—Regular Articles—

Preparation and Evaluation of Solid Dispersion of Meloxicam with Skimmed Milk

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Meloxicam (MLX), a non-steroidal anti-inflammatory drug (NSAID) and a selective COX-2 inhibitor is a water insoluble drug (about 12 μg/ml). In order to improve the aqueous solubility of the drug and its dissolution rate, physical mixture and solid dispersions with skimmed milk were prepared and investigated. Enhancement of aqueous solubility of MLX was observed with solid dispersion of the drug with skimmed milk due to amino acids and surface active agents content in the milk, which can be used for the treatment of gastric disturbance. Rotary vacuum evaporation technique was used to prepare solid dispersion. Results showed that the solubility of solid dispersion of the drug was almost three times greater than the pure drug. Similarly, the solid dispersion of the drug indicated a significant improvement in the dissolution of the drug as compared to the physical mixture and the pure drug. Differential scanning calorimetry, X-ray diffraction and scanning electron microscopic analysis revealed the formation of solid dispersion of the drug with skimmed milk.

Key words——Meloxicam; solid dispersion; skimmed milk powder; dissolution

INTRODUCTION

Meloxicam (MLX), 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-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, osteo arthritis and other joint diseases. It has comparable efficiency and greater gastric tolerability in comparison to conventional NSAIDs.[1] 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 solubility and the dissolution of the drugs. The solid dispersion method is one of the effective approaches to achieve this ideal goal particularly for drugs with poor aqueous solubility in which the drug is incorporated into a water-soluble polymer matrix.[2—5] In order to eliminate or reduce gastrointestinal disorders of non-steroidal drugs, amino acids are suggested either as additives in the peroral application[6] or in the form of amino acid salts.[7] In this study, skimmed milk (SM) has been chosen as a drug carrier due to its surface active agent and amino acid content.[8] Additionally, the milk is proposed against the gastric disturbance caused by non-steroidal drugs with anti-inflammatory effects.[9] Besides solubility and dissolution studies, differential scanning calorimetry, powder X-ray diffraction and scanning electron microscopic analysis were performed to determine the physicochemical properties of the physical mixture (PM) and the solid dispersion (SD) in comparison to the pure drug.

MATERIALS AND METHODS

Materials Skimmed milk (fat content 1.5% maximum) procured from Hisar-Jind Co-op Milk Producers Union Ltd., Jind (Haryana, India). The Meloxicam B.P. was obtained as gift sample from Sun Pharmaceuticals Ltd. (Mumbai, India) and all other chemicals/solvents used were of analytical grade.

Methods

Preparation of Skimmed Milk Powder 100 ml of skimmed milk was dried in a rotary vacuum evaporator (Steroglass, Germany) at 100 rpm, 35°C under vacuum for 6 h. The obtained powder was dried in an oven (100 ml SM yielded about 12.10 g powder) and passed through a sieve no (75—150 μm) and stored in airtight container till further use.

Preparation of Solid Dispersion (SD) Meloxicam (1 g) was mixed in 50 ml of SM in a water bath at

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a temperature of 50℃ and stirred for 30 min using a magnetic stirrer. The resulting suspension was dried in a rotary vacuum evaporator at 100 rpm, 35℃ under vacuum for 6 h forming solid dispersion of the drug in a powder form. The obtained powder was dried in an oven and passed through a sieve (75—150 μm) and stored in an airtight container till further use.

Preparation of Physical Mixtures (PM) 1 g of MLX was uniformly mixed with 6.05 g of powdered SM using a spatula in a mortar. The prepared mixtures were stored in airtight container till further use.

Drug Content SD or PM equivalent to 10 mg of MLX were weighed accurately and mixed with suitable quantity of methanol. The suspension was filtered through 0.22 μm nylon disc filter and drug content was analyzed at 362 nm using UV spectrophotometer (Perkin Elmer EZ 301, USA). Each sample was analyzed in triplicate.

Solubility Studies Pure MLX (20 mg), its physical mixture and solid dispersion with skimmed milk (141 mg equivalent to 20 mg MLX) under test, was placed in a glass stoppered flask containing 20 ml of distilled water. 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.

Differential Scanning Calorimetry (DSC) The DSC thermograms were recorded using a differential scanning calorimeter (Q 10 TA Instruments, USA). Approximately 2 to 5 mg of each sample was heated in an open aluminum pan from 30 to 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/s. 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 aluminum 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.

Dissolution Studies *In vitro* dissolution studies of MLX, PM and SD were carried out using USP paddle method by dispersed powder technique.[3] Samples equivalent to 15 mg of MLX was added to 900 ml of 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, filtered through 0.45 μm nylon filter disc. An equal volume of fresh dissolution medium was replaced (maintained at the same temperature) in order to keep the total volume constant. The filtered samples were suitably diluted, if necessary, and assayed spectrophotometrically at 362 nm.

RESULTS AND DISCUSSION

The drug content of the prepared SD and PM was found to be in the range of 99.1 and 101.4% indicating the applications of the present method for the preparation of SDs with high content uniformity.

In order to determine the interaction between MLX and SM, DSC studies were performed on the individual components. The DSC curve of MLX (Fig. 1) showed one endothermic peak at nearly 257℃, corresponding to its melting point, whereas SM's endothermic peaks at 139, 165 and 203℃.[10] The DSC plots of the PM showed the addition of both SM and drug peak, while the drug in PM exhibited a reduction in endothermal peak height compared to pure drug alone. Since the DSC peak value of SD is broader and away from the melting point of MLX, it could be concluded that there is a formation of a complex[11] between MLX and SM. Disappearance of the specific peak of the drug indicated the drug interaction with the carrier.

The X-ray powder diffraction pattern (Fig. 2) of the pure drug exhibits its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity, whereas SM exhibits a diffraction spectrum, typical of mostly amorphous materials not showing any detectable diffraction peaks. In the case of SD, absence and reduction of major MLX diffraction peaks indicated the presence of the drug mostly an amorphous form (in SD). Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the binary systems with those of a reference. The

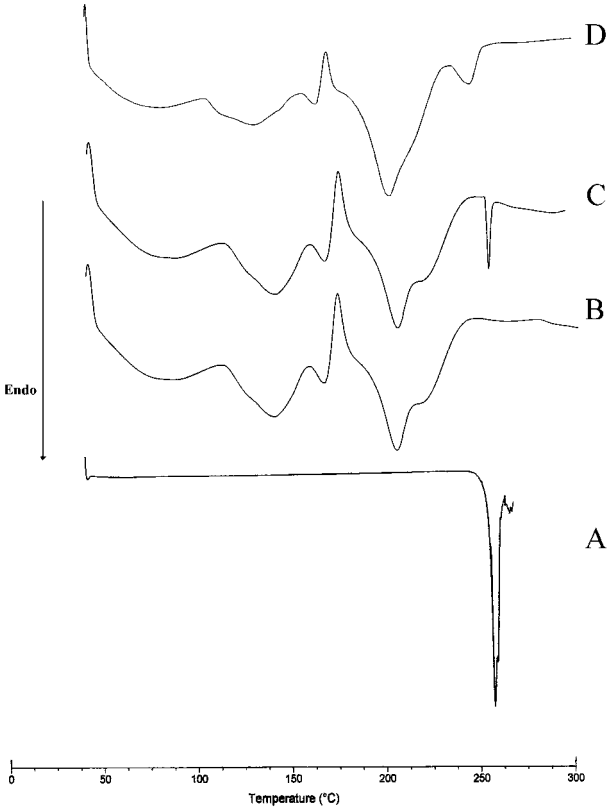

Fig. 1. DSC Thermograms of Meloxicam (A), Skimmed Milk Powder (B), Physical Mixture (C) and Solid Dispersion of Meloxicam with Skimmed Milk Powder (D)

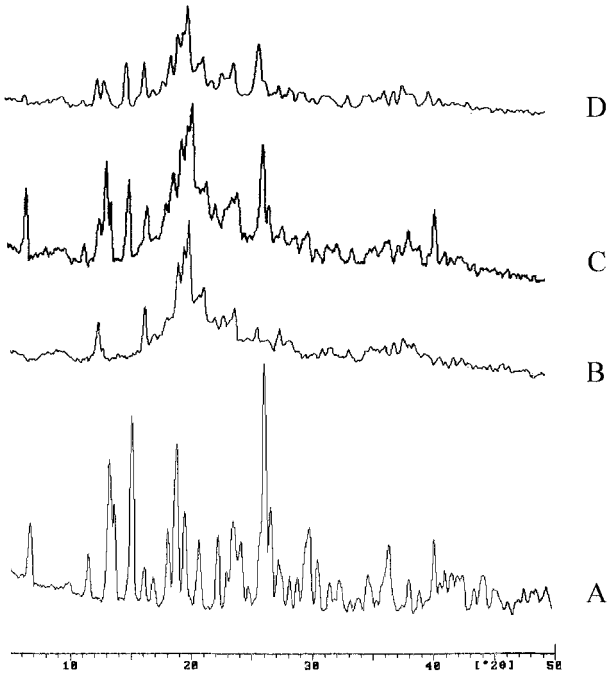

Fig. 2. Powder X-ray Diffraction Spectra of Meloxicam (A), Skimmed Milk Powder (B), Physical Mixture (C) and Solid Dispersion of Meloxicam with Skimmed Milk Powder (D)

relationship used for the calculation of crystallinity was relative degree of crystallinity (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.[12] Pure drug peak at 15.1° (2θ) was used for calculating RDC of PM and SD. The RDC values of physical mixture and solid dispersion were 0.2276 and 0.1294 respectively. Suggesting, the MLX present in the solid dis-

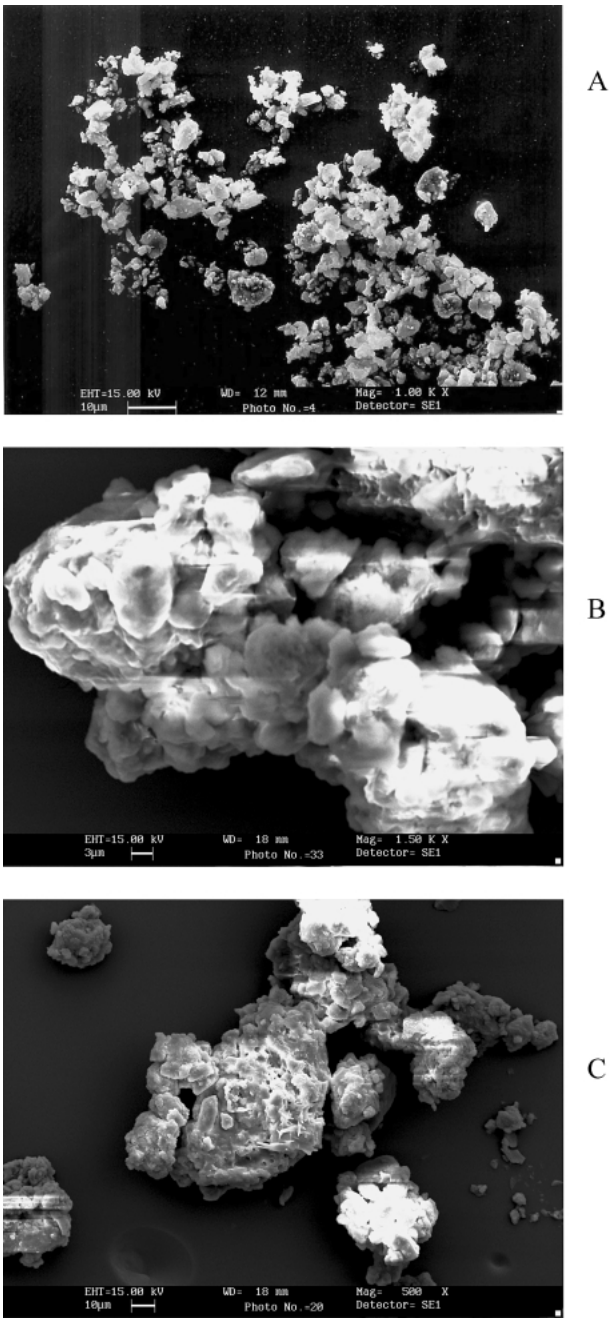

Fig. 3. SEM Photographs of Meloxicam (A), Physical Mixture (B), and Solid Dispersion of Meloxicam with Skimmed Milk Powder (C)

persion would be mostly in amorphous state and only a with few partially crystallized drug molecules.[13]

In the X-ray diffraction spectrum of the PM, it was possible to detect crystals of MLX as the particle size was greater than the SD. However, the particle size of MLX in PM and the pure drug was similar. Based on these results, it can be concluded that the enhancement in solubility and dissolution may be attributed to the surface active agents and enzymes content[14] of SM (in the case of PM) followed by, reduction of particle size and formation of an amorphous state (in the SD form).

The surface morphology of the MLX and its binary systems was examined by SEM analysis. Figure 3 shows some selected SEM images of representative samples. The MLX crystals appeared as fine needles with smooth surfaces, partially agglomerated in bundles. The SEM results show that in the case of PM, the particle size of MLX was approximately the same and some crystals of MLX could be seen in PM. In SD, MLX particles were in almost amorphous form, which indicated a reduction in particle size. These observations provide the evidence of solid dispersion formation and are in accordance to the results obtained from XRD and DSC studies.

Solubility of MLX in SD was nearly three times (36.48 μg/ml), whereas in PM 2.4 times (29.72 μg/ml) higher than in the pure drug (12.41 μg/ml) (Table 1).

The dissolution of poorly water-soluble drugs requires a dissolution medium entirely 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.[15] 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 deflocculation. It is easy to understand that a biorelevant medium needs similar surface activity as biofluids. Studies on sodium lauryl sulphate have shown to satisfy these needs.[16] Based on these facts, dissolution of pure meloxicam, physical mixture and solid dispersion were carried out in distilled water containing 0.25 w/v% sodium lauryl sulphate. The dissolution profiles of SD and PM of MLX with SM are shown in Fig. 4. The dissolution of the pure drug was found to be the least. Incorporation of MLX with

Table 1. Solubility of Meloxicam as Plain Drug in PM and SD with SM in Distilled Water at Room Temperature (28°C)

Form of drug	Solubility (μg/ml)
Pure drug	12.41±0.27
PM	29.72±0.83
SD	36.48±1.26

* $n=3$

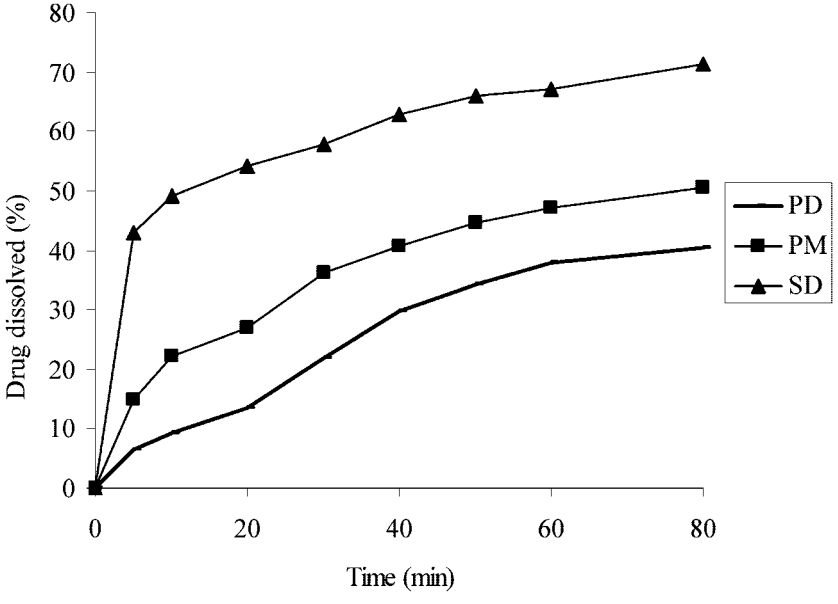

Fig. 4. Dissolution Profile of Meloxicam in Physical Mixture (PM), Solid Dispersion (SD) along with Pure Meloxicam Alone (PD)

SM especially in SD form significantly improved the dissolution of the drug as compared to the PM and the pure drug.

It can be concluded that, SD with SM was found to be more suitable form for MLX in terms of solubility and dissolution when compared with PM. However, the PM of MLX with SM also gave better results than the pure drug. On other hand, investigations on pharmacological activity and side effects of gastrointestinal disturbance of non-steroidal drugs with the same therapeutic activity showed increase in the pharmacological activity and decrease in gastrointestinal disturbance.[9] Thus, it can be concluded to formulate SD of MLX with SM with a decreased therapeutic dose and less gastrointestinal disturbance for peroral and parenteral applications.

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