



Received on 08 April 2019; received in revised form, 23 August 2019; accepted, 24 December 2019; published 01 January 2020

PREPARATION AND CHARACTERIZATION OF ATENOLOL- β -CYCLODEXTRIN ORALLY DISINTEGRATING TABLETS

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Keywords:

Atenolol,
Inclusion complex, β -cyclodextrin,
Orally disintegrating tablets

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ABSTRACT: Atenolol is a hypertension drug that has a low solubility characteristic in water and gastric fluid. The rate of absorption of the drug with poor solubility characteristics is determined by the dissolution process. In this study, an attempt has been conducted to increase the dissolution of atenolol by increasing its solubility. The solubility of atenolol has been enhanced by the inclusion complex using β -cyclodextrin made by several methods (physical mixing, kneading, and solvent evaporation). Evaluation and characterization of atenolol- β -cyclodextrin inclusion complex consist of drug content, dissolution test, Fourier Transformed Infrared analysis (FT-IR), Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD) and Scanning Electron Microscope (SEM). The results of the drug content analysis, dissolution test, and characterization showed that atenolol- β -cyclodextrin inclusion complex, which has been made by the solvent evaporation method was the best approach. Therefore, a solvent evaporation method was chosen to formulate orally disintegrating tablets of atenolol- β -cyclodextrin using direct compression technique. Orally disintegrating tablets of atenolol- β -cyclodextrin were prepared using croscopovidone as disintegrant. The results of pre-compression test and the post-compression test revealed that orally disintegrating tablets of atenolol- β -cyclodextrin inclusion complex disintegrate within 8.17 ± 0.41 sec. *In-vitro* dispersion time in simulated saliva was found to be 45.33 ± 0.58 sec and the percentage of atenolol dissolved from this formula was 92.22% in 30 min. Hence, this formula shows good physicochemical characteristics and fulfill pharmaceutical quality requirements of orally disintegrating tablet.

INTRODUCTION: Atenolol is a drug to treat high blood pressure and has been widely used in hypertension therapy¹. Atenolol is slightly soluble in water.

The solubility of atenolol in water (25 °C) is approximately 13.3 mg/ml². Low solubility characteristic of atenolol in water and gastric fluid caused the bioavailability of atenolol is about 50% following oral administration¹. The rate of absorption of the drugs which have low solubility characteristics determined by the rate of dissolution³.

The rate of dissolution can be increased by several methods such as decrease the particle size using micronization and nanoparticle techniques, solid

<p>QUICK RESPONSE CODE</p> 	<p>DOI: 10.13040/IJPSR.0975-8232.11(1).68-79</p>
<p>This article can be accessed online on www.ijpsr.com</p>	
<p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(1).68-79</p>	

dispersion, salt formation, co-crystal, inclusion complex, etc.^{4, 5} Inclusion complex is one of the approaches which has been used in the pharmaceutical field to improve the dissolution of poorly soluble drugs, taste masking of bitter drugs, and enhance the stability of several drugs^{6, 7}. Cyclodextrins are commonly used in the inclusion complex system because of its structure. Cyclodextrins are cyclic oligosaccharides consist of a macrocyclic ring of glucose subunits joined by α -1, 4 glycosilic bonds⁸. Cyclodextrins have several types regarding the number of glucopyranose units. In general, Cyclodextrins which consist of 6 (α CD), 7 (β CD), or 8 (γ CD) (α -1,4) -linked D-glucopyranose units are widely used as host molecules in inclusion complex approach⁹. Cyclodextrins in the three-dimensional structure described as a truncated cone with a hydrophilic exterior. The interior structure of cyclodextrins molecules consists of carbon groups of glucopyranose units; therefore the interior is more hydrophobic compared to the exterior part^{9, 10}. Regarding its structure, cyclodextrins can induce poorly soluble drugs in their cavity. While the exterior part contact with the medium, cyclodextrins will reveal the drugs which are entrapped in their cavity. Through an inclusion complex approach, cyclodextrins molecules can convert poorly soluble crystalline drugs into water-soluble amorphous drug/cyclodextrins complexes

The results from the previous research revealed that β -cyclodextrins was the most commonly employed in inclusion complex formation. The size cavity of β -cyclodextrins are suitable for the majority of drugs; therefore β -cyclodextrins can entrap the hydrophobic drugs well. Another reason for the use of β -cyclodextrins is the ease of its production and low cost¹⁰. The big molecular cavity of β -cyclodextrins increases the possibilities of the drug to be entrapped in the cavity. In general, one molecule of cyclodextrins will trap one molecule of the drug in their cavity¹¹. The ability of β -cyclodextrins to form inclusion complex is influenced by the size, molecular weight, shape, and the characteristics of the drug¹¹. The inclusion complex of drug molecules with β -cyclodextrins can affect several pharmacokinetic characteristics of the drug, including (i) enhancement of the dissolution process for poorly soluble drugs, therefore improves the bioavailability of these

drugs, (ii) reducing the toxicity of the drugs through application of the lower doses, and (iii) control the release of the drugs¹².

The interaction between cyclodextrins as host molecules and the drugs as guest molecules are mainly through hydrophobic interactions, electronic effects, van der Waals forces, and steric factors. Hydrogen bonds also play a significant role in the cyclodextrins cavity to entrap the drug molecules¹³. An inclusion complex of atenolol and β -cyclodextrins is promising to develop in order to increase the solubility of atenolol, hence the dissolution rate of atenolol will be enhanced. Moreover, an inclusion complex of atenolol with β -cyclodextrins is also giving opportunities for pre gastric absorption of atenolol¹⁴. An inclusion complex of atenolol with β -cyclodextrin in 1:1 ratio was the best ratio, based on the evidence from previous studies¹⁵. In this study, an inclusion complex of atenolol with β -cyclodextrins was prepared using a 1:1 ratio. The preparation method to produce inclusion complex determines the characteristics of the obtained inclusion complex, hence it must be studied to find the most appropriate method.

The objective of this study is to prepare inclusion complexes of atenolol- β -cyclodextrins by different methods such as physical mixture, kneading, and solvent evaporation method. The inclusion complexes which are obtained from each method are then characterized to evaluate the thermal characteristic by differential scanning calorimetry (DSC). The crystallographic state of these inclusion complexes is also observed by X-ray powder diffractometry (XRD). Fourier transform infrared (FT-IR) apply to predict the possible interaction between atenolol and β -cyclodextrins.

The morphology of the inclusion complex is evaluated by Scanning Electron Microscopy (SEM). The inclusion complex, which performs the best characteristics, then formulated into orally disintegrating tablets to increase patient compliance, especially in geriatric patients. Orally disintegrating tablets are characterized by high porosity, low density, and low hardness. When administered, an *in-situ* suspension is created in the oral cavity as the tablet disintegrates and is subsequently swallowed.

Tablets were prepared by using crospovidone as a disintegrant, aspartam, mannitol direct compress, Avicel PH 102[®], mint flavor, magnesium stearate, and Aerosil[®]. Crospovidone was added to facilitate drug release and consequently improve the solubility of the drugs¹⁶. Tablets were prepared by using a direct compression technique. The direct compression method is chosen because this method is simple and cost-effective¹⁷.

MATERIALS AND METHODS:

Materials: Materials that were used in this study consists of atenolol pharmaceutical grade(p.g) (Refarmed Chemicals, Lugono Switzerland), β -cyclodextrin (Roquette, France), ethanol (EtOH) pro analysis (p.a) (Merck), crospovidone (Kollidon[®] CL) p.g (BASF South East Asia Pre-Ltd), magnesium stearate p.g (Faci Asia Pacific PTE LTD), aspartame f.g (Ajinomoto Co. Inc.), aqua demineralisata (Laboratorium of qualitative chemistry University of Surabaya), manitol DC p.g (Roquette Freses, France), aerosil p.g (Brataco), mint flavor f.g (KH Roberts), sodium dihydrogen phosphate ($\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$) p.a (Merck), disodium hydrogen phosphate ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$) p.a (Merck), natrium acetate trihydrate (CH_3COONa) p.a. (Riedel), acetic acid glacial (CH_3COOH) p.a (Merck), methanol (MeOH) pro-HPLC (Mallinckrodt Chemicals), Avicel PH 102[®] p.g (Mingtai Chemical Co. LTD), talk (Brataco), and filter paper No 41 (Whatmann[®])

Methods:

Preparation of atenolol- β -cyclodextrin Inclusion Complex: The Inclusion complex of an atenolol- β -cyclodextrin was prepared using a 1:1 ratio. Three different methods (physical mixture, kneading, and solvent evaporation method) have been utilized to prepare these inclusion complexes.

Physical Mixture: The physical mixture of atenolol and β -cyclodextrin was prepared by mixing individual components using a mortar and a stamper until a homogeneous mixture was obtained. This mixture then stored in airtight containers.

Kneading Method: Kneading method was the first method to prepare the inclusion complex of atenolol- β -cyclodextrin. A homogeneous mixture of atenolol and β -cyclodextrin is kneaded by

ethanol to obtain the slurry mass. The slurry mass was grinding for 1 h until the solvent evaporated to produce a paste-like mass. This paste then dried at 50 °C in a tray dryer for 4 h. The dried inclusion complex powder, then sieved using sieve No. 60 and stored in airtight containers¹⁸.

Solvent Evaporation Method: The initial step to prepare the inclusion complex by this method was dissolved atenolol in ethanol, continuing with the addition of β -cyclodextrin into this solution. This mixture was stirred for 2 h using a magnetic stirrer, then this mixture was placed in a water bath (90 °C) to evaporate the solvent. The inclusion complexes were obtained as a crystalline powder pulverized. The inclusion complexes were sieved by using siever no. 60 and stored in airtight containers until further use¹⁸.

Characterization of atenolol- β -cyclodextrin Inclusion Complex:

Fourier Transform Infrared Spectrophotometry (FT-IR): The interaction between atenolol and β -cyclodextrin was observed by the FT-IR transmission spectrum of atenolol, β -cyclodextrin, and inclusion complex using the potassium bromide (KBr) disc technique^{2,14}. All the spectrum acquired were scanned between 400 and 4000 cm^{-1} .

Differential Scanning Calorimetry: Thermal characteristics of atenolol, β -cyclodextrin, and an inclusion complex of atenolol- β -cyclodextrin were studied using Mettler Toledo differential scanning calorimeter. The scanning rate was 10°C/min and the scanning was conducted between 40°C until 200 °C¹⁸.

Powder X-Ray Diffraction (XRD): The crystallographic state of atenolol, β -cyclodextrin, and an inclusion complex of atenolol- β -cyclodextrin was investigated using X-ray diffractometer (Phillips) in the range 2θ (5-50°) at room temperature¹⁴.

Scanning Electron Microscopy (SEM): The surface morphology of atenolol, β -cyclodextrin, and an inclusion complex of atenolol- β -cyclodextrin was observed by a scanning electron microscope. The samples were coated with gold to provide a conductive layer for observing images at 15 KV.

Drug Content Analysis of atenolol- β -cyclodextrin Inclusion Complex: The drug content in the atenolol- β -cyclodextrin inclusion complex was determined by preparing the inclusion complex powder equivalent to 25 mg of atenolol. The powder then was dissolved and extracted by acetate buffer pH 4.6 in a 100 ml volumetric flask. The solution then filtrated through the Whatman no. 41 filter paper. 10 ml of the filtrate was pipette and transferred into a 25 ml volumetric flask, diluted with acetate buffer pH 4.6. The concentration of atenolol was determined by measuring the absorbance λ 274 nm, using a UV-Visible double beam spectrophotometer (Shimadzu UV-1800).

Dissolution Test of atenolol- β -cyclodextrin Inclusion Complex: Dissolution test of inclusion complex was studied the USP apparatus II (Paddle method) in the Hanson[®] dissolution apparatus at 50 rpm for 60 min. Dissolution studies were carried out using 900 ml of acetate buffer pH 4.6 as a dissolution medium. The dissolution medium was maintained at 37 ± 0.5 °C. The samples of dissolution medium (10 ml) were withdrawn at specified time intervals (2, 4, 6, 8, 10, 15, 30, 45 and 60 min). The concentration of atenolol in the samples of the dissolution medium was analyzed using UV-visible, double beam spectrophotometer (Shimadzu UV-1800) at λ 274 nm. The dissolution parameters were calculated from this test.

TABLE 1: FORMULA OF ATENOLOL- β -CYCLODEXTRIN ORALLY DISINTEGRATING TABLETS

Components	Total per tablet (mg)
Atenolol- β -cyclodextrin	133.41
Crospovidone	30
Avicel PH 102 [®]	94.88
Manitol DC	23.88
Aspartame	9
Mint flavor	3
Magnesium stearate	1.5
Talk	3
Aerosil 200 [®]	1.5
Total	400

Preparation of Powder Mixture of Orally Disintegrating Tablets of atenolol- β -cyclodextrin: The powder mixture was prepared by mixing several components such as atenolol- β -cyclodextrin inclusion complex, Aerosil[®], Avicel[®] PH 102, crospovidone, aspartame, manitol DC, and mint flavor for 10 min in tumbling mixer. The

composition of an orally disintegrating tablet of atenolol- β -cyclodextrin tabulated in **Table 1**. The powder mixture then was evaluated before the compression step (pre-compression test).

Pre Compression Evaluation of the Powder Mixture: The powder mixture of orally disintegrating tablets of atenolol was evaluated by several parameters such as bulk density, tapped density, compressibility, Hausner ratio, flowability, angle of repose, and moisture content.

Bulk Density: Bulk density of powder mixture calculates by dividing the total mass of powder mixture (m) and the bulk volume of the powder (Vb). Bulk density was measured by pouring 40 grams of powder mixture into a measuring cylinder. The volume of the powder mixture was recorded, then the bulk density was calculated using equation¹⁹:

$$\text{Bulk density} = m / Vb$$

Where m is the mass of powder mixture, Vb is the bulk volume of the powder.

Tapped Density: Tapped density of the powder mixture was determined using the tapping machine. The powder mixture was poured into a measuring cylinder and transferred into the tapping machine to evaluate the volume of the powder (Vt) after being tapped 500 times in tapping machine²⁰. The tapped volume (Vt) was noted and the tapped density was determined by this formula

Flowability and Angle of Repose: The powder mixture (± 100 g) was poured through a wide funnel that raised vertically to determine the angle of repose and flow speed of the powder mixture.

The height of the heap (h) and the radius of the base (r) were recorded, then the angle of repose was determined according to this formula:

$$\text{Tan } \theta = h / r$$

Where θ is the angle of repose, h is the height of the heap, and r is the radius of the heap in cm.

Time for the powder mixture to fall down through a funnel was used to calculate the flow speed of the powder mixture.

Compressibility Index and Hausner Ratio: The determination of the compressibility index and Hausner ratio are performed to evaluate the flowability of the powder. The compressibility index can be calculated by comparing the bulk density (Db) and tapped density (Dt) of the powder²¹. The calculation of the compressibility index has been performed utilizing this equation:

$$\text{Compressibility index} = \frac{Dt - Db}{Dt} \times 100$$

Where Dt is the tapped density of the powder and Db is the bulk density of the powder.

Hausner ratio is an indirect index to predict powder flow²⁰. Hausner ratio can be calculated by the following formula.

$$\text{Hausner ratio} = \frac{Dt}{Db}$$

Where Dt is the tapped density of the powder and Db is the bulk density of the powder.

Moisture Content: The moisture content of the powder was determined by analyzing approximately 5 g of the powder. This evaluation was done by using the moisture content analyzer. The moisture content of the powder can be calculated using this equation:

$$\% \text{ MC} = \frac{W - W_0}{W_0} \times 100\%$$

Where W is the weight of wet mass and W₀ is the weight of dry mass

Preparation of Atenolol Orally Disintegrating Tablets: The powder mixture was lubricated and then prepared for the compression process. The compression process was conducted by compress the powder mixture using the Erweka® tablet compression machine. The powder was compressed into 300 mg tablet using 11 mm flat punches.

Post Compression Evaluation: Orally disintegrating tablets of atenolol-β-cyclodextrin tablets were evaluated for organoleptic, dimension, hardness, friability, wetting time, water absorption ratio, *in-vitro* dispersion time, disintegration, drug content, and dissolution.

Organoleptic: The orally disintegrating tablets were inspected in several parameters such as color, shape and taste.

Dimension: The dimension of the tablets was evaluated by vernier caliper to measure the thickness and diameter of 10 tablets. Evaluation of the tablet dimension was conducted to ensure the uniformity of tablet size and predict the problem during the compression process.

Hardness: The hardness or crushing strength of the tablets was determined using a Monsanto hardness tester. The force required to break a tablet in the diametric axis was recorded as the hardness of the tablets²¹.

Friability: Weighed amount of dedusted tablets equal to 6.5 grams were subjected to the rotating drum of ERWEKA® rolling and impact durability tester. These tablets were placed in the rolling and impact durability tester at 25 rpm for 4 min²². % Friability was calculated by this following equation:

$$\% \text{ Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where W₁ was the weight of the tablet before the tablets subjected to the friability test and W₂ was the weight of the tablet after the friability test.

Wetting Time and Water Absorption Ratio: Wetting time test was conducted to predict the hydrophilicity and the penetration rate of water into the structure of the tablets. Orally disintegrating tablet of atenolol-β-cyclodextrin was placed carefully on the surface of filter paper containing 10 ml eosin solutions. The time of eosin solution to reach the surface of the tablets was determined²³. The water absorption ratio was also determined during this test through the amount of the water which is penetrating into the inner structure of the tablet. Water absorption ratio (R) was determined using this equation:

$$R = \frac{W_a - W_b}{W_b} \times 100$$

Where W_b and W_a were tablet weight before and after the water absorption test

In-vitro dispersion time: In-vitro dispersion time test was conducted to evaluate the ability of orally disintegrating tablets to disperse in the small amount volume of saliva. One tablet was placed in a tube containing 10 ml of simulated saliva solutions (phosphate buffer pH 6.8 with

temperature 37 ± 0.5 °C). The time for the tablets dispersed completely was determined²⁴.

In-vitro Disintegration Time: The disintegration test was performed using the method which has been stated in the compendia. Six tablets were placed in each tube of the USP disintegration apparatus. The apparatus was equipped with 900 ml distilled water maintained at 37 ± 0.5 °C as the immersion fluid. *In-vitro* disintegration time of the tablets was determined and recorded²⁵.

Drug Content: Twenty tablets were powdered using a mortar and a stamper. The powder sample (equivalent to 25 mg of atenolol) was weighed accurately and dissolved in 10 ml of methanol. This solution then extracted using acetate buffer pH 4.6 in a 100 ml volumetric flask. The filtrate of this solution then was transferred in a 25 ml volumetric flask and diluted using acetate buffer pH 4.6. The concentration of atenolol in this solution was assayed by a UV-Visible double beam spectrophotometer, then the drug content in each tablet was calculated^{19,26}.

Dissolution Test: The dissolution test was performed using USP dissolution testing apparatus II at 50 rpm for 120 min. The dissolution medium

was acetate buffer pH 4.6 and the temperature was maintained at 37 ± 0.5 °C. An aliquot (10 ml) of the dissolution medium was sampled at a specific time interval. The aliquot was replaced with fresh acetate buffer pH 4.6 in each sampling interval. The amount of atenolol dissolved in each time interval was analyzed by UV-visible, double beam spectrophotometer (Shimadzu UV-1800) at λ 274 nm. The dissolution parameters of the tablets were determined²⁶.

RESULTS AND DISCUSSION:

Characterization of atenolol- β -cyclodextrin Inclusion Complex: The atenolol- β -cyclodextrin inclusion complex was found to be white powders and no odor.

Fourier Transform Infrared (FT-IR) Spectrophotometry: Fourier transform infrared (FT-IR) study was conducted to evaluate the interaction between atenolol and β -cyclodextrin. This study also predicted the formation of a new bond between atenolol and β -cyclodextrin in the inclusion complex. An infrared spectrum of atenolol, β -cyclodextrin, physical mixture of atenolol- β -cyclodextrin, and an inclusion complex of atenolol- β -cyclodextrin can be seen in **Fig. 1**.

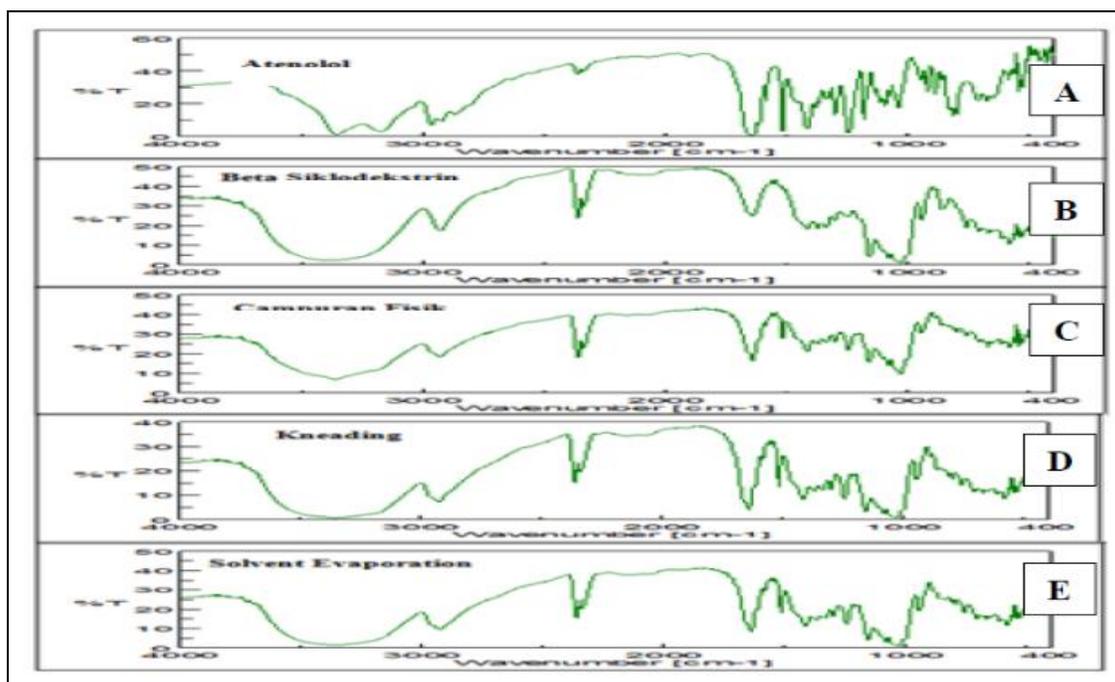


FIG. 1: INFRARED SPECTRUM OF INCLUSION COMPLEXES OF ATENOLOL- β -CYCLODEXTRIN (A) INFRARED SPECTRUM OF ATENOLOL (B) INFRARED SPECTRUM OF β -CYCLODEXTRIN (C) INFRARED SPECTRUM OF PHYSICAL MIXTURE OF ATENOLOL-B-CYCLODEXTRIN (D) INFRARED SPECTRUM OF AN INCLUSION COMPLEX ATENOLOL- β -CYCLODEXTRIN BY KNEADING METHOD (E) INFRARED SPECTRUM OF AN INCLUSION COMPLEX ATENOLOL- β -CYCLODEXTRIN BY SOLVENT EVAPORATION METHOD

Infrared spectrum of pure atenolol showed peaks in 3354.57 cm^{-1} and 3173.29 cm^{-1} indicated -CO-NH group, 2964.05 cm^{-1} (=CH), 1636.03 cm^{-1} (-C=O, NH primer) and $1515,78\text{ cm}^{-1}$ (-N-C=O, NH secondary). As shown in the figure, atenolol had a carbonyl band of $1725\text{-}1685\text{ cm}^{-1}$. Atenolol also showed the carbonyl band in $1725\text{-}1685\text{ cm}^{-1}$. The infrared spectrum of the physical mixture revealed no significant change regarding the specific peaks of atenolol. Whereas, the inclusion complex, which is prepared by kneading and a solvent evaporation method performed a significant decrease of the carbonyl band intensity. This phenomenon can be predicted because of the intermolecular hydrogen bonds between atenolol and β -cyclodextrin. This condition caused by the restriction of atenolol packing in cyclodextrin cavity²⁷. Moreover, in inclusion complexes that had been prepared by kneading and solvent evaporation method, two

functional groups (-CO-NH) had been bounded by functional OH groups of β -cyclodextrin through hydrogen bonding²⁷. The sharp peak of atenolol at 3354 cm^{-1} broadened in the inclusion complex spectrum. Moreover, peak in wavelength 3174 cm^{-1} , resulting from -NH vibrations in atenolol structure was disappeared in the atenolol- β -cyclodextrin inclusion complex spectrum. This condition caused by a complex interaction with β -cyclodextrin

Differential Scanning Calorimetry (DSC): Thermal behavior of atenolol, physical mixture of atenolol- β -cyclodextrin, and an inclusion complex of atenolol- β -cyclodextrin were studied in order to analyze the complex formation. The DSC thermogram of atenolol, physical mixture of atenolol- β -cyclodextrin, and an inclusion complex of atenolol- β -cyclodextrin are shown in **Fig. 2**.

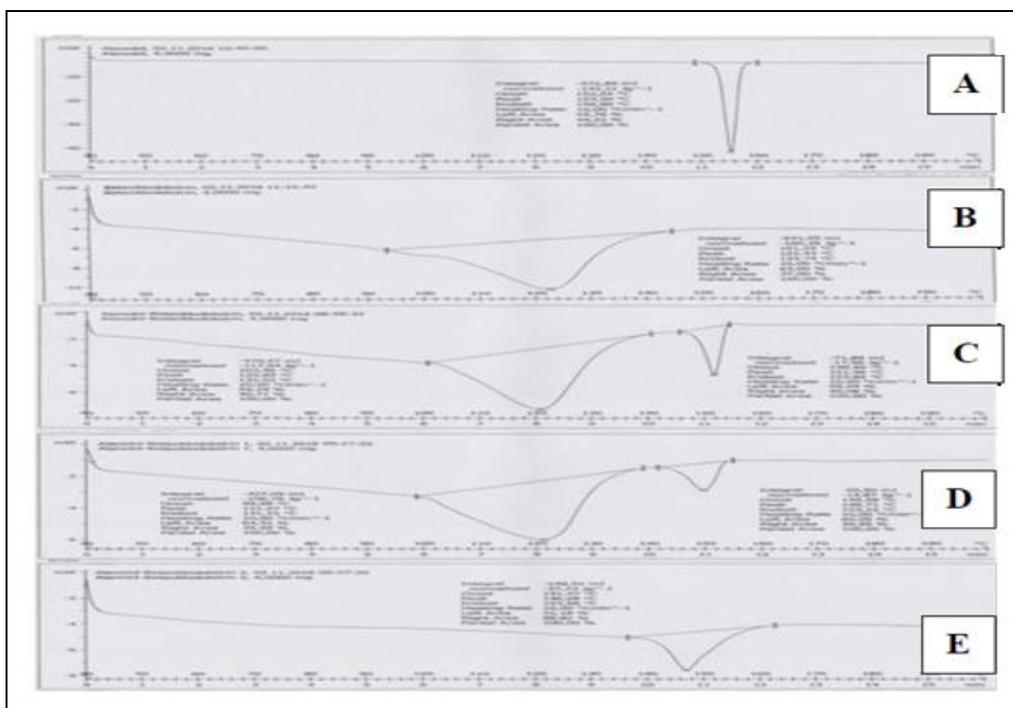


FIG. 2: DSC THERMOGRAM OF (A) DSC THERMOGRAM OF ATENOLOL (B) DSC THERMOGRAM OF β -CYCLODEXTRIN (C) DSC THERMOGRAM OF PHYSICAL MIXTURE OF ATENOLOL- β -CYCLODEXTRIN (D) DSC THERMOGRAM OF INCLUSION COMPLEX ATENOLOL- β -CYCLODEXTRIN BY KNEADING METHOD (E) DSC THERMOGRAM OF AN INCLUSION COMPLEX ATENOLOL- β -CYCLODEXTRIN BY SOLVENT EVAPORATION METHOD

The DSC thermogram of atenolol showed that this molecule has an endothermic peak at $153.50\text{ }^{\circ}\text{C}$, according to its melting point. The β -cyclodextrin showed a broad endothermic peak, which is approximately located at $122.43\text{ }^{\circ}\text{C}$ due to the release of water molecules from the structure. Physical mixture showed two endothermic peaks at $120.89\text{ }^{\circ}\text{C}$ and $151.46\text{ }^{\circ}\text{C}$.

Inclusion complex, which was prepared by kneading method showed two endothermic peaks at $121.27\text{ }^{\circ}\text{C}$ and $149.71\text{ }^{\circ}\text{C}$, while the solvent evaporation method produces the inclusion complex which revealed one endothermic peak at $146.68\text{ }^{\circ}\text{C}$. The complete disappearance of atenolol indicates that the inclusion complex is formed with optimum condition¹⁸.

Powder X-Ray diffraction (XRD): The X-ray diffraction patterns of pure atenolol, as well as the atenolol- β -cyclodextrin inclusion complexes

obtained by using kneading method and solvent evaporation method, are represented in **Fig. 3**.

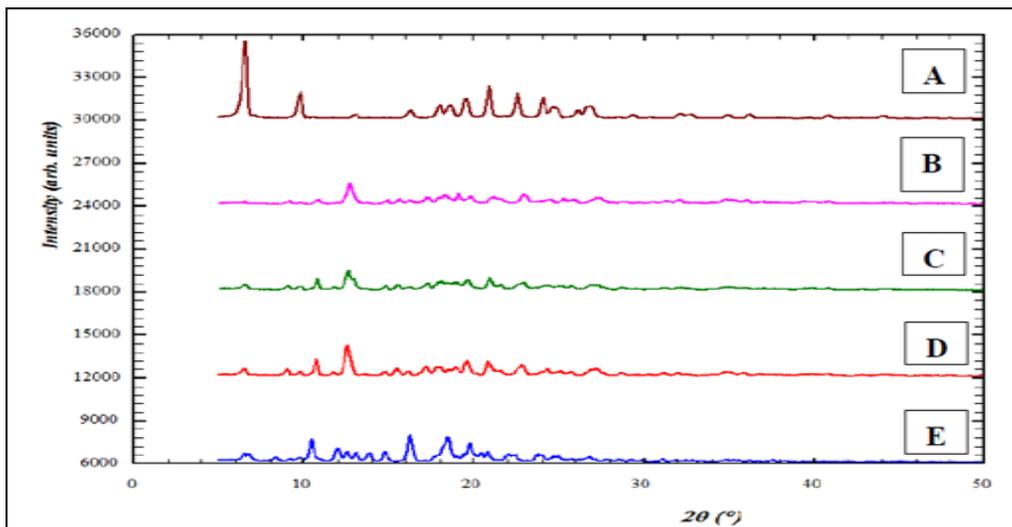


FIG. 3: X-RAY DIFFRACTION PATTERN OF (A) ATENOLOL (B) β -CYCLODEXTRIN (C) PHYSICAL MIXTURE OF ATENOLOL- β -CYCLODEXTRIN (D) INCLUSION COMPLEX OF ATENOLOL- β -CYCLODEXTRIN BY KNEADING METHOD (E) INCLUSION COMPLEX OF ATENOLOL- β -CYCLODEXTRIN BY THE SOLVENT EVAPORATION METHOD

Analysis of the crystallographic aspect was conducted to determine the difference of the crystal structure of the inclusion complex compare to pure drug. The results showed that there was a decrease in the peak intensity of atenolol in inclusion complex formation. The highest reduction of the

peak intensity of atenolol showed by the inclusion complex, which was prepared using the solvent evaporation method. Inclusion complex characterized as a new solid phase with lower crystallinity compared to the pure drug.

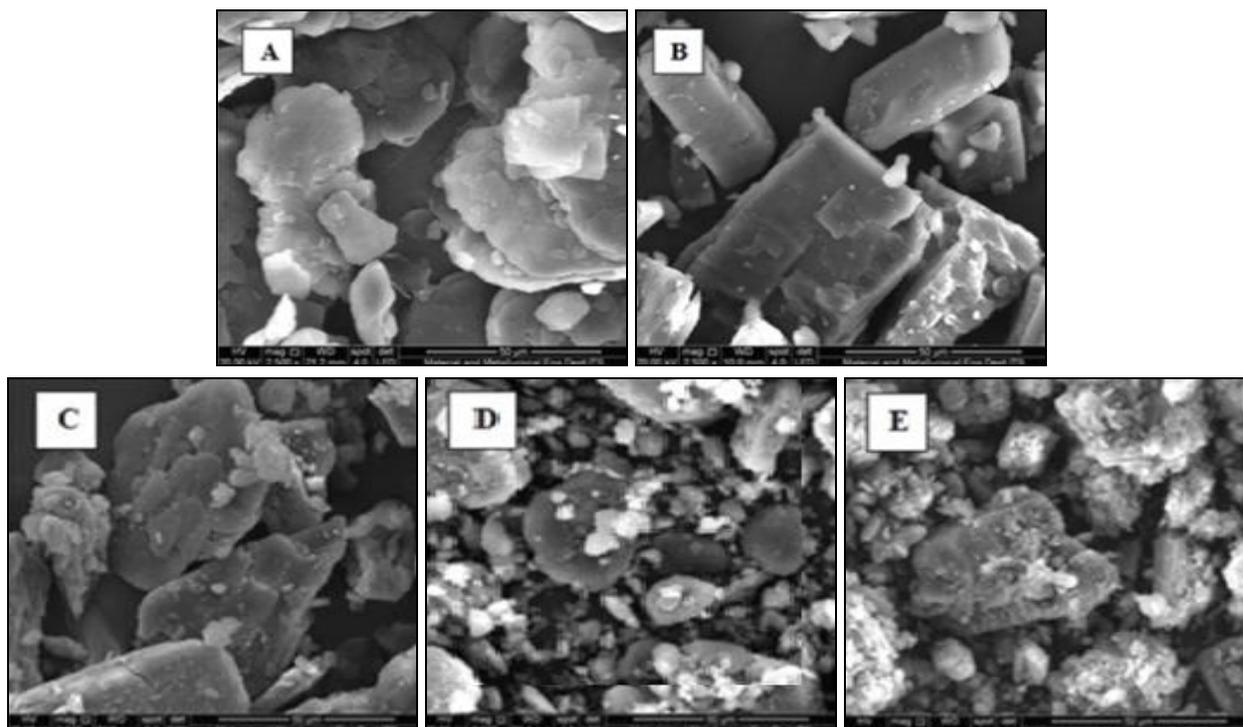


FIG. 4: SCANNING ELECTRON MICROSCOPY (SEM) IMAGES OF (A) ATENOLOL (B) β -CYCLODEXTRIN (C) PHYSICAL MIXTURE OF ATENOLOL- β -CYCLODEXTRIN (D) INCLUSION COMPLEX OF ATENOLOL- β -CYCLODEXTRIN BY KNEADING METHOD (E) INCLUSION COMPLEX OF ATENOLOL- β -CYCLODEXTRIN BY THE SOLVENT EVAPORATION METHOD

Scanning Electron Microscopy (SEM): The SEM study showed the morphology and microscopy photography of the drug and its inclusion complex. The representative images are shown in **Fig. 4**.

The shape of pure drug particles was irregular. The physical mixture images showed that only a small amount of atenolol which was attached to the surface of β -cyclodextrin. The inclusion complex, which is prepared by the kneading method observed that the drug particles attach at the surface of β -cyclodextrin. Moreover, the inclusion complex, which is prepared by the solvent evaporation method showed that atenolol particles attached and incorporated into β -cyclodextrin. The solvent evaporation inclusion complex was poor of crystal structure, lack distinct crystal faces, and incorporated completely in β -cyclodextrin structure²⁸.

Drug Content: UV spectrophotometry was used to determine the drug content of the inclusion complex of atenolol- β -cyclodextrin. The results showed that the drug content of physical mixture was $91.47 \pm 1.22\%$, the inclusion complex, which was produced by kneading method was $92.59 \pm 0.90\%$, and the inclusion complex, which was

produced by solvent evaporation method was $95.40 \pm 0.97\%$.

Dissolution Test of atenolol- β -cyclodextrin Inclusion Complex: Dissolution profile of inclusion complex, which was prepared by physical mixing, kneading method, and solvent evaporation method. The dissolution profiles are as shown in **Fig. 5**.

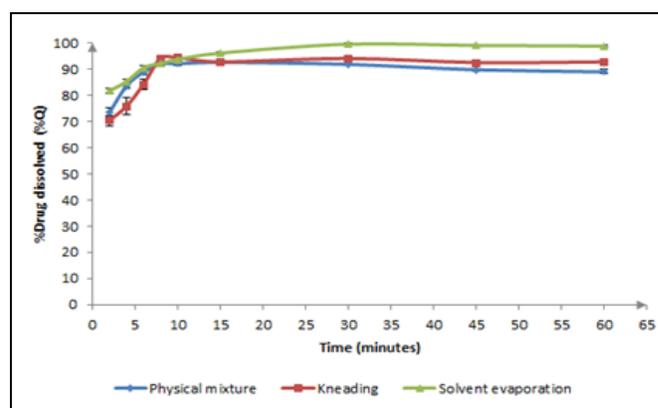


FIG. 5: DISSOLUTION PROFILE OF INCLUSION COMPLEX ATENOLOL- β -CYCLODEXTRIN WHICH MADE BY PHYSICAL MIXING, KNEADING METHOD, AND SOLVENT EVAPORATION METHOD

The Dissolution parameter of the inclusion complex shown in **Table 2**.

TABLE 2: DISSOLUTION PARAMETER OF INCLUSION COMPLEX

Method	%Q (30 min)	TQ% (min)	AUC (0-60 min)	%ED	Kr (min)
Physical mixture	$91.96\% \pm 0.00$	4.49 ± 0.34	5321.93 ± 13.75	$88.70\% \pm 0.23$	0.0046 ± 0.00
Kneading	94.05 ± 0.45	7.61 ± 1.65	5400.46 ± 25.72	$90.01\% \pm 0.43$	0.0138 ± 0.00
Solvent evaporation	99.56 ± 0.45	5.19 ± 1.62	5710.12 ± 14.54	$95.17\% \pm 0.24$	0.0537 ± 0.01

The dissolution profiles of physical mixture and inclusion complexes showed that the solvent evaporation method exhibited a little faster dissolution rate than the physical mixture and produced by the kneading method. An Inclusion complex of atenolol- β -cyclodextrin prepared by the solvent evaporation method is promising to develop into orally disintegrating tablets. The inclusion complex, which was produced by the solvent evaporation method was continued to develop into orally disintegrating tablets.

Pre Compression Evaluation: Precompression evaluation was conducted to predict the ability of powder mixture to be compressed into an orally disintegrating tablet. The ability of the powder to flow was a parameter that was evaluated during this test. The flowability of the powder blend also must

be determined to predict the ability of powder blend to fulfill the dies during the compression stage. The flow properties of the powder mixture can be determined by analyzing the compressibility index (%) and Hausner ratio²⁸. The results of the compressibility index and Hausner ratio revealed that the powder mixture had poor flow character.

The results of flow velocity and angle of repose were found that the powder can not flow well in a glass funnel. This was due to the high percentage of fines in the powder mixture. The powder mixture which had a high percentage of fines, was more adhesive or cohesive. The flow of the powder in this situation was not influenced by gravitation force²⁸. This problem can be solved by decreasing the fines percentage and controlling the particle size distribution.

Moisture content evaluation of powder mixture was conducted to determine that the powder mixture had sufficient moisture content to be compressed. The results showed that the powder mixture had a high moisture content ($6.21\% \pm 0.23$). The high moisture content of powder mixture probably caused by the excipient which was hygroscopic, such as β -cyclodextrin, crospovidone, and Avicel[®] PH 102. The powder mixture which had high humidity will be more cohesive so that this mixture did not flow well. Therefore the weighing process, the mixing process, and the tableting process must be conducted in a room in which the humidity and temperature are controlled well. The results of the pre-compression evaluation are tabulated in **Table 3**.

TABLE 3: THE RESULTS OF PRE COMPRESSION EVALUATION OF ATENOLOL- β -CYCLODEXTRIN ORALLY DISINTEGRATING TABLETS

Parameters	Result
Compressibility index (%)	$33.67 \pm 0.00\%$
Hausner Ratio	1.508 ± 0.000
Moisture content (%)	$6.21 \pm 0.23\%$

Post Compression Evaluation: Atenolol orally disintegrating tablets were white, round shape, no odor, sweet and mint flavor. Tablet means thickness and diameter were almost uniform in the formula. Orally disintegrating tablets of atenolol- β -cyclodextrin performed good mechanical strength during hardness test. The hardness of orally disintegrating tablets of atenolol- β -cyclodextrin was 2.49 ± 0.41 kg. The specification of tablet hardness in orally disintegrating tablets is 2.0-4.0 kg²⁹. Friability and abrasion values of orally disintegrating tablets of atenolol were below 1%. This result indicating that orally disintegrating tablets of atenolol-cyclodextrin have good mechanical resistance. The results of the post-compression evaluation are tabulated in **Table 4**.

TABLE 4: POST COMPRESSION PARAMETERS OF ATENOLOL- β -CYCLODEXTRIN ORALLY DISINTEGRATING TABLETS

Parameter	Result
Organoleptic	White, round shape, no odor, sweet and mint flavor
Drug content	$100.01 \pm 1.1\%$
Diameter	1.10 ± 0.00 cm
Thickness	0.41 ± 0.00 cm
Hardness	2.49 ± 0.41 kg
Disintegration time	8.17 ± 0.41 sec
Dispersion time	45.33 ± 0.58 sec
Friability	$0.26 \pm 0.21\%$

The wetting time for orally disintegrating tablets of atenolol- β -cyclodextrin was 124.67 ± 3.79 sec. The faster the wetting time of the tablets, the faster the tablets will be disintegrated when contact with the media. The water absorption ratio test was conducted to predict the amount of water that can be absorbed by orally disintegrating tablets. Orally disintegrating tablets which have lower water absorption ratio were more preferable to develop. This was due to the orally disintegrating tablets only need a small amount of water to disperse in the media³⁰. Orally disintegrating tablets of atenolol- β -cyclodextrin possess appropriate wetting time and water absorption ratio.

The disintegration time of atenolol- β -cyclodextrins tablets was 8.17 ± 0.41 seconds. These results showed that orally disintegrating tablets of atenolol- β -cyclodextrins fulfill the specification which has been stated in compendia (<1 min)³¹. *In-vitro* dispersion time was also conducted to predict the ability of orally disintegrating tablets to be dispersed in a small amount of saliva in the oral cavity. Orally disintegrating tablets of atenolol- β -cyclodextrins dispersed in 45.33 ± 0.58 seconds. Crospovidone characteristic which promotes capillary activity and hydration enhances the tablets to disperse rapidly without forming gel formation on the surface of the tablets³².

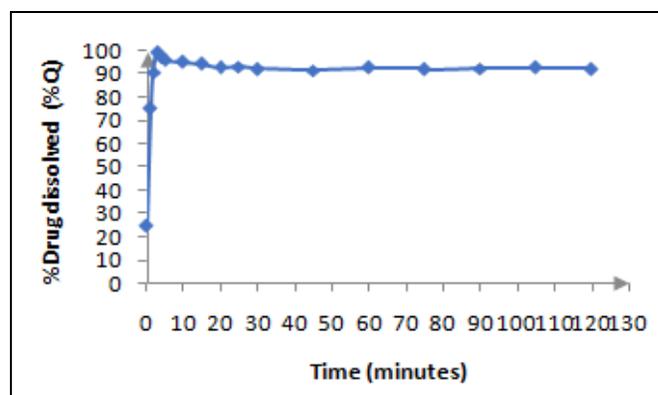


FIG. 6: DISSOLUTION PROFILE OF ORALLY DISINTEGRATING TABLETS OF ATENOLOL- β -CYCLODEXTRIN

The dissolution profile of orally disintegrating tablets of atenolol- β -cyclodextrin showed in **Fig. 6**. The results from the dissolution study showed that orally disintegrating tablets atenolol- β -cyclodextrin meet the specification of compendia. The specification stated that the minimum amount of drug dissolved in 30 min is 85%.

The amount of drug dissolved from this formula was 92.22%, so it can be concluded that this orally disintegrating tablet met the specification.

CONCLUSION: The results from this study showed that the solvent evaporation method produces the best physicochemical characteristics of the inclusion complex of atenolol- β -cyclodextrin. Consequently, the solvent evaporation method was chosen to produce the inclusion complex of atenolol- β -cyclodextrin which further developed into orally disintegrating tablets. Orally disintegrating tablets of atenolol- β -cyclodextrin with sufficient mechanical strength, fast dispersion and disintegration time, and the acceptable taste was produced from this study.

ACKNOWLEDGEMENT: The authors are thankful to DRPM KEMENRISTEK DIKTI, Indonesia, for providing research grants in 2017 (No. 24/SP-Lit/LPPM-01/Dikti/FF/V/2017) to support this research.

CONFLICTS OF INTEREST: There is no conflict of interest during this research.

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How to cite this article:

Rani KC, Parfati N and Stephanie: Preparation and characterization of atenolol- β -cyclodextrin orally disintegrating tablets. *Int J Pharm Sci & Res* 2020; 11(1): 68-79. doi: 10.13040/IJPSR.0975-8232.11(1).68-79.

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