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Water Solubility Enhancement of Atorvastatin by Solid Dispersion Method

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ABSTRACT

Atorvastatin is currently used as calcium salt for the treatment of hypercholesterolemia. It is insoluble in aqueous solution of pH 4 and below; it is very slightly soluble in water and pH 7.4 phosphate buffer. In the present study, an attempt was made to enhance the solubility and dissolution characteristics of atorvastatin calcium using solvent evaporation method. HPMC was used as the polymer in different drug to polymer ratios. From the study it was found that HPMC at a drug to polymer ratio of 2:1 improves the water solubility of the drug by 2 folds when prepared as solid dispersions by solvent evaporation method.

Key words: Solid dispersions, solvent evaporation method, atorvastatin, HPMC.

INTRODUCTION

Most new chemical entities (NCEs) are poorly water soluble drugs, not well-absorbed after oral administration and the oral delivery of such drugs is frequently associated with low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality (Tang *et al*., 2007). But due to many advantageous features of this oral rout of drug administration most of the new chemical entities (NCE) under development now-a-days are intended to be used as a solid dosage form that originates an effective and reproducible *in-vivo* plasma concentration after oral administration (Vasconcelos *et al*., 2007). To overcome the problems associated with oral absorption and bioavailability issue, various strategies have been utilized including prodrug formation (Murtha and Ando, 1994), complexation (Ghorab and Adeyeye, 2001), microcapsulation (Adeyeye *et al.,* 1994), the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrines, nanoparticles, solid dispersions, self emulsifying drug delivery system (Shakhtshneider *et al.,* 1996; Craig, 2002; Gao and Morozowich 2006; Rane *et al.,* 2007; Tang *et al.,* 2007, Uddin *et al*., 2010) etc. However ahead of all, solid dispersion is the most promising method to the scientists due to the ease of preparation, ease of optimization and reproducibility of the manufacturing method (Chiou and Reigelman, 1971; Ford, 1986; Law *et al.,* 1991; Leuner and Dressman, 2000). Atorvastatin is currently used as calcium salt for the treatment of hypercholesterolemia. It is insoluble in aqueous solution of pH 4 and below; it is very slightly soluble in water and pH 7.4 phosphate buffer. The intestinal permeability of atorvastatin is high at the physiologically relevant intestinal pH. The drug is absorbed more in the upper duodenum and in the upper small intestine regions. However, it is reported that the absolute bioavailability (*F*) of atorvastatin is 12% after a 40 mg oral dose (Zhang *et al., 2009*). In the present study, an attempt was made to enhance the solubility and dissolution characteristics of a poorly soluble model drug, atorvastatin calcium using solid dispersion technology.

MATERIALS AND METHODS

Experimental material: Atorvastatin calcium was purchased from Dr. Reddy's Laboratory Ltd., India. Hydroxy Propyl Methyl Cellulose (HPMC 6cps) and ethanol were obtained from Samsung, Korea and Merck, Germany respectively. **Reagent:** Di-sodium hydrogen phosphate and sodium di-hydrogen ortho-phosphate (Merck, Germany) and all other ingredients used were of analytical

grade. **Equipment:** USP dissolution tester-Apparatus-II (VEEGO, India); UV-VIS Spectrophometer (UV mini-1204, SHIMADZU CORP., Koyoto, Japan); Digital pH meter (pH 211 Microprocessor pH Meter, HANNA Instruments, Romania); Electronic balance (M-310, Denver Instruments, USA); Sieve (Endecott's Test Sieve, Endecotts Limited, England), glass vials, mechanical stirrer, water bath, dessicator etc.

Preparation of the solid dispersion

Solvent evaporation method (Spenlehauer *et al.*, 1989; Bodmeier and McGinity, 1987) was used to prepare the solid dispersions. Required amount of drug and polymer (Table 1) were mixed in glass vials. Ethanol as solvent was added to the mixture and continuous stirring was ensured for proper mixing of drug and polymer. The mixed mass was kept in an open beaker and the solvent was allowed to be evaporated. The formulations were kept in a dessicator for further treatment. The solidified mass was then crushed, size reduced in a mortar and pestle and sieved through a 150 micron sieve. All glass vials were labeled with care and kept in dessicator. Samples for dissolution studies were taken from the vials.

Table 1: Different ratios of atorvastatin with HPMC.

Code	Atorvastatin calcium (mg)	HPMC 6cps (mg)	Atorvastatin calcium:HPMC
F-1	500	125	4:1
F-2	500	250	2:1
F-3	500	500	1:1
F-4	500	1000	1:2

Physical mixture of atorvastatin calcium and polymer at the same ratio were prepared for comparing the release pattern of the solid dispersions.

Preparation of phosphate buffer pH 7.4

Phosphate buffer at pH 7.4 was prepared with di-sodium hydrogen phosphate and sodium di-hydrogen ortho-phosphet. To prepare one liter of phosphate buffer 1.421 g di-sodium hydrogen phosphate and 0.227 g sodium di-hydrogen ortho phosphate were weighed out carefully and dissolved in 1 liter of distilled water. The pH of the buffer solution was adjusted using a pH meter.

In vitro dissolution study

These studies were conducted at a temperature of 37±0.5℃ on an USP specification dissolution rate test type II apparatus (Paddle apparatus) with six sections assembly according to the USP 30 procedure (USP 30 and NF 25, 2007). For *in vitro* dissolution studies, phosphate buffer pH 7.4 was used as dissolution media. Water-bath temperature was fixed & confirmed to be 37±0.5℃ before starting the experiment. The medium was preheated to 37℃ and then a quantity of 900 ml was added to each vessel. The apparatus was then assembled and paddle rotation was started and adjusted at 100 rpm and the system was allowed to equilibrate for 15 minutes. After that the paddle rotation was stopped and fixed amounts of solid dispersion containing 50mg equivalent atorvastatin from each batch were placed in the vessels. The apparatus was immediately operated at 100 rpm. Each vessel, vessel position and corresponding sample result were assigned the same code. The duration of the experiment was 60 minutes for each set of sample. 10 ml of sample was withdrawn from the media at pre-determined intervals of 5, 10, 15, 20, 30, 45, 60 minutes. Each and every time 10 ml of dissolution sample was compensated by adding 10 ml fresh phosphate buffer. The sample solutions were diluted and analyzed at 239nm for atorvastatin by UV-VIS spectrophotometer. The amount of drug present in the samples was calculated from calibration curve constructed from the standard solution of USP reference standard test drug (Figure 1).

RESULTS AND DISCUSSION

Effect of HPMC in different drug to polymer ratios on dissolution of atorvastatin can be found in figure 2. It is evident from the current study that the prepared solid dispersions showed better dissolution profile in comparison to raw drug, physical mixtures and atorvastatin with ethanol. Maximum 48.89% of drug release was attained over the 60 minutes dissolution study in case of

raw drug and incase of solidified drug after dissolving in solvent (methanol) the %realease after 60 minutes was 55.61%. Formulation 1 (coded as F-1, drug to polymer ratio 4:1) and formulation 2 (coded as F-2, drug to polymer ratio 2:1) showed better dissolution profile (93.37% and 95.71% of drug release in 60 minutes respectively).

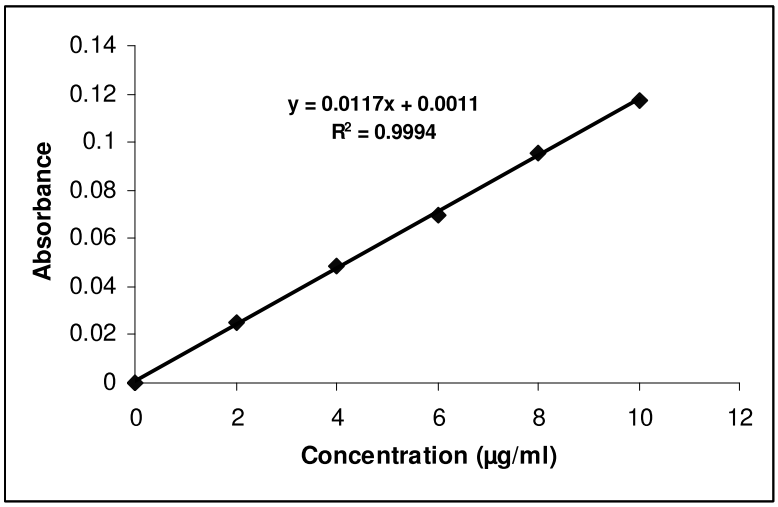

Figure 1: Calibration curve of atorvastatin using phosphate buffer pH 7.4 as media.

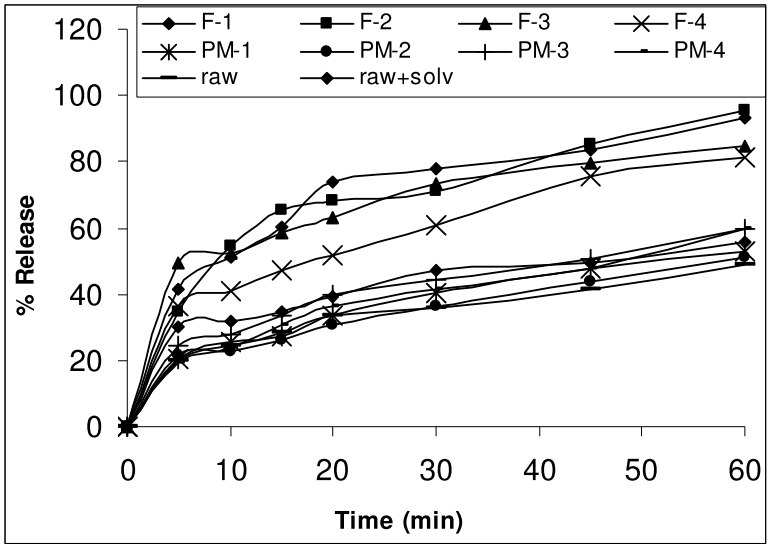

Figure 2: Percent release of atorvastatin from solid dispersions prepared in different polymer ratios of HPMC 6cps (F=formulation, PM=physical mixture).

Formulation 3 (coded as F-3, drug to polymer ratio 1:1) and formulation 4 (coded as F-4, drug to polymer ratio 1:2) showed improved dissolution time in comparison to raw drug (85.00% and 81.13% respectively over a 60 minutes dissolution study). If we consider the physical mixtures in 4:1, 2:1, 1:1 and 1:2 drug to polymer ratio (53.11%, 50.96%, 59.92% and 59.57% of drug release over 60 minutes respectively) we can found that dissolution was improved slightly in comparison to raw drug which indicates that the polymer affect the water solubility and hence dissolution of drug to some extent.

HPMC, a cellulosic polymer showed improved drug release or dissolution profile when solid dispersions were prepared. But from this study no conclusion could be made about the mechanism of enhancement of water solubility. It is also not evident from the data that a higher polymer

concentration gave better dissolution. In a previous study (Uddin *et al*., 2010) it was concluded that solid dispersion systems have a potential usage as controlled release drug delivery system. From the current study it is found that increasing drug to polymer ratio may probably decrease the rate of drug release and thus may also be useful in formulating controlled release drugs.

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