KETOPROFEN ENCAPSULATION OPTIMIZATION WITH CHITOSAN-ALGINATE CROSS-LINKED WITH SODIUM TRIPOLYPHOSPHATE AND ITS REALEASE MECHANISM DETERMINATION USING *IN VITRO* DISSOLUTION

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ABSTRACT

Encapsulation optimization of ketoprofen with chitosan-alginate matrix cross-linked with sodium tripolyphosphate (STTP) and determination of its release mechanism has been carried out in succession by sonication-centrifugation method and in vitro dissolution test, respectively. The matrix is made by varying the concentration of chitosan, alginate and STTP using Box-Benhken design method. Ketoprofen mixing with chitosan matrix sonication performed at 20kHz frequency of ultrasonic waves for 30 mintues and centrifuged at 15 000 rpm speed (27200 x g) for 20 minutes. Determination of coating efficiency, the amount of chitosan nanoparticles and the kinetics associated with release mechanism performed using spectrograph-photometer UV/VIS, SEM and in vitro dissolution test, respectively. The result of the matrix constituent optimization was two formula being elected, F and M formula with composition of chitosan, alginate and STPP, respectively are 1.75% (w/v), 0.75% (w/v), 5.0% (w/v) and 1:50% (w/v), 0.625% (w/v), 4.0% (w/v). The efficiency of coating for both formula are 80.43% and 78.84% respectively with average particle size ranged from 200-8000 nm, and the nanoparticle percentage are 23.90% and 26.81%, respectively. Encapsulation of both formulas shows that the drugs release is controlled in both acidic and alkaline medium. Ketoprofen release kinethic from nanoparticle matrix for F and M formula in acidic medium followed the model of the first-order kinetics and Hixson-Crowell respectively, while in alkaline medium it followed Hixson-Crowell and order 0 model respectively.

Keywords*: ketoprofen, chitosan-alginate-STPP, dissolution efficiency, kinethics*

1. INTRODUCTION

Research on the changing shape of microparticles to form nanoparticles are currently being developed. Nanoparticles are defined as solid particles with a size about 10-1000 nm [1]. Preparation of nanoparticle technology is highly depend on the method of preparation that being used, wheter it is in nanosphere particles form, or nanocapsule. In drug delivery systems, nanoparticle acts as a carrier by dissolving, trapping, encapsulate, or attach the drugs in the matrix. Several advantages of using nanoparticles as drug delivery systems include (1) the particle sizze and surface characteristics of the nanoparticle can be easily manipulated in accordance with the targeted treatment, (2) nanoparticles organize and extend the drug release during the transport of drugs to the target (3) drug can be incorporated into nanoparticle system without chemical reactions, and (4) nanoparticle system can be applied to a variety of treatment goals, because the nanoparticle enter the circulatory system and carried by the blood to the target of treatment [1].

Sugita *et al*. [2] has succeded in making more manageable ketoprofen delivery system using chitosan modified with alginate and glutaraldehyde as crosslinker. The addition of alginate have a role as *interpenetrating agent*, and also acts as a reinforcing material for chitosan-chitosan network so the gel structure become stronger and increase the gel properties [3-4]. Ketprofen chosen as a model because it is not water soluble, low biovilabiliy and fast elimination time ranged from 1.5-2 hours, so the drug should be consumed frequently [5-6]. Therefore, it required a pharmaceutical dosage that can minimize these defficiency. Nanospher/microsphere form pharmaceutical dosage where the drug being trapped and or adsorpt in a drug carrier system is a pharmaceutical dosage that can control drug carrier and find the target right after oral prescription.

Chitosan, alginate and glutaraldehyde concentration that being used are 1,75%; 0,625% and 4,5% respectively. Mixing of chitosan solution modified with ketoprofen add to surfactant tween 80 with 30% concentration stirred with magnetic stirrer for 2 hours. This formula produce microsized particle ranged 0,15–6 µm and able to control ketoprofen release in acidic medium about 0,69%, while in alkaline medium ketoprofen release reach 90%, however its dissolution efficiency is still low which is only 30.44%. Ketoprofen release kinetic in acidic medium was dominated with order 1, while alkaline medium it followed order 0 and Hixson-Crowell [2].

Glutaraldehyda as crosslinker for drug delivery system commonly being avoid because its toxic property. Sugita *et al*. [7] conducted a modification with changing glutaraldehyde crosslingker with STPP, while the concentration used is still similar with previous study and stirring method using magnetic stirrer was subtituted with ultrasonication at 20 kHz frequency for 15-60 minutes. Ultrasonication time range 15-60 minutes resulted mixed nano and microparticle range 150nm-13,5µm with nanoparticle precented and ketoprofen adsorbtion efficency are 7,13-53,23 % and 0,52-73,31 %, respectively.

Due to particle physical property is different with previous study and the amount of nanoparticle is better, so the aim of this research is to optimize chitosan alginate nanoparticle synthesis with STPP as crosslinker using varied chitosan, alginate and STPP concentration at best ultrasonication time and tween 80 surfactant concentration from previous research [7]. The method of synthesis is modified with addition of centrifugation treatment after ultrasonication using 15000 rpm (27200 × *g*) for 20 minutes, and detemine release kinetic using *in vitro* dissolution test formula. This modification methods is expected to increase the amount of nanoparticle and its encapsulation efficency. Varying concentration of chitosan, alginate and STPP is conducted using Box-Behnken experimental design. *In vitro* dissolution test used according to Farmakope Indonesia [8]. Result of this test hopefully can describe this speed and model of release mechanism.

2. EXPERIMENTAL SECTION

2.1 Materials

Chitosan was obtained from Bratachem with deacetylation degree (DD), and molecular weight specifications of 70.15%, and 3×10^5 g/mol, respectively. The other materials used were aquadest, acetic acid 98%, sodium tripolyphosphate (STPP), filtering paper, ethanol, Tween-80, alginate, chloride buffer solution (KCl-HCl)-water pH 1.2, phosphate buffer solution (KH_2PO4-NaOH)-water pH 7.4, and ketoprofen active compound which was obtained from PT Kalbe Farma.

2.2 Instrumentations

Ketoprofen encapsulation was conducted by ultrasonik with model US-150, Beckman centrifugation and Buchi 190 spray dry. Ketoprofen concentration that release from microcapsule was measured by UV-1700 PharmaSpec spectrophotometer, the microcapsule's morphology characterization was conducted by SEM JEOL JSM-5310LV and the dissolution test was conducted using Hansen paddle.

2.3Procedure

2.3.1Box- Behnken Formula Combination production

Formula combination production was begin with determination of maximum and minimum concentration for each component that being used. Combinating formula of chitosan, alginate, and STPP concentration was conducted to determine the effect of each component against nanoparticle characteristic. At early stage, each component value was entered, including chitosan 1.50–2.00% (w/v), alginate 0.500–0.750% (w/v), and STPP 4.0–5.0% (w/v) into Box-Behnken program. This whole data concentration was processed using Box-Behnken model with 3 level 3 factorial to gain reprersentative data spread. Those data processing produced a concentration value combination of all of component used in nanoparticle synthesis. The analysis resulted 15 formula as recomended optimum combination, with some formula replication. Formula replication with same material composition was occured at the combination formula near the center point. This formula only made once so we got 13 formula that being used in ketoprofen nanoparticle production.

2.3.2 Ketoprofen Encapsulation Process [7]

As much as 228.6 ml of 1.75% (w/v) chitosan solution in 1% (v/v) acetic acid solution was mixed with 38.1 ml of 0.625% (w/v) alginate solution with magnet stirring until homogenous. After that, 7.62 ml of 4.5% (v/v) STPP was added to the mixture and then stirred until homogenous. This solution, then was sonicated at frekuensi 20 kHz dengan lamanya waktu pengadukan 30 menit. As much as 250 ml 0.8% (w/v) ketoprofen solution in 96% ethanol was mixed with chitosan-alginate so the weight ratio of chitosan-ketoprofen becomes 2:1. After that, 5 ml of 3.0% Tween-80 was added to the mixture and sonicated during 30 minutes before they were centrifugated at 15000 rpm (27200 × *g*) for 20 minutes. Same treatment was applied to the others formulations. Nanoparticle was produced using a spray dryer. 13 formula that being used are presented in table 1. Nanocapsule characterization using Scanning Electron Microscope (SEM). The capsule's morphology characterization was conducted to the empty, and filled ketoprofen nanocapsule using scanning electron microscope (SEM) and it was only conducted to formulae which have encapsulation efficiency over than 50%.

2.3.3 Encapsulation efficiency [9]

Buffer phosphate at pH 7.4 was used to extract ketoprofen from the nanocapsule. As much as 25 mg nanocapsules of each variant was digested, then extracted with 50 ml of buffer phosphate at pH 7.4 for 24 hours, then the extract was

filtered. The extracted ketoprofen concentration was measured by UV spectrophotometer at 257 nm. The obtained absorbance were used to calculate the ketopfofen concentration via a standard curve. For correction, blank of khitosan-alginat nanoparticle was also determined.

Table 1. Nanoparticle Formula Based on Box-Behnken Experimental Design

Formula Code	Concentration % (b/v)		
	[Kitosan]	[Alginat]	[STPP]
A	1.75	0.50	4.0
B	1.75	0.75	4.0
C	1.75	0.50	5.0
D	2.00	0.50	4.5
E	1.50	0.75	4.5
F	1.75	0.75	5.0
G	2.00	0.75	4.5
H	1.75	0.625	4.5
I	2.00	0.625	5.0
J	2.00	0.625	4.0
K	1.50	0.50	4.5
L	1.50	0.625	5.0
M	1.50	0.625	4.0

2.3.3.1 Standard Curve Construction

The absorbance of ketoprofen solution in pH 7.4 phosphate buffer with 10 ppm concntration was measured using spectrophotometry at 200-300 nm wavelength. The obtained maximum wavelength was used for the next analysis. Standard curve produced with ketoprofen concentration series of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 ppm. The obtained data is a curve that relate the connection between ketoprofen concentration and absorbance.

2.3.4 *In vitro* dissolution test [11]

The dissolution test was conducted using the type 2 dissolution device (paddle method). The microcapsule was weighted (500 mg) and placed at the dissolution chamber. The test was conducted on gastric medium (pH 1.2) for 3 hours and intestinal medium (pH 7.4) for 6 hours at 37 ± 0.5 °C with paddling speed 150 rpm. Fifteen milliliters of aliquots were sampled every 15 minutes from the gastric and intestinal medium. After each time an aliquot was taken, the removed volume was replaced with the new medium solution with the same volume and temperature. The dissolution medium volume was 500 ml. Aliquot's ketoprofen concentration was measured at 258.6 nm (for dissolution at pH 1.2) and 260 nm (for dissolution at pH 7.4). The dissolution kinetic was studied by plotting the ketoprofen release percentage versus dissolution time and then determines the reaction order and the ketoprofen release model.

2.3.5 Drug Release Kinetics [12-13]

Drug release kinetic can describe release rate and model. Generally, drug release kinetic was controlled with oreder 0 and 1. Order 0 reaction can be described as: $[A]_t = [A]_o - kt$ atau $Q = kt$.....(1)

With $[A]_t$ is trace drug concentration in drug dosage after t, $[A]_o$ is initial drug concentration, Q is the release percentage, and k is rate efficient. While order 1 reaction is describe as:

$\ln [A]_t = \ln [A]_o - kt$.....(2)

Drug release from initial dosage can take place with erosion or diffusion mechanism. On the mechanism of erosion, eroded so that the drug dosage apart when in contact with the liquid medium. The mechanism of drug release by erosion following the Fick's first law derived from the order one of this reaction:

$$\frac{dW}{dt} = \frac{DS[Cs - C]}{h} \quad \text{.....} \quad (3)$$

with $\frac{dW}{dt}$ was dissolution mass rate, S was the barrier surface area, D was diffusion coefficient, C_s was drug concentration in saturation state, C was drug concentration in the medium. h was the membrane thickness, and t was the time. The diffusion process is commonly seen in drug dosage using coating and expressed by Higuchi equation, which was developed from Fick's law:

$$\frac{dQ}{dt} = \left(\frac{ADCs}{2t}\right)^{1/2} \text{ atau } \quad Q = (2DACs)^{1/2} t^{1/2} \quad \text{.....(4)}$$

with $\frac{dQ}{dt}$ was drug release rate, A was amount of drugs per unit volume of the matrix, d was the diffusion coefficent of the drug through the matrix, *Cs* was the solubility in the matrix, t was the time, and Q was the amount of drug released per unit are of the matrix. If value $(2DACs)^{1/2}$ = k, then equation (4) become equation (5).

$$Q = kt^{1/2} \quad \text{.....} \quad (5)$$

Besides Higuchi model, the diffusion release can be described also by kinetic modeling approach proposed by Korsmeyer-Peppas through this equation (6):

$$Q = kt^{n} \quad \text{.....} \quad (6)$$

Q is the fraction of drug released at t time, k is the rate coefficient, and n is the release exponent. The release of the drug can be described through erosion kinetics model approach by Hixson through the equation below:

$$Qo^{1/3} - Qt^{1/3} = kt \quad \text{.....} \quad (7)$$

Qt is the amount of drug released at t time, Q_0 is the initial amount of drug in the dosage, and *k* rate cooeficient.

3. RESULT AND DISCUSSION

3.1 Characterization, calculation of coating efficiency and particle size

The nanoparticle obtained in this study had a visual form such as fine grains that are yellowish, brittle, ad hygroscopic. Morphology analysis of nanoparticle by SEM showed that the surface of the chitosan-alginate nanoparticle gel without addition of ketoprofen look rounded (spherical) and shriveled to the size range of 277 – 6000 nm (Figure 1a). Nanoparticles of chitosan-alginate gel with the addition of ketoprofen (1b) shows a spherical shape, smooth, and not shriveled to the size range 400 – 5000 nm. SEM analysis and determination of nanoparticle sized ≤1000 nm percentage is only made to the formula that has a coating efficiency of over 50%, eight formula is being chosen. Formula that gives 50% and more nanoparticle coating efficiency are presented in the Table 2.

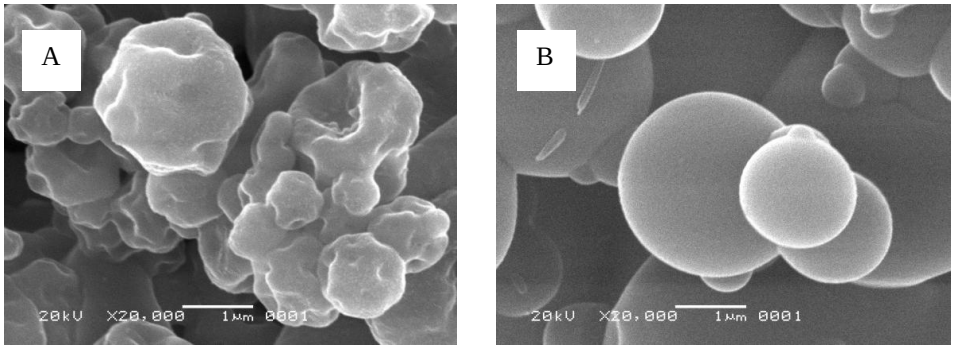

Figure 1 SEM photograph of nanoparticle coated with chitosan-alginate nanoparticle gel crosslinked with triphosphate without ketoprofen (a), and with addition of ketoprofen (b) at 20000× magnification.

Data of coating efficiency and the percentage of nanoparticle then inserted into the combination formula on Box-Behnken programs as response variables. Furthermore, the data were analyzed to obtain three dimensional curves (Figure 2. and 3.) that can be used to see the effect of the combination formula to the amount of nanoparticle.

Table 2. Formula scoring base on amount of (%) of nanoparticle and adsorption efficiency

Formula	DP	EP	NP	Standard Normal		Weighing (0.5)		Total Score	Best Formula
				EP	NP	EP	NP		
A	400–5152	59.79	30.90	-0.68	1.66	-0.34	0.83	0.490	3
D	428–3055	54.54	16.07	-1.21	-0.46	-0.61	-0.23	-0.830	8
F	416–7700	80.43	23.90	1.41	0.66	0.71	0.33	1.040	2
H	550–4722	73.78	14.03	0.74	-0.75	0.37	-0.38	-0.006	4
I	571–8857	58.97	16.55	-0.76	-0.39	-0.38	-0.20	-0.580	5
K	526–6315	64.99	11.66	-0.15	-1.09	-0.07	-0.55	-0.620	6
L	550–10550	60.63	14.28	-0.59	-0.72	-0.29	-0.36	-0.650	7
M	220–8180	78.84	26.81	1.25	1.07	0.63	0.54	1.170	1

Explanation: DP = Particle size range (nm), EP = Adsorption Efficiency (%), NP = % Nanoparticle

Figure 2a shows the effect of chitosan and alginate concentrations on the coating efficiency at 4.0 % (w/v) STPP concentration with the highest effeciency reached 78.84%. In the same STPP concentration, an increasing number of chitosan and alginate tend to reduce the efficiency of the coating. At 4.5% (w/v) STPP concentration, the highest efficiency was 73.78% (Figure 2b), an increasing number of chitosan more than 1.75% (w/v) and increasing number of alginate more than 0.625% (w/v) tend to decrease the efficiency. At 5% (w/v) STPP concentration have 80.43% highest efficiency (Figure 2c), the chitosan optimum amount that produced highest efficiency is 1.75% (w/v), while optimum amount of alginate is 0.750% (w/v). According to Figure 2 it can be seen that efficiency value is fluctuated in accordance with optimum composition of matrix affect the ability of nanoparticles to adsorb or entrap ketoprofen.

Figure 3 shows the effect of chitosan and alginate concentration to the total nanoparticles at 4.0% (w/v) concentration. The highest percentage is 30.90%, and the increasing amount of chitosan tend to decrease naoparticle amount. It also happend at 4.5 and 5.0% (w/v) STPP concentration that have highest percentage of 16.07 and 23.90% respectively (Figure 3b and 3c). These results are different with Wahyono *et al.* [10] that stated if increased STPP concentration and increased chitosan concentration at 3.5% tend to increase the amount of ketoprofen nanoparticle. The affect of alginate amount in Figure 3a shows that at 4.0% (w/v) STPP concentration, addition of alginate tend to decrease the amount of nanoparticle. Otherwise, at 4.5 and 5.0% (w/v) STPP concentration (Figure 3b dand 3c), nanoparticle number tend to increase correspond to alginate concentration increase. Figure 3 also shows that STPP concentration increase tend to decrease nanoparticle number. This is due to STPP act as crosslinker and strengthen ketoprofen nanoparticle matrix so the chitosan was stronger and hard to break into smaller pieces.

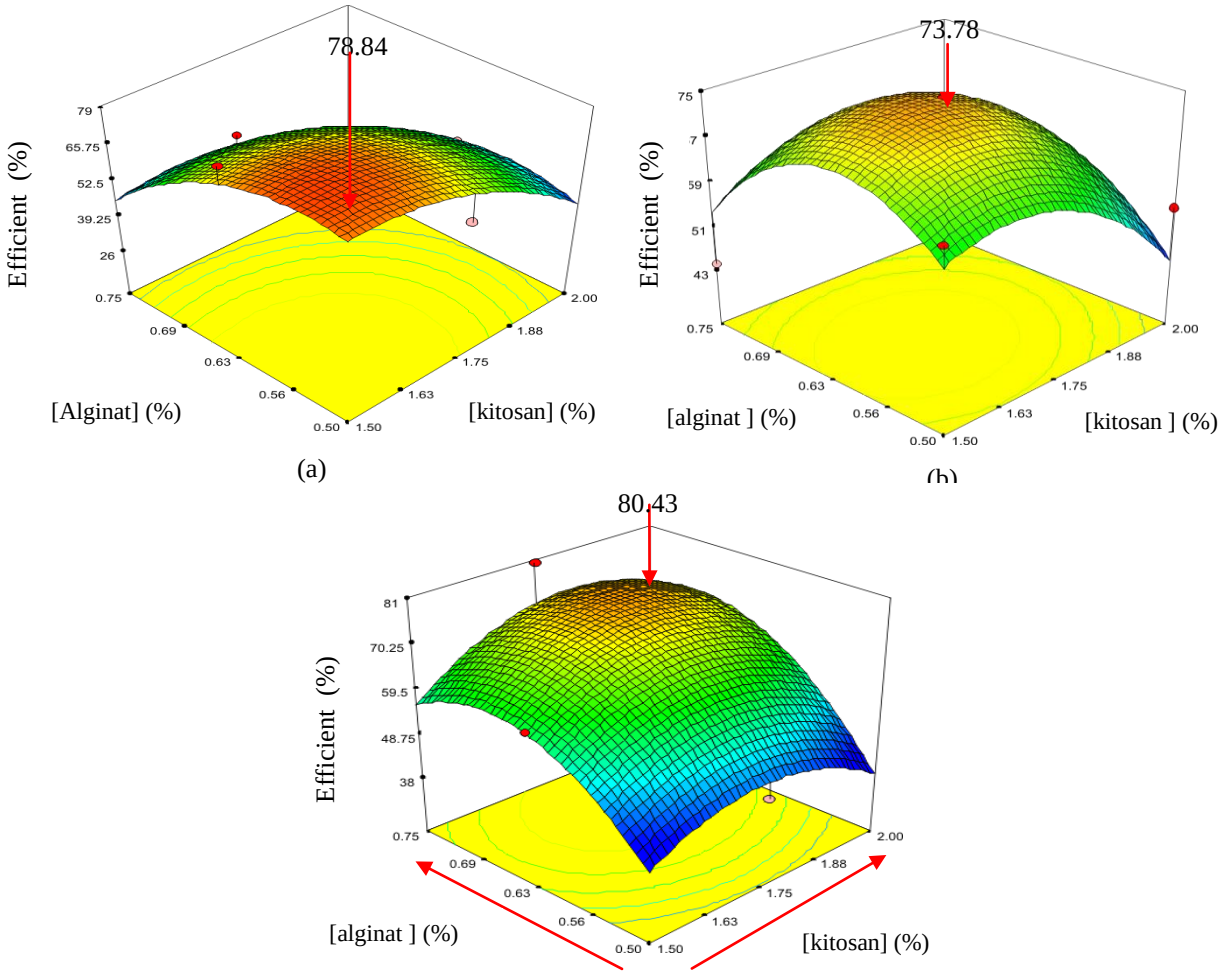

Figure 2 Chitosan and alginate concentration effect on encapsulation efficiency with 4.0% (b/v) (a), 4.5% (b/v) (b), dan 5.0% (b/v) (c) STPP concentration.

3.2 Formula Selection Based on Efficiency Value and Chitosan nanoparticle Number

Selection of the best ketoprofen nanoparticle formula is based on weighting of the efficiency value and the amount of nano sized particles (Table 2). Weighting is conducted using the method of selection under the assumption that each criterion has equal importance in determining the best formula. Selection method using the selection criteria based on standard normal distribution with parameters $\mu = 0$ and $\sigma = 1$. In these circumtances, a random variable, in this case is all the criteria, converted to standard normal values, which are then given scores by the composition percentage of each of the assessment criteria. Selection index is the sum of normal value product of the raw and composition percentage of assessment criteria. Selection stage is done by determining the average value and defficiency standard and nanoparticle amount of each formula, to be converted into standard normal value. Standard normal value for each criteria then multiplied 0.5 because each criteria considered important.

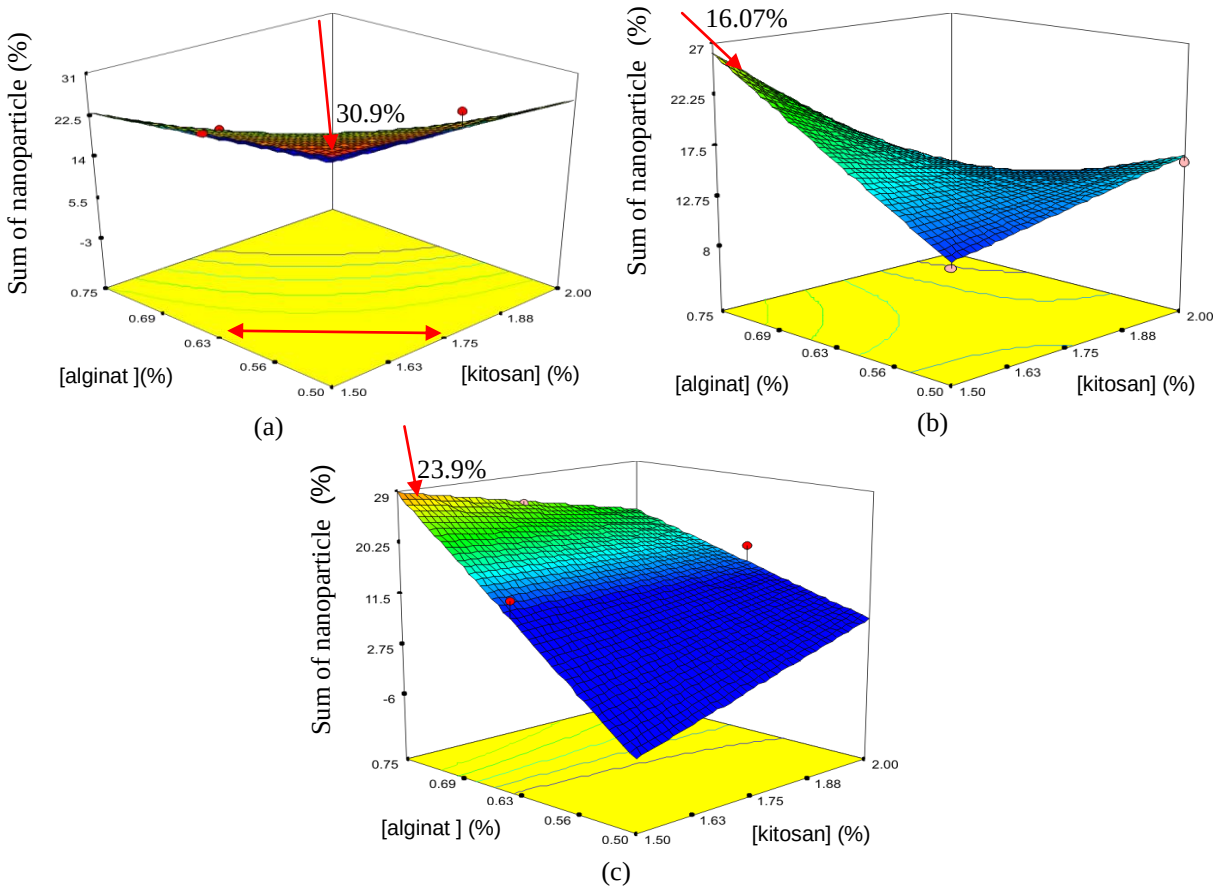

Figure 3 Chitosan and alginate concentration effect on nanoparticle amount with 4.0% (b/v) (a), 4.5% (b/v) (b), dan 5.0% (b/v) (c) STPP concentration.

M and F formula are stated as number 1 and 2 best formula. Being compared with Sugita *et al.* [7] and Wahyono study [10] (Table 3), percentage of nanoparticle number (NP) for both M and F formula are lower, but have more narrow particle size range and larger coating efficiency. The low percentage of nanoparticle allegedly due to the use of alginate gel matrix that causing gel matrix become stronger so it is harder to break at ultrasonication process. Higher concentration of STPP and chitosan with similar alginate concentration in Sugita *et al.* [7] study is suspected causing the gel become more tight so ketoprofen gel is difficult to extract, resulting in a lower coating efficiency. Meanwhile, the centrifugation process is longer at higher speed in Wahyono *et al.* [10] study are suspected to cause rapid extraction of ketoprofen from chitosan and lost during the process, thus reducing the coating efficiency.

3.3 Ketoprofen Release from the Chitosan Matrix

Dissolution testing of nanoparticles in this study was only conducted on the M and F formula. In vitro dissolution done in acidic (pH 1.2) and (pH 7.4) alkaline medium. The rate of ketoprofen release from chitosan-alginate matrix with STPP cross linker in acidic (pH 1.2 buffer) and alkaline medium (pH 7.4 buffer) are shown in Figure 4. In the second medium, the performace of coated ketoprofen release of M and F formula show that they are still able to control the release of ketoprofen in acidic medium and maximum release occured in alkaline medium. Release percentage of ketoprofen in acid medium coated by the two formulas are still high, about 40% when compared with Sugita *et al*. [2] research, ketoprofen release is only about 10%. Differences arising from the use of different crosslinker. This study used STPP which is poly-anionic, while Sugita *et al*. [2] used glutaraldehyde which is neutral. The addition of glutaraldehyde on reinforcing chitosan matrix structure through Schift alkaline interaction forming covalent bonds to form an imine, while STPP reinforcing chitosan matrix through ionic interaction. The matrix density of chitosan crosslinked with glutaraldehyde is higher than ionic crosslinked matrix. Denser matrix of chitosan would prevent the release of ketoprofen that being coated in.

Table 3. Result comparison between M and F formula to previous research [7] and [10]

Observed Parameters	Formula yang diamati			
	Formula M	Formula F	Sugita *et al.* [7]	Wahyono *et al.* [10]
Chitosan % (b/v)	1.50	1.75	1.75	3
Alginate % (b/v)	0.625	0.75	0.625	-
STPP % (b/v)	4.0	5.0	4.5	0.84
Surfactant	Tween 80 3%	Tween 80 3%	Tween 80 3%	Asam Oleat 1.5 mg/mL
Treatment	sonication: 30 minutes; Centri-fugation: 15000 rpm for 20 minutes	sonication: 30 minutes; Centri-fugation: 15000 rpm for 20 minutes	sonication: 15 minutes	sonication: 30 minutes; Centrifugation:20000 rpm for 20 minutes
EP	78.84	80.43	36.79	72.48
NP	26.81	23.90	53.23	58.08
DP	428–3055	416–7700	187–7500	556–1104

The value of the release rate constant (k) at acid medium dissolution is lower than in the alkaline medium. Release kinetic model in both acid and alkaline medium are determined using graphical method, with observing determination highest coefficient value (R^2) that obtained from curve that relate between ketoprofen release percentage and time using kinetic approach. Based on R^2 value, it can be seen that F formula ketoprofen release in acid and alkaline medium followed order 1 and Hixson-Crowell equation respectively, while the M formula in acid and alkaline medium followed Hixson-Crowell and order 0, respectively. Release mechanism that showed by oreder 1 and 0 equation support erosion mechanism theory, while Hixson-Crowell equation show that the drug released through diffusion mechanism that followed by erosion [14]. The study is in line with research conducted by Sugita *et al.* [2], the release mechanism of ketoprofen in acid medium is dominated by the first order, whereas in alkaline medium order-0 and Hixson-Crowell. This study is different from research conducted by Shoaib *et al.* [12], Sarvanan *et al.* [13], Sugita *et al.* [15], and Kim *et al.* [16] with the release kinetics is represented by a model of Korsmeyer-Peppas and Higuchi. Sugita *et al.* [15] observed that the release of ketoprofen double coated chitosan-guar gum and sodium alginate-$CaCl_2$, whereas three other studies in order to observe the release of ibuprofen from excipient hydroxypropyl methylcellulose tablets (HPMC) [12], cephalexin of tablets with HPMC excipients [13] and the active compounds surelease of pellets with excipients sodium alginate [16]. Matrix as a carrier different shows different patterns of release, but the mechanism remains the same through diffusion alone or diffusion coupled with erosion. On the mechanism of erosion, ketoprofen release occurs due to erosion of coating layer. The erosion of coating polymer can be caused by the hydrolysis reaction that allows ketoprofen released from the coating system [17].

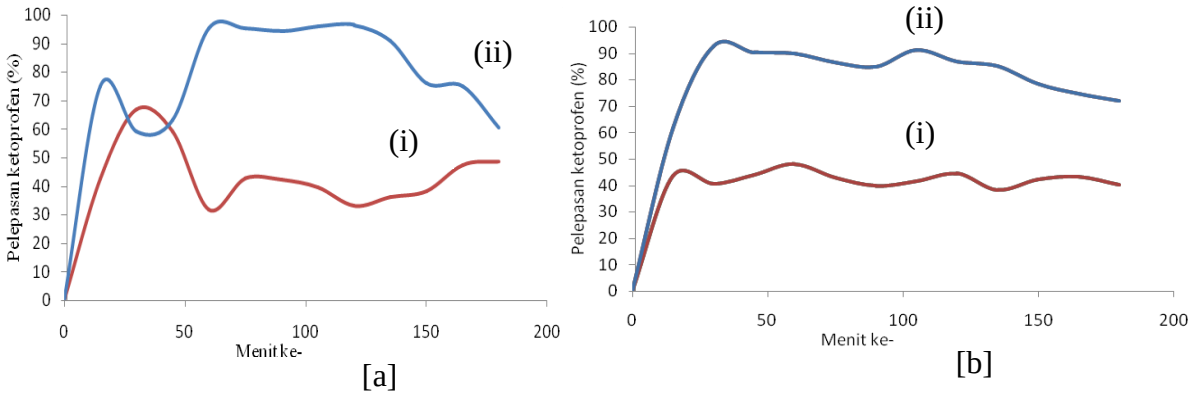

Figure 4 Ketopofen release in acid (i) and alkaline (ii) medium at M (a) and F (b) formula

The release of ketoprofen through the mechanism of diffusion in nanoparticles may happen in two ways, reservoir diffusion swelling (Figure 5a) and diffusion matrix swelling (Figure 5b). Drug release occurs because the nanoparticles absorb liquid buffer system which causes the gel to expand (swelling). This swelling increases the fluid in the system and enlarge the nanoparticles pores and nanoparticle size which allows the drug to diffuse out of the network expands to the external environment [18]. Drug release in reservoir diffusion selling occurs in the nanosphere system, while the drug release matrix diffusion swelling occurs in the nanocapsule system. On the mechanism of erosion, ketoprofen release occurs due to erosion of coating layer. Coating polymer erosion can be caused by the hydrolysis reaction that allows ketoprofen came off from the coating system [18]. This erosion process can occur in two ways, bulk erosion process (Figure 6a), and surface erosion process (Figure 6b).

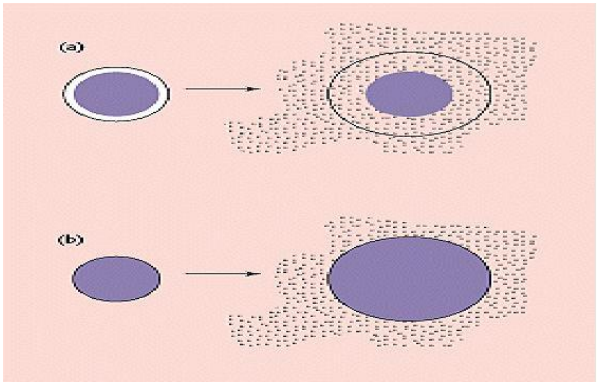

Figure 5 (a) shows reservoir diffusion swelling and (b) show matrix diffusion swelling [18].

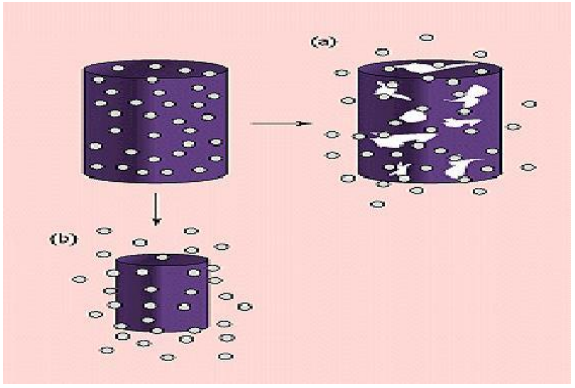

Figure 6 (a) shows bulk erosion process and (b) shows surface erosion process [18].

4. CONCLUSSION

Optimization of ketoprofen coating using chitosan-alginate cross-linked with STPP resulted two selected formula M and F with composition of chitosan, alginate and STPP, respectively, 1.50% (w / v), 0625% (w / v), 4.0% (w / v) and 1.75% (w / v), 0.75% (w / v), 4.5% (w / v); efficiency coating for both formulas M and F, respectively, 78.84% and 80.43%, both of which have a range of sizes particles (400-8000) nm with its nanoparticle percentages are respectively 26.81% and 23.90%. Encapsulation of the second formula shows controlled drugs release in both acidic and alkaline medium medium. Ketoprofen release from nanoparticle matrix for M and F formula in acid medium followed Hixson-Crowell kinetics and order 1 model of reaction speed, while in alkaline medium it is followed order 0 and Hixson-Crowell kinetic model, respectively

5. ACKNOWLEDGEMENT

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