Research Article

Fabrication and Evaluation of Solid Dispersion Containing Simvastatin

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ABSTRACT

Hyperlipidemia or hyper lipoproteinemia or dyslipidemia is the presence of elevated or abnormal levels of lipids or lipoproteins in the blood. Lipid and lipoprotein abnormalities are extremely common in general population and are regarded as a highly modifiable risk factor for cardiovascular diseases due to influence of cholesterol and its more common in elderly patients. 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. The objective of the present study was to enhance the dissolution rate of Simvastatin by making a molecular dispersion of drug in the polymeric matrix of Pluronic F-127. These solid dispersions were analyzed for the percent yield, drug content**,** solubility, SEM, XRD, DSC and *in vitro* dissolution profile. Dissolution study of the solid dispersions shows the enhancement of dissolution rate of Simvastatin. The stability study of the formulations as per ICH guideline Q1A in stability chamber both at intermediate and accelerated conditions ascertained that the formulations are stable at wide range of storage conditions.

Keywords: Pluronic F-127, Simvastatin, Solid dispersion, Stability study.

INTRODUCTION

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.[1] Oral bioavailability of a drug depends on its solubility and/or dissolution rate, therefore efforts to increase dissolution of drugs with limited water solubility is often needed. Improvement in the dissolution rate of the poorly soluble drugs after oral administration is one of the most crucial challenges in modern pharmaceutics. Many methods are available to improve these characteristics including salt formation, micronization and addition of solvent or surface-active agents. In this study Pluronic F-127 was selected as carrier and solid dispersion was prepared by melting/fusion method *the* method of solvent evaporation.[2]

The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability.[3] There are various techniques such as, Particle size reduction, micronization, physical modifications, nano-suspension, modification of crystal habit such as, polymorphs, pseudo polymorphs, complexation, solubilization, salt formation, and use of cyclodextrin which can enhance the solubility & dissolution rate of insoluble drug but this techniques having some practical limitations, solid dispersion technique overcome this practical limitations. However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. Solid dispersion technique can be used to enhance the solubility; dissolution rate and absorption of several insoluble drugs.[4] The term solid dispersion refers to group of solid products consisting of at least two different components, generally a hydrophilic matrix and hydrophobic drugs.[5]

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-hydroxy acid 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.[6]

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.[7]

MATERIALS AND METHODS

Simvastatin was obtained from Apex Laboratories, Chennai, as a gift sample. Pluronic F-127 was obtained from Sigma-Aldrich, India. Sodium hydroxide (NaOH), potassium di-hydrogen phosphate was purchased from SD fine chemicals limited, Mumbai. All the chemicals used were of analytical grade.

Preparation of Simvastatin Solid dispersion

Solid dispersion of Simvastatin was prepared by conventional fusion method. Solid dispersion with carrier i.e., Pluronic F-127 was prepared in different drug: carrier ratios like; 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7 and 1:8. First the Pluronic F-127 was melted at 70±4 °C for 7-8 min in a porcelain dish on water bath under constant stirring, followed by the additional of drug powder to the molten carrier and stirring for an additional 5 min until a homogenous dispersion was formed. The solid dispersion was allowed to solidify at room temperature. After 24 hrs of storage in desiccators, the solid dispersions was pulverized and passed through sieved no. 100; the particle size fraction of 150-200 µm was used for all studies.[5] Eight formulations were prepared by changing the ratios of the drug and as shown in Table 1.

Table 1: Composition of Simvastatin solid dispersion

Formulation code	Drug : carrier ratio
BD-1	01:01`
BD-2	01:02
BD-3	01:03
BD-4	01:04
BD-5	01:05
BD-6	01:06
BD-7	01:07
BD-8	01:08

Characterization of Simvastatin solid dispersion

Percent yield

The percent yield of Simvastatin solid dispersions was determined by using the following formula[2];

$$\%\ Yield = \frac{Weight\ of\ prepared\ solid\ dispersion}{weight\ of\ drug + carrier's} \times 100$$

Drug content

Solid dispersion equivalent to 10 mg of Simvastatin was weighed accurately and dissolved in 10 ml of methanol. The stock solution was further diluted suitably in methanol and analyzed by UV-Visible spectrophotometer at 239 nm[2].

Saturation solubility studies

Excess amount of the drug and its solid dispersion formulation were placed in glass stoppered flask containing 10 ml of pH 1.2 hydrochloric acid (HCl) buffer with 0.1% SLS and also in pH 7.2 phosphate buffer. The amount of drug solubility was determined using UV-Visible spectrophotometer at 239 nm[2].

X-Ray powder diffractometry (XRD)

X-ray diffraction analysis was employed to detect the crystallinity of Simvastatin and its respective solid dispersions, which were conducted using a Rigaku Miniflex Bench top X-ray diffractometer (Tokyo, Japan).[7]

Differential scanning calorimetry (DSC)

All dynamic DSC studies of pure drug and its solid dispersion formulations were carried out on Shimadzu thermal analyzer (TA-60WS). A few milligrams of sample, were hermetically sealed into aluminium pans and heated under nitrogen atmosphere with the heating rate of 10 ^{o}C/min.[4]

Scanning electron microscope (SEM) studies

The surface morphology of Simvastatin solid dispersion sample was determined using scanning electron microscope (Model Bruker Nano X flash detector 5010, Germany), at the required magnification at normal room temperature.[6]

Dissolution study of Simvastatin solid dispersions

10 mg equivalent weight of pure Simvastatin was taken for each formulation and dissolution study was done in 6 stages USP Apparatus II (rotating paddle type). 900ml of pH 7.2 phosphate buffer was taken as dissolution medium. The temperature was maintained at 37±0.5 °C stirring speed was adjusted to 75 rpm. 5ml sample was withdrawn at 05 minutes interval and same volume of distilled water was added to it. Then all the samples are measured in UV Spectrophotometer (Shimadzu UV-1700) at 239 nm against appropriate blank.[6,7]

Stability Study

The stability study of the formulations was done according to ICH guideline Q1A in stability chamber. The stability study was performed at intermediate and accelerated conditions in closed containers at specific storage conditions (Table 2). In both cases samples were analyzed for drug content at 0, 3 and 6 months to find out the effect of temperature and humidity on product stability.

Table 2: Different stability study condition according to the ICH guideline

Study	Storage condition	Minimum time period	Sampling interval
Intermediate (IM)	30 ± 2 °C/65% RH ± 5% RH	6months	0, 3 & 6 months
Accelerated (AC)	40 ± 2 °C/75% RH ± 5% RH	6months	0, 3 & 6 months

RESULTS AND DISCUSSION

Percent yield and drug content

Percentage yield of solid dispersions was calculated and reported in Table 3. The highest percentage yield (94.51±0.85 %) was found in solid dispersion having drug to carrier ratio of 01:06, and lowest yield (87.23±0.94 %) was observed in drug to carrier ratio of 01:02. As seen in Table 3, the drug content analysis showed that the drug loading was high (>87 %) and there was proper distribution of the drug in the carrier i.e., Pluronic F-127. The drug content evaluation of different batches of solid

dispersion showed that the drug content was in the range of 87.13±1.49 - 92.89±0.95 % of the total amount of the drug added to carrier.

Table 3: Yield and drug content of Simvastatin solid dispersions containing drug and carrier in different ratios

Drug : Carrier ratio	Percentage yield (%)*	Drug content (%)*
01:01	89.12±1.22	88.93±1.87
01:02	87.23±0.94	90.24±1.06
01:03	93.41±1.58	89.11±1.54
01:04	88.78±1.03	92.13±1.23
01:05	92.68 ±1.19	91.86±1.73
01:06	94.51±0.85	92.89±0.95
01:07	90.95±1.06	87.13±1.49
01:08	88.19±1.43	90.83±1.15

*mean ± SD n = 3

Saturation solubility studies

The saturation solubility of the Simvastatin solid dispersion containing drug and carrier in different ratios, in pH 1.2 HCl buffer with 0.1% SLS and phosphate buffer of pH 7.2 is graphically represented in Figure 1. The solubility values of solid dispersion for drug carrier ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7 and 1:8 were found to be 29.23, 44.18, 57.43, 69.86, 83.77, 91.52, 105.93 and 109.61 µg/ml and 34.33, 48.54, 62.79, 78.34, 89.14, 98.47, 112.81 and 118.9 µg/ml respectively in pH 1.2 HCl buffer with 0.1% SLS and pH phosphate buffer of 7.2. The increase in solubility of Simvastatin by Pluronic F-127 may be due to the increased wettability of Simvastatin and formation of soluble complex between water soluble polymeric carrier and poorly soluble drug. On the basis of solubility it was found that solid dispersion containing drug and carrier in 1:7 had sufficient solubility among all other prepared solid dispersions. Based on the solubility data obtained, the solid dispersion containing drug and carrier in the ratio 1:7 can be used for the further studies in formulation of compression-coated tablets.

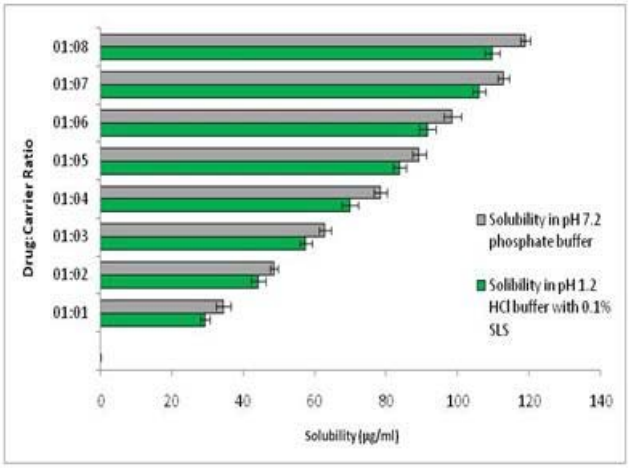

Figure 1: Solubility studies of Simvastatin solid dispersion prepared by different drug and carrier ratio in pH 1.2 HCl buffer with 0.1% SLS and pH 7.2 phosphate buffer.

SEM studies

The SEM images for Simvastatin API and solid dispersion formulation containing drug and carrier in ratio of 1:7 are shown in Figure 2. The Simvastatin API microphotograph (Figure 2A) shows crystalline rectangular shape nature, whereas an image of solid dispersion (Figure 2B) reveals irregular particles with absence of any crystalline material.

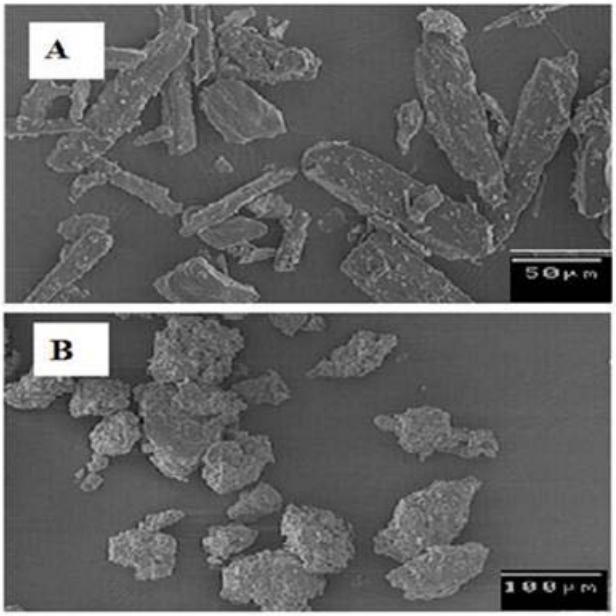

Figure 2: SEM of: (A) Simvastatin API; (B) solid dispersion formulation containing drug and carrier in ratio of 1:7.

XRD studies

X-ray diffractogram of Simvastatin API, pure Pluronic F-127 polymer and solid dispersion formulation containing drug and carrier in ratio of 1:7 is shown in Figure 3. The peaks of Simvastatin API were found at 2 θ angles of 10.96, 17.76, 18.78, 22.4 and 28.54 degrees, indicating its crystalline nature. In contrast the solid dispersion formulation containing drug and carrier in 1:7 ratio showed reduction in intensity of major peaks and disappearance of minor peaks, indicating the conversion of crystalline drug into semi crystalline nature. Decrease in crystallinity of the drug may contribute to enhancement of dissolution of the drug.

DSC studies

The Figure 4 shows the DSC thermogram of Simvastatin API, pure Pluronic F-127 and optimized formulation of solid dispersion. The DSC curve of pure Simvastatin API and pure Pluronic F-127 showed sharp endothermic peaks at 140.12°C and 54.57°C, respectively. The endothermic peak corresponding to melting of Simvastatin was absent in the DSC thermogram of solid dispersion. It might be due to the conversion of crystalline form of Simvastatin into the amorphous form in the solid dispersion or the dissolution of crystalline Simvastatin into the molten carrier[234].

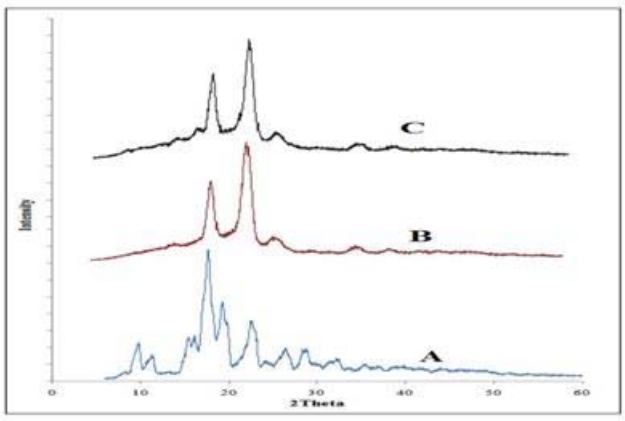

Figure 3: XRD diffractograms of (A) Simvastatin API; (B) pure Pluronic F-127 polymer; (C) solid dispersion containing drug and carrier in 1:7 ratio.

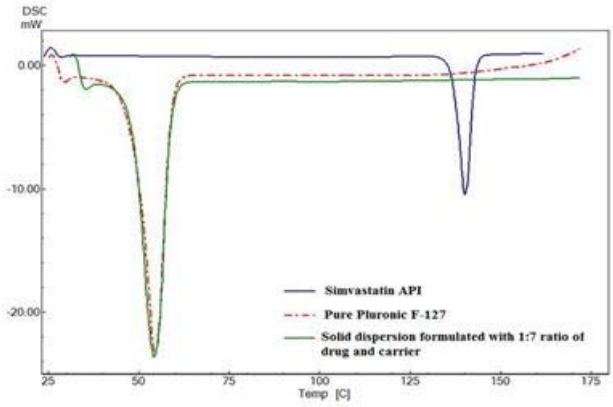

Figure 4: DSC thermogram of Simvastatin API, pure Pluronic F-127 carrier and optimized solid dispersion formulation.

In-vitro dissolution studies

The formulation of solid dispersion of Simvastatin with Pluronic F-127 as carrier was screened for the selection of suitable drug: carrier concentration ratio. This carrier was found to be encouraging since it did not undergo any chemical change during the preparation of solid dispersion. The solid dispersion of Simvastatin with Pluronic F-127 showed a marked increase in the dissolution rate in pH 7.2 phosphate buffer. Dissolution of the Simvastatin increased with increasing proportions of carrier and T50% and T80% values were least with the solid dispersion containing drug: carrier in 1:1 ratio. The formulations containing drug and carrier in the ratio of 1:7 showed satisfactory drug release proving that higher concentration of matrix formed with Pluronic F-127 in ratio 1:7 increased the dissolution rate. These observations (Table 5) indicate the enhanced dissolution of Simvastatin with increase in the concentration of carriers possibly due to the increased wet-ability of the drug by the carrier, drug particle size reduction in the course of the solid dispersion preparation, polymorphic transformation of drug crystals and chemical interactions between drug and carrier.

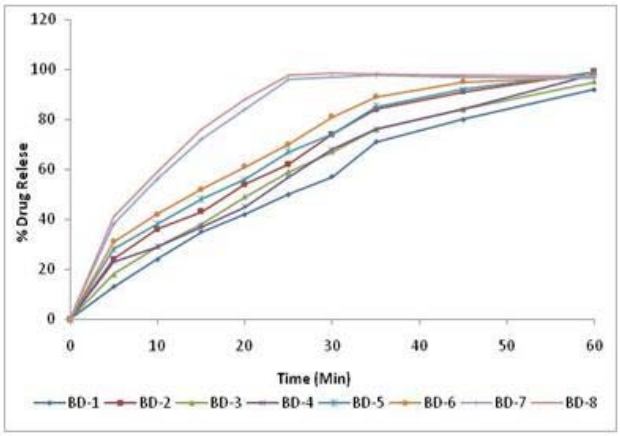

Figure 5: Dissolution profile of different Simvastatin solid dispersion formulations.

Stability studies

All the formulations (BD-1 to BD-8) were kept at intermediate and accelerated conditions in stability chamber in the closed container. A portion of the sample was taken out at 0, 3 and 6 months and interval and tested them for drug content. The result (Table 4) shows no significant changes in appearance and also in drug content. The highest percentage of degradation was observed in formulation BD-5 after 6 months of storing in accelerated condition is found 1.79%. Hence it can be said that the formulations are stable at wide variation in storage condition for long time.

Table 4: Drug content analysis after stability study of intermediate (IM) and accelerated (AC) conditions

Formulation code	Drug content (%)					
	0 months		3 months		6 months	
	IM	AC	IM	AC	IM	AC
BD-1	98.2	98.2	99.1	99.4	98.2	97.9
BD-2	97.6	97.6	98.6	99.1	97.9	98.2
BD-3	98.4	98.4	98.9	98.5	99.8	98.0
BD-4	99.2	99.2	99.4	97.3	98.5	98.3
BD-5	97.7	97.7	98.2	98.5	99.1	98.1
BD-6	99.4	99.4	97.6	98.9	97.3	98.2
BD-7	98.6	98.6	99.2	97.8	98.6	98.1
BD-8	99.1	99.1	98.3	98.6	98.4	97.9

CONCLUSION

Solid dispersion of Simvastatin can be prepared with Pluronic F-127 by fusion technique. Solid dispersion of Simvastatin by the above mentioned method increases the dissolution rate of Simvastatin. The stability of the drug i.e., Simvastatin is not affected by dispersing it in the Pluronic F-127 carrier. The formulations can be stored without any significant degradation for long time. Among the formulations prepared, optimum dissolution was found with the formulation prepared with 1:7 drug: carrier ratio. Hence it can be concluded that preparation of solid dispersion of Simvastatin with Pluronic F-127 can be useful in enhancing the dissolution and improvement of the bioavailability of the drug.

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