In-vitro diffusion study of ibuprofen-β-cyclodextrin inclusion complex nanogel

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ABSTRACT

The inclusion complex is one way to enhance active substance solubility, affecting medicine dissolution and penetration. The inclusion complex is formed by utilizing β-cyclodextrin as the host of the active compounds. The Ibuprofen (2-(4-isobutyl-phenyl)propionate) is a propionate acid derivative and classified in class II of the Biopharmaceutic Classification System, which has low dissolutions and high permeability. This study aims to develop a nanogel containing ibuprofen-β-cyclodextrin inclusion complex with the ratio of 1:1, 1:2 and 2:1; and to compare the in-vitro diffusion profile with pure ibuprofen gel. The inclusion complex of ibuprofen-β-cyclodextrin was prepared using the coprecipitation method with the three molar comparison ratio of 1:1, 1:2, and 2:1. The *in-vitro* study was performed using the gel-based viscolam, comparing the three formulas of ibuprofen-β-cyclodextrin with pure ibuprofen gel. The ibuprofen concentration of each gel tested in the experiment was 1%. The particle size characterization of ibuprofen-β-cyclodextrin inclusion complex gel resulted in having nanoparticle size (510 nm). This characteristic indicates that the inclusion complex gel could enhance the cumulative release amount of ibuprofen compared with pure ibuprofen gel with a relatively smaller particle size (156 nm). Pure ibuprofen and inclusion complex powder size measured to be 763 nm and 957 nm, respectively. The ibuprofen-β-cyclodextrin inclusion complex gel with a molar ratio of 2:1 demonstrated an increase in in-vitro diffusion profile of ibuprofen with a cumulative release amount of 740.3 µg.cm^{-2}. Meanwhile, pure ibuprofen gel had the cumulative release amount of 294.74 µg.cm^{-2}. The gel containing ibuprofen-β-cyclodextrin inclusion complex could enhance the cumulative release amount of ibuprofen compared to pure ibuprofen gel. The ibuprofen-β-cyclodextrin inclusion complex gel at a ratio of 2:1 exhibited an increase in the diffusion of ibuprofen *in-vitro*.

Keywords: ibuprofen, β-cyclodextrin, inclusion complex, Franz diffusion cell, *in-vitro* diffusion profile

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INTRODUCTION

The purpose of inclusion complex formation is to improve drug solubility. This form will also affect the percutaneous drug penetration. Ibuprofen (IBP) is an arylacetic acid derivative which has high antipyretic and analgesic activity (Katzung et al., 2012). Based on the Biopharmaceutic Classification Systems, IBP is classified as class II with high permeability and low solubility. Drug with low solubility will also have a low dissolution rate resulting in imperfect absorption and low bioavailability (Chaudhary and Patel, 2013).

β-cyclodextrin (BCD) is an oligosaccharide that belongs to the cyclodextrin group. The formation of the IBP inclusion complex with BCS occurs where the BCD acts as a host with the IBP molecule as the guest. The inner cavity of cyclodextrins is hydrophobic, allowing hydrophobic drug molecules to be confined in it to form an inclusion complex with non-covalent bonds. In contrast, the outer cavity is hydrophilic so that the drug complex dissolves easily in water (Liu, 2008).

IBP orally is available commercially in both solid and liquid form. However, the limitation of IBP solubility in the gastrointestinal fluid cause a low rate of drug dissolution. Therefore, this problem can be countered by preparing a transdermal type of drug, the nanogel. Nanogel is a drug delivery system through the skin or transdermal with particle size around 1-1000 nm. Several advantages of nanogel form over cream are that the nanogel is relatively more comfortable to be applied with a cooling sensation. Furthermore, this type could increase drug penetration rate due to its small particle size (Agustin et al., 2007)

The ability of the active substances to penetrate the lower layers of the skin determines the effectiveness of transdermal drug administration. A drug needs to penetrate the stratum corneum, which is the outermost part of the skin, to reach the lower layers of the skin. In principle, the entry of the penetrant into the stratum corneum is the partition coefficient of the penetrant (Loftsson and Brewster, 1996). Hydrophilic drugs will penetrate the stratum corneum through transcellular transport, while lipophilic drugs will penetrate through intercellularly. The entry of drug molecules from the skin surface into the tissue under the skin and end up in the blood circulation occurs by passive diffusion called transdermal (Patil et al., 2010).

This study was conducted to develop a nanogel containing ibuprofen-β-cyclodextrin inclusion complex with the molar ratio of 1:1, 1:2, and 2:1; followed by *in-vitro* diffusion profile comparison to pure ibuprofen gel.

MATERIALS AND METHODS

Materials

Ibuprofen (IOL Chemical & Pharmaceutical LTD, India), β- cyclodextrin (Roquette, France), viscolam MAC 10 (Lamberty, Italy), HT Tuffryn Polysulfone membrane (Pall Corporation, USA), ethyl eter, phosforic acid, potassium hydrogen phosphate, propylene glycol, triethanolamine, glycerine, propylparaben, methylparaben and sodium hydroxide (Sigma-Aldrich, USA) and rat skin (male rat, 3 months old, 250 gram, Wistar). Other chemicals and reagents were of analytical reagent grade.

Methods

Preparation of IBP-BCD inclusion complexes using coprecipitation method

Preparation of the inclusion complex of ibuprofen (IBP) in β-cyclodextrin (BCD) was performed using the coprecipitation method at a molar ratio of 1:1, 1:2 and 2:1. The molecular weights of IBP and BCD are 206.28 g/mol and 1135 g/mol, respectively. The BCD was diluted and homogenized in aquadest using a magnetic stirrer at 50℃, followed by adding NaOH into the solution. After that, IBP was added and homogenized at 60°C for ±10 hours. After that, precipitation was formed by evaporating the water content in an oven at 70°C. The precipitation powder was then refined using mortar (Agustin et al., 2007).

Determination of ibuprofen concentration in inclusion complexes

The powder of the IBP-BCD inclusion complex was weighed with three different molar ratio of 1:1, 1:2, and 2:1, which equivalent to 10 mg of pure IBP. Later, each formulation was diluted in 100 ml of phosphate buffer saline (PBS) pH 7.4. Ibuprofen concentration was determined using a spectrophotometer with a wavelength of 223 nm. The experiment was conducted in triplicate repetition (Widjaja et al., 2014).

Partition coefficient determination in phosphate buffer pH 7.4 and chloroform (1:1)

Powder IBP-BCD inclusion complex with the molar rate of 1:1, 1:2 and 2:1, equivalent with 125mg pure IBP powder, was diluted in 25 mL PBS with pH 7.4. The solution was put into a separating funnel and added with an equal volume of chloroform, and mixed until it reached equilibrium. After that, let the solution sit still until it was divided into two fractions. The water fraction was taken to determine the IBP-BCD inclusion complex concentration using an ultraviolet spectrophotometer with a wavelength of 223 nm. The same procedure was also done to pure IBP powder. All of the experiment was done in triplicate replication (Sinko, 2011).

Partition coefficient determination in phosphate buffer pH 7.4 and skin

Powder of IBP-BCD (100 mg) was added into 10 mL PBS pH 7.4 and was homogenized for 25 hours at 25°C. The initial IBP concentration was determined using an ultraviolet spectrophotometer with a wavelength of 223 nm.

The rat skin was shaved and cleaned using 1% trypsin. Later, 100-150 mg of treated rat skin was put into the test solution with specified volume and was homogenized for another 24 hours at 25°C. Following that, filter the solution and evaluate the final IBP concentration using an ultraviolet spectrophotometer with a wavelength of 223 nm.

The same procedure was also conducted in pure IBP powder. The experiment was done in triplicate repetition. The partition coefficient was calculated after equilibrium with the following equation:

$$P = \frac{(C_0 - C_1) / W_{skin}}{C_1 / V}$$ ……………..………………………………………….........……………......(1)

Information :
C_0 = Concentration of IBP in phosphate buffer pH 7,4 (mg/mL)
C_1 = Concentration of IBP after shaking with the skin (mg/mL)
W_{skin} = Weight of skin (mg)
V = Volume of test solution when the skin was inserted (mL)
(Sinko, 2011)

Preparation of nanogel

In this study, pure IBP gel and IBP-BCD inclusion complex gel was prepared with the molar rate of 1:1, 1:2 and 2:1. Each formula contains 1% of IBP, which have anti-inflammation property. The gelling agent used in the preparation was 5% of Viscolam MAC 10, which is emollient with a non-irritating transparent gel texture (Edityaningrum and Rachmawati, 2015; Nurdianti, 2015; Rachmawati et al., 2013). The nanogel formulation is shown in Table 1**.**

Table 1. Formulation of nanogel preparation

Formulation	(% w/w)			
	F1	**F2**	**F3**	**F4**
IBP pure	1	-	-	-
IBP-BCD (1:1) inclusion complex	-	1	-	-
IBP-BCD (1:2) inclusion complex	-	-	1	-
IBP-BCD (2:1) inclusion complex	-	-	-	1
Viscolam MAC 10	5	5	5	5
Propylene glycol	15	15	15	15
Glycerin	5	5	5	5
Triethanolamine	q.s	q.s	q.s	q.s
Propylparaben	0.02	0.02	0.02	0.02
Methylparaben	0.18	0.18	0.18	0.18
Aquadest	Ad 100	Ad 100	Ad 100	Ad 100

To make the nanogel, pure IBP powder and IBP-BCD powder respectively combined in propylene glycol and mixed using a magnetic stirrer. After that, the mixture of glycerine, propylparaben and methylparaben was added, followed by the gradual addition of aquadest and viscolam MAC 10. Finally, the pH level was adjusted using triethanolamine until it reached around 6-7 and thick viscosity before the gel was evaluated.

Characterization and performance evaluation of nanogel
Organoleptic
Organoleptic observation, including shape, colour and smell, was done on the prepared nanogel (Priani et al., 2018).

Homogeneity
A little bit of nanogel was placed evenly between two glass objects to observe the sample's homogeneity under a microscope (Priani et al., 2018).

pH
The acidity level was measured using a pH meter at room temperature. Firstly, the electrode was calibrated using the buffer solution (pH 4 and 7). After that, the electrode was immersed into the prepared gel until the pH value was shown on the screen (Priani et al., 2018).

Dispersibility
The prepared gel (0.5g) was put on a flat glass (20 x 20 cm). A load was put on top of the gel until it weights 150 g. After 5 minutes, the spreading diameter was measured (Priani et al., 2018).

Viscosity and rheology
The rheological properties determination of gel was performed by Brookfield digital viscometer (RV D 220). The viscosity of preparation was measured at varying rotational speeds of the spindle (10; 20; 50; 100; 50; 20; 10 rpm). The viscosity measurement was done using spindle number 62 at the speed of 50 rpm (Priani et al., 2018; Sabale and Vora, 2012).

Drug Content
About 0.5 g of gel, which equals to 5 mg IBP powder, was diluted in 50 mL of PBS pH 7.4 (100 µg/mL). Later, around 1 mL of the solution was diluted in 9 mL of PBS pH 7.4 (10 µg/mL). Following that, the IBP concentration was measured using an ultraviolet spectrophotometer with a wavelength of

223 nm. The standard IBP concentration was required to be within the range of 90%- 110% (BPOM RI, 2014).

Particle size determination

The particle size of gel was determined using Particle Size Analyzer (Beckman Coulter LS 13 320) directly without dilution in comparison with pure IBP powder dispersed in aquadest 1% w/v (Priani et al., 2018).

In-vitro diffusion study of nanogel

The in vitro diffusion evaluation was performed to compare between IBP-BCD inclusion complex gel with pure IBP gel. The experiments were conducted using HT-Tuffryn membrane in Franz diffusion cells with a diffusional area of 3.14 cm^2 and 0.2 μm pore size. The receiver compartment was filled with 15 mL of phosphate buffer solution at a pH 7.4 (37 ± 0.5°C, 600 rpm). The prepared gel (1 g) was applied directly into the membrane. 5.0 mL samples of the receiving compartment were collected at 10, 20, 30, 45, 60, 90, 120, 150, 180, 240, 300 dan 360 minutes. The aliquots absorption was measured using a spectrophotometer (Shimadzu UV-1800) at the maximum wavelength of IBP (223 nm). The receptor phase was replaced at each sampling time by 5.0 mL of phosphate buffer solution (Figueiredo et al., 2016; Priani et al., 2018). This experiment was done in triplicate replication.

The total amount of IBP that penetrated, per diffusion area (μg/cm^2), was determined using the following standard formula (Iskandarsyah et al., 2017):

$$Q = \frac{[C_n.V + \sum_{i=1}^{n-1} C_i.S]}{A} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots(2)$$

Information   :
Q   = total IBP that penetrated per diffusion area (μg/cm^2)
Cn   = concentration of IBP (μg/mL)
V   = volume of the Franz diffusion cell
$\sum_{i=1}^{n-1} C_i$ = concentration of IBP (μg/μL) in the first sample until n-1
S   = sampling volume (mL)
A   = membrane area (cm^2)

RESULT AND DISCUSSION
Preparation of IBP-BCD inclusion complex using coprecipitation method

The IBP-BCD inclusion complex was prepared in three different molar rates (1:1, 1:2 and 2:1) using the coprecipitation method based on precipitation reaction. In this method, IBP and BCD would precipitate simultaneously into a complex form upon passing through its saturation point (Widjaja et al., 2014). There were several necessary processes in the coprecipitation method used to prepare the inclusion complex, including dilution, homogenization, and coprecipitate formation process. In the dilution process, the BCD was diluted in aquadest until it reached the desired molar concentration. Following that, the homogenization process was done to make sure that the IBP was distributed evenly in the solution. Thus, it could ease the binding process of IBP and formed an inclusion complex with BCD. Lastly, the coprecipitate formation process was completed by the absorption of ions during precipitation due to the mixture of IBP and BCD crystal formation with the help of NaOH (pH 12) solution as the catalyst (Widjaja et al., 2014).

The formation of the inclusion complex was affected by polarity, hydrogen bond, and molecular affinity. The polar water molecules moved out of the inner cavity of BCD, which was nonpolar, to the polar outer surface area of the complex. This event led to the increase of hydrogen bond formation. Further, the interaction between IBP molecules and the solvent was decreased, which led to increasing hydrophobic interaction due to the inclusion of IBP molecules into the nonpolar inner cavity of BCD.

Those interactions also elevated the affinity of BCD. Hence, The formed bond between IBP and BCD could not be broken when it was diluted later on (Frömming and Szejtli, 1994)

Determination of IBP concentration in an inclusion complex

The determination of total IBP concentration in the IBP-BCD inclusion complex was done to evaluate the successful formation of the inclusion complex. The IBP concentration in the inclusion complex was found to be different in each formula with a different molar rate, as shown in Table 2.

Based on the result, the IBP-BCD inclusion complex with a molar ratio of 2:1 presented the highest IBP concentration (97.46%). In this case, the polarity of IBP was significantly affecting the amount of IBP molecule that went into the inner cavity of BCD. IBP have a carboxyl functional group (COOH), which is polar. However, the presence of nonpolar groups such as alkyl and benzene rings significantly decreased the polarity of IBP. Thus, it enabled the nonpolar BCD cavity to bind with the nonpolar group from two IBP molecules, which formed the inclusion complex (Liu, 2008).

Table 2. IBP concentration in an inclusion complex

Sample	IBP concentration (%)
IBP-BCD (1:1) inclusion complex	86.130 ± 0.16
IBP-BCD (1:2) inclusion complex	74.590 ± 0.09
IBP-BCD (2:1) inclusion complex	97.460 ± 0.21

Partition coefficient determination

The partition coefficient is a concentration ratio of a compound inside of two solvents that do not mix with each other. The determination of partition coefficient aims to evaluate drug absorption ability on the human skin membrane, which consist of the lipid bilayer. The principle of determining the partition coefficient is the occurrence of equilibrium between the two phases, namely polar and nonpolar. If the partition coefficient value is more than one, it indicated that the dissolved compound is more prominent in the nonpolar phase. Meanwhile, if the partition coefficient value is less than one, then the dissolved compound is more prominent in the polar phase (Sinko, 2011).

In this study, PBS pH 7.4 was used as a polar solvent, and chloroform was used as a nonpolar solvent. The rat skin was used to represent human skin, consisting of a lipid bilayer (Agustin et al., 2007). The result of partition coefficient determination from IBP-BCD inclusion complex powder with the molar rate of 1:1, 1:2 and 2:1 as well as pure IBP powder was displayed in Table 3.

Table 3. Partition coefficient determination

Sample Powder	Partition coefficient[1]	Partition coefficient[2]
Pure IBP	1.380 ± 0.11	0.703 ± 0.06
IBP-BCD (1:1) inclusion complex	0.780 ± 0.03	0.24 ± 0.07
IBP-BCD (1:2) inclusion complex	1.280 ± 0.16	0.772 ± 0.02
IBP-BCD (2:1) inclusion complex	0.829 ± 0.06	1.021 ± 0.14

Information :

1) Partition coefficient in phosphate buffer solution pH 7.4 and chloroform (1:1)

2) Partition coefficient in phosphate buffer solution pH 7.4 and skin

All of the partition coefficients of IBP-BCD inclusion complex powder (molar rate 1:1, 1:2 and 2:1) in PBS pH 7.4 and chloroform solution showed relatively lower value than the pure IBP powder. This result proved that the inclusion complex formation could increase the solubility of IBP. Thus, it was more hydrophilic compared to the pure form of IBP (Sinko, 2011).

On the other hand, the partition coefficient value of pure IBP in PBS pH 7.4 solution and rat skin was relatively lower than the other IBP-BCD inclusion complex. This condition demonstrated that

pure IBP was more challenging to penetrate the skin membrane. Meanwhile, the partition coefficient value of the IBP-BCD inclusion complex in the skin solution relatively higher compared to pure IBP. It revealed that the inclusion complex form relatively increased IBP penetration capability through the membrane compared to its pure form (Saravana Kumar et al., 2013).

The result of partition coefficient determination in both PBS and chloroform as well as PBS and skin solution showed that IBP-BCD inclusion complex with a molar ratio of 2:1 had the most favourable value.

Characterization and performance evaluation of nanogel

Organoleptic evaluation result showed that all four gel formula could be categorized as homogenized semisolid form with the distinctive smell of IBP. The first formula (F1) had an opaque colour with a relatively thinner consistency because it only contained pure IBP powder dispersed in the gel carrier. Meanwhile, the other three formulas contained the IBP-BCD inclusion complex (F2, F3, F4) and displayed transparent colour except in F3. The pH level of all four formulas was within an ideal range for topical gel product, around 6-8.

A spreadability test was performed to evaluate the ability of the gel product to spread when it was applied to the skin. The standard of topical spreadability is within the range of 5-7 cm. F1 possessed the highest spreadability value due to its thinner consistency compared to the other three formulas of inclusion complex gel (F2, F3, F4). In addition, the IBP concentration in all four formula reached the standard topical drug, which was within the range of 90% and 110% (BPOM RI, 2014).

The viscosity and rheology test was done to evaluate the gel's consistency reflecting the liquid's resistance to flow. The higher the viscosity value signifies the stronger resistance or, the thicker the product is. All four gel formulas held different viscosity value. The viscosity values of the gel containing the IBP-BCD inclusion complex (F2, F3, F4) were generally higher than the gel with pure IBP (F1). At 50 rpm, they had a viscosity value according to the optimum viscosity of the gel system (2000-4000 cps) (Garg et al., 2002). The increase of viscosity was suspected to occur due to the presence of BCD, a cyclic oligosaccharide molecule with a high molecular weight. Based on the viscosity and rheology test result, it can be concluded that the gel was categorized as a non-newton liquid with thixotropic rheology. Thixotropic rheology is characterized by a decrease in viscosity on the application of force, and the value of the turning point becomes small (Figure 1). The thixotropic type is considered an ideal system for topical preparation due to its ease of application to the skin (Priani et al., 2021; Sinko, 2011).

The organoleptic observation and characterization of the three IBP-BCD inclusion complex formulas compared with pure IBP gel display favourable criteria except for the formula with the molar ratio of 1:2 (Table 4).

Table 4. Characterization and performance evaluation of nanogel

Formulation	Organoleptic	pH	Dispersibility (cm)	Viscosity (cPs)	Drug content (%)
F1	Opaque, homogen	6.98 ± 0.3	7.52 ± 0.4	1832	101.76 ± 0.15
F2	Clear, homogen	7.28 ± 0.4	7.10 ± 0.5	2659	95.88 ± 0.10
F3	Almost clear, homogen	7.33 ± 0.1	7.01 ± 0.2	3866	90.14 ± 0.09
F4	Clear, homogen	7.40 ± 0.5	7.20 ± 0.1	2495	96.82 ± 0.11

Information :
F1 = Pure IBP gel
F2 = IBP-BCD (1:1) Inclusion complex gel
F3 = IBP-BCD (1:2) Inclusion complex gel
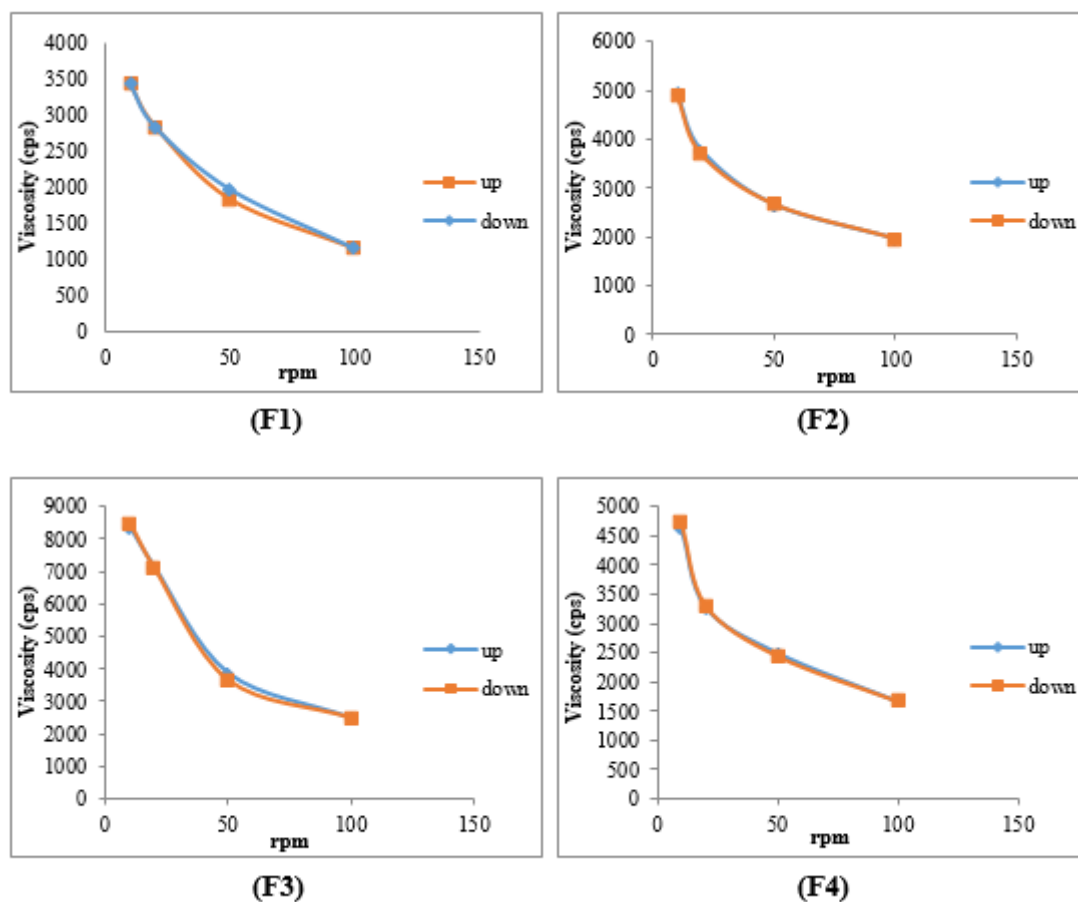F4 = IBP-BCD (2:1) Inclusion complex gel

Figure 1. Rheology of pure IBP gel (F1), IBP-BCD 1:1 inclusion complex gel (F2), IBP-BCD 1:2 inclusion complex gel (F3), IBP-BCD 2:1 inclusion complex gel (F4)

Particle size determination

Particle size measurement showed that both pure IBP powder and IBP-BCD inclusion complex and the gel products were characterized as nanoparticle (1-1000 nm) (Table 5). The particle size of pure IBP powder was smaller than the IBP-BCD inclusion complex due to the combination of molecules that resulted in a bigger particle size. Meanwhile, the gel product of both pure IBP and inclusion complex encountered a decrease in particle size. This condition occurred due to dissolving and stirring in the gelling process. However, this condition is favourable because the smaller its particle size will increase diffusion and penetration ability of the topical preparation product (Patil et al., 2010; Sinko, 2011).

Table 5. Particle size determination

Sample	D_{mean} (nm)
Pure IBP powder	763
Pure IBP gel	156
IBP-BCD (2:1) inclusion complex powder	957
IBP-BCD (2:1) inclusion complex gel	510

In-vitro **drug release study of nanogel**

In-vitro diffusion test was done to evaluate the percutaneous cumulative release ability of IBP from pure IBP gel and IBP-BCD inclusion complex with the molar ratio of 1:1, 1:2 and 2:1. Concurrently, it also determined the best formula from three IBP-BCD inclusion complex gel formulation.
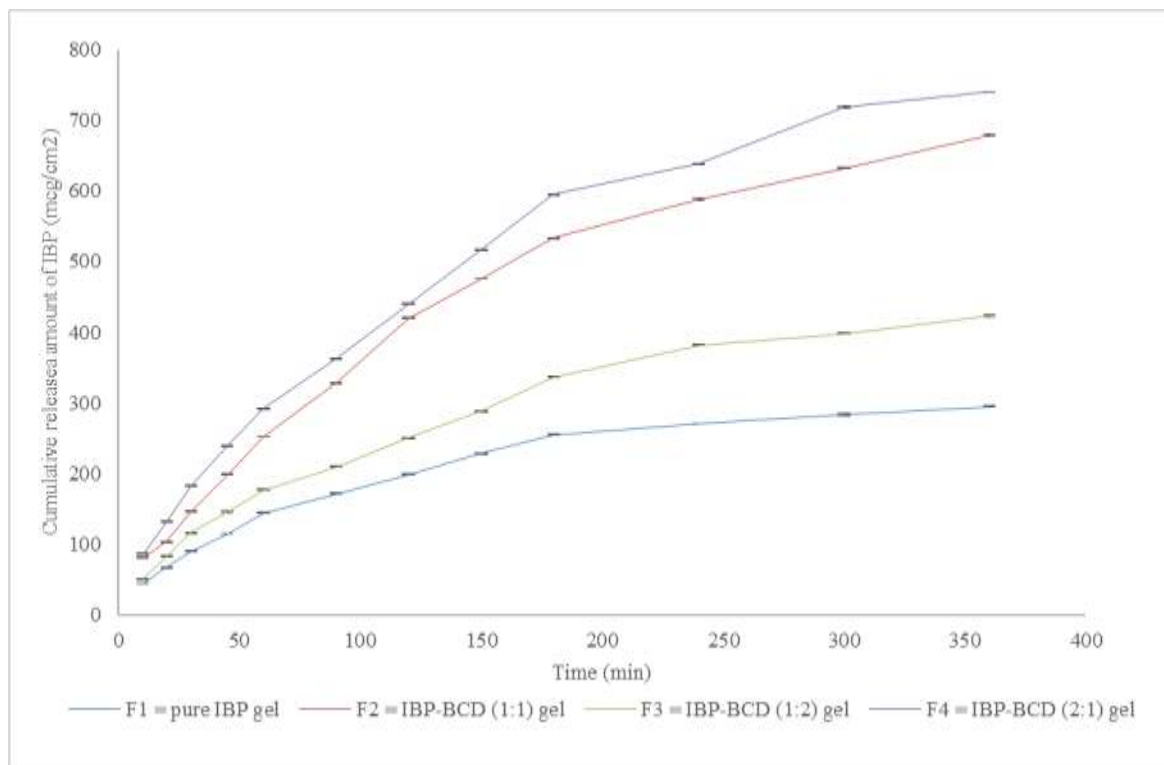

Figure 2. The cumulative release amount of IBP from pure IBP gel (F1), IBP-BCD 1:1 inclusion complex gel (F2), IBP-BCD 1:2 inclusion complex gel (F3), IBP-BCD 2:1 inclusion complex (F4)

The *in-vitro* diffusion study showed that the gel containing the IBP-BCD inclusion complex could enhance the cumulative release amount of IBP compared to pure IBP gel (Figure 2). The total cumulative release of IBP within 6 hours in the *in vitro* diffusion test for pure IBP gel was 294.74 ± 0.12 µg.cm^{-2}, IBP-BCD inclusion complex (1:1) was 678.78 ± 0.19 µg.cm^{-2}, IBP-BCD inclusion complex (1:2) was 423.23 ± 0.07 µg.cm^{-2} and IBP-BCD inclusion complex (2:1) was 740.3 ± 0.14 µg.cm^{-2}.

The transdermal nanogel drug delivery system using viscolam MAC 10 as a gelling agent has been shown to reduce the particle size of IBP. It provides more surface area to release drugs, thereby increasing the rate of release of IBP. The pure IBP gel had a relatively slower IBP release rate than the IBP-BCD inclusion complex gel, even though its particle size was considerably smaller (156 nm). It confirmed that the formation of inclusion complex could increase the total cumulative release of IBO in the nanogel drug delivery system (Priani et al., 2021)

The IBP-BCD inclusion complex (2:1) displayed the best *in vitro* diffusion profile. This formula was more polar compare to other formulas with different molar rate. It formed a complex from two IBP molecules at a time, which its nonpolar part (alkyl group and benzene ring) enter the inner cavity (nonpolar) of the BCD molecule. Meanwhile, the polar part (carboxyl group) was exposed outside

with the polar outer surface of the BCD molecule (Liu, 2008; Sugawara and Nikaido, 2014). The partition coefficient value of the IBP-BCD inclusion complex (2:1) was close to 1, proven that the affinity of nonpolar and polar phase was the same. Thus, it was easier to penetrate (Sinko, 2011)

CONCLUSION

The gel containing ibuprofen-β-cyclodextrin inclusion complex could enhance the cumulative release amount of ibuprofen compared to pure ibuprofen gel. The ibuprofen-β-cyclodextrin inclusion complex gel at a ratio of 2:1 exhibited an increase in the diffusion rate of ibuprofen in the *in-vitro* diffusion study.

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