Original Research Article

Solid-state characterization of lacidipine/PVP $K_{29/32}$ solid dispersion primed by solvent co-evaporation

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Abstract

Background: Lacidipine (LCDP) is a 1,4-dihydropyridine derivative categorized as an anti-hypertensive Ca2+ channel blocker having very low solubility, and thus very low oral bioavailability, which presents a challenge to the formulation scientists. Homogeneous distribution of poorly water-soluble drugs like LCDP in polyvinylpyrrolidone (PVP), a hydrophilic carrier, is definitely a suitable way to improve the bioavailability of such drugs. **Materials and Methods:** The aim of the study was to develop a combined thermal, imaging, and spectroscopic approach, and characterize physical state, dissolution behavior, and elucidation of drug–PVP interaction in LCDP/PVP solid dispersion (SD) using differential scanning calorimetry (DSC), X-ray diffractometry (XRD), fourier transform infrared (FTIR) spectroscopy, and hot stage microscopy (HSM), which is the prerequisite for the development of a useful drug product. **Results:** Dissolution studies of LCDP and its physical mixture with PVP showed less than 50% release even after 60 min, whereas SD of LCDP/PVP ratio of 1:10% w/w showed complete dissolution within 45 min. DSC and powder XRD proved the absence of crystallinity in LCDP/PVP SD at a ratio of 1:10% w/w. The FTIR spectroscopy indicated formation of hydrogen bond between LCDP and PVP. In the SD FTIR spectra, the –NH stretching vibrations and the –C=O stretch in esteric groups of LCDP shift to free –NH and C=O regions, indicating the rupture of intermolecular hydrogen bond in the crystalline structure of LCDP. **Conclusion:** Solid-state characterization by HSM, DSC, XRD, and FTIR studies, in comparison with corresponding physical mixtures, revealed the changes in solid state during the formation of dispersion and justified the formation of high-energy amorphous phase.

Key words: Differential scanning calorimetry, fourier transform infrared spectroscopy, lacidipine, polyvinylpyrrolidone, solid dispersion, solubility, X-ray diffractometry

INTRODUCTION

Lacidipine (LCDP) is chemically a 1,4-dihydropyridine derivative as shown in Figure 1a, which is pharmacologically a calcium channel blocker used as an anti-hypertensive drug. LCDP works by blocking calcium channels in the arterial wall those are present in the muscle cell. Calcium is needed by muscle cells in order for them to contract; so, by depriving them of calcium, LCDP causes the muscle cells to relax. Relaxing and widening of the small arteries decreases the resistance that the heart has to push against in order to pump the blood around the body, which reduces the pressure within the blood vessels.[1] LCDP is completely absorbed from the gastrointestinal tract (GIT) providing its complete dissolution.[2] But the quandary is that LCDP has very low solubility,[3] which presents a challenge to the formulation scientists. When an active agent is administered orally, it must first dissolve in gastric and/or intestinal fluids before it permeates the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption.

One of the most important tasks in drug discovery and development is to enhance the oral bioavailability by improving the dissolution of poorly water-soluble drugs. Salt formation, solubilization, particle size reduction, and solid dispersion formation are the approaches most often used to reach this goal. The formulation of hydrophobic drugs as solid dispersions is a significant area of research aimed at improving their dissolution, and thus enhancing the bioavailability.[4] In the solid dispersion system, the solubility of drug can be improved by changing drug crystallinity to an amorphous state and reducing the particle size for better wettability.[5] The rationale behind such a strategy is that a highly disordered amorphous state has a lower energetic barrier to overcome in order to enter a solution than

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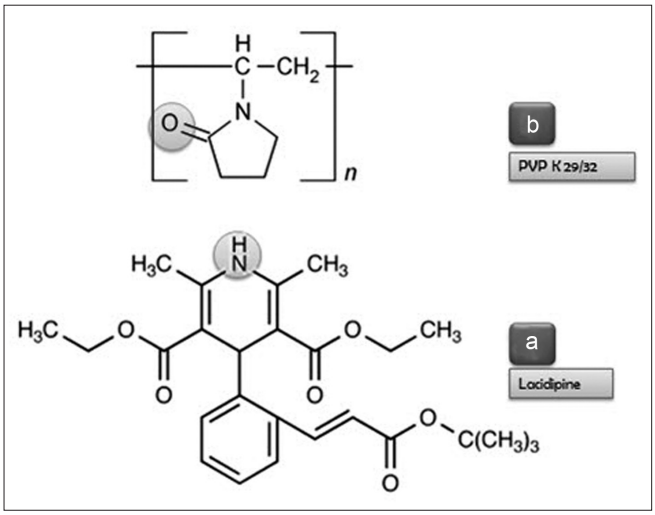

Figure 1: Chemical structure of (a) lacidipine and (b) polyvinylpyrrolidone (PVP)

a regularly structured crystalline state. On the other hand, the presence of the carrier might also cause the creation of a micro-environment in which the drug solubility is improved.[6,7] The high molecular weight compound, polyvinylpyrrolidone (PVP), as shown in Figure 1b, is a synthetic polymer made up of linear groups of 1-vinyl-2-pyrrolidone monomers. PVP (povidone), a polymeric lactam, has low toxicity, strong hydrophilic properties, and physiological tolerance which offers enhancement of Drug Release (DR) and bioavailability of drugs with very low solubility.[8] One of the outstanding properties of the soluble PVP products is their universal solubility in hydrophilic and hydrophobic solvents. So, it is extensively employed as a carrier for the preparation of solid dispersions to improve the solubility of hydrophobic drugs.[9,10] Enhancement of DR is caused by the inhibition of crystallization of drugs, which is mostly offered by the anti-plasticizing effect of PVP and by PVP's surface adsorption and efficient steric hindrance for nucleation and crystal growth. Understanding the basic forces that hold molecules together is important for understanding how molecules interact with each other. These interactions affect mainly the solubility and stability of drugs.[11,12]

Taking all the above into account, the solid dispersions of LCDP in PVP $K_{29/32}$ were prepared using solvent evaporation technique. The main focus of this research work is on the molecular level analysis of the drug molecular state in solid dispersions and interactions between drug and carrier by combination of differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), and Fourier Transform Infrared (FTIR) spectroscopy with hot stage microscopy (HSM) imaging technique.

MATERIALS AND METHODS

Materials

LCDP, an active pharmaceutical ingredient, was procured from Cadila Pharmaceuticals limited, India. PVP (Plasdone® $K_{29/32}$), purchased from ISP Pharmaceuticals, Mumbai, India. Absolute alcohol (ethanol 99.6% v/v) was procured from Sigma Aldrich, Bangalore, India and was used as a common solvent. Unless otherwise stated, all other materials were of analytical grade.

Preparation of LCDP solid dispersion

Solid dispersions of LCDP in PVP $K_{29/32}$ (mass ratio of LCDP to PVP $K_{29/32}$ is from 1:1 to 1:14) were prepared by solvent evaporation method. In brief, accurately weighed quantities of PVP $K_{29/32}$ were dissolved in ethanol, followed by addition of accurately weighed quantities of LCDP to the solution, which was allowed to dissolve completely by ultrasonication at room temperature for about an hour. When a clear solution was obtained, the solvent was evaporated under reduced pressure. The resulting product was dried under vacuum in a desiccator over anhydrous $CaCl_2$ to a constant weight for at least 24 h at room temperature. The dried product was ground in a mortar and passed through a sieve BSS 60# and stored in a desiccator until further evaluation.

Dissolution test

The dissolution studies were performed using Electrolab® dissolution tester based on USP Method II (paddle). The samples, LCDP drug powder *per se*, the LCDP/PVP physical mixture (PM) and the solid dispersion (SD) at different LCDP:PVP ratios of 1:1, 1:2, 1:4, 1:6, 1:8, 1:10, 1:12, and 1:14, containing equivalent to 4 mg of LCDP, were sealed in hard gelatin capsules, then put into 500 ml of purified water with 1% w/v polysorbate 20 thermostatically maintained at 37 ± 0.5°C at a rotation speed of 50 rpm in USP Type II dissolution apparatus. At appropriate time intervals, 5 ml of the sample was withdrawn from midway zone between the surface of medium and top of the rotating paddle not less than 1 cm from the vessel wall and filtered (Millex® AP, Millipore, 0.4 µm). The same volume of solution which was withdrawn was replaced by fresh medium for correction. The absorbance of the standard preparation and the sample test preparation was measured on a suitable spectrophotometer (Systronic®, 2201) at 284 nm against dissolution medium (purified water with 1% w/v polysorbate 20) as blank.

Hot stage microscopy

HSM was performed using an Olympus BX51 (Olympus® Opticals. Tokyo, Japan) polarizing optical microscope equipped with a Linkman THMS600 hot stage (Linkman Scientific Instruments Ltd., Surrey, England) and linkman TMS94 programmable temperature controller. Samples (LCDP, PVP $K_{29/32}$, its PM and its SD in 1:10% w/w) were heated at 2°C/min from room temperature to 200°C.

Differential scanning calorimetry

Thermal analysis of the samples (LCDP, PVP $K_{29/32}$, its PM and its SD in 1:10% w/w) was carried out with a DSC-8 (Perkin Elmer®, Massachusetts, USA). About 10 mg of sample was weighed into a non-hermetically sealed aluminum pan. The samples were heated from 25 to 250°C at a heating rate of 5°C/min. The instrument was calibrated by using indium. All the DSC

measurements were made in nitrogen atmosphere and the flow rate was 100 ml/min.

Powder X-ray diffractometry

Powder X-ray diffractometry (PXRD) of the samples (LCDP, PVP $K_{29/32}$, its PM and its SD in 1:10% w/w) was performed with an X'pert PRO X-ray (PANalytical®, Almelo, The Netherland) over 5°–60° at 2θ range at a scan rate of 1° per min, where the tube anode was Cu with Kα of 0.154 nm monochromatized with a graphite crystal. The pattern was collected with 40 kV of tube voltage and 40 mA of tube current in step scan mode (step size of 0.05, counting time of 1 s/step).

Fourier transform infrared spectroscopy

FTIR spectra of the samples (LCDP, PVP $K_{29/32}$, its PM and its SD in 1:10% w/w) were obtained on a spectrum GX FTIR spectrophotometer (Systronics®, Ahmedabad, India). The Ground samples were mixed thoroughly with KBr, an infrared-IR grade transparent matrix. The KBr disks were prepared by compressing the powder. Then, scans were obtained from 4000 to 400 cm^{-1} at a resolution of 1 cm^{-1}.

RESULTS AND DISCUSSION

Dissolution tests

As the volume of dissolution medium was 500 ml purified water with 1% w/v polysorbate 20 in this study, it was sufficient to provide a sink condition for the dissolution of as much as 4 mg of LCDP. Dissolution profiles of the LCDP drug powder, the LCDP/PVP PM at different LCDP/PVP ratios of 1:1, 1:2, 1:4, 1:6, 1:8, 1:10, 1:12, and 1:14, and the SD at different LCDP/PVP ratios of 1:1, 1:2, 1:4, 1:6, 1:8, 1:10, 1:12, and 1:14 were recorded as same the dissolution condition. The dissolution rate of LCDP drug powder was limited, with a total of less than 8% dissolution after 45 min. The LCDP/PVP PM showed enhanced dissolution rate as compared to LCDP *per se* due to the solubilization effect of PVP, as represented in Figure 2a. After being formulated into SD, the dissolution profiles at different LCDP/PVP ratios increased greatly. At LCDP/PVP ratio of 2:1, it was only comparable to that of 1:2 PM. However, when LCDP/PVP ratios increased from 1:1 to 1:14, an abrupt increase in dissolution rate, over 75% within 45 min, was observed and there was little difference among several ratios from 1:8 to 1:14. The comparison between the 2:1 SD and the 1:2 PM highlighted the effect of incorporation of LCDP into SD. It was suggested that the increase in dissolution rate of SD was attributed to the changes in the solid state during the formation of dispersion. It might be owing to the formation of high-energy amorphous phase. Several authors have reported abrupt change in dissolution rate as the content of PVP in a SD kept increasing. This phenomenon has been studied by Doherty and York, and a change from "crystalline drug-controlled" to "polymer-controlled" mechanism was found to explain the abrupt increase in dissolution rate when PVP content increased over a critical point.[13,14] In this study, special attention has been paid to the "abrupt increase" region, i.e. the LCDP/PVP ratios between 1:6 and 1:8, as represented in Figure 2b. There was "gradual increase" in dissolution rate from the LCDP/PVP ratio of 1:1 to a ratio of 1:6 when significantly improved LCDP dissolution was achieved, as represented in Figure 2b. The results indicate that after 1:8% w/w, SD should be "polymer controlled," and up to 1:6% w/w, SD should be "crystalline drug controlled." The results with 1:6 and 1:8 SD did not support a transition point of "crystalline drug-controlled" to "polymer-controlled" dissolution, but a transition range.

Hot stage microscopy

HSM is used to characterize the interaction of many drugs with the polymer. Characteristic drug crystals, dispersed or adhered to the surface of spherical particles of PVP, were detectable only in PMs, whereas original morphology of both drug and PVP disappeared in co-evaporated and co-ground SD system in 1:10% w/w, which appeared as aggregates of glassy flakes, making it impossible to differentiate the two components. When this system was heated at 2°C/min from room temperature to 200°C, both an increase of crystal size and drug crystallization in the rim of PVP plates were detected; finally, melting of the drug was seen at about 180°C, as represented in Figure 3. Increase in crystal size during heating is attributed to the opening of drug–PVP intermolecular binding.[15]

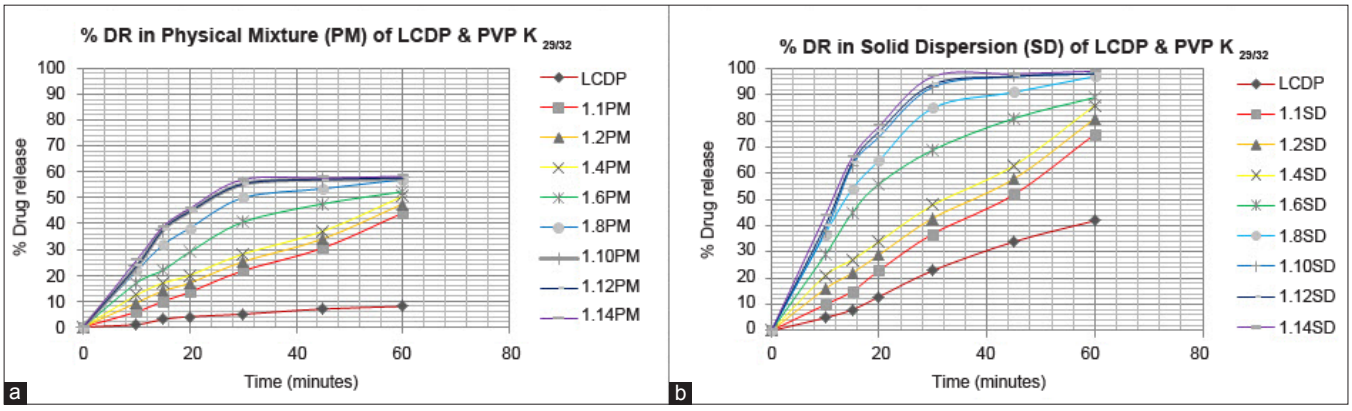

Figure 2: Scatter plots for % drug release from (a) LCDP + PVP $K_{29/32}$ physical mixture (in x:y% w/w) and (b) LCDP + PVP $K_{29/32}$ solid dispersion (in x:y% w/w)

Differential scanning calorimetry

The DSC diagram of LCDP, represented as A in Figure 4, exhibited a sharp endothermic peak at 180.6°C, indicating the melting point of LCDP. During scanning of PVP, a broad endotherm ranging from 70°C to 130°C, represented as B in Figure 4, was observed, indicating the loss of water due to extremely hygroscopic nature of PVP.[16] The PM of LCDP/PVP (1:10) showed the broad endothermic peak of LCDP around 180°C and the broad endothermic peak belonging to PVP simultaneously, represented as C in Figure 4, with about 11°C decrease in melting onset temperature of the drug, suggesting that the drug has to be melted gradually in the polymer matrix. This was because PVP $K_{29/32}$ had a glass transition temperature at 169.0°C, with a result of the drug to be melted in the liquid phase of PVP $K_{29/32}$ with increase in the temperature. LCDP/PVP SD (1:10) showed endothermic peaks that may be ascribed to PVP; however, the endothermic peak of LCDP disappeared in LCDP/PVP (1:10) SD, seen as D marked in Figure 4.

Powder X-ray diffractometry

Crystallinity is indicated by the presence of sharp peaks that are absent in the case of amorphous drugs.[17,18] The inhibitory effect of PVP on the crystallization of many drugs may be due to the interaction of the drugs with PVP, resulting in a change

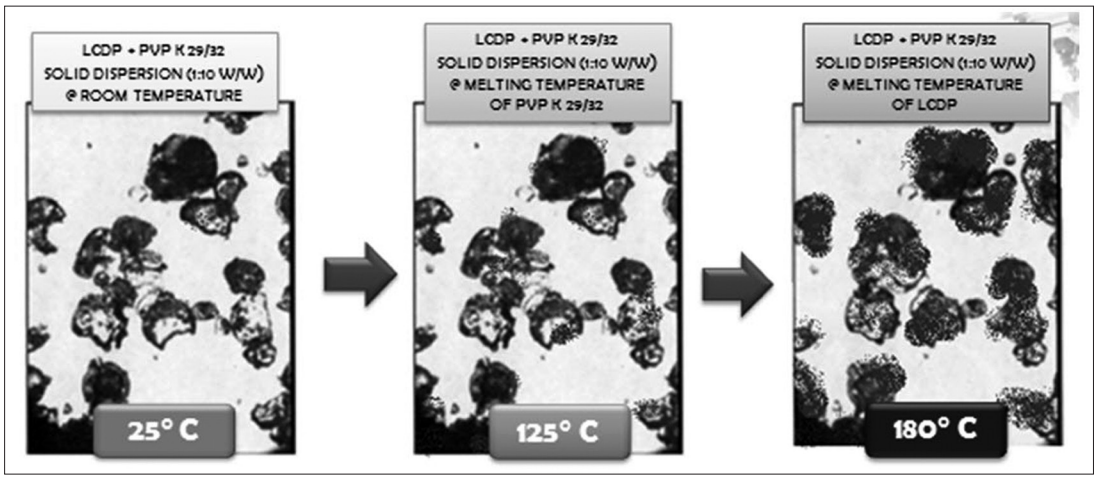

Figure 3: Hot stage microscopy of LCDP–PVP SD (1:10% w/w)

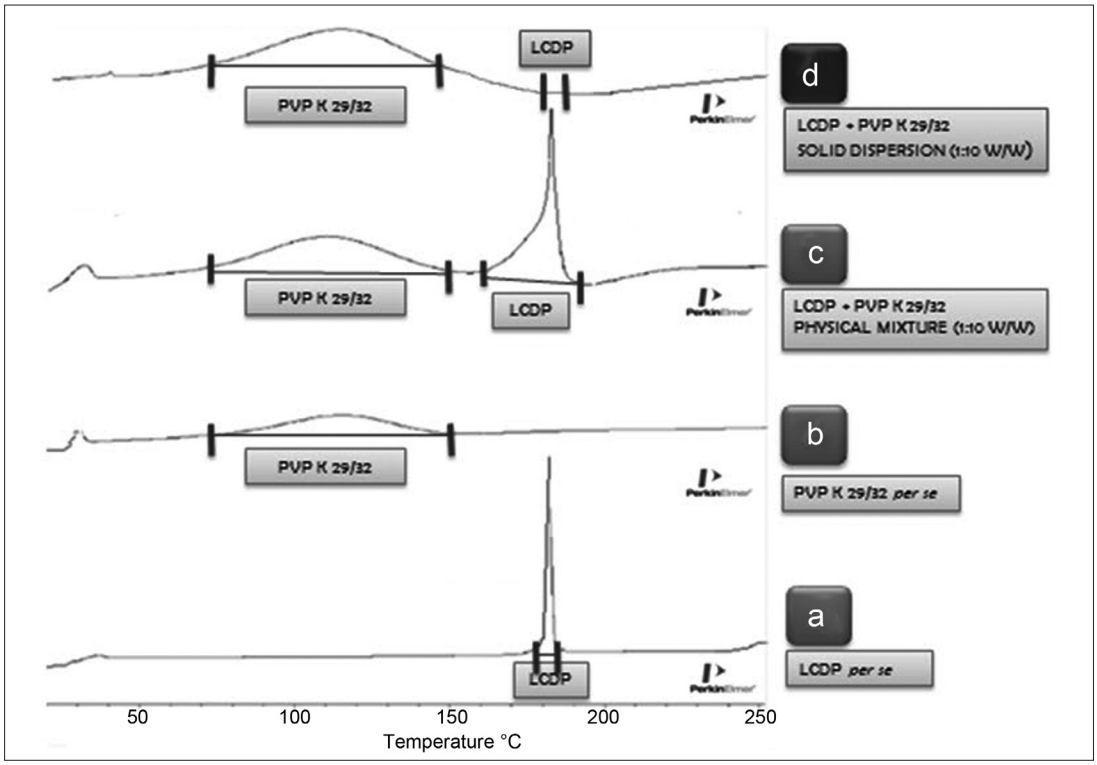

Figure 4: DSC scans of: (a) LCDP per se; (b) PVP $K_{29/32}$ per se; (c) LCDP + PVP $K2_{9/32}$ physical mixture (in 1:10% w/w); and (d) LCDP + PVP $K_{29/32}$ solid dispersion (in 1:10% w/w)

in the molecular mobility of the drugs, ultimately leading to an amorphous form of the drugs. In X-ray diffractogram, LCDP shows characteristic peaks at 7.61°, 13.31°, 14.71°, 17.22°, 23.54°, 25.32°, 26.35°, and 27.95°, represented as A in Figure 5, while PVP does not show any characteristic peak within the observed range of 5°–40° (2θ), represented as B in Figure 5. The diffractograms of the LCDP/PVP PM show the characteristic peaks of LCDP, represented as C in Figure 5, and it looks like a superimposition of that of PVP and LCDP. The diffractogram of LCDP/PVP (1:10%w/w) SD, represented as D in Figure 5, is more like that of PVP, indicating absence of LCDP crystalline form.

Fourier transform infrared spectroscopy

As seen in "A" marked in Figure 6, the characteristic absorption peaks of LCDP appeared at 3348.2, 2977.4 to 2808, 1705 to 1652, and 1627 cm^{-1}, respectively, denoting stretching vibration of –NH, –CH–, –C=O, and –C=C functional groups. The characteristic absorption peaks of PVP appeared at 3454.32 and 1654.48 cm^{-1} corresponding to –OH and the carbonyl on the pyrrolyl ring stretching vibration, represented as B in Figure 6. In the PM spectrum, the characteristic peaks of both LCDP and PVP could be observed, and the spectrum can be regarded as a simple superimposition of that of LCDP and PVP, seen as C marked in Figure 6. However, obvious changes occurred in the feature and fingerprint region of the FTIR spectra of LCDP/PVP (1:10) SD, represented as D in Figure 6. In the feature region, the 3350 cm^{1} NH stretching vibration peak of LCDP disappeared in the SD. It seemed that intermolecular hydrogen bond between –NH of LCDP and –C=O of PVP has formed. The –CH3 and –CH2– stretching vibration (approximately at 2890 cm^{-1}) was also influenced by the formation of hydrogen bond between the N atoms on the pyridine ring and the O atom on carbonyl group of PVP, and their peaks were hardly discernible in the SD spectrum. In general, the variation in absorption peaks of all functional groups was within the range of ±20 wave numbers, which strongly suggested the formation of intermolecular hydrogen bonds between LCDP and PVP, rather than more stable chemical bonds. The formation of hydrogen bond with energy below 42 kJ/mol between drugs and PVP, far less than the covalent bond, was beneficial not only to improve the dissolution rate, but also to enhance the stability and to slow down the aging of solid dispersions. PVP is capable of forming hydrogen bond either through the nitrogen or carbonyl group on the pyrrole ring.[19] However, steric hindrance precludes the involvement of nitrogen atom in intermolecular interactions, thus making the carbonyl group more favorable for hydrogen bonding.[20]

CONCLUSIONS

The enhancement of dissolution rate was obtained by SD containing 1:10 mass ratio of LCDP:PVP $K_{29/32}$. The results of DSC and XRD indicate that LCDP was present in an amorphous or molecular state in the SD and the presence of hydrogen bonding interaction between the >NH of LCDP and –C=O of PVP $K_{29/32}$ in SD was confirmed by combining FTIR. The amorphous state of LCDP coupled with the presence

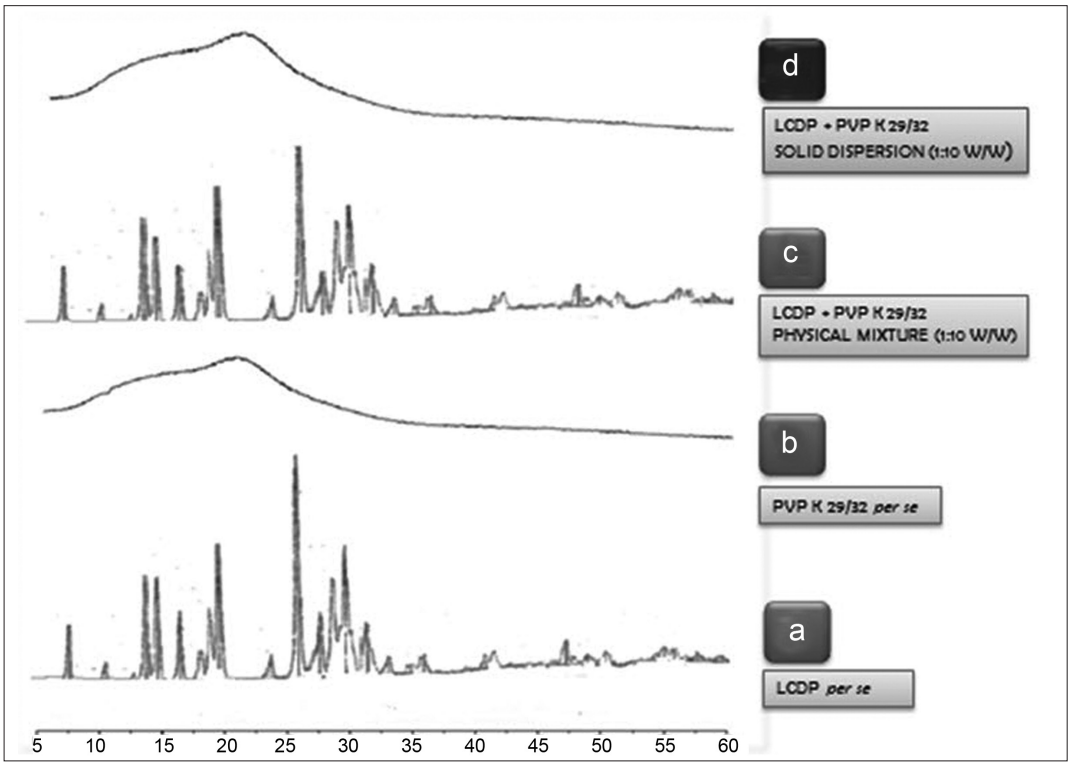

Figure 5: XRD scans of: (a) LCDP *per se*; (b) PVP $K_{29/32}$ *per se*; (c) LCDP + PVP $K_{29/32}$ physical mixture (in 1:10% w/w); and (d) LCDP + PVP $K_{29/32}$ solid dispersion (in 1:10% w/w)

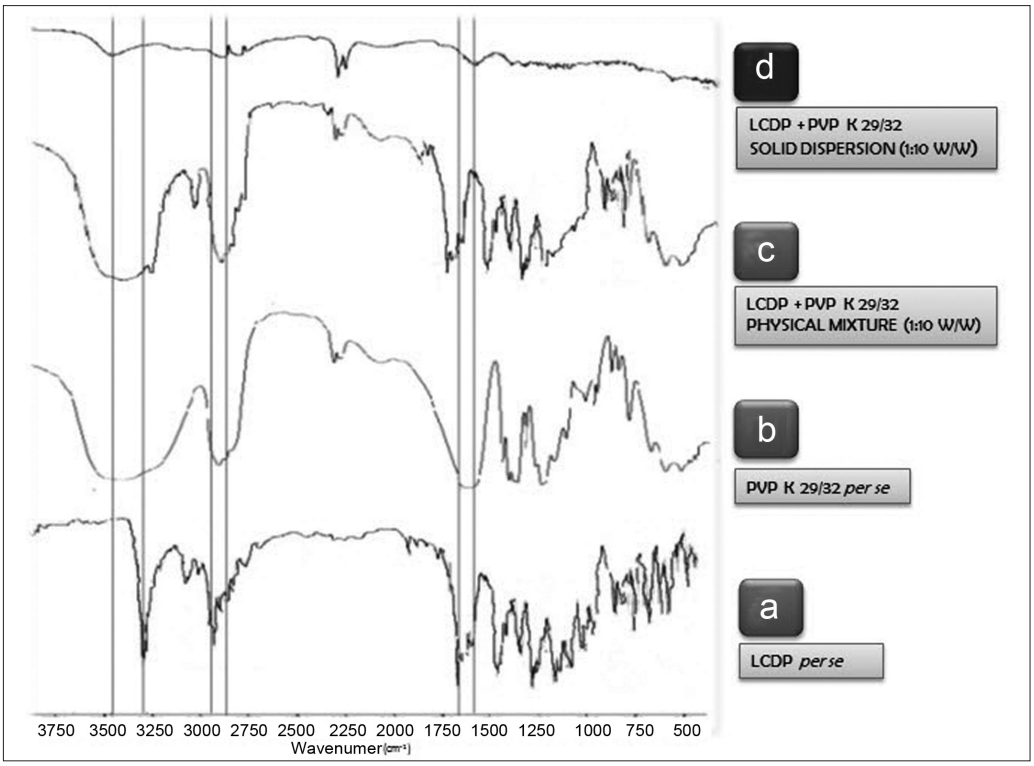

Figure 6: FTIR scans of: (a) LCDP *per se*; (b) PVP $K_{29/32}$ *per se*; (c) LCDP + PVP $K_{29/32}$ physical mixture (in 1:10% w/w); and (d) LCDP + PVP $K_{29/32}$ solid dispersion (in 1:10% w/w)

of hydrogen bond between LCDP and PVP $K_{29/32}$ was the main cause for the marked enhancement of dissolution rate. These results confirmed that LCDP–PVP $K_{29/32}$ SD prepared by the solvent evaporation could be used as a means of enhancing LCDP dissolution rates.

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