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Use of biopolymer of polycaprolactone as matrix of verapamil hydrochloride microcapsule

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ABSTRACT

A microencapsulation study of verapamil hydrochloride with biopolymer polycaprolactone (PCL) as coating material using emulsification solvent evaporation method (W/O) has been carried out. Variations comparison verapamil hydrochloride with polycaprolactone were 1: 1, 1: 2, 1: 3 for each speed of stirring 400 rpm, 700 rpm and 900 rpm. Span 80 was used as the emulsifier. Microcapsules were characterized by X-ray diffraction (XRD), Scanning Electron Microscopy (SEM), Fourier Transform Infra-Red (FTIR), particle size distribution and dissolution profiles. The results showed, the microcapsules were spheric with sizes range between 10 – 30µm. The dissolution profiles showed a decrease in dissolution rate compared to the active substance microcapsules verapamil hydrochloride. The highest encapsulation efficiency was 72.42% for F9 (formula 9) with a ratio of 1: 3 (verapamil HCl: PCl) with stirring speed of 900 rpm. Statistical analysis using Annova one direction between the active substance verapamil hydrochloride and microcapsules with the percent dissolution efficiency showed a significant different results compared to the active substance. In conclusion, the greater the number of PCL coating is used, the greater the inhibition of the release of verapamil hydrochloride from microcapsules. Release kinetics model of verapamil hydrochloride from microcapsules followed the Langenbucher equation.

Keywords: microcapsules, polycaprolactone, emulsification solvent evaporation method, verapamil hydrochloride

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INTRODUCTION

Verapamil hydrochloride is a class of calcium channel blocker drugs that is widely used in the clinic for the treatment of hypertension, angina pectoris, and cardiac arrhythmias. Oral bioavailability of verapamil is very low, only about 10 to 23%, due to first-pass metabolism by the liver and excreted metabolites reformed in urine (70%) and feces (15%). Moreover, the short elimination half-life is approximately 2-8 hour. Therefore, to obtain the optimal therapeutic effect, verapamil hydrochloride must be given by repeated doses [1].

Drugs with short elimination half-lives require considerable amount of drug in each unit dose to maintain a sustained therapeutic effect. To avoid repeated use of drugs and avoid undesirable side effects (fluctuations in plasma drug levels), it is necessary to design a drug in a sustained-release dosage forms. Pharmaceutical preparations in solid form diversely designed to be able to release the active compound into the body and to be absorbed quickly. However, there is also a solid dosage form designed to release the drug slowly so that the therapeutic effect is constant over time and prolong drug action, one of preparation these are slow-release preparation (sustained release). Sustained-release dosage forms are designed fora single dose unit use as an initial dose followed by a maintenance dose that peak levels can be maintained in a long time [2].

One technology that can be done by microencapsulation. Microencapsulation is a process by the use of an active ingredient, both liquids and solids, and coating materials, which form relatively thin on tiny particles of solid and liquid substances with a very small particle sizes between 1-5000 µm [3].

Previous microcapsules are widely used in medicine are made of glass, glass, or polymer non-biodegradable as drug coating material. Such materials will be in the body in quite a long time, since it cannot be degraded by body, can cause new problems for health [4]. Lately, an alternative has been developed using biodegradable polymers for drug encapsulation. This is due to the ability of biodegradable polymer that can be degraded by hydrolysis in the body and biocompatible (does not cause danger to the body).

Polycaprolactone (PCL) is a synthetic biodegradable polymer which belong to aliphatic polyesters group that has been used as a coating material for microencapsulation. Polycaprolactone is used as a coating material due to well permeability and mechanical strength, and its long degradation time is suitable for use as a drug coating material [5].

There are several methods that can be used in the manufacture of microcapsules, such as emulsification solvent evaporation method. In this method, the process of microcapsules formation begins with separation of emulsion droplets at dispersed phase in the carrier phase to form small droplets. If the agitation is stopped, it will show the microcapsules are formed down to the bottom of the container [6]. Solvent evaporation techniques for producing microcapsules can be used in a wide variety of different core materials liquids or solids. The core material can be a material that is soluble in water and insoluble in water [7].

The decisive step of emulsification process is the droplet formation and size distribution of the microspheres produced. Therefore, this method can affect the efficiency of encapsulation, drug release rate and the percentage of manufacturing of microspheres [8].Solvent chosen for this method is also one of the important factors to produce either microcapsules. Some of the criteria that must be fulfilled by solvent are: dissolve the polymer used, having a low solubility in the continuous phase, has the ability to evaporate the high and low boiling point, and has a low toxicity. Therefore, in this study used dichloromethane or methylene chloride, which is generally used in the method of microencapsulation solvent evaporation because of high evaporation upon ability, and low boiling point [9].

Polycaprolactone is a hydrophobic polymer which is widely used in the manufacture of sustained-release dosage forms of drugs that dissolve in water. In this study polycaprolactone is used as microcapsule wall-forming (former wall) which can inhibit the release of verapamil hydrochloride. Inhibition effect the of verapamil hydrochloride release from microcapsules was investigated through in vitro dissolution test, compared to the pure form of verapamil hydrochloride.

The aims of this study was to make microcapsules verapamil hydrochloride with polycaprolactone as forming a wall using the solvent evaporation method into sustained-release preparations.

EXPERIMENTAL SECTION

Equipments: Magnetic Stirrer (IKA, Germany), Fourier Transform Infrared (Jasco), UV-Vis spectrophotometer (UV-1700 Pharma Spec, Japan), analytical balance (Shimadzu AUX 220, Japan), optical microscope, dissolution test (SR & PLUS), pH meter (Accumet basic AB18), and Scanning Electron Microscopy (JEOL, Japan), X-ray diffractometer (PAN Analytical, Netherland), filter paper, drying cabinets, glass tools used at laboratories.

Materials: Verapamil hydrochloride (Kimia Farma, Indonesia), Biopolymer polycaprolactone (Aldrick Chemical), Span 80 (PT. BRATACO, Indonesia), paraffin liquid (PT. BRATACO, Indonesia), dichloromethane, n-hexane (PT. BRATACO, Indonesia).

Methods

Preparation of Verapamil HCl microcapsules

Polycaprolactone was dissolved in dichloromethane while verapamil hydrochloride was dissolved in a solution of biopolymer (M_1). In another beaker, Span 80 was dispersed in liquid paraffin (M_2). M1 was added slowly into the M_2 and stirred with a speed variation of 400, 700, and 900 rpm until all the dichloromethane evaporated. Microcapsules were collected by sedimentation and washed with n-hexane four times, then filtered and dried at room temperature.

Table 1.Microcapsules formulation

Materials	Formula			
	F0	Fl	F2	F3
Verapamil HCl (mg)	-	500	500	500
Polycaprolactone (mg)	500	500	1000	1500
Dichloromethane(mL)	20	20	20	20
Span 80 (mL)	1	1	1	1
Liquid Paraffin (mL)	100	100	100	100

Evaluation of microcapsules

a. IR spectroscopy analysis

Microcapsules in the form of powder, infrared absorption was measured by using Fourier Transform Infrared (FT-IR).

b. Particle size distribution

The particle size distribution was carried out by using Optilab. Optilab was mounted on a microscope ocular lens, calibrated the instrument, and then connected to a computer. Samples were placed on the glass objects and objects placed on the table. The particles will be visible on the laptop screen and counted as many as 300 particles.

c. *Verapamil HCl assay in microcapsules*

The microcapsules were weighed as much as 50 mg, then crushed and put in a 25 mL volumetric flask and diluted with methanol to the mark. 5 ml of the filtrate was pipetted into a 25 mL volumetric flask, dilute with methanol to mark boundaries. The measurement was performed at wavelength of maximum absorption of verapamil hydrochloride using a UV spectrophotometer. Each of these formulas do with repetition 3 times.

d. Scanning electron microscopy (SEM)

Sample was placed on the sample holder aluminum with a thickness of 10 nm, then observed at various magnification SEM tool (Phenomm pro-X, Netherlands). Voltage is set at 5 kV and current of 12 mA.

e. X-Ray powder diffraction

The sample was placed on the glass and leveled to prevent particle orientation during sample preparation. Samples was analyzed at room temperature by using a diffractometer. Measurement conditions were as follows: target metals Cu, Kα filter, the voltage at a current of 40 mA kV, the analysis carried out in the range of 2 theta 5-35o.

f. *Dissolution test*

Dissolution test was done in medium of phosphate buffer pH 7.4 and 900 ml at 37 ± 0.5°C. A number of microcapsules which is equivalent to 120 mg was inserted into the dissolution chambers. At 10, 20, 30, 45, 60, 120, 240 and 360minute,5 mL of solution was pipetted. At each pipetting, the solution in the container is replaced with the same dissolution medium. Then the absorbance measurements was carried out by using UV-Vis spectrophotometer at the wavelength of maximum absorbance. Each formula was done triplicate [10].

RESULTS AND DISCUSSION

The microcapsules process was started by dissolving polycaprolactone in solvent dichloromethane, then verapamil hydrochloride was added into that solution. On the other container, span 80 and liquid paraffin and then was mixed with a variety stirring speed of 400 rpm, 700 rpm, and 900 rpm. At the same time, verapamil and polycaprolactone stirring in dichloromethane was dropped into the dispersion phase. This stirring will produce emulsion verapamil with polycaprolactone. Over stirring, dichloromethane would evaporated, thus the emulsion began to rupture and formed granules microcapsules in the dispersion phase [11]. This mixing process was done for 6 hours continuously. Once formed, the microcapsules were separated from the carrier phase by means of cast ponder then washed with n-hexane. This washing was done repeatedly until the microcapsule obtained free from dispersion phase. Then microcapsules was dried at room temperature until all the n-hexane evaporates.

The FTIR spectroscopy verapamil hydrochloride microcapsules can be seen in Figure 1, where the valleys were formed showed clusters owned by verapamil as an active ingredient and polycaprolactone as a coating material. No new functional groups was formed in microcapsules, which indicated the absence of interaction between the two substances in microcapsules formed (Fig.1).

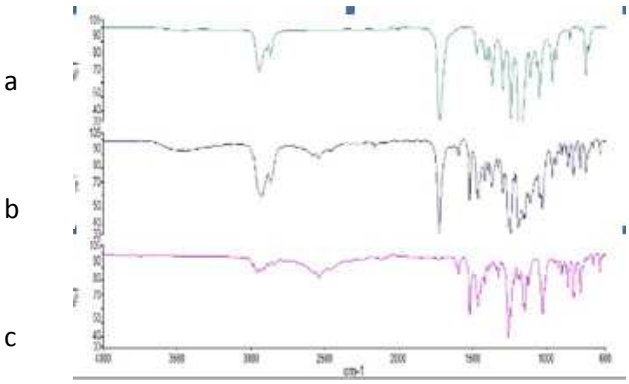

Figure 1. FTIR spectrum of a). polycaprolactone, b). microcapsuled c). verapamil hydrochloride

The SEM showed that verapamil HCl microcapsules with variations at stirring rate of 400 rpm, 700 rpm and 900 rpm at a magnification of 2500x had irregular and porous crystal form, but the microcapsules without the active substance has a more refined shape, dense and more porous. At the other magnification, microcapsules with different speeds show irregularly shaped. There was no uniform microcapsule size aggregated, which is likely due to the size of the resulting particles so small that the particles come together and form aggregates. This data shows that the stirring speed does not affect the morphology of the microcapsules. In this study also showed that verapamil hydrochloride is compatible with the coating polycaprolactone (Fig.2).

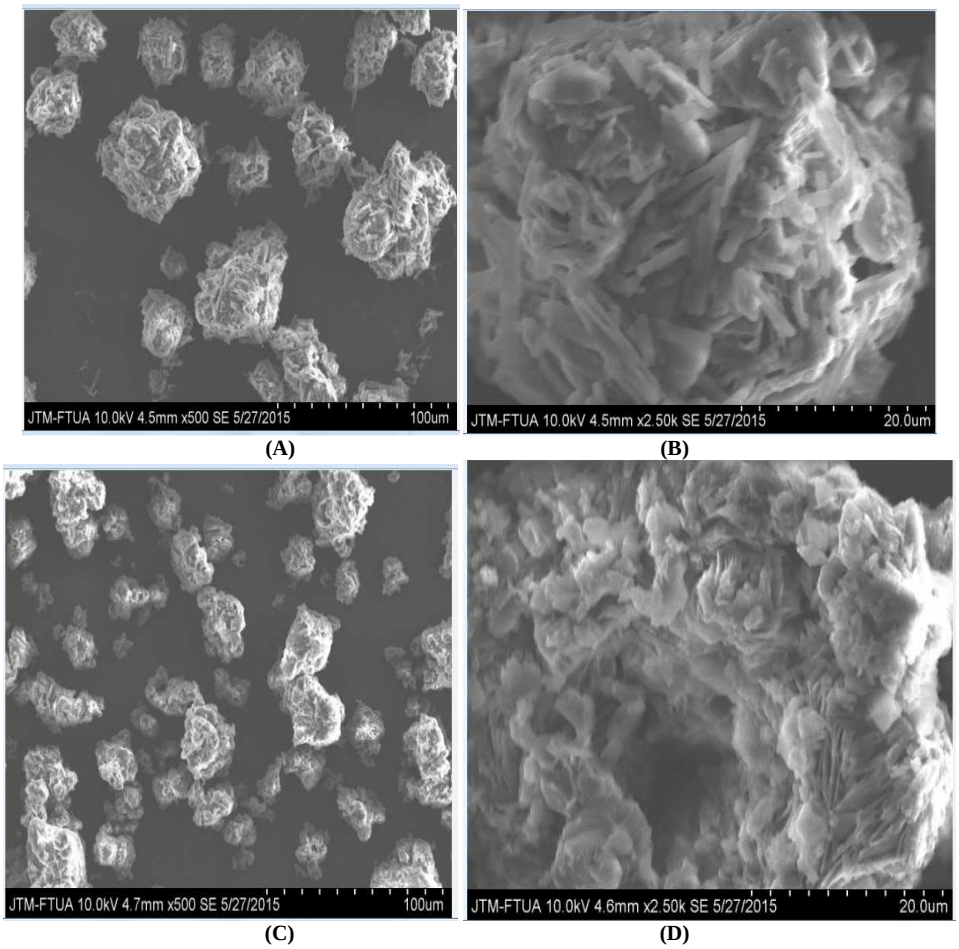

Figure 2. Scanning Electron Microscope (SEM) of (A) verapamil HCl microcapsules Formula 9 (F9) at 500x magnification, (B) verapamil HCl microcapsules at 2500x magnification, (C) empty microcapsules at 500x magnification, (D)empty microcapsules at 2500x magnification

The particle size distribution generally showed that the particle size of the microcapsules as a whole lies between 1.0 – 100µm. Most particle size range in Formula 1, Formula 2, were in the same range, such as in the range 10,1µm - 20 µm with frequencies 50.67% and 74.67% respectively and Formula 3 is in the range of 20.1 µm - 30 µm with a frequency of 37%, while the microcapsules with a speed of 700 rpm in the formula 4 was in range between 1.0 –

10µm. Most particle size range in Formula 1, Formula 2, were in the same range that the frequency of 51%, the formula 5 is in the range of 10.1– 20 µm with a frequency of 60.67%, the formula 6 is in the range of 20.1 – 30µm with a frequency of 34.33%, and at a speed of 900 rpm, the formula 7, 8 and 9, were in the range of 10.1 – 20µm with each frequency in the formula 7 (50.67%), formula 8 (54%), and the formula 9 frequency (56.67%) (Fig.3.).An earlier study using polycaprolactone as a coating material with emulsification solvent evaporation method found that stirring speed at the time of dispersion causes particle size distribution is not uniform due to the high speed stirring emulsion can break droplet easily due to high collisions between stirrer with large droplets that already exist. [12].From the study by [12], it was found that a more uniform size microspheres at 500 rpm than speed of 400 rpm. Data shows the higher the stirring speed, the particle size tends to be smaller and increasing the amount of coating causes an increase in the thickness of the walls of the microcapsules are formed [13]. The particle size obtained qualified microcapsules made using emulsification solvent evaporation method was between 1-5000 µm [7].

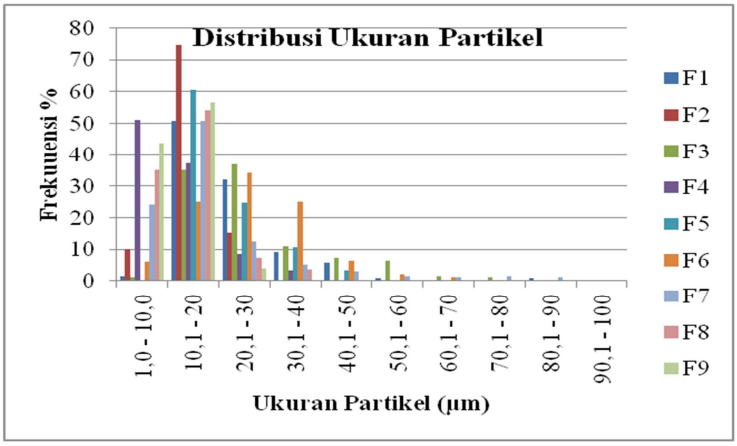

Figure 3. Particle size distribution of verapamil HCl microcapsules

X-ray diffraction peaks at microcapsules showed the same characteristics of the active substance verapamil hydrochloride and polycaprolactone. A decline in the intensity of the interference peak indicated the degree of crystallinity decrease but the degree of amorphous increasing with increasing concentration of the coating due to the heat release process. Microcapsules with a ratio of 1: 1, 1: 2, 1: 3 peak decline much interference as compared to a peak at angle 2θ active substance verapamil pure and this can be seen in (Figure 4), where the diffraction angle formula 1: 1 diffraction angle 2θ = 24.01 (high peak of 25015.29 4865.015); 21,37º (high peak of 85459.98 26306.46); 18,11º (high peak of 52942.52 10271.32); 16,77º (high peak of 11079.36 8302.92); and 10,59º (high peak of 8841.719 4264.086), and so on formula 1: 2 and 1: 3. This indicated that the microcapsules verapamil hydrochloride and polycaprolactone form of amorphous and did not produce a new crystalline phase (molecular compounds).

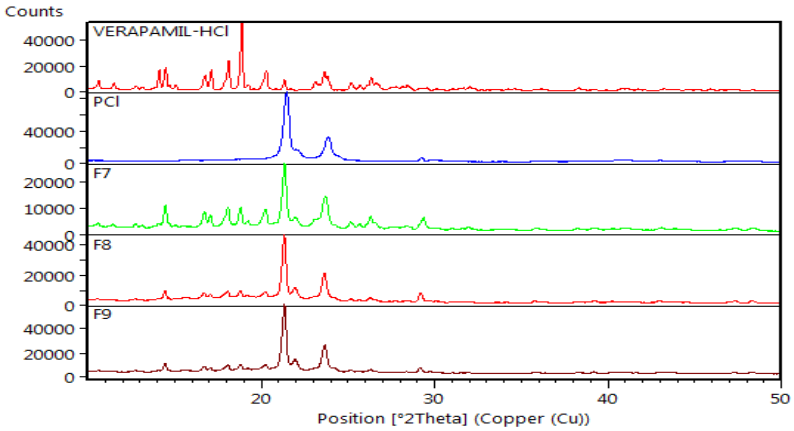

Figure 4. X-ray diffractogram of verapamil HCl-PCL and verapamil hidroklorida microcapsules

Determination of recovery of the active substance generally showed that the increasing number of polycaprolactone as a coating material the verapamil microcapsules were found in the greater number. This due to the increasing coating material was used, the greater the ability of the coating for coating the core material [14]. Reacquisition verapamil hydrochloride in each formula with a stirring speed of 400 rpm variation 67.27% ± 2.88; 1,02dan 68.87%

± 68.97% ± 0.54, stirring rate of 700 rpm 70.83% ± 3.02; 70.96% ± 1.24 and 71.19 ± 1.06%, while the encapsulation efficiency with 900 rpm stirring rate 71.96% ± 1.77; 72.18% ± 0.53 and 72.42 ± 0.60%. Data shows that verapamil hydrochloride encapsulated could not reach 100%.This was likely due to the verapamil hydrochloride did not participate during the process of sedimentation cast, while verapamil hydrochloride was wasted along with liquid paraffin [15] and stirring rate affects encapsulation efficiency of the active substance in the microcapsules, whereby increasing stirring speed, the encapsulation efficiency also increased (Table 2).

Table 2.The results of microcapsules and recovery of the active substance in the microcapsules

Formula of microcapsules	Weight of microcapsules (gram)	Theory weight (gram)	% recovery	% Loading ± SD	Encapsulation efficiency (%)
F1	0,8045	1	80,45	33,64±1,44	67,27±2,88
F2	1,3797	1,5	91,98	34,43±0,51	68,87±1,02
F3	1,975	2	98,75	34,49±0,27	68,97±0,54
F4	0,4735	1	47,35	35,42±1,51	70,83±3,02
F5	1,257	1,5	83,80	35,48±0,62	70,96±1,24
F6	1,7871	2	89,36	35,59±0,53	71,19±1,06
F7	0,5032	1	50,32	35,98±0,89	71,96±1,77
F8	1,4	1,5	93,33	36,09±0,27	72,18±0,53
F9	1,276	2	63,80	36,23±0,30	72,42±0,60

The dissolution test verapamil hydrochloride microcapsules using polycaprolactone as a coating material released verapamil hydrochloride from microcapsules very slow compared to the active substance verapamil hydrochloride powder. This was presumably due to absorption of polymer polycaprolactone obtain any active substance that caused the drug release from the microcapsules very slow [16]. The dissolution results verapamil hydrochloride microcapsules with stirring speed variation where the formula 3, formula 6 and formula 9, release lower than the other formulas. After 6 hours of dissolution process, the amount of active substance dissolved in the formula 3 was 19.075% ± 0.744, formula 6; 18.894% ± 0.275 and formula 9: 21.607% ± 0.384. It can be concluded that the greater the amount of polycaprolactone release verapamil hydrochloride in microcapsules slowly because of the thick walls of the microcapsules. Decrease in the speed of release of verapamil hydrochloride from microcapsules caused by polycaprolactone hydrophobic and difficult to dissolve, as a result of penetration of liquid to diffuse slower and smaller. Hence, the time required to release a number of active substances to be longer [6].

In addition, an increase in mixing speed also affect the dissolution rate also due to the smaller particle size and perfection of the coating is affected by the length of stirring. It is also caused by the change of crystalline form into amorphous (Fig.5). [17].

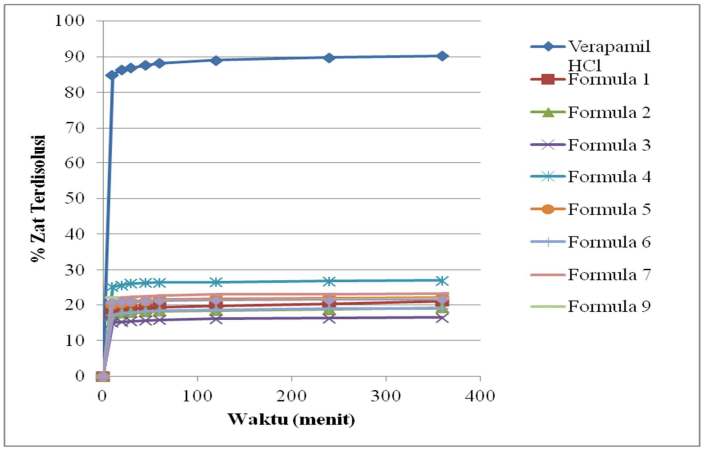

Figure 5. Dissolution profile of verapamil HCl microcapsules in buffer phosphate medium pH 7.4

The calculation of average efficiency of dissolution showed that the dissolution efficiency for the microcapsules at speed of 400 rpm, for a formula 1 = 19.57 ± 0.719%, the formula 2 = 18.22 ± 0.340%, formula 3 = 7.41 ± 0.051%, at a speed of 700 rpm formula 4 = 25.97 ± 0.411%, the formula 5 = 21.53 ± 0.072%, the formula 6 = 18.33 ± 0.110%, while the stirring speed of 900 rpm, the formula 7 = 22.78 ± 0.217% , formula 8 = 21.26 ± 0.210%, formula 9 = 21.06 ± 0.298%. This result found that the increasing amount of polycaprolactone used as the coating could decrease the efficiency of verapamil hydrochloride which indicated a slowdown in the release of active substances from the microcapsules and efficiency of verapamil hydrochloride does not affect the speed variation of stirring.

From the results of the one-way ANOVA statistic test, the value f was calculated by significance <0.05 which indicated that the efficiency of the active substance verapamil hydrochloride and microencapsulated formula 1 to formula 9 give significantly different results [18, 19]. Duncan test, as the further test, was done to look for significance differences of each formula. This showed that the addition of the polymer to give effect to the release of active substances from the microcapsules in each formula.

Determination of kinetics model verapamil hydrochloride in the microcapsules was carried out based on zero-order equations, first order, Higuchi equation, the equation Langenbucher, and Korsemeyer-Peppas equation. Among five models, kinetics of verapamil hydrochloride microcapsules followed Langenbucher equation model, which had the highest linearity that was close to one. Langenbucher equation implies that the kinetics of release of the active substance in the dissolution medium the process of diffusion and erosion microcapsules then accumulation in the fraction solution which means no lag time or the beginning of a slow release.

CONCLUSION

The results of this study concluded that biopolymer polycaprolactone can be used as a coating material in the manufacture of verapamil hydrochloride sustained-release microcapsules. Variations mixing speed emulsion gave effect to the efficiency of encapsulation, where the higher the stirring speed, the greater percent encapsulation efficiency, which found from Formula 9 (72.42% ± 0.60). The particle size distribution showed the higher stirring speed, the smaller the particle size and increasing the number of coating material caused an increase in the thickness of the walls of the microcapsules are formed. According to kinetics models of active substances release, Verapamil HCl microcapsuled followed Langenbucher, which is that the kinetics of the release of active substances in the test medium the process of diffusion and erosion microcapsules then accumulation in the fraction solution which means no lag time or the beginning of a slow release.

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