Enhancement of dissolution profile of poorly aqueous soluble atorvastatin calcium by binary and ternary solid dispersion techniques

M. R. Sarkar\textsuperscript{1*}, A. Hossin\textsuperscript{2}, A. S. M. M. Al-Hossain\textsuperscript{1}, K. M. Y. K. Sikdar\textsuperscript{1}, S. Z. Raihan\textsuperscript{3} and M. H. Hossain\textsuperscript{4}

\textsuperscript{1}Department of Pharmaceutical Technology, University of Dhaka, Bangladesh
\textsuperscript{2}Executive, Square Pharmaceutical Limited, Bangladesh
\textsuperscript{3}Department of Clinical Pharmacy and Pharmacology, University of Dhaka, Bangladesh
\textsuperscript{4}BCSIR Laboratories, BCSIR, Dhaka-1205

Abstract

Atorvastatin calcium (ATV) is an HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitor commonly known as a cholesterol-lowering agent. As a poorly water-soluble drug its absolute bioavailability is very low. To increase the water solubility as well as oral bioavailability, different hydrophilic carriers were used in different ratios (1:0.5, 1:1 and 1:2) to prepare reproducible binary and ternary solid dispersion formulations of ATV by simple physical mixing (PM) and fusion or melting technique. In vitro dissolution studies results revealed that in all cases, the cumulative percent drug release from ATV ternary SD formulations were greater than binary formulations, some marketed products and pure ATV powder. The order of the carriers in enhancing the drug release was found as kollidon 90F > pregelatinized starch > lutrol > kollidon 12F (99.1%, 98.8%, 96% and 95% respectively) for ternary SD formulations whereas pure ATV powder and marketed products showed cumulative percentage release 70.8%, 68.9% (B1) and 73.1% (B2), respectively. The best-out performed ternary SD formulation ATV:Kollidon 90 F (1:2) were further characterized using FT-IR and SEM. SEM analyses indicated conversion of crystal drug to amorphous form and FT-IR data suggested that little or no interaction between the drug and polymer.

Keywords: Hydrophilic polymers; Physical mixing; Fusion method; Solid dispersion; Dissolution

Introduction

Improving the oral bioavailability of poorly aqueous soluble drugs remains the most difficult aspects in the current drug development process (Ali and Al-Khedairy, 2019; Sharma et al., 2009). It is estimated that nearly 40% of API with current market approval and about 90% of molecules/chemical entities in the discovery pipeline have been shown very low aqueous solubility (Kalepu and Vijaykumar, 2015; Lawrence, 1999). Drugs belong to class II of the Biopharmaceutics Classification System (BCS), tend to have a low dissolution (%) rate and poor or low oral bioavailability (Frizon et al., 2013). These drugs are associated with slower absorption rate from the oral route which is a most natural, convenient and safe route for drug administration, therefore drug dissolution is considered the rate-limiting step (Charman, 2000). If solid oral dosages forms are not released completely in the gastrointestinal area, they might show poor bioavailability particularly for drugs which belong to BCS class II. To enhance the solubility of poorly water-soluble drugs, numerous formulation strategies have been investigated and developed (Kalepu and Vijaykumar, 2015; Pabari et al., 2014; Sharma et al., 2009). Several approaches and techniques like physical, chemical and other modifications or techniques such as crystal engineering, particle size reduction, use of surfactant, salt formation, hydrotropic, prodrugs, pH adjustments, micro-emulsion, complexation, co-solvency, micelles and nano crystallization have frequently been implemented to increase the dissolution rate and water solubility of poorly soluble drugs (Chaudhary et al., 2012;
Atorvastatin is an inhibitor of HMG-CoA reductase which catalyzes the transformation of hydroxymethyl glutarate to mevalonate and this molecule is extensively used for lowering total cholesterol (TC), apolipoprotein B (Apo B), triglycerides (TG) as well as low-density lipoprotein cholesterol (LDL-C) (Ali and Al-Khedairy, 2019; Bobe et al., 2011; Narasiah et al., 2010; Sarkar et al., 2014). It is a statin medication belongs to BCS class II drugs whose absolute bioavailability has reported less than 12% due to its’ very low phosphate buffers (pH 7.4) and water solubility (Ahjel and Dumitru, 2009; Mukhtar et al., 2005). As mentioned previously due to its low oral bioavailability, improvement of water solubility of this drug is a valuable approach to improve therapeutic efficacy and solid dosage form design. Different techniques have been implemented to increase the aqueous solubility of atorvastatin such as nano-suspension, co-crystals, Microwave induced solubility enhancement, spray-drying and supercritical antisolvent (SAS) process, self-emulsifying drug delivery systems, cyclodextrin complexation and solid dispersion approaches (Arunkumar et al., 2009; Kim et al., 2008; Maurya et al., 2010; Naqvi et al., 2020; Palem et al., 2009; Rodde et al., 2014). The solubility and dissolution rate of atorvastatin have been improved by solid dispersion approach through different hydrophilic polymers such as PEG 6000, polyvinylpyrrolidone-K30, Soluplus®, PVP VA64, HPMC, Poloxamer 188 (Bobe et al., 2011; Dong et al., 2018; Ha et al., 2014; Hu et al., 2014; Jahan et al., 2013; Shamsuddin et al., 2016). The dissolution profile of atorvastatin was studied and reported to our previous publications (Sarkar et al., 2012; Sarkar et al., 2014) using physical mixing and fusion techniques. Improved dissolution rates of atorvastatin from SD formulations compared to the pure active has been reported (Sarkar et al., 2012; Sarkar et al., 2014). Previously pregelatinized starch, poloxamer 407, hydroxypropyl methylcellulose and sodium carboxymethyl cellulose were used to prepare binary solid dispersion (SD) of atorvastatin calcium and increased the cumulative per cent release from 74% to 96% after 60 minutes (Sarkar et al., 2012). In another study, both physical mixture and melt solvent techniques were implemented to formulate the solid dispersion of atorvastatin with PVK30 and Kollicoat IR and successfully enhanced the solubility of this API (Sarkar et al., 2014).

In this study, reproducible binary and ternary solid dispersion formulations of atorvastatin using simple physical mixing and fusion technique has been prepared and investigated for dissolution rate. The primary objective of the current study was to improve the aqueous solubility, dissolution profile and release rate of the atorvastatin calcium using solid dispersion approach. The polymers kollidon 90F, kollidon 12F, lutrol, and pregelatinized starch were used to prepare binary and ternary SD formulations are very cheap and widely used in different solid dosage forms. After extensive literature search, it was found that these hydrophilic polymers were not previously investigated with this API to formulate solid dispersion formulations.

Material and methods

Atorvastatin calcium was collected from Beximco Pharmaceuticals Ltd., Bangladesh. Pregelatinized starch, lutrol, kollidon 90F, PEG 6000 and kollidon 12F were purchased from BASF, Germany. Electronic balance of Metlar Toledo, Japan, USP dissolution apparatus II of Electrolab, Scanning Electron Microscopy (SEM), JEOL, Japan, double beam UV-spectrophotometer of Shimadzu, Japan and Fourier Transform Infrared Spectroscopy (FTIR) machine of Perkin Elmer, USA were used to conduct the study. All these instruments are available in Department of Pharmaceutical Technology Laboratory and CARS, university of Dhaka, Bangladesh.

Preparation of atorvastatin-hydrophilic polymer binary and ternary solid dispersion formulations

Physical mixtures of atorvastatin calcium with the hydrophilic polymers were formulated by simply mixing them for 15 minutes using a mortar-pestle (Table I). 100 mg Polyethylene glycol 6000 (PEG 6000) was taken in an aluminum pan on a hot plate and allowed to melt at a temperature 60-65 °C (Sarkar et al., 2012). Different ratios of atorvastatin calcium (ATV) and hydrophilic polymers were added in the PEG (molten). The
pregelatinized starch reported to our previous study showed for PM techniques. A physical mixture of atorvastatin and ratio for all the investigated excipients. Therefore, for ternary Atorvastatin-pregelatinized starch cumulative percentage release. On the other hand, kollidon 12F increased the dissolution release rate to 95%. Both these drug, the release was 71% after 60 minutes, whereas release atorvastatin-pregelatinized starch ternary SD formulation were higher than their physical mixture formulations. That (SAS) process, self-emulsifying drug delivery systems, (Ahjel and Dumitru, 2009; Shamsuddin 2014; Hu et al., 2014) using physical mixing and fusion 2011). The scanning resolution of FT-IR was performed at 1 cm-1 over the region of 4000–500 cm-1 (Sikdar 2011). Asif et al., 2009; Kim et al., 2008; Maurya et al., 2009; Rodde et al., 2012). In another Sar, Hossin, Al-Hossain, Sikdar, Raihan and Hossain 167 formulation was to improve the aqueous solubility, dissolution profile and (Fig. 5). Overall, the order of the carrier in enhancing the release of 90F, 12F, lutrol and pregelatinized starch) showed excellent surface of pure atorvastatin calcium converted into the rough catalyzes the transformation of hydroxymethyl glutarate to calcium would also be improved. After analyzing, there were no significant shifts in the FT-IR The SEM photomicrographs showed that the long plate products (B1 and B2) was checked for 60 minutes (Fig. V). FT-IR is a drug characterizing technique that helps to find out mixture was continuously stirring with a glass rod to assure homogenous mixing. The mixtures were then cool down to room temperature (30 °C) to get the dry and solid mass of the drug and polymer mixtures. Mortar-pestle was used to pulverize the mixtures. Prepared formulations were then filled in airtight small vials (5 ml) and the vials were kept and preserved in a desiccator until further use (Sarkar et al., 2014).

In vitro dissolution study

In vitro dissolution assays of atorvastatin calcium (ATV), binary (PM) and ternary solid dispersion (SD) formulation was done in USP type II paddle-type apparatus (mentioned previously) using distilled water (900 ml) maintaining the temperature at 37 °C and paddle rotation at 50 rpm (Iqbal et al., 2020; Sarkar et al., 2012; Sarkar et al., 2014). Each time, 5 ml of dissolution medium (distilled water) was withdrawn from the dissolution apparatus at predetermined 5, 10, 20, 30, 40, 50 and 60 min time intervals and 5 ml fresh distilled water was added to maintain the sink (900 ml) condition (Sarkar et al., 2012; Sarkar et al., 2014). The collected samples (5 ml each) were filtered through filter paper/cotton and analyzed for atorvastatin content in UV-VIS spectrophotometer. The lambda max was used to collect the absorption data at 248 nm. The calibration curve, FT-IR and SEM analyses were performed using standard methods described previously (Bobe et al., 2011; Sarkar et al., 2014).

Drug release kinetics analysis

Different kinetics models like Higuchi, Hixson-Crowell, zero order and first order models were performed to determine the drug release kinetics of the ternary solid dispersion formulations (Kayes et al., 2019). Moreover, one way analysis of variance (ANOVA) was performed among the optimized physical mixing (PM) and solid dispersions (SD) formulations for determining how the drug released significantly from these formulations.

Results and discussion

The dissolution profile of atorvastatin calcium was investigated in distilled water medium for 60 minutes. Cumulative release percentage was gradually increased from 48% (10 min) to 70.8% (60 min) (Fig. 1) (Sarkar et al., 2014). So, different polymers having dissolution enhancing

![Fig. 1. Cumulative percentage (%) release of pure atorvastatin calcium powder in distilled water](image_url)
properties such as kollidon 90F, kollidon 12F, lutrol, pregelatinized starch were used to prepare solid dispersion formulations with atorvastatin with an aim to increase dissolution profile of atorvastatin.

Table II. Different kinetic parameters of atorvastatin (ATV) release for binary physical mixing (PM) formulations (Sarkar et al., 2012)

| PM               | Ratio Drug-Polymer | Zero Order | First Order | Higuchi Model | Hixson-Crowell Model |
|------------------|--------------------|------------|-------------|---------------|---------------------|
|                  | R²     | K₀     | R²     | K₁     | R²     | Kₘ     | R²     | K_HC   |
| PMK12 (Kollidon 12F) | 1:0.5   | 0.74   | 63.345 | 0.91   | -0.5816 | 0.94   | 0.0125 | 0.86   | 1.584   |
|                  | 1:1     | 0.72   | 65.059 | 0.91   | -0.6397 | 0.93   | 0.0119 | 0.85   | 1.695   |
|                  | 1:2     | 0.75   | 68.927 | 0.94   | -0.7261 | 0.94   | 0.0116 | 0.89   | 1.8722  |
| PMK90 (Kollidon 90F) | 1:0.5   | 0.67   | 60.572 | 0.84   | -0.5763 | 0.88   | 0.0121 | 0.79   | -1.5435 |
|                  | 1:1     | 0.64   | 65.137 | 0.85   | -0.6872 | 0.88   | 0.011  | 0.78   | -1.7692 |
|                  | 1:2     | 0.60   | 66.761 | 0.83   | -0.7863 | 0.86   | 0.0102 | 0.75   | -1.9316 |
| PML (Lutrol)      | 1:0.5   | 0.72   | 62.893 | 0.89   | -0.582  | 0.93   | 0.0124 | 0.84   | -1.5793 |
|                  | 1:1     | 0.74   | 65.498 | 0.91   | -0.6476 | 0.93   | 0.012  | 0.86   | -1.7124 |
|                  | 1:2     | 0.73   | 73.749 | 0.96   | -0.9081 | 0.94   | 0.0107 | 0.90   | -2.197  |
| Pure ATV         | -       | 0.71   | 55.183 | 0.85   | -0.4424 | 0.92   | 0.0139 | 0.81   | -1.2683 |

Drug release study of atorvastatin calcium from binary solid dispersion formulations

Atorvastatin-Kollidon 90F binary SDs was prepared by physical mixing (PM) technique where atorvastatin-kollidon 90F ratio was maintained at 1.0:0.5 (PMK90 A), 1.0:1.0 (PMK90 B) and 1.0:2.0 (PMK90 C). Release of atorvastatin was checked for 60 minutes and it was observed that high amount of Kollidon 90F improved the release rate of atorvastatin from 71% to 89%. For pure drug powder, the cumulative release was 71% after 60 minutes of dissolution, whereas release value was approximately 82.0% from PMK90 A. As the content of kollidon 90F was increased, release data were also found to be increased accordingly. For 1:1, approximately 84.0% and for 1:2 it was 88.0% (Figure 3). Hydrophilic polymer kollidon 90F improves the bioavailability of some hardly soluble drugs (Herbrink et al., 2018). Kollidon 90F forms a water-soluble complex with some drug. It also accelerates the dissolution rate of the poorly aqueous soluble drug from solid dosage forms such as lovatatin (Sarkar et al., 2021). Tantishayakul et al (1999) also reported about this dissolution enhancement property of kollidon 90F where they used kollidon 90F to increase the dissolution of piroxicam. Kollidon 90F is an excellent
polymer for increasing solubility, dissolution profile of the poorly soluble drug.

Atorvastatin-kollidon 12F binary SDs formulations were prepared by simple physical mixing technique. Release value was found approximately 78% at 1:0.5 ratio. As the concentration of kollidon 12F was increased, release data were also found to be increased accordingly. For 1:1 (PMK12 B), the cumulative release was approximately 82% and for 1:2, it was 86% respectively (Figure 3). The dissolution enhancement of BCS class II drugs has been reported previously when kollidon 12 F was used as a carrier (Chowdary and Rao, 2000; Herbrink et al., 2018).

Chowdary and Rao (2000) reported the enhanced dissolution profile of itraconazole using kollidon 12F.

Binary SD formulation of atorvastatin-lutrol was prepared and screened for atorvastatin release rate. Release value was approximately 80% for 1:0.5 ratio and 91.2% for 1:2 (Figure 3) ratio, which was significantly higher than the 1:0.5 and 1:1 ratios (Table II, p < 0.05). Previously, the dissolution profile of repaglinide and olanzapine was increased by lutrol, (Cavallari et al., 2013; Patel et al., 2011).

The investigation of the release curve of the drug for PMs was done to check the goodness of fit of the various model
for PM techniques. A physical mixture of atorvastatin and ATV for ternary SD was Higuchi model (Table V and Figure 6). The solubility and dissolution rate of atorvastatin have been reported to our previous publications (Sarkar et al., 2011; Narasaiah et al., 2014). The solubility and dissolution rate of atorvastatin have been found to be increased than the physical mixture. For pure drug powder, the dissolution profile of atorvastatin calcium was made highly water soluble using different polymers in a certain ratio (1:0.5, 1:1 and 1:2). In this study, poorly soluble and low bioavailable atorvastatin calcium was converted into amorphous forms by crystalline atorvastatin calcium was made highly water soluble by polymeric matrix. The dissolution profile of atorvastatin calcium was enhanced the dissolution rate of atorvastatin by hydrophilic dispersion formulation. Ternary formulation of atorvastatin hydrophilic polymer and microcrystalline cellulose and lactose were used to prepare solid dispersion (SD) formulations. Among the ternary SD formulations (1:1 Between Groups, 1:2 Between Groups), the dissolution rate of atorvastatin from 55% to 85% using different polymers in a certain ratio (1:0.5, 1:1 and 1:2). The dissolution profile of atorvastatin calcium was fusion method. The dissolution profile of atorvastatin calcium was performed to determine the drug-excipient interactions as well as the stability of the drug in a solid dispersion formulation (Miyazaki et al., 2011; Frizon et al., 2014; Hu et al., 2012). The collected samples (5 ml) were used to check the goodness of fit of the various model (Table III). The results confirm that the release curve was a zero-order kinetics. However, the dissolution data was to improve the aqueous solubility, dissolution profile and solubility of low aqueous soluble drug, solid dispersion approaches were higher than the other polymers reported previously when kollidon 12 F was used as a carrier for atorvastatin-Kollidon 90F binary SDs formulations. When the release surface of pure atorvastatin calcium converted into the rough surface. That was hypothesised that the bioavailability of atorvastatin was increased than their physical mixture formulations. That was to improve the aqueous solubility, dissolution profile and enhancement of dissolution profile of poorly aqueous soluble atorvastatin calcium was done in USP type II paddle-type apparatus (mentioned previously due to its low oral bioavailability, atorvastatin-Kollidon 90F formulations. When the release surface of pure atorvastatin calcium converted into the rough surface of atorvastatin-Kollidon 90F formulations. When the release surface of pure atorvastatin calcium converted into the rough surface.

**Table III. ANOVA (Analysis of Variance) of the optimized PMs of atorvastatin (Sarkar et al., 2012)**

| PM          | Ratio ATV:Polymer | Source of Variation | SS      | df | MS       | F       | P-value | Fcrit |
|-------------|-------------------|---------------------|---------|----|----------|---------|---------|-------|
| PMK12       | 1:0.5             | Between Groups      | 2730.08 | 1  | 2730.08  | 11.76   | 0.01    | 4.965 |
|             |                   | Within Groups       | 2320.83 | 10 | 232.08   |         |         |       |
| PMK90       | 1:1               | Between Groups      | 3400.33 | 1  | 3400.33  | 14.85   | 0.003   | 4.965 |
|             |                   | Within Groups       | 2289.33 | 10 | 228.93   |         |         |       |
|             | 1:2               | Between Groups      | 3710.08 | 1  | 3710.08  | 15.14   | 0.003   | 4.965 |
|             |                   | Within Groups       | 2450.83 | 10 | 245.08   |         |         |       |
| PML         | 1:0.5             | Between Groups      | 3136.33 | 1  | 3136.33  | 14.66   | 0.003   | 4.965 |
|             |                   | Within Groups       | 2139.33 | 10 | 213.93   |         |         |       |
|             | 1:1               | Between Groups      | 4695.13 | 1  | 4695.13  | 22.024  | 0.001   | 4.965 |
|             |                   | Within Groups       | 2131.79 | 10 | 213.18   |         |         |       |
|             | 1:2               | Between Groups      | 5980.87 | 1  | 5980.87  | 28.654  | 0.0003  | 4.965 |
|             |                   | Within Groups       | 2087.28 | 10 | 208.73   |         |         |       |
|             | 1:0.5             | Between Groups      | 2914.08 | 1  | 2914.083 | 12.810  | 0.005   | 4.965 |
|             |                   | Within Groups       | 2274.83 | 10 | 227.483  |         |         |       |
|             | 1:1               | Between Groups      | 3267.00 | 1  | 3267.00  | 13.962  | 0.004   | 4.965 |
|             |                   | Within Groups       | 2340.00 | 10 | 234.00   |         |         |       |
|             | 1:2               | Between Groups      | 5034.80 | 1  | 5034.80  | 19.788  | 0.001   | 4.965 |
|             |                   | Within Groups       | 2544.43 | 10 | 254.44   |         |         |       |
pregelatinized starch reported to our previous study showed following SD the ratio was fixed at 1:2. Release study was carried out ratio for all the investigated excipients. Therefore, for ternary in vitro were higher than their physical mixture formulations. That 90F ternary SD formulation (1.0:2.0) showed nearly 99.1% drug, the release was 71% after 60 minutes, whereas release physical mixture._dispersion formulation. Ternary formulation of 9). The order of the fitted model for the ternary SDs of ATV percentage release was found to be increased compared to was checked for 60 minutes (Figure 4). The release was atorvastatin-pregelatinized starch ternary SD formulation the surface of pure atorvastatin calcium converted into the rough forms, Microwave induced solubility cyclodextrin complexation and solid dispersion approaches. Poloxamer 188 (Bobe Iqbal, et al., 2014) using physical mixing and fusion approaches. The polymers kollidon 90F, kollidon 12F, lutrol, and pregelatinized starch) showed excellent formulations of atorvastatin prepared by polyethylene glycol was implemented to formulate the solid dispersion of crystals, Microwave induced solubility approach to improve therapeutic efficacy and solid dosage forms. Preparation of atorvastatin-hydrophilic polymer binary and ternary solid dispersions which indicates the crystalline atorvastatin calcium was converted into amorphous form after the ternary SD formulation. So, it was hypothesised that the bioavailability of atorvastatin using different polymers in a certain ratio (1:0.5, 1:1 and was to improve the aqueous solubility, dissolution profile and different kinetics models like Higuchi, Hixson-Crowell, zero formulations with atorvastatin with an aim to increase hydrophilic polymers were added in the PEG (molten). The mixture was continuously stirring with a glass rod to assure from the dissolution apparatus at predetermined 5, 10, 20, 30, 5 ml of dissolution medium (distilled water) was withdrawn and allowed to melt at a temperature 60-65 °C (Sarkar, Hossin, Al-Hossain, Sikdar, Raihan and Hossain, et al., 2012). Different ratios of atorvastatin calcium (ATV) and was taken in an aluminum pan on a hot plate and screened for atorvastatin release rate. Release value was approximately 80% for 1:0.5 ratio and 91.2% for 1:2 (Figure 3). The release value was approximately 82.0% from kollidon 90F where they used kollidon 90F to increase the carrier (Chowdary and Rao, 2000; Herbrink et al., 2014). This indicates the different polymers having dissolution enhancing also found to be increased accordingly. For 1:1, approximately 84.0% and for 1:2 it was 88.0% (Figure 4). Drug release study of atorvastatin from ternary solid dispersion (SD) formulations prepared by fusion method. Atorvastatin ternary solid dispersion (SD) formulations were prepared by fusion/hot melting technique. In PM formulations, improved dissolution has been found for 1:2

| Formulations | Source of Variation | SS     | df  | MS   | F     | P-value | F_{crit} |
|--------------|---------------------|--------|-----|------|-------|---------|---------|
| SDK90        | Between Groups      | 6538.00| 1.00| 6538.00 | 24.37 | 0.001   | 4.965   |
|              | Within Groups       | 2682.81| 10.00| 268.28 |       |         |         |
| SDK12        | Between Groups      | 4602.083 | 1   | 4602.083 | 15.29 | 0.003   | 4.965   |
|              | Within Groups       | 3010.833 | 10  | 301.08  |       |         |         |
| SDPS         | Between Groups      | 5495.520 | 1.00| 5495.520 | 18.488| 0.002   | 4.965   |
|              | Within Groups       | 2972.400 | 10.00| 297.240 |       |         |         |
| SDL          | Between Groups      | 5461.333 | 1.00| 5461.333 | 20.083| 0.001   | 4.965   |
|              | Within Groups       | 2719.333 | 10.00| 271.933 |       |         |         |

(Table II). The results confirm that the release curve was a poor fit to zero-order kinetics. However, the dissolution data were best fitted to the Higuchi model. The order of goodness to fit of different models for PMs was found: Higuchi model>First order>Hixson Crowell>Zero order.
Atorvastatin-pregelatinized starch ternary SD formulation (1:2) was prepared and the cumulative percentage of dissolution was 96%. Atorvastatin-kollidon 90F, Soluplus®, PVP VA64, HPMC, and PEG 4000 increased the release rate up to 91.66% (Shamsuddin et al., 2014). Solid dispersion (SD) formulations compared to the pure active material showed enhanced dissolution rate of atorvastatin by hydrophilic polymer kollidon 90F which improved the release of atorvastatin from the ternary SD formulation. So, it can be concluded that the solubility of atorvastatin calcium was increased in its ternary SD formulations. In this study, reproducible binary and ternary solid dispersion formulations were prepared by fusion/hot melting technique. In PM formulation, the order of the carrier in enhancing the release of atorvastatin was kollidon 90F > pregelatinized starch reported to our previous study showed dissolution method where dissolution physical mixture.

Overall, the order of the carrier in enhancing the release of atorvastatin was kollidon 90F > pregelatinized starch, poloxamer 407, hydroxypropyl cellulose, and increased the cumulative percentage of dissolution than the physical mixture.

Fig. 6. FT-IR spectroscopy of (a) pure atorvastatin powder, (b) ternary solid dispersion formulation of atorvastatin and kollidon 90F (1:2), (c) binary atorvastatin and kollidon 90F (1:2) formulation and (d) pure Kollidon 90F

Fig. 7. Scanning electron microscopic (SEM) analyses of a. pure atorvastatin, b. ternary solid dispersion formulation atorvastatin and kollidon 90F (1:2) and c. binary formulation atorvastatin and kollidon 90F (1:2)
ratio for all the investigated excipients. Therefore, for ternary SD the ratio was fixed at 1:2. Release study was carried out following in vitro dissolution method where dissolution media was water and study was performed for 60 minutes as for PM techniques. A physical mixture of atorvastatin and pregelatinized starch reported to our previous study showed 96% (1:2 ratios) cumulative percentage release of atorvastatin after 60 min (Sarkar et al., 2012). Atorvastatin-pregelatinized starch ternary SD was prepared by fusion technique. Release of atorvastatin from atorvastatin-pregelatinized starch ternary SD formulation was checked for 60 minutes (Figure 4). The release was found to be increased than the physical mixture. For pure drug, the release was 71% after 60 minutes, whereas release value was approximately 98.8% from ternary solid dispersion formulation. Ternary formulation of atorvastatin-lutrol (1:2) was prepared and the cumulative percentage release was found to be increased compared to binary formulations (91% vs 96%). Atorvastatin-kollidon 90F ternary SD formulation (1.0:2.0) showed nearly 99.1% cumulative percentage release. On the other hand, kollidon 12F increased the dissolution release rate to 95%. Both these were higher than their physical mixture formulations. That indicates the fusion method is more effective than the physical mixture.

As for PM, the best fitted model of the dissolution data of ATV for ternary SD was Higuchi model (Table V and Figure 9). The order of the fitted model for the ternary SDs of ATV

![Comparison of pure ATV, PM and SD with marketed brands](image1)

**Fig. 8.** Comparison of pure ATV, PM and SD with marketed brands B1 and B2

![Higuchi model release curves](image2)

**Fig. 9.** Higuchi model release curves of ATV from physical mixtures (PMs) of ATV with Kollidon 12 (a), Lutrol (b) and Kollidon 90 (c). Higuchi release curves of pure ATV and ATV solid dispersion formulations (d) with Kollidon 12, Lutrol and Kollidon 90.
and polymers were: Higuchi model> Hixson Crowell> First order> Zero order

The dissolution profile of ATV of two common marketed products (B1 and B2) was checked for 60 minutes (Fig. V and Fig. 8). The cumulative releases were 68.9% (B1) and 73.1% (B2) which are also found to be lowered than the solid dispersion formulations. Among the ternary SD formulations the highest ATV release rate was found for atorvastatin-kollidon 90F formulations. When the release data of ATV from atorvastatin-kollidon 90F formulation was compared to the marketed product, it was found much higher (Fig. 5).

Overall, the order of the carrier in enhancing the release of atorvastatin was found as atorvastatin calcium ternary SD > atorvastatin calcium binary SD > pure atorvastatin calcium. In all cases, ternary solid dispersion showed a better cumulative percentage of dissolution than the physical mixture. The order of the carriers in enhancing the release of atorvastatin was found as kollidon 90F > pregelatinized starch > kollidon 12F > pure atorvastatin. Dong et al, (2018) enhanced the dissolution rate of atorvastatin by hydrophilic carrier poloxamer 188. Croscarmellose sodium, microcrystalline cellulose and lactose were used to prepare solid dispersion (SD) formulations of atorvastatin by Asif Iqbal et al, (2020). Bobe et al, (2011) previously increased the dissolution rate of atorvastatin from 55% to 85% using mannitol, PVP-K30 and PEG 4000. Solid dispersion (SD) formulations of atorvastatin prepared by polyethylene glycol 4000 increased the release rate up to 91.66% (Shamsuddin et al., 2016). The polymers used in the current study (kollidon 90F, 12F, luteol and pregelatinized starch) showed excellent dissolution profile and, in some instances, performances were higher than the other polymers reported previously (Bobe et al., 2011).

Characterization of the best formulation

FT-IR is a drug characterizing technique that helps to find out the drug-excipient interactions as well as the stability of the drug in a solid dispersion formulation (Miyazaki et al., 2011). The scanning resolution of FT-IR was performed at 1 cm⁻¹ over the region of 4000–500 cm⁻¹ (Sikdar et al., 2019). After analyzing, there were no significant shifts in the FT-IR peaks. However, there were some slight shifts of the peaks in binary and ternary solid dispersions which indicates the formation of solid dispersions with the respective carriers (Fig. 6).

The SEM photomicrographs showed that the long plate surface of pure atorvastatin calcium converted into the rough surface after fusion by the carriers (Fig. 7). Therefore, the crystalline atorvastatin turned/converted into an amorphous form (sarkar et al., 2014). This indicates the significant enhancement of water solubility as well as it was hypothesised that the bioavailability of atorvastatin calcium would also be improved.

Conclusion

In this study, poorly soluble and low bioavailable atorvastatin calcium was made highly water soluble using different polymers in a certain ratio (1:0.5, 1:1 and 1:2) by using physical mixing and SD techniques (1:2). After the dissolution profile study, it was found that ternary SD formulations gave higher drug release after one hour compared to the physical mixers, the pure drug and the marketed product. The order of the carriers enhancing the Atorvastatin calcium found was like kollidon 90F > pregelatinized starch > luteol > Kollidon 12F > pure atorvastatin. Moreover, there were no significant shifts in the FT-IR peaks and the SEM images showed that the longer plate-like form of atorvastatin calcium is converted into the rough surface when the SD was formulated by fusion with the carriers. That means the crystalline atorvastatin calcium was converted into amorphous form after the ternary SD formulation. So, it can be concluded that the solubility of atorvastatin calcium was increased in its ternary SD formulations. However, to describe the more precise characterization of the SDs of atorvastatin calcium (ATV), DSC (Differential Scanning Calorimetry) and XRD (X-ray Diffraction) analysis is necessary to perform.

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