MCO Membranes: Enhanced Selectivity in High-Flux Class

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BACKGROUND

One of the unmet needs in hemodialysis is the adequate removal of uremic toxins over a broad molecular weight range. As synthetic membranes are less selective than the glomerular membrane, current hemodialysis membranes do not remove higher molecular weight toxins appropriately. Consequently, patients on hemodialysis have higher levels of middle and large molecular solutes in plasma.

Membrane innovation is currently directed towards enhanced removal of uremic toxins and increased membrane permeability. During the last decade, some experience has been gathered with high permeability membranes such as high cut-off (HCO) membranes. Pilot trials with **HCO** membranes indicated that expanded toxin removal might benefit the patient by decreasing the general inflammatory state.

Medium cut-off membranes were designed to deliver expanded toxin removal as observed with **HCO** membranes while retaining albumin (65 kDa)1 so that they are appropriate for regular use in conventional treatment schedules and treatment mode (i.e. 4-hour treatments, three times weekly in Europe).

OBJECTIVE

The aim of this study was to present the characterization of four prototypes of novel **MCO** membranes by dextran filtration[¥]. In addition, the sieving properties of the membranes before and after blood contact were reported, and the pore size during operation (i.e. hemodialysis treatment) was compared to the size of uremic toxins and vital proteins.

[¥]Fractional clearance studies to measure the size selectivity associated with glomerular filtration have universally employed dextran as a test transport probe. It is neither secreted nor reabsorbed by the renal tubules, so its clearance is easily measured.[2]

METHODOLOGY

Four different types of prototype devices denoted as **MCO** membrane 1 to **MCO** membrane 4, which differ in permeability, were investigated. As reference, a HCO device (**Theralite** dialyzer) and a conventional high flux membrane (**Revaclear** dialyzer) were also tested. All devices were manufactured by Gambro Dialysatoren GmbH, Hechingen, Germany. The membrane material was a polyarylethersulfone/polyvinylpyrrolidone blend.

Membranes were characterized in minimodules with the same surface area, nominal length, inner diameter and wall thickness. The minimodules were immersed in water before the filtration experiments. Minimodules intended for characterization after contact with blood for simulating in vivo operation conditions were initially perfused with blood (bovine) for 40 minutes and rinsed afterwards with water.

Dextran solutions were prepared, and filtration experiments were carried out. For experiments run on **MCO** membrane 4, the dextran solution included one additional fraction of 150 kDa, to allow for sieving coefficient (SC) calculation with similar precision as the other **MCO** membranes.

RESULTS

Characterization of the **MCO** high-flux membranes by dextran sieving profiles in aqueous solution (pristine; before blood exposure).

As shown in Figure 1, the sieving curves for the **MCO** membranes are located at the molecular weights between that of the conventional high-flux membrane and **HCO** membrane in aqueous solution (pristine; before blood exposure). The **MCO** membrane sieving curves are similar to the ficoll sieving curve for the glomerular membrane; blood purification membranes should mimic the filtration spectrum of the natural (glomerular) membrane.

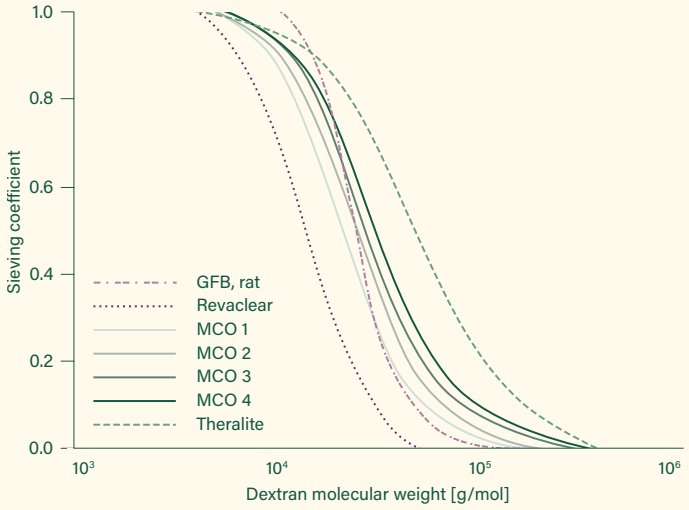

FIGURE 1. Characteristic in vitro dextran sieving curves measured in aqueous solution (pristine/before blood exposure) for different types of blood purification membranes: high-flux (Revaclear, MCO membranes 1-4), HCO (Theralite). Data for glomerural membrane added for comparison (rat specimen, ficoll filtration, measured in vivo).

The values for Medium Weight Retention Onset (MWRO), Medium Weight Cut Off (MWCO) and pore radius (i.e. effective Stokes-Einstein radius calculated from MWCO) are depicted for the four membranes, as well as the conventional high flux membrane and **HCO** membrane in Table 1. The differences between the **MCO** membranes are evident from 1 to 4, showing increased MWRO and MWCO values which indicate increased permeability.

Membrane	Before blood exposure			After blood exposure		
	MWRO [kDa]	MWCO [kDa]	Pore radius [nm]	MWRO [kDa]	MWCO [kDa]	Pore radius [nm]
Revaclear	5.7 ± 0.5	32 ± 3	3.9 ± 0.1	4.4 ± 0.3	14.2 ± 0.2	2.68 ± 0.02
MCO 1	9.4 ± 0.2	56 ± 3	5.0 ± 0.1	5.0 ± 0.4	18.1 ± 0.8	3.0 ± 0.1
MCO 2	10.0 ± 0.6	64 ± 3	5.4 ± 0.1	5.84 ± 0.09	18.2 ± 0.3	3.0 ± 0.1
MCO 3	11.3 ± 0.4	81 ± 9	6.0 ± 0.3	6.32 ± 0.06	22.7 ± 0.8	3.3 ± 0.1
MCO 4[a]	12.1 ± 0.7	99 ± 7	6.5 ± 0.2	6.77 ± 0.06	25 ± 5	3.5 ± 0.3
Theralite	15 ± 1	300 ± 100	10 ± 2	8.1 ± 0.8	40 ± 8	4.3 ± 0.4

Table 1. Characterization of MCO hemodialysis membranes, conventional high-flux and HCO membranes, based on dextran sieving experiments before and after blood exposure. Values are + standard deviation for n=3.*Experiments with **MCO** membrane 4 included one dextran fraction of 150 kDa.

The parameters describing the pore size distribution calculated from the sieving profiles for the same membranes are detailed in Table 2. The presented values assess the mean and broadness of the pore size distribution. The values of the mean of the distribution increase with membrane permeability. The variance of the respective distribution is larger as the pore sizes increase. The pore size distribution for all membranes is narrower after blood contact, indicating that the selectivity of synthetic membranes improves during the operation.

Membrane	Before blood exposure		After blood exposure	
	Mean [nm]	Variance [nm]	Mean [nm]	Variance [nm]
Revaclear	3.0 ± 0.3	2 ± 1	2.42 ± 0.08	0.587 ± 0.003
MCO 1	4.1 ± 0.2	4.7 ± 0.8	2.5 ± 0.1	0.6 ± 0.2
MCO 2	4.0 ± 0.2	4.6 ± 0.4	2.55 ± 0.07	0.7 ± 0.1
MCO 3	4.40 ± 0.03	6.4 ± 0.1	2.9 ± 0.1	1.3 ± 0.4
MCO 4	4.8 ± 0.2	8.8 ± 0.4	3.3 ± 0.6	3 ± 3
Theralite	5.1 ± 0.3	11 ± 2	3.4 ± 0.2	2 ± 1

Table 2. Mean (pore radius) and variance of the log-normal pore size distribution for the 4 MCO prototype membranes, conventional high-flux and HCO membranes before and after blood exposure. Values are average ± standard deviation for n=3. Adapted from Boschetti-de-Fierro et al.

The challenge in developing novel high-flux membranes with toxin removal capabilities similar to **HCO** membranes while retaining albumin adequately resides in the membrane manufacturing process. Increasing pore sizes usually leads to an increase in the broadness of the pore size distribution, causing undesirable albumin permeation. Controlled membrane manufacture allows some improvement in this direction. As can be seen, the **MCO** 4 membrane shows similar mean pore size to **Theralite** (HCO), while having a 20% smaller variance. The less permeable versions, **MCO** 1 and **MCO** 2 membranes, show mean pore size around 4 nm with less than half the variance of **Theralite**. This indicates that the **MCO** membranes offer enhanced selectivity compared to **HCO** membranes.

Membrane Classification After Blood Contact

The sieving curves before and after exposing the **MCO** membranes to blood are shown in Figure 2. After blood exposure, the sieving curves were shifted toward lower molecular weights, and the sieving profiles indicate that the **MCO** membranes are less permeable than the glomerular membrane.

The natural formation of the protein layer on top of the synthetic membrane during hemodialysis gradually affects the solute removal during the first 40 minutes of treatment. This phenomenon is illustrated by the comparison of the sieving characteristics before and after blood contact. While the pristine **MCO** membrane allows the passage of molecules above 70 kDa to some extent, the sieving profile of the **MCO** membranes (as that of every artificial membrane) shifts towards lower molecular weights during operation. This circumstance is a compromise to deliver a tailored removal after the inevitable membrane fouling. As the hemodialysis treatment time is around 4 hours in Europe, this means that during more than 80% of the treatment blood purification is accomplished by a membrane the performance of which is governed by protein fouling. The **MCO** membranes show sieving profiles close to that of the natural kidney after the formation of the protein layer, thereby maintaining the required performance along the treatment.

The effective pore size is an indication for the biggest molecules that will pass through the membranes. The effective pore size of the **MCO** membranes is between 3.0 and 3.5 nm after blood contact/formation of the protein layer (see Table 1), indicating that the membranes retain albumin (hydrodynamic radius of 3.51 nm) (65 kDa)[1] during treatment. Additionally, the least permeable **MCO** membrane has an effective pore radius of 3.0 nm during treatment (Table 1), which should allow adequate removal of large uremic toxins, up to lambda free light chains (λ-FLCs) (45 kDa)[1] with a hydrodynamic radius of 2.8 nm. See Table 3 for hydrodynamic radius (Rh) for albumin and representative middle and large uremic toxins.

Molecule	R_h [nm]	Comments	Ref.
β2 microglobulin	1.7	calculated from the diffusion coefficient in free solution	16
Tumor necrosis factor (TNFα)	1.9-2.3	depending on its aggregation state, influenced by concentration and pH	17
Free light chains (FLC) monomeric state (mostly κ-FLC)	2.3	Stokes' radius determined by chromatography	18
Free light chains (FLC) dimeric form (mostly λ-FLC)	2.8	Stokes' radius determined by chromatography	18
Albumin	3.51	calculated from the intrinsic viscosity (agrees with Stokes' radii from diffusion and sedimentation coefficient)	19

Table 3. Hydrodynamic radius (Rh) for albumin and some representative middle and large toxins. Adapted from Boschetti-de-Fierro et al.

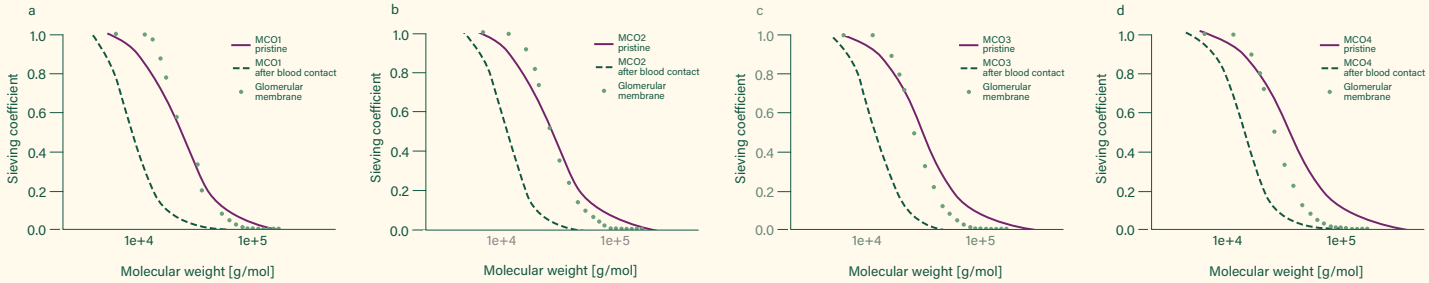

Figure 2. Characteristics of sieving curves for MCO high flux membranes before (solid line) and after blood contact (dashed line), for (a) MCO 1, (b) MCO 2, (c) MCO 3, (d) MCO 4. The data for the glomerular membrane has been added for comparison (rat specimen, ficoll filtration, measured in vivo).

Based on the data presented, it can be presumed that some albumin permeation takes place even after the formation of the protein layer for the most permeable membrane **MCO** 4. This effect, if properly controlled, is not necessarily detrimental to the patients. Albumin loss is tolerated to some extent, as demonstrated in peritoneal dialysis patients where weekly albumin losses of 21–42 g/1.73 m^2 are accepted and not linked to outcome detriment.

CONCLUSION

The novel **MCO** membranes provide for large pore sizes with appropriate pore size distribution and permeability close to that of the natural kidney. Their MWCO values suggest that, when used in hemodialysis treatments, they allow for removal of an expanded range of uremic toxins compared to conventional high-flux membranes. A formation of a protein layer on top of the synthetic membrane during hemodialysis restricts the removal of molecules above 3.5 nm in radius, ensuring the retention of albumin during a treatment, while still optimizing removal of large uremic toxins.

Tailored pore sizes of MCO membrane promote removal of an expanded range of uremic toxins, while ensuring retention of albumin. The unique design of the MCO membrane allows for a filtration profile that's closer to the natural kidney.

References:

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2. Editorial Review, Change Selectivity in Kidney Ultrafiltration, *Kidney International*. 1995; 47:1242-1251.