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DRUG-EXCIPIENTS INTERACTION AND SOLUBILITY ENHANCEMENT STUDY OF SIMVASTATIN

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Abstract

Aim: The purpose of the present study is drug polymer interaction of drug Simvastatin (SV) with different polymers like Chitosan, glycin and beta cyclodextrin(β-CD), were tested analytically and comparison of the results was done and report any possible interactions between them. Previously it was reported that SV forms inclusion complexes with β- Cyclodextrin (β-CD) thereby increasing the solubility of SV in water and this is confirmed here in the present study by use of phase solubility studies and aqueous solubility. **Method:** The analytical techniques used for the purpose are Fourier Transform Infrared Spectroscopy (FTIR) and Differential scanning calorimeter (DSC) to characterize any drug-polymer interactions and formation of inclusion complex. The complexes were prepared by simple Kneading techniques and were evaluated for phase solubility and aqueous solubility. **Result:** The FTIR and DSC study indicate no interaction occurs between drug- polymers and revealed that no endothermic and characteristic diffraction peaks of SV was observed in the inclusion complexes. The study indicated the conversion of crystalline form of SV into the amorphous form. Aqueous solubility profiles were markedly increased in inclusion complexes, compared with the drug alone and physical mixture this study is done so that future formulations can be prepared based on these results. **Conclusion:** Simvastatin is compatible with polymers and solubility of drug was increase by formation of inclusion complex with beta cyclodextrin (β-CD).

INTRODUCTION

Simvastatin was approved by the FDA in December 1991. It decreases total cholesterol, LDL cholesterol, triglycerides, and apolipoprotein B, while increasing HDL. It is use in patients with coronary heart disease, diabetes, peripheral vessel disease, or history of stroke or other cerebrovascular disease[1].

Simvastatin is a synthetic derivative of a fermentation product of *Aspergillus terreu*s. Simvastatin is structural analog of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme). Like other agents, it inhibits the enzyme hydroxymethylglutaryl-CoA (HMG-CoA) reductase. It has an extremely high affinity for this enzyme and was considered the most potent agent of the HMG-CoA class until atorvastatin was approved.

Simvastatin is rapidly absorbed from the gastrointestinal tract after oral administration but undergoes extensive first-pass metabolism in the liver. It is inactive lactone prodrug and hydrolyzed in the gastrointestinal tract to the active ß hydroxy derivative.The drug (SV) is practically insoluble in water and poorly absorbed from the gastro intestinal (GI) tract [2, 3].

Therefore, it is very important to introduce effective methods to enhance the solubility and dissolution rate of drug, substantially leading to its bioavailability. Cyclodextrins (CDs) are cyclic oligosaccharides, which are produced by enzymatic degradation and have been recognized as useful pharmaceutical excipients[4]. Complexation with cyclodextrins has been reported to enhance the solubility, dissolution rate and bioavailability of poorly water soluble drugs[5,6].

The hydrophobic cavity within each Cyclodextrin (CD) offers an attractive environment for inclusion complex formation. The internal diameters of β-CD are appropriate for much small molecule drugs7 Inclusion complex formation with hydrophobic drugs offers an attractive solution to limited solubility for active pharmaceutical candidates[7]. Cyclodextrin and its derivatives play an important role in the formulation development due to their effect on solubility, dissolution rate, chemical stability, and absorption of a drug[8].

In the present study, physical mixtures of the drug (SV) in solid form along with a series of polymers of both natural and synthetic origin were prepared and they were analyzed by using Fourier Transform Infrared (FTIR) spectroscopy and Differential scanning calorimeter (DSC), to characterize any drug-polymer interactions and formation of inclusion complex.

This study is done so that future formulations can be prepared based on these results.

MATERIALS AND METHOD

Materials:

Simvastatin was kindly gifted by Alembic Bioarc pharmaceutical pvt. Ltd., Baroda, Gujarat, India. and the drug was used without further purification. Chitosan obtain as a gift sample from Cognis Pharmaceutical, Germany and used as it procure. All the solvents and chemicals used in study were of AR grade.

Methods:

Preparation of Inclusion complex (Kneading method) [9]

The required quantities of the drug (Simvastatin) and β-CD were weighed accurately in a ratio of 1:1using equation 3. Homogenous slurry of cyclodextrin was prepared in a mortar by adding water: Methanol mixture (1:1) in small quantities. Simvastatin (SIM) powder was then added to this slurry in portions, with continuous kneading until it forms a dry mass.

$$\text{Utility constant} \frac{K * S0 \ X \ M\,(cd) \ X \ M.wt(Drug)}{1 + K * S0 \ X \ M.wt(cd) \ X \ M(Drug)} \quad \ldots\ldots\ldots (1)$$

Where,

M (cd)	Workable amount of cyclodextrin	?
M.Wt (cd)	Mole. Wt of cyclodextrin	1135mg
M(Drug)	Dose of drug	20mg
M.Wt (Drug)	Mole. Wt of Drug	418.56 mg
K	From phase solubility curve	405.84 mol^{-1}

So	Aqueous solubility of drug in absence of beta cyclodextrin	0.071mM
Utility constant		1

EVALUATION

First, formation of a genuine inclusion complex of 1:1 molar ratio was evaluated using different techniques, including FT-IR and DSC study.

Melting point of drug

Melting point of the drugs was determined by taking a small amount of drug in a capillary tube closed at one end and was placed in theil's melting point apparatus and the temperature at which the drug melts was noted. Average of triplicate readings was noted.

Fourier Transform Infrared Spectroscopy (FT-IR) study

FT-IR spectra were recorded for pure drug, individual excipients, physical mixture of drug with excipients and inclusion complex of drug with a Bruker Alpha FT-IR Spectrophotometer using KBr zinc selanide optics of 0.01 g sample between wavelengths 400 to 4000 cm^{-1} and resolution was 2 cm^{-1}.

Differential scanning calorimeter study

DSC scans were recorded for pure drug, excipients, physical mixture of drug with excipients, and inclusion complex of drug using DSC- Shimadzu 60 with TDA trend line software. All samples were weighed (8-10 mg) and heated at a scanning rate of 10°C/min under dry nitrogen flow (20 ml/min)between 50 and 300° C. Aluminum pans and lids were used for all samples. Pure water and indium were used to calibrate the DSC temperature scale and enthalpy response.

Phase solubility study for simvastatin[9]

Phase solubility studies were performed to determine the stoichiometric proportions of simvastatin with β-CD. The data was used to determine the stability constant of the complexes. For this, the stock solution of 20mM β-CD was prepared using distilled

water. These stock solutions were diluted with distilled water to give molar solutions in the range of 2 to 12 mM β-CD. 50mg of Simvastatin is added to distilled water containing β-CD and transferred to 25ml stopper conical flask. The mixture was shaken for 72hrs. Aliquots of 2ml were withdrawn and filtered immediately using 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for Simvastatin by measuring absorbance at 238nm against blank. The experiments will conduct in triplicate. The apparent solubility constant (K) according of complexes is being calculated from the phase-solubility diagram using following equation

$$K = \frac{\text{Slope}}{S0\ (1-\text{slope})} \quad \ldots\ldots (2)$$

The slope is obtained from the initial straight line portion of the plot of simvastatin against cyclodextrin concentration, and S_0 is the equilibrium solubility of Simvastatin in water.

Aqueous solubility[10]

An excess amount of sample was added to 5 ml of the distilled water in test tubes sealed with stoppers. The test tubes were vortex-mixed for 5 min. and then sonicated for 30 min. They were kept in a constant temperature shaking bath maintained at 37 ± 0.5°C until reaching equilibrium (48 h). A portion of the solution was withdrawn and then filtered with a nylon disc filter (0.45 µm) and adequately diluted with methanol. The amount of drug solubilized will be determined at 238 nm by UV-spectrophotometer. The results were reported as the average of triplicate runs in each run

Drug content[10]

Inclusion complexes prepared by kneading method was assay for amount of drug present by dissolving a 10 mg equivalent amount of powder was determined by, dispersing the powder mixture in 10 ml of methanol and suitably diluted with methanol and UV absorbance was measured at 238 nm. Drug concentration was determined from standard graph of drug.

RESULT AND DISCUSSION

The pre and post preparation parameters for all the formulations were evaluated. The preformulation parameters evaluated for the formulation ingredients are as follows.

Melting point of drug

The melting point of simvastatin was found to be 135^0C to 138^0C. Which is same as reported in literature review.

Fourier Transform Infrared Spectroscopy (FT-IR) study[11]

Identification of simvastatin

The FT-IR spectrum of simvastatin is presented in Figure 1. The spectrum of simvastatin shows a broad band at 3546.37cm^{-1}, 2929.77 cm^{-1}, 1695.05 cm^{-1}, 1465.93 cm^{-1}, 1266.50 cm^{-1}, 1162.95 cm^{-1}, 1071.88 cm^{-1}. Which co-relates with the peaks of standard simvastatin sample as mentioned in Table 1.

Figure 1: FT-IR spectrum of pure Simvastatin

Table 1: Characterization of peak in FT-IR spectrum of pure Simvastatin

Identification of beta cyclodextrin

As observed in Figure 2, the FTIR spectrum of β-CD presents the prominent peaks in the region of 3227.0cm^{-1}, 1642 cm^{-1}, 1152cm^{-1}, 1022cm^{-1}. Other peaks of beta cyclodextrin mentioned in Table 2.

Figure 2: FT-IR spectrum of beta cyclodextrin

Table 2: Characterization of peak in FT-IR spectrum of beta cyclodextrin

Identification of chitosan

The FT-IR spectrum of chitosan is presented in Figure 3. The broad band at 3450 cm^{-1} is due to the amine N-H symmetric stretching vibration which might be due to deacetylation of chitosan. Other peaks of chitosan mentioned in Table 3.

Figure 3: FT-IR spectrum of chitosan

Table 3: Characterization of peak in FT-IR spectrum of chitosan

Identification of Glycine

The FT-IR spectrum of glycin is presented in Figure 4. Other peaks of glycin mentioned in Table 4.

Figure 4: FT-IR spectrum of glycine

Table 4: Characterization of peak in FT-IR spectrum glycine

Drug- excipients compatibility study

FT-IR spectroscopy was used to study the possible interactions between SIM and excipients. There is no significant difference in the FT-IR spectra of pure drug, physical mixture of drug and excipients.

In Figure 5, all major peaks of SIM observed at wave numbers 3546.37 cm^{-1} (free O–H stretching vibrations); 3011 and 2929.7 (C–H stretching vibrations); and 1266.50 $cm^{-1}$and 1162.95 cm^{-1} (stretching vibration of ester and lactones carbonyl functional groups) are retained in physical mixtures and summation of parent drug and polymer peaks with less intensity in comparison to pure drug and were more broader. Which clearly indicate that no interaction exists between pure drug and excipients.

Figure 5: FT-IR spectrum of a) Physical mixture of simvastatin and beta cyclodextrin, b) Physical mixture of simvastatin,beta cyclodextrin, chitosan and glycine

FT-IR study of drug loaded inclusion complex

FT-IR spectra of SIM loaded inclusion complex seen in Figure 6, shows almost similar wave number as that of pure drug, but the intensities of the peaks were less than in comparison to pure drug and were more broader. Thus this proves that there is weak interaction between simvastatin and other polymers. This interaction may be because of the complex formation between SIM and β-CD[12].

Inclusion complexes show considerable differences such as overlapping of O-H and C-H group peak resulting broadening of the peak was observed. These modifications clearly indicate the presence of host guest interaction suggesting the formation of stable hydrogen bonds between SIM and β-CD. However other peaks corresponding pure drug such as O-H, C-H (bending), C-O, C-H (stretching), can be clearly detected at the lower frequencies. This indicates that overall symmetry of the molecule might not be significantly changed[10].

Figure 6: FT-IR spectrum of Simvastatin loaded Inclusion complex

Differential scanning calorimeter study

Drug- excipients compatibility study using Differential scanning calorimeter (DSC)

In Figure 7 DSC thermogram of SIM exhibits a sharp melting endotherm at 139.38°C. In DSC thermogram of physical mixture of SIM- β-CD and with other excipients showed same melting endotherm of drug which suggesting that there is no physical or chemical interaction between drug and excipients. Table 5 shows Comparison of thermogram value of drug with physical mixture of excipients.

Figure 7: DSC thermogram of a) simvastatin and b) Physical mixture of simvastatin and beta cyclodextrin c) Physical mixture of simvastatin, beta cyclodextrin, chitosan and glycine

Table 5: Comparison of thermogram value of drug with physical mixture of excipients

DSC study of drug loaded inclusion complex

Differential scanning calorimeter (DSC) can be used for the recognition of inclusion complexes. When guest molecules are embedded in β-CD cavities, their melting, boiling or sublimation points generally shift to a different temperature or disappear. SIM loaded inclusion complex (1:1) was examined by DSC and their thermo grams are shown in Figure 8. SIM thermogram exhibits a single, sharp melting endotherm at139.38^{O}C with fusion enthalpy of -95.16 J/g. The thermal curve of SIM and β-CD (1:1) complex prepared by kneading method showed peak at 139.97°C with fusion enthalpy of -29.86 J/g corresponding to its melting point. Due to the release of water molecules the thermo grams of inclusion complexes prepared by kneading method showed endothermic peaks at 102.21°C.

Figure 8: DSC thermogram of Simvastatin loaded Inclusion complex (1:1)

Phase solubility of Drug in β-cyclodextrin (in water)

The phase solubility profiles of SIM in β-CD are presented in Figure 9. The phase solubility diagram of SIM- β -CD complex could be classified as AN-type according to Higuchi and Connors. The plot shows that the aqueous solubility of drug increases linearly as a function of β-CD. The linear host –guest correlation with slope of less than 1 suggested the formation of 1:1 complex. SIM-β-CD complex presented a slope of (0.0296) with an R^2 value of 0.958. The apparent solubility constant, Ks value obtained from the slope of linear phase

solubility diagram was found to be 405.84 M^{-1} with β-CD. The K1:1 value showed that SIM formed stable complexes with β-CD. Table 6 shows Slope and K value for drug in beta cyclodextrin.

Figure 9: Phase solubility curve of Simvastatin in β-CD at λ_{max} 238nm

Table 6: Slope and K value for drug in beta cyclodextrin

Aqueous solubility of drug loaded Inclusion complex

At the end of 48 hours aqueous solubility of SIM was found to be 73.39µg/ml,81.73 µg/ml, 78.47 µg/ml, and 163.86 µg/ml in water 1.2 pH, 6.8 pH and 7.4 pH respectively. While pure simvastatin has 0.76 µg/ml solubility in water. Figure 10 shows no. of times increases solubility in water, 1.2 pH, 6.8 pH, and 7.4 pH is 96.57, 107.55, 103.26, and 215.61 respectively.

Figure 10: Aqueous solubility of Simvastatin in different solvent

Drug content of drug loaded Inclusion complex at 238nm in different solvent

The % drug content for 1:1 SIM loaded inclusion complex was found to be 96.43±0.051**,** 92.79±0.029**,** 93.48±0.038 and 94.32±0.059 in methanol, 1.2pH, 6.8pH, and 7.4 pH respectively.

CONCLUSION

DSC and FT-IR testing indicates that the drug is compatible with the excipients. From phase solubility diagram it was concluded that SIM- β -CD complex could be classified as AN-type stable inclusion complex with beta-cyclodextrin The linear host –guest correlation with slope of less than 1 suggested the formation of 1:1 complex with 405.84 M^{-1} Ks value with β-CD.

Aqueous solubility of SIM was found to be increases in water, 1.2 pH, 6.8 pH, and 7.4 pH is 96.57, 107.55, 103.26, and 215.61 respectively. The % drug content for 1:1 SIM loaded inclusion complex was found to be higher with low standard deviation.

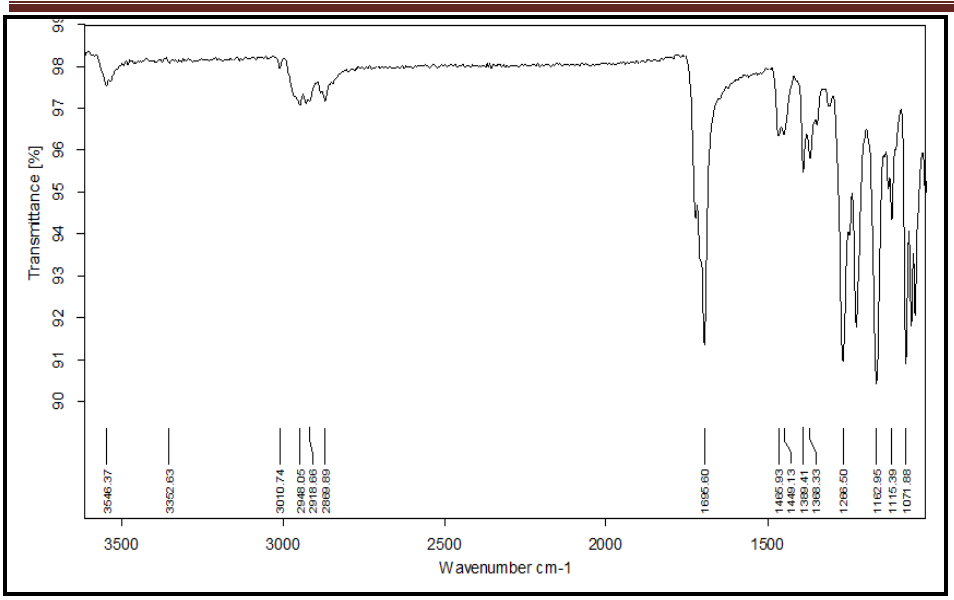

Figure 1 FT-IR spectrum of pure Simvastatin

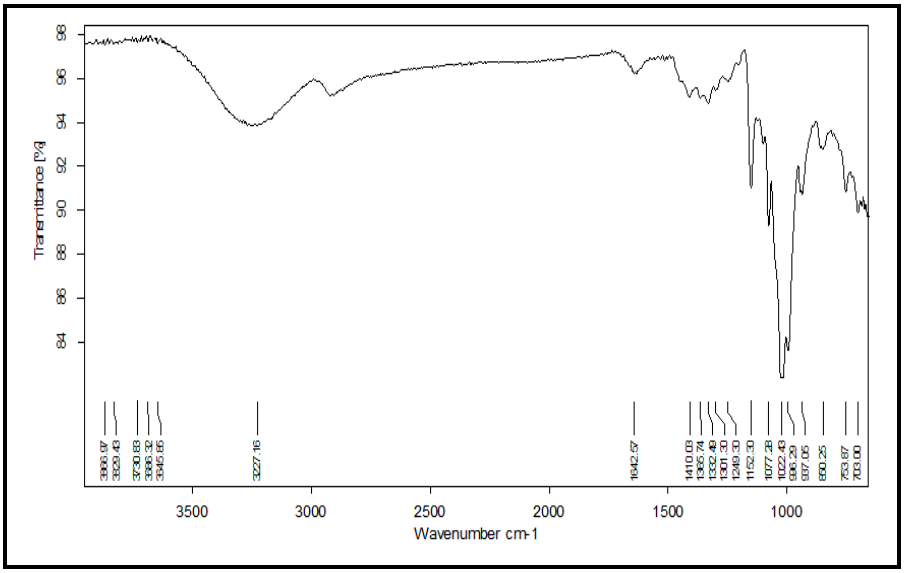

Figure 2 FT-IR spectrum of beta cyclodextrin

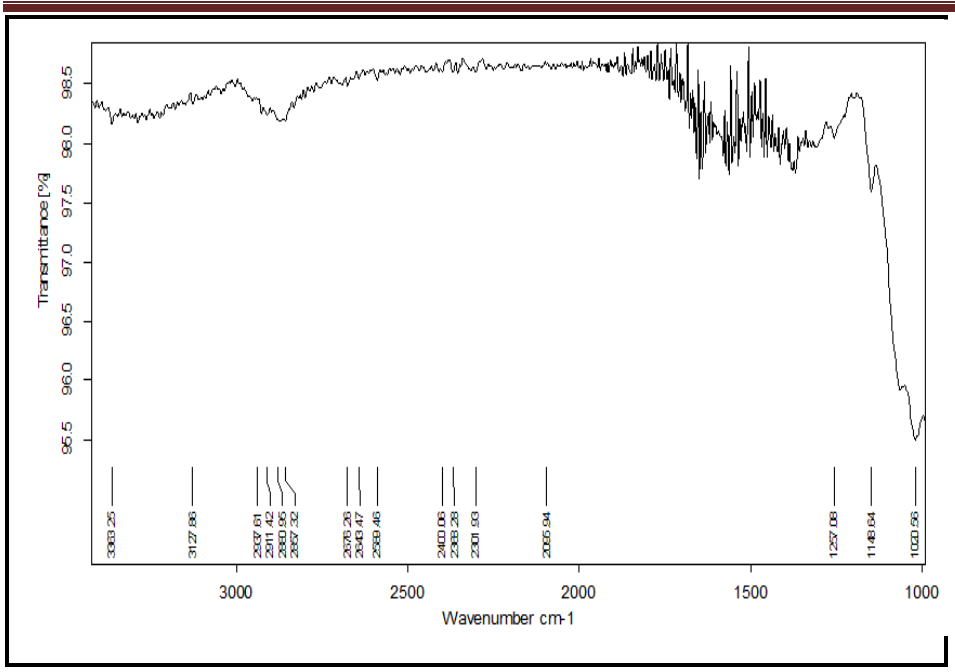

Figure 3 FT-IR spectrum of chitosan

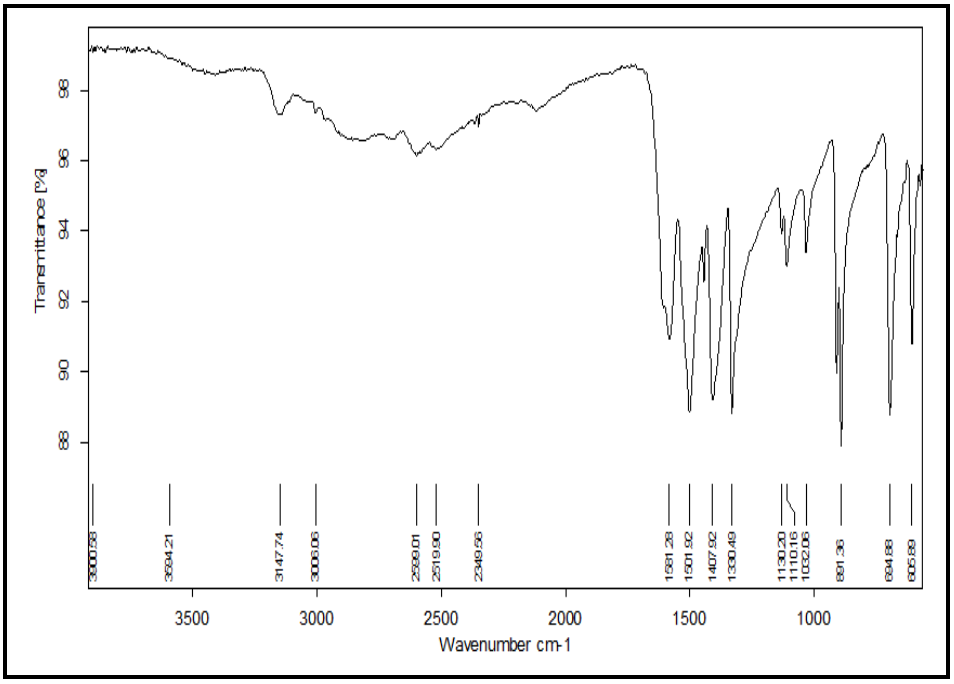

Figure 4 FT-IR spectrum of glycine

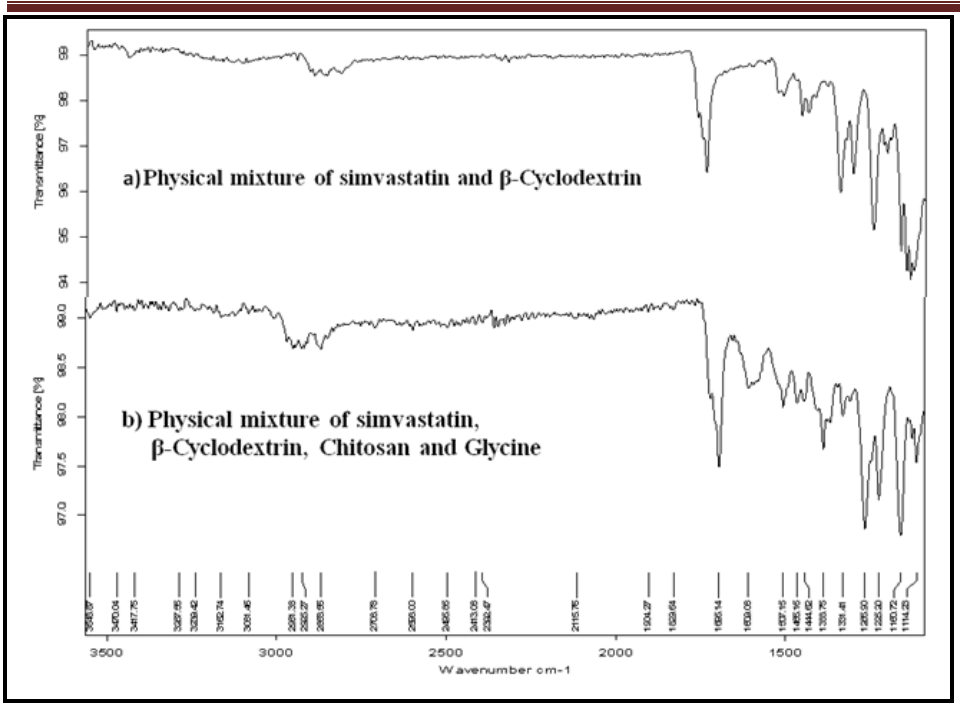

Figure 5 FT-IR spectrum of a) Physical mixture of simvastatin and beta cyclodextrin, b) Physical mixture of simvastatin,beta cyclodextrin, chitosan and glycine

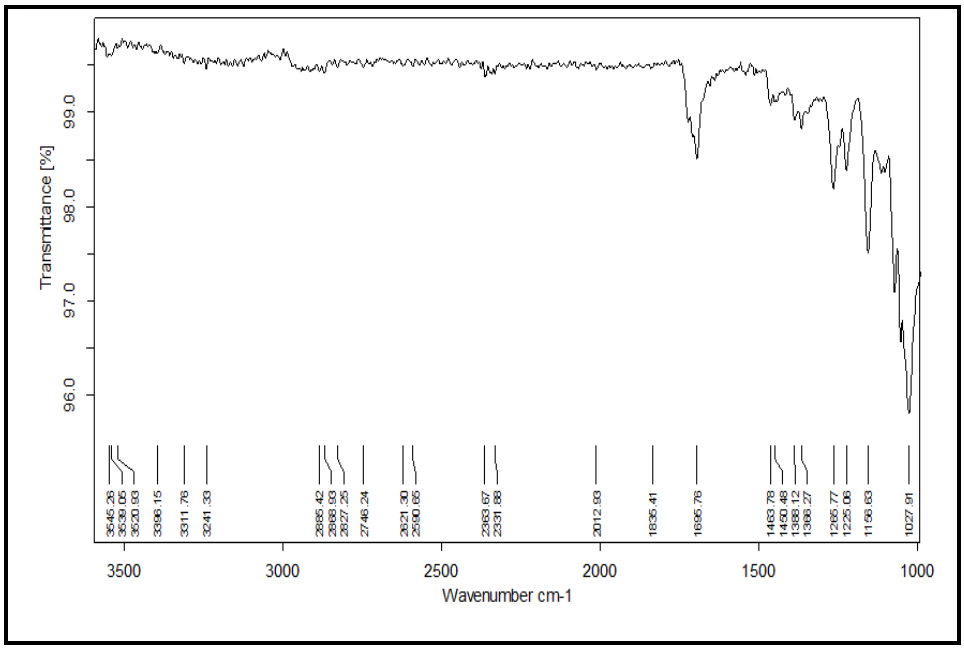

Figure 6 FT-IR spectrum of Simvastatin loaded Inclusion complex

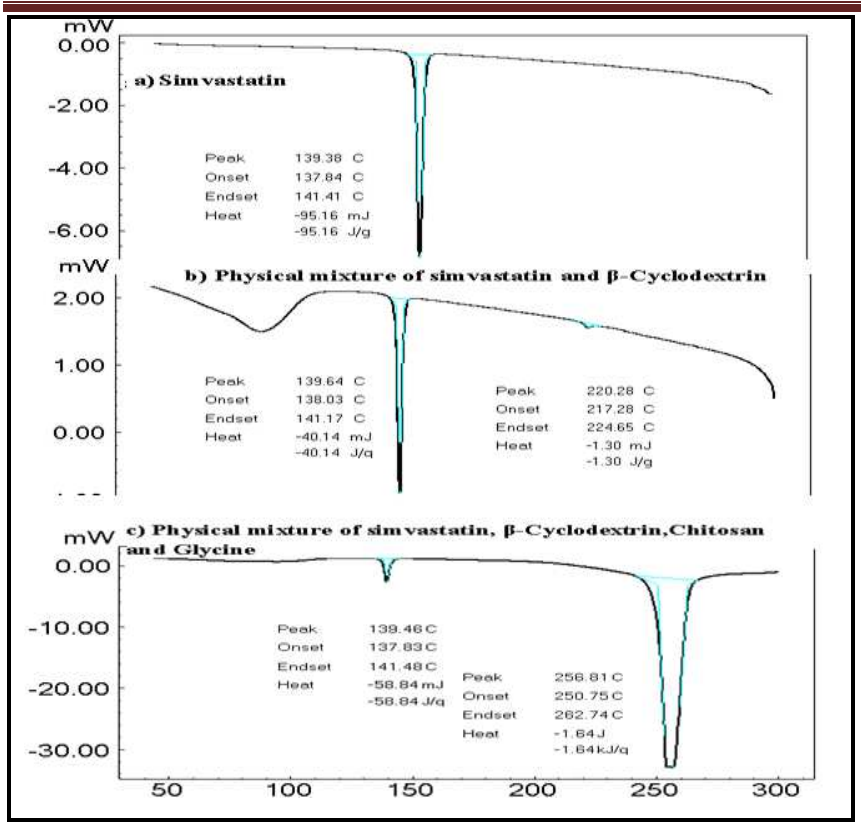

Figure 7 DSC thermogram of a) simvastatin and b) Physical mixture of simvastatin and beta cyclodextrin c) Physical mixture of simvastatin, beta cyclodextrin, chitosan and glycine

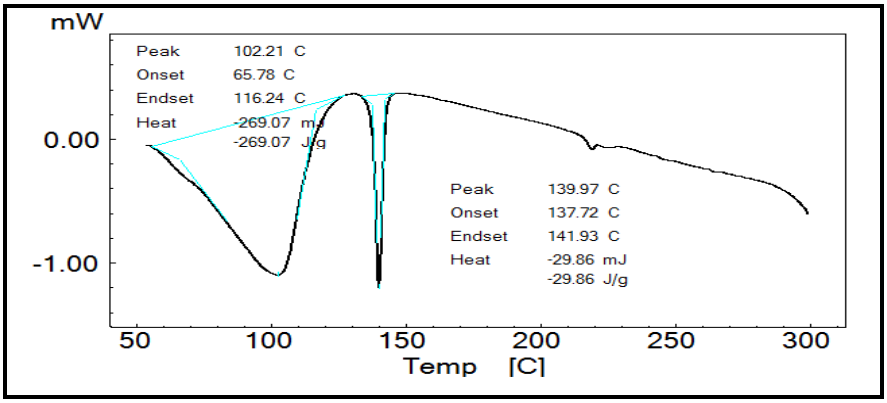

Figure 8 DSC thermogram of Simvastatin loaded Inclusion complex (1:1)

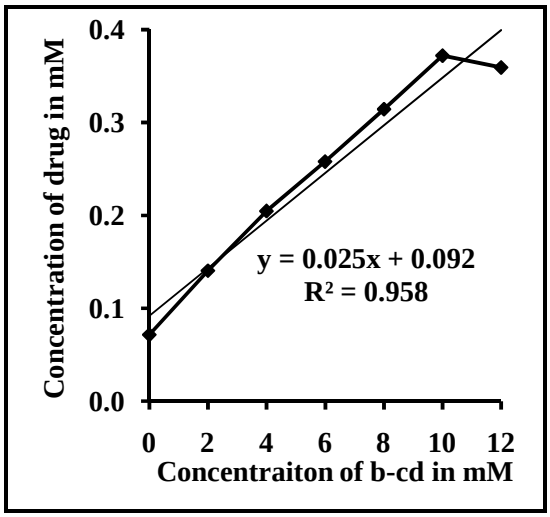

Figure 9 Phase solubility curve of Simvastatin in β-CD at λ_{max} 238nm

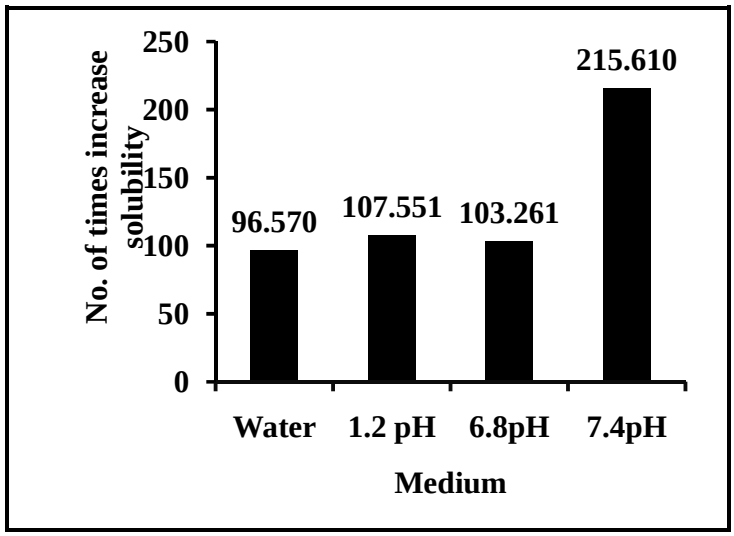

Figure 10 Aqueous solubility of Simvastatin in different solvent

Table 1

Characterization of peak in FT-IR spectrum of pure Simvastatin

Sr.No	Functional group	Standard wave number cm^{-1})	Peak observed in simvastatin API (cm^{-1})
1	Free O-H stretch	3546	3546.37
2	Methyl C-H symmetric stretch; Methylene C-H asymmetric stretch	2924	2929.7
3	Ester C=O stretch	1697	1695.05
4	Methylene C-H symmetric bend; Methyl C-H asymmetric bend	1461	1465.93
5	Lactone -C-O-C bend	1268	1266.50
6	Ester -C-O-C- bend	1164	1162.95
7	Secondary alcohol C-O stretch	1072	1071.88
8	N-H stretching	1568	1567

Table 2

Characterization of peak in FT-IR spectrum of beta cyclodextrin

Sr.No	Functional group	Peak observed in beta cyclodextrin (cm^{-1})
1.	O-H stretching (broad)	3227
2.	O-C (2-bands)C=O (amide I band)	1642
3.	O-H bending (in-plane), α- CH_2 bending, CH_2 deformation	1410
4.	O-H bending (in-plane)	1332
5.	C-C-C bending	1152
6.	O-H (H-bonded), usually broad C-O	1077,1022
7.	=C-H & $=CH_2$ streching, C-H bending & ring puckering	937, 860,753
8.	cis-RCH=CHR	703

Table 3

Characterization of peak in FT-IR spectrum of chitosan

Sr.No.	Functional group	Peak observed in chitosan (cm^{-1})
1.	N-H symmetric stretching vibration	3450
2.	OH stretching	3367
3.	C-H stretching vibration	2924
4.	NH bending (amide II) (NH_2)	1560,1639 ,1319
5.	C=0 stretching (amide I) 0=C-NHR.	1647
6.	CH_2 bending	2927, 2884, 1411, 1321, 1260
7.	CH_3 wagging	1380 and 1384
8.	>CO-CH3 stretching vibration	1083
9.	Confirmed a saccharide structure	1000.56, 1171

Table 4

Characterization of peak in FT-IR spectrum glycine

Sr.No	Functional group	Peak observed in Glycine (cm^{-1})
1.	O-H (free),	3594
2.	CH_2 deformation	3147
3.	O-H (very broad) (acids) stretching	3005,2599,2519
4.	NH_2 scissoring (1°-amines)	1581
5.	C-H banding	1501
6.	C-O-H bending	1407
7.	O-H bending (in-plane)	1330
8.	N-H (1°-amines), 2 bands, O-H (H-bonded), usually broad C-O	1130,1110,1032
9.	C-H bending & ring puckering, (1°-amines) NH_2 & N-H wagging (shifts on H-bonding), C-H deformation streching	891,694
10.	C-H deformation streching	605

Table 5

Comparison of thermogram value of drug with physical mixture of excipients

Sr.No	Sample	$T_{onset\ of\ peak}$ (^0C)	T_{peak} observed (^0C)	ΔH J/g
1	Simvastatin	137.84	139.38	-95.16
2	Physical mixture of simvastatin and beta cyclodextrin	138.03	139.64	-40.14
3	Physical mixture of simvastatin, beta cyclodextrin, chitosan and glycine.	137.83	139.46	-58.84

Table 6

Slope and K value for drug in beta cyclodextrin

Slope	K (mol^{-1})
0.0296	405.84

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