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Formulation and Evaluation of Solid Dispersion of Celecoxib

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Abstract

The aim of this study was to develop celecoxib (CLX) -polyvinylpyrrolidone (PVP) solid dispersion nanoparticles with and without surfactant using the supercritical antisolvent (SAS) process. The effect of different surfactants such as gelucire 44/14, poloxamer 188, poloxamer 407, Ryoto sugar ester L1695, and D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) on nanoparticle formation and dissolution as well as oral absorption of CLX -PVP K30 solid dispersion nanoparticles was investigated. Spherical CLX solid dispersion nanoparticles <300 nm in size were successfully developed using the SAS process. Analysis by differential scanning calorimetry and powder X-ray diffraction showed that CLX existed in the amorphous form within the solid dispersion nanoparticles fabricated using the SAS process. The CLX -PVPTPGS solid dispersion nanoparticles significantly enhanced *in vitro* dissolution and oral absorption of CLX relative to that of the unprocessed form. The area under the concentration-time curve (AUC0 24 h) and peak plasma concentration (Cmax) increased 4.6 and 5.7 times, respectively, with the CLX -PVP-TPGS formulation. In addition, *in vitro* dissolution efficiency was well correlated with in vivo pharmacokinetic parameters. The present study demonstrated that formulation of CLX -PVP-TPGS solid dispersion nanoparticles using the SAS process is a highly effective strategy for enhancing the bioavailability of poorly water-soluble CLX.

Keywords: Bioavailability, Celecoxib, Nanoparticles, Solid dispersion, Supercritical antisolvent

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Introduction

Celecoxib (CLX) is a nonsteroidal anti-inflammatory drug. It is a selective cyclo-oxygenase 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 coadministration of CLX and chemotrophic agents in cancer treatment protocols. According to the biopharmaceutical classification system (BCS), CLX can be categorized as Class II drugs (poorly water-soluble and highly gastrointestinal permeability). In this class, dissolution is the rate limiting step for absorption from the gastrointestinal tract. The pharmacological response of drug therapy is mainly dictated by the availability of the drug at the target receptor site. An important criterion is a sufficient drug plasma concentration after administration. Therefore, the goal of each drug delivery system is to have an adequate therapeutic blood level for a certain period of time, except for some pathological conditions where a local action is required, for example, antacids. Different routes of drug administration are available; oral, intravenous, by inhalation, etc. Oral drug delivery is by far the most favorable and preferred route, as it is considered as safe, convenient for the patient and the compliance is generally good. Mostly 80% of all marketed products CLX drugs are oral products.[1] To achieve therapeutically active range of bioavailability after oral administration of the active pharmaceutical ingredients (API) some steps needs to be consider. First, the drug substance needs to be dissolved in the fluids of the gastro-intestinal tract. After dissolution, an absorptive step is necessary to transport the API to the blood stream. This can occur either passively or actively, but efflux mechanism and presystemic metabolism can counteract the uptake and thereby reduce the bioavailability. When the drug passes the gastrointestinal membranes, it enters the hepatic portal circulation. Here first pass metabolism can result in API metabolites that can be more or less active than the original API. Subsequently the drug reaches the general circulation and can be distributed and transported to its site of action. A final step is the excretion of the drug out of the body.[2] The pharmaceutical industry today looks toward a more rational approach with respect to drug discovery. This leads to overall problems with both solubility and permeability of the newly discovered molecules.[2] Obviously the interpretation of solubility and permeability has to be seen as a function of the drug potency. A drug is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1–7.5. Another important factor is the dissolution rate, an API needs to be dissolved before its absorption.[3] Poor solubility and poor permeability are both critical, but not equally, because of the lack of "safe" formulation-approaches to enhance the latter. Altering the permeability of the enterocytes often implicates toxicity issues. The chemical modification of the drug is safer, but this results in the formation of a new chemical entity. Poor solubility, on the other hand, can be tackled more easily by formulation-approaches. This can be understood if we consider the modified Noyes-Whitney equation:[4]

$$dM/dt = AD (Cs-Ct)/h \quad (1)$$

Where dM/dt is the dissolution rate, A is the specific surface area of the drug particle,

D is the diffusion coefficient,

h is the diffusion layer thickness surrounding the dissolving particle,

Cs is the saturation solubility and Ct is the drug concentration at time t.

According to this equation, an increase of the surface area, by reducing the particle size of the solid compound, and/

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or optimizing the wetting characteristics of the compound surface are possibilities to improve the dissolution rate. Another approach could be reducing the diffusion layer thickness and last, to improve the apparent solubility of the drug in physiologically relevant conditions. Nevertheless a check of a new API's potency, solubility/dissolution rate and permeability is necessary. Therefore, drug compounds can be divided into four classes according to the BCS depending on *in vitro* solubility and *in vivo* permeability data.[5] Although adaptation and extensions have been suggested[6] the BCS as described by Amidon is still widely used to classify drug compounds into four classes [Figure 1]:

Class 1: High Solubility – High Permeability, Class 2: Low Solubility – High Permeability, Class 3: High Solubility – Low Permeability, Class 4: Low Solubility – Low Permeability

Different Approaches for Improvement in Dissolution Performance

Various pharmaceutical strategies are available to improve aqueous solubility and dissolution rate of poorly soluble drug compounds: For example, co-crystals, salt formation, micronization and nanonization, complexation with cyclodextrins, encapsulation in ordered mesoporous silica materials, self-emulsifying systems, and solid dispersions.

Solid Dispersions

Chiou and Riegelman defined a solid dispersion for the 1st time in 1971 as "a dispersion of one or more active ingredients in an inert carrier or matrix at the solid state, prepared by the melting, solvent, or melting-solvent method".[7] Sekiguchi and Obi first reported the manufacturing of a solid dispersion in 1961. A eutectic mixture of sulfathiazole and urea was formulated by thoroughly mixing of the two components and heating it just above the eutectic point using an electric furnace. The sample was stirred rapidly in an ice-bath for solidification.[8] Another approach used by Tachibana and Nakamura deals with dissolution of β-carotene and a water-soluble drug in a solvent, after which the solvent was removed by evaporation. The co-precipitate resulted in colloidal drug dispersion on exposure to water.[9]

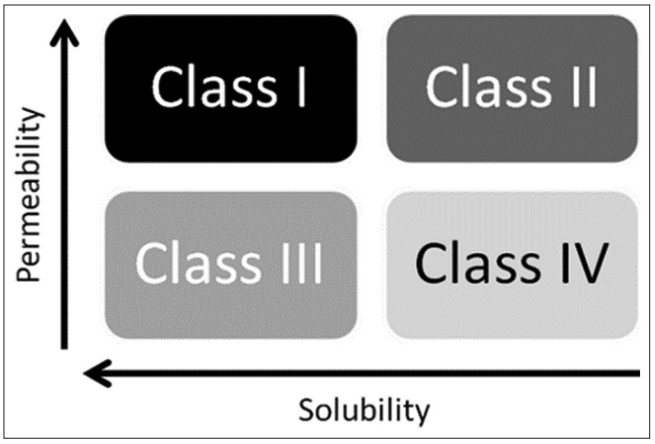

Figure 1: BCS

Types of solid dispersion

1. Simple eutectic mixtures.
2. Solid solutions.
3. Glass solution and suspension.
4. Amorphous precipitations in a crystalline carrier.

Simple eutectic mixtures

These are prepared by rapid solidification of the fused melt of two components that show complete liquid miscibility and negligible solid-solid solubility. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components, for example, - paracetamol-urea.

Solid solutions

In the solid solution drug particle size is reduced to its molecular size. Thus, a solid solution can achieve dissolution rate faster, comparison to corresponding eutectic mixture. According to their miscibility, solid solutions can be classified into two types: (1) Continuous solid solutions- The two components are miscible in the solid state in all proportions and (2) discontinuous solid solutions - here each components solubility within the other component is limited.

Suspension and glass solutions

A glass suspension is a mixture in which within the glassy solvent precipitated particles are suspended whereas glass solution refers as homogeneous glassy system where a solute dissolves in it. Glasses do not have sharp melting points, instead, they soften progressively on heating. The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solutions.[10]

Amorphous solid solution

The solute molecules are dispersed molecularly within the amorphous solvent in an amorphous solid solution [Figure 2]. Chiou and Riegelman were the first to report the formation of an amorphous solid solution using griseofulvin in citric acid, to improve dissolution properties of drug. Other carriers those were used in early studies included urea and sugars such as sucrose, dextrose, and galactose. Recently, organic polymers such as polyvinyl pyrrolidone, polyethylene glycol and various cellulose derivatives have been utilized for this purpose [Table 1].

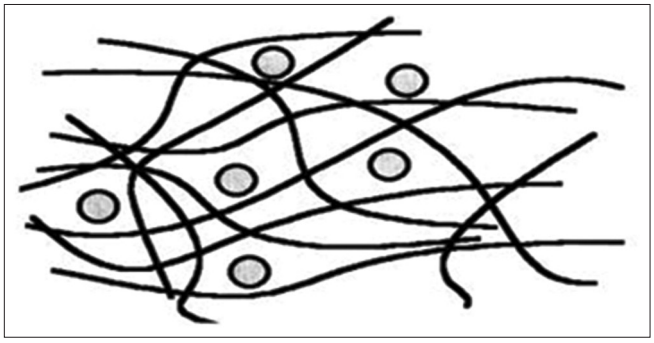

Figure 2: Amorphous solid solution

Selection of suitable carrier

A carrier should meet the following criteria:

1. It should be non-toxic
2. It should have intrinsic rapid dissolution property
3. It should be readily soluble in water
4. The carrier chosen for fusion processes should be chemically, physically, and thermally stable and should have low melting point
5. It should solidify rapidly into stable dispersion by rapid and complete crystallization. The carrier and drug should be miscible in liquid state
6. Drug and carrier must co-crystallize
7. The carrier has must to increase the aqueous solubility of the drug
8. Carrier should must be compatible chemically with the drug and in the solid state and should not form strongly bonded complex with high association constant.

Particles with Improved Wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions.[11] It was observed that even carriers without any surface activity, such as urea[12] improved drug wettability. On the contrary, carriers having good surface activity such as cholic acid and bile salts significantly increase the wettability of the drug. When used can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.[13,14]

Particles with Higher Porosity

Particles in solid dispersions have been found to have a higher degree of porosity.[15] The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate.[16] The increased porosity of solid dispersion particles also hastens the drug release profile.

Drugs in Amorphous State

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility.[17,18] The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process.[19] In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form.[20,21]

For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.[22] Increase in absorption rate and bioavailability.

Disadvantages of Solid Dispersion

1. Amorphous or molecularly dispersed drugs are often susceptible to changes during the storage
   - Hygroscopic drugs are also very moisture sensitive consequently high humidity have resulted in decreased dissolution
   - Other problems are tackiness and decomposition during preparation.[21]

Application of Solid Dispersions

The solid dispersion technique may possess various pharmaceutical applications.

1. To get distribution of a small amount of drug in solid state homogeneous.
2. Help in stabilizing unstable drug and decrease the pre-systemic inactivation of drugs.
3. To deliver liquid and gaseous matter in a solid dosage forms.
4. For formulation a fast release primary dose in a sustained released dosage form.
5. Sustained release regimen of soluble drugs can be formulate by poorly soluble or insoluble carriers.

Aim and Objective

Aim

The objectives are as follows:

1. To formulate and evaluate of solid dispersion of CLX.
2. To enhance the solubility of poorly water soluble drug (CLX) by solid dispersion method.
3. To enhance the solubility and dissolution rate of CLX to improve its overall oral bioavailability.

Objective

Thus, objective of present investigation is to enhance the solubility and dissolution rate of CLX to improve its overall oral bioavailability. The solid dispersions of CLX were formulated by solvent evaporation method using hydrophilic polymers. Attempts have also been made to characterize (evaluate) solid dispersion by Differential scanning calorimetric (DSC), FTIR, Powder X-ray Diffraction (PXRD), and *in vitro* drug release studies.

Materials and Methods

Materials

CLX and ingredients used in the studies were Polyethylene glycol 400, Polyethylene glycol 600, Potassium dihydrogen phosphate, and sodium hydroxide Polyvinyl pyrrolidone, Polyvinyl pyrrolidone K25, methanol and ethanol were provided by *Magnus Pharma Lab Pvt. Ltd. Birgunj, Nepal* as gift. Analytical grade ingredient was used in the studies.

Methods

Preformulation Studies

Physicochemical characterization of drug and polymers

The drug and carriers (PEG 4000, PEG 6000, PVP, and PVP K25) were characterized for the following parameters:

Physical Appearance

Drug powder was visually inspected to check color, appearance, and other physical characteristics.

Melting Point Determination

Melting point of pure drug (CLX) was determined using digital melting point apparatus (Labindia-MR-VIS, Mumbai, India) by capillary method. The sample was filled in the capillary tube closed at one end and placed into melting point apparatus. The temperature was increased slowly and the temperature at which drug sample turned into liquid state was recorded as the melting point of the drug under test.

Ultraviolet (UV) Absorption Maxima

The UV spectrum of CLX in phosphate buffer pH 7.2 was recorded using UV spectrophotometer (Hitachi, model AU 2701, Japan). The drug (10 mg) was accurately weighed and dissolved in 100 ml of phosphate buffer pH 7.2. An aliquot of 1 ml of solution was diluted to 5 ml with phosphate buffer pH 7.2 in a separate volumetric flask. This solution was taken in quartz cell and scanned at wavelength range of 400–200 nm using phosphate buffer pH 7.2 as blank, to get the wavelength of maximum absorption λ_{max}. The λ_{max} was found to be 252 nm.

Solvent Evaporation Method

Certain amounts of CLX and PVP-K25 were dissolved in the minimum amount of methanol to obtain clear viscous 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.

DSC Analysis

Thermal analysis was carried out with the help of DSC equipment (Perkin Elmer, model DSC7, USA). The samples were hermetically sealed in flat-bottomed aluminum pans and heated over a temperature range of 25–200°C at heating rate of 10 °C/min.

Preparation of Standard Curve of CLX in Phosphate Buffer pH 7.2

1. Preparation of 0.2 M potassium dihydrogen phosphate
   Potassium dihydrogen phosphate (27.218 gm) was dissolved in sufficient distilled water to make 1000 ml.
1. Preparation of 0.2 M sodium hydroxide
   Sodium hydroxide (8 gm) was dissolved in sufficient distilled water to make 1000 ml.

Preparation of Phosphate Buffer pH 7.2

Placed 250 ml of 0.2 M potassium dihydrogen phosphate and 173.5 ml of 0.2 M sodium hydroxide in a 1000 ml volumetric flask and sufficient distilled water was added to produce 1000 ml.

Preparation of standard curve

CLX (10 mg) was weighed accurately and dissolved in 10 ml of methanol. An aliquot of 1 ml was taken in 100 ml volumetric flask volume was made up to 100 ml with phosphate buffer pH 7.2 to obtain a stock solution of 10 μg/ml. From this stock solution, aliquots of 1 ml, 2 ml, 4 ml, 6 ml, 8 ml, and 10 ml were taken and transferred to 10 ml volumetric flask and volume was made up to 10 ml with phosphate buffer pH 7.2 to prepare the solution of conc. ranging from 1 μg/ml to 10 μg/ml, respectively. The absorbance of these solutions was measured at 252 nm against a blank phosphate buffer pH 7.2. Each experiment was repeated 3 times and average was calculated. Standard curve was then plotted between concentration (μg/ml) and absorbance. Data are shown in Table 2.

Equilibrium Solubility Determination of Pure drug and Polymer Selection

The ability of CLX and different polymers to form a molecular dispersion was determined by solubility studies.

The equilibrium solubility of CLX and the solubility of drug with different polymers (PEG 4000, PEG 6000, PVP, and PVP K25) in phosphate buffer pH 7.2 were determine. The studies were carried out by incorporating excess amount of pure drug (CLX) in 25 ml volumetric flasks containing 10 ml of phosphate buffer pH 7.2 without polymers or in 5% solution of each polymer in phosphate buffer pH 7.2 and placed in an water bath shaker (Scientech, India) maintained at 80 rpm speed and at 37 °C for 24 h. After 24 h, the suspensions were withdrawn from the volumetric flasks and filtered through Whatman filter paper no.42. The filtered solutions were suitably diluted with phosphate buffer pH 7.2 (wherever necessary) and assayed by UV Spectrophotometer (Hitachi, model AU 2701, Japan) at 252 nm. Each determination was repeated thrice and the mean was reported.

Results and Discussion

Preformulation Studies

Characterization of drug

Physical appearance

CLX was white crystalline powder.

Melting point

Melting point of CLX was determined by capillary method and results are given in Table 3.

Melting point of CLX was found to be 163-164 °C (reported melting point 160–164°C).

UV absorption maxima

The absorption maxima (λ_{max}) of CLX in phosphate buffer (pH 7.2) was found to be at 252 nm (reported λ_{max} = 254nm) [Figure 3].

Table 1: Standard curve of celecoxib in Phosphate Buffer pH 7.2

Serial number	*Concentration of celecoxib (μg/ml)*	*Absorbance*
1	1	0.077
2	2	0.1
3	4	0.259
4	6	0.448
5	8	0.653
6	10	0.816

DSC analysis

The DSC analysis was performed to confirm the melting points and purity of CLX and PVP K25. DSC thermograms of (a) CLX and (b) PVP K25 have been shown in Figure 4. The DSC trace recorded for CLX sample shows a sharp endothermic peak at about 163.56 °C corresponding to the melting of CLX. The thermogram of the PVP K25 showed broad endotherms due to melting around 77.52 °C. The melting points so obtained confirmed the purity of drug and excipients.

Preparation of Standard Curves

Standard curve of CLX in phosphate buffer (pH 7.2)

Standard curve of CLX in phosphate buffer (pH 7.2) was obtained by plotting different concentrations of the drug against absorbance. The absorption maxima (λ_{max}) of CLX in phosphate buffer (pH 7.2) were found to be at 252. The calibration curve is shown in Figure 5.

Equilibrium Solubility Determination and Polymer Selection

Solubility of CLX in the presence of polymers (PEG 4000, PEG 6000, PVP and PVP K25) is shown in Table 4. Solubility of CLX was 3.47 µg/ml in phosphate buffer pH 7.2, while the solubility of CLX in the presence of polymers (5% w/v) such as PEG 4000, PEG 6000, PVP and PVP K25 were 6.86, 8.82, 26.27 and 28.88 µg/ml respectively at the same pH. Thus, the solubility of CLX was increased almost 2 times, 2.5 times, 7.5 times and 8.3 times in the presence of PEG 4000, PEG 6000, PVP, and PVP K25, respectively. CLX had the highest solubility in polymer PVP K25, indicating excellent affinity between CLX and PVP K25 to form a molecular dispersion.

Table 2: Observation of melting point

Active ingredient	*Melting point (°C)*	
	Reported	*Observed*
Celecoxib	160–164	163–164

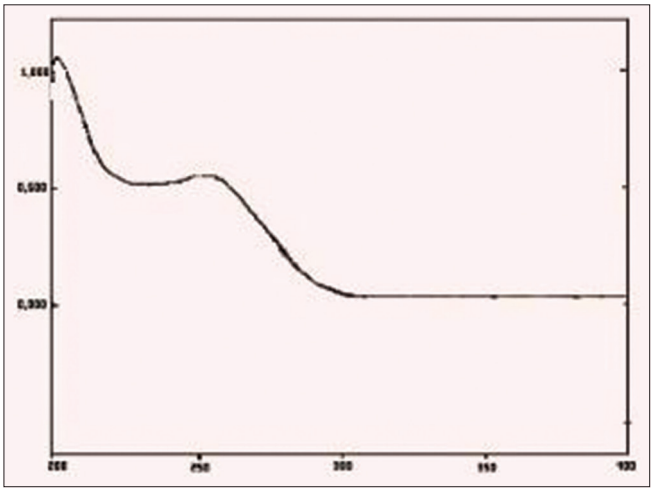

Figure 3: UV scan of CLX in phosphate buffer (pH 7.2)

Drug Polymer Interaction Studies

DSC analysis

The DSC analysis of CLX and physical mixture (1:1) was performed to confirm the absence of drug and carrier interactions. The DSC thermograms of the pure drug CLX (a), physical mixture of CLX and PVP K25 in the ratio of 1:1 (b) has been shown in Figure 6. The DSC thermograms of drug and physical mixture show decrease in the melting point of drug. The melting point of drug was observed at 160.14°C. This decrease in melting point might be due to dilution effect of polymer [Figure 7].

Preparation of CLX Solid Dispersions

Based on the solubility studies with different polymers (5% w/v), solid dispersions of CLX with PVP K25 were prepared in different ratios [Table 5].

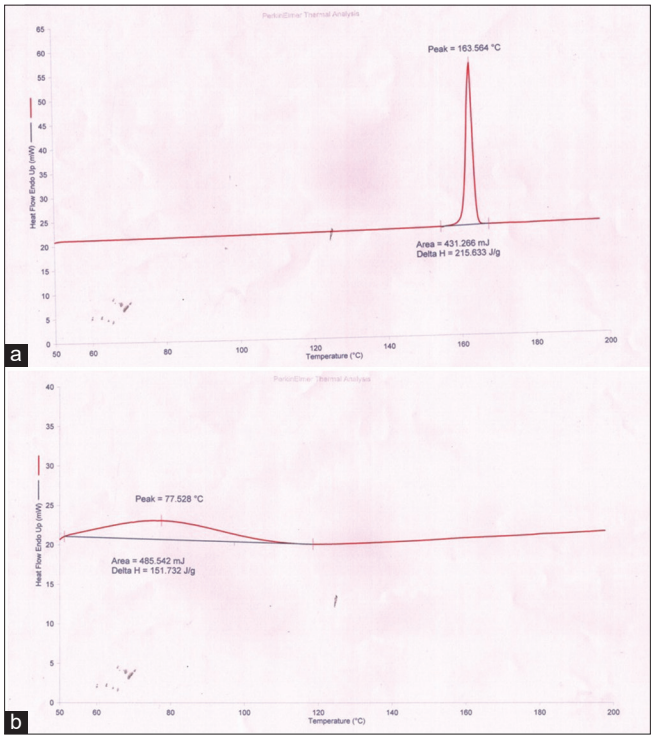

Figure 4: DSC thermograms of (a) CLX and (b) PVP K25

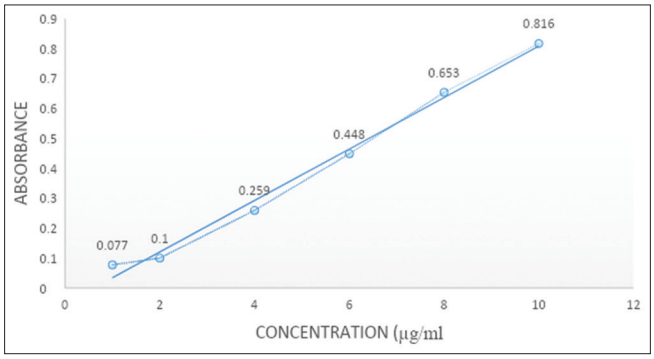

Figure 5: Standard curve of CLX in phosphate buffer (pH 7.2)

Characterization of CLX Solid Dispersion

Equilibrium solubility determination of solid dispersion

Solubility of CLX in solid dispersions with PVP K25 in different ratios is shown in Table 6. Solubility of CLX was 3.47 µg/ml in phosphate buffer pH 7.2, while the solubility of solid dispersions PM, S1, S2, S3, S4, and S5 was found to be 5.46, 17.55, 26.37, 33.93, 39.09, and 44.23 µg/ml, respectively, at the same pH. Thus the maximum solubility of CLX was increased up to 12.7 times in S5 preparation [Figure 8].

Drug content

Drug content of the various formulations is given in Table 7. The drug content of the prepared solid dispersion was found to be in the range of 16.06-49.48% w/w.

DSC study

DSC thermograms of CLX and solid dispersion S5 (1:5) are shown in Figure 9. CLX showed a melting endotherm at temperature at 163 °C. In case of PVP K25 solid dispersion, the DSC thermogram of CLX solid dispersion S5 at 1:5 ratio revealed the disappearance of the characteristic peak of the drug. This could be attributed to dilution effect of PVP K25.

Table 3: Solubility study of CLX with or without different polymers (5% w/v) in phosphate buffer pH 7.2

Serial number	*Polymer (5% w/v)*	*Eq. sat. solubility (µg/ml)*
1	Pure drug (celecoxib)	3.47±0.48
2	PEG 4000	6.86±0.67
3	PEG 6000	8.82±0.56
4	PVP	26.27±1.07
5	PVP K25	28.88±0.89

PVP: Polyvinylpyrrolidone

Table 4: Preparation of celecoxib solid dispersions

Assigned code	*Solid dispersion*	*Drug: Polymer ratio*	*Method employed*
PM	Celecoxib: PVP K25	1:1	Physical mixture
S1	Celecoxib: PVP K25	1:1	Solvent evaporation
S2	Celecoxib: PVP K25	1:2	Solvent evaporation
S3	Celecoxib: PVP K25	1:3	Solvent evaporation
S4	Celecoxib: PVP K25	1:4	Solvent evaporation
S5	Celecoxib: PVP K25	1:5	Solvent evaporation

Table 5: Equilibrium solubility of pure drug and solid dispersions

Solid dispersion	*Equilibrium solubility (µg/ml)*
Pure drug	3.47±0.48
PM	5.46±0.46
S1	17.55±1.05
S2	26.37±1.34
S3	33.93±0.95
S4	39.09±1.56
S5	44.23±1.03

Table 6: Percentage drug content

Formulation	*Percentage drug content (w/w)*
PM (1:1)	49.48±0.23
S1 (1:1)	49.37±0.45
S2 (1:2)	33.01±0.35
S3 (1:3)	24.73±0.78
S4 (1:4)	19.21±1.09
S5 (1.5)	16.06±1.30

PXRD

Powder X-ray diffraction studies were done to investigate the crystalline status of the sample. The peak position (angle of diffraction) is an indication of crystal structure and peak heights are the measures of samples crystallinity in a diffractogram.

Figure 10 shows the PXRD diffractograms of plain CLX, PVP K25 and solid dispersion (S5). The diffractogram of pure CLX exhibited a series of intense peaks at 2θ, 0–50° the most indicative are 10.83, 12.98, 14.81, 16.07, 17.91, 19.62, 21.43, 22.25, 23.40, 25.34, and 29.41°. The respective signal heights were in the order of 150, 144, 197, 166, 202, 248, 238, 250, 236, 126, and 190 cts, respectively, which were indicative of the high crystallinity. Similarly, solid

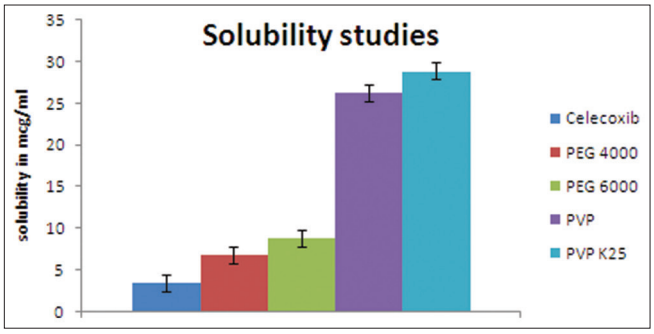

Figure 6: Solubility of CLX alone and in the presence of different polymers (5% w/v) in phosphate buffer pH 7.2

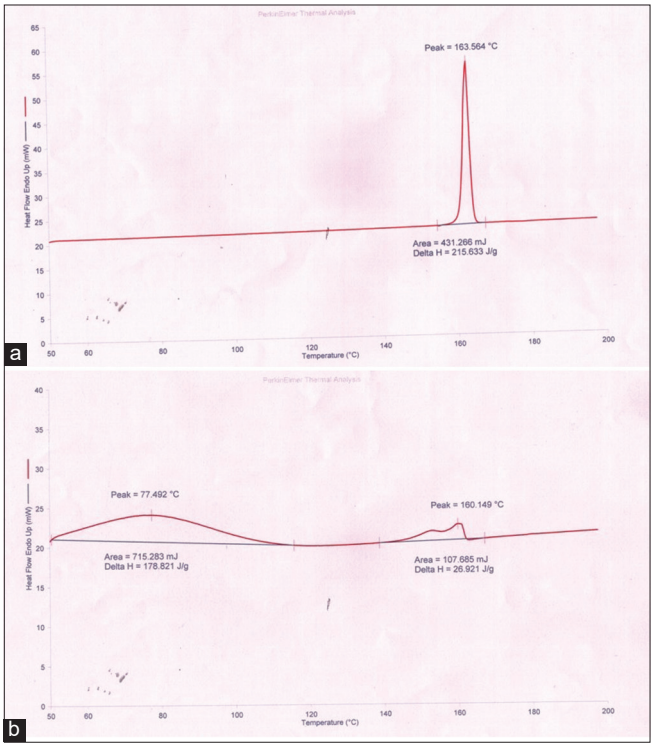

Figure 7: DSC thermograms of (a) CLX and (b) physical mixture (1:1)

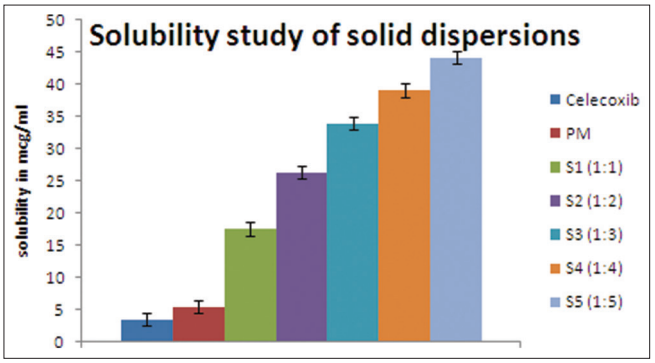

Figure 8: Solubility of CLX alone and solid dispersions in phosphate buffer pH 7.2

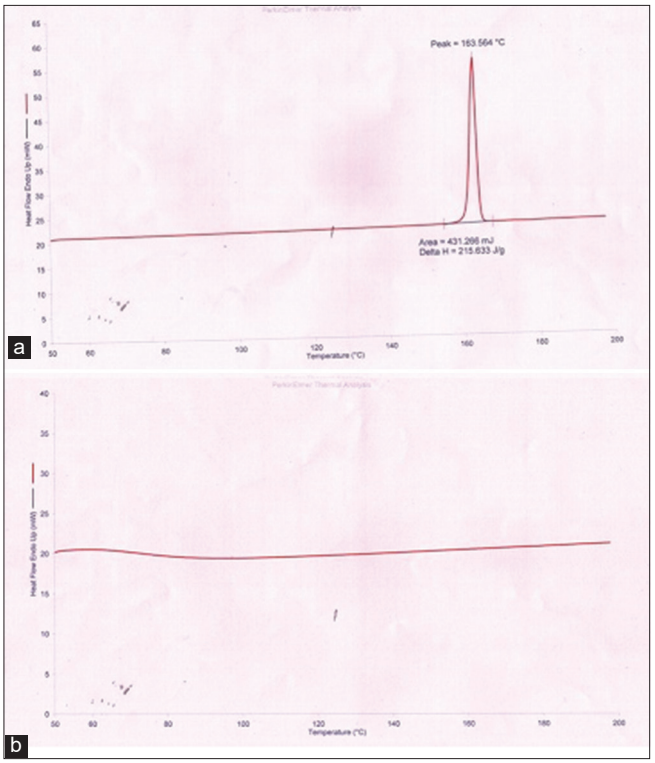

Figure 9: DSC thermograms of (a) CLX and (b) Solid dispersion S5 (1:5)

dispersion S5 showed very weak signals at scattering angles of 10.79 and 20.97 with their respective intensities of 169 and 201 cts, indicating significant loss of crystallinity and conversion into amorphous state of the drug in solid dispersion [Table 8].

In vitro Dissolution Studies

The dissolution rate of pure CLX was extremely low: only about 12.6% of drug was dissolved after 120 min. This might be attributed to the poor wettability and the hydrophobic nature of pure CLX, which exhibited tendency to form large aggregates upon dissolution study that caused the powder to float on the surface of the dissolution medium. The aggregation caused reduction in effective surface area of drug particles available for dissolution. Figure 11 shows the dissolution profile of CLX from solid dispersions prepared with different drug: carrier ratio. The dissolution rate of

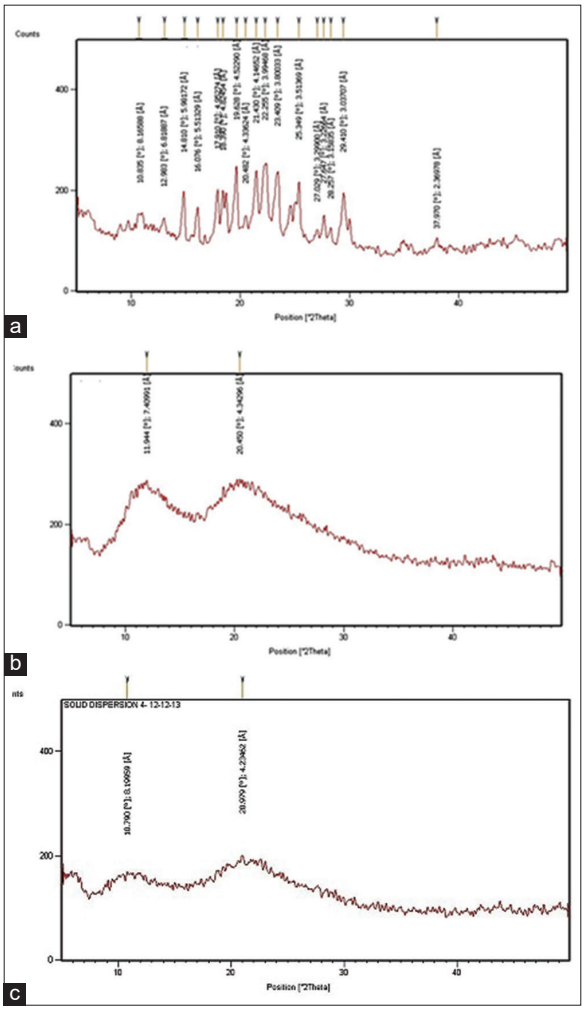

Figure 10: PXRD pattern of (a) celecoxib (b) PVP K25 (c) solid dispersion S5 (1:5).

Table 7 : Powder X-ray diffractometry pattern analysis of celecoxib, polyvinylpyrrolidone K25 and solid Dispersion S5 (1:5)

Peak number	*Celecoxib*			*PVP K25*			*Solid dispersion S5*		
1	2θ	D	I	2θ	D	I	2θ	D	I
2	10.83	8.16	150	11.9	7.40	286	10.79	8.19	169
3	12.98	6.81	144	20.4	4.34	285	20.97	4.23	201
4	14.81	5.98	197						
5	16.07	5.51	166						
6	17.91	4.95	202						
7	18.39	4.82	199						
8	19.62	4.52	248						
8	20.48	4.33	149						
9	21.43	4.14	238						
10	22.25	3.99	250						
11	23.40	3.80	236						
12	24.14	4.51	165						
13	25.34	3.51	217						
14	27.02	3.29	122						
15	27.64	3.22	150						
16	28.25	3.15	126						
17	29.41	3.03	190						

PVP: Polyvinylpyrrolidone

CLX from all prepared solid dispersions significantly increased when compared to the plain drug. The increased dissolution rate

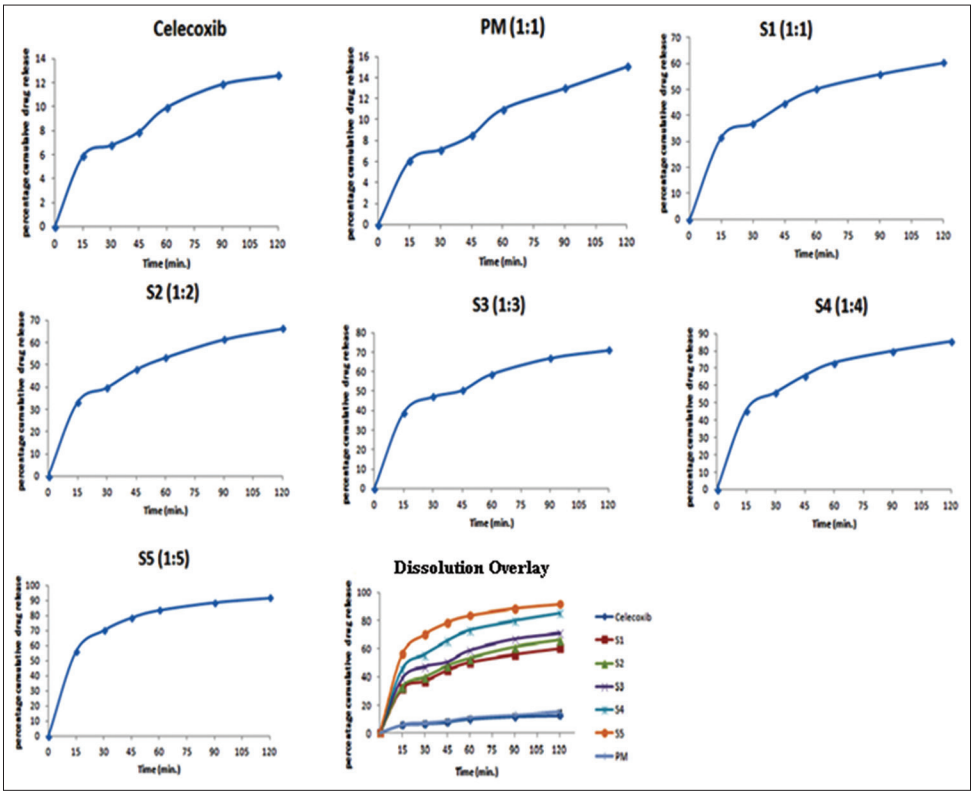

Figure 11: *In vitro* release profile of CLX, PM, and solid dispersions S1, S2, S3, S4, and S5

Table 8: *In vitro* cumulative % drug release from solid dispersions

Time (min)	*Percentage cumulative drug release (±SD, n=3)*						
	Pure drug	*PM*	*S1*	*S2*	*S3*	*S4*	*S5*
0	0	0	0	0	0	0	0
15	5.87±0.19	6.06±0.17	31.73±0.32	33.16±0.25	38.91±0.31	45.74±0.35	56.31±0.2
30	6.78±0.35	7.16±0.07	37.07±0.66	39.76±0.26	47.15±0.12	55.97±0.15	70.26±0.24
45	7.9±0.26	8.51±0.07	44.82±0.32	47.86±0.29	50.49±0.26	65.78±0.17	78.68±0.2
60	9.94±0.26	11.01±0.09	50.35±0.25	53.25±0.45	58.74±0.43	73.18±0.27	83.62±0.45
90	11.89±0.39	13±0.11	56±0.62	61.4±0.84	66.99±0.29	79.93±0.29	88.74±0.15
120	12.6±0.17	15.06±0.08	60.37±0.28	66.26±0.45	71.03±0.16	85.43±0.2	91.73±0.32

SD: Standard deviation

of CLX from solid dispersions can be attributed to several factors such as solubilization effect of the carrier, conversion to amorphous state, improved wettability of CLX, increased surface area due to decreased particle size and inhibition of particle aggregation. It was also noticed that increase in the drug: carrier ratios led to increase in the average percent of CLX dissolved.

Solid dispersion S5 (1:5 ratio) yielded maximum enhancement in dissolution of CLX when compared to other ratios. The dissolution of CLX from solid dispersion prepared using PVP K25 at a ratio of 1:5 was 7.3 fold higher than that of plain drug. This might be due to each single crystallite of the drug being encircled by the soluble carrier (PVP K25) which could readily dissolve and cause water to wet the drug particle.

Conclusion

It can be concluded from DSC and PXRD studies that CLX exists mainly in amorphous form in prepared solid dispersion with PVP K25. The solid dispersion (S5) has shown highest saturation solubility (44 µg/ml) and dissolution rate (92%). Inferences drawn from *in vitro* studies suggest improved dissolution performance of CLX solid dispersions. There was 12-13 fold increase in solubility and 7 fold increase in dissolution rate when compared with pure CLX. Therefore, solid dispersion may be an alternative approach to address poor bioavailability of the CLX. However, further studies are needed to comment more in this respect.

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