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Preparation and characterization of celecoxib solid dispersions; comparison of poloxamer-188 and PVP-K30 as carriers

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ABSTRACT

Objective(s): Solid dispersion formulation is the most promising strategy to improve oral bioavailability of poorly water soluble drugs. The aim of this study was to compare the effect of polyvinylpyrrolidone K30 (PVP) and poloxamer-188 (PLX) as carrier in solid dispersion formulations of celecoxib (CLX).

Materials and Methods: Solid dispersions of CLX:PVP or CLX:PLX were prepared at different ratios (2:1, 1:1, 1:2, 1:4, 1:6) by solvent evaporation and melting methods, respectively. The characterization of samples was performed using differential scanning calorimetery (DSC), X-Ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FT-IR). The Gordon-Taylor equation was used to estimate the T_g of solid dispersion systems and the possibility of the interaction between CLX and PVP. Also, the dissolution rate of all samples was determined.

Results: DSC and XRPD analyses confirmed the presence of amorphous state of drug in solid dispersion systems. FT-IR studies showed CLX could participate in hydrogen bonding with PVP whilst no specific interaction between CLX and PLX was observed. Both PVP and PLX enhanced the dissolution rate of drug in solid dispersion samples. The dissolution rate was dependent on the ratio of drug: carrier. Interestingly, the solid dispersion samples of PLX at 2:1 and 1:1 drug: carrier showed slower dissolution rate than pure CLX, whilst these results were not observed for PVP.

Conclusion: The effect of PVP on dissolution rate enhancement was more pronounced compared to the other carrier. Having a higher Tg and more effect on dissolution rate, PVP could be considered as a more suitable carrier compared to PLX in solid dispersion formulation of CLX.

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Introduction

Celecoxib (CLX) is a selective cyclo-oxygenase 2 (COX-2) inhibitor that has been widely used in the treatment of osteoarthritis, rheumatoid arthritis and acute pain. In addition, several studies have shown the therapeutic benefits of co-administration of CLX and chemotropic agents in cancer treatment protocols (1, 2). According to the biopharmaceutical classification system (BCS), CLX can be categorized as class II drugs (poor water-solubility and high gastrointestinal permeability). In this class, dissolution is the rate limiting step for absorption from the gastrointestinal tract (3). Low solubility of CLX (~5 µg/ml) results in incomplete and high variability in absorption after oral administration (1, 4). Hence, increasing the solubility and dissolution rate is the most efficient strategy to improve oral bioavailability of this drug. Moreover, CLX with the needle shape crystals shows undesirable properties like cohesiveness, poor flowability and handling problems (5) which could cause some problems during the production of its dosage forms.

Various formulations have been used to overcome these drawbacks. Among the several formulation strategies, solid dispersion systems have been widely used to improve the dissolution and oral bioavailability of poorly water soluble drugs. Solid dispersion is a solid state in which the active pharmaceutical ingredient (API) could be dispersed

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particularly or molecularly in an inert amorphous or crystalline carrier. In these systems, reduction in drug particle size (sometimes to the molecular level), and conversion of the crystalline structure of API to the amorphous state, could lead to enhancement of the dissolution rate and oral bioavailability of poorly water soluble drugs (6). In addition, the use of hydrophilic carriers like polyethylene glycols, PVPs, PLXs, etc. in solid dispersion systems could improve the wettability of hydrophobic drugs.

PVPs have suitable solubility in water and therefore could be used as hydrophilic carriers in solid dispersion systems (7). These polymers are also good candidates for preparation of solid dispersion systems using solvent evaporation method due to their good solubility in most of the solvents. PVP-K30 has been used in various solid dispersion formulations in order to enhance the solubility and dissolution rate of poorly water soluble drugs (8, 9). Andrews *et al* prepared solid dispersion of CLX and PVP-K30 and showed that PVP could improve the dissolution of CLX (5). Furthermore, PVP-K30 with high T_g value around 154°C could prevent mobilization and recrystallization of drug following long time storage and improve amorphous state stability of drugs (5). PLX-188 is nonionic surfactant and a block copolymer composed of polyoxyethylene and polypropylene blocks which has been widely used as wetting and solubilizing agent. PLX-188 could be used in preparation of solid dispersion systems using melting process due to its low melting point (56-57°C) and it has been shown that the solubility and dissolution rate of poorly water soluble drugs have been improved using PLX-188 in solid dispersions (10, 11). However there is no report about the use of this carrier in preparation of solid dispersion of CLX. This study has been performed to evaluate the PLX as carrier in preparation of solid dispersion systems of CLX and to compare the PVP-K30 and PLX in terms of their effect on dissolution profile.

Materials and Methods

Materials

CLX was purchased from Arastoo chemical company (Iran), PVP-K30 and PLX-188 (Lutrol F68) were purchased from Sigma-Aldrich (Germany) and sodium dodecyl sulfate was obtained from Merck (Germany). All other solvents and chemicals were of analytical grade.

Preparation of solid dispersions

Solid dispersions of CLX:PVP or CLX:PLX-188 were prepared at drug:carrier ratios of 2:1, 1:1, 1:2, 1:4 or 1:6. For PVP, solvent evaporation method and for PLX, melting method was used.

Solvent evaporation method

Certain amounts of CLX and PVP-K30 were dissolved in the minimum amount of methanol to obtain clear viscose solution. The solvent was removed at 40°C in oven until complete drying of solid dispersions systems. The solid dispersions were then pulverized using a mortar and pestle, passed through 60-mesh sieve (250 µm) and stored in a desiccator until use for further studies.

Melting method

The required amounts of CLX and PLX were blended in a beaker and immersed in a boiling water bath to allow PLX to melt. The molten mixtures were stirred continuously and after 5 min, were rapidly quench cooled in an ice bath. The dispersions were then stored for an hour in refrigerator and then pulverized using a mortar and pestle, passed through 60-mesh sieve (250 µm) and stored in a desiccator until use for further studies.

Preparation of physical mixtures of drug/carrier

The physical mixtures of CLX and carriers were prepared by mixing the sieved fractions (less than 250 µm) of drug and carrier at the same ratio of solid dispersion systems using mortar and pestle.

Preparation of amorphous CLX

Amorphous CLX was prepared by melting the pure CLX at 170°C under nitrogen atmosphere and then rapidly cooling in an ice bath as previously described (5). The prepared amorphous CLX was used for DSC analysis.

Solid dispersion characterization

Determination of saturation solubility

The saturation solubility studies were performed on pure CLX, physical mixtures and solid dispersion samples. Sample of 5 mg was added to 25 ml volumetric flasks containing double-distilled water and stirred at 100 rpm in an air bath at 25°C for 48 h. The resulting suspension was filtered through a 0.22 µm filter. Concentration of CLX was determined spectrophotometrically at 253 nm. The solubility of each sample was determined in triplicates and the mean value and standard deviations were reported.

Differential scanning calorimetry (DSC)

DSC analyses were conducted using a DSC 822e Mettler-Toledo (Mettler Toledo, Switzerland) equipped with a refrigerated cooling system and calibrated using indium standard. Samples of pure CLX, solid dispersions and physical mixtures (3–5 mg) were placed in aluminum pans that were sealed with a lid. The crimped aluminum pans were heated from 20 to 200°C at a scanning rate of 10°C/min. Nitrogen was used as atmosphere at a flow rate of 80 ml/min. Onset temperatures and melting points of the samples were automatically calculated using STARe Ver. 10.00 (Mettler Toledo, Switzerland).

Table 1. Dissolution efficiency (DE), mean dissolution time (MDT) and saturation solubility for pure celecoxib (CLX) and CLX: PVP samples

Drug: carrier	DE%	MDT (min)	Saturation solubility (µg/ml)
CLX	42	17	2±0.73
CLX:PVP 2:1 PM	36	21	3±0.36
CLX:PVP 1:1 PM	39	21	3±0.53
CLX:PVP 1:2 PM	42	19	4±0.94
CLX:PVP 1:4 PM	44	16	4±0.59
CLX:PVP 1:6 PM	49	15	5±0.63
CLX:PVP 2:1 SD	43	11	2±0.83
CLX:PVP 1:1 SD	81	1	3±0.43
CLX:PVP 1:2 SD	86	1	3±0.51
CLX:PVP 1:4 SD	86	2	5±0.38
CLX:PVP 1:6 SD	89	3	5±0.66

Table 2. Dissolution efficiency (DE), mean dissolution time (MDT) and saturation solubility for pure celecoxib (CLX) and CLX:poloxamer (PLX) samples

Drug:carrier	DE%	MDT (min)	Saturation solubility (µg/ml)
CLX	42	17	2±0.73
CLX:PLX 2:1 PM	36	21	2±0.57
CLX:PLX 1:1 PM	38	21	3±0.43
CLX:PLX 1:2 PM	42	17	3±0.61
CLX:PLX 1:4 PM	56	10	4±0.83
CLX:PLX 1:6 PM	59	9	6±0.84
CLX:PLX 2:1 SD	9	24	2±0.77
CLX:PLX 1:1 SD	15	28	3±0.52
CLX:PLX 1:2 SD	68	3	4±0.93
CLX:PLX 1:4 SD	80	5	5±0.76
CLX:PLX 1:6 SD	80	6	5±0.43

Gordon-Taylor calculations

The Gordon-Taylor equation shown below, was used to predict the theoretical T_{gmix} of binary solid dispersion samples of CLX:PVP. These values were compared to the experimentally determined T_g.

$$T_{gmix} = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k_{w2}}$$

$$K \approx \frac{T_{g1}\rho_1}{T_{g2}\rho_2}$$

T_{g1} and T_{g2} are the glass transition temperatures, and w_1 and w_2 are the weight fractions of the two components. K is estimated from the true density (ρ) and T_g of pure CLX and PVP. The true densities of PVP and amorphous CLX were determined to be 1.18 and 1.35g/cm^3, respectively. This study was only performed on CLX:PVP solid dispersion samples. The T_g of binary mixtures of CLX:PLX could not be detected in DSC experiments and in addition, the melting point of PLX is much lower than T_g of CLX.

X-ray powder diffraction studies (XRPD)

X-Ray powder diffraction patterns were obtained for selected samples using a Bruker, D8 Advance, Germany diffractometer, with Cu Kα radiation. X-ray diffraction data were collected in the range of 5°-40° (2θ) with 0.05 steps.

Fourier transforms infrared spectroscopy (FT-IR)

The FT-IR spectra of selected samples were obtained using a Perkin Elmer spectrum BX FTIR (PerkinElmer, Waltham, MA). Samples were previously prepared with potassium bromide (KBr), at 1:5 (sample:KBr) weight ratio. The KBr discs were prepared by compressing the powders at a pressure of 7 tones for 2 min in a hydraulic press and scanned against a blank KBr disk at wave numbers ranging from 4000 to 450 cm^{-1} with resolution of 1.0 cm^{-1}.

Dissolution studies

Dissolution studies were carried out in an automated dissolution tester (Pharmatest, PTWS 3E, Germany) using the USP Apparatus 2 (paddle) method. The bath temperature and paddle speed were set at 37°C and 50 rpm, respectively. Dissolution medium was 1 liter of distilled water containing 0.25% (w/v) sodium dodecyl sulfate (SLS). A certain weight of samples equivalent to 40 mg CLX was added directly to the vessels. Samples were taken from the vessels through sintered filter by a peristaltic pump (Alitea, Sweden), and assayed at 253 nm by a multi-cell transport spectrophotometer (Shimadzu, Japan) based on calibration curve obtained for CLX at this wavelength. The dissolution of each sample was determined in triplicate.

Dissolution parameters

The dissolution efficiency (DE) is defined as the area under the dissolution curve (y) up to a certain time t and expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time (12).

$$DE\% = \frac{\int_0^t y.dt}{y_{100}.t} \times 100$$

Another parameter that describes the rate of dissolution is the mean dissolution time (MDT). MDT is calculated using the following equations.

$$MDT = \sum \bar{t}_i . \Delta M_i / \sum \Delta M_i$$

$$\bar{t} = (t_i + t_{i+1})/2$$

$$\Delta M_i = \left(M_{i+1} - M_i\right)$$

Where t_i^- is the midpoint of the time period during which the fraction ΔM of the drug has been released from sample (13).

Results

Saturation solubility of CLX

Table 1 and 2 show the saturation solubility of pure CLX, and CLX in physical mixture or solid dispersion samples. The results of the solubility studies indicated that pure CLX has very low solubility in water at 25°C (2±0.73 µg/ml). As it is shown in Table 1 and 2, the saturation solubility of CLX was increased by the presence of PVP-K30 and PLX-188 in physical mixtures and solid dispersion samples. By increasing the concentration of the carrier in the physical mixtures and solid dispersion samples the saturation solubility of CLX was also increased.

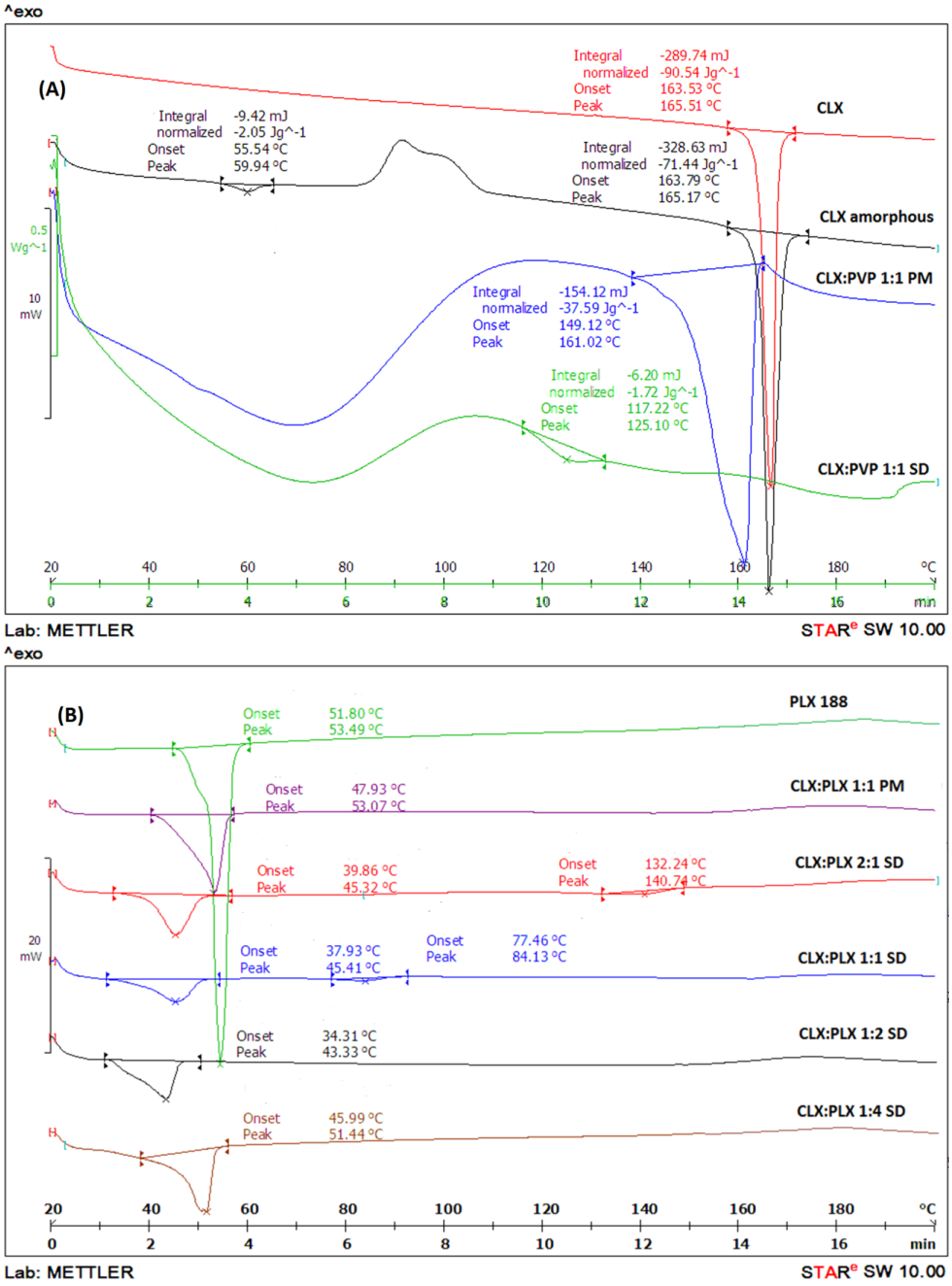

Figure 1. Differential scanning calorimetry (DSC) thermograms of solid dispersion (SD) samples and physical mixtures (PM) at different drug: carrier ratios. (A) CLX:PVP solid dispersions. (B) CLX:PLX solid dispersions
CLX: Celecoxib, PLX: Poloxamer 188; PVP: Polyvinylpyrrolidone K30

Differential scanning calorimetry (DSC)

Figure 1 shows the DSC traces of pure CLX in crystalline and amorphous states, physical mixture (PM), and solid dispersion (SD) systems with PVP-K30 and PLX-188. As it is shown in Figure 1(A) pure CLX exhibited a sharp endothermic peak at 165.51°C whilst the amorphous CLX showed T_g at 59.94°C, a recrystallization exotherm at 72.31°C and a sharp melting endotherm at 165.17°C. Physical mixture of CLX:PVP at the ratio of 1:1 (expanded view) showed a broad melting peak with onset temperature and endothermic peak at 149.12°C and 161.02°C, respectively. However, in the thermogram of SD sample with PVP a broad endothermic peak appeared at 125°C which was the Tg of the SD sample and the peak related to melting point of drug was not observed.

Figure 1B exhibits a sharp endothermic melting peak for PLX-188 at 53.49°C. This Figure also shows the absence of CLX melting endothermic peak for PM and SD samples.

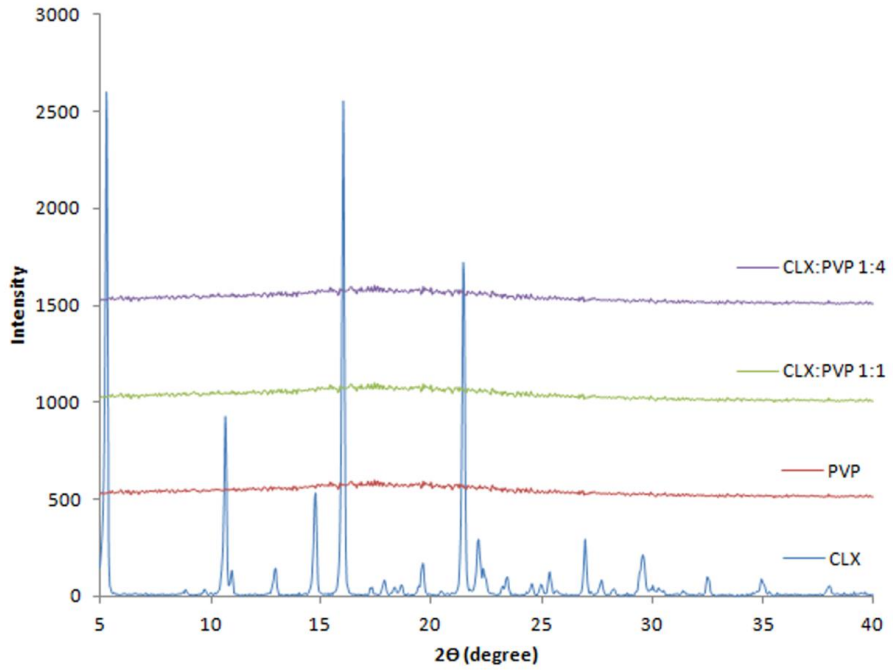

Figure 2. X-ray powder diffractions (XRPD) of pure celecoxib (CLX), polyvinylpyrrolidone K30 (PVP) and their solid dispersion samples at different drug: carrier ratios

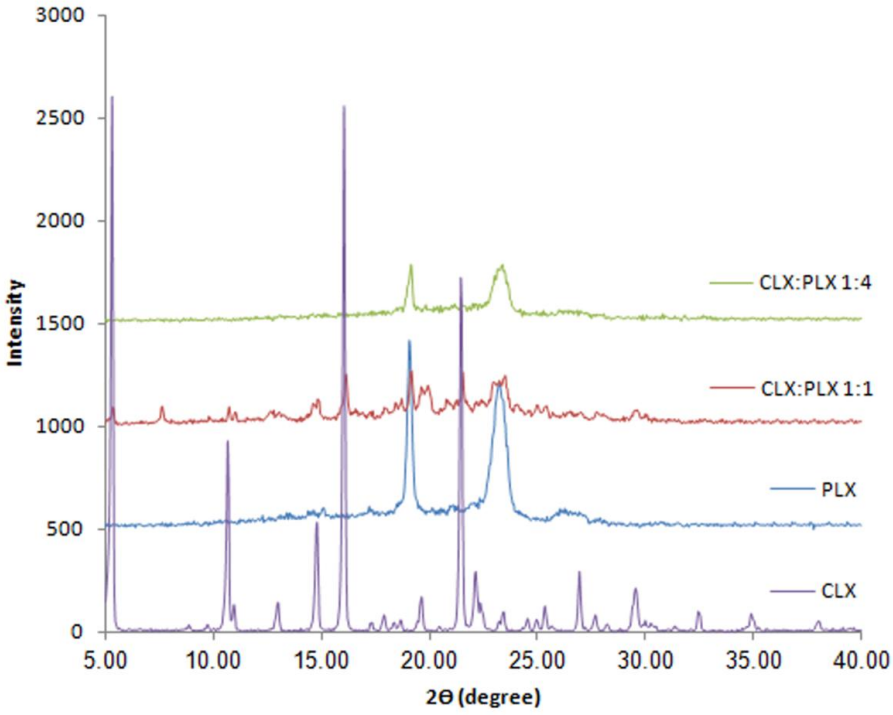

Figure 3. X-ray powder diffractions (XRPD) pattern of pure celecoxib (CLX), poloxamer 188 (PLX) and their solid dispersion samples at different drug: carrier ratios

X-ray powder diffraction studies (XRPD)

XRPD pattern for CLX and its solid dispersions with PVP-K30 and PLX-188 are shown in Figures 2 and 3. X-ray diffraction of CLX showed sharp peaks at 2θ values of 5°, 10.5°, 16° and 21.5°. PVP showed completely amorphous state with the absence of any diffraction peaks whilst PLX-188 showed two peaks at 19° and 23°. As it is shown in Figure 2, there are no peaks for all solid dispersion samples of drug and PVP-K30.

In solid dispersion samples of drug and PLX-188 at the ratio of 1:1, the intensity of the characteristic peaks in the XRPD pattern of crystalline CLX has been reduced. By increasing the ratio of polymer, these characteristic peaks were completely vanished at the ratio of 1:4 CLX:PLX (Figure 3). The peaks at

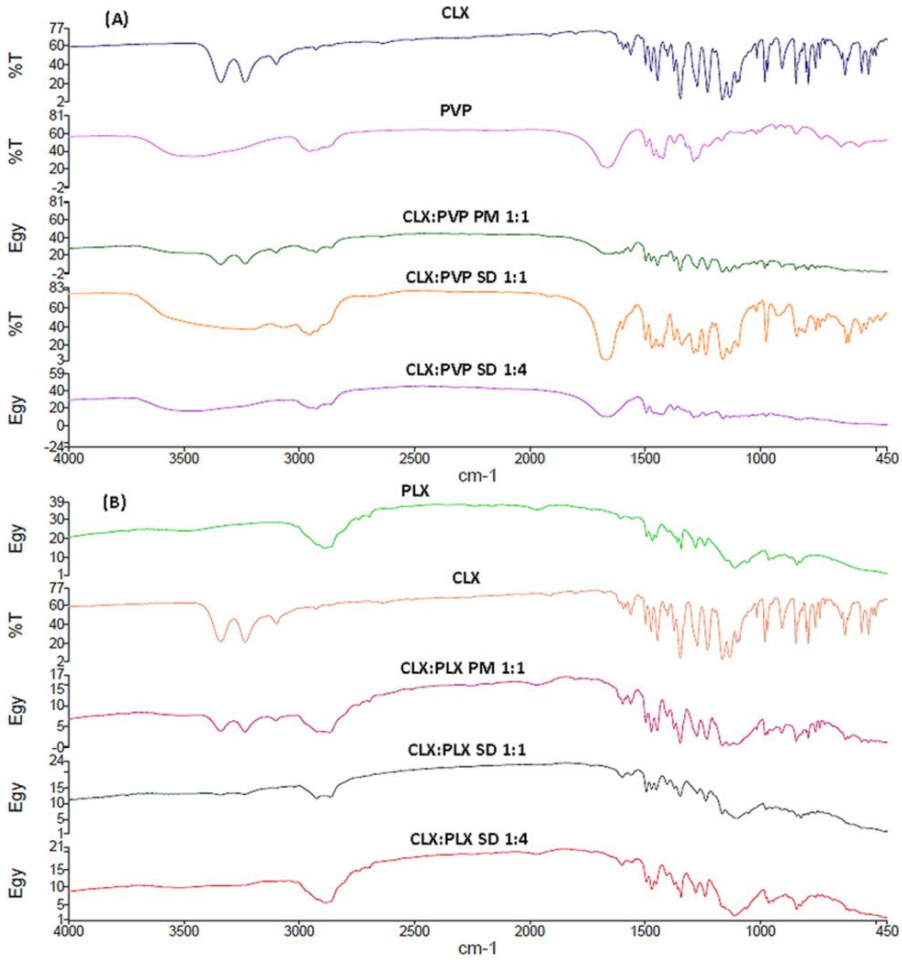

Figure 4. Fourier transform infrared spectroscopy of pure celecoxib (CLX), its physical mixtures (PM), and solid dispersion (SD) samples with polyvinylpyrrolidone K30 (PVP) (A) and poloxamer 188 (PLX) (B)

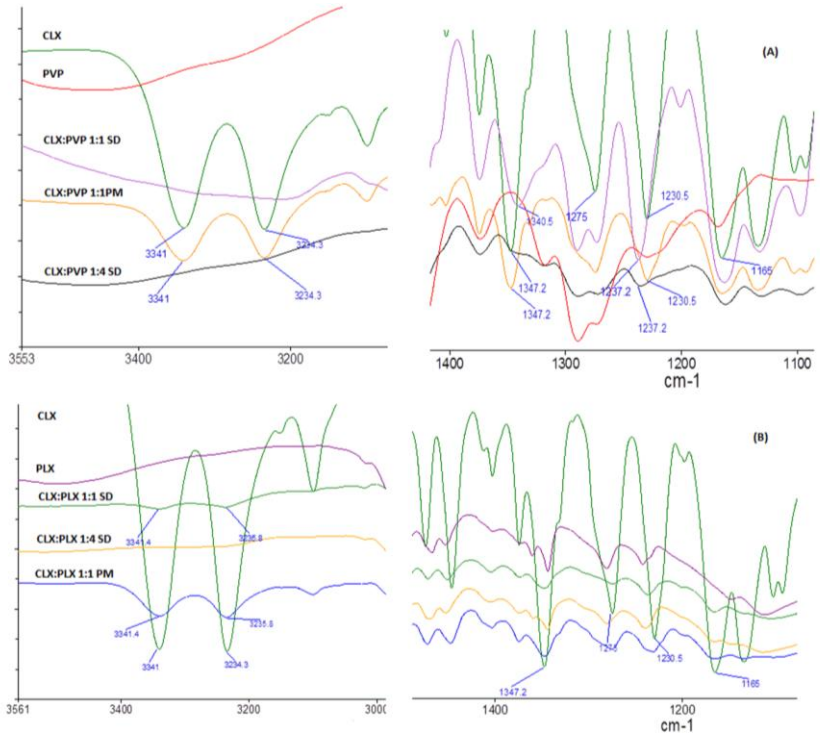

Figure 5. Fourier transform infrared spectroscopy of pure celecoxib (CLX), its physical mixtures (PM), and solid dispersion (SD) samples with polyvinylpyrrolidone K30 (PVP) (A) and poloxamer 188 (PLX) (B), (expanded view)

2θ value of 19° and 23° which are related to PLX, show lower intensity compared to pure PLX.

Fourier transform infrared spectroscopy (FT-IR)

Figures 4 and 5 show the FT-IR spectra of pure CLX, PVP and PLX, their physical mixtures and solid dispersion samples. As it is shown in Figures 4 and 5, CLX showed its characteristic peaks at 3341 and 3234 cm^{-1} which were related to N-H stretching vibration of sulfonamide group, 1347 and 1165 cm^{-1} for the S=O asymmetric and symmetric stretching and 1230 and 1275 cm^{-1} for symmetric and asymmetric C-F stretching. The intensity of the characteristic peaks has been reduced in solid dispersion samples compared to its physical mixture.

Dissolution studies

The dissolution profiles of pure CLX, PM and SD samples with PVP-K30 (A and B) or PLX (C and D), are shown in Figure 6. As it is shown in Figure 6 (A and B, C and D), the presence of PVP or PLX could improve the dissolution rate of CLX in PM and SD samples.

Discussion

Differential scanning calorimetry (DSC)

It has been previously reported that drug/polymer intermolecular interactions play a critical role in the stabilization of amorphous solid dispersion formulations. This stabilization of high energy amorphous systems is mostly dependent on drug/polymer miscibility and glass transition temperature of solid matrix (14). So, it is important to have an analytical method that allows the investigation of physicochemical properties. Methods such as DSC, XRPD, FTIR and dissolution test are often used for this purpose.

DSC analyses were performed in order to investigate the thermal behavior of the components of the samples. In solid dispersion or physical mixture samples, absence or shifting of the melting point of the drug to the lower temperature indicates the possibility of drug/polymer miscibility. Moreover, in solid dispersion samples, absence or shifting of the T_g of drug to the higher temperature has been previously reported (14, 15). As it is shown in Figure 1A, the absence of melting point of CLX in solid dispersion samples at the ratio of 1:1 CLX:PVP indicates the conversion of CLX to an amorphous state, while the presence of single peak of T_g at 125.10ºC proves the miscibility of CLX in the PVP. The observed T_g value is significantly higher than that of amorphous CLX, suggesting that the molecular mobility of CLX within the SD samples could be reduced. Moreover, calculation of theoretical T_g values according to Gordon-Taylor equation (89°C) and comparison with experimental value (125°C), confirmed a positive deviation from the ideal behavior. These results are indicative of a strong interaction between CLX and PVP and increased rigidity of the matrix network of their solid dispersion systems and hence the stabilization of formulation (14). Similar results have been also reported by Andrews *et al* (5). In addition, the absence of recrystallization exotherm indicates that PVP-K30 inhibited the mobility and hence recrystallization of CLX when it was heated above T_g.

As it is shown in Figure 1B, the PLX-188 showed the melting point at 53.49°C which is in agreement with the literature data (10). Absence of CLX melting endothermic peak in 1:1 PM is attributed to the dissolution of CLX in the molten PLX. Figure 1B clearly shows the formation of eutectic mixture in solid dispersion systems. Samples with CLX:PLX 1:2 ratio exhibited the lowest melting point at 43.33°C. Samples with 2:1 and 1:1 ratios also produced eutectic mixtures with melting points at 45.32°C and 45.41°C, respectively. In these samples, presence of a very small and broad melting endothermic peak could be attributed to the excess amount of CLX which did not form an eutectic mixture with PLX. Similar results have been reported for solid dispersion systems of PLX-188 and ibuprofen (10). As the drug is miscible with PLX-188, during the preparation of solid dispersions, the drug molecules could penetrate into the crystalline structure of PLX and this could prevent the formation of crystalline state after the mixture is being cooled. As a result, PLX could be formed with weaker structure, compared to its primary form. Hence, it could be melted at lower temperature and could show a broad melting peak (16).

In general, solid dispersion samples containing PVP-K30 and CLX could be more stable than those containing PLX and CLX due to higher T_g. This could reduce the possibility of recrystalization of CLX during storage.

X-ray powder diffraction studies (XRPD)

X-ray diffraction analysis of CLX showed sharp peaks at 2θ values of 5°, 10.5°, 16° and 21.5° indicating the crystalline nature of CLX (17). PVP showed completely amorphous state with absence of any diffraction peaks, whilst PLX-188 showed two peaks at 19° and 23° corresponding to the crystalline structure of PLX (16). As it is shown in Figure 2, there are no peaks in all solid dispersion samples of drug and PVP-K30. This indicates that the CLX has been completely converted to an amorphous state in the presence of PVP-K30. In solid dispersion samples with the ratio of 1:1 drug to carrier, CLX is completely amorphous and by increasing the ratio of polymer, no remarkable changes could be detected in XRPD pattern.

In solid dispersion samples of drug and PLX-188 at the ratio of 1:1 drug to carrier, the intensity of the

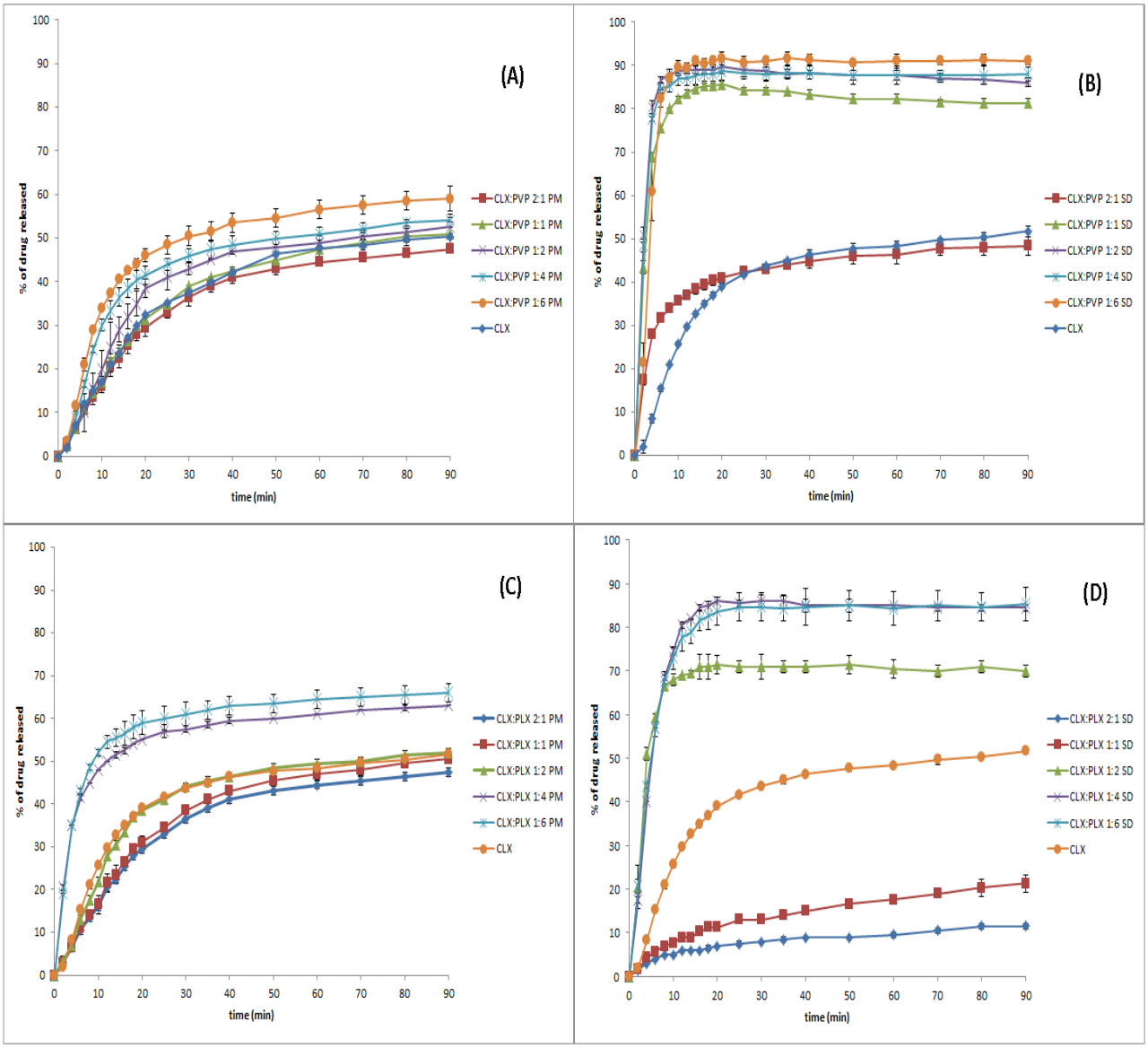

Figure 6. Dissolution profiles of pure celecoxib (CLX) and its physical mixtures (PM) with polyvinylpyrrolidone K30 (PVP) (A), solid dispersions (SD) with polyvinylpyrrolidone K30 (PVP) (B), physical mixtures (PM) with poloxamer 188 (PLX) (C) and solid dispersions (SD) with poloxamer 188 (PLX) (D)

characteristic peaks in the XRPD pattern of crystalline CLX has been obviously reduced. However, by increasing the ratio of polymer, these characteristic peaks were completely diminished at the ratio of 1:4 CLX:PLX (Figure 3). The peaks at 2θ value of 19 and 23 which are related to PLX, show lower intensity compared to pure PLX due to dilution of polymer with CLX. The XRPD results confirmed the results of DSC studies and accounted for the formation of the amorphous state of CLX in the presence of PVP-K30 and PLX in solid dispersion samples.

Fourier transform infrared spectroscopy (FT-IR)

The interaction between API and carrier in solid dispersion systems usually results in noticeable changes in the FT-IR spectra. So, FT-IR has been employed in addition to DSC and XRPD to study the molecular interactions between the drug and carrier. As it is shown in Figures 4 and 5, CLX showed its characteristic peaks related to N-H stretching vibration of sulfonamide group, the S=O asymmetric and symmetric stretching and symmetric and asymmetric C-F stretching (5, 17). The intensity of the characteristic peaks has been reduced in solid dispersion samples compared to its physical mixture as shown in Figures 4 and 5. It has been reported that there is a possibility of intermolecular hydrogen bonding between CLX and PVP (5). In FT-IR spectra of CLX:PVP solid dispersion samples, the two CLX bands at 3341 cm^{-1} and 3234 cm^{-1} are broadened or lost, suggesting that the N–H group in CLX is engaged in hydrogen bonding (18). In addition, the symmetrical stretching vibration of C–F at 1230 cm^{-1} positively shifted to 1237 cm^{-1}. Also, a negative shift to lower wavenumber (from 1347 cm^{-1} to 1340 cm^{-1})

was observed in asymmetric stretching of SO_2 group. Since that sulfonamide group can participate as proton donor (NH_2) and proton acceptor (SO_2), these changes might indicate the intermolecular hydrogen bonding of CLX molecules (5, 17). The intermolecular hydrogen bond has been previously reported in amorphous form of CLX, whilst no intermolecular hydrogen bond has been observed in crystalline form of CLX because of its spatial conformation (17). These results are in agreement with those published previously (19). In Figures 4A and 5A, negligible shift in the position of C=O stretching vibration band related to PVP could be observed in solid dispersion samples. This could indicate the absence of hydrogen bonding between CLX and PVP. However, the negligible shift of C=O bond in PVP could be due to the high content of PVP in solid dispersion samples as shown by other studies (19). Failure of FT-IR spectroscopy in detecting the shift of C=O bond in PVP, has been reported to be due to the marked difference in the number of molecules of CLX and PVP available for interaction. As PVP is a polymeric compound with large number of C=O groups compared with NH2 groups of CLX, the number of nonbonded C=O groups are more than those which are engaged in hydrogen bonding and this results in negligible shift in the C=O stretching vibration band (19). Gupta *et al* showed that even at low content of PVP in solid dispersion systems of CLX and PVP, the bands of N-H and S=O stretching vibrations for CLX were observed at positions characteristic of amorphous CLX and the authors concluded that in binary solid dispersion of CLX and PVP, both CLX-CLX and CLX-PVP hydrogen bond exist and the hydrogen bond between CLX and PVP could limit the molecular motions in the amorphous state of the drug and assist its stability.

As it is shown in Figures 4B and 5B, the intensity of doublet peak related to NH_2 groups of CLX has been reduced in SD samples of CLX:PLX compared to physical mixture. In addition, this doublet peak disappeared in CLX:PLX at 1:4 SD sample. There is no identifiable shift in the wavenumbers of S=O and C-F of CLX in SDs and PM. These observation indicated the probability of the formation of hydrogen bond between CLX and PLX in solid dispersion samples particularly at high drug:carrier ratio (1:4).

Dissolution studies

As it is shown in Figure 6A and 6B, the presence of PVP-K30 could improve the dissolution rate of CLX in both PM and SD samples; however, solid dispersion samples showed much higher dissolution rate compared to PMs. The drug:carrier ratio affected the dissolution profiles for both PM and SD samples, but the effect was more pronounced for SD samples. In other words, the ratio of drug:carrier considerably affected the dissolution profiles of solid dispersion samples so that at 2:1 drug:carrier ratio the dissolution profile for SD sample was resembled the pure CLX, whilst increase in carrier ratio to 1:1 resulted in dissolution of 80% of drug in less than 10 min. Increase in carrier ratio to 1:2 in SD samples, increased the dissolution rate and efficiency markedly (Figure 6B and Table 1). It should be mentioned that further increase in drug:carrier ratio up to 1:6 hardly affected the dissolution profile in SD samples with PVP-K30. The results also indicate that the percent of dissolved drug has increased to more than 80% in SD samples at 1:1 and higher ratios of drug:carrier. This effect might be due to the improved solubility of CLX in the presence of PVP-K30 (Table 1). Moreover, PVP-K30 as a hydrophilic carrier could enhance the wettability of drug and hence improves the dissolution rate of SD samples (20).

Nearly similar results with some exceptions were shown for PLX samples. It could be observed that PLX has a major influence on dissolution rate of CLX in both PM and SD samples and the ratio of PLX plays a critical role on the amount and rate of dissolution. As it is shown in Figure 6C, in PMs at the ratio of 2:1 and 1:1 drug:carrier, the dissolution rate slightly decreased compared to pure CLX, whilst increase in the ratio of carrier (e.g to 1:4 or 1:6), increased the dissolution rate. However, in SD samples at 2:1 or 1:1 drug:carrier ratio (Figure 6D) the rate of drug dissolution decreased dramatically compared to pure CLX. The reduction in dissolution rate of solid dispersion samples at lower carrier ratio could be attributed to the PLX properties. In solid dispersion samples with low amount of carrier, the presence of PLX is not sufficient to disperse the CLX molecularly among carrier molecules and hence the drug molecules form aggregates due to their lipophilisity and make amorphous clusters. This corresponds to glass suspension type of solid dispersion systems (21, 22). When this system comes into contact with the dissolution medium, PLX forms a viscose gel layer around the drug clusters. This viscose gel slows down the diffusion of dissolution medium through it and therefore, small lumps appear in dissolution vessels which are difficult to dissolve. In solid dispersion samples with higher amount of polymer, the drug molecules could be dispersed molecularly among polymer chain and therefore, the formation of glassy solution type of solid dispersion system would be easy. This type of solid dispersion system could dissolve quickly after contact with dissolution medium.

In general, considering dissolution profiles, dissolution efficiency, MDT and drug:carrier ratio, it could be claimed that as a carrier, PVP-K30 is more suitable than PLX-188 for improvement of the dissolution rate of CLX in their solid dispersion systems. It was shown that the enhancement effect of PVP-K30 on dissolution rate of CLX was significantly higher at similar drug:carrier ratio and PVP could

improve dissolution profile of CLX at very lower concentration compared to PLX-188.

Conclusion

The results of this study showed that both PVP-K30 and PLX-188 are potential carriers for improvement in dissolution profile of CLX, a poorly water-soluble drug. The ratio of drug:carrier was the most important factor to achieve dissolution enhancement. PVP-K30 could be considered as a more suitable carrier as its effect on dissolution rate and efficiency was more prominent at lower concentrations. Moreover, solid dispersions of CLX:PVP with higher T_g could be more stable during storage.

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References

1. Dolenc A, Kristl J, Baumgartner S, Planinsek O. Advantages of celecoxib nanosuspension formulation and transformation into tablets. Int J Pharm 2009; 376:204-212.
2. Lu GW, Hawley M, Smith M, Geiger BM, Pfund W. Characterization of a novel polymorphic form of celecoxib. J Pharm Sci 2006; 95:305-317.
3. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharm 2004; 58:265-278.
4. Seedher N, Bhatia S. Solubility enhancement of Cox-2 inhibitors using various solvent systems. AAPS Pharm Sci Tech 2003; 4:1-9.
5. Andrews GP, Abu-Diak O, Kusmanto F, Hornsby P, Hui Z, Jones DS. Physicochemical characterization and drug-release properties of celecoxib hot-melt extruded glass solutions. J Pharm Pharmacol 2010; 62:1580-1590.
6. Vasconcelos TF, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today 2007; 12:1068-1075.
7. Leuner C, Dressman JB. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000; 50:47-60.
8. Khodaverdi E, Khalili N, Zangiabadi F, Homayouni A. Preparation, characterization and stability studies of glassy solid dispersions of indomethacin using PVP and isomalt as carriers. Iran J Basic Med Sci 2012; 15:820-832.
9. Sethia S, Squillante E. Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. Int J Pharm 2004; 272:1-10.
10. Newa M, Bhandari KH, Li DX, Kwon T, Kim JA, Yoo BK, *et al.* Preparation, characterization and *in vivo* evaluation of ibuprofen binary solid dispersions with poloxamer 188. Int J Pharm 2007; 343:228-237.
11. Ghareeb MM, Abdulrasool AA, Hussein AA, Noordin MI. Kneading technique for preparation of binary solid dispersion of meloxicam with poloxamer 188. AAPS Pharm Sci Tech 2009; 10:1206-1215.
12. Al-Hamidi H, Edwards A, Mohammad MA, Nokhodchi A. To enhance dissolution rate of poorly water-soluble drugs:glucosamine hydrochloride as a potential carrier in solid dispersion formulations. Colloids Surf B Biointerfaces 2010; 76:170-178.
13. Costa FO, Sousa JJ, Pais AA, Formosinho SJ. Comparison of dissolution profiles of Ibuprofen pellets. J Control Release 2003; 89:199-212.
14. Baird JA, Taylor LS. Evaluation of amorphous solid dispersion properties using thermal analysis techniques. Adv Drug Deliver Rev 2012; 64:396-421.
15. Janssens S, Van den Mooter G. Review: physical chemistry of solid dispersions. J Pharm Pharmacol 2009; 61:1571-1586.
16. Fousteris E, Tarantili PA, Karavas E, Bikiaris D. Poly (vinyl pyrrolidone)-poloxamer-188 solid dispersions prepared by hot melt extrusion - Thermal properties and release behavior. J Therm Anal Calorim 2013; 1-11.
17. Chawla G, Gupta P, Thilagavathi R, Chakraborti AK, Bansal AK. Characterization of solid-state forms of celecoxib. Eur J Pharm Sci 2003; 20:305-317.
18. Fouad EA, El-Badry M, Mahrous GM, Alanazi FK, Neau SH. The use of spray-drying to enhance celecoxib solubility. Drug Dev Ind Pharm 2011; 37:1463-1472.
19. Gupta P, Thilagavathi R, Chakraborti AK, Bansal AK. Role of molecular interaction in stability of celecoxib-PVP amorphous systems. Mol Pharm 2005; 2:384-391.
20. Gupta VR, Mutalik S, Patel MM, Jani GK. Spherical crystals of celecoxib to improve solubility, dissolution rate and micromeritic properties. Acta Pharm 2007; 57:173-184.
21. Sarkari M, Brown J, Chen X, Swinnea S, Williams RO, Johnston KP. Enhanced drug dissolution using evaporative precipitation into aqueous solution. Int J Pharm 2002; 243:17-31.
22. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm 2002; 54:107-117.