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Kuo-Jen Hwang[a]; Yu-Chin Chang[a]
[a] Department of Chemical and Materials Engineering, Tamkang University, Tamsui Taipei Hsien, Taiwan

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The Use of Cross-Flow Microfiltration in Purification of Liposomes

Kuo-Jen Hwang* and Yu-Chin Chang

Department of Chemical and Materials Engineering, Tamkang University, Tamsui, Taipei Hsien, Taiwan

ABSTRACT

The use of cross-flow microfiltration for purification of liposome vesicles is studied. The liposomes are concentrated while the phospholipid monomers are rejected or permeated through the filter membrane during filtration. Effects of operating conditions, such as cross-flow velocity and filtration pressure, on the filtration rate, the cake properties, the rejection coefficient of phospholipid, and the separation efficiency are discussed. The experimental results show that the filter cake formed by liposome vesicles exhibits a very high compressibility and specific filtration resistance. Cake resistance plays a major role on the overall filtration resistance. The filtration rate attenuates quickly at the beginning of filtration, due to the deposition and the compression of liposome vesicles. After a period of time, the filtration rate gradually approaches a pseudo-steady

*Correspondence: Kuo-Jen Hwang, Department of Chemical and Materials Engineering, Tamkang University, Tamsui, Taipei Hsien 25137, Taiwan; Fax: +886-2-26209887; E-mail: kjhwang@mail.tku.edu.tw.

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value. An increase in applied filtration pressure causes an increase in the filtration rate at the pseudo-steady state, the membrane and the cake resistances, and the separation efficiency. On the other hand, the filtration rate at a pseudo-steady state increases, whereas the cake resistance decreases with the increase in cross-flow velocity. However, the effects of operating conditions on internal membrane fouling are negligible. A theory based on the basic filtration equation and the force balance model of particle deposition is proposed for estimating the filtration rate at a pseudo-steady state. The experimental data agree very well with the model calculations. A lower cross-flow velocity or filtration pressure gives the phospholipid monomers more opportunities to penetrate the cake and the membrane into filtrate. Therefore, the rejection coefficient increases with the increase in filtration pressure or cross-flow velocity. Compared with the conventional "dead-end" cake filtration, the use of cross-flow microfiltration in the purification of liposomes is an efficient method.

Key Words: Cross-flow microfiltration; Liposome; Purification; Microfiltration.

INTRODUCTION

Liposomes play an increasingly important role in the applications of medicine, gene therapy, and vaccines over the past 10 years. Various kinds of functional liposomes were prepared using different methods, such as the conventional film method,[1] reverse-phase evaporation method, dry-reconstitution method, and freeze-and-thaw method. In the past, many researchers in this field paid attention to the preparation methods of functional liposomes; however, many problems occurred in the manufacturing processes. One of these problems was the purification of liposomes from the preparation solution. The phospholipid monomers and other impurities should be removed in purification operations for reuse. In general, the columns packed with various kinds of molecular sieves were most commonly used. Although this method has a relatively high separation efficiency, it is very expensive and rather timeconsuming in the manufacture of liposomes.

Cross-flow microfiltration keeps the suspension flow parallel to the filter membrane in order to limit the growth of filter cake. Comparing this mode of filtration with the conventional "dead-end" cake filtration, cross-flow microfiltration has many advantages, such as thinner cake, lower filtration resistance, higher filtration rate, and longer operation time. Therefore, cross-flow microfiltration has been widely used in many industrial processes for separation of fine particles, microbes and colloids from liquids.

Liposome vesicles are deformable. They have a highly compressible property when they are filtered and formed a filter cake under pressure. As a result, a compact cake layer with very high filtration resistance is often constructed next to the membrane surface.[2–4] Since this layer plays a major role in the overall filtration resistance, how to reduce the resistance of this layer or to increase the filtration rate becomes the most important problem in research on these types of filtration.

In this article, cross-flow microfiltration is used to purify liposome vesicles. The effects of filtration pressure and cross-flow velocity on the filtration rate, the filtration resistance, the cake properties, the rejection coefficient of phospholipid, and the separation efficiency are discussed.

THEORY

Basic Filtration Theory

Particles are carried by liquid and deposited onto the filter membrane to form a filter cake during filtration. The basic filtration equation can be expressed as:

$$q = \frac{\Delta P}{\mu(R_t)} = \frac{\Delta P}{\mu(R_c + R_{if} + R_m)} \tag{1}$$

where q = the filtration rate; ΔP = the filtration pressure; μ = the viscosity of fluid; and R_t, R_c, R_{if}, and R_m = the overall filtration resistance, the filtration resistances due to cake formation, and due to the internal fouling in the membrane pores, and the clean membrane resistance, respectively.

In general, cake resistance plays a major role on the filtration rate when the particle size is larger than the membrane pore size. This resistance can be given by

$$R_c = \alpha_{av} w_c \tag{2}$$

where α_{av} and w_c = the average specific filtration resistance and the mass of cake, respectively. The cake mass can be estimated based on the material balance, that is,

$$w_c = \rho_s(1 - \varepsilon)L_c \tag{3}$$

where ρ_s = the particle density and ε = the average cake porosity. Furthermore, the relationships between α_{av} and the filtration pressure can be expressed as the following empirical equation:[5]

$$\alpha_{av} = A\Delta P^n \tag{4}$$

where A and n = empirical coefficients.

Force Balance Model for Particle Deposition

When particles are arriving at the membrane surface, whether they can deposit stably or not is determined from the external forces exerted on them.[6–9] These external forces include the drag forces, the inertial lift force, the gravity force, and the interparticle forces. Since the gravity and the inertial lift forces are three to five orders of magnitude smaller than the drag forces or the net interparticle force for such fine particles in most operating conditions, it is reasonable to neglect these forces in the force analysis. Therefore, the force balance model at the critical condition can be expressed as:[7,9]

$$F_{dx} = f_c(F_{dy} + F_i) \tag{5}$$

where f_c = the friction coefficient, F_i = the interparticle force, and F_{dx} and F_{dy} = the drag forces in the directions of cross-flow and filtration, respectively.

On the basis of the force analysis on the depositing particles in a two-parallel-plate cross-flow microfiltration,[9] Eq. (5) can be simplified to:

$$q_s = C_1\gamma_w + C_2 \tag{6}$$

for a uniform particle size distribution. Once the empirical coefficients, C_1 and C_2, are determined from experimental data, a linear relationship between filtration rate and wall shear rate can be obtained from Eq. (6). Since the cross-sectional area for suspension flow will be reduced due to the cake formation, the shear rate at the membrane surface for laminar flow can be estimated by[9]

$$\gamma_w = 6u_s\frac{H}{(H - L_c)^2} \tag{7}$$

in which u_s = the original cross-flow velocity and H = the clearance between two plates of the filter. A relationship between filtration rate and cake thickness can then be obtained by substituting Eq. (7) into Eq. (6), that is,

$$q_s = C_3\frac{u_sH}{(H - L_c)^2} + C_2 \tag{8}$$

where $C_3 = 6C_1$. The coefficients in the above equation can be obtained from the line in the plot of q_s vs. $u_sH/(H - L_c)^2$ at the pseudo-steady states.

Prediction of Filtration Rate at Pseudo-steady State

Once the values of R_{if}, R_m, and the empirical coefficients in Eq. (4) are measured or determined from experimental data, Eq. (1) can be employed to relate the filtration rate and the cake thickness under a given filtration

pressure. Therefore, the filtration rate and the cake thickness at a pseudo-steady state can be estimated by solving Eqs. (1) and (8) simultaneously under a given cross-flow velocity and filtration pressure.

EXPERIMENTAL METHODS AND MATERIALS

Preparation of Liposomes

Multilamellar liposomes were prepared using the conventional film method.[1] Lecithin and cholesterol manufactured by ACROS Corp. (Piscataway, NJ, USA) were used as the lipid mixtures and were dissolved in a solvent of 2 : 1 (V/V) chloroform and methanol mixture. The solution was mixed well for about 10 min and then dried in a vacuum rotary evaporator until a dried lipid film was coated on the round-bottom flask wall. The lipid mixture was hydrated and dispersed with deionized water to prepare a 0.1%wt. milklike liposome suspension. The suspension was agitated using an ultrasonic vibrator during the above procedures. The prepared suspension was then used in experiments after 24 h. The true density (excluding water content) of the liposome vesicles was measured as 992 kg/m^3. A transmission electronic microscope (TEM) photo of liposome vesicles is shown in Fig. 1(a), and the vesicle shape was close to a sphere. The size distribution of the vesicles was measured on a volume basis using a laser scattering particle sizer (HORIBA LA-910, Kyoto, Japan) and is shown in Fig. 1(b). The vesicle diameters ranged from 0.1 to 2.0 μm with an average value of 0.4 μm. The pH value of the suspension was 7.5, and the suspension temperature was kept at 25°C using a thermostat.

Cross-Flow Microfiltration

Cross-flow microfiltration was carried out using a two-parallel-plate type cross-flow microfilter. A schematic diagram of the filtration system is shown in Fig. 2. The filtration channel was 4.5×10^{-4} m in height, 0.1 m in length, and 5.0×10^{-3} m in width; thus, a filtration area of 5.0×10^{-4} m^2 was used in experiments. The isopore membrane consisting of polycarbonate (manufactured by Millipore Corp., Bedford, MA, USA) with a uniform pore diameter of 0.1 μm was used in experiments.

The prepared liposome suspension was mixed well in the suspension tank and then pumped into the cross-flow microfilter using a circulation pump. The cross-flow velocity was controlled and measured using a rotameter, and the filtration pressure was adjusted using a needle valve. The concentrate was recycled back into the suspension tank, while the filtrate was collected

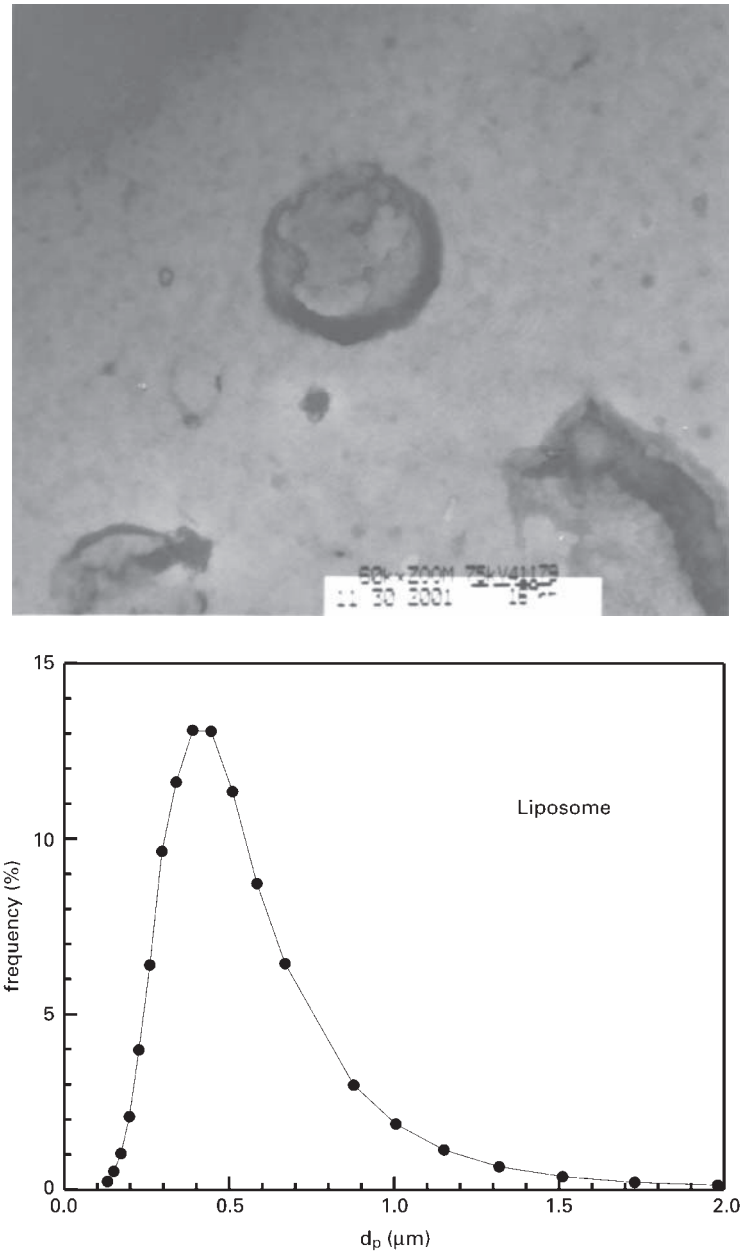

Figure 1. (a) TEM photo of liposomes (×60,000). (b) Size distribution of liposomes (on the volume basis).

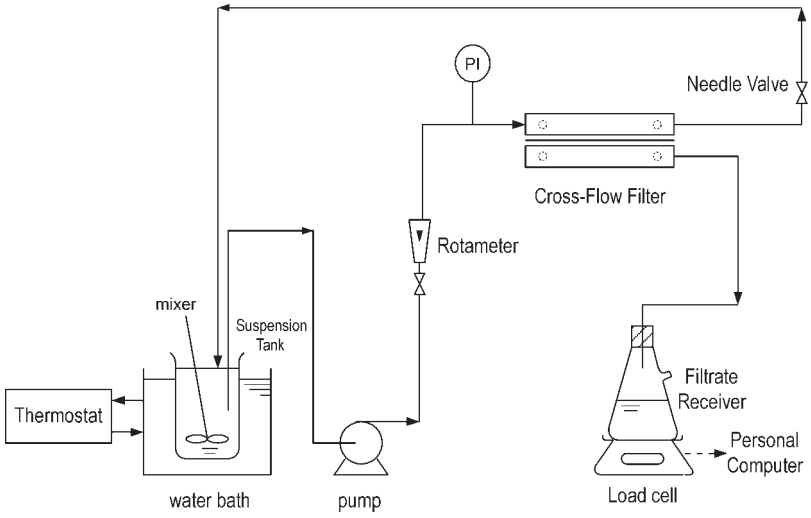

Figure 2. A schematic diagram of cross-flow microfiltration system.

in a filtrate receiver. The filtrate was weighed using a load cell placed under the receiver, and the filtration data of filtrate weight vs. time were recorded on a personal computer. As soon as the experiments were terminated, the filter cakes were carefully picked up and sent out for analysis of their mass and the water inside and outside liposomes using a thermal gravimetric analyzer (TGA). The details of the TGA analysis method have been described in previous studies.[10,11] The cross-flow velocities used in experiments ranged from 0.15 to 0.45 m/sec, and as a result, the wall shear rates ranged from 0.23 to 0.66 sec^{-1}. Under such conditions, the Reynolds number ranged from 100 to 400, which indicated the suspension under a laminar flow.

Measurement of Phospholipid Concentration

The phospholipid concentration in a suspension was measured using an UV/Visible spectrophotometer at the wavelength of 970 nm. The GSTrap FF column manufactured by Amersham Pharmacia Biotech. Corp. (Uppsala, Sweden) was used to separate the liposome vesicles from unencapsulated material in a suspension. Because the phospholipids could be entrapped completely by the molecular sieves packed in the column, their fraction in a suspension could be known by measuring the phospholipid concentrations before and after the suspension flowed through the column.

RESULTS AND DISCUSSION

Figure 3 shows the time courses of filtration rates, q, before 30 min under various filtration pressures, ΔP, at the same cross-flow velocity, $u_s = 0.15$ m/sec. The filtration rates attenuate very quickly at the beginning of filtration, due to the deposition and the compression of liposomes. Liposome vesicles are carried by liquid toward the filter membrane, and some of them may deposit on the membrane surface. The deposited liposomes result in a very high filtration resistance, since the liposome vesicles exhibit a serious shape deformation, even under low filtration pressure. The cake properties will be discussed in detail later. When the filtration time exceeds 500 sec, the filtration rate under each condition gradually approaches a pseudo-steady value, because the cake growth is limited by the cross-flow of suspension. Under such a condition, all major external forces exerted on a depositing liposome vesicle have the same order of magnitude,[4,9] the vesicle is very difficult to deposit stably on the cake surface, and the filtration rate then remains almost constant. Although an increase in filtration pressure leads to a higher driving force of filtration, it also leads to a thicker cake with a

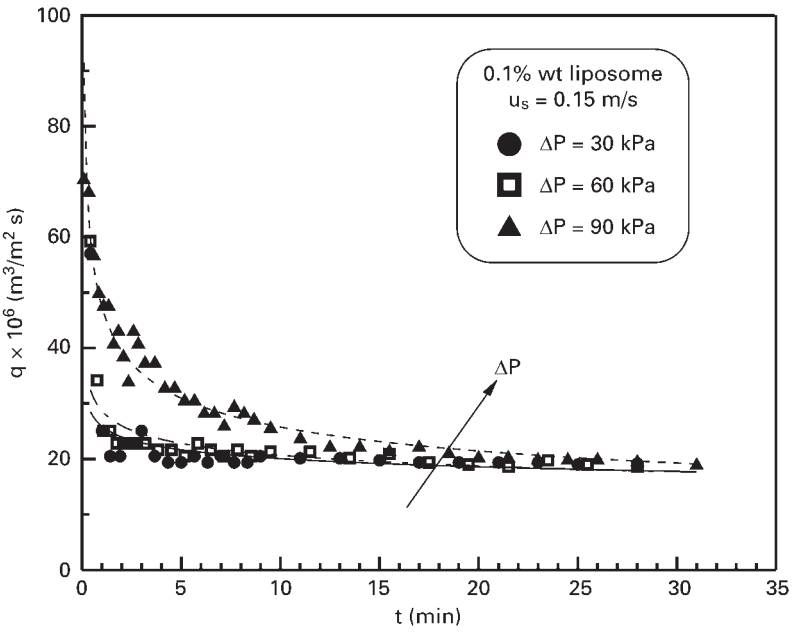

Figure 3. Time courses of filtration rates during cross-flow microfiltration under various filtration pressures.

more compact structure, and thus, a higher filtration resistance. This is the reason filtration pressure has less effect on the filtration rate.

In order to know the magnitudes of filtration resistances from various sources in the cross-flow microfiltration of liposomes, these resistances at pseudo-steady states are analyzed and compared in Figs. 4 and 5. In these figures, R_c, R_i, and R_m are the resistances of the filter cake, the internal fouling in membrane pores, and the clean membrane, respectively. The values of R_m are measured by flowing clean deionized water through the membrane. The overall filtration resistances, R_t, under various conditions can be calculated using the basic filtration equation, Eq. (1). As soon as the experiments are terminated, the suspensions are suddenly changed to clean, deionized water. Once the filter cakes are swept away from the membrane surfaces by the cross-flow, the sums of R_i and R_m can be measured under such conditions. Therefore, the values of R_i can be calculated from the known values of R_m, while R_c can be obtained by subtracting the sums of R_i and R_m from the overall resistances. Figures 4 and 5 show the effects of filtration pressure and cross-flow velocity, respectively, on the filtration resistances at pseudo-steady states. It can be found that the filtration resistance of the filter cake plays the major role on the overall filtration resistance in all conditions. The

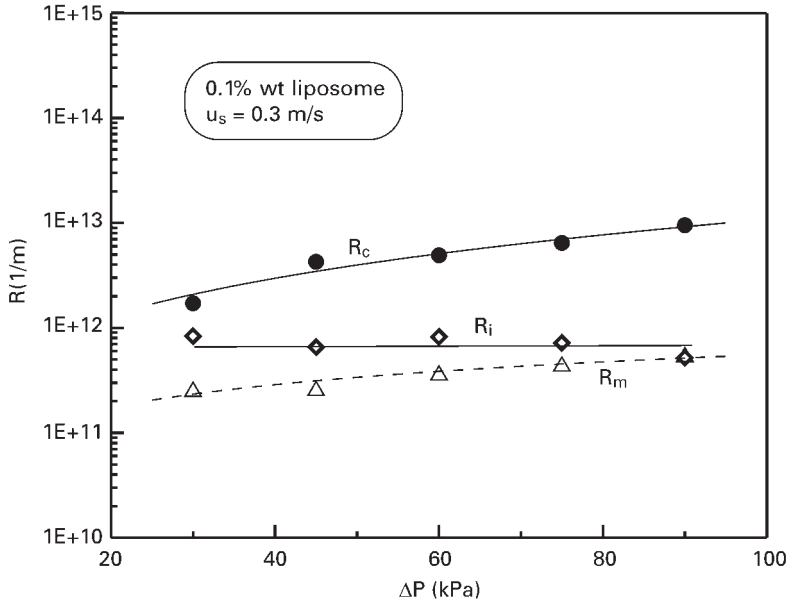

Figure 4. Effect of filtration pressure on various sources of filtration resistances.

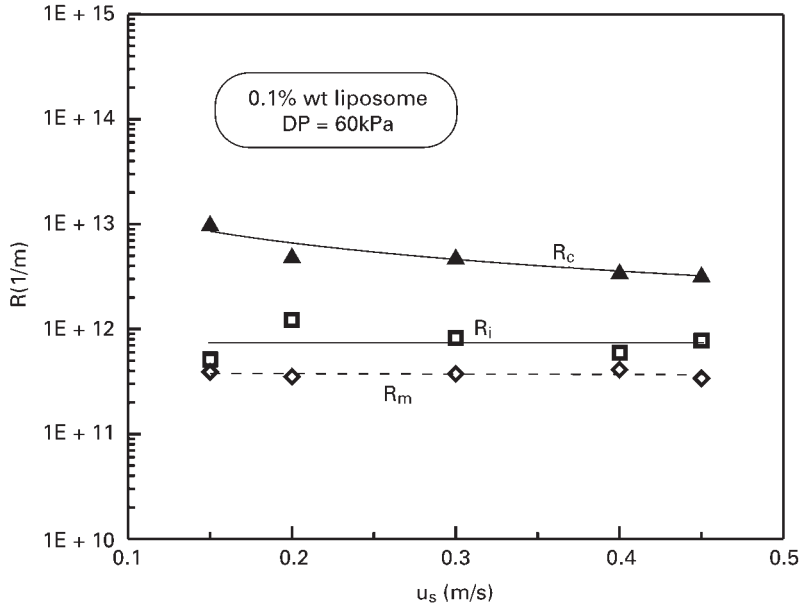

Figure 5. Effect of cross-flow velocity on various sources of filtration resistances.

values of R_c are 10–30 times greater than those of R_m, while the values of R_i are twice the value of R_m within the operating conditions of this study. The values of R_c increase with increase in filtration pressure but with decrease in cross-flow velocity. These are because the cake masses increase with the increase in filtration pressure but with the decrease in cross-flow velocity.[4,7,8] Furthermore, the filter cake may also be compressed to a more compact structure under a higher filtration pressure. The constant R_i implies that the internal fouling or blocking of phospholipid in the membrane does not vary obviously within the operating conditions. Furthermore, the clean membrane resistance increases with the increase in filtration pressure, but has no significant effect on the overall filtration resistance. Based on the above analysis, understanding the cake properties under various conditions becomes the essential step for grasping the cake filtration resistance as well as the filtration rate.

In order to understand the effects of operating conditions on the cake properties, the mass and porosity of cakes and the water content inside the liposome vesicles under various filtration pressures are measured using a TGA. Some of the results of these properties at filtration times of 3 min (180 sec) and 167 min (10,000 sec) are listed in Table 1. The cake porosity is defined as the volume fraction of the void among the liposome vesicles

Table 1. The cake mass, cake porosity, and water content inside the liposomes in the filter cakes formed under $u_s = 0.3\,m/sec$.

		Filtration pressure (kPa)				
		30	45	60	75	90
Cake mass ($\times 10^{-3}\,kg/m^2$)	$t = 180$ sec	3.22	2.74	5.71	4.91	3.37
	$t = 10{,}000$ sec	5.40	6.05	9.92	13.42	7.65
Water content inside liposome vesicles (vol.%)	$t = 180$ sec	58.1	57.5	53.5	50.0	47.8
	$t = 10{,}000$ sec	54.5	51.3	46.7	44.3	44.7
Cake porosity (—)	$t = 180$ sec	0.189	0.184	0.167	0.143	0.143
	$t = 10{,}000$ sec	0.143	0.143	0.143	0.141	0.141

in a cake, which reflects the space ratio to supply for fluid flow. It can be found from Table 1 that an increase in filtration pressure decreases the cake porosity; in other words, a more compact cake will be formed under a higher filtration pressure. The shape deformation of liposome vesicles can be expected because the cake porosities shown in this table are far lower than those of random packing of spherical particles ($\varepsilon = 0.4–0.6$). It can be noticed that the cake properties are more or less different between $t = 3$ and 167 min. This is because the equilibrium state of the cake properties cannot be attained instantaneously when deformable particles are filtered.[11] The data also show that the cake is compressed to a compact structure at the beginning period of filtration. This is the reason the filtration rate decays very quickly at the time (Fig. 3). On the basis of the results of previous research,[4,9] the mass and growth rate of a filter cake are dependent strongly on the velocity ratio of filtrate to cross-flow of suspension and the specific filtration resistance of cake. An increase in filtration pressure results in a higher filtration rate, but also in a more compact cake. This indicates that the specific filtration resistance of cake also increases with increase in filtration pressure. These tendencies are the same as those in previous studies.[3,4,7,8] According to the basic filtration theory, Eq. (1), these opposite effects lead to variation of cake mass due to a small change of filtration pressure, which is probably an irregular trend. The other data listed in this table describe the water content in the liposome vesicles. Although a little water in the liposomes may be squeezed out during cake compression, about 45–60% of cake volume is still occupied by this kind of water. Since the water content of the liposome vesicles remains almost constant during filtration, it can be considered to be a portion of liposomes themselves. The water content in the liposome vesicles decreases, as expected, with increase in filtration pressure.

The average specific filtration resistance of cake, α_{av}, can be calculated by Eq. (2) once the cake resistance and the cake mass are measured. The average specific filtration resistances of cakes under various pressures are shown in Fig. 6. Compared with the data of Hwang and Lin,[9] the values of liposomes α_{av} are two orders of magnitude higher than those of rigid submicron particles of the same size; therefore, one can understand how difficult it is to filter liposomes. A power-type empirical equation, Eq. (4), can be obtained by regressing the experimental data in Fig. 6, and the power raised on the pressure term is 0.714, which indicates a high cake compressibility.[2]

Figure 7 shows a plot of q_s vs. $u_s H/(H - L_c)^2$ at the pseudo-steady states under various operating conditions. The regressed straight line demonstrates that Eq. (8) can be employed for estimating cake formation in cross-flow microfiltration. Once the coefficients in Eq. (8) are evaluated from the slope and intercept of the line, this equation can be used to relate the filtration rate and the cake thickness at pseudo-steady states.

According to the proposed theory, the filtration rate and cake thickness at the pseudo-steady state can be estimated by solving Eqs. (1) and (8) simultaneously under a given cross-flow velocity and filtration pressure. Figure 8 shows a comparison of filtration rates at pseudo-steady states between the experimental data and the model calculations under various operating conditions. This figure

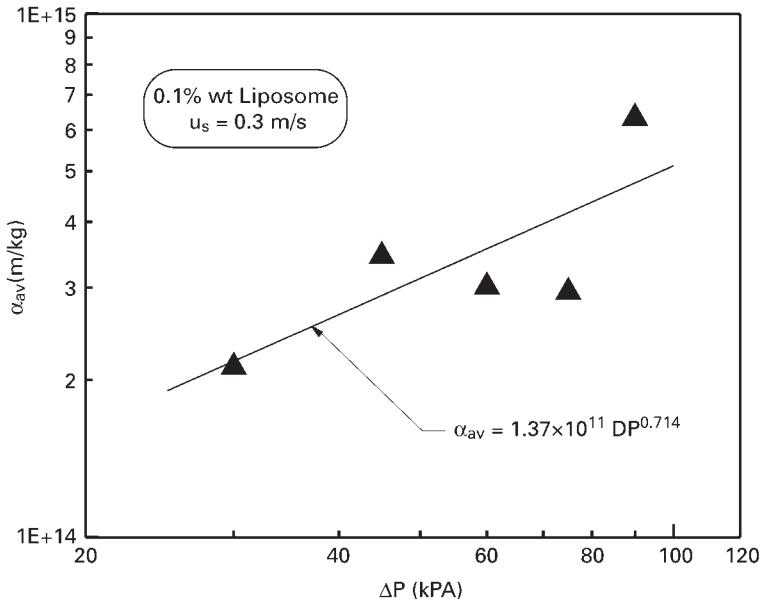

Figure 6. Plot of α_{av} vs. ΔP.

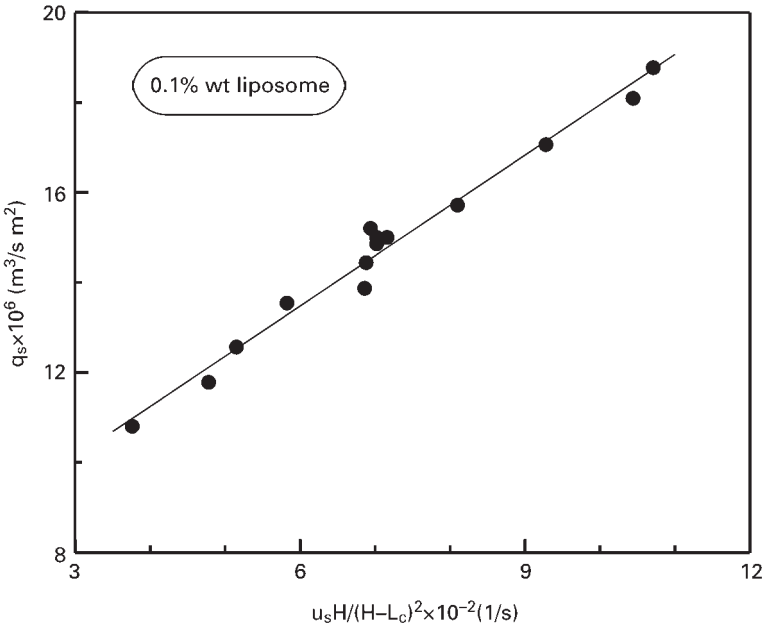

Figure 7. Plot of q_s vs. $u_s H/(H - L_c)^2$.

depicts that the filtration rate increases with both increase in cross-flow velocity and filtration pressure, but the effect of cross-flow velocity is more dominant. The filtration rate increases over two times when cross-flow velocity increases from 0.15 to 0.45 m/sec. This trend can be expected because of a thinner cake formed under a higher cross-flow velocity.[4,7,8] As a result, a higher filtration rate is then given, due to the lower filtration resistance. On the other hand, only a slight increase can be observed as the filtration pressure increases for about three times. This is due to the formation of a compact, thicker cake under a higher filtration pressure, which has been discussed previously. The good agreement between the experimental data and the model calculations demonstrates the reliability of the proposed model of this study. The filtration rates at pseudo-steady states can be predicted accurately under various operating conditions.

Some unencapsulated phospholipid monomers in suspension may be penetrated through the formed cake and the membrane into filtrate, while the others are rejected by the filter cake and re-entrained back into the bulk flow. The rejection coefficient is defined as

$$R_{\text{rej}} \equiv 1 - \frac{C_p}{C_b} \tag{9}$$

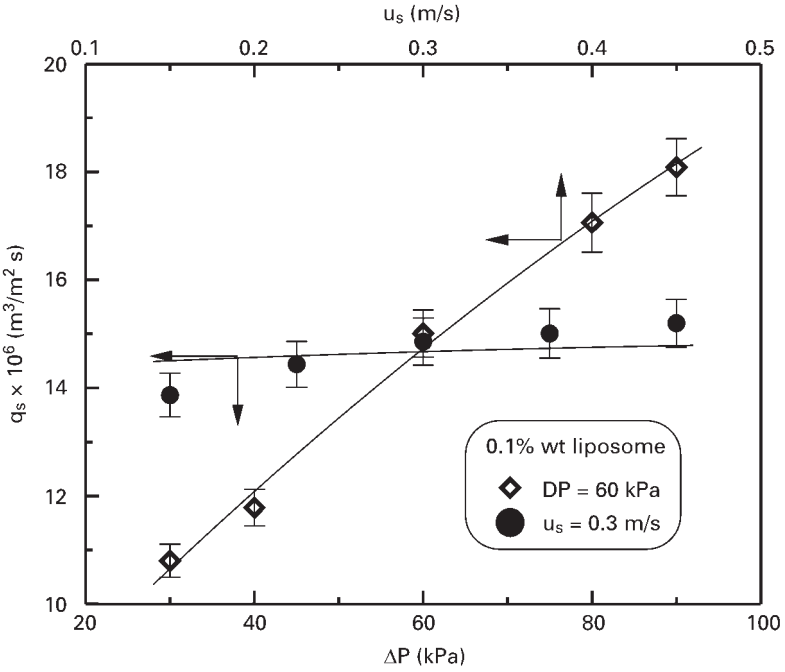

Figure 8. Effects of cross-flow velocity and filtration pressure on the filtration rates at pseudo-steady states.

where C_p and C_b = the concentrations of phospholipid in filtrate and in bulk suspension, respectively. Figure 9 shows the rejection coefficients of phospholipid monomers under various pressures for two different cross-flow velocities. It can be seen that the rejection coefficient increases with the increase in filtration pressure. This is because a thicker cake formed under a higher filtration pressure will reject more phospholipids.[12] Moreover, since more phospholipids will be swept away from the cake surface due to a higher wall shear stress, a higher rejection coefficient is obtained under a higher cross-flow velocity.

In order to discuss the effect of cross-flow velocity on the rejection coefficient in more detail, a set of typical results of rejection coefficients are measured and shown in Fig. 10. It can be noticed that no evident effect of cross-flow velocity on the rejection coefficient can be observed when the velocity is less than 0.2 m/sec. Under such a low velocity, the shear stress acting on the cake surface is not large enough to sweep the phospholipids away; all phospholipids arriving at the cake surface will be transported into the filtrate.

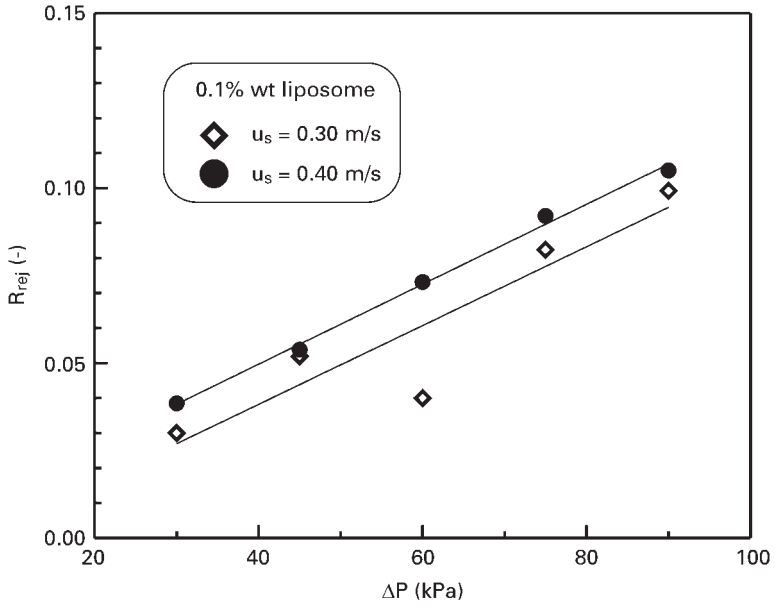

Figure 9. Effect of filtration pressure on the rejection coefficient of phospholipids.

As a result, the rejection coefficient is equal to zero. However, the effect of cross-flow velocity becomes dominant as its value is larger than 0.3 m/sec, and a sudden jump of rejection coefficient can be found when the velocity exceeds 0.4 m/sec. This implies that the phospholipids cannot be separated completely from liposome suspensions as the cross-flow velocity is greater than that value.

The symbol E is used to define the separation efficiency of liposomes, which indicates the fraction of liposomes in total mass of solids (solutes) in the concentrate. Therefore, the value of E depends on both the filtration rate and the rejection of phospholipids. Figure 11 depicts the values of E measured 30 min after the beginning of filtration under various conditions. The mass fraction of the liposomes in all solids in the original suspension is measured as 0.73. The value of E increases during microfiltration since some phospholipid monomers are transmitted into the filtrate. This figure shows that the value of E increases with increase in filtration pressure. This is because a higher filtration pressure results in a higher filtration rate, which leads to more phospholipids flowing into filtrate, regardless of the occurrence of a higher rejection coefficient. On the other hand, a minimum value of E occurs as the cross-flow velocity increases from 0.15 to 0.45 m/sec under

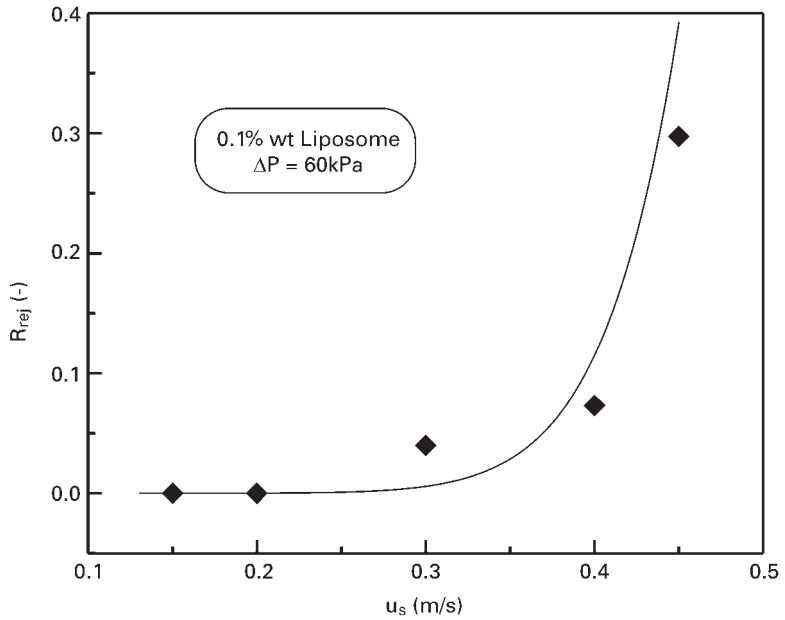

Figure 10. Effect of cross-flow velocity on the rejection coefficient of phospholipids.

$\Delta P = 60$ kPa. In general, the higher filtration rate, which is always obtained under a higher cross-flow velocity, causes more monomers to penetrate through the cake and the membrane. However, the low rejection coefficient occurring at low cross-flow velocity might improve the separation efficiency, due to the high concentration of phospholipids in the filtrate. These contradictory effects cause the occurrence of the minimum E value. In short, in order to obtain higher separation efficiency and higher filtration rate, the optimum conditions are higher filtration pressure and higher cross-flow velocity, according to the above results. But some liposomes may have more opportunities to be decomposed under high shear stresses; this effect should be taken into consideration in the purification processes. The strength of the liposome vesicles in cross-flow microfiltration would be a worthwhile subject in future research.

The received filtrate volumes in cross-flow microfiltration and the conventional dead-end cake filtration under various filtration pressures at $t = 60$ and 180 min are summarized in Table 2. The experimental apparatus of the dead-end cake filtration is the same as that used by the author's in the previous study.[11] One can notice that the received filtrate volumes in

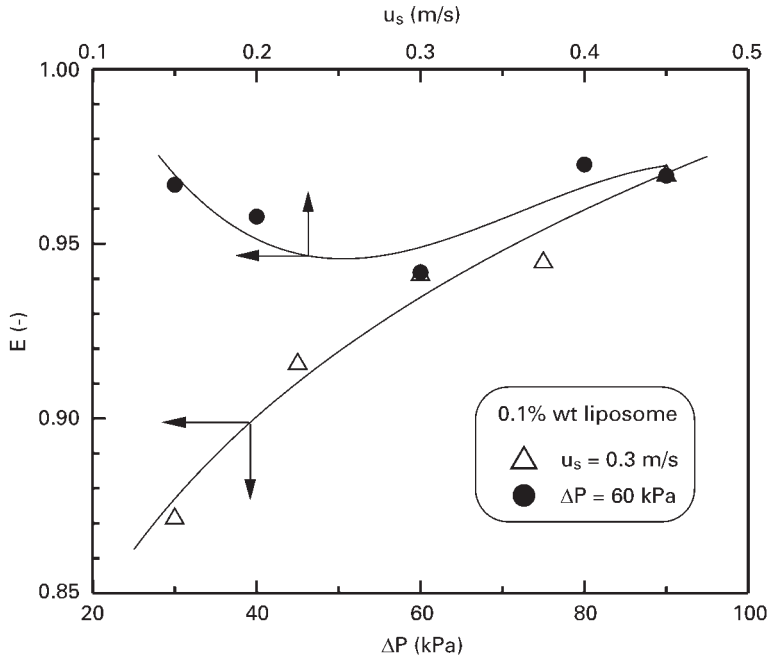

Figure 11. Effects of cross-flow velocity and filtration pressure on the separation efficiency.

cross-flow microfiltration are about six times higher than those obtained in dead-end cake filtration under the same filtration pressure. This fact indicates that the use of cross-flow microfiltration for purification of liposomes is an efficient method.

CONCLUSIONS

Attempts have been made to use cross-flow microfiltration in the purification of liposomes in the preparation process. The liposomes were concentrated during filtration while most phospholipid monomers were separated into filtrate. Effects of cross-flow velocity and filtration pressure on the filtration rate, the cake properties, the rejection coefficient, and the separation efficiency have been discussed. The cake resistance played a major role in all sources of filtration resistances. A compact and highly compressible cake would be formed at the beginning of filtration, which resulted in a sudden drop in filtration rate. The filtration rate at a pseudo-steady state

Table 2. A comparison of received filtrate volumes between the cross-flow microfiltration and the conventional dead-end cake filtration.

	Cross-flow microfiltration ($u_s = 0.3$ m/sec)		Conventional dead-end cake filtration	
	$v \times 10^2$ (m^3/m^2) at $t = 3{,}600$ sec	$v \times 10^2$ (m^3/m^2) at $t = 10{,}800$ sec	$v \times 10^2$ (m^3/m^2) at $t = 3{,}600$ sec	$v \times 10^2$ (m^3/m^2) at $t = 10{,}800$ sec
$\Delta P = 30$ kPa	64.72	157.22	12.48	28.31
$\Delta P = 45$ kPa	69.77	160.16	11.23	27.22
$\Delta P = 60$ kPa	66.26	165.93	10.48	25.52
$\Delta P = 75$ kPa	70.53	166.28	10.81	25.63
$\Delta P = 90$ kPa	74.61	175.1	10.34	25.26

increased slightly with increasing filtration pressure; however, it increased over two times as cross-flow velocity increased from 0.15 to 0.45 m/sec. The filtration rates at pseudo-steady states could be related with cross-flow velocity and filtration pressure using the proposed model. Moreover, the increase in cross-flow velocity or filtration pressure would increase the rejection of phospholipid and increase the fraction of liposome vesicles in the concentrate. Compared with the conventional "dead-end" cake filtration, the high operation capacity demonstrated that the use of cross-flow microfiltration in the purification of liposomes was an efficient method.

NOMENCLATURE

A	the empirical coefficient in Eq. (4) (m/kg)
C_1	the empirical coefficient in Eq. (6) (m)
C_2	the empirical coefficient in Eq. (6) (m/sec)
C_3	the empirical coefficient in Eq. (8) (m)
C_b	the concentrations of phospholipid in bulk suspension (kg/m^3)
C_p	the concentrations of phospholipid in filtrate (kg/m^3)
E	the separation efficiency of liposomes (—)
F_{dx}	the drag force whose direction is parallel to suspension cross-flow (N)
F_{dy}	the drag force whose direction is parallel to filtrate flow (N)
F_i	the net interparticle force (N)
f_c	the friction coefficient between particles (—)
H	the clearance between two plates of the filter (m)

L_c	cake thickness (m)
n	the empirical coefficient in Eq. (4) (—)
q	filtration rate (m^3/m^2 sec)
q_s	filtration rate at pseudo-steady state (m^3/m^2 sec)
R_c	filtration resistance of cake (m^{-1})
R_i	filtration resistance due to membrane fouling (m^{-1})
R_m	filtration resistance of clean membrane (m^{-1})
R_{rej}	rejection coefficient defined in Eq. (3)
R_t	overall filtration resistance (m^{-1})
u_s	the original cross-flow velocity (m/sec)
v	filtrate volume per unit area (m^3/m^2 sec)
t	filtration time (sec)
w_c	cake mass (kg/m^2)

Greek Letters

α_{av}	average specific filtration resistance of cake (m/kg)
ε	average cake porosity (—)
γ_w	the shear rate on the membrane surface (sec^{-1})
ΔP	filtration pressure (N/m^2)
μ	fluid viscosity (Pa sec)
ρ_s	particle density (kg/m^3)

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