Research Article
Available online at www.ijpras.com

ISSN 2277-3657

Volume 4, Issue 1 (2015):51-56

International Journal of Pharmaceutical Research & Allied Sciences

Solubility Enhancement of Atorvastatin Calcium by Using Microwave Assisted Solid Dispersion Preparation Method

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Subject: Pharmaceutics

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 6000 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 solubility 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 respectively and further characterized by FTIR. The results of FTIR revealed that no chemical interaction between the drug and the polymer exist. All the formulations showed a marked increase in drug solubility with the increase in the concentration of PEG 6000. But the dispersion prepared by microwave induced fusion method shows more solubility than conventional hot melt method for preparation of solid dispersion.[1]

Keywords: *Atorvastatin Calcium (ATC), solid dispersion, Fusion Method, Microwave Irradiation Method, Polyethylene Glycol (PEG) 6000*.[1]

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. 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.[1]

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.

Class I :-
This class show 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 :-
Class II showing 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 :-
This show 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 :-

It is 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: Hydrochlorothiazide, Furosemide, Meloxicam etc. Atorvastatin Calcium is a BCS class II drug and having water solubility problem. 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. It is known that the aqueous solubility lesser than 1 g/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. 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. 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 water soluble drugs. Sekiguchi and Obi (1961) developed a method to enhance the bioavailability of poorly water-soluble drugs, which was later termed as solid dispersion. 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. 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 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. 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 6000 as carrier. 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 solubility study, Fourier transform infrared (FT-IR) Spectroscopy, and also performed to compare the physicochemical and absorption properties of pure drug and amorphous form (fusion induced processed drug).

Methods of Preparation of Solid Dispersions

Various methods have been developed for preparation of solid dispersions, these methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, demixing (partially or complete), and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control.

The brief description of the methods of preparations of solid dispersion is as follows:-

1. Solvent evaporation method:-

In solvent evaporation method drug is dissolved in organic solvent at its saturation solubility with continuous stirring for some time. Polymer is suspended in sufficient amount of water (up to wet mass of polymer). The drug solution is poured at once into polymer suspension. The entire solvent is evaporated. The mass obtained is dried.

2. Melting fusion method:-

This method involves the preparation of physical mixture of a drug and a water soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved.

3. Solvent melting method:-

Accurately weighed drug is dissolved in organic solvent. The solution is incorporated into the melt of mannitol and cooled suddenly

and mass is kept in desiccator for complete drying. The solidified mass is crushed, pulverized and passed through sieve.

4. Kneading method:-

A mixture of accurately weighed drug and carrier is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved.

5. Co-Grinding method:-

Accurately weighed drug powder and the carrier are mixed for some time using a blender at a specified speed. The mixture is then charged into the chamber of a vibration ball mill. A certain number of steel balls are added. The powder mixture is ground. Then the sample is collected and kept at room temperature in a screw capped glass vial until use.

6. Co-precipitation method (co-evaporates):-

Accurately weighed carrier is dissolved in water and drug is dissolved in organic solvent. After complete dissolution, the aqueous solution of carrier is then poured into the organic solution of the drug. The solvents are then evaporated. The dispersion is pulverized with pestle and mortar, sieved and dried.

7. Spray drying method:-

Accurately weighed amount of drug with lipid carrier are dissolved in methanol to obtain a clear solution. This solution is then spray dried using a laboratory scale dryer. The sample is stored over silica gel in a vacuum desiccator.

8. Gel entrapment technique:-

Carrier which have tendency to swell is dissolved in suitable organic solvent to form a clear and transparent gel. The drug is then dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by glass mortar and sieved.

9. Direct Filling:-

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug.

10. Lyophilization technique:-

This is a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular Lyophilization dispersion.

11. Electro spinning method:-

It is clear that the electro spinning technology used in the polymer industry combines solid dispersion technology with nanotechnology. In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give an on woven fabric, or they can be collected on a spinning mandrel. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength.

12. Supercritical fluid (SCF) technology:-

Supercritical CO2 antisolvent induces the precipitation about 100-fold faster than the liquid antisolvent, not allowing enough time for the drug and the polymer domains to separate out. Thus, supercritical CO2 precipitation can provide a more dispersed solid mixture. Supercritical CO2 -based precipitation is superior to the liquid based precipitation or the milling process.

13. Dropping solution method:-

The dropping method facilitate the crystallization of different chemicals and produces round particles from melted solid dispersions. In laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipette and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate. It does not use organic solvents and, therefore, has none

of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods.

Materials and Methods

Materials

Atorastatin Calcium was obtained as a gift sample from Mylan Pharmaceuticals Ltd. Nashik, India. while PEG 6000, 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 6000 were weighed according to different weighed ratio, as shown in table 1.

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 ATC was added with continuous stirring until dissolution. Solidification was allowed to occur at room temperature. The product was stored in a desiccators 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 6000 were prepared using the microwave induced fusion method. The finalized ratio was found to be 1: 2 w/w. First, ATC and PEG 6000 were weighed in a ratio of 1: 2 w/w followed by gentle mixing and subjected to microwaves for different times such as 5, 6 and 7 minutes at a constant chosen power of 700 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 desiccators for 24 h and then the product was pulverized using a mortar and pestle. The pulverized powders were passed through an 80# sieve[3].

Table 1: It shows the formula for the preparation of Atorvastatin Calcium Solid Dispersions.

Drug: PEG 6000	A1 (1:1)	A2(1:2)	A3 (1:3)
Drug (ATC)	500 mg	500 mg	500 mg
PEG 6000	500 mg	1000 mg	1500 mg

Solubility Studies

Solubility studies were performed according to the method described by Higuchi and Connors. The saturation solubility of drug and SDs with PEG 6000 (1:1, 1:2 and 1:3 w/w) in water was determined by adding an excess of drug and SDs to 50 ml distilled water 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 and analyzed by Jasco V-630 UV spectrophotometer at 242 nm.

Fourier Transform Infrared Spectroscopy (FTIR)

The KBr discs of Atorvastatin, PEG 6000 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.

Result and Discussion

Pre formulation study

1. **Melting point**

The melting point of Atorvastatin calcium is found to be 159-160 ^{0}c.[2,3]

2. **Solubility**

Atorvastatin Calcium practically insoluble in water, freely soluble in alcohol sparingly soluble in acetone, freely soluble in dichloromethane.[4]

3. UV –Visible spectrometric studies

Standard calibration curve in methanol Calibration curve of Atorvastatin Calcium in methanol was carried out. Were table 2 and fig 1 shows the concentrations of ATC in methanol and the respective absorbance.

Table 2: It shows the standard Calibration Curve Data of Atorvastatin Calcium in methanol at 247 nm.

Sr. No	Conc.(ug/ml)	Absorbance
1	2	0.1550
2	4	0.2418
3	6	0.3541
4	8	0.4467
5	10	0.5642

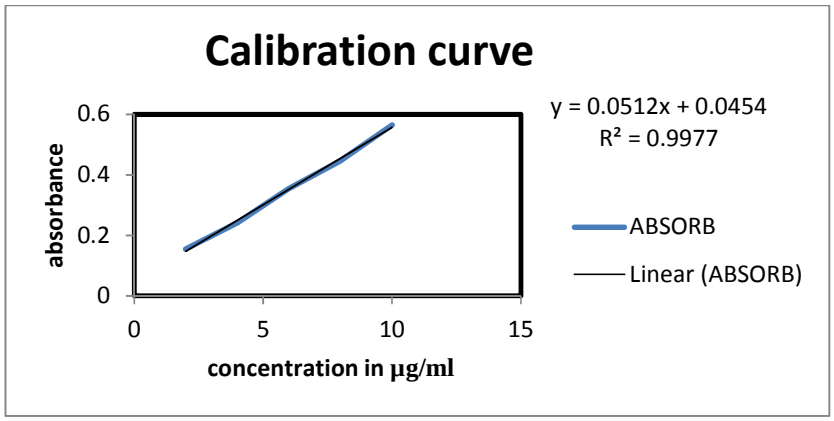

Fig 1: Chart showing calibration curve of ATC in methanol

Phase Solubility Studies:-

Solubility profile of Atorvastatin Calcium with PEG 6000 are shown in table The solubility of Atorvastatin calcium in water , without PEG 6000 was found to be mg /ml. The solubility of Atorvastatin Calcium increased as a linear function of carrier concentration. All dispersion shows enhanced solubility but higher in case of solid dispersion prepared by PEG 6000 in (1:3), as shows in table 3 and 4.

Table 3: It shows the solubility of Atorvastatin Calcium from various physical mixtures in distilled water.

Sr. no.	Physical mixture (Drug:PEG6000)	Solubility in mg/ml
1.	1:1	0.2990
2.	1:2	0.3121
3.	1:3	0.3500

Table 4: It shows the solubility of Atorvastatin Calcium from various solid dispersions in distilled water.

Sr. no.	Solid Dispersion (Drug:PEG6000)	Solubility in mg/ml Hot melt method	Solubility in mg/ml microwave method
1.	1:1	0.2990	0.3129
2.	1:2	0.3721	0.4124
3.	1:3	0.4676	0.6527

FT-IR spectroscopic studies:-
The FT-IR absorption spectra of Atorvastatin Calcium and PEG6000 were carried out and the spectra was found to exhibit characteristics absorption bands by table 5 shows in following range.

Table: 5 Shows the characteristics IR absorption bands at following range

Sample	IR ranges	Functional group
ATC	3240,1627,1620,1180,1100,3600, 828 cm-1	N-H, C=O, C=C, C-O, C-N, O-H.
PEG6000	3425 cm-1, at 1109 cm-1 and at 2889 cm-1	O-H, C-O-C and C- H Stretch.

Conclusion

Solid dispersion of Atorvastatin Calcium using carrier PEG 6000 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, analysis. The results of FTIR revealed that no chemical interaction between the drug and the polymer exist. All the formulations showed a marked increase in solubility in water and drug release with the increase in the concentration of PEG 6000. The solid dispersion prepared by microwave assisted method showing more solubility than conventional fusion method.[1]

"Cite this Article"

Taral M .N. "Solubility Enhancement of Atorvastatin Calcium by Using Microwave Assisted Solid Dispersion Preparation Method" Int. J. of Pharm. Res. & All. Sci. 2015;4(1):51-56

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