A novel and innovative drug delivery system in fast dissolving oral film of glimepiride-betacyclodextrin inclusion complexes

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Abstract. Delivery system in fast dissolving oral film is the system in which drug can be released immediately without drinking water and can be dissolved in saliva, then absorbed into the body through the oral cavity. Glimepiride is classified in the Biopharmaceutics Classification System class II which has a low solubility in water. Formation of glimepiride inclusion complexes using betacyclodextrin is known to increase solubility while suppressing the bitter taste of glimepiride. The purpose of this study was to develop FDOF preparations containing glimepiride-betacyclodextrin (1:2) inclusion complexes made by co-grinding technique. The development of the FDOF formula begins with the orientation of the formula which varies the concentration of crospovidone as superdisintegrant and PEG 400 as plasticizer. The FDOF were made from two formulas, with one formula containing glimepiride-betacyclodextrin (1:2) inclusion complexes and the other formula containing pure glimepiride as the active ingredient, using the solvent casting method with HPMC E5 LV as the film forming agent. The final evaluations of FDOF include organoleptic, weight variation, film thickness, surface pH, disintegration time, drug content, dissolution rate, percent elongation, tensile strength and folding endurance tests. The best FDOF formula from optimization process contain HPMC E5 LV 35% as film forming agent, PEG 400 15% as plasticizer and 8% crospovidone as superdisintegrant. From the results of final preparation evaluation, FDOF containing glimepiride-betacyclodextrin (1:2) inclusion complexes proved to be better than FDOF containing pure glimepiride.

1. Introduction
Glimepirid (GMP) is available commercially in the form of conventional oral tablet that generally a not so convenient form for elderly patients that commonly have type II diabetes mellitus. This inconvenience can decrease those patients discipline in taking the medication for a long period of time. One of the strategy to overcome this problem is to develop medical preparation (dosage) in the form of fast dissolving oral film (FDOF). The delivery system of this dosage begins at the tongue where the film instantly dissolved without the help of drinking water. The medicine is released and dissolved into saliva and then directly absorbed into the body through mouth cavity and also through the digestive system [1]. Some of the obstacles in making the FDOF are the low solubility of GMP and its bitter taste, so in order to make the FDOF, some specific techniques are required to handle this obstacle.

The complex inclusion technique with betacyclodextrine was developed in this research to increase the solubility of GMP and also to suppress the bitterness of the taste. Cyclodextrine is an oligosacharide that has torus shape and has lipophilic group on the inside of its cavity and hidrophilic group on the outer surface and has sweet taste. This structure enables cyclodextrine to form non-covalent inclusion complexes with many other molecules [2]. Among the cyclodextrine group, BCD is the most commonly
used to develop formula for drug delivery system. Because, taste and disintegration time are the two conditions that need to meet the FDOF quality standard, so in the dosage development process, the studies were concentrated in the method of complex inclusion making and the in the search of the most optimum material for the filler and disintegrator.

In the previous research, the making of fast disintegrating oral tablet (FDOT) that contain GMP-BCD complex inclusion has been done with mole ratio of 1:2, and using solvent evaporation method. The resulting FDOT has a sweet taste, short wetting time, short dissolving time, and a higher dissolution rate compared with the FDOT that has only contain pure GMP [3].

In this research the production of GMP-BCD inclusion complex was done with 1:2 mole ratio using the co-grinding method. This method was chosen to maximize the sweet taste because no organic solvent is used in this method that usually left a bitter taste even though the solvent had already been evaporated. the next step is to choose the best ratio to form the complex inclusion based on characterization results. The profile of FDOF that use GMP-BCD inclusion complex was then compared to FDOF that use pure GMP.

2. Method

The development of the FDOF formula began with formula orientation which varies crospovidone concentration as superdisintegrant and PEG 400 as plasticizer. FDOF were made into two formulas containing GMP-BCD inclusion complex (1:2) and pure GMP as the active ingredient [4]. The method used in this step was solvent casting with HPMC E5 LV as the film forming agent. The evaluation on the end result of FDOF were organoleptic, weight variety, film thickness, surface pH, dissolving time, drug content, dissolution rate, elongation percentage, tensile strength, and folding durability evaluations.

2.1. Preparation of Fast Dissolving Oral Film (FDOF)

FDOF was made using solvent casting method by varying the superdisintegrant and plasticizer through basic formula orientation which then followed by evaluation. The FDOF basic formula orientation is given in Table 1.

| Material          | Formula | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|-------------------|---------|----|----|----|----|----|----|----|----|
| HPMC E5 LV (%)    |         | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 |
| PEG 400 (%)       |         | 15 | 15 | 15 | 15 | 10 | 10 | 10 | 10 |
| Crospovidone (%)  |         | 2  | 4  | 6  | 8  | 2  | 4  | 6  | 8  |
| Menthol (mg)      |         | 33,3 | 33,3 | 33,3 | 33,3 | 33,3 | 33,3 | 33,3 | 33,3 |
| Ethanol (mL)      |         | 0,67 | 0,67 | 0,67 | 0,67 | 0,67 | 0,67 | 0,67 | 0,67 |
| Distilled Water (mL)|     | 0,85 | 1  | 1,1 | 1,25 | 0,75 | 0,95 | 1,05 | 1,2 |

2.2. Performance evaluation of FDOF

There are 10 different types of test that was performed to evaluate the performance of the FDOF. Here are the methods of those tests.

2.2.1. Organoleptic test. In this test, the FDOF physical properties that being evaluated were form, size, flexibility, color, odor, and taste [5]. This test was done on orientation formula, and the FDOF that contains GMP-BCD complex inclusion then compared to the FDOF that contains pure GMP as the active ingredient.

2.2.2. Weight variety test. This test was done by weighing five FDOF using digital analytical scale that represent the side part and the middle part of the film. The result was then averaged. This test was done
on orientation formula, and then FDOF that contains GMP-BCD complex inclusion compared to the FDOF that contains pure GMP as the active ingredient.

2.2.3. **Film thickness test.** Each of the FDOF thickness was measured on five different points using micrometer caliper, and the result was being averaged [5]. This test was done on orientation formula, and the FDOF that contains GMP-BCD complex inclusion compared to the FDOF that contains pure GMP as the active ingredient.

2.2.4. **Surface pH test.** This test was performed by placing FDOF samples on the petri dishes and then moistened with aquadest. The pH value then registered when the pH meter electrode touches the film surface [6]. This test was done on orientation formula, and then FDOF that contains GMP-BCD complex inclusion was compared to the FDOF that contains pure GMP as the active ingredient.

2.2.5. **In-vitro disintegration time test.** Some FDOF sample was placed on petri dish that has 10mL 6.8 pH phosphate buffer. The time that it took for FDOF to disintegrate is the in-vitro disintegration time. There were five FDOF’s needed for each formulation [5]. This test was done on orientation formula, and the FDOF that contains GMP-BCD complex inclusion compared to the FDOF that contains pure GMP as the active ingredient.

2.2.6. **Drug content test.** This test was performed by taking FDOF samples with the size of 3 x 2 cm that represent five molding area (middle part and four corner) was taken in the right amount and then dissolved in methanol. Then the samples were diluted using 7.4 pH phosphate buffer, and after that the solution was filtered using filter membrane. GMP content was determined using UV-visible spectrophotometer after being diluted with 7.4 pH phosphate [5]. This test was done on orientation formula, and the FDOF that contains GMP-BCD complex inclusion then compared to the FDOF that contains pure GMP as the active ingredient.

2.2.7. **In-vitro dissolusion drug release test.** In-vitro dissolution test was done using paddle (type II USP apparatus) in temperature 37 ± 0,5°C with 75 rpm stirring speed in a 500 mL of 7.4 pH phosphate buffer medium with aliquote samples were taken as much as 5 mL every 2,4,6,8,12,14,16,18, and 20 minutes’ time interval and then replaced by the same amount new dissolution medium. The samples obtained then filtered and determined the content using UV spectrophotometer [5]. This test was done on orientation formula, and the FDOF that contains GMP-BCD complex inclusion compared to the FDOF that contains pure GMP as the active ingredient.

2.2.8. **Percent elongation test.** This test was performed by pulling FDOF samples using special pulling tool. Weights were added gradually on the tool to increase the pulling force until the FDOF sample was broken. The elongation was determined by recording the distance that were displayed by the pointer on a sheet of paper before the FDOF breaking. Percent elongation was calculated using the formula [7]:

\[
\text{percent elongation} = \frac{L_1}{L_0} \times 100\%
\]

With, \(L_1 = \text{length increase (mm)}\), \(L_0 = \text{initial length (mm)}\).

2.2.9. **Tensile strength test.** A 2x2 cm² FDOF sample that is free from bubble and physical damage is put between two clamp that were positioned 3 cm from each other. A cardboard was attached on the FDOF surface using clamp or double tape to prevent damage of FDOF because of indention or the clamp. During the measurement, the FDOF was pulled downward by adding weights gradually to the clamp until the FDOF was ripped off. Tensile strength was measured when FDOF was ripped off using the formula [7]:
\[
Tensile \ strength \left( \frac{kg}{mm^2} \right) = \frac{\text{Force at break (kg)}}{\text{FDOF area cross section (mm}^2)}
\]

2.2.10. Folding endurance test. This test was done by folding a sample of FDOF repeatedly at the same time until it was broken. The number of folding until the FDOF is broken is its folding endurance [7].

3. Results and discussion

3.1. Preparation of Fast Dissolving Oral Film (FDOF)

The first step in the preparation phase is to perform some FDOT formula orientation. The results from formula orientation can then be evaluated to find the most optimum result. Based on optimization result and FDOF orientation basis, F4 was found to be the best formula. This result is shown in Table 2.

| Table 2. Evaluation of FDOF basis formula optimization. |
|---------------------------------------------------------|
| Formula | Weight Variety (mg) | Basis |
| F1      | 7.38 ± 5.4          | 0.05 ± 0 | 9.12 ± 1.19 |
| F2      | 9.58 ± 1.3          | 0.05 ± 0 | 8.74 ± 4.38 |
| F3      | 13.62 ± 1.19        | 0.05 ± 0 | 5.47 ± 2.9  |
| F4      | 14.1 ± 0.67         | 0.05 ± 0 | 4.77 ± 2.05 |
| F5      | 9.64 ± 3.1          | 0.05 ± 0 | 8.58 ± 2.97 |
| F6      | 10.48 ± 1.14        | 0.05 ± 0 | 7.59 ± 1.15 |
| F7      | 10.84 ± 1.47        | 0.05 ± 0 | 5.66 ± 2.04 |
| F8      | 11.96 ± 1.0         | 0.05 ± 0 | 3.66 ± 0.16 |

After the optimum formula was obtained, then come the phase of FDOF preparation. The FDOF was made based on the best result of orientation formula evaluation which was made into two formulas. Formula F4-A was the formula which contain GMP-BCD (1:2) inclusion complex as its active ingredient, while formula F4-B was the formula that has pure GMP as the active ingredient. These results are shown in Table 3.

| Table 3. Formula of FDOF preparation. |
|----------------------------------------|
| Material | FDOF Formula |
|          | F4-A | F4-B |
| Inclusion Complex GMP-BCD (eq. To 5 mg GMP) | 28,16 | -    |
| Glimepiride (mg) | -     | 5     |
| HPMC E5 LV (%) | 35    | 35    |
| PEG-400 (%) | 15    | 15    |
| Crospovidone (%) | 8     | 8     |
| Menthol (mg) | 33.3  | 33.3  |
| Ethanol 96% (mL) | 0.67  | 1.87  |
| Distilled water (mL) | 2.15  | 1.25  |
3.2. Evaluation of FDOF

Table 4. Organoleptic of FDOF.

| Formula | Organoleptic | Shape          | Texture and Flexibility | Color    | Odor              | Taste                     |
|---------|--------------|----------------|--------------------------|----------|-------------------|---------------------------|
| F4-A    | A bit menthol like | Rectangle | Smooth on one side, a bit coarse (rough), quite flexible | Orange   | A bit menthol like | A bit bitter to tasteless |
| F4-B    | A bit bitter | Rectangle | Smooth on one side, a bit coarse (rough), quite flexible | Grayish white | A bit menthol like | bitter                   |

Table 5. Evaluation of FDOF.

| Formula | Evaluation of FDOF | Weight Variety (mg) | Film Thickness (cm) | Disintegration time (Sec) | Surface pH | Drug Content (%) |
|---------|---------------------|---------------------|---------------------|---------------------------|------------|------------------|
| F4-A    |                     | 62.50 ± 0.25        | 0.127 ± 0.001       | 34.18 ± 1.19              | 7.00 ± 0.1 | 91.8 ± 0.59      |
| F4-B    |                     | 54.16 ± 1.01        | 0.108 ± 0.02        | 33.14 ± 1.73              | 7.04 ± 0.08 | 141 ± 9.15       |

Table 6. Evaluation of percent elongation, tensile strength and folding durability.

| Sample of FDOF | Percent elongation (%) | Tensile strength (kg/mm²) | Folding durability (times) |
|----------------|-------------------------|----------------------------|---------------------------|
| F4-A           | 65.12 ± 1.6             | 1.283 ± 0.231             | >600                      |
| F4-B           | 22.9 ± 0.58             | 1.135 ± 0.004             | 200                       |

Figure 1. In vitro drug release.
From organoleptic evaluation test result, it was found that formula F4-A had better taste than F4-B, this result proves that the forming of complex inclusion can cover the bitter taste of GMP since BCD has sweet taste.

The result of surface pH test shows that formula F4-A had 7.00 ± 0.1 pH value and formula F4-B had 7.04 ± 0.08 pH value. From this results it can be seen that FDOF were in the neutral pH. FDOF dosage with acid or base pH can irritate patient’s mouth cavity so that it would be inconvenient for him/her.

Formulas F4-A and F4-B had disintegration time of less than one minute, which qualify the standard of FDOF.

GMP content on formula F4-A was 91.8% ± 0.59% and for F4-B was 141% ± 9.15%. By referring to the standard of GMP content in a dosage, which is 85-115% with SD value of not more than 6 [8,9], it can be concluded that formula F4-A met the standard while formula F4-B is not. Formula f4-A can met the standard because the active ingredient GMP was in the form of complex inclusion with BCD such that its solubility was increased and the homogenization process becomes easier and faster in the dosage. F4-B was not met the standard because GMP practically insoluble in water and hardly soluble in ethanol such that the homogenization process is difficult in the dosage. Moreover, GMP that form agglomeration can also affect its distribution in the dosage.

F4-A FDOF showed higher values of elongation percentage, tensile strength, and folding durability, compared to F4-B FDOF [9,10]. These results can be understood by the fact that the hydrogen bond formed at the fabrication of GMP-BCD inclusion complex, strengthen its interaction with HPMC E5 LV as film forming agent and PEG 400 as plasticizer, besides the usage of crospovidone at the optimal concentration that was obtained from previous formula optimization [11,12].

From Figure 1 can be concluded that FDOF with GMP-BCD complex inclusion as active ingredient can increase dissolution rate because the outer layer of the complex is easily moisted and dissolved compared to FDOF that contain pure GMP as the active ingredient [13,14]. The comparison of the dissolution rate from GMP-BCD inclusion complex and pure GMP FDOFs at the 20th minutes are 92.8% and 69.7% respectively. Moreover, because the hydrogen bonding from the GMP as the guest in the inclusion inside the BCD’s cavity as the host creates hidrophilic environment that helped to increase the solubility and dissolution rate of GMP [15,16,17].

4. Conclusion

Development of optimal orientation formula resulted in the FDOF formula that contain 35% HPMC E5 LV as film forming agent, 15% PEG 400 as plasticizer, and 8% crospovidone as superdisintegrant. FDOF formula that contain 1:2 GMP-BCD complex inclusion active ingredient was proven to reduce the bitter taste of GMP, had a dissintegration time of less than one minute, neutral surface pH (7 pH), had drug content that met the standard, the amount of dissolved ingredient at the 20th minutes were significantly higher. Percent elongation, tensile strength, and also folding durability were also higher compared to the FDOF that uses pure GMP as its active ingredient.

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