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IMPROVEMENT SOLUBILITY OF ATORVASTATIN CALCIUM USING SOLID DISPERSION TECHNIQUE

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Keywords:

Physical mixing; Melt Solvent method; Kollicoat IR; poorly water-soluble drug; solid dispersion.

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ABSTRACT: This study focused on an investigation of dissolution property of solid dispersion system consisting of drug, exipients, and carrier. The purpose of this study was to enhance the dissolution of Atorvastatin Calcium, a practically water-insoluble drug by preparation of solid dispersion using hydrophilic polymers and a carrier PEG 6000. Solid dispersion formulations were prepared by using The Melt Solvent and physical mixing method. Physical mixtures (PMs) of atorvastatin and hydrophilic polymer Kollicoat IR and PVK 30 were prepared at 1:0.5, 1:1 and 1:2 ratios. Melt Solvent method was used to prepare solid dispersion of atorvastatin, PVK 30 and kollicoat IR at 1:2 ratio. Solid dispersions were characterized by differential scanning calorimetry, scanning electron microscopy and dissolution tests. Characterization studies revealed that solid dispersion of Atorvastatin prepared by Melt Solvent methods showed better dissolution compare to Physical mixing and pure atorvastatin due to the conversion of atorvastatin into a less crystalline and/or amorphous form. The order of dissolution enhancement was Kollicoat IR > PVK30 in solid dispersions as well as in physical mixtures. Improvement of dissolution was significantly greater in solid dispersions prepared by Melt solvent method than in physical mixtures. The differential scanning calorimetric studies indicated that a decreased crystallinity of the solid dispersions obtained revealed that a portion of Atorvastatin was in an amorphous state. This was because of Kollicoat IR and PVK 30 affected the crystallinity of the drug could be considered as an important factor in enhancement the dissolution rate. It is known that amorphous drug represents the most ideal case for fast dissolution.

INTRODUCTION: Atorvastatin is a selective competitive inhibitor of HMG CoA reductase. Atorvastatin reduces total cholesterol, LDL-cholesterol in patients with mixed dyslipidemia. It also decreases the VLDL-cholesterol and triglyceride[1]. Atorvastatin inhibits the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, an originator of sterols, including cholesterol. By preventing de novo cholesterol synthesis, they reduce the intracellular source of cholesterol [2].

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Atorvastatin calcium ([*R*-(*R**, *R**)] – 2 - (4-fluorophenyl) - β, γ- dihydroxy-5-(1-methylethyl)-3-phenyl-4- [(phenylamino) carbonyl]-1Hpyrrol- 1-heptanoic acid) is hemi-calcium salt **(Figure 1)**.

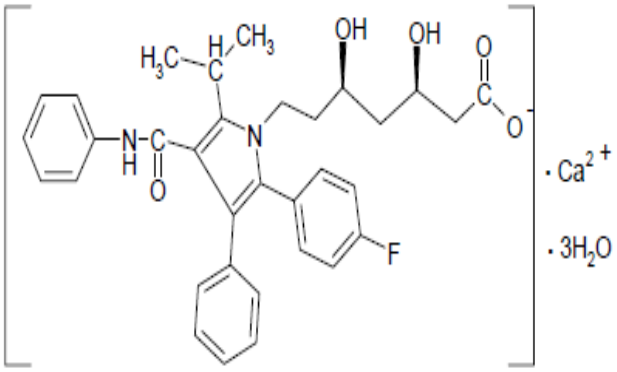


FIGURE 1: CHEMICAL STRUCTURE OF ATORVASTATIN CALCIUM

Atorvastatin is very slightly soluble in water and phosphate buffers at pH 7.4 and acetonitrile, freely soluble in methanol. The intestinal permeability of atorvastatin is high at the physiologically intestinal pH (6 – 6.5). However, it is reported that the absolute bioavailability of atorvastatin is 12% after a 40 mg oral dose [3].

Atorvastatin have very low and erratic oral bioavailability due to their lower water solubility. Therefore, it is vital to design effective methods to boost their dissolution, hence their oral absorption.
The enhancement of oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. Though salt formation, particle size reduction and solubilization have commonly been used to raise dissolution rate and thereby oral absorption and bioavailability of such drugs, there are some practical drawbacks of these techniques [4].

Solid dispersions have been considered as an effective method for improving drug dissolution rate and their saturation solubility in the gastrointestinal fluids [5].

Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by Melt Solvent, solvent, or solvent Melt Solvent methods [6]. This system provides the possibility of reducing the particle size of drugs and transforms the drug from the crystal-like stucture to the shapeless amorphous state, and/or to locally increase the saturation solubility [7]. To prepare solid dispersions of a poorly soluble drug with water-soluble polymers is a promising method for improving the dissolution characteristics and bioavailability of the drug[8]. The binary and ternary solid dispersions were prepared to enhance the dissolution of poorly soluble drugs to improve oral absorption of these drugs [9–11]. Many water-soluble carriers have been employed for preparing solid dispersions, such as polyethylene glycols, polyvinylpyrrolidone [12], mannitol, hydroxypropyl methylcellulose [13], poloxamer [14], etc.

In the research, an effort has been made to increase solubility of Atorvastatin calcium by solid dispersion using physical mixing (PM) and Melt Solvent technique using PVK30 and Kollicoat IR.

MATERIALS AND METHODS:

Materials

Atorvastatin Calcium was provided as generous gift from Beximco Pharmaceutical, Bangladesh (Analytical grade). Kollicoat IR and PVK 30 were obtained from BASF (Germany).All other materials and reagents were of analytical grade of purity. This experiment was carried out from July 2013 to April 2014.

Preparation of Binary Physical Mixture of atorvastatin-polymer:

Physical mixtures of Atorvastatin Calcium with Kollicoat IR and PVK 30 were prepared by mixing in a mortar and pestle for 10 minutes. The binary mixtures of drug-polymers were then stored in desiccators at a room temperature until further use and were letter-coded as PM (physical mixture) **(Table 1)**.

TABLE 1. ASSIGNMENT OF PRODUCT CODE TO DIFFERENT FORMULATIONS PREPARED BY PHYSICAL MIXING AND MELT SOLVENT METHOD

S. No.	Polymer	Formulation Combination		Assigned Code of the formulated batches	
		Physical Mixing (ATV: P)	Melt Solvent Method (C:ATV:P)		
1		1:0.5	5:1:0.5	PM_1	MS_1
2	Kollicoat IR	1:1	5:1:1	PM_2	MS_2
3		1:2	5:1:2	PM_3	MS_3
4		1:0.5	5:1:0.5	PM_4	MS_4
5	PVP K30	1:1	5:1:1	PM_5	MS_5
6		1:2	5:1:2	PM_6	MS_6

ATV = atorvastatin calcium; P = polymer; C = Carrier, PEG 6000; PM = physical mixing; MS = melt-solvent

Preparation of Ternary Solid Dispersion by Melt Solvent Method:

Accurately weighed amount of Polyethylene glycol 6000 was placed in an aluminum pan on a hot plate and melted at a temperature around 55°-60° C. Accurately weighed amount of atorvastatin calcium & polymer were added in the molten PEG with continuous stirring to assure homogenous mixing. The mixtures were then allowed to cool-down to room temperature to get the dry and solid mass of the mixtures. The mixtures were then pulverized in a mortar-pestle and sieved through a 30-mesh sieve to have solid-dispersion (SD) powders of uniform-size. The SD powders were then stored in desiccator at the ambient temperature until further use. SD powders were letter-coded as MS (melt-solvent) **(Table 1).**

Physicochemical Characterization

Differential scanning calorimetric studies

Differential scanning calorimetry (DSC) is frequently the pharmaceutical thermal analysis technique of choice because of its ability to provide detailed information about both the physical and energetic properties of substances.

The pure drug and solid dispersions were examined by DSC 60 (Shimadzu, Japan) where 5-6 mg samples were placed in aluminum pan at a heating rate of 10^{o}C/min with purging of dry nitrogen at a constant rate of 20 ml/min. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. DSC was used to determine crystalinity of atorvastatin, Kollicoat IR, PVK 30, PM3, PM6, MS3, MS6 formulations.

Scanning Electron Microscopy (SEM)

The scanning electron microscopy (SEM) analysis was carried out using scanning electron microscope (JSM 6100, Jeol, Japan). Samples of Pure drug (Atorvastatin), physical mixtures formulations and solid dispersion were mounted onto the stubs using double-sided adhesive tape and then coated with a thin layer of gold palladium alloy (150–200A°). The scanning electron microscope was operated at an acceleration voltage of 20 KV, working distance (12–14 mm). The selected magnification was ×500. SEM was used to investigate particle shape of pure atorvastatin, MS_3 and MS_6 formulation.

***In - vitro* release studies**

In-vitro dissolution studies of pure atorvastatin calcium, binary PM, and ternary SD powder equivalent to 10 mg of atorvastatin were performed in USP type II paddle type apparatus (ELECTRO LAB, India) using 900mL distilled water maintaining at 37±0.5° C as dissolution medium and 50 rpm as the paddle rotation speed. Each time, 10mL of dissolution medium was withdrawn at predetermined time intervals and 10mL fresh distilled water was added immediately to maintain the sink condition. Dissolution mediums withdrawn were filtered through 0.45 m filter paper and analyzed for drug content by a UV-VIS spectrophotometer at a of 248 nm.

RESULTS AND DISCUSSION:

Differential Scanning Calorimetry

Figure 2 (a) and **2 (b)** show the DSC thermogram of pure atorvastatin, pure Kollicoat IR, PM_3, MS_3, pure PVP K30, PM_6, MS_6. Pure atorvastatin showed an endothermic peak at 158.55° C. This endothermic-melting peak of atorvastatin was observed in a very smaller extent in the thermograms of both PM_3 and PM_6 suggesting the presence of the drug at its crystalline form. But, the melting peak of the drug was totally absent in the thermograms of both ternary formulations (MS_3 and MS_6) suggesting the entrapment of the drug crystals inside the molten PEG. This might also due to the fact that drug might also transform from its crystalline form to amorphous form in the SD formulations[15].

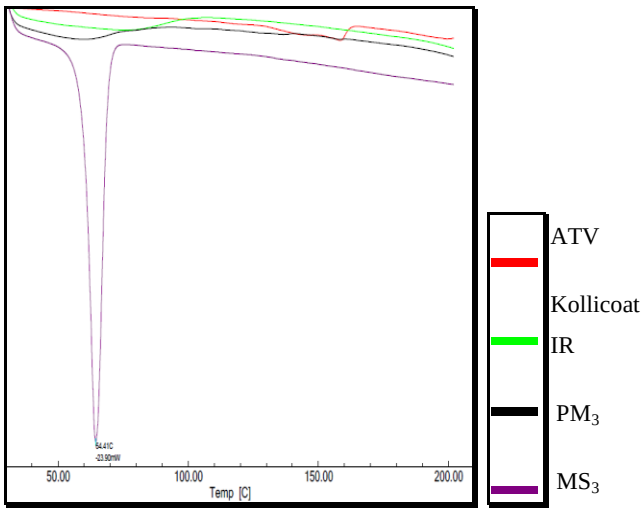


FIGURE 2(a). DIFFERENTIAL SCANNING CALORIMETRIC THERMO GRAMS OF ATORVASTATIN, KOLLICOAT IR & POLYETHYLENE GLYCOL 8000, PM AND MS MIXTURE

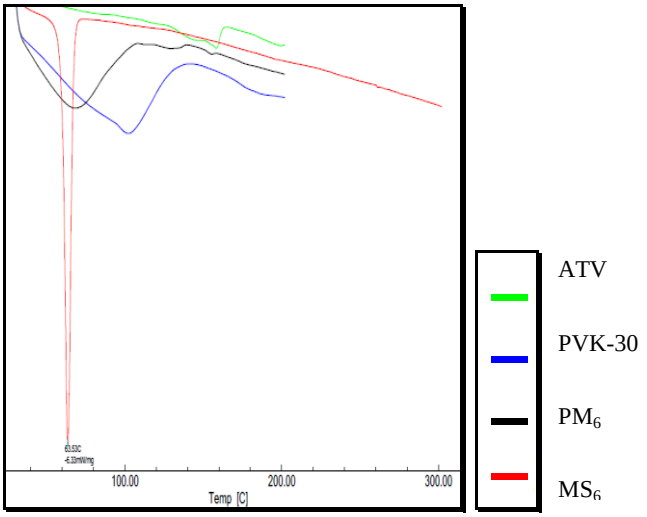
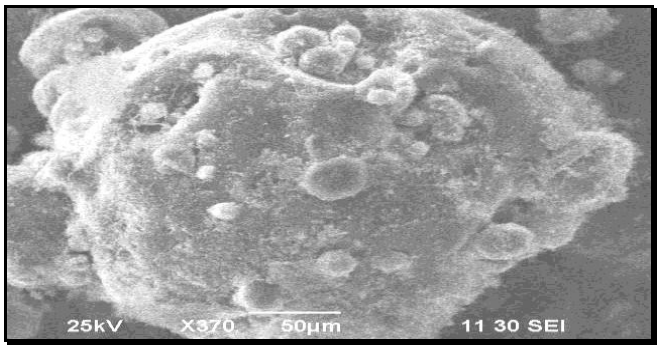


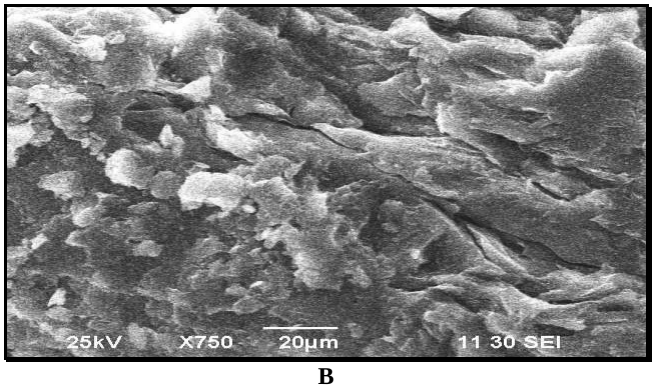
FIGURE 2(b). DIFFERENTIAL SCANNING CALORIMETRIC THERMO GRAMS OF ATORVASTATIN, PVK-30 & POLYETHYLENE GLYCOL 8000, PM AND MS MIXTURE.

Scanning Electron Microscopy (SEM)

SEM study indicated **Figure 5.** Those pure drug particles were irregular in shape, while the physical mixture of the drug and carrier shows that drug particle remains dispersed and physically adsorbed on the surface of the carrier particles. The solid dispersion of Atorvastatin, Kollicoat IR, PVK 30 and PEG 600 showed a homogeneous dispersion indicating that the atorvastatin molecules were dispersed uniformly in carrier of solid dispersion prepared by melting method at 1:2 ratios, assuming amorphous solid dispersion state.



A



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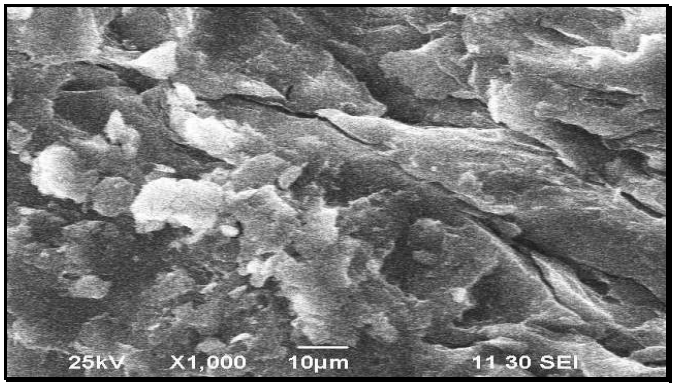

C

FIG.3. SCANNING ELECTRON MICROSCOPY PHOTOGRAPH OF PURE ATV (A), MS_3 (B) AND MS_6 (C) FORMULATIONS.

In- vitro release studies

In vitro dissolution studies were conducted on three times of each of the formulations (formulations PM_1, PM_2, PM_3, PM_4, PM_5, PM_6, MS_1, MS_2, MS_3, and MS4 MS_5 and MS_6).The cumulative released of atorvastatin in dissolution media was 55% after 60 minutes which is shown in **Figure 4(a)**. The mean cumulative percent of Atorvastatin released from PM_1, PM_2, PM_3, PM_4, PM_5 and PM_6 formulations prepared by physical mixing, at different time intervals is shown in **Fig. 4(b)**.

It was observed that the rate of release for PM_1, PM_2, PM_4, and PM5 was lower than PM_3 and PM_6. As 80% and 82% ATV was found to be released in case PM_3 and PM_6 (1:2 ratio) after 60 minutes of dissolution. The increase in dissolution rate of drug in the presences of carriers could be attributed to an increasingly effective solubilization process. Because of the formation of unstructured/amorphous phases, the dissolution percentage is very high since the drug simply dissolved along with the hydrophilic polymers. Therefore, the improve aqueous solubility and little viscosity of Kollicoat IR and PVK 30 enhances the dissolution process.[16]

On the other hand the formulations MS_1, MS_2, MS_3, MS_4 MS_5 and MS_6, produced by Melt Solvent technique showed maximum release after 60 miniutes which were nearly 100 % for Kollicoat IR (MS_3) and 90% for PVK 30 (MS_6) respectively which were much higher than MS_1, MS_2,MS_4, MS_5 and all other physical mixing formulations shown in Figure.4(b). Various studies have shown that Kollicoat IR and PVK30 inhibit crystallinity of drugs and resulting in amorphous nature of drug in

the solid dispersions. Crystallization inhibition was attributed to two effects: the interactions between the drug molecule and the hydrophilic polymer due to hydrogen bonding and the entrapment of the drug molecules in the hydrophilic polymeric matrix. In presence of PVP K-30 and Kollocoat IR, drug had better wettability; hence the dissolution of drug was greater in the form of solid dispersion [17]. The order of dissolution enhancement was Kollicoat IR > PVK30 in solid dispersions as well as in physical mixtures.

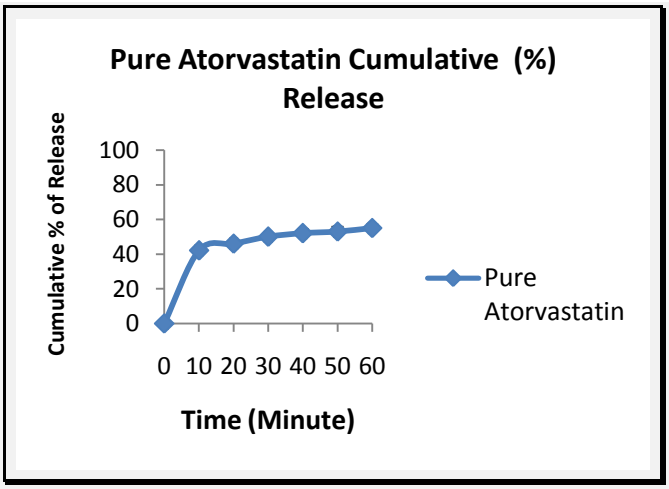

FIGURE 4(a): PURE ATORVASTATIN CUMULATIVE (%) RELEASE CURVE

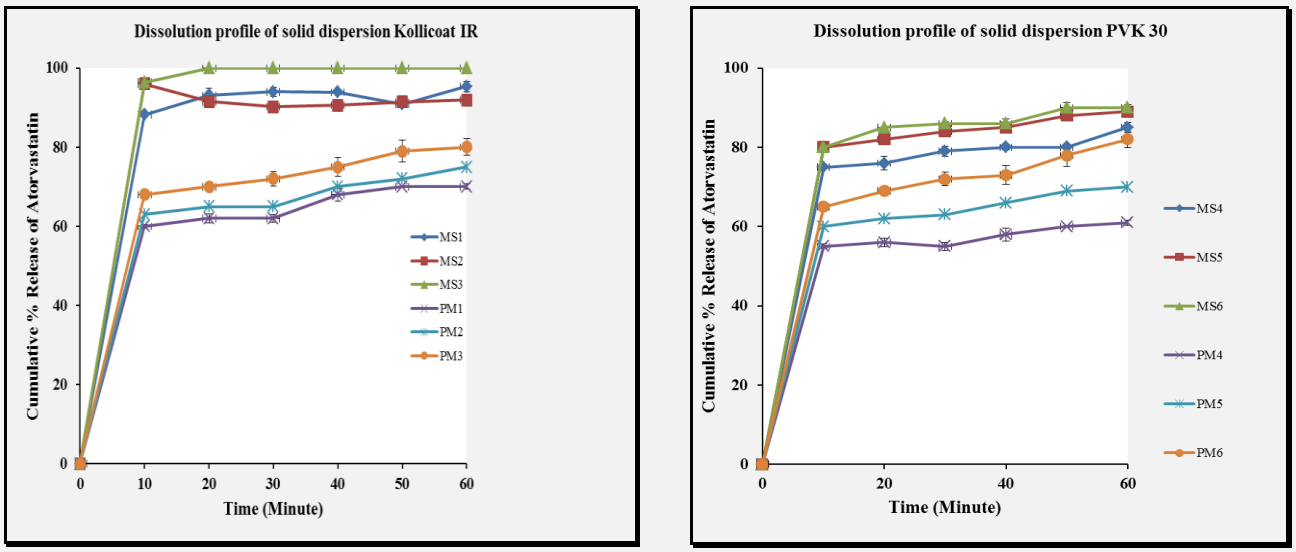

FIGURE 4(a): PM AND MS FORMULATIONS CUMULATIVE (%) RELEASE CURVES

CONCLUSIONS: The study has demonstrated that dispersions of Atorvastatin calcium into water-soluble carrier like Kollicoat IR and PVK 30 changed the crystallinity of Atorvastatin calcium according to type and amount of the polymer. The formation of Atorvastatin calcium –Kollicoat IR/PVK 30 solid dispersion destroyed almost completely the crystallinity of the drug and represents a suitable modification for improving its availability. Kollicoat IR and PVK 30 tested in this study was sufficient for conversion of Atorvastatin calcium to amorphous form. However, it also decreased the crystallinity of Atorvastatin calcium. Which ultimately improve solubility of drug. The study also shows that dissolution rate of Atorvastatin can be enhanced to considerable extent by solid dispersion technique with Kollicoat IR and PVK 30.

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