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Formation of the Gel Layer of Polymers and Its Effect on the Permeation Flux in Crossflow Filtration of *Corynebacterium glutamicum* Broth

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ABSTRACT

The behavior of the permeation flux in crossflow filtration of *Corynebacterium glutamicum* broth was studied. In the beginning of filtration the permeation flux changed in accordance with the cake filtration model. The permeation flux agreed with the value calculated from the weight of the cell layer formed on the membrane per unit filtration area and the specific resistance of the cell layer measured in dead-end filtration. After cell deposition on the membrane, permeation resistance rapidly increased. The increase was due to the formation of the gel layer of the proteins and polysaccharides in the supernatant of the broth. When the circulation flow rate was raised, the weight of the cell layer reduced. However, the beginning of the rapid increase of permeation resistance came earlier and the apparent specific resistance of the cell layer increased. The higher the circulation flow rate, the higher the permeation flux at the beginning of the rapid increase of resistance. When the transmembrane pressure was lowered or the cell concentration was raised, the beginning of the rapid increase of the permeation resistance came earlier. The permeation flux at which the formation of the gel layer began was almost constant, even if the transmembrane pressure and the cell concentration were changed.

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INTRODUCTION

Separation of cells from microbial broth is one of the important processes in the bioindustry (1, 2). In conventional fermentation processes, centrifugation and dead-end filtration have been used. Crossflow filtration, in which the formation of a cake (cell layer) on a filtration membrane is repressed by shear stress to yield high permeation flux, has been receiving increased attention. Many theoretical and experimental studies have been made to find the relationships between the permeation flux and the filtration conditions in the crossflow filtration of suspensions (1, 3–7). Theoretical models and experimental data show that permeation flux is proportional to shear stress to the 0.33–2.0th power. Thus various methods utilizing inserts (protuberances) (8), high speed rotating disc filters (9), Taylor vortex (10), and Dean vortex (11, 12) have been proposed to increase the shear stress on the membrane in crossflow filtration. However, conventional filtration and centrifugation have in most cases not been replaced by crossflow filtration in the bioindustry. One reason is that the permeation flux at a high shear stress is not as high as the flux estimated from studies using simple suspensions. Some researchers have pointed out that the physical and chemical properties of microbial broths influence permeation flux in crossflow filtration. Nagata et al. showed that magnesium ammonium phosphate precipitate formed during steam sterilization of the medium increased the permeation resistance of the cell layer in crossflow filtration of *Bacillus polymyxa* broth (13). Kroner et al. indicated that polypropylene glycol used as an antifoam increased the filtration resistance (14). Shimizu et al. showed that the increase of the ratio of broken cells in suspension decreases permeation flux in crossflow filtration (15). The influence of polymers in a broth or suspension on the permeation flux in crossflow filtration has been suggested (13, 16, 17). We have studied some cases where the permeation flux was not increased with a rise in the shear stress. In crossflow filtration of suspensions and broths of rod-shaped bacteria, the cells in the cake formed on the membrane are arranged by the shear to form a dense cake layer with high resistance (shear-induced arrangement) (18–20). In the crossflow filtration of baker's yeast cultivated in molasses medium, the fine particles increase the permeation resistance of the cell layer and thus the permeation flux does not increase with a rise in the shear stress [shear-induced size classification (21–23)].

For this paper we studied permeation behavior in the crossflow filtration of the broth of *Corynebacterium glutamicum*, which is used for the industrial production of amino acids. The permeation flux was remarkably reduced by the formation of a gel layer on the surface of the cell layer which had initially formed on the filtration membrane. The dependence of the permeation flux on the filtration conditions is also discussed.

EXPERIMENTAL

Strain and Cultivation

Corynebacterium glutamicum FKU173 was used in this study. The cell was cultivated in a medium containing 0.5% yeast extract (Difco Laboratories, Detroit, MI), 0.5% Polypepton (Nippon Pharmaceutical Co., Tokyo, Japan), 0.5% NaCl, and 1.0% glucose at 30°C with reciprocal shaking (120 strokes/min). The initial pH of the medium was adjusted to 7.0 with 1 N KOH. The microorganism was inoculated into 100 cm^3 of the medium in a 500-cm^3 shaking flask as a seed culture. After 24 hours of cultivation, 8 cm^3 of the seed medium was inoculated into 400 cm^3 of the medium in a 2000-cm^3 shaking flask as a main culture. The main culture was also cultivated for 24 hours.

Filtration Membrane

A microfiltration membrane, C045 (Toyo Roshi Co., Tokyo), was used for both dead-end and crossflow filtration experiments. The membrane was a screen-type filter with a nominal pore size of 0.45 μm.

Measurement of Specific Resistance

The specific resistance was measured by an unsteady-state method at 20°C in dead-end filtration. A broth was filtered with the aid of pressure from a nitrogen gas cylinder. A module with a filtration area of 38.1 cm^2 and a depth of 7 cm was used for the measurement of the specific resistance. The viscosity of the permeate was measured with an Ostwald viscometer at 20°C. The specific resistance of the microbial cake was calculated from the change in permeate volume with time as described elsewhere (24).

Crossflow Filtration

Crossflow filtration was performed at 20°C using a thin-channel-type module made of polycarbonate having a filtration area of 24 cm^2 (2.4 cm in width and 10 cm in length). The channel depth was 2.4 mm. A broth was circulated with a rotary pump (RM10, Nakamura Metal Co., Osaka, Japan) equipped with a variable-speed drive (Ringcorn RXM-400, Shimpo Industry Co., Kyoto, Japan) (Fig. 1). The permeate was returned to a reservoir tank to keep the cell concentration constant. After the filtration experiment we measured the weight of the cake formed on the membrane. The circulation flow rate, the transmembrane pressure, and the cell concentration were 5–60 cm^3/s (linear velocity: 0.09–1.0 m/s), 25–98 kPa, and 6–26 kg-wet cell/m^3, respectively. The broth was concentrated by centrifugation (8000*g*) and appropriately diluted with the supernatant of the broth.

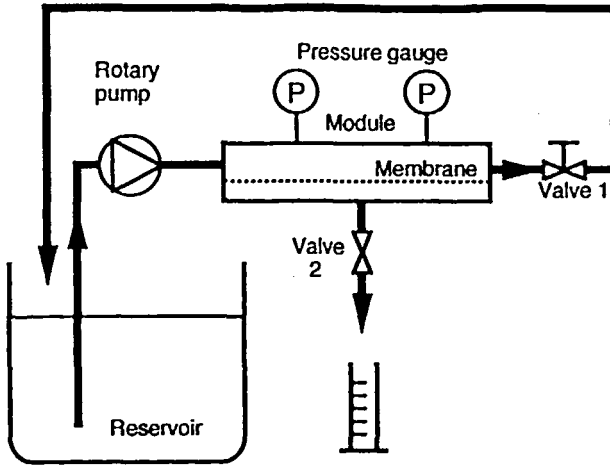

FIG. 1 Schematic diagram of crossflow filtration apparatus.

Analytical Methods

Concentrations of proteins (including small peptides) and sugars were determined by the Lowry method (25) and the phenol-sulfuric acid method (26), respectively. The water content of the gel layer formed in the crossflow filtration of the supernatant of the broth was determined from the decrease of the mass after lyophilization.

Scanning Electron Microscopy

The cross section of the cell layer was observed with a scanning electron microscope by the method described elsewhere (22) with minor modifications. The cell layer formed on the membrane during filtration was fixed with 2.5% glutaraldehyde in 0.1 M sodium phosphate buffer, pH 7.4, at room temperature for 2 hours. The cell layer was dehydrated in a series of 50, 70, 80, 90, 95, and 100% ethanol solutions. Then ethanol was substituted for by *t*-butanol. The layer was frozen at −20°C and dried with a freeze-dryer (ES-2030, Hitachi, Tokyo). The cell layer was cracked to observe a cross section. The sample was sputter-coated with gold and palladium (E-101, Hitachi) and viewed with a scanning electron microscope (S-2150, Hitachi) at 15 kV.

RESULTS

Specific Resistance of *C. glutamicum*

The cell concentration of *C. glutamicum* broth was 13–14 kg/m^3. The concentrations of the proteins, including peptides and sugars in the superna-

tant of the broth, were 2.9 and 3.6 kg/m^3, respectively. In dead-end filtration the permeation flux J decreased with an increase of the permeate volume per unit filtration area v. A linear relationship was observed between $1/J$ and v (data not shown). It indicates that the permeation behavior followed the cake filtration model (27). The specific resistance α was calculated using Eq. (1) from the slope of the relationship $d(1/J)/dv$, the transmembrane pressure ΔP, the viscosity of the permeate μ, and the cell concentration C.

$$\alpha = \frac{\Delta P}{\mu C}\frac{d(1/J)}{dv} \tag{1}$$

The viscosity was 1.06 mPa·s. The specific resistance measured was correlated with Eq. (2) in the transmembrane pressure of 25–98 kPa.

$$\alpha = 1.1 \times 10^{12} \times \Delta P^{0.34} \tag{2}$$

Changes in Permeation Flux and Resistance during Crossflow Filtration

Figure 2 shows the courses of the permeation flux and the weight of the cell layer per unit filtration area w in crossflow filtration of *C. glutamicum* broth. The circulation flow rate, the transmembrane pressure, and the cell concentration were 30 cm^3/s, 49 kPa, and 14 kg/m^3, respectively. The weight of the cell layer was almost constant after 900 seconds of filtration. However,

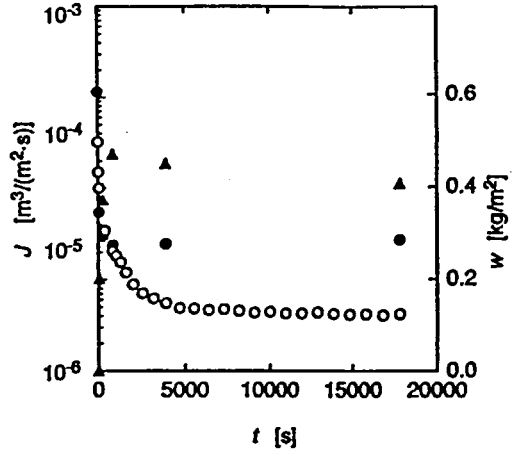

FIG. 2 Changes in permeation flux and cell deposition during crossflow filtration of *C. glutamicum* broth. Circulation flow rate = 30 cm^3/s, ΔP = 49 kPa, and C = 14 kg/m^3. (○) Experimental permeation flux; (●) permeation flux calculated with the cake weight and the specific resistance measured in dead-end filtration; (▲) cake weight per unit filtration area.

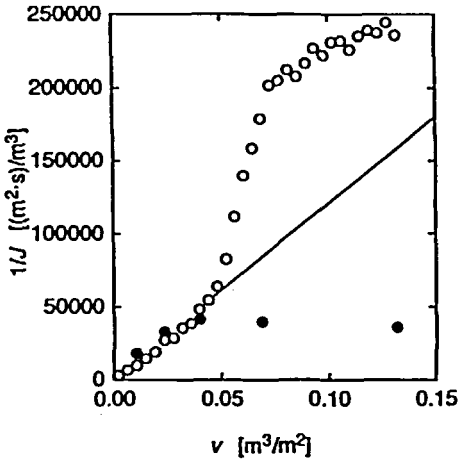

FIG. 3 Plots of $1/J$ vs v for the data from Fig. 2. (○) Experimental value; (●) value calculated with the weight of the cell layer and the specific resistance. The solid line shows the result in dead-end filtration.

the permeation flux decreased after 900 seconds and reached a constant value at 4000 seconds. The permeation flux calculated from w using Eq. (3) and J_{cal} are also shown in Fig. 2,

$$J_{cal} = \frac{\Delta P}{\mu(R_m + \alpha w)} \tag{3}$$

where R_m is the membrane resistance. The value of R_m was evaluated to be 3.7×10^{10} m^{-1} by measuring a permeation flux for a fresh membrane. The experimental flux and the calculated value agreed well until 900 seconds while the experimental flux decreased to one-fifth the calculated value at 3600 seconds. Figure 3 shows a plot of $1/J$ vs v in crossflow filtration. The plot is useful to analyze the change in permeation resistance since the value of $1/J$ is proportional to the permeation resistance ($R_m + \alpha w$) at a constant pressure (20, 22, 27, 28). The experimental value of $1/J$ increased linearly as in dead-end filtration until $v = 0.05$ m^3/m^2, where the filtration time was 900 seconds. Then the experimental data deviated upward from the line. The value of $1/J_{cal}$ reached a nearly constant value when the value of v was more than 0.07 m^3/m^2.

Formation of a Gel Layer in Crossflow Filtration

Figure 4 shows the cross sections of the near surface of the cell layers formed on the filtration membrane in the crossflow filtration shown in Fig.

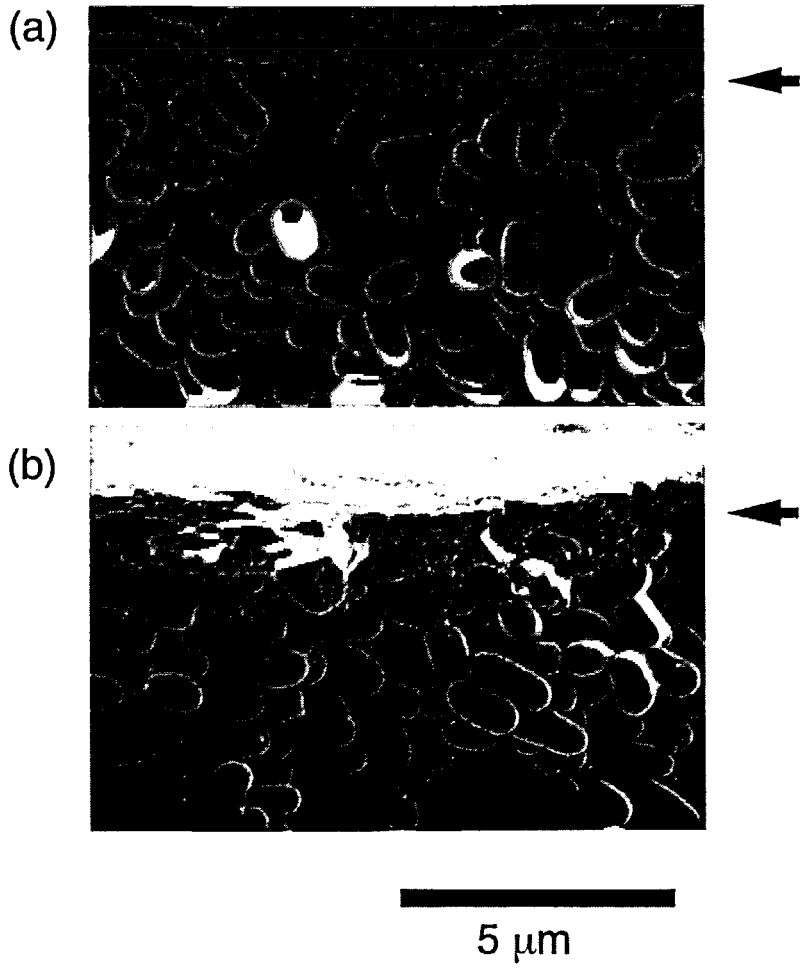

FIG. 4 Cross section of the cake layer formed in crossflow filtration of *C. glutamicum* broth. (a) After 900 s; (b) after 3600 s. The photos show the parts of the near surface. Circulation flow rate = 30 cm^3/s, ΔP = 49 kPa, and C = 14 kg/m^3. The arrows show the edges between the upper surface of the cake and the cross section.

2. The filtration times for Figs. 4(a) and 4(b) were 900 seconds (v = 0.05 m^3/m^2) and 3600 seconds (v = 0.07 m^3/m^2), respectively. The cell layer consisted of only *C. glutamicum* cells at 900 seconds while a gel layer was observed on the surface of the cell layer at 3600 seconds. Figure 5 shows a plot of $1/J$ vs v in the crossflow filtration of the supernatant of the broth. In

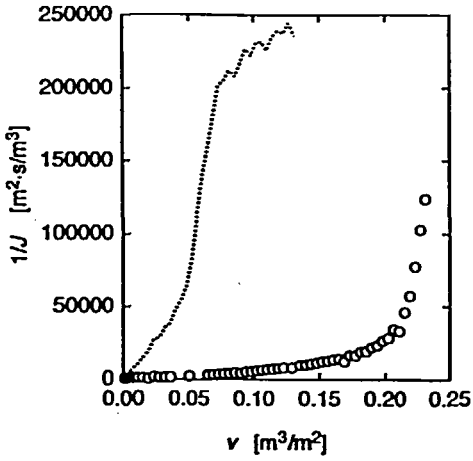

FIG. 5 Plots of $1/J$ and v for the crossflow filtration of the supernatant of *C. glutamicum* broth. Circulation flow rate = 30 cm³/s and ΔP = 49 kPa. The broken line shows the result of crossflow filtration of *C. glutamicum* broth.

the beginning of the filtration, the permeation resistance was much lower than in the crossflow filtration of the broth. When the value of v exceeded 0.20 m^3/m^2, the filtration resistance began to increase rapidly. After 3600 seconds of filtration where v was 0.20 m^3/m^2, a gel layer was formed on the filtration membrane. The wet weight of the gel layer per unit filtration area was 8.3×10^{-4} kg/m^2. Since the gel layer was insoluble in water, the components of the gel were neither analyzed by a high performance liquid chromatography nor an electrophoresis. The gel layer was soluble in the reagents for the Lowry method and the phenol-sulfuric acid method. The gel layer consisted of 55% water, 25% sugar, and 20% protein. The concentrations of the protein and sugar in the permeate were 2.8 and 3.4 kg/m^3, respectively. The concentrations in the permeate decreased little from those in the retentate.

Effect of the Circulation Flow Rate on the Permeation Flux

Figure 6(a) shows the permeation flux in the crossflow filtration of *C. glutamicum* broth at different circulation flow rates. The permeation fluxes were almost the same at the beginning of filtration. At 1000 seconds the lower the circulation flow rate, the higher the permeation flux. However, the permeation flux decreased with increasing circulation flow rate when the filtration time exceeded 3600 seconds. Figure 6(b) shows plots of $1/J$ vs v.

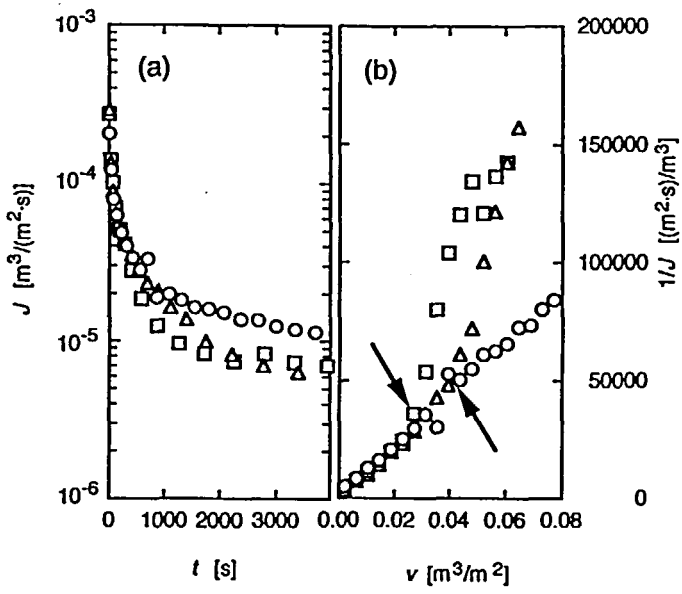

FIG. 6 Effect of circulation flow rate on permeation flux in crossflow filtration of *C. glutamicum* broth. $\Delta P = 49$ kPa and $C = 14$ kg/m^3. Circulation flow rate: (○) 5 cm^3/s; (△) 30 cm^3/s; (□) 60 cm^3/s. (a) J vs t; (b) $1/J$ vs v.

The permeation resistance increased linearly as in dead-end filtration at the circulation flow rate of 5 cm^3/s. At 60 cm^3/s the resistance began to increase rapidly when the value of v reached around 0.03 m^3/m^2 at flow rates of 30 and 60 cm^3/s. The permeation flux reached a nearly constant value of 5×10^{-6} m^3/(m^2·s). Table 1 shows the weight of the cell layer per unit filtration area and the apparent specific resistance of the cell layer at 3600 seconds of filtration. The higher the circulation flow rate, the lower the weight of the cell layer. The specific resistance of the cell layer increased with a rise of the circulation flow rate as discussed later.

Effect of the Transmembrane Pressure on the Permeation Flux

Figure 7(a) shows the permeation flux in crossflow filtration at different transmembrane pressures. The permeation flux increased as the transmembrane pressure was raised. A rapid increase of the permeation resistance was observed at the three transmembrane pressures in Fig. 7(b). The higher the transmembrane pressure, the larger the value of v at the initiation of the rapid

TABLE 1
Weight and Apparent Specific Resistance of the Cake Formed in Crossflow Filtration of *C. glutamicum* Broth. Filtration Time = 3600 seconds

Circulation flow rate (cm^3/s)	Transmembrane pressure (kPa)	Cell concentration (kg/m^3)	Weight of cake per unit filtration area (kg-wet/m^2)	Apparent specific resistance (10^{12} m/kg)	Ratio of specific resistance[a] (—)
0[b]	49	14	1.16	4	(1)
5	49	14	0.97	4	1
30	49	14	0.45	16	4
60	49	14	0.24	27	7
30	25	14	0.42	9	2
30	49	14	0.57	16	4
30	98	14	0.70	19	3
30	49	6	0.32	22	5
30	49	13	0.37	23	6
30	49	26	0.44	22	6

[a] The ratio of the specific resistance to that obtained in dead-end filtration at the same transmembrane pressure.
[b] The result from a dead-end filtration.

increase of resistance. The rapid increase began when the value of $1/J$ reached 4000–5000 $(m^2 \cdot s)/m^3$ at the three pressures. The weight of the cell layer per unit filtration area increased as the transmembrane pressure was raised (Table 1).

Effect of the Cell Concentration on the Permeation Flux

Figure 8(a) shows the permeation flux in crossflow filtration at different cell concentrations. The permeation flux decreased as the cell concentration increased. The permeation resistance began to increase rapidly when the value of $1/J$ reached 4000–5000 $(m^2 \cdot s)/m^3$ at the three cell concentrations in Fig. 8(b) as in the case of the crossflow filtration at different transmembrane pressures (Fig. 7b).

DISCUSSION

The increase of the permeation resistance was larger in crossflow filtration of *C. glutamicum* broth than in dead-end filtration (Fig. 3). The formation of a gel layer was observed on the surface of the cell layer which had deposited at the beginning of filtration under a scanning electron microscope (Fig. 4).

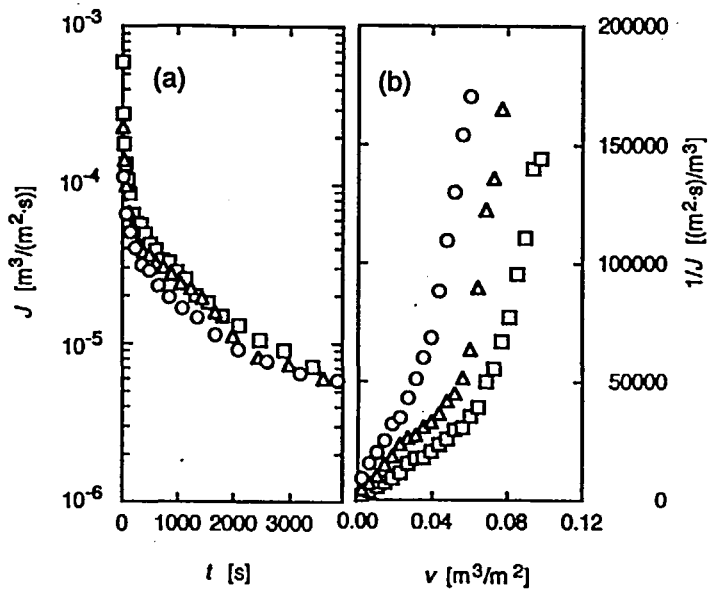

FIG. 7 Effect of transmembrane pressure on permeation flux in crossflow filtration of *C. glutamicum* broth. Circulation flow rate = 30 cm³/s and C = 14 kg/m³. Transmembrane pressure: (○) 25 kPa; (△) 49 kPa; (□) 98 kPa. (a) J vs t; (b) $1/J$ vs v.

The specific resistance of the gel layer formed on the membrane in the crossflow filtration of the supernatant of the broth (Fig. 5) was 7.0×10^{15} m/kg-wet gel or 1.6×10^{16} m/kg-dry gel. The value on a wet basis was 1800 times the specific resistance of the cell layer at 49 kPa. In Fig. 4 the thickness of the polymer gel was 1.2 μm. The weight of the gel layer per unit filtration area was 1.2×10^{-3} kg/m² on a wet weight basis on the assumption that the density of the gel was nearly equal to that of water (1.0×10^3 kg/m³). The calculated increase of the value of $1/J$ was 1.8×10^5 (m²·s)/m³ when the gel layer formed. This agrees well with the increase appearing in Fig. 3, 1.5×10^5 (m²·s)/m³. The agreement supports the formation of the gel layer of polymers as the cause of the increase in the permeation resistance.

Assuming that the gel layer formed from $v = 0.20$ to 0.23 m³/m², in Fig. 5 the value of C_p was calculated to be 1.2×10^{-2} kg/m³ from the dry weight of the gel layer per unit filtration area (3.7×10^{-4} kg/m²). The value of C_p calculated from the slope during the crossflow filtration in Fig. 3 (6.1×10^6 seconds) and the specific resistance of the gel layer (1.6×10^{16} m/kg-dry gel) by using Eq. (3) was 1.8×10^{-2} kg/m³. These results indicates that the

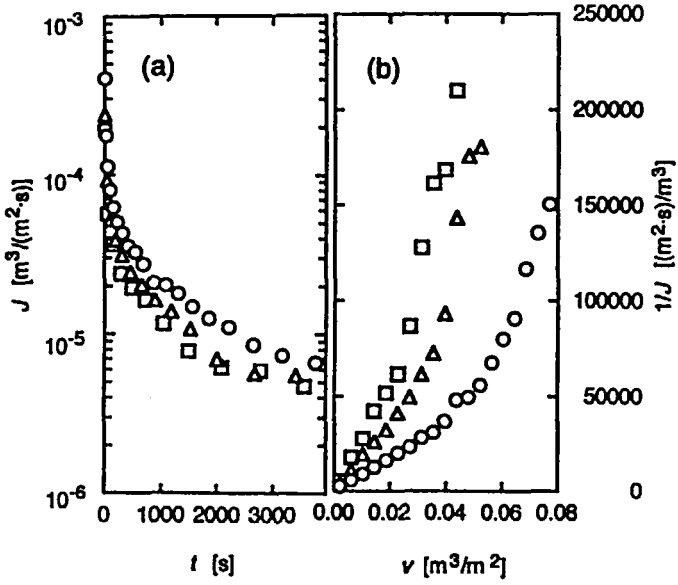

FIG. 8 Effect of cell concentration on permeation flux in crossflow filtration of *C. glutamicum* broth. Circulation flow rate = 30 cm³/s and ΔP = 49 kPa. Cell concentration: (○) 6 kg/m³; (△) 13 kg/m³; (□) 26 kg/m³. (a) J vs t; (b) $1/J$ vs v.

polymer components—the concentration of which is one-hundredth of the cell concentration—reduced the permeation flux significantly. In this study the polymers in the gel layer were not analyzed in detail since we could not to solubilize the layer. However, the components were probably polymers such as proteins and polysaccharides since they gelatinized on the cell layer in crossflow filtration. The polymers were thought to be secreted from *C. glutamicum* cells during crossflow filtration or cultivation.

A similar phenomenon has been observed in the crossflow filtration of broth of yeast cultivated in molasses medium. In this case a trace amount of fine particles in molasses deposited on the surface of the cell layer increased the permeation resistance severely. The concentration of fine particles was one-tenth that of the yeast concentration (22).

The permeation flux in the crossflow filtration of *C. glutamicum* broth decreased with increasing flow rate (Fig. 6), a tendency opposite to the dependence of permeation flux on the flow rate usually observed (1, 3–7). The beginning of the rapid increase of permeation resistance came earlier when the circulation flow rate was raised (Fig. 6b) because of shear-induced size

classification (21). The same phenomena were observed in crossflow filtration of the broth of yeast cultivated in molasses (22).

The shear stress on the surface of the cell layer, τ, was calculated to be 0.5, 2.2, and 6.3 Pa at a circulation flow rate of 5, 30, and 60 cm^3/s, respectively, when the filtration channel is assumed to be a rectangular duct (29, 30). The permeation flux calculated using Eq. (3) from the weight of the cell layer formed after 3600 seconds of crossflow filtration and the specific resistance measured in dead-end filtration, J_{cal}, was 1.2×10^{-5}, 2.5×10^{-5}, and 4.6×10^{-5} $m^3/(m^2 \cdot s)$ for a flow rate of 5, 30, and 60 cm^3/s, respectively. The rapid increase of the permeation resistance seemed to start when the circulation flow rate reached approximately J_{cal} at a flow rate of 30 and 60 cm^3/s (arrows in Fig. 6b). On the other hand, the rapid increase of the resistance was not observed when the circulation flow rate was 5 cm^3/s. The specific resistance of the cell layer formed at 3600 seconds agreed with the value measured in dead-end filtration (Table 1). At a flow rate of 5 cm^3/s the cells would keep depositing at 3600 seconds as in dead-end filtration. These results support the model in which the gel layer is formed after the end of the formation of the cell layer. There is a relationship between J_{cal} and the shear stress on the cell layer τ, expressed by.

$$J_{cal} = 1.5 \times 10^{-5} \times \tau^{0.6} \tag{4}$$

The dependence of J_{cal} on τ ($\tau^{0.6}$) was similar to that in crossflow filtration of suspensions of yeast and latex (1, 30–33). This fact suggests that the cell layer formed at the beginning of crossflow filtration of *C. glutamicum* broth as in the crossflow filtration of suspensions of spherical particles.

The steady-state permeation flux after the formation of the gel layer became higher as the circulation flow rate was raised. The permeation flux reached the steady-state value of 8×10^{-6} $m^3/(m^2 \cdot s)$ at 1800 seconds when the flow rate was 60 cm^3/s (Fig. 6a). The steady-state flux was 4×10^{-6} $m^3/(m^2 \cdot s)$ at a flow rate of 30 cm^3/s (Fig. 2). The steady-state permeation flux increased proportionally to the circulation flow rate. However, the permeation flux at a circulation flow rate of 5 cm^3/s was the highest through 3600 seconds of filtration. The backflushing or backpulsing method (20, 22, 34–37) is more effective for increasing permeation flux in crossflow filtration than is raising the shear stress (8–12).

The permeation flux slightly increased when the transmembrane pressure was raised (Fig. 7a). The value of v at which the rapid increase of the permeation resistance began became large with a rise in the pressure (Fig. 7b). The permeation flux at which there was a rapid increase of the resistance was 2×10^{-5} $m^3/(m^2 \cdot s)$ at all transmembrane pressures. The shear stress on the surface of the cell layer was 2–3 Pa at the three pressures in Fig. 7. The permeation flux at which the rapid increase of the resistance began was almost

independent of the transmembrane pressure. The permeation resistance increased rapidly after the permeation flux reached about 2×10^{-5} $m^3/(m^2 \cdot s)$ when the cell concentration was varied. The shear stress was 2.0–2.2 Pa at the three cell concentrations. The value of J_{cal} calculated by Eq. (3) was proportional to the cell concentration to the -0.2nd power. The dependence of the permeation flux at the end of cell deposition on the cell concentration was lower than that of the flux on the shear stress.

CONCLUSIONS

In the crossflow filtration of *C. glutamicum* broth the formation of the gel layer of the proteins and polysaccharides in the broth on the initially deposited cell layer increased the permeation resistance significantly. The weight of the cell layer decreased and the rapid increase of the permeation resistance came earlier when the circulation flow rate was raised. The permeation flux at which there was a rapid increase of the resistance was almost constant when the transmembrane pressure and the cell concentration were varied.

NOMENCLATURE

C	cell concentration (kg/m^3)
C_p	polymer concentration (kg/m^3)
J	permeation flux [$m^3/(m^2 \cdot s)$]
J_{cal}	permeation flux calculated with the specific resistance measured in dead-end filtration and the weigh of cake per unit filtration area [$m^3/(m^2 \cdot s)$]
ΔP	transmembrane pressure (Pa)
R_m	resistance of membrane (m^{-1})
t	filtration time (s)
v	permeate volume per unit filtration area (m^3/m^2)
w	cake weight per unit filtration area (kg/m^2)
α	specific resistance of cell layer (m/kg)
μ	viscosity of permeate (Pa·s)
τ	shear stress (Pa)

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