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# Enhancement of dissolution rate of atorvastatin calcium using solid dispersions by dropping method

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**Abstract:** The objective of the present investigation was to study the effect of polyethylene glycol 4000 (PEG 4000) and polyethylene glycol 6000 (PEG 6000) on *in vitro* dissolution of Atorvastatin Calcium (ATC) from solid dispersions. Initial studies were carried out using physical mixtures of the drug and carrier. Solid dispersions were prepared by the dropping method. Atorvastatin was formulated as physical mixtures and solid dispersions (dropping method) using 1:1, 1:2 and 1:3 ratios of drug and carriers (PEG 4000 & PEG 6000). Saturation solubility study for pure drug, physical mixtures and solid dispersions were carried out in water and pH 6.8 phosphate buffer solutions (PBS). The *In vitro* dissolution studies were carried in pH 6.8, higher *in vitro* dissolution of solid dispersions was recorded compared to their corresponding physical mixtures and the pure drug. The prepared solid dispersions showed marked increase in the saturation solubility and dissolution rate of Atorvastatin than that of pure drug. PEG 6000 in 1: 3 drug to carrier ratio exhibited the highest drug release (89.65%) followed by PEG 4000 (80.03%) in the same ratio formulated as solid dispersions using 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.
**Key words:** solid dispersions, Atorvastatin calcium, dropping method and PEG-4000 & 6000.

## Introduction:

Atorvastatin Calcium (ATC) is an Anti-hyper lipidemic agent and is used in the treatment of obesity and is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol[1].

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[2]. Poorly water-soluble drugs show unpredictable absorption, since their bioavailability depends upon dissolution in the gastrointestinal tract[3, 4, 5]. The dissolution characteristics of poorly soluble drugs can be enhanced by several methods[6, 7, 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. 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 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[14] techniques.

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[15], which is advantageous for the manufacture of solid dispersions. ATC was chosen as a model candidate because of its low dissolution rate and solubility-limited bioavailability.

## Materials and Methods

### Materials

Atorvastatin Calcium (ATC) was a gift sample from Dr.Reddy's laboratory, Hyderabad, poly ethylene glycol 4000 and 6000 were 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 (1:1, 1:2 and 1:3) with PEG 4000 and PEG 6000 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, F3, F4, F5 and F6 formulations were shown in **table no: 1.**

### Preparation of Solid Dispersion by Dropping Method:

For the preparation of the ATC solid dispersions prepared by dropping method, containing different weight ratios of ATC in PEG 4000 and PEG 6000. The composition of S1, S2, S3, S4, S5 and S6 formulations was shown in **table no: 1**. The PEG was melted in a porcelain dish at 58 $^0$C (±1$^0$C) and a measured amount of ATC 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

### Phase solubility studies:

Phase and saturation solubility studies were performed according to the method described by Higuchi and Connors[16].The saturation solubility of drug and SDs with PEG 4000 (1:1, 1:2 and 1:3 w/w) and PEG 6000 (1:1, 1:2 and 1:3 w/w) in distilled water and phosphate buffer (pH 6.8) were 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 UV spectrophotometer at 245nm, Elico SL-150, India.

### FT-IR Spectroscopy:

Fourier transmitted Infrared (FT-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.

**Table: 1 Composition of ATC Physical Mixtures and Solid Dispersions**

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | S1 | S2 | S3 | S4 | S5 | S6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ATC | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 |
| PEG-4000 | 80 | 160 | 240 | - | - | - | 80 | 160 | 240 | - | - | - |
| PEG-6000 | - | - | - | 80 | 160 | 240 | - | - | - | 80 | 160 | 240 |

**Drug content estimation[17]:**
The drug content in each solid dispersions 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* drug dissolution studies:**
Dissolution rate studies were performed in pH 6.8 phosphate buffer at 37 ± 0.5 $^0$C, using 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 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) [18]. 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[19].

## Results and Discussion:

The drug content in physical mixtures, solid dispersions with PEG 4000 and PEG 6000 as reported in **table: 2** were found to be in the range of 96.2% to 99.6%. Therefore, dropping method used in this study appears applicable for the preparation of solid dispersions without affecting drug content.

The mechanisms responsible for improved drug dissolution may be drug/ carrier interactions in solid state or drug/carrier interactions in liquid state or both. When the physical mixture is added to the dissolution medium, it may simply happen that the carrier, which dissolves first, modifies the hydrophilicity/lipophilicity or wettability of the drug or it may form a weak complex with the drug at the particle surface, resulting in drug dissolution. An increase in the saturation solubility of the drug can explain the improved dissolution of solid dispersions as per the Noyes and Whitney equation[20], since the saturation solubility of a compound is dependent on the size of the particles. Since it is possible to achieve reduction in particle size with a solid dispersion system, the saturation solubility studies were performed with these systems. The results on saturation solubility indicated that the solubility was enhanced by 35 % compared to atorvastatin calcium.

**Table: 2 Solubility studies and drug content for 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 | 96.75±0.012 |
| F-2 | 46.87 ± 1.24 | 72.76 ± 1.21 | 97.87±0.025 |
| F-3 | 57.79 ± 1.35 | 81.89 ± 2.35 | 98.69±0.022 |
| F-4 | 35.59 ± 1.12 | 63.78 ± 1.19 | 98.54±0.031 |
| F-5 | 46.87 ± 1.24 | 72.76 ± 1.21 | 97.25±0.053 |
| F-6 | 57.79 ± 1.35 | 81.89 ± 2.35 | 99.25±0.043 |
| S-1 | 36.22 ± 1.05 | 65.12 ± 1.13 | 97.24±0.021 |
| S-2 | 48.86 ± 1.87 | 73.52 ± 1.15 | 98.35±0.013 |
| S-3 | 58.92 ± 1.46 | 83.42 ± 1.76 | 98.77±0.026 |
| S-4 | 38.52 ± 1.15 | 67.96 ± 1.27 | 99.42±0.041 |
| S-5 | 47.83 ± 1.45 | 74.67 ± 1.41 | 96.20±0.036 |
| S-6 | 59.56 ± 1.39 | 95.72 ± 1.48 | 99.60±0.023 |

**Figure: 1 Comparison of Release Profiles Using PEG-4000&6000 by Physical Mixtures with Pure Drug**

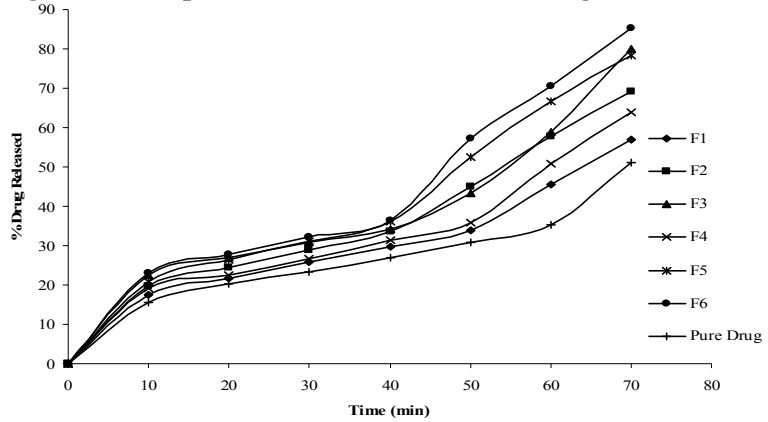
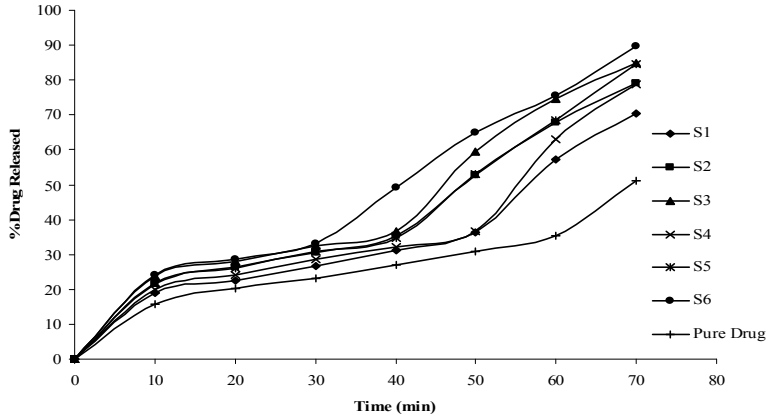



**Figure: 2 Comparison of Release Profiles Using PEG-4000 & 6000 by solid dispersions with Pure Drug**




**Solubility Studies:**

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 polymer was observed and the prepared formulation with PEG 6000 1:3 presented higher dissolution concentration as compared with the other formulations obtained with different ratios (1:1 and 1:2). Maximum solubility in Phosphate buffer solution was observed in dropping method 1:3 (Drug: PEG 6000) ratio 95.72 ± 1.48 µg/mL, when compared with that of pure ATC (57.06 ± 0.67 µg/mL).

***In Vitro* drug release:**

The dissolution profiles of ATC for solid dispersion and physical mixture performed in 6.8 phosphate buffer were studied. The comparative cumulative release of ATC at various time intervals from the physical mixtures and solid dispersions made by using various concentrations of PEG 4000 and PEG 6000 are shown in **Figure: 1&2.** Dissolution of the pure drug, ATC, in PBS (pH 6.8) was only 51.06 %. Prepared physical mixtures and solid dispersions showed improvement in dissolution characteristics. In the first 30 minutes, physical mixtures of PEG 4000 (1:1, 1:2 and 1:3) showed 25.86, 28.97 and 30.71 % drug release 26.70, 30.57 and 32.44 % drug release from solid dispersions (1:1, 1:2 and 1:3). In the first 30 minutes, physical mixtures of PEG 6000 (1:1, 1:2 and 1:3) showed 26.70, 30.19 and 32.11% drug release 28.48, 32.71 and 34.97 % drug release from solid dispersions (1:1, 1:2 and 1:3). After 60 min, physical mixtures with PEG 4000 showed 45.50, 57.64 and 58.89 % drug release, whereas solid dispersions with PEG 4000 showed 57.34, 66.76 and 73.55 % and PEG 6000 showed 63.13, 69.64 and 77.63 % drug release, respectively.

Dissolution of the pure drug was found to be 35.26 % in 60 minutes. Almost half of the drug was dissolved from physical mixtures and solid dispersions in the first 30 minutes. After 60 min, solid dispersions with PEG 4000 (1:3) showed 58.89 % release whereas maximum release was obtained with PEG 6000 (1:3) and was 77.63%.

Possible mechanisms of increased dissolution rates of solid dispersions have been proposed by

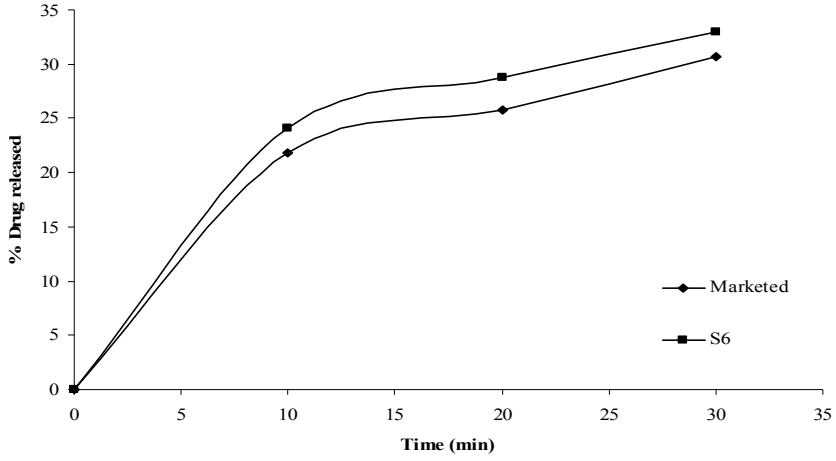
Ford[21]. A reduction of crystallite size, solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of the drug from the dispersion, dissolution of the drug in the hydrophilic carrier, drug conversion to amorphous state and finally, a combination of the mentioned mechanisms. The increased dissolution rate in these cases can thus be attributed to several factors, such as the solubilization effect of the carrier, conversion to amorphous state, and improved wettability of atorvastatin calcium. In general, dissolution may be described by two processes: the rate of the interfacial or solid solvent reaction leading to solubilization of the molecule, and the rate associated with the diffusional or transport process of the solvated molecule to the bulk part of the dissolution medium. Water readily forms hydrogen bonds with the polar groups such as OH present in PEG 4000 and PEG 6000 and the $-CH_3$ and C=0 groups in atorvastatin calcium. The strength of bonds between water and PEG and water and drug molecules may be stronger than or comparable with that between the molecules of the solid dispersions[22]. Upon contact, water molecules solvate the polymers and atorvastatin molecules, either in the crystalline or in amorphous form, and break the hydrogen bonds in the drug-carrier complexes.

**Table: 3 Dissolution Kinetics of ATC Physical Mixtures and Solid Dispersions Formulated With PEG-4000 & 6000**

| 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 | 0.469 | 18.51 | 25.49 |
| F2 | 0.9526 | 0.9257 | 0.9281 | 0.9185 | 0.9558 | 0.523 | 20.83 | 30.48 |
| F3 | 0.9638 | 0.8790 | 0.8956 | 0.8815 | 0.9068 | 0.483 | 23.22 | 31.77 |
| F4 | 0.9209 | 0.9176 | 0.9154 | 0.9052 | 0.9261 | 0.475 | 19.60 | 26.95 |
| F5 | 0.9543 | 0.9359 | 0.9235 | 0.9209 | 0.9556 | 0.560 | 22.50 | 34.13 |
| F6 | 0.9693 | 0.9123 | 0.9146 | 0.9029 | 0.9424 | 0.550 | 23.91 | 36.30 |
| S1 | 0.9420 | 0.9110 | 0.8951 | 0.8949 | 0.9285 | 0.530 | 19.51 | 28.09 |
| S2 | 0.9530 | 0.9180 | 0.9035 | 0.8991 | 0.9391 | 0.553 | 22.48 | 33.58 |
| S3 | 0.9587 | 0.9157 | 0.9105 | 0.8983 | 0.9428 | 0.555 | 24.36 | 37.05 |
| S4 | 0.9320 | 0.8770 | 0.8744 | 0.8783 | 0.9043 | 0.535 | 20.91 | 29.78 |
| S5 | 0.9483 | 0.8886 | 0.8905 | 0.8832 | 0.9209 | 0.549 | 22.68 | 33.67 |
| S6 | 0.9714 | 0.9212 | 0.9250 | 0.9149 | 0.9553 | 0.589 | 24.72 | 40.19 |

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

**Figure: 3 *In-vitro* Release Profiles of Atorvastatin Calcium Solid Dispersion (S6) And Marketed Tablet (Lipitor)**



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. The corresponding release rate constant values were shown in **table: 3**. 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: 3**. The slope values (n) obtained to decline Between 0.469 to 0.589 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 (S6) and marketed tablet (**Lipitor**).The above results indicated that the increasing concentration of PEG-6000 content enhanced the drug release. The release kinetics of ATC prepared from different methods of solid dispersions was observed and tabulated.

**Figure: 4 FT-IR Spectra of Atorvastatin Calcium**

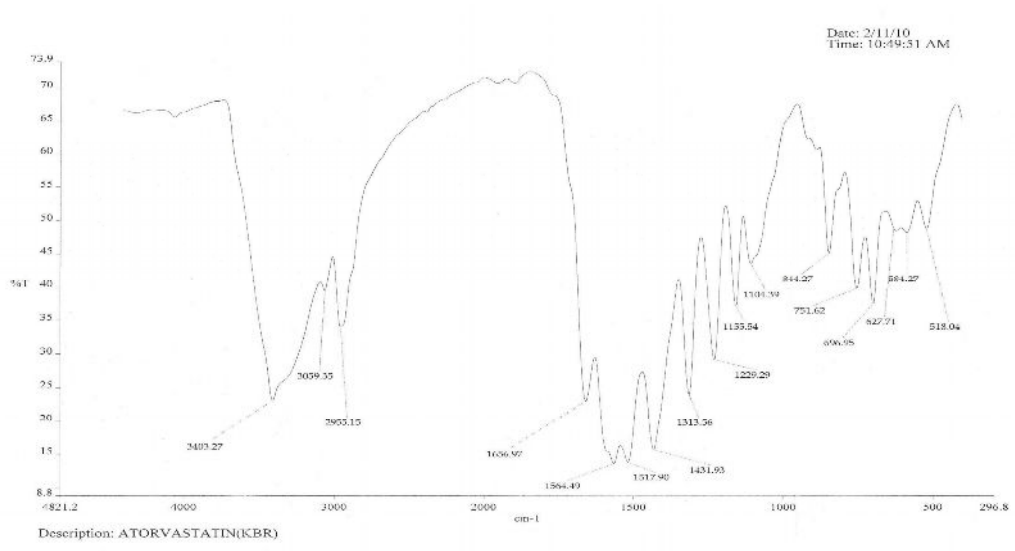



**Figure: 5 FTIR Spectra of ATC& PEG-4000 Mixture**

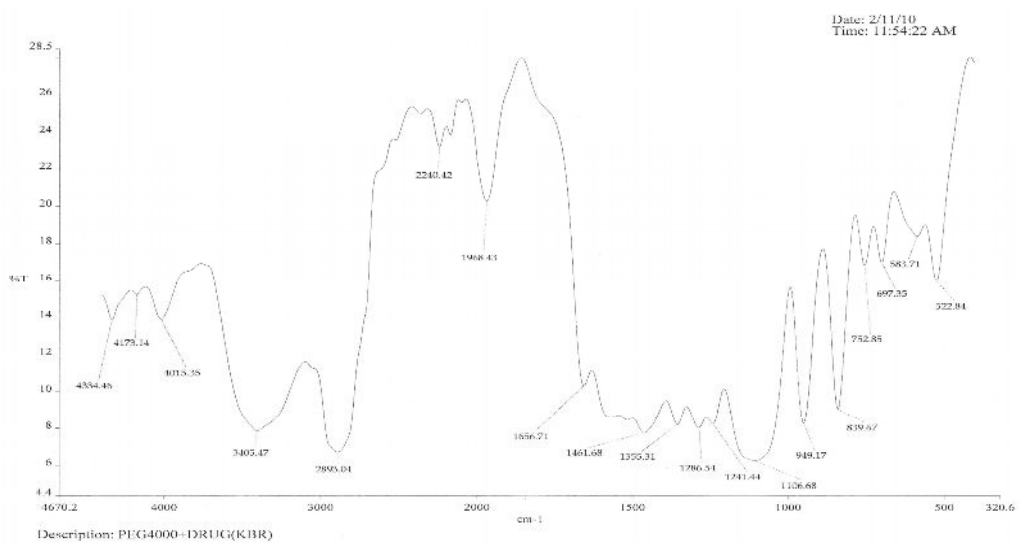
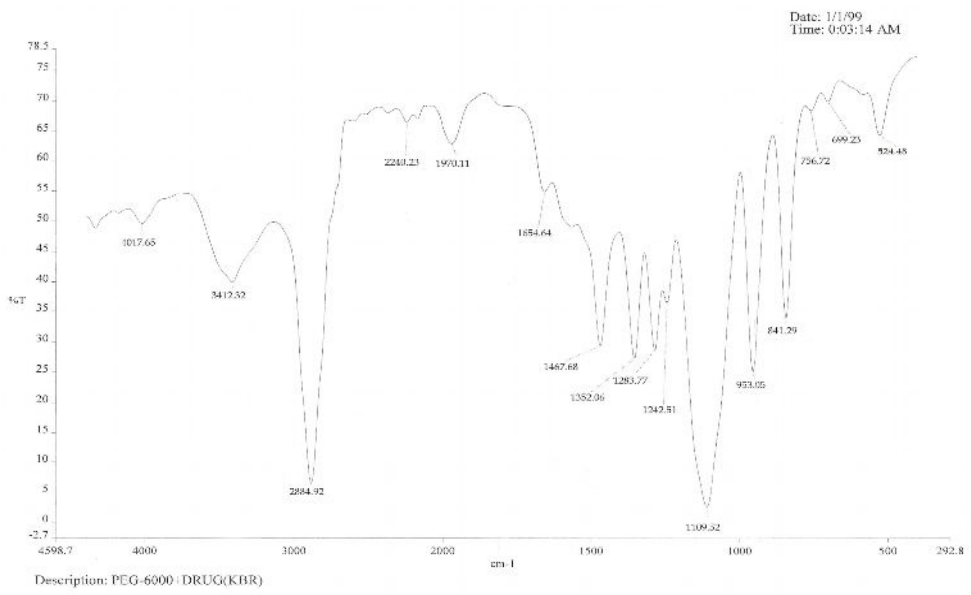


**Figure: 6 FTIR Spectra of ATC& PEG-6000 Mixture**




**Spectroscopy studies:**

The IR spectra of pure ATC and solid dispersions are shown in **Figures 4, 5, & 6**. 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-4000 and PEG-6000. These observations indicated the compatibility of PEG-4000 and PEG- 6000 with ATC.

## Conclusion:

The prepared solid dispersions were extended to various characterizations. The solubility and dissolution studies showed there is a possibility of improved solubility of ATC through solid dispersion with Poly ethylene glycol 6000 than with Polyethylene glycol 4000. The dissolution rate of ATC from solid dispersions with PEG 6000 improved to more than 38.63 % compared to the pure drug. Further, all the solid dispersions performed better than the corresponding physical mixtures. Also, the saturation solubility of the drug when formulated into solid dispersion with the polymer was higher than that of phase solubility achieved in the presence of the polymer (physical mixture). IR spectra indicated no well-defined interaction between the drug and polymer. A maximum increase in dissolution rate was obtained with Atorvastatin Calcium: PEG 6000 solid dispersion with a weight ratio of 1:3. PEG 6000 dispersion by dropping method showed faster dissolution rate when compared with that of PEG 4000 and pure drug.

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