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Research Article

FORMULATION AND EVALUATION OF SOLID DISPERSION OF ATORVASTATIN CALCIUM

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ABSTRACT
The present study was designed to improve the solubility and hence enhance the dissolution of hydrophobic drug Atorvastatin calcium (ATC) in order to increase its bioavailability. Solid dispersion of atorvastatin calcium using carrier PEG 4000 was formulated in different ratios by conventional fusion and microwave induced fusion method. In particular, the Microwave technology has been considered in order to prepare an enhanced release dosage form for poorly water soluble drug ATC. Their physicochemical characteristics and dissolution properties were compared to the corresponding dispersions and pure drug. Three different formulations were prepared using Conventional fusion method and Microwave induced fusion method in different ratios i.e., 1:1, 1:2, 1:3 and 1:1, 1:2, 1:3 respectively, were further characterized by FTIR, DSC and SEM analysis. The results of FTIR revealed that no chemical interaction between the drug and the polymer exist. DSC studies showed that the drug was in amorphous state completely entrapped by the polymer. SEM studies showed the surface morphology of the solid dispersion. All the formulations showed a marked increase in drug release with the increase in the concentration of PEG 4000 when tested for their *in vitro* studies. Formulation T5 showed the best release with a cumulative release of 86.15 % in 30 minutes, when compared to the pure drug and marketed formulation. The microwave assisted method was found to be better than conventional fusion method for preparation of solid dispersion.
Keywords: Atorvastatin Calcium (ATC), solid dispersion, Fusion Method, Microwave Irradiation Method, Polyethylene Glycol (PEG) 4000.

INTRODUCTION

The enhancement of the bioavailability of poorly water soluble drugs is one of the greatest challenges of drug development. Amongst them is the dispersion of the drug into an inert, hydrophilic polymer matrix[1]. There is general consensus in the pharmaceutical industry that poorly water-soluble drug candidates are becoming more prevalent. If a drug candidate has reasonable membrane permeability then often the rate-limiting process of absorption is the drug dissolution step. This is characteristic of compounds which can be categorized as biopharmaceutical classification system (BCS) class II.[2] Drugs in this class are expected to have a variable dissolution profile due to the formulation and *in vivo* variables that, in turn, affect the absorption.[3] The aqueous solubility lesser than 1 µg/ml will definitely creating a bioavailability problem affecting the efficacy of a drug. Poorly water-soluble drugs show unpredictable absorption, since their bioavailability depends upon dissolution in the gastrointestinal tract. 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.[4] Several techniques are commonly used to improve dissolution and bioavailability of poorly water-soluble drugs, such as size reduction, the use of surfactants, the formation of solid dispersions and the transformation of crystalline drug to amorphous state.[5] Among the physical modifications, the preparation of solid dispersions has become one of the most active areas of research in the pharmaceutical field with a view to improve the bioavailability of poorly soluble drugs. Sekiguchi and Obi (1961) developed a method to enhance the bioavailability of poorly water-soluble drugs, which was later termed solid dispersion.[6] 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. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid and excess drug precipitates as fine colloidal particles or oily globules of submicron size.[7] Recently a novel approach based on the use of microwave irradiation has been proposed for the preparation of SD. Microwaves irradiation (MW) is a well-known method for heating and drying materials. Microwaves, with their ability to penetrate any substance, allow the production of heat in any point of the sample at the same time. This is due to the presence in it of molecules characterized by a dipolar moment able to absorb microwave energy and convert it into heat. This phenomenon occurs when the microwave frequency is close to the resonance frequency of the polar molecules. The efficient heating of materials by microwaves depends on the capacity of a specific material to absorb microwave energy. Microwave energy has been employed to change the crystalline state of a drug, instead of conventional heating.[8] In this study drug-carrier systems were prepared by MW irradiation using Atorvastatin calcium as a model drug (Class II) in the presence of PEG 4000 as carrier. Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase and is commonly used as atorvastatin calcium. Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)- b,d-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. Atorvastatin calcium is a white to off white crystalline powder that is insoluble in aqueous solutions of pH 4 and below, which are the conditions typically present in the stomach of a subject. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol and freely soluble in

methanol. Atorvastatin is rapidly absorbed after oral administration, with time to reach peak concentrations (Tmax) within 1– 2 h. The fraction absorbed (%) and absolute bioavailability of atorvastatin are approximately 30 % and 12 %, respectively. The low systemic availability is attributed to pre systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.[9] Our research aimed to improve the bioavailability of atorvastatin calcium by modification of its solid state properties using conventional fusion and microwave induced fusion methods. Their physicochemical properties in the solid state were characterized by powder X-ray diffraction (XRD), Fourier transform infrared (FT-IR) Spectroscopy, Differential scanning calorimetry (DSC), Scanning electron microscopy (SEM), Solubility and dissolution and were also performed to compare the physicochemical and absorption properties of pure drug and amorphous form (fusion induced processed drug).

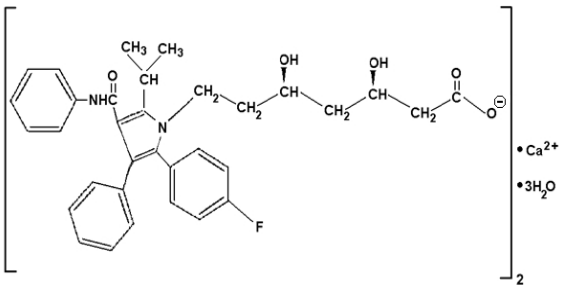

Figure 1: Structure of Atorvastatin Calcium

Biopharmaceutical Classification System

The BCS was first devised in 1995 by Amidon *et al* and since then it has become a benchmark in the regulation of bioequivalence of oral drug products. The BCS serves as a guiding tool to improve the efficiency of drug development by proper selection of dosage form and bioequivalence tests, to recommend a class of immediate release (IR) solid dosage forms, for which bioequivalence may be assessed based on *in vitro* dissolution tests and to lay the effect of excipients on drug permeability[10].

Class I: High permeability and solubility
Formulation independent

The bioavailability of class I compounds is determined only by delivery of the drug solution to the intestine. Examples: Benzapril, Loxoprofen, Sumatriptan etc.

Class II: High permeability but low solubility
Formulation dependent

The bioavailability of class II compounds is limited by drug solubility/dissolution. Examples: Valsartan, Nimesulide, Loratadine, Aceclofenac etc.

Class III: Low permeability but high solubility
Dependent on barrier properties

The bioavailability of class III compounds is limited by intestinal permeability. Examples: Gabapentine, Topiramate, Atropine etc.

Class IV: Low permeability and low solubility
Formulation and barrier properties dependent

The bioavailability of class IV compounds is limited both by solubility/dissolution and intestinal permeability. Examples: Hydrochlorthiazide, Furosemide, Meloxicam etc[11].

Need of Solubility Enhancement

According to recent estimates, nearly 40 % of new chemical entities are rejected because of poor solubility i.e. biopharmaceutical properties. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.

Bioavailability

It is measurement of the extent of therapeutically active drug that reaches systemic circulation and is available at the site of action. It is one of the essential tools in pharmacokinetics, as bioavailability must be considered when calculating dosages for non intravenous routes of administration. Poor aqueous solubility is caused by two main factors

1. High lipophilicity and
2. Strong intermolecular interactions which make the solubilization of the solid energetically costly.

Solubility of active pharmaceutical ingredients (APIs) has always been a concern for formulators, since inadequate aqueous solubility may reduce development of products and limit bioavailability of oral products. Solubility plays an essential role in drug disposition, since the maximum rate of passive drug transport across a biological membrane, the main pathway for drug absorption, is the product of permeability and solubility. Among the five key physicochemical screens in early compound screening, pKa, solubility, permeability, stability and lipophilicity, poor solubility tops of the list of undesirable compound properties. Compounds with insufficient solubility carry a higher risk of failure during discovery and development since insufficient solubility may compromise other properties, influence both pharmacokinetic and pharmacodynamic properties of the compound, and finally may affect the ability of the compound to develop as API. Currently only 8 % of new drug candidates have both high solubility and permeability[12].

MATERIALS AND METHODS

Materials

Atorastatin Calcium was obtained as a gift sample from Cipla Pharmaceuticals ltd. Baddi Distt. Solan (HP), India while PEG 4000, Sodium starch glycollate, lactose, talc, magnesium stearate and all the other chemicals used were of pharmaceutical grade.

Methods

Solid dispersions were prepared by Fusion Method and Microwave irradiation induced fusion method in three different ratios. Atorvastatin Calcium and Polyethylene glycol 4000 were weighed according to different weighed ratios.

Conventional Fusion Method

The solid dispersions were obtained by the conventional fusion method. PEG 4000 was heated to a molten mass at 55

– 60°C and to this a weighed amount of ATC was added with continuous stirring until dissolution. Solidification was allowed to occur at room temperature. The product was stored in a dessicator for 24 h and then pulverized using a porcelain mortar and pestle. The pulverized powders were passed through an 80# sieve.

Microwave Induced Fusion Method

Solid dispersions with different ratios of ATC and PEG 4000 were prepared using the microwave induced fusion method. The finalized ratio was found to be 1: 2 w/w. First, ATC and PEG 4000 were weighed in a ratio of 1: 2 w/w followed by gentle mixing for 5 minutes using a mortar and pestle. A fixed amount of this mixture was subjected to microwaves for different times such as 5, 6 and 7 minutes at a constant chosen power of 590 W in a microwave instrument. Only one beaker at a time was placed inside the microwave. The samples were exposed in the microwave for a predetermined time interval. The beaker was then placed at room temperature for solidification. Solid dispersions were collected and stored in the dessicator for 24 h and then the product was pulverized using a mortar and pestle. The pulverized powders were passed through an 80# sieve[13].

Solubility Studies

Solubility studies were performed according to the method described by Higuchi and Connors. The saturation solubility of drug and SDs with PEG 4000 (1:1, 1:2 and 1:3 w/w) in 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 48 h at 37^0C ± 0.5^0C. 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 241.5 nm.

Fourier Transform Infrared Spectroscopy (FTIR)

The KBr discs of Atorvastatin, PEG 4000 and finalized solid dispersion were prepared using electrically operated KBr Press Model SHIMADZU FTIR-5300 Fourier transform spectrophotometer was used to record IR spectra of the prepared discs, to confirm any interaction of Atorvastatin with other excipients of dispersion[14].

Differential Scanning Calorimetry (DSC)

Atorvastatin, PEG 4000, physical mixtures and solid dispersions were examined by a differential scanning calorimeter at a heating rate of 10°C/min from 30°C to 300°C in nitrogen atmosphere.

Scanning Electron Microscopy (SEM)

The Solid dispersion was examined by Scanning electron microscope to investigate the surface morphology and homogeneity of the particles. The samples of finalized formulation were sputter-coated with gold at room temperature before examination to render the surface of particles electro-conductive. The scanning range was 450 to 4,000 cm−1 and the resolution was 1 cm^{-1}.

***In vitro* Release Studies**

Drug release profile of complexes were obtained by USP II dissolution apparatus using Phosphate buffer pH 6.8 (900 ml) as dissolution medium at 75 rpm (37 ± 0.5°C). The samples were withdrawn at fixed interval, filtered (pore size 0.22 µm), diluted suitably with dissolution medium and analyzed for ATC content spectrophotometrically at 241.5 nm[15].

Formulation Studies

Tablets containing complexes (equivalent to 10 mg ATC) prepared by Fusion method and Microwave method were formulated using various excipients and evaluated for various pre-compression studies. The blend was compressed on rotary press tablet machine using concave shape, 150 mg punch. Further subjected to various post compression studies. Drug release profile from tablets was determined using 6.8 pH buffers as dissolution medium at 75 rpm (37 ± 0.5°C).

RESULT AND DISCUSSIONS

Method of Preparation

Fusion Method

In this method the polymer was melted at over a thermostatically controlled hot plate at its respective melting point and the drug was incorporated into the molten carrier mass in three different ratios 1:1, 1:2, 1:3. The blend was heated at the corresponding temperature for 5 minutes, followed by flash cooling on an ice bath. The solid dispersions thus obtained, were dried in oven at 30°C to remove moisture if present. The dried solid dispersion was pulverized through 80'mesh sieve and stored in the dessicator for further use. The cooled granules were stored in sealed bags for their evaluation. The prepared samples were compared for their solubility and dissolution rate. The dispersions obtained were tacky. (Table 1)

Microwave Irradiation Fusion Method

Solid dispersions with different ratios of ATC and PEG 4000 were prepared using the microwave irradiation fusion method. First, ATC and PEG 4000 were weighed in a ratio of 1:1, 1:2, 1:3 w/w followed by gentle mixing for 5 minutes using a mortar and pestle. A fixed amount of these mixtures were subjected to microwaves for 5 minutes, 6 minutes, 7 minutes at a constant chosen power of 590 W in a microwave instrument. Only one beaker at a time was placed inside the microwave. The samples were exposed in the microwave for a predetermined time interval. The beakers were then placed at room temperature for solidification. Solid dispersions were collected and stored in a dessicator for 24 h and then the product was pulverized using a mortar and pestle. The pulverized powders were passed through a 80# sieve. (Table 2)

Solubility Studies

Solubility studies were performed according to the method described by Higuchi and Connors. 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 Phosphate buffer in conical flask and were rotated in a orbital shaking incubator for 48 h at 37 ^{0}C ± 0.5^0C. The saturated solutions were filtered through a 0.45 µm membrane filter, suitably diluted with water, phosphate buffer and analyzed by UV spectrophotometer at 241.5 nm. (Table 3, 4)

IR Spectroscopy

The FT-IR spectrum of Atorvastatin Calcium is shown in Figure 2. IR spectra of pure Atorvastatin Calcium reveal the presence of peak at 3365 indicates the presence of n-H stretching, presence of peak at 3272 indicate that presence of

asymmetric O-H stretching and peak at 3056 cm^{-1} indicates presence of symmetric O-H stretching in sample specimen., FT-IR spectra verified the purity and authenticity of the procured sample. IR Spectra of pure drug and solid dispersion of Atorvastatin Calcium with PEG 4000 prepared by fusion method and microwave induced fusion method. From the FTIR study it was found that some of the peaks of the drugs were shifted broadened, some present with reduced intensity and some vanished. This was referred to formation of a complex between the drug and carrier. Complexation was leading to formation of an amorphous form of drug with PEG 4000 by solid dispersion leading to improve the dissolution rate of drug. (Figure 2-5)

Differential Scanning Calorimetry (DSC)

A frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC) (Kerc and Srcic, 1995). In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. The thermal behaviour of solid dispersion of ATC-PEG complex was studied using DSC in order to confirm the formation of complex. DSC thermogram of ATC-PEG and inclusion complexes is shown in (Figure 6-9). The DSC thermogram of ATC showed an endothermic peak at 156.80 ^{o} C corresponding to its melting point. The DSC thermogram of solid dispersion of ATC-PEG Complex showed endothermic peak at different temperature by different method of preparation, which is different from the pure drug, which gives clear evidence that there is formation of the complex. (Figure 6-9)

X-Ray Diffraction Studies (XRD)

The analytical tools such as X-ray diffractometry are usually employed in the pharmaceutical field to characterize the solid drug substance. The powder X-ray diffraction is used for detection of crystalline phases in mixed system. However, too much crystallinity causes brittleness. The crystallinity parts give sharp narrow diffraction peaks and the amorphous component gives a very broad peak. Amount of crystallinity in the material can be calculated by the ratios between these intensities. The X-RD pattern (Figure 10-13) of pure drug presented several diffraction peaks at $2\theta = 17.0750$, 21.5875 and 19.4395 indicating the crystalline nature of the drug. The XRD of solid diapersion of ATC-PEG 4000 exhibited crystallinity with reduced intensity when compared with that of Atorvastatin Calcium. In Figure 12 and 13 the Atorvastatin Calcium peaks with reduced peak height area were observed, the diffractrograms of solid dispersions are super imposable with the X-ray diffractrograms of pure PEG 4000, indicating reduced crystallinity of Atorvastatin Calcium. Some major peaks displayed in XRD pattern of pure Atorvastatin Calcium disappeared in XRD pattern of ATC-PEG 4000 solid dispersion indicating existence of amorphous solid state of Atorvastatin Calcium in the solid dispersion of ATC-PEG 4000. (Figure 10-13)

Scanning Electron Microscopy

SEM images of Atorvastatin Calcium, PEG 4000 and solid dispersions are shown in Figure (14-17) respectively. The parent Atorvastatin Calcium crystals were in the form of rod shaped or irregular crystals, which is in confirmation with the earlier report. This rod shaped form of Atorvastatin Calcium leads to very poor flow and compressional difficulties. In case of solid dispersions it was difficult to distinguish the presence of Atorvastatin Calcium crystals. Atorvastatin Calcium crystals appeared to be incorporated into particles of the PEG 4000. (Figure 14-17)

***In Vitro* Dissolution Study**

The *in vitro* release profile of Atorvastatin Calcium and all solid dispersions ATC 1, ATC 2, ATC 3, ATC 4, ATC 5 and ATC 6 are shown in Table 5 and 6. Figure 18 and 19 showed the comparison of cumulative percent drug released versus time. In all the cases, cumulative percent released was much greater than pure Atorvastatin Calcium. Figure 18 and 19 showed the dissolution rate of ATC solid dispersion with polymer (PEG 4000). The dissolution rates were enhanced with increasing concentration of polymer. Higher dissolution rates were shown by the solid dispersions of drug with PEG 4000 as compared to the pure drug. By comparing the solid dispersions, the better dissolution profile was shown by microwave induced fusion method as compared to the solid dispersions prepared with fusion methods. (Table 5 and 6, Figure 18 and 19)

Dissolution Efficiency

Dissolution efficiency of pure Atorvastatin Calcium and solid dispersions prepared with ATC and PEG 4000 by two methods at 10 minutes were calculated which is shown in Table 7. ATC 5 formulation showed maximum dissolution efficiency at 10 minutes. With this we can say that formulation prepared by microwave method (1:2) is best formulation. (Table 7, Figure 20)

Preparation of Tablet

The solid dispersion of ATC-PEG was formulated into tablet by direct compression method equivalent to 10 mg dose. The all excipients were passed through sieve # 60. All the above ingredients were properly mixed together. Talc and magnesium stearate were mixed. The mixture was then compressed in to tablet by using rotary single punch tablet machine. The formulation of tablet is shown in (Table 8). The formulations were developed by using different conventional technologies. The formulations given in the Table T1, T2 and T3 were prepared from solid dispersion prepared by fusion method. The formulations T4, T5 and T6 were prepared by solid dispersion prepared from Microwave irradiation method. (Table 8)

Evaluation of Tablet

General Appearance

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance and tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet Thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Table 1: Compositions of S.D containing ATC and PEG 4000 with Fusion method

Formulation code	Drug : carrier ratio
ATC 1	1:1
ATC 2	1:2
ATC 3	1:3

Table 2: Composition of S.D containing ATC and PEG 4000 with Microwave irradiation Fusion method

Formulation code	Drug : carrier ratio
ATC 4	1:1
ATC 5	1:2
ATC 6	1:3

Table 3: Solubility of S.D with Fusion method

Formulation code	Solubility (µg/ml)
ATC 1	395 ± 1.732
ATC 2	458 ± 2.88
ATC 3	368 ± 1.154

Data are expressed as mean ± S.D. (n = 3)

Table 4: Solubility of S.D with microwave induced Fusion method

Formulation code	Solubility (µg/ml)
ATC 4	412 ± 1.154
ATC 5	528 ± 1.732
ATC 6	483 ± 1.732

Data are expressed as mean ± S.D. (n = 3)

Table 5: Dissolution profile of pure ATC and PEG 4000 with Fusion method

Time (min)	Pure Drug	ATC 1	ATC 2	ATC 3
5	2.29 ± 0.122	20.16 ± 0.405	26.91 ± 0.405	27.42 ± 0.464
10	8.06 ± 0.032	25.21 ± 0.691	52.51 ± 0.465	32.17 ± 0.777
15	15.96 ± 0.137	36.08 ± 0.656	55.70 ± 0.577	44.70 ± 0.748
20	21.97 ± 0.185	44.74 ± 0.327	59.29 ± 0.537	51.08 ± 0.428
25	24.81 ± 0.127	48.83 ± 0.321	60.85 ± 0.700	54.72 ± 1.832
30	28.14 ± 0.121	51.17 ± 0.445	63.18 ± 0.854	57.14 ± 2.051

Data are expressed as mean ± S.D. (n = 3)

Table 6: Dissolution profile of pure ATC and PEG 4000 with Microwave induced fusion method

Time (min)	Pure Drug	ATC 3	ATC 4	ATC 5
5	2.29 ± 0.122	24.33 ± 0.395	52.26 ± 0.460	44.29 ± 0.892
10	8.06 ± 0.0.032	40.53 ± 0.330	67.69 ± 0.328	54.27 ± 0.975
15	15.96 ± 0.137	48.44 ± 0.435	70.79 ± 0.535	68.27 ± 0.572
20	21.97 ± 0.185	56.18 ± 0.325	75.84 ± 0.431	73.99 ± 0.445
25	24.81 ± 0.127	61.52 ± 0.435	82.16 ± 0.461	79.83 ± 0.233
30	28.14 ± 0.121	64.23 ± 0.440	84.75 ± 0.334	82.29 ± 1.334

Data are expressed as mean ± S.D. (n = 3)

Table 7: Dissolution efficiency of solid dispersions prepared by different methods

Formulation code	% DE_{10}
Pure ATC	3.408 ± 0.248
ATC 1	18.17 ± 0.379
ATC 2	29.50 ± 0.308
ATC 3	23.98 ± 0.513
ATC 4	24.13 ± 0.253
ATC 5	47.79 ± 0.230
ATC 6	40.08 ± 0.977

Data are expressed as mean ± S.D. (n = 3)

Table 8: Composition of Finalized solid dispersion tablets

Ingredients	T1	T2	T3	T4	T5	T6
SD 1:2	30	30	30	30	30	30
MCC	60	60	60	60	60	60
SSG	3	6	9	3	6	9
Mannitol	53	50	47	53	50	47
Talc	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2

Table 9: Weight Variation in tablets

Average Weight of Tablet	% Deviation
80 mg or less	± 10
80 mg to 250 mg	± 7.5
250 mg or more	± 5

Table 10: Characterization of selected solid dispersion tablets

Formulation code	Thickness (mm)	Hardness ($kg/cm^{2)}$	Weight variation (mg)	Friability (%)	Disintegration time (sec)
T1	2.83 ± 0.011	3.23 ± 0.152	146 ± 1.52	0.53	12
T2	2.85 ± 0.023	2.93 ± 0.152	150 ± 1.52	0.54	9
T3	2.75 ± 0.015	3.0 ± 1.0	146 ± 1.52	0.62	8
T4	2.82 ± 0.017	2.73 ± 0.057	153 ± 1.0	0.50	15
T5	2.56 ± 0.011	2.23 ± 0.152	144 ± 2.51	0.57	8
T6	2.70 ± 0.020	2.76 ± 0.152	151 ± 0.152	0.62	7

Data are expressed as mean ± S.D. (n = 3)

Table 11: Dissolution profile of Atorvastatin Calcium from marketed tablet and selected solid dispersion tablets

Cumulative Mean Percent Released ± S.D.			
Time	**Marketed Formulation**	**T2**	**T5**
5	24.48 ± 0.138	27.13 ± 0.206	53.59 ± 0.138
10	33.67 ± 0.286	53.74 ± 0.138	68.4 ± 0.24
15	40.83 ± 0.206	56.12 ± 0.095	71.13 ± 0.138
20	44.70 ± 0.201	57.21 ± 0.206	77.44 ± 0.138
25	46.46 ± 0.201	58.76 ± 0.236	82.81 ± 0.138
30	51.69 ± 0.206	61.22 ± 0.144	86.15 ± 0.236

Table 12: Comparison of Drug Release Data before and after Storage

Time (Minutes)	T5 (Before Storage)	T5 (After Storage)
5	53.59 ± 0.138	52.7 ± 0.241
10	68.4 ± 0.240	67.47 ± 0.206
15	71.13 ± 0.001	70.23 ± 0.127
20	77.44 ± 0.138	77.37 ± 0.118
25	82.81 ± 0.138	81.83 ± 0.215
30	86.15 ± 0.2360	84.37 ± 0.245

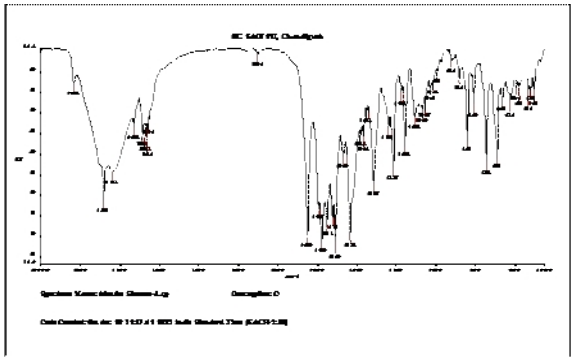

Figure 2: FTIR Spectrum of ATC

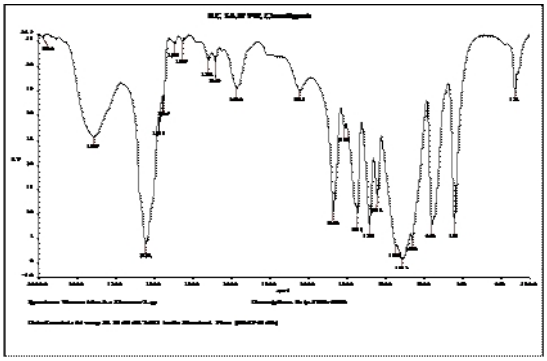

Figure 3: FTIR Spectrum of PEG 4000

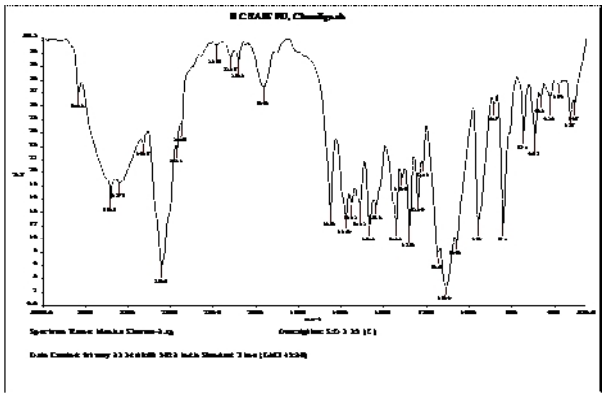

Figure 4: ATC: PEG 4000 (1:2) with Fusion method

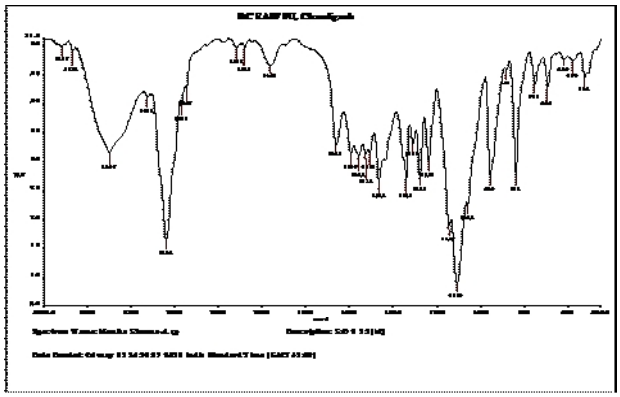

Figure 5: ATC: PEG 4000 (1:2) with Microwave induced fusion method

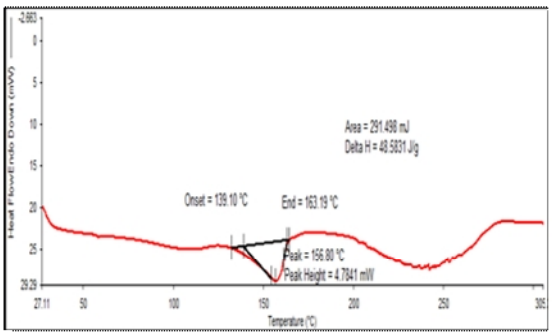

Figure 6: DSC of ATC

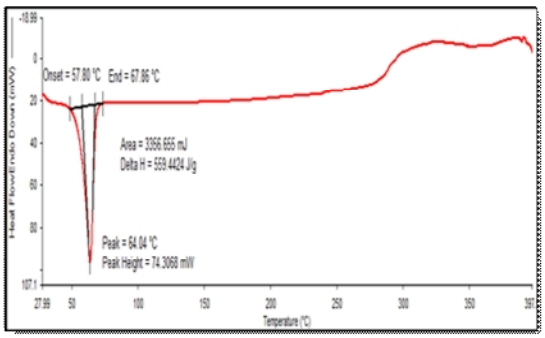

Figure 7: DSC of PEG 4000

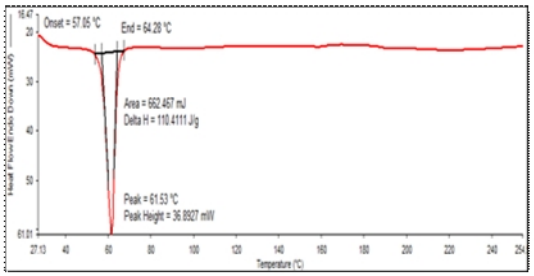

Figure 8: DSC of Fusion method

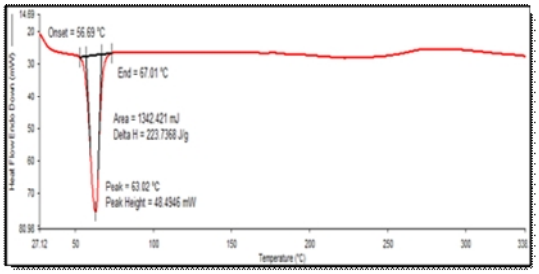

Figure 9: DSC of Microwave method

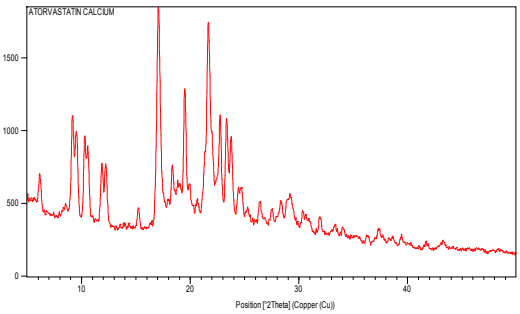

Figure 10: XRD of ATC

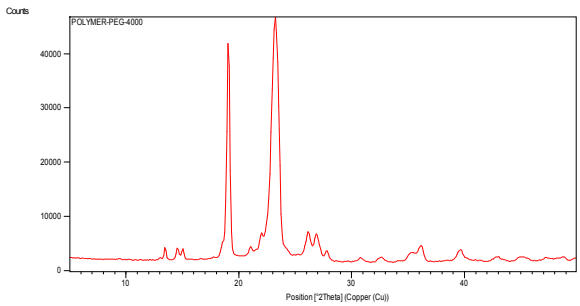

Figure 11: XRD of PEG 4000

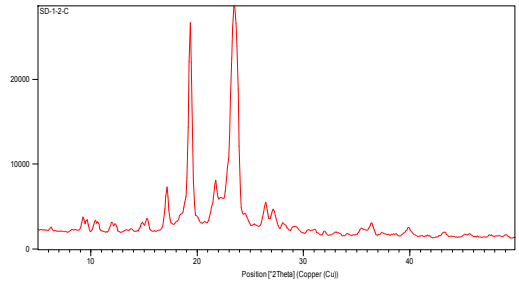

Figure 12: XRD of Fusion method

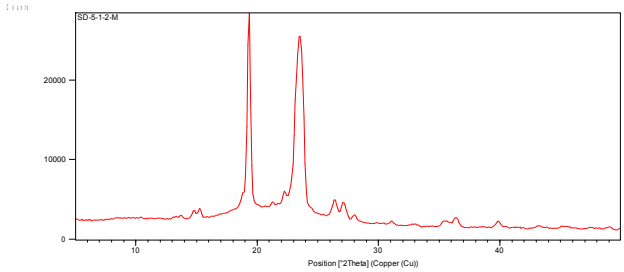

Figure 13: XRD of Microwave method

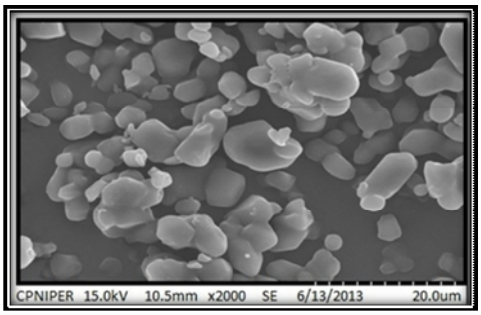

Figure 14: SEM of ATC

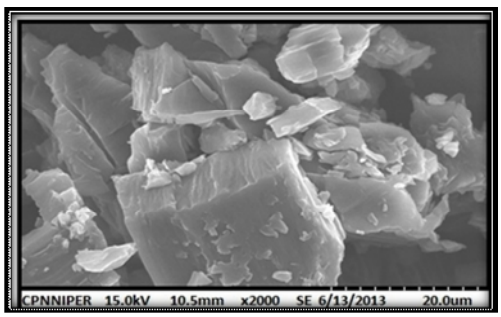

Figure 15: SEM of PEG 4000

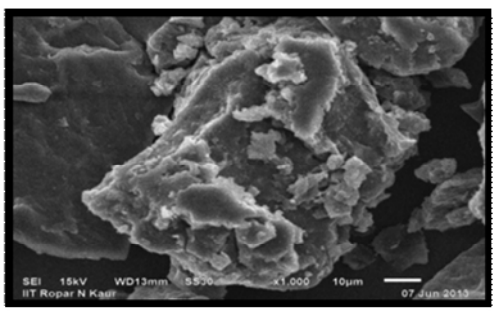

Figure 16: SEM of S.D of Fusion method

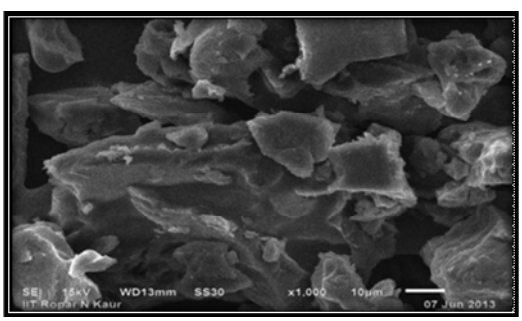

Figure 17: SEM of S.D of Microwave method

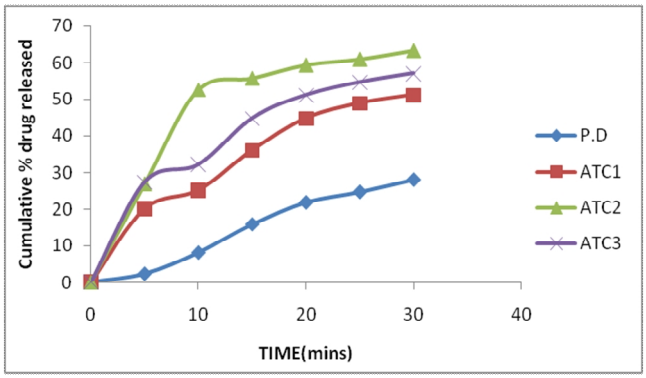

Figure 18: *In vitro* dissolution profile of ATC and PEG 4000 with Fusion method

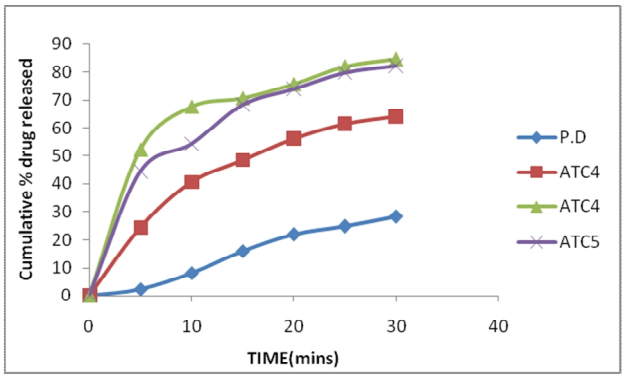

Figure 19: *In vitro* dissolution profile of ATC and PEG 4000 with Microwave Fusion method

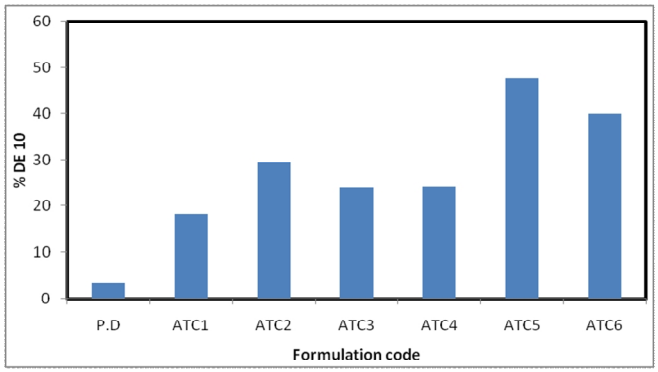

Figure 20: Comparison of % DE_{10} of different formulations

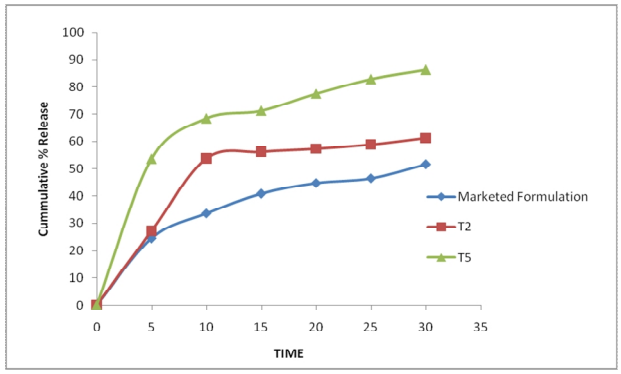

Figure 21: Dissolution profile of Atorvastatin Calcium from marketed tablet and best formulation (T2, T5)

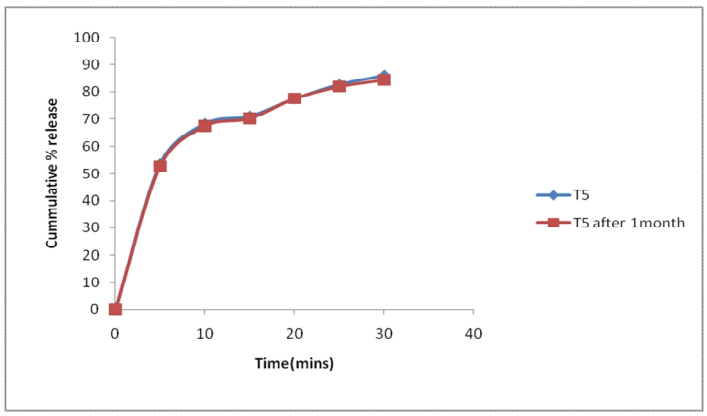

Figure 22: Comparison of Drug Release Data before and after Storage

Weight Variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in Table 9.

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

Friability (F)

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre –weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. The friability (F) is given by the formula[16]. (Table 10)

$$F = \frac{W_{initial} - W_{final}}{W_{initial}}$$

Where, W initial – Weight of tablets before friability,
W final – Weight of tablets after friability

Hardness, % friability, weight variation and Thickness of tablet are given in (Table 10). The hardness of tablet was in the range 2.5-3.1 kg/ cm^2. The percent weight loss in the friability test was less than 1 %.

***In Vitro* dissolution study**

In-vitro drug release rates from different tablets prepared from two selected solid dispersions and marketed formulation were determined in 900 ml of pH 6.8 phosphate buffer at 37°C with a stirrer rotation speed of 75 rev/min using the USP dissolution test apparatus with a paddle stirrer (method II). A 5-ml sample of dissolution medium was withdrawn at 5, 10, 15, 20, 25, 30, minutes using a cannula and syringe. The samples were suitably diluted and assayed spectrophotometrically at 241.5 nm. Each dissolution rate test was repeated three times. Comparison between two selected prepared formulation and marketed formulation is given below in Table 11 and Figure 21. From all the batches i.e. T1, T2, T3, T4, T5 and T6, T2 and T5 shows maximum release. Those were selected and compared with marketed formulation.

Stability Studies

From the above batches ATC 5(T5) showed maximum dissolution properties. The tablets of Batch ATC 5(T5) were packed in Polythene pouch and charged for accelerated stability studies at 40°C in a humidity chamber having 75 % RH. Samples were withdrawn after 1 month interval. The drug dissolution profile of exposed sample was carried out. The results of accelerated stability studies are shown in Table 12 and Figure 22.

There was no significant variation in the *in vitro* drug release profile over a period of one month as shown in Figure 22. The similarity factor was calculated for comparison of the dissolution profile before and after stability studies. The f_2 value was found to be more than 50 (~ 80.30) which indicated a close similarity between both the dissolution profiles. Hence, the results of the stability studies confirmed that the developed formulation is very stable which can be seen in Figure 22.

CONCLUSION

Atorvastatin calcium exhibits high permeability through biological membranes, but its absorption after oral administration is limited by its low dissolution rate due to its very low aqueous solubility. Hence, the use of the Fusion technique was chosen to enhance the dissolution properties of ATC. The ATC solid dispersions were prepared using PEG 4000 as the carrier. XRD studies of SD of ATC showed complete inhibition of crystallinity in the ATC solid dispersion by Fusion method and Microwave fusion method. It is transformed into an amorphous form which has the highest energy and solubility. The DSC study confirmed the absence of any interaction between the drug and excipients used in the preparation of ATC solid dispersions. The hardness, friability, weight variation and disintegration tests were within acceptable limit. The *in vitro* dissolution study confirmed enhanced drug release from formulation prepared by Microwave Irradiation method. It was observed that aging had no significant effect on the hardness, disintegration time and dissolution profile of the ATC tablets.

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