

floating Dike

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Sustained release of captopril tablet with floating system using a cross-linked matrix of alginate

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Abstract

Captopril has a short biological half life 2-3 hours and has been used for long-term treatment of hypertension. The properties of captopril such as absorbed well in the stomach, freely water-soluble, instability in intestinal environment, and bioavailability about 65%. This study aimed to determine the physical characteristics and drug release profile of captopril tablet sustained release with floating system using a cross-linked matrix of alginate with calcium chloride as a crosslinker. Matrix system was obtained by forming alginat cross-linked with a calcium chloride. HPMC K4M was used to help cross-linked reaction. Tablet was prepared by wet granulation with varying levels of sodium alginate and calcium chloride. Dissolution test is carried out by paddle method in HCl pH 1,2; 100 rpm; and $37 \pm 0,5^{\circ}\text{C}$ for 8 hours. Amount of captopril released determined by measuring the captopril dissolved using UV spectrophotometry at λ 205 nm. The result showed that this tablet having physical characteristics suitable with the general requirements for tablets. Drug release profile of captopril tablet sustained release with floating system using a cross-linked matrix of alginate with calcium chloride as a crosslinker capable keeping release of captopril up to 8 hours (third formula) about 51,226% (DE) and followed zero order kinetics.

Keywords: sustained release tablet, captopril, floating systems, cross-linked, alginate

Introduction

Drugs with a high frequency of use can cause problems such as fluctuations in drug concentration in the blood and the patients are often less regular using drugs that can affect the therapeutic process (Shargel, 2005). Captopril has a half-life 2-3 hours making it suitable for slow-release tablet are prepared. Development of slow-release captopril tablets will provide some benefit to patients who need to take this drug on an ongoing in a long time. Some of these advantages include increased patient compliance in treatment, reducing the frequency of drug administration, and reduce fluctuations in blood concentrations of drugs that reduce the risk of side effects. Captopril have properties well absorbed in the stomach, easily soluble in water, easily oxidized in the intestinal pH, and the bioavailability less than the maximum that should be considered the development

strategy of slow-release captopril tablets are strong enough to hold the release of the drug and can survive in the stomach in a long time (Seta *et al*, 1988). Captopril is passively absorbed in the stomach and the proximal small intestine and partly absorbed with the help of the peptide, while more than 40% eliminated via urine in the form of intact (Nur *et al*, 2000).

Dosage form that can be retained in the stomach called gastroretentive drug delivery system (GRDDS). GRDDS can improve control of drug delivery is well absorbed in the stomach. Residence time in the stomach can be improved by mucoadhesive delivery system attached to the mucosal surface, delivery systems that can increase the size of the drug so it retained because it can not pass through the pylorus, and delivery systems to control the density so that it can float (floating) in gastric fluid (Gohel *et al*, 2004).

According to Arora (Arora *et al.*, 2005) one of the method to extend the residence time of tablets in the stomach is floating system and the system is considered as one method of effective and applied in dealing with bioavailability. Drugs in the floating system is released slowly at a speed that can be determined and reduced fluctuations in plasma drug concentrations (Chawla *et al.*, 2003). Floating system can be achieved by lowering the dosage so that the density is smaller than the density of liquid gastric (Zou *et al.*, 2008). Carrier that can be used is a polymer which has a density of light that can also affect the release of drug from the dosage (Garg and Gupta, 2008). Polymers used in the floating system is quite diverse, there's even a few modifications. One of polymer modification in the floating system is a cross-link (Kroschwitz *et al.*, 1992).

Cross-links is a bond of a polymer chain with other polymer chains that form the three dimensional structure as a result of chemical reactions. In cross-link alginate with calcium chloride, a calcium ion will replace two sodium ions in the alginate to form a cross-link. This cross-link structure causes the molecular motion is limited and obstructed the swelling of polymer in a particular medium, so it should be able to improve the drug release profile of the preparation (Kroschwitz *et al.*, 1992). Cross-link reaction of sodium alginate with calcium chloride in low pH produce calcium alginate are not soluble in water and insoluble in pH 1.2. In the acidic conditions in the stomach, the swelling of calcium alginate gel is rare, the drug will most likely be released by diffusion through the insoluble matrix (Tønnesen and Karlsen, 2002).

Based on the description, it is necessary to develop captopril in slow-release dosage forms with a floating system using alginate cross-link matrix with calcium chloride as a crosslinker, which is expected to release the drug at a controlled rate and stay in the stomach for a long time to improve the bioavailability.

Methods

Materials. Captopril, HPMC K4M, Ac-di-Sol, talc (obtained from PT Kimia Farma), sodium alginate, calcium chloride, magnesium stearate, distilled water, HCl 0.01 N.

Methods. Manufacture of slow-release tablet dosage forms. Slow-release tablet captopril floating system using alginate cross-link matrix prepared according to a formula that can be seen in Table 1. The granules prepared by the method wet granulation. Preparation of granules by wet granulation method is done by swelling a sodium alginate using distilled water to form alginate gel and can be flowed. Sodium alginate has been swelled which is weighed according to the formula and then mixed with captopril until homogeneous (mixture 1). Avicel PH102 was mixed homogeneously with 1/5 ac-di-sol (mixture 2). HPMC K4M, calcium chloride, and 3/5 ac-in-sol was mixed until homogeneous (mixture 3). Mixture 1 and mixture 2 mixed until completely homogeneous (mixture 4), then added a few drops of distilled water until it forms a mass of tablets. Mixture of 3 and 4 blended until completely homogeneous to form granules or inner phase in the mass of tablets. The granules are sieved using 16 mesh sieve and then dried in an oven at 50°C (dry). Dry granules sieved again with 18 mesh sieve, then add 1/5 ac-di-sol, talc and magnesium stearate sequentially and mixed until homogeneous. Mass obtained is then compressed into tablets.

Table 1. Formula slow release captopril tablet floating system

Component	F1	F2	F3	F4	F5
Kaptopril (mg)	25	25	25	25	25
Natrium alginat (%)	6	8	10	12	14
Kalsium klorida (%)	9	7	5	3	1
HPMC K4M (%)	57	57	57	57	57
Ac-di-sol (%)	5	5	5	5	5
Avicel PH102 (%)	20	20	20	20	20
Mg Stearat (%)	1	1	1	1	1
Talk (%)	2	2	2	2	2
Total (mg)	200	200	200	200	200

Flow properties of granule test. Flow properties of granules test performed by the method of baring angle and the flow time.

a. Angle of repose

The measurement is carried out by inserting the granules into a flow meter at a height of free-standing on graph paper on a horizontal set. The flow meter cover is opened so that the granules out and accommodated on a plane. (R) is the radius of the base of the conical pile and (h) is a cone-shaped stack height. Repose angle of the granules can be calculated by the equation:

$$\tan \alpha = \frac{h}{r} \text{ atau } \alpha = \arctan \frac{h}{r}$$

Description: α = angle of repose

h = height of pile

r = radius of pile of granules
or $\frac{1}{2}$ d (Voight, 1995).

b. Flow time

Flow time test carried out by weighing 100 grams of granules, inserted into the flow meter/funnel the stem end is closed. Funnel lid is opened and the granules are allowed to flow until the end, calculated flow time of granules¹¹. Granules are said to be good when the flow rate has a 10 g/sec or about 100 grams of granules can flow out of the funnel in less than 10 seconds (Lieberman *et al*, 1989).

Evaluation of tablets

a. Physical Appearance

Tests carried out by organoleptis physical appearance, including examination of the uniformity of color, presence or absence of odor, surface shape, and presence or absence of defects (damage) physical (Banker and Anderson, 1986).

b. Uniformity of size

Diameter and thickness of the tablet was measured by using a long slide and then analyzed according to the requirements of uniformity in the size of the tablet in the Pharmacopoeia. Otherwise stated, the diameter of the tablet not more than three times and not less than one-third times the thick tablet (Anonymous, 1979).

c. Uniformity of weight

Up to 20 tablets that have been cleaned of dust were weighed individually and

average weight was calculated, then matched with the percentage deviation of the weight table in Indonesian Pharmacopoeia. Should not exceed 2 tablets, each of which weighs deviate from the mean weight is greater than the price specified in column A. Besides, no one else tablet weight deviates from the average weight of more than the price set column B (Anonymous, 1979).

d. Hardness test

One tablet is placed in the middle and perpendicular to the hardness tester, first scale the zero position, then slowly rotated the tool to break tablets. Read the scale achieved when broken or crushed tablets. In general, a good tablet has a hardness between 4-10 kg (Anonymous, 1995).

e. Friability test

A total of 20 tablets that have been cleaned weighed, then put in friabilator. The tool is run 4 minutes, or 100 times a round. Tablets were taken and cleaned of particles attached to the tablet, weighed again, calculated the percentage difference in weight or shrinkage. The total weight of the tested tablets should not be reduced by more than 1% of initial weight test. Friability equation is as follows:

$$F\% = \frac{(W_o - W_t)}{W_o} \times 100\%$$

f. Floating test

Observation of swelling behaviour and floating done visually, the way: the tablet is inserted in 100 mL beaker glass contained HCl solution pH 1.2. Swelling behaviour and the floating observed for 5 hours. Good results were swelled and floating more than 5 hours (Arora *et al*, 2005).

g. Drug release test

i. Determination of the maximum wavelength

ii. Determined with make the curve correlation between the absorbance with the wavelength of the captopril standard solution at a certain concentration¹⁶. Using the

- wavelength range between 197-250 nm (maximum wavelength of captopril by USP 29 is 205 nm). Wavelength used is the wavelength are having of maximum absorbance.
- iii. Preparation of captopril standard curve
 - iv. Captopril standard curve obtained by making a series of captopril solution in HCl medium at pH 1.2, the concentration is 0.008; 0.010; 0.012; 0.014; 0.016 mg/ mL. Absorbance of each concentration was measured by UV-vis spectrophotometer at a wavelength of maximum. Absorbance data obtained and graphed against the concentration to obtain the regression equation and curve (Gandjar and Rohman, 2007).
 - v. Testing of drug release
 - vi. Drug release test were performed using the method of dissolution testing. Dissolution testing performed using a type 2 (paddle) at agitation speed of 100 rpm in HCl medium pH 1.2 as much as 900 mL at $37 \pm 0.5^\circ\text{C}$ for 8 hours. As many as 5 mL aliquot was taken at minute 5, 10, 15, 30, 45, 60, 120, 180, 240, 300, 360, 420, and 480. Amount of captopril released determined by measuring the captopril dissolved using UV spectrophotometry at a maximum wavelength. Furthermore the amount of captopril released can be calculated using regression equations derived from standard curves of captopril (Wadher *et al*, 2011).

Data Analysis. Analysis of the physical properties of the drug and drug released from tablet using statistical analysis one way ANOVA at 95% confidence level. To determine the kinetics and mechanism of drug release from tablet carried out by comparing the value of the regression coefficient based on the zero-order kinetics equation, first order, and Higuchi equation.

Results and Discussion

The flow properties of granule showed baring angle and the flow time are qualified. Analysis of baring angle with one way ANOVA showed significance ($0.078 > 0.05$) it was explained that baring angle of granule between the formula not differ significantly. The results of the analysis of flow time by one way ANOVA showed significance ($0.01 < 0.05$). Then tested LSD, obtained that only the formula 5 is significantly different than the other formulas.

The test of repose angle and flow time describe the flow properties of granule when the tableting process is running. Flow properties of granule is very important because it affects the uniformity of the compression and tablet weight uniformity (Lieberman *et al*, 1989). Granules or powders that have a repose angle of less than or equal to 30° usually indicate that the material can flow freely, if the angle is greater than or equal to 40° the flow is less well (Lachman *et al*, 1994). The size of the baring angle influenced by the shape, size, granules moisture, gravity and friction forces inter-particle, if the tensile force and friction forces is small it will be faster and easier flow. The flatter the resulting cone, baring angle gets smaller and the faster the flow properties of powders [11, 13].

Based on the formula 1 to formula 5, the increased contents of sodium alginate and reduced calcium chloride result a more rapid flow time. More rapid flow time on formula 5, this happens because the granules in the formula 5 has a relatively larger size. Larger granules in the formula 5 is possible because of the granules mass during granulation relatively more humid because there is residual sodium alginate are not bound by the crosslinker is calcium chloride, sodium alginate is carrying water, causing the mass becomes more humid as sodium alginate has a hydrophilic properties (Brunetti and Martin, 2006) and the granulation process forming granules with a size larger. According to Lieberman (Lieberman *et al*, 1989), large granules will have a small inter-

granules contact so that the resulting flow time was faster.

The test of physical appearance showed that visually color tablets of formula 1 to 5 are increasingly off-white, it is because the contents of sodium alginate are increasing. Sodium alginate used in this study is a light brown. Surface shape and consistency of the tablet of formula 1 and formula 3 is smooth and compact, the formula 4 is rather rough

and compact, and the formula 5 coarse and rather compact. Granule formula 5 in addition to having a larger size also has the ability to form a compact mass after a given pressure (compactibility) is relatively low so that when compressed by the same pressure with the other formulas produced tablets with slightly rough surface and rather compact (Ansel, 2005).

Table 2. Experiment results

No.	Evaluation	F1	F2	F3	F4	F5
1.	Baring angle (x°)	27,147±1,196	28,733±0,451	28,733±1,020	29,063±0,549	27,967±0,333
2.	Flow time (seconds)	2,283±0,112	2,237±0,032	2,267±0,232	2,137±0,130	1,637±0,025
3.	Colour	White	White	White	White	White
4.	Odor	Sulfida	Sulfida	Sulfida	Sulfida	Sulfida
5.	Surface shape	Smooth and compact	Smooth and compact	Smooth and compact	Rather rough and compact	Rough and rather compact
6.	Physical damage	No	No	No	No	No
7.	Thickness of Tablet (cm)	0,397±0,005	0,388±0,008	0,344±0,007	0,450±0,008	0,421±0,008
8.	Diametre of Tablet (cm)	0,810±0,000	0,810±0,000	0,810±0,000	0,810±0,000	0,810±0,000
9.	Average of weight uniformity (mg)	205,5	199,1	196,0	205,7	204,1
10.	Hardness of tablets (kg)	7,65±0,474	7,80±0,587	8,85±0,530	6,75±0,486	4,60±0,516
11.	Friability (%)	0,207±0,049	0,199±0,109	0,180±0,107	0,396±0,071	2,199±0,429
12.	DE480 (%)	74,957	56,039	51,226	60,936	52,066
13.	Release kinetics of captopril regression data					
a.	Zero Order	0,8503	0,8442	0,9025	0,9228	0,8484
b.	Higuchi	0,9074	0,9663	0,9842	0,9556	0,9256
c.	First Order	0,8447	0,9628	0,9317	0,8507	0,8893

The results test of size uniformity showed that all tablets meet the test requirements of the physical properties of the uniformity of thickness and diametre size of the tablet because it is still within the permissible range of the diametre should be no more than three times as thick tablet and should not be less than one third of the tablet thickness (Anonymous, 1979). Based on this analysis it can be concluded that the tablets have been prepared to have a uniform size. Size uniformity of the tablets can be assumed that there is uniformity of content of captopril in tablets.

All the weight uniformity test data showed that all of formula eligible weighting

uniformity based on the Indonesian Pharmacopoeia Third Edition, because none of the tablets deviated from 7.5% and 15% of the average tablet weight (Anonymous, 1979). Tablet weight is determined by filling a number of granules residing in the compression chamber and associated with the flow properties of granules. Tests on the uniformity of tablet weight is also done by calculating the CV (Coefficient Variation) and the results showed that the weight of each tablet formula qualify, since there is no formula that has a CV value of more than 5%. Tablet with a good weight uniformity can be assumed that the contents of the active substance in the tablet is also uniform,

so the therapeutic effect resulted identical (Voight, 1995).

All formula meets the requirements of tablet hardness. Tablet hardness is determined by the compactibility and compressibility granule. Compactibility and compressibility very important associated with the easily of granules to be compressed so as to produce a hard tablet. Granules that has a poor compressibility and compactibility will require high pressure to be compressed into tablets (Ansel, 2005). Results of ANOVA test obtained 0.000 significance. Results of hardness test showed significant differences between the formula, except between formula 1 and formula 2.

Friability more than 1% is usually considered as a tablet is not good¹³. All formula meets all requirements friability except the formula 5. Friability determined by the bound inter-granules and the influence of compactibility and compressibility granules. Results of ANOVA test obtained significance (0.001) < 0.05. Further tested LSD, obtained results that only the formula 5, which differed significantly compared to other formulas.

The results of floating test captopril tablets with alginate cross-link matrix, as shown in Figure 1, Figure 2, Figure 3, and Figure 4, respectively.

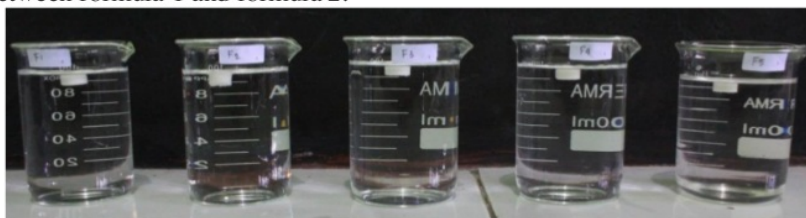


Figure 1. Floating test 0 minute



Figure 2. Floating test 180 minute

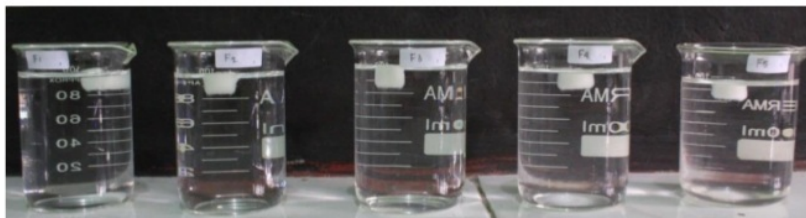


Figure 3. Floating test 300 minute

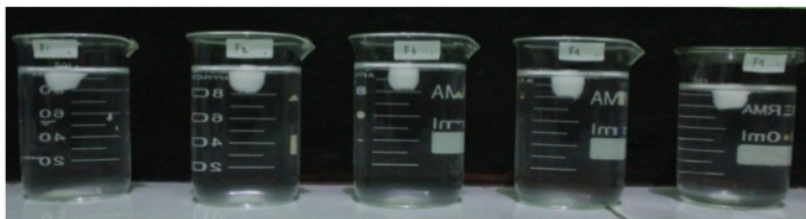


Figure 4. Floating test 1 day

At the beginning of the test, each tablet of the five formulas immediately float and gradually swell. During the 5-hour period, tablets still in the form and afloat with the swelling surface. Tablet floatation due to the selection of excipients that have a smaller density than water (Wikarsa and Valentina, 2011). Crosslinking sodium alginate with calcium chloride aided with HPMC K4M produces matrix strong enough to maintain the integrity of the tablet during the floating test. When the tablet in contact with the medium, ac-in-sol which serves as disintegrant and sodium alginate which have swelling properties will form pores in the layer of HPMC K4M so that the tablet directly to float and then HPMC K4M hydrated then tablets can swell.

Tablet attached to the wall surface of the beaker glass, this was due to sodium alginate has bioadhesive properties (Rowe *et al.*, 2006). After settling in period of 24 hours of tablet still afloat but the gel-like consistency was formed shortly after that the tablets is sinking. Tablets can float in the long term (more than 24 hours), because there is an excipient that has a small density and sodium alginate has bioadhesive properties so

attached to the beaker glass walls and can withstand tablet still afloat.

The maximum wavelength of captopril in the wavelength range between 197-250 nm and obtained the maximum wavelength is 205 nm. USP 29 (2007) states that the maximum wavelength of captopril tablets is 205 nm and the absorbance were relatively stable at HCl pH 1.2, this indicates that the maximum wavelength obtained in the experiment is in agreement with theory.

Captopril standard curve obtained by making a series of captopril solution at pH 1.2 in HCl medium, namely the concentration of 0.008; 0.010; 0.012; 0.014; 0.016 mg/mL. Absorbance of each concentration was measured by UV-vis spectrophotometer at a wavelength of 205 nm. Absorbance data obtained and graphed against the concentration to obtain the regression equation and curve. Data are presented in Figure 5. Drug release test performed using the method of dissolution testing. Dissolution profile with a slow-release tablet captopril floating system using alginate cross-links matrix is presented in Figure 6.

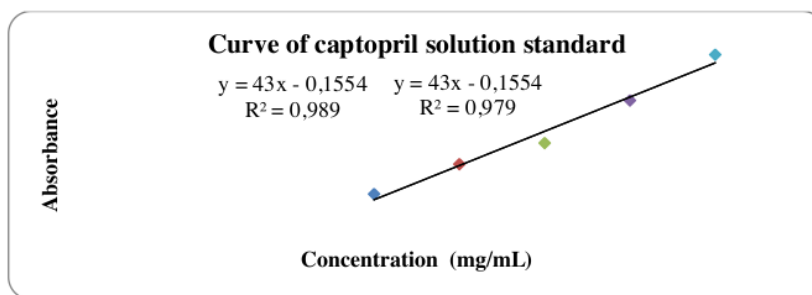


Figure 5. Curve of captopril solution standard

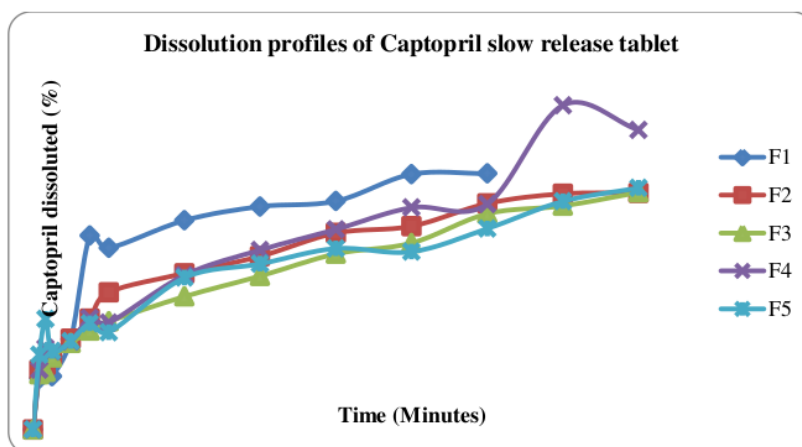


Figure 6. Dissolution profiles of Captopril slow release tablet

Based on Figure 6 drug release from slow-release tablet captopril floating system using a matrix of alginate cross-links with calcium chloride as the crosslinker has a slow-release effect, where in 8 hours of formula 1 are able to release the drug as much as 100% after hours-6; formula 2 able to release the drug as much as 72.199%; formula 3 is able to release the drug as much as 72.395%; formula 4 can release the drug as much as 91.385; and formula 5 can release the drug as much as 73.739%. Content variation of sodium alginate with calcium chloride can affect the release of the drug in dosage form. In addition to the observation of drug release profile also calculated the value of dissolution efficiency (DE).

Dissolution efficiency is the parameters that describe the ability of drug release from a preparation at a certain time. This method is a comparison of the area under the curve and the dissolution rate at the same time. Dissolution efficiency calculated by comparing area under the curve dissolution with the rectangular area 100% of active substances are dissolved at the certain time. DE method can be described the entire process of dissolution until at a certain time, so all points on the curve describing the dissolution. In addition disclosure DE method is identical to the disclosure of trial data in vivo (Khan and Rhodes, 1975). The area under the curve dissolution rate calculated based on the equation:

$$[AUC]_{t_{n-1}}^{t_n} = \frac{C_{n-1} + C_n}{2} (t_n - t_{n-1})$$

Where $[AUC]_{t_{n-1}}^{t_n}$ area under the curve at the time area between t_n dan t_{n-1} ; C_n is the concentration of active substance dissolved at the time t_n ; C_{n-1} is the concentration of active substance dissolved at the time t_{n-1} (Khan and Rhodes, 1975).

Results of DE_{480} calculation showed that the variation of sodium alginate (10%) with calcium chloride (5%) is the formula 3 has the smallest value of DE_{480} . This suggests that the cross-link formed will affect the release of drug from the dosage form. Cross-link was formed lead to the molecular motion is restricted and inhibited the development of polymer in the medium (Kroschwitz *et al*, 1992) and with the help of HPMC K4M will form a solid matrix to hold the drug release.

Drug release from slow-release preparations, ideally regardless constantly from start to finish or follow the model of zero-order kinetics (Ansel, 2005). Kinetics of release of captopril was determined by the equation:

$$\text{Zero Order : } F = a_1 + b_1 \cdot t \quad \dots\dots\dots(1)$$

$$\text{First Order : } \ln(100\% - F) = a_2 - b_2 \cdot t \quad \dots\dots\dots(2)$$

$$\text{Higuchi : } F = a_3 + b_3 \cdot \sqrt{t} \quad \dots\dots\dots(3)$$

Where F is the amount of drug released at time t ; a_1 , a_2 , a_3 is intercept and b_1 , b_2 , b_3

are slope. Release kinetics of captopril was determined by direct regression of the amount of drug dissolved versus time (zero order), Wagner equation (first order) (Wagner, 1971) and Higuchi equations.

The value of the correlation coefficients obtained can be concluded that the order of the reaction is more dominant in the kinetics of drug release is to follow the Higuchi kinetics equation. When the number of drug released from the matrix is proportional to the root of the time it is said to follow a zero-order kinetics (Higuchi, 1963).

If drug released controlled by the matrix erosion so the correlation between the amount of drug released versus time is linear (Lipidus and Lordi, 1968). If the amount of drug released versus root of time is linear so controlled release by diffusion matrix. Based on research results that showed the linearity of the correlation between the amount of drug released versus time and the amount of drug released versus root of time, the release mechanism of captopril cross-link matrix alginate with calcium chloride controlled both mechanism i.e diffusion and erosion. Diffusion mechanism is more dominant, it can be seen the value r for the equation of the curve captopril dissolved to the root of time closest to 1 compared to the time line captopril dissolved.

The results showed that the formula captopril slow-release tablet with floating system using alginate cross-link matrix is able to maintain the release of captopril to 8 hours and release mechanism follows zero order kinetics. The development of this formula can be done with the study of absorption in in vitro fertilization, i.e. by doing drug permeation studies, aiming as screening process against a potential cure for transfers orally.

Conclusion

Captopril sustained release tablets using a system of floating alginate matrix cross linkage with calcium chloride has physical characteristics that meet the general requirements for tablets (physical appearance, uniformity of size, uniformity of

weight, hardness, and friability), except formula 5 which has friability 2.199%. Profile of drug release shows that the coherency matrix of alginate crosslinked with calcium chloride was able to keep the release of captopril to 8 hours, proven formula 2 which releases the drug at least 72.199% with the release kinetics followed zero-order kinetics. The mechanism of release is a combination of erosion and diffusion.

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