Optimization and Assessment Orally Disintegrating Tablet of Using Biopolymer Combination

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Abstract. Orally Disintegrating Tablet (ODT) or a crushed tablet in the mouth is one of the most useful drug preparations for geriatric and pediatric patients who have difficulty swallowing conventional tablets. This research aims to determine the effect of single and combination biopolymers. The optimization of the disintegration time of ODT preparations did by 11 formulas printed with direct press technique. It consisted of single biopolymers and combinations of Chitosan, Xanthan gum, Carboxymethyl cellulose, and Maltodextrin. Evaluation of ODT preparations begins with an evaluation of formulation, which includes the flow rate test, fixed angle, and compressibility index. The evaluation of the formulated ODT measured by size and weight uniformity test, hardness test, rigidity test, and wetting time test. Also, in vitro and in vivo disintegration test. All formulas meet the ODT physical quality requirements. ODT 8 is an ODT formula that uses a disintegrant combination of biopolymer Chitosan and Maltodextrin. It shows the fastest disintegration time is 19 seconds. The statistical test showed a significant difference between the ODT formula to the optimization of disintegration time with a value of p < 0.05. ODT with a biopolymer combination has a faster disintegration than ODT with a single biopolymer.

1. Introduction

Natural polymers, known as biopolymers produced or derived from renewable natural resources, can be decomposed and do not produce toxins. Biopolymers are much glimpsed by industry for several reasons, namely unlimited natural resources, bio-compatible and biodegradable (can be described), have good mechanical properties, have been designed and optimized naturally to fulfill a certain task, easy to make derivatives with the nature as desired.

The most common biopolymers found in nature and in various industries are cellulose groups, for example Carboxymethyl cellulose (CMC). The second largest biopolymer is chitin, like chitosan [1]. Xanthan gum and Maltodextrin are also many other classes of biopolymers [2]. Maltodextrins are oligosaccharides belonging to prebiotics. Starches of this group provide more benefits in the food industry, even pharmaceuticals [3]. Some biopolymers derived from natural polysaccharides that have binding and expanding properties (swelling) in the air are suitable to be formulated as disintegrants (crushers) that can provide instant disintegration in ODT preparations. Drug delivery systems are a means of strategy for product development and extending the product life cycle in the pharmaceutical market. In order to assist patients, several rapidly destroyed drug delivery systems have been developed [4]. One of them is Orally Desintegrating Tablet (ODT). ODT or crushed tablets in the mouth is one of the most useful drug dosage to geriatric and pediatric patients who have difficulty in swallowing conventional tablets or capsules [5]. According to the FDA (Food and Drugs
Administration, USA), ODT is defined as a solid dosage form containing the active compound of the drug, which can be destroyed rapidly, usually in seconds, when placed on the tongue. The main criterion of ODT is rapidly destroyed in the oral cavity with the help of saliva in 15 to 60 seconds [6]. The desiccant (desintegrant / superdesintegrant) is used to meet the criteria by which the tablet is destroyed at a set time limit. Based on the description above, the researchers are interested in conducting research by formulating biopolymers into crushers in ODT preparations.

2. Methodology

2.1. Materials
The ingredients in this study are Chitosan, Xanthan gum (Qingdao Rich Trading Co., Ltd., China), Carboxymyl Cellulose (Qingdao Rich Trading Co., Ltd., China), Maltodextrin (Zhucheng Dongxiao Biotechnology Co., Ltd.), China, Avicel® PH 102 (DMV-Fonterra Excipient GmbH & Co KG, Germany), Manitol (Qingdao Bright Moon Seaweed Group Co., Ltd., China) Magnesium stearic, Talkum.

2.2. Methods
ODT’s are made in 500 mg direct print with tablet weight and 12 mm cross section. biopolymer was used as a desintegrant. The composition of ODT seen can be seen in Table 1.

| Formulation | Code | Z.A | K | XG | Mal | CMC | Talk | Mg.S | Man | AVL | Total (mg) |
|-------------|------|-----|---|----|-----|-----|------|------|-----|-----|------------|
| ODT₁        | 50   | 75  | - |   |     | 2.5 | 2.5  | 35   | 335 | 500 |
| ODT₂        | 50   | -   | 75 | -  |     | 2.5 | 2.5  | 35   | 335 | 500 |
| ODT₃        | 50   | -   | - | 75 | -   | 2.5 | 2.5  | 35   | 335 | 500 |
| ODT₄        | 50   | -   | - |   | 75  | 2.5 | 2.5  | 35   | 335 | 500 |

Description :
K = Chitosan = (Desintegrant)Biopolymer
XG = Xanthan Gum = (Desintegrant)Biopolymer
Mal = Maltodextrin = (Desintegrant)Biopolymer
CMC = Carboxymethyl Cellulose = (Desintegrant)Biopolymer
AVC = Avicel = Material Filler
Man = Mannitol = Sweetener Material
Talk = Talkum = Lubricant
Mg.S = Magnesium Stearate = Lubricant Material

Each material is weighed and then put into the mixture and mixed until homogeneous. The homogeneous mixture is then printed directly with the tablet press machine.

2.3. Evaluation of Time Destroyed In Vitro
One tablet is inserted in each tube of basket and used water temperature 37° ± 2° as medium, then tool run. The crushed time of the tablet is recorded that since the basket containing the tablet is raised down until the tablet is destroyed. Tablets declared destroyed if no part of the tablet left behind dikasa [7].

2.4. Evaluation of Wetting Time Test
The time of wetting the tablet is slowing down using a simple procedure. Circular filter paper is available in a 8.5 cm diameter petri dish, then 8 ml of Ponceau color is 0.1% b / v in distilled water
into the petri dish. The test is carried out with one tablet on the paper base in the petri dish, gradually. The time needed to make the surface of the tablet uses the color of wetting [8].

2.5. Evaluation of time destroyed In Vivo

This test uses 6 volunteers. Before the test runs, each volunteer is required to wake his mouth, then attach one ODT tablet on top of their tongue and leave the tablet completely destroyed. The time it takes for the tablet to crumble without chewing is calculated, after which the tablet is immediately spit out. Repeat 3 times for each volunteer. The end point for the crushed time of the mouth is the time when the tablet wrapped in the tongue becomes crushed (the tablet is not intact anymore).

3. Result And Discussion

Result of Time Destroyed In Vitro

| Formulation Code | Average First Disintegration Time | Average Total Disintegration Time |
|------------------|----------------------------------|----------------------------------|
| ODT1             | 9 seconds                        | 24 seconds                       |
| ODT2             | 10 seconds                       | > 15 minutes                     |
| ODT3             | 1 minutes                        | 3 minutes                        |
| ODT4             | 5 minutes                        | > 15 minutes                     |

Description:
* = 3 repetition treatments

Based on Table 2 it can be concluded that the formula which has a total disintegration time below 30 seconds is ODT1 which contains chitosan as disintegrant. Chitosan as disintegrant (ODT1) gives 24 seconds of disintegration, Although chitosan is known to be unable to dissolve in water, it can dissolve easily in acids, but the expanding power of this compound is so strong that when in direct contact with chitosan water as disintegrant it expands rapidly. According to [9], the disintegrant material is added to facilitate the breaking or breaking of the tablet when in contact with liquids, it can also function to draw water into the tablet, expand and cause the tablet to break. This mechanism also applies to maltodextrin compounds which are not only easy to expand but are also easily soluble in water. Because it is easily soluble in water, maltodextrin in the formula (ODT3) has the ability to add sticky power (cohesion) between particles when in contact with water, so that the density of granules will be higher which causes the disintegration time to be a little longer, when compared to disintegration chitosan in formula (ODT1).

Table 4.1 also shows that some formulas that have a disintegration time do not comply with ODT requirements, which is> 15 minutes. Some of these formulas are ODT2 (xanthan gum); ODT4 (CMC). Based on this description, it can be concluded that CMC and xanthan gum in this study cannot be said to be disintegrated in ODT formulations because they cannot provide instant disintegration time. This shows that the above formulas are also not suitable for conventional tablet disintegration, so it is more appropriate to use excipients in slow-release dosage formulations or controlled release.

This can be caused because xanthan gum is one type of soluble fiber so that it has the properties to form a gel if it mixes with liquid (liquid) and decreases disintegration power [10]. Likewise with CMC, which not only can be disintegrant but also as thickener, so CMC is able to bind water when in contact with water and water molecules are trapped in the gel structure formed by CMC, so that the disintegration power decreases and decays slowly, not instantaneously [11]. This can be overcome by formulating CMC or xanthan gum as a disintegrant with the right concentration so that the disintegration power is still better than the binding capacity when in contact with liquids. Based on the description above, the researchers chose the ODT1 formula as a formula with the fastest in vitro disintegration time to be evaluated in the wetting and disintegration stages in vivo.
Result of Wetting Time Test

Wetting time is one of the important parameters in ODT evaluation. The time of wetting is used as an indicator of the destruction of tablets in the oral cavity [12]. Table 3 has presented the results of ODT wetting time evaluation in this study.

| ODT1 | Wetting time (detik) | Wetting time average (detik) |
|------|----------------------|-----------------------------|
| Tablet 1 | 49,45 |  |
| Tablet 2 | 52,02 | 50,60 |
| Tablet 3 | 50,34 |  |

Table 3 Results of Wetting Time Evaluation

**Figure 1. Wetting Time Test**

| Tablet 1 | 0 detik | 30 detik | 49,45 detik |
|----------|---------|----------|-------------|
| Tablet 2 | 0 detik | 30 detik | 52,02 detik |
| Tablet 3 | 0 detik | 30 detik | 50,34 detik |
Table 3 shows that the ODT1 formula fulfills the expected criteria for ODT in this study, because the average wetting time of tablets is <60 seconds, which is 50.60 seconds. Wetting time is related to disintegration time. According to [13], the rapid destruction of oral tablets is a contribution from the use of disintegrant and pores forming. This porosity can make saliva to penetrate into the tablet which in turn causes increased disintegration time.

Result of Time destroyed In Vivo

Evaluation of disintegration time in vivo is a parameter needed to determine the disintegration time of ODT in the mouth. The end point for disintegration time in the mouth is the time when the tablets placed on the tongue are destroyed until there are no intact lumps [14]. Table 4 has presented the results of the in vivo ODT disintegration time evaluation.

Table 4 Results of Evaluation of Tablet Disintegration Time In Vivo

| ODT1   | Disintegration time in vivo (seconds) | Disintegration time in vivo average (seconds) |
|--------|-------------------------------------|---------------------------------------------|
| Volunteer 1 | 60,49                                      | 60,55                                      |
|         | 60,56                                      |                                             |
|         | 60,60                                      |                                             |
| Volunteer 2 | 60,52                                      | 60,12                                      |
|         | 60,29                                      |                                             |
|         | 59,57                                      |                                             |
| Volunteer 3 | 60,31                                      | 59,65                                      |
|         | 60,20                                      |                                             |
|         | 58,45                                      |                                             |

The results of the in vivo ODT1 disintegration test can be seen in Table 4 which shows that all formulas met the expected criteria as ODT in this study, because the average disintegration time of tablets obtained was about 59 to 60 seconds. The fastest average in vivo disintegration time is 59.65 seconds indicated by the third volunteer, this is in accordance with the expected ODT criteria which is <60 seconds. This indicates that the tablet will be destroyed when in contact with saliva in the mouth. Longer in vivo disintegration time than wetting time can be caused due to the low amount of saliva (about 2 ml) in the mouth [15].
Figure 2. Evaluation of Tablet Disintegration Time In Vivo

| Tablet 1 | 0 detik | 30 detik | 60,31 detik |
|----------|---------|----------|-------------|
| Tablet 2 | 0 detik | 30 detik | 60,20 detik |
| Tablet 3 | 0 detik | 30 detik | 58,45 detik |
CONCLUSION
Biopolymers can be used as disintegrants with different abilities. Biopolymers of CMC and xanthan gum provide unintentional disintegration power, whereas Chitosan and Maltodextrin biopolymers can provide instant disintegration so that they are suitable to be used for disintegrant in the formulation of Orally Disintegrating Tablet.

ACKNOWLEDGEMENT
We would like to thank academic community of University of Muslim Nusantara Al Washliyah for all their scientific help and support throughout this study.

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