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Microwave induced solubility enhancement of poorly water soluble atorvastatin calcium

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Abstract

Objectives The objective of the present investigation was to enhance the solubility and dissolution rate of atorvastatin calcium (ATR) by a solid dispersion technique using poly-(ethylene glycol) 6000 (PEG 6000).

Methods Microwave energy was used to prepare an enhanced release dosage form of the poorly water soluble drug ATR with PEG 6000 as a hydrophilic carrier. After the microwave treatment, the drug and hydrophilic polymer get fused together to form a solid dispersion. An in-vivo study was performed to determine the lipid-lowering efficacy (cholesterol, high density lipoprotein and triglyceride) of the solid dispersions using a Triton-induced hypercholesterolemia model in rats.

Key findings An increase in the solubility of ATR was observed with increasing concentration of PEG 6000. The optimized ratio for preparation of solid dispersions of ATR with PEG 6000 was 1 : 12 w/w by conventional fusion and the microwave induced fusion method. Differential scanning calorimetry and powder X-ray diffraction studies of the solid dispersions confirmed the conversion of some crystalline ATR into the amorphous form. Scanning electron microscopy images also showed conversion of some crystalline ATR into the amorphous form. The in-vitro study showed that solid dispersions increased the solubility and dissolution rate of ATR, and thus may improve its bioavailability compared with plain ATR. The solid dispersion formulation prepared by the microwave induced fusion method significantly ($P < 0.05$) reduced serum lipid levels in phases I and II (18 h and 24 h) of the Triton test compared with plain ATR.

Conclusions The microwave induced fusion method could be considered as a simple, efficient method to prepare solid dispersions of ATR with significant enhancement of the in-vitro dissolution rate as well as in-vivo activity.

Keywords atorvastatin calcium; bioavailability; microwave induced fusion; solid dispersions; solubility enhancement

Introduction

The solubility behaviour of drugs remains one of the most challenging aspects of formulation development.[1,2] In fact, most new chemical entities are poorly water soluble drugs, not well absorbed after oral administration.[3] Similarly, most promising new chemical entities, despite their high permeability, are generally only absorbed in the upper small intestine, absorption being significantly reduced after the ileum. Thus, there is a small absorption window,[4] and if these drugs are not completely released in this gastrointestinal area, they will have low bioavailability. Therefore, one of the major challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability.[5,6] By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side-effects. Solid dispersions are a very successful approach to improving drug release and oral bioavailability of poorly water soluble drugs.[7] These can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties.[8,9] By reducing the particle size of the drug to almost the molecular level, locally increasing the saturation solubility, the drug wettability, bioavailability may be significantly improved. The conversion of drug from the crystalline to the amorphous state

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is mainly achieved by two different methods: melting and solvent evaporation.[10,11]

The fusion method is also referred to as the melt method and is most suitable for crystalline materials.[12] In this method, materials are melted using a physical mixture at the eutectic composition followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. Poly(ethylene glycol) (PEG) is a hydrophilic polymer often used to prepare solid dispersions with the fusion method. PEG has been used extensively to improve the dissolution and bioavailability of drugs.[13,14]

A novel approach based on the use of microwave irradiation has become a recognized method for heating and drying materials.[15] Microwave equipment uses electromagnetic waves between the infrared and radio frequencies over the range of 0.3–300 GHz that pass through material and cause the molecules to oscillate, generating heat. During conventional heating, the surface of the material heats first and then the heat moves inward. Microwave heating generates heat inside the material and heats the entire volume at about the same rate. 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 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 through microwaves depends on the capacity of a specific material to absorb microwave energy. Recently, the use of microwaves has become very attractive in organic chemistry. In fact, compared with conventional heating (i.e. conduction, convention or radiation with infrared light) microwave irradiation offers several advantages such as rapid volumetric heating, no overheating at the surface, addressable heating, energy saving and low operating cost.[16]

Microwave energy has been used to change the crystalline state of a drug instead of conventional heating. It has been reported that microwave energy can influence the crystalline status of the drug and the time of exposure plays an important role in achieving the amorphous state of the drug, thus improving its dissolution rate.[16] The application of microwaves represents a promising alternative to conventional preparative methods of solid dispersions of drugs as the microwave induced method involves much shorter preparation times.[16]

In this study, microwave irradiation was applied for the preparation of solid dispersions of the poorly water soluble drug atorvastatin calcium (ATR). ATR, a synthetic lipid-lowering agent, is an inhibitor of 3-hydroxy-glutarly-coenzyme A (HMG-CoA) reductase, which catalyses the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis.[17] As ATR belongs to BCS class II, its intestinal permeability is high at the physiologically relevant intestinal pH. It is reported that the oral bioavailability of ATR is 14%.[18] ATR is insoluble in aqueous solution of pH 4 and below, it is very slightly soluble in water and pH 7.4 phosphate buffer. In this study, we investigated the effect of using microwave energy to enhance the solubility, dissolution rate and bioavailability of the poorly water soluble ATR.

Materials and Methods

Materials

ATR and PEG 6000 were obtained as gift samples from Ind-Swift Ltd (New Delhi, India) and Unitop Chemicals Pvt Ltd (Mumbai, India) respectively. All other materials used were of analytical reagent grade.

Preparation of solid dispersions

Physical mixture

The physical mixture of ATR and PEG 6000 was prepared simply by mixing using a mortar and pestle in different ratios such as 1 : 1, 1 : 3, 1 : 6, 1 : 9 and 1 : 12 w/w. Ratio optimization was carried out by a solubility determination method.

Conventional fusion method

The solid dispersions were obtained by the conventional fusion method. PEG 6000 was heated to a molten mass at 55–60°C and to this a weighed amount of ATR 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 ATR and PEG 6000 were prepared using the microwave induced fusion method. The optimized ratio was found to be 1 : 6 w/w. First, ATR and PEG 6000 were weighed in a ratio of 1 : 6 w/w followed by gentle mixing for 5 min using a mortar and pestle. A fixed amount of this mixture (2 g) was subjected to microwaves for different times such as 3, 4, 5 and 6 min at a constant chosen power of 590 W in a microwave instrument (CATA-2R, Catalyst Systems, Pune, India). 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.

Characterization of solid dispersions

Solubility study

The solubility of ATR, physical mixture and solid dispersions prepared by the conventional fusion method and microwave induced fusion method was determined in pH 6.8 phosphate buffer at 37 ± 0.5°C. For each preparation, an equivalent of 10 mg of drug was added to 10 ml of buffer in glass vials with caps. The vials were kept on a glass shaker incubator maintained at 37 ± 0.5°C for 24 h. After that the solution was filtered through a 0.45-μm Millipore filter and the filtrate was analysed using a UV spectrophotometer (UV-1700; Shimadzu, Tokyo, Japan) at 241 nm.[19]

In-vitro drug release study

In-vitro drug release rates from different solid dispersions 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 (TDT-08L; Electrolab, Mumbai, India) with a paddle stirrer (method II). A 5-ml sample of dissolution medium was withdrawn at 5, 10, 15, 30, 45, 60, 90, 105 and 120 min using a cannula and syringe. The samples were suitably diluted and assayed spectrophoyometrically at 241 nm. Each dissolution rate test was repeated three times.[20]

Fourier transform infrared spectroscopy

Fourier transform infrared (FTIR) spectra of ATR, PEG 6000, physical mixture and solid dispersions prepared by the microwave induced fusion method were obtained on a FTIR-8400S (Shimadzu) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 450–4000 cm^{-1} and the resolution was 1 cm^{-1}.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) curves of ATR, PEG 6000, physical mixture and solid dispersions prepared by the microwave induced fusion method were obtained using a DSC-60 (Shimadzu) at a heating rate of 10°C/min from 30 to 450°C in a nitrogen atmosphere.

Powder X-ray diffraction

Powder X-ray diffraction patterns of ATR, PEG 6000, physical mixture and solid dispersions prepared by the microwave induced fusion method were recorded using a diffractometer (PW 1140; Mettler Toledo, Columbus, OH, US) and Cu-kα radiation. The diffractometer was run at a scanning speed of 2°/min and a chart speed of 2°/2 cm per 2θ.

Scanning electron microscopy

Scanning electron microscopy photographs of ATR and solid dispersions prepared by the microwave induced fusion method were obtained using a scanning electron microscope (JSM 6390; JEOL, Peabody, MA, US) with a 10-kV accelerating voltage.

In-vivo evaluation of solid dispersions

The animal experiment was carried out in full compliance with the protocol approved by institutional animal ethical committee (registration no. 651/02/C/CPCSEA under the Committee for the Purpose of Control and Supervision of Experiments on Animals, India). The in-vivo study was carried out according to a previously reported method.[21] Male Wistar rats, 150–200 g, were divided into four groups of six animals. The animals were maintained at 22 ± 3°C and 30–70% relative humidity. The rats were fasted overnight and then intraperitoneally injected with 250 mg/kg Triton WR 1339 (isooctyl-polyoxyethylene phenol) (tyloxapol; Sigma Chemical Co, St Louis, MO, US) dissolved in 0.9% saline. Control groups of rats were given the vehicle (saline solution) and experimental groups were given plain ATR (25 mg/kg bodyweight) and the solid dispersion formulation (equivalent to 25 mg/kg atorvastatin). The rats were restrained by hand and the oral dosing was performed without anaesthesia by intubation using an 18-gauge feeding needle (the volume fed was 1.0 ml in all cases). Blood samples were withdrawn at 18 and 24 h. Serum was separated by centrifugation at 16 770 g/min and was used for biochemical analysis. Serum cholesterol, triglycerides and high density lipoprotein (HDL) were estimated in control, Triton, plain drug and solid dispersion formulation groups by reported methods.[21] Statistical analysis of the collected data was performed using non-parametric one-way analysis of variance (Kruskal-Wallis test followed by Dunn's-test) to evaluate the individual differences between the treatment groups.

Results

Characterization of solid dispersions

Solubility study

Solubility data for ATR, physical mixture and solid dispersions prepared by the conventional fusion method and microwave induced fusion method are given in Table 1. Solubility data showed that PEG 6000 significantly ($P < 0.05$) enhanced the solubility of ATR from solid dispersions prepared by the microwave induced fusion method when compared with plain ATR. Ratio optimization data are shown in Table 2 and suggest significant enhancement of solubility in the case of the 1 : 12 ratio of ATR to PEG 6000. Although significant solubility enhancement was observed in the case of the 1 : 12 ratio, the 1 : 6 ratio of ATR to PEG 6000 was considered for further study as there were insignificant differences in the solubility enhancement when the 1 : 6 ratio was compared with the 1 : 12 ratio. This also decreased the amount of polymer to be used.

In-vitro release study

Figure 1 shows the in-vitro dissolution profiles of ATR and solid dispersions prepared by the conventional fusion method and the microwave induced fusion method. Statistical tests such as the Kruskal-Wallis test followed by Dunn's test were employed to check individual differences in dissolution rate in different groups at each time point. The results of the statistical analysis suggest significant enhancement of dissolution

Table 1 Solubility study of atorvaststin calcium, physical mixture and solid dispersions

Product	Solubility (μg/ml)
Atorvaststin calcium	0.2952 ± 0.014
Physical mixture	0.4238 ± 0.003
Solid dispersions: conventional fusion method	0.5970 ± 0.019
Solid dispersions: MW 6 min	0.8858 ± 0.004*

Solid dispersions prepared by the microwave (MW) induced fusion method had an exposure time of 6 min. $n = 3$. *Significant.

Table 2 Ratio optimization of atorvastatin calcium and poly(ethylene glycol) 6000

Drug to polymer ratio	Solubility enhancement (fold)
1 : 1	1.01
1 : 3	1.20
1 : 6	1.43
1 : 9	1.46
1 : 12	1.49*

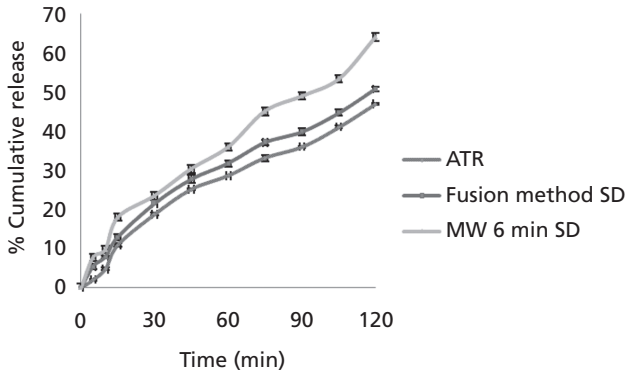


Figure 1 Dissolution profiles of atorvaststin calcium and solid dispersions prepared by conventional fusion and microwave induced fusion methods. ATR, atorvastatin calcium; fusion method SD, solid dispersions prepared by the conventional fusion method; MW 6 min SD, solid dispersions prepared by the microwave induced fusion method with an exposure time of 6 min.

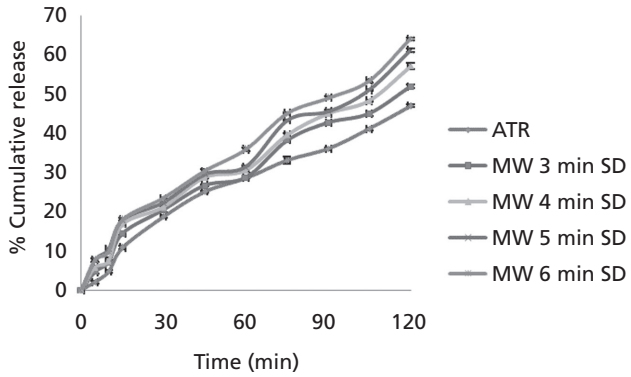


Figure 2 Dissolution profiles of atorvaststin calcium and solid dispersions prepared by the microwave induced fusion method. ATR, atorvastatin calcium. Solid dispersions (SD) were prepared by the microwave (MW) induced fusion method with different exposure times (3, 4, 5 and 6 min).

rate of ATR from solid dispersions prepared by the microwave induced fusion method at all time points ($P < 0.05$) when compared with plain ATR. Figure 2 shows the dissolution profile of ATR and the microwave induced fusion method at different exposure times such as 3, 4, 5 and 6 min, respectively. From the dissolution profile it is evident that the solid dispersions improved the dissolution rate of ATR to a great extent (30% increase in dissolution rate). When the data from Figure 2 are treated in a statistically similar manner as those of Figure 1, a significant enhancement ($P < 0.05$) of the dissolution rate was observed in the case of solid dispersions prepared by the microwave induced fusion method with exposure times of 5 and 6 min when compared with plain ATR. These findings are in agreement with previously reported results by Papadimitriou *et al*,[16] who found the dissolution rate of tibolone to be slightly higher in the case of dispersions prepared by microwave irradiation, possibly due to the smaller size of the tibolone particles in the dispersions prepared by microwave irradiation.

Table 3 Percentage drug release in dissolution efficiency of atorvastatin calcium and solid dispersions

Product	% Release	
	60 min	120 min
Atorvastatin calcium	28.61 ± 0.17	46.97 ± 0.29
Solid dispersions: conventional fusion method	31.72 ± 0.74	50.82 ± 0.61
Solid dispersions: MW 3 min	28.75 ± 0.29	51.90 ± 0.48
Solid dispersions: MW 4 min	30.61 ± 0.78	57.09 ± 0.79
Solid dispersions: MW 5 min	31.46 ± 0.24	61.14 ± 0.50*
Solid dispersions: MW 6 min	35.92 ± 0.42	64.09 ± 0.30*

Solid dispersions prepared by the microwave (MW) induced fusion method had exposure times of 3, 4, 5 or 6 min. $n = 3$. *Significant.

Table 3 summarizes the percentage drug release in dissolution efficiency at 60 and 120 min. Table 3 shows the dissolution profile of ATR and solid dispersions prepared by conventional fusion and the microwave induced fusion method. The microwave induced fusion method showed a significant enhancement in dissolution rate ($P < 0.05$) compared with plain ATR at 60 and 120 min.

Fourier transform infrared spectroscopy

FTIR spectra of ATR, PEG 6000, physical mixture and solid dispersions prepared by the microwave induced fusion method are presented in Figure 3.

Differential scanning calorimetry

The DSC curves of ATR, PEG 6000, physical mixture and solid dispersions prepared by the microwave induced fusion method are shown in Figure 4.

Powder X-ray diffraction

Powder X-ray diffraction spectra of pure ATR, PEG 6000 and solid dispersions prepared by the microwave induced fusion method are presented in Figure 5.

Scanning electron microscopy

The scanning electron microscopy photomicrographs of ATR shown in Figure 6 show the longer crystals with very specific morphology, whereas for solid dispersions prepared by the microwave induced fusion method, a decrease in crystallinity due to molecular dispersion of ATR in the polymer matrix was observed.

In-vivo evaluation of solid dispersions

The in-vivo study was performed to evaluate the pharmacodynamic potential of a developed formulation compared with plain ATR using a Triton induced hyperlipidaemia model; Triton is a nonionic surfactant that induces hyperlipidaemia by inhibiting peripheral lipoprotein lipase enzymes responsible for removal of lipid particles from the body. The administration of Triton leads to transient elevation of lipid levels, which reach a peak at 18 to 24 h after administration (phase I) and start to lower again the following day (phase II). Atorv-

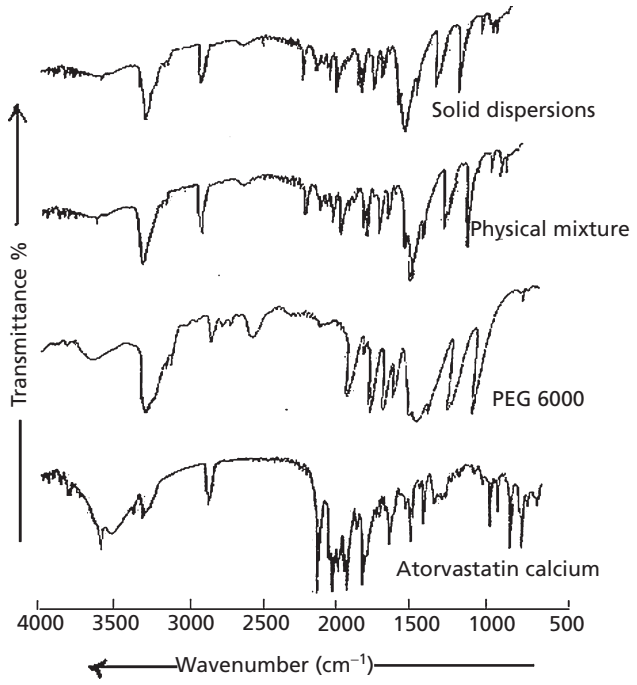


Figure 3 Fourier transformed infrared spectra of atorvastatin calcium, PEG 6000, physical mixture and solid dispersions prepared by the microwave induced fusion method with an exposure time of 6 min.

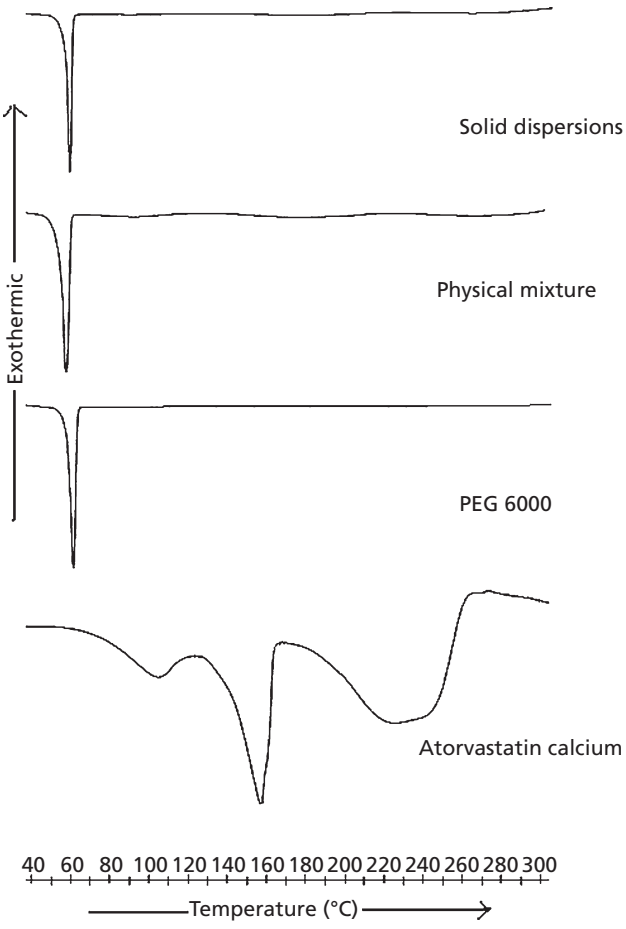


Figure 4 Differential scanning calorimetry curves of atorvastatin, PEG 6000, physical mixture and solid dispersions prepared by the microwave induced fusion method with an exposure time of 6 min.

astatin is a liver selective, competitive inhibiter of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutarly-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. The precise mechanism by which ATR exerts its antihyperlipidaemic effect is by lowering plasma lipids apparently by inhibiting synthesis and also by stimulating the catabolism of triglyceride-rich lipoproteins. ATR and its solid dispersion formulations were found to affect the serum lipid level in both phase I and phase II. Results of the in-vivo evaluation are shown in Table 4. Statistical tests such as Kruskall Wallis and Dunn's test were applied for comparison among various treatment groups and suggest significant enhancement of bioavailabity from solid dispersions prepared by the microwave induced method compared with plain ATR ($P < 0.05$).

Discussion

Optimization of the drug to polymer ratio was done by solubility determination using pH 6.8 phosphate buffer. The ratio optimization results are shown in Table 2. Drug and polymer in the ratio of 1 : 12 significantly enhanced the solubility when compared with the 1 : 1 ratio. However, for further study we used the 1 : 6 ratio as the observed differences in solubility enhancement were not significant between the 1 : 6 and 1 : 12 ratio of ATR to PEG 6000. The dissolution enhancement of ATR from the drug–polymer system can be attributed to a number of factors including loss of crystallinity, that is conversion from the crystalline to amorphous form, increased wettability and dispersibility. Results of the FTIR study showed characteristic peaks of ATR between 3700 and 3000 cm^{-1}, specifically at 3670, 3363, 3254, 3055, 2874, 2360, 1651 and 1577 cm^{-1}. The peak at 3670 cm^{-1} indicated free O-H stretching, which was reduced in terms of intensity or nearly not found in the case of solid dispersions prepared by the microwave induced fusion method, which may be due to molecular dispersion of crystalline ATR in PEG 600. Other peaks at 3363 cm^{-1} (N-H stretching), 3254 cm^{-1} (asymmetrical O-H stretching) and 3055 cm^{-1} (symmetrical O-H stretching) were seen in the ATR spectra. PEG 6000 showed a C-H stretching 2885 cm^{-1}, a C-O stretching 1110 cm^{-1} and an O-H stretching at 3419 cm^{-1}. The above characteristic peaks also appear in the spectra of all physical mixtures at the same wavelength. Thus, from the FTIR study it cannot be concluded that true solid dispersions were achieved.

In the case of the DSC curves, the first small endothermic peak at 100°C was possibly due to the loss of water from trihydrate ATR. The second endothermic peak in the DSC curve at 156.89°C was attributed to ATR corresponding to its melting point. The third broad peak around 220°C to 260°C may be due to degradation product of ATR. PEG 6000 showed a characteristic peak at 61.47°C. The DSC curves of the physical mixture as well as solid dispersion prepared by microwave induced fusion method showed endothermic peaks

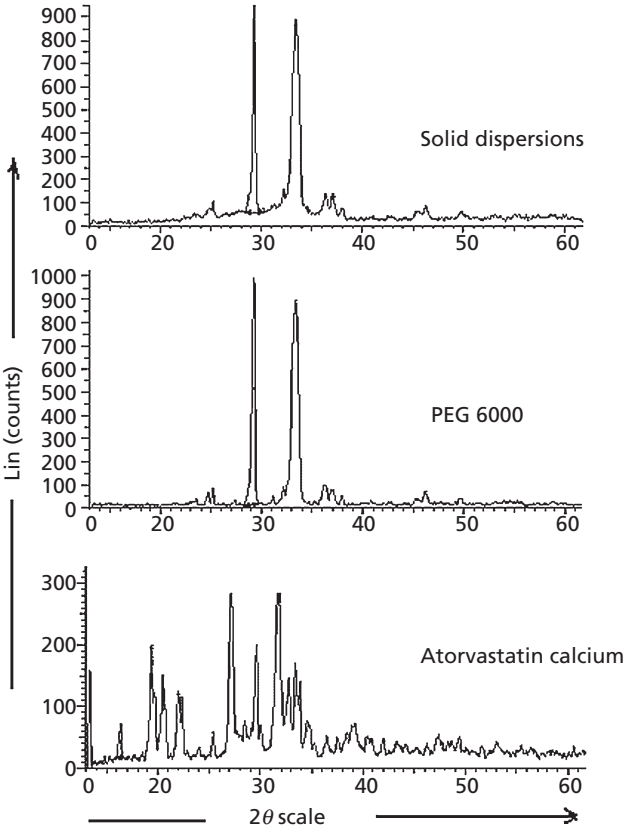


Figure 5 Powder X-ray diffraction patterns of atorvastatin calcium, PEG 6000 and solid dispersions prepared by the microwave induced fusion method with an exposure time of 6 min.

corresponding to the melting point of PEG 6000. The absence of an ATR peak in case of physical mixture and solid dispersions suggests molecular dispersion of the drug in PEG 6000.

The X-ray diffractograms of ATR showed sharp peaks at different angles (2θ) 6.24°, 9.26°, 10.36°, 11.92°, 15.38°, 17.10°, 19.54°, 21.70°, 22.75° and 23.38°, showing a typical crystalline pattern. All major characteristic crystalline peaks appear in the diffractograms of solid dispersions prepared by the microwave induced fusion method but were of low intensity, which indicates conversion of some crystalline ATR to the amorphous form. Scanning electron microscopy showed that ATR originally showed longer crystals in a plate shaped form, whereas in solid dispersions prepared by the microwave induced fusion method it forms a rough surface into which drug and polymer get completely fused to form a uniform single component and converts crystalline drug to the amorphous form which result in remarkable solubility, dissolution rate enhancement and thus may improve bioavailability of ATR.

Table 4 shows the effect of treatments on serum lipid levels in phase I and II (18 and 24 h). ATR produced a fall in serum cholesterol (184 ± 11 mg/dl), triglyceride (396 ± 17 mg/dl) and protective HDL (33 ± 0.22 mg/dl) levels. The solid dispersions prepared by the microwave induced fusion method, as expected, performed better than plain ATR, resulting in a significant reduction in serum cholesterol (118 ± 1.2 mg/dl), triglycerides (323 ± 11 mg/dl) and increase in protective HDL (59 ± 0.22 mg/dl) levels in phase I ($P < 0.05$). It has been reported that there is a natural tapering in cholesterol and triglyceride values in phase II of the Triton test.[21] However, this normal clearance of serum lipid in phase II of the Triton test can also be triggered by the presence of a drug in the circulation. ATR is known to stay in the blood circulation for a long time, as it has a biological half-life of 14 h. Thus, a longer duration of action is guaranteed provided there is an optimal initial plasma drug level, which is generally determined by the bioavailability of the drug. We also evaluated the effect of ATR and the solid dispersions in phase II of the Triton test. As seen from Table 4, ATR lowered cholesterol (209 ± 3.7 mg/dl), triglyceride (469 ± 3.7 mg/dl), and protective HDL (29 ± 0.24 mg/dl). The solid dispersions, as expected, performed better than ATR, resulting in a significant reduction of serum cholesterol (147 ± 0.9 mg/dl), triglycerides (412 ± 11 mg/dl) and increase in protective HDL (69 ± 0.38 mg/dl) levels in phase II ($P < 0.05$). Thus, the greater lipid-lowering activity of the solid dispersions prepared by the microwave induced fusion method in both phases I and II of the Triton test can be explained by the fact that the solid dispersions resulted in complete dissolution of ATR, which could have increased absorption and thereby a higher plasma drug concentration (higher bioavailability). The low bioavailability of ATR is attributed to its poor aqueous solubility. The observed differences in pharmacodynamic activity and the results from the in-vitro dissolution studies suggest that the solid dispersions prepared by the microwave induced fusion method significantly reduce ($P < 0.05$) cholesterol and triglycerides levels, and increase protective HDL levels owing to greater solubilization of ATR from the solid dispersions compared with plain ATR.

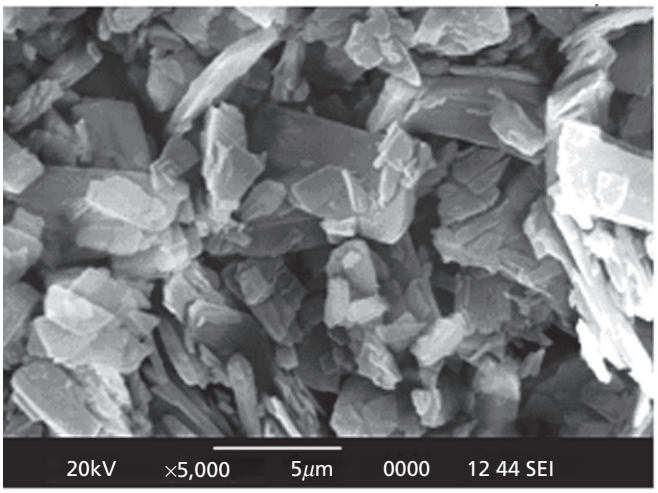
Conclusions

Solid dispersions of ATR with PEG 6000 prepared by the microwave induced fusion method significantly improved its dissolution rate ($P < 0.05$). Increased wetting and the solubilizing effect of PEG 6000 as well as the molecular dispersion of the drug in solid dispersions and alteration of the surface properties of the drug particles might be responsible for the enhanced dissolution rate. The in-vivo performance of the solid dispersions prepared by the microwave induced fusion method showed an enhancement in the solubility and dissolution rate of ATR from solid dispersions compared with plain ATR and thus significantly enhance its bioavailability ($P < 0.05$). A plasma study needs to be performed in order to further establish the findings of the indirect in-vivo method.

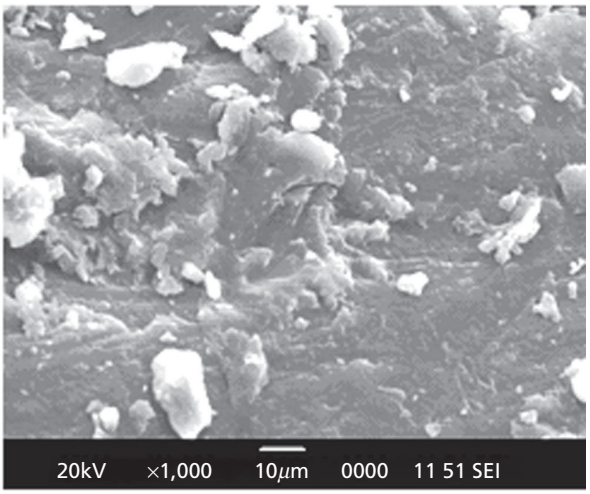
Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.



Atorvastatin calcium



Solid dispersions MW 6 min

Figure 6 Scanning electron microscopy photographs of atorvastatin calcium and solid dispersions prepared by microwave induced fusion method with an exposure time of 6 min.

Table 4 In-vivo evaluation of atorvastatin calcium solid dispersions

Treatment group	Triglyceride (mg/dl)	Cholesterol (mg/dl)	High density lipoprotein (mg/dl)
Phase I (18 h)			
Triton	432 ± 10	227 ± 0.98	31 ± 0.32
Atorvastatin calcium	396 ± 17	184 ± 11	33 ± 0.43
Solid dispersions: MW 6 min	323 ± 3*	118 ± 1.2*	59 ± 0.22*
Phase II (24 h)			
Triton	534 ± 37	310 ± 2.4	26 ± 0.24
Atorvastatin calcium	469 ± 3.7	209 ± 3.7	29 ± 0.24
Solid dispersions: MW 6 min	412 ± 11*	147 ± 0.9*	44 ± 0.26*

Solid dispersions prepared by the microwave (MW) induced fusion method had an exposure time of 6 min. All values are given as the mean ± SEM, $n = 6$. *Significant.

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