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Preparation and Characterization of Co-grinding Tablet of Meloxicam with PVP K-30

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ABSTRACT

Preparation of tablets dosage form from co-grinding of meloxicam with PVP K-30 has been done. Meloxicam and PVP K-30 in a weight ratio of 1:3 were grounded for 2 hours. The interaction of co-grinding solids state were evaluated by FT-IR. Tablets were prepared by direct compression method in three formulas: co-grinding of meloxicam (F1), physical mixtures meloxicam (F2), and intact meloxicam tablet (F3). The evaluations conducted for tablets were weight variation, size variation, hardness test, friability test, disintegration time, and tablet dissolution. Dissolution test was carried out for 60 minutes in phosphate buffer pH 7.5. The dissolution test results for F1, F2, and F3, were $71.65\% \pm 2.32$; $51.66\% \pm 5.38$; $35.71\% \pm 2.96$, respectively. Co-grinding meloxicam tablet showed the highest dissolution rate compared to physical mixture and intact meloxicam tablet ($p < 0.05$).

Keywords: Co-grinding, meloxicam, PVP K-30, tablet, dissolution test

INTRODUCTION

Meloxicam (4-hidroxy-2methyl-N-(5-methyl-2-thiaolyl)-2H-1,2benzothiazine-3-carboxamide 1,1-dioxide) is a non-steroidal anti-inflammatory drug (NSAID) of the group oxicam derivative. It is used to treat rheumatoid arthritis, symptomatic osteoarthritis and other joint pains [1]. Meloxicam is practically insoluble in water and acidic mediums. According to the biopharmaceutical classification system (BCS), this drug is categorized as class II, low solubility but high permeability [2]. For poorly water soluble drugs, the oral absorption is rate limited by dissolution process. The dissolution rate of poorly water soluble drugs can be improved by phase transformation of solid drugs into its high energetic amorphous forms [3,4]. One of the strategies used for the amorphization drugs is by co-grinding the poorly water soluble drug with a hydrophilic polymer such as PVP K-30, PEG, gelatin and HPMC [5,6]. Previous study from our group showed that preparation of co-ground product of meloxicam-PVP K-30 by ball milling apparatus result in an improvement of meloxicam dissolution rate significantly. Co-grinding meloxicam-PVP K-30 generated an amorphous phase [7]. The purpose of the present work was to prepare a co-ground product of meloxicam -PVP K-30 (ratio 1:3) into tablet dosage form. The tablet dosage form was evaluated for physical properties and dissolution rate profile.

MATERIALS AND METHODS

Materials

Meloxicam (Indofarma Ltd, Indonesia), PVP K-30 (Delta Chemical, Indonesia), methanol (Bratachem, Indonesia), distilled water, Avicel® PH 102 (Kimia Farma, Indonesia). Aerosil®, Potassium dihydrogen Phosphate, NaOH were purchased from Bratachem Ltd, Indonesia.

Methods

Co-grinding process

Co-grinding was prepared by mixing meloxicam and PVP K-30 with a weight composition ratio of 1: 3 (5 g: 15 g). The mixture was milled using ball milling apparatus for 2 hours. A physical mixture of meloxicam – PVP K-30 with a weight ratio similar was prepared as comparison and intact meloxicam as control.

Formulation and evaluation of tablet

Co-ground of meloxicam and PVP K-30, a physical mixture meloxicam and intact meloxicam was mixed with Aerosil® and Avicel® PH 102, then homogenized and formed tablet by direct compaction method. The moisture content, bulk and tapped density, flowability, Hausner ratio, and compressibility of powder mixture were tested. 100 Tablets were formulated and each tablet was 150 mg. The formula composition can be seen in Table 1. Tablets formed are tested uniformity of weight and size, hardness, friability, and disintegration time.

Table 1. Formulation of meloxicam tablet 150 mg

Materials (mg)	F1	F2	F3
Co-grinding meloxicam-PVP equal to 15 mg meloxicam	61,692	-	-
Physical mixture meloxicam – PVP equal to 15 mg meloxicam		61,789	-
Intact meloxicam	-	-	15
Aerosil®	0,75	0,75	0,75
Avicel® PH 102	85,558	87,461	134,25

(F1: co-grinding meloxicam-PVP, F2: physical mixing meloxicam-PVP, F3: intact meloxicam)

Dissolution rate profile

In vitro dissolution rate was carried out at 75 rpm speed in phosphate buffer pH 7.5 (900 mL) medium at $37 \pm 0.1^\circ\text{C}$ for 60 minutes according to USP 2009. The amount of dissolved meloxicam was determined by spectroscopy UV-VIS. Dissolution test was conducted for meloxicam co-grinding tablet, meloxicam-physical mixture tablet, and intact meloxicam tablet.

Spectroscopic Infra-Red analysis

The sample was placed on the ATR crystal to cover all surfaces of the crystal. Absorption spectra were recorded with (Fourier Transform Infrared) at wavenumber $4000\text{--}500\text{cm}^{-1}$. Analyses was performed for intact meloxicam, co-grinding meloxicam and physical mixture.

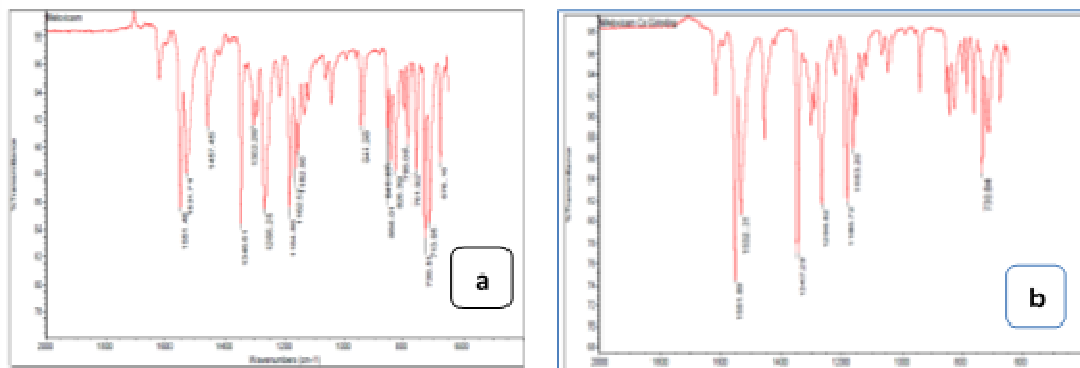
Data Analysis

Data from this study was analyzed statistically using analysis of variance (ANOVA) using SPSS 19.

RESULTS AND DISCUSSION

Spectroscopy infra-red analysis

FT-IR spectroscopy analysis was done to observe the spectrum formed from the powder mixture of co-grinding and physical mixture of meloxicam with PVP compared to intact meloxicam. The test results showed that there was no shift of wave number in the fingerprint region of a physical mixture and co-grinding mixture, which is relatively the same as intact meloxicam. It indicated that, there was no chemical interaction between meloxicam and PVP K-30 after co-grinding process. The infra-red spectrum is shown in Figure 1.



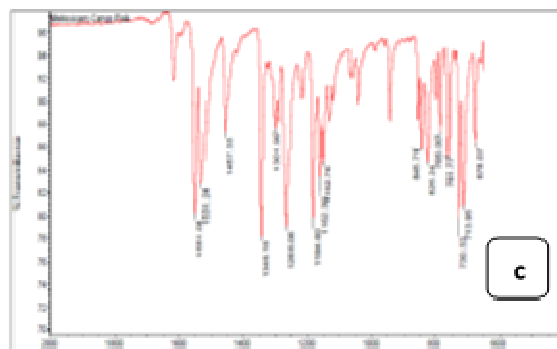


Figure 1. FT-Infra red spectrum of (a) intact meloxicam, (b) co-grinding of meloxicam, (c) physical mixture of meloxicam

Evaluation of powder

General evaluation for powder has been done included moisture content, Flow rate, bulk and tapped density, Hausner Ratio and compressibility test. The results obtained were compared to the requirements in the literature. The test results of the powder evaluation is shown in Table 2.

Evaluation of moisture content showed that co-ground products and physical mixture of meloxicam met the requirements which was in range of 3-5%, while the intact meloxicam was 2.1%. This indicated that intact meloxicam was drier compared to the modified meloxicam. The flowability of a powder is of critical and importance factor in manufacturing tablet dosage forms in order to get uniformity of feed as well as reproducible filling of tablet dies. Meanwhile, high dose variations will occur [8]. A powder has good flow rate at >10g/s. Flow rate of co-grinding meloxicam mixture, meloxicam physical mixture and intact meloxicam were 5.5 g/s, 3.8 g/s and 7.3 g/s, respectively. This results indicated that the flowability of sample were relatively poor. Poor flow property was likely caused by additional, PVP which is hygroscopic material that tends to absorb moisture from the air causing the formulation blend difficult to flow. Results of testing the bulk and tapped, Hausner ratio and compressibility were in accordance with the flow rate.

Table 2. Evaluation formulation blend

Test	F1	F2	F3
Moisture content (%)	4.5	3.5	2.1
Flow rate (g/s)	5.5 g/s	3.8 g/s	7.3 g/s
Bulk density (g/ml)	0.50	0.46	0.44
Tapped density (g/ml)	0.61	0.61	0.61
Hausner ratio	1.22	1.32	1.38
Compressibility (%)	18.03%	24.59%	27.87%

(F1: co-grinding meloxicam-PVP, F2: physical mixing meloxicam-PVP, F3: intact meloxicam)

Evaluation of tablet dosage form

Meloxicam tablets were manufactured for 150 mg in weight which containing 15 mg meloxicam for each tablet. The result of tablets evaluation is shown in Table 3.

Table 3. Tablets evaluation

Evaluations of tablets	Formula		
	F1	F2	F3
Average weight (mg)	147.55 ± 1.12	147.9 ± 0.91	148.7 ± 0.48
Thickness (mm)	2.87 ± 0.04	2.93 ± 0.03	2.93 ± 0.03
Diameter (mm)	6.58 ± 0.03	6.58 ± 0.01	5.50 ± 0.01
Hardness(Kg/cm ²)	8.1 ± 0.74	7.4 ± 0.63	5.1 ± 0.32
Friability (%)	0.23	0.37	0.03

(F1: co-grinding meloxicam-PVP, F2: physical mixing meloxicam-PVP, F3: intact meloxicam)

Differences in the size of each formula can be caused by the presence of additional materials such as PVP that affecting tablet size. Uniformity of the tablet size can affect tablet appearance which will also affect patient acceptance. All tablet formulation (F1, F2, and F3) in this study met the requirement of meloxicam tablet including weight, thickness, size and friability [8]. The hardness of tablet for each formula also met the requirement, which the proceeded meloxicam had greater hardness compared to intact meloxicam. This result was likely due to the different amount of PVP in the tablet. PVP can also act as a binder, which causes the connectivity of power becomes greater and tablet is likely to have great hardness. If the tablet hardness is relatively low, tablet will be easily broken,

whereas if the tablet has a higher hardness, the tablet will have a longer disintegration time. This is in accordance with the disintegration time of this study, where the disintegration of co-grinding and physical mixture of meloxicam tablet were 16.93 and 16.62 minutes, while intact meloxicam tablets was 1.20 minutes.

Dissolution profile of tablet dosage form

Dissolution test was performed on the three formulas (F1, F2, and F3) of meloxicam tablet. The profile of meloxicam tablet dissolution test results can be seen in Figure 2. The amount of meloxicam dissolved in co-grinding meloxicam tablet was the highest compared to physical mixture meloxicam tablet and intact meloxicam tablet. An increase in dissolution rate of meloxicam tablet dosage was likely caused by solubilization effect of PVP K-30 in dissolution medium, and changes in the crystalline state of meloxicam into the amorphous phase by grinding [9,10]. However, this result was relatively low according to United State Pharmacopeia 2009, which stated that the amount of meloxicam dissolved within 30 minutes was not less than 70% [11]. This likely due to the hardness tablet for both co-grinding and physical mixture of meloxicam as discussed previously.

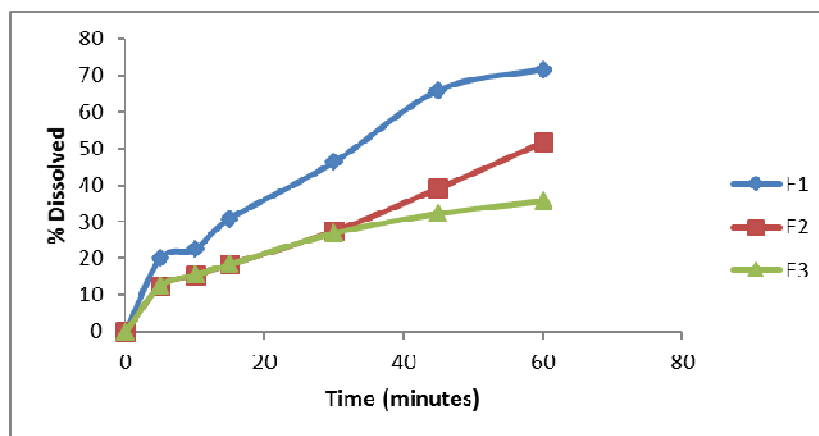


Figure 2. Meloxicam tablet dissolution profile; F1: Tablet of a mixture of meloxicam co- ground-PVP, F2: Tablets of a physical mixture of meloxicam-PVP, F3: Tablet intact meloxicam

CONCLUSION

The co-grinding technique can be used to increase dissolution rate of meloxicam tablets compared to tablets results of physical mixture and intact meloxicam tablets significantly ($p < 0.05$).

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