

Characterization of Piroxicam Nanoparticles in Orally Disintegrating Tablet (ODT)

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Abstract : Tablet is one of oral dosage forms, which is widely used because it is convenient to carry, the duration of drug action can be controlled, and their taste and smell can be improved by particular technique. However, some patients, especially pediatrics and geriatrics, often have difficulty in swallowing conventional tablets even with a lot of water. Therefore, orally disintegrating tablet (ODT) is developed to solve this problem. In the administration of ODT, tablets are placed on the tongue and will disintegrate rapidly in a very short time, less than one minute. Piroxicam, a nonsteroidal anti-inflammatory and analgesic, needs fast onset of action. So, it is necessary to formulate it into ODT.

Piroxicam microparticles were reduced to nanoparticles by using high energy milling (HEM) E3D and evaluated by scanning electron microscope (SEM), particle size analyzer (PSA), and X-ray diffraction (XRD). After the size was reduced, the piroxicam nanoparticles were formulated into ODT. The ODT was evaluated for its drug content, hardness, friability, disintegrating time, and wetting time.

The research findings show that particle sizes of drugs are in range of 455-772.9 nm, indicate that the preparation of piroxicam nanoparticles from piroxicam microparticles is successful. The characterization results of piroxicam nanoparticles ODT show that it fulfilled all of the criteria of ODT.

Keywords: nanoparticles, piroxicam, milling, orally disintegrating tablet.

Introduction

Oral administration route is the most favorable route for administering drugs because it is convenient so that can enhance patients compliance and is relatively cheap in therapy cost.¹ One of the widely used oral dosage form is tablet. Tablet is one of oral dosage forms, which is widely used because it is convenient to carry, the duration of drug action can be controlled, and their taste and smell can be improved by particular technique. However, some patients, especially pediatrics and geriatrics, often have difficulty in swallowing conventional tablets even with a lot of water.²

A study shows that more than 26% patients have difficulty in swallowing tablet. Therefore, clinicians and pharmacists are demanded to take regard of this problem in developing correct drug formulation for patients. Formulations of drugs that can dissolve and disintegrate rapidly in mouth without drinking water are considered to be an answer for this problem. This kind of drugs will give greater advantages than conventional tablets do, more convenient to use, and have the potential to increase patients compliance.³

The drug formulation intended above is orally disintegrating tablet (ODT). According to FDA (Food and Drugs Administration, USA), ODT is a solid dosage form that contains drug active ingredients, that can disintegrate rapidly, usually in seconds, when placed on the tongue. ODT will dissolve rapidly just by contact with saliva, without the need to drink water. ODT dosage form is also has faster dissolution and absorption rate and higher bioavailability compares to conventional tablets.⁴ Moreover, drugs side effects caused by first pass metabolism in the liver can be reduced.⁵

ODT can be formulated by using several methods. The easiest and the cheapest method is direct compression method.⁶ Three basic approaches in developing ODT are maximizing pore structure of the matrix of tablet, adding disintegrants, and using water soluble ingredients in the formulation.⁷ The two last approaches are applied in this study.

Experimental Methods

Apparatus

Tablet compression machine (Ateliers), Strong Cobb hardness tester (Erweka), disintegration tester (Erweka), dissolution tester (Erweka), friabilator (Roche), UV-Vis spectrophotometer (Shimadzu mini 1240), high energy milling (HEM) E3D with ceramic ball (diameter of 2 mm) as milling media, particle size analyzer (Delsa™ Nano, Beckmann Coulter), and other laboratory glassware (Pyrex).

Material

Piroxicam (Nantong JingHua Pharmaceutical, Co. Ltd), crospovidone, croscarmellose sodium (Ac-Di-Sol®, FMC BioPolymer), microcrystal cellulose (Ceolus®, Asahi Kasei Chemicals Corp.), aspartame, talcum, and Mg Stearate (PT. Brataco), hydrochloric acid, methanol (E. Merck), and distilled water.

Preparation of piroxicam nanoparticles

As much as 5 g of piroxicam size 13 μ m and ceramic balls with diameter of 2 mm (1:10) were put into the chamber of high energy milling (HEM) E3D machine, and the machine were ran at speed 1400 rpm for 30 hours. The obtained particles were characterized by using scanning electron microscope (SEM), X-ray diffractometer (XRD), and particle size analyzer (PSA).

Preparation of piroxicam nanoparticles ODT

The tablets were prepared by using direct compression method. The components of the formulation were shown in Table 1.

Table 1. Formula of piroxicam nanoparticles ODT

Components	Amount (mg)
Piroxicam nanoparticles	10
Crospovidone	5
Croscarmellose Na	5
Microcrystal cellulose	167
Aspartame	10
Mg Stearate	2
Talcum	1
Total	200

Drug content determination

Twenty tablets of each formula were accurately weighed and powdered. Then, weighed the powder equivalent with 5 mg of piroxicam. The powder was then put in a 100 ml flask, dissolved with 5 ml of methanol, and this solution was diluted with 0.1 N HCl solution. The solution was filtered and the first few drops of filtrate were discarded. As much as 5 ml of the filtrate was withdrawn, put in a 50 ml flask, and diluted with 0.1 N HCl solution. This solution was then measured for its absorbance by using UV spectrophotometer at a wavelength of 334 nm.

As for drug content determination, calibration curve was made from piroxicam stock solution with concentration of 2 ppm, 3.5 ppm, 5 ppm, 6 ppm, and 7 ppm. The calibration curve was then used to calculate the regression equation and the drug content.

Hardness test

Hardness test was carried out on 6 tablets of each formula. The method: each tablet is placed perpendicular between the anvil and the punch of Strong Cobb hardness tester, then clamped by turning the adjustment bolt until light marks "stop" light. Pressed a button to put pressure on the tablet until the tablet was broken and the scale's needle stops. Numbers on the scale are appointed by the needle and then recorded. This is the value of the hardness of the tablet.

Friability test

Twenty tablets of each formulation were weighed and the weight was recorded (a gram). The tablets were then put into Roche friability tester and the friability tester was ran for 4 minute (100rpm). Once completed, the tablets were removed, cleaned from dust, and then weighed again (b gram).

$$\text{Friability} = \frac{(a - b)}{a} \times 100\%$$

Disintegration time test

The disintegration time of ODT was measured by 3 type of test: using disintegration tester, modified test, and test in the oral cavity.

Disintegration time test using a disintegration tester: one tablet was inserted in each tube of disintegration tester basket, and then ran the tool. Water was used as a medium with temperature of 37 ± 2 °C.

Modified disintegration time test: one tablet was inserted into a 9 cm diameter petri dish that contained 9 ml distilled water. The time for the tablet to disintegrate completely was noted.

Oral cavity disintegration time test. This test used 6 volunteers. Before starting the test, each volunteer was required to rinse his/her mouth. One ODT was placed on the tongue and let to disintegrate completely, and the time needed was noted.

Wetting time test

A piece of tissue paper (11 cm x 10 cm) was folded in half, then placed on a 9 cm diameter petri dish containing 9 ml Ponceau 4R (a red dye) solution. One tablet is placed on the tissue paper, then the time needed for perfect wetting of the tablet was noted. The wetting time is the time it takes to make the upper surface of the tablet into the red. The test was carried out on 6 tablets of each formulation of ODT.

Results and Discussion

Characterization of piroxicam nanoparticles

The result of scanning electron microscope (SEM) showed that the size of piroxicam particles after being milled with high energy milling (HEM) E3D for 30 hours were smaller than 1000 nm. This indicated that the milling process has succeeded to make piroxicam nanoparticles. The result of SEM was shown in Figure 1.

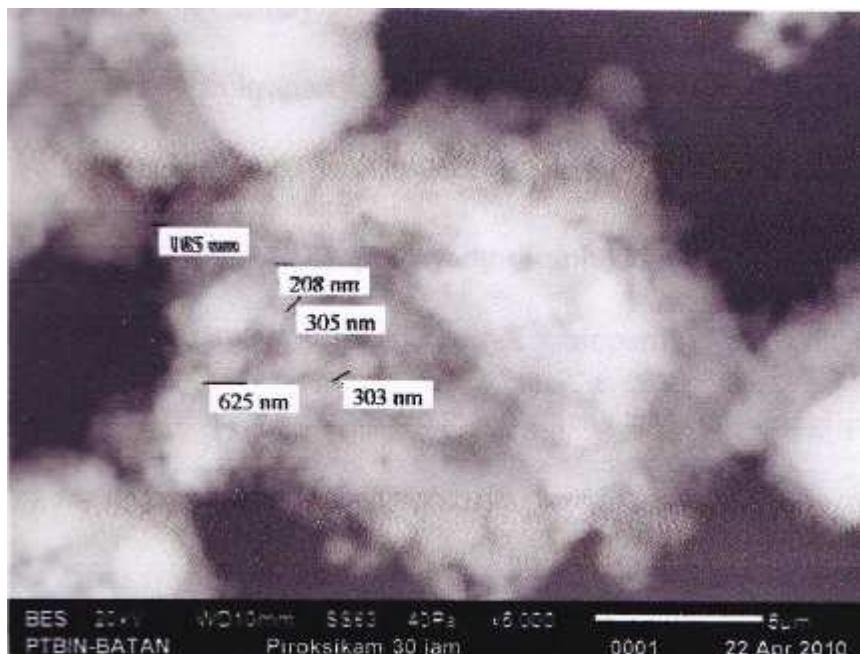


Figure 1. Piroxicam particles size observed with SEM after milling by HEM E3D for 30 hours (zoomed 5000x)

The same result was also showed by particle size analyzer (PSA). The particles size after analyzed by PSD was between 455 – 772.9 nm. Figure 2 showed the distribution of piroxicam nanoparticles.

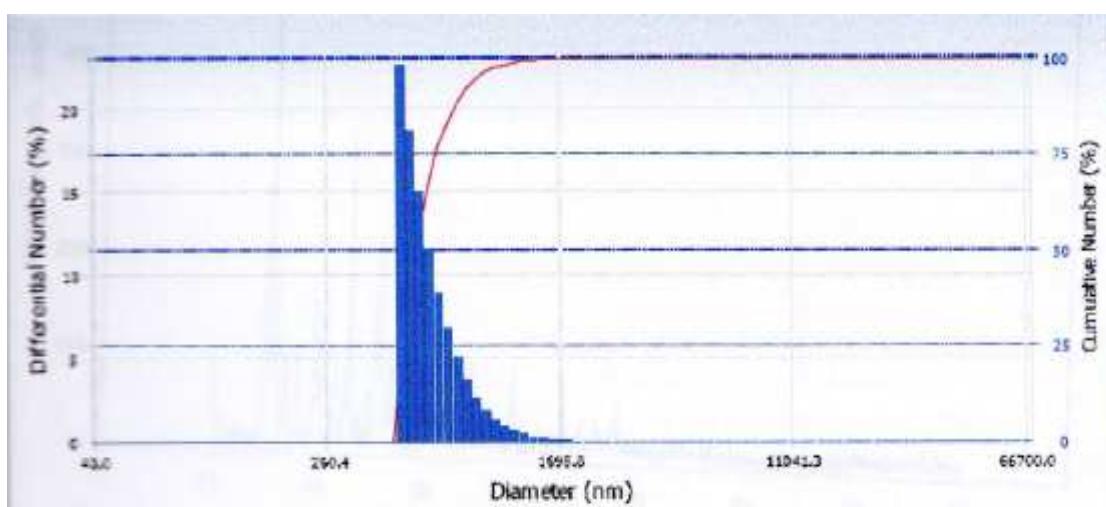


Figure 2. Distribution of piroxicam particles size after milling by HEM E3D for 30 hours.

X-ray diffraction of piroxicam microparticles showed four peaks with high intensity at area of 10-28° (2θ) and five peaks with low intensity at area more than 30° (2θ). The almost similar diffraction patterns was also observed in x-ray diffraction of piroxicam nanoparticles. Figure 3 showed the x-ray diffraction of piroxicam microparticles and piroxicam nanoparticles.

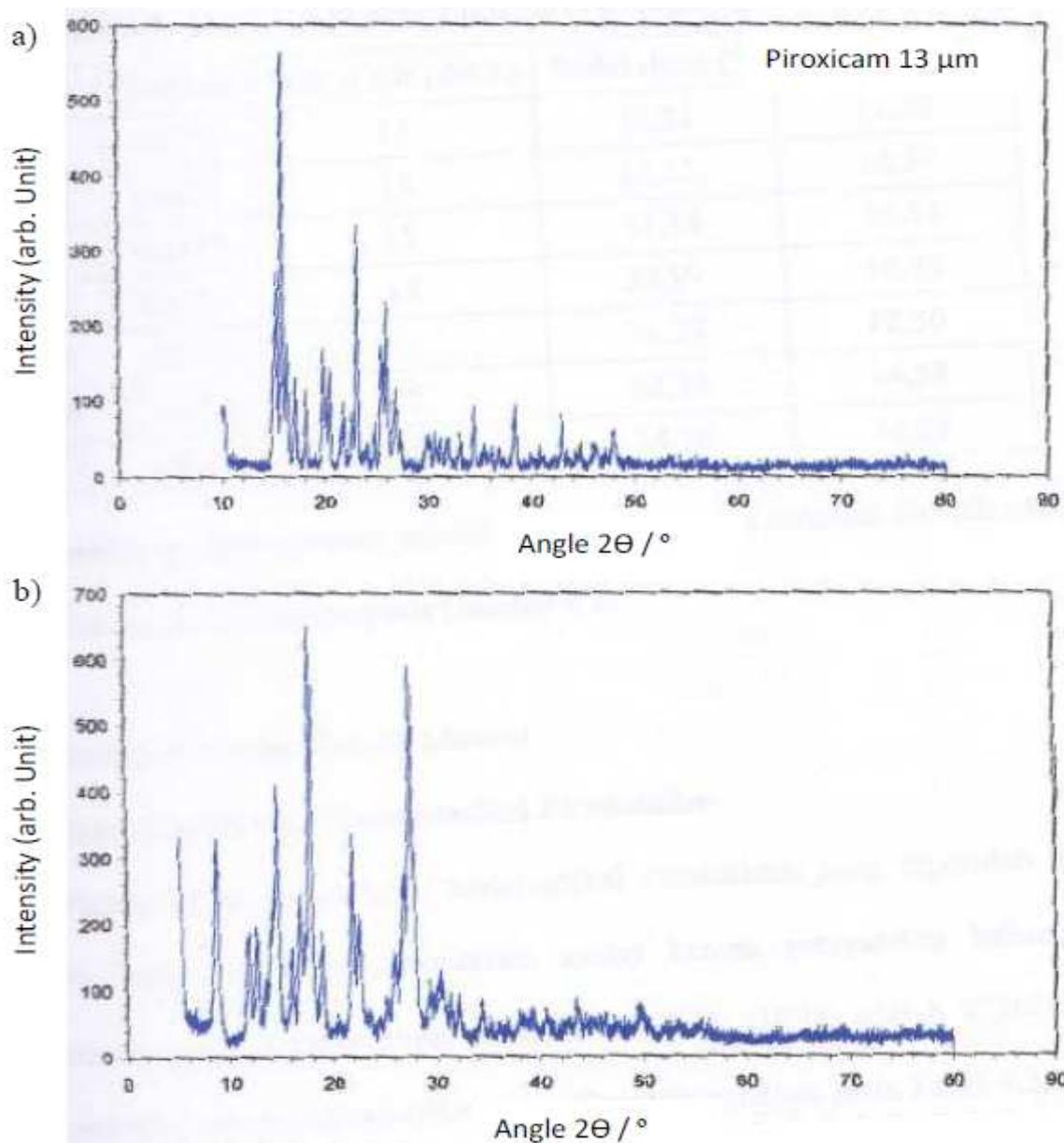


Figure 3. X-ray diffraction of a) piroxicam microparticles and b) piroxicam nanoparticles.

The almost similar diffraction patterns indicated that the tested particles were the same substances, i.e. piroxicam. These findings were proven further by content determination by using UV spectrophotometer. The differences between the two diffraction patterns were only at the intensity and the area of peaks. These indicated that there was a difference in particles size before and after milling. The expanding in area indicated the reducing in particles size. The reduction of particles size were thought due to conduction or the lost of mechanic energy during milling.⁸

Characterization of piroxicam nanoparticles ODT

The results of characterization of piroxicam nanoparticles ODT were showed in Table 2.

Table 2. The results of characteristics evaluation of piroxicam nanoparticles ODT

Drug Content (%)	Hardness (kg)	Friability (%)	Disintegration Time (second)			Wetting Time (second)
			<i>Disintegration tester</i>	<i>Modified test</i>	Oral cavity test	
93.21±2.93	3.66±0.15	0.41	8.50±0.84	48.17±3.43	38.00±3.69	33.16±3.06

In this study, piroxicam nanoparticles assay was performed by using procedure that specified in Pharmacopoeia of The People's Republic of China (2005). Thus, the requirement of piroxicam ODT nanoparticles content was also referred to the literature, that is 90-110%⁹. The results of the assay showed that the ODT formulion in this study has met this requirement.

The hardness of the ODT prepared was lower than that of conventional tablet, which in in range of 4-8 kg¹⁰. This was due to ODT was designed to disintegrate and to dissolved rapidly. The tablet was so porous to be able to absorbed water rapidly¹¹.

Friability value showed the effect of physical stress to tablet in packaging and distribution process. The problem that usually exist in ODT is that ODT is quiet fragile¹¹. However, the ODT prepared in this study still fulfilled the friability requirement, that is ≤ 0.8%¹⁰. This relatively good friability was due to the used of additional ingredients that have good compressibility.

Disintegration time tested by using a disintegration tester was relatively very fast because the superdisintegrant rapidly absorbed the water when ODT was completely submerged in the medium, as well as the effect of stirring rate of the disintegration tester which was higher if compared to the peristaltic motion of the tongue. In the modified disintegration time test, there was no stirring movement and the volume of medium used was relatively less. In oral cavity test, the disintegration time was a bit faster than in the modified disintegration time test, because in oral cavity test there was peristaltic motion of the tongue that did not exist in the modified disintegration time test.

Wetting time is an important parameter in the evaluation of the disintegration of ODT because disintegration rate is highly depends on the rate of tablet wetting process¹². The result of the wetting test indicated that the ODT has a good wettability.

Conclusion

The milling process by high energy milling (HEM) E3D at 1400 rpm for 30 hours has succeeded to reduce the size of piroxicam from microparticles into nanoparticles. The formulation of piroxicam nanoparticles as ODT has met the requirement of drug content that specified in Pharmacopoeia of The People's Republic of China. The hardness was lower than conventional tablet because ODT is more porous than conventional tablets. The friability and disintegrating time has met the requirement. The piroxicam nanoparticles ODT also has a good wettability.

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