Original Paper

Blood Purification

Blood Purif 2012;34:34–39
DOI: 10.1159/000339816

Received: December 30, 2011
Accepted: May 30, 2012
Published online: August 17, 2012

Experimental First-Pass Method for Testing and Comparing Sorbent Polymers Used in the Clearance of Iodine Contrast Materials

George O. Angheloiu[a, c] Heribert Hänscheid[f] Xiaoyan Wen[b] Vincent Capponi[d]
William D. Anderson[a, e] John A. Kellum[b]

[a]Heart and Vascular Institute and [b]CRISMA Center, Department of Critical Care Medicine, Presbyterian Hospital, University of Pittsburgh Medical Center, Pittsburgh, Pa., [c]Department of Cardiology, DuBois Regional Medical Center, Dubois, Pa., [d]Cytosorbents Inc., Monmouth Junction, N.J., and [e]Exempla Healthcare, Denver, Colo., USA; [f]Department of Nuclear Medicine, University of Würzburg, Würzburg, Germany

Key Words
Adsorption · Acute renal failure · Sorbents · Iodine contrast

Abstract
Background: Sorbents have been shown to adsorb iodinated radiocontrast media. ***Objective:*** In this study we describe a simple method to compare various sorbents in terms of capacity to adsorb radiocontrast media. ***Methods:*** Iodixanol solution was injected into columns filled with three types of sorbent at filtration velocities of increasing magnitude. Two variables of interest – contrast removal rate and matched iodine retention (MIR) – were calculated to measure the adsorption efficiency and the mass of contrast iodine adsorbed versus sorbent used, respectively. ***Results:*** The highest contrast removal and MIR for Porapak Q, CST 401 and Amberlite XAD4 were 41, 38 and 16% ($p = 0.22$ and 0.0005 for comparisons between Porapak Q-CST 401 and CST 401-Amberlite XAD4) and 0.060, 0.055 and 0.024, respectively ($p = 0.18$ and 0.0008). Extrapolation to a clinical scenario may suggest that removal of 8 ml iodixanol could be achieved by masses of sorbents of 43, 47 and 107 g, respectively. ***Conclusion:*** In this study we set a benchmark for comparing the radiocontrast-adsorbing efficiency of polymer sorbents during first-pass experiments, using a readily available methodology.

Introduction

Sorbents have been shown to adsorb iodinated radiology contrast media [1, 2]. Accordingly, sorbents exhibit promising potential in the prevention of contrast-induced acute kidney injury (CI-AKI) by removing iodine contrast media from the patients' circulatory system during or after radiology, cardiology or neurology procedures.

No study has yet set a benchmark for assessing and comparing the adsorbing efficiency of various sorbents for radiocontrast materials. In this study we described a method to compare the iodine contrast-adsorptive capacity of sorbent materials in standard single-pass experiments, and used this method in the particular example of three sorbents: Porapak Q (Waters Corp.), Amberlite XAD4 (Rohm & Haas), and CST 401 (Cytosorbents).

CST 401 is a polymer resin sorbent that has been used in ex vivo experiments directed at removing iodine contrast media [2]. This agent has been processed to be used in biological media without creating significant adverse interactions with the circulating blood cells. It has been employed in human sepsis clinical trials [3], and also in in vitro experiments that showed good contrast-filtering efficiency [2]. The two other sorbents (Amberlite XAD4 and Porapak Q) have found so far industrial applications

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0253–5068/12/0341–0034$38.00/0

Accessible online at:
www.karger.com/bpu

George O. Angheloiu
Department of Cardiology, DuBois Regional Medical Center
100 Hospital Avenue
DuBois, PA 15801 (USA)
Tel. +1 814 371 2200, E-Mail goangheloiu@drmc.org

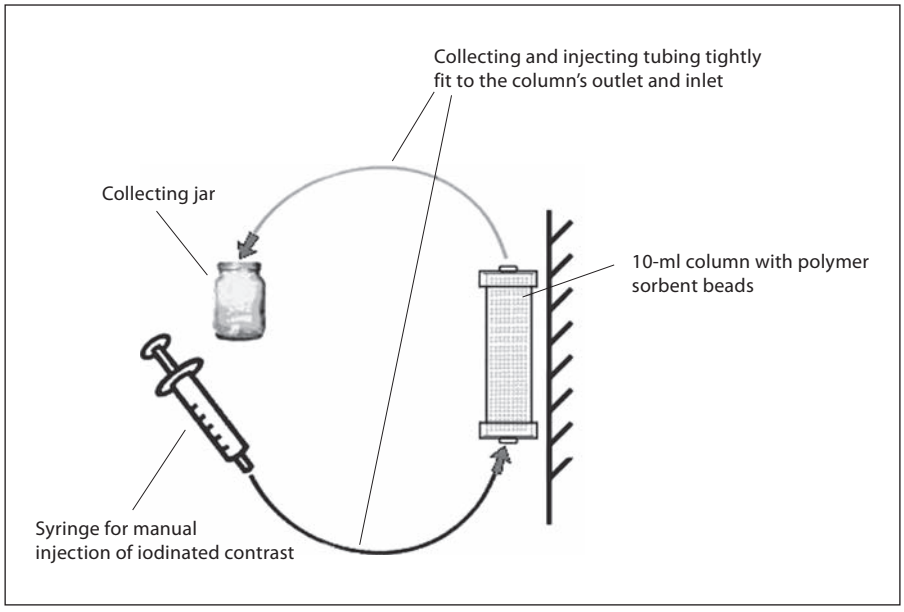

Fig. 1. Experimental set-up.

Table 1. Physical properties and total mass of the three sorbents used

Sorbent	Diameter of beads, μm	Surface area m^2/g	Total mass g
Porapak Q	149–125	550	6
Amberlite XAD4	490–690	725	5.54
CST 401	425–1,000	850	6.05

in areas such as removal of solvents and low molecular weight molecules [4], or analysis of complex compounds such as atmospheric gases or organic substances, respectively [5]. Porapak Q is a 50–80 mesh ethylvinylbenzene divinylbenzene copolymer [6], while Amberlite XAD4 is macroreticular cross-linked aromatic polymer [7]. Physical properties of the three polymers are listed in table 1.

Methods

Experimental Design

Experiments have been performed using 10-ml columns, made of a plastic non-adsorbing inert material (fig. 1). Three columns were filled with the three sorbents; the material was then compacted carefully by dripping 99% isopropyl alcohol, while slowly shaking the columns for the sorbent to settle. Further amounts of sorbent material were added to fill the columns completely. After packing, the alcohol was actively flushed out and columns were left open allowing for complete evaporation of the alcohol. Adequate sealing was insured by means of a rubber molding and an inlet-provided cap at the distal and proximal ends of the columns. Inert plastic filters were placed on top of the column's inlet/outlet orifices to prevent migration of the beads. The sorbent mass was measured at 7 days or more following the packing. This parameter was calculated by subtracting the mass of the empty vial and sealing from the vial filled with sorbent in a dry form. Columns were suspended on a vertically positioned stand (fig. 1). Tubing used for the iodine contrast media injection was perfectly sealed to the proximal and distal caps, not allowing air leakage into the columns.

The contrast solution was prepared by mixing a total 11.137 liter normal saline with 113 ml iodixanol (Visipaque, 320 mg of iodine/ml; GE Healthcare). For each experimental cycle, 250 ml solution, containing 2.5 ml of iodixanol, was injected in a first-pass manner into the columns in an antigravitational direction. Figure 1 depicts a simplification of the experimental set-up. The injection was performed manually at five flow velocities of increasing magnitude: 10, 30, 60, 120 and 240 ml/min, respectively. To achieve this goal the infusion was timed uniformly against a chronometer over a set interval of time (30 or 10 s) to achieve each particular inflow velocity: 5 ml/30 s, 15 ml/30 s, 30 ml/30 s, 20 ml/10 s and 40 ml/10 s, for a total time of 24, 8, 4, 2 and 1 min, respectively. Flow velocity for each inflow rate, temperature (23°C), column volumes (10 ml), and total volume of fluid mix (250 ml) were kept equal for all three sorbents. During one experimental run, pressures were measured on the inflow course of the setup, using Omega and SCAN pressure gauges.

Great care was placed into assuring that no air bubbles were injected into the columns during the experiments. The first 5 ml of outflow mix were discarded, since they contained the saline left after each interim column cleaning (corresponding to the void space of the column). The remaining filtered outflow mix was collected in a jar. Experiments were repeated three times for each

velocity and for each type of sorbent. Two 1-ml samples from the outflow fluid mix were collected in 1.5-ml transparent plastic jars and submitted for iodine concentration measurements by means of X-ray fluorescence. The outflow concentration represented the mean concentration of the collected bolus of fluid mix. For greater accuracy, the inflow concentration was measured from the contrast solution prepared as above. Contrast removal rate and matched iodine retention (MIR) were calculated for each sorbent and velocity as an average of the three experiments.

The columns were initially prepped and subsequently cleaned after each first-pass experiment by slowly injecting them with 200 ml of 99% isopropyl alcohol followed by 100 ml of normal saline. Extreme care was given to avoid introducing air into the columns. The integrity of the process was verified by assuring during one cleaning run that there was no contrast left in an aliquot of normal saline collected from the cleaning outflow fluid.

Contrast Material Assay

Iodine concentration in the samples was measured by X-ray fluorescence as previously described [8]. The samples were irradiated by γ-rays from a radioactive ^{241}Am source (activity: 11 GBq, half-life: 432 years) providing a highly constant photon beam of 59.5 keV γ-radiation (emission probability: 0.36 per decay). These photons are in general well suited to excite iodine by the photoelectric effect thus inducing X-ray fluorescence radiation. The photon beam was collimated and the measuring volume was well defined for sample tubes with fixed dimensions. The intensity of the fluorescence radiation is in general directly proportional to the number of iodine atoms in the target volume. A low-energy high-purity Germanium detector (Canberra GL2015-7935.7LB) powered by a γ-ray spectrometer (Ortec Spectrum Master 92X-II) was used to monitor the fluorescence radiation. For a typical sample tube, the background count rate was about 0.1 counts per second (cps) if the tube was filled with pure water free of iodine, the detection efficiency (background corrected net count rate) was approximately 0.01 cps/(μg/ml), and the limit of detection 20 μg/ml in a 100 s count. For each experiment, two 1-ml vials were submitted. Measurements were performed twice for each sample submitted and the total of four measurements averaged for the final result.

Contrast Removal Rate and Retention

For reasons of consistency, all calculations used the outflow and inflow contrast concentrations as provided by the X-ray fluorescence assay. The measured inflow concentration was 3.48 mg/ml – in reasonable agreement with the effective value (3.2 mg/ml of iodine, +9% deviation). All measurements were compared to the measured inflow concentration to compensate for systematic errors potentially introduced by the sampling procedure, sample manipulation, transport, and measurement.

The sorbent column contrast removal rate was calculated as a percentage ratio: (inflow contrast concentration – outflow contrast concentration)/(inflow contrast concentration), where the inflow and outflow fluid were referred to in connection with the column of polymer sorbent beads.

The adsorption capacity of each column was labeled as MIR, which expresses the amount of contrast iodine (in mg) adsorbed by 1 mg of sorbent. The variable was calculated as a ratio between the mass of contrast absorbed during each first-pass cycle and the mass of the sorbent. The mass of contrast adsorbed was computed as a product of 250 ml (volume of fluid mix passed through the column) and the difference (inflow contrast concentration – outflow contrast concentration).

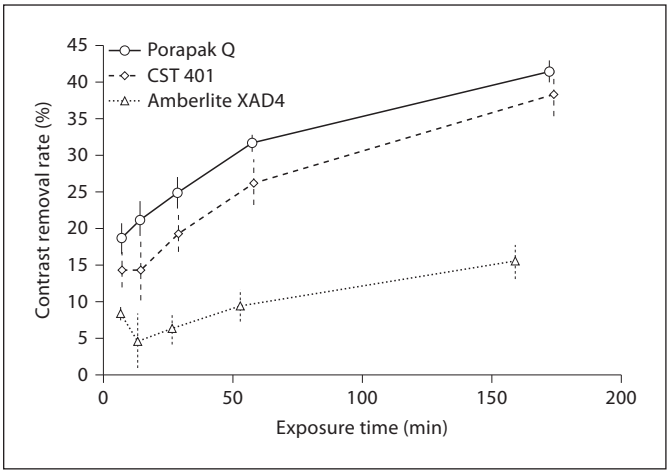

Fig. 2. Iodine contrast removal rate of three polymer sorbent materials plotted as a function of exposure time. Exposure time was defined as the time of interaction between 1 mg of contrast iodine and 1 mg of sorbent. Vertical bars represent standard deviations.

The contrast removal and MIR were expressed as function of a parameter called exposure time. This was defined as the interval of time during which 1 mg of sorbent makes contact with 1 mg of contrast iodine while contrast solution was being passed through the column at a certain velocity. The exposure time was calculated as the ratio of the total sorbent mass (mg) and the velocity of the contrast through the column (iodine mg/min), and expressed in minutes. This variable is a modified version of the residence time, defined as the time spent by a particle inside a volume of interest while traversing it [9]. Since our investigation focuses on the interaction between the mass sorbent and the contrast molecules, while being able to keep all experimental setting identical for the three sorbents, we decided to replace the column's volume with the mass of sorbent for obtaining the exposure time. In a clinical scenario the volume of contrast would be proportionally higher, and a similar reasoning for applying the chosen formula would apply.

Statistical Methods

We used the Student test with a p value of ≤ 0.05 for rejecting the null hypothesis.

Results

The mass of sorbent packed in the 10-ml columns is listed in table 1. The contrast removal versus exposure time was depicted in figure 2. Highest values were 41% for Porapak Q, 38% for CST 401, and 16% for Amberlite XAD4 ($p = 0.22$ and 0.0005 for comparisons between Po-

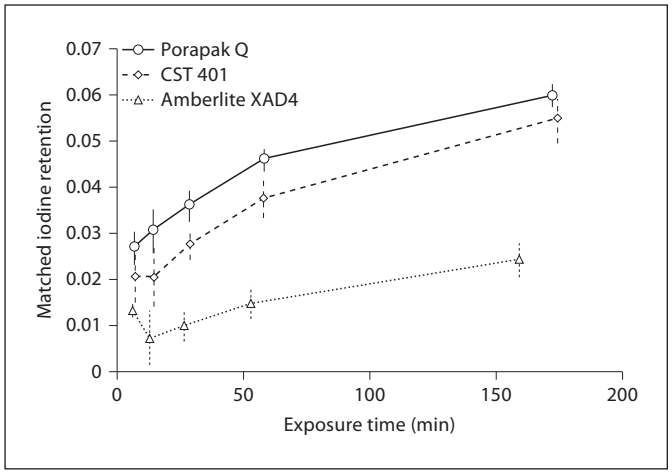

Fig. 3. MIR of three polymer sorbent materials plotted as a function of exposure time. Vertical bars represent standard deviations.

rapak Q-CST 401 and CST 401-Amberlite XAD4). A similar pattern was seen in the graphic depicting MIR (fig. 3). MIR values at the longest exposure time were 0.060, 0.055 and 0.024, respectively ($p = 0.18$ and 0.0008, respectively).

As expected, both variables were higher with higher exposure times, hence lower contrast solution filtration velocities. The exposure time, as indicated by its formula, was inversely proportional to the filtration velocity and directly proportional to the mass of sorbent used.

The column inflow and column average pressures as a function of flow velocity are depicted in figure 4. One can notice that with lower flow velocities (higher exposure times) the pressures were equal for all sorbents, and they diverged for velocities >120 ml/min.

Discussion

Our study is the first to test and compare the properties of various sorbent polymers vis-à-vis the adsorption of iodine contrast media, in our particular case iodixanol – a non-ionic iso-osmolar contrast agent used with predilection in patients with impaired renal function.

CI-AKI is a life-threatening condition and is a result of using intravenous or intra-arterial iodine-based contrast material in patients with predisposing conditions such as prior renal impairment, congestive heart failure, diabetes, shock, acute myocardial infarction or dehydration [10].

Efforts have been concentrated in the medical and technology research to devise efficient CI-AKI prevention methods. Hemodialysis is known to remove contrast, but has not been able to prevent CI-AKI [11], while hemoperfusion appears to provide some benefit to predisposed patients undergoing coronary interventions, however at the cost of longer procedural times [11–13].

Sorbent polymers have been used with success to remove iodine contrast in animal and in vitro experiments [1, 2]. No human studies investigating these molecules have been published to date, and no study has answered the question of how to compare iodine contrast removal efficiency. In this report, we compare the contrast removal efficiency of three sorbent molecules using first-pass experiments.

Contrast Removal Rate and Matched Iodine Retention

We defined the exposure time as the amount of time during which 1 mg of contrast iodine is exposed to 1 mg of sorbent while injecting the contrast solution with velocities of increasing magnitude. We used this parameter as the independent variable, starting from the hypothesis that the contrast adsorption is proportional with the time that the molecules of contrast and sorbent remain in contact.

We defined the contrast removal rate as the percentage of iodine mass extracted during a first-pass and MIR as the mass of contrast iodine (expressed in mg) that binds to 1 mg of sorbent beads at velocities (i.e. exposure times) of varying magnitudes. In our particular experiment, all three sorbents were able to remove iodinated contrast with a contrast removal varying in a decreasing manner between Porapak Q, CST 401 and Amberlite XAD4. As expected, this parameter varied proportionally with the exposure time. MIR had a profile similar with the contrast removal rate.

We used in this study three sorbents that likely are, in comparison to other adsorptive materials such as ion-exchange resins, best suited for adsorbing non-ionic agents such as iodixanol. As demonstrated in table 1, the size of bead is much lower for Porapak Q than for the other two sorbents. One can imagine that improved design for sorbents with a current larger size (CST 401 and Amberlite XAD4), with new beads harboring lower diameter and hence larger adsorbent surface areas, could improve the radiocontrast-adsorptive capacity of these agents.

The experimental set-up was designed in a manner to generate excellent data consistency (as demonstrated by fig. 2 and 3): we performed each experiment in three consecutive series and measured the contrast concentration

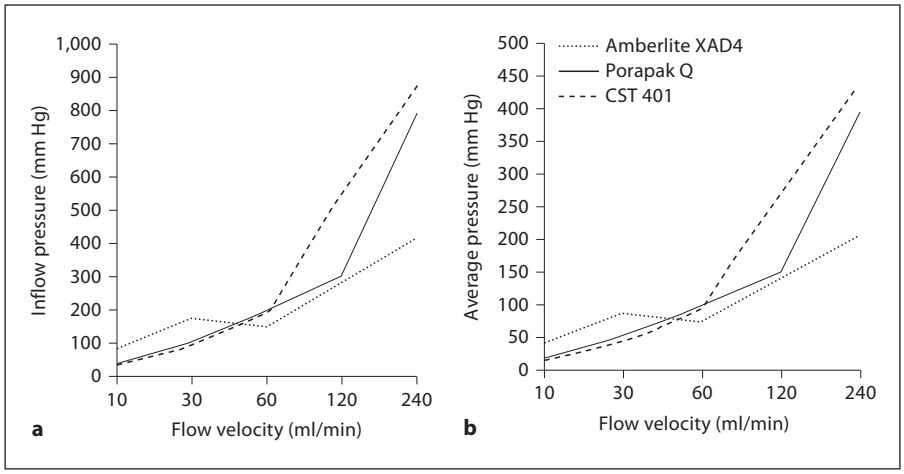

Fig. 4. Column inflow (**a**) and column average pressures (**b**) as function of flow velocity.

twice in two different batches for each experimental repeat. Contrast flow through the columns was directed in an antigravitational manner assuring a uniform contrast-sorbent contact, with all experimental settings (temperature, flow, velocity, column volumes) kept constant for all three sorbents. All these features allowed an accurate comparison between the three sorbents.

The inflow and average pressures were equal for all three sorbents in the velocity regimen <120 ml/min (fig. 4). The highest contrast adsorption difference between sorbents was detected in exactly the same velocity bracket, suggesting that the column pressure may have only a small influence on the contrast absorption in the physiologic range – <200 mm Hg.

Clinical Significance

Our data serves as a benchmark for comparing various sorbent materials ahead of clinical studies and for tracking their efficiency in a longitudinal manner. The importance of a standardized exposure time lies in the possibility of comparing experiments performed at various filtration velocities, and potentially different masses of contrast and sorbent. MIR allows one to compare various sorbents irrespective of the mass of materials used in each particular experiment.

The three agents showed only a mild tendency for plateauing with lower velocities (10 and 30 ml/min), indicating that with longer exposure times (using either lower filtration velocities or higher sorbent masses) we could obtain better removal rates. In a parallel study that mimicked suctioning of contrast from the cerebral venous circulation, we used a larger 500-gram column of CST 401. In consecutive first-pass experimental cycles where we injected 8 ml of iodixanol at a much lower exposure time (between 10 and 15 min) than the peak value used in the current study (170–180 min), the initial removal rate was approximately 95%, which proves that sorbent hemadsorption can potentially remove the entire volume of contrast injected in a clinical first-pass set-up [2].

Using as an example the case of Porapak Q, experiments at a velocity of 10 ml/min (or peak exposure time of close to 180 min) MIR was 0.06, which indicates that 1 mg of sorbent adsorbed 0.06 mg of contrast iodine. Extrapolating our data to a first-pass clinical scenario such as diagnostic invasive arterial angiography where one may use boluses of 8 ml of iodixanol containing 2,560 mg of iodine immediately suctioned on the venous side, the mass of sorbent beads needed to adsorb the entire quantity of contrast using a similar exposure time of 170 min would be close to 43, 47 and 107 g for the three types of sorbent (Porapak Q, CST 401, and Amberlite XAD4, respectively). This may again suggest that complete removal of contrast is possible in a clinical first-pass set-up, in keeping with other results obtained by our group [2].

This extrapolation needs to be considered carefully in procedures where larger volumes of contrast are administered and subsequently allowed to distribute throughout the body before eventually being suctioned and filtered, such as contrast-enhanced CT angiography. Iodixanol distribution volume was found in human pharmacokinetics to be equal to 0.28 l/kg [14], which would suggest larger volumes of filterable blood, hence implying a steady-state experiment instead of a first-pass type of removal procedure [15]. Theoretical approaches such as the Freundlich equation or Langmuir isotherms apply to the steady-state experimental set-up and hence were not used here.

Limits, Future Studies

In this study we used a relatively low mass of contrast and sorbent beads in columns of low volume, which were kept constant throughout the experiments, with the only independent variable parameter being the contrast filtration velocity. Although our results indicate that in theory complete adsorption of contrast is possible even with higher quantities of contrast (such as 100 ml of iodixanol), it is possible that using larger volumes of contrast with larger volume columns, such as required by an eventual clinical application, might result in different contrast adsorption kinetics due to a different architecture of the column with uneven exposure of the beads to the contrast and subsequent varying results. Further experiments with larger volume columns are needed to confirm our current results.

All our experiments were done in a first-pass manner, similarly with a clinical procedure where the operator administers small boluses of contrast to the patient (such as in a cardiac catheterization) that could eventually be subsequently suctioned and filtered separately in single-pass runs, such as cerebral angiography or any type of invasive angiography.

The vehicle used in our experiments was normal saline which, although an isotonic solution, does not contain major blood components such as proteins that could eventually interfere with the contrast adsorption. Further studies are needed to evaluate the sorbents' performance while using blood as an experimental vehicle.

Conclusion

This is the first experimental study to establish an in vitro method for assessing and comparing the iodine contrast adsorption capacity of sorbent materials. The simplicity of the experiment, the novelty of the concept (testing of radioiodine contrast removal sorbents), as well as the novelty of the various performance parameters make this investigation a benchmark study. Further studies are needed to better plan the sorbents' clinical use and track improvements in their materials' design.

Disclosure Statement

This study was funded in part by a grant from Cytosorbents Inc. who also generously provided the CST 401 polymer. The sponsor had no role in the design, execution or interpretation of the results of the study.

References

1 Michishita I, Fujii Z: A novel contrast removal system from the coronary sinus using an adsorbing column during coronary angiography in a porcine model. J Am Coll Cardiol 2006;47:1866–1870.
2 Angheloiu GO, Haenscheid H, Reiners C, Anderson WD, Kellum JA: In vitro catheter and sorbent-based method for clearance of radiocontrast material during cerebral interventions (manuscript submitted).
3 http://02c390e.netsolhost.com/news41.htm.
4 http://www.rohmhaas.com/ionexchange/pharmaceuticals/xad.htm.
5 http://www.waters.com/waters/partDetail.htm?partNumber=WAT027060&locale=en_US.
6 Lee DS, Kim NS: Identification of fragrances from chestnut blossom by gas chromatography-ion trap mass spectrometry. Bull Korean Chem Soc 2002;23:1647–1650.
7 Amberlite XAD4 – Technical Data Sheet http://www.dow.com/assets/attachments/business/process_chemicals/amberlite_xad/amberlite_xad4/tds/amberlite_xad4.pdf.
8 Reiners C, Hänscheid H, Lassmann M, Tiemann M, Kreissl M, Rendl J, Bier D: X-ray fluorescence analysis of thyroidal iodine content with an improved measuring system. Exp Clin Endocrinol Diabetes 1998;106(suppl 3):S31–S33.
9 Ghirelli F, Leckner B: Transport equation for local residence time of a fluid. Chem Eng Sci 2004;59:513–523.
10 McCullough PA, Soman SS: Contrast-induced nephropathy. Crit Care Clin 2005;21:261–280.
11 Deray G: Dialysis and iodinated contrast media. Kidney Int Suppl 2006;100:S25–S29.
12 Marenzi G, Marana I, Lauri G, Assanelli E, Grazi M, Campodonico J, Trabattoni D, Fabbiocchi F, Montorsi P, Bartorelli AL: The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. N Engl J Med 2003;349:1333–1340.
13 McCullough PA: Contrast-induced acute kidney injury. J Am Coll Cardiol 2008;51:1419–1428.
14 Svaland MG, Haider T, Langseth-Manrique K, Andrew E, Hals PA: Human pharmacokinetics of iodixanol. Invest Radiol 1992;27:130–133.
15 DiLeo MV, Kellum JA, Federspiel WJ: A simple mathematical model of cytokine capture using a hemoadsorption device. Ann Biomed Eng 2009;37:222–229.