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# Formulation of Ibuprofen Orally Disintegrating Tablets (ODTs) by Lyophilization Method using Gelatin and Mannitol

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**Abstract: Background:** Orally Disintegration Tablet (ODTs) are solid dosage forms containing active pharmaceutical ingredient (API) which disintegrate rapidly, usually less than 60 seconds without the need of water when placed on the tongue. Ibuprofen, which is practically water insoluble, shows low bioavailability. Lyophilization is one of the technique that can solve this problem in ODTs formulation.
**Objectives:** To formulate Ibuprofen ODTs by using lyophilization technique and to determine the effect of formulation process and the excipients.
**Methods:** Ibuprofen ODTs were formulated by using water soluble matrix consisting gelatin 5% and mannitol in the ratio 0:200; 50:150; 100:100; 150:50; 200:0. The resulting tablets were evaluated using parameters such as: hardness, friability, disintegration time in vitro, modified disintegration time, disintegration time in the oral cavity, wetting time, water absorption ratio, drug content determination, weight uniformity, and dissolution.
**Result:** The results showed that ibuprofen Orally Disintegrating Tablets fulfilled the requirements for all parameters except for F5 formula that did not produce physical shape intact tablet. ODTs used higher amount of gelatin 5% showed faster disintegration time [19 s (F1); 29.2 s (F2); 36 s (F3) and 57.5 s (F4)]. In contrast, the higher amount of mannitol used in ODTs formula, tablet hardness were also higher. *In vitro* drug release of all formulation ODTs showed fast drug release in the first minute where the F1 97.77%; F2 89.66%, 87.80% F3; F4 72.97%, much different with pure ibuprofen only release 27.15%. From ANOVA test using SPSS program 15.0 ($p < 0.05$) showed significant differences dissolution profiles between all ODTs formula with pure ibuprofen.
**Conclusion:** Ibuprofen ODTs formulated by lyophilization process caused changing in the crystal into the amorphous form. Gelatin 5% acts as binder and disintegrant while mannitol affects the hardness of ODTs.
**Keywords:** orally disintegrating tablet, ibuprofen, gelatin, mannitol, lyophilization.

## Introduction

Orally Disintegrating Tablets are solid dosage form containing active ingredients that disintegrate and dissolve rapidly without the need of water in less than 3 minutes when placed on the tongue. The drugs that have low solubility in water (poorly soluble drug) are often a problem for this tablet formulation because they show low bioavailability. One of the most successful processes to overcome this problem is lyophilization[1,2].

Lyophilization is a process known as "freeze drying", related to the removal of water from products in the frozen state at extremely low pressures[3]. This technique can improve the solubility of drugs that have low solubility in water because when the lyophilization process occurs, porous structure of the matrix and many

amorphous form of the active ingredient will be form[4,5]. Ibuprofen, a compound included in the model of biopharmaceutical classification system (BCS) II, which is high permeability but low solubility, is used as active ingredient in ODT formulations. The primary objective of this study is to formulate Orally Disintegrating Tablets (ODTs) and to study the effect of excipients and the manufacturing process on the resulting ODTs.

Orally Disintegrating Tablets of ibuprofen were made using materials that are readily soluble in water, i.e. 5% gelatin as binder as well as disintegrant and mannitol as filler that affect the hardness of tablets as well as sweetener that can cause a cold sensation in the mouth. These materials were added to the five ODT formulations in varying amounts in order to see the effect of the two materials.

## Experimental Methods

### Apparatus

The apparatus used in this study were the freezer, freeze dryer (VirTis), disintegration tester (Copley), paddle-type dissolution tester, friabilator (Copley), hardness tester (Copley), spectrophotometer UV / Visible (1240 UVmini Shimadzu), mixer, stopwatch, digital balance (Henherr BL-H2), and other laboratory equipments.

### Materials

The materials used for this study were ibuprofen (Dexa Medica Company), gelatin gel with strength of 140 bloom, mannitol, NaOH p.a. (E. Merck), potassium phosphate mono-base p.a. (E. Merck), and CO2-free distilled water.

### Preparation of Ibuprofen ODTs

Ibuprofen ODTs were prepared by lyophilization process. The formula of ibuprofen ODTs can be seen in Table 1.

**Table 1.:** Formula of ibuprofen ODTs by lyophilization process, using a combination of 5% gelatin and mannitol as matrix with various concentrations.

| Formula | Materials (mg) | | | Total |
|---|---|---|---|---|
| | Ibuprofen | 5% Gelatin | Mannitol | |
| F1 | 200 | 200 | 0 | 400 |
| F2 | 200 | 150 | 50 | 400 |
| F3 | 200 | 100 | 100 | 400 |
| F4 | 200 | 50 | 150 | 400 |
| F5 | 200 | 0 | 200 | 400 |

Solution of 5% gelatin was freshly made for each ODTs formula, i.e. by scattering 5 grams of gelatin powder into cold water, allowed to expand, heated over a water bath until dissolved, made up to 100 ml by adding hot water, and used while hot. Then, all materials were weighed. Put 5% gelatin solution and mannitol into the mortar, add the ibuprofen mixed until homogeneous. The mixture was transferred to a glass beaker, stirred by using a mixer, and put in a blister with diameter of 13 and weight of 400 mg. Then put in the freezer until the preparation hardened and freeze dried the preparation to form lyophilization ODTs.

### Tablets evaluation

The resulting tablets were evaluated using parameters such as: hardness, friability, disintegration time *in vitro*, modified disintegration time, disintegration time in the oral cavity, wetting time, water absorption ratio, drug content determination, uniformity of dosage, and dissolution.

### Drug content determination

Twenty tablets of each formula were accurately weighed and powdered. Then, weighed the powder equivalent to 50 mg of ibuprofen. The powder was then put in a 100 ml volumetric flask, dissolved with 0.1 N NaOH and made up to 100 ml. The solution was filtered and the first few drops of filtrate were discarded. As

much as 11.5 ml of the filtrate was withdrawn, put in a 25 ml volumetric flask, and diluted with 0.1 N NaOH solution. This solution was then measured for its absorbance by using UV spectrophotometer at its maximum wavelength, and the content of ibuprofen was calculated. In Indonesia Pharmacopeia IV Edition, ibuprofen tablet must contained active ingredient not less than 90.0% and not more than 110.0% of the amount listed on the label.

**Hardness test**

Hardness test was carried out on 6 tablets of each formula by using hardness tester (Copley) Placed the tablets in the space provided on the device with a sleeping position, set the tool and pressed the button. The number shown in the digital screen when the tablet broke was the hardness of the tablets. The hardness requirements for ODT are 0.1 to 3 kP.

**Friablility test**

Ten tablets of each formulation were cleaned from dust and weighed. The weight was recorded (a gram). The tablets were then put into Copley friability tester and the friability tester was ran for 4 minute at speed of 25 rpm. Once completed, the tablets were removed, cleaned from dust, and then weighed again (b gram). The weight reduction showed friability value, expressed in percent of the initial weight of the tablet. Tablet friability value is considered good enough when 0.1-0.9%[6].

**Disintegration time test**

***Desintegration test by using desintegration tester (Copley) / In Vitro test***

This test was conducted on six tablets of each formulation with 800 ml water at 37º ± 2º C as medium. Each of the tablets was put into the baskets of the desintegration tester and the disintegration tester was ran at speed 30 times per minute. At the end of the time limit as specified in the monograph, the baskets were lifted and the six tablets was observed. All tablets should be disintegrate perfectly.

Requirement: the time required to disintegrate the tablet is less than one minute[7].

***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 volunteers to test four ODT formula that perfectly formed. 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[8].

**Wetting time test and water absorption ratio**

Circular filter paper placed in a 9 cm diameter petri dish filled with 9 ml of distilled water containing water soluble dyes (methylene blue). One tablet was placed gently in the middle of the petri dish, and then recorded the perfect wetting time of the tablets. Wetting time is the time it takes to make the top surface of the tablet to absorp color. The tablet was weighed before and after wetted. Water absorption ratio was calculated by the formula R = (wa - wb) / wb x 100% where wb is the weight of the tablet before absorbs water and wa is the weight of the tablet after absorbed water[9]. The test was carried out on 6 tablets.

**Weight uniformity test**

This test was conducted on ten tablets taken randomly from each formula. The tablets were weighed one by one. Calculate the average weight for a tablet. From the results of drug content determination test, count the active ingredient of each tablets by assuming that each tablet was homogeneously distributed. The

requirements for weight uniformity is between 85.0 to 115.0% of that stated on the label, and the relative standard deviation is less than or equal to 6.0%[10].

**Analysis of X-ray Diffraction Patterns**

Ibuprofen powder and Ibuprofen ODT from lyophilized process were recorded on X-ray diffraction system using Cu radiation source, voltage of 40 kV, and current of 30 mA. Observations were made at 2θ and scanning speed of 0,020 º per second.

**Dissolution test**

The dissolution test was performed by using type 2 dissolution tester (paddle method) with medium of 900 ml phosphate buffer at 37º ± 0.5º C with rotation speed of 75 rpm within 60 minutes. At certain intervals of time, 1 ml samples were withdrawn and put into 25 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 maximum wavelength. Then the cumulative percent of drug release was measured. This test was conducted on six tablets.

## Results and Discussion

Of the five formulas, there was a formula that did not produce physically intact tablet, i.e. F5. This happened because this formula only contained one mannitol as the matrix without 5% gelatin which served as matrix binder. The results of the evaluation of ibuprofen ODT formulated by lyophilization process using 5% gelatin and mannitol as matrix can be seen in Table 2.

**Table 2.** The results of the evaluation of ibuprofen ODT formulated by lyophilization process using 5% gelatin and mannitol as matrix

| Formula | Drug content (%) | Hhardness (kg) | Friability (%) | Disintegration time (second) | | | Wetting time (second) | Water absorption (%) | Weight uniformity | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | In vitro | Modified test | Oral Cavity test | | | Drug content and SD | RSD |
| F1 | 100,6583 ± 0,31093 | 2,08 ± 0,3332 | 0,89 | 19,00 ± 0,00 | 82,10 ± 0,32 | 7,1 | 52,95 ± 0,7064 | 65,93 ± 1,57 | 100,84 ± 1,73 | 0,86 |
| F2 | 100,7300 ± 0,44583 | 2,34 ± 0,2913 | 0,70 | 29,17 ± 1,17 | 90,97 ± 0,31 | 12,5 | 60,50 ± 0,4604 | 54,95 ± 3,68 | 100,88 ± 1,61 | 0,80 |
| F3 | 100,0150 ± 0,90612 | 2,35 ± 0,1319 | 0,66 | 36,00 ± 2,28 | 94,10 ± 0,30 | 15,3 | 62,27 ± 1,6367 | 51,31 ± 1,85 | 100,89 ± 0,33 | 0,16 |
| F4 | 100,8100 ± 0,46312 | 2,65 ± 0,2619 | 0,55 | 57,50 ± 2,59 | 111,10 ± 0,26 | 21,2 | 90,47 ± 0,5317 | 43,24 ± 1,49 | 101,18 ± 0,69 | 0,34 |

Based on this study results, the content of ibuprofen in various formula that produced intact tablets by the lyophilization process, can be seen in Table 2, has met the requirements applied in Indonesia Pharmacopeia IV Edition, which is 90.0% to 110.0%.

Orally Disintegrating Tablets (ODT) was designed to have a rapid disintegration and dissolution, so that tablets generally have high porosity to ensure rapid absorption of water into the tablet[8]. Therefore, in general, ODT has a lower hardness than conventional tablet hardness (4-8 kg). In this study, we found that the higher the amount of mannitol added, the higher was the hardness. This was due to the nature of mannitol to produce stiffness in tablet and thus affected the hardness of tablets resulted by lyophilization process[4,11].

Friability or weight loss experienced by each type of tablet was good, if the range between 0.1 to 0.9%[6]. The results of friablility tests in this study were in accordance to the requirements, which were ranging from 0.55% to 0.89%.

Table 2 showed that the *in vitro* disintegration time of all ODT formulas was faster than that of modified test because the matrix used was water soluble so that it has a rapid absorption of water when the ODT submerged in the medium as well as the effect of stirring rate of disintegration tester. In modified disintegration time test, the medium was used relatively less and there was no stirring. The disintegration time of *in vivo* test in the oral cavity showed the fastest disintegration time than the other two types of disintegration time test. This was presumably due to the peristaltic movements of the tongue and the effect of saliva in the oral cavity. Although the movement was not faster than the stirring rate in disintegration tester tool and the fluid in the mouth was less than the medium used in other two types of disintegration time test, test in the oral cavity was affected by the pH of saliva which was alkaline, so that it helped to speed up the tablet disintegration time.

In addition, the results also indicated that the higher the 5% gelatin used, the disintegration time was faster. This was because in the lyophilized formulation process, water was removed by sublimation which induced the formation of amorphous pore structure of the tablet. The more the amount of 5% gelatin used, the more water was removed and the more porous structure was formed. So the disintegration time was faster.

The wetting time of each formula was not more than 3 minutes. It can be seen that the higher the amount of 5% gelatin used, the wetting time was faster. This was presumably due to the higher the amount of 5% gelatin used, the amount of water removed from the tablet in the freeze drying process was also higher, so that the pores were formed even more. Consequently penetration/absorption of water occured faster. This led to the time required for the tablet to be perfectly wetted became faster.

From Table 2, it can be seen that the higher amount of 5% gelatin in a formula, then the percentage of water absorption was higher. This was because the nature of gelatin that can expanded when came in contact with water. By the nature of this inflatable gelatin, water can be absorbed even more.

X-ray diffraction of ibuprofen showed an intense sharp peak. This indicated the crystalline nature of the drug as shown in Figure 1a. The similar X-ray diffraction patterns were observed in the results of the analysis of all ODT formula (Figure 1b, 1c, 1d and 1e), which indicated that the same substances contained in all ODT formula. The difference lay on the lower intensity of the peak. This showed crystal form of the drug changing to the amorphous form[12].

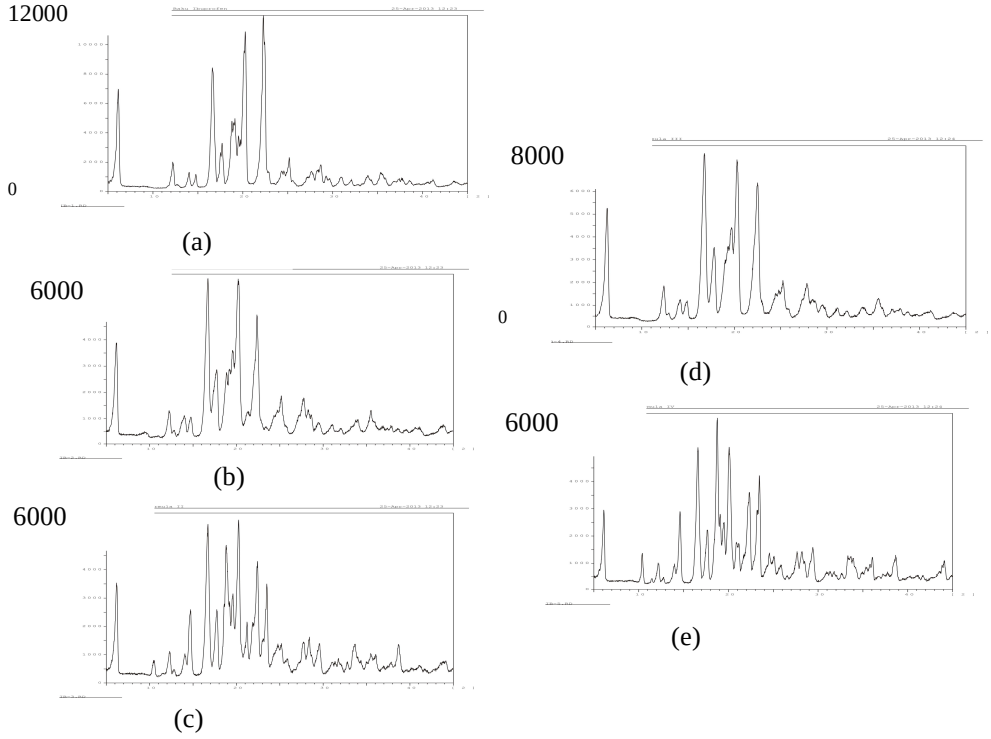

**Figure 1**. Results of X-ray diffraction patterns of: (a) ibuprofen; (b) ODT F1; (c) ODT F2; (d) ODT F3; and (e) ODT F4.

The dissolution test results can be seen in Figure 2.

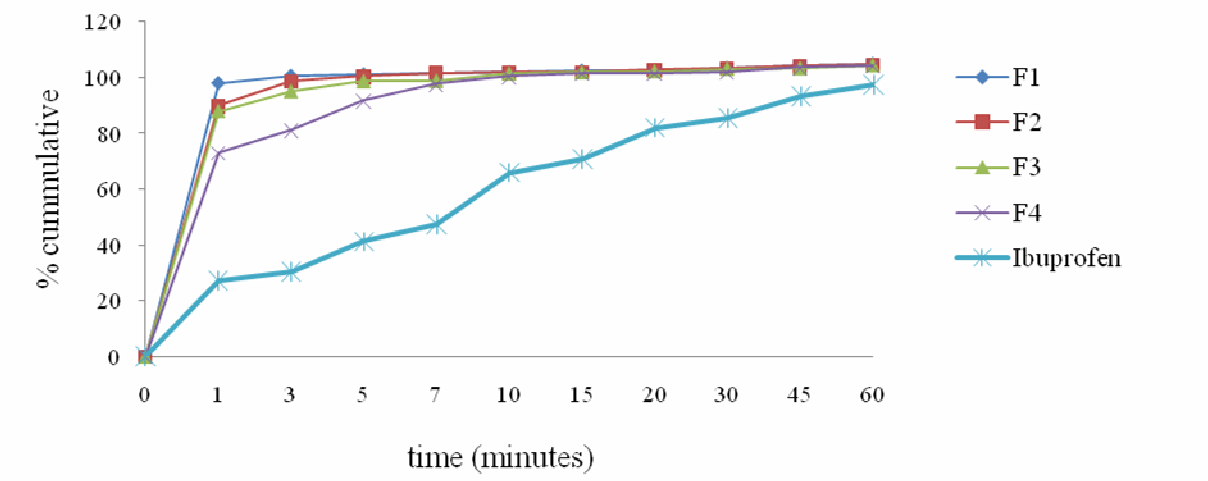


**Figure 2.** Percent cummulative versus time of ibuprofen ODT and pure ibuprofen

For comparison, dissolution test was also performed on pure ibuprofen obtained from Dexa Medica Company, Indonesia. All ODT formula already showed high percent cumulative, i.e. F1 of 97.77%; F2 of 89.66%; F3 of 87.80%; and F4 of 72.97%. These results showed a significant difference from that of pure, which only 27.15% in the first minute. This was because ODT formulated by using 5% gelatin with lyophilization process. Like has been explained before, in this lyophilization process water was removed by sublimation which induced the formation of amorphous pore structure of the tablet. The more amount of 5% gelatin used, the more water was removed and the more porous structure was formed. Thus, it increased the solubility of drug.

## Conclusion

Ibuprofen ODT formulated by the lyophilization process causes changes in the crystalline form of the active compound into an amorphous form and 5% gelatin serves as a binder as well as disintegrant thus increasing disintegration time and dissolution rate of water-insoluble drugs. Mannitol act as filler and can affect the hardness of ODT formed due to its nature.

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