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Preparation and Characterization of Nanoparticles for Dissolution Rate Enhancement of Ibuprofen

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Abstract: Ibuprofen is a non-steroid anti-inflammatory drugs (NSAIDs) used for treating pain, inflammatory, and fever. This research was conducted to reducing the size of ibuprofen, characterization and dissolution test methodology. In reducing the size of ibuprofen, milling method at 1400 rpm for 30 hours was used. The characterization of standard ibuprofen (SI) and nanoparticle ibuprofen (NI) used a particle size distribution, scanning electron microscopy, X-ray diffraction, differential thermal analyzer, while dissolution test methodology used a dissolution tester. The particle size of ibuprofen obtained after being reduced was 0,5 -1μm smaller than standard ibuprofen of 40μm, melting point and x-ray diffraction of nanoparticle ibuprofen showed similar results with standard ibuprofen. The dissolution rate of ibuprofen was increasing with the reducing of particle size (nanoparticle size) compared to standard ibuprofen. Nanoparticle ibuprofen showed maximum peak levels at minute 120 of a 22.77% and standard ibuprofen had 48.77% at pH, while the (pH 7.2) nanoparticle ibuprofen showed maximum peak levels at minutes 135 of a 100.26% and standard ibuprofen had 101.05%. The difference in solubility and particle size influence the dissolution, absorption, and effectiveness rate.
Keywords: Ibuprofen, anti-inflammatory, nanoparticle, dissolution rate.

Introduction

Ibuprofen is one drug that is difficult to dissolve in water and almost insoluble which is caused by its hidrophobic structure.[1,2]Ibuprofen also has highly cohesive strength, which is resulting in a poor current strength. Ibuprofen can be classified as a non-steroid anti-inflammatory drugs(AINS) often used as analgesic, anti-inflammation, and anti-pyretic.[3] A low dosage ibuprofen is as effective as aspirin and acetaminophen for a common indication,[4] and has the same effectiveness with indomethacin.[5]Enantiomer R and S(+)ibuprofen for the most part were used in treating low to medium pain which are associated with dysmenorrhea, headache, migraine, post-operation and spondylitis treatment, osteoarthritis, rheumatoid arthritis, and disruption on soft tissue.[6] Dentists more often give ibuprofen for treating acute or chronic sharp pain in the mouth.

Dissolution rate or the time it took for a relatively insoluble drugs to dissolve in water has been a regular problem found in the pharmacy industry. Ibuprofen is a compound that can be classified into low dissolution with high permeability,[7]the classification is based on *Biopharmaceutical Classification System* (BCS) II. Drugs with a low dissolution, the rate of dissolution is a main factor in the absorption process of the drugs.[8] For most of drugs, dissolution is a determining factor for the *onset of action* speed and therapeutic activity, thereby the efforts to increase dissolution rate in a drug is needed.[9]

One step that could be taken to increase dissolution rate is by reducing the size of ibuprofen particles to nano scale. This kind of particles are often called with the name nanoparticles. Nanoparticles could be obtained by using several of methods including crushing, grinding, spray drying, and frozen drying. The most common

method is a mill media; a technology for reducing particle size and had been proven its reliability.[10] Transformation on ibuprofen physical characters can also be expected to change its bioavailability profile.[11]

Based on the explanation above then this research will conduct a creation of nanoparticles ibuprofen and physical characterization, a dissolution and availability test, then a test on analgesic effect which will be compared with standard ibuprofen.

Experimental

Materials

Materials being used includes analysis materials with a high level of purity. Ibuprofen (Hubei Granules-Biocause Pharmaceutical, Co. Ltd) and other chemical materials from Merck© such as HCl, KH_2PO_4, NaOH, and methanol. Laboratory glasses equipment, analytic scale (vibra) for high energy milling (HEM), ceramic ball with diameter of 2 mm, x-ray diffraction, scanning electron microscope, differential thermal analyzer, particle size distributor, dissolution test device (Erweka), and spectrophometer UV-Visible (Shimadzu, 1800).

Methods

Nanoparticles ibuprofen was prepared by using a milling method, which is one of effective methods to produce nanoparticles. Ibuprofen with standard size and ceramic balls with diameter of 2mm was put into the chamber with 1:10 scale. Next, it was accelerated by 1400 rpm for 30 hours until the size of the particles produced would be less than 100nm.[2]

Characterization of Standard and Nanoparticles Ibuprofen

a) Particle Size Distribution (PSD)

Particle size from standard and nanoparticles ibuprofen was measured directly after precipitation with dynamic laser light scattering (Analysis of Particles Size). Before the analysis, the drugs suspension was melted using 0.2 mg/ml pure water.[2]

b) Scanning Electron Microscope (SEM)

Surfacesmorphology of standard and nanoparticles were observed using a SEM devices with the accelerated voltage of ± 1.5 – 20 kV.[2,12]

c) X-Ray Diffraction (XRD)

Standard and nanoparticles ibuprofenwere stored in the system of x-ray diffraction using Cu radiation source, 40 kV voltage, and 30 mA current. The observation was conducted with the scanning speed of 0.05º per second.[12]

Dissolution Testing

The profile of ibuprofen was determined by using a certain device called a dissolution apparatus which refer to the method apparatus type II.[13]Standard ibuprofen was put into a capsule and given a ring-shaped-mass. Then it was put into a container with certain pH in a 37 temperature ± 0.5ºC and mixing speed of 100 rpm. A sample taking was conducted between the interval of 0-120 minutes for acid pH and 0-135 minutes for alkali pH. Sample taking was conducted from the same position; the middle point between the surface of dissolution medium and the top part of the row was not less than 1cm from the container wall.[14]This solution then measured on a wave length (λ) of 264 nm. The same test was conducted toward nanoparticles ibuprofen.[2]

Results and Discussion

Characterization of Standard and Nanoparticles Ibuprofen

a) Particle Size Distribution (PSD)

The testing on particle size distribution of nanoparticles ibuprofen was shown on Figures 1 which illustrated that there was 94.5% of ibuprofen with the particle size of 50-100 nm , 4.7% for ibuprofen with the particle size of 100-150 nm, and 0.5% for ibuprofen with the particle size more than 150 nm. This result showed that the most particles found in nanoparticles ibuprofen were in the size of 50-150 nm and the size of

those particles was different with the 40 µm size of standard ibuprofen. Based on the research by Mansouri*et al*,[2]standard ibuprofen has particles in the size of 90-245 µm while the nanoparticles ibuprofen has particles in the size of 200-450 nm.

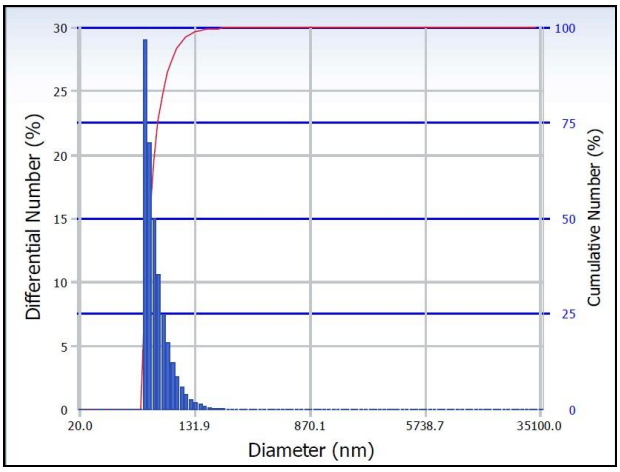

Figure 1. Particle size distribution of nanoparticles ibuprofen

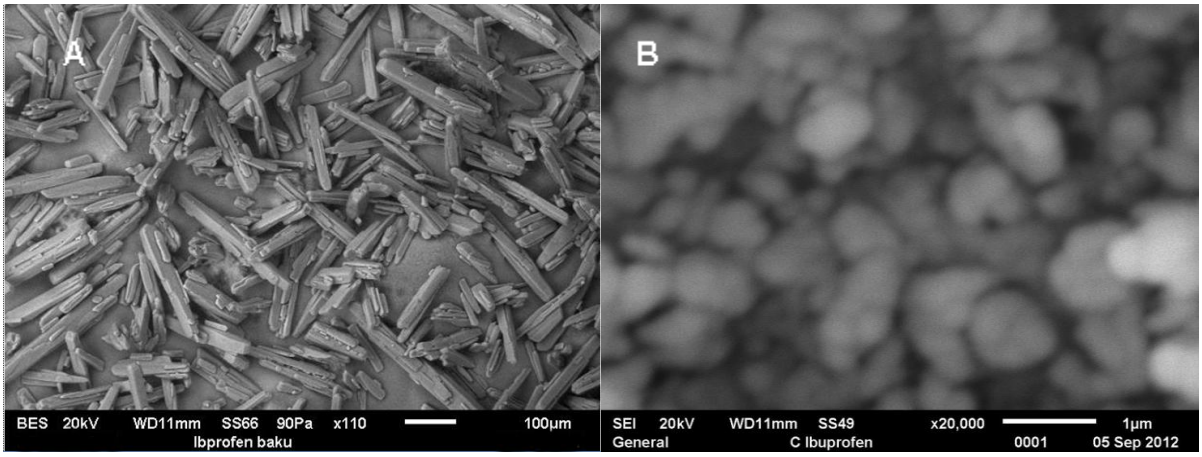

Figure 2. Form of standard ibuprofen (A) and nanoparticles ibuprofen (B)

b) Scanning Electron Microscope (SEM)

Based on the data on particle size distribution, a standard ibuprofen has particles in 40 µm size, while nanoparticles ibuprofen producing particles that mostly in the size of 50-100 nm. This result can be seen in the result of scanning electron microscopy (SEM) in Figures 2 which illustrated how the size of particles in nanoparticles ibuprofen were smaller than in standard ibuprofen. In the result, standard ibuprofen formed as crystal with coarser surface while nanoparticles ibuprofen has a smoother surface and formed as amorf. Based on the research conducted by Chen *et al*,[15]nanoparticles ibuprofen being tested produced particles in spherical form and the size of 34.8 nm.

c) Differential Thermal Analyzer (DTA)

Differential thermal analyzer testing of standard and nanoparticles ibuprofen can be seen in Figures 3; how standard ibuprofen has melting point in the temperature of 101.5ºC while nanoparticles ibuprofen's melting point is in the temperature of 100.9ºC. The difference of particle size really influences the melting point of a substance, because the bigger the size of the particles being used then the harder for melting process.[16] Research conducted by Chen *et al*,[15] mentioned about how there was a difference between the standard ibuprofen's melting point of 81ºC with the one that the poly-(methyl vinyl eter-co-maleic anhydride) covered nanoparticles ibuprofen had of 164.3ºC.

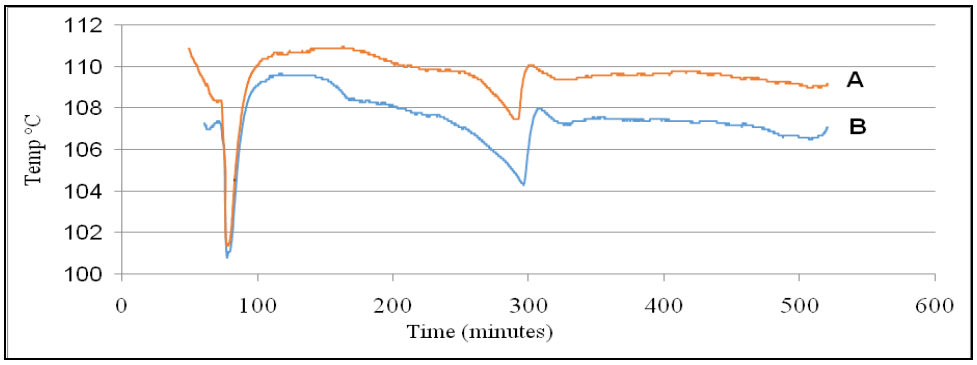

Figure 3. Melting point of standard ibuprofen (A) and nanoparticles ibuprofen (B)

Dissolution rate study

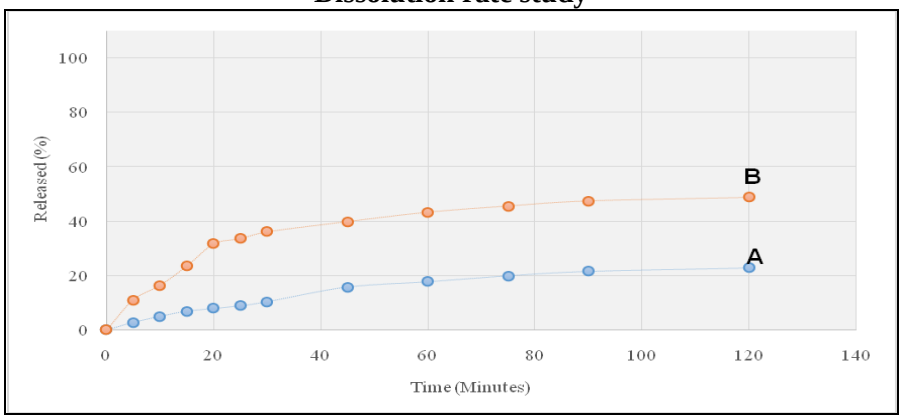

Figure 4. Dissolution rate of standard (A) and nanoparticles ibuprofen (B) on acid pH

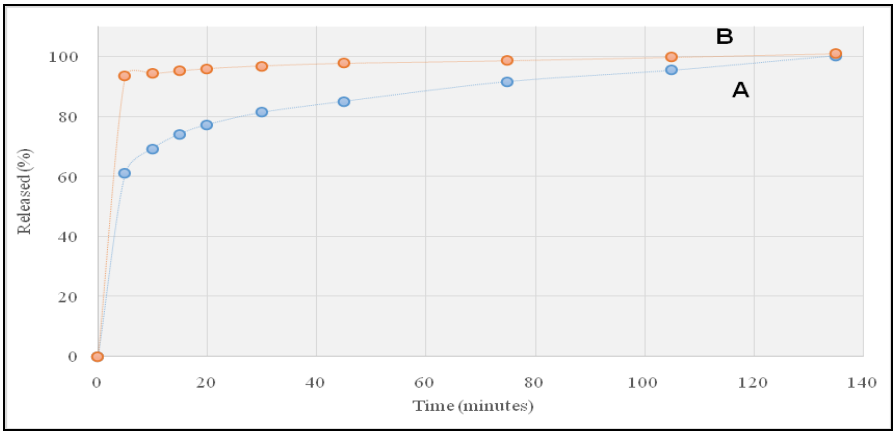

Figure5. Dissolution rate of standard (A) and nanoparticles ibuprofen (B) on alkali pH

The differences on how the substance being soluble, size of the particles, form of the crystals, and pH could give a significant difference on dissolution. The effect of the differences on standard and nanoparticles ibuprofen's particles size toward the dissolution rate can be seen in Figures 4.From the observation of Figures 4, it is obvious that nanoparticles ibuprofen more easily dissolved than microparticles. Nanoparticles ibuprofen dissolve more quickly in synthetic gastric liquid (acid pH), it reached the amount of 31.741% in minutes 20, while microparticles ibuprofen only reached 7.92% and the top amount was reached in minutes 120 with the result could reach 22.77%, while nanoparticles ibuprofen reach 48.77%. By that, it can be concluded that nanoparticles ibuprofen has dissolution rate 2.14 times more than microparticles ibuprofen due to the fact nanoparticles ibuprofen has smaller size of particles size which help it to dissolve in acid pH while ibuprofen has pKa of 4.5-4.6.[17]Dissolution test using synthetic intestine liquid (alkali pH) showed that nanoparticles ibuprofen dissolve quickly in 5 minutes reaching 93.58%, while microparticles ibuprofen reached 61.00% (Figures 5), this fact proves that it took more time for microparticles ibuprofen to reach the same amount like nanoparticles ibuprofen where in 135 minutes microparticles ibuprofen reached 100.26%, while nanoparticles

ibuprofen reached 101.05%. This fact concludes that nanoparticles ibuprofen more quickly to dissolve in medium because its small size particles based on the measurement conducted using particle size distribution. Based on Directorate General of Drugs and Food (BPOM) in 1995, ibuprofen can be classified as substance that insoluble in water and a compound type of Biopharmaceutical Classification System (BCS) II, where it has a high level of permeability and low level of dissolving.[7] The amount obtained on synthetic intestine liquid (alkali) also fulfill the requirement from United States Pharmacopeia,[13] which is the amount obtained should not be less than 80% (Q) in 60 minutes.

Discussion

Reducing the particles of ibuprofen using milling method resulting particle size about 50-100 nm, smaller than particles in standard ibuprofen of 40 µm. The particles form of nanoparticles ibuprofen are smaller, smoother, and amorf, compared with standard ibuprofen. The dissolution rate comparison of nanoparticles ibuprofen on acid pH was 1.54 times faster compared with standard ibuprofen. The same process also happened on alkali pH where nanoparticles ibuprofen's dissolution rate was 4 times faster than standard ibuprofen.

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