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

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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;

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Friedrich *et al.,* 2006; Frizon *et al.,* 2013; Lai *et al.,* 2011; Merisko-Liversidge and Liversidge, 2008; Shamsuddin *et al.,* 2016; Sharma *et al.,* 2009). To increase the water solubility of low aqueous soluble drug, solid dispersion is considered one of the most common and effective methods (Shamsuddin *et al.,* 2016). In solid dispersion technique, the solubility of the poorly water-soluble drug is increased using different hydrophilic carriers in which the drug is molecularly dispersed (Chiou and Riegelman, 1971). Crystalline drugs are transformed into amorphous forms by different hydrophilic polymers in solid dispersion approach (Choi and Park, 2017).

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; Narasaiah *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 hodrophilic 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

Table I. Formulations were prepared by physical mixing (PM) and fusion/melting method

Formulations code	PML	PMK90	PMK12	SDPS	SDL	SDK90	SDK12
Atorvastatin (mg)	10	10	10	10	10	10	10
Lutrol (mg)	5/10/20	-	-	-	20	-	-
Kollidon 90F (mg)	-	5/10/20	-	-	-	20	-
Kollidon 12F (mg)	-	-	5/10/20	-	-	-	20
Pregelatinized starch (mg)	-	-	-	20	-	-	-
PEG 6000	-	-	-	100	100	100	100

PML: Physical Mixing Lutrol; PMK90: Physical Mixing Kollidon 90F; PMK12: Physical Mixing Kollidon 12F; SDPS: Solid dispersion Pregelatinized starch; SDL: Solid dispersion Lutrol; SDK90: Solid dispersion Kollidon 90F; SDK12: Solid dispersion Kollidon 12F; 5/10/20 mg: 1:0.5, 1:1 and 1:2 ratios of atorvastatin and polymers.

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
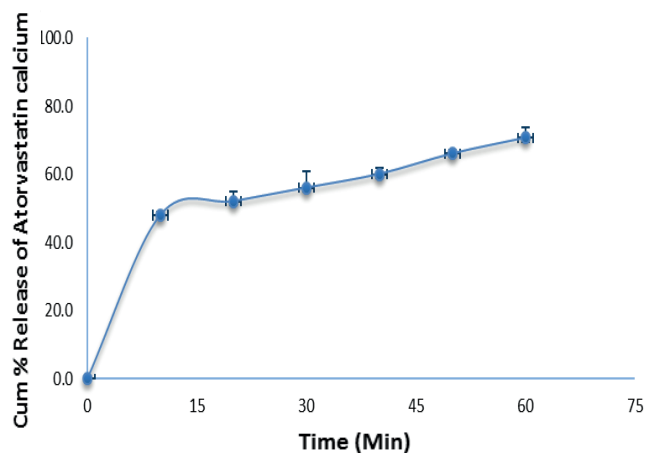

Fig. 1. Cumulative percentage (%) release of pure atorvastatin calcium powder in distilled water
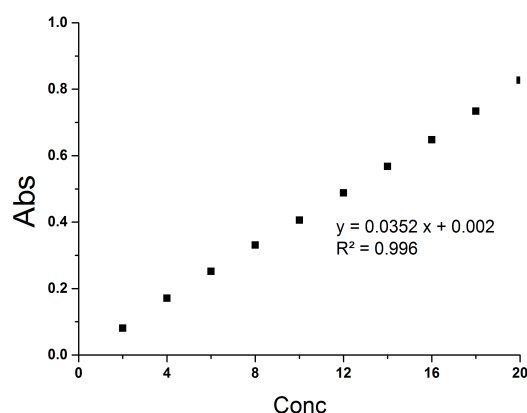
Fig. 2. Calibration curve atorvastatin calcium in distilled water

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.

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 lovastatin (Sarkar *et al.,* 2021). Tantishaiyakul *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

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	
		R^2	K_0	R^2	K_1	R^2	K_h	R^2	K_{HC}
	1:0.5	0.74	63.345	0.91	-0.5816	0.94	0.0125	0.86	1.584
PMK12 (Kollidon 12F)	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
	1:0.5	0.67	60.572	0.84	-0.5763	0.88	0.0121	0.79	-1.5435
PMK90 (Kollidon 90F)	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
	1:0.5	0.72	62.893	0.89	-0.582	0.93	0.0124	0.84	-1.5793
PML (Lutrol)	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
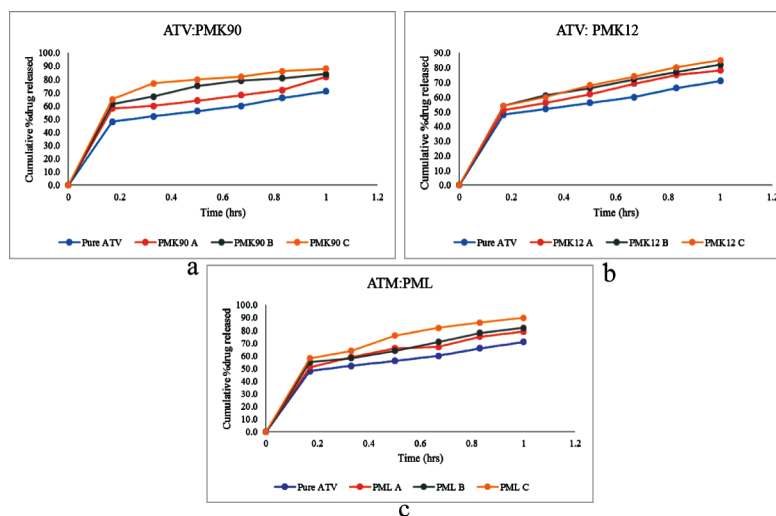
Fig. 3. Cumulative % release (Zero order) of atorvastatin from atorvastatin-kollidon 90F (a), kollidon 12F (b) and lutrol (c) binary SD prepared by physical mixing technique
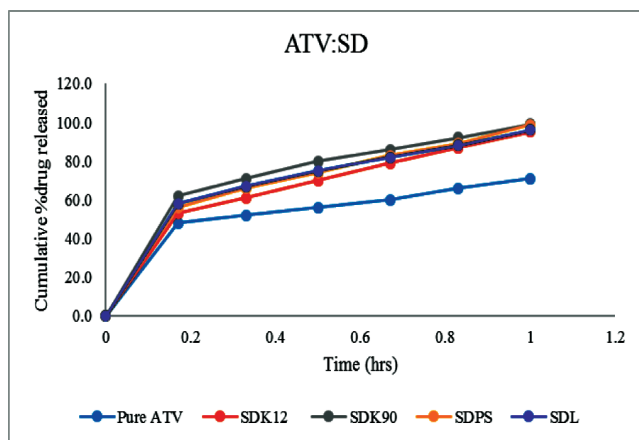

Fig. 4. Cumulative percentage release (zero order) of atorvastatin from ternary SD formulation prepared by fusion technique
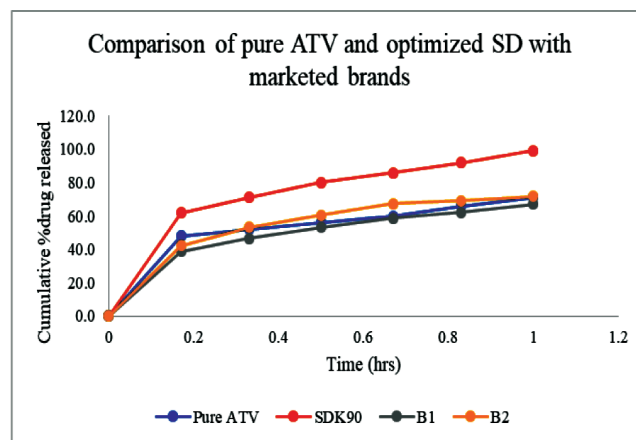

Fig. 5. Comparison of pure ATV and optimized SD with marketed brands

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

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	F_{crit}
PMK12 (Kollidon 12F)	1:0.5	Between Groups	2730.08	1	2730.08	11.76	0.01	4.965
		Within Groups	2320.83	10	232.08			
	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			
PMK90 (Kollidon 90F)	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			
PML (Lutrol)	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			

Table IV. Kinetic parameters of atorvastatin (ATV) release from ternary solid dispersion (1:2 ratios) formulations (Sarkar *et al.,* 2012)

SD	Zero Order		First Order		Higuchi Model		Hixson-Crowell Model	
	R^2	K_0	R^2	K_1	R^2	K_h	R^2	K_{HC}
SDK12	0.82	79.654	0.95	-1.1351	0.98	0.0107	0.96	-2.5635
SDK90	0.75	79.938	0.87	-1.6761	0.94	0.01	0.94	-3.0945
SDPS	0.80	81.46	0.85	-1.5604	0.97	0.0103	0.94	-3.0095
SDL	0.77	77.94	0.94	-1.1904	0.96	0.0105	0.94	-2.6024
Pure ATV	0.71	55.183	0.85	-0.4424	0.92	0.0139	0.81	-1.2683

Table V. ANOVA analysis of the optimized SDs of atorvastatin

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	4602.08	15.29	0.003	4.965
	Within Groups	3010.833	10	301.08			
SDPS	Between Groups	5495.520	1.000	5495.520	18.488	0.002	4.965
	Within Groups	2972.400	10.000	297.240			
SDL	Between Groups	5461.333	1.000	5461.333	20.083	0.001	4.965
	Within Groups	2719.333	10.000	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.

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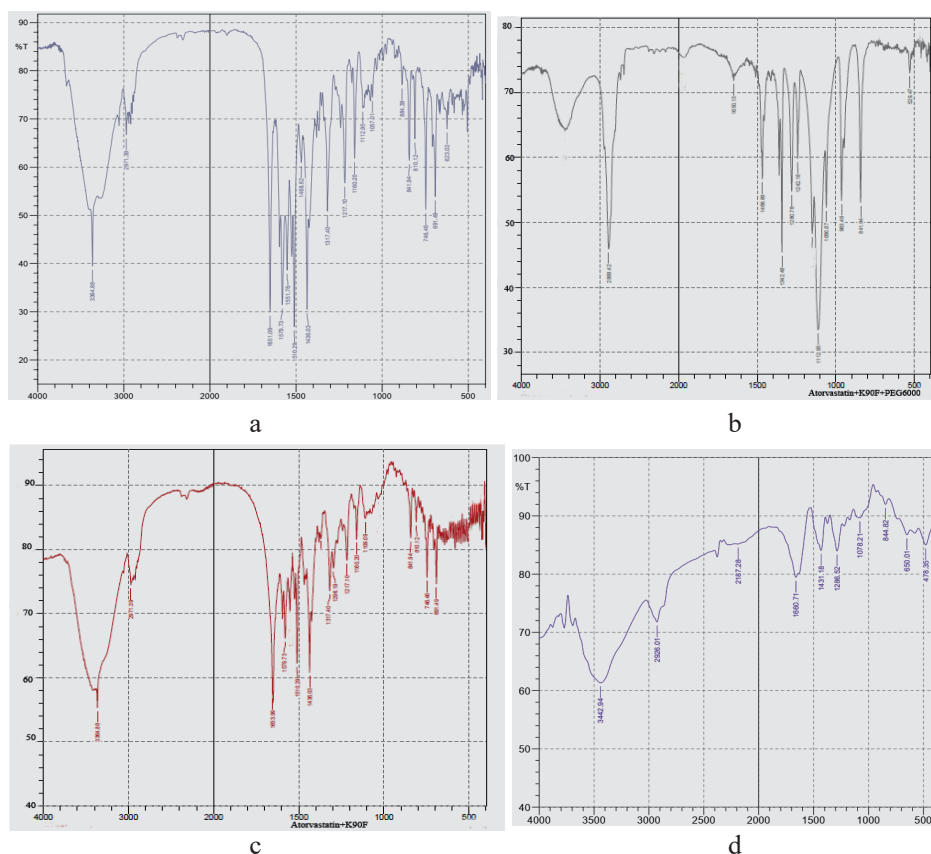
Fig. 6. FT-IR spectroscopy of (a) pure atorvastatin powder, (b) ternary solid dispersion formulation of atorvastatin and kollidon 90F (1:2), (c) binary atorvastatin and kollidon 90F (1:2) formulation and (d) pure Kollidon 90F
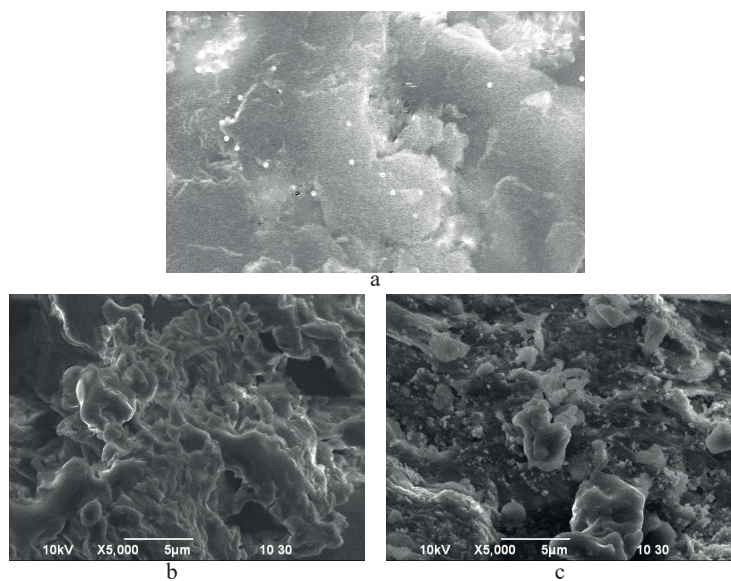

Fig. 7. Scanning electron microscopic (SEM) analyses of a. pure atorvastatin, b. ternary solid dispersion formulation atorvastatin and kollidon 90F (1:2) and c. binary formulation atorvastatin and kollidon 90F (1:2)
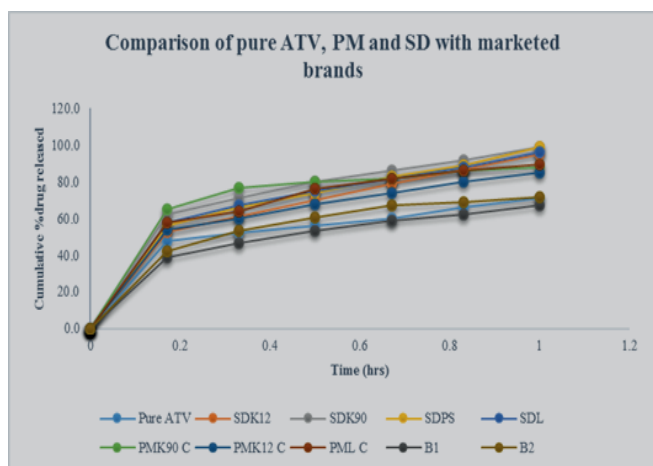
Fig. 8. Comparison of pure ATV, PM and SD with marketed brands B1 and B2

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
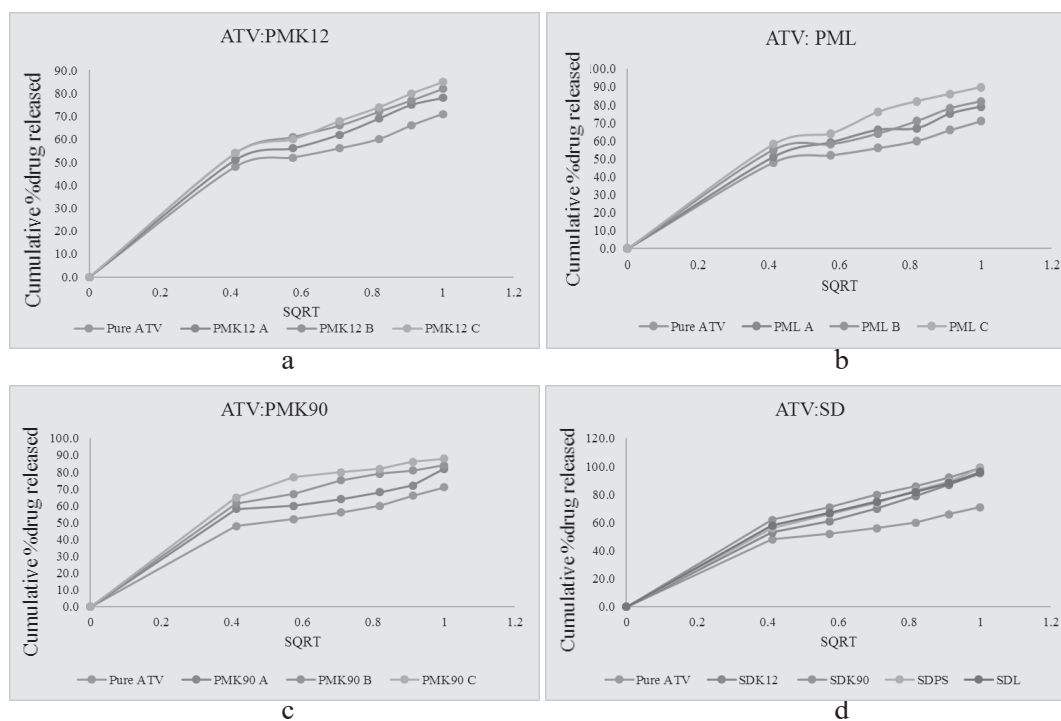

Fig. 9. Higuchi model release curves of ATV from physical mixtures (PMs) of ATV with Kollidon 12 (a), Lutrol (b) and Kollidon 90 (c). Higuchi release curves of pure ATV and ATV solid dispersion formulations (d) with Kollidon 12, Lutrol and Kollidon 90.

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, lutrol 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 > lutrol> 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.

References

Ahjel S and Dumitru L (2009), Enhancement of solubility and dissolution rate of different forms of atorvastatin calcium in direct compression tablet formulas, *Farmacia.* **57**(3): 290-300.

Ali S and Eman Al-Khedairy E (2019), Solubility and Dissolution Enhancement of Atorvastatin Calcium using Solid Dispersion Adsorbate Technique, *Iraqi J. Pharm. Sci.* **28**(2): 105-114. DOI: 10.31351/vol28iss2.

Arunkumar N, Deecaraman M, Rani C, Mohanraj KP and Kumar KV (2009), Preparation and solid state characterization of atorvastatin nanosuspensions for enhanced solubility and dissolution, *Int J Pharm Tech Res.* **1**(4): 1725-1730.

Bobe K, Subrahmanya C, Suresh S, Gaikwad D, Patil M, Khade T, Gavitre B, Kulkarni V and Gaikwad U (2011), Formulation and evaluation of solid dispersion of atorvastatin with various carriers, *Pharmacie Globale*. **2**(1):1-6.

Cavallari C, Fini A and Ceschel G (2013), Design of olanzapine/lutrol solid dispersions of improved stability and performances, *Pharmaceutics*. **5**(4): 570-590. DOI: .org/ 10.3390 /pharmaceutics 5040570.

Charman WN (2000), Lipids, lipophilic drugs, and oral drug delivery—some emerging concepts, *J. Pharm. Sci.* **89**(8): 967-978. https://doi.org/ 10.1002/ 1520-6017 (200008) 89:8<967:: AID- JPS1> 3.0.CO;2-R.

Chaudhary A, Nagaich U, Gulati N, Sharma V, Khosa R (2012), Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review, *J Adv Pharm Educ Res*. 2(1):32-67.

Chiou L and Riegelman S (1971), Pharmaceutical applications of solid dispersion systems, *J. Pharm. Sci.* **60**(9): 1281-1302.

Choi S and Park S (2017), Design of PVP/VA S-630 based tadalafil solid dispersion to enhance the dissolution rate, *Eur J Pharm Sci.* **97**: 269-276. https://doi. org/10.1016/ j.ejps.2016.11.030.

Chowdary R and Rao S (2000), Investigation of dissolution enhancement of itraconazole by solid dispersion in superdisintegrants, *Drug Dev. Ind. Pharm.* **26**(11): 1207-1211. https://doi.org/10.1081/DDC- 100100993.

Dong W, Su X, Xu M, Hu M, Sun Y and Zhang P (2018), Preparation, characterization, and in vitro/vivo evaluation of polymer-assisting formulation of atorvastatin calcium based on solid dispersion technique, *Asian J. Pharm. Sci.* **13**(6): 546-554. https://doi.org/10.1016/ j.ajps.2018.08.010.

Friedrich H, Fussnegger B, Kolter K and Bodmeier R (2006), Dissolution rate improvement of poorly water-soluble drugs obtained by adsorbing solutions of drugs in hydrophilic solvents onto high surface area carriers, *Eur. J. Pharm. Biopharm.* **62**(2): 171-177. https://doi.org/10.1016/ j.ejpb.2005.08.013.

Frizon F, Eloya J, Donaduzzi C, Mitsui M and Marchetti J (2013), Dissolution rate enhancement of loratadine in

polyvinylpyrrolidone K-30 solid dispersions by solvent methods, *Powder Technol*. **235**: 532-539. https://doi.org/10.1016/ j.powtec.2012.10.019.

Ha ES, Baek I, Cho W, Hwang S and Kim M (2014), Preparation and evaluation of solid dispersion of atorvastatin calcium with Soluplus® by spray drying technique, *Chem. Pharm. Bull.* **62**(6): 545-551. https://doi.org/ 10.1248/cpb.c14-00030.

Herbrink M, Groenland S, Huitema A, Schellens J, Beijnen J, Steeghs N and Nuijen B (2018), Solubility and bioavailability improvement of pazopanib hydrochloride, *Int. J. Pharm.* **544**(1): 181-190. https://doi.org/10.1016/ j.ijpharm.2018.04.037.

Hu L, Gu D, Hu Q, Shi Y and Gao N (2014), Investigation of solid dispersion of atorvastatin calcium in polyethylene glycol 6000 and polyvinylpyrrolidone, *Trop. J. Pharm. Res.* **13**(6): 835-842. DOI: 10.4314/tjpr.v13i6.2.

Iqbal A, Hossain M, Shamim M, Islam M, and Siddique M (2020), Formulation, *in vitro* evaluation and characterization of atorvastatin solid dispersion, *Trop. J. Pharm. Res*. **19**(6): 1131-1138. DOI: 10.4314/tjpr.v19i6.2.

Jahan R, Islam M, Tanwir A and Chowdhury J (2013), In vitro dissolution study of atorvastatin binary solid dispersion, *J. Adv. Pharm. Technol.* **4**(1): 18-24. DOI: 10.4103/2231-4040.107496.

Kalepu S and Vijaykumar N (2015), Insoluble drug delivery strategies: review of recent advances and business prospects, *Acta Pharmaceutica Sinica B.* **5**(5): 442-453. https://doi.org/ 10.1016/j.apsb. 2015.07.003.

Kayes K, Islam M, Hamidur R and Saqueeb N (2019), A comparative study on Naproxen Sodium tablets formulating with different super disintegrants, *GSC biol. pharm. sci.* **9**(3):076-084. https://doi.org/ 10.30574/gscbps.2019. 9.3.0234.

Kim J, Kim M, Park H, Jin S, Lee S and Hwang S (2008), Physicochemical properties and oral bioavailability of amorphous atorvastatin hemi-calcium using spray-drying and SAS process, *Int. J. Pharm.* **359**(1-2): 211-219. https://doi.org/ 10.1016/j .ijpharm. 2008.04. 006.

Lai F, Pini E, Angioni G, Manca M, Perricci J, Sinico C and Fadda A (2011), Nanocrystals as tool to improve piroxicam dissolution rate in novel orally disintegrating tablets, *Eur. J. Pharm. Biopharm.* **79**(3): 552-558. https://doi.org/ 10.1016/j.ejpb. 2011.07.005.

Lawrence X Yu (1999), An integrated model for determining causes of poor oral drug absorption, *Pharm. Res.* **16**(12): 1883-1887. https://doi.org/ 10.1023/A: 1018911728161.

Maurya D, Belgamwar V, and Tekade A (2010), Microwave induced solubility enhancement of poorly water soluble atorvastatin calcium, *J. Pharm. Pharmacol.* **62**(11): 1599-1606. https://doi.org/ 10.1111/j.2042-7 158.2010.01187.x.

Merisko-Liversidge EM and Liversidge GG (2008), Drug nanoparticles: formulating poorly water-soluble compounds, *Toxicol. Pathol.* **36**(1): 43-48. https://doi.org/10.1177/0192623307310946

Miyazaki T, Aso Y, Yoshioka S and Kawanishi T (2011), Differences in crystallization rate of nitrendipine enantiomers in amorphous solid dispersions with HPMC and HPMCP, *Int. J. Pharm.* **407**(1-2): 111-118. https://doi.org/ 10.1016/ j.ijpharm. 2011.01.035

Mukhtar RYA, Reid J and Reckless JPD (2005), Pitavastatin, *Int. J. Clin. Pract.* **59**(2): 239-252. https://doi.org/ 10.1111/j.1742-1241. 2005.00461.x

Naqvi A, Ahmad M, Minhas MU, Khan KU, Batool F and Rizwan A (2020), Preparation and evaluation of pharmaceutical co-crystals for solubility enhancement of atorvastatin calcium, *Polym. Bull.* **77**: 6191-6211. https://doi.org/10. 1007/s00289- 019-02997-4

Narasaiah L, Reddy K, Kishore K and Raj Ku (2010), Enhanced dissolution rate of atorvastatin calcium using solid dispersion with PEG 6000 by dropping method, *J. Pharm. Sci. & Res*. **2**(8): 484-491.

Pabari R, Jamil A, Kelly J, Ramtoola Z (2014), Fast disintegrating crystalline solid dispersions of simvastatin for incorporation into orodispersible tablets, *Int. J. Pharm. Investig.* **4**(2): 51-59. DOI: 10.4103/2230-973X.133029.

Palem CR, Patel S and Pokharkar VB (2009), Solubility and stability enhancement of atorvastatin by cyclodextrin complexation, *PDA J Pharm Sci Technol.* **63**(3): 217-225.

Patel M, Pandya N and Bhaskar VH (2011), Preparation, characterization and in vitro evaluation of repaglinide binary solid dispersions with hydrophilic polymers, *Int J Drug Dev & Res.* **3**(2): 111-121.

Rodde M, Divase G, Devkar T and Tekade A (2014), Solubility and bioavailability enhancement of poorly aqueous soluble atorvastatin: in vitro, ex vivo, and in vivo studies, *BioMed Res. Int.* **2014**: 463895. https://doi. org/10.1155/ 2014/463895.

Sarkar R, AL-Hossain M, Islam S, Faroque ABM (2012), Effect of Hydrophilic Swellable Polymers on Dissolution Rate of Atorvastatin Using Simple Physical Mixing Technique, *Ind. J. Novel Drug. Del.* **4**(2): 130-138.

Sarkar M, Hossain A, Sultana R and Faroque A (2014), Improvement solubility of atorvastatin calcium using solid dispersion technique, *Int. J. Pharm. Sci.* **5**(12): 5405-5410.

Sarkar M, Sikdar K, Hossain A and Sharmin N (2021), Improving the drug dissolution profile of poorly aqueous soluble lovastatin using hydrophilic polymers by solid dispersion and physical mixing techniques, *Natl J Physiol Pharm Pharmacol* . **11**(2): 216-221. DOI: 10.5455/njppp. 2021.11.123 47202022122020.

Shamsuddin, Fazil M, Ansari H and Ali J (2016), Atorvastatin solid dispersion for bioavailability enhancement, *J. Adv. Pharm. Technol.* **7**(1): 22-26. DOI: 10.4103/2231-4040.169873.

Sharma D, Soni M, Kumar S, Gupta G (2009), Solubility enhancement—eminent role in poorly soluble drugs, *Res J Pharm Technol.* **2**(2): 220-224.

Sikdar K, Ahamed A, Alam M, Sarkar M and Sajeeb B (2019), Formulation and in-vitro evaluation of bilayer tablets of atenolol and amlodipine, *Bangladesh Pharmaceutical Journal.* **22**(2): 153-169.

Tantishaiyakul V, Kaewnopparat N and Ingkatawornwong S (1999), Properties of solid dispersions of piroxicam in polyvinylpyrrolidone, *Int J Pharm.* **181**(2): 143-151. https://doi. org/10.1016/S0378 -5173(99)00070-8.