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Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2010, 2(3):304-311

ISSN No: 0975-7384
CODEN(USA): JCPRC5

Improved dissolution rate of Atorvastatin calcium using solid dispersions with PEG-4000

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ABSTRACT

The solid dispersion was defined as the dispersion of one or more active ingredients in an inert carrier or matrix. The purpose of the study was to improve the physicochemical properties of Atorvastatin calcium (ATC) like solubility, dissolution properties and stability of poorly soluble drug by forming dispersion with PEG 4000 as water soluble carrier. ATC was formulated by physical mixtures and solid dispersions (dropping method) using 1:1, 1:2 and 1:3 ratios of drug and carrier (PEG 4000). The Phase and saturation solubility study, in vitro dissolution of pure drug, physical mixtures and solid dispersions were carried out. The prepared dispersions showed PEG was found to be effective in increasing the saturation solubility and dissolution rate of ATC than that of pure drug. The dispersion with PEG 4000 (1:3) by dropping method showed faster dissolution rate (85.038%) as compared to other dispersions with PEG 4000 (1:1 and 1:2) whichever prepared by physical mixture and dropping method. The FT-IR shows the complexation and there were no interactions. Finally solid dispersion of ATC: PEG 4000 prepared as 1:3 ratio by dropping method showed excellent physicochemical characteristics and was found to be described by dissolution release kinetics and was selected as the best formulation in this study.

Key words: Atorvastatin calcium (ATC), solid dispersion, dropping method and poly ethylene glycol (PEG) 4000.

INTRODUCTION

The aqueous solubility lesser than 1 μg/ml will definitely creating a bioavailability problem affecting the efficacy of a drug. Up to 40 percent of new chemical entities discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs [1]. Poorly water-soluble drugs show unpredictable absorption, since their bioavailability depends upon dissolution in the gastrointestinal tract [2, 3, 4]. The dissolution characteristics of poorly soluble drugs can be enhanced by several methods [5, 6, 7]. Lipophilic molecules, especially those belonging to the biopharmaceutics classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges, like incomplete release from the dosage form, poor bioavailability, increased food effect, and high inter-patient variability [8].

Alteration of the solid state at the particle or molecular level involves a physical change in the drug and is an attractive option for improving drug solubility [9]. Particle size reduction by micronization or nanonization can enhance the dissolution rate; however, the apparent solubility remains unaltered. At the molecular level, polymorphs offer a limited solubility advantage because of a small difference in free energy. In contrast, amorphous systems with excess thermodynamic properties and lower energetic barrier can offer significant solubility benefits [10]. This solubility benefit can be further enhanced by preparing solid dispersions (SDs). SDs contributes by slowing devitrification, enhancing wettability and modulating the properties of the solvent [11]. Solid dispersions (SDs) with superior pharmaceutical properties can be formulated into suitable dosage forms especially for geriatric population which exhibits variable drug responses due to many age related physiological changes coupled with disease states. Geriatric patients with lower GI motility and gastric emptying, fluctuating gastric pH and reduced intestinal blood flow rate exhibit variable absorption upon administration of solid dosages forms. Solid dispersion is one of the effective and widely used techniques for dissolution enhancement [12]. The two basic procedures used to prepare solid dispersions are the melting or fusion [13] and solvent evaporation techniques [14].

Atorvastatin Calcium is an Anti-hyper lipidemic agent and is used in the treatment of obesity and is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol [15].

Polyethylene glycol (PEG) is used for the preparation of solid dispersions. A particular advantage of PEGs for the formation of solid dispersions is that they have good solubility in many organic solvents. The melting point of PEGs lies below 65 ^{0}C in all cases [16], which is advantageous for the manufacture of solid dispersions. Additional attractive features of PEGs include their ability to solubilize some compounds [17] and also improve compound wettability. Therefore, in the present study, PEG 4000 was chosen as a suitable polymer for the preparation of solid dispersions. Solid dispersions were then evaluated by dissolution and FT-IR spectroscopy.

EXPERIMENTAL SECTION

Materials

Atorvastatin Calcium was a gift sample from Dr.Reddy's lab, Hyderabad, poly ethylene glycol 4000 was purchased from Merk, Mumbai, Potassium dihydrogen orthophosphate (Qualigens fine chemicals, Mumbai), Sodium hydroxide (Finar chemicals ltd. Ahemdabad) and methanol (Research-Lab fine chemicals industries, Mumbai). All required chemicals were analytical grade.

Methods

Preparation of Physical Mixture:

Physical mixtures of ATC at three different mass ratios with carrier (1:1, 1:2 and 1:3) were prepared in a glass mortar by light trituration for 5 minutes. The mixtures were passed through a sieve (60). The prepared mixtures were then filled in hard gelatin capsules, sealed and stored in a dessicator until further use. The composition of F1, F2 and F3 formulations was shown in **table no: 1**.

Table: 1 Composition of Atorvastatin Calcium Physical Mixtures and Solid Dispersions

Ingredients(mg)	F1	F2	F3	S1	S2	S3
ATC	80	80	80	80	80	80
PEG-4000	80	160	240	-	-	-
PEG-4000	-	-	-	80	160	240

ATC: Atorvastatin Calcium; PEG: Poly Ethylene Glycol

Preparation of Solid Dispersion by Dropping Method:

For the preparation of the ATC solid dispersion prepared by dropping method, containing different weight ratios of ATC in PEG 4000. The composition of S1, S2 and S3 formulations was shown in **table no: 1**. The PEG was melted in a porcelain dish at 58^0C ($\pm1^0$C) and a measured amount of ATC was added and stirred. The melted drug-carrier mixture was pipetted and placed into an adjustable heating device to keep the temperature constant. The melted drug-carrier mixture was dropped onto a stainless steel plate, where it solidified into round particles. The temperature of the stainless steel plate was <20 ^{0}C. The round particles (equivalent to 80 mg of ATC) were placed into hard gelatin capsules (size no. 2) for further investigations.

Physicochemical Characterization

Solubility Measurements:

Phase and saturation solubility studies were performed according to the method described by Higuchi and Connors (18).The saturation solubility of drug and SDs with PEG 4000 (1:1, 1:2 and 1:3 w/w) in distilled water and phosphate buffer (pH 6.8) was determined by adding an excess of drug and SDs to 50 ml distilled water or Phosphate buffer in conical flask and were rotated in a orbital shaking incubator for 96 hrs at 37 ^{0}C ±0.5 ^{0}C. The saturated solutions were filtered through a 0.45 μm membrane filter, suitably diluted with water, phosphate buffer and analyzed by Elico SL-150 UV spectrophotometer at 245nm.

FT-IR Spectroscopy:

Infrared (IR) spectroscopy was conducted using Thermo Nicolet Nexus 670 Spectrophotometer and the spectrum was recorded in the wavelength region of 4000 to 500 cm^{-1}. The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients) in KBr and compressing into discs by applying a pressure. The pellet was placed in the light path and the spectrum was obtained.

Drug content analysis [19]:
The drug content in each solid dispersion and physical mixture was determined by the UV-Spectroscopic method. An accurately weighed quantity of solid dispersion or physical mixture, equivalent to 80 mg of atorvastatin calcium, was transferred to a 100 mL volumetric flask containing 10 mL of methanol and dissolved. The volume was made up to 100 mL with pH 6.8. The solution was filtered and the absorbance was measured after suitable dilutions by using Elico SL-150 UV-Spectrophotometer at 245nm.

***In-vitro* dissolution studies:**
Dissolution rate studies were performed in pH 6.8 phosphate buffer at 37 ± 0.5 ^{0}C, using 8-station USP type-II apparatus with paddle rotating at 50 rpm. Solid products, solid dispersions as well as physical mixtures, each containing 80 mg of drug were subjected to dissolution. At fixed time intervals, samples withdrawn were filtered and spectrophotometrically analyzed for the drug content at 245 nm. Each test was performed in triplicate (n=3). Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) [20]. The similarity factor (f2) was evaluated to compare ATC release profiles.

$$f2 = 50 \log \{[1+1/n \sum_{t=1}^{n} (Rt - Tt)^2]^{-0.5} \times 100\}$$

Where Rt and Tt were the cumulative percentage of drug released for reference and test assay at time t respectively, n was the number of time points. The FDA suggests that two dissolution profiles are declared to be similar if the value of *f2* is between 50 and 100 [21].

RESULTS AND DISCUSSION

Solid dispersion of ATC containing varying concentration of PEG 4000 was formulated in an attempt to improve the solubility and dissolution rate of ATC. The ATC, physical mixture and solid dispersion were investigated by analytical method and IR spectra. The drug content in physical mixtures and solid dispersions was found to be in the range of 97.2% to 98.9%. Therefore, dropping method used in this study appears applicable for the preparation of solid dispersions without affecting drug content.

Solubility Studies:
The solubility of pure drug in water and in PBS (pH 6.8) was found to be 27.04 ± 0.56 and 57.06 ± 0.67 µg/mL. The solubility of physical mixture prepared using PEG 4000 in the ratio (1:1, 1:2 and1:3) was 35.59 ± 1.12, 46.87 ± 1.24, 57.79 ± 1.35 µg/mL in water and 63.78 ± 1.19, 72.76 ± 1.21, 81.89 ± 2.35µg/mL in PBS. The solubility of SDs using PEG 4000 (1:1, 1:2 and 1:3) in water were found to be 36.22 ± 1.05, 48.86 ± 1.87, 58.92 ± 1.46 µg/ml and in PBS (pH 6.8) 65.12 ± 1.13, 73.52 ± 1.15 and 83.42 ± 1.76 µg/ml respectively. All of the test samples showed an increase in drug solubility (**Table 2**). As the solid dispersion is a metastable form and tends to transform in to the stable form, the drug concentration may tend to decrease with elapse of time during the solubility test. In order to avoid this problem all the solubility test samples of the different formulations were with drawn and analyzed at established time (96hrs). This allowed readily comparing the solubility of different solid dispersions. The solubility of different concentrations of drug and carrier was observed and the prepared formulation with PEG 4000 (1:3) presented higher dissolution concentration as compared with the other formulations obtained with different ratios (1:1 and 1:2). Maximum solubility in PBS was observed in dropping method 1:3 (Drug: PEG 4000) ratio 83.42 ± 1.76 µg/mL, when compared with that of pure ATC (57.06 ± 0.67 µg/mL).

Table: 2 Solubility studies of pure drug and solid dispersions

Formulation code	Solubility (µg/mL)		Drug content (%)
	Water	PBS	
Pure drug	27.04 ± 0.56	57.06 ± 0.67	95.56±0.023
F-1	35.59 ± 1.12	63.78 ± 1.19	98.75±0.126
F-2	46.87 ± 1.24	72.76 ± 1.21	98.27±0.072
F-3	57.79 ± 1.35	81.89 ± 2.35	99.16±0.042
S-1	36.22 ± 1.05	65.12 ± 1.13	99.54±0.083
S-2	48.86 ± 1.87	73.52 ± 1.15	97.78±0.024
S-3	58.92 ± 1.46	83.42 ± 1.76	99.69±0.011

In vitro drug release studies:

The dissolution profiles of ATC for solid dispersion and physical mixture performed in 6.8 phosphate buffer were as shown in **Table: 3**.

Table: 3 *In vitro* dissolution data for pure drug, marketed tablet, physical mixtures and solid dispersions

Time (min)	Cumulative % drug released							
	Pure drug	Marketed tablet	F1	F2	F3	S1	S2	S3
10	15.633	21.84	17.428	19.853	22.632	18.824	21.513	23.705
20	20.175	25.807	21.698	24.515	26.915	22.422	26.503	27.987
30	23.197	30.728	25.867	28.977	30.718	26.702	30.577	32.448
40	26.898	34.935	29.595	33.485	34.207	31.217	35.221	36.614
50	30.883	50.477	34.020	45.123	43.318	36.247	52.813	59.397
60	35.261	63.052	45.501	57.642	58.891	57.340	67.764	74.554
70	51.006	77.222	56.844	69.113	79.923	70.575	79.060	85.038

The dissolution rate was significantly increased when the ATC: PEG 4000 ratio was at 1:3. The mean percentage of drugs for physical mixture after 70 minutes was 56.844, 69.113, 79.923% for 1:1, 1:2, 1:3 respectively as shown in **Figure: 1** and 51.006%, 77.222% for pure drug and marketed tablet. But in the dropping method half fold increase in release rate was observed as 70.575, 79.060 and 85.038% respectively (**Figure: 2**) (This may be due to impact of complexation and bond formation. This may lead improved solubility by reducing particle size).

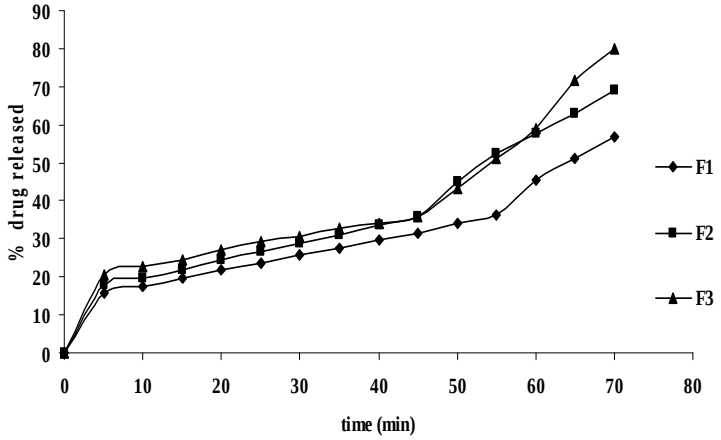

Figure: 1 Dissolution Profiles of Atorvastatin Calcium Physical Mixtures Formulated With PEG-4000

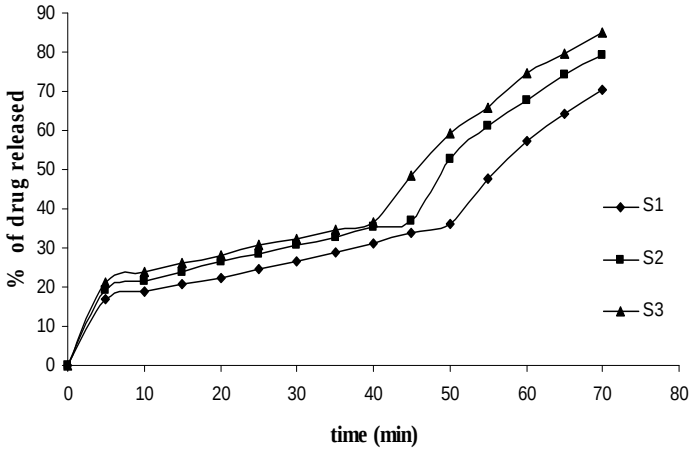

Figure: 2 Dissolution Profiles of Atorvastatin Calcium Solid Dispersions Formulated With PEG-4000

The drug release from all the formulations followed zero order kinetics. To analyze the mechanism of drug release from these formulations, the data were followed Hixson Crowell equation ({fraction unreleased} 1/3 vs. time). The release rate kinetic data & dissolution efficiency at 30 & 60 minutes (DE_{30} & DE_{60}) for these formulations were given in **table 4**. The slope values (n) obtained to decline between 0.5309 to 0.5557 for all formulations for the release of ATC, indicating non-fickian diffusion. The dissolutions profile showed in (**figure: 3**) and similarity factor (***f*₂**), these two formulations were found to be 84.83% indicating the significant differences in between the selected (S3) and marketed tablet (**Lipitor**).The drug release from different formulations followed the order: S3>S2>S1. The above results indicated that the increasing concentration of PEG-4000 content enhanced the drug release.

Table: 4 Dissolution Kinetics of Atorvastatin Calcium Physical Mixtures and Solid Dispersions Formulated With PEG-4000

Formulation code	Correlation Coefficient (R^2)					Slope (n)	$DE_{30\%}$	$DE_{60\%}$
	Zero order	First order	Higuchi	Peppas	Hixson-Crowell			
F1	0.9416	0.9091	0.9195	0.9078	0.9394	0.4692	18.51	25.49
F2	0.9526	0.9257	0.9281	0.9185	0.9558	0.5235	20.83	30.48
F3	0.9638	0.8790	0.8956	0.8815	0.9068	0.4833	23.22	31.77
S1	0.9420	0.9110	0.8951	0.8949	0.9285	0.5309	19.51	28.09
S2	0.9530	0.9180	0.9035	0.8991	0.9391	0.5535	22.48	33.58
S3	0.9787	0.9157	0.9105	0.8983	0.9628	0.5557	24.36	37.05
Marketed	0.9474	0.9221	0.9131	0.8969	0.9410	0.5183	22.63	32.89

**DE_{30} and DE_{60}, dissolution efficiency at 30 and 60 minutes.*

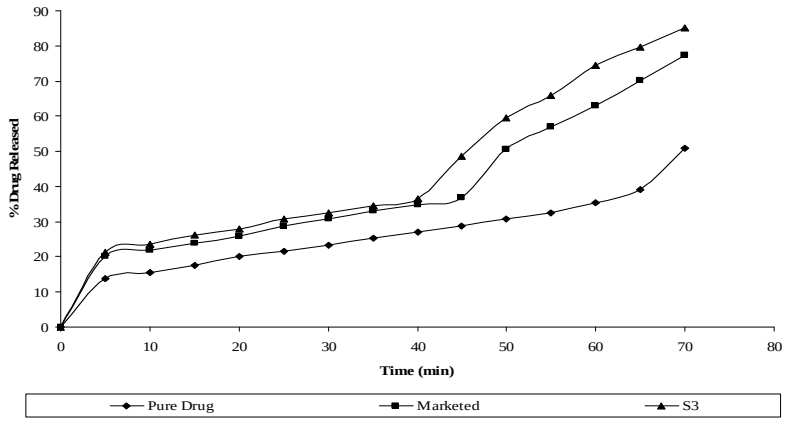

Figure: 3 Dissolution profile of Pure Atorvastatin Calcium, Marketed tablet and Solid dispersion (S3)

FT-IR Spectroscopy studies:

The FT-IR spectra of pure ATC and solid dispersions are shown in **Figures 4 & 5**. The FT-IR spectra of pure ATC showed characteristic peaks at 2955.15 cm^{-1} (C-H - stretching), 1313.56 cm^{-1} (C-N - stretching), 3059.15 cm^{-1} (C-HO - stretching alcoholic group), 1564.97 cm^{-1} (C=O - stretching amidic group), 3403.27 cm^{-1} (N-H - stretching), 1656.97 cm^{-1} (C=C - bending), 751.62 cm^{-1} , 696.95 cm^{-1} (C-F - stretching), 1104.39 cm^{-1} (O-H - bending). It might be the possibility of intermolecular hydrogen bonding between adjunct ATC molecules. The spectrum of pure ATC was equivalent to the spectra obtained by the addition of carrier. This indicated that no interaction occurred with a solid dispersion of drug and lipid carriers. The results revealed no considerable changes in the IR peaks of ATC, when mixed with polymer PEG-4000. These observations indicated the compatibility of PEG-4000 with ATC.

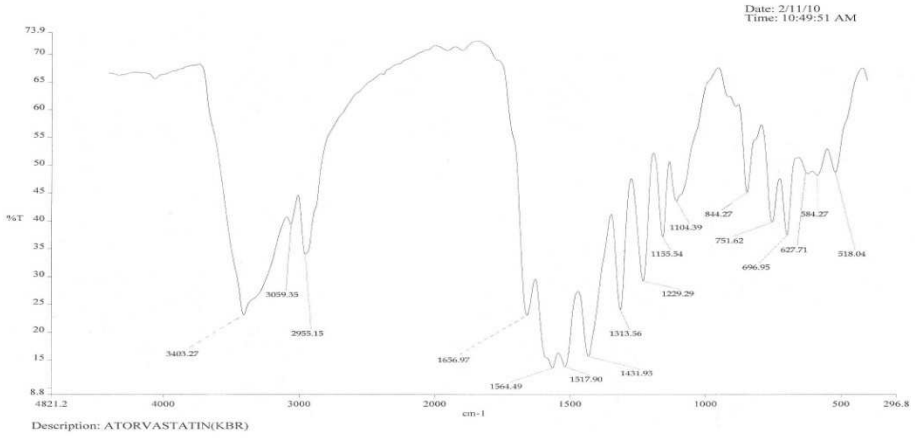

Figure: 4 FTIR Spectra of Atorvastatin Calcium

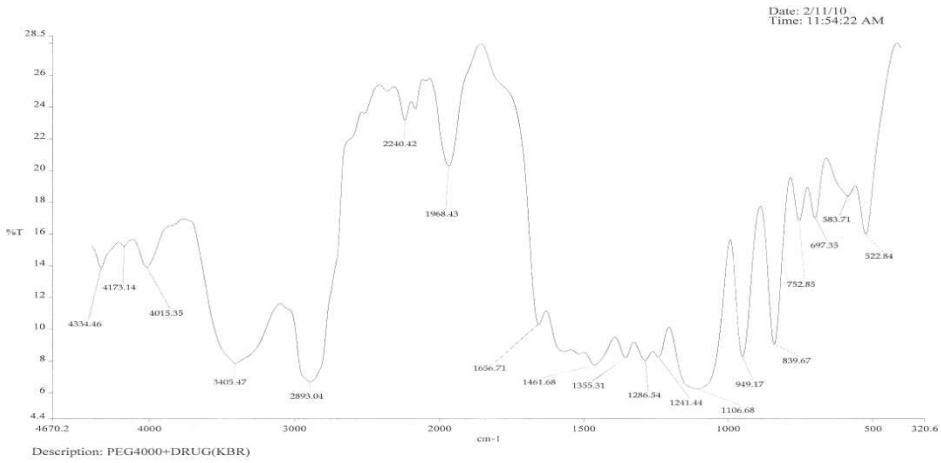

Figure: 5 FTIR Spectra of Atorvastatin Calcium & PEG-4000 Mixture

CONCLUSION

The prepared solid dispersions were extended to various characterizations. FT-IR shows there was no degradation of drug. The solubility and dissolution studies showed there is a possibility of improved solubility of ATC through solid dispersion with Poly ethylene glycol 4000. A maximum increase in dissolution rate was obtained with ATC: PEG 4000 solid dispersion with a

weight ratio of 1:3. PEG 4000 dispersion by dropping method showed faster dissolution rate when compared with that of pure drug.

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