Original Article

Factors influencing the dissolution behavior of meloxicam dispersions

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ABSTRACT

The development of pharmaceutical cocrystals has recently been recognized as a fruitful approach to improving the dissolution rate and hence the bioavailability of drugs belonging to class II in the biopharmaceutical classification system (BCS). Different types of coformers, including ibuprofen, were screened for the potential synthesis of cocrystal solid forms with a non-steroidal anti-inflammatory agent, meloxicam, in an attempt to modify its dissolution rate into favorable higher values. Nine formulations were prepared using the solvent evaporation method, and the products were characterized by differential scanning calorimetry (DSC), in-vitro release studies, and powder X-ray diffraction (PXRD). Data obtained from FTIR, DSC, and PXRD spectra strongly supported the development of a new crystalline state. In addition, formulation F6, which contains meloxicam: oxalic acid dihydrate at a molar ratio of 1:2, exhibited a better dissolution pattern than pure meloxicam and other formulations, therefore, it was selected as the optimum formulation. Among the coformers explored throughout the study, oxalic acid dihydrate successfully produced cocrystals that achieved a significant enhancement in the dissolution rate compared to meloxicam.

Keywords: Pharmaceutical cocrystals, Meloxicam, Oxalic acid, Dissolution

Introduction

Pharmaceutical cocrystals have emerged recently as a promising approach to solve an essential challenge in the pharmaceutical industry, which is the delivery of active pharmaceutical ingredients (APIs) that possess limited aqueous solubility and inadequate bioavailability [1-4]. Cocrystals are often described as crystals that consist of two or more neutral components that are solids under ambient conditions. The two compounds, mainly API and a coformer, are connected through hydrogen bonding between the complementary functional groups. The bonding enable them to form supramolecular synthon, like carboxylic acid ……carboxylic acid, carboxylic acid……amide, carboxylic acid……aromatic nitrogen, and amide……amide [5, 6]. It has been reported that cocrystals have a profound capacity to modulate the physicochemical properties of drugs mainly by causing modifications in the molecular arrangements and /or interactions between molecules in crystal lattices without any alteration in the chemical entity of API or compromising its pharmacological activity [7].

Meloxicam, is designated as 4-hydroxy-2-Methyl-N- [(5-methyl-1,3-thiazol-2-yl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide. Meloxicam is a class II NSAID and is used in the management of pain or inflammation caused by osteoarthritis and rheumatoid arthritis [8]. The property of rapid absorption and rapid onset is always desirable for analgesic agents. For class II drugs, increasing solubility and dissolution rate, which presents the rate-limiting step to drug absorption may cause a remarkable enhancement in clinical response [9]. Therefore, in this study cocrystal formation was screened with different coformers including tartaric acid, citric acid, oxalic acid dihydrate, and saccharin. In addition, ibuprofen was explored as a possible coformer for the production of drug-drug cocrystals

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and ultimately gain a beneficial therapeutic hybrid with meloxicam.

Materials and Methods

Materials

Meloxicam and Ibuprofen were purchased from (Ajanta, India). Citric acid and tartaric acid were obtained from (Panreac Quimica S.L.U., Barcelona). Oxalic acid dihydrate and sodium lauryl sulfate were purchased from (Fluka AG, Switzerland). Saccharin was purchased from (Sigma –Aldrich, Germany).

Synthesis of cocrystals

Fast evaporation method using a rotary evaporator was adopted to prepare the cocrystal formulations **(Table 1)**. Meloxicam and coformers in a molar ratio of (1:1) and (1:2) were dissolved in a solvent mixture consisting of chloroform and methanol (50:50% v/v). Thereafter, the solvent was dried under reduced pressure, temperature of 55°C, and 100 rpm. Finally, round bottom flasks were scraped and powders were sieved and stored for further analysis.

Table 1. Composition of the cocrystal formulations

Formulations	Meloxicam (mg)	Tartaric acid (mg)	Citric acid (mg)	Oxalic acid dihydrate (mg)	Saccharin (mg)	Ibuprofen (mg)
F1 (1:1)	100	42.7				
F2 (1:2)	100	85.4				
F3 (1:1)	100		54.8			
F4 (1:2)	100		109.5			
F5 (1:1)	100			35.9		
F6 (1:2)	100			71.8		
F7 (1:1)	100				52.2	
F8 (1:2)	100				104.4	
F9 (1:1)	100					58.8

Characterization of cocrystals

Differential scanning calorimetric (DSC) analysis

DSC was obtained using SAT PT-1000 Linseis instrument. Samples of pure meloxicam, coformers, and their corresponding formulations were loaded into hermetically sealed aluminum pans and heated at a rate of 10°C/min, and scanned in the range of 0-400 °C under argon atmosphere.

Powder X-ray diffraction (PXRD)

Using a Shimadzu X-ray diffractometer (XRD 6000) equipped with a Cu radiation source at 40 kV and 30 mA, X-ray spectra were obtained. Scanning was performed at ambient temperature from 5 to 80 degrees over 2θ drive axis, with a scan speed of 8 degrees/min and a continuous scanning mode.

FTIR

Using an FTIR spectrophotometer (Shimadzu FTIR-8400S) by the potassium bromide disc method, FTIR spectra were obtained. Briefly, samples of pure meloxicam, coformers, and their corresponding formulations were thoroughly mixed and triturated with potassium bromide. Then, the mixtures were pressed into compacts and analyzed at 400-4000 cm^{-1}.

In-vitro drug release study

Drug release study for the pure meloxicam and formulations (F1 –F9) was done using the USP Type II dissolution apparatus (Vanguard/ USA). Samples of 100 mg of meloxicam or its equivalent amount of cocrystals were weighed and placed in phosphate buffer (900 ml, pH 6.8) containing 1.5 % sodium lauryl sulfate and rotated at 37±0.5°C and 50rpm. 5 ml of samples were collected at each time interval and compensated with an equal volume of buffer solution. The withdrawn samples were filtered through the Whatman filter and spectrophotometrically analyzed at 360 nm. All release studies were performed in triplicates.

Results and Discussion

Differential scanning calorimetric (DSC) analysis

Meloxicam DSC thermogram exhibited a sharp endothermic peak reflecting its melting point at 260.5°C [10]. The DSC thermograms for the prepared formulations displayed different thermal patterns compared to the pure meloxicam. Most formulations except formulation F1 recorded melting points that are lower and/or between those recorded for meloxicam and the coformers, attributed to the formation of new crystalline solids that are characterized by weaker intermolecular forces than the starting crystalline forms [11, 12]. The higher melting point displayed in formulation F1 has been recorded in literature, yet it is not a frequent observation in cocrystals [13]. The DSC thermogram of the selected formulation F6 is shown in **(Figure 1)**.

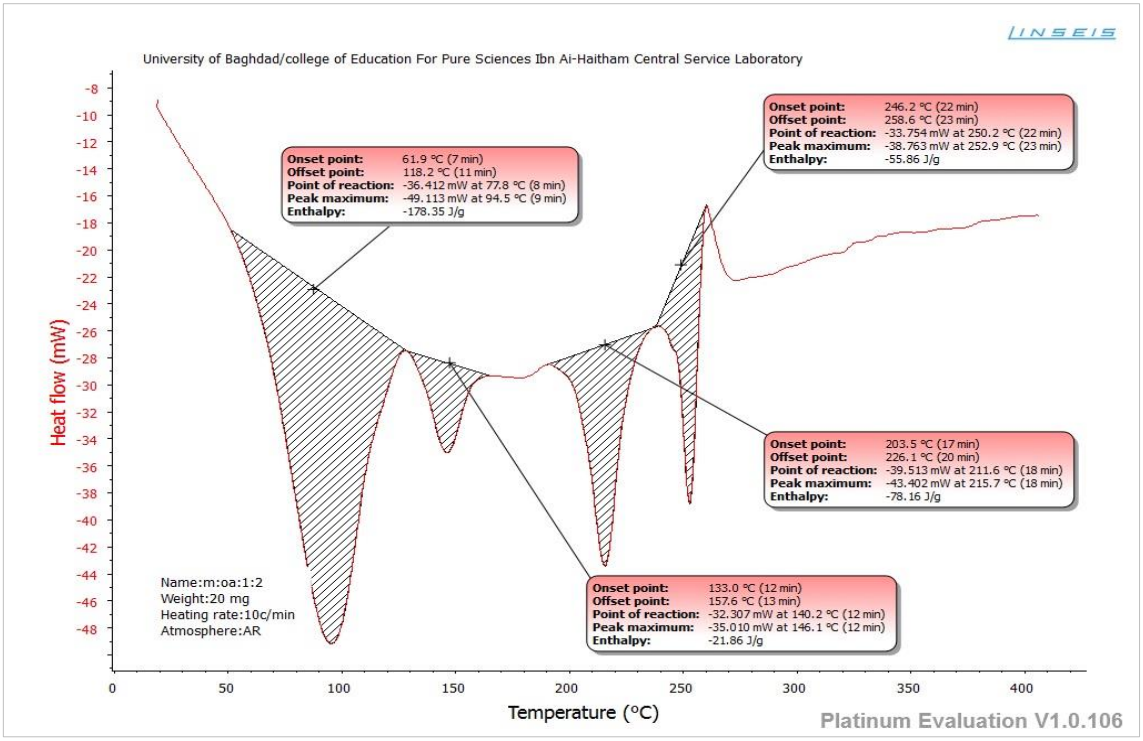

Figure 1. DSC thermogram of F6

PXRD

XRD patterns were analyzed for both the starting materials and the corresponding formulations. Pure meloxicam exhibited characteristic sharp peaks at 13.09°,14.94°,18.69°, and 25.83° indicating its crystalline state [14]. Likewise, coformers showed diffraction patterns that reflected their crystalline nature.

The presence of additional peaks has been noticed in the X-ray spectra of all formulations (F1-F9), suggesting the formation of a new crystalline state [11, 15]. **Figure 2** illustrates the diffraction spectrum of optimum formulation (F6), which exhibits distinct peaks at 8.407°, 16.28°, 18.01°, and 28.95° that are not related to the drug or coformer.

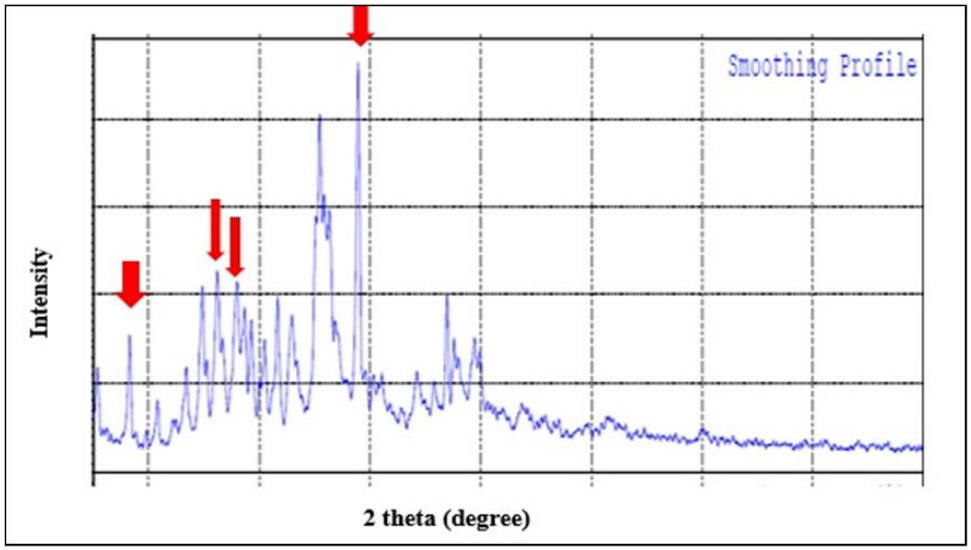

Figure 2. X-ray spectrum of F6

FTIR

FTIR spectrum of pure meloxicam exhibited fundamental peaks at 3290.67, 1618, and 1157.33 cm^{-1} that correspond to N-H, C=O, and S=O stretching vibration, respectively [16]. The fundamental peaks of pure ibuprofen at 1720 and 3000 cm^{-1} were assigned to carbonyl stretching of isopropionic acid and hydroxyl group stretching, respectively [17].

Tartaric acid, citric acid, and oxalic acid dihydrate exhibited a strong absorption band in the region (1760-1690) cm^{-1} related to C=O stretching vibration and the broad band assigned to a hydroxyl group in the region (3300-2500) cm^{-1} [18].

Saccharin revealed peaks at 3093.92 and 1724.42 cm^{-1} that correspond to N-H and C=O stretching vibration, respectively. In addition, peaks at 1180.47 and 1336.71 cm^{-1} correspond to symmetric and asymmetric stretching of the SO_2 group [19].

IR spectra of formulations between meloxicam and organic acids (F1-F6) have demonstrated a reduced intensity and a shift of the absorption bands, assigned to N-H and C=O stretching vibration of meloxicam, towards the lower frequencies. A similar shift was evident for the C=O stretching vibration of the acids. In addition, a significant change in shape and reduced intensity of hydroxyl stretching vibration of the acids was observed. These results suggest the formation of intermolecular hydrogen bonds, thereby indicating cocrystal formation [20, 21].

On the other hand, no alteration in the characteristic absorption bands has been detected in the IR spectra of formulations employing saccharin and ibuprofen as a coformer (F7-F9) when compared to these of meloxicam or the coformer. **Figures 3-5** depict FTIR spectra of meloxicam, oxalic acid dihydrate, and formulation F6, respectively.

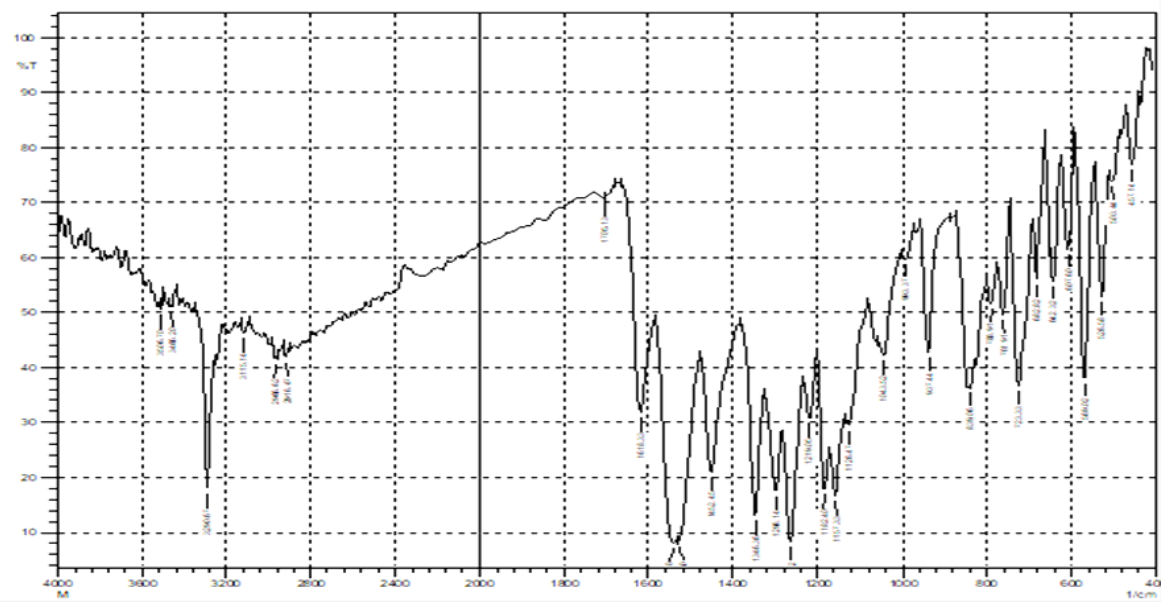

Figure 3. FTIR spectrum of meloxicam

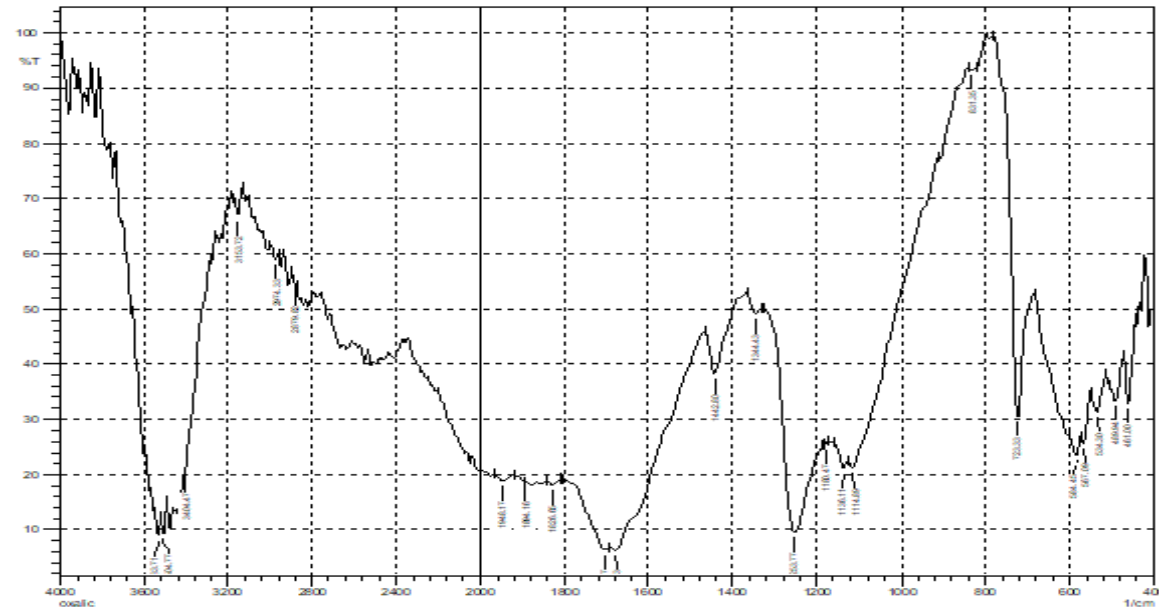

Figure 4. FTIR spectrum oxalic acid dihydrate

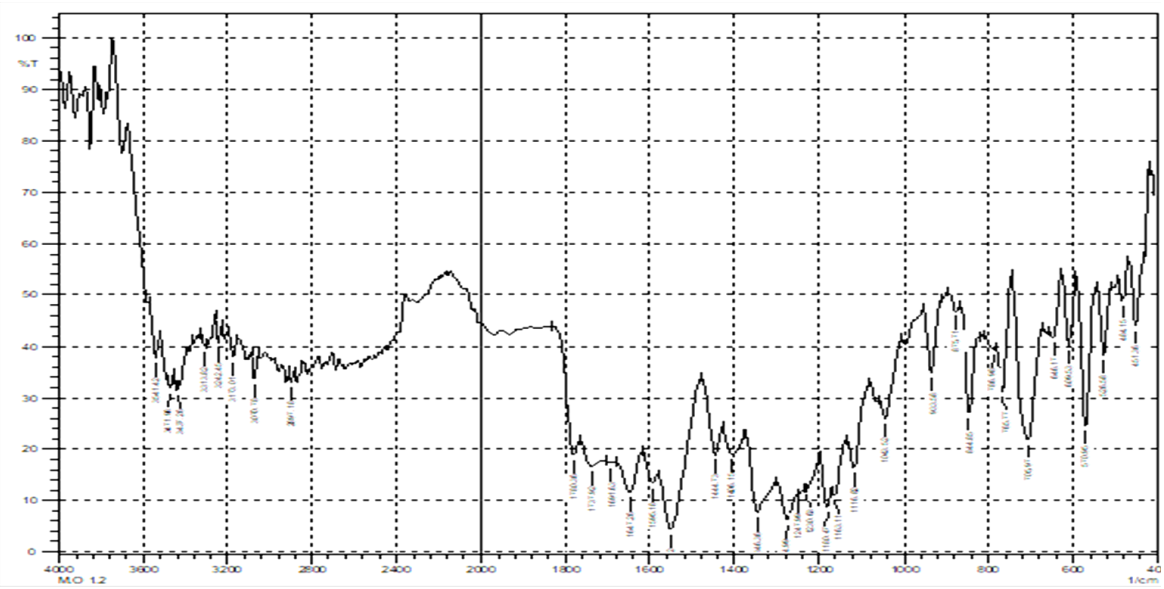

Figure 5. FTIR spectrum of F6

In-vitro release study

In vitro release profiles of pure meloxicam and the prepared formulations (F1-F9) are illustrated in **(Figure 6)**. The dissolution rates were in the following order: F6>F2>F1>pure meloxicam>F5>F3>F4>F8>F9>F7.

Higher dissolution rates achieved by F6, F2, and F1 over that of the pure meloxicam could be attributed to the ability of cocrystals to generate a state of supersaturation (the drug concentration exceeds its equilibrium solubility) during their dissolution [22]. Formulation F6, which contains meloxicam: oxalic acid dihydrate (1:2) was superior compared to pure meloxicam and other formulations as it liberated 87.77% at the end of 120 minutes, while meloxicam released 58.46% at the same time interval. Therefore, F6 was selected as the optimum formulation.

On the other hand, the deterioration in the dissolution rate recorded for the other six formulations may be due to a modulation in the crystal habit leading to densely packed molecules within cocrystals [23].

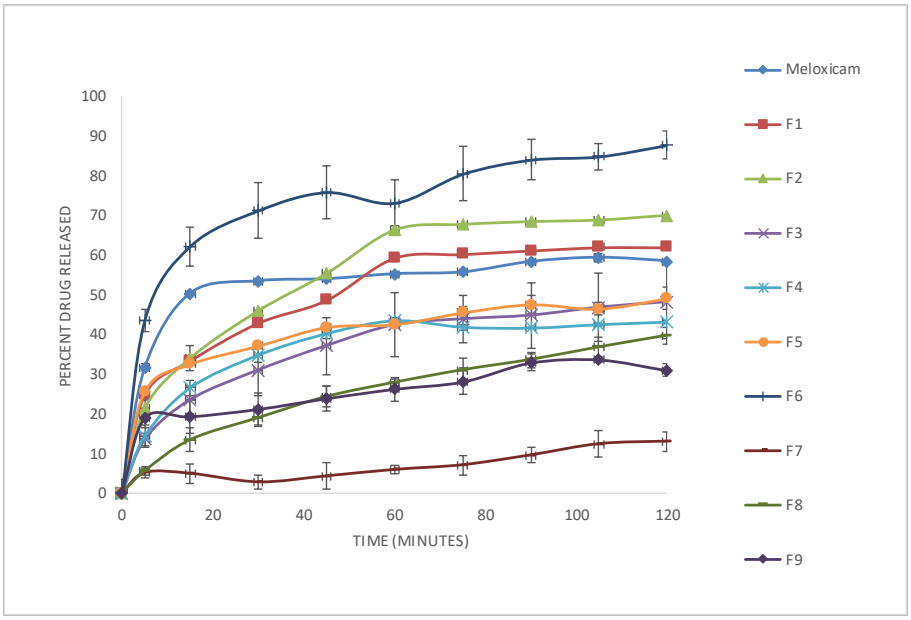

Figure 6. In vitro release profiles of meloxicam, (F1-F9)

Conclusion

It can be concluded that among the coformers explored throughout the study, oxalic acid dihydrate successfully produced cocrystals that achieved a significant enhancement in the dissolution rate compared to meloxicam.

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Ethics statement: None

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