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RESEARCH ARTICLE

Enhancement of Solubility and Dissolution Properties of Lacidipine by Solid Dispersion

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Abstract:
Lacidipine is a 1, 4-dihydropyridine derivative categorized as an anti-hypertensive Ca^{+2} 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 lacidipine in PVP-K30 and Poloxamer-188 is definitely a suitable way to improve the bioavailability of such drugs. Solid dispersion is the most promising strategy to improve oral bioavailability of poorly soluble drugs. The aim of study was to compare the effect of PVP-K30 and Poloxamer-188 as carrier in solid dispersion formulation of lacidipine. Solid dispersion of PVP-K30 or Poloxamer-188 were prepared at different ratios (1: 2, 1: 4, 1: 6, 1: 8 and 1: 10%w/w) by solvent evaporation methods. The characterization of samples was performed using FT-IR, DSC and XRD. Dissolution and solubility studies were also performed. The FT-IR spectroscopic analysis revealed the possibility of intermolecular hydrogen bonding in various solid dispersions. The DSC and XRD studies indicated the transformation of crystalline lacidipine to amorphous lacidipine by the solid dispersion technology. The dissolution rate was dependent on the ratio of drug: carrier. The results obtained showed that the rate of dissolution and solubility were considerably improved when formulated in solid dispersions as compared to pure drug. The order of increasing dissolution rate observed with PVP-K30 and Poloxamer-188 in different concentration was poloxamer-188 > PVP-K30 > pure drug.

Keywords: Lacidipine, Solid Dispersion, Solvent Evaporation, PVP-K30, Poloxamer-188

Introduction

Lacidipine (LCDP) is chemically a 1, 4-dihydropyridinederivative, 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. LCDP is completely absorbed from the gastrointestinal tract(GIT) providing its complete dissolution. But the quandary is that LCDP has very low solubility, 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.[1,2]
The incorporation of drug into hydrophilic carriers has frequently been reported to increase the dissolution rate of poorly soluble drugs, often leading to improved drug bioavailability. Such dosage forms are referred to as solid dispersions. This system provides the possibility of reducing the particle size of drugs to nearly a molecular level, to transform the drug from the crystalline to the amorphous state and/or locally increase the saturation solubility. Several carriers have been employed in preparing solid dispersions; among those is use of PVP-K30 and poloxamer-188. The aim of study was to prepare and characterize solid dispersion of lacidipine with different carriers to improve its dissolution properties. In order to evaluate the effect of these carriers on lacidipine, dissolution and solubility studies were performed. Physical analysis based on differential scanning calorimetry, FI-IR spectroscopy and powder X-ray diffraction was performed to elucidate the structure of dispersions and to detect possible drug-carrier interaction.[3]

Materials and Methods

Materials

Lacidipine and PVP-K30 were obtained as gifts from Cadila Pharmaceuticals limited, India. Poloxamer-188 was purchased from Alpha Chemika, Maharashtra. Ethanol was purchased from RFCL limited, Gujarat.

Phase Solubility Studies[4]

Phase solubility studies were carried out according to Higuchi and Connors. An excess of lacidipine (10mg) was added to 25ml portions of distilled water, each containing variable amount of PVP-K30 and Poloxamer-188 such as 0.5, 1.0, 1.5, 2.0 and 2.5%w/v. All the above solutions with variable amount of PVP-K30 and Poloxamer-188 were shaken for 24 hours using orbital shaker. After shaking, the solutions were filtered and their absorbance noted at 284nm. The solubility of the lacidipine in every PVP-K30 and Poloxamer-188 solution was calculated and phase solubility diagram was drawn between the solubility of lacidipine and different concentration of PVP-K30 and Poloxamer-188.

Preparation of Physical Mixtures of Drug/Carrier[3]

Physical mixtures were prepared by mixing lacidipine with PVP-K30 and Poloxamer-188 for three minutes in a mortar until a homogeneous mixture was obtained. The resulting mixture was sieved through sieve no.100# and then stored in desiccators at room temperature until use.

Preparation of Solid Dispersions[5]

Solid dispersions were prepared with Lacidipine: PVP-K30 and Poloxamer-188 in 1: 2, 1: 4, 1: 6, 1: 8 and 1: 10 weight ratios by solvent evaporation method. Lacidipine was dissolved in ethanol and carrier was added to above solution. The solvent was evaporated at room temperature. The samples were pulverized in a mortar and passed through sieve no. 100#.

Characterization of Solid Dispersion by FT-IR Spectra[6]

FT-IR spectra of the samples (physical mixture and solid dispersion of drug and poloxamer-188 in different ratio) were obtained on a FTIR spectrophotometer. 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 4 $cm^{-1.}$

Characterization of Solid Dispersion by DSC[7]

DSC analysis was performed using a model DT-60 DSC (Shimadzu). Sample was heated in hermetically sealed aluminum pans over a temperature range of 50^0C-300^0C at a constant rate of 10^0C/min under a nitrogen steam.

Characterization of Solid Dispersion by XRD[8]

Vacuum grease was applied over a glass slide to stick the sample. About 100 mg of sample was sprinkled over it to make a layer having a thickness of ~0.5 mm. All the experiments were performed on an X-ray diffractometer (Philips X'Pert MPD, Eindhoven, Netherlands) having a sensitivity of 0.1 mg. The sample slide was placed vertically at an angle of zero degree in the sample chamber. An X-ray beam (Philip Cu target x-all ray tube) of 2kW was allowed to fall over the sample. As the slide moves at an angle of theta degree, a proportional detector detects diffracted X-ray at angle of 2-theta degrees. XRD patterns for poloxamer-188 solid dispersion were recorded using Philips JPCD software for powder diffractometry**.**

In – Vitro Drug Release Study[5]

*I*n vitro dissolution studies of pure drug and solid dispersions were carried out in 900 ml of 1% tween-20 solution at 37 ± 0.2^0C, using USP dissolution test apparatus type-II. Samples equivalent to 25 mg of lacidipine was filled in muslin cloth, tied with paddle and rotated at 50 rpm. At 5 min time intervals, 5ml samples were withdrawn, the initial volume was maintained by adding fresh dissolution medium. The solution was filtered and analyzed at 284nm.

Results and Discussion

Phase Solubility Studies

The phase solubility diagram generated for the solid dispersion between lacidipine: PVP-K30 and Poloxamer 188 presented in figure 1 and 2. This plot shows that the aqueous solubility of the drug increases linearly as a function of PVP-K30and Poloxamer 188 concentration. The solid dispersion stiochiometry was assumed to be 1:1 indicating A type of curve. The value of apparent

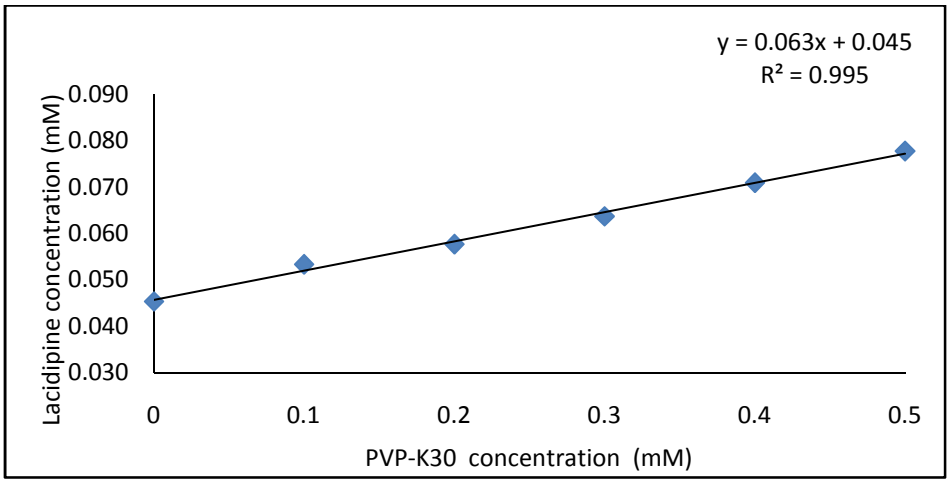

Figure 1: Phase Solubility Study of PVP-K30 Solid Dispersion

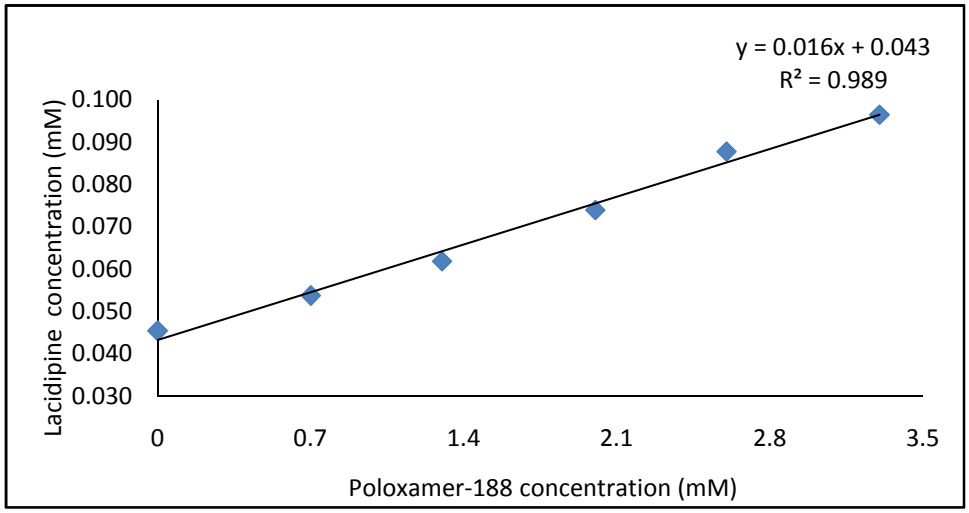

Figure 2: Phase Solubility Study of Poloxamer-188 Solid Dispersion

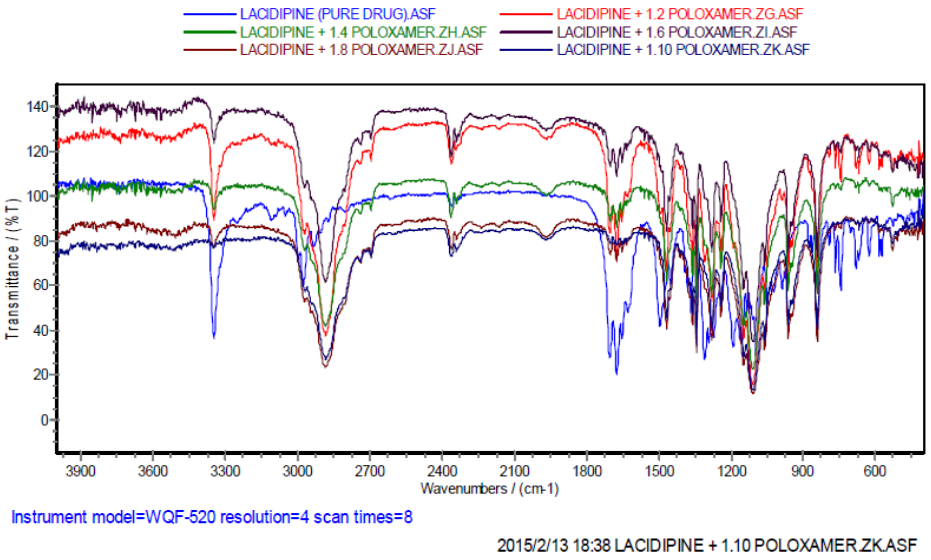

Figure 3: FT-IR Spectra of Pure Lacidipine and Solid Dispersion of Poloxamer-188

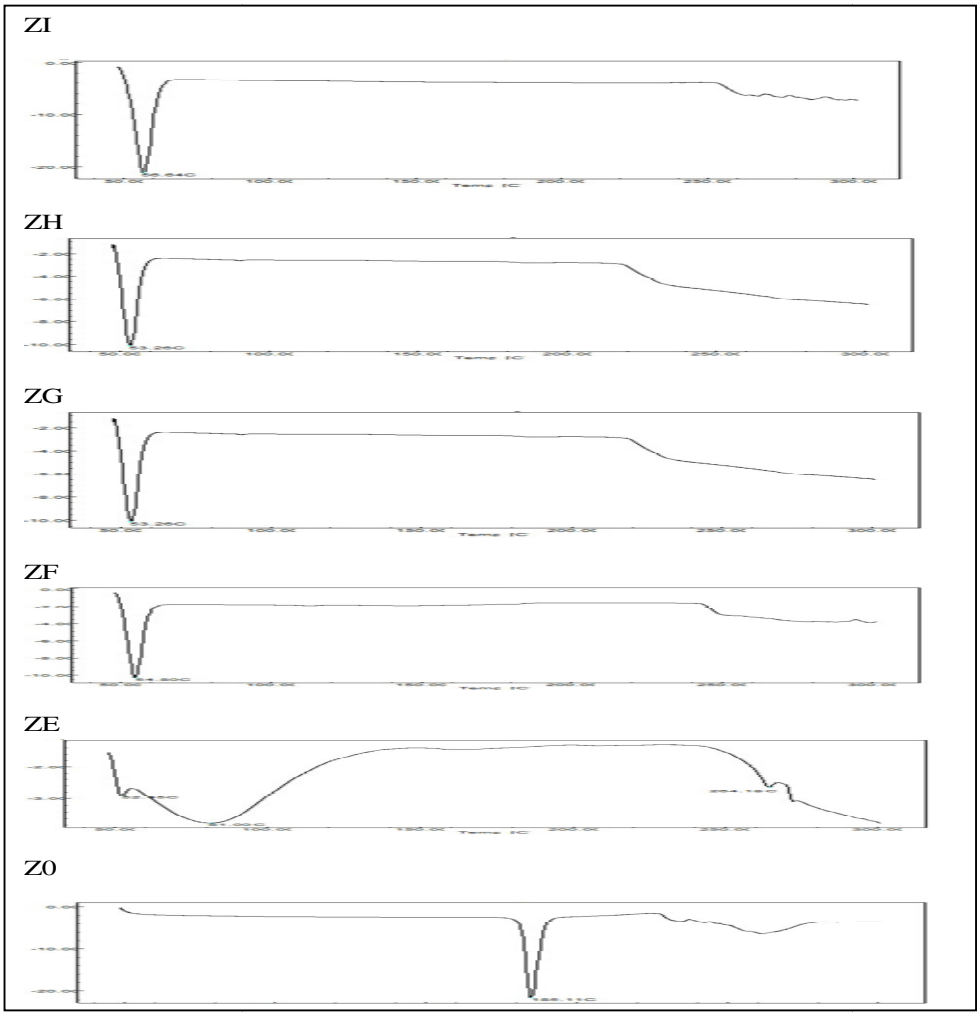

Figure 4: DSC Thermogram of (Z0) pure lacidine (ZE) 1: 2 lacidipine: poloxamer-188 solid dispersion (ZF) 1: 4 lacidipine: poloxamer-188 solid dispersion (ZG) 1: 6

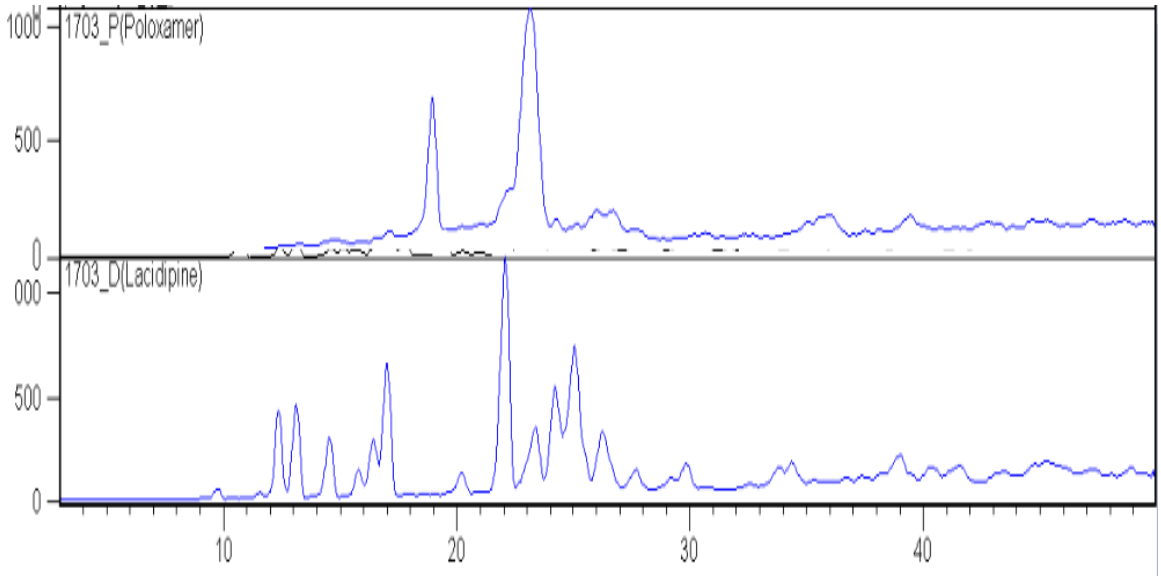

Figure 5 XRDDiffractograms of Poloxamer-188 Solid Dispersion and Pure Drug

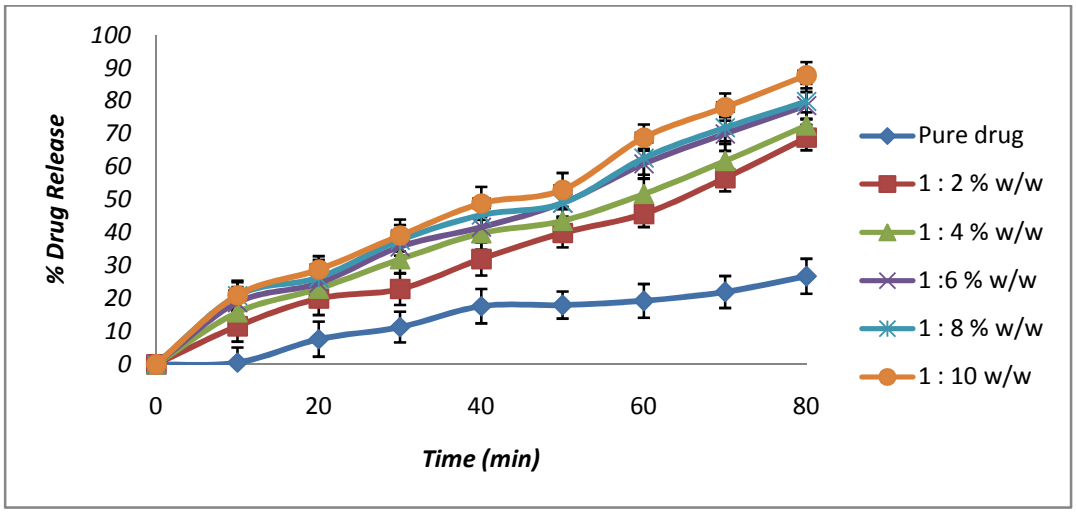

Figure 6: *In vitro* Drug Release Profile of PVP-K30

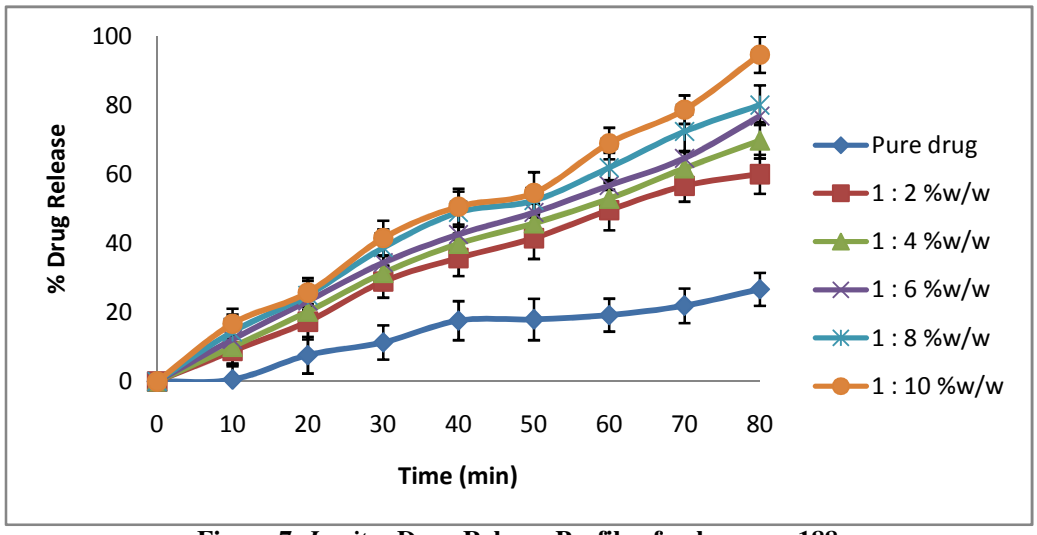

Figure 7: *In vitro* Drug Release Profile of poloxamer-188

stability constant obtained from the slope of phase solubility diagram was 1471.244 $M^{-1}$for PVP K30 and 377.90 $M^{-1}$for Poloxamer 188 which was in the range of 50-2000 M^{-1} and indicates good stability of lacidipine - PVP-K30 solid dispersion at 1:1 ratio.

FT-IR Spectra

The FT-IR spectra of pure drug, Poloxamer-188 solid dispersion samples was shown in figure 3. Lacidipine showed its characteristic peaks at 3357.5 and 2979.5 cm^{-1} which were related to N-H stretching vibration of dihydropyridine ring, C-H structure of aliphatic for streaching. The intensity of the characteristic peaks has been reduced in solid dispersion samples compared to pure drug.

Differential Scanning Calorimetry (DSC)

Figure 4 shows the DSC traces of pure lacidipine in crystalline states, solid dispersion systems with Poloxamer-188. As it is shown in figure 4, pure lacidipine exhibited sharp endothermic peak at 185.11^{0}C. which was ascribed to drug melting point. The absence of drug peak was observed in the DSC thermogram of various solid dispersions. It indicated the possibility of formation of solid dispersion between lacidipine and poloxamer-188.

XRD Analysis

The XRD patterns of pure lacidipine and prepared lacidipine solid dispersion using poloxamer-188 are presented in figure 5. The characteristic peaks appeared in the XRD pattern of the pure lacidipine17^0, 22^0 and

$25.12^{0.}$ (2θ), suggesting that the drug is present as crystalline state. The XRD pattern of lacidipine solid dispersion using poloxamer-188 showed various characteristic peaks of pure lacidipine with/without very small shifting. It was observed that some peaks shown by pure lacidipine were absent, and the intensity of peaks of this lacidipine solid dispersion was found to be markedly reduced when compared to that of the pure lacidipine. These observations indicate that the drug in solid dispersion was amorphous as compared to pure drug.

***In – Vitro* Drug Release Study**

The *in vitro* release profiles of pure lacidipine, solid dispersion with PVP-K30 and poloxamer-188(1: 2, 1: 4, 1: 6, 1: 8 and 1: 10 %w/w) shown in figure 6 and 7. It was observed that the in-vitro release of pure drug was slow than its solid dispersion with PVP-K30 and poloxamer-188. Results indicated that as the concentration of carriers increase, amount of drug release was found to be increased. From the comparison of solid dispersion of PVP-K30 and Poloxamer-188, it was revealed that the solid dispersion prepared using Poloxamer-188 has shown better drug release compared to solid dispersion prepared using PVP K30.

Conclusion

The results of this study showed that both PVP-K30 and poloxamer-188 are potential carriers for improvement in dissolution profile of lacidipine, a poorly water-soluble drug. The ratio of drug: carrier was the most important factor to achieve dissolution enhancement. Poloxamer-188 could be considered as a more suitable carrier as its effect on dissolution rate and efficiency was more prominent at lower concentrations. The finding of this result revealed that the problems of lacidipine like poor solubility and dissolution rate limited absorption and other side effect can be overcome by enhancing solubility of lacidipine.

References

1. Mukharya A, Chaudhary S, et al. Solid state characterization of Lacidipine/PVP K29/32 solid dispersion primed by solvent co-evaporation.*Int. J. Pharm. Inv.* 2012; 2(2): 90-96.
2. Dinda SC, Panda S. Formulation and *in-vitro/in-vivo* assessment of enhanced bioavailability of lacidipine using nano pure technique. *Albanian J. Pharma. Sci.* 2013; 1(1): 33-41.
3. Prasanthi NL, Rao N, Manikiran SS. Studies on dissolution enhancement of poorly water soluble drug using water soluble carriers. *Asian J. Pharm. Cl. Res.* 2010; 3(2): 95-97.
4. Balata G, Mahdi M, Bakera RA. Improvement of solubility and dissolution properties of ketoconazole by solid dispersions and inclusion complex. *Asian. J. Pharm. Cl. Res.* 2010; 5(1): 1-12.
5. Homoyouni A, Sadeghi F, Nokhodchi A, et al. Preparation and characterization of celecoxib solid dispersion; comparison of poloxamer-188 and PVP-K30 as carriers. I*rabian. J. Med. Sci.* 2014; 17(5): 322-331.
6. Dubey A, Kharia AA, Chatterjee DP. Enhancement of aqueous solubility and dissolution of telmisartan using solid dispersion technique. *Int. J. Pharma. Sci. Res.* 2014; 5(10): 4478-4485.
7. Muehlenfeld C, Kann B, Windbergs M. Solid dispersion prepared by continuous cogrinding in air jet mill. *J. Pharma.Sci.* 2013; 4132-4139.
8. Patel JR, Carlton RA et al. Preparation and structural characterization of amorphous spray-dried dispersions of tenoxicam with enhanced dissolution. *J. Pharma. Sci.* 2012; 101(2): 641-661.