Acta Biomaterialia 8 (2012) 2279–2287

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

A novel approach for blood purification: Mixed-matrix membranes combining diffusion and adsorption in one step

Marlon S.L. Tijink [a,b], Maarten Wester [c], Junfen Sun [b,d], Anno Saris [a,c], Lydia A.M. Bolhuis-Versteeg [a], Saiful Saiful [b,e], Jaap A. Joles [c], Zandrie Borneman [b], Matthias Wessling [b,f], Dimitris F. Stamatialis [a,b,*]

[a] Institute for Biomedical Technology and Technical Medicine MIRA, Biomaterials Science and Technology, University of Twente, Faculty of Science and Technology, P.O. Box 217, 7500 AE Enschede, The Netherlands
[b] Membrane Technology Group, University of Twente, Faculty of Science and Technology, P.O. Box 217, 7500 AE Enschede, The Netherlands
[c] Department of Nephrology and Hypertension, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands
[d] State Key Laboratory for Modification of Chemical Fibers and Polymer Materials, College of Material Science & Engineering, Donghua University, North People Rd. 2999, Songjiang, Shanghai 201620, PR China
[e] Chemistry Department, Faculty of Math and Natural Science, Syiah Kuala University, Darussalam, Banda Aceh 23111, Indonesia
[f] Chemical Process Engineering, RWTH Aachen University, Turmstrasse 46, 52064 Aachen, Germany

ARTICLE INFO

Article history:
Received 25 October 2011
Received in revised form 24 February 2012
Accepted 2 March 2012
Available online 9 March 2012

Keywords:
Mixed-matrix membranes (MMM)
Activated carbon
Creatinine
Adsorption
Blood purification

ABSTRACT

Hemodialysis is a commonly used blood purification technique in patients requiring kidney replacement therapy. Sorbents could increase uremic retention solute removal efficiency but, because of poor biocompatibility, their use is often limited to the treatment of patients with acute poisoning. This paper proposes a novel membrane concept for combining diffusion and adsorption of uremic retention solutes in one step: the so-called mixed-matrix membrane (MMM). In this concept, adsorptive particles are incorporated in a macro-porous membrane layer whereas an extra particle-free membrane layer is introduced on the blood-contacting side of the membrane to improve hemocompatibility and prevent particle release. These dual-layer mixed-matrix membranes have high clean-water permeance and high creatinine adsorption from creatinine model solutions. In human plasma, the removal of creatinine and of the protein-bound solute para-aminohippuric acid (PAH) by single and dual-layer membranes is in agreement with the removal achieved by the activated carbon particles alone, showing that under these experimental conditions the accessibility of the particles in the MMM is excellent. This study proves that the combination of diffusion and adsorption in a single step is possible and paves the way for the development of more efficient blood purification devices, excellently combining the advantages of both techniques.

1. Introduction

The prevalence of end-stage renal disease (ESRD) was ~535,000 in the USA in 2008. Of these patients, ~355,000 were treated with hemodialysis. Despite the high health care costs of dialysis treatment (over €50,000 per patient per year), hemodialysis is only partially successful in the treatment of patients with ESRD. Mortality (15–20% per year) and morbidity of these patients remain excessively high, whereas their quality of life is generally low [1]. This is reflected in the expected remaining life years, which are 25.0 years for the general US population, 15.7 for ESRD patients with a kidney transplant and 5.6 years for ESRD patients receiving dialysis treatment [2].

In the last three decades, sorbent technology has been applied in the treatment of severe intoxication and to increase the efficiency of hemodialysis, or replace it, and as a treatment for fulminant hepatic failure. In hemoperfusion (or plasma perfusion), blood (or plasma) is purified by extracorporeal passage through a column containing the adsorbent which can remove or neutralize the substance of interest. Hemoperfusion cannot fully substitute hemodialysis because it does not remove urea and excess fluid. Sorbents used in hemoperfusion help to remove uremic toxins; however, direct blood contact with the adsorbent often causes hemocompatibility issues, especially on the long term [3]. Activated carbon (AC) has a long record as a sorbent in blood purification in the case of intoxications, acute and chronic renal failure as well as liver failure [3–5]. Uncoated activated carbon is a strong adsorbent for uremic toxins [6] whereas polymeric coatings of activated carbon might

* Corresponding author at: Institute for Biomedical Technology and Technical Medicine MIRA, Biomaterials Science and Technology, University of Twente, Faculty of Science and Technology, P.O. Box 217, 7500 AE Enschede, The Netherlands. Tel.: +31 53 489 4675; fax: +31 53 489 2155.
E-mail address: d.stamatialis@utwente.nl (D.F. Stamatialis).

1742-7061/$ - see front matter © 2012 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.actbio.2012.03.008

help to improve hemocompatibility. However, coated activated carbon could still release carbon fragments, even after careful washing, and a double coating process is needed to overcome this problem [7]. In conventional hemoperfusion columns, optimal distribution of blood flow within the packed sorbent bed is very important for adequate use of the adsorption capacity, especially with rather viscous and complex solutions like blood or plasma. Channelling within the column leads to suboptimal adsorption and can induce blood coagulation. Furthermore, micro-particles that can be released into the circulation and can cause emboli are always a concern related to hemoperfusion.

It is obvious that a combination of the strengths of dialysis membranes with the adsorption power of high surface area sorbents can be very beneficial for the blood purification efficacy [8]. In fact, in the late 1970s so-called sorbent membranes were developed. These membranes were even on the market for a certain period, produced by Enka [9–15]. However, due to their quick saturation, manufacturing difficulties, reduced patient convenience and lack of adsorbents with high purity [16–19], they were quickly abandoned. More recently, membrane filtration and adsorption columns are often combined as two separate steps in wearable artificial kidneys [20,21].

In this paper, we propose a novel membrane concept for combining diffusion and adsorption of uremic retention solutes in one step: the so-called mixed-matrix membrane (MMM). In this concept, adsorptive particles are incorporated in a macro-porous membrane matrix. A particle-free membrane layer is introduced on the blood contacting side of the membrane, aiming to improve membrane hemocompatibility and prevent particle release into the circulation and hence emboli formation (see Fig. 1).

Mixed-matrix membranes have been proposed as an alternative for traditional chromatographic columns [22,23]. Compared to conventional columns, they have low flow resistance, which allows the use of smaller particles, resulting in an improved adsorption capacity and adsorption kinetics [24,25]. Furthermore, the particles can be homogenously distributed by embedding them in the matrix, leading to optimal adsorption efficiencies and preventing quick saturation.

Here, for the proof of concept, we prepare and investigate flat sheet MMMs using materials with an excellent record in blood purification. A polyethersulfone (PES)/polyvinylpyrrolidone (PVP) polymer blend is used for the preparation of the macro-porous membrane matrix (PES as a membrane-forming polymer blended with PVP to improve hydrophilicity) and activated carbon is used as adsorptive particle. Creatinine, a small-molecular-weight uremic retention solute, often used as a marker of kidney function, is used as model water soluble solute. The para-aminohippuric acid (PAH) which belongs to the family of hippurates, and is often used as a marker for organic anion transport because of tubular secretion, is used in this study as a model protein-bound solute [26–29].

The study investigates the combination of diffusion and adsorption in a single step, which probably leads to more efficient blood purification devices and will prevent issues related to the use of conventional hemoperfusion columns.

2. Materials and methods

2.1. Materials

Polyethersulfone (PES) (ULTRASON, E6020P, BASF, the Netherlands) was used as membrane material. Polyvinylpyrrolidone (PVP) (K90), (MW ≈ 360,000, Fluka, Sigma–Aldrich, Germany) and extra pure N-Methylpyrrolidone (NMP) (Acros organics, Belgium) were used as additive and solvent, respectively. Ultrapure water, prepared with a Millipore purification unit, was used as non-solvent in the coagulation bath. Activated carbon (Norit A Supra EUR, Norit Netherlands B.V., the Netherlands) was sieved with a 45 μm sieve (Fritsch GmbH, Germany) and used as adsorbent particles (median size 27 μm). The following chemicals were purchased from Fluka, Sigma–Aldrich. Creatinine was dissolved in Tyrode's buffer (pH 7.4) composed of 137 mM NaCl, 5.4 mM KCl, 1.8 mM $CaCl_2$, 0.5 mM $MgCl_2$, 11.9 mM $NaHCO_3$ and 5.5 mM glucose in ultrapure water.

2.2. Membrane preparation

The particle-free membrane layer was prepared using a 15 wt.% PES and a 7 wt.% PVP in NMP solution which was stirred at a roller bank overnight at room temperature. For the MMM, first a mixture of 14 wt.% PES and 1.4 wt.% PVP in NMP solution was prepared and stirred at a roller bank overnight at room temperature, then different amounts of dry activated carbon particles were added. Loadings of 50, 60 and 70 wt.% activated carbon in relation to the amount of PES in the mixed-matrix membrane layer were applied, calculated as:

$$\text{Loading}(\%) = \frac{W_{AC}}{W_{AC} + W_{PES}} \cdot 100 \quad (1)$$

where W_{AC} is the dry weight of activated carbon particles (g) and W_{PES} is the dry weight of PES (g). The mixtures were stirred at least overnight and ultrasound was applied for at least 15 min to break down possible particle clusters. After degassing overnight, all the membranes were prepared by immersion precipitation.

Solutions were cast on a glass plate using a casting knife. A slit of 300 μm and 150 μm for single-layer MMMs and single particle-free membranes were used respectively. An adjustable co-casting knife was used for dual-layer MMMs, see Fig. 2. The heights of the slits of the first and second knife were 300 and 450 μm respectively. Casting was immediately followed by immersion into the coagulation bath, containing 60 wt.% NMP in ultrapure

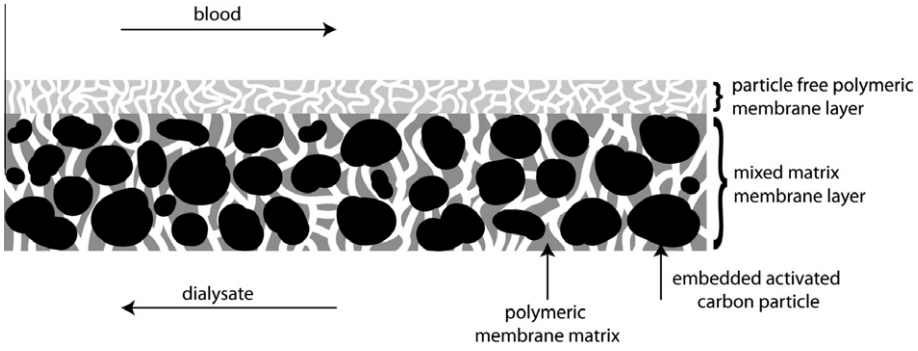

Fig. 1. Concept of dual-layer mixed-matrix membranes for blood purification.

ID	Title	Pages
716	A novel approach for blood purification: Mixed-matrix membranes combining diffusion and adsorption in one step	9