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Solubility Enhancement of Atorvastatin Calcium by Solid Dispersion using Skimmed Milk Powder

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Abstract

Atorvastatin calcium is a BCS class II drug which shows poor bioavailability due to inadequate solubility. Solid dispersions present a promising option to enhance the solubility of poorly water soluble drugs. Atorvastatin calcium has low solubility and low oral bioavailability, so it's a challenge to formulate suitable dosage form. In order to improve aqueous solubility of the drug, solid dispersion of Atorvastatin calcium and skimmed milk were prepared and investigated. Lyophilization technique was used to prepared solid dispersion. The objective of this investigation was to improve the solubility of the poorly water-soluble drug Atorvastatin calcium, using solid dispersion techniques, with skimmed milk powder as a hydrophilic carrier. The effects of the polymer concentration and method of preparation on the solubility rate was studied. The results showed that the solubility of Atorvastatin calcium increases with increasing skimmed milk concentration. The solubility study clearly demonstrated the potential of hydrophilic skimmed milk in enhancing the solubility rate of Atorvastatin calcium. The whole formulation showed distinct enhancement in the solubility. The optimum Atorvastatin calcium to skimmed milk ratio 1:9 enhances the solubility. It was concluded that for improvement of solubility of poorly water soluble Atorvastatin calcium, skimmed milk powder as a carrier can be utilize very well.

Keywords-Skimmed milk, Solid dispersion, Solubility, Atorvastatin calcium

INTRODUCTION

Solubility have major importance in a large number of scientific disciplines and practical applications in processing to the use of medicines [1]. Drugs with poor aqueous solubility are an important issue for pharmaceutical research scientists. [2]. Drugs that are poorly soluble in water are associated with slower drug absorption, eventually leading to inadequate and variable bioequivalence [3]. Drugs are classified on the basis of their solubility and permeability characteristics. The Biopharmaceutical Classification System (BCS) categorizes drugs in four classes: Class I, Class II, Class III, and Class IV. Drugs belonging to BCS Class II are poorly soluble in water, with high permeability [4, 5], and thus are ideal candidates for enhancing bioavailability by simply enhancing solubility. Atorvastatin calcium is a BCS Class II drug. Atorvastatin calcium is used as a hypolipidemic synthetic agent, it is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme. A reductase (HMG CoA), which catalyses the conversion of HMG CoA to mevalonate, an early rate limiting step in the cholesterol biosynthesis pathway[6]. Chemically it is (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1-H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.

It is insoluble in aqueous solutions with pH values less than 4; very slightly soluble in distilled water, phosphate buffer of pH 7.4, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol [7, 8]. Atorvastatin calcium has a plasma half-life of 18–24 hours, much higher than that of other statins. Poor oral bioavailability of Atorvastatin calcium (12%) is mainly attributed to its low aqueous solubility (0.1 mg/mL) and its crystalline nature [9].

In pharmaceutical world from last few eras, more number of poorly soluble drug substances are growing constantly. Consequently, many new approaches have been addressed to improve the solubility and enhance the dissolution rates. [10] So, the challenge for the development scientists is to use various solubilization technologies. For preparation of solid dispersion (SD), commonly used methods include the fusion or solvent processes such as hot melt extrusion, spray drying, solvent co-precipitation and super critical fluid process. [11-13] For the formulation of poorly water soluble drug, SD is established as a firm platform. A successful SD should be simply converted to ultimate dosage form and it must be physically and chemically stable during storage. Development of poor water soluble drug as SD officiating a distinct enhancement in their dissolution rates and is generally assisted by an enhancement in their relative bioavailability. [14]

The advantages of SD method are simple method and its non toxicity. Till now no efforts has been done to prepare SD using skimmed milk. Skimmed milk is very cheap, freely available, biodegradable and it does not show any toxicity issue. So the formulation of SD of Atorvastatin calcium with the use of skimmed milk and restricted water solubility may be a prospective and cost effective way to overwhelm the issue. Skimmed milk used as a carrier in formulation of solid is the best approach for modulating gastric irritation as well as enhancement of the water solubility of the Atorvastatin calcium. [15]

In the present work, we developed a solid dispersion of Atorvastatin calcium using skimmed milk. The skimmed milk is a colloidal suspension of casein micelles, globular proteins and lipoprotein particles. The principal casein fractions are α-s1, α -s2, β-casein and κ-casein. β -casein is

amphiphilic and acts as a detergent molecule with surfactant property. The milk also contains whey proteins with principle fractions of β -lactoglobulin, α -lactalbumin, bovine serum albumin and immunoglobulins [16]. These molecules were found to be surface active with Superior solubility than caseins. The lyophilization procedure was chosen because it provides protection against heat denaturation of protein molecules. The Atorvastatin calcium SD was evaluated for solubility study.

Varying ratios of drug and carrier were formulated and evaluated. To deduce the possible effects of the carrier on the drug, their solid dispersion were formulated and compared with plain drug.

MATERIALS AND METHODS

Atorvastatin calcium was obtained as gift sample from Mylan Lab Ltd, Nashik . Skimmed milk powder procured from Banaskantha Dist. Co-operative Milk Producers Union Ltd, Palanpur 385 001 India and all others chemicals /solvents used were of analytical grade.

Determination of wavelength (λmax) in methanol [17,18]

10 mg of drug was accurately weighed and was diluted to 100 ml using methanol to get a final solution of concentration 100 µg/ml. This solution was used as stock solution. From the stock solutions 1 ml of aliquot was withdrawn and volume made up to 10 ml with methanol to obtain the solution with concentration 10 µg/ml respectively. UV spectrum was recorded in the wavelength range of 200 - 400nm. Wavelength of maximum absorbance was determined.

Construction of Beer's Lamberts plot in methanol [17,18]

The stock solution of methanol was used to prepare different dilutions. The absorbances of different dilutions were measured at 246 nm using methanol as blank by UV-Visible spectrophotometry

Preparation of SD

A SD containing Atorvastatin calcium with skimmed milk powder in varying ratios (Table1) were prepared by lyophilization [19]. The drug and carrier were prepared according to the specified drug-to-carrier ratio. Atorvastatin calcium was dissolved in methanol and the carrier was put in a mortar. The drug solution was introduced to the carrier with slow and continuous trituration until a porous mass was formed. The mass was freeze-dried in a lyophilizer at -40^{o}C. The solid mass was pulverized and passed through sieve of 250 mm to get uniformly sized particles.

Saturation solubility studies [20,21]

Saturation solubility studies were conducted according to the method reported. Pure Atorvastatin calcium SD formulations containing equivalent amounts of drug were placed in a flask with glass topper containing 0.05M phosphate (pH6.8) buffer. The samples were placed on a shaker, agitated for 48h at 37±0.5 ^{O}C until equilibrium was achieved and the aliquots were filtered through 0.45 mm filter. The filtered samples were diluted and assayed using a UV-visible spectrophotometer against a blank prepared as described previously.

RESULTS AND DISCUSSION

UV Spectrophotometric analysis of Atorvastatin calcium calcium

The UV spectrum was recorded in the range 200-400 nm. The Wavelength of maximum absorption (λmax) was determined from the scan and then further preparation of (standard) curve was carried out at the detected wavelength of maximum absorption (λmax).

Wavelength (λmax) of Atorvastatin calcium calcium in Methanol:

Atorvastatin calcium was showing the maximum absorbance at 246.2 nm in methanol. The wavelength of Atorvastatin calcium calcium in methanol shown in fig 1 and Table 2.

Construction of Beer's lamberts plot of Atorvastatin calcium calcium in methanol:

The Beer's lamberts plot for Atorvastatin calcium in methanol was constructed. The regression coefficient of the lines obtained in methanol was found to be 0.9998 which is shown in Table 3 and Figure 2. The linearity in methanol was found in the concentration range of 5-25 µg/ml.

Saturation solubility studies:

From the observation it has been found that there was enhancement in solubility of solid dispersion of Atorvastatin calcium as compared to plain Atorvastatin calcium.

Solid dispersions were prepared in the ratio of 1:1, 1:2, 1:3, upto 1:9 simultaneously they were observed in distilled water, a comparative study shows that as quantity of skimmed milk increases in solid dispersion the solubility rate also get increases and SD having ratio 1:9 was having greater solubility in distilled water.

The observed result in case of pure drug and Polymer solubility in water is mentioned in table 4 , fig. 3 and fig.4.

Table 1 -Preparation of Solid dispersion of Atorvastatin calcium and skimmed milk

Ratio (Drug:Carrier)	Weight of Atorvastatin calcium (mg)	Weight of milk powder (mg)
1:1	100	100
1:3	100	300
1:5	100	500
1:7	100	700
1:9	100	900

Table 2: Table of wavelength (λmax) of Atorvastatin calcium calcium in Methanol

Observed	Reported [19]
246.2 nm	246 nm

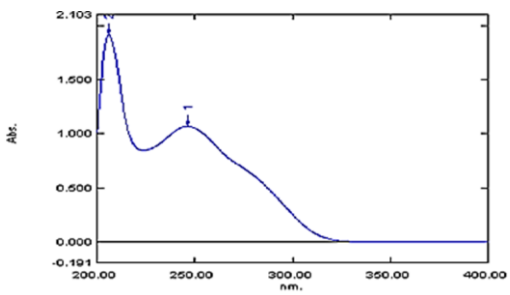

Fig. 1 UV spectra of Atorvastatin calcium calcium in methanol

Table 3: Reading of Construction of Beer's lamberts plot of Atorvastatin calcium calcium in Methanol

Concentration (In ppm)	Absorbance
5	0.185
10	0.301
15	0.433
20	0.566
25	0.691

Table 4: Evaluation of different SD formulations for solubility study

Ratio (Drug:Carrier)	Absorbance	Concentration(mg/ml)
1:1	0.229	0.00692
1:3	0.343	0.01138
1:5	0.420	0.0144
1:7	0.600	0.0217
1:9	0.761	0.0277
Plain drug	0.186	0.00524

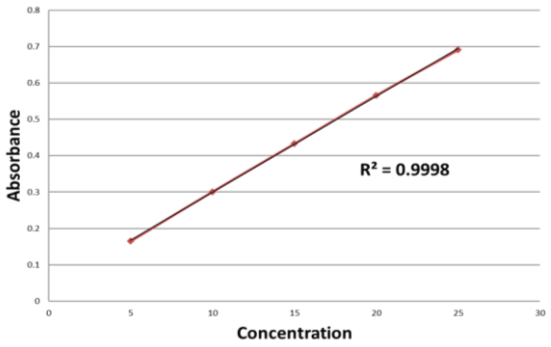

Fig. 2 Construction of Beer's lamberts plot of Atorvastatin calcium calcium in Methanol

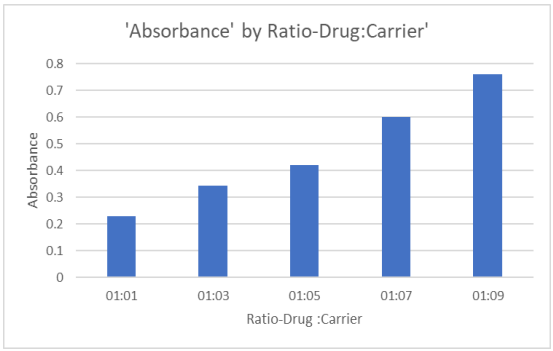

Fig. 3: Overlay of solubility studies of Solid Dispersion of Atorvastatin calcium calcium and Skimmed milk in Distilled Water

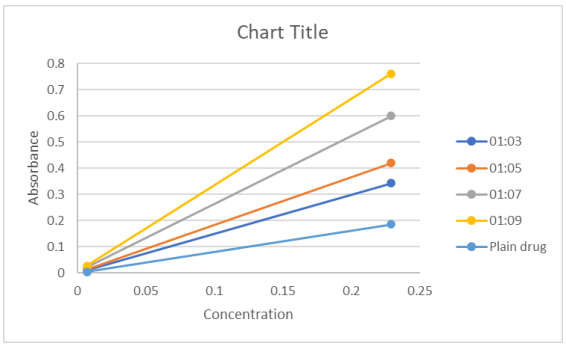

Fig 4- Evaluation of different SD formulations and plain drug of Atorvastatin calcium

CONCLUSION

In the present study we investigated the possibility of preparing an SD of Atorvastatin calcium with skimmed milk by a lyophilization technique. The formulation was successful in significantly enhancing the solubility rate of Atorvastatin calcium. Therefore, the present methodology can be regarded as a commercially feasible technique for improving the solubility of Atorvastatin calcium with skimmed milk as carrier.

Conflict of interests: The authors do not have any conflict of interest to declare.

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