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Molecular Adsorbent Recirculating System (MARS): a Chemical Engineering Analysis of In Vivo Experimental Data

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Dialysis and adsorption units are commonly used in liver support devices for the removal of albumin-bound toxins, such as bilirubin, and water-soluble low-molecular-weight toxins, such as creatinine. In this paper, the consolidated approach of chemical engineers' to process design is applied to the analysis of the performance of a MARS treatment. The theoretical analysis of the detoxification process is used to discuss some clinical data obtained during a MARS treatment session, referring to bilirubin and creatinine concentration in plasma and different parts of the device circuit.

1. Introduction

The treatment of patients suffering from acute and acute-on-chronic liver failure is presently carried out with extracorporeal devices aimed at bringing them out of the acute phase safely or to bridge them to organ transplantation.
The main function provided by these liver support devices (LSDs) is blood detoxification from a wide range of noxious substances, including water-soluble and albumin-bound toxins. In order to remove selectively and effectively also toxins of this latter class, LSDs implement different separation processes that, under a general point of view, consist in some combination of dialysis and adsorption.
One of the most commonly used LSDs in clinical practice is the Molecular Adsorbents Recirculating System (MARS, Gambro, Lund, Sweden). Basically, the detoxification process implemented in the MARS consists in blood dialysis across a special albumin impregnated membrane against a concentrated albumin solution (albumin dialysate). The particular structure of the membrane and the presence of a binder in the dialysate allow also for albumin-bound toxin transfer across the membrane, while the cut-off of the membrane is chosen so as to avoid transfer of albumin and higher molecular weight substances. The albumin dialysate is continuously regenerated by conventional dialysis and adsorption on activated carbon and anionic resin and recirculated (Fig.1).
Analysis and design of the unit operations implemented in MARS as well as other LSDs is a typical competence of chemical engineers; therefore, it is reasonable to believe that

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application of the common methodology of chemical engineering could produce significant improvements in this field.

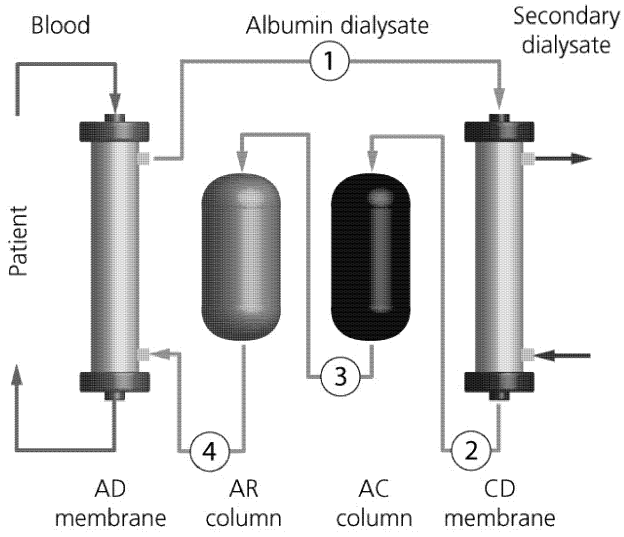

*Figure 1: Schematic representation of the MARS device. The numbers indicate the points at which albumin dialysate samples were collected for the acquisition of the data reported in Table*1 *and* 2.

In this paper, the consolidated approach of chemical engineers' to process design is applied to the analysis of the performance of a MARS treatment.
To that end, mathematical models of dialysis and adsorption processes, with parameters obtained by in-vitro data, were used to simulate single units and the whole detoxification process of MARS. The results obtained allowed to make qualitative and semi-quantitative considerations on the process efficiency, and detect important factors affecting the performance of the device.
The theoretical analysis provided the base for the discussion of some clinical experimental data, obtained during MARS treatment sessions. The data presented refer to two toxins, namely, bilirubin and creatinine, that belong to two different classes of compounds: the former is a standard marker of the clinical state of liver-failure patients and can be considered as representative of the class of strongly albumin-bound toxins, the latter is a water-soluble low-molecular-weight molecule, which is present in plasma as free solute.

2. Theoretical analysis of the detoxification process

Models of dialysis and adsorption units included in MARS were developed previously and used to simulate single parts and the whole detoxification process [Annesini et al. 2005, 2008]. The parameters used in the simulations where obtained by in-vitro data.

Here, only the basic features of the models and the main results of the simulations will be reported.

2.1 Dialysis process

The model of the hollow fiber dialyser combines the toxin transfer rate across the membrane with the toxin mass balance in the feed and dialysate solution.

In the case of toxins not bound to albumin, the model is well known [Galletti et al., 1995]. As for albumin dialysis of strongly albumin-bound toxins like bilirubin, the model is corrected to consider bilirubin partition equilibrium between two albumin containing aqueous phases (which corresponds to equal fractions of free albumin in both phases); furthermore, it is assumed that the driving force for bilirubin transfer is given by the difference between bilirubin-to-free-albumin ratios in the two phases. Consequently, the solute mass balances in the blood-side (superscript α) and in the dialysate-side (superscript β) are given by

$$\frac{dc_{tox}^{\alpha}}{dz} = \frac{K_0 A}{LQ^{\alpha}}\left(\frac{c_{tox}^{\alpha}}{c_{alb}^{\alpha} - c_{tox}^{\alpha}} - \frac{c_{tox}^{\beta}}{c_{alb}^{\beta} - c_{tox}^{\beta}}\right) \tag{1}$$

$$\frac{dc_{tox}^{\beta}}{dz} = \frac{K_0 A}{LQ^{\beta}}\left(\frac{c_{tox}^{\alpha}}{c_{alb}^{\alpha} - c_{tox}^{\alpha}} - \frac{c_{tox}^{\beta}}{c_{alb}^{\beta} - c_{tox}^{\beta}}\right) \tag{2}$$

where A is the membrane area, L the module length, Q the volumetric flow rate and K_0 is a characteristic transport coefficient of the membrane.

An asymptotic clearance value, CL_{∞}, is obtained for $1/Z = Q^{\beta}c_{alb}^{\beta} / Q^{\alpha}c_{alb}^{\alpha} >> 1$

$$\frac{CL_{\infty}}{Q^{\alpha}}\frac{c_{tox}^{\alpha,in}}{c_{alb}^{\alpha}} + \ln\left(1 - \frac{CL_{\infty}}{Q^{\alpha}}\right) = -k \tag{3}$$

where $k = K_0 A / Q^{\alpha} c_{alb}^{\alpha}$.

If the solution to be detoxified has a very low toxin-to-albumin molar ratio, equations (1) and (2) can be analytically integrated to give:

$$\frac{CL}{Q^{\alpha}} = \frac{1 - \exp[k(1-Z)]}{Z - \exp[k(1-Z)]} \tag{4}$$

Equation (4) clearly shows that membrane module clearance increases with increasing $1/Z$, i.e. increasing the dialysate flow rate or its albumin concentration.

It is worth noting that Eq. (4) apply also to dialysis of toxins not bound to albumin, with $Z = Q^{\alpha}/Q^{\beta}$ and $k = PA/Q^{\alpha}$ (where P is the toxin's permeability trough the membrane) while, in this case

$$\ln\left(1 - \frac{CL_{\infty}}{Q^{\alpha}}\right) = -k \tag{5}$$

From a practical point of view, if $1/Z$ is above 1-1.5, a further increase of this parameter should produce a negligible improvement of module clearance; on the other hand

substantial improvement can be obtained with larger k values, i.e with larger modules or more permeable membranes.
Assuming a flow rate of about 170 ml/min in all the compartments of the MARS device and a blood-to-dialysate albumin concentration ratio of 0.36 (plasmatic concentration of albumin is about 40 g/l), $1/Z$ is close to 1 for water-soluble toxins such as creatinine in the CD membrane, and close to 3 for strongly albumin-bound toxins like bilirubin in the AD membrane. This suggests that both dialysers are working close to the limiting value of clearance CL_∞. Furthermore, assuming a $(P\,A) \approx 300$ ml/min for creatinine in the CD module and a $K_0A \approx 2.6$ μmol/min for bilirubin in the AD module [Annesini et al. 2009], $CL_\infty / Q^\alpha \approx 0.82$, and $CL_\infty / Q^\alpha \approx 0.04$, respectively. Such a result suggests that the AD membrane is under dimensioned for the removal of bilirubin.

2.2 Adsorption process

The model of the adsorption columns is obtained by coupling the differential unsteady toxin mass balance in the liquid phase with mass transfer kinetics from the liquid to the adsorbed phase:

$$\varepsilon \frac{\partial c_{tox}}{\partial t} + (1-\varepsilon)\rho \frac{\partial n_{tox}}{\partial t} = D \frac{\partial^2 c_{tox}}{\partial z^2} - v \frac{\partial c_{tox}}{\partial z} \tag{6}$$

where c_{tox} is the toxin concentration in the liquid phase, n_{tox} the toxin adsorbed amount per unit sorbent mass, ε is the bed porosity, ρ is the intrinsic density of the solid adsorbent, v the liquid superficial velocity and D the toxin axial dispersion.
Assuming linear driving force (LDF) mass transfer kinetics, the toxin mass balance in the adsorbed phase may be written as

$$\frac{\partial n_{tox}}{\partial t} = \frac{3}{R} K_c (n^*_{tox} - n_{tox}) \tag{7}$$

where n^*_{tox} is the specific toxin adsorbed amount in equilibrium with the toxin concentration in the liquid phase, R the adsorbent particle radius and K_c is the LDF mass transfer coefficient. Equations (6) and (7) can be integrated with the obvious initial and boundary condition (Dankwerts conditions).
Adsorptive media used in MARS are activated carbon, and anionic resin. Thermodynamics and fixed-bed kinetics of bilirubin adsorption on these media from albumin-containing aqueous solutions have been thoroughly investigated in-vitro (Annesini et al. 2005, 2008, submitted) and the parameters of the model have been estimated. It is worth mentioning some important results of these papers. Firstly activated carbon proved to have a significant affinity for a wide range of toxins, even if its adsorption capacity for negatively charged compounds such as bilirubin is not very high; this latter class of toxins, on the other hand, is highly adsorbed by anionic resin.
Furthermore, bilirubin adsorption on anionic resin resulted to be a very slow process; as a consequence, in operating conditions similar to those used in MARS, bilirubin was not completely removed in the laboratory column.

2.3 Simulation of the MARS device

The models presented in the previous sections can be combined to simulate a complete LSD, including different units as reported by Annesini et al. [2009]. The simulations carried out in the aforementioned work, based on operating conditions used in real MARS treatment sessions, gives an overall bilirubin clearance as low as 3-4% [Annesini et al. 2009]. A two-fold effect of albumin in the dialysate on the overall detoxification process is observed: on one hand, an higher albumin concentration enhances bilirubin transfer to the dialysate in the membrane module, but, on the other hand, impairs the regeneration of dialysate by adsorption. Furthermore, the overall clearance decreases during the treatment, due to the incomplete regeneration and the build-up of bilirubin concentration in the dialysate

3. Analysis of clinical data

In order to validate the considerations presented in the previous paragraph, data were obtained during clinical MARS sessions.

Blood and albumin dialysate samples (withdrawn at the points indicated in Fig.1) were collected and analyzed to measure the concentration of albumin and some important toxins. Sample collection was performed before and at different times after the beginning of the treatment. Table 1 and 2 present an example of the data obtained for total bilirubin and creatinine, respectively, referring to the treatment of two different patients. In both cases, during the treatment, the flow rates of the blood and dialysate circuit were set to 170 ml/min and the concentration of albumin in the dialysate was about 110 g/l.

As for bilirubin, the data show that, although a decrease of the plasmatic concentration was actually observed, the efficiency of the treatment for the removal of this toxin was very low during the session considered. This can be most clearly shown by calculating bilirubin clearances as follows

$$CL = Q_D \frac{C_{(4)} - C_{(3)}}{C_{(patient)}} \tag{8}$$

where $C_{(i)}$ is the toxin concentration measured at point (i) of the albumin dialysate circuit (see Fig. 1 and Tab. 1). The values obtained are only a few percent of the blood flow-rate, in agreement with the prediction of the model. Furthermore, the comparison of the concentration measured at points 2, 3 and 4, shows that, in the albumin dialysate circuit, bilirubin is mainly cleared in the anionic resin column and, to a much lesser extent, in the activated carbon column, while the conventional dialyser is virtually ineffective for the removal of this toxin.

It is significant to point out that the effluent of the resin column contains a non-negligible bilirubin concentration even at early operating times, when the sorbent is far from saturation. This finding, clearly shows that albumin is never completely regenerated. As a consequence, the device performance decreases during the treatment.

As for creatinine, the data reported in Tab.2 show that, as expected, this water-soluble toxin is efficiently cleared by the conventional dialyser. A modest amount of creatinine is also removed in the activated carbon column (10% after 8h), confirming the wide range of non-charged substances that can be cleared by this sorbent medium.

Table 1: Total bilirubin concentration in patient's blood and albumin dialysate at different points of the MARS circuit (see Fig.1) measured during a clinical MARS session

	Total Bilirubin [mg/dl]			
	Before	After 1h	After 3h	After 6h
Patient	16.57	15.56(*)	13.74	11.48
Point 1	-	1.3	1.6	1.1
Point 2	-	1.3	1.6	1.0
Point 3	-	1.2	1.5	0.9
Point 4	-	0.8	1.2	0.9
CL[ml/min]	-	5.5	4.9	3

(*)Extrapolated on the basis of the time course of plasmatic concentration

Table 2: Creatinine concentration in patient's blood and albumin dialysate at different points of the MARS circuit (see Fig.1) measured during a clinical MARS session

	Creatinine [mg/dl]			
	Before	After 10min	After 2h	After 8h
Patient	4.0	-	-	-
Point 1	-	1.7	1.5	1.8
Point 2	-	0.3	0.4	0.9
Point 3	-	0.1	0.2	0.8
Point 4	-	0.1	0.2	0.9

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