COMPARISON OF SOLUTE PERMEABILITY AND REJECTION CHARACTERISTICS OF NORMAL AND HIGH FLUX CELLULOSE HAEMODIALYSIS MEMBRANES

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Summary

Permeability and rejection properties of new, high flux cellulose membranes and fibres have been compared with Cuprophan PM 150. The greater solute and water flux is explained in terms of larger 'pores', which permit greater transport of large molecules.

Introduction

Patient preference for shorter treatment time, together with a desire for more efficient utilisation of clinic facilities, has led to demands for more efficient dialysers. Increases in clearance attained through larger membrane area are necessarily accompanied by enlargements in device weight and blood volume, as well as improved ultrafiltration control. The alternative procedure is to utilise more permeable membranes. However, the most widely used membrane, regenerated cellulose, even when prepared in its thinnest form, has been shown to exhibit a marked diminution of clearance with increasing solute molecular weight [1]. It has been the common understanding among membrane chemists that it would not be possible to achieve high solute permeabilities with cellulose, especially at molecular weights greater than 500 daltons. Thus, there has been a continuing emphasis on the development of new membrane materials from synthetic polymers [2–7].

In this report we present permeability and rejection data for a new set of cellulose sheet and hollow fibre membranes that have significantly increased permeation properties for larger solutes. The cellulose films and fibres investigated retain the hydrophilic properties generally associated with this polymer, but respond to concentration and pressure gradients as if they contained pores characteristic of the more hydrophobic synthetic membranes made from polysulfone or polyacrylonitrile presently being used in haemofilters [8].
Experimental

Sample Preparation

Three types of high permeability Cuprophan* membrane were tested; type 210 PM sheet, type HDF sheet, and type D2-HDF hollow fibre. Comparisons with types 150 PM sheet and type D2-IM hollow fibre were made with data previously obtained in this laboratory.

Sheet membranes were received dry and rinsed in demineralised water 30 min before testing. Hollow fibres were potted into test bundles 16–18cm long containing 160 fibres. Detailed procedures for fibre bundle preparation, including a description of the test device to mount the fibre bundles, have been reported previously [9]. The method used to wash the fibres free of bore packing fluid (isopropyl myristate) varied with fibre type. Type D2-IM fibres were washed with isopropanol, whereas type D2-HFD fibres were washed with Freon 113 (1,1,2-trichloro-2,2,1-trifluoroethane). Fibre bundles were washed by soaking and then flushing the lumens with solvent.

Transport Measurements

A description of methods used to determine flat sheet and hollow fibre membrane diffusive permeability ($P_M$) in this laboratory has been published previously [1,9]. More recently, methods employed by us to determine rejection of solutes by haemofiltration membranes were presented [10].

Solute rejection by the walls of hollow fibres was measured in a device similar to that used to measure diffusive permeability of fibre bundles, except that no dialysate was present. The fibre lumens were perfused with a solution containing the test solutes; the circuit was a closed loop which could be pressurised; fibre exteriors were at atmospheric pressure. Volume flux was determined during timed intervals by the mass of ultrafiltrate collected and a knowledge of the bundle surface area. Rejection was calculated from the circulating solute concentrations in the lumens and in the ultrafiltrate, by analytical methods previously cited. Observed rejections ($R_{obs}$) were corrected for concentration polarisation (using a numerical method based on thin film theory for laminar flow [11]) to provide $R_{corr}$; the latter was fitted to the Spiegler-Kedem equation by a non-linear least-squares procedure to estimate limiting rejection, $\sigma$, and $P_M$.

All data reported were obtained at 37°C and represent true membrane properties free of concentration polarisation, as defined in the general flux equation [12]:

$$J_s = P_M \Delta C + \bar{C}(1-\sigma)J_v$$  \hspace{1cm} (1)

where $\Delta C$ is the concentration gradient across the membrane, $\sigma$ is the limiting rejection, and $\bar{C}$ is the mean solute concentration in the membrane wall, assuming equilibrium at both faces of the membrane. $J_s$ and $J_v$ are solute and volume flux at any point on the membrane.

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Results and Discussion

Figure 1 illustrates the relative diffusivity of various test solutes through each of the membranes tested. Relative diffusivity is calculated as the product of membrane permeability \( P_M \) times the wet thickness (\( \ell \)), divided by the solute diffusion coefficient in saline at 37°C (\( D^{37} \)). This ratio represents the efficiency of transport through the membrane, since the solute could not be expected to move more rapidly through a membrane than through an equivalent path length of saline solution. For a membrane that offers no resistance to transport, the ratio has a value of 1.0; for an impermeable membrane the ratio is zero. All membranes tested follow a pattern of decreasing relative diffusivity with increasing molecular size of the test solute. In Figure 1, responses of the higher flux membranes and fibres show a less pronounced decrease with increasing solute molecular weight than do corresponding lower flux membranes. Comparison of the HDF fibre and the HDF sheet indicates that the fibre has a lower molecular weight "cut-off" than sheet membrane; inulin permeabilities of the sheet are nearly twice as great as those of the fibre as a consequence of this, although urea permeabilities are similar.

Relative diffusivity can be interpreted to be a function of test solute hydrodynamic radius, membrane pore radius, and membrane cross-sectional area available for transport. An analysis of the permeability properties of the membranes
in terms of a pore model based on HTO diffusivity, and hydraulic conductivity leads to estimates of membrane pore sizes and fractional pore area available for transport. Applying such a pore model to the present samples yields the geometrical parameters listed below:

<table>
<thead>
<tr>
<th>Membrane</th>
<th>150 PM</th>
<th>210 PM</th>
<th>HDF</th>
<th>D2-HDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pore radius (cm x 10^8)</td>
<td>17.2</td>
<td>29.9</td>
<td>36.6</td>
<td>49.2</td>
</tr>
<tr>
<td>Fractional Pore Area</td>
<td>0.30</td>
<td>0.34</td>
<td>0.34</td>
<td>0.34</td>
</tr>
</tbody>
</table>

For the sheet membranes the average pore size increases from type 150 PM to 210 PM to the HDF membrane; or in the same order as is found for increases in the hydraulic permeability ($L_p$) (Table I). There are small differences in the fractional area of the membranes available for transport, with the 150 PM membrane having the lowest value.

**TABLE I. Membrane Diffusive Peremeability Data**

<table>
<thead>
<tr>
<th>Solute</th>
<th>Molecular weight</th>
<th>PM x 10^4 (cm/sec)</th>
<th>Cuprophan HDF</th>
<th>Cuprophan 210 PM</th>
<th>Cuprophan 150 PM NIH Ref. Lot No.2</th>
<th>D2-IM</th>
<th>D2-HDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTO</td>
<td>20</td>
<td>24.2</td>
<td>19.7</td>
<td>26.7</td>
<td>25.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>60</td>
<td>13.0</td>
<td>9.49</td>
<td>11.5</td>
<td>9.38</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Phosphate (pH &gt; 7.4) (80% HPO_4^2-)</td>
<td>96</td>
<td>4.58</td>
<td>3.00</td>
<td>2.59</td>
<td>–</td>
<td>5.31</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>113</td>
<td>7.47</td>
<td>5.53</td>
<td>5.82</td>
<td>5.33</td>
<td>8.78</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>180</td>
<td>5.00</td>
<td>3.63</td>
<td>3.75</td>
<td>–</td>
<td>6.52</td>
<td></td>
</tr>
<tr>
<td>Sucrose</td>
<td>342</td>
<td>2.78</td>
<td>2.42</td>
<td>1.76</td>
<td>2.19</td>
<td>4.92</td>
<td></td>
</tr>
<tr>
<td>Raffinose</td>
<td>504</td>
<td>2.73</td>
<td>1.83</td>
<td>1.62</td>
<td>–</td>
<td>3.77</td>
<td></td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>1355</td>
<td>1.67</td>
<td>0.965</td>
<td>0.594</td>
<td>0.603</td>
<td>2.07</td>
<td></td>
</tr>
<tr>
<td>Inulin</td>
<td>5200</td>
<td>0.867</td>
<td>0.332</td>
<td>0.120</td>
<td>0.109</td>
<td>0.517</td>
<td></td>
</tr>
<tr>
<td>Cytochrome C</td>
<td>12400</td>
<td>0.107</td>
<td>0.045</td>
<td>&lt; 0.01</td>
<td>–</td>
<td>0.181</td>
<td></td>
</tr>
<tr>
<td>Myoglobin</td>
<td>17000</td>
<td>0.077</td>
<td>0.02</td>
<td>&lt; 0.01</td>
<td>–</td>
<td>0.166</td>
<td></td>
</tr>
</tbody>
</table>

The increased pore dimensions of the high flux samples are reflected in the increased relative diffusivities shown in Figure 1. The larger pores produce less impedance to solute transport through the membranes. The figure also illustrates the increasing impedance to solute transport through 150 PM membranes as
solute size increases and conversely, the lesser response by membranes having larger pore radii. The change in relative diffusivity is greatest as solute dimensions approach those of the pore.

The D2-HDF fibre was found to have the largest average pore dimensions of any of the samples tested; these approximate the values for the Rhone-Poulenc polyacrylonitrile membrane reported earlier [10]. The fact that the inulin permeability for this fibre is less than for the HDF sheet of the same thickness is an anomaly and will need further study.

Convection of solutes in ultrafiltration (in the absence of dialysis) has been described by Spiegler and Kedem [13] to follow the relationship:

$$C_u = C_0 \left[ 1 - \sigma(e^\beta - 1)/(e^\beta - \sigma) \right]$$  \hspace{1cm} (2)

where $C_u$ is solute concentration in the ultrafiltrate, $C_0$ is solute concentration at the pressurised surface of the membrane, $\sigma$ is the reflection coefficient, and $\beta$ is the Peclet number given by:

$$\beta = J_v(1-\sigma)/P_M$$  \hspace{1cm} (3)

Equations (2) and (3) illustrate that the solute concentration in the ultrafiltrate is a function of both intrinsic membrane properties (via $\sigma$, $P_M$, $L_p$) and the conditions of operation ($J_v$). Experimental measurements of rejection ($R=1 - \frac{C_u}{C_0}$) at increasing transmembrane pressures yield data sets such as shown in Figure 2,

Figure 2. Rejection response as a function of transmembrane volumetric flow rate
where the ordinate has been corrected for concentration polarisation effects. Regression analyses of the data on the basis of equation (2) provide estimates for the limiting rejection \( R_{\infty} \) and diffusive permeability. Limiting rejection is often used to predict ultrafiltration membrane performance; however, in clinical applications it is not the significant factor since haemofilters generally operate at transmembrane volume fluxes \( J_v \) well below the maximum; i.e., for 1.0 m\(^2\) dialysers operated to remove 1 kg/hr, the value of \( J_v \) is 0.1 x 10\(^{-4}\) cm/sec, while a haemofilter removing 60 ml/min through an area of 0.5 m\(^2\) operates at a \( J_v \) equal to 2.0 x 10\(^{-4}\) cm/sec.

To predict solute rejection by a given membrane/solute pair, one must know the coefficients of equation (2). The generally applicable rule is that rejection will be lowest at small transmembrane velocities and will then be governed by the ratio \( J_v(1-\alpha)/P_M \). Thus, either low rejection coefficients or large permeability coefficients will reduce solute rejection.

Comparison of inulin data for the HDF sheet and D2-HDF fibre based on convective measurement provides an interesting contrast with the diffusive data. The sheet HDF has greater limiting rejection for inulin than does the D2-HDF fibre, but diffusive permeability for the latter is lower. Since both membranes have essentially the same wet thickness and apparent pore density, the results can be attributed to two possible causes: either there is a marked difference in the pore size distribution of the two materials, or the fibre pores have some residual charge which impedes the large solute apart from steric factors.

In conclusion, a new series of high flux cellulose membranes (both sheet and hollow fibres) prepared by the cuprammonium process is commercially available. The membranes demonstrate increased permeability properties over standard haemodialysis membranes, making them suitable for applications in high efficiency dialysers and haemofilters.

References


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Open Discussion

FUNCK-BRENTANO (Paris) Have you taken into account the Donnan phenomenon in these calculations?

KLEIN The Donnan effects on the solutes we use are very small, because they are neutral.