Journal of Chemical and Pharmaceutical Research, 2014, 6(11)

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Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(11):263-267

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Enhancement of dissolution rate of Meloxicam by co-grinding technique using Hydroxypropyl methylcellulose

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ABSTRACT

The present study investigates the effect of solid state grinding of meloxicam as a model of poorly water-soluble drug with hydrophilic polymer hydroxypropyl methylcelluloce (HPMC) 6 cps by using ball milling machine on dissolution rate of meloxicam. The ratio of meloxicam to HPMC were 1:1, 1:3, and 1:5. The solid state interaction of co-ground and physical mixture was evaluated by X-raypowder diffraction, thermal DTA, and SEM. The dissolution studies were conducted in USP type II apparatus. The result of X-raypowder diffraction analysis showed that the co-ground of meloxicam with HPMC decreased the drug crystallinity. The endothermic peak of meloxicam from co-ground products shifted to low temperature and peak intensity decreased significantly. X-ray powder diffraction and DTA analysis showedthe transformation of crystalline state of meloxicam to amorphous one by co-grinding with HPMC. SEM results showedthe co-ground mixture has agglomerate form.The highest in dissolution rate was observed with co-ground products of meloxicam and HPMC (ratio 1:3) compared to the intact meloxicam, ground meloxicam and its physical mixture.

Keywords :meloxicam, hydroxypropyl methylcellulose, co-grinding, dissolution rate

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INTRODUCTION

Meloxicam (MEL) is a non steroidal anti-inflammatory drug, belongs to oxicam derivative group that used to relief of rheumatoid arthritis, osteoarthritis, and other joint diseases. MEL is practically insoluble in water and is categorized as a Class II drug of the Biopharmaceutical Classification System (low solubility and high permeability) [1]. The drug with low solubility often shows low bioavailability when administered orally, and the dissolution rate of drug in the gastrointestinal tract fluid becomes a rate–limiting step. Therefore, it is important to increase dissolution rate of MEL [2].

Many strategies have been applied to improve dissolution rate of MEL such as formation of inclusion complex with cyclodextrin, solid dispersion and co-crystal formation [3, 4, 5]. One interesting and simple method developed to increase the rate of dissolution and bioavailability of drugs that are poorly soluble is co-grinding technique with hydrophilic polymers. Co-grinding will enhance the effect of solubilization and bioavailability. Co-grinding technique is a simple and environmental friendly because it does not require organic solvents compared to other solubility enhancement techniques [6, 7]. Hydroxypropyl methylcelluloce (HPMC) is one of a hydrophilic polymer that can be used to improve the solubility, bioavailability, and dissolution rate of poorly soluble drugs [8].

The aim of this present study is toevaluate the mechanism of increase in dissolution rate of MEL in co-ground product with hydroxypropyl methylcelluloce. In addition, solid state interaction between meloxicam and HPMC by co-grinding method was characterized by X-ray powder diffraction, differential thermal analysis, and scanning electronmicroscopy analysis.

EXPERIMENTAL SECTION

Materials

Meloxicam was purchased from Indofarma Ltd. (Jakarta, Indonesia). HPMC was purchased from Pyridam Ltd. (Jakarta, Indonesia) and all other chemicals or solvents were of analytical grade.

Methods

Preparation of Physical Mixtures (PM)

The physical mixtures with ratio (w/w) of meloxicam to HPMC 1:1, was uniformly blended by using spatula in a mortar for 30 minutes. The prepared mixtures were stored in airtight container till further use.

Preparation of Co-Ground Mixtures (CG)

Meloxicam and HPMC with polymer ratios (w/w) of 1:1, 1:3, and 1:5 were co-ground at 100 rpm for 120 minutes using a ball mill apparatus (Pascal Engineering).The process consists of four cycles,with each cycle consists of 30 minutes. After completion of one cycle, the powder was removed from the wall of the vessel with spatula for proper grinding.

X-Ray Powder Diffraction

Analysis of X-ray powder diffraction was performed at room temperature by using a diffractometer. Measurement conditions as follows: the target metals Cu, Kα filter, voltage 35-40kV, current 40 mA, the analysis was performed at 2 the arange of 2-45°. The sample is placed on the sample holder(glass) and leveled to prevent particle orientation during sample preparation

Differential Thermal Analysis (DTA)

Analysis was performed by using a DTA. Heating temperaturewas started from20-250^{0}C, with a heating rate10^{0}C perminute

Scanning Electron Microscopy (SEM)

Samples were placed on the sample holder and coated with gold aluminum with a thickness of10 nm. Samples were observed with various magnification using SEM instrument(JEOL, Japan). Voltage was setat15-20kVand current12 mA.

Dissolution Studies

Dissolution studies were carried out by using USP paddle method. Samples equivalent to 50 mg of meloxicam was added to 900 ml of phosphate buffer pH 7.5 at 37 ± 0,5°C and stirred at 100 rpm. 5 ml of aliquot was withdrawn at different time in intervals. An equavolume of fresh dissolution medium was replaced (maintained at the same temperature). Samples were assayed spectrophotometrically at 362.2 nm.

RESULTS AND DISCUSSION

Grinding is widely used to reduce the particle size of poorly soluble drug to enhance the dissolution rate and bioavailability. This technique is relatively simple and easy to scale up.However, the energetic input during grinding process is often induced the formation of aggregate of fine particles, in addition, it may also lead to solid state transformation, crystal defects, amorphization and increased solid state reactivity [9, 10]. These problems can be solved by co-grinding the poorly soluble drugs with hydrophilic polymer such as gelatin, povidone and PEG [6, 11]. In present study, meloxicam is used as a model of poorly soluble drug and HPMC is a hydrophilic polymer and it is evaluated the effect of co-grinding with polymer on solid state properties of meloxicam and also its impact on dissolution rate of meloxicam powder.

Analysis of the X-ray powder diffraction is a powerful method to characterize solid state interaction and evaluate the effect of grinding on the solid phase and the changes of crystallinity degree in solid compounds from co-ground products. The intact meloxicam shows solid crystalline, it is shown by the presence of sharp characteristicsof interference peaks at 2 value 12.9, 14.8, 18.4 and 25.9 (Fig. 1A). X-ray diffractogram of HPMC shows diffuse pattern indicating its amorphous nature (Fig. 1B). Grounded meloxicam(Fig. 1C) showssimilar interference peaks with intact meloxicam, but the intensity is slightly lower than the intact meloxicam. Itis shown that the crystal defect of crystalline phase of meloxicam during grinding [9]. X-ray diffractionpattern ofphysicalmixture ofMEL-HPMC (1:1) displaysthe high characteristic peaks of MEL which showa high degree of crystallinity (Fig. 1D). X-ray diffraction pattern of co-ground product of MEL – HPMC (1:1; 1:3 and 1:5) is presented in Figure 1E – F. Characteristic of peak intensities of MEL at 2 Θ = 12.9, 14.8, 18.4 and 25.9 is gradually decreased with the increase of polymer HPMC ratio in co-ground mixture. Relative degree of crystallinity (RDC) was calculated by comparing

characteristic peak intensities in the diffractogram of samples with those of the intact drug (RDC = I_{sample} /$I_{intact\ drug}$). One of characteristic peak intensities at 2 Θ = 14.8 was used for calculating RDC of the samples [12]. Peak intensity in diffractogram was determined by using *win PLOTR* software (version March 2007). The RDC of physical mixture (1:1) and co-ground products (1:1; 1:3 and 1:5) were 0.721; 0.512; 0.372 and 0.310 respectively. This result shows a decrease in crystallinity degree of MEL upon co-grinding by hydrophilic polymerof HPMC. Crystalline solid of MEL undergoes transformation phase to amorphous solid. Degree of crystallinity influences of drug dissolution, an amorphous and metastable form will dissolve at fastest rate. It is due to its higher internal energy and greater molecular mobility, which enhance thermodynamic properties compared to crystalline state [13].

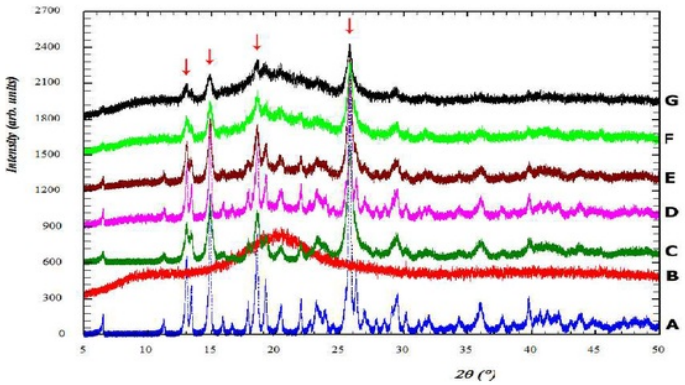

Figure 1 PXRDPattern : (A) intact meloxicam, (B) HPMC, (C) grounded meloxicam, (D) physical mixture 1:1 , (E) co-ground 1:1, (F) co-ground 1:3, and (G) co-ground 1:5

Thermal analysis of DTA was performed to evaluate the interaction between meloxicam and HPMC in the solid state (Fig.2). Meloxicam shows a sharp endothermic peak at a temperature of 254.6°C which is the melting point of meloxicam. DTA thermogram of HPMC showsabroad endothermic peak at 130 – 165 °C which is attributed to the glass transition temperature(Tg)[14]. Thermogram of co-ground meloxicam and HPMC (1:1) exhibits a weak broad endothermic at 149 °C and shifts to lower temperature at 238 °C, suggesting that meloxicam is either disperse in HPMC polymer chains or partially transform the crystalline state to the amorphous one.

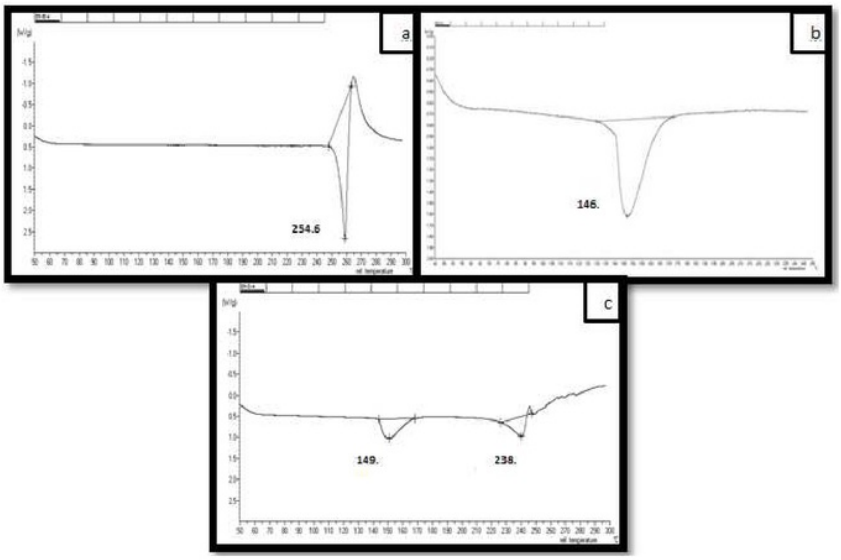

Figure 2 DTAThermograms : (a) intact meloxicam, (b) HPMC and (c) co-ground 1:1

The SEM photographs of MEL, HPMC, physical mixture and co-ground products are presented in Figure. 3. MEL has irregularly shaped particles. Rod-like shape HPMCis sticking together. In physical mixture (Fig. 3C), meloxicam disperses in HPMC, but it can still be distinguished between meloxicam and HPMC. Co-ground product (1:1) has an irregular shape or amorphous state, formed agglomerates and larger size than the physical mixture (Fig. 3D).

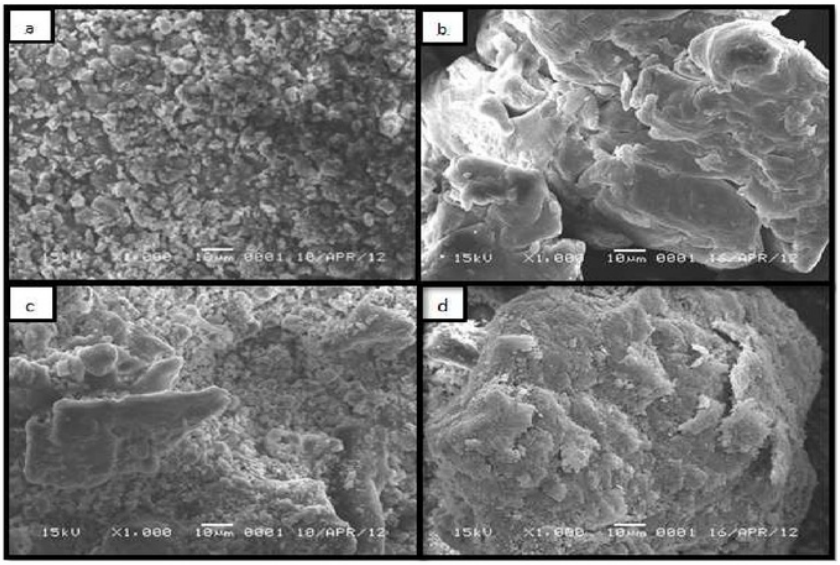

Figure 3 SEM photographs of (a) intact meloxicam, (b) HPMC, (c) physical mixture 1:1,and (d) co-ground 1:1 (1000x magnification)

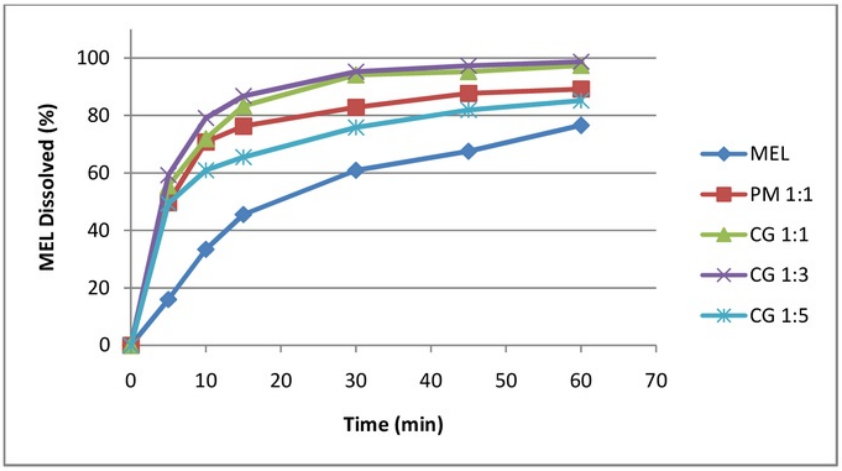

Figure. 4. Dissolution profile for intact meloxicam, physical mixture (1:1), co-ground product (1:1; 1:3 and 1:5)

The dissolution profiles of co-ground products compared tothat of its physical mixture and intact drug are shown in Fig. 4. Dissolution data are presented as dissolution efficiency over 60 minutes in Table 1. Dissolution studies emphasize that there is significant enhancement in the dissolution rate of meloxicam from co-ground products and its physical mixture (1:1) compared to intact meloxicam and ground meloxicam except for co-ground productsof meloxicam – HPMC (1:5). The enhanced drug dissolution rate from co-ground with HPMC could be attributed to the solubilization effect of HPMC as surface active agent that increasing wettability of meloxicam particles in dissolution medium. In addition, in the presence of HPMC, amorphous solid of meloxicam was stabilized and inhibited phase transition into crystalline phase [7, 8]. The increasing HPMC concentration in co-ground products (1:5) reduces meloxicam dissolution rate due to formation of gelatinous and stronger layer around the drug particles which might sustain the release of drug molecules into dissolution medium [7]. The slight increase of dissolution rate of the physical mixtures of MEL-HPMCcan be resulted from the higher wettability of drug particles in presence

of hydrophilic polymer (HPMC), which can reduce the contact angle between solid drug particles and dissolution medium [15]. In general, enhanced dissolution rate of drug molecules from co-ground products can be attributed to the particle size reduction and embeds drug particles into hydrophilic polymer chain and amorphism of crystalline form of insoluble drug by the grinding process.

Table. 1. Percentage of dissolution efficiency (DE)

	DE (%)
MEL	53.38 ± 1.37
Physical mixture 1:1	76.50 ± 0.32
Co-ground 1:1	84.01 ± 0.85
Co-ground 1:3	86.45 ± 0.24
Co-ground 1:5	70.17 ± 0.88

CONCLUSION

In this present study, it is demonstrated that co-grinding technique of MEL with HPMC reduces crystallinity degree of crystalline phase of MEL. In addition, co-ground product of MEL-HPMC (1:3) has the highest dissolution rate.

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