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Physicochemical characterization and dissolution study of spray dried amorphous Lovastatin with Polyvinylpyrrolidone K30

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Abstract

The aim of the present study was to improve the solubility and dissolution of poorly water soluble drug Lovastatin (LVS). Solid dispersions were prepared by using PVPK30 and aerosil 200 by spray drying method, with different drug: polymer ratio (1:1, 1:2, 1:4 and 1:8). These formulations were characterized by the saturation solubility, IR, DSC, PXRD and SEM. The aqueous solubility of LVS was favoured by the presence of polymer PVPK30. In contrast to the very slow dissolution rate of pure LVS, spray dried solid dispersions considerably improved the dissolution rate. This can be attributed to the increased wettability and dispersibility of LVS in polymeric matrix of PVPK30 as well as decreased crystallinity and increase in amorphicity which is confirmed by PXRD, DSC and SEM. IR studies also revealed that there is hydrogen bonding formation between drug LVS and PVPK30. The formulation SD4 showed highest solubility and dissolution rate. Stability study confirmed that there is no recrystallinity of drug over storage for specific period.

Keywords: Lovastatin, Spray drying, PVPK30, Aerosil 200, Solid dispersion

1. Introduction

Aqueous solubility of drug is a key property which governs dissolution, absorption and thus *in-vivo* efficacy^[1]. In the current scenario, most of the drug molecules discovered are lipophilic and exhibits poor aqueous solubility which in turn results in low bioavailability and poses a challenge in developing optimum oral solid dosage form^[2]. Nearly 40% of the new chemical entities currently being discovered are poorly water soluble drugs^[3]. If the drug is having good permeability then the rate limiting step in absorption is the drug dissolution. This is a characteristic of compounds which belong to the biopharmaceutical classification system II (BCS class II)^[4]. Drugs in this class are expected to have a variable dissolution profile due to the formulation and *in-vivo* variables. The aqueous solubility lesser than 1 µg/ml creates problem of bioavailability. Alteration of the solid state at the particle or molecular level involves a physical change in the drug can be used as an option to improve the drug solubility^[5]. Physical modification of lipophilic drugs is done by using several carriers like cyclodextrins, carbohydrates, hydrotropes, dendrimers, polyglycolized glycerides and other methods by use of superdisintegrants, solid dispersions, surfactants melt granulation, particle size reduction^[6]. Conversion of crystalline form of drug to amorphous is one of the strategies which improve the drug solubility.

Pharmaceutical materials that are processed by high energy processes such as spray drying, jet milling and melt extrusion are often rendered at least partially amorphous. This occurs by the virtue of the fact that these processes create conditions that can prevent crystallisation or mechanically disrupt the structure of an existing crystalline material. The high internal energy and specific surface area of the amorphous state relative to the crystalline state can lead to enhanced dissolution and bioavailability^[7].

Lovastatin (LVS) is an antihyperlipidaemic drug. Its principal metabolite that is hydroxy acid is potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, which catalyses the conversion of hydroxy methyl glutarate to mevalonate which is an early and rate limiting step in biosynthesis of cholesterol^[8]. The inhibition occurs due to the structural similarity between the hydroxyacid form of the statins and the HMGCoA intermediate formed. Reduced intracellular cholesterol synthesized induces the hepatic LDL-receptor, which results in increased extraction of LDL cholesterol from the blood and decreased circulating LDL cholesterol. It has been proven that LVS is effective as therapeutic and prophylactic agent in

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the management of major morbidities such as atherosclerosis, peripheral arterial disease and cardiovascular disease. LVS however has low bioavailability, only a small fraction of the administered dose will reach the systemic circulation^[9, 10]. It is a white crystalline powder which has low aqueous solubility, that is 0.4 µg/ml at room temperature^[11]. An increase in aqueous solubility of LVS could be useful to help increase the efficacy of the drug by having it dissolved in the gastrointestinal fluid^[12].

The hydrophilic polymer polyvinyl pyrrolidone K30 (PVP K30) is used as carrier in the preparation of solid dispersions. It shows good water solubility, low toxicity, low melting point, rapid solidification rate, physiological tolerance and economic cost. These properties ensure that PVP K30 is a good carrier polymer for preparing solid dispersion^[13].

Various methods are available for determining the physical nature of solid dispersions. These characterization methods include Infrared spectroscopy, Differential scanning calorimetry, Powder X-Ray Diffraction etc.,^[7, 14].

In the present study, Solid dispersions are prepared by spray drying method. Spray drying of a drug LVS along with the water soluble carrier polyvinyl pyrrolidone K30 (PVP K30) was done. Colloidal silicone dioxide (Aerosil 200), a hydrophilic adsorbent is used for ease of processing and facilitating transport of the final product to the collection vessel. These solid dispersion formulations are prepared by different ratios of drug and polymer. These formulations were characterized by solubility FTIR, DSC, PXRD and dissolution studies. The results are compared with the pure drug. Further accelerated stability studies were also carried out.

2. Materials and Method

2.1 Materials

Lovastatin is obtained as gift sample by Biocon Limited (Bangalore Karnataka). PVP K30 by (BASF) and Aerosil 200 (Degussa). All chemicals and solvents used in this study were of analytical grade reagents.

2.2 Methods

2.2.1 Solid dispersions prepared by spray drying method

Solid dispersions of LVS in PVP K30 containing different ratios (1:1, 1:2, 1:4 and 1:8) were prepared by spray drying method as follows. LVS along with PVP in above said ratios is dissolved in sufficient amount of dichloromethane. To these clear solutions proposed quantity of Aerosil 200 is added to obtain uniform suspensions. Spray drying was carried out using laboratory scale spray dryer (Labultima model LU 222 Mumbai India) under following set of conditions. Inlet temperature 35 °C; outlet temperature 26-28 °C; feed rate 4-6 ml per minute; atomization air pressure 2 kg/cm² and aspiration -250 mm WC. The resulting solid powder was placed in vacuum dryer for 24 hours to remove residual solvents if any. Then the samples are passed through sieve number 100. The samples were stored in desiccator for further studies^[7].

2.2.2 Physical mixtures

Physical mixtures (PMs) having the same weight ratios were prepared by thoroughly mixing appropriate amounts of LVS and PVP K30 in mortar until a homogeneous mixture was obtained. The resulting mixtures were sieved through a sieve number 100. The samples were stored in desiccator for further compatibility studies^[7].

2.2.3 Compatibility studies by infrared spectroscopy

Compatibility studies were carried out for pure drug (LVS), (PVPK30), (Aerosil 200), physical mixtures of polymers (LVS+PVPK30) and solid dispersions prepared by spray drying method (SD4). Infrared spectroscopic analysis was done for the same. Fourier transform infrared spectra of moisture free powdered samples were obtained by using spectrophotometer (FT-IR Shimadzu Co., Japan) by potassium bromide (KBr) pellet method (2mg of sample in 200 mg of KBr). The scanning range was 400-4000 cm⁻¹ and the resolution was 1 cm⁻¹.

2.2.4 Drug content

Solid dispersions equivalent to 10 mg of LVS were weighed accurately and dissolved in suitable quantity of ethanol. The drug content was determined at 238 nm by UV spectrophotometer^[7].

2.2.5 Saturation solubility

To evaluate increase in solubility of Lovastatin (as in solid dispersions) or only by the presence of hydrophilic polymer (as in PMs), saturation solubility measurements were carried out. A known excess amount of solid dispersions were added to 10 ml of phosphate buffer (6.8 pH). Samples were rotated at 20 rpm in a water bath at 25 °C for 48 hours. Samples were then filtered, suitably diluted and analysed spectrophotometrically at 238 nm^[7].

2.2.6 Scanning Electron Microscopy (SEM)

Samples were mounted on double faced adhesive tapes and coated with gold (200Å) under reduced pressure (0.001 torr) for 5 minutes using an ion sputtering device. The gold coated samples were observed under the SEM and photomicrographs of suitable magnifications were obtained^[7].

2.2.7 Differential scanning calorimetry (DSC) analysis

DSC scans of the samples were recorded by using DSC Shimadzu-60. The samples were hermetically sealed in aluminium pans and heated at constant rate of 10°C/min under dry nitrogen flow (100ml/min) between 50 to 300 °C^[9].

2.2.8 Powder X-Ray Diffraction (PXRD) analysis

X-Ray powder scattering measurements were carried out with a D2 Phaser Diffractometer at room temperature using the monochromatic CuKα-radiation at 34 mA and at 38 Kv over a range of 2θ angles from 5° to 90° with an angular increment of 0.05 °/s^[7, 9].

2.2.9 Dissolution studies

The dissolution studies were performed using USP XXIII type 2 apparatus (electrolab India) for 3hrs. Samples of pure LVS and solid dispersions equivalent to 10 mg of the drugs were added to the 900 ml of phosphate buffer (pH 6.8) as dissolution medium maintained at 37±0.5 °C, which was stirred at 100 rpm. At suitable intervals, 5ml samples were withdrawn, filtered (0.22µm), diluted and analysed at 238 nm using UV spectrophotometer. An equal volume of fresh medium at the same temperature was replaced into the dissolution medium after each sampling to maintain its constant volume throughout the test. Each test was performed in triplicate (n=3) and calculated mean values of cumulative drug release were used for plotting curves^[9].

2.2.10 Stability studies

The accelerated stability of SD 4 was checked as per ICH guidelines at 40 °C/75%RH upto 3 months. Periodically (15days, 1 month and 3 months) samples were removed and checked for *in vitro* drug release and presence of crystallinity using PXRD studies [7].

3. Result and Discussion

3.1 Compatibility studies

The spectra of all the samples are shown in figure 1. The spectrum of pure lovastatin presented characteristic peaks at 3539 cm⁻¹ (Alcohol O-H stretching vibrations), 3016 cm⁻¹ (olefinic C-H stretching vibration), 2964 cm⁻¹, 2927 cm⁻¹, 2876 cm⁻¹ (Methyl and methylene C-H stretch in vibration), 1725 cm⁻¹, 1713 cm⁻¹ and 1690 cm⁻¹ (Lactone and ester carbonyl stretch) 1430 cm⁻¹, 1381 cm⁻¹ and 1357 cm⁻¹ Methyl and methylene bending vibration), 1282 cm⁻¹, 1219 cm⁻¹, 1075 cm⁻¹ 1055 cm⁻¹ (Lactone and ester C-O-C bending vibration), 969 cm⁻¹ Alcohol C -OH stretch), and 870 cm⁻¹ (Trisubstituted olefinic C-H wagging) respectively.

The spectrum of PVP showed important bands at 2925 cm⁻¹ C-H stretch and 1653 cm⁻¹ stretching vibration of the carbonyl group, which is most distinct peak in the IR spectrum of PVPK30. The broad peak at 3000-3300 cm⁻¹ (OH stretching vibrations), which was attributed to the presence of water. The spectrum of Aerosil 200 showed the presence of broad prominent peak at 1076 cm⁻¹ (strong Si-O linkage) is characteristic of Aerosil and also there is peak at 3549 cm⁻¹ (O-H stretch).

Upon comparison; the spectra of solid dispersions by spray drying (LV-PVPK30) and physical mixtures; in contrast to the physical mixtures, solid dispersions presented possibility of hydrogen bonding between Lovastatin and PVPK30. Each pyrrolidone moiety of PVP has two groups (=N- AND C=O) that can potentially form hydrogen bond with the drug at molecular level in solid dispersion formulation. Significant broad peaks at 3553 cm⁻¹ and 1695 cm⁻¹ suggested hydrogen bonding interaction between free O-H group of Lovastatin and carbonyl group of PVPK30.

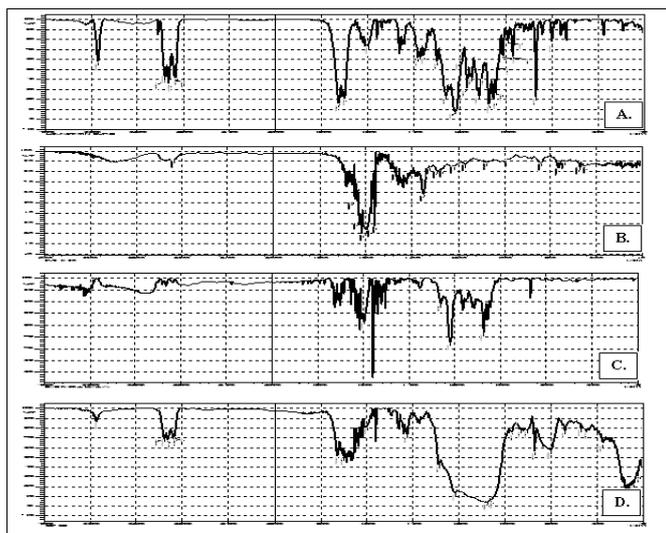


Fig 1: FTIR Spectra of A. Lovastatin B. PVPK30 C. Physical mixture D. SD4

3.2 Preparations of solid dispersions

Optimization of the solid dispersions were carried out by varying different variables such as drug: polymer ratio, processing variables such as temperature; concentration of

suspension/slurry; inlet and outlet temperature and feed rate etc. Dichloro methane was selected as solvent in spray drying method, because of the restriction on maintenance of outlet temperature below 35 °C. Based on drug content, saturation solubility and powder characteristics, the formulations are considered as optimum formulations. Composition of Solid Dispersions (SD) and Physical Mixtures (PM) is shown in the Table 1.

Table 1: Composition of Solid Dispersions and Physical Mixtures of Lovastatin

Type of Formulation	Composition (parts by weight)	
	Lovastatin	PVPK30
SD1/PM1	1	1
SD2/PM2	1	2
SD3/PM3	1	4
SD4/PM4	1	8

The drug content values and Saturation solubility for solid dispersions are given in the Table 2. The low drug content could be possibly due to the loss of drug during processing. Saturation solubility of pure drug is 0.4µg/ml. Saturation solubility is increased in physical mixtures as compared to the pure drug. This could be due to increased wettability. The formulation SD4 is considered to be optimum formulation based on the results of drug content and saturation solubility of 97% and 87.3 respectively. The formulations also shown good flow properties, further increase in polymer concentration will affect the flow properties, which will create problem during processing of solid dispersions.

Table 2: Drug contents and saturation solubilities of solid dispersions

Formulation code	Drug content	Saturation solubility (Solid dispersions)	Saturation solubility (Physical mixture)
SD1	68±0.10%	28.6± 0.3	0.9 ± 0.05
SD2	74±0.45%	46.3± 0.2	3.7 ± 0.04
SD3	85±0.08%	73.4±0.5	6.3 ± 0.04
SD4	97±0.89%	87.3±0.4	3.1± 0.2

3.3 SEM

The microphotographs of pure LVS and optimized formulation SD4 are shown in the figure 2. Pure drug is consisting of mixture of small and bigger crystalline particles. Whereas the particles in SD4 shows porous spherical amorphous particles with smaller size ranges.

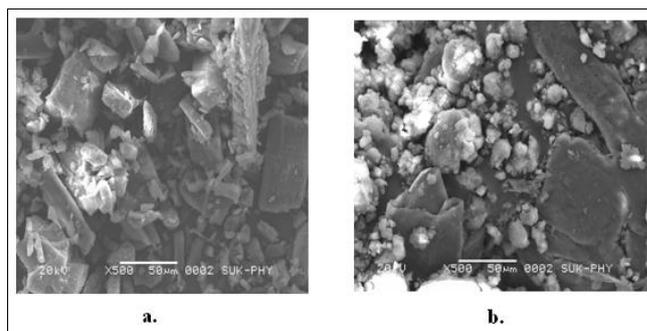


Fig 2: SEM Photomicrographs of a. Lovastatin b. SD4.

3.4 DSC

The thermal behaviour of pure drug LVS, PVPK30 and SD4 was studied by DSC. The DSC curves are shown in the figure 3. The pure LVS shows melting endotherm at 170 °C with enthalpy of fusion (ΔH) of 163.15 mJ/g. The DSC scan of PVPK30 shows a broad endotherm between 80-120 °C due to

presence of moisture residue in PVP K30. The DSC scan of SD4 shows a peak at 80-130 °C due to loss of water and also complete absence of drug peak at 170 °C. This confirms the amorphicity of LVS in solid dispersion inside the PVP matrix as indicated by the results of PXRD.

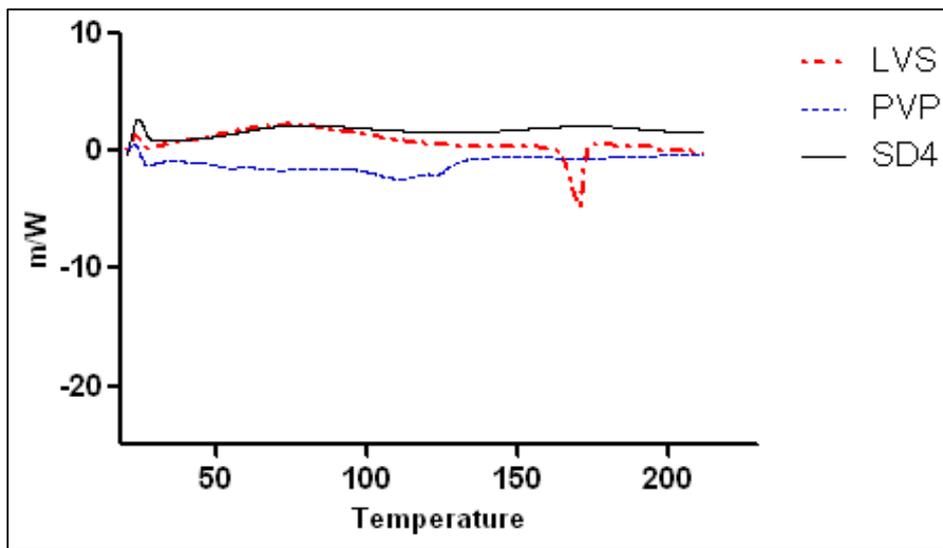


Fig 3: DSC Thermograms of (A) Lovastatin (B) PVP K30 (C) SD4.

3.5 PXRD

PXR Diffractograms of pure LVS and SD4 are shown in the figure 4. The presence of characteristic peaks (at 2θ) in X-Ray diffraction indicates that LVS is present in crystalline material with characteristic diffraction peaks appearing at a diffraction angle of 2θ at 10.69, 12.61, 13.52, 14.74, 15.45, 16.06, 17.11, 17.82, 19.56, 21.31, 22.57, 25.79, 26.96, 30.29, 32.01, 34.65, 35.86 etc. Whereas SD4 showed the absence of any diffraction peaks corresponding to drug indicating the LVS was in the amorphous state.

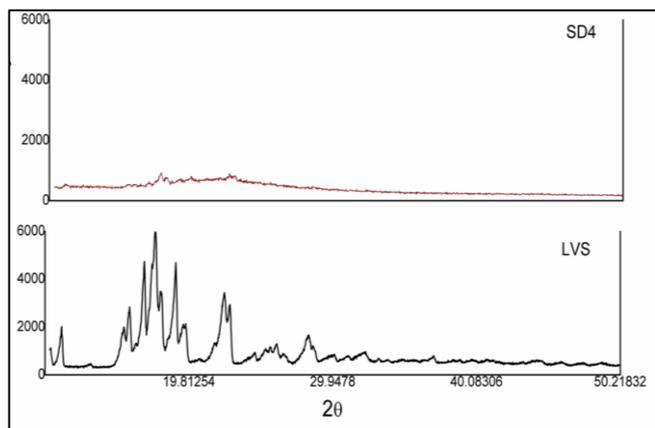


Fig 4: Powder X-ray diffractograms of Lovastatin (LVS) and SD4

3.6 Dissolution studies

Dissolution profiles of pure LVS and solid dispersions over a period of 3 hours are shown in the figure 5. The dissolution rate of pure LVS is very low that is 23.63% drug is dissolved in 3 hours. Solid dispersions of LVS with PVPK30 significantly enhanced the dissolution rate of LVS. SD4 presented highest drug release 93.8 %. This improved drug release is due to the presence of amorphous form of LVS as confirmed by IR, SEM, DSC and PXRD studies.

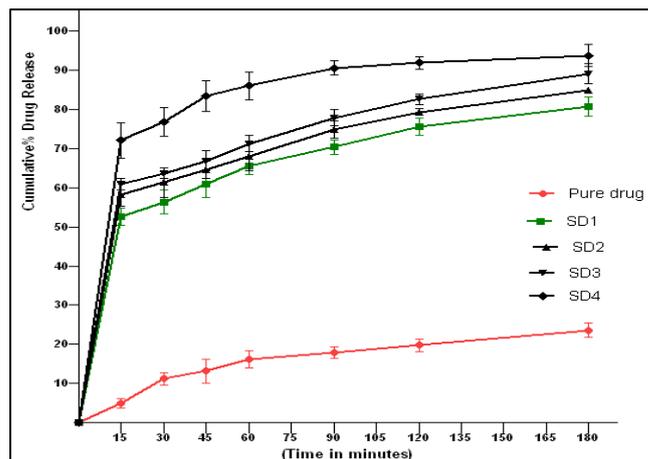


Fig 5: *In-vitro* dissolution profiles of Lovastatin pure drug and solid dispersions (SD1-SD4)

3.7 Stability studies

The evidences from the previous studies carried out say that, the solid dispersions prepared by different methods tend to recrystallize upon storage at high temperature and relative humidity. Hence stability studies were carried out to test the recrystallinity. When SD4 was subjected for dissolution test; at specific interval (15days, 1 month and 3 months); over a period of 3 months, the decrease in invitro drug release was found to be insignificant which is shown in the Figure 6. Also PXRD observations indicated that the presence of amorphicity at specific time intervals of 3 months period. There were no changes found in the powder X-ray diffractograms of SD4, indicating that there were no peaks corresponding to the crystallinity of LVS found in the diffractograms which is shown in the figure 7. This could be attributed to the entrapment of drug molecules in the polymer matrix, which prevents further recrystallization upon storage.

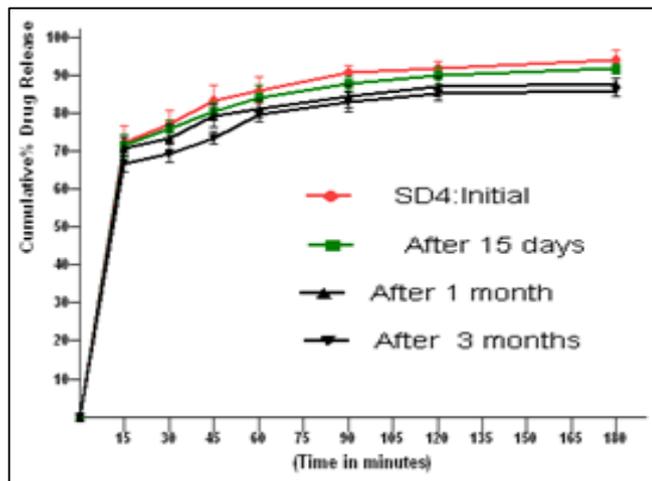


Fig 6: *In-vitro* Dissolution profiles of SD4 during stability study at different time intervals.

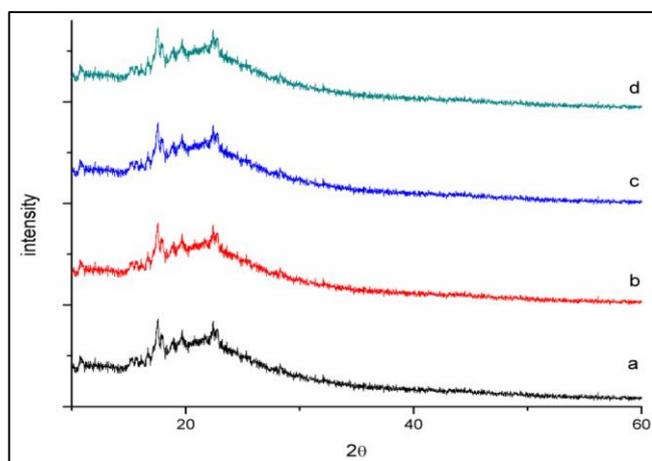


Fig 7: Powder X-ray Diffractograms of SD4 during stability study at different time intervals. (a) Initial (b) 15 days (c) 1 month (d) 3 months.

4. Conclusion

The solubility and dissolution can be enhanced by the SDs of LVS with PVP K30 and aerosil 200. IR studies confirmed that there is hydrogen bonding between the drug LVS and polymer PVP K30 at molecular level in SDs, which could be the reason for enhanced solubility. Conversion of crystalline to amorphous form of LVS is confirmed by DSC, PXRD, SEM and dissolution studies. Stability study results confirm absence of recrystallinity upon storage over a period of 3 months. Hence present study suggests that spray drying method can be successfully used for the preparation of solid dispersions.

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