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RESEARCH ARTICLE

Improving the drug dissolution profile of poorly aqueous soluble lovastatin using hydrophilic polymers by solid dispersion and physical mixing techniques

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ABSTRACT

Background: Improvement of the dissolution rate and solubility of poorly aqueous soluble drugs using solid dispersion (SD) techniques are considered as one of the most attractive processes. The focus of the current research project is to investigate the dissolution property of lovastatin (LVT) using SD technology comprising of drug, excipients, and carrier. **Aim and Objectives:** The main objective of this study is to augment the dissolution profile of LVT, a statin medication belongs to biopharmaceutics classification system Class II drugs and water-insoluble, by applying SD procedures. **Materials and Methods:** The melt solvent/fusion and physical mixing (PM) methods were employed to prepare the SDs. PMs of LVT and hydrophilic carriers such as Kollidon 90F and Kollicoat IR were prepared and investigated at three different ratios (1:0.5, 1:1, and 1:2). SD formulation of LVT was prepared by melt solvent or fusion technique using hydrophilic carriers and polyethylene glycol at 1:0.5:5, 1:1:5, and 1:2:5 ratios. The characterization of the prepared SD formulations was investigated by scanning electron microscopy (SEM) and *in vitro* dissolution studies. **Results:** Physical characterization experiment showed that SD of LVT prepared by fusion technique demonstrated improved dissolution property compared to the PM formulations or pure drug attributable to the conversion of LVT into an amorphous and/or less crystalline form. The results of *in vitro* dissolution enhancement order followed the same trend both in SD formulations and in PMs (Kollicoat IR> Kollidon 90F). The SEM analyses indicated that crystallinity of drug decreased in the SD formulation suggesting a portion of LVT could be in an amorphous state. **Conclusion:** The outcomes suggested a remarkably increased dissolution rate of LVT through SD systems prepared with suitable and correct proportion of polymers by melt solvent method and PM technique when compared with the pure drug dissolution profile. This was because of the hydrophilic carriers which affected the crystal structure of the drug. Hence, this approach of SD technique utilizing the above-mentioned carriers could be employed as a substantial formulation strategy to enhance the *in vitro* dissolution rate which, in turn, may improve the oral bioavailability of the water-insoluble drugs.

KEY WORDS: Solid Dispersion; Fusion Method; Physical Mixing; Biopharmaceutics Classification System Class II Drug; Dissolution Rate

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INTRODUCTION

Drugs belong to Class II and Class IV of the Biopharmaceutics Classification System (BCS), possess an inferior aqueous solubility and tend to have a low dissolution (%) rate and poor bioavailability.[1] These drugs are associated with a poor absorption rate when administered through the oral route,

which is the most natural, safe, and convenient route for drug administration. Hence, dissolution is considered as the rate determining step especially for Class II drugs which show high permeability but low solubility.[2] If solid oral dosage forms are not released completely in the gastrointestinal area, they may impose a critical barrier to the bioavailability predominantly for drugs with reduced water solubility. More than 40% of the currently approved drugs and as high as 90% of the chemical entities in the discovery pipeline exhibit poor gastrointestinal solubility, thus they display slow drug absorption leading to low bioavailability.[3,4] In the last few decades, notable progress has been made in the development of physical and chemical techniques for improving the solubility of drugs in water. Several approaches have been adopted to rise the dissolution rate of poorly soluble drugs including physical, chemical, and other modifications or techniques such as particle size reduction, salt formation, pro-drugs, pH adjustments, micro-emulsion, complexation, cosolvency, and nanocrystallization.[1,5-8] Despite this progress, many of these techniques are not devoid of drawbacks.[9] To overcome the limitations of these strategies and improve drug dissolutions rates, solid dispersion (SD) technique has widely been used. SD is one of the most effective ways to enhance drug release from poorly aqueous soluble drugs.[10,11] In SD approach, crystalline drugs are transformed to amorphous forms by different hydrophilic polymers.[12]

Lovastatin (LVT), a statin medication, belongs to BCS Class II drugs and is prescribed for controlling hyperlipidemia. Its metabolite hydroxy acid is a potent inhibitor of enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which catalyzes the transformation of hydroxymethyl glutarate to mevalonate [Figure 1].[13] Mevalonate is an essential building block for the biosynthesis of cholesterol.[13] LVT is a crystalline white powder exhibiting very little/poor water-solubility (0.4 μg/mL).[14]

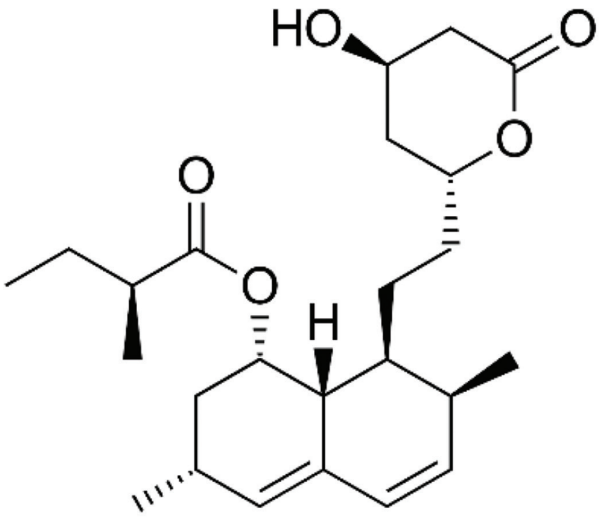

Figure 1: Chemical structure of lovastatin[13]

The partition coefficient of this drug in octanol/water system was reported approximately 1.2×10^4 at room temperature.[13,14] The high partition coefficient indicates its hydrophobicity and hence low aqueous solubility resulting in <5% bioavailability.[13,14] Therefore, improvement of water solubility of this drug is a valuable approach to improve therapeutic efficacy. To address aqueous solubility issue of LVT, different methods have been taken to improve its solubility as well as bioavailability. For examples, nanocrystals complexation with β-cyclodextrin, SD, microemulsion, and drug-dendrimer conjugates approaches have been used.[15-18] Different hydrophilic polymers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), and sodium starch glycolate (Na-SG) have been used to prepare SD formulations. However, in most instances solubility and dissolution rate did not improve to the expected level.[15-18] Therefore, the purpose of the present study was to formulate and evaluate SDs of LVT in hydrophilic carriers Kollidon 90F and Kollicoat IR using PM and fusion techniques. In this work, the aqueous solubility and the *in vitro* drug release rate were improved by employing melt solvent fusion methods to prepare SD formulations with different hydrophilic polymers. We hypothesized that the crystalline structure of the drug would be transformed into an amorphous form through chemical interaction between LVT and hydrophilic carriers, which should improve both drug water solubility and the *in vitro* drug dissolution rate.

MATERIALS AND METHODS

Ethical Permission

The research was conducted *in vitro* only. No animal or human sample or volunteer was used and hence no ethical permission was required from ethics committee. However, the research work was done in the laboratories of the Faculty of Pharmacy, University of Dhaka.

Materials and Instruments

LVT, Kollicoat IR, Kollidon 90F, and PEG-200 were purchased and collected from local vendors and Aristopharma Ltd, Bangladesh. Monobasic potassium phosphate/potassium di-potassium hydroxide, phosphoric acid, hydrochloric acid (37%), hydrogen phosphate, acetonitrile, ethanol, methanol, and chloroform were also purchased from local vendors. All materials, solvents, and reagents were of analytical grade of purity. Instruments such as dissolution tester, ultraviolet–visible spectroscopy (UV-VIS), electronic balance, desiccators, mortar/pestle, and scanning electron microscopy (SEM) were used in the analyses and formulation preparations available in Pharmaceutical Technology Laboratory and CARS, University of Dhaka.

Methods

Formulation of binary PM of LVT-polymer[1]

The LVT drug and the hydrophilic carriers Kollicoat IR and Kollidon 90F were placed in clean mortar at 1:0.5, 1:1, and 1:2 ratios. The mixtures were mixed properly using pestle for 15 min. The prepared binary PMs of LVT-polymers were then placed in desiccators at a room temperature for storage until further use and formulations were marked as PM [Table 1].

Preparation of ternary SD by fusion/melt solvent method[11,19-21]

PEG-200 of accurate amount was placed in an aluminum pan and heated at a temperature around 55–60°C. LVT and hydrophilic polymers were weighed accurately at 1:0.5, 1:1, and 1:2 ratios and added in the molten PEG. The mixture was stirred continuously to ensure proper mixing. The PEG/LVT/polymer mixtures were then allowed to cool-down at room temperature. The prepared ternary molten systems turned into dried solid mass which was pulverized using a mortar-pestle. The formulations were sieved through a 30-mesh sieve to have uniform SD powders. The prepared SD powders of PEG/LVT/polymer were then stored in desiccators at the room temperature for future use and characterization. The SD formulations were coded as SD [Table 1].

Physicochemical characterization[1,8]

Physiological characterization of the SD and PM formulations was performed using SEM. Double-sided adhesive tapes were used to mount the samples of LVT and SD onto the stubs. This formulation samples were then thinly coated with a gold-palladium alloy (150–200A°) to perform the SEM analysis.

In vitro drug release study by dissolution testing[1,11]

In vitro dissolution rate investigation of pure LVT, PMs and ternary SD (PEG/Polymer/Drug) powder formulations (equivalent to 20 mg of LVT) were conducted using a USP type II paddle type apparatus. Distilled water (900 ml) at 37 ± 0.5°C was used as dissolution medium with 50 rpm paddle rotation speed. To maintain the sink condition, at prescheduled time intervals dissolution medium was withdrawn (10 ml) and replenished with fresh distilled water. The collected dissolution liquid was filtered through 0.45 m filter paper which was then analyzed using a UV-VIS spectrophotometer at 238 nm wavelength for drug content determination.

RESULTS

Standard Calibration Curve of LVT

Methanol was used to dissolve LVT and a standard curve was prepared.[22] Appropriately measured LVT was taken and dissolved in 100 ml methanol. The solution was then diluted (2–20 μg/ml) with distilled water and phosphate buffer (pH 6.8) separately to construct calibration curves with water and phosphate buffer, respectively. Absorbance values of these diluted solutions were determined with the help of UV-spectrophotometer at λ_{max} 238 nm, using distilled water and phosphate buffer as blank [Figure 2].

In vitro Dissolution Rate Studies

In vitro dissolution studies of the SD formulations were conducted on three times of each (formulations P1 to P6, SD1 to SD6). The cumulative percent of LVT released from P1 to P6 formulations prepared by PM was calculated at various time intervals [Figure 4]. Higher drug release rates were observed for formulations P3 and P4 when compared with other PM formulations indicating the 1:2 ratio formulations were more effective to enhance the release of API from the mixtures. Among the two P3, P6 formulations, P6 was found to have the highest release rate (72%) than P3 after 60 min of dissolution [Figure 4]. While in formulation P3, around 68% drug release was noted within 1 h. However, in case of other PM formulations, the release rates of drug were below 56% within 1 h. The dissolution rate of pure LVT was also screened and it was found 38% after 1 h [Figure 3]. The order of drug release for PMs of LVT with these hydrophilic polymers can be written as P6>P3>P5>P4>P2>P1 [Figure 4].

The higher dissolution rate of LVT using hydrophilic polymers Kollicoat IR and Kollidon 90F could be ascribed to a progressively enhanced solubilization process.

The SD ternary formulations prepared by dissolving drug and polymer in the same amount of PEG were tested to check

Table 1: Different SD formulations prepared by PM and melt solvent method and their assigned product Code

Polymer	Formulation combination		Assigned Code of the formulated batches	
	PM (LVT: Poly)	Melt solvent method (PEG: LVT: Poly)	PM	SD
Kollidon 90F	1:0.5	5:1:0.5	P1	SD1
	1:1	5:1:1	P2	SD2
	1:2	5:1:2	P3	SD3
Kollicoat IR	1:0.5	5:1:0.5	P4	SD4
	1:1	5:1:1	P5	SD5
	1:2	5:1:2	P6	SD6

LVT: Lovastatin; Poly: Polymer; PEG: Polyethylene glycol; PM: Physical mixing; SD: Melt-solvent solid dispersion

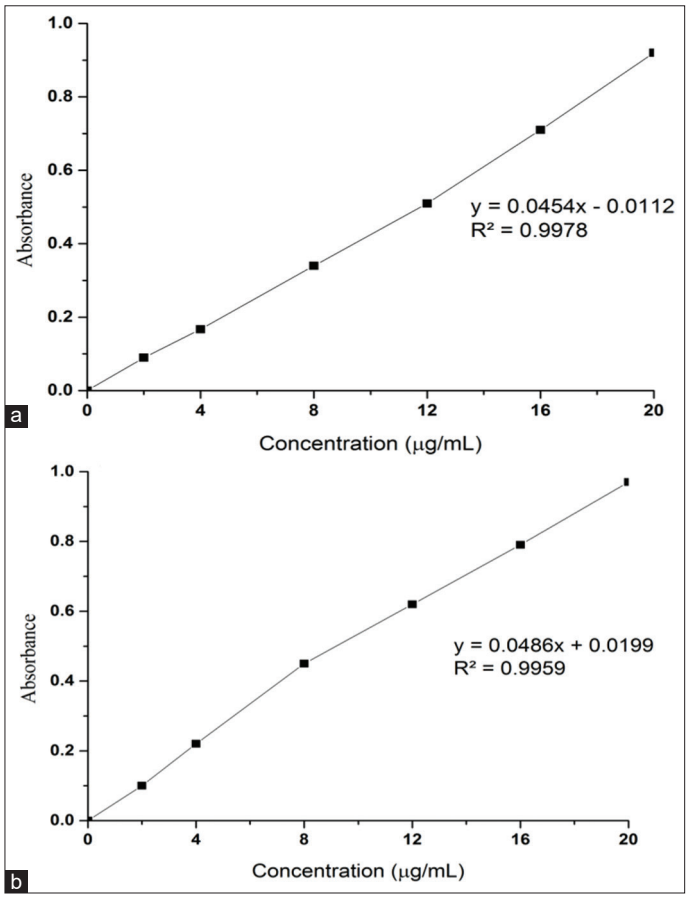

Figure 2: Standard curves of lovastatin in: (a) Distilled water; (b) phosphate buffer (pH 6.8)

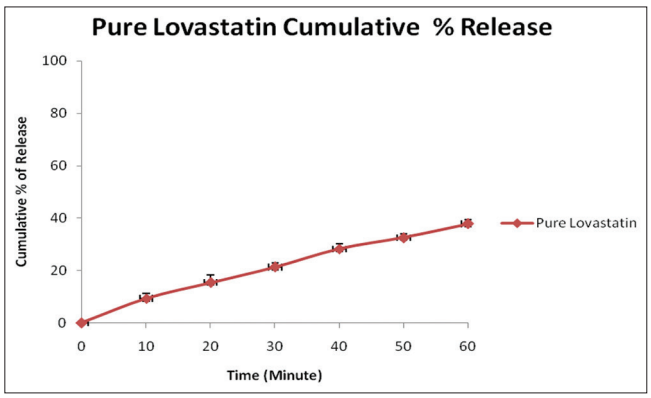

Figure 3: Cumulative release (%) of pure lovastatin

dissolution properties. The formulation SD6, produced by fusion technique showed maximum cumulative release after 1 h which was nearly 87%, much higher than the P6, P5, P3, and P2 [Figures 4 and 5] indicating the SD formulations exhibited a significantly increased dissolution rate compared to the PMs. The release of LVT from SD formulations prepared by melt solvent method with Kollicoat IR was greater when compared with SD3 (82%). The drug release rate was high with Kollicoat IR both as SDs (ternary formulation) and PMs (binary) than the Kollidon 90F. The enhanced mean cumulative release rates of drug from SDs may be due to many factors such as heightened drug wettability, averting drug

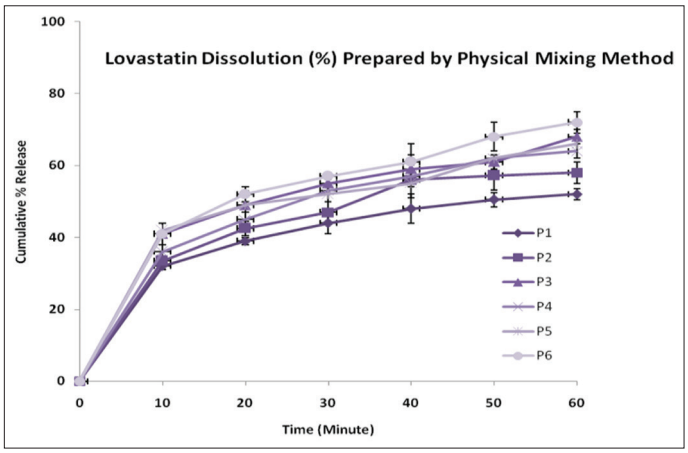

Figure 4: Zero order release curves of lovastatin from physical mixing formulations after 10, 20, 30, 40, 50, and 60 min

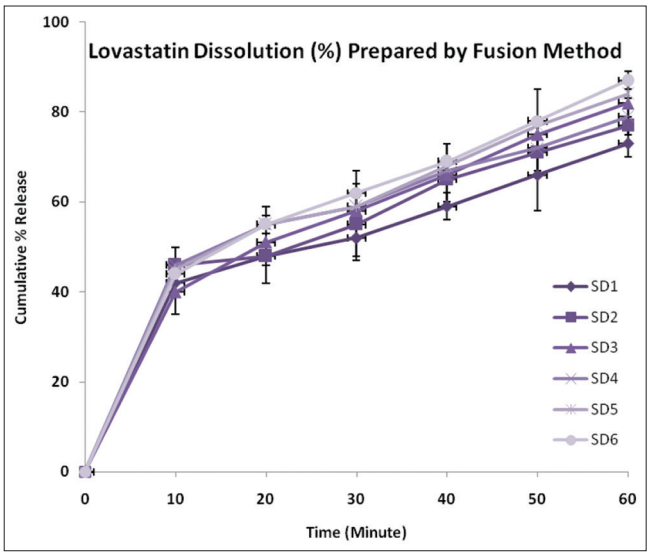

Figure 5: Release percentage of lovastatin after 10, 20, 30, 40, 50, and 60 min from solid dispersion formulations prepared by fusion techniques

aggregation process by the polymers, diminished particle size of drug, and conversion of the crystal form to amorphous form etc.[20,21] The order of drug release from formulations made by melt solvent technique was SD6>SD5>SD3>SD4>SD2>SD1 [Figure 5]. These results confirmed that the high amount (1:2 ratios) of hydrophilic polymer increased the drug release rate from SD formulations.

Observably, LVT was found to be released 72% from the formulations in case of PMs with Kollicoat IR (1:2 ratio) after 60 min of dissolution. It was 68% for Kollidon 90F [Figure 4]. Kollicoat IR increased the LVT release rate to 87% when formulation was prepared by fusion technique. The enhanced drug release rates obtained by using the hydrophilic polymers can be presented as Kollicoat IR>Kollidon 90F. Higher dissolution rates were observed for fusion technique formulations when compared with PM formulations in almost all cases.

SEM Analysis

SEM analysis displayed an irregular shape of the pure LVT particles in SD formulations. The drug particles were found not to be completely homogeneously dispersed and physically adsorbed on the surface of the hydrophilic carrier particles within the binary PM formulations of the LVT and polymer when examined using SEM [Figure 6c and d]. On the other hand, SD formulations containing LVT, PEG, Kollicoat IR, and Kollidon 90F exhibited an evenly distributed mixture indicating that the LVT molecules were homogenously dispersed in the hydrophilic carrier of SD prepared by melting/fusion method at 1:2 ratios [Figure 6a and b]. From the obtained SEM results, it can be inferred that the crystalline drug has converted to amorphous state.

DISCUSSION

In this study, we demonstrated that SD of water insoluble drug LVT with hydrophilic polymers using melt solvent/ fusion technique can be employed to improve its dissolution and hence the bioavailability. First, we showed that the hydrophilic polymers Kollidon 90F and Kollicoat IR improved the dissolution rate of LVT from the binary and ternary SD formulations and the release rates ranged from 52% [Figure 4] to maximum 87% [Figure 5], while the dissolution rate of pure LVT was only 38%. It was also evident that, when comparing the two methods (PM and SD), fusion technique of SD was found to be a better procedure to enhance the drug dissolution rate. Second, for both PM and fusion products of pure drug and polymers, 1:2 ratio formulations showed good dissolution rate compared to other formulations suggesting formulations prepared with high amount of hydrophilic polymers demonstrated superior dissolution rates. For example, the ternary formulations SD6 and SD3 showed much higher dissolution rate than the other corresponding SD formulations [Figure 5]. Third, we found that, formulations containing Kollicoat IR exhibited a greater dissolution profile than Kollidon 90F [Figures 4 and 5]. Reportedly, Kollicoat IR enhanced the dissolution process of omeprazole due to its high aqueous solubility and low viscosity.[19] Finally, the reasoning behind these heightened LVT release rates from the SD formulations using hydrophilic carriers were explained through SEM analyses. The SEM study exhibited that, the crystalline form of the drug was changed to an amorphous state when in SD formulations but not completely in PMs. Taken together, this is the very first study that demonstrated an improved dissolution profile of a water insoluble drug LVT by employing melt solvent/fusion SD method using hydrophilic polymers.

In previous studies, PEG, PVP, and Na-SG have been used to prepare SDs of LVT but in most cases solubility and dissolution rate did not improve to the expected level.[16-18] In this study, it was shown that, SDs of LVT in hydrophilic carriers Kollidon 90F and Kollicoat IR exhibited considerably better dissolution than other polymers such as PEG, PVP, and Na-SG. El-Badry *et al.* also found that Kollicoat IR enhanced the dissolution process of omeprazole due to its high aqueous solubility and low viscosity.[19]

Further studies such as Fourier-transform infrared and differential scanning calorimetry analysis are required to fully

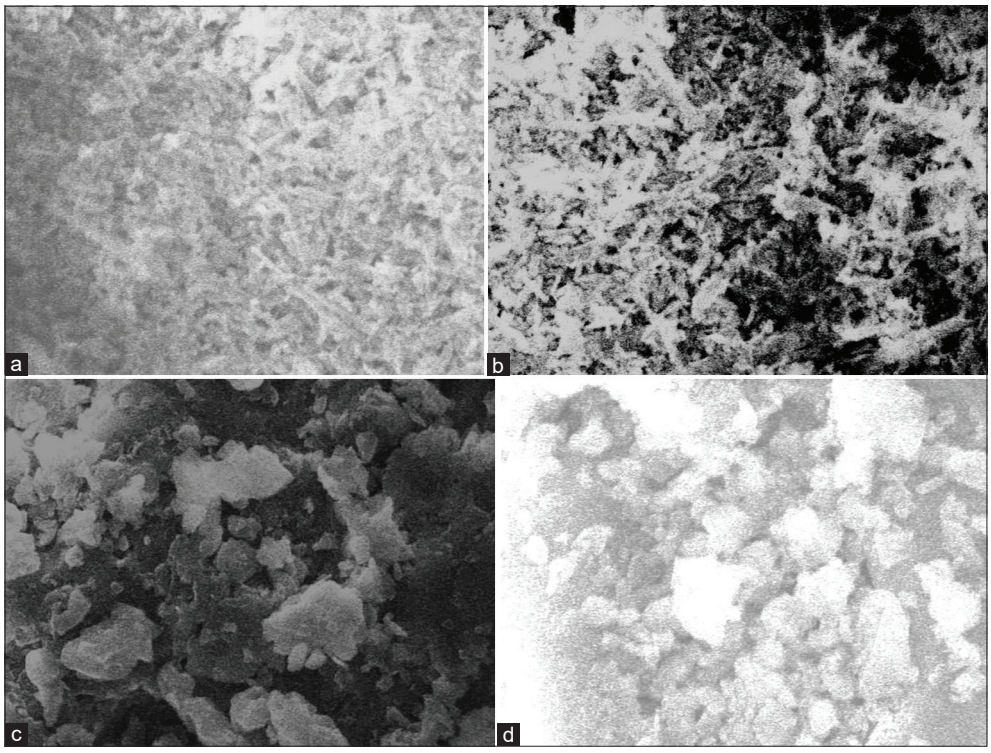

Figure 6: Scanning electron microscopy photograph of (a) SD6, (b) SD3, (c) P6, and (d) P3 formulations

confirm these findings as well as for detail understanding of this solubility enhancement of LVT induced by these hydrophilic polymers. SD formulation of LVT with other hydrophilic polymers such as hydroxy propyl methyl cellulose and poloxamer and other SD techniques such as solvent evaporation, kneading and hot melt extrusion could also be investigated to enhance the dissolution rate. Nevertheless, both techniques used in this study (PM and fusion) are very simple, economic, do not require heavy duty equipment and hence suitable to be adopted industrially as well as by researchers to increase the overall dissolution rate of LVT and/or other water insoluble drugs which may enhance their bioavailability.

CONCLUSION

The present investigation showed that the crystallinity of water insoluble LVT can be changed by dispersing the drug into hydrophilic carriers such as Kollidon and Kollicoat IR. SEM analyses also were in agreement with the reduction of crystallinity of LVT and conversion to amorphous form in the SD formulations, which ultimately improved solubility of drug. This study also demonstrated that the dissolution rate of poorly soluble LVT can be upgraded to a considerable extent employing SD technique with different hydrophilic polymers. These findings can be beneficial in establishing more advanced and feasible techniques to augment the rate of release of LVT, other statin-based small molecules and/or other low aqueous soluble drugs.

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