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DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF ATORVASTATIN CALCIUM POLOXAMER 407 SOLID DISPERSION SYSTEMS

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Abstract

In vitro Dissolution behaviour of a poorly water-soluble drug, atorvastatin calcium (ATC) from its solid dispersion (SD) systems with poloxamer 407 (P407) has been investigated to develop a novel formulation with enhanced dissolution rate. Solid dispersion of drug-carrier ratios (1:0.5, 1:1, 1:1.5 and 1:2) prepared by solvent evaporation method, were premeditated for drug loading, saturation solubility and dissolution behavior. Saturation solubility study and dissolution test were carried out in both phosphate buffer (pH 7.4) media and distilled water. Solid dispersions were found effective to enhance the solubility of ATC significantly in all the media. In the dissolution study, SD at the ratio of 1:1 (drug: carrier) was found to be most effective, showed fastest and higher drug release. The higher ratios of poloxamer 407 (1:1.5 and 1:2) in SD were found to sustain the release rate of drug which might be owing to its gelling tendency in higher proportion at elevated temperature. Fourier Transform Infrared Spectroscopy (FT-IR) of solid dispersions with pure drug revealed no drug-carrier interactions. Thermogram and short term stability studies ensured that the prepared SDs were stable. So, solid dispersion may be an effective technique to prepare immediate and sustain release atorvastatin calcium.

Key words: Solid dispersion, saturation solubility, dissolution time, FT-IR, sustain release.

Introduction

Atorvastatin calcium (Figure 1) is a synthetic anti-hyperlipidemic agent, prescribed in the treatment of obesity. Now a days its importance is rising in risk management of stroke, heart attack and revascularizations procedures in Type 2 diabetic patients, patient with multiple risk factors without evidence of heart disease and CHF patients (Croom and

Plosker, 2005). This potential drug is regarded as class II drug, according to the BCS (Biopharmaceutics Classification System) and characterized by a low water solubility and dissolution rate (Amidon *et al.*, 1995) which results in incomplete absorption. It is insoluble in aqueous solute of below pH 4, sparingly soluble in water and pH 7.4 phosphate buffer. At the physiologically relevant intestinal pH, the intestinal permeability of atorvastatin is found high (Lennernas, 1997). It has small absorption window as only being absorbed from upper small intestine and after the ileum absorption reduces significantly (Streubel *et al.*, 2006). However, the absolute bioavailability (F) of atorvastatin is reported 12% for 40mg oral dose (Corsini *et al.*, 1999). Several approaches can be applied to enhance the dissolution characteristics of this type of poorly soluble drugs (Hoerter and Dressman, 1997; Hancock and Zografi, 1997). Commonly applied methods to increase dissolution rate are salt formation, solubilization, particle size reduction which results into improved oral absorption and bioavailability of such drugs (Galia *et al.*, 1998). Solid dispersion of drug in water soluble polymers is one of the promising techniques (Brahmankar, 2009) of enhancing drug dissolution, because of its ease of preparation, simplicity of optimization and reproducibility (Leuner and Dressman, 2000).

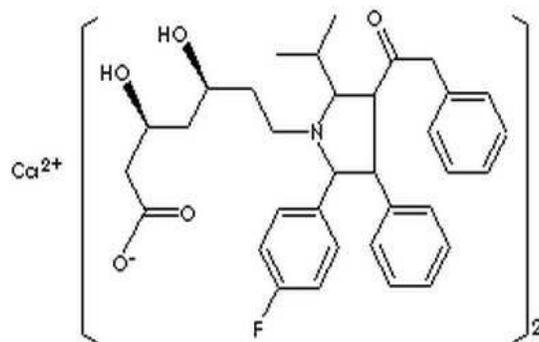


Figure 1: Chemical structure of atorvastatin

Solid dispersion (SD) is either a molecular dispersion or nano-crystals or amorphous nanoparticles of drugs in carrier (Chiou and Riegelman, 1971). It is a two component system consisting of a hydrophilic carrier in which the drug is incorporated by melting (fusion) (Sekiguchi and Obi, 1961), solvent, or melting solvent method (Tachibana and Nakamura, 1965). Increased surface area was offered due to small size of the drug particles in SD which helps in enhancement of drug dissolution (Purvis *et al.*, 2006), as dissolution rate of drug is affected by state and size of the particle. Only a few approaches of SD techniques have been reported to increase the solubility of ATC (Maurya *et al.*, 2010; Lakshmi *et al.*, 2011). Water soluble low melting point synthetic polymers are suitable for preparing SD. In

current times, scope of poloxamer in SD is increased due to its low melting point (56–57°C), wetting properties, in vivo absorption enhancer ability and oral safety. Poloxamers are a group of triblock copolymer, non-ionic surfactants in nature (Chen *et al.*, 2004) and is available in different grades. All of these grades have been proved effective in SD techniques (Saettone *et al.*, 1988). So, the present study was designed to develop atorvastatin calcium–poloxamer 407 SDs by solvent evaporation method and evaluate for their *in vitro* performances.

Materials and Methods

Experimental material

Atorvastatin calcium powder was a gift from Rangs Pharmaceutical Bangladesh Limited. P407 was gift sample from BASF, Bangladesh. Potassium dihydrogen orthophosphate, Sodium hydroxide, methanol and all required chemicals were of analytical grade.

Preparation of Solid Dispersion by Solvent evaporation method

SD of ATC were prepared by solvent evaporation method containing weight ratios of 1:0.5(S1), 1:1(S2), 1:1.5(S3), 1:2(S4) of ATC with P407 as carrier. 500mg of ATC was taken in the vial and 4ml methanol was added in each. The drug was completely dissolved in the solvent. Then different amount of P407 was added in the solution and sonicated it for 1 min. All solutions were dried by hot air. When the solutions were evaporated completely, they were stored in a dessicator for 24 hours. After withdrawn from vials, the formulations were crushed in mortar and pestle and passed through 150 microne sieves.

Evaluation of SDs

Drug content analysis

The drug content in each SD was determined by the UV Spectroscopic method (Arunkumar *et al.*, 2009). Each SD equivalent to 10 mg ATC dissolved in 10 ml of methanol then distilled water was added to make the volume 100 ml. After filtering these solutions, the absorbance of the filtrates was measured by UV-Spectrophotometer at 246 nm.

Solubility Measurements

The saturation solubility of pure ATC and each SDs was determined in distilled water and phosphate buffer (pH 7.4). An excess amount of drug and SDs was added in 50 ml distilled water or Phosphate buffer in a conical flask and were

shaken for the 24 h at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no1, suitably diluted with media and study by UV-VIS spectrophotometer at 246nm.

Drug-polymer interactions study

Interaction between ATC and P407 in SD formulations was studied by Fourier Transform Infrared Spectroscopy (FT-IR). We followed potassium bromide disc method using Infra red spectrophotometer (Shimadzu, IR Prestige, Japan). The selected scanning range was 750–4000 cm⁻¹ and the resolution was 8 cm⁻¹. Number of reference scans was 20. We compared the IR spectra of SDs, pure ATC and respective carrier to identify the interaction.

Thermal study

It was carried out to find out the effect of heating on stability of the drug which is based on thaw point melt method. For this study, the drug is allowed to solidify after heating in capillary melting point tube and the melting point of rapidly solidifying mass was noted.

Preparation of tablet and characterization

Each SDs equivalent of 10mg ATC was compressed to tablet dosage using required excipients (Table 1). Tablets were prepared by direct compression technique in a single punch rotary tableting press (8.00 mm round flat beveled punch) and evaluated for hardness (Monsanto hardness tester) friability (Shimadzu friabilator), weight variation and drug content. Stability studies were also carried out at 40⁰C for sporadic time intervals.

Table 1: Composition of the tablet formulated with Solid dispersion

Ingredients	Amount (mg)
SD(equivalent to ATC)	20
Ludipress	216
Sodium starch glycolate	8
Talc	4
Magnesium stearate	2
Total	250

***In vitro* dissolution studies:**

Dissolution studies of the prepared tablets were conducted in two dissolution media (distilled water and pH 7.4 phosphate buffer) at 37 ± 0.5 °C, using 8 station USP type-I apparatus (Shimadzu, Japan) rotating at 100 rpm. Release pattern of pure ATC powder was also observed. At predetermined time intervals (5, 10, 15, 30, 45, 60 min), 10 ml of sample was withdrawn from each basket, filtered through a 0.45 µm filter paper (model) and then analyzed

spectrophotometrically at 246 nm. Each test was performed in triplicate (n=3) and calculated mean values of cumulative percent of released drug in media were used to plot the release curve.

The drug release rates were characterized by MDT (mean dissolution time), $T_{50\%}$ (Time required for 50% drug release), $T_{80\%}$ (Time required for 80% drug release) and dissolution efficiency (DE). These values were calculated from dissolution data according to the following equations (Mockel and lippold, 1993):

$$T_{50\%} = (0.5/k)^{1/n}$$

$$T_{80\%} = (0.8/k)^{1/n}$$

$$MDT = (n/n+1) \cdot k^{-1/n}$$

$$DE = \frac{\int_{t_1}^{t_2} y \cdot dt}{y_{100} \times (t_2 - t_1)} \times 100$$

Where n is a release exponent and y is the percentage of dissolved product.

Mean dissolution time (MDT) was used to characterize the drug release rate from the dosage form. MDT is inversely proportional to drug releasing ability of the solid dispersions.

Stability study

Short-term stability studies of the all SDs were assessed by keeping them at 40°C for a month to three.

Results

Drug content analysis

Drug content of the solid dispersions was found to be between 94.52 % and 104.83%.

Solubility Studies

The results of saturation solubility (Figure 2) of SDs in phosphate buffer pH 7.4 and distilled water showed that P407 was effective in enhancing solubility in both the media. Solid dispersion have been found to increase the solubility up to 64% in phosphate buffer (pH 7.4) and 71% in aqueous medium in comparison with pure ATC. The solubility of formulated SDs increased with the increase of P407 and was higher than pure ATC in both the media. But P407 greatly improves solubility in relatively lower concentration (S1 and S2). Relatively higher loading (S3 and S4) also increased solubility but no further advantages was offered towards solubility enhancement.

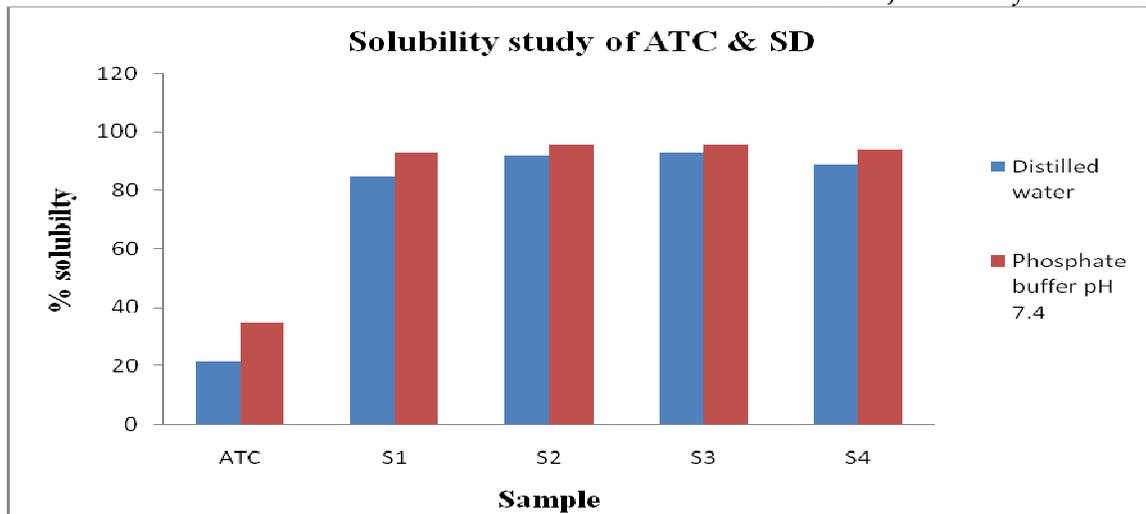
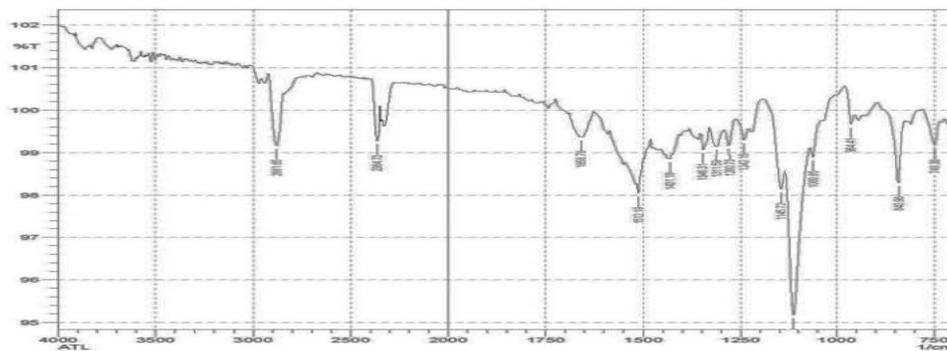


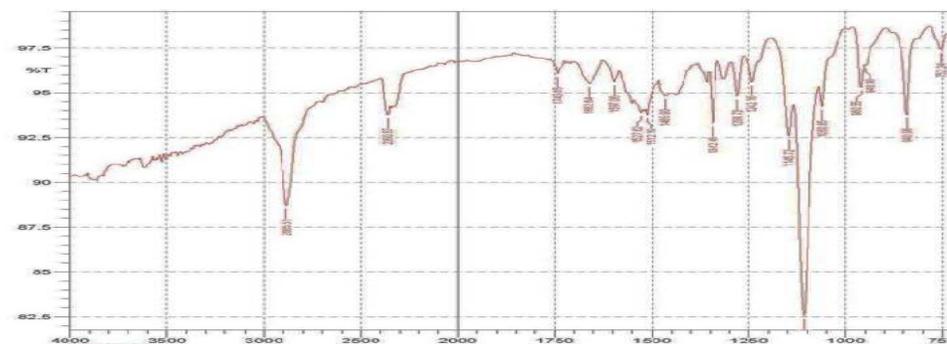
Figure 2: Saturation solubility of Atorvastatin calcium in pure and in solid dispersions with poloxamer 407. Data are expressed as mean \pm S.D. (n=3).

Drug-polymer interactions study

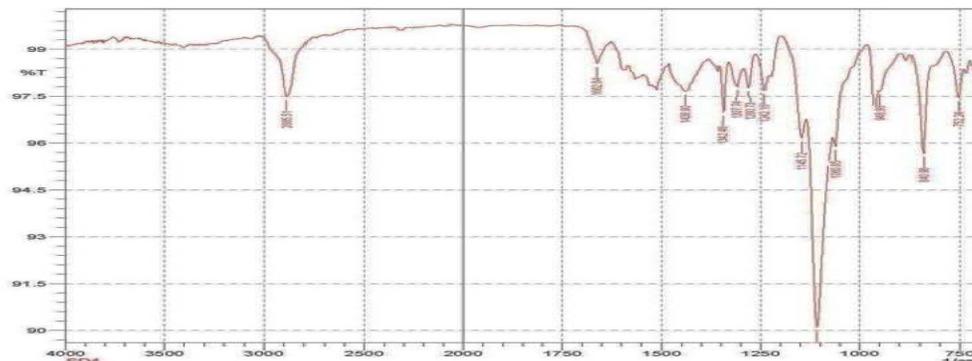
Figures 3 represented the IR spectra of pure ATC, P407 and SDs. IR spectrum of pure ATC (Figure 3a) was identical with the prepared solid dispersions (Figures c, d and e). This indicated that there was no interaction between ATC and carriers in the prepared solid dispersions. In addition, no degradation of drug and carrier due to the high temperature during manufacturing was found from IR spectra.



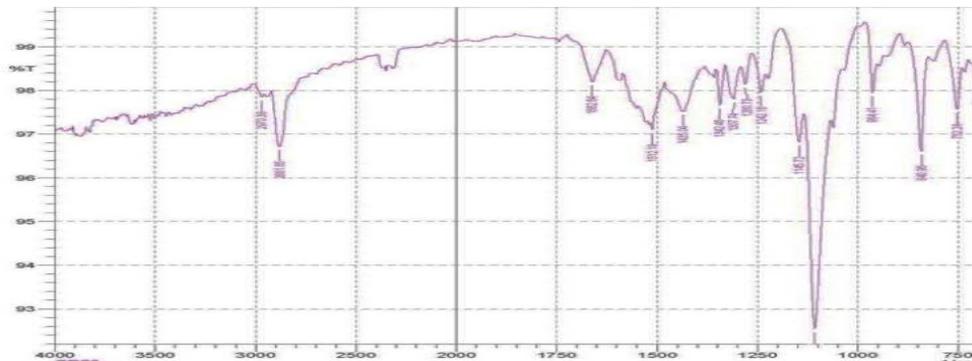
(a)



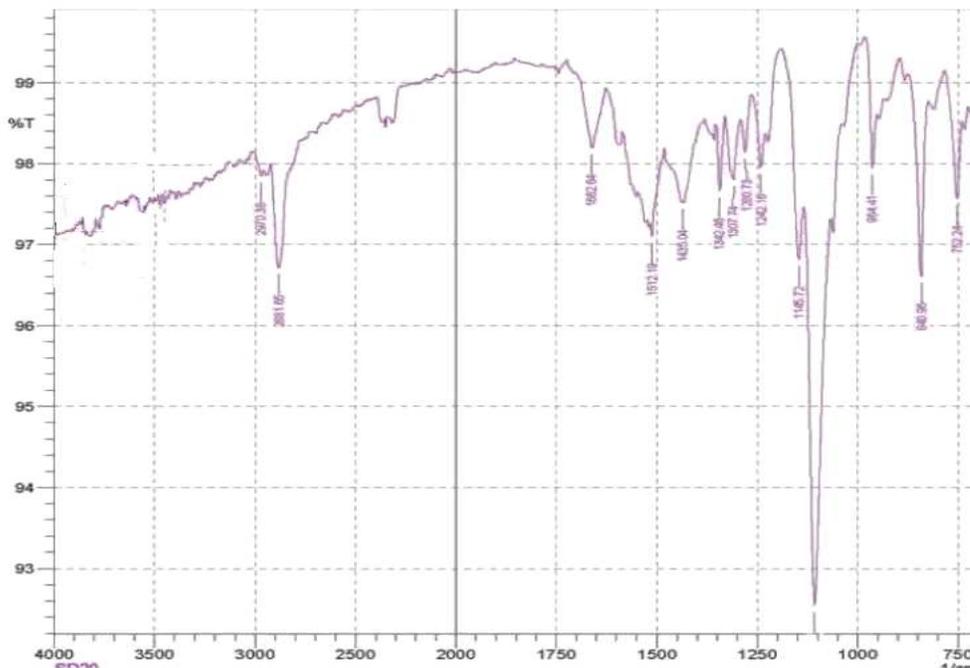
(b)



(c)



(d)



(e)

Figure 3: IR spectrum of a)Atorvastatin calcium (ATC) b)poloxamer 407(P407) c) solid dispersions containing ATC- P407 (1:05) d) solid dispersions containing ATC- P407 (1:1)ratios e) solid dispersions containing ATC- P407 (1:2)ratios.

Thermal study of SDs (Table 2) indicated identical melting point of ATC before and after thermal studies. Characteristic features of pure drug observed in thermograms of each SDs.

Table-2: Thermograms of solid dispersion.

Sl. No	Melting point of Atorvastatin calcium (Before thermal studies) in °C	Melting point of Atorvastatin calcium (After thermal studies) in °C
S1	159	159.7
S2	159.9	160.00
S3	160.2	160.2
S4	160.5	160.5

Result of Tablet evaluation

All parameters of the prepared tablets of SDs were evaluated and found within the specified I.P. limits. The thickness and diameter of the tablets were found to be 2.60 ± 0.51 and 7.3 ± 0.46 mm, respectively. The hardness of the different SDs ranged from 3 to 5 kg/cm². Less than 1% friability was exhibited by all the formulations. Measured weight variation was within the I.P. limits ($\pm 5\%$). The disintegration time was evaluated in all the formulations and found to be 5.31 ± 1.45 min. (I.P. limits uncoated tablet is < 15min).

In vitro drug release pattern

The dissolution profiles of ATC from SDs in phosphate buffer (pH 7.4) and distilled water were shown in Figure 4 and Figure 5. Drug release from SDs in phosphate media was found higher (up to 43.7% within 5 min) than pure ATC (8.3% within 5 min) from the beginning of the dissolution study. Drug release from S1 and S2 increased rapidly after 5 min of dissolution study. Within 45 min 80% and 100% drug was released from S1 and S2, respectively. ATC showed up to 35% dissolution over 60 min and incomplete release upto 5h. S3 and S4 released 20% and 16% ATC, respectively within 15 minutes. Upto 60 min only 50-55% ATC was released from S3 and S4.

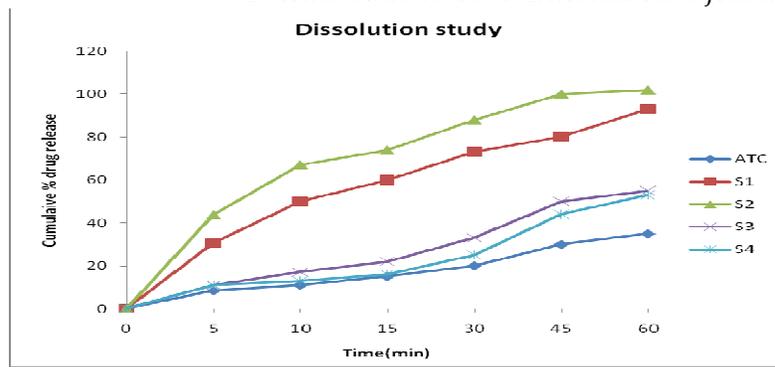


Figure 4: In vitro dissolution profiles of solid dispersion in phosphate buffer (pH-7.4).Data are expressed as mean ± S.D. (n=3)

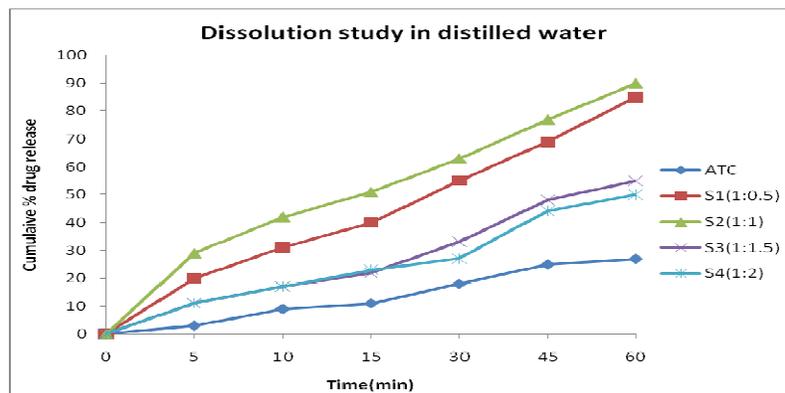


Figure 5: In vitro dissolution profiles of solid dispersion in distilled water.Data are expressed as mean ± S.D. (n=3)

Dissolution studies of SDs in distilled water showed the same pattern of dissolution but slightly low release rate than phosphate buffer media. P407 increased ATC release from SD upto 1:1 ratio then retarded the release.

MDT, $T_{50\%}$, $T_{80\%}$ and % DE were calculated from dissolution data and presented in Table 3. The MDT values of SDs were found to be a function of carrier (P407) loading upto S2 . Then MDT decreased with increase of P407 (S3 and S4).

Table 3: Successive fractional dissolution time ($T_{50\%}$ and $T_{80\%}$), MDT (in min± SD) values and % DE (30min and 60 min) of solid dispersions.

Sample	$T_{50\%}$	$T_{80\%}$	MDT		% DE ₃₀	% DE ₆₀
			Buffer	Water		
S1	9±0.86	42±1.77	15.975± 1.025	19.91±2.03	88.82	72.08
S2	6±1.33	29±0.96	11±0.87	17.55±1.55	129.07	86.70
S3	42±3.06	178±1.86	21.31±2.00	22.86±0.95	18.15	25.21
S4	52±3.08	242±2.04	25.87±1.23	21.8±1.85	10.42	23.41
ATC	300±2.45	450±1.04	22.33±1.77	25±0.956	6.77	10.21

Stability study

Short-term stability study showed that the physical appearance and the drug content of prepared tablets with SDs remained unchanged (no major change). As the tablets of all formulations were stored at 40°C, a minimum shelf life of 2 years could be provided.

Discussion

The oral administration of drug is the most familiar and advantageous over other types of route because of easy production, convenient ease of ingestion and low price. But ATC creates not only bioavailability problem due to low water solubility if administered orally, but also creates serious delivery challenges, like incomplete release from the dosage form, increased food effect and high inter-patient variability. We endeavored to design optimum SD formulations of ATC with Poloxamer 407 which ensure efficient solubility and improved dissolution rate. All the solid dispersions prepared by solvent evaporation technique were found to be granular, fine and free flowing.

The content uniformity test indicated that the drug is evenly dispersed in the powder formulation. Because all the solid dispersions showed the presence of high drug content with low standard deviations before and after short-term stability study. Therefore, solvent evaporation method used in this study found to be reproducible for formulation of SD.

Saturation solubility (for 24 h) of prepared SDs was found is a function of carrier (P407) loading. That means solubility of ATC from prepared SDs increases with the increase of poloxamer 407. Solid dispersion is a metastable form and because of its tendency to renovate into the stable form, the drug concentration may tend to decrease with elapse of time during the solubility test. This problem can be avoided by testing saturation solubility. The mechanisms responsible for improved drug solubility in both the media may be ATC-P407 interactions in solid state or in liquid state or both. Chemical structure of highly water soluble P 407 has the properties to form micelles in aqueous media (Kabanov *et al.*, 2002). When the mixture came in contact with aqueous media, the polymer particles might have hydrated rapidly into polymer solution, solubilizing the adjacent drug particles and subsequently releasing ATC into the media (Chen *et al.*, 2004).

In FT-IR study, the absence of major shift in peak positions, retention of drug peak and the equivalent addition spectra (of ATC and P407) for SDs suggested the absence of interactions in solid state between drug and carrier. The spectrum of SDs of ATV revealed a slight shift in few characteristics peaks with no difference in overall spectrum which indicates

possibility of intermolecular hydrogen bonding between ATC and P407. These results indicated insignificant chemical interaction in the FT-IR spectra of pure drug and solid dispersion. An increase in polymer contents also did not initiate any drug polymer interaction.

SD formulations of poorly soluble drugs facilitate the drug to be dispersed in the dissolution media at the possible quickest rate. This dispersion rate depends on the type of the carrier used and the physical state (crystal/amorphous) of the drug particles. All the prepared SD with P407 showed better dissolution rate than pure drug within 1h. This improvement of dissolution pattern might be due to surface active property (lowering of surface tension between hydrophobic drug and solvent), micell formation of the polymer and improvement of wetting characteristics of the drug (Newa *et al.*, 2007; Zhang *et al.*, 2009). Thus enhancement of dissolution of drug attributed to the dispersibility and wettability of poloxamer.

But dissolution pattern was found varying with different carrier loading. P407 in 33.33% (S1) and 50% (S2) concentration showed quickest and immediate release pattern in both the media. Upto 50% of P407, dissolution rate of ATC increased with the increase of poloxamer. Further increase of P407 (S3 and S4) slow down the dissolution rate and showed sustain release profile. This might be due to the gelling property of P407 at higher concentrations and elevated temperature (Sancheti *et al.*, 2008; Vikrant *et al.*, 2009). This gelling property of P407 may offer a scope of its application in designing modified release formulations.

Lower MDT of S1 (15.975 ± 1.025) and S2 (11 ± 0.87 min) indicates a higher dissolution rate of the formulation. Again, higher % DE₆₀ value of S1 (72.08) and S2 (86.70) indicated the higher extend of drug release from this formulation within 1 h. So both the rate and extent of drug release were apparently increased from S1 and S2 solid dispersions.

Higher MDT and lower % DE₆₀ of S3 and S4 indicated comparatively lower dissolution rate and retarded release from these formulations. So, it is clearly seen that drug-carrier ratio in the SD formulations plays the key role in governing the ultimate dissolution of the drug.

Promising outcome of thermal and stability investigation indicated the consistency of the prepared solid dispersions.

Conclusion

Preparation of solid dispersion of Atorvastatin calcium with poloxamer 407 was found relatively easy, simple, quick, inexpensive and reproducible manner using solvent evaporation method. Both solubility and dissolution rate of

atorvastatin calcium were enhanced in this method. Instant release of free atorvastatin calcium from SDs will consequence to swift absorption and improved bioavailability compared to pure atorvastatin calcium. Preliminary outcome from this work recommended that poloxamer 407 loading in SD exerted a wide variation of drug release pattern. Based on the results, we can say that carrier loading upto certain limit improves dissolution rate, above it modifies the release pattern into delayed release. Thus solid dispersion of drug with P407 might be efficient in formulating both immediate release and sustained release oral dosage form of drug with improved dissolution.

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