

The Effects of Crospovidone and Croscarmellose Sodium as Superdisintegrants On the Characteristics Of Piroxicam Nanoparticles ODT (Orally Disintegrating Tablet)

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Abstract: ODT (Orally Disintegrating Tablet) is a dosage form that designed to disintegrate immediately when placed on tongue. Therefore, the use of appropriate superdisintegrant in the formulation is the key aspect in the development of this dosage form. It is known that crospovidone and croscarmellose sodium are superdisintegrants that can generate good ODT disintegration profiles. However, the differences of their effects are still unknown. In this study, the ODT characteristics prepared by using crospovidone and croscarmellose sodium as superdisintegrants were discussed. Piroxicam nanoparticles ODT were made by using direct compression method. The ODT was evaluated for its drug content, hardness, friability, disintegrating time, wetting time, and dissolution profile. The results showed that ODT formulated using croscarmellose sodium with concentration up to 10% showed better friability, disintegrating time, wetting time, and dissolution profile than ODT formulated with crospovidone.

Keywords: crospovidone, croscarmellose sodium, superdisintegrant, orally disintegrating tablet.

Introduction

During these decades, orally disintegrating tablet (ODT) has received extensive wide attention as an alternative dosage form to increase patient compliance, particularly pediatric and geriatric patients. This is because ODT can dissolve/disintegrate in the mouth without the need to drink water so as to facilitate activities to swallow tablets. ODT will disintegrate rapidly when come to contact with saliva in less than 60 seconds¹. In addition to having a rapid rate of disintegration, ODT has some other clinical advantages such as fast absorption and onset of action, high bioavailability, and avoidance of first pass metabolism².

Direct compression method is the most commonly used method in producing ODT because it is the easiest method in tablet manufacturing, can use conventional manufacturing instrument, short procedure, relatively cheap, can be loaded with thermolabile and moisture sensitive drugs, and can be made into high dose^{1,3}.

Similarly to conventional tablets, ODT formula generally contains diluents, disintegrant, lubricant, coloring agent, flavoring agent, and even sweeteners. Disintegrant plays the most important role to produce fast disintegration, especially when direct compression method was applied².

Understanding of the nature and the effect of disintegrant in formulation have been growing rapidly in these few years, creating a new class of disintegrant called superdisintegrant⁴. Caramella, et al., found that the efficiency of disintegration process was based on force-equivalent concept, which is the ability of disintegrant to transform the water absorbed into swelling force⁵.

The commonly used superdisintegrants are crospovidone and croscarmellose sodium. They both are known to have high efficiency in the use of low concentration (2-5% b/b)⁶. In formulation, the concentration of superdisintegrant can be up to 10-20%, depends on the dose and characteristic of active ingredient and also the desired release rate. Crospovidone is polyvinylpyrrolidone derivative, insoluble in water, rapidly spread and swell in water but does not form gel even though in a long duration. It is the best superdisintegrant and has high surface area-volume ratio. Croscarmellose sodium is a cross-linked sodium salt of carboxymethyl cellulose, highly hydrophilic so that having a large swelling capacity. Both of them are included into modified cellulose group, which is a very important ingredient in orally disintegration system because they produce rapid disintegration.

There have been some studies evaluating the effects of crospovidone and croscarmellose sodium as superdisintegrants on the characteristics of oral solid dosage form^{6,7,8}. However, the differences of their effects on the characteristic of ODT are still unknown. Therefore, this study is aimed to compare the characteristic of ODT formulated by using crospovidone and croscarmellose sodium as superdisintegrants.

Piroxicam is a non steroidal anti-inflammatory drug (NSAID), analgesic, and antipyretic that needs rapid release from its dosage form to achieve pharmacological response in therapy, so it is considered to be an ideal drug to be made into ODT dosage form. Piroxicam is sparingly dissolves in water. To increase its solubility in water, the particle size needs to be reduced into nano scale or nanoparticle. This is due to ODT must rapidly dissolve into saliva, so that its formulation must consist of ingredients that readily dissolve in water⁹.

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), and other laboratory glassware (Pyrex).

Material

Piroxicam nanoparticles with size ranged between 455-772.9 nm (LIPI, Indonesia), 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 nanoparticle ODT

The tablets were prepared by using direct compression method. The components of each formulation are showed in Table 1.

Table 1. Formula of piroxicam nanoparticles ODT varying in the composition of superdisintegrants.

Components (mg)	Formulation Code						
	ODT1	ODT2	ODT3	ODT4	ODT5	ODT6	ODT7
Piroxicam nanoparticles	10	10	10	10	10	10	10
Crospovidone	5	-	10	-	20	-	5
Croscarmellose Na	-	5	-	10	-	20	5
Microcrystal cellulose	172	172	167	167	157	157	167
Aspartame	10	10	10	10	10	10	10
Mg Stearate	2	2	2	2	2	2	2
Talcum	1	1	1	1	1	1	1
Total	200	200	200	200	200	200	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 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.

Dissolution test

The in vitro drug release study was performed by using type 2 dissolution tester (paddle method) with medium of 900 ml of 0.1N HCl solution at 37 ± 0.5 ° C at rotation speed of 75 rpm within 40 minutes. At certain intervals of time, 10 ml samples were withdrawn and filtered. Five milliliters of the filtrate were put into 10 ml volumetric flask and diluted with the dissolution medium (on each sampling occasion, fresh medium with the same sampling volume was added to keep the volume constant). This solution was then measured for its absorbance by using UV spectrophotometer at a wavelength of 334 nm. Then the cumulative percent of drug release was measured.

Results and Discussion

The results of characteristics evaluation of all formulations are showed in Table 2.

Table 2. The results of characteristics evaluation of all formulations.

No.	Formula	Drug Content (%)	Hardness (kg)	Friability (%)	Disintegration Time (second)			Wetting Time (second)
					<i>Disintegration tester</i>	<i>Modified test</i>	Oral cavity test	
1	ODT1	91,75±2,17	3,50±0,52	0,46	8,50±0,84	67,33±1,51	60,00±1,67	54,33±7,12
2	ODT2	94,54±1,83	3,12±0,31	0,47	7,83±0,41	50,83 ±3,76	41,00±3,90	42,33±4,03
3	ODT3	91,18±1,15	3,66±0,31	0,33	7,50±1,05	65,17±2,04	56,00±1,90	53,16±5,85
4	ODT4	92,46±0,88	3,52±0,26	0,31	4,17±0,75	41,33±2,07	32,00±2,37	32,83±3,43
5	ODT5	95,25±2,11	3,62±0,49	0,35	5,67±0,82	63,17±3,97	53,67±4,13	42,33±4,23
6	ODT6	92,68±3,61	3,62±0,33	0,36	6,33±1,03	49,50± 2,81	40,67±3,14	36,66±3,20
7	ODT7	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%¹⁰. The results of the assay showed that all ODT formulions in this study have met this requirement and there is no consistent trend that influenced by the superdisintegrants used in the formulation.

The hardness of ODT in this study was lower compared to that of conventional tablet, which is range between 4-8 kg¹¹. This is because ODT is designed with a rapid rate of disintegration, has a high porosity to water absorption, resulting in decrease of tablet hardness². This study found that there is no correlation between the superintegrants used with tablet hardness.

Meanwhile, friability test results indicate that sodium croscarmellose will provide a better friability compared to crospovidone. Nevertheless, the use of high superdisintegrant (20%) will reduce the friability.

In contrast to the requirements of conventional tablet disintegration time test that uses acid or buffered medium, the medium used in the ODT disintegration time test is water. This is because ODT is designed to disintegrate in the oral cavity and dissolve in saliva, whose composition is mostly water². The results of disintegration time test of all ODT formulations showed that the disintegration time tested by using a disintegration tester was faster than the disintegration time tested in the oral cavity and the disintegration time tested in the oral cavity was faster than the disintegration time tested by modified test.

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.

The disintegration time test results also showed that the used of croscarmellose sodium as superdisintegrant will provide faster disintegration time on ODT than using crospovidone. The higher the concentration of superdisintegrant used, the shorter the time required for the tablet to disintegrate perfectly. However, the use of high concentrations of croscarmellose sodium (20%) showed slower disintegration time than the use of croscarmellose sodium in lower concentration (10%). This was shown by the tablet's core which remained dry and hard, as seen in Figure 1.

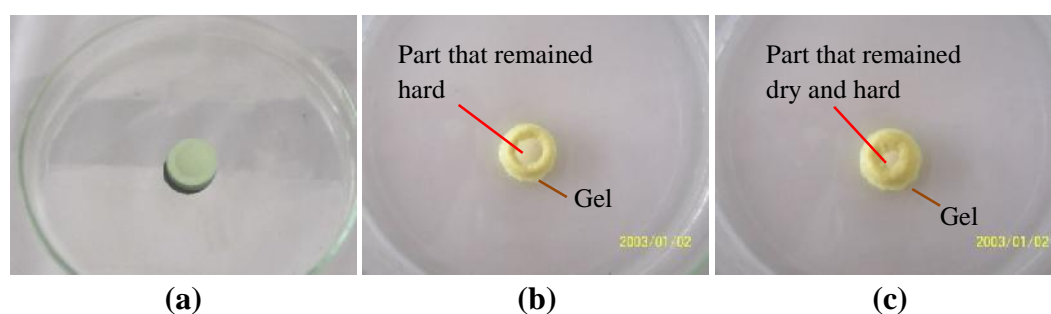


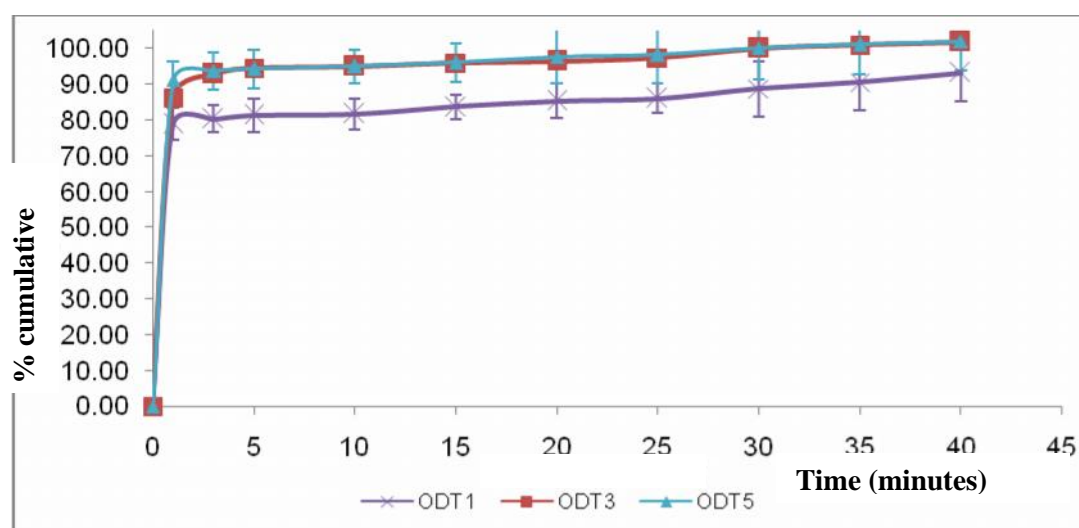
Figure 1. The process of modified disintegration time test. ODT6 with 20% croscarmellose sodium as superdisintegrant: (a) beginning, (b) at 15th second, and (c) at 30th second.

According Camarco, et.al., this happened because at high concentrations, croscarmellose sodium will form a gel that inhibits water penetration into the tablet core¹².

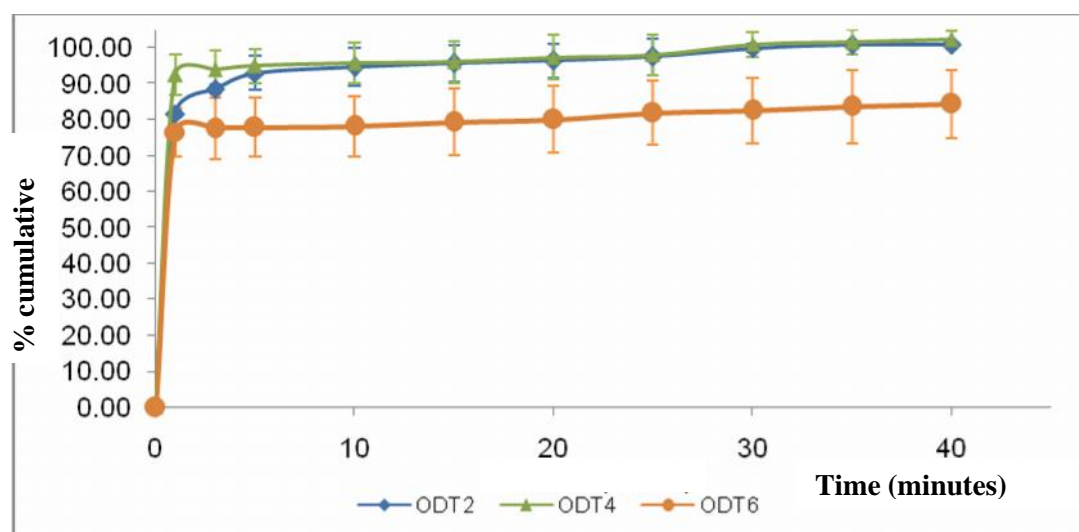
The same conclusion was also obtained for wetting time test. The results of wetting time test also showed that the higher the concentration of superdisintegrants used, the wetting time is shorter. Wetting time in formulation with crospovidone as superdisintegrant is longer than that of formulation with croscarmellose sodium as

superdisintegrant. This is due to the capillarity nature of crospovidone which is difficult soaked in water compared to the properties of croscarmellose sodium which is very hydrophilic. 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 process¹³.

After beginning with the wetting process, ODT will experience the process of disintegration and the subsequent release of active ingredients or dissolution. Dissolution rate is also highly dependent on the rate of disintegration process. This was proven by the results of dissolution test in this study, which were consistent with the results of disintegration time test, ie the higher the concentration of the superdisintegrant used, the higher the % cumulative of drug released at the same time interval, but specifically for ODT that used croscarmellose sodium as superdisintegrant, its % cumulative of drug released decreased with the use of high concentrations of croscarmellose sodium (20%). However, the dissolution profiles of ODT that used croscarmellose is still generally better than that of ODT that used crospovidone. Dissolution profiles of ODT that used croscarmellose sodium and crospovidone as superdisintegrants can be seen in Figure 2.



(a)



(b)

Figure 2. Dissolution profiles comparison of piroxicam nanoparticles ODT with crospovidone (a) and croscarmellose sodium (b).

Meanwhile, the use of combination superdisintegrants at the same concentration, respectively 5% on ODT7 formula (total superdisintegrant is 10%) did not give better results compared to single use of each superdisintegrant with the same total concentration of the formula ODT3 and ODT4. In contrast, % cumulative of drug observed in ODT7 was lower than ODT3 and ODT4. Comparison of dissolution profiles of these three formulas can be seen in Figure 3.

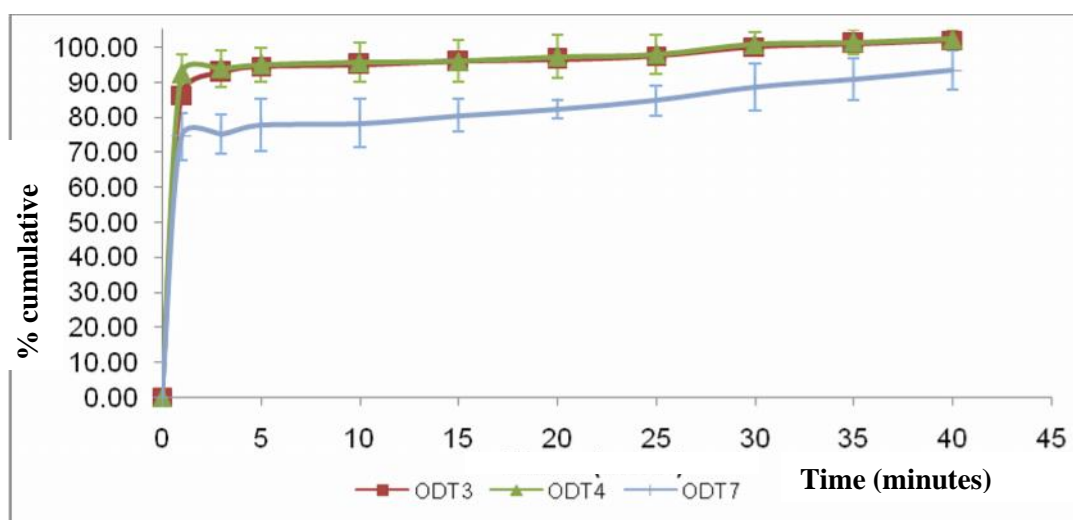


Figure 3. Dissolution profile comparison of piroxicam nanoparticles ODT with total superdisintegrant concentration 10%, ie 10% crospovidone (ODT3), 10% croscarmellose sodium (ODT4), and 5% crospovidone + 5% croscarmellose sodium (ODT7).

CONCLUSION

Although crospovidone and croscarmellose sodium are used with the same function in the formulation and include in the same group of superdisintegrant, that is modified cellulose, both have different characteristics that worthy for attention when they will be used in the development of ODT formula. Overall, the results of this study indicate that croscarmellose sodium will provide better ODT characteristics compared to crospovidone in aspect of friability, disintegration time, wetting time, and dissolution profile. However, the limitation observed is croscarmellose sodium cannot be used in high concentrations (over 20%) in the formulation because it will lead to the formation of a gel that inhibits water penetration into the tablet core that would decrease the rate of wetting and disintegration of the ODT.

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