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The Improvement of the Dissolution and Release Characteristics of Ibuprofen Suppository Through Inclusion Complexes with β-Cyclodextrin

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Abstract.

Ibuprofen is classified as a BCS class II because of its low solubility and high permeability. Inclusion complex formation using β-cyclodextrin is one method to increase a drug's solubility. In addition to the method of increasing the solubility, the choice of dosage form and route of administration has a big role in the success of therapy because it can increase the onset of action of drugs while avoiding side effects. Rectal suppositories can provide a faster antipyretic effect than oral preparations. The purpose of this study was to determine the effect of inclusion complexes formation with β-cyclodextrin in increasing the dissolution rate and release characteristics of ibuprofen suppositories. The suppository formulation used various concentrations of cetylalcohol to increase the consistency of the cocoa butter base. The release characteristics of ibuprofen in suppositories were evaluated, including, organoleptic, melting time, weight diversity, dissolution rate and dissolution efficiency, by comparing ibuprofen inclusion complex suppositories with β-cyclodextrin all three mole ratios, namely 1:1, 1:2 and 2:1, to pure ibuprofen suppositories. The inclusion complex of ibuprofen with β-cyclodextrin at a mole ratio of 2:1 showed to increase the solubility and dissolution rate of ibuprofen in suppositories with good physical and release characteristics.

Keywords: ibuprofen, inclusion complexes, suppository

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1. INTRODUCTION

The rapid increase in body temperature in fever can cause seizures even if only for a short time or is often called febrile seizure [1]. A febrile seizure is a seizure that occurs when the body temperature, i.e., the rectal temperature, rises above 38°C and is caused by an extracranial process. Febrile seizures occur in 2-4% of children aged 6 months to 5 years. The main treatment for fever is the administration of antipyretics. Although the use of antipyretics is not proven to reduce the risk of febrile seizures, experts in Indonesia still agree that giving antipyretics such as paracetamol, ibuprofen, or aspirin can still be given [2]. When compared to other drugs, ibuprofen has a better effect than

paracetamol or aspirin in young children aged 6-24 months with fever because it has a higher temperature lowering effect after 6 hours of the first dose [3]. The dose required for ibuprofen to have an antipyretic effect on children in suppositories is 125 mg [4].

Ibuprofen is classified as Biopharmaceutics Classification System (BCS) class II because of its low solubility and high permeability [5]. For drugs with low solubility and high permeability, the dissolution process is a determining step for drug absorption [6]. Thus, it is necessary to try to increase dissolution by increasing the solubility which aims to accelerate the absorption process and accelerate the onset of drug action.

Many techniques are used to increase the solubility of a drug that is difficult to dissolve in water [7]. One of them is developed through an inclusion complex with β-cyclodextrin compounds which dissolve faster than the drug itself so that it can improve dissolution rate, absorption, bioavailability, and chemical stability of the drug [8].

In addition to the method of increasing the solubility, the choice of dosage form and route of administration has a big role in the success of therapy because it can increase the onset of action of drugs while avoiding side effects. Ibuprofen given orally is a potential cause of gastrointestinal bleeding and can increase the risk of gastric ulcers [9]. Suppositories are solid dosage forms in which one or more active ingredients are dispersed in a suitable base and have a suitable shape to be inserted rectally to give a local or systemic effect [10]. Rectal administration of ibuprofen with suppositories can give a faster temperature lowering effect than oral preparations [4].

The base of the suppository can affect the speed at which the drug is released from the suppository. In this study, the base suppository used was cocoa butter which is a fat-soluble base. Cocoa butter is an ideal base because it has a melting point in the 30-36^{0}C range, so it can melt at human body temperature [10]. The use of cocoa butter in ibuprofen suppositories is more efficient when compared to PEG and Witepsol E75 because it has the fastest dissolution and permeation rates [11]. Cocoa butter is safe, non-toxic, and non-irritating, so it can be used as a base for suppositories [12].

In this study, a complex inclusion method using β-cyclodextrin was carried out to increase the solubility of ibuprofen in cocoa butter-based suppositories. The purpose of this study was to determine the effect of the inclusion complex method with β-cyclodextrin in increasing the percent dissolution and release characteristics of ibuprofen in cocoa butter-based suppositories.

2. METHODS

Preparation of the inclusion complex of ibuprofen (IBP) in β-cyclodextrin (BCD) using the coprecipitation method at a mole ratio of 1:1, 1:2 and 2:1, as shown in **Table 1** [13,14]. It is known that the molecular weights of IBP and BCD are 206.28 g/mol and 1135 g/mol [15-17].

TABLE 1: Preparation of IBP-BCD inclusion complexes.

Mole Ratio of IBP: BCD	IBP (mg)	BCD (mg)
1: 1	206.28	1135
1: 2	206.28	2270
2: 1	412.56	1135

Information:
IBP = Ibuprofen
BCD = Betacyclodextrin

Then carried out characterization of the results of the IBP-BCD inclusion complex with saturation solubility testing for 120 minutes in aquadest solvent, temperature 25 ± 2°C, using an orbital shaker at 150 rpm, compared to pure IBP which was measured spectrophotometrically at a maximum absorption wavelength of 265 nm [15-17].

The preparation of suppositories begins with the optimization of the base formula using variations in the concentration of cetylalkohol in cocoa butter with a weight of 3 grams using the cast molding method, as shown in **Table 2**. The composition of the best suppository base formula is determined based on the results of organoleptic evaluation and melting time test [18].

TABLE 2: Composition of suppository base formula.

Ingredients	Base Formula (mg)		
	1	2	3
Cetylalcohol	150	300	450
Cocoa Butter	2850	2700	2550

Next, the suppositories are made by counting the replacement numbers [18]. The suppository formulation contains the active substance of the IBP-BCD inclusion complex at all three mole ratios which is equivalent to a dose of 125 mg of IBP and pure IBP. The evaluation of the final preparation included organoleptic, weight variability, melting time, percent dissolution and dissolution efficiency compared to suppositories containing pure IBP [18].

Evaluation result data instatistical analysis using Oneway Anova, data normality test using Saphiro Wilk and data homogeneity test using Levene's test [18].

3. RESULTS AND DISCUSSION

3.1. Creation of the IBP-BCD Inclusion Complex

The IBP-BCD inclusion complexes were made at 1:1, 1:2 and 2:1 mole ratio to see the effect of increasing the solubility of IBP on various mole ratios of inclusion complexes with BCD. Meanwhile, the method used in the preparation of the IBP-BCD inclusion complex is coprecipitation. This method involves deposition together between BCD and IBP in a complex when it passes its saturation point. Coprecipitation is a promising method because it is easy to process, uses low temperatures, is simple in equipment and provides adequate yields [13,14]. In the three mole ratios, the IBP-BCD inclusion complexes showed the same organoleptic data, namely in the form of powder, white in color, distinctive aroma with a slightly sweet taste.

3.2. Characterization of the IBP-BCD Inclusion Complex

The powder of the IBP-BCD inclusion complex was characterized by saturated solubility test to see the effect of increasing the solubility of IBP after being complexed with BCD, compared to pure IBP. The saturated solubility test results proved that the solute concentration in IBP in the BCD inclusion complex was higher than that of pure IBP. The highest solute concentration in IBP occurred in the IBP-BCD inclusion complex with the mole ratio of 2:1. This is because the molecular weight of IBP is about five times smaller than the molecular weight of BCD, indicating that IBP has a small molecular diameter, making it possible for two IBP molecules to bind to the non-polar parts of BCD to form an inclusion complex [19]. The saturated solubility test results data on the characterization of the IBP-BCD inclusion complex compared to pure IBP are presented in **Table 3**.

TABLE 3: Saturated solubility test of IBP.

Sample	Concentration (mg / L)
Pure IBP	3.20 ± 0.30
IBP-BCD (1: 1) Inclusion Complexes	7.72 ± 0.27
IBP-BCD (1: 2) Inclusion Complexes	4.40 ± 0.32
IBP-BCD (2: 1) Inclusion Complexes	23.06 ± 0.31

Information:
IBP = Ibuprofen
BCD = Betacyclodextrin

3.3. Base Formula Optimization and Evaluation

Preparation of suppositories using the cast molding method is relatively simple, practical and produces a good appearance of suppositories, weighing 3 grams according to the weight of the suppository according to the 3rd edition of Indonesian Pharmacopoeia, namely 2-3 grams [15].

In the base optimization formula, cetyl alcohol is used as a consistency enhancer from the base used, namely cocoa butter, so that the resulting suppository does not melt easily and does not become brittle. However, the concentration of cetylalkohol use should not be too high because it will cause the suppository to become hard, making it difficult for the manufacture and use and the drug release characteristics of the suppository to not meet the requirements. Therefore, it is necessary to optimize the formula to get the best suppository base formulation by varying the three concentrations of cetylalcohol to see the effect on melting time and base consistency [15].

The evaluation results of the three base formulas show the same homogeneity of color, shape and surface conditions, namely homogeneous yellowish white, tapered shape such as a torpedo, no cracks or holes and no exudate [15].

The melting time test of the suppository base formula was carried out to evaluate the melting or dissolving time of the suppository base [18]. In this evaluation, it was found that the time varies depending on the concentration of cetylalkohol use on the base, the higher the concentration, the more the consistency of the base increases so that the melting time is longer. This is evident in the base formulas 1 and 2 show that the melting time that meets the specifications of suppositories using a cocoa butter base is not more than 30 minutes [18]. While formula 3 does not meet the specifications because it takes more than 30 minutes. Thus formula 1 was chosen as the basis for making further suppository preparations. The results of the evaluation of the melting time of the base suppository formula are summarized in Table 4.

Table 4: Melting time of the suppository base.

Suppository Base	Time (Minute)
1	21.10 ± 0.24
2	24.46 ± 0.32
3	31.05 ± 0.34

3.4. Suppository Formulations

In making suppositories, it is necessary to calculate the replacement number to determine the equivalence of the amount of active ingredient that replaces the base weight in the suppository [18,19]. The results of the replacement number calculation are listed on Table 5.

Table 5: Replacement value.

Suppository	Replacement Value
F1A	0.327 ± 0.18
F1B	0.519 ± 0.04
F1C F1D	0.153 ± 0.03 0.078 ± 0.23

The following is the composition of the suppository preparation formula containing the inclusion complex IBP which is equivalent to the IBP 125 mg dose and the suppository containing pure IBP, is described in full in Table 6.

Table 6: Composition of suppository preparation.

Ingredients	Composition (mg)			
	F1A	F1B	F1C	F1D
IBP-BCD	813.27	1500.60	468.69	-
IBP	-	-	-	125
Cetylalcohol	150	150	150	150
Cocoa Butter	2036.73	1349.40	2381.31	2725
Suppository Weight	**3000**	**3000**	**3000**	**3000**

Information:
IBP = Ibuprofen
BCD = Betacyclodextrin

3.5. Evaluation of IBP Suppositories

The organoleptic evaluation results of all suppository formulas containing the IBP-BCD and pure IBP inclusion complexes showed the same homogeneity of color, shape and surface conditions, namely homogeneous yellowish white, tapered shape like a torpedo, no cracks or holes and did not show any exudates. [10]. In detail, the results of the organoleptic evaluation for suppositories are listed in Table 7.

The melting time test was carried out to determine the crush and softening times of suppositories [18]. The results of the melting time test showed that all formulas met the requirements, namely less than 30 minutes [19,20]. However, suppositories containing pure IBP had a longer melting time than suppositories containing IBP-BCD inclusion

Table 7: Organoleptic of suppository preparation.

Organoleptic	F1A	F1B	F1C	F1D
Homogeneity of color	Yellowish white, homogeneous	Yellowish white, homogeneous	Yellowish white, homogeneous	Yellowish white, Homogeneous
Shape	Torpedo	Torpedo	Torpedo	Torpedo
Surface conditions	No cracks/holes	No cracks/holes	No cracks/holes	No cracks/holes
Exudate	No	No	No	No

complexes at all three mole ratios. This is because the formation of inclusion complexes with BCD can reduce the melting point of IBP.

Thus, suppositories can melt at body temperature and release IBP into the rectal fluid to provide a therapeutic effect in an ideal time of less than 30 minutes. The results of the melting time test results for suppositories containing the IBP-BCD inclusion complex at the three mol ratios as well as the pure IBP suppositories, are described in full in Table 8.

Table 8: Melting time of suppository preparation.

Suppository	Time (Minute)
F1A	24.35 ± 0.25
F1B	23.56 ± 0.23
F1C	25.43 ± 0.24
F1D	27.55 ± 0.26

The weight diversity test was carried out to determine whether the IBP suppository produced had a uniform weight. From the tests conducted, it shows that all formulas meet the specifications, namely the percentage deviation of each suppository is not more than 5% [20]. This proves that the preparation of suppositories has used the right and appropriate design formulas, methods, and procedures. Thus, the resulting suppository is expected to have the same dose and therapeutic effectiveness. The results of the evaluation of the weight diversity of suppositories are found in Table 9.

Dissolution evaluation was carried out to determine the effect of inclusion complex formation with BCD on the dissolving rate of IBP in suppositories in rectal fluid compared to suppositories containing pure IBP.

The results of the dissolution evaluation showed that the four suppository formulas had an increase in the amount of IBP that was dissolved per unit time. However, when compared between the four formulas, F1D has the lowest amount of dissolved IBP with the percent dissolved value at the 120th minute is 35.45%. This proves that the suppository containing pure IBP with low solubility causes a low dissolution rate as well.

Table 9: Percent deviation of suppository weight.

Sample Number	Percent Deviation ± SD (%)				Specification
	F1A	F1B	F1C	F1D	
1	1.89 ± 0.77	2.15 ± 0.87	2.42 ± 3.28	2.77 ± 0.87	<5%
2	1.31 ± 0.20	0.13 ± 0.82	0.85 ± 0.50	1.13 ± 0.82	<5%
3	0.96 ± 2.03	0.29 ± 1.26	4.96 ± 2.90	2.29 ± 1.26	<5%
4	0.62 ± 1.33	2.51 ± 0.39	2.75 ± 0.86	1.51 ± 0.39	<5%
5	0.58 ± 1.98	3.69 ± 1.65	1.64 ± 0.39	3.49 ± 1.65	<5%
6	1.34 ± 2.12	0.42 ± 2.10	1.25 ± 1.30	0.82 ± 2.10	<5%
7	1.03 ± 2.18	4.12 ± 0.83	1.53 ± 1.40	3.12 ± 0.83	<5%
8	1.72 ± 0.69	1.47 ± 0.96	2.39 ± 0.88	2.37 ± 0.96	<5%
9	1.03 ± 0.92	0.58 ± 0.13	2.07 ± 0.77	1.28 ± 0.13	<5%
10	1.72 ± 2.34	1.50 ± 0.49	2.28 ± 2.41	2.50 ± 0.49	<5%

Meanwhile, FIC has the highest percent dissolution value, namely 97.74%, compared to F1A and F1B, which are 60.81% and 47.48%, respectively. This can occur because of the different IBP-BCD mole ratios which affect the dissolution rate.

The dissolution rate profile of suppositories containing IBP-BCD inclusion complexes at the three mole ratios as well as pure IBP suppositories, is listed in **Figure 1.**

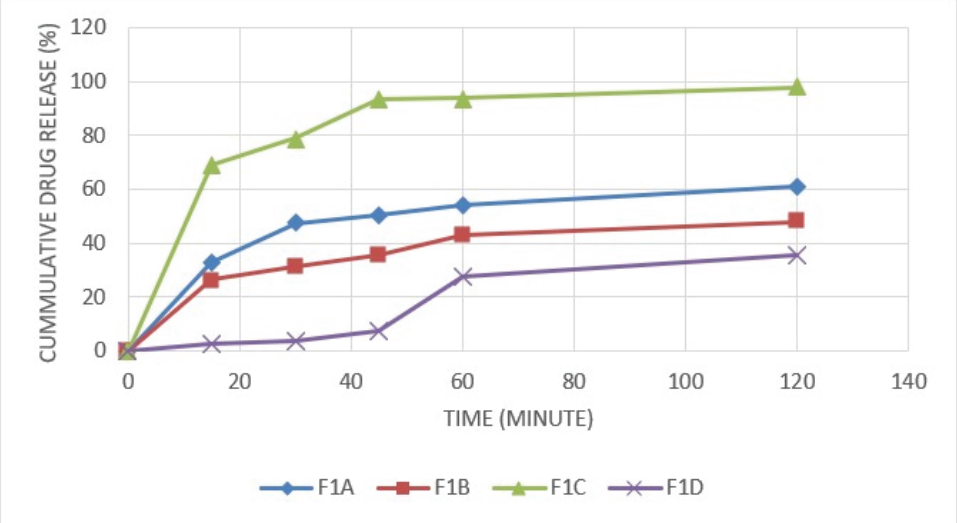

Figure 1: Comparison of percent dissolved Ibuprofen on (F1A) Ibuprofen-Betacyclodextrin (1:1) suppositories, (F1B) Ibuprofen-Betacyclodextrin (1:2) suppositories, (F1C) Ibuprofen-Betacyclodextrin (2:1) suppositories, (F1D) Pure Ibuprofen suppositories.

The results of the calculation of the dissolution efficiency of the four suppository formulas at the 120th minute show that F1C has the highest value compared to others, especially against F1D. This proves that the formation of inclusion complexes can increase the dissolution efficiency of IBP in suppositories. Statistical analysis shows

that the dissolution efficiency of all formulas is significantly different. The results of the calculation of dissolution efficiency at 120 minutes are shown in **Table 10**.

TABLE 10: Dissolution efficiency at 120th minute.

Suppository	Dissolution Efficiency
F1A	44.35 ± 0.27
F1B	33.56 ± 0.65
F1C	85.43 ± 0.48
F1D	17.55 ± 0.26

4. CONCLUSION

Based on the results of the study, it can be concluded that the formation of ibuprofen inclusion complexes with β- cyclodextrin at a mole ratio of 2:1 can significantly increase the solubility and dissolution rate of ibuprofen in suppositories containing 5% cocoa butter base and cetylalkohol and have proven physical and release characteristics. both in terms of organoleptic, melting time and weight diversity.

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