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Citrus maxima Pectin as Superdisintegrant: Preparation and Evaluation of Dextromethorphan Hydrobromide Orodispersible Film

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***Citrus maxima* Pectin as Superdisintegrant: Preparation and Evaluation of Dextromethorphan Hydrobromide Orodispersible Film**

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Abstract. *Citrus maxima* pectin has a function to serve as a superdisintegrant due to its hydrophilicity, its high methoxyl content, and its great affinity for water. It allows the acceleration of the disintegration time of the orodispersible film. This study aims to determine the superdisintegration effect of *Citrus maxima* pectin on orodispersible film characteristics. Initially, *Citrus maxima* pectins were extracted and evaluated for organoleptic properties, qualitative tests, loss on drying, ash content, equivalent weight, and methoxyl content. Orodispersible film of dextromethorphan hydrobromide was formulated in 5 formulas with varying concentrations of 2%, 4%, 6%, 8%, and 10%. The films were evaluated for their organoleptic properties, uniformity of weight, thickness, tensile strength, elongation, pH, disintegration time, determination of content, and drug uniformity. The pectin from *Citrus maxima* has been successfully extracted to produce high purity and to include the type of HMP. Orodispersible film DH has been made and has met compendial standard parameters as they showed to have disintegration time of 48.5-59 seconds, a tensile strength of 20.59 - 32.45 kg/cm², and elongation of 38.8 - 44%. The results showed that the increasing concentration of *Citrus maxima* pectin will accelerate the disintegration time, increase the elongation, and decrease the tensile strength.

1. Introduction

Orodispersible films as thin films have been explored as a novel drug delivery tool and an alternative approach to conventional dosage forms. The films are fast dissolving dosage form, self-administrable, and convenient to swallow (1). Thin films have been proved to possess the capabilities to improve the onset of drug action, to reduce the dose frequency, and to enhance drug efficacy (2). The orodispersible film is intended to rapidly disintegrate and dissolve in the oral cavity by adding superdisintegrant, both natural, semi-synthetic, and synthetic.

Superdisintegrant affects the rate of film disintegration by increasing moisture penetration and dispersion. The bioavailability of the drug is affected by film disintegration. Its mechanism of action is swelling or wicking or chemical reactions or enzymatic action (3). There are two types of superdisintegrant; namely natural and synthetic superdisintegrants. Pectin is a natural superdisintegrant, which is relatively cheaper, its availability is abundant, non-irritating, and non-toxic. Pectin is a polysaccharide found in all plant tissues in the cell walls. This thus becomes an advantage because it is easy to obtain. Malviya et al. states that pectin from mango skin is a good candidate as a superdisintegrant because it has good solubility and high swelling index (4).

Dextromethorphan hydrobromide (DH) is used as a drug model. Dextromethorphan hydrobromide (DH) is an effective and safe antitussive drug found in several over-the-counter cough and cold



medicines (5). In the Indonesian market, dextromethorphan hydrobromide is formulated to various forms of conventional tablets, syrups, and lozenges.

This study used pectin from *Citrus maxima* as a superdisintegrant given its largest pectin sources, which is around 30%. Susilawati et al. stated that the extraction of grass jelly with citric acid could increase methoxyl levels to increase solubility and speed up the time of disintegration (6). The lower the levels of methoxyl in pectin, the more difficult it is to be dissolved in water, and vice versa. At the same time, the higher the level of methoxyl in pectin, the easier the pectin to be soluble in water (7). However, the use of pectin as a superdisintegrant has not been extensively investigated. Therefore, in this study, superdisintegrant concentration in general, was used 1-10% (8).

2. Methodology

Materials

Dextromethorphan hydrobromide (Divi's Laboratories, India), *Citrus maxima* skin powder (BALITTRO, Bogor, Indonesia), citric acid (Monodon Group), HPMC (Dow Chemical Company), glycerol (PT. Putra Primajaya), sucrose (Cap-Bintang Indonesia), menthol (PT. Samiraschem), methylparaben and propylparaben (Ueno-Japan).

Extraction of *Citrus maxima* pectin

The extraction procedure in this study followed the acid heat extraction method, as adopted by Liew et. al., with modifications. A total of 0.25gram of citric acid was dissolved in 250 ml of aquadest to pH 2. It was then added to 50gram *Citrus maxima* skin powder and subsequently refluxed at 70°C for 6 hours. The extract was filtered with a filter cloth. The filtered filtrate was poured into a beaker glass and cooled. 96% alcohol was added with a volume ratio of 1: 1 and deposited for 24 hours. The precipitate was filtered with a filter cloth and washed again with 96% ethanol to remove the acid. Pectin gel was dried in an oven at a temperature of 35-45°C for 24 hours (9). The dried pectin was then weighed.

Characterization of *Citrus maxima* pectin

The extracted pectin was characterized for various physicochemical properties such as organoleptic properties, identification test, determination of moisture, ash content, equivalent weight, and methoxyl content, which are described below:

a. Organoleptic properties and identification test (10)

The organoleptic test of the film was observed using the senses. The test identification procedure was (i) adding 9mL of water to 1g pectin which was then heated over steam until it dissolved then replaced the lost evaporation water. (ii) adding 50mL of water to 0.5g pectin and was stirred until dissolved; the solution was added ethanol P in the same volume. (iii) adding 1mL of NaOH 2N to 5mL solution (0.5 in 50) and was kept at room temperature for 15 minutes (iv) the gel from the previous test added hydrochloric acid 3N; the solution was shaken and precipitated forms that turn white and clumpy when heated.

b. Loss on drying and ash content

A-1 or 2g of sample was weighed in a bottle-weight, which had been preheated at 105°C for 30 minutes and weighed. The sample was flattened on bottom bottle-weight with 5-10mm thickness, dried in an oven with the lid opened at 105°C until constant weight (10). The ash content was determined using a furnace method with a temperature of 550°C (11).

c. Equivalent weight (EW) and methoxyl content (12)

The equivalent weight was measured by weighing carefully 0.5g pectin. A-5mL ethanol 96%, 100mL CO₂-free was distilled in water, and six drops of phenolphthalein indicator was added into Erlenmeyer; 1g NaCl was also added to sharpen the endpoint. The mixture was titrated with 0.1N NaOH until the

indicator was pale pink (pH 7.5) and lasted for at least 30 seconds. The neutral solution was used for the determination of methoxyl content. The methoxyl content was measured by adding 25mL NaOH 0.25N to neutral solution from EW determination. It was then stirred and kept in the solution for 30 minutes in a closed flask. Then, 25mL HCl 0.25N was added to the solution and was titrated with 0.1N NaOH until pale pink. Galacturonic content (% AUA) was calculated from the volume of NaOH obtained from the determination EW and the methoxyl content, as shown in equations (1), (2), and (3).

$$\text{Equivalent weight} = \frac{\text{pectin weight (mg)}}{\text{mL NaOH} \times N \text{ NaOH}}$$

$$\text{Methoxyl content (\%)} = \frac{\text{mL NaOH} \times 31 \times N \text{ NaOH} \times}{100 \text{ sample weight (mg)}}$$

$$\text{Galacturonic acid levels (\%)} = \frac{(\text{meq from NaOH CO}_2\text{-free} + \text{meq from NaOH for methoxyl}) \times 176 \times}{100 \text{ sample weight (mg)}}$$

Orodispersible film DH preparation

Films were prepared by the solvent casting method using pectin extracted as superdisintegrant at concentrations of 2%, 4%, 6%, 8%, and 10% w/w. Pectin and HPMC were dispersed with hot water while being stirred to form a clear gel using a magnetic stirrer. Dextromethorphan hydrobromide, sucrose, methylparaben, and propylparaben were dissolved in hot water. All ingredients were mixed until homogeneous. Menthol was dissolved with 2-3 drops of 96% ethanol, glycerol, and the remaining aquadest was added and stirred until homogeneous. The liquid film was poured into a mold and dried in an oven at 30-40°C for 24 hours. Afterwards, the film was cut to 2×2cm size. One mold is equivalent to 60 sheets with a weight of 250mg.

Table 1. Design formula of orodispersible film DH

| Materials | Quantity (% w/w) | | | | |
|---------------|------------------|-------|-------|-------|-------|
| | F1 | F2 | F3 | F4 | F5 |
| DH | 0,3 | 0,3 | 0,3 | 0,3 | 0,3 |
| Pectin | 2 | 4 | 6 | 8 | 10 |
| HPMC | 2 | 2 | 2 | 2 | 2 |
| Sucrose | 8 | 8 | 8 | 8 | 8 |
| Glycerol | 4 | 4 | 4 | 4 | 4 |
| Methylparaben | 0,18 | 0,18 | 0,18 | 0,18 | 0,18 |
| Propylparaben | 0,02 | 0,02 | 0,02 | 0,02 | 0,02 |
| Menthol | 0,1 | 0,1 | 0,1 | 0,1 | 0,1 |
| Aquadest ad | 100mL | 100mL | 100mL | 100mL | 100mL |

Evaluation of orodispersible film DH

a. Organoleptic properties, uniformity weight, and film thickness

The organoleptic test of the film was observed using the senses. The uniformity of weights was determined by weighing 20 sheets of film one by one, through which the average film weight was calculated. No more than two films should deviate from the average weight higher than the value in column A, and none of the films deviated from the average weight more than the value in column B (IPC, 2014). The film's thickness was calculated using a screw micrometer at five different points, and the average was then calculated.

b. Tensile strength dan elongation

Tensile strength and elongation was determined using Strogaph-R1 (Toyoseiki, Japan) with a force of 100kg. The film was cut with a Dumbbell ASTM-D-1822-L Crosshead at a speed of 25mm/minute.

c. Disintegration time

The film was placed in the middle of a 10cm diameter petri dish filled with 10mL aquadest. Time was measured from the beginning of the film was placed down until it became soft (film rupture). The time was recorded as the film's disintegration time (13).

d. Determination of pH

The acidity level was measured using a pH meter (LaMotte), which was calibrated using buffer pH 4 and pH 7. Electrodes were rinsed with distilled water and dried. pH measurement was carried out on the film solution before it was poured. The electrodes were dipped for ± 1 minute to obtain a stable value (IPC, 2014).

e. Determination of drug content and uniformity

Various concentrations of a standard solution with phosphate buffer pH 6.8 as a solvent were prepared to determine the maximum wavelength and the calibration curve of dextromethorphan hydrobromide. Ten sheets of film were dissolved by phosphate buffer pH 6.8 in a 100mL volumetric flask. The solution was sonified for 15min, which was then filtered. A-1mL of the filtrate was pipetted and diluted in a 10mL volumetric flask. Absorption was measured by UV-Vis spectrophotometer (Shimadzu UV-1601) (14).

Statistically analysis

Disintegration time test data were analyzed using one-way ANOVA to see differences between formulas. It was then followed by Tukey's test with a 95% confidence level ($\alpha = 0.05$).

3. Result and Discussion

Characterization of pectin

Extraction was carried out by hydrolyzing under acidic conditions with the reflux method at 70°C for 6 hours. The yield of pectin was $9.80 \pm 0.23\%$. This result is different from previous studies that obtained pectin as much as 12.1-20.5% with the microwaved-acid extraction method for 60 minutes at an acidity level of 1 to 2.5 (15). Pectin yield and physicochemical characteristics depend on the extraction method used and other parameters such as pH, temperature, extraction time, extraction acid, and liquid-solid ratio (9,16). Previous studies have shown that raw pomelo peels consist of 16.5% cellulose, 3.2% lignin, 6.9% hemicellulose, and 35.4% pectin (17). Pectin, a carbohydrate polymer consisting of connected α - (1,4) galactonic acid units, takes time to soften its structure to extract the pectin. The length of extraction time affects the time of contact or diffusion between the solvent molecule and *Citrus maxima*'s skin. Acidic pH conditions present high concentrations of hydrogen ions in the solvent to stimulate the hydrolysis of protopectin, which is a combination of cellulose compounds with pectin molecules (9) that can release maximum pectin under suitable extraction conditions (acid concentration and treatment temperature-time).

Table 2. Characterization of pectin from *Citrus maxima* peel

| Parameters | Results | Specifications* |
|-------------------|-------------------|-----------------------------|
| Ash content | $1.02 \pm 0,09\%$ | Max 10% |
| Loss on drying | $6.65 \pm 0,64\%$ | Max 12% |
| Equivalent weight | 612.7 mg | 600–800mg |
| Methoxyl content | 9.02% | High: >7.12% Low: <7.12% |
| Galacturonic acid | 80.22% | >65% |

* International Pectin Producers Association/IPPA (2001)

Organoleptically, the pectin obtained was in the form of yellow powder and odorless. The pectin identification test showed the formation of a rigid gel on cooling after heating, forming a bright precipitate after adding ethanol P, a semi gel under alkaline conditions, and a precipitate under acidic

conditions. Purity analysis to ensure pectin quality was carried out by determining moisture content, ash content, equivalent weight, methoxyl content, and galacturonic acid content (12). The study also determined the loss on drying to calculate the maximum limit of the compound lost in the drying process. Compounds that were lost by drying on pectin came from materials added to the extraction process.

Ash content that was calculated at 1.02% indicates the presence of inorganic compounds in pectin. This result is lower than pectin that was successfully extracted from *Citrus maxima* originating in Bangladesh, which was 5.70% (18) and the same as pectin originating from Brunei Darussalam, which was 1.07–2.82% (19). The equivalent weight was a measure of the content of free galactonic acid groups, which were not esterified in the pectin molecular chain. The EW value obtained was 612.7; higher than pectin extracted from *Citrus maxima* at a lower pH (18,19). The results of the methoxyl test showed that pectin included in the category of high methoxyl pectin (HMP) has a value of 9.02% (>7.12%). Pectin methoxyl levels have an essential role in determining pectin solubility's functional properties and can affect the structure and texture of pectin gel (20). The Food Chemical Codex states that galacturonic acid (AUA) content indicates the purity of extracted pectin, and the value should not be less than 65% (18). In this study, the extracted pectin showed high AUA values. Pectin purity or galacturonic acid content depends on pH, not on temperature (21). These results indicated that the pectin from *Citrus maxima* peels has high purity, including high methoxyl pectin.

Evaluation of orodispersible film dextromethorphan hydrobromide

Organoleptic observations from the five formulas showed that the resulting film has a yellowish-white color that is transparent, odorless, non-sticky, and has a sweet taste. The higher the concentration of *Citrus maxima* pectin, the more intense the color of the film. The color of the film is affected by the constituent added; the higher the constituent's amount, the darker the film (22). The difference in *Citrus maxima* pectin concentration affects the color, but it does not affect the odor and adhesiveness. Sucrose in the film formula produces a sweet taste, making patients more readily to accept. Removing the film from the mold is not difficult because the use of glycerol at a concentration of 4% as a plasticizer makes the film not sticky. Drying film was carried out for 24 hours at 30-40°C. If the drying is less than 24 hours, it is difficult to remove the film from the mold because it has not dried completely.

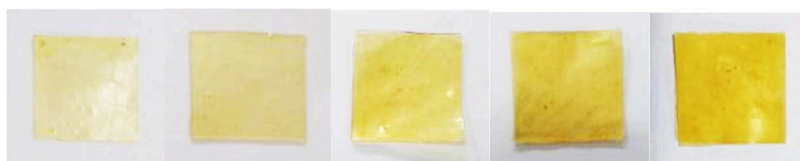


Figure 1. Orodispersible film of dextromethorphan hydrobromide

The evaluation of the film's uniformity weights was carried out to determine the uniformity of weights between films in one molding. The evaluation results of the five formulas can be seen in Table 3. The data shows that the uniformity of weights carried out on 20 edible films has an average deviation percentage that is not large. Films F1 to F5 meet the uniformity requirements of weights i.e., no more than two films that deviate greater than 7.5%, and none of the films deviate greater than 15% (10) with an average weight of 201.45-224.45 mg. The weight difference caused by an increase in the concentration of *Citrus maxima* pectin, which makes the total amount of solids in the film solution poured on a mold of the same size, will affect the film's weights and thickness.

Table 3. The evaluation results of DH orodispersible films

| Parameters | F1 | F2 | F3 | F4 | F5 |
|---------------------------|------------|------------|------------|------------|------------|
| Uniformity of weight (mg) | 201 ± 1,85 | 207 ± 1,95 | 213 ± 1,04 | 218 ± 1,79 | 224 ± 1,67 |

| | | | | | |
|--|------------------|------------------|------------------|------------------|------------------|
| Thickness (μm) | 156.5 ± 17.7 | 173.2 ± 18.1 | 178.7 ± 14.9 | 198.1 ± 9.8 | 203.6 ± 10.9 |
| Tensile strength (kg/cm^2) | $32 \pm 0,35$ | $30 \pm 0,21$ | $26 \pm 0,14$ | $23 \pm 0,24$ | $20 \pm 0,36$ |
| Elongation (%) | $29 \pm 1,64$ | $33 \pm 1,64$ | $37 \pm 1,87$ | $41 \pm 2,00$ | $44 \pm 1,58$ |
| pH | $7,15 \pm 0,02$ | $7,11 \pm 0,01$ | $7,01 \pm 0,07$ | $6,93 \pm 0,08$ | $6,86 \pm 0,04$ |
| Drug content (%) | 92,68 | 90,83 | 93,96 | 95,81 | 91,68 |
| Uniformity of drug (%) | $92,11 \pm 1,76$ | $91,74 \pm 1,95$ | $92,49 \pm 2,24$ | $95,20 \pm 1,74$ | $92,10 \pm 1,27$ |

The thickness test of the film was done using a micrometer screw to the accuracy of 0.01 mm at five different measurement points. This test is essential to ensure the uniformity of film thickness because it is directly related to the accuracy of the doses in the strip. The thickness of the film is usually less than 0.25 mm (23). Based on the evaluation, film thickness ranges from 0.150 to 0.205 mm. The measurement results show a tendency of increased thickness with an increase in the concentration of *Citrus maxima* pectin. This is because the higher concentration of pectin causes an increase in the total dissolved solids in solution, causing film thickness to increase. The increase in the thickness occurs due to differences in the concentration of the filmmaking material. At the same time, the volume of solution poured on each mold is the same, causing the total solids in the film after drying increased, and the polymers that make up the film matrix also increase, resulting in a thicker film. Similarly, the orodispersible film paroxetine hydrochloride was developed by Shinde et al., whereby an increase in film weight is proportional to an increase in film thickness (24).

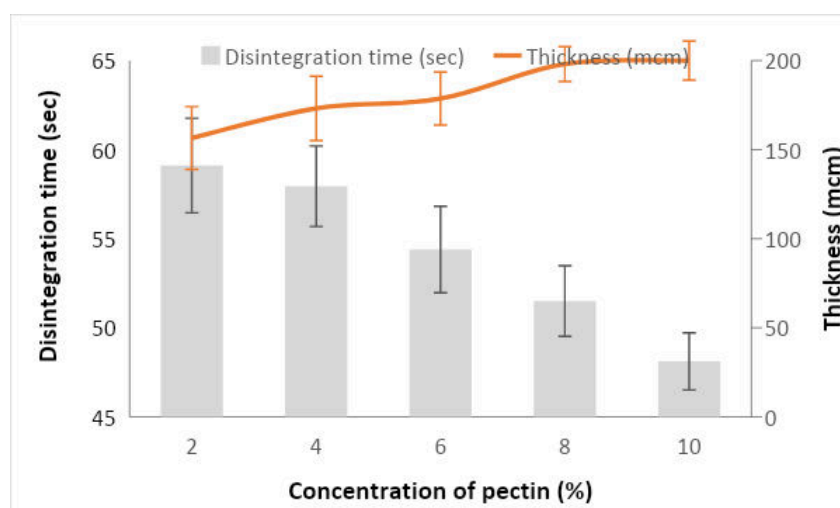


Figure 2. The graph showing the disintegration time decreasing against pectin concentration increasing and thickness of the orodispersible film

Superdisintegrant is a material that can disintegrate rapidly, which is expected to break the film into smaller fragments when it comes in contact with liquid or biological media (salivary fluid). This is closely related to the value of the disintegration time of the film. Superdisintegrant generally has a disintegration time of less than one minute. Based on the evaluation in this study, the film disintegration time ranged from 48.5 to 59 seconds—a higher *Citrus maxima* pectin concentration as a superdisintegrant makes film to disintegrate rapidly. The increasing number of pectin components (hydrophilic) causes an increase in the percentage of film solubility (25). Previous studies stated that the increase in pectin hydrogel formation in tablets due to increased water absorption capacity would increase the swelling index. The water absorption capacity is associated with the absorption rate due to the porous structure, thus facilitating faster disintegration (26). Another study discovers that pure pectin-based films have a higher swelling degree than pectin-alginate-based films (27). Another factor affecting the disintegration time value is methoxyl content. The methoxyl pectin level has an essential role in determining pectin solubility's functional properties and it can thus increase solubility and

accelerate disintegration time (20). The lower methoxyl pectin levels, the more difficult it is to dissolve in water. Whereas the higher of methoxyl pectin levels will make it easily soluble in water (7). In this research, this pectin belongs to high-methoxyl pectin, which is 9.07%. The more concentrations of *Citrus maxima* pectin used, the more methoxyl levels in the film can increase the solubility and film disintegration time.

The results of statistical tests on disintegration time which began with the normality test using the Kolmogorov-Smirnov analysis showed the value of sig (0.903) > α (0.05), which means that H₀ is received and that the data is typically distributed. Meanwhile, the homogeneity test showed the value of sig (0.839) > α (0.05), which means that H₀ is received and that the data is declared homogeneous. Furthermore, the data analyzed by one-way ANOVA showed a sig value < 0.05, which showed that H₀ is rejected and indicated an interaction between concentration and disintegration time. Afterwards, this study continued with the Tukey test, which showed that a 2% interval using *Citrus maxima* pectin as a superdisintegrant produced a significantly different disintegration time value on DH orodispersible film.

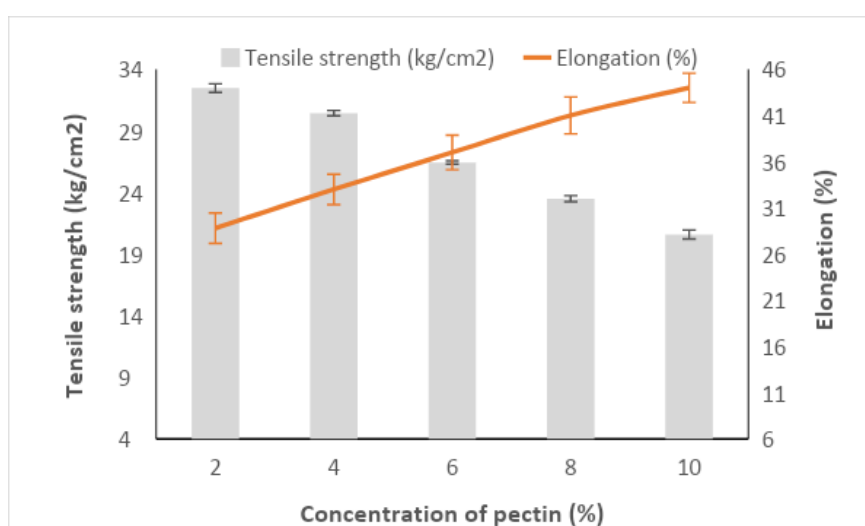


Figure 3. The graph of tensile strength dan elongation test on DH orodispersible film

The graph of the effect of increasing pectin levels on tensile strength and elongation of DH orodispersible film is shown in Figure 3. Based on the evaluation results, the films' tensile strength values ranged from 20.59 to 32.45 kg/cm², while the percentage of the films' elongation ranged from 28.8 to 44.0%. Tensile strength is the maximum force that a film can withstand until it breaks. Another study also found that pectin-based films with various types of plasticizers decreases the tensile strength of the films as the concentration of the plasticizer increases (28). This phenomenon is similar to the decrease in tensile strength that occurred in this orodispersible film. One possible reason for the high tensile strength for low pectin concentrations is the predominance of the strong hydrogen bonds produced by the HPMC-HPMC intermolecular interactions during the HPMC-pectin attraction. However, the addition of pectin at a concentration of 2% to 10% caused a decrease in the film's tensile strength. When the pectin concentration increased from 2% to 10%, the film showed the highest reduction value of 34% (down to 20.59 kg/cm²) in tensile strength. Tensile strength is an important parameter whereby its measurement is usually followed by a measurement of percent elongation.

The increase in pectin concentration from 2% to 10% caused an increase in the elongation of the film from 28.8% to 44.0%. Elongation at break is defined as the ability of a film to change shape before breaking. This parameter (% elongation) helps determine the film's flexibility and stretchability. The elongation of polymeric materials depends on the mobility of their molecular chains (28). An increase in films' elongation can explain how pectin decreases the intermolecular bonds between HPMC matrices and replaces them with hydrogen bonds formed between the pectin and HPMC

molecules. Such disruptions and reconstructions of polymer molecular chains reduce stiffness and increase films' flexibility by allowing more chain mobility (28). The resulting film's pH ranged from 6.85 to 7.15, which is in the salivary pH ranged 5.5 to 7.5 This indicates that it was suitable for usage in the oral cavity. The pH of pectin, according to Rowe et al., is 6.0-7.2 (29).

Determining the maximum wavelength of dextromethorphan hydrobromide in phosphate buffer pH 6.8 with a 40ppm concentration using a UV-Vis spectrophotometer produced a maximum wavelength of 277.7 nm. The wavelength is slightly different from the previous literature which stands at 278 nm (30). The resulting absorption is 0.2590, which in the Lambert-Beer equation equals to the ranges of 0.2-0.8. The dextromethorphan hydrobromide calibration curve made using a phosphate buffer stands at pH 6.8. Absorption at these concentrations was measured by absorption using a UV-Vis spectrophotometer at a wavelength to obtain a straight-line equation $y = 0.041 + 0.0070x$ with a correlation value of 0.9999. Based on the measurement data results, the drug contents of F1 to F5 were 92.68%; 90.83%; 93.96%; 95.81%; and 91.68% respectively, with an SBR value of 1.86%. Pharmacopoeia of Indonesia declares that the dextromethorphan hydrobromide content is not less than 98.0% and not more than 102.0% (10). Accordingly, the determination of dextromethorphan hydrobromide levels in each formula are less than the specified standard. This is due to the fact that the small active substance (5mg per film) allows ingredients to remain in the container or mold, decreasing the active substance in each film.

A uniformity test was needed as the dose of DH is 5mg per film. Data result shows SBR values of F1 to F5 were 1.67%; 1.86%; 2.12%; 1.74% and 1.21%, respectively. Pharmacopoeia of Indonesia requirements i.e., SBR value of not more than 2% (10), states that films from F1-F5 except F3 meet the requirements. SBR values that differ from F3 films are caused by the lack of homogeneity among the active substances in the mold which is resulted from lack of stirring which allows one film to be more content than required.

4. Conclusion

The pectin from *Citrus maxima* has been successfully extracted to produce high purity and include the type of HMP. Orodispersible film DH has been made and has met compendial standard parameters. Adding pectin as a superdisintegrant can accelerate disintegration time, increase elongation percent, and decrease tensile strength of dextromethorphan hydrobromide film.

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