JURNAL FARMASI SAINS DAN KOMUNITAS, May 2020, 8-19 Vol. 17 No. 1
p-ISSN 1693-5683; e-ISSN 2527-7146
doi: http://dx.doi.org/10.24071/jpsc.002034

THE INFLUENCE OF β-CYCLODEXTRIN CONCENTRATIONS AS LIGANDS ON INCLUSION COMPLEXES TO INCREASE THE SOLUBILITY OF IBUPROFEN

Rahmah Elfiyani*), Anisa Amalia, Alvin Integra

Faculty of Pharmacy and Science, University of Muhammadiyah Prof. DR HAMKA, Klender-Jakarta Timur, 13460, Indonesia

Received August 12, 2019; Accepted January 21, 2020

ABSTRACT

Ibuprofen is a compound with low solubility but high permeability in water. One method to improve the ability of a substance to dissolve in water is through the formation of inclusion complexes. This study aims to obtain ratio between ibuprofen and β-cyclodextrin which results in inclusion complex with an optimal amount of dissolved ibuprofen. The inclusion complex was made using solvent evaporation method with molar ratio variations of 1: 1, 1: 2, 1: 3, 1: 4 and 1: 5. The results of the inclusion complex were characterized by X-ray diffraction, FTIR, SEM, and DTA. The solubility test was carried out using three different media; they are pH solution 7.4; pH solution 1.5; and distilled water. The solubility test results showed no increase on the ibuprofen solubility of the inclusion complex within medium solutions of pH 7.4 and pH 1.5 whereas in aquades medium there was an increase in the inclusion complex solubility compared to pure ibuprofen. Based on the results, it can be concluded that inclusion complex with molar ratio of 1: 1 shows optimal amount of dissolved ibuprofen compared to other ratio variations in aquadest medium.

Keywords: β-cyclodextrin; ibuprofen; inclusion complexes; solvent evaporation.

INTRODUCTION

In a study conducted by Octavia *et al*. (2015), it was found that pure ibuprofen could not be dissolved for more than 70% in 30 minutes. Such compound requires a method to increase its solubility to improve the bioavailability of drugs (Yasir *et al*. 2010). Other studies investigating the increase of ibuprofen solubility have been carried out in the form of solid dispersion by the methods of solvent evaporation and melting dispersion (Gupta *et al*., 2011). This study uses relatively toxic organic solvents which will leave residue on the results of ibuprofen solid dispersion.

Another way to improve the solubility of drugs that are difficult to dissolve in water is through the inclusion complex, through which can improve the speed of dissolution, absorption, bioavailability, and chemical stability of the drug (Loftsson & Brewster, 1996). Inclusion complex is a form of inserting non-polar compounds (substrates) into a container of another compound (ligand) (Ketan *et al*., 2012). β-cyclodextrin compound is one of cyclodextrin types that can be used as a ligand in the formation of inclusion complex. It is because β-cyclodextrin has relatively large cavity diameter of up to 6Å and good water solubility of 1 part in 20 parts of water (Rowe *et al*., 2012).

Based on the explanation above, this research will produce an inclusion complex with a variation of ibuprofen:β-cyclodextrin ratio using the solvent evaporation method due to an increase in ibuprofen solubility. The purpose of this study is to obtain ratio of ibuprofen:β-cyclodextrin which produces inclusion complex with an optimal amount of dissolved ibuprofen.

*Corresponding author: Rahmah Elfiyani
Email: *rahmahelfiyani@uhamka.ac.id*

METHODS

The materials used in this study are ibuprofen (Hubei granules-biocause pharmaceutical), β-cyclodextrin (BaoJi GuoKang Bio-Technology), alcohol, aquadest, KCl (Merck), HCl (Merck), KH2PO4 (Merck), and NaOH (Merck). In addition, the instruments used in this study include X-ray diffractometer (Pan Analytical empryren), DTA (Mettler Toledo), UV-VIS spectrophotometer, SEM (SEM-eds JEOL JED350), FTIR spectrophotometer (Agilent), magnetic stirrer (Power MS-H-Pro), rotary evaporator (Butchi), and sieving (Retsch AS 200 digits CA).

Production of inclusion complex

The inclusion complex was made into 5 formulas by varying the molar ratio between ibuprofen:β-cyclodextrin which were 1: 1; 1: 2; 1: 3; 1: 4 and 1: 5 (Table 1). Ibuprofen was dissolved in 50 ml of ethanol (M1) while β-cyclodextrin was dissolved in 50 ml of hot water (60°C) (M2). After that, the M2 clear solution was put into M1 clear solution and stirred using a magnetic stirrer at 300 rpm for 30 minutes. The turbid solution is then evaporated (170 bar, 150 rpm, temperature 40°C). The dried powder formed was sieved using a mesh of 100, then dried in a desiccator for 3 hours (Priotta, 2015).

Characterization of inclusion complexes

Infrared spectra of ibuprofen, β-cyclodextrin and inclusion complexes were recorded using FT-IR spectrophotometer by KBr pellet method. Measurements were made at wavenumbers 400 - 4000 cm-1 (Hiremath *et al*, 2008).

DTA would characterize the solid-state interaction of the inclusion complex, β-cyclodextrin and, ibuprofen. The sample used was approximately 5 mg of ibuprofen, β-cyclodextrin, and inclusion complex at warming temperatures from 30 to 400 °C with a heating speed of 10 °C / minute (Ma *et al*., 2012).

XRD patterns of Ibuprofen, β-cyclodextrins and inclusion complexes were recorded using X-ray diffractometer with Cu anode tube at 5-700 / 2θ intervals. The sample was placed on a plate-shaped holder made of aluminum. Diffractogram would be read automatically on the computer (Asih II, 2011).

Particle morphology was observed using SEM. The powder sample (ibuprofen, β-cyclodextrin, inclusion complex) was placed in an aluminum sample holder and coated with gold with thickness of 10 nm. Samples were then observed for the enlargement of SEM devices. The voltage was set at 20 kV and the current was 12 mA (Octavia *et al*, 2015).

Solubility test

A total of 100 mg of standard ibuprofen and inclusion complex results were dissolved into 20 ml of ethanol each, put into a 100 ml volumetric flask and dissolved with the medium (buffer pH 1.5/ distilled water) until the boundary mark. It was stirred using a magnetic stirrer at a speed of 150 rpm for 15 minutes. A sample of 10 ml was taken and filtered with a 0.45 µm filtrate membrane. Absorption was measured at maximum wavelength using spectrophotometer. The solubility test was also carried out on solvent buffer pH 7.4 without the addition of ethanol to help to dissolve ibuprofen.

DATA ANALYSIS

Solubility test data on dissolved ibuprofen levels were analyzed using non-parametric analysis of Friedman because the data were not normally distributed and were not homogeneous.

Tabel 1. Formula of Inclusion Complex

	F 1	F 2	F 3	F 4	F 5
β-cyclodextrine (g)	283,75	567,5	851,25	1135	1418,75
Ibuprofen (g)	51,55	51,55	51,55	51,55	51,55

RESULTS AND DISCUSSION

FTIR

The results of FTIR characterization from ibuprofen, β-cyclodextrin and inclusion complexes can be seen in Figure 1 and Table 2. Inclusion complexes showed the presence of β-cyclodesktrin and ibuprofen groups. In formula 1 there were wavelengths of 1701.5 cm^{-1} and 1459.3 cm^{-1} which were the peaks in ibuprofen, a slight shift in wavelength from 1461 cm-1 to 1459 cm-1 (Barmi *et al*., 2018). In formula 2, a shift in wavelength from 3283.8 to 3280.1 belonged to β-cyclodextrin (Silverstein et.al., 1981), but there was no aromatic peak of ibuprofen. The wavelength of ibuprofen aromatic group was not seen in formulas 3, 4 and 5 as well. Carboxylic group wavelength shift from 1701.5 to 1735.1 belonged to ibuprofen in formula 3, formula 4 and formula 5. This indicated a weak interaction between ibuprofen and β-cyclodextrin (Hiremath *et al*., 2008). From these results, it was known that there was a shift in wavelength and appearance of ibuprofen, and wavelengths of β-cyclodextrin which indicated an interaction between ibuprofen and β-cyclodextrin

.

Tabel 2. Wave Number of FTIR

	Distance wave number (cm^{-1})	β-cyclodextryn (cm^{-1})
(O-H)	2500-3300	3263,3
(C-H) aromatis	1000-1275	1099,6
(C-O) alcohol dan fenol	1000-1300	1077,2
	Distance wave number (cm^{-1})	Ibuprofen (cm^{-1})
(C=O) carboxylic acid	1701	1701.5
(C=C) aromatic	1461	1460
	Distance wave number (cm^{-1})	Inclusion complex (cm^{-1})
O-H	2500-3300	3265-3280,1
C-H	1000-1275	1104.1
C-O	1000-1300	1079.1
C=O carboxylic acid	1701	1701.5-1735.1
(C=C) aromatic	1461	1459

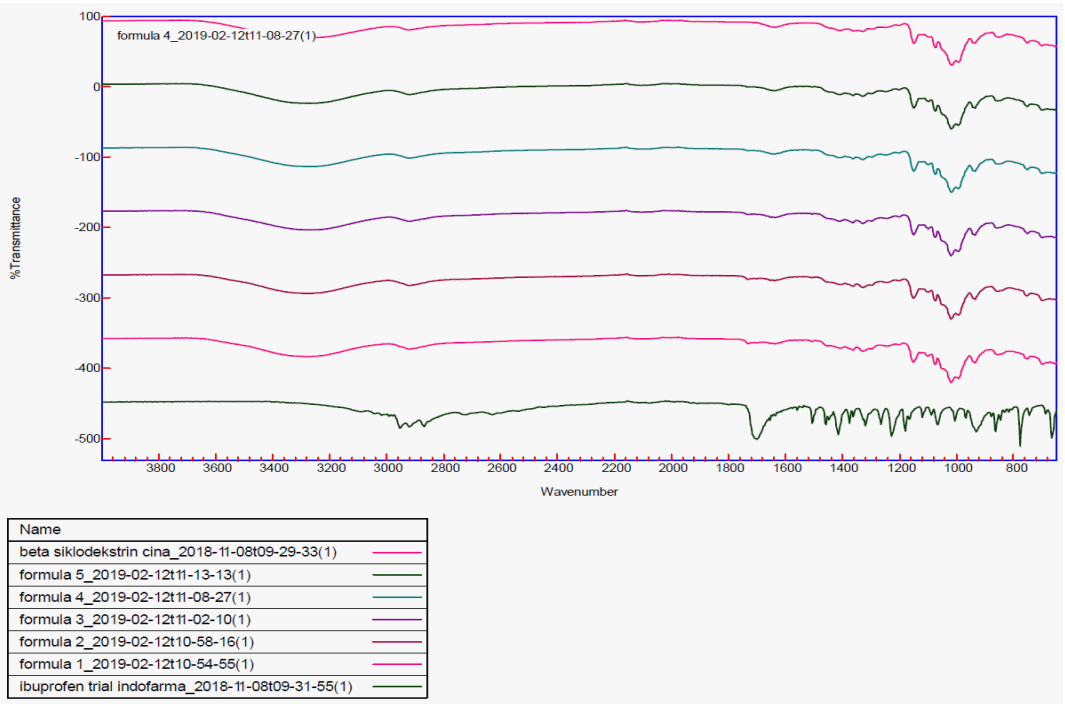
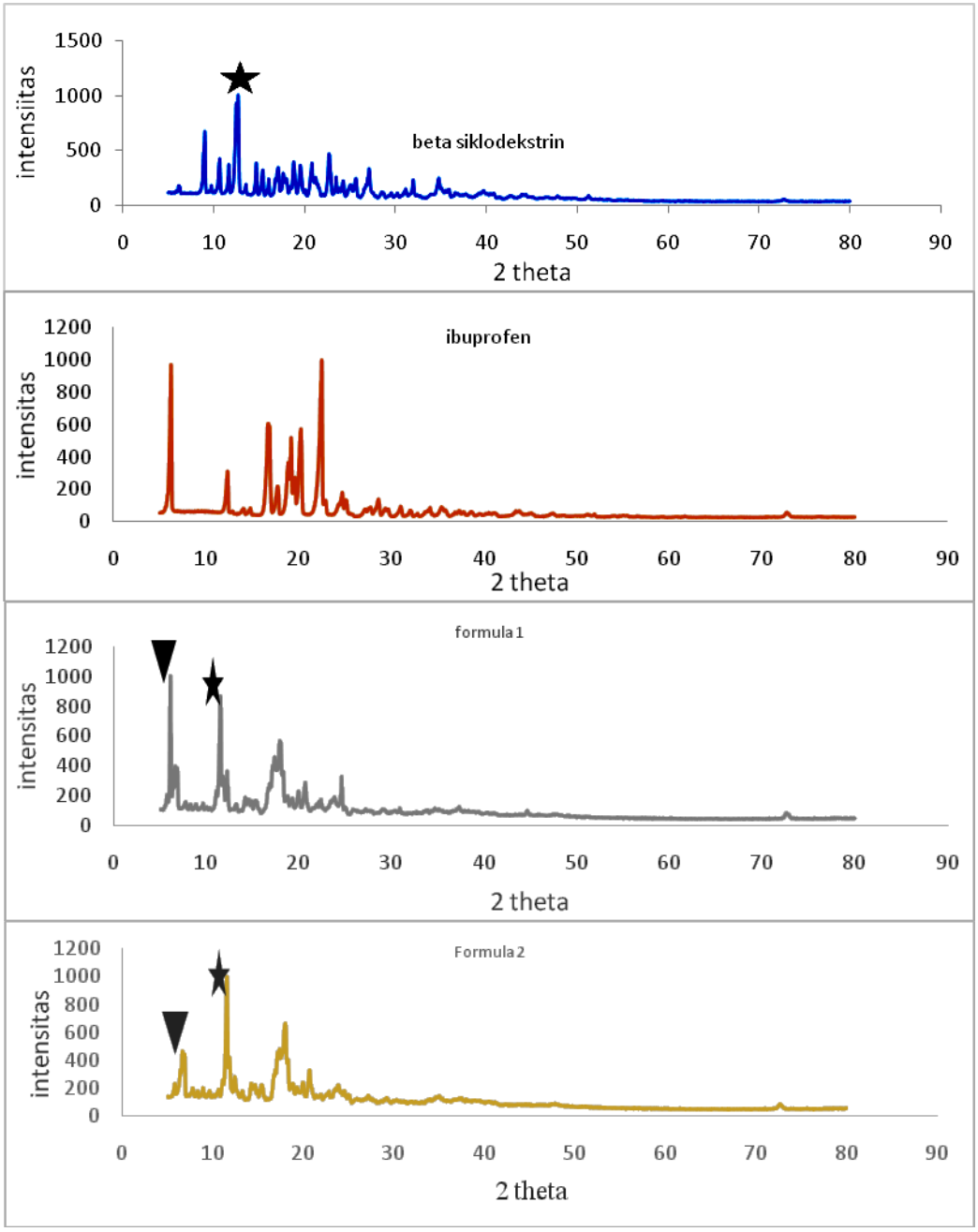


Figure 1. IR Spectrum of ibuprofen, β-cyclodextrin and inclusion complex.

X-ray Diffractometry

It can be seen in Figure 2. In formula 1, the inclusion complex was formed due to the bonding of ibuprofen and β-cyclodextrin so that the peaks in formula 1 and formula 2 were not too many. With the increase on the number of β-cyclodextrin, the peaks were increasingly visible until formula 5, but did not cover the peak of ibuprofen. The diffraction pattern formed from formula 1 to formula 5 was increasingly seen approaching β-cyclodextrin diffraction pattern with increasing peaks similar to β-cyclodextrin. This signifies that ibuprofen molecule has entered the structure of β-cyclodextrin cavity so that it looks dominant β-cyclodextrin diffractogram (Rini *et al*., 2015). The decrease in height of peak intensity indicates a change in the structure so that the results of the inclusion complex are amorphous (Pamudji *et al*., 2014; Barmi *et al*., 2018).



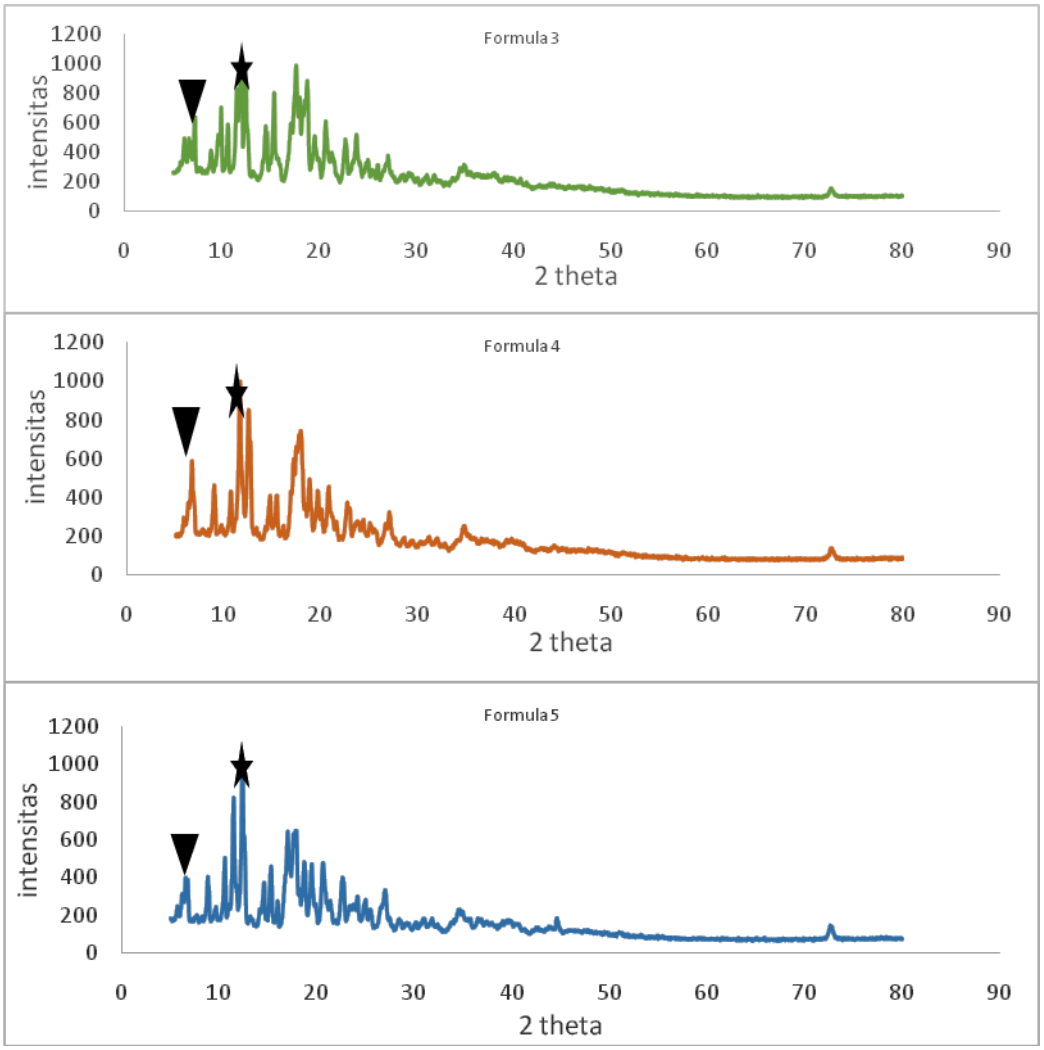


Figure 2. XRD result of ibuprofen, β-cyclodextrin and inclusion complex.

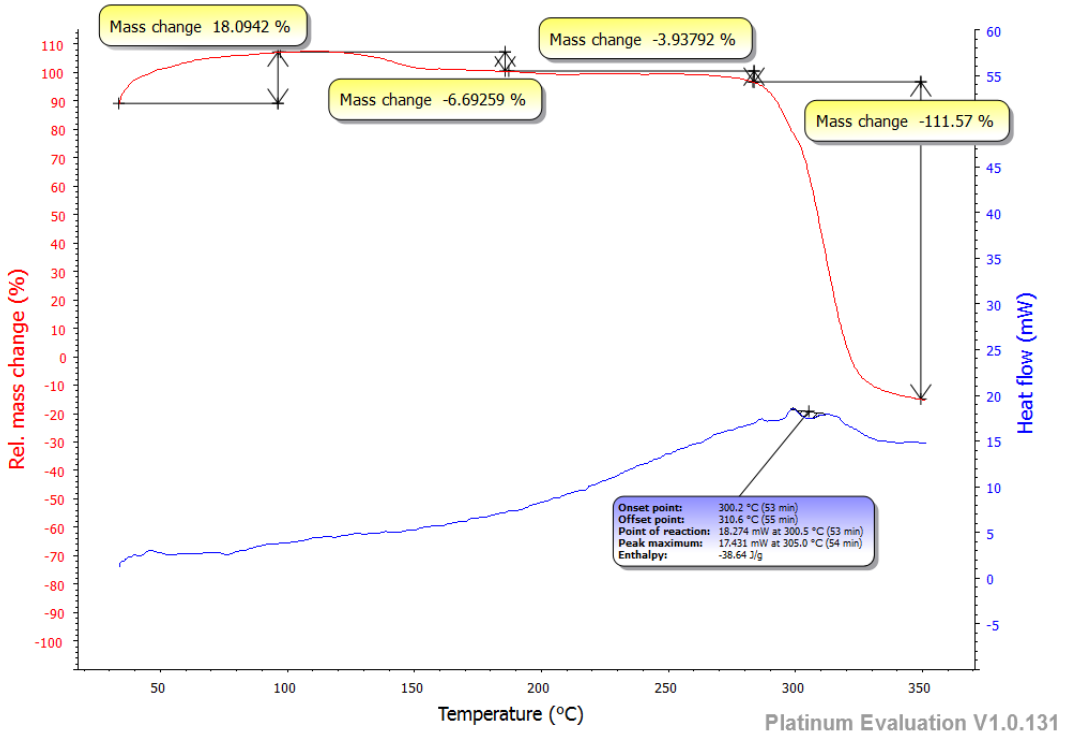
Differential Thermal Analysis

Formula 1 and formula 2 showed an endothermic process at a temperature of 2900°C - 3200°C. Endothermic changes can occur due to oxidation of organic compounds (Setabudi *et al*., 2012). However, formula 3 experienced an exothermic process at a temperature range of 2940°C - 3020°C and at that temperatures there was a change in mass. Meanwhile, in formula 4 and formula 5, exothermic process was directly followed by endothermic process. Exothermic process usually occurs due to the formation of crystals during the heating process which is often referred to solidification.

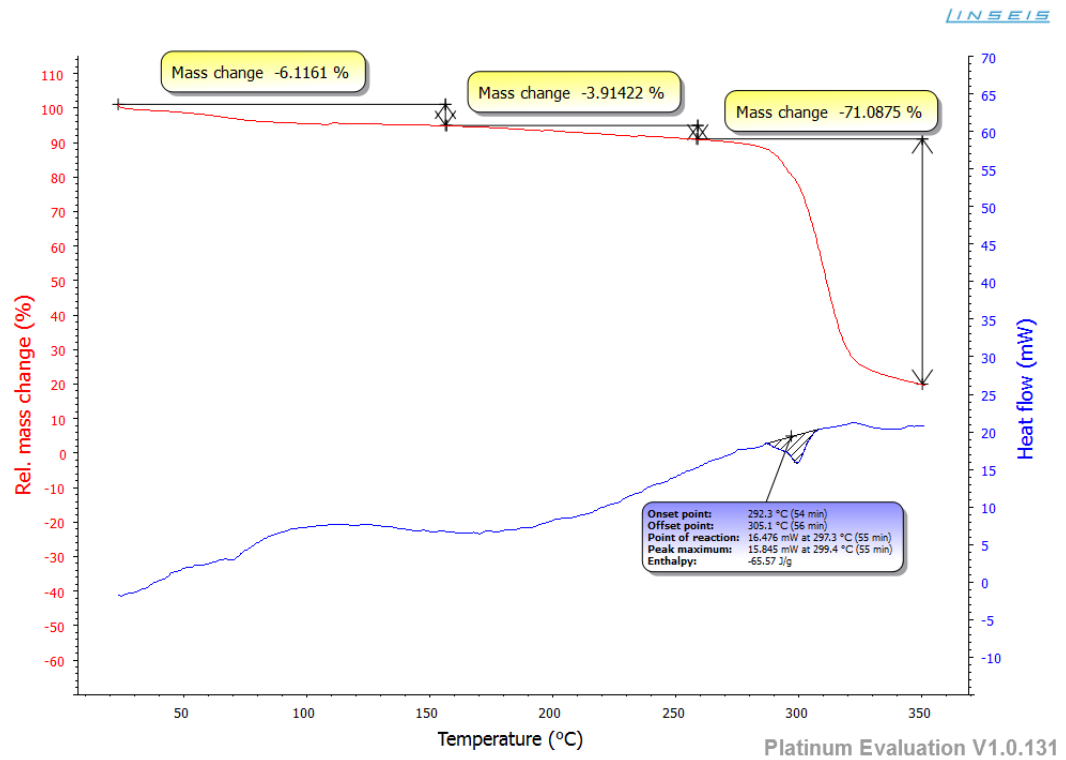
In all results (Figure 3) on inclusion complex, dehydration which usually occurs at temperatures of around 1000°C is absent this time due to the disappearance of ibuprofen melting point. Ibuprofen loses its peak because it has entered the cavity of β-cyclodextrin so that it does not show endothermic points at these adjacent temperatures (Hirameth 2008; Manca *et al*., 2005).

Scanning Electron Microscope

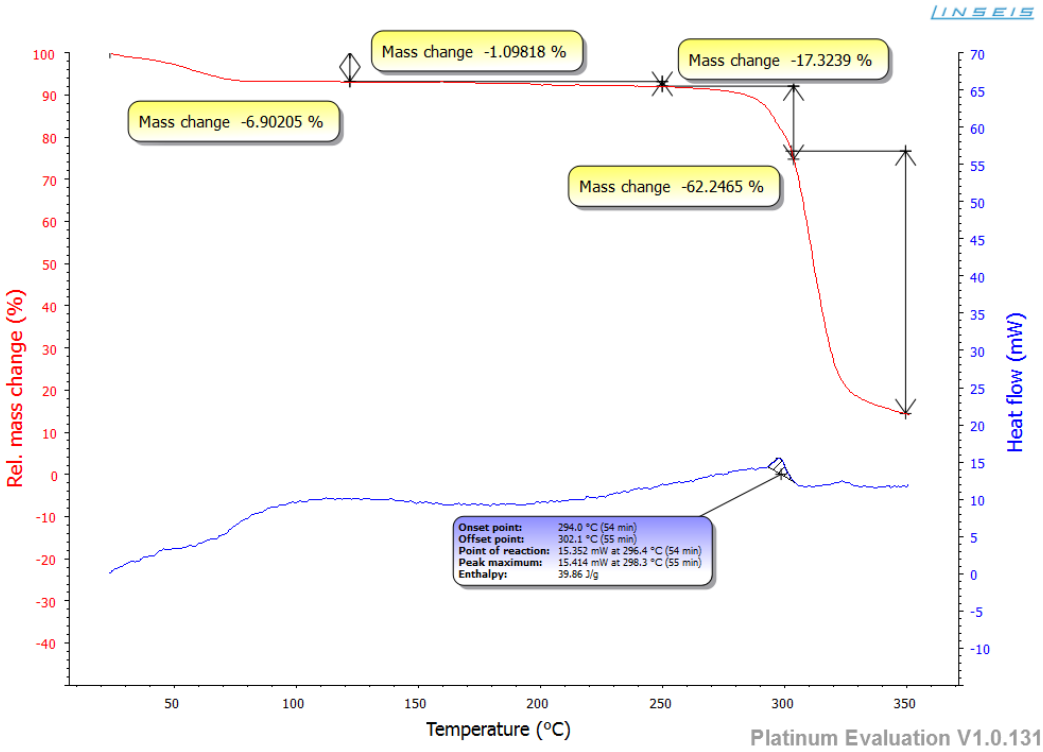
The results of pure ibuprofen examination showed a long cylindrical rod shape while β-cyclodextrin was seen as a lump with a rough and irregular texture. In the results of inclusion complex, all formulas appear to have no form that resembles ibuprofen and β-cyclodextrin. In fact, almost all are irregular in shape (Figure 4).


Mass change 18.0942 %
Mass change -6.69259 %
Mass change -3.93792 %
Mass change -111.57 %
Onset point: 300.2 °C (53 min)
Offset point: 310.6 °C (55 min)
Point of reaction: 18.274 mW at 300.5 °C (53 min)
Peak maximum: 17.431 mW at 305.0 °C (54 min)
Enthalpy: -38.64 J/g
Rel. mass change (%)
Heat flow (mW)
Temperature (°C)
Platinum Evaluation V1.0.131

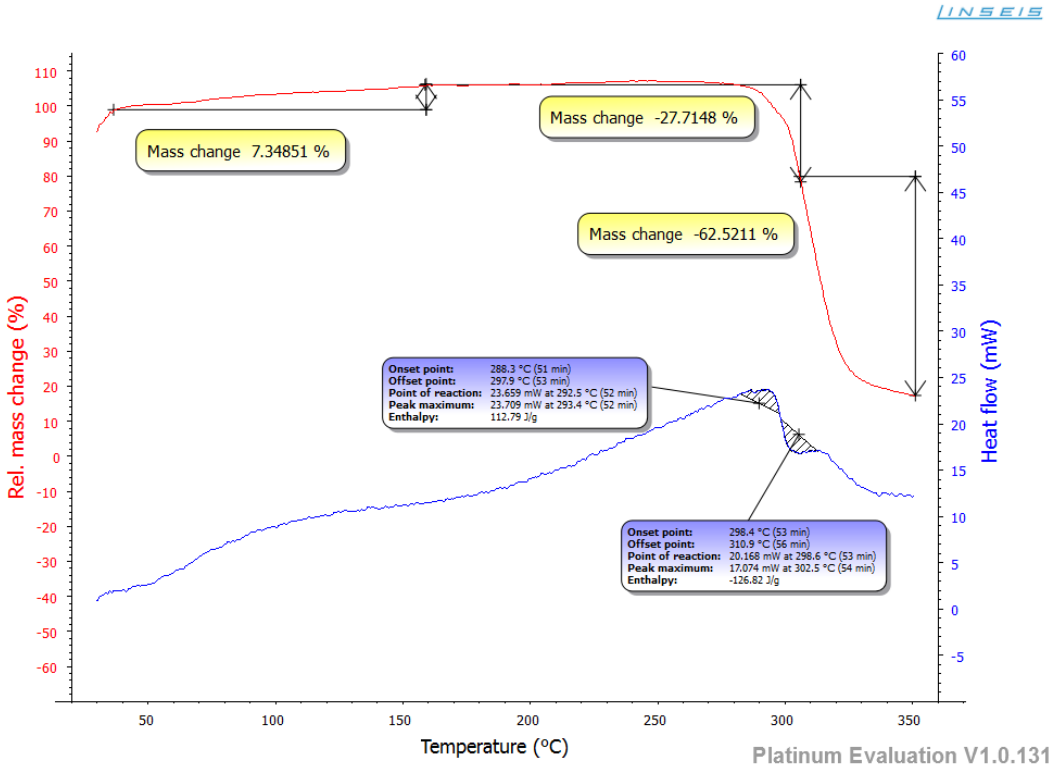
(a)


Mass change -6.1161 %
Mass change -3.91422 %
Mass change -71.0875 %
Onset point: 292.3 °C (54 min)
Offset point: 305.1 °C (56 min)
Point of reaction: 16.476 mW at 297.3 °C (55 min)
Peak maximum: 15.845 mW at 299.4 °C (55 min)
Enthalpy: -65.57 J/g
Rel. mass change (%)
Heat flow (mW)
Temperature (°C)
Platinum Evaluation V1.0.131

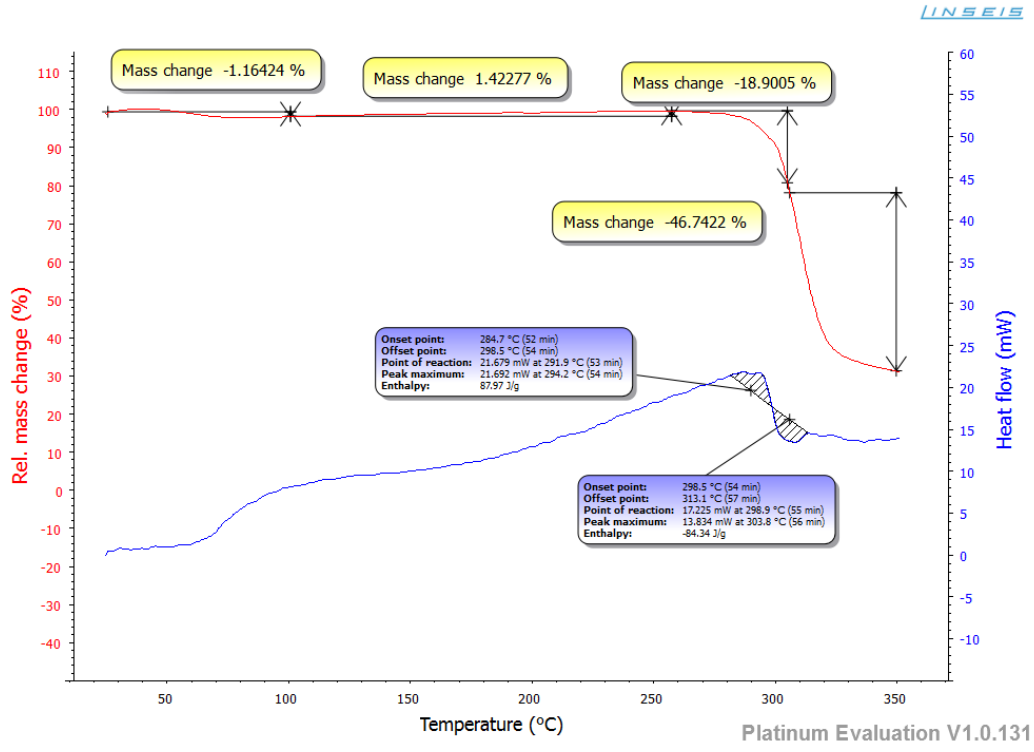
(b)


Mass change -1.09818 %
Mass change -17.3239 %
Mass change -6.90205 %
Mass change -62.2465 %
Onset point: 294.0 °C (54 min)
Offset point: 302.1 °C (55 min)
Point of reaction: 15.352 mW at 296.4 °C (54 min)
Peak maximum: 15.414 mW at 298.3 °C (55 min)
Enthalpy: 39.86 J/g
Rel. mass change (%)
Heat flow (mW)
Temperature (°C)
Platinum Evaluation V1.0.131

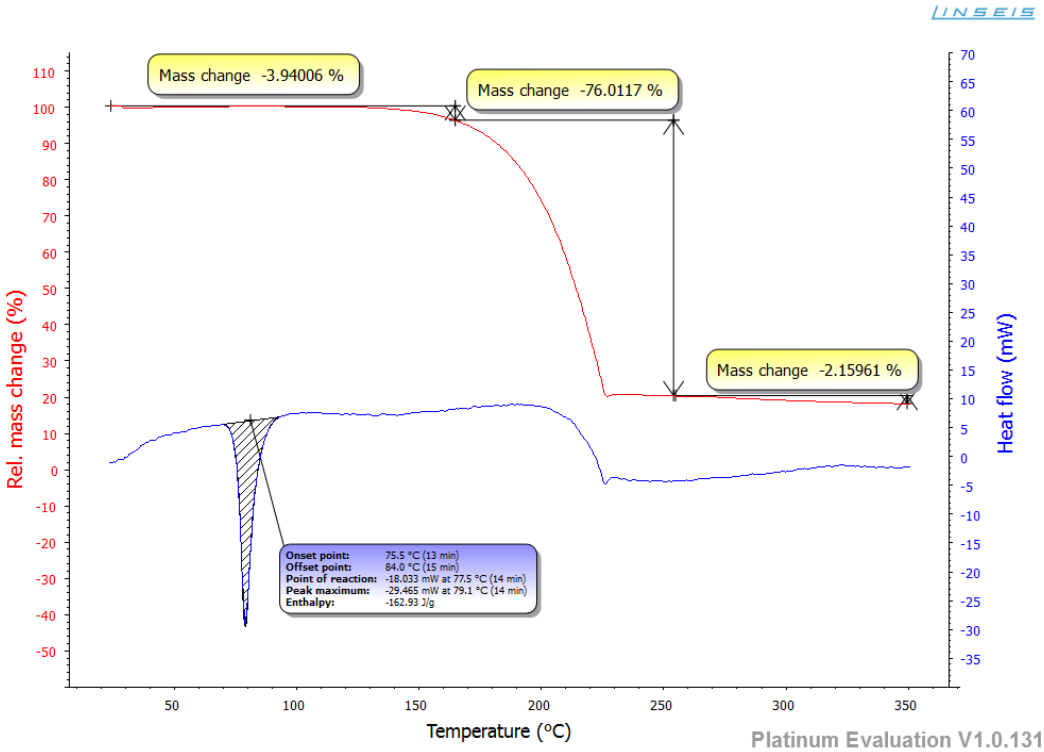
(c)


Mass change 7.34851 %
Mass change -27.7148 %
Mass change -62.5211 %
Onset point: 288.3 °C (51 min)
Offset point: 297.9 °C (53 min)
Point of reaction: 23.659 mW at 292.5 °C (52 min)
Peak maximum: 23.709 mW at 293.4 °C (52 min)
Enthalpy: 112.79 J/g
Onset point: 298.4 °C (53 min)
Offset point: 310.9 °C (56 min)
Point of reaction: 20.168 mW at 298.6 °C (53 min)
Peak maximum: 17.074 mW at 302.5 °C (54 min)
Enthalpy: -126.82 J/g
Rel. mass change (%)
Heat flow (mW)
Temperature (°C)
Platinum Evaluation V1.0.131

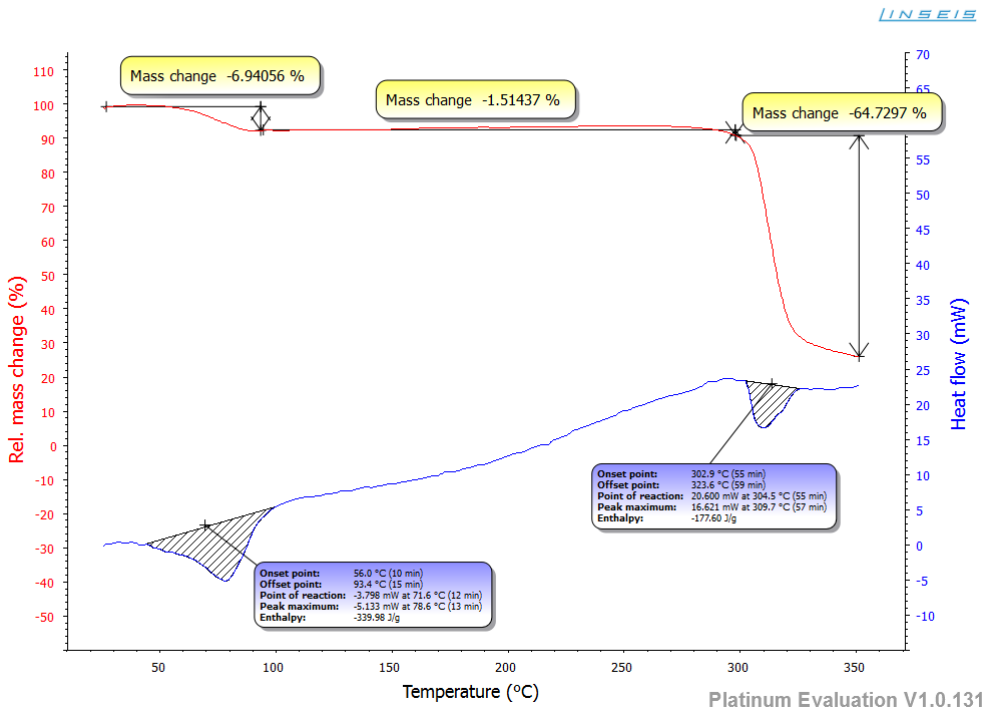
(d)


Mass change -1.16424 %
Mass change 1.42277 %
Mass change -18.9005 %
Mass change -46.7422 %
Onset point: 284.7 °C (52 min)
Offset point: 298.5 °C (54 min)
Point of reaction: 21.679 mW at 291.9 °C (53 min)
Peak maximum: 21.692 mW at 294.2 °C (54 min)
Enthalpy: 87.97 J/g
Onset point: 298.5 °C (54 min)
Offset point: 313.1 °C (57 min)
Point of reaction: 17.225 mW at 298.9 °C (55 min)
Peak maximum: 13.834 mW at 303.8 °C (56 min)
Enthalpy: -84.34 J/g
Rel. mass change (%)
Heat flow (mW)
Temperature (°C)
Platinum Evaluation V1.0.131

(e)

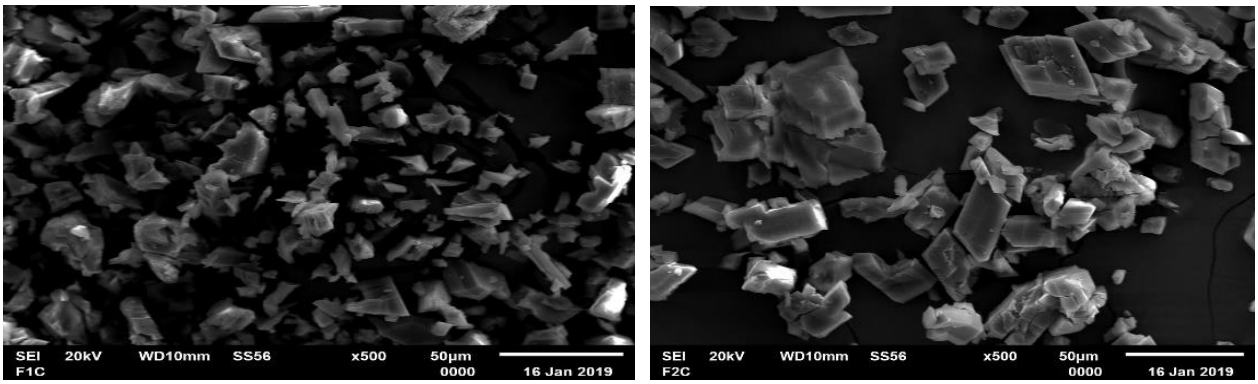

Mass change -3.94006 %
Mass change -76.0117 %
Mass change -2.15961 %
Onset point: 75.5 °C (13 min)
Offset point: 84.0 °C (15 min)
Point of reaction: -18.033 mW at 77.5 °C (14 min)
Peak maximum: -29.465 mW at 79.1 °C (14 min)
Enthalpy: -162.93 J/g
Rel. mass change (%)
Heat flow (mW)
Temperature (°C)
Platinum Evaluation V1.0.131

(f)



(g)

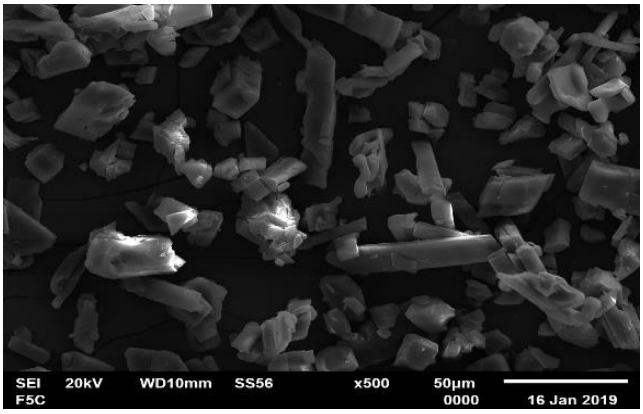
Figure 3. DTA result: (a) Formula 1, (b) Formula 2, (c) Formula 3, (d) Formula 4, (e) Formula 5, (f) ibuprofen, (g) β-cyclodextrin.



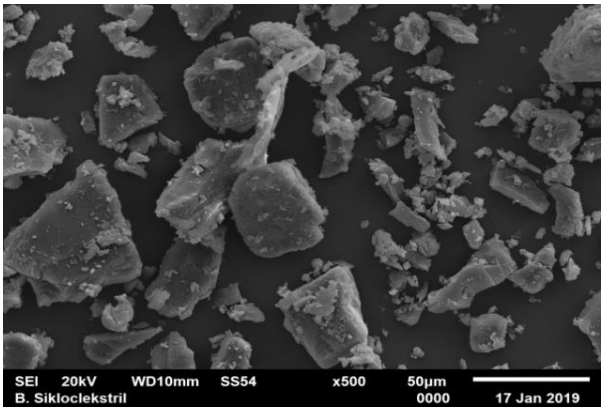
Formula 1 Formula 2

Formula 3 Formula 4

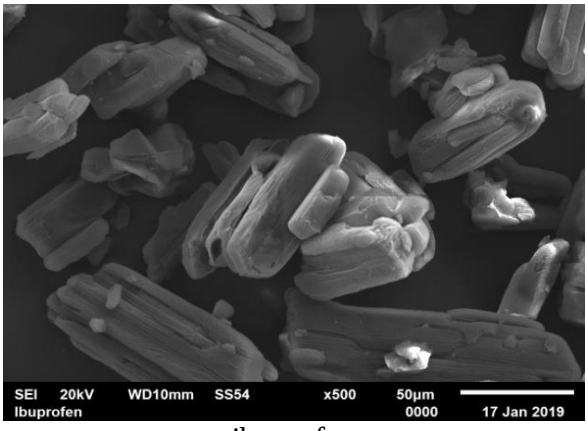
Figure 4. SEM results



Formula 5



β-cyclodextrin



ibuprofen

Figure 4. SEM results (*Continued*)

Solubility Test

One of the most common methods in evaluation inclusion complexation is phase solubility. A phase solubility diagram is constructed by plotting the molar concentration of dissolved solute found on the vertical axis against the concentration of complexing agent added on the horizontal axis. Two general types of phase solubility profiles are generated; Type A where soluble complexes are formed, and Type B where complexes of limited solubility are formed (Higuchi & Connors, 1965).

The results (Figure 5) show that the addition of β-cyclodextrin to the inclusion complex at solution of pH 7.4 and pH 1.5 follows the type BI diagram which means that there is no increase in the solubility of ibuprofen with the addition of β-cyclodextrin at ratios of 1: 1, 1: 2, 1: 3, 1: 4, and 1: 5. As with the aquadest medium, there is an increase in the solubility of ibuprofen in formula 1 (ratio 1: 1) compared to pure ibuprofen, and the solubility type follows type Bs diagram.

Curve Bs shows the formation of a complex that increases the total solubility of the compound (similar to type A diagram). More addition of complexing agents producing solubility of the complex is reached. As additional compound goes into solution, some solid complexes precipitate. Further addition of complexing agents beyond point z results in depletion of the compound from solution by complex formation. Curve BI is interpreted similarly except that the complex formed is so insoluble that no increase in solubility is observed (Mosher & Thompson, 2007).

Statistical analysis of the solubility test results shows that sig < 0.05 based on which it can be concluded that the 2 variables (ratio of ibuprofen:β-cyclodextrin and the type of medium) generate different solubility results

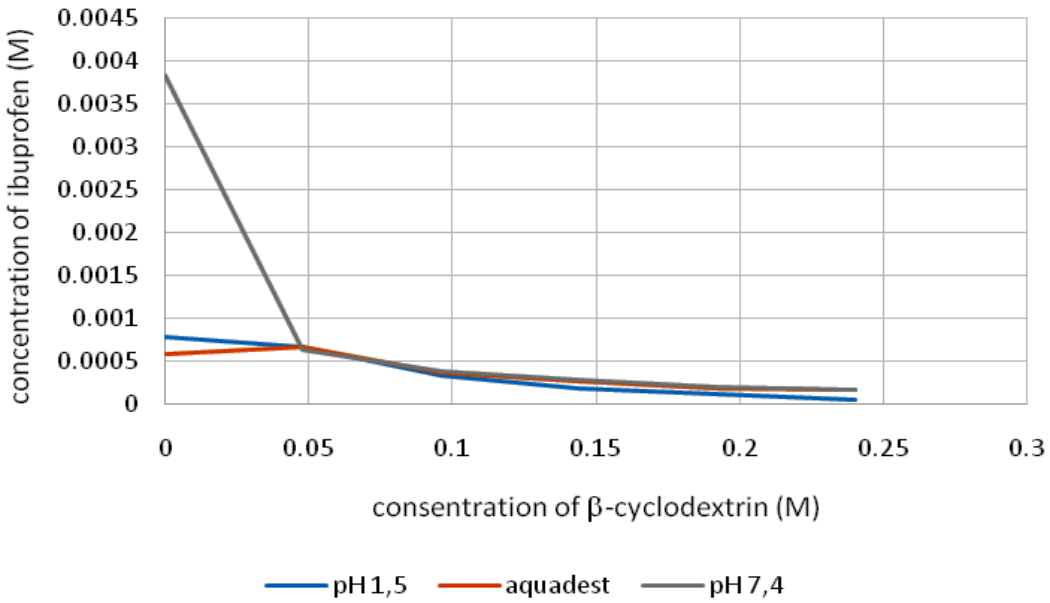


Figure 5. Solubility phase diagram of inclusion complexes

CONCLUSION

The inclusion complex is not able to increase the solubility of ibuprofen within solution medium of pH 7.4 and pH 1.5. Meanwhile, in the aquadest medium, the formation of inclusion complexes can increase the solubility of ibuprofen at ratio of 1: 1.

ACKNOWLEDGMENT

This research was supported by a grant from the LEMLITBANG UHAMKA (Research and Development Institute of Muhammadiyah Prof. DR HAMKA University) with contract number of 247/F.03.07/2019.

REFERENCES

Asih, I.I., 2011. Pembuatan Kompleks Inklusi Glikalizid-Beta Siklodekstrin dan Perbandingan Kecepatan Disolusi Glikalizid Dari Sediaan Tablet. *Skripsi*. Fakultas MIPA Universitas Indonesia, Jakarta. pp. 24-25.

Barmi, H., Lia, A., Desi, S., Julia, A.S., 2018. Pembentukan kompleks Inklusi ibuprofen kombinasi polimer β-siklodekstrin dan Hydroxypropyl Metylcelulose (HPMC) menggunakan teknik kneading. Riset Informasi Kesehatan, 7(1).

Gupta, M.M., Patel, M.G., Patel, N.S., Madhulika, K., 2011. Enhancement of Dissolution Rate Of Ibuprofen by Preparing Solid Dispersion Using Different Methods. *International Journal of Pharmacy and Pharmaceutical Sciences*, 3(3), 204-206.

Higuchi, T., Connors, K.A., 1965. Phase-solubility Techniques. In Advances in Analytical Chemistry and Instrumentation Vol. 4. John Wiley & Sons, Inc. New York, 117–212.

Hiremath, S.N., Raghavendra, R.K., Suntil, F., Danki, L.S., Rampure, M.V., Swamy, P.V., Bhosale, U.V., 2008. Dissolution Enhancement of Gliclazide by Prepartion of Inclution Complexs with Beta-cyclodextrin. *Asian Journal of Pharmaceuties*, 73-76.

Ketan, T., Salvjni, Anurdha, K., Gajjar, Jignasa, K., 2012. Importance and Enhancment Techniques: A Review. Institute of Pharmacy. Nirma University. Gujarat. India.

Loftsson, T.D., Hrciinsdottir, M., Masson, 1996. Evaluation of Cyclodextrin Solubilization of Drugs, *International Journal of Pharmaceutics, (*302), 18-28.

Ma, S., Yong, W., Xiaojun, S., Fulin, Y., 2012. Formulation of Berberine Hydrochloride and Hydroxypropyl-β-Cyclodextrin Inclusion Complex with Enhanced Dissolution and Reduced Bitterness. *Tropical Journal of*

Pharmaceutical Research, 11 (6), 871-877.

Manca, M.L., Marco, Z., Guido, E., Donatella, V., Chiara, S., Giuseppe, L., Anna, M.F., 2005. Diclofenac-*β*-Cyclodextrin Binary Systems: Physicochemical Characterization and In Vitro Dissolution and Diffusion Studies. *AAPS PharmSciTech*, 2005, 6(3), 464-472.

Mosher, G., Thompson, D.O., 2007. Complexation: Cyclodextrins dalam Encyclopedia of Pharmaceutical Technology, 3rd Edition. New York, 671-676.

Octavia, M.D., Novety, O., Halim A., 2015. Karakterisasi Kompleks Inklusi Ibuprofen Beta Siklodekstrin dengan Menggunakan Teknik Penggilingan Bersama. Sekolah Tinggi Ilmu Farmasi Padang.

Pamudji, J.S., Mauludin, R., Lestari, V.A., 2014. Improvement of Carvedilol Dissolution Rate Trough Formation of Inclusion Complex With β-Cyclodextrin. *International Journal of Pharmacy and Pharmaceutical Sciences*, 6(4), 228-233.

Priotti, J., Ferreira, M.J.G., Lamas, M.C., Leonardo, D., Salomon, C.J., Nunes, T.G., 2015. *First Solid-state NMR Spectroscopy Evaluation of Complexes of Benznidazole with Cyclodextrin Deerivatives.* Centro de Qumica Estrutural, Instituto Superior Technico, Lisboa.

Rini, A., Fathya, I.L., Auzal H., 2015. Pembentukan dan Karakterisasi Kompleks Inklusi Fenilbutazon dan β-siklodesktrin dengan Metoda Co-grinding. *Jurnal Ilmiah Farmasi*.

Rowe, R.C., Sheskey, P.J., Cook, W.G., Fenton, M.E., 2012. Handbook of Pharmaceutical Excipient. Seventh Edition. Pharameutical Press. USA.

Setaibudi, A., Rifan, H., Ahmad, M., 2012. Karakterisasi Material: Prinsip dan Aplikasinya pada Peneltian Kimia. First Edition. UPI PRESS. Bandung, 21-22.

Silverstein, R.M., Bassler, G.C., Morrill, T.C., 1981. Spectrometric Identification of Organic Compounds. Fourth Edition. New York, 108-120.

Yasir, M., Asif, M., Kumar, A., Anggarval, A., 2010. *Biopharmaceutical Classification System: An Accunt. Internasional Journal of PharmTech Research.* CODEN. USA, 1681-1690.