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COMPARATIVE EVALUATION OF DIFFERENT CARRIERS TO ENHANCE SOLUBILITY AND DISSOLUTION OF POOR WATER SOLUBLE DRUG

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ABSTRACT

The aim of this study was to investigate the effect of different carriers on solubility and in vitro dissolution of poorly water soluble drug meloxicam (MLX). Solid dispersions with Polyethylene glycol-6000 (PEG6000), Poloxamer 188 (Plx188), Poloxamer 407 (Plx407) and inclusion complexes (ICs) with β cyclodextrin (β-CD) were prepared by different methods in three different weight ratios. All SDs and ICs were evaluated for percentage practical yield, drug content, solubility and dissolution studies and characterized by FTIR and powder X-ray diffraction studies. The improvement of solubility using polymers was in the following order: Plx188 > Plx407 > PEG6000 > β-CD. In Dissolution studies, maximum drug release (99.46% at 90 min) were obtained in 1:3 ratios of MLX to Plx188. Solid dispersion of MLX with Plx188 by fusion method in 1:3 ratios can be used to formulate fast dissolving solid dosage form to enhance drug dissolution.

KEYWORDS: **Meloxicam • Solid dispersion • Poloxamer • β –cyclodextrin • Dissolution study**

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INTRODUCTION

Meloxicam is a nonsteroidal anti inflammatory and anti-pyretic agent. It is generally used in the treatment of rheumatoid arthritis, osteoarthritis and other joint pains [1,2]. Meloxicam is BCS class II drug and practically insoluble in water (8µg/ml) that delays its absorption from the gastrointestinal tract which directly influences the Cmax, Tmax, as well as the bioavailability of the drug [3].Various techniques have been used to improve the solubility/dissolution rate of poorly water-soluble drugs. Among them, the solid dispersion technique [4-7] and complexation with cyclodextrins [7-9] are used most frequently. The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix in solid state, prepared by melting (fusion), solvent evaporation or melting solvent method. Solid dispersion is a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly in amorphous particles (clusters) or in crystalline particles [10]. Solid dispersions offer many advantages, improved wettability of the powder, greater reduction in the particle size compared to conventional mechanical milling, generation of particles with higher porosity, and presence of powder in the amorphous state, all of which may contribute to enhance dissolution rate and solubility of the poorly soluble compound [11]. In solid dispersions, hydrophilic polymers have commonly been used as carriers. The most popular polymeric carriers used for solid dispersion formulation are polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) due to their water solubility and ability to form solid solution [12]. Recently Poloxamers have also shown promise to be excellent carriers for the preparation of solid dispersions because Poloxamers have the capability to alter physical properties such as hydrophobicity, surface charge, flocculation/dispersion, floatation and wetting properties [13-16]. Cyclodextrins and their derivatives play an important role in improving the therapeutic efficacy of drugs with poor solubility and/or stability problems. They are capable of alleviating the undesirable properties of drug molecules through the formation of inclusion complexes [9,17]. The aim of the present work was to compare the efficiency of different types of carriers (PEG 6000, Plx188, Plx407 and β-CD) and several methods of preparation of SDs and ICs on solubility and in vitro dissolution of MLX.

MATERIALS AND METHODS

Meloxicam was obtained from Siemen Laboratories, Haryana, India. β-cyclodextrin was purchased from Fine chemicals, Hyderabad. PEG-6000 was purchased from Loba Chemie Pvt. Ltd., Mumbai, India. Plx-407 and Plx-188 were purchased from Sigma-Aldrich. All other reagents and chemicals were of analytical grade.

Preparation of Inclusion complexes with β-cyclodextrine

Co-grinding method

Calculated amount of MLX and β-CD were weighed, mixed together and blended thoroughly by triturating in mortar pastel for 30 min then passed through 40 # sieve.

Kneading method

Add required amount of β-CD into solvent [water-DMF (1:1)] and made paste. Drug is then added to paste and kneaded for one hour. Dried it in the oven at 50°C then passed through it through 40 # sieve.

Table 1
Compositions and batch codes of inclusion complexes and solid dispersions

Composition	Method	Drug: Carrier ratio	Batch code
MLX: β-CD	Co-grinding	1:2	F1
		1:3	F2
		1:4	F3
	Kneading	1:2	F4
		1:3	F5
		1:4	F6
MLX: PEG 6000	Co-grinding	1:2	F7
		1:3	F8
		1:4	F9
	Fusion	1:2	F10
		1:3	F11
		1:4	F12
MLX: Plx 188	Co-grinding	1:2	F13
		1:3	F14
		1:4	F15
	Fusion	1:2	F16
		1:3	F17
		1:4	F18
MLX: Plx 407	Co-grinding	1:2	F19
		1:3	F20
		1:4	F21
	Fusion	1:2	F22
		1:3	F23
		1:4	F24

Preparation of solid dispersions
Solid dispersions of MLX with PEG 6000, Plx 188 and Plx 407 were prepared by co-grinding method and fusion method.

Co-grinding method
Calculated amount of MLX and carrier were weighed, mixed together and blended thoroughly by triturating in mortar pastel for 30 minutes. The resultant mixtures were passed through 40 # sieve.

Fusion method
The required amount of carrier melted in porceline dish on water bath at 52-55°C. MLX was added to the melted carrier and stirred for 1-2 min and allow it for cooling and passed it through 30, 40 then 60 # sieves.

Evaluation of solid dispersions
Percent practical yield (PY)
Percentage practical yield were calculated to know about percent yield or efficiency of any method thus it helps in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation. PY (%) = [Practical Mass (Solid dispersion) / Theoretical Mass (Drug + Carrier)] × 100 The result was shown in Table 2.

Drug content
Drug content was determined by dissolving solid dispersion (equivalent to 7.5 mg of MLX) in small volume of methanol and further diluted with freshly prepared phosphate buffer (pH 7.4) in a 100 ml volumetric flask. The content of MLX was determined spectrophotometrically at 362nm using Shimadzu 1800 UV-visible spectrophotometer. The results were shown in Table 2.

FTIR studies
Spectra for MLX and solid dispersions and inclusion complexes were recorded in a FT-IR (BRUKER) spectrophotometer in order to study any kind of interaction between drug and carrier. The results were shown in figure 1.

Solubility study
MLX and solid dispersions equivalent to 7.5 mg of MLX were added to 10 ml distilled water in screw-capped test tubes, vortexed for 3 min, and shaken at room temperature for 24 hrs. Undissolved solid dispersions suspended in the distilled water were centrifuged at 8,000 rpm for 10 min and the clear supernatants obtained were filtered through 0.22 µm membrane filter then diluted with distilled water, and analyzed spectroscopically at 362 nm. The results were shown in Table 2.

In vitro drug release studies

The *in vitro* dissolution characteristics of SDs and ICs with highest solubility for each carrier (F4, F12, F17 and F23) were compared with the pure drug. *In vitro* dissolution studies of colorless hard gelatin capsules containing pure MLX and four optimized batches (F4, F12, F17 and F23) were performed using the US Pharmacopoeia model digital tablet dissolution test apparatus-2 (Lab India, DISSO 2000) at the paddle rotation speed of 75 rpm in 900 ml of phosphate buffer (pH 7.4). The dissolution rate was studied by placing MLX (7.5 mg) and solid dispersions (equivalent to 7.5 mg of drug) in dissolution medium. A 5 ml aliquot was withdrawn at different time intervals, filtered (through 0.45µm membrane) and replaced with 5 ml of fresh dissolution medium. The samples were estimated for dissolved MLX by measuring absorbance at 362 nm.

Angle of Repose

The flowability properties of the optimized solid dispersions were determined by measuring angle of repose in triplicate. The angle of repose was measured by passing solid dispersions through a sintered glass funnel of internal diameter 27 mm on the horizontal surface. The radius (r) of the cone base was determined and height (h) of the heap formed was measured with a cathetometer. The angle of repose (Φ) was calculated from the following equation.

$\Phi = \tan^{-1}(h/r)$.

Contact Angle

Wettability of pure drug and optimized SD were determined by measuring contact angles. Pure drug powder or optimized SD (250 mg) was compressed into a pellet by a hydraulic press at 5,000 kg/cm2 pressure (1 min). Deionized Water (10-20 µl) was placed from a microsyringe on the horizontal particle surface (pellet) then drop was photographed after 3 s for the determination of contact angle [18].

XRD Studies

The powder XRD pure MLX and solid dispersions (MLX with poloxamer-188) was recorded using an X-ray Diffractometer (Diffractometer system, XPERT-PRO) using Cu radiation generated at 40 Kv and 30 mA and scanning rate was 2°/min over a 2θ range of 10-80 [19].

RESULTS AND DISCUSSION

Percent practical yield (PY)

The percentage practical yield for all the formulations of solid dispersions was found to be between the range of 93.34± 1.18 to 98.85 ± 0.41 (n = 3). There is minimum loss of formulation occurred in preparation of solid dispersions by co-grinding method than kneading and fusion method. The results are shown in Table 2.

Drug content

The percentage drug content for all the formulations of solid dispersions was found to be between the range of 97.23 ± 1.16 % to 100.14 ± 0.26 % (n = 3). The fusion method for SDs preparation and kneading method for ICs with β-CD preparation results more uniform dispersion with high content uniformity than formed by co-grinding method. So it shown higher % drug content. The results are shown in Table 2.

Solubility study

With increase in the drug to polymer ratio increase in MLX solubility was found in SDs with PEG 6000 while vice-versa results were found in β-CD ICs. Solubility studies showed that highest solubility has been obtained in SDs by fusion method with poloxamers than β-CD ICs and PEG 6000 SDs. With Plx188 and Plx407 drug solubility was found to be increased up to the ratio 1:3 further increase in the polymer concentration there is no effect on solubility of drug was found. Mechanism involve an increase in solubility of drug with poloxamers is micellar solubilization. The improvement of solubility using polymers was in the following order: Plx188 > Plx407 > PEG 6000 > β-CD.]

Table 2
Evaluation of physical parameters of inclusion complexes and solid dispersions.

Batch	% Practical Yield ± SD (n=3)	Drug content (%)±SD (n=3)	Solubility (mg/ml) ± SD (n=3)
F1	98.85 ± 0.41	99.12 ± 0.35	0.974± 0.012
F2	97.41± 0.75	98.67 ± 1.06	0.946± 0.015
F3	97.44± 0.45	98.26 ± 0.51	0.885± 0.022
F4	96.13± 1.14	99.69 ± 0.86	1.178± 0.011
F5	95.27± 1.65	99.01 ± 1.04	1.108± 0.012
F6	93.34± 1.18	98.27 ± 0.84	0.984± 0.018
F7	98.12± 0.35	99.52 ± 0.46	0.893± 0.010
F8	97.84± 1.15	98.74 ± 1.12	1.038± 0.012
F9	97.11± 1.04	99.24 ± 1.08	1.121± 0.015
F10	95.26± 1.25	97.23 ± 1.16	1.016± 0.010
F11	95.43± 1.14	98.02 ± 0.89	1.152± 0.017
F12	93.16± 1.42	97.54 ± 1.32	1.203± 0.010
F13	98.04± 0.45	99.02 ± 1.40	0.917± 0.012
F14	98.13± 0.36	99.18 ± 0.16	1.285± 0.014
F15	98.01± 0.65	99.02 ± 0.20	1.108± 0.018
F16	96.84± 0.55	98.06 ± 1.21	1.289± 0.012
F17	96.88± 0.34	100.04 ± 0.45	1.489± 0.011
F18	95.31± 1.25	98.56 ± 1.40	1.385± 0.015
F19	98.09± 0.63	100.14 ± 0.26	0.928± 0.012
F20	98.53± 0.45	99.38 ± 1.06	1.219± 0.012
F21	98.06± 1.05	100.02 ± 0.55	1.047± 0.012
F22	95.34± 1.02	98.78 ± 1.06	1.301± 0.012
F23	96.14± 0.51	99.18 ± 1.05	1.426± 0.012
F24	95.48± 0.86	98.56 ± 1.14	1.216± 0.012

FTIR Study

Figure 1 shows the spectrum of MLX and optimized formula of SDs and IC. The spectrum of MLX shows characteristic peaks at 3,285.68 cm−1 (N-H stretching vibrations), 1,611.29 cm−1 (C = N stretching vibrations), and 1,168.49 cm−1 (S = O stretching vibrations), respectively. The spectrum of solid dispersion exhibited significant decrease in intensity of characteristic peaks of MLX which may be due to intermolecular hydrogen bonding. The spectra peaks of drug are almost unchanged in the optimized formula of SDs and IC which indicates that the overall symmetry of molecule is not significantly affected.

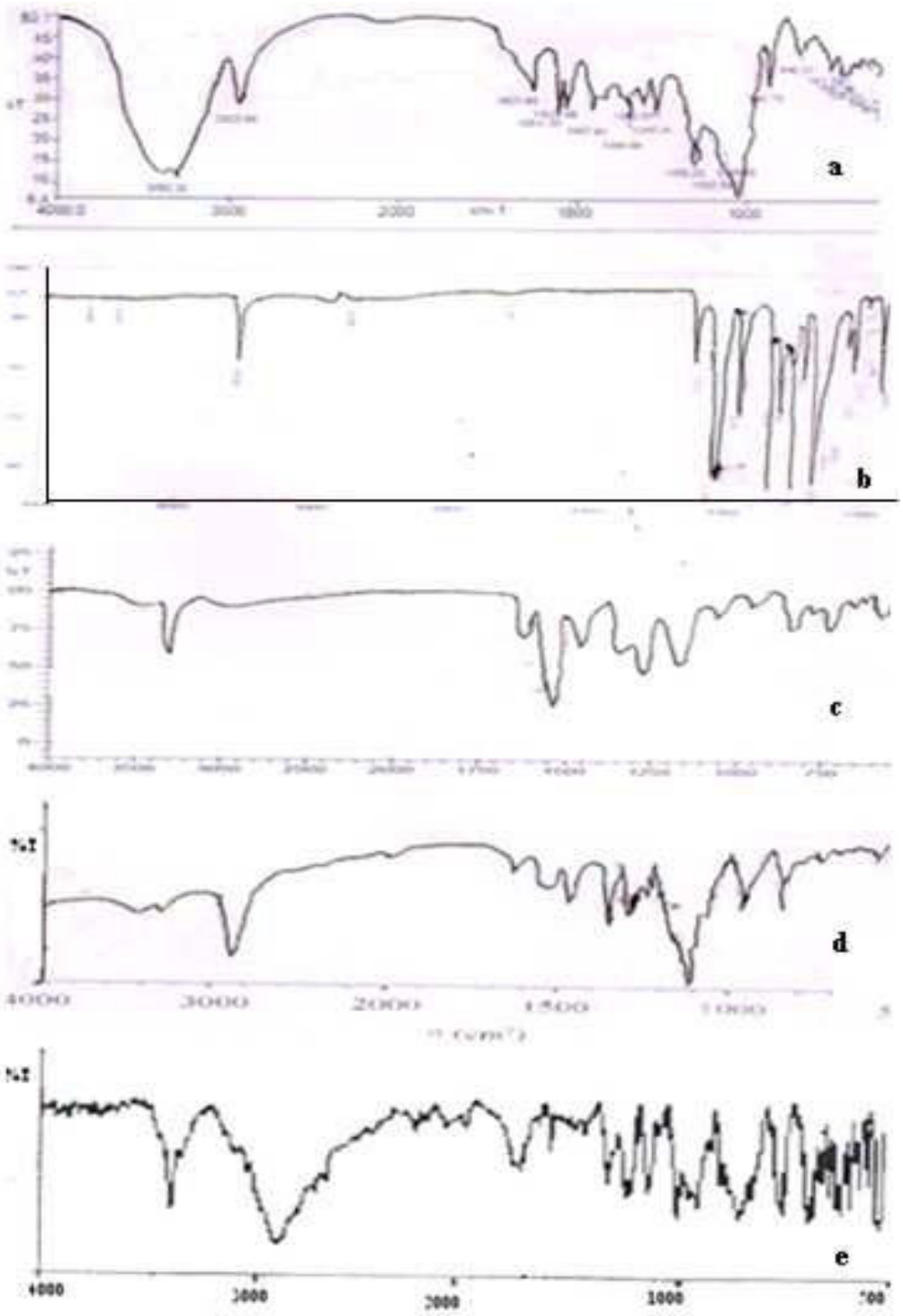

Figure 1
FTIR Spectra of (a) MLX (b) MLX & β-CD (c) MLX & Plx188 (d) MLX & Plx407 (e) MLX & PEG 6000

In vitro dissolution

All SDs and ICs of MLX showed improved dissolution when compared with pure drug. Dissolution profiles of pure drug and different SD batches F4, F12, F17 and F23 are shown in figure 2. The highest drug release was obtained for SD batch F17 than F4, F12 and F23. The drug release from F17 SD was slower at 5 and 10 minutes but became faster at 30, 60 and 90 minutes than other three batches. The percentage drug release at 90 minutes from bathes F4, F12, F17 and F23 were 78.45 ± 1.18%, 84.65 ± 1.48%, 99.46 ± 0.32% and 93.92 ± 1.02% respectively. In vitro dissolution studies reveal that solid dispersion of MLX with Plx188 with 1:3 ratios shows maximum cumulative drug release due to wettability and hydrophilic nature of carrier.

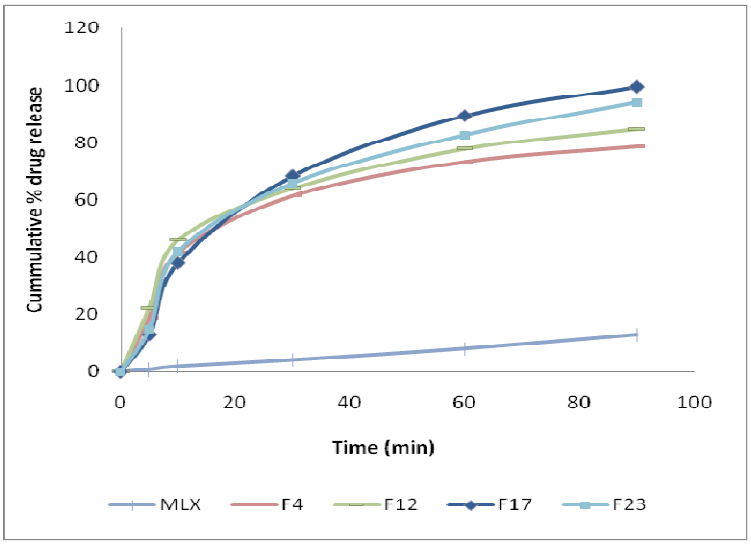

Figure 2
Dissolution profiles of MLX, F4, F12, F17 and F23 solid dispersions.

Angle of Repose

The angle of repose of optimized SD (F17) was found to be 29.68.4 ± 0.31 which indicates good free flowability.

Contact Angle

Measured contact angle of optimized SD (F17) was 36°. Wettability of optimized SD was significantly improved compared with MLX pure drug (78°).

Powder X-ray Diffraction Analysis (XRD)

XRD patterns of MLX, Plx 188 and optimized SD (F17) are shown in figure 3. In the x-ray diffractograms of MLX, sharp peaks at a diffraction angle (2θ) of 13°, 15°, 18.5°, and 26° indicate the presence of crystalline drug, while solid dispersion shows sharp peaks at 19° and 23.5°. These data reveal that the typical drug crystalline peaks were still detectable (with reduced intensity and less number) in the SD. This results confirms the presence of little amount of crystalline drug in the SD. The XRD of solid dispersion exhibits peaks less than the sum of the number of peaks of MLX and PXM in their pure forms. This suggests that crystallinity of both MLX and Plx188 is reduced in the SD (F17) which may contribute to enhancement of dissolution of the MLX [19].

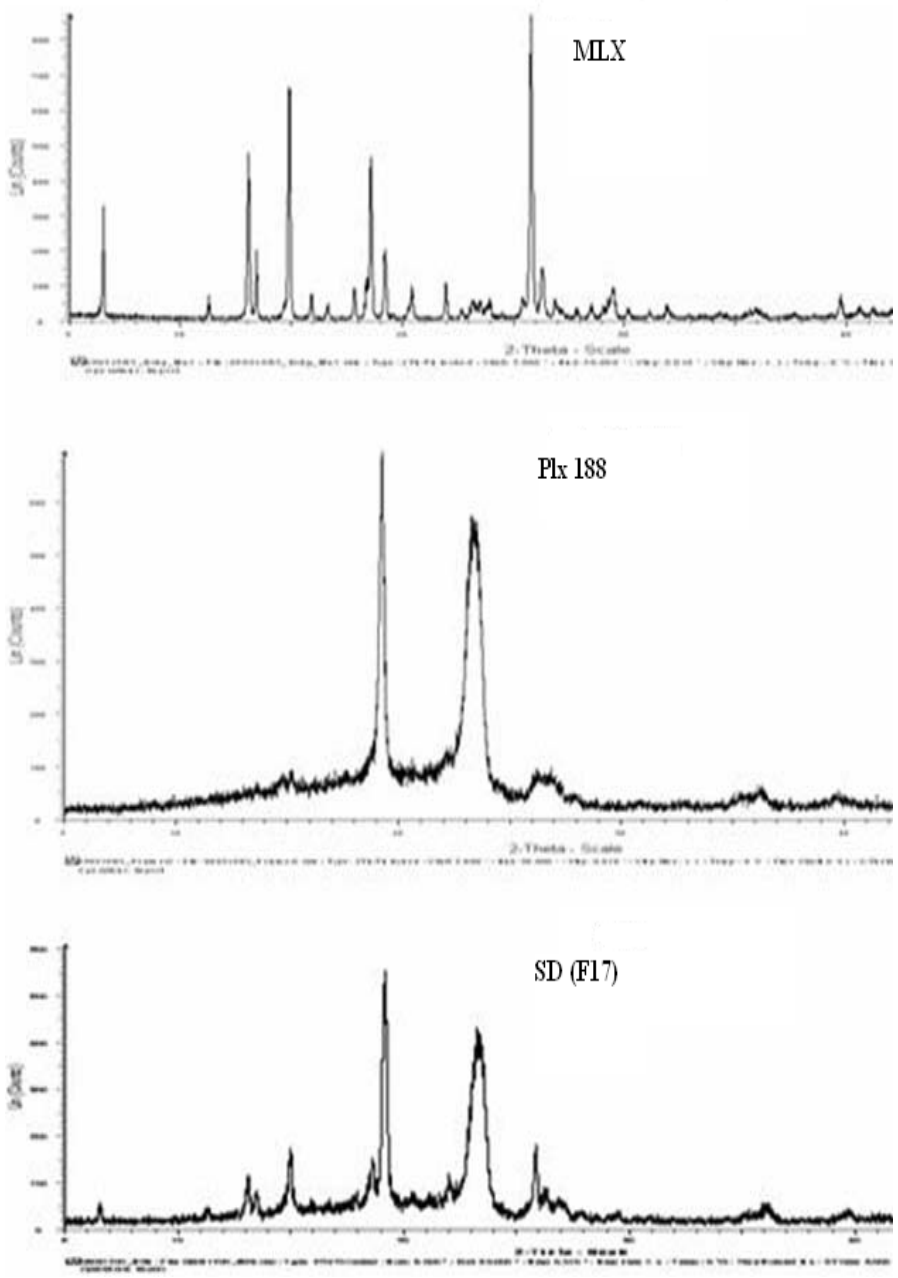

Figure 3
Powder x-ray diffraction spectra of MLX, Plx188, and Optimized formula of solid dispersion of MLX and Plx188 (F17).

CONCLUSION

The results of presented study confirm that the solubility and dissolution of MLX are improved by SDs with PEG 6000, Plx-188, Plx-407 and ICs with β-CD. Solid dispersion of MLX with Plx188 (1:3 ratio) prepared by fusion method shows maximum solubility and cumulative percent drug release than others. In vitro dissolution studies and characterization studies reveal that solid dispersion of MLX with Plx188 shows enhancement of MLX dissolution due to wettability and hydrophilic nature of carrier and the conversion of MLX into a less crystalline and/or amorphous form. So it may be concluded that SD of MLX with plx188 can be used in manufacturing of fast dissolving solid dosage forms to enhance MLX solubility and dissolution.

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