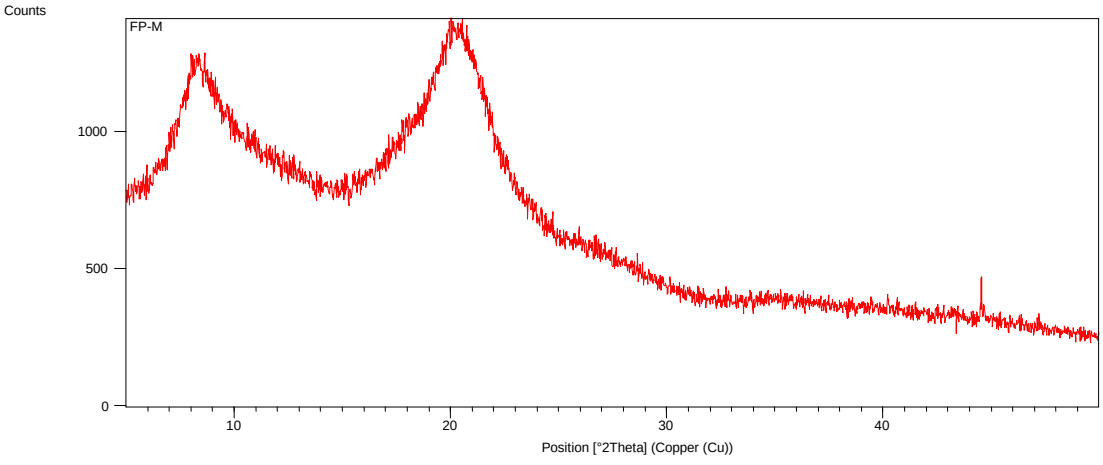

Figure 6: X-ray diffraction of Simvastatin with HPMC/MC

Infrared spectroscopy

The spectrum of solid dispersions exhibited significant decrease in intensity of O-H stretching vibrations which may be due to intermolecular hydrogen bonding. The spectra peaks of drug were almost unchanged in the optimized solid dispersions which indicate that the overall symmetry of molecule was not affected

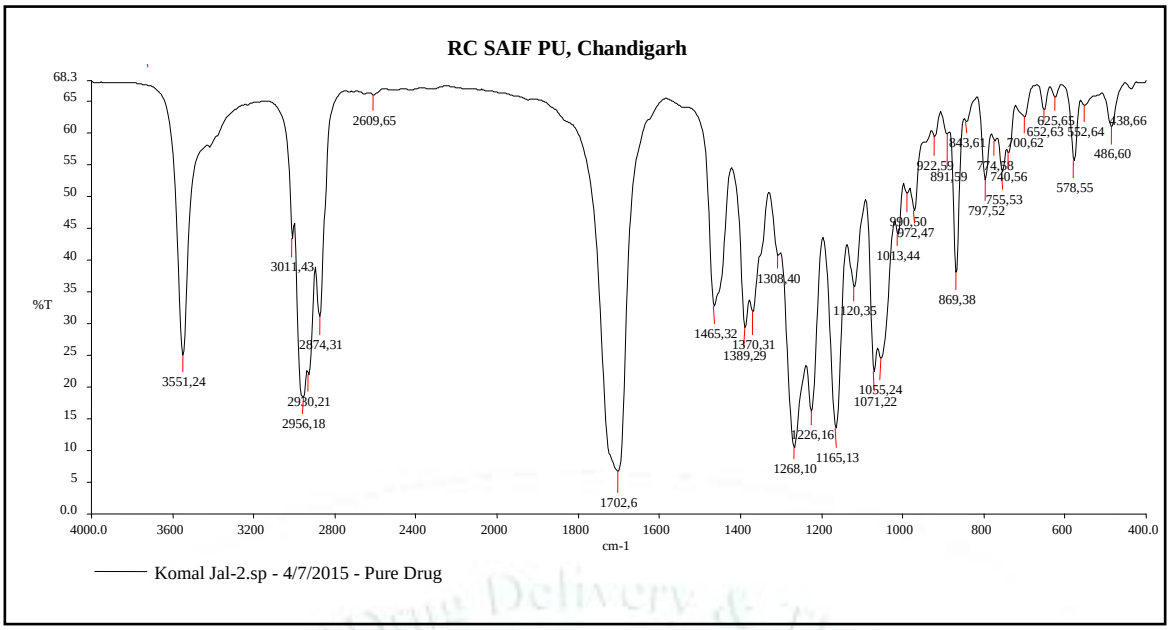

Figure 7: IR Spectra of Simvastatin

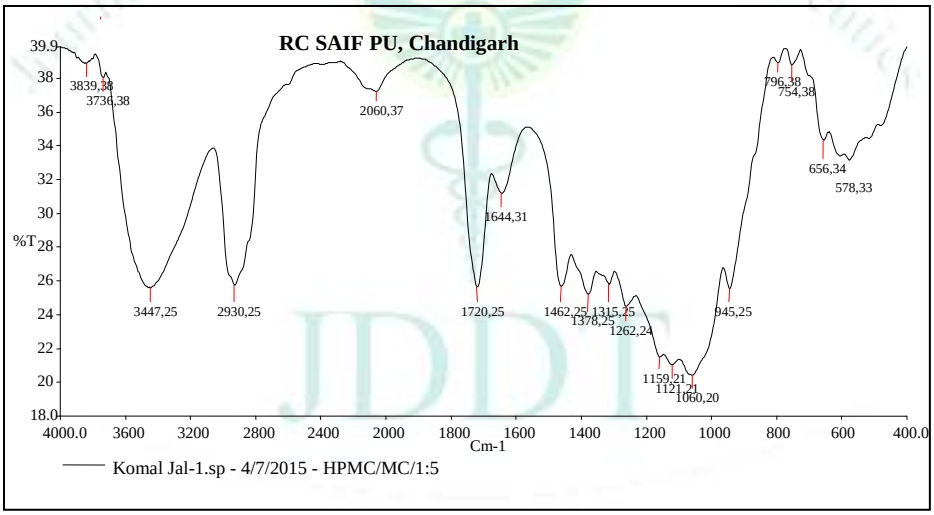

Figure 8: IR Spectra of optimized solid dispersion with (HPMC/MC)

Optimized formulation

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

Table 9: Dissolution efficiency and yield of optimized formulations

Optimized formulation	$\%DE_{60}$	% Yield
100:500	65.44	90.27
100:500	53.41	89.26
100:250:250	60.90	92.54

Table 10: Evaluation parameters of optimized solid dispersion (HPMC) after stability

Time period (in days)	**0**	**7**	**14**	**21**	**30**
Color appearance	No change in color	No change in color	No change in color	No change in color	No change in color
Drug release	-	-	-	-	95.47

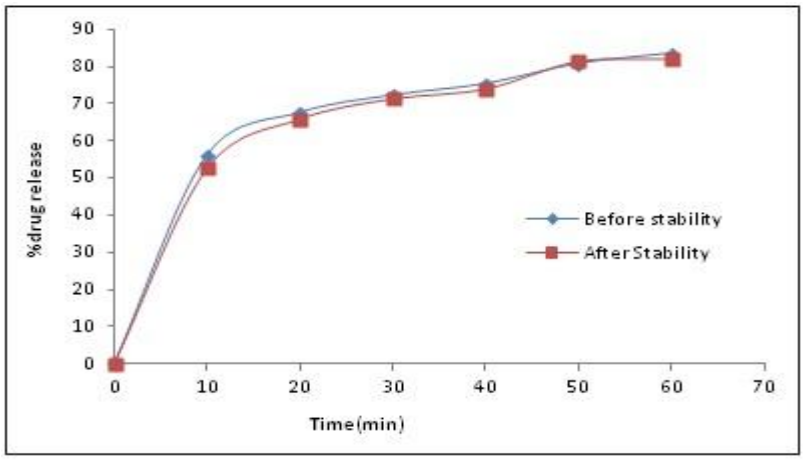

Figure 9: Drug Release Data of Before and After Storage (Sim/HPMC)

Table 11: Evaluation parameters of optimized solid dispersion (MC) after stability

Time period (in days)	**0**	**7**	**14**	**21**	**30**
Color appearance	No change in color	No change in color	No change in color	No change in color	No change in color
Drug release	-	-	-	-	91.17

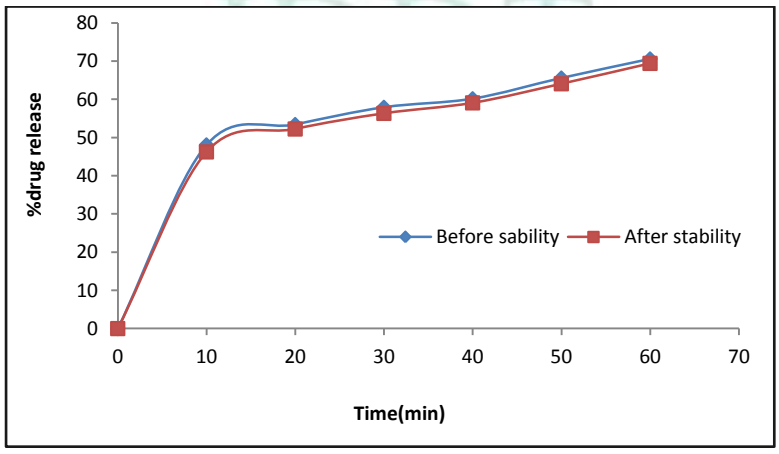

Figure 10: Drug Release Data of Before and After Storage (Sim/MC)

Table 12: Evaluation parameters of optimized solid dispersion (HPMC: MC) after stability

Time period (in days)	**0**	**7**	**14**	**21**	**30**
Color appearance	No change in color	No change in color	No change in color	No change in color	No change in color
Drug release	-	-	-	-	93.23

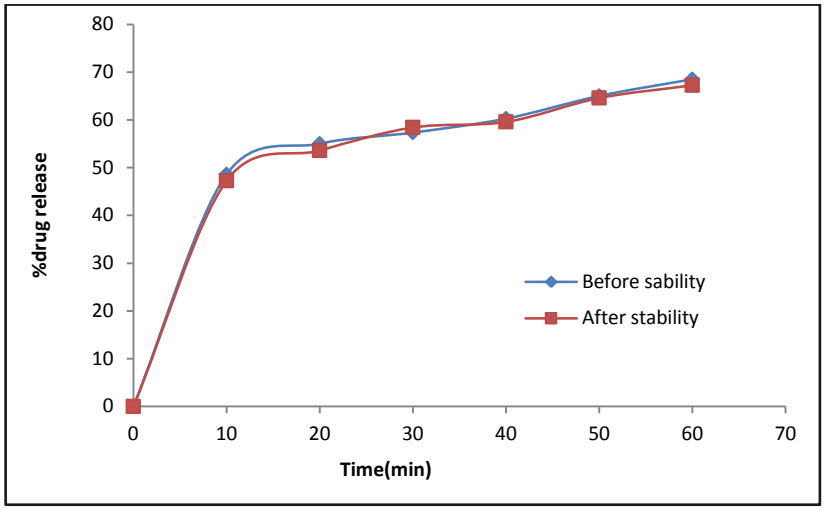

Figure 11: Drug Release Data of Before and After Storage (Sim/MC: HPMC)

From all above the dissolution data, it shows that there will no change from the above dissolution data and graph, that there is no change to be observed in prepared optimized solid dispersion. The value to be calculated from the equation and drug release value is 93.23 that is become met similar with the standard so that the optimized solid dispersion was stable after the stability studies.

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