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Characterization and Improvement Dissolution Profile of the Hydrochlorothiazide-β-Cyclodextrin Inclusion Complex using Kneading Method

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Abstract

Hydrochlorothiazide is a drug antihypertensives are classified into Biopharmaceutics Classification System (BCS) class IV, so required technique formulation to improve solubility, one of them with complex inclusion. The inclusion complex was prepared with a kneading method with a comparison amount of hydrochlorothiazide - β- cyclodextrin 1:1 (F1) mol, 2:1 (F2) mol, and a physical mixture prepared in a ratio of 1:1 mol. This research aims to see the effect of complex formation inclusion on dissolution rate and characteristics of physicochemical properties of hydrochlorothiazide. Complex inclusions formed are characterized by scanning electron microscopy (SEM), and infrared spectrophotometer (FT-IR). X-ray diffraction, differential scanning calorimetry (DSC), and dissolution profiles. Characterization of physicochemical results analysis diffraction X-rays show that powder complex inclusion hydrochlorothiazide with β-cyclodextrin experiences decline peak intensity approaches a more amorphous nature. Characterization results FT-IR analysis shows No interaction chemistry exists between hydrochlorothiazide β-cyclodextrin. SEM analysis shows morphology substance active Already coated with β- cyclodextrin. DSC analysis shows a decline in enthalpy of the complex inclusions that indicate physical interactions form a simple eutectic mixture. Research results show that complex inclusion hydrochlorothiazide - β-cyclodextrin can repair characteristic physicochemical and can increase hydrochlorothiazide dissolution profile in a way significant ($p<0.05$) compared with powder The physical mixture with the highest dissolution results was shown by the F1 inclusion complex (82.843 %).

Keywords: Inclusion Complex, Hydrochlorothiazide, β-cyclodextrin, Dissolution Profile

1. Introduction

An important physicochemical property of a medicinal substance is solubility, especially the solubility of the system in water. A drug must have water solubility to be therapeutically effective. Relatively insoluble compounds often show absorption that is not perfect or uncertain [1].

Hydrochlorothiazide is a drug that has diuretic properties. This compound can cause more urine excretion. Diuretics work to increase the excretion of sodium, chloride, and water. Hydrochlorothiazide is a prototype group of thiazides and is recommended for some cases of mild to moderate hypertension in combination with various other antihypertensives [2,3]. Hydrochlorothiazide is a derivative of chlorothiazide and is used as an anti-hypertension drug. The diuretic effect is milder but lasts longer, namely 6 to 12 hours. The strength of the hypothesis is stronger so it is widely used as a first choice for mild to moderate hypertension [4].

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The Biopharmaceutics Classification System (BCS) groups drugs based on solubility and permeability, namely the most important thing that influences the bioavailability of medicine inside the body. Hydrochlorothiazide classified as BCS class IV, which has low solubility and low permeability when administered orally (low solubility and low permeability drugs). this nature limits the bioavailability of hydrochlorothiazide in the body. Cyclodextrin is one possible pharmaceutical strategy used to improve solubility from hydrochlorothiazide [5,6].
Inclusion complexes are complexes formed from guest chemical molecules trapped in cavities or channels host molecules because Van der Waals style without existing bond covalently formed. The complex formed is a complex that is hydrophilic on the outside so that it becomes a drug compound that is difficult to dissolve late and can increase solubility, dissolution rate, bioavailability, and stability drugs [7,8].
The process of inclusion complex formation is mainly influenced by the hydrophobic nature of the interacting drug compounds (guests) with a part in cavity cyclodextrin. Apart from that, interactions are also influenced by the shape and size of the drug compound. Physical properties chemistry compound. The drug can change due to the formation of inclusion complexes. The complex formed can increase the solubility, dissolution rate, bioavailability, and stability of medication [5,7].
Inclusion complexes formed in the solution can be detected by increasing solubility compound and so on can determine the constant stability of the complex. Complex inclusion in circumstances congested can characterized by spectrophotometer infrared, method analysis heat, diffractometer X-rays, and with chromatography thin layer [5,7].
Cyclodextrin is an oligosaccharide Cyclic consists of glucose molecules, and can form inclusion complexes with various molecules. Form molecule cyclodextrin No cylindrical but shaped toroidal with the inside of the compound being hydrophobic while the outside is hydrophilic. Cyclodextrin is capable of forming an inclusion complex with water-insoluble drugs. This inclusion complex has proven can repair stability, solubility, dissolution rate, and bioavailability something compound medicine [8].
Based on the above, this research formulated to increase the solubility of Hydrochlorothiazide which is difficult to dissolve in water in the form of an inclusion complex with Beta cyclodextrin made using the kneading method. It is hoped that the formation of the hydrochlorothiazide β-cyclodextrin compound inclusion complex formed can improve the physicochemical properties and increase the dissolution profile of hydrochlorothiazide compared to pure hydrochlorthiazide and its physical mixture.

2. Material and Method

2.1 Material

Hydrochlorothiazide (Ipca Laboratories Limited), β-cyclodextrin (PT Signa Husada), HPLC grade methanol (PT. Merck), Aquabidestilata (Ikhapharmindo), Hydrochloric Acid (PT. Merck) and Distilled Water (PT. Brataco).

2.2. Preparation of inclusion complex

Hydrochlorothiazide inclusion complex – β-cyclodextrin made with mole ratios of 1: 1 (F1) and 2:1 (F2) using kneading method. β-Cyclodextrin and hydrochlorothiazide are put into a mortar, homogenized, and added with a small amount of water then stirred until it becomes a semi-dry mass, then the mass is dried. Complex inclusions are stored in a desiccator [9].

2.3 Preparation of Physical mixture

Hydrochlorothiazide physical mixture - β-Cyclodextrin is made with a mole ratio of 1:1 . The ingredients are mixed in a mortar until homogeneous. Then sifted using a 40 mesh sieve, the physical mixture that has been made is stored in a desiccator [10,11].

2.4 Characterization Inclusion Complex Hydrochlorothiazide - β- cyclodextrin

2.4.1 Scanning Electron Microscopy (SEM) Analysis

Test carried out to compound single hydrochlorothiazide, beta-cyclodextrin, physical mixture, and complex inclusion with Scanning Electron Microscopy (Hitachi S-3400N, Japan). The sample is placed on a 1 cm stand that has been covered with carbon tabs and then flattened. Adjust the conditions with the vacuum used and set

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the voltage at 10 V, then vacuum it. After vacuumed sample Can observed with choose 1000× magnification on the monitor [10].

2.4.2 FT-IR spectroscopic analysis

Test carried out to compound single hydrochlorothiazide, beta-cyclodextrin, mixture physical and inclusion complexes with an FT-IR Spectrophotometer (Perkin Elmer, USA). Tests were carried out on samples that had been prepared using the disc method. Spin the location sample one way clockwork, then set the background order (> 50 scanning), then insert the sample into a clean and dry sample holder. Then analyzed in numbers waves 400-4000 cm^{-1} [12].

2.4.3 X-Ray Diffraction Analysis

Test carried out to compound single hydrochlorothiazide, beta-cyclodextrin, and a physical mixture and complex inclusion with Diffractometer X- -rays (X'Pert Pro PANalytical, Netherlands). The instrument was set up using Ni-filtered, Cu-K radiation, voltage 40 kV, and current 30 mA radiation spread in the crystal region of the sample, which was measured with a vertical goniometer. Patterns were obtained between 10 ^{o} and 100° at room temperature. The sample is prepared and inserted into the holder and then compacted using a holder press machine to obtain the desired peak. After the sample preparation is complete, it is inserted into the XRD tool and the results will be visible on the monitor [10].

2.4.4 Differential Scanning Calorimeter (DSC) Analysis

Test carried out to compound single hydrochlorothiazide, mixture physical and complex inclusion with Differential scanning calorimetry (Setaram 131 EVO, France). DSC analysis was performed with way, tool calibrated use indium accordingly standard, then the sample was weighed ± 5 mg and put in receptacle aluminum, heated and measured from temperature 30-300^{o} C, with speed warmup constant 10^{o} C per minute with the flow of nitrogen gas in an endothermic process [11].

2.4.5 Determination dissolution profile hydrochlorothiazide - β-cyclodextrin in complex inclusion

The dissolution test was carried out using type 1 (basket) dissolution test equipment. The cylindrical flask container was filled with 900 ml of 0.1 N HCl medium at a temperature of 37 ± 0.5 ^{0}C. Equivalent test powder with 50 mg hydrochlorothiazide was put in a basket that coated with filter paper, dipped into a cylindrical container and the stirrer rotated at a speed of 100 rpm. Then pipette 5 ml of dissolution solution, at time intervals of 5, 10, 15, 30, 45, and 60 minutes. Every pipetting is replaced with a dissolution medium of the same temperature so that the volume of the dissolution medium is always constant. Absorption solution that has been pipetted of the dissolution medium is measured in length wave uptake maximum 271.4 nm with UV-VIS spectrophotometry and calculated amount of dissolvable hydrochlorothiazide [12].

3. Result and Discussion

3.1 Scanning Electron Microscopy (SEM)

The results of particle shape analysis using SEM at 1000x magnification show characteristics from hydrochlorothiazide, beta-cyclodextrin, physical mixture, and complex inclusion. SEM results of hydrochlorothiazide seen form solids crystal with form no orderly chunk with a surface clean (Figure 1a), β-cyclodextrin seen like large, hollow chunks with an irregular surface texture (Figure 1b) [11]. SEM results were mixed physics hydrochlorothiazide and beta-cyclodextrin with a 1:1 ratio, visible morphology of each component hydrochlorothiazide and β-cyclodextrin. This because no happen interaction between hydrochlorothiazide with beta-cyclodextrin (Figure 1c). SEM results are complex inclusion hydrochlorothiazide –beta-cyclodextrin F1 (Figure 1d) and F2 (Figure 1e), crystals hydrochlorothiazide and beta-cyclodextrin difficult differentiated, where beta-cyclodextrin looks like envelop hydrochlorothiazide form something aggregates with irregular and uneven shapes. This matter shows that the complex inclusion of Hydrochlorothiazide - beta-cyclodextrin produces the compound Hydrochlorothiazide as an substance active (guest molecules) that enters the toroidal cavity of β-cyclodextrin as a polymer carrier (host molecule).

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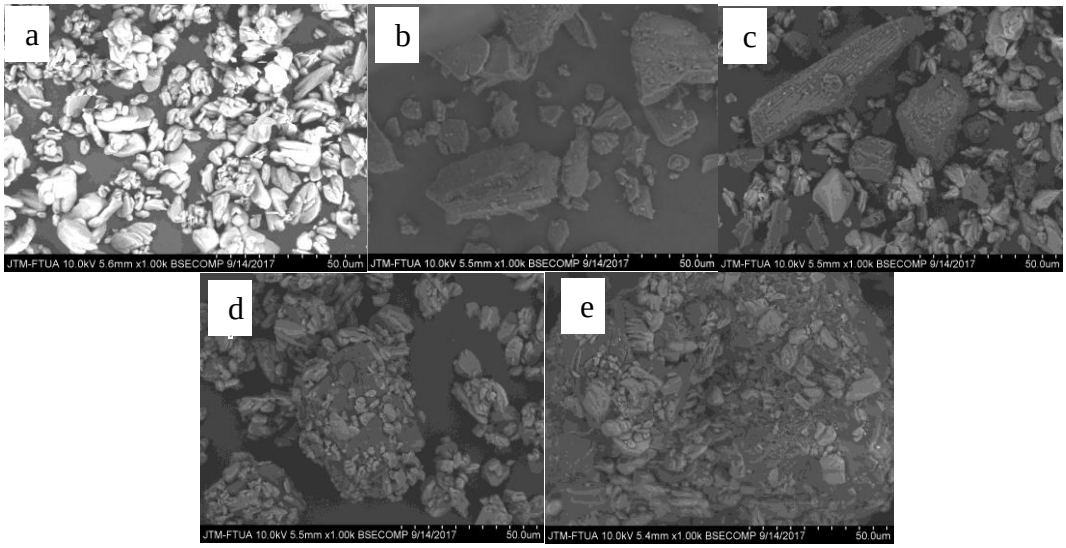

Figure 1. SEM morphology 1000x magnification (a) Hydrochlorothiazide, (b) β-cyclodextrin, (c) Physical mixture, (d) Inclusion Complex F1 (1:1), (e) Inclusion Complex F2 (2:1).

3.2 FTIR Spectrophotometer

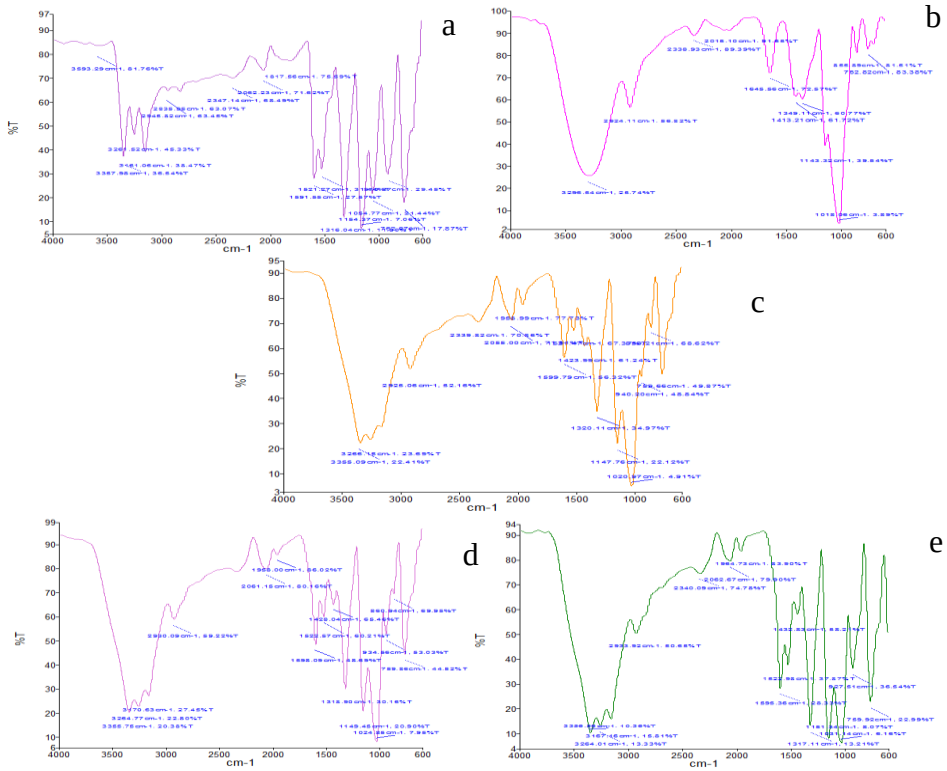

Figure 2. FT-IR spectrum (a) Hydrochlorothiazide, (b) β-cyclodextrin, (c) Physical mixture, (d) Complex inclusion F1 (1:1), and (e) Complex Inclusion F2 (2:1).

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Characterization results on the powder FT-IR spectrum hydrochlorothiazide (Figure 2a), it can be seen that there is an NH functional group at a wave number of 3553.25 cm^{-1}, a C=O functional group at a wave number of 1817.56 cm^{-1}, a CO function on numbers wave 1154.27 cm^{-1} [11]. The FT-IR spectrum of beta-cyclodextrin (Figure 2b) shows a wide peak at wave number 3289.08 cm^{-1} which indicates the existing group OH function. and at a wave number of 2925.54 cm^{-1} indicates the presence of CH bonds [11]. Mixed FT-IR spectrum physical (Figure 2c) shows the dominant absorption bands for hydrochlorothiazide, namely at the wave number 3355.09 cm^{-1}; 3266.15 cm^{-1}, 3170.63 cm^{-1}, there is also a peak indicating the presence of a functional group from beta-cyclodextrin at wave numbers 2930.09 cm^{-1} and 2061.15 cm^{-1}. The appearance of peaks indicates the presence of functional groups belonging to hydrochlorothiazide and beta-cyclodextrin showing that No there is interaction between hydrochlorothiazide with beta-cyclodextrin. The FT-IR spectra of F1 (Figure 2d) and F2 (Figure 2e), are present peak showing exists group function hydrochlorothiazide namely in numbers wave 3355.75; 3355.55 cm^{-1} which indicates the OH functional group, at wave number 2930.09; 2933.92 cm^{-1} which shows exists group CH function, on numbers wave 1958.99; 1958.00 cm^{-1} which indicates the presence of the C=O functional group. Disappearance part peak hydrochlorothiazide shows exists interaction between hydrochlorothiazide with betacyclodextrin in making complex inclusion between hydrochlorothiazide with betacyclodextrin.

3.3 Diffraction X Rays (XRD)

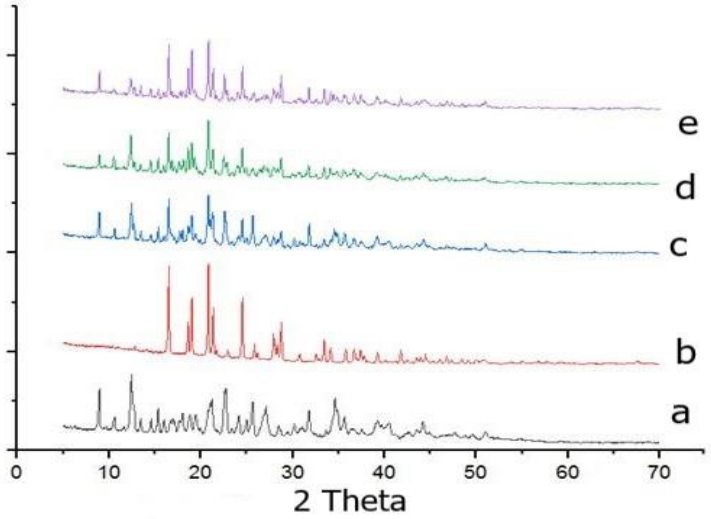

Figure 3. X-RD diffractogram (a) Hydrochlorothiazide (b) β-cyclodextrin, (c) Physical mixture, (d) Inclusion Complex F1 (1:1), (e) Inclusion Complex F2 (2:1).

Diffractogram x-rays (Figure 3) show the diffraction pattern from peak typical interference _ from compound single hydrochlorothiazide, beta-cyclodextrin, physical mixture, and inclusion complexes formed. Diffractogram hydrochlorothiazide (Figure 3a), shows typical crystalline peaks at 2θ angles 16.41264^{O}, 20.68773^{O}, 24.40521^{O} with peak interference 5435.6; 5232.0; 3636.5 [11]. Diffractogram beta-cyclodextrin (Figure 3b) shows characteristics crystalline at an angle of 2θ, namely 19.85130^{O} [11]. Diffractogram physical mixture hydrochlorothiazide-beta cyclodextrin (Figure 3c) shows the physical mixture hydrochlorothiazide-beta cyclodextrin Still there are peaks crystalline characteristic of both substances which gives different X-ray diffraction patterns. Diffractogram complex inclusions F1 (Figure 3d) and F2 (Figure 3e) show a decline in intensity peak crystalline very significant hydrochlorothiazide compared to Crystalline peaks formed in physical mixtures, which means that the crystal form decreases and leads to amorphous formation. An amorphous substance is shown by a pattern with an irregular structure and arranged without direction. Diffractogram substance crystal composed of a regular structure so that the distance between the planes parallel can measured and on the pattern diffractogram seen intense peaks [11]. Decline degrees of crystallinity cause solubility

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hydrochlorothiazide to become tall. The results of X-ray diffraction analysis show that the pressing process will cause bonding to occur between substance actives and excipients so that substance activity is included by excipients. Included particle substance active inside cavity beta-cyclodextrin that will produce a different crystalline lattice from the grille beginning as well as followed with decline degrees crystallinity caused by changes on the surface experienced crystals emphasis.

3.4 Differential Scanning Calorimetry (DSC)

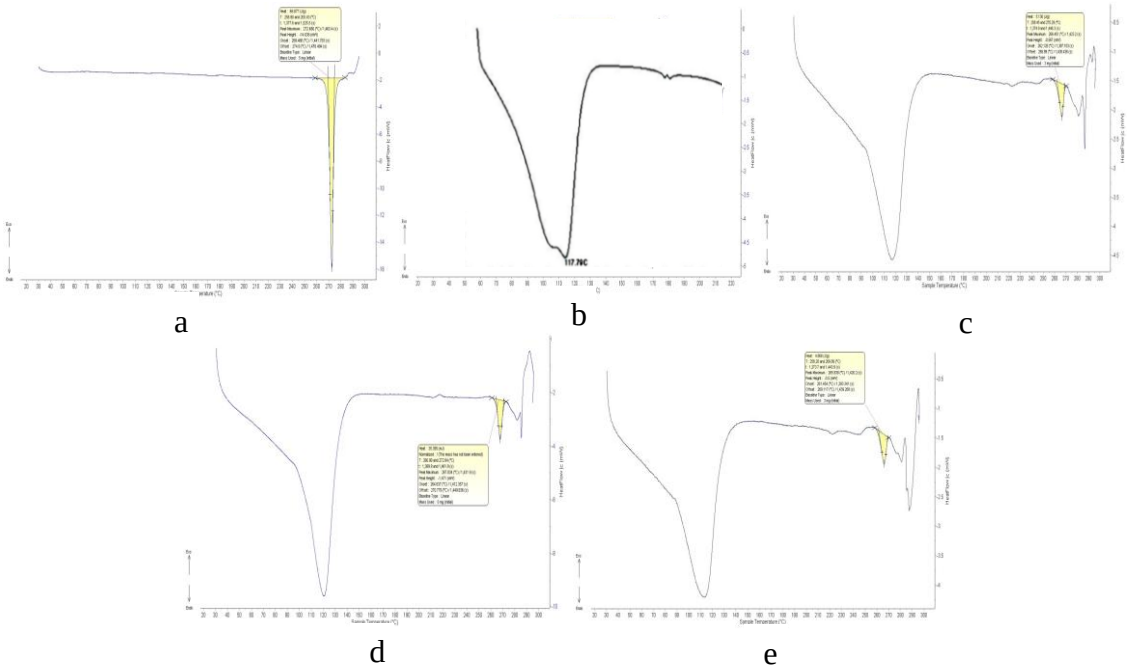

Figure 4. Thermogram (a) Hydrochlorothiazide, (b) β-cyclodextrin, (c) Physical mixture, (d) Complex Inclusion F1 (1:1), (e) Inclusion Complex F2 (2:1).

Thermogram hydrochlorothiazide showing peak endothermic at a temperature of 272.656^{o}C which is incident smelting from hydrochlorothiazide with need energy warmup amounting to 69,877 J/g (Figure 4a) [11]. Visible characteristics own sharp intensity from peak endothermic all-around point boiling signify hydrochlorothiazide is used in the form of crystalline powder. β-cyclodextrin thermogram shows peak endothermic at a temperature of 117.79^{o}C (Figure 4b) [11]. Thermogram physical mixture hydrochlorothiazide-β-cyclodextrin with enthalpy amounting to 35,395 J/g with endothermic peak 267.637^{o}C (Figure 4c). Thermogram complex inclusion F1 (1:1) with enthalpy 8.506 J/g and endothermic peak 265.6^{o}C (Figure 4d). Thermogram of the inclusion complex F2 (2:1) with enthalpy 19.121 J/g and endothermic peak hydrochlorothiazide and β-cyclodextrin at 267.302^{o}C (Figure 4e). Thermogram physical mixture and complex inclusion show a decline in intensity enthalpy from hydrochlorothiazide pure. This shows a decline in crystallinity becoming amorphous because energy heating is required to melt material active, cyclodextrin, mixture physical and complex inclusion more a little. This result is comparable to the XRD results, which are higher XRD peak then the more the peak is high endothermic from DSC results. These results also show that hydrochlorothiazide has experienced a change from crystalline to amorphous form. These DSC results are also comparable to SEM data, where seen from form morphology that hydrochlorothiazide pure Already included into the Beta cyclodextrin is made with complex inclusion.

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3.5 Dissolution Profile

Dissolution profile using 0.1 N HCl media with type 1 (basket) equipment. The results of determining the dissolution profile of complex inclusions, physical mixtures (CF), and Hydrochlorothiazide (HCT) show that in physical mixtures and complex inclusions there is a significant increase in the dissolution profile ($p<0.05$) compared to hydrochlorothiazide, with the percentage of dissolved substances in the 60th minute respectively is F1 of 82.84%, F2 of 73.0404%, physical mixture of 69.2547%. The percentage of dissolution profile results from this complex inclusion is in accordance with the requirements of the Ind Farmakope Indonesia Ed. V which states that Hydrochlorothiazide dissolves no less than 60% within 60 minutes [13].

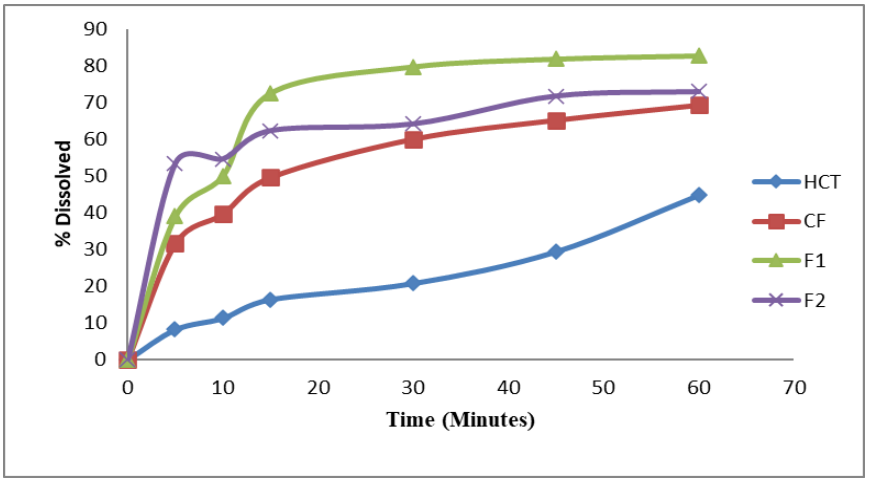

Figure 5. Hydrochlorothiazide (HCT) dissolution profile curve, physical mixture (CF), complex inclusions F1 (1:1) and complex inclusions F2 (2:1) in 0.1 N HCl medium

4. Conclusion

Based on the research conducted, it can be concluded that the formation of a hydrochlorothiazide and β-cyclodextrin inclusion complex can improve the physicochemical properties compared to a physical mixture and hydrochlorothiazide. The inclusion complex of Hydrochlorothiazide with β-cyclodextrin increased the dissolution profile of Hydrochlorothiazide significantly ($p<0.05$) with the amount of Hydrochlorothiazide dissolved at 60 minutes for Hydrochlorothiazide, physical mixture, inclusion complex F1, F2 respectively 44.872%, 69.2547 %, 82.8429%, and 73.0404%. The best dissolution percentage was shown by the F1 inclusion complex (1:1) with the highest dissolved percentage, namely 82.8429%.

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