Shmmon Ahmad[1] and Harpinder Kaur Gill[1]

[1]Chandigarh College of Pharmacy

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POLYMORPHISM AND SOLID STATE TRANSITION OF ANTIHYPERLIPIDEMIC DRUG SIMVASTATIN: PREPRATION, CHARACTERIZATION AND OPTIMIZATION BY USING CCD & RSM

Shmmon Ahmad* and Harpinder Kaur Gill.

Departments of Quality Assurance, Chandigarh College of Pharmacy, Landran, Mohali, Punjab -140307.

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***Correspondence for Author**
Shmmon Ahmad
Departments of Quality Assurance, Chandigarh College of Pharmacy, Landran, Mohali, Punjab - 140307.

ABSTRACT

Recently it has been growing interest in investing solid state transition forms prepared by different technique. The majority of drugs are administered in solids form. Among all newly discovered chemical entities about 40% drugs are lipophillic and fail to reach market due to their poor aqueous solubility. Problem of solubility is a major challenge for formulation scientist, which can be resolved by different technological approaches. Simvastatin belong to class of antihyperlipidemic drugs having very low solubility and falls in category II Class of BCS. Polymorphism and solid state transitions change the solid-state property which is significantly influence the performance of the final product such as solubility, Melting Point, Dissolution Rate and flow property. Optimization process like RCM and CCD design was used to study the effect of variables such as solubility and melting point for quality determination of formulation. Solvent evaporation method is used in this study to prepare new transition form. This technique has more advantages and it is preferred method over others such as spray drying, sonication and homogenization. Through the characterized analysis (SEM, XRD, ATR, DSC, Solublity and melting point) of optimised form, given reliably confirmation data that the new solid state transition forms is amorphous form. It is more soluble than crystalline form.

KEYWORDS: Polymorphism, Solid state transition, Simvastatin, Dissolution, DSC, SEM, ATR.

INTRODUCTION

Polymorphism

Polymorphism is the ability of a particular solid substance to exist in multiple solid states forms as a result of different arrangements and/or confirmations of its molecules. These crystalline forms are chemically similar but structurally dissimilar. For example the diamond and graphite are polymorphs of carbon.

Each crystal polymorphs has a well-defined region of thermodynamic stability in the phase diagram of the substance, and first-order phase transitions from one polymorph to another are observed through changes in temperature T or pressure *P* (P. H. Poole).[1]

Crystalline Form

Crystalline form contains highly ordered arrangement of molecules and atoms held together by non-covalent interactions. Inorganic salt (sodium chloride) we can consider as a simple example the unit cell.

Amorphous Form

Amorphous form increase intermolecular distance due which increase the absorption surface. Main advantage as compared to conventional crystalline drugs is their considerably improved solubility and bioavailability.

- Higher dissolution rate (can give better bioavailability)
- Better compression characteristics
- Optimum stability of macromolecules

Phase transition

Phase transition is the process of transformation of one polymorph into another, which may also occur on storage or during processing. Two types of polymorphous transitions are distinguished, Enantiotropic and Monotropic (D.Giron).[2] Both enantiotropism and monotropism are important properties of polymorphs. Uncontrolled phase transitions of unstable polymorphs into more stable ones are a big problem of pharmaceutical industry. Thermal analysis techniques are being used extensively for determination of the thermodynamic relationships between different phases: enantiotrope or monotrope transitions between true polymorphs, transitions between different solvates or hydrates and polymorphs, glass transition of amorphous form (B.Kratochvíl).[3]

A phase transition is the transformation of a thermodynamic system from one phase or state of matter to another one by heat transfer. The term most commonly used to describe transition between solid, liquid and gases state of matter. In the three states of matter, solids possess the most structural diversity. Whereas gases and liquids consist of discrete molecules that are randomly distributed due to thermal motion, solids consist of molecules, atoms, or ions that are statically positioned. Solid can be further divided in Crystalline and amorphous solids (B.D.Fahalman).[4]

Now-a-days various varieties of pharmacological molecules have been discovered. But the great majority of these molecules have poor bioavailability, mostly of these molecules associated with their low solubility in water, low absorption of drugs in to systemic circulation. So the manufacturing units highly concentrate on the investigation of crystal polymorphism to optimize the physicochemical properties and assure the stability of API before the drug product development (Vellaisamy).[5] Among these drugs, simvastatin is the most frequently used, despite its poor solubility in water (M. Rúbia).[6] Problem of solubility is making a challenge to researcher, which can be resolved by different technological approaches (M.Limbachiya).[7] Simvastatin belong to class of antihyperlipidemic drugs having very low solubility and falls in category II Class of BCS (M. Rao).[8] This class represents the drugs having low solubility and high permeability. This category of drugs needs special attention and modifications to show better solubility and hence bioavailability. A number of methodologies can be adapted to improve solubilisation of poor water soluble drug and further to improve its bioavailability. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and then such drugs shows good bioavailability (A.Chaudhary).[9]

There are many Physical and chemical properties that vary among Solid state transitions as listed in **Table 1** (D.Singhal).[10]

Table 1: List of physical and chemical properties that differ among various Solid state transitions.

Packing properties	Molar volume and density, refractive index, Electrical and thermal conductivity and Hygroscopicity.
Thermodynamics Properties	Melting and Sublimation temperatures, internal energy enthalpy, heat capacity, entropy, free energy and chemical potential
Spectroscopic properties	Electronic, vibrational and nuclear spin transitions.

Kinetic properties	Dissolution rate, rate of solid state reactions, stability, Bioavailability, T_{max}, C_{max} and AUC
Surface properties	Surface free energy, surface chemistry, colour morphology
Mechanical properties	Hardness, tensile strength, compatibility handling, flow and blending

The physical properties of the solid state can be seen in crystals and powders in both drugs and pharmaceutical excipients. They are of interest because they can affect both the production of dosage forms and the performance of the finished product (A.T.Florence).[11]

MATERIAL AND METHODS

Materials

Simvastatin was kindly gifted by Ranbaxy Laboratories Ltd. Mohali, India and the drug was used without further purification. Distilled water was prepared in laboratory. All the solvents and chemicals used in study were of AR grade/all materials used for study conformed to USP-24 standards.

Method

Solid state transition was performed by crystallisation from single solvent evaporation method (A.Poornaprajna).[12] In this method, product was obtained by dissolving weighed amount of drug in water immiscible solvent Dichloromethane in a beaker at 10-55°C. It was kept on magnetic stirrer for different time in between 3-50min. The undissolved drug was filtered off. When the solvent concentrated, then added Petroleum ether as anti-solvent and this solution was kept on water bath at 5-10°C for 30min with continuous stirring. The saturated solution was evaporated on water bath. After 2-4 hours crystals were obtained.

Optimization

Throgh Polymorphisim/solid state transitions we can obtain various form which have different properties (listed in Table1). So optimisation should be, based on parameters such as solubility, hygroscopicity, crystallinity, stability, and ease of production. Optimization process like RCM (Response Surface Methodology) and CCD (Central Composite Design) design was used to study the effect of variables such as solubility and melting point for quality determination of formulation. RCM is a collection of mathematical and statistical techniques based on the fit of a polynomial equation to the experimental data, which must describe the behaviour of a data set with the objective of making statistical provisions. A

CCD model was used to statistically optimize the formulation factors on the melting point (y_1) and new transition form solubility (y_2), Details of the design are listed in table 2.

Table 2: Relationship between coded and actual values of the variables used in formulation of solid state transition form.

Formulation factors	Coded level of variables	
	-1	+1
X_1 = Heating temperature	20	55
X_2 = Heating Time	10	40

For each factor, the experimental range was selected on the basis of the results of preliminary experiments and the feasibility of preparing the new solid state transition form at the extreme values. The value range of the variables was: heating temperature (x_1): 10-55°C and heating time (x_2): 10-40min. The design consists of 13 experiments. The details of the design are shown in **Table 3**. Each experimental run was repeated thrice.

Table 3: Observed responses in central composite design for new transition from, Influence of formulation variables on Melting point.

Run Sample	A:Temp degree C	B:time Minutes	Solubility mg/ml	Melting point degree C
1	12.7	25	0.026	110
2	37.5	25	0.086	115
3	37.5	3.78	0.062	112
4	37.5	25	0.088	76
5	37.5	25	0.08	110
6	62.2	25	0.064	58
7	55	40	0.174	58
8	37.5	25	0.085	108
9	20	40	0.067	57
10	37.5	46.2	0.0784	114
11	20	10	0.0664	110
12	55	10	0.0544	112
13	37.5	25	0.0654	65

A design matrix comprising of 13 experimental runs was constructed and the responses were modelled by the following polynomial model:

$$y = b_0 + b_1x_1 + b_2x_2 + b_{11}x_1^2 + b_{22}x_2^2 + b_{12}x_1x_2 + b \quad \text{.....(1)}$$

The ranges for each of the variables in were chosen taking into account our preliminary experiments. Table 3 shows the experimental results concerning the tested variables on mean melting point and solubility. These two responses were individually fitted to a second order polynomial model. For each response, the model which generated a higher F value was identified as the best fitted model. Each obtained model was validated by ANOVA. Three dimensional response surface plots were drawn for the optimization of new transition form. These types of plots are useful in studying the effects of two factors on the response at one time, when the third factor is kept constant.

Melting Point is a critical factor for Solid state transition. Stability and various compression factors are directly affected by melting point. Generally higher melting point of product show good stability and decrease the chance sticking, picking, weight variation in tablet, because lower melting point product melt during compression and stick with punch and create problem.

$Melting\ point(Y_1)$ =108.7315648+1.714856731* Temp -2.06293771* time - 0.000952381*Temp * time-0.029265306* $Temp^2$ $^{+}$0.024611111* $time^2$ .....(2)

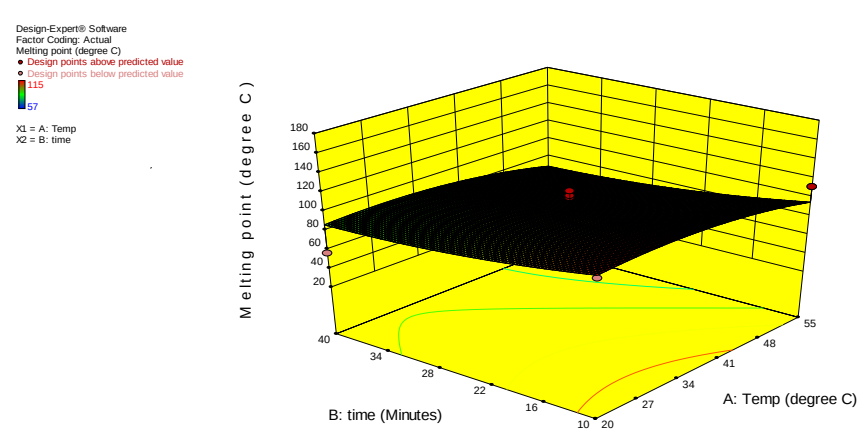

Figure 1: Three dimensional response surface plots showing the effect of variables on responses: - Melting point.

A positive value in regression equation for a response represents an effect that favours the optimization (synergistic effect); while a negative value indicates an inverse relationship (antagonistic effect) between the factors and the response (M.Singh).[13]

The reduced quadratic model was found to be non significant with an F value of 0.85 ($p < 0.0500$), which indicates that response variable Y_1 and the set of formulation variables were significantly not related. The high R^2 value indicated that 37.79% of variation in melting point was explained by the regression on formulation factors.

Table 4: Comparison of the experimental and predicted values of new transition form prepared under the predicted optimum conditions.

S.No	Response	Predicted value	Experimental value	Bias (%)[a]
1	Melting Point Y_1	112.9	110	2.56
2	Solubility (mg %) Y_2	6.98	6.64	5.00

$$^{a}Bias = \frac{predicted\ value - experimental\ value}{predicted\ value} \times 100$$

Influence of Preparation Factors on Solubility

In this study, the solubility of new transition form reached up to 6.64% (Table 4). High solubility is advantageous since it transports enough drugs at the target site and increase the residence time of the drug. The high solubility of optimised form can be attributed to several factors.

The optimised variables show a good fit to the reduced quadratic model (Equation 3) with an F value of 5.71 ($p < 0.0500$), which indicates that response variable Y_2 and the set of formulation variables were significantly related. The high R^2 value indicated that 71.3% of variation in solubility was explained by the regression on formulation factors.

The statistical analysis of the results generated a quadratic response for optimised form solubility is as follows

$Solubility(\%)\ (Y_2) = 0.113196873 - 0.001770904*Temp - 0.003055057*Time + 0.000113333*Temp*Time$ .....(3)

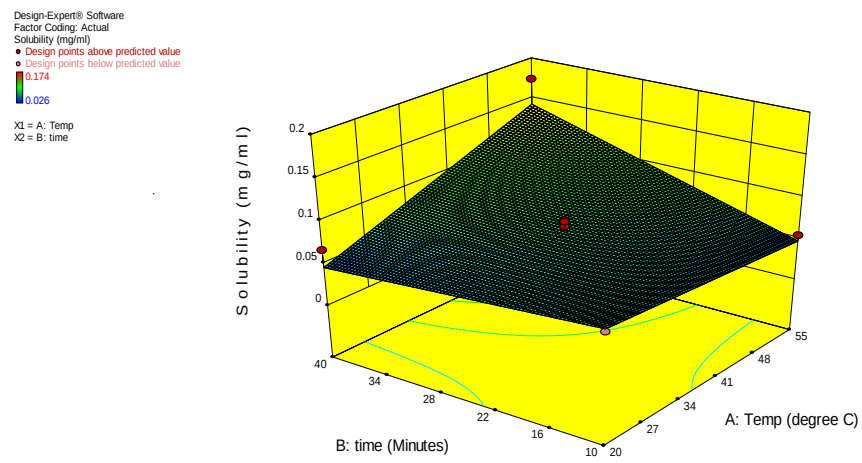

Figure 2: Three dimensional response surface plots showing the effect of variable on the response: - Optimised form solubility.

EVALUATION

Tenth formulation was selected which have highest solubility. The Optimised form was evaluated by different techniques including Dissolution studies, SEM, DSC, XRD and ATR.

Dissolution (In Vitro release) Study

Dissolution testing of optimized form was performed according to USP 32 (USP).[14] Apparatus 2 (paddle) at 50 rpm; 37 ± 0.5°C; 900mL of pH 7.0 phosphate buffer (0.01 M) with 0.5% SDS(sodium dodecyl sulphate). The dissolution medium was prepared by dissolving 4.5 gm of sodium dodecyl sulphate in 900 mL of water and adjusting the pH to 7.0 with monobasic sodium phosphate. SDS was added in concentrations of 0.1–0.5% w/v. Simvastatin release was quantified by UV spectrophotometric analysis of the dissolution samples at 237.5 nm.

The dissolution studies were carried for 30min, at 37±05ºC paddles rotating at 50 rpm. The 5ml aliquots sample were withdrawn and analyzed after 5, 10, 15, 30 minutes and same quantity was replaced to dissolution medium (N.Singla) (G.Singhvi).[15][16]

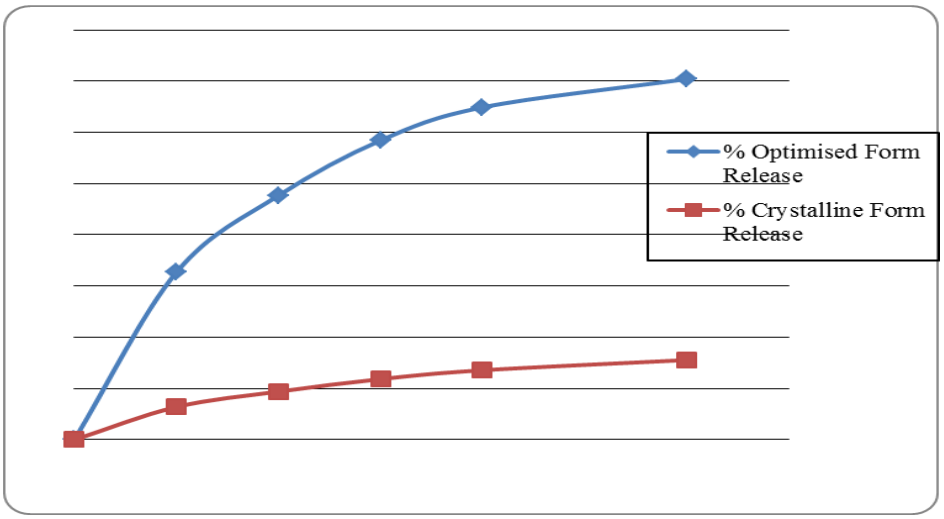

Figure 3: *In vitro* release profile of simvastatin pure drug and optimised transition form.

The dissolution profiles of the optimised form and pure drug (SIM) are shown in **Figure 3.** It is evident that the dissolution rate of optimised form was higher as compared to the pure drug. Simvastatin drug substance showed poor dissolution profile i.e. only 15.57 % of drug was released at the end of 30 minutes, where as Solid state transition form showed excellent release 70.42 % drug at the end of 30 minutes.

The improved dissolution due to amorphous form with decrease particle sizes its deposition on the surface of the carrier and improved wettability. *In vitro* dissolution profile shows that percentage drug release is good in Solid state transition form.

Screening Electron Microscopy

For their external morphology studies of unchanged drug and Solid state transition form the SEM was used. The sample were visualized using scanning electron microscopy (JSM-6510 from SAI Labs, Thapar University, Patiala) operated at 10Kv. The small amount of powder samples was manually dispersed on a metal stub with double adhesive tape and coated with Platinum/Palladium alloy under vacuum. The shape and surface characteristic of the Optimised form and pure drug was observed in electron micro analyzer and photographs (C.T.K.H.Stadtlander) (K.Dandu).[17][18]

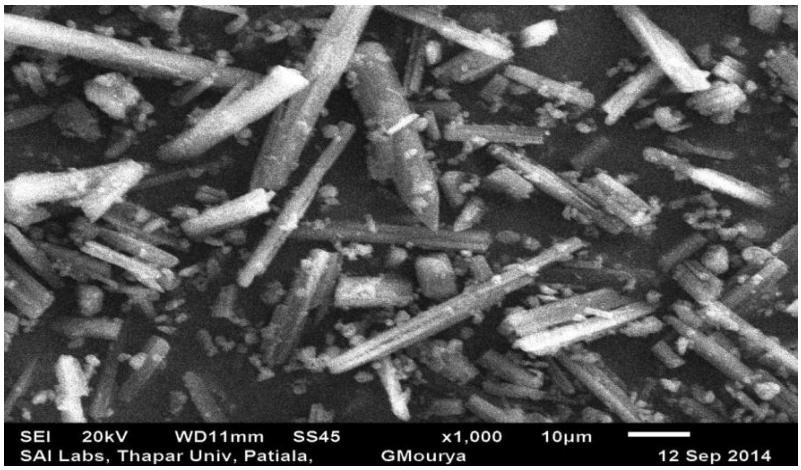

Figure 4: SEM of pure drug simvastatin.

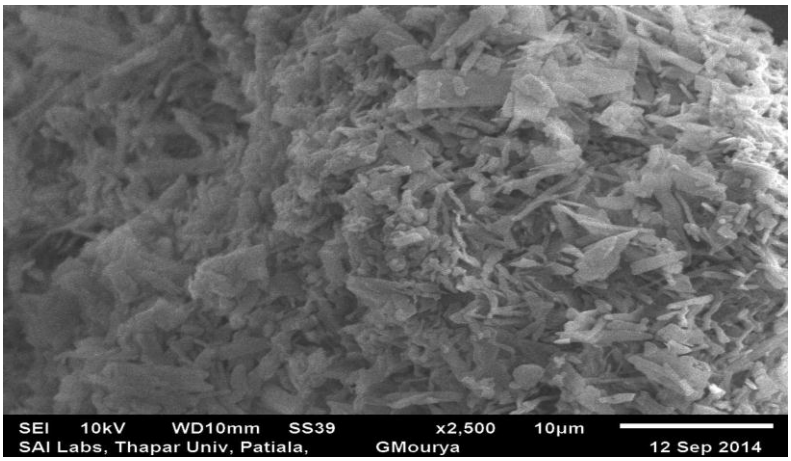

Figure 5: SEM of optimized Solid state transition form.

DSC thermograms of drug

The Differential scanning calorimetry of drug was carried out by (DSC Q10 V9.4 Build 287 USA) instrument. Samples weighing between 1 and 10 mg were loaded into open aluminium pan and placed into the DSC cell. The cell had a nitrogen purge flowing at approximately 40cm^3/min. The DSC was used to analyze the samples from 10–350°C with a 10°C/min heating rate. Obtained DSC thermograms were match to reference simvastatin thermograms (P.Pandya).[19]

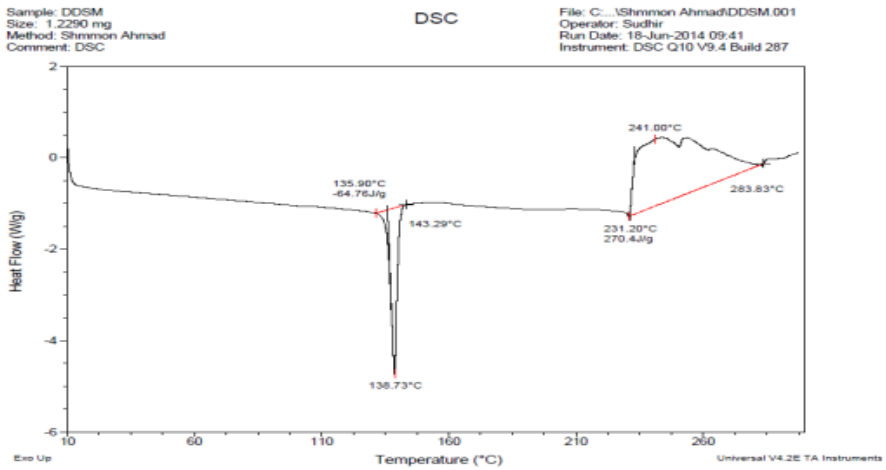

Figure 6: DSC thermogram of pure Drug.

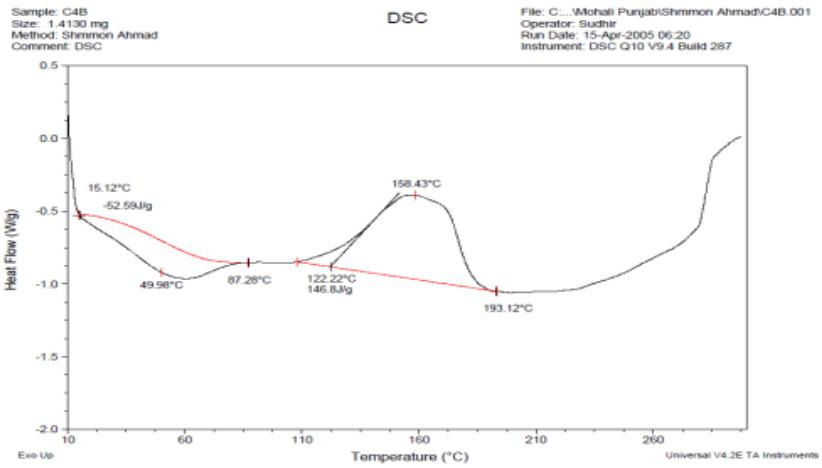

Figure 7: DSC thermograms of optimised solid state transition form.

DSC and their thermo grams of simvastatin drug are shown in **Figure 6.** SIM thermograms exhibits a single, sharp melting endotherm at 138.73°C which is corresponding to its melting point with onset 135.90°C, endset 143.29°C and fusion enthalpy of -64.76 J/g.

Due to the conversion of SIM crystalline to amorphous form the thermograms of optimised form showed endothermic peaks at less temperature 49.98°C with onset 15.12°C, endset 87.28°C and fusion enthalpy of -52.59 J/g **(Figure 7**). Amorphous forms of simvastatin show a higher recrystallization tendency at the higher temperature conditions. The amorphous form was cold crystallised by heating and showed an exothermic peak at 158.43°C with fusion enthalpy 146.8J/g.

Attenuated Total Reflectance (ATR)

Attenuated Total Reflectance (ATR) spectra of moisture free powdered samples of simvastatin pure/Solid state transitional form were obtained using a spectrophotometer (Bruker Alpha). The procedure consists of placed the powdered sample on the crystal. The scanning range was 400-4000 cm $^{-1}$ and the resolution was 4 cm-1. Polystyrene was used to check the spectrophotometer calibration (D. Mandal).[20]

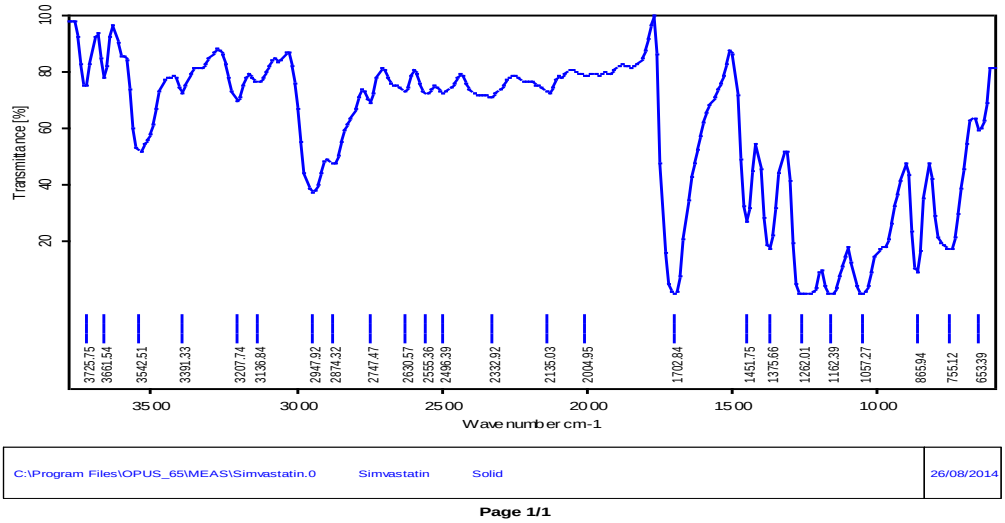

Figure 8: ATR spectra of pure form simvastatin.

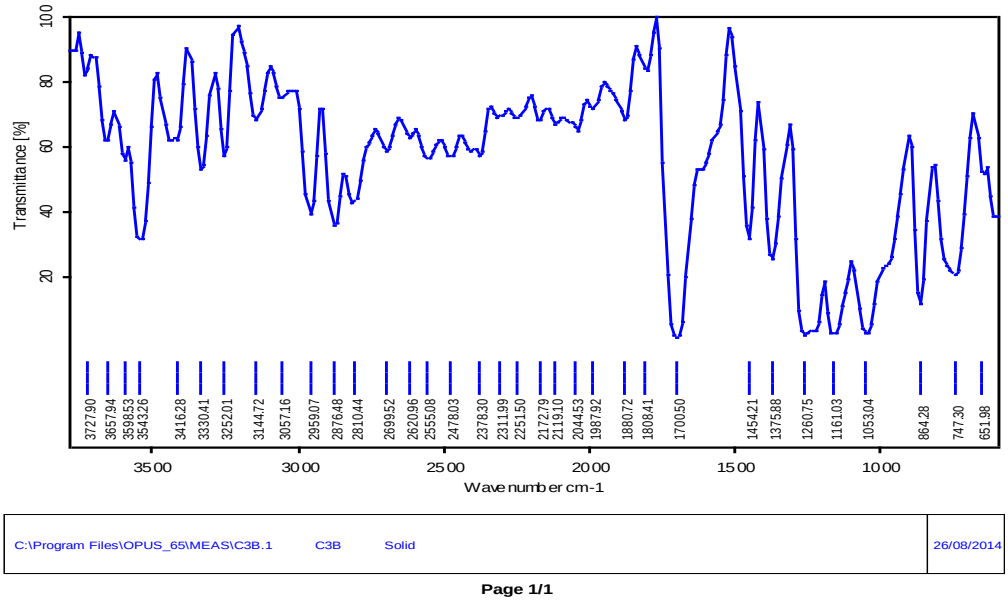

Figure 9: ATR Spectra of optimised form.

Spectra 8 and 9 show ATR spectrum of simvastatin and simvastatin optimised form. Spectra of simvastatin 1702.84cm^{-1} (C=O), 1057.27cm^{-1} (C-O), 3542.51cm^{-1} (OH bonded) and 1262.01cm^{-1} (lactones -C-O-C- bend).

All above peak appear in drug optimised form. It indicates that there was no interaction between drug and solvent DCM. But the intensity of the peak at 3598.53 cm^{-1}(free O-H) and 2959.07cm^{-1} (methyl C-H) is higher than pure simvastatin. The OH bond region (3650–3200 cm^{-1}) showed significant peak shifts and broadening, which indicated that amorphization is associated with a change in intermolecular hydrogen bonding.

CONCLUSION

Solid state transitions of drug Simvastatin were prepared successfully using solvent evaporation technique. The preparation method was simple and inexpensive to obtain reproducible optimised form with an enhanced impact on solubility and *in-vitro* release.

An increase in solubility was obtained when the optimised form were obtained at 20ºC for 10 minutes. The temperature and heating time were optimised by design expert Software Version 9. All the studies have been reported to be carried out at 10-55ºC for heating time near about 10-40 minutes.

Solubility of optimized form was 0.0664mg/ml, whereas the pure drug showed a solubility of 0.0192mg/ml. Therefore the optimised solid state transition form of simvastatin showed solubility enhancement by 3-4 folds as compared to the crystalline form. Solubility enhancement is the key to ensure the goals of a good formulation like good oral bioavailability, reduce frequency of dosing and better patient compliance combined with a low cost of production.

The optimized solid state transition form also shows valuable increased *In vitro* release in comparison to crystalline simvastatin. Optimised form showed a release of 70.42 % release as compared to 15.57% release in case of crystalline simvastatin. Higher dissolution rate have greatest influences on their absorption characteristics from the GIT and also the biological availability of the drug.

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