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The effect of milling process on phenylbutazone prior to inclusion complex with ß-cyclodextrin

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ABSTRACT

Phenylbutazone(PBZ) is a Non Steroid Anti Inflammatory Drug (NSAID). It is practically insoluble in water. The objective of this study was to find out the millinginfluence on PBZ prior to inclusion complex with β-cyclodextrin (β-CD). The milling process of intact PBZ was carried out in a ball mill with time variation 1 and 4 hours. Preparation of inclusion complex was done by kneading method with molar ratio of milled PBZ and β-CD was 2:1. Physical mixture and PBZ without milling process were also prepared with the same ratio of PBZ and β-CD as comparisons. The characterization of intact PBZ, physical mixture and PBZ-β-CD inclusion complexes were done by Infra-Red spectroscopy, Scanning Microscopy electron (SEM), Differential Thermal Analyzer (DTA), X-ray Powder Diffraction (XRPD). Dissolution test was done using basket method in a 900 ml phosphate buffer as medium at speed 100 rpm and temperature 37°C ± 0.5 for 60 minutes. X-Ray spectrum showed a decrease of peak intensity of inclusion complexes. SEM depicted the aggregation of PBZ. Meanwhile, the dissolution showed a decreasing on milled PBZ after inclusion complex withβ-CD compared to PBZ without milling. In conclusion, milling process on PBZ created aggregation which decreased the dissolution of inclusion complex of PBZ - β-CD .

Keywords: Phenyl butazone, β-cyclodextrin, inclusion complex, milling, characterization

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INTRODUCTION

The solubility of a poorly soluble drug can be altered in many ways, such as modification of drug crystal forms, addition of co-solvents and surfactant, micronisation and complexation with cyclodextrin[1,2]. Among these possibilities the cyclodextrin approach is one of particular interests. Phenylbutazon (PBZ) is a pyrazolone derivative mainly used as anti inflammation for cronic gout [3]. PBZ is practically insoluble in water[4].The poor solubility and wettability of PBZrender difficulties in pharmaceutical formulation either for oral or parental use, which may lead to variation in bioavailability. To overcome these problems, increasing the aqueous solubility of PBZ is an important goal.

Milling process can reduce particles sizebecomes smaller which expected to increase the surface area in contact with the drug solvent, thus increasing the dissolution rate [5, 6]. Moreover, drugs complexation with cyclodextrin have been reported increasing solubility of drugs, enhanced bioavailability, improved stability, masking of bad test or odor, reduced volatility, transformation of liquid or gas into solid form reduced side effect, and the possibility of a drug release system, etc [7-9]. Thus, this study was proposed to investigate the influence of milling process of PBZ before the inclusion complex of PBZwith β-cyclodextrin. PBZ was milled prior to complexation with β-cyclodextrin. The characterizations of drug, β-CD and complex inclution using differential thermal Analyse (DTA), powder X-ray diffractometry (PXRD) and FTIR, dissolution rate profile of complexes were performed.

MATERIALS AND METHODS

Materials

PBZ was obtained as a gift sample from PT. Dexa Medica (Indonesia). β-CD was purchased from PT. Sigma Husada (Indonesia), NaOH and KH_2PO_4 were purchased from Bratechem (Indonesia). All materials were used as received.

Milling of PBZ

Milling process of PBZ using a Ball Mill (Pascal® L9FS) with variations in time of 1 hour and 4 hours at 100 rpm.

Preparation of Complexes with β-CD

Physical Mixture

PBZ with β -CD at 2:1 molar ratios were mixed in a mortar for about one hour with constant trituration, and stored in a desiccator.

Kneading Method

PBZ with β-CD at 2:1 molar ratios were prepared by kneading method, which β-CD was placed in a mortar and small quantity distilled water to get β-CD slurry. Then, PBZ was incorporated slowly into the slurry and trituration was continued for one hour. The slurry was dried at 45^{o}C for 24 hours, pulverized and stored in desiccator[10,11]. Formula 1 (F1) was prepared with PBZ without miling, Formula 2 (F2) was prepared with1 hour milled PBZ, and Formula 3 (F3) was prepared with 4 hour milled PBZ.

Powder X-ray diffractometry (PXRD)

Powder X-RD patterns of intact PBZ, β-CD, physical mixture and complex inclutions were recorded by using an automated Philips Holland –PW 1710 scanner with filter Cu radiation over the interval 5-60°/2θ. The operation data were as follows: voltage 35 kV, current 20 mA, filter Cu and scanning speed 1°/min.

Fourier transform infrared (FTIR) spectroscopy

Fourier transform IR spectra were recorded on FT/IR-4100 type A. The spectrum were recorded for intact PBZ, β-CD , physical mixture and complex inclutions. Samples were prepared in KBr disc (2 mg sample in 200 mg KBr).The scanning range was 400-4000 cm^{-1}.

Scanning Electron Microscopy (SEM)

The microscopy of intact PBZ, β-CD , physical mixture and complexes were recorded by using SEM Jeol.Powder sample was placed in an aluminum sample holder and coated with gold to a thickness of 10 nm. Samples were then observed at setting of voltage was 20 kV and current 12 mA.

In Vitro dissolution studies

The dissolution of the inclusion complexes were compared with those of intact PBZ and physical mixture of PBZ and β-CD . The dissolution studies were performed according to the USP XXX, using rotating basket method. The sample, corresponding to 50 mg of PBZ, was placed into hard gelatin capsules. The dissolution medium was 900ml of phosphate buffer (pH 7.5). The stirring speed of the paddle was 100 rpm, and temperature was maintained at 37°C ± 0.5°C. The samples (5 ml) were withdrawn at various time intervals, which was filtered through whattman filter paper and analyzed by UV spectrophotometer at 264,5 nm [4].

RESULTSAND DISCUSSION

Powder X-ray diffractometry

Powder X-ray diffractometry was used to record the diffraction patterns of intactPBZ, milled PBZ, physical mixture, and inclusion complexes. X-ray diffraction patterns of intact PBZ showed diffraction peaks in crystalline state (Figure. 1). PBZ crystalline peaks seen at2Θ angle: 15:51, 20.91, and 21:03. β-CD was also seen in a crystal stateat diffraction peaksof2Θ angle: 12:45, 20.89, and 22.63. The peak intensity of inclusion complex of F1, F2 and F3 and PBZ- β-CD physical mixture were lower than intactPBZ. Decreasing in the intensity of the interference peaks indicateda change in the degree of crystallinity. The change in the degree of crystallinityis due tothe structure becomes more amorphous [11]. Therefore, solubility of amorphous PBZ is expected higher than in the intact form [11].

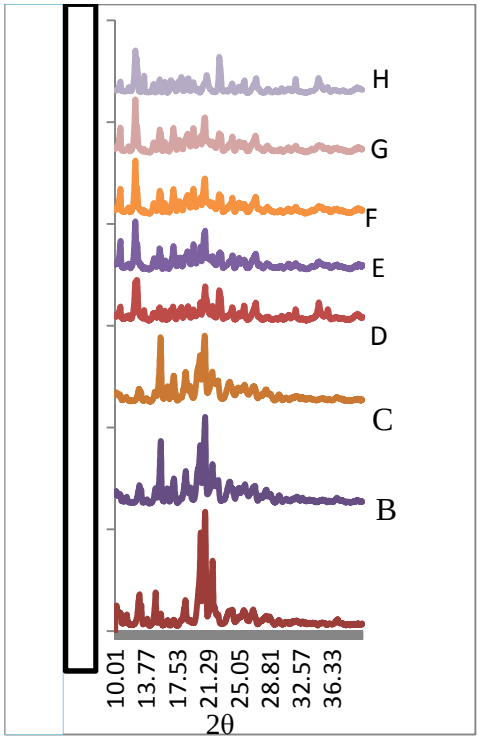

Figure 1.PXRD Spectrum of (A) intactPBZ, (B) 1 hour milled PBZ, (C) 4 hours milled PBZ, (D) β-CD, (E) PM, (F) F1, (G) F2,and (H) F3

Fourier transform infrared (FTIR) spectroscopy

FT-IR spectrum of intactPBZ gives a peak wave number at 1714.13 cm^{-1} which indicates the presence of carbonyl groups, 1486.52$cm^{-1}$for C = C aromatic and 1293.59 $cm^{-1}$for CH absorption as shown in Figure. 2. FT-IR spectrum of β-CD showed broad peaks wave numbers at 3500 - 3000 cm^{-1} which indicated the presence of alcohol and OH groups in complex molecules such as cellulose, saccharides, polymers and other molecules that have a very strong group absorption. The FTIR spectrumof inclusion complex of PBZ and β-CDshowed an increase at wave number due to the insertion of the benzene ring into the β-cyclodextrin richelectroncavity and an increasing in electron cloud density, which will lead to increase the frequency. Moreover, due to changes in the micro part of the β-CD, it lead to the formation of hydrogen bonds and van der Waals forces during their interaction to form inclusion complexes [12].

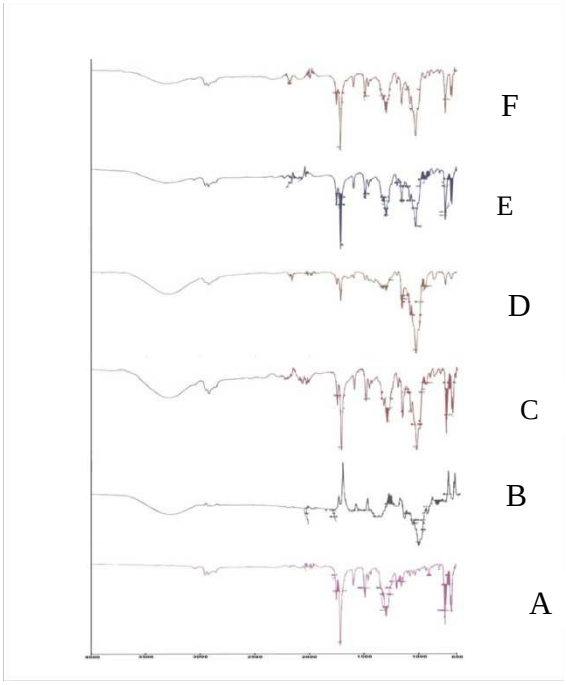

Figure 2. FT-IR Spectra of (A) intact PBZ, (B) 1 hour milled PBZ, (C) 4 hours milled PBZ, (D) β-CD, (E) PM, (F) F1,(G) F2,and (H) F3

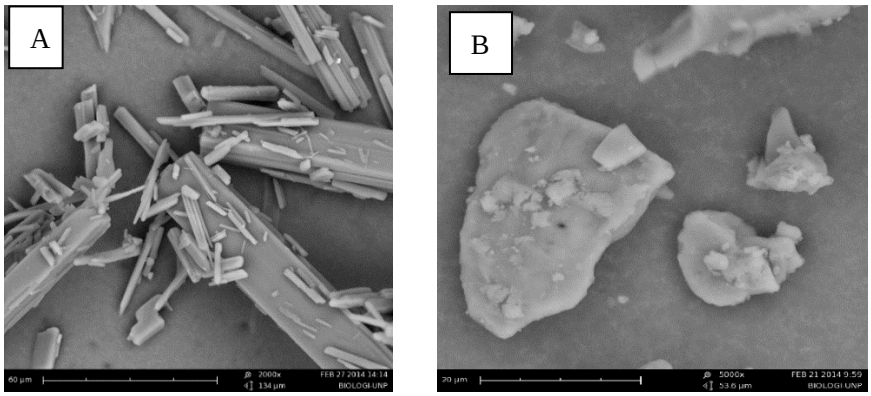

Figure3. SEM of (A) intact PBZand (B)β-CD

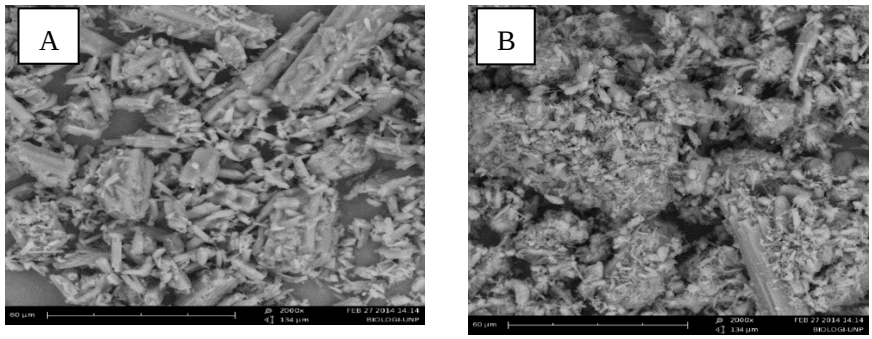

Figure 4. SEM photo of (A) 1 hour milled PBZ milling and (B) 4 hours milled PBZ

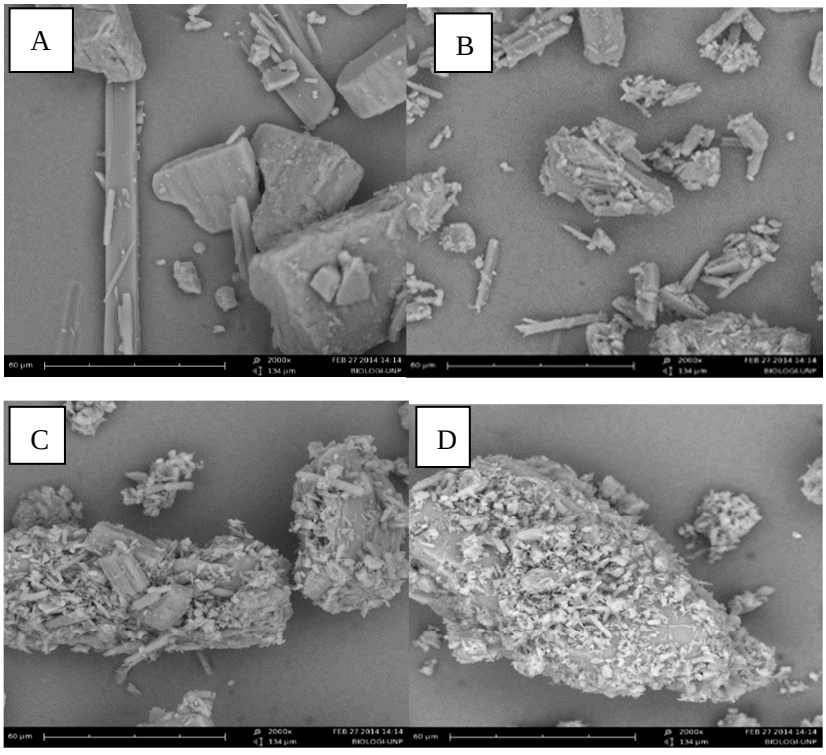

Figure 5. SEM of PM (A) PM, (B) FI, (C) F2 and, (D) F3

Scanning Electron Microscopy (SEM)

The SEM of intact PBZ showed an irregular cylinder shape, while β-CD looked like the stem as a shown in Figure 3. PBZ which milled for 1 and 4 hour showing the aggregation, which the longer the milling time the more aggregation shown (Figure 4).Physical mixture, complex inclusion in F1, F2 and F3 (Figure5) formed inclusion

complexes in small amount,which appear many of PBZwere outside of β-CD surfaces. In addition, in F2 and F3 the aggregation was formed.In PBZ which has been grinded for 1 hour the aggregation formed, and 4 hours milling aggregates formed more bigger (Figure.5).

***In Vitro* dissolution studies**

Dissolution of intact PBZ, physical mixture, inclusion complex of F1, F2 and F3 in the 60 minute were 89.16%, 95.34,99.34%, 91.92%, 52.64%, respectively (seen in Figure 6). Inclusion complex F1 showed a faster dissolution rate than pure drug and other complexes. The milling process on PBZ decreased the dissolution rate of PBZ that complexes with β-CD, the longer of the milling process, the rate of dissolution is getting smaller. The milling process on PBZ causing aggregation and agglomeration of fine particles as also shown in SEM due to increasing surface energy and Van der Waals forces between molecules to form agglomerates. [11]

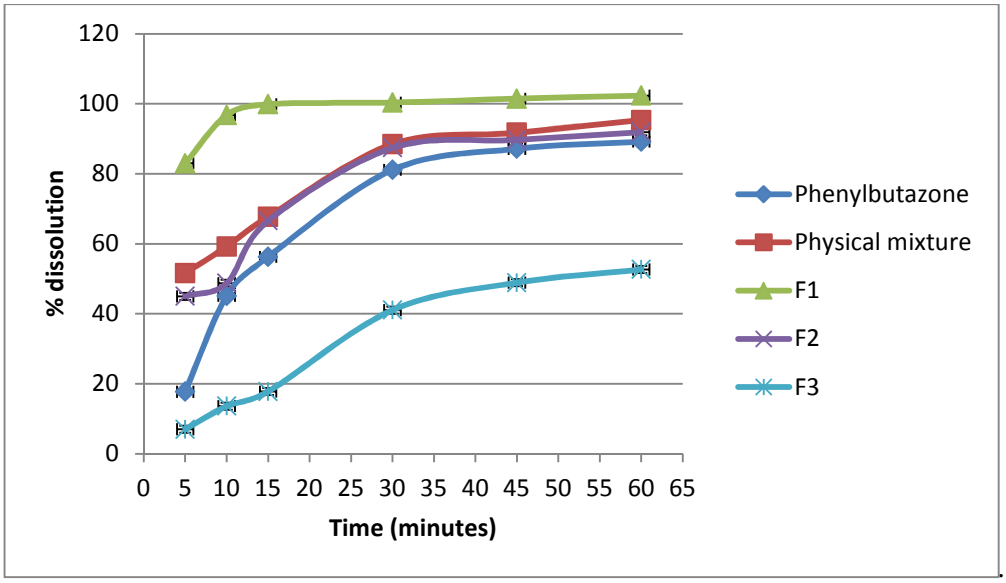

Figure6.Dissolution profile of PBZ, Physical mixture, F1, F2, and F3

CONCLUTION

Milling process on PBZ causing aggregation which resulted in the decreasing dissolution of inclusion complex PBZ - β-CD

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