Concentration of Benzylpenicillin Sodium by Polyimide Nanofiltration Membrane

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ABSTRACT: In this work, a nanofiltration membrane prepared from soluble polyimide (HQDPA-DMMDA) was used to concentrate benzylpenicillin sodium solutions at 10 and 14°C. Three benzylpenicillin sodium solutions with the concentration of 7.2, 13.0, and 19.7 g/L were used. The pressure varied from 0.5 to 2.0 MPa. The rejection reached 85% for the solution of 19.7 g/L under 2.0 MPa. To the solution of 7.2 g/L, the largest permeation flux was 9.5 kg/m^2 h. Temperature had a slight influence on flux, but the influence on rejection was complicated. A sharp increasing phenomenon of rejection appeared under 0.5 MPa when the concentration was 19.7 g/L. This was elucidated by Martínez-Landeira's works on benzylpenicillin's colloids. J Appl Polym Sci 104: 3077–3081, 2007

Key words: nanofiltration; polyimide; antibiotics; benzylpenicillin

INTRODUCTION

Antibiotics are very useful for human beings. They are mainly produced by fermentation. One of the major problems in the production of fermentation is the concentration and purification of antibiotics from the fermented broth.[1,2] The conventional steps are: filtration (removal mycelial cells), solvent extraction (isolation and purification), and subsequent crystallization. During solvent extraction, antibiotics are extracted into an immiscible organic phase, such as *n*-butylacetate at certain pH value, and concentrated by vacuum distillation. The purification cost may vary from 20 to 50% of the total production cost.[2]

Membrane separation technologies have an improved efficiency and reduced operating cost in comparison with the traditional concentration processes. For the antibiotic's production of fermentation, ultrafiltration (UF) was applied to remove the emulsifying agents by some researchers on lab and pilot scale.[1,2] Nanofiltration (NF) is a relative new membrane separation technology.[3] NF is a pressure driven membrane process, falling in between reverse osmosis (RO) and UF. The molecular weight cut-offs (MWCO) of NF membranes are from 200 to 1000 Da. The molecular weights (MW) of most antibiotics are in the range of 200–1200 Da, coincident with the range of MWCO of NF membranes. So, NF is fit for the direct concentration and purification of antibiotics from the ultrafiltrated broths.[1,2,4] Compared with RO, NF can provide many advantages, such as lower operating pressure, larger permeation flux, and removing inorganic ions with significant charges.[2] Benzylpenicillin (penicillin G) is a widely used antibiotics produced by fermentation. To our knowledge, few studies on concentration of benzylpenicillin sodium by NF were carried out until now.

Polyimides are special engineering plastics. They are often used as gas separation membrane materials for their rigid polymeric chains and large free volumes. Polyimides can resist many organic solvents. Soluble polyimides can be prepared easily as separation membranes by phase inversion methods.[5,6] Polyimide (HQDPA-DMMDA), (1,4-bis (3,4-dicarboxyphenoxy) benzene dianhydride (HQDPA)-2,2′-dimethyl-4,4′-methylene dianiline (DMMDA)) is a new soluble polyimide. It was as an excellent separating membrane material in recent years for the dehumidification of compressed air, separation of water/ethanol, methanol/MTBE, and H_2/N_2.[7–10]

In this work, nanofiltration membrane was prepared with polyimide (HQDPA-DMMDA) by phase inversion technique. Benzylpenicillin sodium solutions were concentrated at different conditions by the NF membrane. The distinct advantage of self-prepared membrane over commercial membranes is the structure of self-prepared membrane can be adjusted by ourselves to fit the mixture systems,

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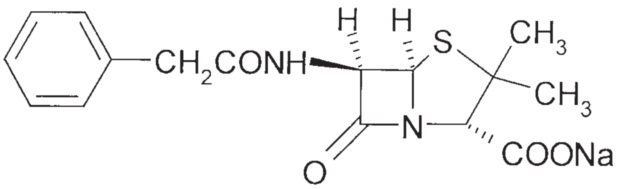

Figure 1 Chemical structure of benzylpenicillin sodium.

although the separation properties of self-prepared membrane may be lower than commercial membranes at this stage.

EXPERIMENTAL

Materials

Benzylpenicillin sodium was purchased from the General Pharmaceutical Factory of Harbin Pharmaceutical Group, China. Figure 1 shows the chemical structure. The molecular weight is 356.38.

Polyimide (HQDPA-DMMDA) was purchased from Changchun Institute of Applied Chemistry, China. Figure 2 shows the chemical structure.

NF membrane preparation

The membrane was prepared by the immersion precipitation phase inversion method. The procedure was as follows. First, (HQDPA-DMMDA) was dissolved in a mixture of *N*-methyl-2-pyrrolidone (NMP) and acetone to form a casting dope. The mass ratio of polyimide, NMP, and acetone were 8:18:8. After filtering and degassing, the polymer solution was cast on PET nonwoven fabric support (MF110, Vilene, Japan) at 40°C. The relative humidity was 40–50%. Then, after exposing in air for 15 s, the formed membrane with nonwoven fabric support was immerged in a water bath to form the asymmetric membrane structure. The membrane was used for NF experiments after three times of solvent exchanging process with distilled water in 24 h. NMP and acetone were purchased from Tianjin Kermel Chemical Reagents Development Centre, China. Figure 3 shows the cross section picture of the NF membrane characterized with a SEM (FEI Quanta 200, USA). The magnification times are 2000×.

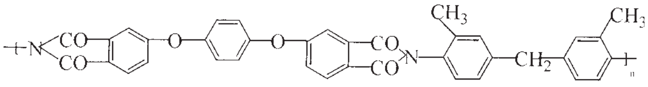

Figure 2 Chemical structure of (HQDPA-DMMDA).

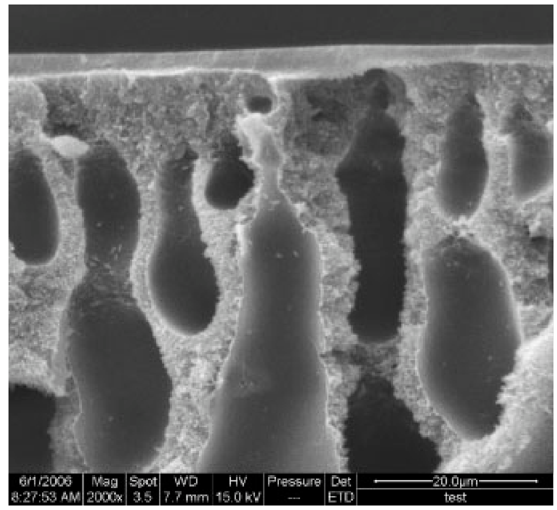

Figure 3 Cross section of (HQDPA-DMMDA) NF membrane.

NF concentration experiments

NF equipment

The NF equipment was a self-made apparatus. Figure 4 shows the schematic drawing of the NF equipment. The membrane was supported by a porous stainless steel disc in the cell (6). The effective filtration area was 50.3 cm^2.

Experimental conditions

The experiments were carried out at 10 and 14°C since penicillin is very sensitive to hydrolysis at temperature higher than 15°C.[2] The temperature was maintained by the refrigerating apparatus (2) and a cooling coil inside the feed tank (1). The transmembrane pressure varied from 0.5 to 2.0 MPa, which

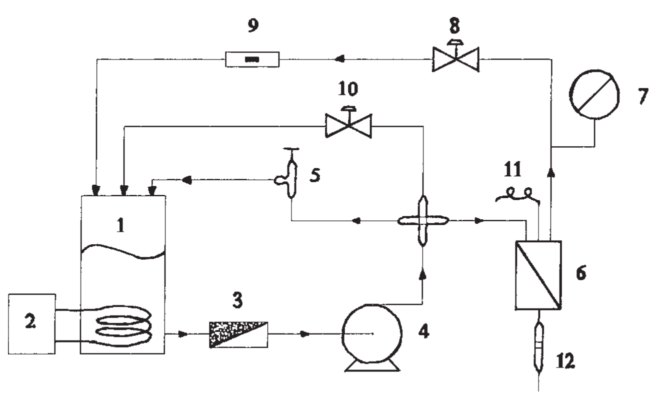

Figure 4 Schematic drawing of NF experimental equipment. (1) feed tank, (2) refrigerating apparatus, (3) safe filter, (4) pump, (5) safe valve, (6) membrane cell, (7) pressure meter, (8) back pressure valve, (9) flowmeter, (10) bypass valve, (11) thermal couple, (12) permeation.

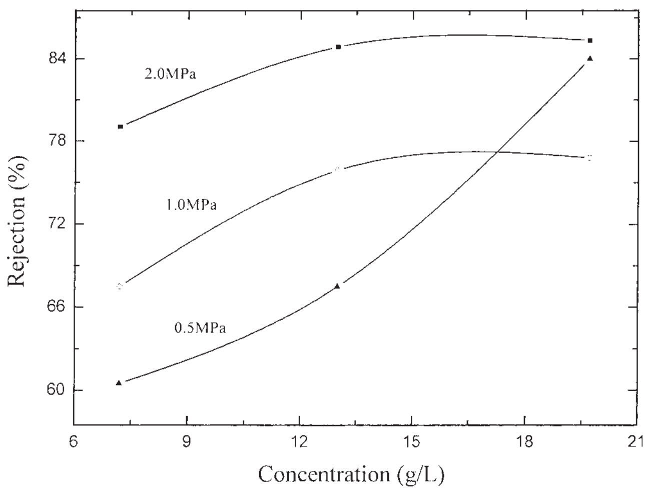

Figure 5 Rejection versus concentration at 10°C.

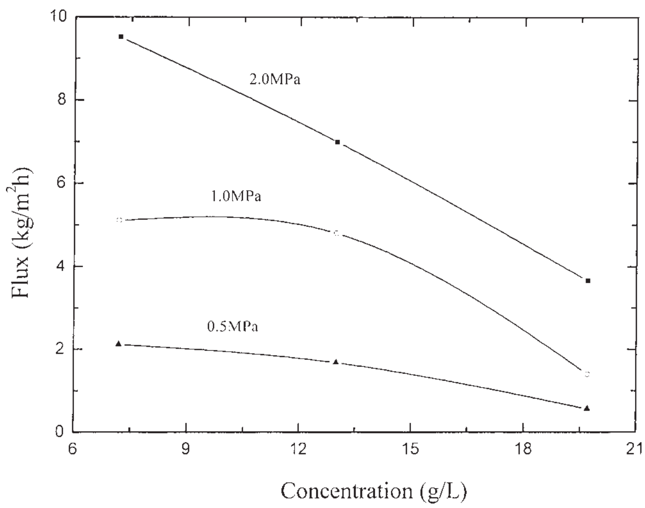

Figure 6 Flux versus concentration at 10°C.

was adjusted through controlling the back pressure valve (8) and bypass valve (10).

The feed solutions of benzylpenicillin sodium were prepared by dissolving benzylpenicillin sodium in distilled water containing NaH_2PO_4, Na_2HPO_4. The pH value of feed solutions was maintained at 6, measured by a pH meter (Sartorius PB-10, Germany). Three feed solutions with different concentration of benzylpenicillin sodium were used. The concentration was 7.2, 13.0, and 19.7 g/L, respectively. The concentrations changed slightly during the NF experiments, so they were taken as constant. NaH_2PO_4, Na_2HPO_4 were purchased from Tianjin Kermel Chemical Reagents Development Centre, China.

NF parameters

The rejection R is defined as follows to represent the rejection ability of the NF membrane:

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

where C_p and C_f are the concentrations of benzylpenicillin sodium in the permeation and feed side, respectively. The concentrations in the feed side and permeation were measured by a UV–vis spectrophotometer (T6, Beijing Purkinje General Instrument, China). Permeation flux was measured by an electronic balance (AR2140, Ohaus, Pine Brook, NJ).

RESULTS AND DISCUSSION

Figure 5 shows the rejection versus concentration under three operating pressures at 10°C. Figure 6 shows the flux versus concentration at the same conditions. In Figure 5, the rejection increases when pressure and concentration of benzylpenicillin sodium increase. For the solution of 19.7 g/L, the rejection reaches 85% under 2.0 MPa. In Figure 6, the flux increases with the increasing of pressure, but decreases with the increasing concentration for each pressure. The largest flux is 9.5 kg/m^2 h for the solution of 7.2 g/L at 10°C.

In Figure 5, the rejection for 19.7 g/L increases sharply under 0.5 MPa, but the flux does not decreased rapidly (Fig. 6). Figure 7 shows the same phenomenon for the solution of 19.7 g/L at 14°C. Figure 8 shows the flux versus pressure for the solution of 19.7 g/L at 14°C. Generally, the increasing rejection corresponds with the decreasing flux for the membrane separating technologies. So, the phenomenon seems *abnormal*. A new colloidal result about benzylpenicillin sodium found by Martínez-Landeira et al. may give an explanation to the phenomenon.

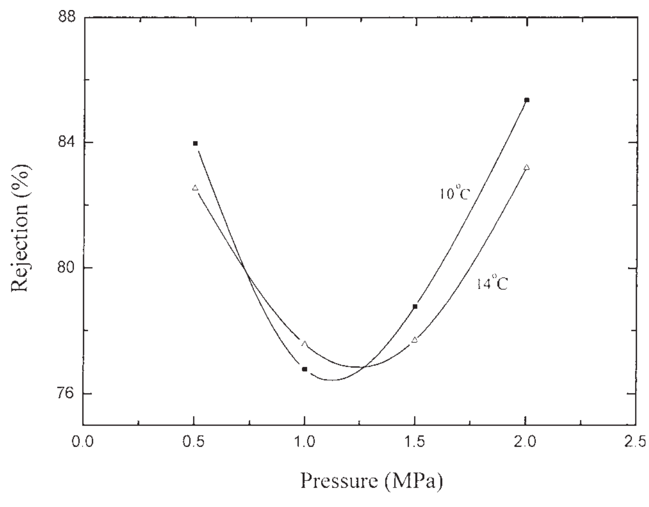

Figure 7 Rejection versus pressure for the solution of 19.7 g/L.

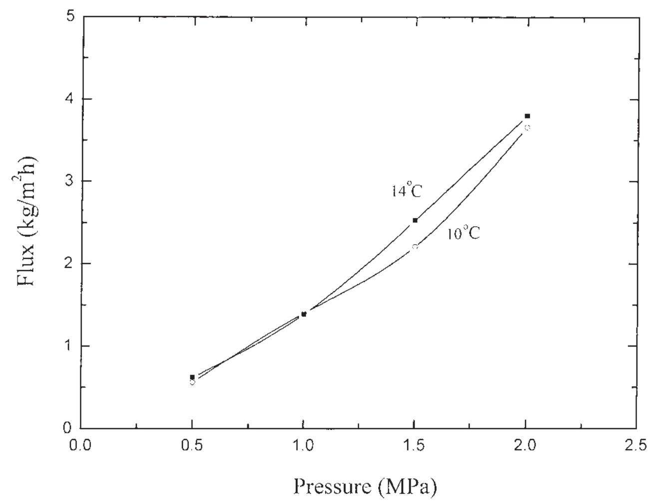

Figure 8 Flux versus pressure for the solution of 19.7 g/L.

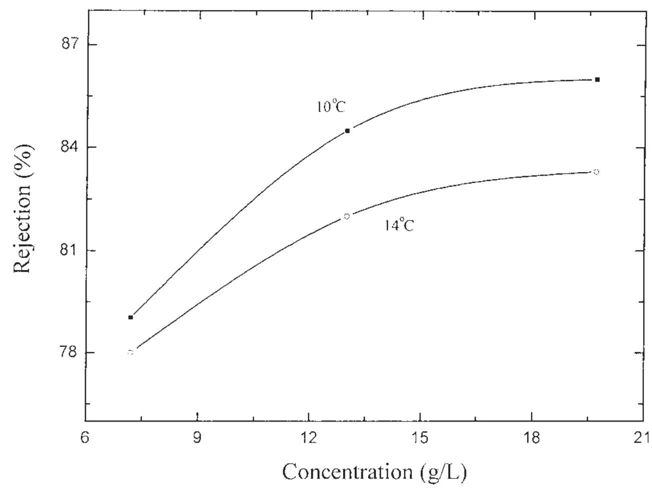

Figure 10 Rejection versus concentration under 2.0 MPa.

Braeken et al. investigated the influence of molecular size and hydrophobicity of dissolved organic compounds in aqueous solution on retention of some commercial NF membranes. They found that molecular size of organic compound has big influence on the retention when the molecular size of the organic compound, compared to the MWCO of NF membrane, increases.[11] Martínez-Landeira et al. found that benzylpenicillin could form aggregates in aqueous solution at certain condition.[12] At 15°C, the critical premicelle concentration (cpc) of benzylpenicillin sodium was 0.11 mol/kg, and the critical micelle concentration (cmc) was 0.26 mol/kg. Benzylpenicillin formed dimers at cpc, then these dimers self-assembled into micelles at cmc.[12] In our NF experiment, the concentration of 19.7 g/L equals to 0.055 mol/kg, which is smaller than cpc and cmc.

However, the concentration polarization always exists in any membrane process. The solute concentration at the membrane surface is much higher than that in bulk solution because of the reversible accumulation of the rejected solute.[13] It is impossible to measure the solute concentration at the membrane surface directly. Some concentration polarization models based on chemical engineering are complicated.[13] So, in the experiment, the concentration of benzylpenicillin at the membrane surface can reach to cpc if concentration polarization is enough strong. When benzylpenicillin sodium formed dimer, the molecular size increased. According to Braeken et al.'s conclusion, the rejection will increase sharply. It is inconsequent that this phenomenon does not appear under 1.5 and 2.0 MPa (Fig. 5). The possible reason is that pressure has some influences on the aggregates at the polarization layer. However, the experimental verification will be complicated, and the question goes beyond the research contents of this experiment.

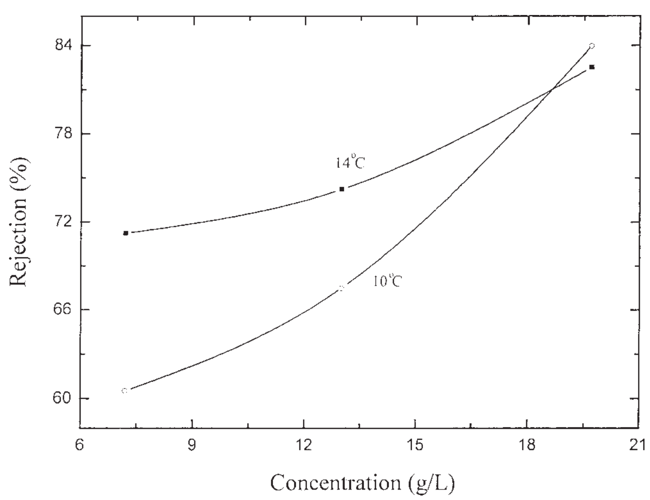

Figure 9 Rejection versus concentration under 0.5 MPa.

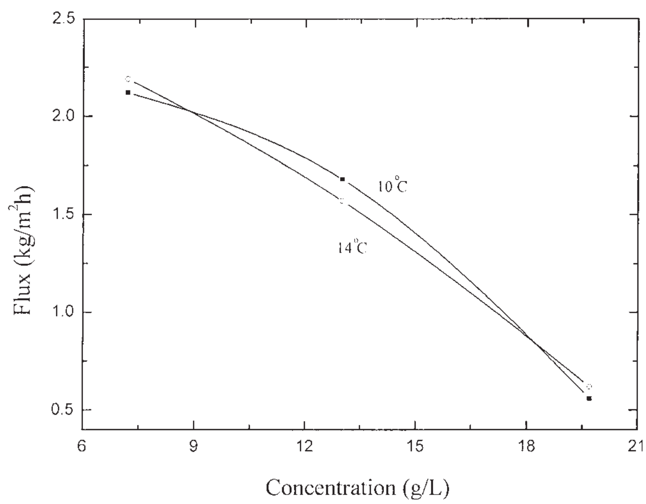

Figure 11 Flux versus concentration under 0.5 MPa.

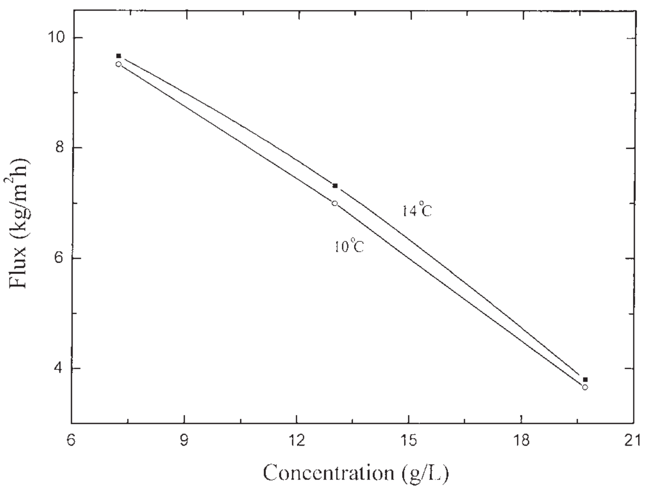

Figure 12 Flux versus concentration under 2.0 MPa.

The influences of temperature on rejection and flux are shown in Figures 9–12. From Figures 9 and 10, the impact of temperature on rejection is different under 0.5 and 2.0 MPa. It is difficult to explain the temperature behavior with a single NF mechanism because the permeation performance of solute are decided by several factors, such as pressure potential, concentration potential, membrane structure, and temperature.

The influences of temperature on flux under 0.5 and 2.0 MPa are similar (Figs. 11 and 12). The flux decreases slightly when the temperature decreases from 14 to 10°C. The reason is that the permeation is almost pure water, and the decreasing temperature increases the viscosity of water.

CONCLUSIONS

In this research, a nanofiltration membrane prepared from soluble polyimide (HQDPA-DMMDA) by the immersion precipitation phase inversion method was used to concentrate benzylpenicillin sodium solutions at 10 and 14°C. The concentration of three benzylpenicillin sodium solutions was 7.2, 13.0, and 19.7 g/L, respectively. The pressure varied from 0.5 to 2.0 MPa. The rejection reached 85% for the solution of 19.7 g/L under 2.0 MPa. To the solution of 7.2 g/L, the largest permeation flux was 9.5 kg/m^2 h. Temperature had a slight influence on flux, but the influence on rejection was complicated. In addition, a sharp increasing phenomenon of rejection appeared under 0.5 MPa when the concentration was 19.7 g/L. This was elucidated by Martínez-Landeira's works on benzylpenicillin's colloids.

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