Effect of Carriers on Solid Dispersions of Simvastatin (Sim): Physico-Chemical Characterizations and Dissolution Studies

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Abstract

The aim of the present work was to improve the solubility and dissolution rate of simvastatin (SIM), a drug used for the treatment of hyperlipidemia. Two systems were used: solid dispersions with PEG 4000 and PEG 6000 prepared using the fusion method in various ratio of 1:1, 1:3, and 1:5 and inclusion complexes with HP-β-cyclodextrin obtained by kneading method in a ratio of 1:1 with drug SIM. The formulations were characterized in liquid state by phase solubility studies and in the solid state by differential scanning calorimetry, X-ray powder diffraction, and FTIR spectroscopy. The aqueous solubility of SIM was studied in the presence of PEG 6000. The dissolution profiles of solid dispersions and inclusion complexes were determined and compared with those of SIM alone and the physical mixture. Inclusion complex prepared with HP-β-cyclodextrin by kneading method showed highest dissolution rate of SIM. Dissolution studies indicated that the dissolution rate were markedly increased in these solid dispersions systems compared with those in physical mixtures and pure drug alone. The increase in dissolution rate strongly depended on the type, ratios of drug to carriers and selection of the method of preparations of solid dispersions. The solid dispersions compound prepared in the ratio of 1:1 by the HP-β-cyclodextrin by kneading method showed the higest improvement in wettability and dissolution rate of SIM due to the amorphous formed and approximately 100% of drug dissolved within 60 min. So this amorphous SDs could be useful for further formulation as a suitable competitave dosage forms.

Keywords: Solid dispersion, Simvastatin, PEG 4000, PEG 6000, HP-β-cyclodextrin, Dissolution Studies.

INTRODUCTION

Simvastatin (SIM) is a lipid lowering agent derived synthetically from a fermentation product of Aspergillus terreus. After oral ingestion, SIM, an inactive lactone, is hydrolyzed to the
corresponding β-hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) reductase, the enzyme that catalyses an early and rate-limiting step in the biosynthesis of cholesterol [1]. SIM is a white, crystalline, nonhygroscopic powder, practically insoluble in water (30 mcg/ml), and 0.1 (N) HCl (60 mcg/ml). It is generally considered that compounds with very low aqueous solubility will show dissolution rate limited absorption and hence poor absorption, distribution and target organ delivery. Its biological half life (3 hours) is very short and it is well absorbed from GIT but its bioavailability is only 5% indicating extensive first pass metabolism in liver [2].

In order to improve the solubility and bioavailability of poorly water soluble drugs many methods are used. Solid dispersions [3-4] and cyclodextrin inclusion complexes [5, 6] are actually among the most frequently used.

An important influence on the properties of such solid dispersions (SDs) and inclusion complexes is the method of preparation and the type of the carrier used [7-11]. The methods used to prepare SDs include physical mixing, melting method [12] and methods used for inclusion complexes are physical mixing and kneading.

Among the carriers used in the formation of solid dispersions, polyethylene glycol is used most commonly. It shows excellent water solubility and varies significantly in molecular weight, ranging from 200 to in excess of 300,000 [13].

Hydroxypropyl-β-cyclodextrin (HP-β-CD) is known to form inclusion complexes with many pharmaceutical compounds and appears to possess promising properties for the improvement of drug release, since it has the complexing properties of cyclodextrins and much greater solubility in water than β-cyclodextrin. HP-β-CD is also useful in the formulation of parenteral preparations due to its low cytotoxicity, weak haemolytic activity and only minor irritating effect [5, 14].

The present study was planned to improve the aqueous solubility and dissolution rate of simvastatin by preparing its solid dispersions with polyethylene glycol 4000 (PEG 4000) and PEG 6000 employing two methods such as fusion cooling and simple physical mixing and cyclodextrin inclusion complexes with hydroxypropyl-β-cyclodextrin employing two methods such as physical mixing, and kneading.

In order to analyze the prepared products, selective physical determinations based on X-ray diffractometry, IR spectroscopy and differential scanning calorimetry (DSC) were used. Solubility diagrams and dissolution studies were also carried out.

MATERIALS AND METHOD

2.1. Materials
Simvastatin was received as gift sample by Aurobindo Pharma. Ltd., (Hyderabad, India), polyethylene glycol (PEG) 4000 and 6000 were gifted by Trizma chemical co. and Hydroxypropyl-β-cyclodextrin purchased from Merck Ltd., Mumbai, India. All other chemicals and solvents used in this study were of analytical grade.

2.2. Phase solubility studies
Phase-solubility studies were performed according to the earlier method reported by Higuchi and Connors, 1965 [15]. The amounts of Simvastatin, that exceeded its solubility, were
transferred to Franz diffusion cell containing 30 ml phosphate buffer (pH 6.8) with different concentrations (0, 0.5, 1.0, 2.0, and 5.0% w/v) of PEG 6000. The contents were stirred on electromagnetic stirrer (Remi, India) at 37±0.5 °C for 24 hours. After equilibrium attainment, the samples were filtered, suitably diluted and analyzed spectrophotometrically for drug content at the wavelength of 238 nm using spectrophotometer (VARIAN, Carry 50, BIO, USA). All assays were performed in triplicate.

2.3. Preparation of solid dispersions (SDs) and inclusion complex

2.3.1. Solid dispersions prepared by melting method

Three SDs preparations containing different weight ratios of simvastatin in PEG 4000 or PEG 6000 (1:1, 1:3, 1:5 and denoted as SDPEG 4000 1/1, 1/3, 1/5 or SDPEG 6000 1/1, 1/3, 1/5, respectively) were prepared by the melting method.

The carrier (PEG 4000 or PEG 6000) was melted in a water bath at 70 °C, the drug was added in the solid state and the mixture stirred until homogeneity was attained. The mixture was then cooled rapidly in a freezing mixture of ice and stored in a desiccator for 24 hours. Subsequently, the dispersion was ground in a mortar and sieved through 80 #.

2.3.2. Preparation of inclusion complex by kneading method

1:1 molar ratio of Simvastatin and hydroxypropyl-β-cyclodextrin were wetted in a glass mortar for 20 min, then kneading with 50% (v/v) alcohol for 45 min. The pasty mass obtained was dried at 60 °C. The dried mass was passed through sieve 80 and stored overnight in desiccator and denoted as KNCD.

2.3.3. Preparation of physical mixture

Physical mixtures (PMs) having the same weight ratios were prepared by thoroughly mixing appropriate amounts of Simvastatin and PEG 4000, PEG 6000 or Hydroxypropyl-β-cyclodextrin in a mortar until a homogeneous mixture was obtained. The resulting mixtures were sieved through 80 # sieve and denoted as PMPEG 4000 1/1, 1/3, 1/5, PMPEG 6000 1/1, 1/3, 1/5 and PMCD 1/1 respectively.

2.4. Characterization of solid dispersion

2.4.1. Infrared (IR) spectroscopic analysis

Fourier-transform infrared (FTIR) spectra of moisture free powdered samples of simvastatin, its PMs, SDs and inclusion complex with PEG 4000, PEG 6000 and hydroxypropyl-β-cyclodextrin were obtained using a spectrophotometer (JASCO FTIR-410, Ireland) by potassium bromide (KBr) pellet method. The scanning range was 400-4000 cm\(^{-1}\) and the resolution was 4 cm\(^{-1}\). Polystyrene was used to check the spectrophotometer calibration.

2.4.2. Powder X-Ray diffraction (PXRD) analysis

The physical state of simvastatin in the various preparations was evaluated by X-ray diffraction. Powder X-ray diffraction patterns of all samples were determined using Ultima III, Rigaku, Japan with a CuKα anode at 40 kV and 30 mA and at a scan rate of 1° min\(^{-1}\) from 20 range from 5° to 40°. The positions and intensities of diffraction peaks were considered for the identification and comparison of crystallinity of the drug or carrier.

2.4.3. Differential scanning calorimetry (DSC) analysis

DSC scans of the powdered samples were recorded using Perkin Elmer Thermal Analysis, USA. All samples were weighed from 1.18 to 2.784 mg and heated at a scanning rate of 10 °C/min in a nitrogen atmosphere.
°C min⁻¹ under dry nitrogen flow (20 ml min⁻¹) between 32 to 310 °C. Tin pans and lids were used for all samples. Pure water and indium were used to calibrate the DSC temperature scale and enthalpic response.

2.5. Drug content analysis
The drug contents of physical mixture, solid dispersions and KNCD were analyzed using a UV-spectrophotometer (VARIAN, Carry-50, BIO, USA) by dissolving the sample contain 2.0 mg equivalent weight of simvastatin in 100 ml methanol, followed by further dilution of 1 ml alcoholic solution and volume made up to 10 ml with water. After suitable dilution, the absorbance of the above solution was measured at 238 nm against appropriate blank solution. Each test was performed in triplicate.

Table 1: % Actual Amount of Simvastatin Recovered From Formulations

<table>
<thead>
<tr>
<th>CARRIERS</th>
<th>PEG 4000 (MEAN ±SD) (n=3)</th>
<th>PEG6000 (MEAN ±SD) (n=3)</th>
<th>HPB CD (MEAN±SD) (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio (SIM: Carrier) 1:1</td>
<td>95.88±3.92</td>
<td>99.16±4.56</td>
<td>111.96±3.92</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>99.64±4.24</td>
<td>112.28±4.88</td>
</tr>
<tr>
<td></td>
<td>1:5</td>
<td>100±1.24</td>
<td>110±3.92</td>
</tr>
</tbody>
</table>

2.6. Dissolution studies
Dissolution studies were performed using USP apparatus II (Electro Lab, India). Pure simvastatin and all the other products (PMs, SDs, and KNCD) prepared as described earlier were included in this study. Samples of each preparation equivalent to 10 mg of simvastatin were spread over the surface of the dissolution medium (900 ml of phosphate buffer at pH 6.8) maintained at a temperature of 37±0.5 °C, stirring at 50 rpm. The samples were withdrawn at predetermined time intervals, filtered, diluted with methanol and analyzed using a UV-spectrophotometer (VARIAN, Carry-50, BIO, USA) at 238 nm. Each test was performed in triplicate.

2.7. Data analysis
Results are expressed as mean values and standard deviation (±S.D.) and the significance of the difference observed was analyzed by the Student’s t-test. In all tests, a probability value of P < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

2.6.1. Phase solubility studies
The phase solubility curve of simvastatin in the presence of PEG 6000 at 37 °C is shown in Figure 1. According to Higuchi and Connors [15] the phase solubility diagram of SIM-PEG 6000 could be classified as A_L type. The curve showed a linear increase in simvastatin solubility as a function of PEG 6000 concentration with a slope of 0.0031 (R² = 0.9922) in the concentration range (0–0.00025 moles/30ml) investigated. It has been found that at the highest polymer concentration (5% w/w), the solubility increased approximately 3.5 fold with PEG 6000 at 37 °C.
Fig 1. Phase solubility profile of SIM-PEG 6000 in phosphate buffer pH 6.8

2.6.2. Characterization of SDs
2.6.2.1. FTIR spectroscopic analysis
FTIR has been used to assess the interaction between carrier and guest molecules in the solid state. The FTIR spectra of all samples are shown in Figure 2. Important vibrations detected in the spectrum of drug, polymers and formulations are described as follows:

The spectrum of pure simvastatin presented characteristic peaks at 3550.31 cm⁻¹ (alcoholic O-H stretching vibration), 2963.09 cm⁻¹ and 2875.34 cm⁻¹ (methyl and methylene C-H asymmetric and symmetric stretching vibration), 1704.76 cm⁻¹ (lactone C=O and ester C=O stretching), 1464.67, 1388.50 cm⁻¹ (methyl and methylene C-H bending vibration), and 1267.19, 1226.51, 1164.79 and 1121.40 cm⁻¹ (lactone and ester C-O-C bending vibration), respectively. Important variations detected in the spectrum of PEG 4000 are the alcoholic O-H stretching at 3432.67 cm⁻¹, methylene C-H stretching vibration at 2886.92 cm⁻¹, methyl and methylene C-H bending vibration at 1468.53, 1345.11, 1280.50 cm⁻¹ and C-O ether stretching vibration at 1111.76 cm⁻¹. The spectrum of PEG 6000 are alcoholic O-H stretching at 3469.31 cm⁻¹, methylene C-H stretching vibration at 2885.95 cm⁻¹, methyl and methylene C-H bending vibration at 1468.53, 1345.11, and 1281.47 cm⁻¹ and C-O ether stretching vibration at 1108.87 cm⁻¹ and the spectrum of HP-β-CD are alcoholic O-H stretching at 3395.07 cm⁻¹, methyl and methylene C-H stretching vibration at 2929.34 cm⁻¹ and C-O ether stretching vibration at 1033.66 cm⁻¹.

The spectras of PMPEG 4000 1/3, PMPEG 6000 1/3, SDPEG 4000 1/3, and SDPEG 6000 1/3 and KNCD 1/1 can be simply regarded as the superposition of those of Simvastatin and PEG 4000, PEG 6000 or HP-β-CD and any characteristic peaks of physical mixtures and SDs were not changed when those were compared with the pure drug SIM. It can be concluded that no strong chemical interaction occurred between drug and polymers.
2.6.2.2. Differential scanning calorimetry (DSC)

DSC enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic or exothermic phase transformations) [16]. The thermal behavior of the prepared solid dispersions and inclusion complexes of simvastatin with PEG 6000 was studied by DSC.

The thermograms for pure Simvastatin, PEG 6000, HP-β-CD and their PMs, SDs and inclusion complex are shown in Fig-3. The thermogram of simvastatin was typical of a highly crystalline compound, characterized by a sharp endothermic peak at 140 °C which corresponded to its melting. DSC scan of PEG 6000 showed single sharp endotherm at 65 °C due to melting of PEG 6000 whereas during scanning of HP-β-CD a broad endotherm ranging from 34 to 60 °C was observed, due to the presence of residual moisture in HP-β-CD. DSC thermogram of PMPEG 6000 1/3 showed a sharp endothermic peak at 65 °C due to melting of PEG 6000, showing no peak at 140 °C for drug. In case of SDPEG 6000 1/3 the endothermic peak of PEG was shifted to lower temperature indicating some type of interaction between drug and PEG. In case of KNCD 1/1 the endothermic peak of drug was retained and showing no interaction between them because endothermic peak at 140 °C was suppressed and not given a sharp peak of SIM indicates that simvastatin may present as amorphous or as a solid solution inside the matrix in these samples. PMPEG 6000 1/3 and SDPEG 6000 1/3 showed complete absence of SIM peak indicates that simvastatin may present as amorphous or as a solid solution inside the PEG matrix in these samples and that was further confirmed by the XRD analysis.
2.6.2.3. Powder X-Ray Diffraction (XRD) Studies
Powder X-ray diffractograms of pure simvastatin, its PMs, SDs with PEG 4000 or PEG 6000 and inclusion complexes with HP-β-CD are shown in Fig-4. The presence of numerous distinct peaks in the X-ray diffraction spectrum indicates that simvastatin was present as a crystalline material. PEG 4000 and PEG 6000 also exhibited distinct patterns with diffraction peaks but the spectrum of HP-β-CD was characterized by the complete absence of any diffraction peak which is characteristic of an amorphous compound.

Fig 4. Powder x-ray diffractograms of SIM (A), PEG 4000 (B), PMPEG 4000 1/3 (C), SDPEG 4000 1/3 (D), PEG 6000 (E), PMPEG 6000 1/3 (F), SDPEG 6000 1/3 (G), HP-β-CD (H), HP-β-CDPM (I) AND KNCD 1/1 (J).
PMPEG 4000 1/3, PMPEG 6000 1/3, SDPEG 4000 1/3 and SDPEG 60001/3 showed presence of characteristic diffraction peaks of both drug and polymer indicating simvastatin was present as crystalline material in these samples. As shown in Fig-4 it has been clearly confirmed that in case of pure HP-β-CD (H) did not show any distinct peaks and that was further suppressed in KNCD 1/1 (J), but exhibited distinct peaks in case of HP-β-CDPM (I). So, it may be concluded that the drug was present in an amorphous form in SD of HP-β-CD (1/1) prepared by kneading method. Moreover, no other peaks than those which could be assigned to pure simvastatin and PEG or HP-β-CD were detected in all samples.

2.6.2.4. Dissolution studies
The dissolution rate profiles of simvastatin and its PMs, SDs and inclusion complexes are reported in Fig 5. Pure simvastatin was characterized by only 29.52% drug release within 3 hrs in phosphate buffer (pH 6.8). Release rate from SDs and inclusion complexes were evidently higher than the dissolution rate of drug alone. Corresponding physical mixture, also demonstrated higher dissolution profile which may be due to an improved wettability of the drug particles at the early stages of dissolution process. Dissolution of SDs was incomplete even after 3 hrs (66.44% using PEG 6000). But the SD of KNCD (1/1) released completely within 60 min. A very high increase of the drug dissolution rate in case of KN system may be probably due to several reasons: the formation of soluble inclusion complex, amorphization of the drug and consequent solubility increase, better wettability and reduction of particle size.

CONCLUSIONS
Amorphous KNCD solid dispersion was formed at the lower ratios of 1:1 for drug: HP-β-CD. FTIR analysis indicated no differences in intermolecular hydrogen bonding interactions between SIM and HP-β-CD among solid dispersions. The absence of SIM melting was observed for the amorphous solid dispersion, as expected. DSC thermograms exhibited broad endotherms for physical mixtures of drug: HP-β-CD, as a consequence of solid state
interaction induced by heating. This phenomenon was not observed for drug: HP-β-CD physical mixtures. According to dissolution study, drug releases from physical mixtures were higher than that of pure drug, possibly caused by the increase in drug wettability. Solid dispersions exhibited better dissolution rates than physical mixtures, resulted from the increase in drug wettability, reduce drug particle size, or prevent drug aggregation. The maximum result was obtained from amorphous solid dispersion of drug: HP-β-CD 1:1 which showed about a 100% drug dissolve with in 60 min which was much more higher as compared with drug (22 % drug dissolve after 3 hrs) alone.

Among numerous ways of enhancing drug dissolution, solid dispersion of drug in a water soluble polymer is one of the promising techniques. An obstacle of solid dispersion technology in pharmaceutical product development is that a large amount of a carrier, ie, more than 50% to 80% wt/wt, was required to achieve the desired dissolution. This high percentage of carrier causes consistency of product performance at the time of manufacturing. This is a major consideration in that the number of market products arising from this approach has been less than expected.

Recently, combined carriers have been used and a higher increase in drug dissolution was reported. However, those reported solid dispersions were still a very low percentage of drugs loading in the system, which required an extremely high amount of carrier. High drug loaded solid dispersion with high drug dissolution enhancement is not an easy task since the drug presented in such a system is in complete crystal has high crystallinity. Therefore, the strategy of high drug loaded solid dispersion systems with enhanced drug dissolution still needed to be improved.

Solid state characterization indicated SIM was present as amorphous material when it was entrapped in carrier’s matrix with HP-β-CD and it has not any strong interaction with the carriers.

In contrast to the low solubility of pure drug and slow dissolution rate of physical mixtures of SIM, the dispersion of the drug in the carriers considerably enhanced the dissolution rate. This can be attributed to improved wettability and dispersibility, as well as decrease of the crystalline and increase of the amorphous fraction of the drug. Solid dispersion prepared with HP-β-CD showed the highest improvement in wettability and dissolution rate of SIM which may be an effective and promise competitive dosage form in the recent market.

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REFERENCES