Temperature effects on separation of Gd$^{3+}$ from Gd-DTPA-folate using nanofiltration method

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Abstract. MRI is one of the best techniques in medical diagnostics. Contrast agents are used to improve the visual of organs that are difficult to distinguish through MRI. Gd-DTPA-folate is one of the specific contrast agents against cancer diagnosis, because it has a high affinity to folate receptors. In the complexing Gd-DTPA-folate, does not rule out the complexity step runs imperfectly, so there is still Gd$^{3+}$ in the Gd-DTPA-folate complex. The separation of Gd$^{3+}$ from the Gd-DTPA-folate complex is important to eliminate toxic effects on the contrast agent. This study aims to determine the effect of temperature on the separation of Gd-DTPA-folate from Gd$^{3+}$ with nanofiltration. The method are preparation Gd-DTPA-folate from GdCl$_3$.6H$_2$O and DTPA-folate by reflux method, then separated Gd-DTPA-folate complex from Gd$^{3+}$ with nanofiltration at variation temperature ($40, 41, 42, 43, 44^\circ C$). Then, the values of flux and rejection coefficients were analyzed. The results showed that the optimum temperature for the separation of Gd$^{3+}$ from Gd-DTPA-folate was achieved at 42.6$^\circ C$ with the rejection coefficient of 24% and the permeate flux of 403 L.m$^{-2}$.h$^{-1}$.

1. Introduction

Nowadays, rare earth elements have become a global issue. This relates to its role in various advanced technological [1,2]. One of the most popular uses of rare earths is in the medical field are Magnetic Resonance Imaging. MRI becomes one of the best techniques in medical diagnosis. On MRI diagnostic requires a contrast agent designed to increases visual contrast between normal and diseased tissues. One of the most commonly used contrast compound in MRI is gadolinium [3].

The contrast compound which has been recommended by Food and Drug Agency USA is Gd-DTPA under the trade name Magnevist®. Development of a contrast agent MRI (Targeted Contrast Agent) based on folic acid has begun. The Gd-DTPA-folate as a targeted contrast agent is expected to be used to detect the presence of ovarian cancer, breast cancer, and various epithelial cancers such as cervical, bowel and renal cancers [4]. The use of Gd-DTPA-Folate as a contrast agent must be comply the requirements, including the concentration of Gd$^{3+}$ ions and the free DTPA ligand should be small. The presence of Gd$^{3+}$ ions in the contrast agent should be as minimal as possible or within the maximum range of tolerance is 0.150 ppm because of its can toxicity to the human body [5,6]. Therefore, a special method is required that can separate Gd$^{3+}$ from the Gd-DTPA-Folate complex.

Membrane separation technique has become one of the alternative methods that produce very little waste. The principle of separation by membrane is based on differences in molecular weight size with
MWCO membrane. Nanofiltration is one type of membrane that has MWCO 300-1000 Da that allows separation at the scale of small molecules and ionic molecules [6]. The advantage of the nanofiltration method when compared to other techniques is high separation efficiency, no additional reagents, green chemistry, and easy to use [7]. Sorin et al. has conducted a study on the separation of gadolinium (III) using nanofiltration assisted by a complexity step which observes the effect of pH, pressure, flux, ionic strength, and temperature. The objective of the study is to determine the effect of temperature on the separation of Gd-DTPA-folate from Gd³⁺ by nanofiltration method.

2. Methods
The materials use were Akua milliq-Q (Central Laboratory, Padjadjaran University), glacial acetic acid (pa), gadolinium chloride hexahydrate (pa, Sigma Aldrich), diethylentriaminepentaacetate-folate (pa, Sigma Aldrich), Dow FilmTec TW30-1812-50 nanofiltration membrane made Of polyamide material with a pore size of 0.1 nm and a surface area of 150 cm², sodium hydroxide (sigma aldrich), sodium hydroxide (pa), and orange xylenol.

Synthesis of Gd-DTPA-Folate. DTPA-Folate solids weighed as much as 10.7514 g then dissolved with akua milliq-Q up to 250 mL. GdCl₃.6H₂O solid weighed 4.6079 g then dissolved with akua milliq-Q until 250 mL, the solution mixture was refluxed for 1 hour at temperature constant. After that, the reflux solution cooled and then measured pH. Furthermore, added sodium hydroxide 3 M to pH 7. Then the pure solution is dried using a freeze dryer. The obtained solids were weighed 0.3 g, dissolved in 100 mL of akua milli-Q [1,2].

Separation of Gd-DTPA-Folate Complex with Nanofiltration, Laboratory-scale nanofiltration membrane system was prepared. 100 mL of the Gd-DTPA-folate complex solution was placed into a feed container containing 2,000 mL of a akua milli-Q. A certain amount of akua milli-Q was passed through the membrane for 60 minutes until the membrane reached a stable state. The Gd-DTPA-folate solution as the feed solution was passed through the membrane under 6 bar of pressure and the temperature variation (40, 41, 42, 43, 44 °C) with a cross-flow system. The permeate and retentate collected every 15 mins, then calculated permeate flux for each temperature variation [1,2].

The permeate flux was calculated by measuring the permeate volume (V) across the membrane per membrane surface area (A) and times (t) for each of the temperature conditions according to the equation [6]:

\[ J = \frac{V}{A \times t} \]  

Rejection coefficient was measured by utilizing a visible light spectrophotometer to calculate the feed concentration (Cᶠ) and permeate concentration (Cₚ) [6]:

\[ R = \left( 1 - \frac{C_p}{C_f} \right) \times 100\% \]  

3. Results and Discussion
Table 1 shows that the increasing of temperature can lead to a decreasing concentration of Gd³⁺ in the Gd-DTPA-folate complex after separating process with the nanofiltration membrane. This is because the larger pore membranes that cause Gd³⁺ will easily pass through the membrane and out as permeate. The concentration of Gd³⁺ on permeate is greater than that of retentate. It means, Gd³⁺ comes out more through the membrane so that it can be separated with the complex.
Table 1. Comparison of Gd$^{3+}$ concentrations in feed, permeate, and retentate solutions at variation of temperature separation

| Temperature (°C) | Feed (ppm) | Permeate (ppm) | Retentate (ppm) |
|------------------|-------------|----------------|-----------------|
| 40               |             | 0.199          | 0.163           |
| 41               |             | 0.219          | 0.158           |
| 42               | 0.333       | 0.240          | 0.151           |
| 43               |             | 0.259          | 0.142           |
| 44               |             | 0.281          | 0.132           |

The separation with nanofiltration is based on differences in molecular size. A smaller molecular sizes than the membrane pore in this case is Gd$^{3+}$ (157,25 Da) will be easy to pass through the membrane pores, whereas the particles that have larger molecular sizes than the membrane pores are Gd-DTPA-folate (1011 Da ) will be rejected on the surface of the membrane. Thus, this causes fouling of Gd-DTPA-folate complex particles on the membrane surface which keeps the membrane pores covered by large complex molecules and causes Gd$^{3+}$ to be rejected on the membrane surface, so Gd$^{3+}$ cannot entirely pass through the membrane pores [1,2].

Effect of Temperature on Permeate Flux and Gd$^{3+}$ Rejection Coefficient. The optimal conditions of membrane performance are expressed by the magnitude of the permeate flux and the rejection of the metal ions in the feed solution. One that can affect the value of flux and rejection is the temperature parameter.

Figure 1 shows the effect of temperature variation on flux permeate, with flux value at variation 40; 41; 42; 43; 44 °C are 390.625 L.m$^{-2}$.h$^{-1}$, 393.082 L.m$^{-2}$.h$^{-1}$; 397.772 L.m$^{-2}$.h$^{-1}$; 403.551 L.m$^{-2}$.h$^{-1}$; 410.509 L.m$^{-2}$.h$^{-1}$. Based on the results experiment, the value of permeate flux increases with increasing temperature. The higher temperature causes the permeate flux is higher too. Increasing temperature causes decreasing viscosity of the solution, this is because the distance between the particles in the solution is getting away so that the friction force gets smaller. If the viscosity Gd$^{3+}$ solution getting smaller, particles will more easily pass through the membrane pores so that the solution will be faster to flow out of the membrane as permeate. In accordance with the formula for determining the permeate flux of Eq.(1), that the permeate flow rate velocity (t) is inversely proportional to its flux value (J). If the permeate solution flows faster then it will take less time for the permeate solution out of the membrane, thus causing the flux value to be greater.

![Figure 1. Effect of temperature on Gd$^{3+}$ rejection coefficient and permeate flux](image-url)
Contrast to the permeate flux, the increasing temperature causes decreasing the Gd\(^{3+}\) rejection coefficient. The amount of rejection coefficient generated at temperature 40; 41; 42; 43; 44 °C respectively of 40.24; 34.23; 27.93; 22.22; 15.62%. The higher of feed temperature causes the greater concentration of Gd\(^{3+}\) on the permeate due to the larger pore size, making it easier for Gd\(^{3+}\) in the feed solution to pass through the membrane pore and came out as permeate. Based on Equation (2), that permeate concentration value (C\(_p\)) affects the rejection coefficient (\%R). Where the rejection coefficient is inversely proportional to permeate concentration, it means that the higher permeate concentration (C\(_p\)) will cause the rejection coefficient (\%R) to become smaller. Based on that, hence in this research got coefficient value of rejection which getting smaller with increasing of temperature variation.

Based on Figure 1, it is known that the optimum temperature at the Gd-DTPA-folate separation from Gd\(^{3+}\) is achieved at a temperature of 42.6 °C. This can be seen from the graph curve showing the existence of the intersection of rejection coefficient value with permeate flux. At the optimum temperature, the rejection coefficient value is 24% and the permeate flux value is 403 L.m\(^{-2}\)h\(^{-1}\). Rejection coefficient value, 24% is still low compare with the literature about 50-90% [1,2].

4. Conclusion

Temperature affects the separation of Gd\(^{3+}\) from Gd-DTPA-folate, where the higher operating temperature causes the permeate flux value to increase, and the Gd\(^{3+}\) rejection coefficient will decrease. The optimum conditions of the separation of the Gd-DTPA-folate complex occurred at a temperature of 42.6 °C with a rejection coefficient of 24% and a permeate flux value of 403 L.m\(^{-2}\)h\(^{-1}\).

5. References

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