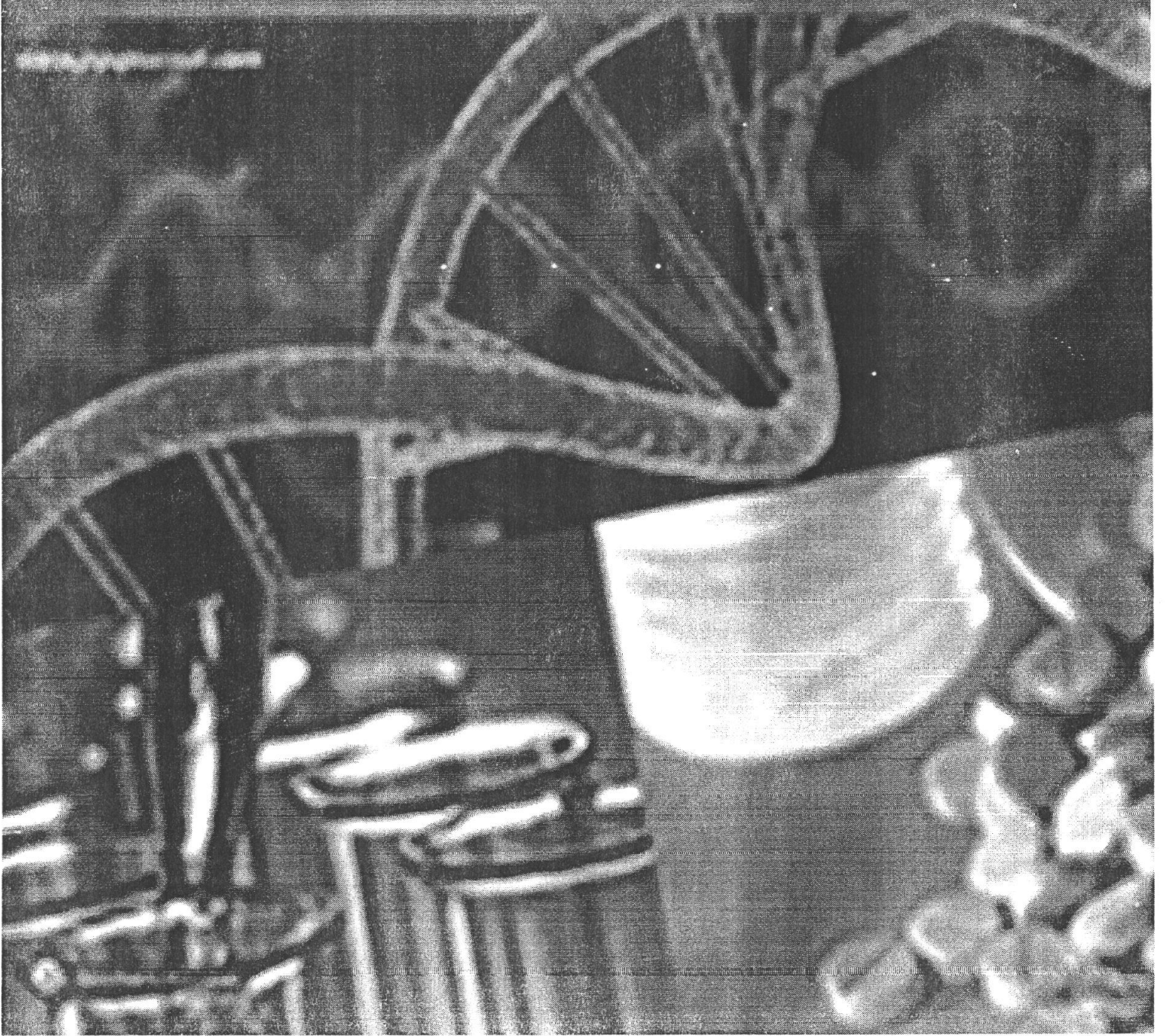


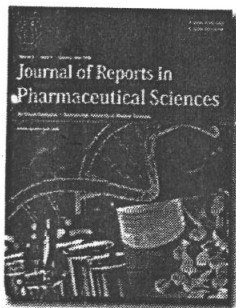
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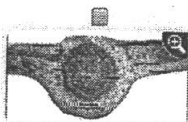








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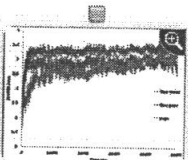


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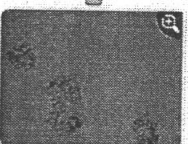


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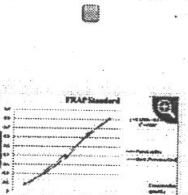


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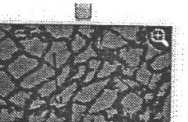
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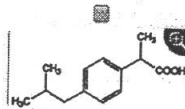
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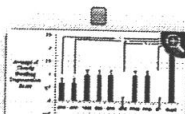


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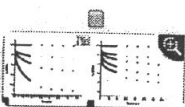


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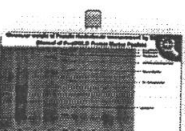


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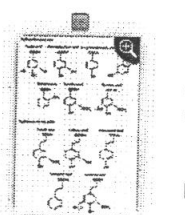
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## Experimental Design Approach in Erythropoietin-alginate Microsphere Preparation with Different Concentrations of Drug and Polymer

### Abstract

**Background:** Microspheres as drug delivery system has been selected to increase stability of Erythropoietin (EPO) to achieve efficacy. **Aim:** Aim of this research was to determine effect of polymer and EPO concentrations on the characteristics. **Materials and Method:** Microspheres involved sodium alginate as polymer and CaCl<sub>2</sub> as a crosslinker. The concentrations of sodium alginate used were 2% and 3%, and EPO were 5000 IU and 10000 IU. Formula of microspheres which consist of 2% and 3% of alginate and 5000 IU EPO were called F1 and F2 respectively, whereas microspheres using 2 and 3% alginate and 10000 IU EPO was named F3 and F4 respectively. Characterization including morphology, particle size, swelling index, and yield of microspheres prepared by ionotropic gelation aerosolization technique. Design of Experiment (DoE) was used to analyze the formula. **Results:** Results showed that particle sizes of EPO-alginate microspheres were  $3.36 \pm 0.126 \mu\text{m}$ ,  $3.42 \pm 0.098 \mu\text{m}$ ,  $3.88 \pm 0.131 \mu\text{m}$  and  $3.95 \pm 0.151 \mu\text{m}$  for F1, F2, F3 and F4 respectively. The swelling index measurement based on mass and particle size of microspheres of all formulas showed an index of less than 10. Respectively, yield was  $77.84 \pm 0.290\%$ ,  $86.65 \pm 0.191\%$ ,  $91.89 \pm 0.210\%$ , and  $94.65 \pm 0.252\%$  for F1 to F4. Using the ANOVA factorial design, it was found that increasing sodium alginate concentration significantly increased yield, while increasing EPO concentration significantly increased particle size and yield of microspheres. Both sodium alginate and EPO concentrations did not affect swelling index of microspheres. Range concentrations of sodium alginate and EPO that produced optimal characteristics of microspheres can be observed in the feasible area of design space overlaid contour plot generated from DoE study. **Conclusion:** EPO-alginate microspheres demonstrated the prospective as carrier and DoE is potential for further optimized formulations.

**Keywords:** Aerosolization, Ca-alginate microspheres, characteristics, design of experiment, erythropoietin

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### Introduction

Erythropoietin (EPO) is a glycoprotein that can penetrate the blood-brain barrier and interact with neural receptors to produce neuroprotective functions, which can be used for prophylaxis and Parkinson's therapy.<sup>[1,2]</sup> EPO is a protein that has a weakness, namely its risk to be denatured at high temperatures and under extreme pH conditions of <3 and >9, and its necessity for frequent invasive administrations to produce neuroprotective function.<sup>[3,4]</sup> Therefore, it is necessary to select an appropriate drug delivery system in order to achieve efficacy and safety.

Microspheres are microparticles composed of homogeneous mixtures or dispersions of active ingredients and entrapment materials.<sup>[5]</sup> The recommended dry

microsphere size for the subcutaneous route is 3.5–5  $\mu\text{m}$  to reduce the potential for inflammation in the tissues.<sup>[6]</sup> The desired microspheres are in the form of a dry suspension to maintain the stability of the active ingredient, which can then be reconstituted before use. Another advantage of microspheres is that it can reduce side effects due to precipitous drug release.<sup>[7]</sup>

The manufacture of microspheres by ionotropic gelation method with aerosolization technique is performed by spraying a polymer solution in a crosslinked solution with the advantages that the drug is encapsulated to become stable, has a uniform particle size of <8  $\mu\text{m}$ , has a spherical shape, is produced easily and through quick process, has safety in manufacture, and ensures low cost due to not using organic solvents.<sup>[8]</sup>

In the process of making microspheres, a polymer and a crosslinker are required.

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The most commonly used polymer is sodium alginate. This polymer in the form of hydrophilic polysaccharides isolated from the brown algal cell wall. The benefits of sodium alginate are that it is biocompatible, biodegradable, safe, and cheap.<sup>[9]</sup> The most frequently used crosslinkers are Ba<sup>2+</sup> and Ca<sup>2+</sup> divalent cations. At the selected level of 1 M, calcium chloride (Ca<sup>2+</sup>) crosslinker is safer and affects the rate of drug release (ovalbumin model), causing it to be slower and more controlled than barium chloride (Ba<sup>2+</sup>) crosslinker.<sup>[10,11]</sup> Then, the selected drying technique was freeze-drying using 5% maltodextrin lyoprotectant to ensure stability and produce a smooth and spherical microsphere and make the release of the active ingredient more controllable, constant, and predictable.<sup>[8,12]</sup>

From the above process, EPO-alginate microspheres would be formed, which can be reconstituted and injected subcutaneously in the patient. The alginate microspheres will release EPO without subsequent microsphere movement from the subcutaneous tissue. In general, the release of the active ingredient from the microsphere includes two stages. The first stage is the stage when the dissolution medium diffuses and stabilizes the hydrodynamic pressure in the microsphere. The second stage is the process of drug release from the microsphere.<sup>[13]</sup> EPO is released from alginate microspheres and diffuses from the subcutaneous tissue to blood circulation, going into the brain, penetrating the blood-brain barrier, interacting with neural receptors, and then, producing indirect neuroprotective effects.<sup>[11]</sup>

The characteristics of the microsphere are influenced by formula variables such as active ingredient content, polymer type, polymer content, crosslinker solution content, crosslinking time, and pH.<sup>[12]</sup> Levels of polymer and active ingredient content used greatly affect microsphere characteristics. With increasing polymer levels in the microspheres, there is an increase in microsphere mean diameter, swelling index, and yield, as long as the quantities of polymer and crosslinker are sufficient.<sup>[11,12]</sup> According to Hariyadi *et al.*, an increase of 1%, 1.5%, and 2.5% in sodium alginate polymer content in the ovalbumin-alginate microsphere leads to increased microsphere particle sizes.<sup>[11]</sup> In another study, a content increase of 2% and 3% in sodium alginate polymers in the albumin-alginate bovine serum microsphere results in increased microsphere particle size with a spherical shape and smoother surface.<sup>[14]</sup> On the other hand, increased content of antigen model active ingredient leads to an increase in microsphere particle size and yield as long as levels of polymer and crosslinker are sufficient to form microspheres.<sup>[15]</sup>

This study was conducted to determine the effect of polymer content of sodium alginate and EPO on several characteristics, namely morphology (shape and surface), size, swelling index, and yield of EPO-alginate microspheres. The preparation of EPO-alginate microspheres was carried out through ionotropic gelation method with aerosolization technique using 2% and 3% sodium alginate polymer and 5000 IU and 10,000 IU of EPO crosslinked with CaCl<sub>2</sub> 1 M solution.

## Materials and Methods

### Materials

Pharmaceutical grade recombinant human EPO (Daewoong Pharmaceutical Co., Ltd, Gyeonggi, Republic of Korea); pharmaceutical grade sodium alginate (Sigma-Aldrich Inc., St. Louis, MO, USA); pharmaceutical grade CaCl<sub>2</sub>·2H<sub>2</sub>O (Solvay Chemicals International); Na<sub>2</sub>HPO<sub>4</sub> pro analysis (Merck, Darmstadt, Germany); KH<sub>2</sub>PO<sub>4</sub> pro analysis (Merck, Darmstadt, Germany); NaCl pro analysis (Sigma-Aldrich Inc., St. Louis, MO, USA); pharmaceutical grade Maltodextrin (Brataco Chemicals, Jakarta, Indonesia); HCl pro analysis (Merck, Darmstadt, Germany); NaOH pro analysis (Merck, Darmstadt, Germany); and demineralized water are used.

### Research method

#### *Erythropoietin-alginate microsphere formula design*

The formula design of EPO-alginate microspheres of F1 to F4 were presented in Table 1.

#### *Erythropoietin-alginate microspheres production*

Sodium alginate (2 g) was dissolved into 100-ml demineralized water; EPO was dispersed into alginate solution and was stirred until it became homogeneous. The resulting Erythropoietin-alginate solution was sprayed using aerosol spray with a hole size of 35 μm, a constant pressure of 40 psi, and a spraying distance of 8 cm into 200 ml of CaCl<sub>2</sub> and was stirred constantly for 30 min at the speed of 1000 rpm. The formed microspheres were centrifuged at a speed of 4000 rpm for 6 min and then washed using distilled water 2–3 times. The washed microspheres were suspended in a 5% maltodextrin solution and then dried using freeze-dryer (Eyela FD-81, Tokyo, Japan) at -45°C for 30 h.

#### *Erythropoietin-alginate microsphere evaluation*

##### Particle size distribution examination

The evaluation of EPO-alginate microsphere size distribution was performed using 400 × optical microscope magnification (Axioscope 40-Zeiss, LLC, USA). This evaluation was performed by placing wet microspheres on the glass object and observing as many as 300 particles.

**Table 1: Erythropoietin-alginate microspheres formulas with different sodium alginate and erythropoietin content**

Materials	Function	Formula			
		F1	F2	F3	F4
Erythropoietin	Active ingredient	5000 IU	5000 IU	10000 IU	10000 IU
Sodium alginate	Polymer	2%	3%	2%	3%
CaCl <sub>2</sub> solution	Crosslinker	1 M	1 M	1 M	1 M
Crosslinking time	-	30 min	30 min	30 min	30 min
Maltodextrin	Lyoprotectant	5%	5%	5%	5%

Then, the average diameter was determined, and a microsphere size distribution curve was created. The average diameter was calculated using the formula:

$$d_{vs} = \frac{nd^3}{nd^2}$$

Microsphere shape and surface morphology

The evaluation of EPO-alginate microsphere shape and surface evaluation was performed using a scanning electron microscope (SEM) (Fei Inspect S50, Japan). This evaluation was performed by placing a sample on the handle of the preparation with an adhesive material containing metal grains, such as the metal Pt. The gold in the chamber was evaporated so that the gold steam coated the entire surface of the microparticles. The surface of the gold-coated microparticle was observed with SEM to observe the shape and surface morphology of its microspheres.

Infrared spectra examination

The spectrophotometric evaluation using Fourier-transform infrared (FTIR) spectrophotometer (Perkin Elmer Instrument), India, was performed to determine which microspheres were formed. This evaluation can be done by weighing 1 mg of the microsphere formula with dried KBr powder. Afterward, the microspheres were compressed with hydrophilic presses equipped with a steam puller so that the result obtained is a light-penetrating, light-permeable plate. The resulting infrared spectra were compared with EPO, alginate, and maltodextrin spectra.

Thermal analysis results using differential thermal analysis

A melting point evaluation was conducted to determine whether microspheres have been formed. This evaluation can be done by weighing 3–5 mg samples, then putting it into a sample pan with a crucible aluminum type that has a maximum temperature of 350°C, and then closed. Then, the sample pan was inserted into the sample holder. A heating with a heating rate of 5°C/min, and the equilibrium time was obtained after the initial melting temperature was reached. The peak results of the melting point obtained were compared with the peak of the alginate melting point and CaCl<sub>2</sub>.

Moisture content determination

The moisture content (MC) determination on EPO-alginate microspheres can be performed using the moisture analyzer (Mettler Toledo HB43-S Greifensee, Switzerland). This evaluation can be performed by weighing 0.5 g of microspheres and inserting them into the moisture measurement tool. The tool would work for 10 min. The MC was calculated by the formula:

$$MC = \frac{\text{initial weight} - \text{resulting weight}}{\text{resulting weight}} \times 100\%$$

Determination of swelling index

About 100 mg of dry microspheres was laid in 10 ml of phosphate-buffered saline pH 7.4. Swelling index observations were performed at 24- and 30-h intervals. The expanding microspheres were then filtered, and the microsphere surface is wiped with filter paper until the filter paper did not become wet anymore. Samples were laid in a 37°C oven for 2 h, which were then carefully weighed to obtain constant final sample weight.<sup>[16]</sup>

Swelling Index Mass

$$= \frac{\text{sample weight at time } t - \text{initial sample weight (mg)}}{\text{initial sample weight (mg)}}$$

Yield determination

The yield value was determined by the ratio of the total weight of the dry microspheres obtained to the amount of weight of EPO, sodium alginate, and maltodextrin. The yield value can be calculated using the formula:

$$\text{Yield (\%)} = \frac{\text{total microsphere weight (mg)}}{\text{alginate weight} + \text{erythropoietin weight} + \text{maltodextrin weight (mg)}} \times 100\%$$

A factorial design ANOVA statistical analysis using the SPSS 21 program (International Business Machines Corporation, IBM, New York, USA) with 95% confidence degree ( $\alpha = 0.05$ ) was performed on particle sizes, swelling indices, and yield data. A free sample *t*-test was performed to determine the compatibility of the swelling index mass and size at the same time. A paired *t*-test was performed to determine the difference of swelling indices at different observation times. In addition, data processing was also performed using Factorial Design 2<sup>2</sup> design of experiment (DOE) in Minitab 17 software to determine the main effect plot, contour plot, and overlaid contour plot, as well as the range of polymer content of sodium alginate and EPO content to produce the optimal microsphere characteristics, including microsphere size of 3.15–3.85 μm, swelling index of 1–2, and yield of 85%–100%.

## Results

### Physical characteristics of erythropoietin-alginate microspheres

Organoleptic observations were performed on dried EPO-alginate microspheres of F1, F2, F3, and F4 with maltodextrin lyoprotectant. There was a uniform result,



namely white and odorless powder. Furthermore, the MC of EPO-alginate microspheres F1, F2, F3, and F4 was examined using a moisture analyzer. The examination obtained the results in Table 2 of 9.23% ±0.243%, 9.36% ±0.212%, 9.79% ±0.204%, and 9.53% ±0.200% for each formula according to the requirement that the microsphere MC is <10%.<sup>[17]</sup>

DTA thermogram of EPO-alginate microspheres of F1, F2, F3 and F4 showed the melting points and melting heats for each respective formula of 163.5°C and 77.8 J/g, 172.3°C and 58.9 J/g, 163.9°C and 167 J/g, and 204.9°C and 211.9°C. These data indicated that melting points of EPO-alginate microspheres of F1, F2, and F3 were in the range of the melting points of sodium alginate (143°C) and CaCl<sub>2</sub> (176°C), thus it can be inferred that interaction was occurred between sodium alginate and CaCl<sub>2</sub> to form microspheres.<sup>[18]</sup> The endothermic peaks of the EPO-alginate F4 microspheres showed melting at 204.9°C; 211.9°C is probably the polymorphic result of the microsphere after the freeze-drying process. The intensity of the endothermic peak and the enthalpy of the EPO-alginate microspheres is higher than that of the polymer and the crosslinker materials because a stable system of Ca-alginate has been formed, requiring higher energy to melt the EPO-alginate microspheres.<sup>[19]</sup>

From the results of FTIR spectral examination of the four formulas in Figure 1, the uptake of the amide-specific group of EPO amide (C = O) is present in all formulas, indicating that EPO is stable during the encapsulation process.<sup>[18]</sup> From the results of the examination, the peak of amide uptake was found in all four formulas with F1

wavenumbers (1641.31/cm), F2 (1646.27/cm), F3 (1639.54/cm), and F4 (1633.39/cm). However, the absorption of the NH stretching groups of all formulas on the wavenumber is 3267.56/cm is undetected because there is an overlap with a wider OH group uptake. There was also showed that the absorption of specific groups of guluronate fingerprints of Na-alginate, maltodextrin, and asymmetric carboxylate salt groups were occurred due to crosslinking reactions, which indicated by FTIR that Ca-alginate microspheres have been formed. Other research was also studied formation of crosslinked calcium alginate microspheres by using FTIR spectroscopy.<sup>[20]</sup>

### Morphology and particle size of microspheres

The results showed that the shape of wet microspheres of formula F1, F2, F3, and F4 was spherical and of a smooth surface [Figure 2]. The SEM results in Figure 1 of all microspheres of the formula showed that the microspheres were spherical shaped and had a smooth surface. The addition of lyoprotectant maltodextrin can cause hydrogen bonding between maltodextrin and the polar surface of microspheres, which can cover the microsphere surface cavity and prevent microsphere formation caused by water sublimation from microspheres during the drying process by freeze-drying method.<sup>[21]</sup>

In the observation of wet microspheres with optical microscope, the average particle diameter (dvs) of particle sizes of EPO-alginate microspheres F1, F2, F3, and F4 was 3.36 ± 0.126, 3.42 ± 0.098, 3.88 ± 0.131, and 3.95 ± 0.151 μm, respectively [Figure 3]. These results indicated that the mean diameter of the microsphere size increases with increasing content of sodium alginate polymer and the content of EPO used. The increased particle size of the microspheres may be affected by ions in the microsphere system.<sup>[22]</sup> Increased levels of partially negatively charged (more active COO group) EPO will repel the COO group of alginate, causing chain extension, increasing the viscosity of the polymer solution, and enlarging the droplet, thus increasing the particle size of the microsphere.<sup>[23,24]</sup>

### Swelling index of microspheres

Examination of swelling index of EPO-alginate microspheres was performed based on mass and particle size of microspheres at 24 and 30 h. The obtained swelling

**Table 2: Moisture content examination**

Formula	Replication	MC (%)	Average±SD (%)
F1	R1	8.95	9.23±0.243
	R2	9.38	
	R3	9.36	
F2	R1	9.17	9.36±0.212
	R2	9.59	
	R3	9.33	
F3	R1	9.56	9.79±0.204
	R2	9.95	
	R3	9.86	
F4	R1	9.33	9.53±0.200
	R2	9.73	
	R3	9.54	

SD: Standard deviation, MC: Moisture content

**Table 3: Swelling index of microspheres based on mass and particle size**

Formula	Based on mass		Based on particle size	
	t=24 h	t=30 h	t=24 h	t=30 h
	Swelling Index±SD	Swelling Index±SD	Swelling Index±SD	Swelling Index±SD
F1	1.25±0.188	1.78±0.230	1.15±0.258	1.80±0.168
F2	1.43±0.240	2.16±0.167	1.32±0.231	1.98±0.179
F3	1.29±0.163	1.89±0.106	1.22±0.214	1.92±0.203
F4	1.49±0.224	2.21±0.299	1.36±0.115	2.13±0.200

SD: Standard deviation

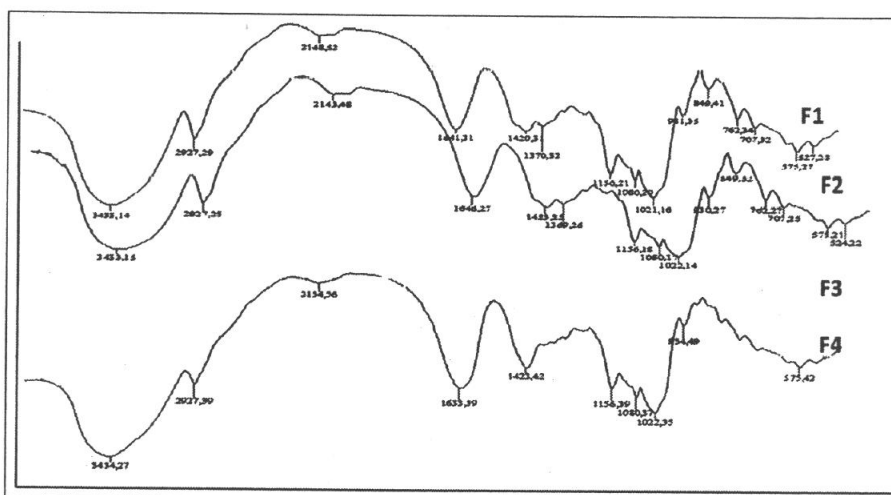


Figure 1: FTIR spectrophotometer of microspheres formula using 5000 IU EPO, alginate 2% and CaCl<sub>2</sub> 1M (F1), 5000 IU EPO, alginate 3% and CaCl<sub>2</sub> 1M (F2), 10000 IU EPO, alginate 2% and CaCl<sub>2</sub> 1M (F3) and 10000 IU EPO, alginate 3% and CaCl<sub>2</sub> 1M (F4)

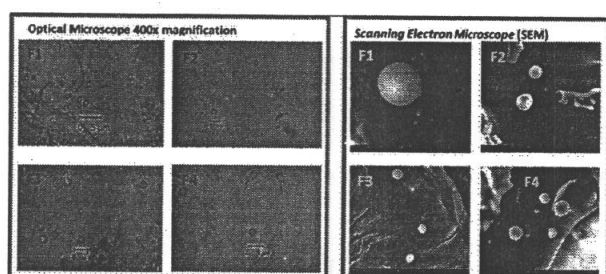


Figure 2: The shape and surface of EPO-alginate microspheres of F1, F2, F3, and F4

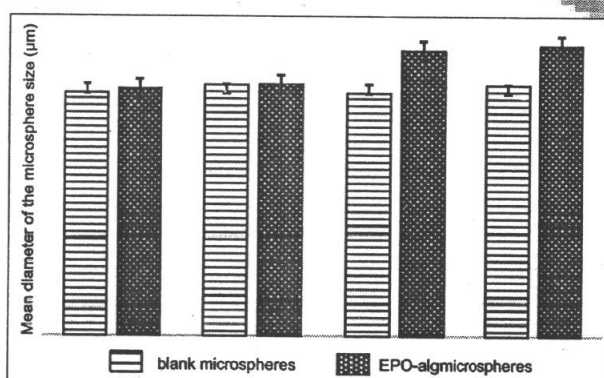


Figure 3: Histogram of blank microspheres and erythropoietin-alginate microspheres

index results are based on mass at 24 and 30 h and based on particle sizes at 24 and 30 h, respectively, on EPO-alginate microspheres as seen in Table 3.

There was no significant difference between the swelling index results based on mass and based on the particle size at the same time of observation. In addition, there was a significant difference between the swelling index results

at 24 and 30 h of observation, both based on mass and particle size. Based on the analysis with ANOVA factorial design, it was found that sodium alginate and EPO polymer content had no significant effect on swelling index based on mass or particle size both at 24 and 30 h of observation on EPO-alginate microspheres.

The swelling index data can be used to predict drug release from the microspheres accompanied with the data of the drug levels released per unit time.<sup>[22]</sup> However, due to the limited number of EPO-alginate microspheres in the absence of assay data, this study only observed swelling indices at two observation times, each of which was replicated three times. The swelling index data of EPO-alginate microspheres ranged from 1.25 to 2.13. The values of an equilibrium state swelling index resulting in the controlled release of alginate microspheres in saline phosphate buffer are in the range of 1–2.<sup>[17,20,25-26]</sup> It is desirable that EPO-alginate microspheres can expand by a swelling index of 1–2 for 48 h to obtain a controlled release of EPO from alginate microspheres [Figure 4].

For the yield examination of F1, F2, F3, and F4, the yield of 77.84 ± 0.290%, 86.65 ± 0.191%, 91.89 ± 0.210%, and 94.65 ± 0.252% were obtained. Based on ANOVA factorial design analysis, it can be seen that both the sodium alginate polymer and the EPO content significantly influence the yield of EPO-alginate microspheres F1, F2, F3, and F4 [Figure 5].

#### Design of experiment

The results of data analysis with Minitab 17.0 software (Minitab inc., PA, USA) using main effect plot to observe the effect of polymer content of sodium alginate and EPO content showed that increased sodium alginate polymer did not affect particle size, increased swelling index based on microsphere mass and particle size at 24 and 30 h,



and increased the yield of the EPO-alginate microspheres. On the other hand, an increased concentration of EPO increased the particle size, did not affect swelling index based on microsphere mass and particle size at 24 and 30 h, and increased the yield of EPO-alginate microspheres.

The results of data analysis using Pareto chart found that EPO was the most influential factor on particle size and EPO-alginate microsphere yield as shown in Figure 6. In the result of overlaid contour plot, the range of polymeric sodium alginate and EPO content was obtained, which can be used to produce optimal microsphere characteristics that include wet EPO-alginate microsphere particle sizes

of 3.15–3.85  $\mu\text{m}$ . Swelling index based on mass and size of 1–2<sup>[25,17]</sup> and the yield of EPO-alginate microsphere of 85%–100% was found in the feasible area of design space.

The optimal amount of polymer and crosslinking may affect the particle size of the microsphere.<sup>[10]</sup> In this study, the amount of sodium alginate polymer is less than that of  $\text{CaCl}_2$  crosslinker used, so no alginate polymer can be bonded by  $\text{Ca}^{2+}$  to thicken the microsphere layer. Ultimately, microsphere particle size did not increase with the addition of 2% and 3% sodium alginate polymers.<sup>[10]</sup> Meanwhile, an increase in negative partially charged EPO levels will deny alginates that are also negatively charged, resulting in chain extension and increased viscosity of the solution to form droplets of enlarging microsphere particles.<sup>[23,24,27]</sup> Increased levels of sodium alginate polymer and the active ingredient content used may result in higher microsphere yield.<sup>[10]</sup>

From the above description, it can be concluded that the sodium alginate polymer significantly affects the yield. Meanwhile, EPO significantly affected the particle size and

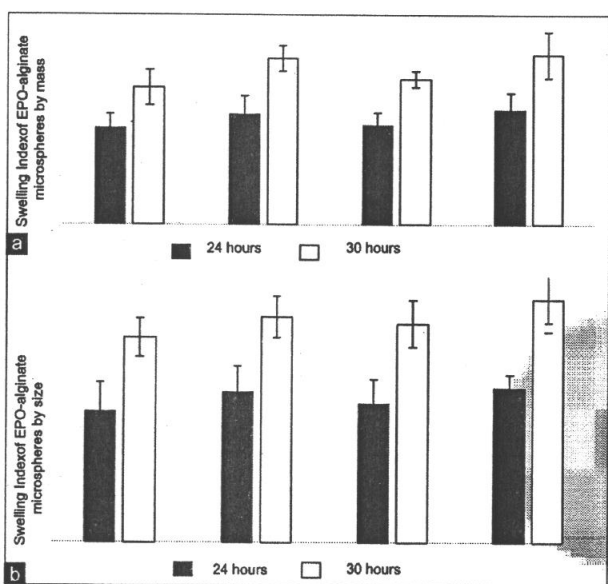


Figure 4: Swelling index of erythropoietin-alginate microspheres (a) based on mass and (b) based on size

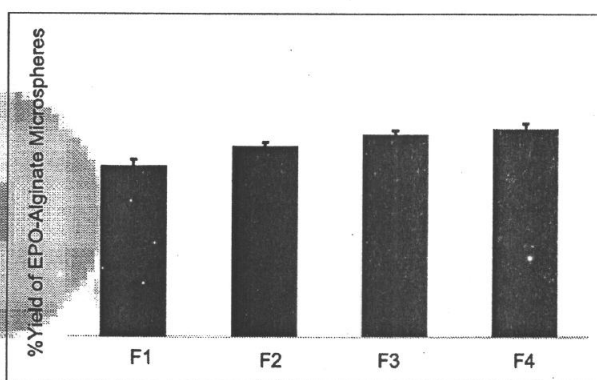


Figure 5: Microspheres yield

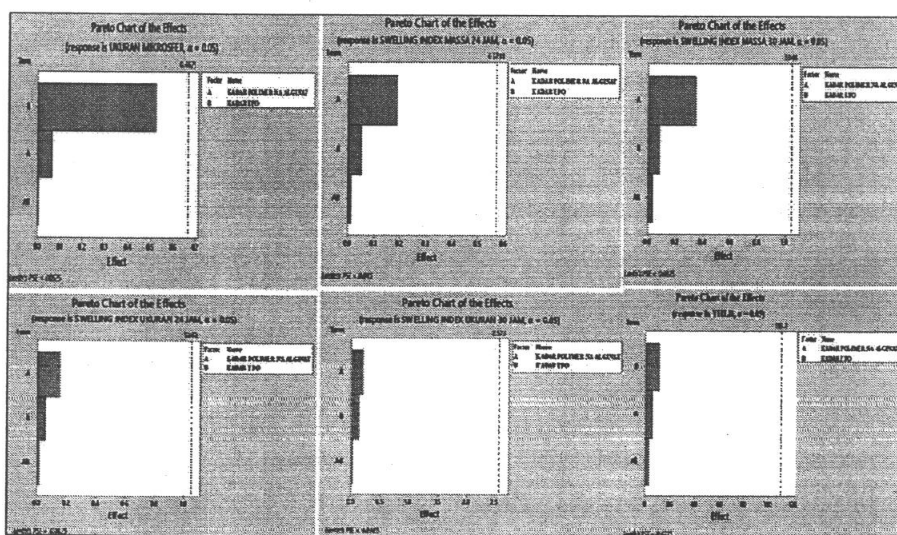


Figure 6: The Pareto chart of sodium alginate and erythropoietin polymer content to the size, swelling index of the mass and size at 24 and 30 h, and the yield of erythropoietin-alginate microspheres

yield of EPO-alginate microspheres. In addition, it is suggested that subsequent research optimizes the assaying method and the release test of EPO from alginate microspheres.

### Conclusion

EPO-alginate microspheres prepared using ionotropic gelation method with aerosolization technique using 2% and 3% sodium alginate polymer levels and EPO 5000 IU and 10,000 IU levels have spherical shapes with smooth surfaces. Increased levels of sodium alginate polymer can significantly increase yield, while elevated levels of EPO can increase particle size and yield significantly. The range of sodium alginate polymer and EPO content, which contained characteristics including particle size, swelling index based on mass and particle size, and optimum yield is found in the feasible area of design space as a result of overlaid contour plots with a sodium alginate content range of 2%–2.6% and an EPO content range of 7500–9500 IU.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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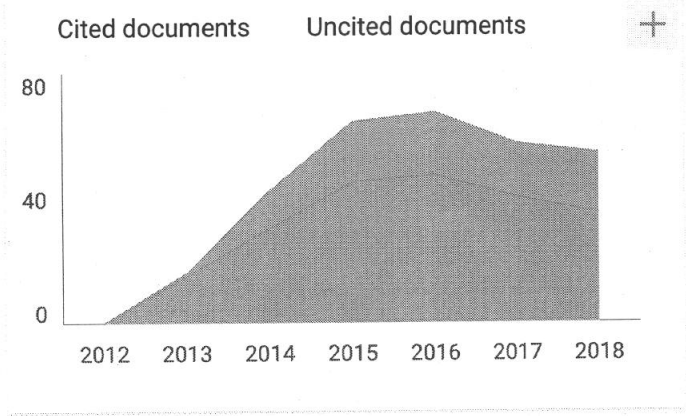
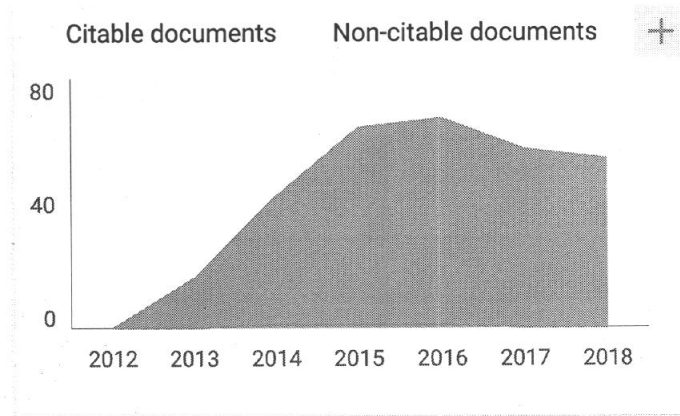
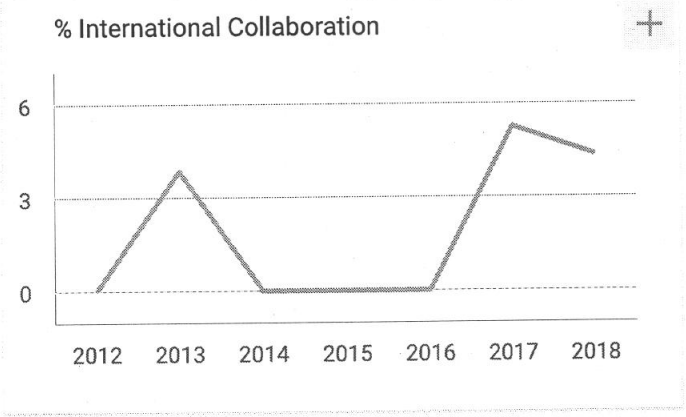
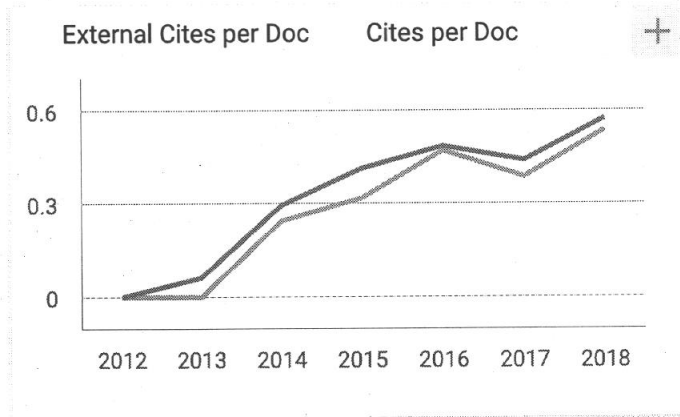
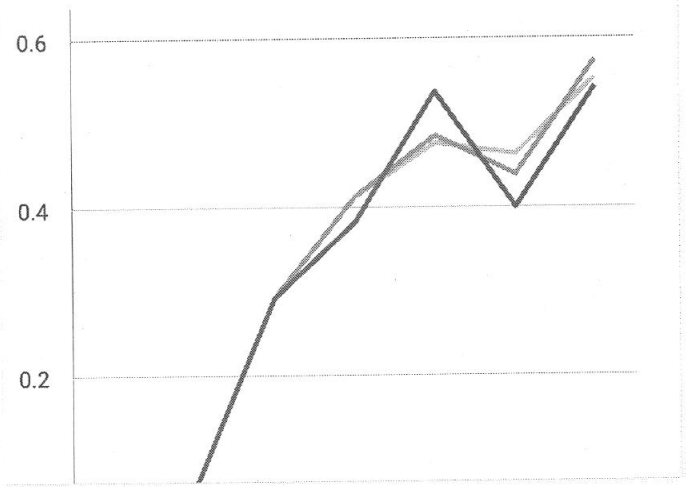
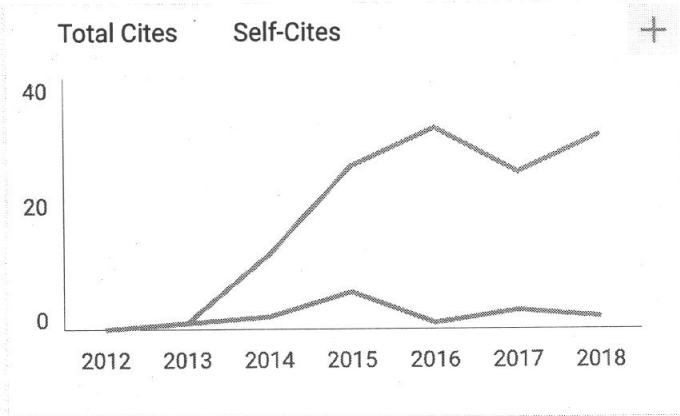
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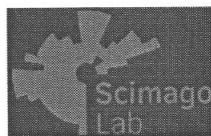
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