EVALUATION OF SOLUBILITY OF SIMVASTATIN USING β-CYCLODEXTRIN BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Simvastatin is a poorly soluble drug exhibiting poor dissolution pattern. Simvastatin-β cyclodextrin dispersions were prepared with a view to study the influence of β-CD on solubility and dissolution of this poorly soluble drug Simvastatin. Solid dispersions of Simvastatin were prepared using different ratios of β-CD as carrier by Physical mixture, solvent evaporation method, Kneading method and Fusion Method. They were evaluated for drug content, moisture content, FTIR spectral studies, solubility, *in-vitro* dissolution and release kinetics. The solubility profile indicated that there is increase in solubility of Simvastatin when β-CD concentration is increased. The solid dispersion complex of drug (1:5 ratios) was giving better dissolution profile as compared to pure drug and other solid dispersions (1:1 and 1:3). This in turn can improve the bioavailability. FT-IR shows the complexation and compatibility of drug and carrier.

KEY WORDS:β-cyclodextrin.

INTRODUCTION

Simvastatin (SV) a well-known plasma cholesterol-lowering agent, after administration it is converted to active form (hydroxy acid) which is a potent competitive inhibitor of 3-hydroxy-3-methyl glut aryl co-enzyme (HMG-Co A) reductase, which catalyses the rate limiting step of cholesterol biosynthesis[1]. Simvastatin reduces morbidity and mortality associated with coronary heart disease and is prescribed with more than US $ 5 billion worldwide sale annually[2]. In 2007 Simvastatin have been among the most widely prescribed drugs in the world. The drug is isolated from molds such as Aspergillus. Its water solubility is 30µg/ml because of its poor aqueous solubility[3], it leads to low effective concentration in biofluids and therefore poor bioavailability[4].Improvement of the aqueous solubility in such a case is a valuable goal that leads to enhancing therapeutic efficacy[5].

To improve the solubility of Simvastatin several systems have been reported. For example, the Simvastatin crystal with 40µm dimensions was developed, yielding an improvement in its dissolution[6]. Self-micro emulsifying drug delivery system of Simvastatin containing oil, surfactant and co-surfactant showed

an increase in both in vitro dissolution rate and in vivo bioavailability compared with commercial Simvastatin tablets[7]. Solid dispersion (SD) of amorphous Simvastatin in hydrophilic polymers can be also used to achieve this goal[8].

Among the various approaches to improve the dissolution rate of poorly soluble drugs, the preparation of SD has often proved to be successful[9,10,11,12,13]. Solid dispersion (SD) technology was most widely used technology[14,15,16]. In solid dipersions, the drug is dispersed in an inert water soluble carrier at solid state. Cyclodextrins have been extensively used to improve the solubility of poorly water soluble drugs[17, 18]. Also it enhances bioavailability, stability and protects drugs against physicochemical and enzymatic degradation[19, 20.] Cyclodextrins are a group of cyclic oligosaccharides obtained from the enzymatic degradation of starch.

The aim of this study was to formulate Simvastatin (SV) solid dispersion (SD) by incorporating β -cyclodextrin (β-CD) with the drug Simvastatin to improve the aqueous solubility, dissolution rate for the improvement oral bioavailability. Also to study the effect of β-CD incorporation on the properties of this lipophilic drug molecule Simvastatin.

MATERIALS AND METHODS

Simvastatin (SV) was obtained as gift sample from ISP Hong-Kong India Pvt.Ltd, (Hyderabad), β-cyclodextrin were purchased from (Qualigens chemicals, Mumbai). All the chemicals used in the study were of analytical and pharmaceutical grade.

Preparation of Physical mixture (PM)

Simvastatin and β-CD were accurately weighed at various drug-to-carrier weight ratios (1:1, 1:3 and 1:5) and thoroughly blended in glass mortar for 5 min then passed through sieve no.100 and stored in desiccators over fused calcium chloride for further study. The composition of various batches is shown in Table 1[21].

Preparation of solid dispersion

Solvent Evaporation method (SEM)

The SD of Simvastatin with carrier at various drug-to-carrier weight ratios (shown in table 1) were prepared by solvent evaporation method[22] by dissolving 50mg of Simvastatin in methanol in a beaker and carrier was added and mixed to dissolve to get a clear solution. Then it was evaporated at ambient temperature and the resulting semi-wet mass was passed through sieve.no.100 mesh size. The granules were dried at room temperature for 1hour and further dried at 65°C for overnight in hot air oven. The products were kept in desiccators for further study.

Kneading Method (KM)

Simvastatin and β-CD in different ratios (shown in table) were taken. β-CD was added to the mortar, small quantity of 40% water was incorporated while triturating to get wet mass[22]. Then slowly drug was incorporated into the slurry and triturating was further continued for 1h. wet mass was further air dried. By the at 45°C for 24 hours, pulverized and passed through sieve No.100 and stored in desiccators over fused calcium chloride for further study.

Fusion Method (FM)

The accurately weighed amount of carrier β-CD was melted in a porcelain dish at 80-85°C.Calculated amount of Simvastatin was incorporated with thorough mixing for 1-2 minutes followed by quick cooling. The ratio of drug and carrier in the ratio of 1:1, 1:3 and 1:5 were prepared by the modified technique[23].

EVALUATION

Solubility Studies

The solubility studies on pure drug, physical mixture and solid dispersion prepared by solvent evaporation method[24-26], fusion method and kneading method were conducted in a thermostat shaker water bath by shaking for 96 hours at 37º C± 0.5º C. Finally the solution was filtered by using Whatmann filter paper (Grade 41, Himedia) and after suitable dilutions the drug concentration was determined using UV-Vis spectrophotometer (shimadzu, japan) at 238nm. All the solubility measurements were performed in triplicate.

Fourier Transform Infrared (FT-IR) Spectroscopy

The FT-IR spectra were recorded on samples of pure drug and solid dispersion prepared by the above methods in different ratios of carrier (w/w) in a KBr pellet technique. The pellets were prepared on KBr press under hydraulic pressure of 150 kg/cm^2; the spectrums were scanned over the wave number range 3600-400 Cm^{-1} at ambient temperature with resolution of $4cm^{-1}$ using FT-IR model – 2500 apparatus.

Drug Content Analysis

An accurately weighed quantity of solid dispersion equivalent to 50mg of Simvastatin was taken into a 100ml volumetric flask and dissolved in minimum quantity of buffer (water with 5% SDS) then the volume made using buffer. The samples was diluted suitably and assayed for drug content using a double beam UV/Vis spectrophotometer (shimadzu, japan) by detecting its wavelength at a maximum absorbance[26].

In Vitro Dissolution Studies

The dissolution of the samples was studied using dissolution apparatus I (USP XXIV) basket method. The Dissolution medium was 900ml of distilled water, maintained at 37±0.5°C with the stirring speed of 100rpm. Accurately weighed samples of different ratio of drug to carrier (PM,KM,SEM and FM), equivalent to 50mg of Simvastatin were filled in zero size hard gelatin capsule by hand filling method and placed in basket of dissolution apparatus. A 5.0ml aliquate sample solution was withdrawn at predetermined time intervals and filtered through 0.45µm Millipore filter. An equal volume of fresh dissolution medium was immediately replaced to maintain sink condition. The concentration of Simvastatin at each sampling time was analyzed at 238nm using UV-Vis spectrophotometer. The experiments were performed in triplicate. With the help of standard curve equation concentration were found using absorbance value.

RESULT AND DISCUSSION

In the present work Simvastatin was complex with highly water soluble carrier β-cyclodextrin in molar ratio 1:1, 1:3 and

1:5 by four different methodologies like Physical mixture, Fusion method, Solvent evaporation method and Kneading method. The Solid dispersion was characterized by FT-IR and physicochemical evaluation (Table 2). FT-IR spectroscopy was used to study the possible interaction between Simvastatin and the carrier in the solid dispersion. The FTIR spectra of drug-carrier solid dispersion did not differ from that of Simvastatin and displayed absorption bands as in IR spectra of Simvastatin showing the drug was not degraded in the presence of β-cyclodextrin and any other stress conditions showed in (Figure 1-3).

The solubility of the Simvastatin and solid dispersion was studied using distilled water and was observed that the prepared solid dispersion ratio 1:5 exhibits maximum solubility as compared with the other ratio 1:1 and 1:3. In fusion method and solvent evaporation method, the solubility was found to be 45 µg /ml and 40 µg /ml for physical mixture and 38µg /ml for kneading method (Table 2). When concentration of β-cyclodextrin is increased, the solubility of Simvastatin also increased. The carrier is in torus shape with hydrophilic outer surface and a liphophilic central cavity. These properties form inclusion complexes with liphophilic molecules[-28-31]. The Drug-CD complex exhibit good aqueous solubility which is different from that of the free drug. This is because of changes in many of the physicochemical properties of drug without alteration of the intrinsic pharmacokinetic[32, 33].

The drug content for all the batches was estimated spectrophotometrically at 238nm and shown (Table 2).

Solid dispersion formulated by different methods showed marked enhancement in the dissolution of drug as compared to plain drug powder and is clearly evident from the percentage drug release represented in (Table 2 and Figures4-7).Solid dispersion prepared by fusion method shows improved dissolution at the end of 60 min which is 44.41%. The ratio 1:5 showed better in vitro release when compared with that of pure drug which is 28.78 % at the end of 60min. The solid dispersion prepared by fusion method and solvent evaporation method showed 1.5 fold increase in dissolution. This is due to increased wet ability and dispersibility of drug by the carrier. Hydrophilic carrier will help to improve wetting property and reduce the interfacial tension between hydrophobic drug and dissolution medium[17].

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Table 1: Composition of inclusion complex batches

S.No	Batch Code	Drug:Carrier ratio (Molar)	Drug (mg)	Carrier (mg)
1	PM1	1:1	50	50
2	PM2	1:3	50	150
3	PM3	1:5	50	250
4	SEM1	1:1	50	50
5	SEM2	1:3	50	150
6	SEM3	1:5	50	250
7	KM1	1:1	50	50
8	KM2	1:3	50	150
9	KM3	1:5	50	250
10	FM1	1:1	50	50
11	FM2	1:3	50	150
12	FM3	1:5	50	250

Table 2: Physicochemical evaluation of Simvastatin Solid Dispersion.

S.No	Batch Code	% Yield	Moisture content (%)	Drug content (%)	Solubility (µg/ml)	% Drug Release
1	PM1	85±1.3	6±0.6	97±1.3	22	21.38
2	PM2	93±0.9	6±0.7	98±1.0	30	31.19
3	PM3	98±0.4	5±0.6	97±0.8	40	39.06
4	SEM1	84±1.2	7±0.8	98±0.9	20	31.49
5	SEM2	95±0.8	6±0.7	97±1.2	39	38.33
6	SEM3	98±0.5	7±0.8	96±1.0	45	43.15
7	KM1	84±0.9	6±0.6	96±0.8	29	30.39
8	KM2	94±0.9	6±0.5	97±1.4	34	33.13
9	KM3	97±0.6	7±0.6	98±1.2	38	37.92
10	FM1	86±0.7	5±0.7	97±0.8	34	32.75
11	FM2	94±0.8	6±0.7	98±1.0	40	39.35
12	FM3	96±0.9	6±0.6	98±1.0	45	44.41
13	Pure Drug	-	5±0.6	99±0.8	28	28.78

N=3±SD

Table 3: Kinetics of Simvastatin from Prepared Solid Dispersions 1:5 ratio.

Kinetic model/Method	PM	FM	SEM	KM
Zero Order	0.8514	0.9582	0.6332	0.912
First Order	0.8513	0.8513	0.8373	0.8513
Higuchi	0.933	0.9433	0.7249	0.9361
Korsmeyer-Peppas	0.9371	0.943	0.7177	0.9377
Hixson-Crowell	0.9089	0.9186	0.798	0.9333

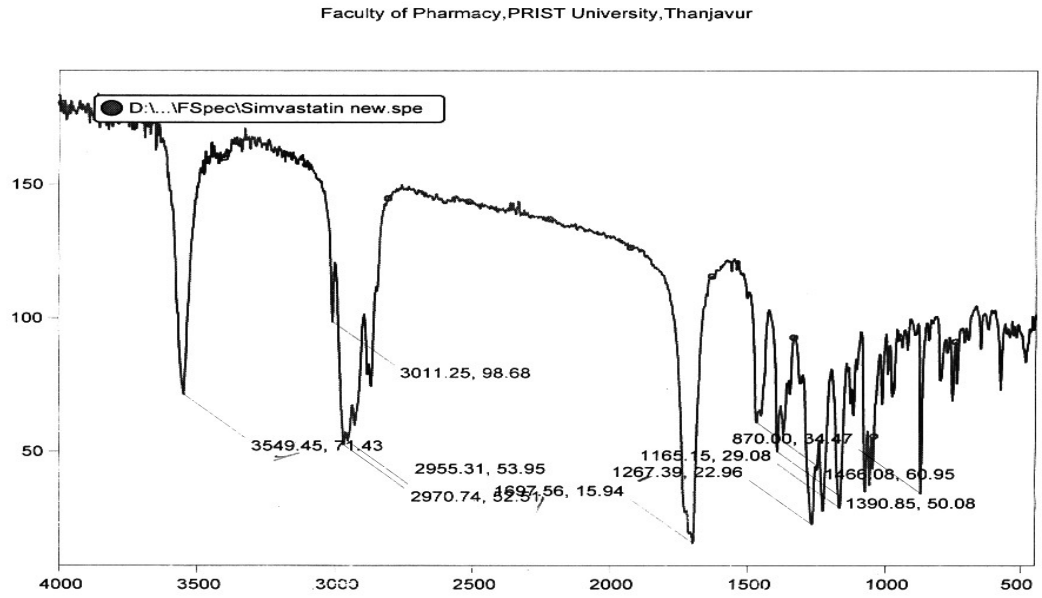

Fig 1- FT-IR spectrum of Simvastatin Solid Dispersions prepared by physical mixture

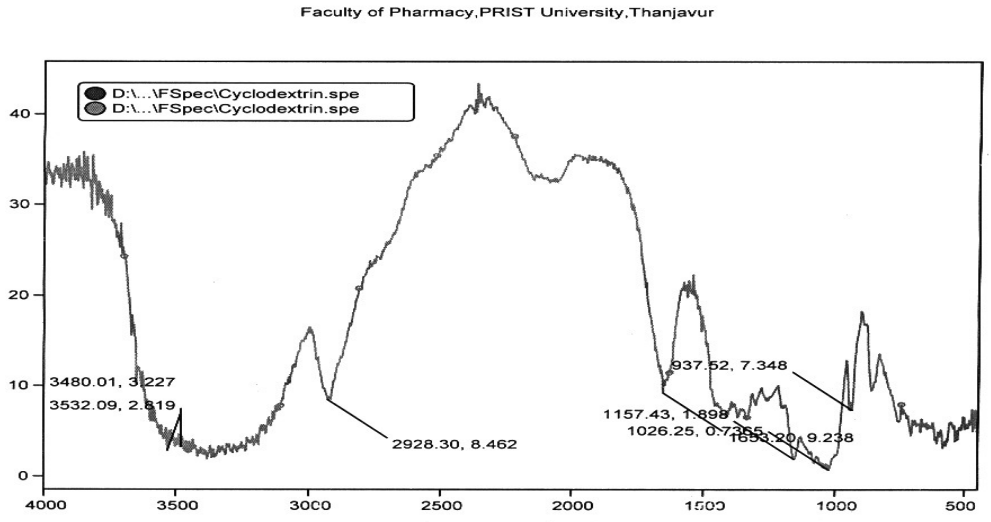

Fig 2- FT-IR spectrum of β-cyclodextrin

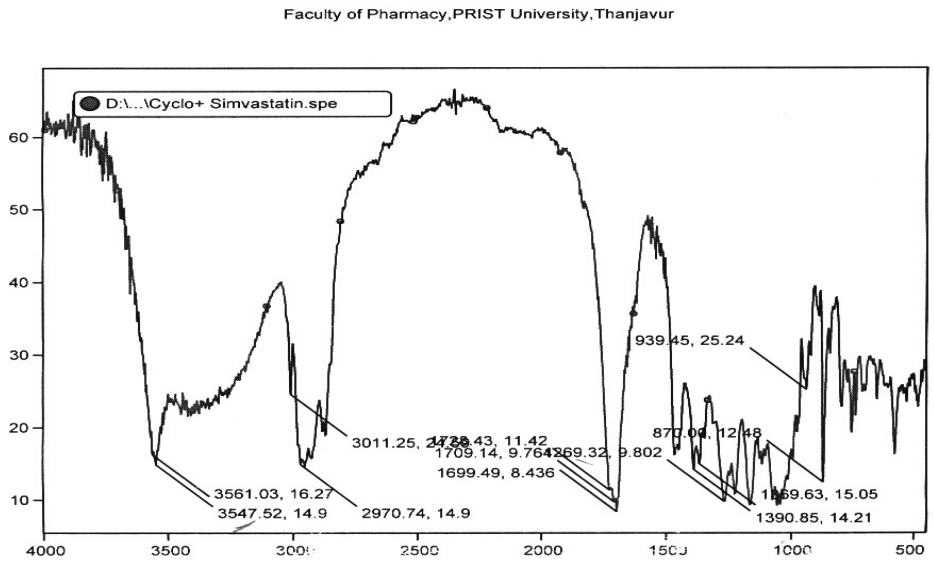

Fig 3- FT-IR spectrum of Solid dispersions prepared by Physical mixture

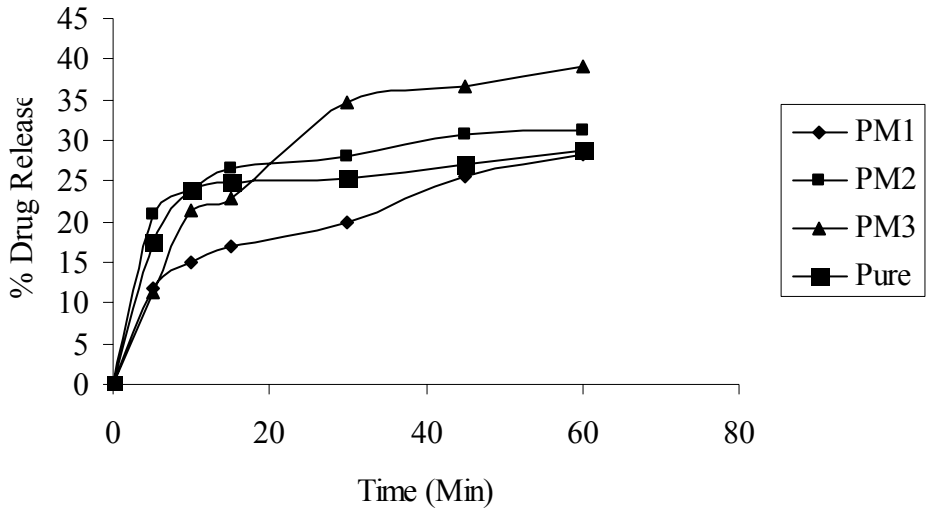

Fig 4- *In- vitro* release profile of Physical mixture and pure drug. (Drug : cyclodextrin) PM1= 1:1, PM2= 1:3 and PM3= 1:5.

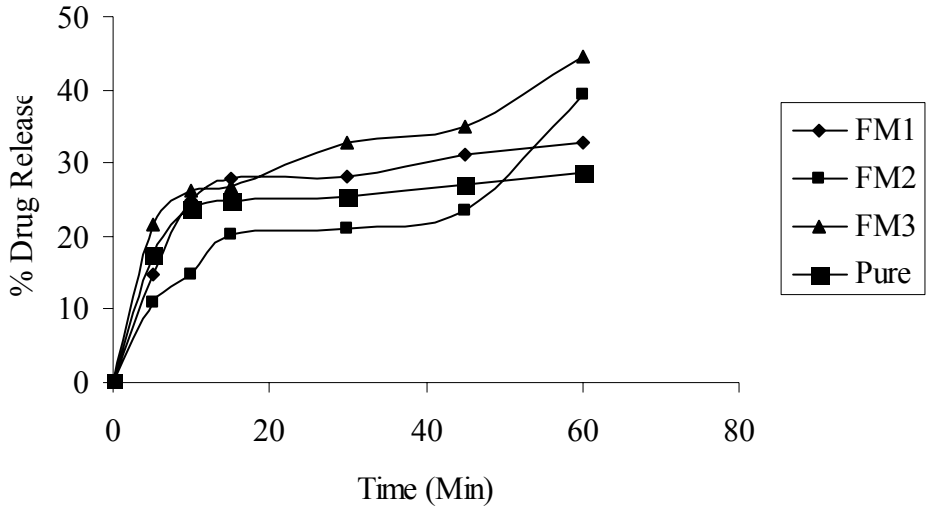

Fig 5- *In-vitro* release profile of Solid dispersions prepared by Fusion method and compared to pure drug. . (Drug : cyclodextrin) FM1= 1:1, FM2= 1:3 and FM3= 1:5.

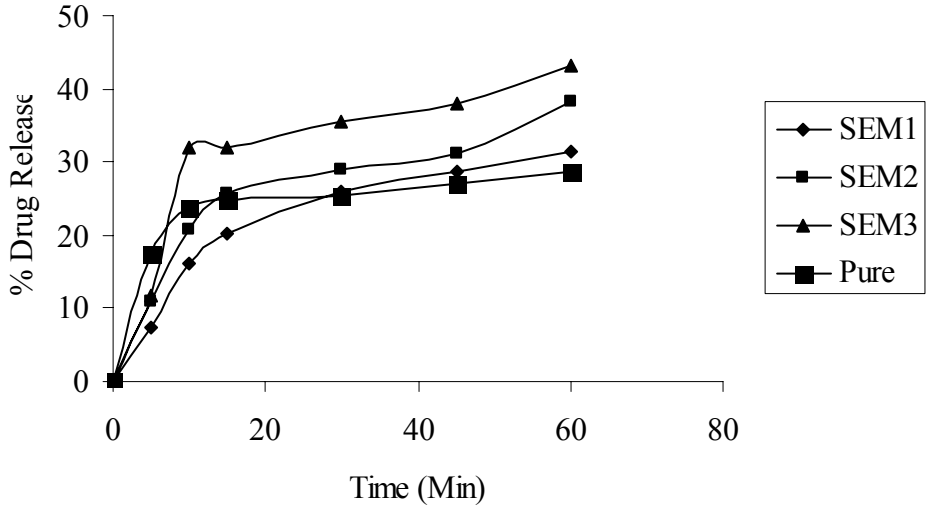

Fig 6- *In-vitro* release profile of Solid dispersions prepared by Solvent evaporation method and compared to pure drug. . (Drug : cyclodextrin) SEM1= 1:1, SEM2= 1:3 and SEM3= 1:5.

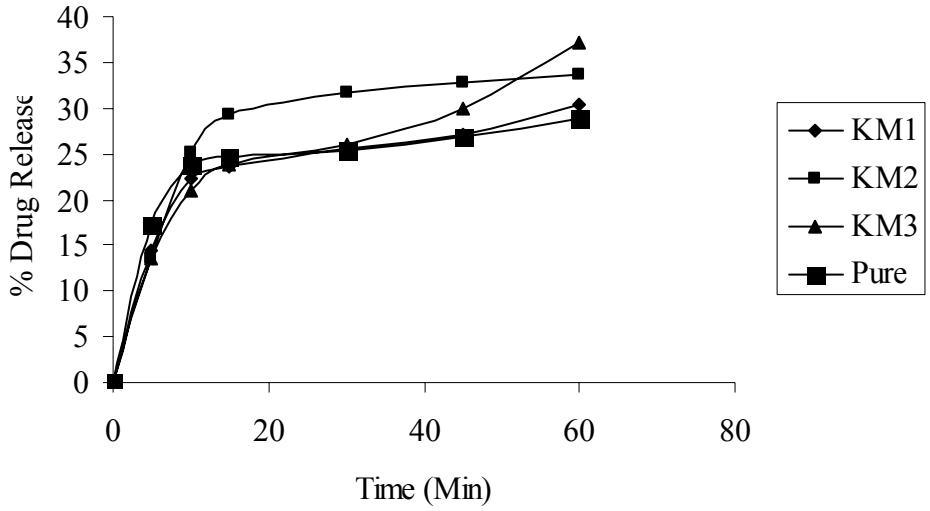

Fig 7- *In-vitro* release profile of Solid dispersions prepared by Kneading method and compared to pure drug. . (Drug : cyclodextrin) KM1= 1:1, KM2= 1:3 and KM3= 1:5.