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Cross-flow filtration as a method of separating fungal cells and purifying the polysaccharide produced

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Abstract. Cross-flow filtration (CFF) has been investigated as a method of separating filamentously growing fungal cells and purifying the polysaccharide produced. The effects of transmembrane pressure, module geometry (e.g. channel height or tube diameter), tangential feed velocity and cell as well as polysaccharide concentration are discussed. Apart from these experiments, influences by the recirculation pump used are shown.

List of symbols

b_f	–	fouling index
b	–	factor refering to the behaviour of the sublayer
C	$kg \cdot m^{-3}$	concentration
C_g	$kg \cdot m^{-3}$	solute concentration at the membrane
C_b	$kg \cdot m^{-3}$	solute concentration in the bulk phase
D	s^{-1}	shear rate
k	$m \cdot s^{-1}$	mass-transfer coefficient
K	$mPa \cdot s^n$	consistency index
n	–	flow behaviour index
P_w	$m^3 \cdot s^{-1} \cdot m^{-2}$	rate of permeation
P_{w1}	$m^3 \cdot s^{-1} \cdot m^{-2}$	rate of permeation at 1 minute
P'_w	$m^3 \cdot s^{-1} \cdot m^{-2}$	rate of permeation at the beginning
p	Pa	pressure
Q	m^2	largest cross-section of a particle
q	m^2	smallest cross-section of a particle
Re	–	Reynolds number
R_f	m^{-1}	fouling resistance
R_m	m^{-1}	membrane resistance
t	s	time
w	$m \cdot s^{-1}$	tangential feed velocity

Greek symbols

λ	–	friction factor
ΔpTM	Pa	transmembrane pressure
η	$mPa \cdot s$	shear viscosity
η_{sp}	–	specific viscosity (rel. increase of viscosity $\eta_{sp}=\eta_{rel}-1$)
$[\eta]$	$m^3 \cdot kg^{-1}$	intrinsic viscosity
ν_w	$m^2 \cdot s^{-1}$	kinematic viscosity
ϱ	$kg \cdot m^{-3}$	density

Indices

b	bulk
cell	cells
f	fouling
g	gelling
PS	polysaccharide
rel	relative
sp	specific
w	water

1 Introduction

The downstream processing of cell cultures and the purification of the biosynthetical substances produced represent one of the main tasks of bioengineering. Most processes of cell separation, e.g. centrifugation or dead-end filtration, which were commonly used in the past, are time-consuming and expensive. Centrifugation did not meet the requirement of minimizing running costs either. The energy needed to create high gravitational forces to overcome the low density difference of the culture broth system constitutes one third of the operating costs. On the other hand, dead-end filtration consumes less running costs, but the resistance to permeation flow increases as cell deposits build up upon the filter medium. Thus, decreasing rates of permeation are observed in the first few minutes of the filtration period, leading to very low values.

Yet apart from this decisive disadvantage, dead-end filtration is very useful when low shear-stress is required for separation. Compared to all these conventional separation techniques CFF offers some improvements in permeation rate, operating time and economy. CFF technique and its feasibility in varying the design of membrane modules permit special adaptation to the bioproduct that has to be separated and purified. Beside these advantages of CFF the separation of cell suspensions or purification of bioproducts involves some problems encountered in dead-end filtration. Fouling, cell deposition on the membrane surface and gel-polarization are the main factors affecting the efficiency of the CFF process.

The formation of such dense and sometimes compressive layers offers additional resistance to the rate of permeation. This would also affect the retention characteristics of the membrane. In order to minimize the problem of layer forma-

tion, several complementary approaches were undertaken [1]. Technical solutions such as flat-channel-modules or tubes have been investigated which now meet the requirement of increased rates of permeation [2]. These systems utilize fluid mechanics established by tangential feed flow. The consequence is lateral motion of particles countercurrent to permeate flow. Particularly, the creation of high speed profiles using modified flow channel geometries, e.g. open channel systems or turbulence producing spacers within the flow channel have been described in several papers [3, 4].

The present work investigates the influence of starting procedures and the behaviour of the rate of permeation during the concentration runs of fungal cell suspensions and macromolecular polysaccharide solutions. Modified concentration polarization models are used to describe the obtained experimental results. Further investigations were performed to study the dependence of the rate of permeation on transmembrane pressure and tangential feed velocity.

In addition to these experiments, the shear-stress created by the CFF system including the recirculation pump was investigated.

2 Materials and methods

2.1 Microorganism and polysaccharide

The filamentously growing fungus Schizophyllum commune, ATCC 38548, secretes an extracellular neutral polysaccharide. It consists of a backbone chain of 1,3-β-D-glucopyranose units with 1,6-bounded β-D-glucopyranose at about every third glucose molecule in the basic chain [5, 7] (Fig. 1).

In water the polysaccharide behaves as rodlike triple helix with pseudoplastic flow characteristics [6]. During cultivation pseudoplasticity depends on the length of the chain produced by the fungus at the outer cell-wall [8]. Batch cultivation with Schizophyllum commune was carried out in a 50-dm-bioreactor (Braun Diessel Biotech, Melsungen, FRG) with three 6-flat-bladed turbine impellers.

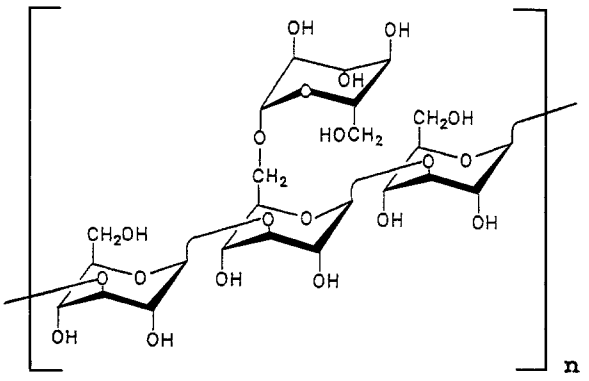

Fig. 1. Primary structure of Schizophyllan

All cultivations performed showed polymer formation associated with growth and required oxygen limitation for enhanced productivity. The fungus reached its stationary phase after substrate consumption. Under substrate limiting conditions polymer degrading enzymes (glucanases) are released into the medium. In order to prevent synthesis of these enzymes, the cultivation was terminated after 96 h.

Light scattering measurements of the polysaccharide produced resulted in an absolute molar mass of $11 \cdot 10^6$ g/mol.

2.2 Filtration equipment

The cell separation experiments were performed at 20 °C with ceramic tube modules (PSK CER MSP005194, Millipore, Eschborn, FRG) of two different pore sizes (0.45 and 1.0 μm) and a membrane area of 0.14 m^2 of each module.

Microfiltration employed in purification and concentration of were assayed at the same temperature (20 °C) with a Prostak system (Millipore, Eschborn, FRG). One or three Prostak modules arranged in line were tested alternatively. The flat membranes consisted of 0.1 μm hydrophilic PVDF Durapore material. The membrane area of one module was 0.17 m^2 (2-flat membranes/stack). The membranes were cleaned according to the recommendation of the manufacturer after each run.

2.3 Rheological characterization

The flow behaviour of aqueous Schizophyllan solutions was measured by a rotary viscometer (RV 100, Haake, Karlsruhe, FRG).

The viscous characteristics of the polymer obtained can be described by the power law model of Ostwald and de-Waele over a wide range of shear rates (0.3–300 s^{-1}):

$$\eta = K \cdot D^{(n-1)} \tag{1}$$

The flow behaviour index n is in reverse proportion to the extent of pseudoplasticity.

Previous investigations [7] have shown that – depending on cultivation time – alterations in the viscous behaviour are caused solely by change in molecular weight. Thus, it is important to adjust optimal parameters such as temperature, aeration rate, impeller speed and cultivation time in order to obtain highly molecular polysaccharide solutions. In addition to these characterizations the intrinsic viscosity [η], representing the specific volume of a randomly coiled polymer molecule, was measured (Zimm-Crothers-viscometer, Krannich, Göttingen, FRG).

3 Theory

Conventional cell separation has been carried out in a dead-end mode using the plate-and-frame filter press. The particular advantage of this technique is a cell-cake of relatively low moisture content. The primary disadvantage of the dead-end filtration device is that the resistance to permeate

flow increases as the cell deposit builds up on the filter medium. This will be influenced by sticky and highly molecular materials.

Unfortunately, the separation of cells using cross-flow techniques involves many of the problems encountered in dead-end filtration. However, the cell suspension can be kept moving at such a velocity that the deposition of cells or cell adhering polymer on the membrane surface is minimized.

In the case of stationary conditions, meaning constant temperature, transmembrane pressure tangential flow velocity as well as constant cell and/or polymer concentration, changing of the rate of permeation P_w can be expressed by Eq. (2):

$$P_w = P_{w1} \cdot t^{-b} . \tag{2}$$

Here, declining rates of permeation are due to adsorption of solutes at the membrane surface, which is expressed quantitatively by the exponent b.

In order to describe the build-up of solutes at the solution-membrane-interface the known model of concentration polarization can be used. This model is based on the balance between the convective drag of solutes toward the membrane surface and their back-diffusion. In the case of completely retained solutes the expression for the rate of permeation is Eq. (3):

$$P_w = k \cdot \ln (C_g/C_b) , \tag{3}$$

with C_g and C_b as the interface and bulk concentrations, respectively; k is the mass transfer coefficient.

In many concentration experiments the gel-polarization model has been used successfully for describing the alteration of the rate of permeation as a function of bulk concentration and tangential feed velocity. Yet it has not proved useful for suspensions with large particles (larger than a few microns) or of highly molecular solutes. In this case a lack of conformity between theory and experiment is observed [8].

In order to overcome this difference between prediction and observation new models have been proposed. Some of these models are based on fluid mechanical forces used to increase back-migration of particles away from the membrane surface. Equation (4) describes the relationship between the static and dynamic fluid pressure responsible for adherence of particles at the membrane surface or transportation along the flow channel [9].

$$0.5 \cdot \varrho \cdot w^2 > p \cdot (Q/q) \cdot \lambda . \tag{4}$$

In order to prevent deposition of particles on the membrane the value of dynamic fluid pressure must be greater than the value of the right-hand side of Eq. (4). Thus, optimal rates of permeation can be achieved by varying tangential feed velocity with respect to relatively low static pressure.

In the case of high permeable membranes a "solid-flux model" has been proposed assuming that the decline of the rate of permeation along with the concentration of suspended solids (particles) is proportional to the rate of permeation itself [10]:

$$dP_w/dC_b = -b \cdot P_w . \tag{5}$$

Integration results in:

$$P_w = \exp (-b\, C_b) \cdot P'_w . \tag{6}$$

This model is based on the further assumption that back-migration of particles from the sublayer or membrane surface is negligible and that particles that reach the solid-solution-interface adhere completely. Plots of $\ln P_w$ vs. C_b can be useful in deciding either gel-polarization without back-diffusion (Eq. (6)) or gel-polarization with back-diffusion (Eq. (3)) is more appropriate.

4 Results and discussion

In order to realize cell separation, ceramic tube modules of two different pore sizes (0.45 and 1.0 μm; filtration area 0.14 m^2) were investigated.

Purification and concentration runs were carried out with cell-free polysaccharide solutions of 0.05% (w/v). The filter unit alternatively consisted of one or three flat-membrane modules (Prostak). Thus, the filtration area could be varied from 0.17 to 0.51 m^2. Full retention of the polysaccharide was obtained at a maximum pore size of 0.1 μm and at a maximum cut-off of 10^6 Dalton, respectively.

As previously reported [10], typical values of the average rate of permeation for ceramic tube modules range from 50 to 100 $dm^3/(h \cdot m^2)$. Comparable values were also obtained here. Using flat-membrane modules (Prostak) average rates of permeation of 30 to 40 $dm^3/(h \cdot m^2)$ could be achieved.

4.1 Factors influencing filtration

4.1.1 Fouling

In the case of cell separation one problem arises from migration of small particles into larger pores of the filter medium. Furthermore, the adsorption (fouling) of macromolecules, e.g. proteins, contributes to the reduction in permeability. Unfortunately, the initial contamination of the membrane cannot be removed even by reverse-flow cleaning following the filtration process. Only extended cleaning with chemical agents, e.g. NaOCl, would restore initial permeabilities.

A quantitative description of the adsorption can be expressed by the membrane resistance R_m. The determination of R_m had been performed by water flux measurements before the filtration experiments were executed.

Using Eq. (7), the slope of the plots of P_w vs. ΔpTM results the membrane resistance. Here, the dependence of the rate of permeation upon transmembrane pressure is based on the assumption of laminar flow through porous material [11, 12]:

$$P_w = \Delta pTM/(32 \cdot v_w \cdot R_m) . \tag{7}$$

Table 1. Membrane resistances of the ceramic tube membranes (CTM) and polymeric flat membranes (PFM)

	R_m $[m^{-1} \times 10^{10}]$	R_f $[m^{-1} \times 10^{10}]$
PFM, 0.1 µm	5.65	0.06
CTM, 0.45 µm	2.61	0.15
CTM, 1.0 µm	0.40	1.32

The determination of the fouling resistance R_f was performed after the membranes had been rinsed with utmost care. All water flux experiments were carried out with deionized water at 20 °C. The calculated values of R_f (Eq. (8)) and R_m can be taken from Table 1. Thus:

$$P'_w = \Delta pTM/(32 \cdot v_w \cdot [R_m + R_f]) . \quad (8)$$

The R_f values give an idea of the problems of cell separation from highly viscous culture broths when using microfiltration membranes. Free migration of cell particles and macromolecules into the pores of the membrane during the first minutes of filtration change the permeability considerably. This initial deposit is irreversible; it cannot be removed neither by changing cross-flow conditions nor by back-pulsing or augmented wall shear-stress.

4.1.2 Initial filtration conditions

In Figs. 2 and 3 the behaviour of initial rates of permeation is presented. A comparison of the two ceramic tube modules shows a change in behaviour of the rate of permeation with increasing pore diameter. In the case of the module with 0.45 µm pores steady-state conditions were already reached after 0.5 h. With regard to the module with 1.0 µm pores steady-state conditions could not be ensued. Migration of cell particles into the pores on the one hand and migration of macromolecules (e.g. polysaccharide and proteins) through the membrane on the other hand prevented the formation of steady-state conditions. Thus, cell separation with microfiltration membranes involves two main problems:

a) the adsorption of macromolecules at inner walls of the pores, and
b) the adsorption of particles and macromolecules at the membrane surface.

Subsequent formation of sublayers (gel-polarization) can successfully be controlled by tangential feed velocities, so cell separation with the aid of cross-flow microfiltration requires pores of a suitable diameter that guarantees full retention of cell particles and free permeation of the product. The attempt to find such conditions is also represented in Figs. 2 and 3. For comparison, the two membranes of various pore diameter were tested using the same culture broth, tangential feed velocity and temperature. In both cases full retention of cells was given. Unfortunately, in the case of 0.45 µm full retention of the polysaccharide was given just as well after

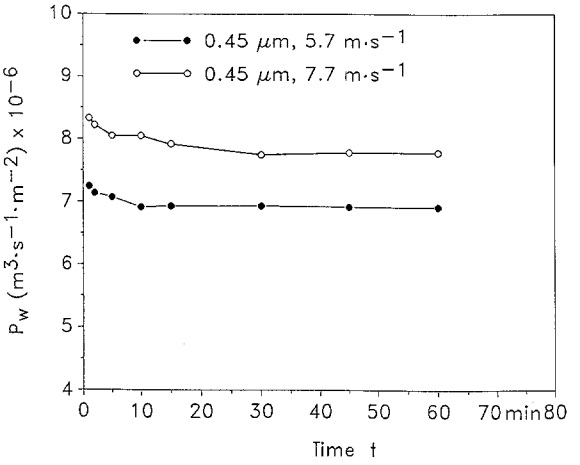

Fig. 2. Fouling: effect of tangential feed velocity; ceramic tube module, 0.45 µm. $C_{cells} = 0.03\%$ (w/v), $C_{PS} = 0.12\%$ (w/v), $\Delta p =$ 140 kPa, $\Delta p = 120$ kPa

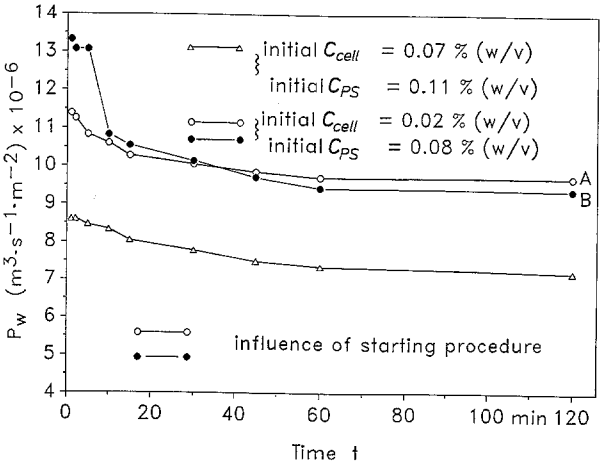

Fig. 3. Fouling: effect of different cell- and polysaccharide concentrations and different starting procedures. A) fast opened permeate valve, B) slowly opened permeate valve; the opening was stopped after the permeate pressure had reached zero. Ceramic tube module, 1.0 µm, $w = 7.7$ m · s^1, $\Delta p = 145$ kPa

the adsorption layer had been built up. Only in the case of 1.0 µm pores did the samples of the permeate contain the polysaccharide. Unfortunately, the polysaccharide concentration of the permeate was decreasing during the filtration process in consequence of the changed retention characteristic of the membrane. In order to overcome such problems, the optimization of the initial concentration of cells and polysaccharide is necessary as well as the optimization of temperature, tangential feed velocity and transmembrane pressure. The starting procedure of a filtration process is important, too. In order to prevent immediate migration of solutes/cells into the pores of the membrane, the opening of the permeate valve should be stopped after the permeate pressure had reached zero. Figure 3 shows the influence of two different starting procedures. It is indicated that such a controlled starting procedure will at last lead to higher rates of permeation.

4.1.3 Tangential feed velocity

The cross-flow experiments with the Prostack flat membrane module were carried out at a tangential feed velocity resulting in Reynold's numbers of 1800 to 7500 corresponding to shear rates of 1100 to 2600 s^{-1}. These values represent a compromise between the various requirements for operation, such as the given geometrical design of the module or the performance of the recirculation pump. Plots of P_w vs. ΔpTM (Fig. 4) make clear that in the case of two different tangential feed velocities transmembrane pressures greater than 0.8 bar do not contribute further to increased rates of permeation. Thus, an efficient control of layer formation involves limiting operating pressures. Higher transmembrane pressures are combined with increased transportation of particles and/or solutes toward the membrane surface. This could remarkably reduce the effectiveness of the tangential feed velocity with regard to gel-layer thickness.

Cross-flow experiments with the ceramic tube module were carried out with turbulent flow ($Re = 11\,000-31\,000$ and shear rates of 3000–8500 s^{-1}) in consequence of module geometry. Generally, the change from laminar to turbulent flow is indicated at $Re = 2300$ which is the critical Reynolds number. In the case of cross-flow filtration the critical Reynolds number changes from 2300 to nearly 6000 [12] depending on the module geometry.

Figure 5 indicates that the rate of permeation increases in proportion to the shear rate. With regard to the Prostak-flat-membrane module the slope of the plots is 0.7, which is in conformity with the 0.5 to 0.7 power dependency expected of a system operating in region controlled by laminar flow and mass-transfer [10]. In the case of the ceramic tube module the slope of the plots varies from 1.0 to 1.1, which is higher than the 0.8 to 1.0 power dependency of a system operating in a region controlled by turbulent flow and mass-transfer [3]. This result indicates that modified models or other models of concentration polarization than the usual ones must be used to describe the microfiltration of highly viscous culture broths containing cells.

4.1.4 Concentration

Separation and concentration experiments (separation of cells from culture broths containing a polysaccharide and concentration of cell-free polysaccharide solutions) were performed with the ceramic tube module of 1.0 µm pores and with the Prostak-flat-membrane module of 0.1 µm pores, respectively. The ceramic tube module of 0.45 µm pores was not used as a result of full retention of the polysaccharide after a few minutes of filtration.

With regard to the ceramic tube module, the cell separation experiment was carried out with low cell and polysaccharide concentrations due to the results of the time dependency of the rate of permeation. The initial concentrations amounted to: a) $C_{cells} = 0.021\%$ (w/v) and b) $C_{PS} = 0.08\%$ (w/v).

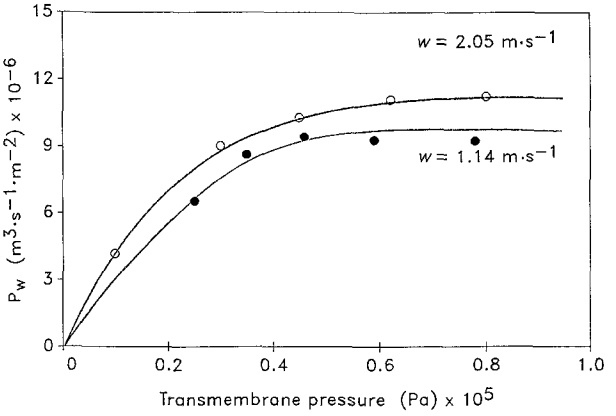

Fig. 4. Influence of the transmembrane pressure at different tangential feed velocities; Prostak flat membrane module, 0.1 µm

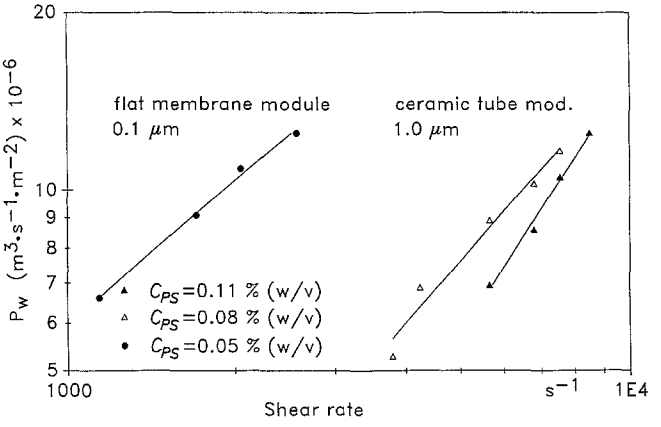

Fig. 5. Influence of shear rates in consequence of augmented tangential feed velocities; flat membrane module $\Delta p = 30$ kPa, ceramic tube module, $\Delta p = 110$ kPa

The dependency is indicated in Figs. 6 and 7. In the case of cell concentration plots, no significant difference between the model of solid flux and the model of concentration polarization can be observed. The plots of the polysaccharide concentration indicate the effects arising from gel-layer formation. Free permeation of polysaccharide molecules through the membrane decreases with time and increasing viscosity of the culture broth (Fig. 6).

In order to solve the problem of the declining permeability of the polysaccharide such effects as higher temperature and steady-state conditions are still under investigation. With regard to the polysaccharide concentration runs with the aid of the Prostak-flat-membrane module (Figs. 8 and 9) one observes a sigmoidal curve which can be subdivided into three sections: 1) gel-layer formation, 2) constant operation phase and 3) final reduction in rates of permeation resulting from the incease in viscosity. The plots further indicate that according to the concentration polarization model as well as to the solid flux model no linear relationship is given. Only in the case of $\log(P_w)$ vs. C_b linearity can be stated with respect to the third section of the curve in Fig. 8. Here the

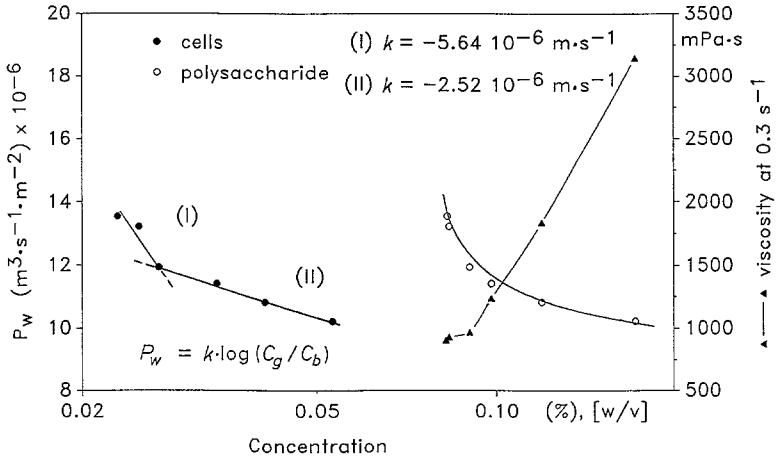

Fig. 6. Cell separation: dependence of the permeation rate upon concentration (with regard to Eq. (3)); ceramic tube module 1.0 µm. The increase of culture broth viscosity in consequence of higher concentration is also indicated

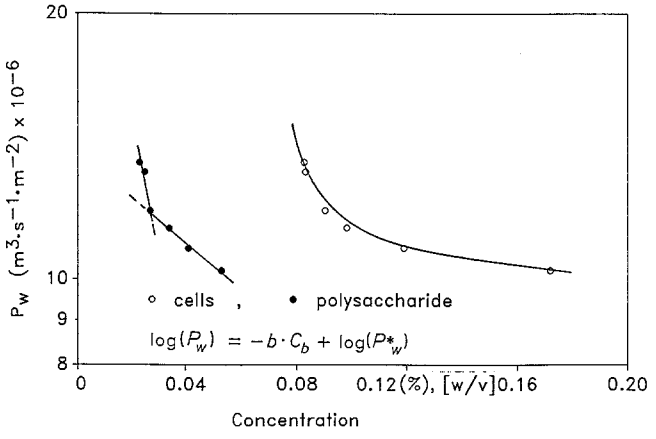

Fig. 7. Cell separation: dependence of the permeation rate upon concentration (with regard to Eq. (6)); ceramic tube module, 1.0 µm

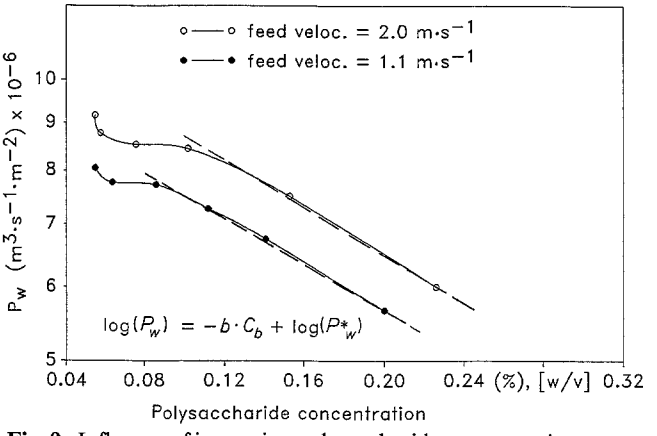

Fig. 9. Influence of increasing polysaccharide concentrations at two different tangential feed velocities. The plots refer to Eq. (3); Prostak flat membrane module, 0.1 µm, $C_{PS} = 0.05\%$ (w/v)

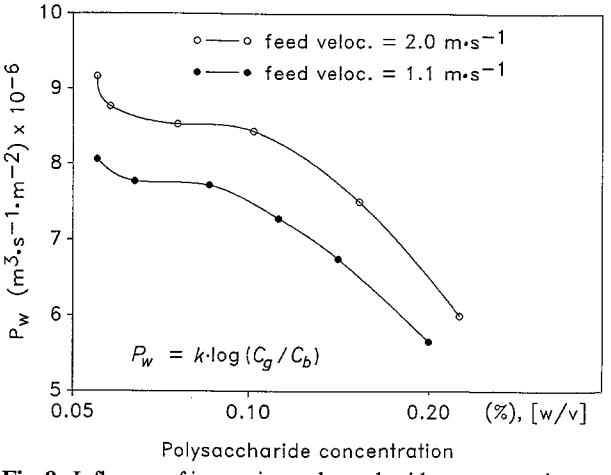

Fig. 8. Influence of increasing polysaccharide concentrations at different tangential feed velocities. The plots refer to Eq. (6); Prostak flat membrane module, 0.1 µm, $C_{PS} = 0.05\%$ (w/v)

correlation coefficients are $r^2 = 0.995$ and $r^2 = 0.997$, respectively.

In conformity with literature [13] the observed decrease in rates of permeation in the last part of the concentration run cannot be ascribed solely to the decrease in Reynolds numbers. The compressibility of the material forming the layer would lead to reduced permeability as well. With regard to microfiltration membranes with larger pores clogging does contribute to a further loss of permeability.

In the case of purification of cell-free polysaccharide solutions the protein content of the solutions could be reduced by more than 70% (Fig. 10). Purifications performed in a "cross-flow diafiltration mode" resulted in a reduction of more than 90% of protein content. Full protein removel could not be achieved in consequence of layer formation (layer compaction) which contributes to higher retention.

4.2 Shear stress produced by the WAUKESHA pump and CFF system

There are two main criteria of product quality: 1) high purity and 2) high viscosity of the polysaccharide solutions. Considering its relatively high molecular weight ($11 \cdot 10^6$ g/mol) the polysaccharide should not be exposed to vigorous shear stress. The extent of shear stress depends mainly upon flow channel geometry, tangential feed velocity (wall shear stress) and the circulation pump.

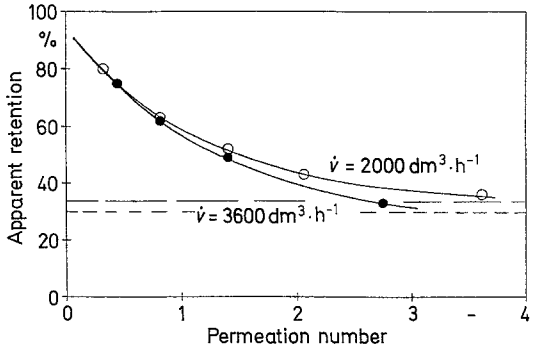

Fig. 10. Retention characteristic of the Prostak flat membrane module with regard to the feed protein concentration; initial C_{prot} = 0.038% (w/v)

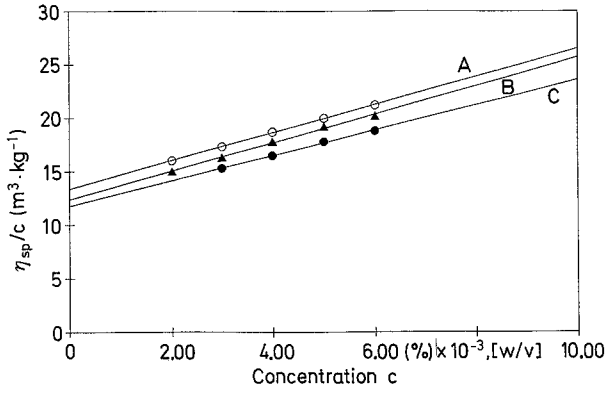

Fig. 11. Shear stress produced by the WAUKESHA pump and cross-flow filtration system (Prostak)

Table 2. Comparison of the recirculation pumps tested. The shear stress is expressed by the relative decrease of the viscosity of polysaccharide solutions of 0.05%

Pump	Used volume [$m^3 \times 10^{-3}$]	Feed stream [$(m^3 \cdot s^{-1}) \times 10^{-3}$]	Relative decrease of viscosity [%]
Amicon gear-pump [1]	5	0.3	46
Millipore mohno-pump [2]	10	1.0	33
Filtron sinus-pump [3]	10	1.0	20
Waukesha circuit-piston-pump [4]	10	1.0	5

[1] Amicon GmbH, Witten, FRG; [2] Millipore, Eschborn, FRG; [3] Filtron, Karlsruhe, FRG; [4] Intertechnik, Elze, FRG

In Table 2 four different circulation pumps, which were tested with respect to their shear stress, are presented. The investigations were carried out with polysaccharide solutions containing polysaccharide of 0.05% (w/v). After 1 h of recirculation the viscosity was measured anew (0.3 to 300 s^{-1}, 40 °C). The relative decrease in viscosity is indicated in Table 2. Thus, the WAUKESHA circuit-piston-pump resulted in very low shear stress. In order to verify this result, samples of the polysaccharide solution were dialysed and the intrinsic viscosity subsequently measured (Fig. 11; before shear stress: curve A; after shear stress: curve B). The influence of the Prostak-flat-membrane module was investigated as well.

The plots of graph C in Fig. 11 present the shear stress produced by the WAUKESHA pump and the Prostak module. It can be seen that the recirculation pump is the mainly contributes to the decrease in viscosity.

5 Conclusions

Cross-flow filtration offers an economical and practical alternative method for separating cells and product purification, respectively. Yet in some cases it involves many of the problems encountered in dead-end filtration. However, high cross-flow velocities and reversed flow cleaning (depending on the filter housing/material) contribute to minimizing deposition of cells or macromolecules at the membrane surface. In the case of fungal cell separation from highly viscous culture broths cross-flow filtration could be combined with a coarse preseparation of cells with the aid of highly porous filter material such as sieves or gauze integrated in a continuously working flow bioreactor.

Further optimization of parameters, e.g. tangential feed velocity, transmembrane pressure, temperature and initial concentration of solutants/cells, make such dynamic filtration processes competitive with conventional separation/filtration devices. In order to overcome problems arising from highly viscous culture broths, product purification should be performed in a "cross-flow diafiltration" mode. Thus, steady-state conditions would not only contribute to reduced layer formation but would minimize problems arising from increased viscosities as well.

Regarding to the economic point of view such a process should be easy to integrate into a continuously working production plant. Nevertheless, it must be kept in mind that the downstream processing of biotechnical products will amount to the majority of the production costs.

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