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Design and Development of Solid Dispersions of Simvastatin for Enhancing the Solubility

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ABSTRACT

The aim of the present work was to improve the solubility and dissolution rate of simvastatin, a drug used for the treatment of hyperlipidemia. Simvastatin is a selective competitive inhibitor of HMG CoA 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 carriers and solid dispersion was prepared with PEG 4000 and PVP-K30. These solid dispersions were analyzed for the solubility and In-vitro dissolution profile, solid dispersion of drug with PEG 4000 had shown enhanced solubility with improved dissolution rate. Further FTIR, X-Ray studies were carried out. Solid dispersion prepared with PEG 4000 in 1:5 ratio shows the presence of amorphous form confirmed by the characterization study .The study also shows the that dissolution rate of Simvastatin can be enhanced to considerable extent by solid dispersion technique with PEG4000.

Key words: Hyperlipidemia, solid dispersion, PEG4000, PVP-K30.

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INTRODUCTION

Simvastatin is a cholesterol-lowering agent widely used to treat hypercholesterolemia[1]. It lowers plasma cholesterol by inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol[2]. Simvastatin belongs to BCS class II having low solubility (1.45µg/ml) and therefore low oral bioavailability (5%)[3]. Simvastatin has the disadvantage of low bioavailability due to not being soluble in water and its intestinal metabolism by CYP3 enzyme.[4]Poor aqueous solubility presents great challenges to further development of these agents. Hence it is important to enhance the aqueous solubility, dissolution rate, and bioavailability of drug from its oral solid dosage forms.

Solid dispersions have traditionally been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubilities and dissolution rates as compared with crystalline material. Drugs molecularly dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement, which result in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution process and drug solubility and wettability may be increased by surrounding hydrophilic carriers.[5]

In the present study, solid dispersions were prepared by a solvent evaporation method using two different carriers at different drug–carrier ratios (PEG 4000 and PVP-K30) and evaluated for different parameters like drug content, *in vitro* drug release studies.

MATERIALS AND METHODS

Materials

Simvastatin was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. All other chemicals and reagents were of analytical grade.

Preparation of Solid Dispersions:

Solid dispersions of simvastatin were prepared by employing solvent evaporation and kneading methods.

Solvent evaporation:

Simvastatin and carriers (PEG 4000 and PVP-K30) in various proportions *viz.* 1:1,1:2,1:3,1:4 and 1:5 (drug: carrier) were prepared by solvent evaporation method as follows. To the solution of simvastatin in ethanol, the aqueous solution of carrier (PEG 4000 or PVP-K30) was added.

Then allowed to evaporate the solvent by placing it in vacuum drier for 3hours at a temperature of 40ºC and the dried sample was stored in a desiccators for overnight. Then the dried sample was ground in a mortar and passed through # 100.[6]

Evaluation of Solid Dispersions:

The formulated solid dispersions were evaluated for following parameters:

Analysis of simvastatin using a UV- Visible spectrophotometer:

Standard stock solution of the drug(1000µg/ml) was prepared by dissolving 100mg drug in 5ml of methanol and further diluted with Phosphate buffer P^H 7 containing 0.5% SLS. The concentrations of 2-10 µg/ml were prepared. The calibration curve was obtained by analyzed spectrophotometrically at 238nm by UV-Visible spectrophotometer [7]. Calibration curve was plotted by taking concentration (µg/ml) on x-axis and absorbance on y-axis.

Drug content:

Solid dispersions equivalent to 10 mg of simvastatin were accurately weighed and dissolved in the ethanol. The solution was filtered, suitably diluted and analyzed spectrophotometrically at 238 nm by UV-Visible spectrophotometer. The actual drug content was calculated using the following formula[8].

$$\% \text{ Drug content} = \frac{\text{Actual amount present in solid dispersion}}{\text{Theoretical amount present in solid dispersion}} \times 100$$

***In vitro* drug release studies:**

In vitro drug release studies of pure drug as well as solid dispersions were performed using USP XXII type 2dissolution apparatus (Electro lab, Mumbai, India). Solid dispersion equivalent to 10 mg of simvastatin was accurately weighed and subjected for dissolution in 900 ml of Phosphate buffer pH 7containing 0.5% sodium lauryl sulphate at a temperature of 37±0.5ºc and stirring speed of50 rpm. Aliquot of 5ml was withdrawn at regular intervals of time (i.e 5 min) and replenished the same volume with fresh medium. The samples were analyzed spectrophotometrically at 238 nm by UV-Visiblespectrophotometer[9].

Powder X-Ray Diffractometry:

The X-ray diffractograms were obtained using on X-Ray diffraction instrument (Philips Analytical X'Pert PRO) with Cu radiation, at a voltage of 40kV and current of20mA[10].

Infra red spectrum:

IR spectrums of simvastatin and solid dispersions were carried out using FT-IR based on the KBr pellet method. The spectra were scanned over a wave number range of2000 to 400 cm–1[11].

RESULTS AND DISCUSSION:

Drug content for all solid dispersions were in the range of 98.45-99.76 %. (Table 1)

Table1: List of Solid dispersions formulated by Solvent evaporation at different ratios

Formulation Code	Carrier	Drug: carrier ratio	Drug content
F1		1:1	98.67
F2		1:2	99.12
F3	PEG4000	1:3	99.24
F4		1:4	98.45
F5		1:5	99.69
F6		1:1	99.23
F7		1:2	99.34
F8	PVP K30	1:3	98.78
F9		1:4	99.44
F10		1:5	99.76

Higher the drug content in solid dispersions was shown that low standard deviations, indicates that the drug was uniformly dispersed in the formulation. These results revealed that the method used in this study appears to be reproducible for preparation of solid dispersion. The dissolution profiles of simvastatin pure drug and solid dispersions with PEG 4000 and PVP K30 prepared by solvent evaporation method was shown in figure 1and 2.

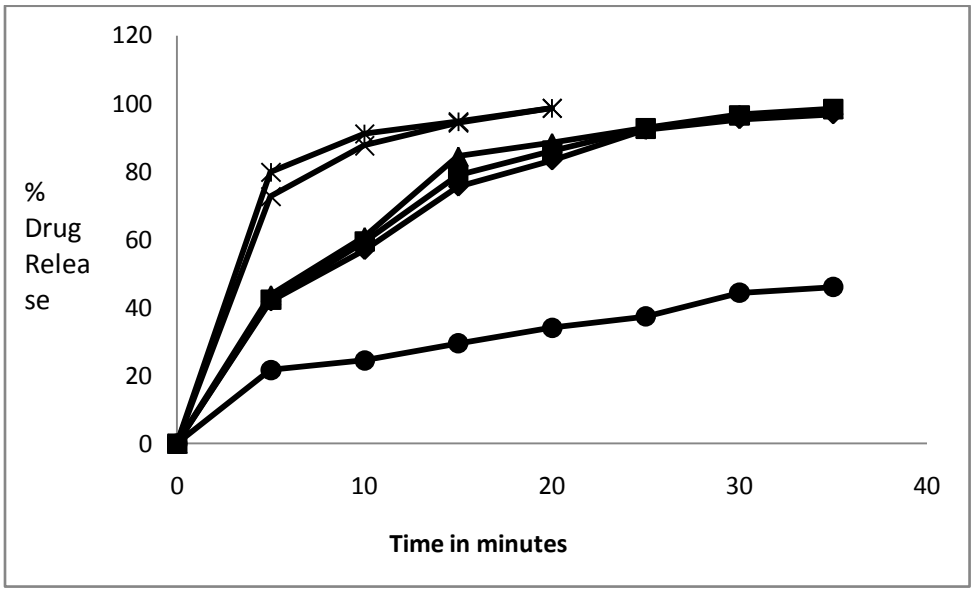

Figure1: *In vitro* dissolution profiles of simvastatin-PEG 4000 solid dispersions prepared by solvent evaporation method.

F1 -(▼) - solid dispersions prepared with PEG4000 in 1:1 ratio
F2 - (■)-solid dispersions prepared with PEG4000 in 1:2 ratio
F3 - (▲)- solid dispersions prepared with PEG4000 in 1:3 ratio
F4-(×)- solid dispersions prepared with PEG4000 in 1:4 ratio
F5- (✳) - solid dispersions prepared with PEG4000 in 1:5 ratio

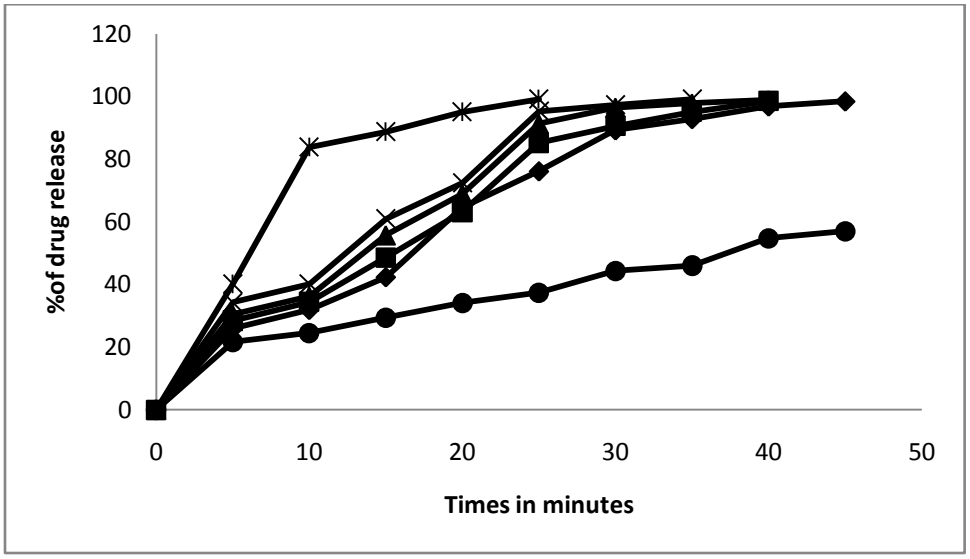

Figure2: *In vitro* dissolution profiles of simvastatin-PVP K30 solid dispersions prepared by solvent evaporation method

F6 - (◆) - solid dispersions prepared with PVPK-30 in 1:1 ratio
F7 - (■) - solid dispersions prepared with PVPK-30 in 1:2 ratio
F8 - (▲) - solid dispersions prepared with PVPK-30 in 1:3 ratio
F9 -(×) -solid dispersions prepared with PVPK-30 in 1:4ratio
F10 - (✳) - solid dispersions prepared with PVPK-30 in 1:5 ratio

It was evident that solid dispersions exhibit faster dissolution than the free drug. The improvement in the dissolution rate varies with the carrier and carrier ratio. The *in vitro* dissolution studies of the solid dispersion prepared by solvent evaporation with PEG 4000 at 1: 5 ratio showed 98.67% release in 20 minutes. Enhancement in dissolution rate was may be due to improved wettability which can lower the interfacial tension between poorly soluble drug and dissolution medium (Table 2)

Table 2: In-vitro Dissolution parameters of Simvastatin solid dispersions prepared by Solvent evaporation at different weight ratios.

Formulation Code	Zero order	First order	K_1 (min-1)	T_{50} (min)	T_{90} (min)
F1	0.8348	0.9731	0.111	6.2	20.6
F2	0.9246	0.9785	0.123	5.6	18.7
F3	0.8355	0.9636	0.137	5.0	16.8
F4	0.6673	0.9455	0.173	4.0	13.3
F5	0.6567	0.9747	0.215	3.2	10.7
F6	0.9520	0.9549	0.077	8.9	29.6
F7	0.6299	0.9623	0.092	7.5	25.0
F8	0.9357	0.9559	0.101	6.8	22.7
F9	0.7858	0.9757	0.129	5.3	17.8
F10	0.8429	0.9763	0.170	4.1	13.5

X-Ray Diffraction patterns of pure drug and solid dispersions were showed in the figure 3 and 4 respectively. The peak position (angle of diffraction) is an indication of crystal structure and the peak height is the measure of simple crystallinity. The pure drug shows a highly crystalline nature, indicated by numerous intense peaks.

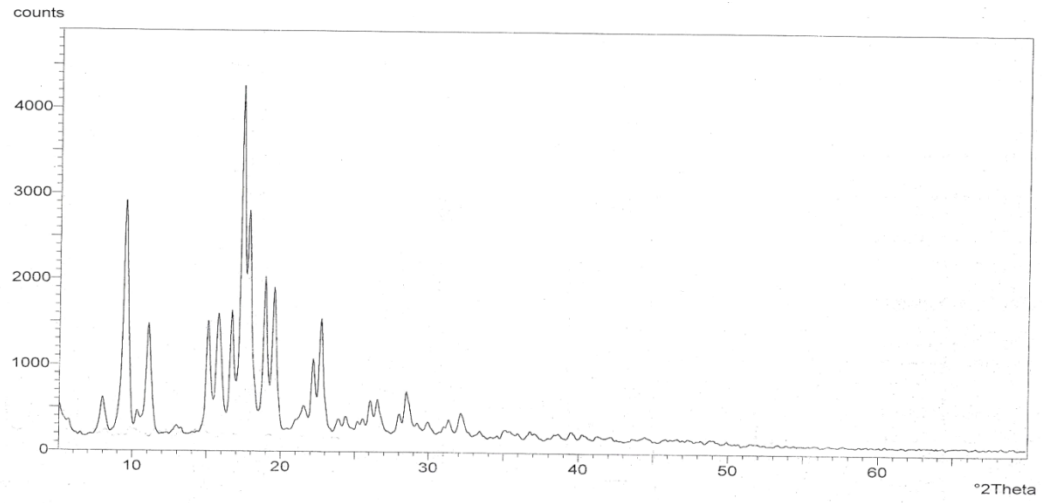

Figure 3: X- ray diffraction pattern of Simvastatin

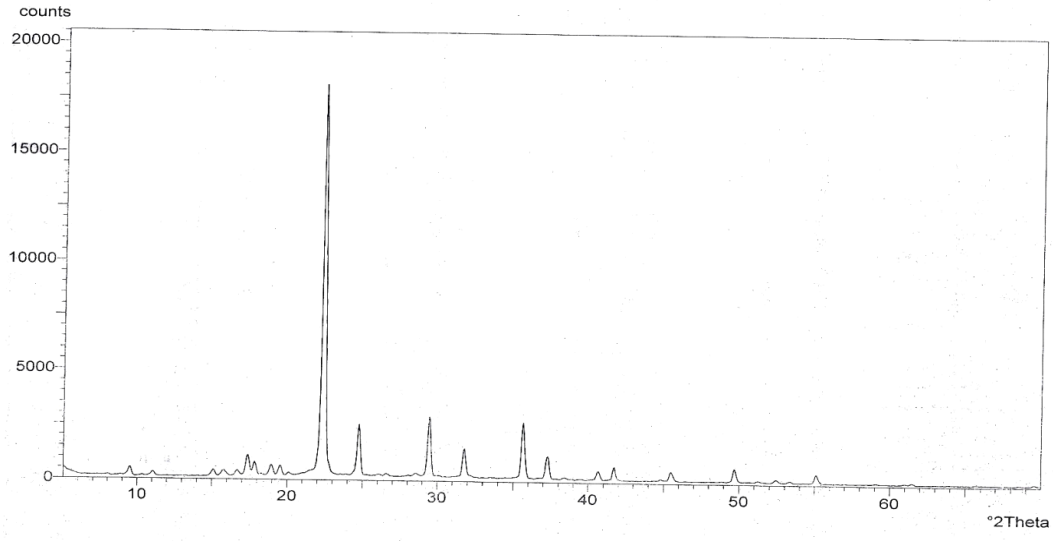

Figure 4: X- ray diffraction pattern of simvastatin PEG4000 solid dispersion (1:5).

On the other hand solid dispersion was shown decrease in crystallinity, evidenced by the absence of several intense peaks.

FTIR spectroscopy was used to study the possible interactions between simvastatin and PEG 4000 in the solid dispersion. There was no significant difference in the FTIR spectra of pure drug and solid dispersion (figure5and 6).

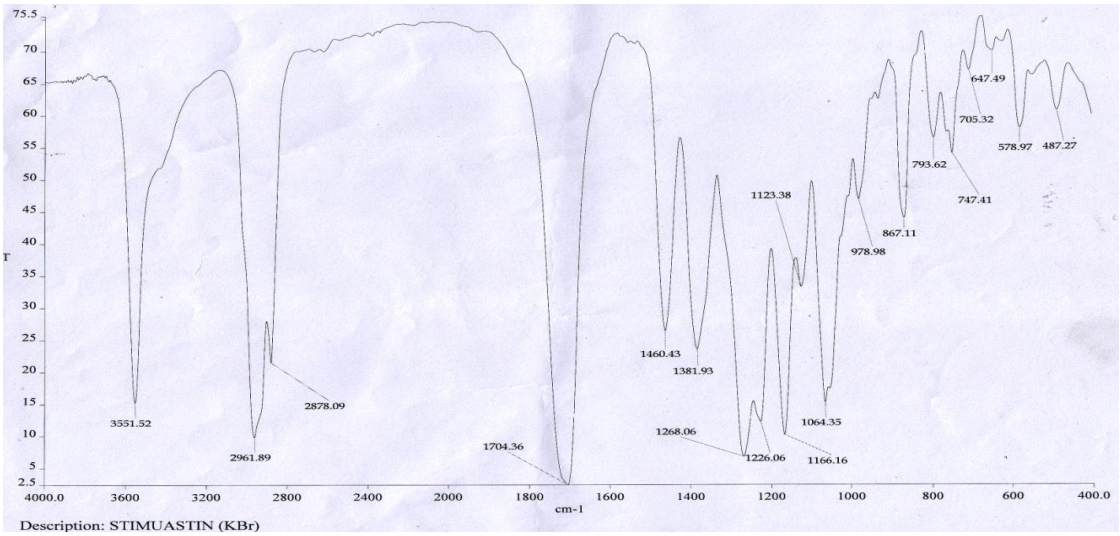

Figure 5: IR spectra of simvastatin

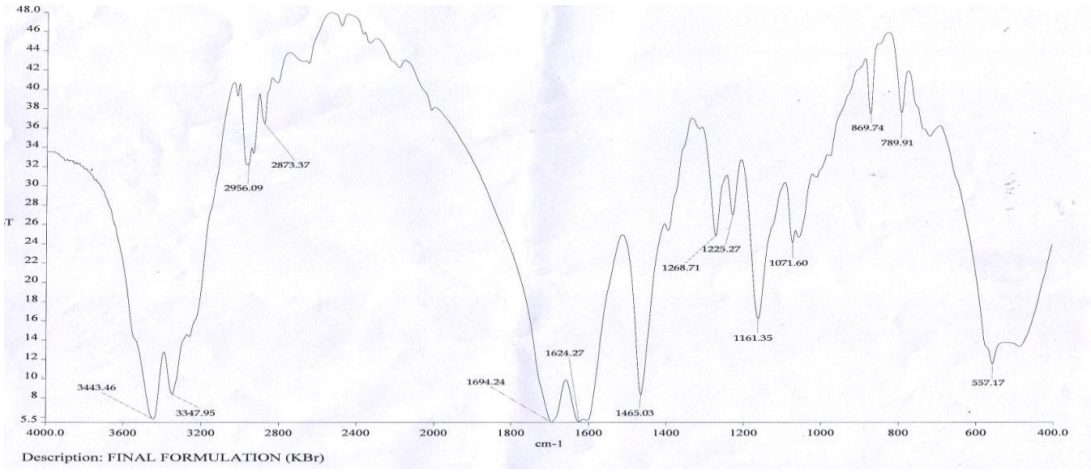

Figure 6: IR spectra of Simvastatin: PEG4000 Solid dispersion (1:5)

CONCLUSION:

From the *in-vitro* dissolution studies of the solid dispersions, the higher drug release was obtained from solid dispersions prepared by solvent evaporation method and with a carrier PEG 4000(1:5). The present work concluded that solid dispersion technology can be used successfully to enhance the dissolution rate of poorly soluble drug Simvastatin.

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