Improving solubility and dissolution of meloxicam by solid dispersion using hydroxypropyl methylcellulose 2910 3 cps and nicotinamide

by Retno Sari

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Improving solubility and dissolution of meloxicam by solid dispersion using hydroxypropyl methylcellulose 2910 3 cps and nicotinamide

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Abstract:
Background: Solid dispersion (SD) represents a good method for enhancing the solubility of poorly water-soluble drugs. Meloxicam (MLX), a nonsteroidal anti-inflammatory drug has poor solubility in water. Hydroxypropyl methylcellulose (HPMC) 2910 3 cps, a hydrophilic carrier and nicotinamide (NC), a hydrotropic agent can be used as matrix of SD. The aim of this study is to investigate the effect of HPMC 2910 3 cps and NC as SD matrix on the solubility and dissolution rate of MLX.
Methods: The SD of MLX was prepared by solvent evaporation method using methanol as solvent. The SD formulations composed of HPMC and NC in different ratios (1:1:1, 1:2:2, 1:2:1, 1:2:2). The physical state of MLX SD were characterized by Differential Thermal Analyzer (DTA), Fourier Transform Infrared Spectroscopy, powder X-ray diffractometer (PXRD), Scanning Electron Microscopy (SEM). The solubility and dissolution of the MLX SD were also evaluated.
Results: The results of differential thermal analysis (DTA) showed that the melting point of MLX SD was lower than MLX further the X-ray diffractogram showed a decrease of the crystallinity of MLX in SD. Those indicated that MLX was dispersed molecularly in SD. The SD showed a widening transmission peak at 3000–3500 cm^{-1} which resembled the peak of pure MLX transmission. It indicated that intermolecular hydrogen bonds were formed between MLX, HPMC, and NC. The solubility and the dissolution efficiency (ED_{60}) of SD with MLX-HPMC 2910 3 cps-NC = 1:2:1 increased 3.59 times and 1.50 times higher then MLX substance.
Conclusions: MLX-HPMC-NC SD system increased the solubility and dissolution of MLX. The SD with MLX-HPMC 2910 3 cps-NC ratio of 1:2:1 had the highest solubility and ED_{60} compared to the other SD formulas.

Keywords: dissolution, hydroxypropyl methylcellulose 3 cps (HPMC 3 cps), meloxicam (MLX), nicotinamide (NC), solubility, solid dispersion

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Introduction

Solid dispersion (SD) is one of the most promising strategies to improve the oral bioavailability of poor water-soluble drugs. The term "solid dispersion" refers to the dispersion of one or more active ingredients in an inert carrier or matrix in the solid state [1]. The SD method is commonly applied to increase the dissolution rate and bioavailability of poorly soluble drugs due to its simple, cost-effective, and beneficial characteristics [2].

Meloxicam (MLX) is a Biopharmaceutics Classification System (BCS) class II compound, an oxicam derivative nonsteroidal anti-inflammatory drug with anti-inflammatory, antipyretic, analgesic activities, and low gastrointestinal toxicity. Poor wettability and low solubility of MLX (6 μg/mL) [3] cause slow oral absorption and poor bioavailability. Application of the SD could be a key factor for improving the solubility and bioavailability of MLX.

The solubility and dissolution rate are two of the critical factors in the absorption process, especially for oral administration. The bioavailability of an active pharmaceutical ingredient with low solubility given orally depends on the dissolution rate of the dosage form [4]. The mechanism of SD to improve the dissolution rate

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is by dispersing the drug molecularly in polymeric carriers thereby causing size reduction and surface area enhancement [5].

The SD consists of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly in amorphous particles (clusters) or in crystalline particles [6].

Hydroxypropyl methyl cellulose (HPMC), a cellulose derivative, is a hydrophilic polymer that can improve the solubility of the crystalline drug. HPMC exhibits a high capability to form a solid solution with poor water-soluble drugs. It is reported that HPMC with a low viscosity, such as HPMC 3 cps, is commonly used as a matrix in the SD [7].

HPMC-nicotinamide (NC) is well known to increase the solubilities of drugs such as nifedipine, nitrendipine [7], [8], atorvastatin [9] when formed as a SD with these drugs. NC as a hydrotropic agent exhibited a salting in effect on the HPMC solutions resulting in an increase in gelation temperatures. These effects are considered to be due to the hydrogen bonding of NC to HPMC molecules, which was suggested by a shift to a longer wavelength of the ultraviolet (UV) spectra of aqueous NC solutions by the addition of HPMC. These results suggest that NC has an affinity with the hydrophilic groups of HPMC [8].

The objective of this study was to determine the characterization, solubility, and dissolution of MLX-HPMC 2910 3 cps-NC SD. The physicochemical characterization was investigated by Fourier transform infrared (FTIR) spectroscopy, differential thermal analysis (DTA), powder X-ray diffraction (XRD), and scanning electron microscopy (SEM). The solubility and dissolution test of MLX were studied to determine the effect of SD on the solubility and the dissolution efficiency of MLX.

Materials and methods

Materials

Materials used in this study were of pharmaceutical grade. MLX was supplied by Dexa Medica, Palembang, Indonesia; HPMC 2910 3 cps was purchased from Vivapharm, Surabaya, Indonesia; NC was purchased from Western Drugs Limited, India. Sodium lauryl sulfate (SLS) and methanol (pro analytical) were obtained from Merck (Germany).

Methods

Preparation of MLX-HPMC-NC SD

The SD of MLX-HPMC-NC was prepared in the ratios 1:1:1 (SD1), 1:1:2 (SD2), 1:2:1 (SD3), and 1:2:2 (SD4) (w/w) by dissolving MLX in methanol and HPMC, and NC in water. For SD1, 250 mg MLX was dissolved in 750 mL ethanol, and 250 mg HPMC and 250 mg NC each were dissolved in 20 mL water. The mixture solution was evaporated at room temperature. Then the dispersions were sieved (50-mesh) and stored in a desiccator.

Preparation of the MLX-HPMC-NC physical mixture

The powders of MLX, HPMC, and NC were each sieved (50-mesh). The physical mixture (PM) was prepared by mixing MLX-HPMC-NC at ratios 1:1:1 (PM1), 1:1:2 (PM2), 1:2:1 (PM3), and 1:2:2 (PM4) (w/w) in a mortar.

DTA evaluation

The thermal analysis of the samples was performed using DTA (Mettler Toledo FP85 TA Cell, Swiss). The temperature was calibrated with indium. A sample of 5–7 mg was placed on a closed aluminum pan. The DTA was programmed at a temperature range of 30 °–300 °C with a heating rate of 10 °C per min.

PXRD evaluation

The PXRD evaluation was conducted at room temperature (±25 °C) using a diffractometer (X'Pert Phillips, Netherlands). The measurement conditions were Cu metal target, Kα filter, 35 kV voltage, and 40 mA current. The analysis was performed at the range of 2 theta 5–50°. The sample was placed on the sample holder and leveled to prevent the orientation of the particles during sample preparation.

FTIR evaluation

A dispersion about 1% of a powder sample in potassium bromide was prepared to form a pellet. Infrared spectra of the samples were observed using infrared spectrophotometer (Spectra One, Perkin Elmer, USA) at a wavenumber range of 400–4000 cm^{-1}.

SEM evaluation

The powdered sample was placed on a n aluminum holder and coated with gold with a thickness of 10 nm. The samples were then observed at 2500 magnification using SEM (Jeol JSM-7900F, Japan). Voltage and current were set at 20 kV and 12 mA.

MLX solubility test

The solubility test on SD and PM of MLX-HPMC-NC and MLX was performed at room temperature (28 °C ± 0.5 °C). Precisely, 15 mg of MLX or the PM and SD with the equivalent amount of 15 mg meloxicam were accurately weighed and put into 4 ml of distilled water and stirred in a circulating water bath (Julabo PURA 22, Germany) for 6 h. Subsequently, 4 ml of the samples were taken and filtered with 0.45 µm membrane filter (Millipore, USA). Samples were measured using UV-vis spectrophotometer (Hitachi UH5300, Japan) at a maximum wavelength of 362 nm.

MLX dissolution test

The dissolution test was carried out using a dissolution test apparatus (Erweka DT 700, Germany) with paddle mixer. A sample equivalent to 15 mg of MLX was added to 900 mL distilled water containing 0.5% w/v SLS at 37 °C ± 0.5 °C and stirred at 50 rpm. A 5.0 mL sample was withdrawn at time intervals 5, 10, 20, 30, 40, 60, and 120 min and filtered with 0.45 µm membrane filter. The samples were determined by UV-visible spectrophotometer (Hitachi UH5300, Japan) method at a wavelength of 362 nm. The amount of MLX dissolved was calculated. To determine the difference in dissolution profile among the groups, the dissolution efficiency at 60 min (DE_{60}) was calculated and statistically analyzed using one-way analysis of variance (ANOVA) test at $\alpha = 0.05$.

Results

DTA evaluation

Thermal analysis of DTA was performed to evaluate the interaction between MLX, HPMC, and NC in the solid state. The thermograms of MLX, PM1, PM2, PM3, PM4, SD1, SD2, SD3, SD4 were shown in Figure 1. MLX had an endothermic peak at 255 °C (41.7 J/g) which was the melting point of MLX. It indicated that MLX was in the crystalline form [10]. The thermogram of HPMC had a widened endothermic peak around 220 °C indicating a glass transition condition, and NC had an endothermic peak at 131 °C. From Figure 1, two endothermic peaks of all PMs of PM1, PM2, PM3, PM4 were observed at 114.9 °C and 220 °C; 120.4 °C, and 219 °C; 107.9 °C and 230 °C; 113.8 °C and 229.7 °C. The SD thermogram also had two endothermic peaks, the SD1, SD2, SD3 endothermic peak with melting temperature of 91 °C and 221.1 °C; 113.6 °C and 241.7 °C; 93.0 °C and 214.6 °C, and the SD4 had three endothermic peaks at 100.5 °C, 224.3 °C, and 287.0 °C. The shifting of the endothermic peak indicated that MLX had dispersed molecularly within the HPMC and NC [11].

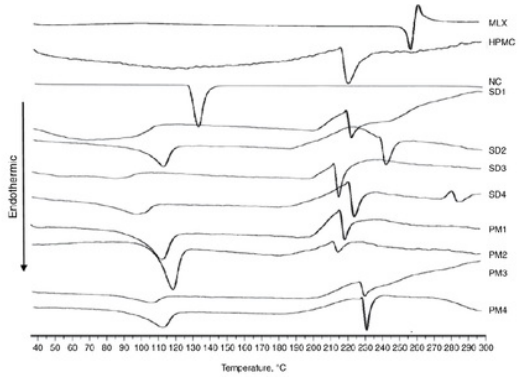

Figure 1: Differential thermal analysis thermograms of meloxicam (MLX), hydroxypropyl methylcellulose (HPMC), nicotinamide (NC), solid dispersion (SD)1, SD2, SD3, and SD4, physical mixture (PM)1, PM2, PM3, and PM4.

PXRD evaluation

The results of PXRD analysis in Figure 2 showed the diffraction pattern of MLX crystalline phase with specific interference peaks at angle 2θ = 13.3, 14.9, 18.5, 22.6, 25.8. In the diffractogram of the PM, specific peaks of MLX emerged, indicating that the crystallinity of MLX remained unchanged in the PM. The diffractogram of SD showed decreases in the intensity of diffraction peaks and the loss of diffraction peaks at 2θ = 14.9 and 22.6, respectively. Some peaks of MLX also appeared in SD but with lower intensities, suggesting a decrease of MLX crystalline in SD form.

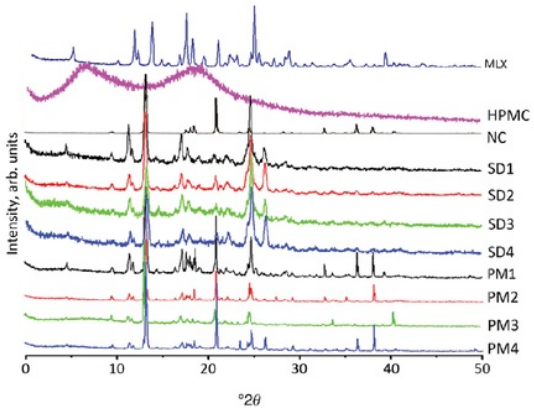

Figure 2: X-ray diffractograms of MLX, HPMC, NC, SD1, SD2, SD3, SD4, PM1, PM2, PM3, and PM4.

FTIR evaluation

The FTIR spectra of MLX, HPMC, NC, PM1, PM2, PM3, PM4, SD1, SD2, SD3, and SD4 were presented in Figure 3. The FTIR spectroscopy is used to examine the changes in physical and chemical structures of a material [12]. In the infrared spectrum, the absorption bands of specific aromatic functional groups of MLX were 3282 cm^{-1}, (secondary amine strech), 2966 cm^{-1} (C-H stretch), 1615 cm^{-1} (NH_2 scissoring vibrations), and 1150 cm^{-1} (S=O strech). The HPMC had an absorption band of specific functional groups, C-O-C at a wavenumber of 1050 cm^{-1}, and –OH group at a wavenumber of 3425 cm^{-1}. The NC had absorption bands of specific funcional groups, 3347 and 3150 (N-H amine primer stretch), and 1613 cm^{-1}(NH_2 stretch). The spectra of the SD system showed that the absorption band had widened and shifted at 3300–3500 cm^{-1}, similar to the absorption band of the MLX.

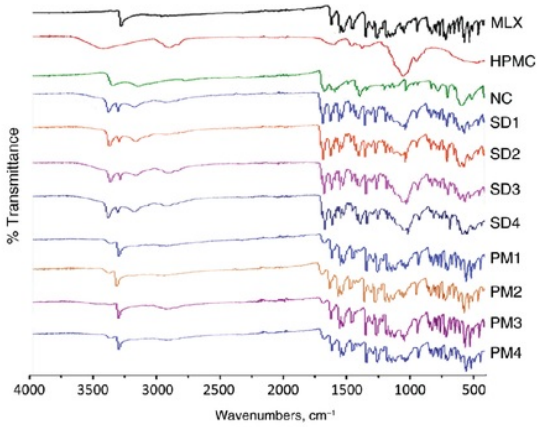

Figure 3: Infrared spectrograms of MLX, HPMC, NC, SD1, SD2, SD3, SD4, PM1, PM2, PM3, and PM4.

SEM evaluation

The results of morphological observations on crystal habit of MLX, PM3, SD3 were shown in Figure 4. The surface morphology of the PM3 observed using SEM showed MLX dispersing in the HPMC and NC matrix. The MLX showed a crystalline form with rectangular shapes, HPMC showed the prismatic form and fibrous shape, and the NC showed a crystalline form. From the SD3 morphology, it was observed that SD3 had a different morphology from the PM3. The particles of each component were no longer visible. It proved that the SD of MLX-HPMC 2910-NC was successfully formed.

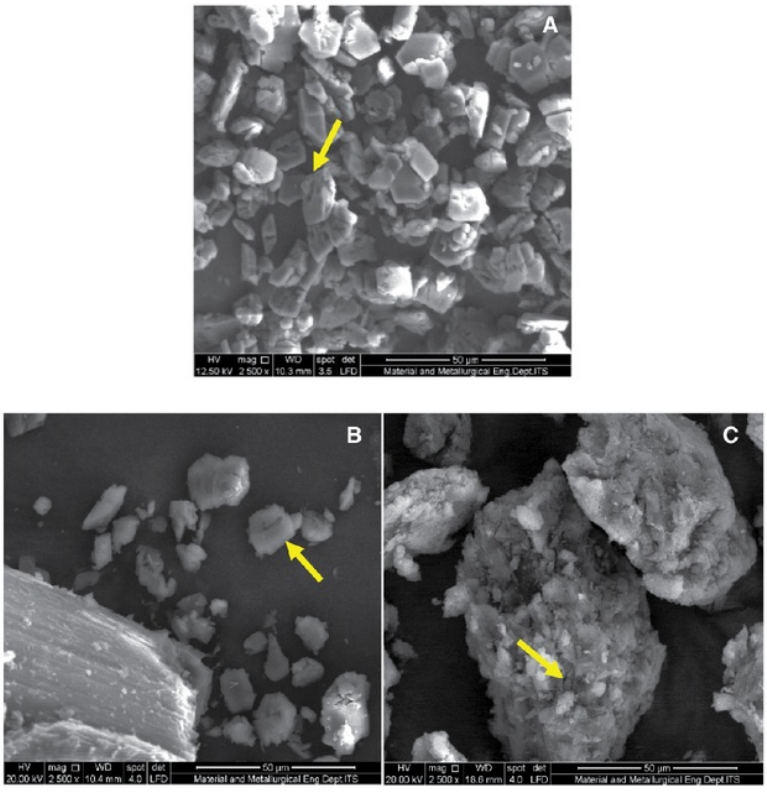

Figure 4: Scanning electron microscopy micrograph of MLX (A), PM3 (B), and SD3 (C) at magnification 2500×. Yellow around indicated specific crystal morphology for each sample.

Solubility test

The solubility test result in Figure 5 showed that all SDs had greater solubility compared to MLX and PM. The solubility of MLX from SD was increased up to 3.6 times and 2.5 times compared to MLX substances and PM, respectively. The solubility enhancement of SD was due to the formation of molecular dispersion of MLX in the HPMC 2910 as hydrophilic matrix and NC as hydrotropic agent. The solubility test showed that the percentage of MLX dissolved increased following the increasing in HPMC amount. The results of the one-way ANOVA statistical analysis showed that the solubility of MLX and all PM and SD composition were significantly different at $p < 0.05$, except between PM2 and MLX; PM2 and PM1.

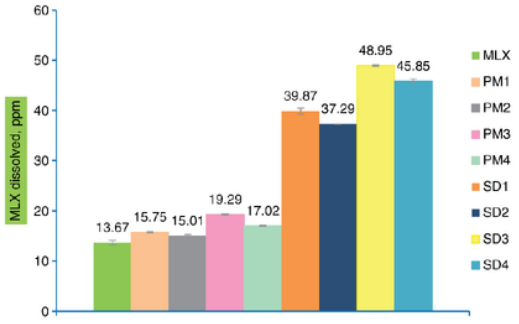

Figure 5: The solubility profile of MLX, HPMC, NC, PM1, PM2, PM3, PM4, SD1, SD2, SD3, SD4 in distilled water at 28 °C ± 0.5 °C.

Dissolution test

The dissolution test results of MLX, HPMC, NC, PM1, PM2, PM3, PM4, SD1, SD2, SD3, and SD4 were presented in Figure 6. The dissolution efficiency at 60 min (DE_{60}) (Table 1) showed that the solubility of MLX from SD became 1.5 times higher than the MLX substance. But the one-way ANOVA statistical analysis at p value < 0.05 followed by Tukey's post-hoc test which showed that the DE_{60} among the SD formula were not significantly different. However, DE_{60} was as follows: MLX < PM1 < PM2 < PM3 < PM4 < SD1 < SD2 < SD4 < SD3.

Table 1: Dissolution efficiency at 60 min of meloxicam (MLX), physical mixture (PM), and solid dispersion (SD) of MLX-hydroxypropyl methylcellulose (HPMC) 2910, 3 cps-nicotinamide (NC) at various ratios (n = 3).

Mean	MLX	PM 1	PM2	PM3	PM4	SD1	SD2	SD3	SD4
ED_{60} (%)	56.08	76.54	76.90	78.76	79.62	82.16	82.56	84.13	83.45
SD	1.55	5.17	4.73	4.04	4.92	0.44	0.40	0.57	0.12

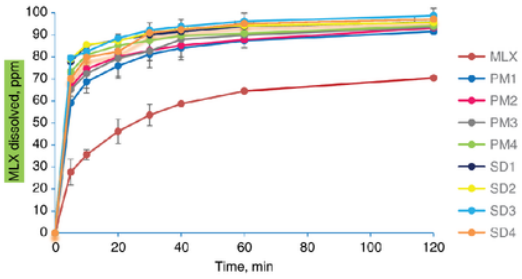

Figure 6: Dissolution profile of MLX, HPMC, NC, PM1, PM2, PM3, PM4, SD1, SD2, SD3, and SD4 in distilled water containing 0.5% w/v sodium lauryl sulfate (SLS) at 37 °C ± 0.5 °C.

Discussion

From the thermograms of PM and SD, it was seen that there were two endothermic peaks except for SD3 with a high amount of HPMC. At SD4 with ratio HPMC 2910 and NC = 2:2, three endothermic peaks were observed at 100.5°, 224.3°, and 287°. The peak appeared at 287° and was similar to the MLX peak as at the higher ratio of HPMC and NC (2:2) there was more hydrogen bonding between NC and HPMC that affected the interaction between the HPMC 2910 with the MLX. All SDs showed the shifting of the melting point to a lower temperature and the decrease in the enthalpy value. It was due to the decreasing bond energy among molecules that could reduce the energy required to melt the substance. The decrease and/or loss of endothermic peak means a decrease in crystallinity and the MLX was molecularly dispersed in the HPMC and NC matrix [12]. The results in PXRD demonstrated the changes of MLX crystallinity to amorphous form. However, in SD system, an amorphous form of MLX may not be totally obtained. The reasons could be the particle size reduction and the interaction between MLX and the polymer. The amorphous form may be present but only partially since the DTA thermogram and PXRD diffractogram showed some crystal peaks of MLX. The intensity of SD3 system was lowest compared to other SD. It indicated a decrease in the peak intensity of the diffractogram of the SD system as the amount of HPMC increased. As the amorphous form is generally more soluble than the crystalline form, the decrease in drug crystallinity leads to the enhancement in drug solubility and release rate, which could improve the drug bioavailability [13], [14]. The characteristic peaks in FTIR spectroscopy representing specific functional groups were detected in all the samples; the widening and shifting of the peak in SD indicate that intermolecular hydrogen bonds are formed between MLX, HPMC, and NC. The SD3 showed a solid aggregate and only slightly visible small MLX crystals were dispersed within the HPMC and NC matrix [15] indicating the formation of the SD.

The solubility of MLX had increased by the formation of SD system, due to the physical changes that decrease the particle size. Particle size reducing can enhance the particle surface area which contacts with the solvent. In addition, the SD3 showed the highest solubility. This is possibly due to a higher amount of polymer used in SD3 that inhibit crystal formation, which in turn increased its solubility [16]. The dissolution study showed that MLX has the lowest dissolution profile due to its hydrophobic characteristics. The SD3 had the highest dissolution efficiency caused by the higher amount of HPMC. The HPMC could coat the MLX and increased wetting effect. It also prevent aggregation of MLX so the particles retained in small particle size. The particle size reduction increased the particle surface area which contacts with media, so it enhance the dissolution of MLX in SD system [12]. NC increased the dissolution of the drug because of the pyridine ring, and the hydrophilic amide group on NC has hydrotropic properties which can help increase the solubility. The bond between NC and water (solvent) makes self-aggregation occur. NC interacts with HPMC and MLX solutes to form complexes; this complex causes higher solubility in water [17], [18].

Conclusions

The present study indicated that MLX-HPMC-NC SD had lower crystallinity compared to the MLX substance and the PM, which resulted in an increase in the solubility and the dissolution of MLX. The SD3 (1:2:1) had the highest solubility and ED_{60} compared to the other formula. The solubility and the dissolution (ED_{60}) of SD3 increased up to 3.6 times and 1.5 times more than the MLX substance. These findings may contribute to the enhancement of the bioavailability of MLX that could further improve the drug efficacy.

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Competing interests: Authors state no conflict of interest.

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