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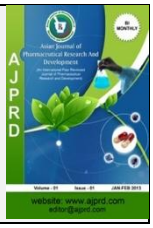

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Research Article

Characterization of Celecoxib β-Cyclodextrin Inclusion Complexes Using Solvent Evaporation Method

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A B S T R A C T

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) used for the treatment of pain and inflammation. Celecoxib is included in class II in the Biopharmaceutis ClassificationAsystem drug (BCS) which has low solubility and high permeability. This study aims to increase the solubility and dissolution rate of celecoxib by characterizing the inclusion complex of celecoxib β-cyclodextrin. Inclusion complexes were prepared by the solvent evaporation method using a water-soluble polymer, β-cyclodextrin. The inclusion complexes were prepared in a 1: 1 ratio between celecoxib and β-cyclodextrins. As a comparison, a physical mixture with the same composition was made. Powder mixtures of physics and inclusion complexes characterized by physicochemical properties include: FT-IR spectroscopy analysis, DSC analysis, assay and dissolution test. The dissolution test was determined by the paddle method. The results of characterization of the inclusion complex using FT-IR spectrophotometry showed a shift in the wave number as well as the physical interaction between celecoxib and β-cyclodextrin. The results of the DSC (Differential Scanning Calorimetry) decreased the enthalpy and melting point between celecoxib, the physical mixture and the inclusion complex. The dissolution test showed an increase in dissolution rate at 60 minutes, namely Celecoxib 55.03%, physical mixture 61.58% and inclusion complex 67.53%.

Keywords: celecoxib, β-cyclodextrin, inclusion complex, *solvent evaporation, dissolution test*

A R T I C L E I N F O: Received; 05 Sept. 2021; Review Complete; 25 Nov. 2021 Accepted; 29 Nov. 2021 Available online 15 Dec. 2021

Cite this article as:

Rosaini H, Sandra N, Asra R, Halim A, Characterization of Celecoxib β-Cyclodextrin Inclusion Complexes Using Solvent Evaporation Method, Asian Journal of Pharmaceutical Research and Development. 2021; 9(6):41-47

DOI: http://dx.doi.org/10.22270/ajprd.v9i61037

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INTRODUCTION

One of the physico-chemical properties which is an important consideration in the formulation of medicinal preparations is solubility. A drug must be soluble in water for it to be therapeutically effective. In order for a drug to enter the circulatory system and produce a therapeutic effect, it must first be in solution. Compounds with low solubility (water solubility less than 10 mg / mL) can cause incomplete, unstable, slow absorption resulting in a decreased therapeutic response[1].

There are several drugs that have problems regarding solubility, such as drugs for BCS class II and drugs for BCS class IV. Class II BCS drugs are drugs that have poor solubility and high permeability.

Meanwhile, class IV BCS drugs are drugs that have poor solubility and low permeability[2]. One example of a class II BCS drug is celecoxib. Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) that is used for the treatment of pain and inflammation. Celecoxib has poor solubility which is practically insoluble in water. A drug should have good solubility so that it can be absorbed and work according to the desired effect[3].

β-cyclodextrin is a cyclic oligosaccharide compound containing 7 D - (+) - glucopyranose units which are bound by β-1,4 bonds. β-cyclodextrin has the ability to form inclusion complexes with various molecules. The shape of the β-cyclodextrin molecule is not cylindrical but rather choroidal with the inside of the compound being hydrophobic while the outside is hydrophilic[4]. The most commonly used cyclodextrin derivatives are β-

cyclodextrins. β-cyclodextrins are relatively inexpensive, commercially available and capable of forming inclusion complexes with a number of guest molecules[5].

Inclusion complexes are complexes formed from two molecules through non-covalent interactions. The process of forming the inclusion complex is mainly influenced by the hydrophobic nature of the medicinal compound (guest) that interacts with the interior of the cyclodextrin cavity. In addition, the interaction is also influenced by the shape and size of the drug compound. The physicochemical properties of drug compounds can change due to the formation of inclusion complexes that can increase the solubility, dissolution rate, bioavailability and stability of the drug[6].

Evaporation of the solvent *(solvent evaporation)* is one method that is used to dissolve the drug and the cyclodextrin separately on two solvents were intermingled, mixing both of these solutions aim to obtain the dispersion molecule drug dealer and complexing finally the solvent evaporated under vacuum to obtain inclusion compounds powder solid. The resulting mixture was stirred and evaporated under vacuum at 45ºC. The dry mass is then crushed and passed on a 60-mesh sieve. This method is quite simple and economical[7].

This study aims to improve the solubility and dissolution rate of celecoxib through techniques evaporation of the solvent*(solventevaporation)*with a polymer that is soluble in water, namely β-cyclodextrin and the complex formed is characterized by analysis "Forier Transform Infra Red" (FT-IR) analysis " Differential Scanning Calorimeter" (DSC), assay and dissolution test.

RESEARCH METHODS

Tools

The tools used in this study include: Laboratory standard glassware, Analytical digital scales (Precisa Type XB 220A, Switzerland), *FT-IR Spectrophotometer* (Thermo Scientific Nicolet iS10 FT-IR), dissolution testing apparatus (Copley, Scientific Type NE4- COPD, UK), *UV-Vis Spectrophotometer* (Shimadzu Type 1800, Japan), *Differential scanning calorymetry* (Setaram DSC 131 Evo, France), Oven (*LABO FCD-3000 Serial)*, desiccators, sonicators, and other tools that support research.

Material

The materials used include: Celecoxib (Shanghai Huirui Chemical Technology.Co.LTD, Hong Kong), b-cyclodextrin (Shanghai Huirui Chemical Technology.Co.LTD, Hong Kong), Methanol (Brataco), Aquadest (Bratachem), HCL 0.1 N (Brataco).

Work procedures

Preparation of Physical Mixture Formulas and Celeoxib β-cyclodextrin Inclusion Complexes

Table I. The physical mixture formula (CF) and the inclusion complex using the solvent evaporation method were prepared with a 1: 1 mol ratio between celecoxib and β-cyclodextrin.

Table I. Inclusion complex formulas

Material	Amount weighed (g)	
	CF	F1
Celecoxib	3,8137	3,8137
β-siklodekstrin	11,35	11,35
Amount	15,1637	15,1637

Preparation of Celecoxib Mixed Physical and β-cyclodextrin

Physical mixture of celecoxib and β-cyclodextrin are made in the ratio 1: 1 mol, then each material separately crushed first, then mixed and crushed until homogeneous. The mixture is divided into 5 parts and each part is taken and stirred in the mortar using a spatula 3-5 times and flattened again. The treatment was carried out 3 times. After the mixing process is complete store the physical mixture in a container and store it in a dry place protected from light.

Preparation of Celecoxib and β-cyclodextrin inclusion complexes using theSolvent Evaporation Method

Celecoxib and β-cyclodextrin were prepared using the solvent evaporation method based on a ratio of 1: 1 mol. Celecoxib powder was put into beaker glass and dissolved with methanol while β-cyclodextrin was dissolved with distilled water. To the celecoxib solution, the β-cyclodextrin solution was added slowly while stirring. Then the resulting solution mixture is dried in an oven at a temperature of 40-50 ºC until dry. The resulting solid is scraped off and crushed in a mortar, then stored in a desiccator.

Characterization of Celecoxib and β-cyclodextrin Inclusion Complexes

FT-IR Spectrophotometric Analysis

The test was carried out with the raw material of celecoxib, physical mixture, and preparation of the celecoxib β-cyclodextrin inclusion complex using the kBr disc method and it was analyzed at a wave number 400-4000cm^{-1}, take the IR absorption spectrum of the sample. This analysis will show spectra describing functional groups[8].

Analysis *Differential Scanning Colorimetry* (DSC)

DSC measurement is done by means of a calibrated before use using indium then 3 mg of celecoxib sample is weighed and put into containers cruicible pan, heated and measured by a temperature of 30^{o} C to 250^{o} C. The constant heating speed10^{o} C / min with drainage nitrogen gas 10 ml / minute[9].

Determination of Celecoxib Levels

Preparation of Main Solution

Celecoxib is weighed as much as 25 mg then dissolved with methanol in a 50 mL volumetric flask and the volume

is sufficient to mark the limit, then homogenized, in order to obtain a solution concentration of 500 µg / mL.

Determination of the Maximum Wavelength of Celecoxib

A total of 10 mL of celecoxib mother liquor was piped and put in a 50 mL volumetric flask, diluted with methanol solvent to the limit mark and homogenized to obtain a concentration of 100 µg / mL. Then pipette 1 mL of the solution into a 10 mL volumetric flask, then dilute it with solvent to mark the limit and homogenize it, so that a concentration of 10 µg / mL is obtained. Then the maximum wavelength was measured with a UV-VIS spectrophotometer at a wavelength of 200-400 nm and the maximum wavelength of celecoxib was obtained.

Preparation of Celecoxib Calibration Curves.

Mains solution pipette from a concentration of 100 µg / mL of 0.6 mL; 0.8 mL; 1 mL; 1.2 mL and 1.4 mL, then put into a 10 mL volumetric flask, suffice it with methanol until the limit mark is then homogenized to obtain concentrations of 6, 8, 10, 12, and 14 µg / mL. Then the uptake of each solution was measured at the maximum wavelength of celecoxib.

Determination of Celecoxib Levels in Physical Mixture and Inclusion Complexes

Each formula was weighed equivalent to 25 mg Celecoxib by weighing Celecoxib 25 mg, and physical mixture 0.0998, and inclusion complex 00998. Then put in a 50 mL volumetric flask then dissolved with methanol and the volume is sufficient to the limit mark, so that a concentration of 500 µg / mL is obtained, then the 10 mL pipette solution is put in a 50 mL volumetric flask with enough methanol to obtain a concentration of 100 µg / mL, then pipette 1 mL of the solution into a 10 mL volumetric flask, dilute with solvent to the limit mark and homogenized, to obtain a concentration of 10 µg / mL. Then the absorbance was measured with a UV-VIS spectrophotometer at the Celecoxib wavelength. The test was carried out three times. Celecoxib content was determined with a wavelength of 252 nm.

Dissolution

Test The dissolution test was carried out using a paddle-type dissolution test device. The dissolution flask was filled with 900 mL of 0.1 N HCl dissolution medium. The temperature is set at 37 ± 0.5°C with a rotating speed of 100 rpm for 1 hour. Then we weighed celecoxib, β-cyclodextrin physical mixture and celecoxib-β-cyclodextrin inclusion complex equivalent to 100 mg, then put into the dissolution medium. The solution in the dissolution flask is taken as much as 5 mL at 5, 10, 15, 30, 45, and 60 minutes and replaced with a new dissolution medium at each time of collection with the same volume and temperature at pipetting. Each pipette solution was put in a vial and tested for absorbance using UV-Vis Spectrophotometry. The dissolution test was carried out three times[10].

Data analysis

Data from the dissolution of inclusion complexes and physical mixtures were determined by determining the kinetics model of drug release based on the zero order, first order, Higuchi and Korsmeyer-Peppas equations and the dissolution efficiency was determined. Dissolution efficiency data were processed statistically using SPSS 20 with one-way ANOVA, followed by Duncan's continued test.

RESULTS AND DISCUSSION

This study was conducted to increase the solubility of a drug in the form of an inclusion complex. Celecoxib is used as an active substance which is a non-steroidal anti-inflammatory drug that is included in the *Biopharmaceutics Classification System* Class II(BCS), where drugs have poor solubility and high permeability[11]. Celecoxib has poor water solubility, which is practically insoluble in water, so it can affect the rate at which drugs are absorbed in the body. Increase its solubility by adding a polymer, namely β-cyclodextrin, using the inclusion complex technique.

FT-IR Spectroscopic Analysis FT-IR

spectroscopic analysis was carried out to see if there was a shift in the spectrum formed from the inclusion complex celecoxib β-cyclodextrin and to identify functional groups or structures in a compound. Every bond in a compound absorbs infrared light. These bonds can experience stretching (stretching) or bonding (wrinkling). The fingerprint area can also be used to identify a sample by comparing the absorption spectrum of the sample with the absorption spectrum of a comparison compound. Analysis using spectroscopy is also to determine whether there is a chemical interaction between celecoxib and β-cyclodextrin[12]. The results of infrared spectrum analysis on celecoxib show the presence of NHgroups$_2$ at wave number 3332.89 cm^{-1}, functional group S = O at wave number 1345.47 cm^{-1}, CN functional group at wave number 1373.82 and CF at number wave 1273.96 cm^{-1}. The infrared spectrum on β-cyclodextrin is the presence of the CH functional group at wave number 2937.16 cm^{-1}, and the OH functional group at wave number 3318.08 cm^{-1}. The characteristics of the infrared spectrum in the physical mixture of NH_2 at wave number 3330.36 cm^{-1}, the functional group S = O at wave number 1345.69 cm^{-1}, the CN functional group at a wavelength of 1373.79 cm^{-1} and the CF functional group at wave number 1274.26 cm^{-1}. The results of the infrared spectrum characteristics in the inclusion complex show the presence of the NHfunctional group$_2$ at wave number 3333.13 cm^{-1}, the S = O functional group at wave number 1346.15 cm^{-1}, the CN functional group at a wavelength of 1374.14 cm^{-1} and the CF functional group at wave number 1229.08 cm^{-1}. From the analysis of celecoxib FTIR spectrum results, physical mixtures, inclusion complexes, there is a wave shift. This indicates that there is an interaction between celecoxib and β-cyclodectrin, which means that inclusion complexes have been formed by the solvent evaporation method, and the absence of missing or increased functional groups indicates that there is no chemical interaction between celecoxib and β-cyclodextrins.

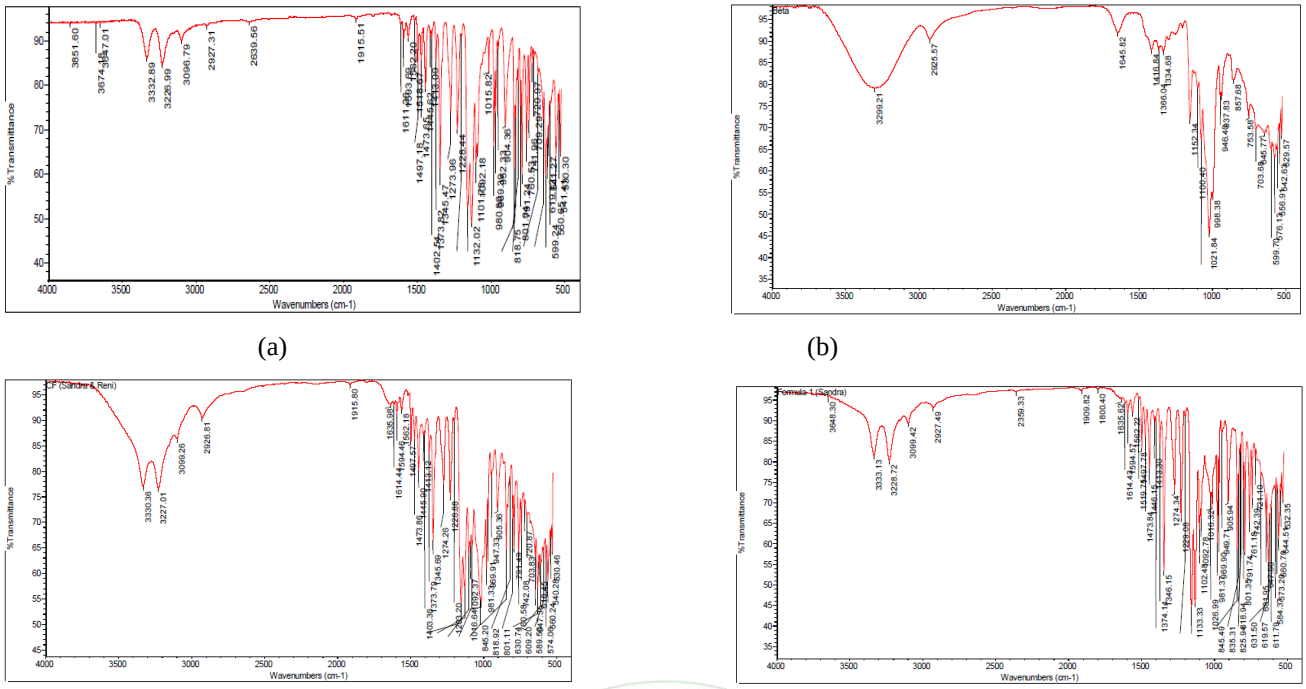
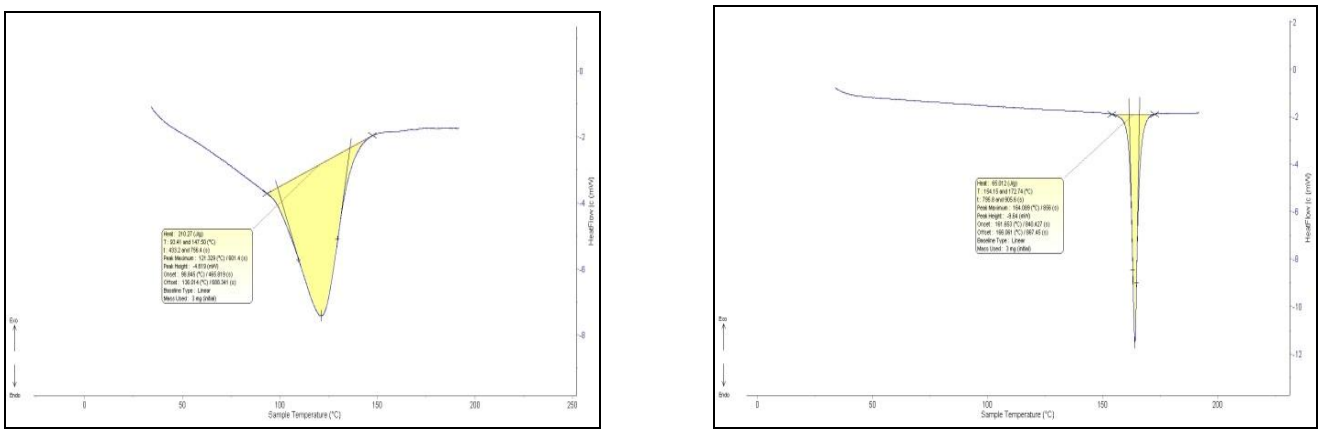
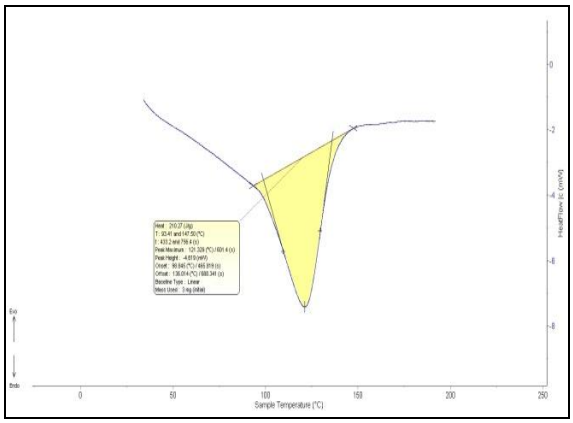


Figure 1: (a). Spectrum FT-IR celecoxib, (b). Spectrum FT-IR β-cyclodextrin, (c). FT-IR spectrum of physical mixture, (d). FT-IR spectrum complex inclusions.

Differential Scanning Calorymetry (DSC)

Analysis Thermal analysis using the DSC tool is used to determine the heat capacity and enthalpy of a material and is able to measure the amount of heat absorbed or released during the transition[13]. The results of the celecoxib thermogram showed a sharp endothermic peak at a temperature of 164.08^{o} C, which was a melting event of celecoxib with an enthalpy of 65.012 J / g. The results of the β-thermogram showed an endothermic peak at a temperature of 121.32^{o} cyclodectrin C with an enthalpy of 210.27 J / g. In the physical mixture there is an endothermic peak at a temperature of 108.59 ° C with an enthalpy of 87.65 J / g and at a temperature of 163.87 ° C with an enthalpy of 13.827 J / g. And for the inclusion complex of celecoxib β-cyclodextrin, the endothermic peak is seen at a temperature of 108.27 ° C with an enthalpy of 74.169 J / g and at a temperature of 163.51 ° C with an enthalpy of 38.286 J / g. From the results of the DSC thermogram, it can be seen that there is a decrease in the enthalpy value and melting point of the active celecoxib, the physical mixture and the inclusion complex, the enthalpy in the physical mixture = 13.827 and the inclusion complex = 38.286, where the decrease in the enthalpy for the physical mixture is better than the inclusion complex.which indicates the occurrence of physical interactions and no new endothermic peaks are formed, which means that there are no chemical interactions.





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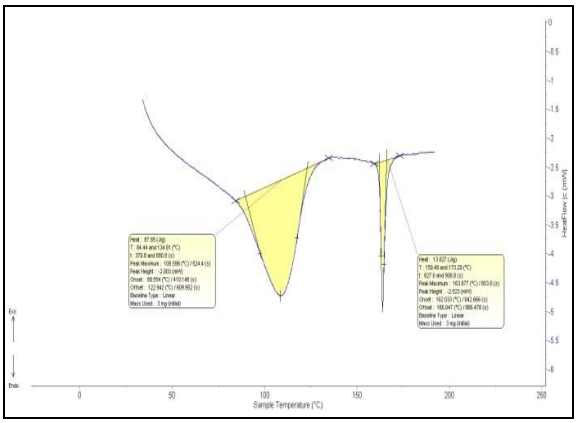

(d)

Figure 2: (a). Celecoxib thermogram, (b). B-cyclodextrinthermogram, (c). Physical mixed thermogram, (d). Inclusion complex thermogram.

The Determination of Celecoxib β-Cyclodextrin concentration of celecoxib and β-cyclodextrin was determined using a Uv-Vis spectrophotometer. Determination of the content begins with the determination of the maximum absorption wavelength using methanol with a concentration of 10 ppm and obtained a maximum wavelength of 252.00 nm with an absorbance of 0.537. While the wavelength of maximum absorbance shown at the *European Pharmacopoea 8th* 2014 that is 251 nm, it means that the results obtained by researchers at the maximum wavelength of celecoxib are close to the referenced literature.

The calibration curve of celecoxib in methanol was made with a concentration of 6 µg / mL, 8 µg / mL, 10 µg / mL, 12 µg / mL, 14 µg / mL and obtained a line regression equation y = 0.05028x– 0.03138 with a value of r = 0.99977.

From the research that has been done, the results of celecoxib level determination were obtained 100.62%, where these results are in accordance with the range of requirements for celecoxib levels listed in the *European Pharmacopoea 8th ed* 2014, namely celecoxib levels not less than 98% and not more than 102.00 %. The results of celecoxib content determination in the physical mixture, the inclusion complex obtained CF = 98.42%, and KI = 98.68%. Of all the assay results obtained were in accordance with the requirements stated[14].

Dissolution Test

Determination of the dissolution test of celecoxib, physical mixture, and inclusion complex was carried out using 0.1 N hydrochloric acid medium. Determination of celecoxib wavelength The maximum absorption in hydrochloric acid medium 0.1 N with a concentration of 100 ppm obtained a wavelength of 252.40 with an absorbance of 0.25. The calibration curve of celecoxib in 0.1 N hydrochloric acid medium was made with concentrations of 100 µg / mL, 120 µg / mL, 140 µg / mL, 160 µg / mL, and 180 µg / mL in order to obtain the regression equation y = 0.00496x - 0 , 23735 with a regression coefficient value, 0.99920.

In the determination of the dissolution test of celecoxib, physical mixture, and inclusion complexes, it shows that in the physical mixture and the inclusion complex there is an increase in the percentage of dissolution, the increase in dissolution rate is due to the effect of adding β-cyclodextrins, it is seen that in the inclusion complex system there is an increase in the dissolution rate. The increase in dissolution percentage can be seen in the dissolution percentage of each formula.

The percent dissolution in the 60th minute of the physical and complex mixture is CF = 61.58%, and KI = 67.53%. The increase in dissolution percentage was influenced by the formation of β-cyclodextrin inclusion complexes using the solvent evaporation method. It can be concluded that the addition of β-cyclodextrin and the solvent evaporation method can increase the dissolution percentage.

Another parameter used for dissolution evaluation is dissolution efficiency[15]. The dissolution efficiency value is the AUC (*Area Under Curve*) value of the amount of drug dissolved per time, as in the study of *bioavailability / bioequivalence* this value can also be used to compare the amount and rate of drug dissolution in general.

The average calculation of the dissolution efficiency obtained from the area under the curve shows the dissolution efficiency values for celecoxib, physical mixture, and the inclusion complex, namely CB = 49.83%, CF = 54.40%, KI = 58.84%. These data indicate that the inclusion complex has the greatest efficiency.

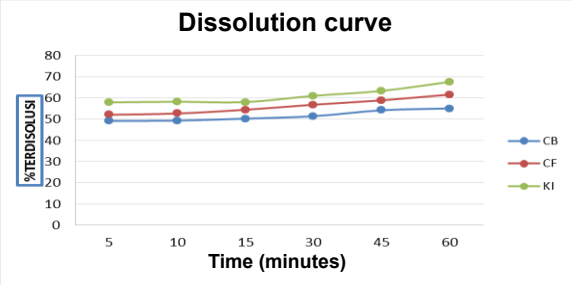

Figure 3: Dissolution curves of celecoxib, physical mixture, and inclusion complexes.

In the dissolution kinetics analysis of celecoxib, physical mixture, and inclusion complexes were carried out based on kinetics models of order 0, order 1, *Higuchi*, and *Korsemeyer-peppas*[16]. Of the four kinetics models, the correlation coefficient of thekinetics model equation *Higuchi* is the closest to one. The y line regression equations for celecoxib, physical mixture, and inclusion complexes are CB: y = 1.1529x + 45.912 (r = 0.9486), CF: y = 1.7253x + 47.661 (r = 0.9841), and KI : y = 1.706x + 52.676 (r = 0.8925).

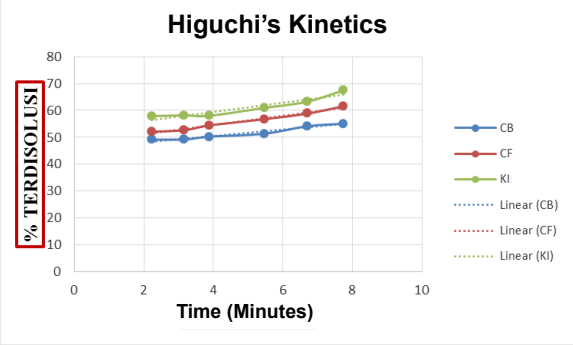

Figure 4: Higuchi kinetic model

From the results of the research conducted, the best formula was shown by the inclusion complex with the solvent evaporation time of 60 minutes, because the best dissolution results were 67.53% and the dissolution efficiency was 58.84%. This shows that there has been a significant increase in the dissolution rate and at the time of the evaporation process the molecules in the solution have undergone a hydrogen bonding reaction. This is due to the addition of β-cyclodextrin, where celecoxib is trapped into the β-cyclodextrin cavity.

Data Analysis

Analysis Statistical analysis of the dissolution efficiency of celecoxib β-cyclodextrin was carried out by one-way ANOVA test using SPSS 20. From the ANOVA calculation results showed the value of F count = 5.460 with Sig. = 0.045 (<0.05), which means that$_{Ho\ is}$ rejected. This shows that the average dissolution efficiency of celecoxib, physical mixture, and inclusion complexes is different, namely an increase in the formation of inclusion complexes on the results of dissolution efficiency. The results of Duncan's continued test show that the average dissolution efficiency is divided into 2 subsets, where the dissolution efficiency of celecoxib lies in subset 1, the physical mixture and the inclusion complex is in subset 2. It can be concluded that there are differences in dissolution efficiency between celecoxib, physical mixtures, and inclusion complexes, which means that there is an increased dissolution rate in the formation of the inclusion complex from celecoxib.

CONCLUSION

Based on the research that has been done, it can be concluded that:

There was a change in physicochemical characterization after the formation of the celecoxib β-cyclodextrin inclusion complex using the solvent evaporation method. Where seen in the physicochemical evaluation of physical mixtures and inclusion complexes on FT-IR, there was a shift in wave numbers between celecoxib, physical mixture and inclusion complexes, and no new functional groups formed, and in DSC there was a decrease in enthalpy and melting point between celecoxib, a physical mixture. and the inclusion complex, the enthalpy in the physical mixture = 13.827 and the inclusion complex = 38.286, where the decrease in the enthalpy of the physical mixture is better than the inclusion complex. This is due to the formation of inclusion complexes in the evaporation that have not been able to inclusion completely.

There is an effect of β-cyclodextrin on the dissolution rate of celecoxib on the formation of inclusion complexes and an increase in the dissolution rate of inclusion complexes.

Suggestion

It is recommended that the next researchers conduct further research on the characterization of the inclusion complex of celecoxib β-cyclodextrin using the solvent evaporation method.

REFERENCES

1. Ansel, H. C. (2008). Pengantar bentuk sediaan farmasi. (Edisi 4). Penerjemah: F.Ibrahim. Jakarta: Universitas Indonesia Press.

2. Reintjes, T. (2011). *Solubility enhancement with BASF pharma polymers solubilizer compendium*. Germany: Pharma ingredients & services.

3. J. Fort. Celecoxib, a COX-2-specific inhibitor: the clinical data. Am J.Orthop,1999;(28):13–18.

4. Loftsson, T., & Brewster, M. E.Pharmaceutical applications of β-siklodekstrin, drug solubilization and stabilization. J Pharm Sci. 1996; 85(10):1017-1024.

5. Loftsson T, Jarho P, Masson M, Jarvinen T. Cylodextrin in Drug Delivery, Expert Opinion Drug Delivey, 2005; 2:335-351

6. Duchene, D. (2011). Cyclodextrin And Their Inclusion Complexes, In Bilensoy, E. Cyclodextrin In Pharmaceutics, Cosmetics and Biomedicine. John Wiley & Sons, Inc., New Jersey, Canada.

7. Patil, J. S., Kadam, D. V., Marapur, S. C., & Kamalapur, M. V. Inclusion Complex System ; A novel technique to improve the solubility and bioavailability of poorly soluble drugs. *International Journal of Pharmaceutical Sciences Review and Reserch, 2010;* 2, (2), 29-34.

8. Sahoo, S., Chakraborti, K,C., Misrha,C, S., Nanda, Nath., Upendra & Naik, S. FTIR and XRD Investigations Of Some Flouroquinolones. *International Journal Of Pharmacy and Pharmacetical Sciences.*2011; 3(3).

9. Liu, Y., Sun, C., Hao, Y., Jiang, T., Zheng., & Wang,S. Mechanism of dissolution enhancement and bioavaibility of poorly water soluble celecoxib by preparing stable amorphous nanoparticles. Journal of pharmacy & pharmaceutical sciences,2008; 13(4):589.

10. Reddy, M.N., M., Rehana, T., Ramakrishna, S., Chowdary, K. P.R., &Diwan,P.V.β-cyclodextrin complexes of celecoxib: molecular-modeling, characterization, and dissolution studies. *AAPS PharmSci,2004; 6(1)*.

11. Jouyban-Gharamaleki, V., Soleymani, J., Jouyban-Gharamaleki, K., Suleymanov, T. A., & Jouyban, A. Solubilization of celecoxib, lamotrigine and phenytoin using ethanol and a nonionic surfactant. Journal of Molecular Liquids, 2017; 243:715–719.

12. Dachriyanus. (2004). Analisis struktur sensyawa organik secara spektroskopi. Padang: Andalas Universitty Press.

13. Ginting, A., Sutri, I., & Jan, S. Penentuan Parameter Uji dan Ketidakpastian Pengukuran Kapasitas Panas Pada Differentian Scanning Calorimeter. J. Tek. Bhn. Nukl.2005; 1(1):1-57.

14. European Pharmacopoeia Commission. (2014) . European Directorate for the Quality of Medicines &Healthcare European Pharmacopoeia 8th Edition, Strasbourg : Council Of Europe .

15. Kementerian Kesehatan Republik Indonesia. (2014). Farmakope Indonesia. (Edisi V). Jakarta: Kementrian Kesehatan Republik Indonesia.

16. Rowe, R. C., Sheskey, P. J., & Quinn, M. E. (2009). *Handbook of pharmaceutical exipients* (6th ed). London: Pharmaceutical Press.