Formulation and evaluation fast disintegrating film salbutamol sulfate using HPMC E15

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Abstract. The aim of the study was to formulate and evaluate Fast Disintegrating Film salbutamol sulfate with HPMC E15 polymer using a solvent casting method. FDF salbutamol sulphate preparations with variations of HPMC E15 polymer concentration (F1 = 30%, F2 = 40%, F3 = 50% and F4 = 60%). Film of salbutamol sulphate was evaluated organoleptic, thickness, uniformity of weight, folding endurance, PH surface, moisture loss, moisture uptake and in vitro disintegration time. The result showed that film of salbutamol sulphate produce flexible and semi-transparent films. Evaluation results of thickness, weight, folding endurance, surface pH, moisture loss and moisture uptake and film disintegration time of all formulas met the requirements, except the uniformity of weight at F4, time of disintegration of F1, F2, F3 and F4 because high concentration of polymer and not added surfactant and superdisintegrant.

1. Introduction

The development of science and technology in the pharmaceutical, new drug dosage forms have been developed and one of which is in the oral route preparation. Oral route preparation have been chosen to be developed because they are noninvasive and easy in administration. One of the preparations which includes the oral route is tablets, where in particular conventional tablets still have some disadvantages such as unpleasant or bitter taste, many patients have difficulty swallowing tablets especially for pediatric and geriatric patients [1], then the bioavailability is relatively low because first pass hepatic metabolism occurs [2].

To overcoming disadvantage of conventional tablets, an alternative dosage form of FDT (Fast Disintegrating Tablet) has been developed which can disintegrate rapidly in the oral cavity without having to use drinking water so that problems for pediatric and geriatric patients who have difficulty swallowing tablets can be overcome. However, FDT (Fast Disintegrating Tablet) preparation also still have weaknesses where the tablets are easily brittle and have not been able to eliminate the risk of choking [3]. Therefore, in this study we will further develop FDT (Fast Disintegrating Tablet) preparations into FDF dosage forms (Fast Disintegrating Film).

FDF (Fast Disintegrating Film) is a thin film preparation that will be much preferred by patients because of the ease of administration (the film is placed on the tongue or other mucous tissue in the mouth without having to use drinking water), so that complaints from pediatric and geriatric patients are difficult swallowing tablets can be overcome [4]. In addition, because the preparation is in the form of film, it will avoid the risk of choking, avoiding fragility due to the flexible nature of the film and will have a much larger surface area with a faster dissolution time [3].
The criteria for the ideal active ingredient for rapid disintegration films are small to larger molecular weights, have a pleasant taste, can to penetrate the oral mucosal tissue, have good strength and solubility in the air and saliva [3], active substances which can be incorporated up to 15 mg [5]. Many drugs that can be formulated as antiemetics, antihistamines, antidepressants, antiepileptics, vasodilators, and anti-asthma [6].

Antiasthma is in the form of drugs such as bronchodilators, corticosteroids, anticholinergics used in the treatment of asthma [6]. Asthma itself is a disease that complies with provisions that support prevention, wheezing, coughing, secret hypersecretion, and bronchial hyperactivity [7]. Currently there are an estimated 300 million people who experience asthma throughout the world. According to the World Health Organization's Global Burden of Disease Study, estimating that asthma causes 346,000 individuals to die every year worldwide [8]. Although asthma cannot be cured, but by doing management that can control asthma [9].

One of the drugs that used to relieve asthma symptoms is salbutamol sulfate. Salbutamol sulfate is a selective group of β2 adrenergic agonists and bronchodilators, where the characteristics have relatively small doses and easily soluble in water [10], will be useful if formulated into preparation for disintegrating films with a wide area of possibilities. Onset of action is faster and penalties for asthma can be resolved immediately.

The important in formulating rapid disintegration films is polymers for film formation which usually consist of hydrophilic polymers [4], and in this study using HPMC E15. HPMC E15 has the ability to make films that are flexible, transparent, tasteless, colorless, and also soluble in water [11].

Based on the background above, the problem that can be formulated is how to preparation of film formulations salbutamol sulfate using HPMC E15 polymer.

The purpose of this study was to formulate and evaluation of salbutamol sulfate film using HPMC E15 polymer.

2. Method
In this study, preparation of fast disintegrating film using solvent casting method. The film fast disintegrating film was made in 4 formulations. The formulation can see in Table 1. HPMC E15 dissolving in distill water and added PEG 400 and mixing with ultraturax with 1000 rpm for 15 minutes. Salbutamol sulphate and sweetener dissolving in distill water. The solution of polymer and salbutamol sulphate, sweetener mixing with ultraturax 1000 rpm for 1 hour. The solution pour on petri dish and dried on room temperature for 3 hour. After of that, dried in oven at temperature 40°C for 24 hour. Film was removed from the petri dish and cutting in size 2x3 cm (equivalent with dose of salbutamol sulphate 2 mg).

Film of salbutamol sulphate was evaluated organoleptic, thickness, uniformity of weight, folding endurance, PH surface, moisture loss, moisture uptake and in vitro disintegration time.

| Ingredients            | Function         | FORMULA (%) |
|------------------------|------------------|-------------|
|                        |                  | F1          | F2          | F3          | F4          |
| Salbutamol sulphate    | Active agent     | 2 mg        | 2 mg        | 2 mg        | 2 mg        |
| HPMC E15               | Film forming     | 30          | 40          | 50          | 60          |
| PEG 400                | Plastisizer      | 20          | 20          | 20          | 20          |
| Stevia                 | Sweetener       | 40          | 40          | 40          | 40          |
| Methyl paraben         | Preservative     | 0.2         | 0.2         | 0.2         | 0.2         |
| Prophyl paraben        | Preservative     | 0.02        | 0.02        | 0.02        | 0.02        |
| Brilliant blue FCF     | Coloring agent  | Qs          | Qs          | Qs          | Qs          |
| Distill water          | Solvent         | Qs          | Qs          | Qs          | Qs          |

*weight of film = 70 mg.
3. Results and discussion

3.1. Results

![Figure 1](image_url). Formula fast disintegrating film salbutamol sulphate.

**Table 2.** Evaluation thickness of film.

| Evaluation | F1     | F2     | F3     | F4     |
|------------|--------|--------|--------|--------|
| Thickness (mm) | 0.050  | 0.063  | 0.063  | 0.083  |
|             | 0.053  | 0.080  | 0.073  | 0.080  |
|             | 0.063  | 0.063  | 0.070  | 0.077  |
|             | 0.073  | 0.060  | 0.077  | 0.077  |
|             | 0.050  | 0.063  | 0.077  | 0.070  |
|             | 0.073  | 0.080  | 0.077  | 0.083  |
| Mean        | 0.060  | 0.068  | 0.073  | 0.078  |
| Standard deviation | 0.011  | 0.009  | 0.005  | 0.005  |

**Table 3.** Uniformity of weight (mg).

| Evaluation uniformity of weight film | F1     | F2     | F3     | F4     |
|-------------------------------------|--------|--------|--------|--------|
| weight (mg)                         | 66.9   | 78.00  | 77.8   | 91.9   |
|                                     | 67.7   | 80.4   | 85.5   | 97.5   |
|                                     | 72.1   | 76.4   | 80.7   | 90.3   |
|                                     | 70.6   | 76.3   | 89.1   | 90.7   |
|                                     | 66.3   | 77.2   | 84.4   | 86.1   |
|                                     | 74.9   | 79.7   | 83.6   | 98.5   |
| Mean                                | 69.75  | 78.00  | 83.52  | 92.50  |
| SD                                  | 3.3762 | 1.7170 | 3.9117 | 4.6989 |
| KV                                  | 4.8405 | 2.2012 | 4.6838 | 5.0799 |
### Table 4. Evaluation folding endurance (times).

| Formula | F1 | F2  | F3  | F4  |
|---------|----|-----|-----|-----|
| Folding endurance (time) | 107 | 140 | 179 | 257 |
| | 103 | 137 | 179 | 253 |
| | 111 | 144 | 187 | 248 |
| Mean | 107 | 140,3333 | 181,6667 | 252,6667 |
| SD | 4 | 3,5119 | 4,6188 | 4,5092 |

### Table 5. pH surface.

| Formula | F1 | F2 | F3 | F4 |
|---------|----|----|----|----|
| pH surface | 6.8 | 6.8 | 6.9 | 6.8 |
| | 6.8 | 6.8 | 6.9 | 6.8 |
| | 6.8 | 6.8 | 6.9 | 6.8 |
| Mean | 6.8 | 6.8 | 6.9 | 6.8 |
| SD | 0 | 0 | 0 | 0 |

### Table 6. Moisture loss film.

| Formula | Initial Weight (mg) | Final weight (mg) | Calculation | % Moisture loss film |
|---------|---------------------|------------------|-------------|----------------------|
| F1 | 66.3 | 60.3 | \( \frac{66.3 \text{ mg} - 60.3 \text{ mg}}{66.3 \text{ mg}} \times 100 \) | 9.0498 |
| F2 | 79.7 | 75.6 | \( \frac{79.7 \text{ mg} - 75.6 \text{ mg}}{79.7 \text{ mg}} \times 100 \) | 5.1443 |
| F3 | 83.6 | 76.1 | \( \frac{83.6 \text{ mg} - 76.1 \text{ mg}}{83.6 \text{ mg}} \times 100 \) | 8.9713 |

### Table 7. Moisture uptake film.

| Formula | Initial weight (mg) | Final weight after exposed (mg) | Calculation | % Moisture uptake film |
|---------|---------------------|-------------------------------|-------------|----------------------|
| F1 | 66.9 | 68.1 | \( \frac{68.1 \text{ mg} - 66.9 \text{ mg}}{66.9 \text{ mg}} \times 100 \) | 1.793 |
| F2 | 76.3 | 82.1 | \( \frac{82.1 \text{ mg} - 76.3 \text{ mg}}{76.3 \text{ mg}} \times 100 \) | 7.602 |
| F3 | 85.5 | 89.6 | \( \frac{89.6 \text{ mg} - 85.5 \text{ mg}}{85.5 \text{ mg}} \times 100 \) | 4.795 |
| F4 | 98.5 | 101 | \( \frac{101 \text{ mg} - 98.5 \text{ mg}}{98.5 \text{ mg}} \times 100 \) | 2.538 |

### Table 8. Disintegration time of film.

| Formula | F1 | F2 | F3 | F4 |
|---------|----|----|----|----|
| Disintegration time (second) | 88 | 170 | 393 | 649 |
| | 89 | 163 | 422 | 612 |
| | 91 | 165 | 447 | 678 |
| Mean | 89.3 | 166 | 434.5 | 663.5 |
| SD | 1.5275 | 3.6056 | 17.6777 | 20.5061 |
3.2. Discussion
Salbutamol sulfate as an active substance formulated into a fast disintegration film using a variation of HPMC E15 polymer as a film, PEG 400 additive as a plasticizer, stevia sugar as sugar, methyl paraben and propyl paraben as preservative, FCF brilliant blue as a dye and aquadest as a solvent.

In this formulation, salbutamol sulfate with strength of dose 2 mg / strip was formulated into fast disintegrating film using a solvent casting method. The casting solvent method is chosen because it is easy and suitable for laboratory scale research. In the casting solvent method, the hydrophilic polymer is dissolved in aquadest and the active substance and other excipients are dissolved in the appropriate solvent then a solution is made and added to the petri dish then dried. Aquadest includes salbutamol sulfate which is easily soluble in water, except methyl paraben and propyl paraben are dissolved in ethanol 96%. Salbutamol sulfate was dissolved in the solvent then stirred using ultraturax at a speed of 1000 rpm with a during 1 hour. The homogeneous solution was poured into a petri dish (d = 13.6 cm) and dried in an oven at 40 °C for 24 hours. The dried film is removed from the petri dish and cut 2x3 cm then put in a plastic clip and stored in a tightly closed container filled with silica gel to prevent the film from getting wet. Films obtained from each formula were evaluated includes organoleptics, thickness, weight uniformity, folding endurance, surface pH, moisture loss, moisture uptake and in-vitro disintegration time.

Organoleptic tested included color, aroma, taste, film surface and film approval. One of the acceptability of drugs is the physical form of the drug, attractive color, aroma, and taste can increase consumer interest in the preparation [12]. The color of the film for each formula is blue because it added brilliant FCF blue. The aroma on each formula is odorless because in each formula no one receives flavorings. The taste in each formula still shows a rather bitter taste. In addition to adding stevia sugar as a growing sweetener with a considerable contribution of 40%, it shows stevia sugar with a concentration of 40% less effective to cover of the taste required from active substances. While for the surface texture of each formula that shows the surface of the film that is smooth and semitransparent. Formula of Fast disintegrating film salbutamol sulfate can see at figure 1.

Film thickness is needed in terms of its correlation with the dose of the drug in the film. The film thickness determined between 5-200 μm is a good film and the standard deviation of film thickness should not exceed 5% [13,14]. Variation in film thickness from F1, F2, F3 and F4 showed 0.0500-0.0833 mm (50-83 μm) where each formula has a standard deviation of less than 5% means having a film thickness that is in accordance with what is required. The table of thickness can see at table 2.

Uniformity weight of film purpose to ensure every film have uniform of weight and dose. Six films were taken randomly and then weighed and calculated the average weight of the film, while the Permatasari was coefficient variation of weight of film not exceed from 5% [12]. Films weighing at formula F1, F2, F3 and F4 produce varying weights of 66.3 mg to 98.5 mg with variation coefficients from F1, F2 and F3 meeting requirements that are less than 5%. The table of uniformity of film can see at table 3. Whereas for F4, the required coefficient of variation in film weight is 5.08% because ovens that have an uneven airflow cause the thickness in one petri dish to be different between the edge and center of the cup, so that the coefficient of variation in F4 film weight is more than 5%.

Folding endurance to known flexibility of film and can influence fragility of the film. Folding endurance with a value of ≥300 times will require good film approval, and Maheswari confirms that good folding endurance of film ranges from 100-150 times [15]. The results of the average folding resistance test for F1, F2, F3 and F4 show mixed results, from the results obtained by the highest average folding resistance for F4 which is as much as 252.67 folds and the lower F1 as many as 107 folds. This means that the resulting folding resistance value is still in accordance with the required folding endurance. The results of the folding endurance test are obtained conclusively with film formation, which increases the formation concentration by increasing the folding endurance of the film. Folding endurance of film can see at table 4.

pH measurement of surface of film is done to known the presence of irritating effects on the oral mucosa. It is expected that the surface pH of the film reacts to neutral pH or the pH of normal human saliva [12]. Gitting reporting as the pH of non-stimulating saliva is called between 6.49-7.28 [16]. pH
measurements were carried out using a pH meter, based on the measurement results obtained by the pH value of F1, F2, and F4 which was 6.8 while the pH value of F3 was 6.9. These results indicate the pH value is still in the range of normal human salivary pH so it will not irritate the oral mucosa. pH of FDF salbutamol sulphate can see at table 6. 

Moisture loss and moisture uptake of film description of stability of film at physicochemical under normal conditions in dry and humid conditions [17]. The results of the moisture loss for each result for F1, F2, F3 and F4 are 9,05%; 5,14%; 8,97%; and 9,03%. Variation of moisture loss film is caused by the influence of drying time in non-uniform oven. The highest percentage of moisture uptake by F2 is 7,60%, where F2 is a formula that has the lowest percentage among other formulas, showed that the film has lowest loss moisture because it has a small moisture content (this film will remain dry) causing this film is more hygroscopic so it has a large of moisture uptake. Moisture loss and moisture uptake of film salbutamol sulphate can see at table 5.

In-vitro disintegration time of film is an important parameter in determining a good film preparation. The faster the disintegration time produced, the better the film preparation is used to release the active ingredient until it has an effect on the body [12]. The disintegration time of film between 5-30 seconds [18]. Disintegration time results of F1, F2, F3 and F4 shows its disintegration in seconds to 89,33; 166; 434,5 and 663,5. The disintegration time of all formula exceed 30 seconds, it means that it does not meet the required because at formulation of the salbutamol sulphate disintegration film there is no added surfactants and superdisintegrants which can shorten the disintegration time of the film. The surfactant itself can be used as a solvent or wetting agent so that the film can be destroyed in a few seconds and can release active substances [15]. Lakshmi reported that formulation disintegrating films that added superdisintegrants have fast disintegrating time compared with films formulated without superdisintegrants [19]. This is what changes the time of disintegration of the film preparation for the rapid disintegration of salbutamol sulfate for longer. Disintegration time of film can see at table 8.

The disintegration time is influenced by polymer concentration, film weight, film thickness and folding endurance. To understand the correlation, analyzed using tolerance analysis. Difference analysis is one of the statistical techniques used to find correlations between variables or more that are quantitative in nature. The coefficient correlations is a coefficient that reflects the level of relationship between causes of responses or more [12]. Responses that uses SPSS®16 by using Pearson conversations, because the resulting data is normally distributed by increasing the amount paid.

The correlation between thickness-weight response, folding endurance -thickness, disintegration time-thickness, folding endurance -weight, disintegration time-weight, and disintegration time-folding endurance -disintegration time resulting correlation value of > 0,95 which indicates a positive linear relationship significant (p-value <0.05) except for weight-thickness having a significant effect (p-value <0,01). The results of conversation analysis use SPSS®16 along with the conversion graphic. The correlation results showed that if the weight is increasing, so that folding endurance and disintegration time of the film will increasing too. This is because there is a difference in the variation of HPMC E15 polymers on each formula higher (F1 = 30%, F2 = 40%, F3 = 50% and F4 = 60%) so that the resulting film will add more numbers with increased polymer concentration increases. With increasing thickness, the weight of the film will increase, then with a film thickness that increases also the number of folds (folding resistance) of the film will increase because the number of folds needed to make the broken film will be much more. When folding endurance films increases, resulting film strength and flexible with regard to the good polymer bonds. It needs the disintegration media to take longer to break the bonds between polymers and cause the films disintegration time to be longer [12].

4. Conclusion
The study concluded that the evaluation of the Fast disintegrating film of salbutamol sulphate included organoleptic, thickness, uniformity of weight met the requirements but didn’t with in vitro disintegration time.
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