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Enhanced Dissolution Rate of Atorvastatin Calcium using Solid Dispersion with PEG 6000 by Dropping Method

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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 like solubility, dissolution properties and stability of poorly soluble drug by forming dispersion with Poly Ethylene Glycol (PEG) 6000 as water soluble carrier. Atorvastatin was formulated by physical mixtures and solid dispersions (dropping method) using 1:1, 1:2 and 1:3 ratios of drug and polymer (PEG-6000). The saturation solubility was carried using water and phosphate buffer solution (PBS) and showed marked increase in the saturation solubility than that of pure drug. Higher *in vitro* dissolution of solid dispersions was recorded compared to their corresponding physical mixtures and the pure drug. The dispersion with PEG-6000 (1:3) by dropping method showed faster dissolution rate (89.65%) as compared to other dispersions with PEG-6000 (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 Atorvastatin: PEG-6000 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: *Solid Dispersion, Dropping Method, Water Soluble Carrier, Atorvastatin calcium and PEG-6000.*

Introduction:

Atorvastatin calcium is anti-hyper lipidemic drug that is poorly soluble in water, having a biological half-life of 14 hrs 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 [1].

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 [2], which is advantageous for the manufacture of solid dispersions. Additional attractive features of PEGs include their ability to solubilize some compounds [3] and also improve compound wettability.

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 [4]. Poorly water-soluble drugs show unpredictable absorption, since their bioavailability depends upon dissolution in the gastrointestinal tract [5, 6, 7]. The dissolution characteristics of poorly soluble drugs can be enhanced by several methods [8, 9, 10]. 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 [11].

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 [12]. 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 [13]. 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 [14]. 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 [15]. The two basic procedures used to prepare solid dispersions are the melting or fusion [16] and solvent evaporation [17] techniques.

Therefore, in the present study, PEG 6000 was chosen as a suitable polymer for the preparation of solid dispersions. Solid dispersions were then evaluated by dissolution and FT-IR spectroscopy.

Materials and Methods:

Materials

Atorvastatin Calcium was a gift sample from Dr.Reddy's lab, Hyderabad, India. Poly ethylene glycol 6000 was purchased from Merk, Mumbai, Potassium dihydrogen orthophosphate (Qualigens fine chemicals, Mumbai, India), Sodium hydroxide (Finar chemicals ltd. Ahemdabad, India) and methanol (Research-Lab fine chemicals industries, Mumbai, India). All required chemicals were analytical grade.

Methods

Preparation of Physical Mixture:

Physical mixtures of atorvastatin calcium at three different mass ratios (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 no: 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 1.

Preparation of Solid Dispersion by Dropping Method:

For the preparation of the Atorvastatin Calcium (ATC) solid dispersion prepared by dropping method, containing different weight ratios of ATC in PEG 6000. The composition of S1, S2 and S3 formulations was shown in Table 1. The PEG was melted in a porcelain dish at 58 ^{0}C ($\pm1^0$C) and a measured amount of Atorvastatin Calcium were 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, physical mixtures and SDs with PEG 6000 (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, physical mixture 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 6000

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-6000	80	160	240	-	-	-
PEG-6000	-	-	-	80	160	240

ATC: Atorvastatin calcium; PEG-Poly Ethylene Glycol

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:

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 [19].

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 (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 R_t and T_t 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:

The drug content in physical mixtures and solid dispersions was found to be in the range of 95.56 % to 99.6 %. Therefore, dropping method used in this study appears applicable for the preparation of solid dispersions without affecting drug content.

Solubility Studies:

The results of saturation solubility studies are given in Table 2. 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 6000 in the ratio (1:1, 1:2 and 1:3) 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 ± 2.35 µg/mL in PBS. The solubility of SDs using PEG 6000 (1:1, 1:2 and 1:3) in water were found to be 38.52 ± 1.15, 47.83 ± 1.45, 59.56 ± 1.39 µg/mL and in PBS (pH 6.8) 67.96 ± 1.27, 74.67 ± 1.47 and 95.72 ± 1.48 respectively.

Table 2: Solubility studies and drug content of pure drug, physical mixtures 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	98.54±0.031
F-2	46.87 ± 1.24	72.76 ± 1.21	97.25±0.053
F-3	57.79 ± 1.35	81.89 ± 2.35	99.25±0.043
S-1	38.52 ± 1.15	67.96 ± 1.27	99.42±0.041
S-2	47.83 ± 1.45	74.67 ± 1.41	96.20±0.036
S-3	59.56 ± 1.39	95.72 ± 1.48	99.60±0.023

PBS: Phosphate Buffer solution

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	19.102	20.958	23.161	20.044	21.870	24.073
20	20.175	25.807	22.469	26.455	27.674	24.243	26.028	28.739
30	23.197	30.728	26.705	31.191	32.112	28.484	30.715	32.970
40	26.898	34.935	31.455	36.105	36.378	32.300	34.877	49.303
50	30.883	50.477	35.914	52.431	57.332	36.668	53.108	64.958
60	35.261	63.052	50.701	66.778	70.421	63.139	68.644	75.635
70	51.006	77.222	64.010	75.351	82.393	78.784	84.631	89.652

All of the test samples showed an increase in drug solubility. 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 withdrawn and analyzed at established time (96hrs). This allowed readily comparing the solubility of different solid dispersions.

Table 4: Dissolution Kinetics of Atorvastatin Calcium by Physical Mixtures and Solid Dispersions Formulated With PEG-6000

Formulation code	Correlation Coefficient (R^2)					Slope (n)	$DE_{30\%}$	$DE_{60\%}$
	Zero order	First order	Higuchi	Peppas	Hixson Crowell			
F1	0.9209	0.9176	0.9154	0.9052	0.9261	0.4756	19.60	26.95
F2	0.9543	0.9359	0.9235	0.9209	0.9556	0.5601	22.50	34.13
F3	0.9693	0.9123	0.9146	0.9029	0.9424	0.5508	23.91	36.30
S1	0.9320	0.8770	0.8744	0.8783	0.9043	0.5359	20.91	29.78
S2	0.9483	0.8886	0.8905	0.8832	0.9209	0.5496	22.68	33.67
S3	0.9714	0.9212	0.9250	0.9149	0.9553	0.5895	24.72	40.19

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

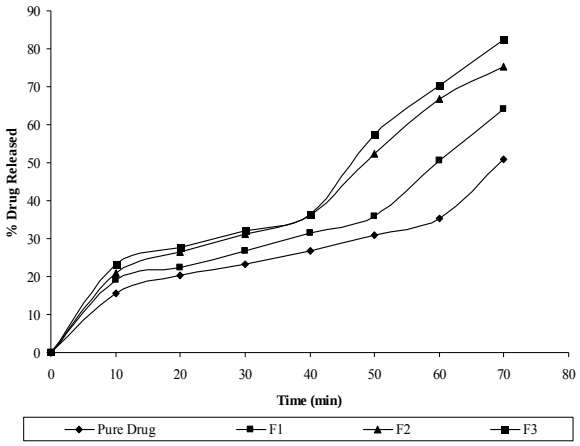

Figure 1: Dissolution Profiles of Atorvastatin Calcium Physical Mixtures Formulated With PEG-6000.

The solubility of different concentrations of drug and polymer was observed and the prepared formulation with PEG 6000, 1:3 (Drug: Carrier) 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 6000) ratio 95.72 ± 1.48 µg/mL, when compared with that of pure Atorvastatin Calcium(57.06 ± 0.67 µg/mL).

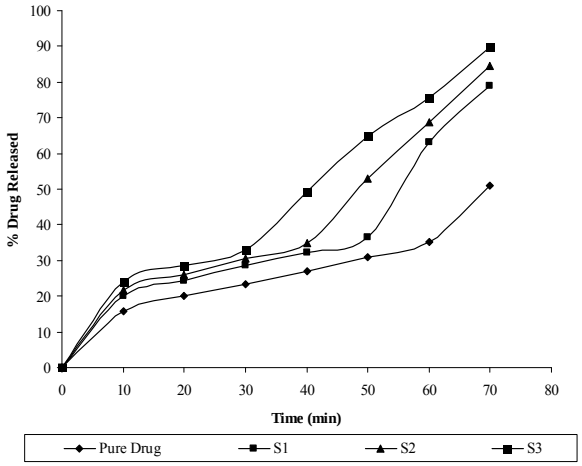

Figure 2: Dissolution Profiles of Atorvastatin Calcium pure drug and Solid Dispersions.

In Vitro drug release:

The dissolution profiles of Atorvastatin Calcium for solid dispersion and physical mixture performed in 6.8 phosphate buffer were as shown in Table 3. The dissolution rate was significantly increased when the Atorvastatin Calcium: PEG 6000 ratio was at 1:3.

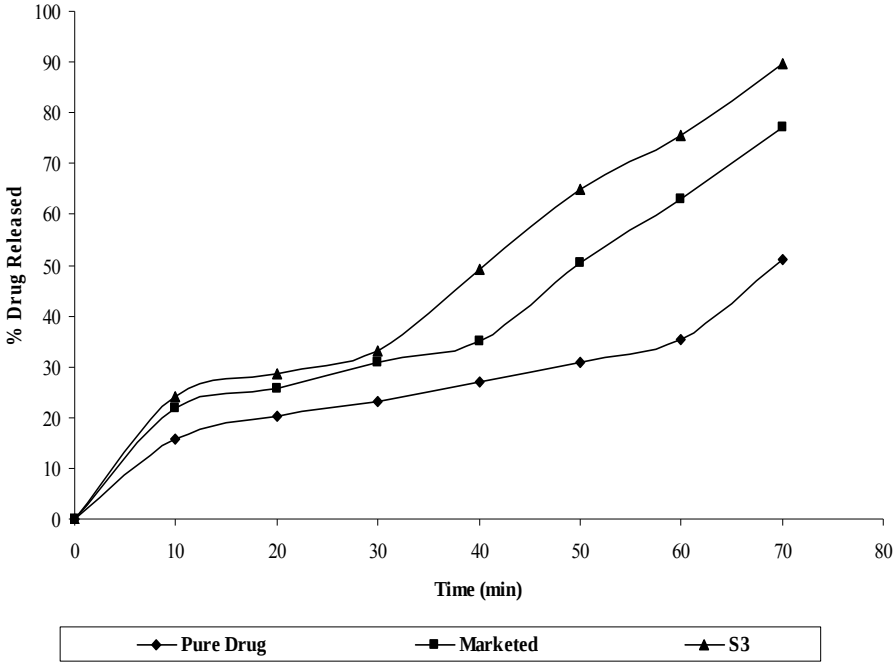

Figure 3: Dissolution profile of Pure Atorvastatin Calcium, Marketed tablet and Solid dispersion (S3)

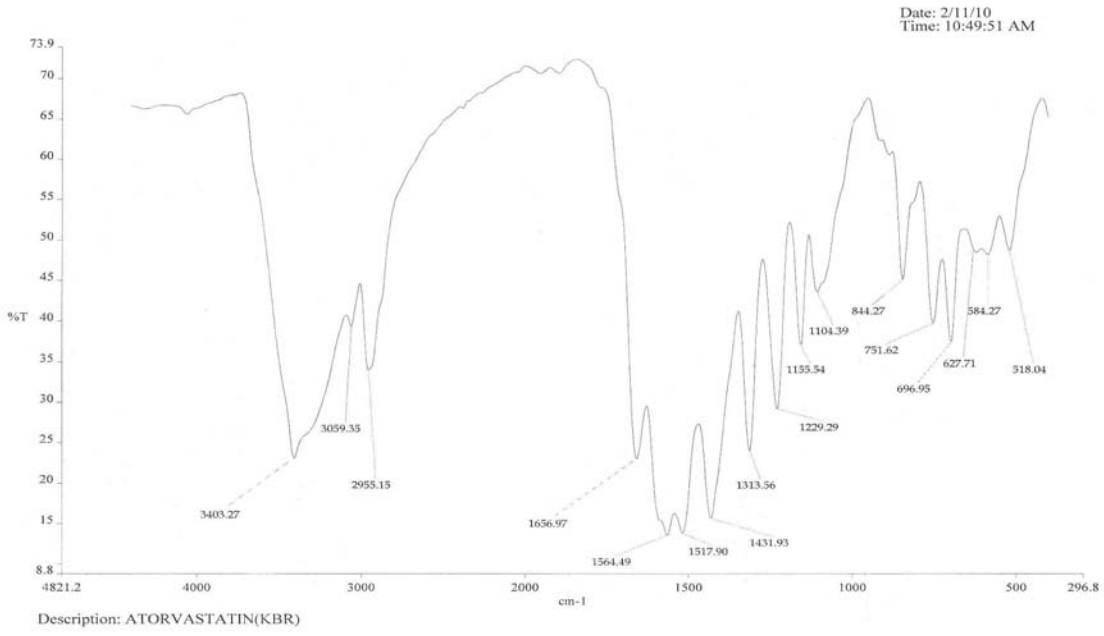

Figure 4: FTIR Spectra of Atorvastatin Calcium

The mean percentage of drugs for physical mixture after 70 minutes was 64.01%, 75.35%, 82.39% for 1:1, 1:2, 1:3 respectively as shown in Figure 1 and 51.01%, 77.22% for pure drug and marketed tablet. But in the dropping method half fold increase in release rate was observed as 78.78%, 84.63% and 89.65% respectively as shown Figure 2 (This may be due to impact of complexation and bond formation.

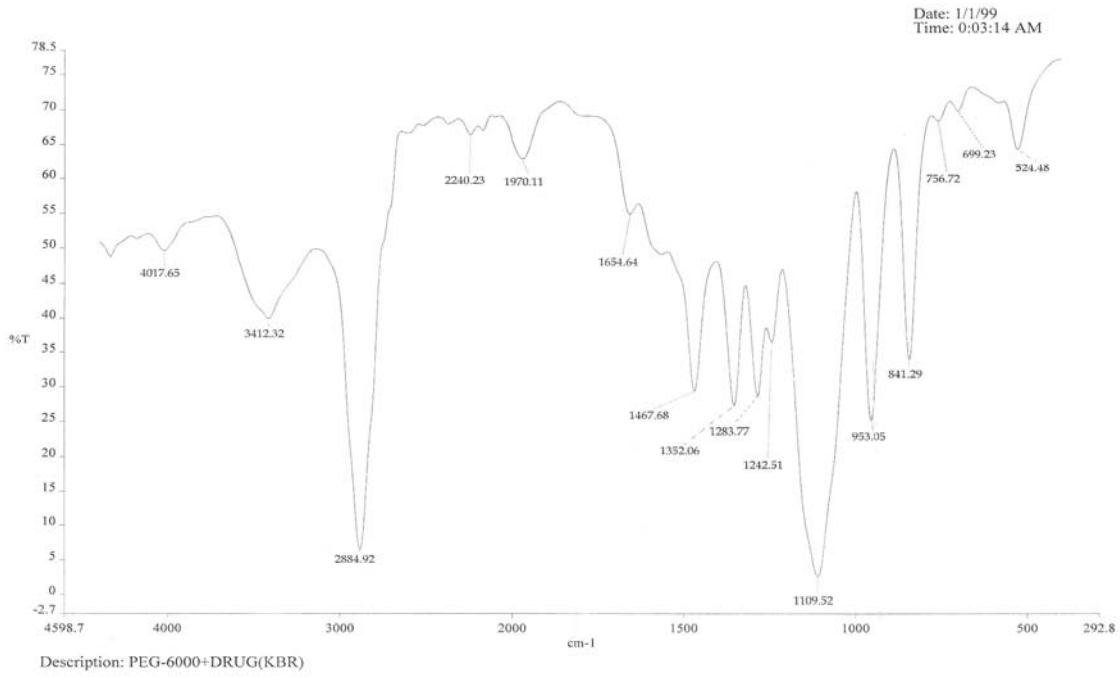

Figure 5: FTIR Spectra of Atorvastatin Calcium & PEG-6000 Mixture

This may lead improved solubility by reducing particle size).The drug release from all the formulations followed zero order kinetics, as the plot observed in between amount of drug released Vs time was found to be linear. 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 kinetics & 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 0.4756 to 0.5895 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 80.58% 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-6000 content enhanced the drug release.

Spectroscopy studies:

The IR spectra of pure ATC and solid dispersions are shown in Figures 4 & 5. The 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-6000. These observations indicated the compatibility of PEG-6000 with ATC.

Conclusion:

The prepared solid dispersions were extended to various characterizations. FTIR shows there was no degradation of

drug. The solubility and dissolution studies showed there is a possibility of improved solubility of Atorvastatin Calcium through solid dispersion with Poly ethylene glycol 6000. A maximum increase in dissolution rate was obtained with Atorvastatin Calcium: PEG 6000 solid dispersion with a weight ratio of 1:3 (drug: carrier). PEG 6000 dispersion by dropping method showed faster dissolution rate when compared with that of pure drug and physical mixtures. Finally it could be concluded that solid dispersion by dropping method for Atorvastatin Calcium using hydrophilic polymers would improved the aqueous solubility, dissolution rate and thereby enhancing its systemic availability.

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