Adsorption Mass Transfer Zone of Vancomycin in Cartridges With Styrene-Divinylbenzene Sorbent

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Cartridges for hemoadsorption containing styrene-divinylbenzene sorbent are used for multiple conditions, such as intoxication. The mass transfer zone comprises the extension along the longitudinal span of the cartridge where adsorption occurs. The aim of this experiment is to evaluate the mass transfer zone for vancomycin in the HA380 cartridge. The experiment was carried out twice. A saline solution with vancomycin passed through a HA380-modified cartridge at 100 ml/min in a single-pass fashion. The cartridge had four openings along its longitudinal dimension, at 3, 6, 9, and 12 cm. In both experiments, the collection of aliquots occurred at minute 4, in the four openings and pre- and post-cartridge, and an additional sample from the effluent bag at the end of each experiment. In the second experiment, an additional sampling of the same six sites occurred at minute 14. The sigmoidal shape of the curve for the mass transfer zone of vancomycin was similar to the theoretical one. In experiment one, at minute 4, vancomycin clearance was 98.75 ml/min. In experiment two, vancomycin clearance at minutes 4 and 14 was 93.76 and 93.20 ml/min, respectively. This implies an adequate and optimal design of the HA380 cartridge. *ASAIO Journal* 2024; XX:XX–XX

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Hemoadsorption treatments with cartridges containing styrene-divinylbenzene sorbents are currently used in a vast array of clinical scenarios, including intoxication, cytokine release syndrome from different etiologies, hyperbilirubinemia associated or not with acute liver failure, rhabdomyolysis, and uremia.[1–4] In light of the growing interest in hemoadsorption, exploring in-depth technical aspects of the therapy may foster improvements. One notable technical feature is the region where the decaying of the concentration of a solute marker molecule occurs along the longitudinal span of the cartridge, which is defined as the mass transfer zone (**Figure 1**). This zone represents the expected region where the removal of a compound takes place because the reduction in its concentration along the passage into the cartridge is proportional to the mass adsorbed. The formal definition postulates that this zone starts from the region where the solute concentration is 95% of the inlet concentration until the region where the solute concentration is 5% of the inlet concentration.[5] Furthermore, determining the mass transfer zone describes the efficiency of the cartridges, and assessing the mass transfer zone is useful to guide manufacturers in defining the amount of sorbent present in each cartridge and the cartridge's dimensions.[2]

There are few data to quantify the mass transfer zone, and most studies only quantify the pre-cartridge (inlet extremity) and post-cartridge (outlet extremity) concentration of the solutes.[6–9] The acquisition of samples of the solution during its passage through the cartridges is not feasible because there are no sampling ports in the commercially available cartridges.

We hypothesized that the progressive reduction in the concentration of a small-middle molecule (vancomycin) dissolved in a saline solution passing through a modified cartridge would graphically represent the theoretical concept of mass transfer zone. Our group has already explored the removal capacity of this sorbent for vancomycin.[10–12]

We interposed a modified commercial cartridge with sampling ports in a single-pass circuit. We planned to measure vancomycin concentration at different sites along the longitudinal dimension of the cartridge simultaneously. Through an *in vitro* experiment, the aim of this study was to determine the mass transfer zone of vancomycin in a cartridge for hemoadsorption and vancomycin adsorptive clearance.

Materials and Methods

Study Design

The authors carried out an *in vitro* experimental study emulating an extracorporeal circuit applied for hemoadsorption.

The study aimed to determine the mass transfer zone of a commercial adsorption cartridge. The elements in the circuit were a blood tubing circuit for hemodialysis, a peristaltic pump, and a modified cartridge packed with sorbent resin. The cartridge was interposed in the circuit downstream of the peristaltic pump. A solution containing vancomycin was propelled into the circuit in a single-pass fashion. The solution samples were collected in four different regions of the cartridge simultaneously. We performed the experiment twice.

Circuit

The circuit was connected to the GALILEO machine (IRRIV Foundation, Vicenza, Italy), in which a peristaltic pump for human hemoadsorption therapy propels the solution, see **Figure 2**. A 1,000 ml glass reservoir (Schott 1000 DURAN; Sigma-Aldrich, Darmstadt, Germany) with a stir bar contained the solution. The reservoir remained over a hotplate magnetic stirrer (VELP Scientifica S.r.l., Usmate Velate, Italy). A blood tubing system for hemodialysis (ArtiSet, Gambro Dasco S.p.A., Medolla, Italy) had its inlet extremity connected to the reservoir and the outlet extremity connected to an effluent bag (MEDICA S.p.A., Medolla, Italy). The modified cartridge was connected downstream of the pump and was held in an upward position, with the inlet port facing downward. The circuit was primed with saline solution.

Modified Cartridge

The authors utilized an HA380 cartridge (Jafron Biomedical, Zhuhai City, China). **Table 1** describes the device specifications. The cartridge contains sorbent resin (double crosslinked styrene-divinylbenzene copolymers) in the form of porous beads with an average diameter of 800 µm. The housing (cylinder) of polycarbonate has 19 cm on its longitudinal axis (considering the caps) and 6 cm in diameter, a total volume of 400 ml, and a priming volume of 150 ml (when already filled with the resin).

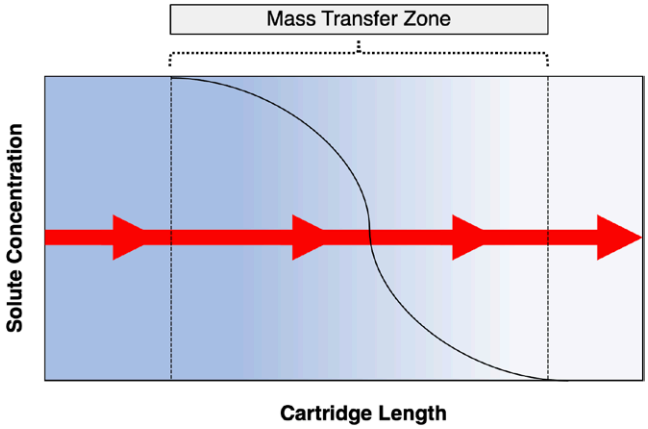

Figure 1. The mass transfer zone is the region that extends along the longitudinal axis of the cartridge. It represents the decay in the solute's concentration during the passage of the solvent through the cartridge. The point at which the solute concentration is indetectable denotes the end of the mass transfer zone. The decay in the solute concentration occurs by its removal through adsorption. The red line with arrows represents the blood flow direction from left to right. The progressive reduction in the background color represents the clearance of the solute from a darker area of the highest concentration toward a lighter area with minimal concentration.

The cartridge was emptied, the resin discarded, four holes were drilled 3 cm apart from each other in the longitudinal axis, and a 200 cm intravenous administration tubing system (Three stop, Aries S.r.l., Mirandola, Italy) was inserted into each hole. The tip of the line was located in the inner part of the cylinder, as depicted in **Figure 3**. The priming volume of the line was 1.6 ml. On the day of the experiment, all the resin from a new cartridge was transferred to the modified one.

Vancomycin Sampling and Measurement

Vancomycin (Zengac, Fisiopharma S.r.l., Palomonte, Italy) was added to a 3,000 ml bag and dissolved in a 0.9% NaCl solution (Na 154 mmol/L), up to a concentration of 40 mg/L. The solution was transferred to three glass reservoirs, each containing 1,000 ml, and pumped at 100 ml/min at a constant temperature of 37.0°C. The 3 ml aliquots were obtained after 4 minutes to ensure that the saline priming solution (~150 ml) contained in the cartridge was displaced by the vancomycin solution. In the second experiment, we collected additional samples at 14 minutes in all sites to explore if partial sorbent saturation could influence the mass transfer zone. After each collection, a syringe filled with air was connected to the lines, and 3 ml was pushed into each site. The airflow forced the remaining solution in the line to return to the circuit. The sampling sites were identified as S0, upstream of the cartridge; S1, S2, S3, and S4, distancing 3, 6, 9, and 12 cm from the inlet port, respectively (**Figure 4**). The S5 site was placed downstream of the outlet port. In both experiments, we measured vancomycin concentration in the effluent bag at the end of the experiment.

The samples were immediately analyzed using a turbidimetric immunoassay method (QMS assay [Thermo Fisher Scientific, Waltham, MA]), in the ILab 650 platform (Instrumentation Laboratory, Werfen, Bedford, MA). The experiment was terminated after all the 3,000 ml of the vancomycin solution passed through the cartridge, allowing the calculation of the total vancomycin mass adsorbed. This volume was drained into an effluent bag. Because the solution flow was 100 ml/min, the time to collect all the solution in the effluent bag was 30 minutes.

Parameters and Calculations

a. Calculation of single-pass solute clearance (ml/min) is obtained with the following formula: "a minus sign if missing after Cinlet in the formula"

$$\text{Vancomycin clearance} = \frac{(C_{\text{inlet}} - C_{\text{outlet}})}{C_{\text{inlet}}} \bullet Q_S, \quad (1)$$

where C_{inlet} (mg/L) is the pre-cartridge vancomycin concentration, C_{oulet} (mg/L) is the post-cartridge vancomycin concentration, and Q_S is the solution flow (ml/min).

b. Total vancomycin mass adsorbed is measured with the following formula:

$$\text{i. Mass adsorbed} = \text{Vanco}_{\text{initial}} - \text{Vanco}_{\text{final}}, \quad (2)$$

where $\text{Vanco}_{\text{initial}}$ is the total vancomycin mass added into the initial 3,000 ml bag, and $\text{Vanco}_{\text{final}}$ is the total vancomycin mass in the effluent bag at the end of the experiment.

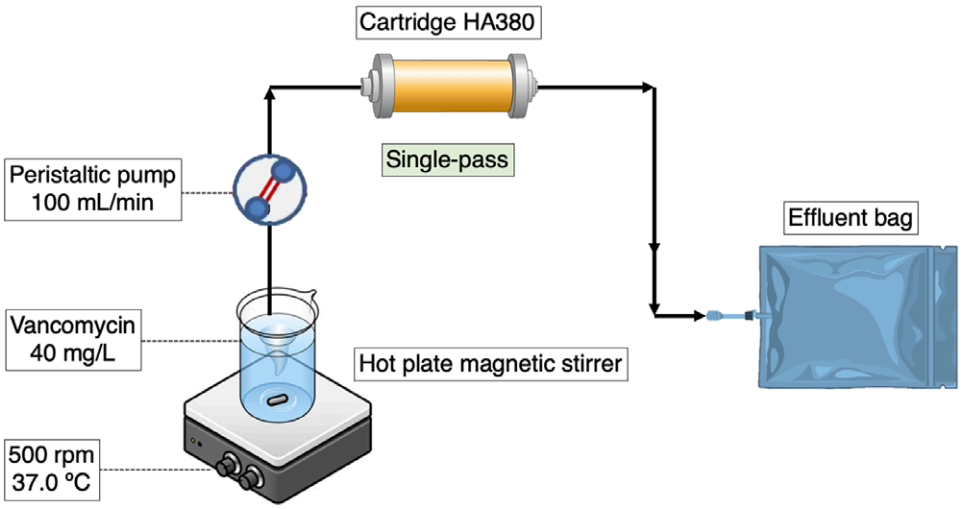

Figure 2. Experimental circuit setup. A peristaltic pump propels a saline solution containing vancomycin from a reservoir through an HA380-modified cartridge in a single-pass fashion. The fluid is collected in an effluent bag.

Table 1. Device Technical Data

Adsorbent material	Double crosslinked styrene-divinylbenzene copolymers
Mean pore size	3.34 nm
Mean bead diameter	~800 µm
Cartridge volume	400 ml
Adsorbent volume*	380 ml
Priming volume*	150 ml
Housing material	Polycarbonate
Mesh (net rack)	Polyester
O-ring seals	Silicone
Blood flow range	100–700 ml/min
Effective adsorption area	54,000–60,000 m^2
Sterilization	Gamma irradiation
Manufacturer	Jafron
Commercial name	HA380

*Information provided by the manufacturer.

$$\text{ii. Vanco}_{\text{initial}} = C_{\text{initial}} \bullet V, \quad (3)$$

where $C_{initial}$ is the vancomycin concentration (mg/L) in the initial bag, and V (mL) is the total solution volume.

$$\text{iii. Vanco}_{\text{final}} = C_{\text{final}} \bullet V, \quad (4)$$

where C_{final} is the vancomycin concentration (mg/L) in the effluent bag at the end of the experiment.

Data Analysis

Due to the simple design of the experiment, specific statistical analyses were unnecessary. Data were plotted in Excel (Microsoft, Redmond, Washington).

Results

Mass Transfer Zone

In the first experiment, samples were drawn from the cartridge after 4 minutes, while in the second experiment, samples were collected after 4 and 14 minutes. **Figure 5** depicts the mass transfer zone in the first and second experiments.

Clearance and Mass Adsorbed

Vancomycin clearance in experiment one at 4 minutes was 98.75 ml/min. In experiment two, the drug clearance at 4 and

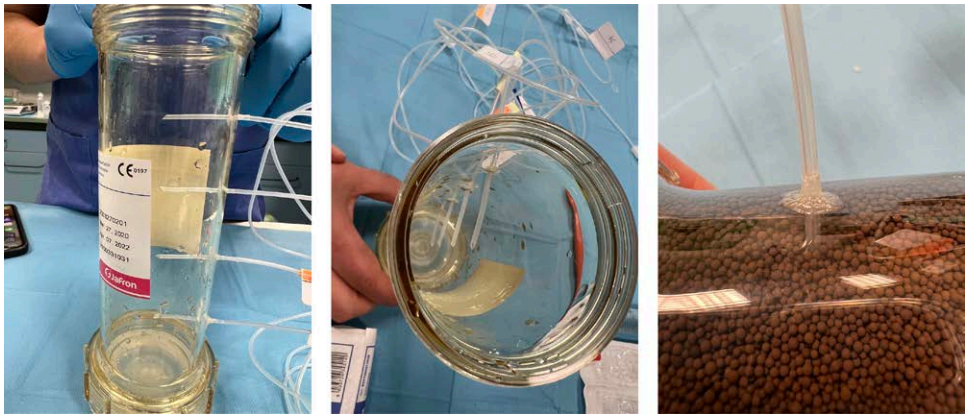

Figure 3. HA380-modified cartridge. The images in the left and in the middle show the modified cartridge emptied. The tip of the tubes was positioned in the center of the polycarbonate cylinder. The image on the right demonstrates the cartridge filled with sorbent material with a spherical shape (beads), and the position where the tube perforates the cylinder.

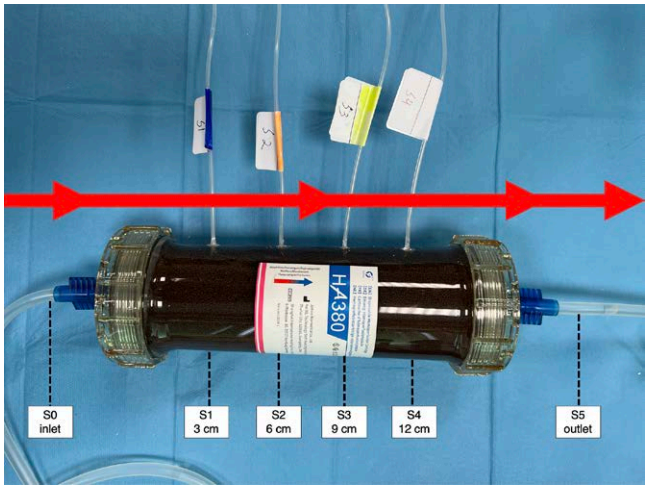

Figure 4. Representation of the modified cartridge and the sites to obtain aliquots of the solution. The sites S0 and S5 are not shown in this image and were represented by the boxes pre- and post-cartridge regions. The red line with arrows represents the solvent flow direction from left to right.

14 minutes was 93.76 and 93.2, respectively. An aliquot was drawn from the effluent bag at the end of the experiments to determine vancomycin concentration. In experiment one, the vancomycin total mass was 96 mg, and 92.7 mg were adsorbed, that is, removal of 96.6%. In experiment two, the vancomycin total mass was 105.9 mg, and 97.8 mg was adsorbed, resulting in a removal of 92.3%.

Discussion

The current study demonstrates a strong reduction in vancomycin concentration along the solvent passage through the cartridge. Our results point out that the mass transfer zone for a small-middle molecule in a cartridge with styrene-divinylbenzene sorbent covered all the cartridge length and that the adsorption process took full advantage of the cartridge's dimensions. Ideally, all the target compounds should be removed from the liquid phase while passing through the device. When the concentration of a solute in the outlet of a cartridge is still significant, it indicates that not all the solute mass was cleared from the solvent and this situation is termed the flow-through condition.[13,14] The flow-through condition might be a consequence of inadequate cartridge design, insufficient sorbent mass, and sorbent wasting or saturation. In chemical engineering, a packed bed is defined as a hollow vessel filled with a packing material. In our experiment, the former is the polycarbonate cylinder, and the latter is the styrene-divinylbenzene beads.[15] The intent of the packed bed is to optimize the interface between the solid surface (adsorber) and the compound in the fluid phase (adsorbate).[16] The HA380 cartridge displays a randomly packed bed structure because the particles (beads) are free to move and relocate in the cylinder.

The flow-through condition might also occur when not all the sorbent surface is exposed to the liquid medium because the interphase flow (*i.e.*, flow in between the beads) is not uniform, and some regions, represented by a fraction of the beads, are more permeated than others, the so-called channeling effect. We could anticipate channeling is not significant in the HA380 and other commercial cartridges from previous data about fluid dynamics analysis published by our group.[14,17]

Channeling effect can also be prevented by choosing a packing density between 40% and 60%. Packing density can be defined as the ratio between the sorbent volume (excluding the volume of the pores) and the volume of the recipient (*i.e.*, the cartridge).[18] For the HA380, the packing density is approximately 60%.

Vancomycin is an antimicrobial member of the glycopeptide drug class. It has a molecular weight of 1,449 Da, and according to the current classification of middle molecules, it is subclassified as a small-middle molecule (molecular weight 500–15,000 Da).[19] We have chosen to explore this molecule because of its known adsorption kinetics and affordability for acquisition and analysis. Vancomycin can be used as a surrogate for other middle molecules, such as myoglobin and interleukin 6. Furthermore, we opted for a vancomycin concentration of 40 mg/L because recent consensus guidelines recommend the assessment of peak and trough concentrations of vancomycin, allowing an "area under the curve-guided dosing."[20,21] It is postulated that a peak concentration of 40 mg/L and a trough concentration of 15–20 mg/L could provide adequate area under the curve for specific pathogens.[22] In both experiments, vancomycin single-pass removal surpassed 90%. These findings are clinically meaningful, reinforcing the understanding that dose adjustments of the medications should be a concern in patients undergoing hemoadsorption treatments using styrene-divinylbenzene sorbent. Recently, Furukawa *et al.*[23] published a preclinical experiment in sheep measuring the removal of vancomycin and gentamicin with the HA380 cartridge. The authors concluded that an increment of approximately 30% in the dose of vancomycin is justified for patients undergoing hemoadsorption with this cartridge.

Limitations of our study include evaluating one solvent flow (i.e., 100 ml/min), a single baseline solute concentration, only assessing one or two time points, and using saline as the sole solvent. Furthermore, we were not able to attain precisely the desired initial vancomycin concentration. We presume that during the dilution of vancomycin powder in the glass vial, not all the content was aspirated, explaining the lower-than-expected concentration in the initial bag. Moreover, we collected an additional series of samples at minute 14 only in the second experiment. This variable (*i.e.*, timing of sampling) may be relevant because partial saturation of the sorbent might "shift to the right" the mass transfer zone curve. The influence of other variables such as solvent flow, solute concentration, competitive adsorption in the case of the presence of two or more compounds, progressive saturation of the sorbent, and use of other solvents such as plasma and whole blood warrant further evaluation. Finally, we observed divergence in the reduction of vancomycin concentration in the S2 site (6 cm from the inlet port), **Figure 5**. In experiment one, at minute 4, the concentration dropped by 44.8%. In experiment two, at minute 4 and at minute 14, the reduction was 79.6% and 59.8%, respectively. We speculate that the higher reduction at minute 4 in experiment two might have occurred because some beads were inadvertently aspirated and trapped in the line and had more contact with the fluid phase, **Figure 6**. We presume this issue was partially solved in the sampling at minute 14 because the beads observed in the line were flushed back into the cartridge and were not seen in the line.

In conclusion, this *in vitro* study demonstrates that the reduction in the solute concentration occurred progressively,

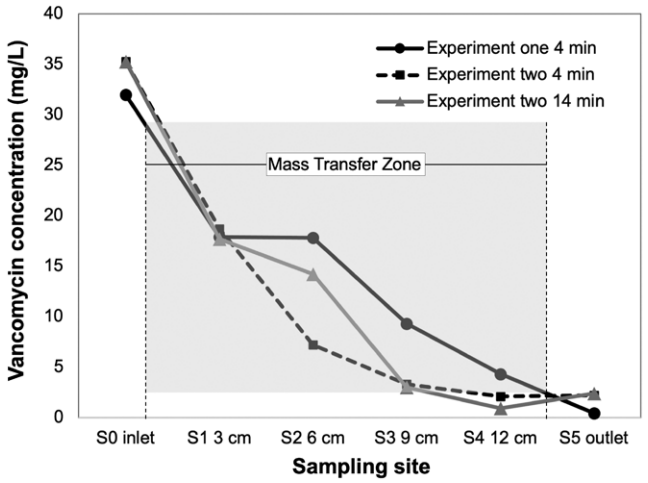

Figure 5. Vancomycin mass transfer zone. The curves demonstrate the reduction in vancomycin concentration along the passage of the solution through the cartridge. The labels in the horizontal axis represent the sampling sites in the circuit (S0 inlet and S5 outlet) and in the cartridge (S1, S2, S3, and S4). In the first experiment, the aliquots were drawn simultaneously at minute 4. In the second experiment, the aliquots were drawn at minute 4 and minute 14. The gray zone delimited by the dashed vertical lines represents the mass transfer zone, where the solute concentration ranges from 95% to 5% of the pre-cartridge concentration.

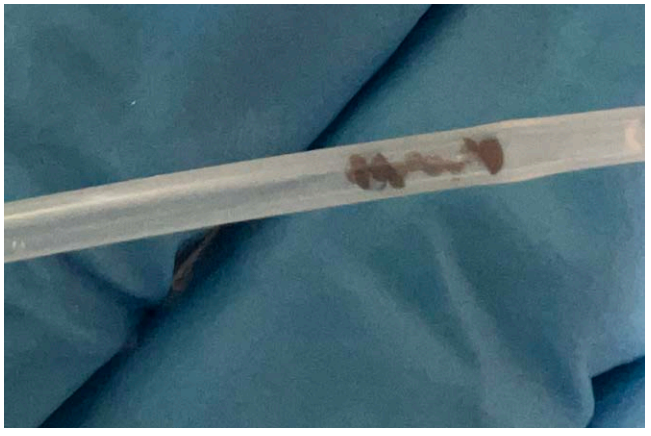

Figure 6. Sorbent beads are trapped inside the line at the S2 site (6 cm from the inlet port). This could increase the contact of the solution passing through the line and the sorbent, falsely increasing the removal of the solute and not necessarily representing the solute concentration inside the cartridge.

resembling the theoretical sigmoidal shape of the mass transfer zone curve. This implies an adequate and optimal design of the cartridge. In addition, the study of mass transfer zone is crucial for design improvement and further development of cartridges for hemoadsorption.

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