RESEARCH ARTICLE

Solubility enhancement and development of dispersible tablet of meloxicam

Nazma Inamdar, Kiran Bhise, Shakeel Memon

Department of Pharmaceutics, Allana College of Pharmacy, Pune, Maharashtra, India

The present research work investigates enhancement of dissolution profile of meloxicam using solid dispersion (SD) with various polymers. The work also describes the formulation of dispersible tablet (DT) and effervescent tablet of meloxicam. PEG 6000, PEG 8000, PEG 20000, Lutrol F-127, and β-cyclodextrin were selected for the preparation of SD. The SDs were prepared by melting and solvent evaporation methods. Dissolution studies were performed for plain meloxicam, SDs, and tablet formulations. Infrared spectroscopy and differential scanning calorimetry were performed to identify the physicochemical interaction between drug and carriers. Dispersible tablets and effervescent tablets were compared with tablet containing plane drug for dissolution profile. Dissolution of DT improved significantly in SD product (<95% in 1 min).

Key words: *Effervescent tablets, meloxicam, melting method, solid dispersion, solvent evaporation method*

INTRODUCTION

Meloxicam is an oral nonsteroidal anti-inflammatory drug. It is reported to be selective inhibitor of cyclo-oxygense-2 and used in the management of rheumatoid arthritis, for the short-term symptomatic treatment of acute exacerbations of osteoarthritis, and for the symptomatic treatment of ankylosing spondylitis.[1]

The rate and extent of dissolution of the active ingredient from any dosage form often determines the rate of extent of absorption of the drug.[2] In case of a meloxicam that is poorly water soluble, dissolution may be the rate-limiting step in the process of drug absorption.[3] Drug with poor water solubility have been shown to be unpredictably and slowly absorbed compared with drugs of higher solubility. Therefore, a better oral, parenteral, or topical formulation can be developed by increasing the water solubility of the drugs.[4]

Solid dispersion (SD), which was introduced in the early 1970s,[5] is an effective method for increasing the dissolution rate of poorly soluble drugs, hence, improving their bioavailability.[6] Chiou and Riegelman defined the term SD as 'a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method'. When SD is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs. In addition, in SD, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size.[7]

Address for correspondence:
Nazma Inamdar, Allana College of Pharmacy, Azam Campus, Pune - 411 001, Maharashtra, India. E-mail: nazma13@yahoo.co.in

MATERIALS AND METHODS

Materials

Meloxicam was obtained as gift sample from Techno Drug (Mumbai, India). PEG 6000, PEG 8000, and PEG 20000 were purchased from Loba Chemical (Mumbai). β-Cyclodextrin was purchased from Himedia Lab (Mumbai) and Lutrol F-127 was a gift sample from Transchem Pharma (Mumbai). All reagents and solvents used were of analytical grade.

Melting method

Melting method was used for the preparation of SD of meloxicam with PEG 6000, PEG 8000, PEG 20000, and Lutrol F-127. The drug:polymer ratio (1:1, 1:2, and 1:3) was accurately weighed, mixed in crucible, and the mixture was kept for melting on water bath with constant stirring. The mixture was cooled slowly at room temperature. The product was placed in desiccators over silica gel for 4 days. The solidified product was transferred to a clean mortar, triturated and passed through sieve No. 16 and 20.

Solvent evaporation method

In solvent evaporation method, meloxicam and β-cyclodextrin in (1:1, 1:2, and 1:3) ratio was accurately

weighed and transferred into Petri plate and dissolved in sufficient quantity of chloroform. The solution was stirred for 15 min. It was evaporated with constant stirring; the resulting SD was stored in a desiccator to harden for 4 days. The mass was passed through sieve No. 16 and 20. It was then stored in the desiccator.

Physical mixtures (PMs) were obtained by pulverizing in glass mortar and carefully mixing accurately weighed (1:1, 1:2, and 1:3) amounts of meloxicam and polymers.

Solid state studies

Fourier transform infrared (FTIR) spectroscopy

The samples were mixed with potassium bromide in a ratio of 1:99 in agate mortar and pestle and mixed thoroughly. This mixture was then loaded in FTIR (JASCO - FT/IR-4100, Germany) to get an IR spectrum.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry analysis was performed for optimum SDs, plain meloxicam (MX), PEG 8000, and drug-polymer PMs using DSC-60 (Shimadzu, Japan) on 2 mg sample. Samples were heated in a hermetically sealed aluminum pans in the temperature range of 25-300°C at heating rate of 10°C/min under nitrogen flow of 30 ml/min.

Drug content

Solid dispersion equivalent to 15 mg of meloxicam was dissolved in 100 ml 0.1 N NaOH by vigorous shaking for 20 min. The solution was sonicated for 5 min. The solution was filtered through 0.45-μ filter. Then, 1 ml filtrate was withdrawn and diluted up to 10 ml by 0.1 N NaOH and analysed spectrophotometrically at 360 nm.

Liquid state studies

Solubility studies[8]

Sample equivalent to 15 mg of meloxicam (pure MX, PMs, and SDs) were added to 5 ml of phosphate buffer of pH 7.4, sonicated for 1 h and stirred using magnetic stirrer at room temperature for 42 h. The suspension was filtered (0.45 μ Millipore filter), diluted with phosphate buffer of pH 7.4, and analyzed spectrophotometrically at 360 nm. The average of two experiments was taken.

Dissolution studies[2]

The dissolution studies was accomplished using USP type-I method using an Electrolab Dissolution apparatus (TDT-08L, Electrolab, Mumbai). The dissolution medium was 900 ml of phosphate buffer pH 7.4 maintained at 37 $\pm$ 0.5°C and 50 rpm stirring rate. A weighed amount of sample (equivalent to 15 mg MX) was filled in hard gelatin capsule. The capsule was then placed in to basket that is immersed in to the medium. The sample (5 ml) was withdrawn, filtered, and concentration of MX was determined spectrophotometrically at 360 nm.

Tablet preparation and characterization

The formulation designing for effervescent and dispersible tablet is depicted in Table 1. The granules were prepared by wet granulation technique. The tablets were compressed on 8-station single rotary tablet press (Karnavati - Minipress D-II Link, Mumbai) using 10- and 8-mm standard flat punch. Prepared tablets were evaluated for hardness (Monsanto hardness tester), friability, and disintegration time. *In vitro* dissolution studies were performed similarly as for SD using USP type-II apparatus.

RESULT AND DISCUSION

Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy was performed on meloxicam, the prominent peaks were obtained at 3295, 1617, 1552, 1340, and 1183/cm because of stretching vibration bands of NH, C=O, C-C, and two S=O, respectively. The group frequencies of drug confirmed to the respective structure. In case of SD of meloxicam and polyethylene glycols and Lutrol F-127, both drug and polymers peaks were present. The spectra revealed no difference in the positions of the absorption bands, especially with respect to OH, =O, NH, hence providing the evidence for the absence of hydrogen bonding interaction in solid state between polymers and meloxicam. When the ratio of meloxicam and polymer is same, the peak is sharp, whereas in higher polymer, these peaks are not distinct. In cyclodextrin, the FTIR spectra demonstrated a shift of NH band of meloxicam from 3294 to 3274/cm, which confirm complex formation. The changes in the rest of the spectrum are not significant. The spectra of only optimized SD (MX:PEG 8000) is depicted in Figure 1.

Table 1: Formulation designing

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Meloxicam	15	15	-	-	15	-
MX:PEG 8000 (1:3)	-	-	60	60	-	60
Mannitol	169	135	129	95	25	25
PVP-K30	3	3	-	-	3	-
Citric acid	6	35	6	35	-	-
Sodium bicarbonate	100	105	100	105	-	-
Sodium starch glycolate	-	-	-	-	16	16
Micro-crystalline cellulose	-	-	-	-	134	92
Magnesium-stearate	4	4	2	2	4	4

Each tablet contains 1 mg menthol; 1 mg aerosil; and 1 mg aspartame

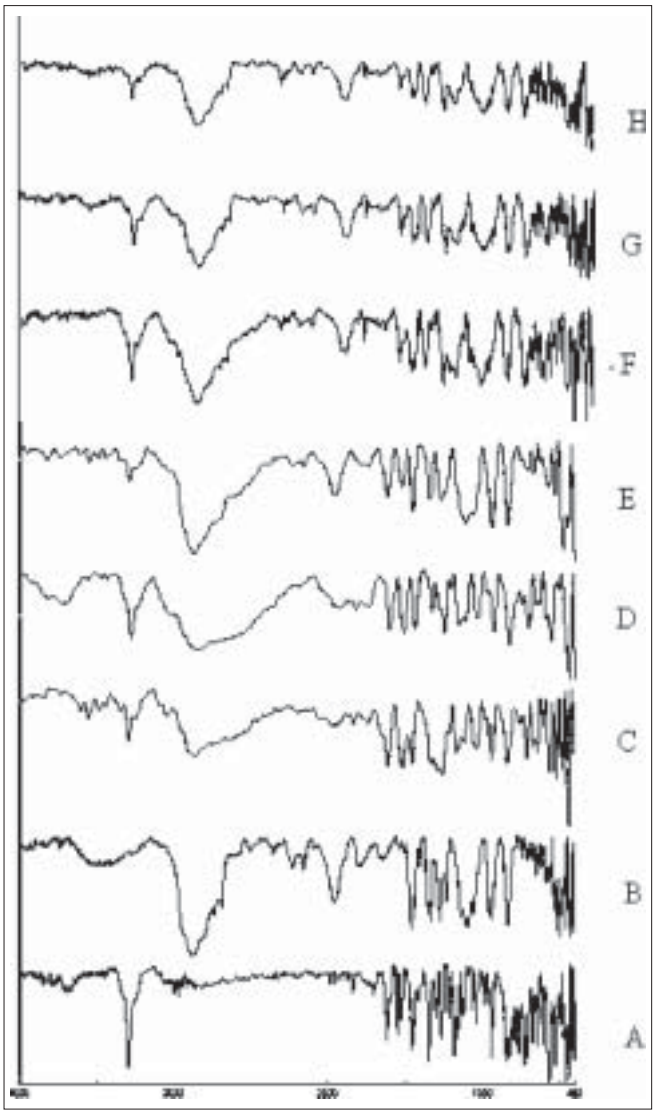

Figure 1: FTIR spectra of (A) meloxicam, (B) PEG 8000, (C) MX: PEG 8000 1:1 PM, (D) MX:PEG 8000 1:2 PM, (E) MX:PEG 8000 1:3 PM, (F) MX:PEG 8000 1:1 SD, (G) MX:PEG 8000 1:2 SD, (H) MX: PEG 8000 1:3 SD

Differential scanning calorimetry

Differential scanning calorimetry scan of pure meloxicam, PEG 8000, PM, and SD are depicted in Figure 2. Meloxicam showed an endothermic peak at 260°C corresponding to its melting point. PEG 8000 shows the thermogram at 60°C corresponding to its melting point. Solid dispersion shows the weakness of endotherm peak as compared to PM because PEG 8000 melts before meloxicam, there is possibility that crystalline meloxicam might dissolve in molten PEG 8000 during the DSC scan and convert to amorphous form. A lack of drug melting endotherm in SD suggests the presence of drug in an amorphous form within the dispersion. Physical mixture has broad peak when compared with SD.

Solubility studies

The data depicted in Table 2 shows that the saturation solubility was higher for SDs as compared to plain drug and PM.

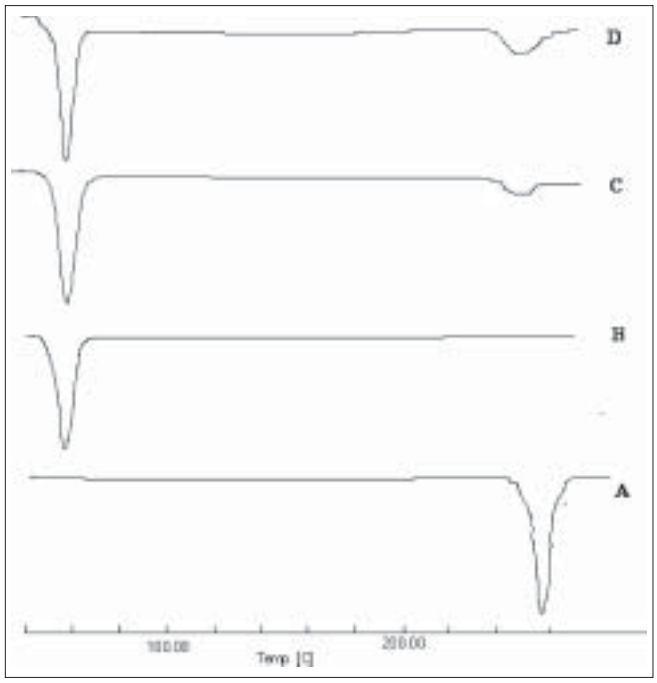

Figure 2: DSC curve of (A) meloxicam, (B) PEG 8000, (C) MX:PEG 8000 1:3 (SD), (D) MX:PEG 8000 1:3 (PM)

Dissolution studies

Dissolution profiles of plane drug and optimized ratio of all SD is shown in Figure 3. The figure indicated that the SD ratio 1:3 of MX:PEG 8000 gives fast dissolution of drug as compared to other polymers and plane drug. Solid dispersion technique has improved the dissolution rate of meloxicam to a great extent. Table 3 summarizes percentage drug dissolved of optimized ratios of all SD in 5 min (DE_5), 10 min (DE_{10}), 30 min (DE_{30}), 60 min (DE_{60}), 90 min (DE_{90}) shows fast dissolution enhancement of drug in SD with PEG 8000 in 1:3 drug:polymer ratio. PEG 8000 has high molecular weight as compared to PEG 6000 because of which it has more repeating unit of helical chain in which the drug molecule is lodged in the cavity. PEG 20000 is having high molecular weight as compared to PEG 8000, but it shows lesser dissolution because PEG 20000 has more repeating units of oxyethylene helical that causes trapping of meloxicam particles. β-Cyclodextrin increases the solubility, but lesser than PEG 8000, whereas Lutrol F-127 gives delay in release of drug.

Tablet preparation and characterization

To formulate dispersible tablet of meloxicam, the SD MX: PEG 8000 (1:3) ratio was selected based on its solubility and *in vitro* dissolution performance.

The use of effervescent mixture and superdisintegrant for preparation of dispersible tablets is highly effective. They accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore fast disintegration occur.

Table 2: Saturation solubility data of meloxicam with various polymers

Composition	Ratio	Solubility in mg/100 ml	
		Solid dispersion	Physical mixture
Meloxicam (plane drug)		0.773	
Melting method			
Meloxicam:PEG 6000	1:1	0.945	0.833
	1:2	0.999	0.856
	1:3	1.142	0.892
Meloxicam:PEG 8000	1:1	1.040	0.943
	1:2	1.250	0.998
	1:3	1.556	1.024
Meloxicam:PEG 20000	1:1	0.962	0.810
	1:2	1.010	0.832
	1:3	1.118	0.875
Meloxicam:Lutrol F-127	1:1	1.301	0.925
	1:2	1.160	0.910
	1:3	1.029	0.859
Solvent method			
Meloxicam:β-cyclodextrin	1:1	1.109	0.860
	1:2	0.971	0.824
	1:3	0.933	0.791

Table 3: Percentage dissolution and dissolution efficiency of plane meloxicam and optimized solid dispersion ratios of all polymers

DE (min)	A	B	C	D	E	F
DE5*	68.57 ± 10.21	91.33 ± 5.30	76.25 ± 1.63	38.31 ± 5.96	6.77 ± 7.63	0.65 ± 0.57
DE10*	71.13 ± 8.62	89.88 ± 2.42	81.37 ± 1.72	43.48 ± 2.13	9.12 ± 13.35	0.79 ± 0.60
DE30*	76.41 ± 5.69	88.85 ± 2.18	87.03 ± 2.23	61.36 ± 2.49	53.76 ± 8.60	2.08 ± 0.59
DE60*	82.60 ± 4.62	89.53 ± 2.59	83.68 ± 3.82	73.69 ± 4.01	78.62 ± 6.80	4.35 ± 0.80
DE90*	85.71 ± 2.11	89.96 ± 2.96	-	78.49 ± 4.16	92.92 ± 6.77	6.44 ± 0.88

A - MX:PEG 6000 1:3; B - MX: PEG 8000 1:3; C - MX: PEG 20000 1:3; D - MX: β-cyclodextrin 1:1; E - MX: Lutrol F-127 1:1; F - meloxicam (plane drug); DE_5, DE_{10}, DE_{30}, DE_{60}, and DE_{90} dissolution efficiency at 5, 10, 30, 60, and 90 min; *All values are mean of three readings ± SD

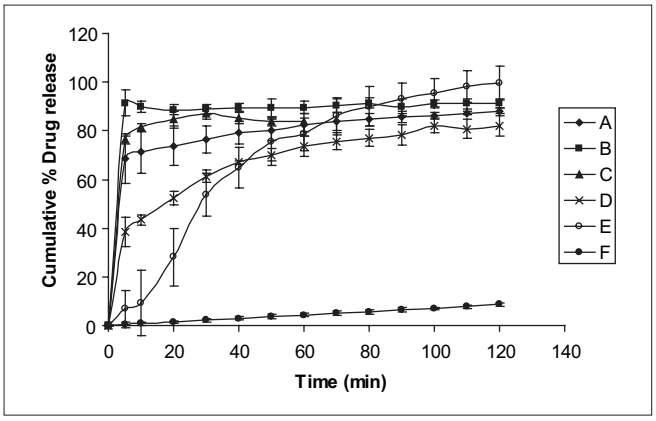

Figure 3: Comparison of all optimized ratios (A) MX:PEG 6000 1:3, (B) MX:PEG 8000 1:3, (C) MX:PEG 20000 1:3, (D) MX:β-cyclodextrin 1:1, (E) MX:Lutrol F-127 1:1, (F) meloxicam (plane drug)

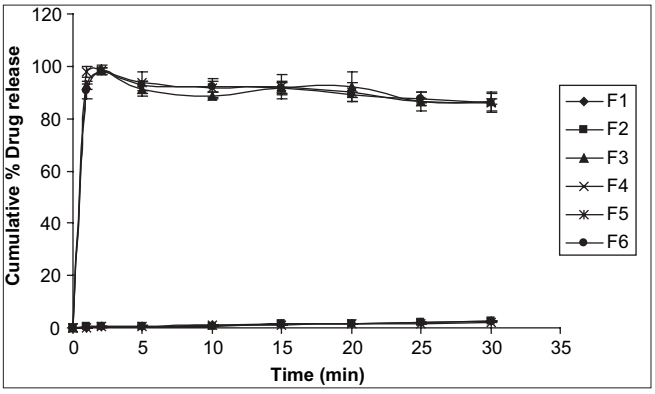

Figure 4: Dissolution of dispersible tablet

This disintegration is reported to have effect on dissolution characteristics.

Effervescent mixture citric acid:sodium bicarbonate (1:3) and sodium starch glycolate were tried to achieve fast dispersion of tablets as shown in Figure 4. The formula of different tablets prepared is summarized in Table 1. However, tablets containing effervescent mixture in 1:3 ratio showed the fast.

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