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Preparation, Characterization and *In vitro* Dissolution Studies of Solid Dispersion of Meloxicam with PEG 6000[1]

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The poor solubility and wettability of meloxicam leads to poor dissolution and hence showing variations in bioavailability. The present study is aimed to increase solubility and dissolution of the drug using solid dispersion techniques. The solid binary systems were prepared at various drug concentrations (5—40%) with polyethylene glycol 6000 by different techniques (physical mixing, solvent evaporation). The formulations were characterized by solubility studies, differential scanning calorimetry, fourier transform infrared spectroscopy and *in vitro* dissolution rate studies. The solubility of drug increased linearly with increase in polymer concentration showing A_L type solubility diagrams. Infrared spectroscopy studies indicated the possibility of hydrogen bonding with polymer. The differential scanning calorimetry and powder X ray diffraction demonstrated the presence of polymer as eutectica or monotectica in solid dispersion along with the physical characteristics of the drug (crystalline, amorphous or a mixture of both). The solid dispersions of the drug demonstrated higher drug dissolution rates than physical mixtures and pure meloxicam, as a result of increased wettability and dispersibility of drug in a solid dispersion system.

Key words——solid dispersion; meloxicam; solubility; dissolution enhancement

INTRODUCTION

Meloxicam (MLX), (4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2H-1, 2-benzothiazine-3-carboxamide-1, 1-dioxide), a non-steroidal anti-inflammatory drug (NSAID) and a selective cyclooxygenase-2 (COX-2) inhibitor, is used in the treatment of rheumatoid arthritis, osteoarthritis and other joint diseases. It has comparable efficiency and greater gastric tolerability in comparison to conventional NSAIDs.[2] Like many NSAIDs, MLX is practically insoluble in water (12 μg/ml). The poor solubility and wettability of MLX leads to poor dissolution and hence, variations in bioavailability. Thus, increasing the aqueous solubility and dissolution of MLX is of therapeutic importance.

A variety of devices have been developed over the years to enhance the drug release and the dissolution of the drugs. The solid dispersion method is one of the effective approaches to achieve this ideal therapy particularly for drugs with poor aqueous solubility by incorporating them into a water-soluble polymer matrix.[3—6] Polyethylene glycol (PEG) is one of the most widely used carriers to prepare solid dispersions.[7—9] (Structure of MLX and PEG 6000 is shown in Fig. 1).

Several attempts have been made to increase the solubility of MLX via rapidly disintegrating tablets,[10,11] cyclodextrins,[12—15] solid dispersions[15,16] and cosolvent systems.[17,18] However, the present study is aimed to formulate the solid dispersion of MLX with PEG 6000 using different drug concentrations in order to improve its aqueous solubility, wettability, *in vitro* dissolution and hence bioavailability of the drug. The solid binary systems were prepared taking different drug/polymer ratios (5—40%) using
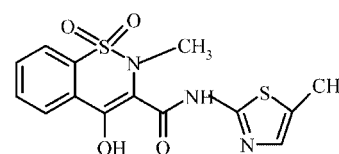
Meloxicam

PEG 6000
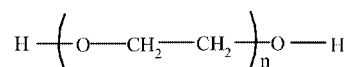
Fig. 1. Molecular Structure of Meloxicam and PEG 6000

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different techniques (physical mixing, solvent evaporation). After assessing the drug content in the solid dispersions, the products were characterized by differential scanning calorimetry, fourier transform infrared spectroscopy, powder X ray diffraction, scanning electron microscopy and *in vitro* dissolution rate studies. The drug polymer interactions in aqueous solutions were investigated by phase solubility analysis.

EXPERIMENTAL

Materials　　The Meloxicam B.P. was obtained as gift sample from Sun Pharmaceuticals Ltd., (Mumbai, India). Polyethylene glycol 6000 was purchased from S.D. Fine Chemicals (Mumbai, India) and all other chemicals/solvents used were of analytical grade.

Preparation of Binary Systems　　Solid dispersions (SD) of different drug content (5—40%) with PEG 6000 were prepared by solvent evaporation method. Accurately weighed quantities of MLX and PEG 6000 were dissolved in dichloromethane. The mixture was stirred and evaporated at 40° in vacuum oven until dry. The dried mass was pulverized and sieved (75—150 μm). The physical mixtures (PM) of MLX and PEG 6000 were prepared by mixing individual components that had previously been sieved (75—150 μm). All the samples were stored in a desiccator over silica gel till further use.

Drug Content　　SDs equivalent to 10 mg of MLX were weighed accurately and dissolved in suitable quantity of Methanol. The drug content was analyzed at 362 nm by UV spectrophotometer (Perkin Elmer, USA). Each sample was analyzed in triplicate.

Solubility Studies　　The effect of different concentrations of PEG 6000 on the equilibrium solubilities of MLX in distilled water at room temperature (28℃) were carried out by adding an excess of MLX (20 mg) to 20 ml of distilled water and varying concentrations of PEG 6000. The samples were placed on a shaker, agitated at 28℃ until equilibrium was achieved (48 h) and the aliquots were filtered through 0.22 μm nylon disc filter. The filtered samples were diluted suitably and assayed spectrophotometrically at 362 nm, a wavelength at which PEG 6000 does not interfere. Three determinations were carried out for each sample to calculate the solubility of MLX.

Infrared Spectroscopy (IR)　　IR spectroscopy was performed on fourier-transformed infrared spec-

trophotometer (1700, Shimadzu). The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectras were scanned over wave number range of 4500—500 cm^{-1}.

Differential Scanning Calorimetry (DSC)　　The DSC thermograms were recorded using a differential scanning calorimeter (Q 10 TA Instruments, USA). Approximately 2—5 mg of each sample was heated in an open aluminum pan from 30—300℃ at a scanning rate of 10℃/min under a stream of nitrogen.

Powder X-ray Diffraction Analysis (XRD)　　Powder X-ray diffraction patterns were recorded using a Powder X-ray diffractometer (Philips PW 1729 X-ray generator computer 1710) under the following conditions: target Cu, filter Ni, voltage 35 kV, current 20 mA, receiving slit 0.2 inches. The data were collected in the continuous scan mode using a step size of 0.01° at 2θ/sec. The scanned range was 5—50°.

Scanning Electron Microscopy (SEM)　　The SEM analysis was carried out using a scanning electron microscope (LEO, 435 VP, UK). Prior to examination, samples were mounted on an aluminium stub using a double sided adhesive tape and then making it electrically conductive by coating with a thin layer of gold (approximately 20 nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 15 kV. The selected magnification was 1000× since it was enough to appreciate the general morphology of the powder under study.

Dissolution Studies　　*In vitro* dissolution studies of MLX, PM and SD was carried out using USP paddle method (Lab India, India) by dispersed powder technique.[4] Samples equivalent to 15 mg of MLX was added to 900 ml distilled water containing 0.25% w/v sodium lauryl sulphate at 37±0.5℃ and stirred at 50 rpm. An aliquot of 5 ml was withdrawn at different time intervals with a syringe filter (pore size 0.45 μm). The withdrawn volume was replenished immediately with the same volume of the prewarmed (37℃) dissolution medium in order to keep the total volume constant. The filtered samples were suitably diluted, if necessary, and assayed spectrophotometrically at 362 nm. Under these experimental conditions, PEG 6000 did not interfere with spectrophotometric assay. The mean of at least three determinations was used to calculate the drug release.

RESULTS AND DISCUSSION

Drug Content The drug content of the prepared SDs was found to be in the range of 99.2—101.6% indicating the applications of the present method for the preparation of SDs with high content uniformity.

Solubility Studies The solubility of the drug increased with the increase in polymer concentration (Fig. 2) and approximately 15-fold rise was noted for the highest concentration of PEG 6000 under study. The solubility of MLX increased linearly with an increase in the concentration of PEG 6000, giving A_L type solubility diagrams.[19] These results are in accordance with the established formation of soluble complex between water-soluble polymeric carriers and poorly soluble drugs.[9,20] However, similar results are not observed with every water insoluble drugs e.g. no enhancement of solubility of norfloxacin (a poorly water-soluble drug) had been reported in the presence of PEG 6000.[21]

FT-IR Spectroscopy The interaction between the drug and the carrier often leads to identifiable changes in the FT-IR profile of SDs. FT-IR spectra for MLX, PEG 6000, SDs and PMs have been depicted in Fig. 3. The spectrum of MLX exhibited characteristic signals at 3290.3 cm^{-1} (N–H stretching vibrations), 1620.1 cm^{-1}, (C=N stretching vibrations), 1153.4 cm^{-1} (S=O stretching vibrations), respec-
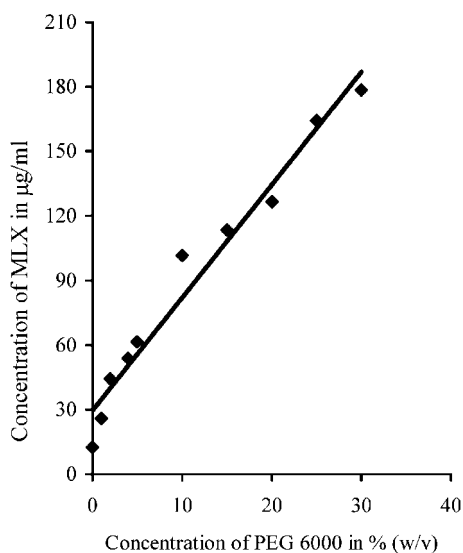
tively. The spectra of PMs were equivalent to the addition spectrum of polymer and the drug indicating no interaction occurring with the simple physical mixture of drug and the polymer. The spectrum of SDs exhibited significant decrease in the intensities of N-H and S=O stretching vibration peaks of MLX, a slight shift along with decrease in intensity of C=N stretching vibrations and hydroxyl stretching vibration peak (3444.6 cm^{-1}). Moreover, the surface of SDs exhibited a C–H stretching vibration peak (2887.2 cm^{-1}) of PEG 6000. These observations indicated possibility of intermolecular hydrogen bonding via N–H, S=O and C=N groups of MLX and hydroxyl groups of PEG 6000. In the low frequency region (1000−400 cm^{-1}) of the spectra of SDs, the peaks characteristic of MLX were almost unchanged. This indicated that although the drug molecule is hydrogen bonded with the polymer, the overall symmetry of the molecule is
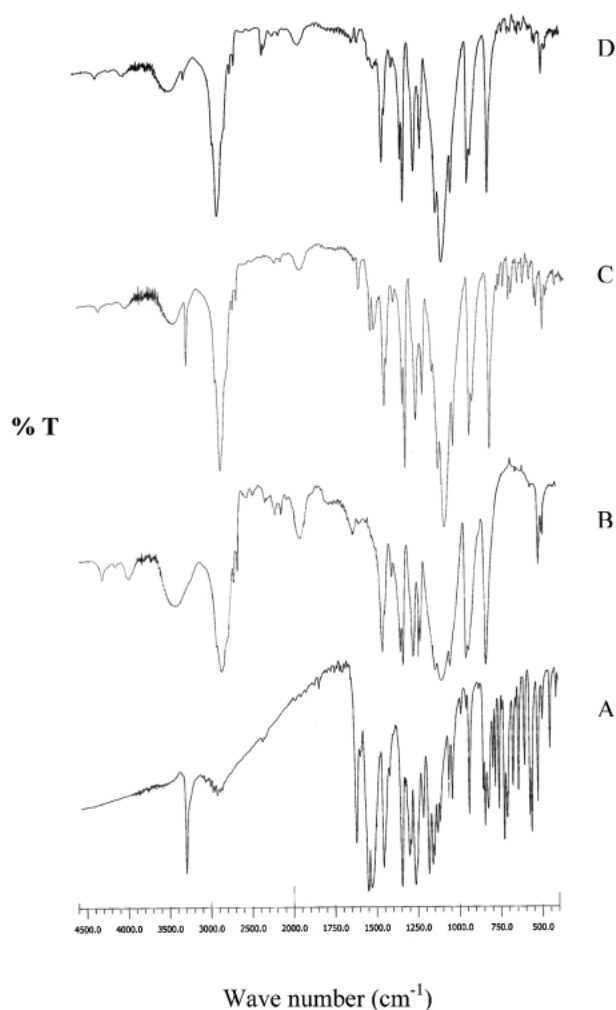

Fig. 2. Effects of Increasing Weight Fractions of PEG 6000 on Solubility of MLX

Each point represents as mean±S.D., $n=3$.

Fig. 3. FT-IR Images of Solid Systems: MLX (A), PEG 6000 (B), PM 10% (C), and SD 10% (D)

not significantly affected.[22)]

DSC Studies   The thermograms of the pure drug (MLX), the carrier (PEG 6000), SDs and PMs are illustrated in Fig. 4. The DSC thermograms of each component exhibited a sharp endothermal peak corresponding to the melting point of MLX (257.38 °C) and PEG 6000 (61.58°C). No differences were apparent between DSC thermograms of PMs and SDs. The complete disappearance of the drug melting peak observed in both PMs and SDs was attributable to the drug dissolution in the melted carrier before reaching its fusion temperature,[23)] the phenomenon, already observed in solid dispersions of other drugs with PEG.[24−26)]

Thermograms of the mixture containing an excess amount of MLX (40%) demonstrated two endothermic transactions. The first transition peak was observed very close to the melting temperature of PEG 6000 whereas; the second minor transition peak corresponds to the melting temperature of the drug gradually shifted to the lower temperature, losing its sharp and distinctive appearance. The disappearance of the drug melting in lower amount of MLX was due to its dissolution in the melted carrier. MLX-PEG 6000 systems were found to be completely miscible in the liquid phases and completely immiscible in the solid state.[19,27,28)] Further, approximately 10% difference in heat of fusion of SDs and PMs indicate a slight reduction in PEG crystillinity.[29)] This type of system is also typical of SDs of Flunarizine,[30)] Naproxen[27)] and Ibuprofen[31)] with PEGs, suggesting the presence of PEG in SDs as eutectica or monotectica, whereas, the drug as crystalline, amorphous or a mixture of both.[32)]

Powder X-ray Diffraction Analysis   The powder XRD patterns of various MLX, PEG 6000 and its binary systems were compared in Fig. 5. The diffraction pattern of the pure drug showed its highly crystalline nature, as indicated by the numerous distinctive peaks. The PEG 6000 alone exhibited two high intensity peaks at 19° and 23°. The lack of the numerous distinctive peaks of the drug in the solid dispersion demonstrated that a high concentration of the drug was dissolved in the solid-state carrier matrix in an amorphous structure. Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the binary systems with those of a reference. The relationship used for the calculation of crystallinity was relative degree of crystallinity
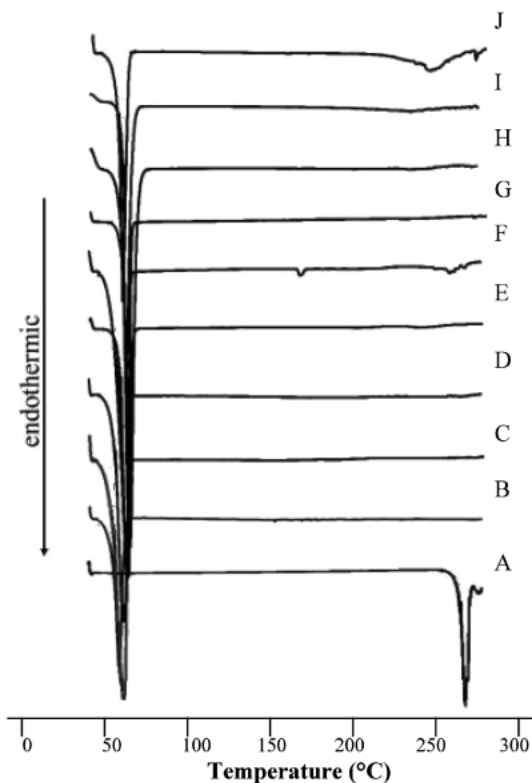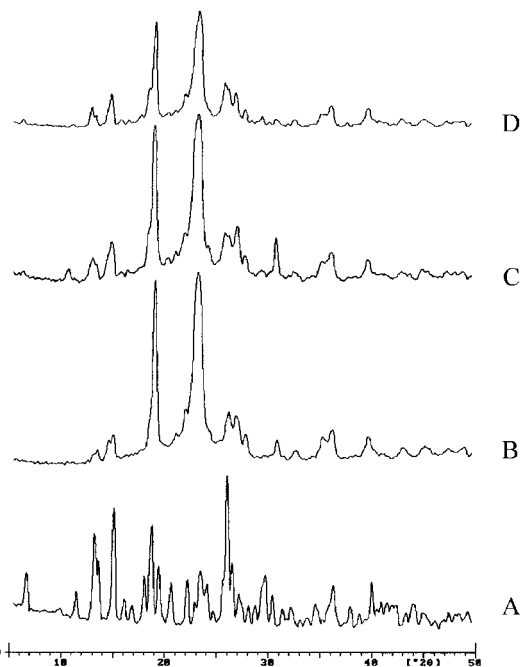

Fig. 4.   DSC Thermographs of Solid Systems: MLX (A), PEG 6000 (B), SD 5% (C), SD 10% (D), SD 20% (E), SD 40% (F), PM 5% (G), PM 10% (H), PM 20% (I), and PM 40% (J)

Fig. 5.   Powder X-ray Diffraction Spectra of MLX (A), PEG 6000 (B), PM 10 % (C), and SD 10 % (D)

$(RDC) = I_{sam}/I_{ref}$, where I_{sam} is the peak height of the sample under investigation and I_{ref} is the peak height at the same angle for the reference with the highest intensity.[15,16] Pure drug peak at 15.1° (2θ) was used for calculating RDC of PM 10% and SD 10%. The RDC values of physical mixture and solid dispersion were 0.2005 and 0.0455 respectively. Suggesting, the MLX present in the solid dispersion would be mostly in amorphous state and only with few partially crystallized drug molecules.[33]

Scanning Electron Microscopy The surface morphology of the MLX and its binary systems was examined by SEM analysis. Figure 6 shows some selected SEM images of representative samples. The MLX crystals appeared as fine needles with smooth surfaces partially agglomerated in bundles. The PEG 6000 exhibited crystalline agglomerates of rather irregular size and shape, which are clearly visible in PMs. The presence of less crystalline drug, uniformly and finely dispersed or adhered to the carrier surface was observed in the SDs. Further, in the solid dispersion containing lower drug content (SD 5%), it is very clear that the drug and polymer are in the state of solid solutions where majority of the drug particles are observed to be dissolved in the polymer. These observations provide the evidence of solid solution formation and are in accordance to the results obtained from FT-IR and DSC studies.

Dissolution Studies The dissolution of poorly water-soluble drugs requires a dissolution medium en-
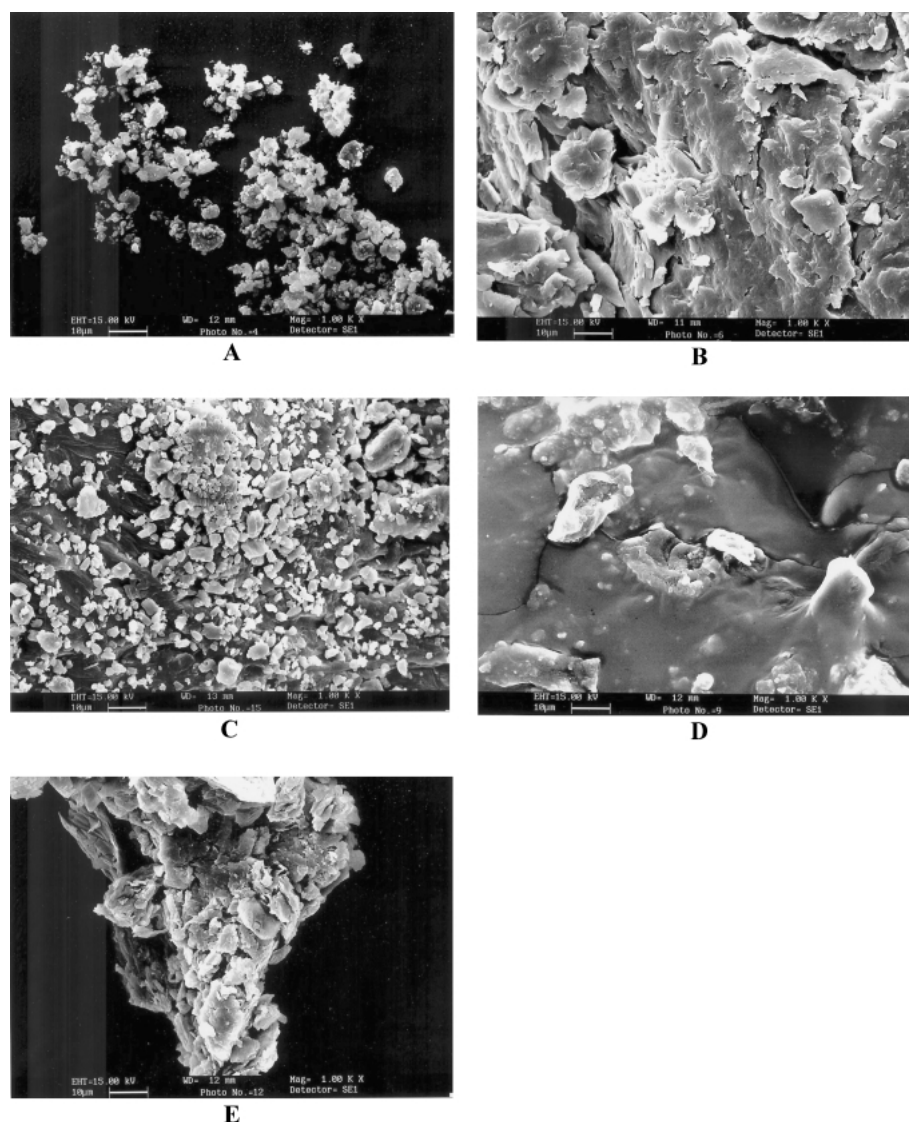

Fig. 6. SEM Images of MLX (A), PEG 6000 (B), PM 5% (C), SD 5% (D), and SD 10% (E)

tirely different from those used for water-soluble drugs. One of the techniques that have been useful in dissolution of insoluble drugs is the incorporation of a small amount of surfactant in the dissolution medium.[6] The use of surfactant in the dissolution medium may be physiologically meaningful, due to the presence of natural surfactants (like bile salts) in the gastrointestinal tract. The ability of surfactants to accelerate the *in vitro* dissolution of poorly water-soluble drugs has been attributed to wetting, micellar solubilization, and/or defocculation. It is easy to understand that a biorelavent medium needs similar surface activity as bio fluids. Studies on sodium lauryl sulphate have shown to satisfy these needs.[34] Based on these facts, dissolution of pure MLX, PM and SD were carried out in distilled water containing 0.25% w/v sodium lauryl sulphate.

It is very clear that the meloxicam dissolution rate increased with increasing PEG 6000 content. However, this effect was significant only in the first phase of the dissolution process (within 1 h). Since solid dispersions of meloxicam with PEG 6000 exhibited enhanced dissolution rate within this time period; it can be assumed that this may improve its rate of absorption *in vivo*. Possible mechanism of increased dissolution rates of solid dispersions have been proposed by Ford[35] and Craig,[3] include: reduction of crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallities, improved wettability and dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier, conversion of drug to amorphous state, and finally, the combination of previously mentioned methods. The increased dissolution rate observed in this case can thus be contributed by several factors such as solubilization effect, conversion to amorphous state, and improved wettability of meloxicam.

In general, dissolution may be described by two processes: the rate of the interfacial or solid-solvent reaction leading to solubilization of the molecule, and the rate associated with the diffusional or transport process of the solvated molecule to bulk part of the dissolution medium. Since water is strongly polar due to its O–H groups, it readily forms hydrogen bonds with polar groups such as O–H present in PEG 6000 and the SO_2 group on the meloxicam.[36] The strength of bonds between water-PEG 6000 and water-drug molecules may be stronger than or comparable with that between the molecules of the solid dispersions. Upon contact, water molecules solvate the PEG 6000 and meloxicam molecules and break the hydrogen bonds between the drug-carrier complex. The dissolution behaviour of pure MLX and MLX from PMs and SDs with PEG 6000 in various weight fractions (5, 10, 20 and 40%) have been shown in terms of dissolution efficiency[37] at 10 min (DE_{10}), percent drug dissolved at 30 min (DP_{30}) and relative dissolution rate at 5 min in comparison to the pure drug (RDR_5) in Table 1, whereas, the dissolution profiles are shown in Fig. 7. DE is defined as the area under dissolution curve up to the time (t) expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

$$\text{Dissolution efficiency (DE)} = \left(\frac{\int_0^t y \times dt}{y100 \times t} \right) \times 100$$

The dissolution efficiency will have a range depending upon the time interval chosen. In any case, constant time interval should be chosen for comparison. In the present investigation, DE_{10} values were calculated from the dissolution data of each product and used for comparison. The increase in dissolution and dissolution efficiency values of PMs could be due to the reduction of the interfacial tension between the hydrophobic drug particles and the dissolution medium, owing to the presence of the hydrophilic polymer and a local solubilizing effect acting during early stages of the dissolution process in the microenvironment surrounding the drug particles.[19,38] The increase in dissolution of MLX observed with increase

Table 1. Percent Drug Dissolved at 30 Min (DP_{30}), Dissolution Efficiency at 10 Min (DE_{10}) and Relative Dissolution Rate at 5 Min (RDR_5) of Pure MLX, Physical Mixtures (PM) and Solid Dispersions (SD)

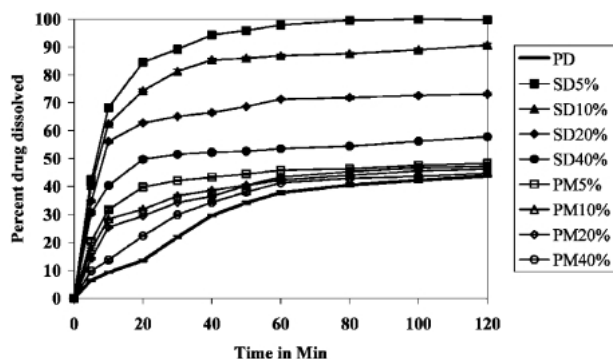| Sample	DP_{30}	DE_{10}	RDR_5
MLX	21.89±0.52	5.55	1
PM 5	42.12±0.21	18.18	3.17
PM 10	36.63±0.34	15.88	2.72
PM 20	34.31±0.21	13.50	2.21
PM 40	29.93±0.36	8.35	1.52
SD 5	89.22±0.66	38.31	6.56
SD 10	81.31±0.83	35.9	6.28
SD 20	65.12±0.35	31.46	5.38
SD 40	51.58±0.39	25.43	4.75

Each value represents as mean±S.D., $n=3$.

Fig. 7. Dissolution Profile of Meloxicam Alone and in Solid Dispersions and Physical Mixtures
Each point represents as mean ±S.D., $n=3$.

in PEG concentration may be attributed due to the increased amorphonising efficiency of PEG in higher concentration.[39] Further, the increase in the drug dissolution profile from SDs has generally been attributed to the reduction of drug particle size within SDs.[40] A poorly water-soluble drug with a strong hydrophobicity results in floating of the drug on the surface of dissolution medium, it is thought that, the better the wettability and dispersibility of a drug in a solid dispersion system, the better the chances of achieving an increase in drug dissolution profile.[41] Moreover, PEG may form a concentrated diffusion layer into which the drug dissolves prior to its release into the aqueous medium.[42]

CONCLUSIONS

The present work demonstrated the preparation of solid dispersions of Meloxicam with polyethylene glycol 6000 by solvent method, with the improved solubility and dissolution properties. The solubility, DSC, FT-IR, XRD and SEM studies clarified the physical state of both the drug and the carrier in the samples. A eutectic system was obtained in which the contribution of the PEG crystals was concentration dependent. The higher dissolution rates exhibited by solid dispersions may imply enhanced oral biavailability due to the increased wetting properties and solubility of drug in the hydrophilic polymer.

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