

## DIFFUSION BEHAVIOR OF KETOPROFEN THROUGH CHITOSAN-ALGINATE MEMBRANES

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## ABSTRACT

Chitosan-alginate membrane diffusion behavior has been investigated for its application in drugs delivery system. Ketoprofen diffusion behavior assay were performed at 37 and 42 °C to membrane thickness ( $h$ ) and donor cell concentration of ketoprofen variations ( $A$ ). The results showed that equilibrium concentrations ( $C_s$ ) of ketoprofen equation was  $27.0087 + 0.09067T - 1.7499h + 0.1030A + 0.0161h^2 - 0.0022A^2 + 0.0040Th - 0.0018TA + 0.0095hA$ . The value of  $C_s$  was closer to the expected therapy concentration at 50 and 75 mg/L with thin membrane (10-34  $\mu\text{m}$ ). Based on Higuchi equation, the model for  $J$  and  $D$  were  $J = 11.0849 - 0.2713T - 0.3132h - 0.7461C_s - 0.0096A - 0.0001h^2 - 0.0131C_s^2 + 0.0002A^2 + 0.0084Th + 0.0275TC_s - 0.0018TA - 0.0059hC_s + 0.0021hA + 0.0037C_sA$  with  $R^2 = 97.9\%$  and  $D = -12.5000 + 0.2266T + 0.1313h + 0.1538C_s + 0.1200A - 0.0009h^2 + 0.0240 C_s^2 - 0.0009A^2 + 0.0015Th - 0.0150 TC_s - 0.0011TA - 0.0096hC_s + 0.0004hA + 0.0039C_sA$  with  $R^2 = 98.7\%$ , respectively. The two dimensional contour maps of  $J$  versus  $A$  and  $h$ , both at 37 and 42 °C, showed an increasing of  $J$  value as  $A$ ,  $h$ , or  $T$  increased.

**Keywords:** ketoprofen, chitosan-alginate, diffusion

## INTRODUCTION

The ability of chitosan to form membrane has been much studied. The membranes chitosan are potential to be used in drug delivery systems. Yamada et al. [1] and Sutriyo et al. [2] have coated ketoprofen anti-inflammatory drugs and propranolol hydrochloride anti-hypertension drugs by chitosan membranes, respectively. However, its fragile membrane property needs to be strengthened by adding glutaraldehyde as a cross-linker and natural or synthetic polymer as an interpenetrating agent. Sugita et al. have been investigated chitosan modified membranes by adding glutaraldehyde and natural hydrocolloid like guar gum [3], alginate [4], carboxymethylcellulose (cmc) [5] and xanthan gum [6], respectively. The chitosan modified are potential for membranes to be used in drug delivery systems. The potential of chitosan-guar gum membranes as drug delivery system have investigated by Nata et al. [7] and Sugita et al. [8] through such ketoprofen diffusion and in vitro dissolution behaviors, respectively.

Nata et al. [7] reported that ketoprofen diffusion through such chitosan-guar gum membrane was initiated by swelling process followed with membrane pores opening that release the drugs content from the matrix. Sugita et al. [8] reported that microphotographs of ketoprofen microcapsules in the gastrointestinal (KCl-HCl solution, pH 1.2) after 30 min of dissolution were shattered, so ketoprofen release became uncontrollable. Guar gum was not hold out to acid solution at pH < 3.0.

Microphotographs of ketoprofen microcapsules in the intestinal (buffer phosphate solution, pH 7.4) after 90 min of dissolution were still controllable and coated of ketoprofen content about 31.5%, but release time was too fast. On the other hand, shelf life of microcapsules are about 18.92 months if kept in climatic chamber at  $(40 \pm 2)$  °C and RH  $(75 \pm 5)\%$  for 3 months [9].

Herdini [10] have been used chitosan-alginate membranes as drug delivery system for curcuma. Sarmiento et al. [11], Van den Berg et al. [12], and Pandey & Khuller [13] have also used it for coating insulin hormone, protein, and antibiotics drug (like rifampicine, isonyazide tuberculosis, pirazynamide), respectively. The membranes were applicable as coating material on slow-released drug preparation and hold out to acid solution at pH < 3.0 [14]. In previous research, Sugita et al. [4] reported that the membrane is also potential for membranes to be used in drug delivery systems. In this research, the membranes could be used to coat a ketoprofen. This membrane has not been investigated practically. Ketoprofen is a non-steroid anti-inflammatory drug (NSAID) with poor-solubility in water. Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur in patients treated chronically with ketoprofen therapy. This weakness can be overcome by microencapsulation the ketoprofen. It is hoped that the microcapsule can control the released of the ketoprofen. Chitosan-alginate membranes are expected to be more effectively coat and control the drug release.

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This paper presents the diffusion behavior of ketoprofen through chitosan-alginate membranes. Membrane diffusion performance has been examined from the amount of released ketoprofen concentration under the equilibrium condition ( $C_s$ ), flux ( $J$ ), and diffusion coefficient ( $D$ ) values resulted from the Higuchi equation calculation. The relation between  $J$ , membrane thickness ( $h$ ), and ketoprofen concentration ( $A$ ) are modeled using response surface method (RSM).

## EXPERIMENTAL SECTION

### Materials

Chitosan was from CV Dinar Cikarang Bekasi with specification of moisture and ash contents, molecular weight, and degrees of deacetylation were 8.49%, 0.15%,  $6.63 \times 10^5$  g/mol and 74.15% respectively; alginate and glutaraldehyde; ketoprofen was from PT Kalbe Farma. Aquades was from Organic Chemistry Laboratory, Institute of Bogor Agriculture.

### Instrumentation

Shimadzu Pharmaspec 1700 UV Spectrophotometer and scanning electron microscopy (SEM) (JEOL-JSM-5310LV). Model of ketoprofen  $C_s$ ,  $J$  and  $D$  were calculated using response surface method (RSM) in Minitab Release 14.

### Procedure

#### Chitosan-alginate Membrane Preparation [9]

Chitosan-guar gum membranes were prepared by mixing 75 mL of 2.25% (w/v) chitosan solution, 5 mL of 0.83% (w/v) alginate solution, and 1 mL of 4.0% glutaraldehyde solution, which was then poured into a 21.40 x 28.25 cm mold. Membranes thickness ( $h$ ) was varied by varying the volume of chitosan solution that was used.

#### Membrane Diffusion in Vitro Assay [7]

Three degrees of donor cell concentration ( $A$ ) were used: 25, 50, and 75  $\mu\text{g/mL}$ , whereas receptor compartment was filled with ethanol-water (1:1) solvent. The instrument was then put into a 37 and 42 °C water bath to keep the temperature. The mixing was assisted by two aerators that applied at both sides of the diffusion cell. A 10.0 mL aliquot was sampled from the recipient cell and the diffused ketoprofen concentration was determined by UV spectrophotometer. Aliquot sampling was performed every 30 min for the diffusion assay at 37 °C during 3 h and every 20 min for the assay at 42 °C during 6 h until the ketoprofen concentration became relatively constant ( $C_s$ ). Substitute solvent (10.0 mL) was

added after each time an aliquot was sampled. Aliquot absorbance was determined at 255 nm.

### Ketoprofen Diffusion Coefficient ( $D$ ) and Flux ( $J$ ) Modeling

Flux ( $J$ ) and  $D$  were calculated by Higuchi equation:

$$D = \frac{Q^2}{2AC_s t} \quad (1)$$

$$J = \frac{dQ}{dt} = \left( \frac{ADC_s}{2t} \right)^{1/2} \quad (2)$$

$$Q = hA - \frac{1}{2} hC_s \quad (3)$$

$dQ/dt$  = drug releasing rate per matrix surface area

$C_s$  = drugs concentration that has been released to the recipient cell under saturated or equilibrium condition (mg/L)

$A$  = total concentration of drug either outside or inside on gel matrix (mg/L)

$H$  = membrane thickness ( $\mu\text{m}$ )

Flux ( $J$ ) and  $D$  relationship mathematical models were obtained using RSM method integrated in Minitab Release 14 software with donor cell concentration ( $A$ ), equilibrium concentration ( $C_s$ ), diffusion temperature ( $T$ ), and membrane thickness ( $h$ ) as the factors. Outputs of this modeling are  $J$  and  $D$  equations and two dimensional contour plots.

## RESULT AND DISCUSSION

### Higuchi Models of $C_s$ , $J$ , and $D$

Table 1 shows the equilibrium concentration ( $C_s$ ), diffusion coefficients ( $D$ ) and flux ( $J$ ) as the results of diffusion assays. The both were derived from Higuchi's Law using linear relationship between time and mass of ketoprofen that passed through the membranes.

The influence of  $T$  on diffusion coefficient in this research was not significant due to the varied number and size of hollow space in membranes. Schmidt et al. [15] reported the dependence of water vapor permeability on the porosity of polyurethane membranes. This behavior may be due to changes in physical properties of the polymeric membrane such as the pore size or possibly the diffusivity of solvent in the membrane [16].

Mathematical model for  $C_s$  obtained by RSM using Minitab14 software is  $C_s = 27.0087 + 0.0906T - 1.7499h + 0.1030A + 0.0161h^2 - 0.0022A^2 + 0.0040Th - 0.0018TA + 0.0095hA$  with  $R^2 = 85.6\%$ .  $R^2$  value for  $C_s$  model is less than 90%. However, statistical analysis of the equation shows that  $A$ ,  $T$ , and  $h$  factors each has significant effects to  $C_s$  value, with  $P$  value less than for every variable at 99% confidence level.

**Table 1.** The  $C_s$ ,  $D$  and  $J$  values that were obtained from diffusion assays

Run	$A \text{ mg L}^{-1}$	$h \text{ (}\mu\text{m)}$	$T \text{ (}^\circ\text{C)}$	$C_s \text{ mg L}^{-1}$	$D \times 10^{-9} \text{ cm}^2 \text{ sec}^{-1}$	$J \times 10^{-12} \text{ gcm}^{-2} \text{ sec}^{-1}$	$t \text{ (hour)}$
1	25	30	37	2.3009	1.1237	0.9034	11.0
2	25	28	37	2.0539	1.0598	0.8107	11.5
3	25	40	37	4.6437	0.9845	1.2599	10.0
4	25	40	37	2.8488	2.1678	1.6372	8.0
5	25	52	37	1.9940	3.4724	1.3868	12.5
6	25	54	37	4.4596	2.0180	1.8297	9.3
7	25	26	42	4.6243	0.6601	1.2936	6.3
8	25	24	42	8.4431	0.4909 <sup>a</sup>	2.0778	3.3
9	25	44	42	3.2485	3.1927	2.5209	5.7
10	25	45	42	6.5359	1.3549	2.2638	6.0
11	25	74	42	4.2635	6.5852 <sup>a</sup>	4.1477	5.7
12	25	56	42	4.4566	3.3786	2.9519	6.0
13	50	20	37	13.1826	0.1985	1.5072	8.0
14	50	20	37	12.6317	0.2798	2.0224	6.0
15	50	30	37	5.2560	1.0674	1.9738	10.0
16	50	30	37	5.8937	0.7826	1.6338	12.0
17	50	48	37	8.4132	1.5952	3.0529	10.0
18	50	32	37	8.0045	0.9398	2.5554	8.0
19	50	28	42	10.1587	0.4635	1.8717 <sup>a</sup>	9.3
20	50	34	42	13.5329	1.0235	4.7113 <sup>a</sup>	4.3
21	50	40	42	5.3249	4.3162 <sup>a</sup>	6.0689 <sup>a</sup>	4.3
22	50	40	42	7.6901	1.4206 <sup>a</sup>	2.9587	8.7
23	50	44	42	8.0554	2.0156	4.0135	7.0
24	50	48	42	12.0614	1.0798	3.0856 <sup>a</sup>	9.5
25	75	30	37	9.2380	1.4895 <sup>a</sup>	4.8876 <sup>a</sup>	6.0
26	75	10	37	12.5404	0.0607	0.8301 <sup>a</sup>	11.5
27	75	40	37	9.7051	1.5023	3.8971	10.0
<b>28<sup>b</sup></b>	<b>75</b>	<b>40</b>	<b>37</b>	<b>11.8413</b>	<b>1.3778</b>	<b>4.4282</b>	<b>8.7</b>
29	75	64	37	3.5943	11.309 <sup>a</sup>	6.5069	10.0
30	75	64	37	9.9641	3.7321 <sup>a</sup>	6.2238	10.0
31	75	10	42	13.3937	0.1382	2.0328	4.7
32	75	10	42	12.6003	0.1562	2.1469	4.4
33	75	32	42	8.0793	1.3637	3.6390	8.7
34	75	30	42	10.4446	1.0595	3.9646	7.3
<b>35<sup>b</sup></b>	<b>75</b>	<b>42</b>	<b>42</b>	<b>13.2440</b>	<b>1.7742</b>	<b>6.1365</b>	<b>6.5</b>
36	75	42	42	12.3458	3.7603 <sup>a</sup>	12.0447 <sup>a</sup>	4.4

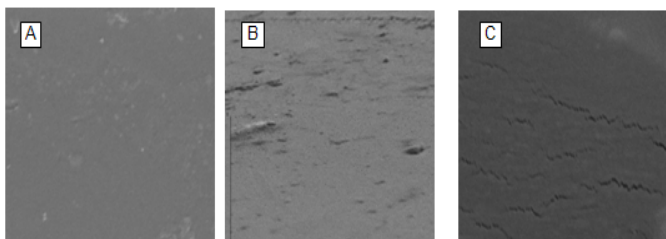
<sup>a</sup> These values were not included in RSM due their large error

<sup>b</sup> These values were used for SEM analysis.

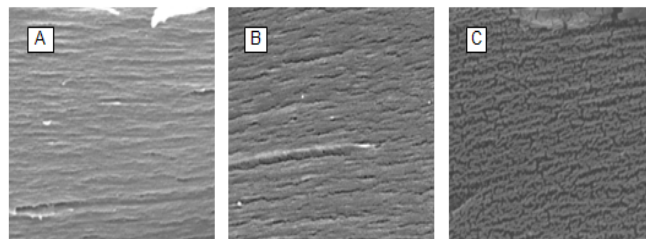
Similar modeling for  $J$  and  $D$  respectively resulting:  
 $J = 11.0849 - 0.2713T - 0.3132h - 0.7461C_s - 0.0096A - 0.0001h^2 - 0.0131C_s^2 + 0.0002A^2 + 0.0084Th + 0.0275TC_s - 0.0018TA - 0.0059hC_s + 0.0021hA + 0.0037C_sA$  with  $R^2 = 97.9\%$  and  $D = -12.5000 + 0.2266T + 0.1313h + 0.1538C_s + 0.1200A - 0.0009h^2 + 0.0240C_s^2 - 0.0009A^2 + 0.0015Th - 0.0150TC_s - 0.0011TA - 0.0096hC_s + 0.0004hA + 0.0039C_sA$  with  $R^2 = 98.7\%$ . Statistical analysis to  $J$  and  $D$  equation also

shows significant effect of  $A$ ,  $C_s$ ,  $T$ , and  $h$  to  $J$  and  $D$  value at 99% confidence level.

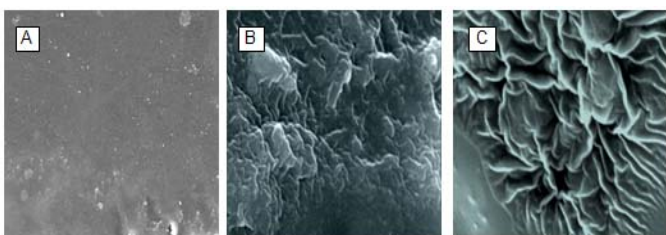
$C_s$  model can be applied to estimate  $A$ ,  $h$ , and  $T$  values needed for obtaining expected ketoprofen therapy concentration as slow-released preparation.  $J$  and  $D$  models can be used to estimate chitosan-alginate membrane diffusion properties for ketoprofen at different  $A$ ,  $T$ ,  $h$ , and  $C_s$  values.



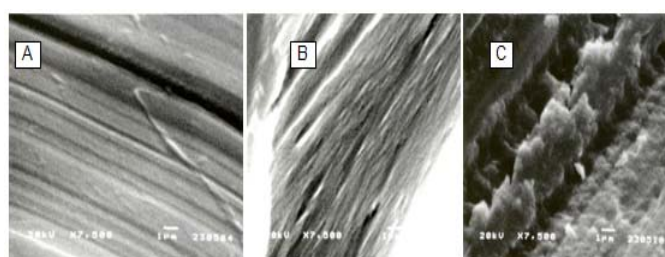
**Fig 1.** Microphotographs of (A) control; (B) run-28; (C) run-35 chitosan-alginate membranes surface (top section) at 10,000 times magnification



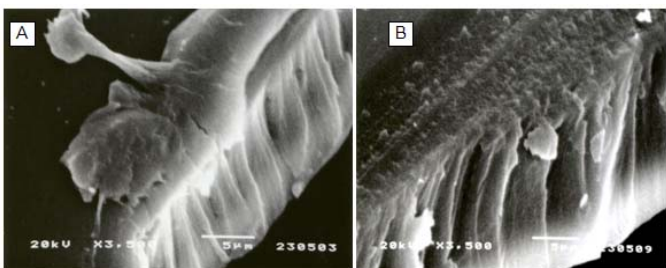
**Fig 2.** Microphotographs of (A) control; (B) run-28; (C) run-35 chitosan-alginate membranes surface (lateral section) at 10,000 times magnification



**Fig 3.** Microphotographs of (A) before diffusion assay; (B) run-3 (curcumin concentration ( $C_d$ ) = 8 g/L;  $T=37$  °C); (C) run-8 ( $C_d$  = 8 g/L;  $T$  = 41 °C) chitosan-alginate membranes surface at 5,000 times magnification [10]



**Fig 4.** Microphotographs of (A) control; (B) run-9; (C) run-25 membranes surface at 7,500 times magnification [7]



**Fig 5.** Microphotographs of (A) control; (B) run-25 membranes cross-section at 3,500 times magnification [7]

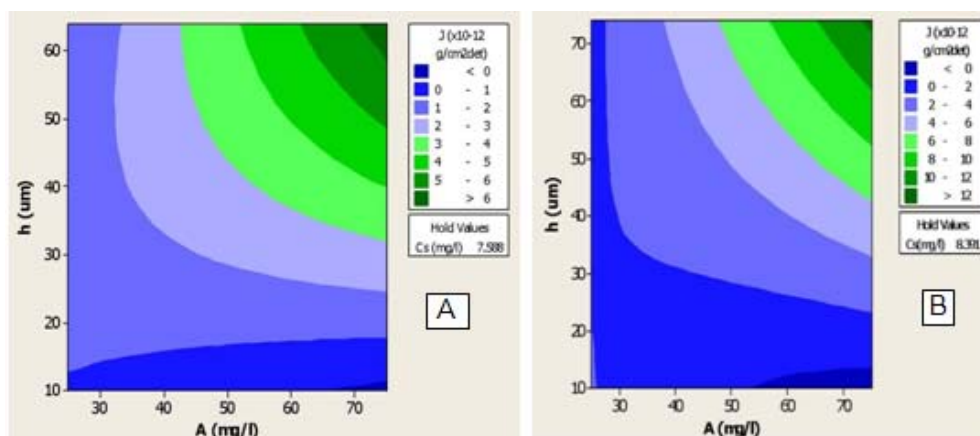
### Membranes Characterization

SEM image at 10,000 times magnification (Fig. 1A) clearly showing that chitosan-alginate membrane surface (top section) doesn't have any pores and look very smooth before diffusion assay. Before diffusion assay, lateral section observation also doesn't show that the membrane has any cavity inside (Fig. 2A). This surface morphology is similar with the result reported by Herdini [10] (Fig. 3A).

The observation of membranes after diffusion assay (Fig. 1B and 2B) showed that the membranes have small hollow space. These holes probably formed due to membrane swelling as the effect of ketoprofen concentration difference and also temperature. Swelling process is estimated to be enhanced when the temperature is raised. It was supported by the observation of run- 28<sup>th</sup> membrane ( $A$  = 75 mg/L;  $T$  = 37

°C;  $h$  = 40  $\mu$ m). In the previous study, Herdini [10] reported that chitosan-alginate membrane that has been used in the curcuma diffusion assay at 37 °C has widely opened pores that dig deep into the membrane (Fig. 3B).

Increasing temperature accommodate membrane swelling to occur more easily. This fact is supported by the 35<sup>th</sup> diffusion assay membrane observation result ( $A$  = 75 mg/L;  $T$  = 42 °C;  $h$  = 42  $\mu$ m). Membrane pores became more widely opened and dig deeper into the membrane (Fig. 1C and 2C). This result is similar with the fact that Mulder [17] has reported, temperature rise will enlarge membrane pore holes due to thermal expansion. Herdini [10] also reported that chitosan-alginate membrane that has been used in the 8<sup>th</sup> diffusion assay at 41 °C has wider cavities, the membrane became porous, wavier, and cruder (Fig. 3C). Santos et al. [18] has reported that increasing temperature give rise to sodium sulfamerazine diffusion coefficient pass through chitosan membrane. Results from the 28<sup>th</sup> and 35<sup>th</sup> diffusion assay are consistent with this. The  $J$  value for the 35<sup>th</sup> assay ( $T=42$  °C), which is  $6.1365 \times 10^{-12}$  g cm<sup>-2</sup> sec<sup>-1</sup>, is higher than the  $J$  value for the 28<sup>th</sup> assay ( $T$  = 37 °C), which is  $4.4282 \times 10^{-12}$  g cm<sup>-2</sup> sec<sup>-1</sup>. This also happened to the  $D$  value obtained; the 35<sup>th</sup> assay  $D$  value ( $1.7742 \times 10^{-9}$  cm<sup>2</sup>/sec) is higher than the  $D$  value for the 28<sup>th</sup> assay ( $1.3778 \times 10^{-9}$  cm<sup>2</sup>/sec) (Table 1). If we relate these facts with the SEM images, this might be due to membrane porosity in the 35<sup>th</sup> is higher than in the 28<sup>th</sup> assay membrane.



**Fig 6.** Relationship curve between A and h versus J at  $T = 37\text{ }^{\circ}\text{C}$  and  $C_s = 7.588\text{ mg/L}$  (A) and  $T = 42\text{ }^{\circ}\text{C}$  and  $C_s = 8.391\text{ mg/L}$  (B)

The results are similarly with Nata et al. [7]. Nata et al. [7] reported that the microphotographs of chitosan-guar gum membranes (Fig. 4) were unporous or had varied porosity due to dense cross-linking between chitosan molecules. It was estimated that small holes in run- 9 membrane ( $C_d = 75\text{ mg/L}$ ;  $T = 37\text{ }^{\circ}\text{C}$ ;  $h = 31\text{ }\mu\text{m}$ ) were caused by swelling process that was enhanced by concentration difference and temperature increase.

The observation of membranes cross-section shows the same results (Fig. 5). It shows that the membranes have hollow space. However, this hollow space did not emerge the surface of the membranes (Fig. 4A). The swelling process on membranes caused the hollow space became larger (Fig. 5B) and membranes pores that are the channel for the hollow space were opened (Fig. 4C). Swelling process is estimated to be enhanced when the temperature is raised. It was supported by the observation of run- 25 membrane ( $C_d = 75\text{ mg/L}$ ;  $T = 42\text{ }^{\circ}\text{C}$ ;  $h = 35\text{ }\mu\text{m}$ ). The membrane became porous, wavier, and cruder (Fig. 4C). However, the pores were not spread throughout the membranes. It was supported by observation of the same membrane, but on the other area. This pore-opening process is very good for drug delivery. The swelling process of the membranes can make the drugs released when the microcapsule interacts with a body liquid.

#### The Influence of Ketopropfen Concentration, Temperature, and Membrane Thickness Effect on Ketopropfen $C_s$

Table 1 show that the equilibrium concentration ( $C_s$ ), diffusion coefficients ( $D$ ) and flux ( $J$ ) as the results of diffusion assays. At ketopropfen concentration of 25, 50, and 75 mg/L,  $C_s$  value varied between 1.9940 and 13.5329 mg/L for membrane that as thick as 10-74  $\mu\text{m}$  at

37 and 42  $^{\circ}\text{C}$ . For ketopropfen concentration of 25 mg/L at 37  $^{\circ}\text{C}$  and 42  $^{\circ}\text{C}$  have a maximum value of  $C_s$  were 4.6437 mg/L and 8.4431 mg/L, respectively that reached by the membrane with intermediate thickness (40  $\mu\text{m}$ ) and the thin membrane (24  $\mu\text{m}$ ), respectively. These  $C_s$  values are still lower than the expected ketopropfen therapy concentration. But, for 50 mg/L ketopropfen concentration at 37  $^{\circ}\text{C}$  and 42  $^{\circ}\text{C}$  have maximum  $C_s$  value were 13.1826 mg/L and 13.5329 mg/L, respectively that obtained by the thin membrane (20  $\mu\text{m}$ ) and the thick membrane 34  $\mu\text{m}$ , respectively. For 75 mg/L ketopropfen concentration at 37  $^{\circ}\text{C}$  and 42  $^{\circ}\text{C}$  have maximum  $C_s$  12.5404 mg/L and 13.3937 mg/L, respectively that obtained by membranes with same thickness (10  $\mu\text{m}$ ). It has been showed that at 50 and 75 mg/L ketopropfen concentration,  $C_s$  values are closer to the expected therapy concentration, 15–25 mg/L. Diffusion time needed to reach  $C_s$  value at applied A, h, and T values are varied between 3.33 and 12.5 h. These suggest that chitosan-alginate is potential to be applied as ketopropfen coating material on slow-released drug preparation, thus ketopropfen administration frequency and its negative side effect can be minimized.

#### The Influence of Ketopropfen Concentration, Temperature, $C_s$ , and Membrane Thickness Effect on Ketopropfen flux ( $J$ )

Fig. 6 show that the two dimensional contour maps of  $J$  to A and h at 37  $^{\circ}\text{C}$  and 42  $^{\circ}\text{C}$ , respectively. Fig. 6a described that at condition  $T = 37\text{ }^{\circ}\text{C}$  and  $C_s = 7.588\text{ mg/L}$  (mean value), maximum  $J$  value were obtained when ketopropfen concentration is high (70–75 mg/L) on the thick membrane (59–64  $\mu\text{m}$ ), while the minimum value of  $J$  were reached when ketopropfen concentration is high (65–75 mg/L) on the thin membrane (10–12  $\mu\text{m}$ ). In other words, the higher

concentration and membrane thickness will generally result in higher flux value. The increasing amount of ketoprofen molecules will give rise to the propulsion force generated, thus membrane swelling and ketoprofen diffusion will be more easily take place. This result probably obtained due to the better porosity of thick membrane than the thin ones. But this suggestion is not reflected in the 35<sup>th</sup> diffusion assay SEM images (Fig. 2C) which shows a quite good porosity for the intermediate thickness membrane (42  $\mu\text{m}$ ).

Similar condition was discovered at  $T = 42\text{ }^\circ\text{C}$  and  $C_s = 8.391\text{ mg/L}$  (mean value) (Fig. 6B). Maximum  $J$  value were obtained when ketoprofen concentration was high (73–75 mg/L) on the thick membrane (72–74  $\mu\text{m}$ ), on the other hand, the minimum value were reached when high concentration (53–75 mg/L) on the thin membrane (10–14  $\mu\text{m}$ ). On this condition, the similar result like in 37  $^\circ\text{C}$  was obtained;  $J$  is proportional with ketoprofen concentration and membrane thickness. Generally, at higher temperature (42  $^\circ\text{C}$ ) the higher  $C_s$  value (mean value  $C_s = 8.391\text{ mg/L}$ ) was obtained than at the lower temperature (37  $^\circ\text{C}$ ) (mean value  $C_s = 7.588\text{ mg/L}$ ). At higher temperature tends to speeds up membrane swelling, thus enlarge pores size then increase ketoprofen molecules flow rate across the membrane. Previously Mulder [17], Ariyaskul et al. [19], Susheelkumar et al. [20], and Chen et al. [21] also reported increased flux as the temperature rise, but membrane selectivity decreased.

## CONCLUSION

Chitosan-alginate membrane with 10–34  $\mu\text{m}$  thickness has potential as ketoprofen coating material in slow-released drug preparation of 50 and 75 mg/l dose at 37  $^\circ\text{C}$  or 42  $^\circ\text{C}$ .  $C_s$  value were obtained at the conditions are closer to the therapy concentration. The two dimensional contour maps of  $J$  versus  $A$  and  $h$  shows increasing  $J$  value as  $A$ ,  $h$ , or  $T$  increased.

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