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Hybrid Sol Gel Coating: A Solution to Prevent Interactions Between Plasticized Poly(vinyl chloride) and Injectable Drugs?

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ABSTRACT: During the infusion of drugs with medical devices in plasticized poly(vinyl chloride) (PVC) release of plasticizers in the injectable solution and/or sorption of drugs on PVC may occur. Thus, patient safety and/or effectiveness of his therapy may be altered. In this study, we assessed the efficiency of a sol gel hybrid coating in preventing plasticizers' release (di-(2-ethylhexyl) phthalate (DEHP)) from PVC matrix and drug sorption into PVC. Remaining concentrations of drugs and plasticizer's concentration released after migration tests were assessed by liquid chromatography. Migration processes were followed by Fourier Transform Infrared – Attenuated Total Reflectance (FTIR-ATR) spectroscopy and PVC surface changes were characterized by scanning electron microscopy (SEM). An evaluation of the mechanical properties of both uncoated and coated polymer was done. The hybrid coating protects PVC from plasticizers leaching. Sorption of drugs tested is also limited. However, the protection against plasticized PVC interactions isn't optimal, probably due to a degradation of the layer, as shown on SEM microphotographs. Furthermore improvements might provide an efficient barrier to advert risks impaired to PVC interactions, to provide patient care safety. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 40145.

KEYWORDS: poly(vinyl chloride); plasticizer; coatings; adsorption; biomedical applications

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INTRODUCTION

Poly(vinyl chloride) (PVC) is used in a wide range of medical devices, such as administration sets for infusion, because of its numerous advantages. The typical characteristics required for tubing for use as for example, an intravenous set, include transparency, flexibility, kink resistance, toughness, ease of bonding with common solvents or adhesives, and suitability for gamma-ray, ethylene oxide or electron beam sterilization, and low cost. As a biomaterial, plasticized PVC has achieved its predominant role in the medical plastics industry by a unique combination of desirable properties. To induce and maintain flexibility and workability of PVC medical devices, plasticizers are added up to a concentration of about 40% to the PVC polymer. Until recently, di-(2-ethylhexyl) phthalate (DEHP) was one of the most commonly used plasticizers for pharmaceutical applications. Since it is not covalently bond to PVC, DEHP can migrate from medical devices when in contact with liquids such as nutrition admixtures, lipophilic drug solutions, or blood[1–4] and so might lead to unwanted exposure of patients. DEHP is classed as a carcinogen, mutagen, or toxic for reproduction chemical compound (CMR1B) under the Regulation of Classification, Labelling and Packaging of substances and mixtures (CLP Regulation)[5] because of its potential toxicity on fertility or reproduction. Several alternatives have been proposed to avoid DEHP leaching. In some cases, industrials replaced PVC by other materials, like polyethylene, silicone, or polyurethane. For other medical devices, the replacement wasn't possible because the chosen materials didn't provide the same compromise of mechanical properties and low cost, which are the most important qualities required for infusion devices. Therefore, in most cases, PVC has been conserved and other plasticizers are used, which might migrate less and have a better toxicological profile. However, there isn't enough data to prove their harmlessness in risky medical situations, especially as most of these plasticizers are known to be endocrine disruptors.[4,6]

To limit plasticizer migration, some authors have proposed physical and chemical techniques such as covalent attachment of the plasticizer to the PVC chain,[7] polyethylene oxide coating,[8] chemical vapor deposition,[9] and nucleophilic substitution of PVC with dithiocarbamate.[10] In a previous study, we also

demonstrate the efficiency of a photopolymerizable hybrid sol gel coating against DEHP release from pharmaceutical PVC bags.[11] The film deposited on the surface of the PVC is an organic/inorganic hybrid layer, generated by the hydrolysis and condensation of a mixture of titanium alkoxide functionalized by an acrylic acid and methacrylate grafted alkoxysilane. The results we obtained are promising in so far as the coating provides not only a barrier against DEHP release but also offers a high good transparency to the coated polymer surface, which is not altered by the treatment.[11]

The other main problem with PVC material is the possible sorption of drugs onto the polymer surface of the medical device, leading to a loss of these drugs. Clinical consequences may be important as the patient doesn't receive the prescribed therapeutic dose. Thus, solutions proposed to reduce release behavior of plasticizers out of PVC-made equipments have to also be efficient against drugs sorption into PVC of medical devices, especially those used for infusion applications (infusion sets, extension sets or bags). PVC plasticized with alternative plasticizers is also affected by these interactions, with the amount of sorption being related to the type of plasticizer used.[12] Physical or chemical techniques mentioned above, which act in protecting PVC against DEHP release, have not kept up on preventing drug sorption into PVC.

So, the aim of this study was:

- to evaluate the efficiency of the barrier effect of our hybrid sol gel on DEHP leaching over time, to know if the protection does last for more than 1 h, as demonstrated in our previous study.[11] Indeed, clinical situations like the infusion of a drug with an PVC infusion set and/or from a PVC bag are often made over a several hours period.
- to check if the hybrid layer could also prevent drug sorption over time into PVC bags.

In addition, migration and sorption tests, surface characterization and mechanical properties of the plasticized polymer were investigated, to verify if the PVC properties of the medical devices are maintained.

The goal is to determine if sol gel coating can be a safe solution to prevent these two types of interactions related to PVC, which must be considered indivisible in terms of patient care security.

EXPERIMENTAL

Hybrid Sol Synthesis and Sample Coating Process

Hybrid sol synthesis and sample coating process were investigated according to Massard et al.[11] process. The inorganic matrix precursor used was methacryloxypropyltrimethoxysilane (MAPTMS) supplied by Sigma Aldrich. This organosilane has a photopolymerizable methacrylate function grafted on an alkoxysilane. In the first step of the sol synthesis, partial hydrolysis and condensation of the organoalkoxysilane was performed under an acid catalysis condition by adding 0.75 equimolar of 0.1*M* HCl with vigorous stirring. Due to its high reactivity, the Sigma Aldrich titanium IV isopropoxide was first complexed with pure acrylic acid (AA) supplied by Sigma in the molar ratio $Ti(OiPr)_4$: AA 1 : 2 and then added to the prehydrolysed medium. The inorganic molar ratio MAPTMS : $Ti(OiPr)_4$ was 10 : 1.

The co-hydrolysis and condensation of the previous mixture were performed by dropping in the medium under vigorous stirring, a total amount of deionized water to reach a final molar ratio H_2O :MAPTMS was 3 : 2 and H_2O : $Ti(Oi\ Pr)_4$ was 3 : 2.

Under non actinic light, the photoinitiator in the form of 3 wt% of Sigma Aldrich 2,2-dimethoxy-1,2-diphenylethane-1-one was added to the solution. The solution was stirred overnight and stored away from light. Final hybrid sol composition is 10 : 1 : 2 who stands for the molar ratio MAPTMS : $Ti(OiPr)_4$: AA.

Then, the films were dip coated on a PVC DEHP-plasticized substrate (6 × 1 cm) supplied by Macopharma (Macoflex® bags). The withdrawal speed was of 25 cm/min. Just after the coating, the samples were irradiated for 20 min with a polychromatic fluorescent UV lamps (Philips TDL 8 W (total optical power, 1.3 W), 300 mm long, wavelength range 350–400 nm) in a configuration providing about 0.7 mW/cm^2 at the sample surface.

DEHP Migration Test

Thirty PVC strips of 6 × 1 cm were soaked into a 6 mL solution of ethanol 96% (Sigma Aldrich) in a hemolysis tube during 30 min, 60 min, 3 h, 24 h, and 48 h. For each time analysis, three coated samples were used to quantify DEHP leaching and three uncoated samples were used as controls. One milliliter of the ethanolic solution was removed to measure the DEHP concentration. Ethanol was chosen to respect the conditions of migration described in the European Standard EN 1186-15. DEHP released from PVC was quantified by high performance liquid chromatography. For each sample, the surface was observed by SEM and FTIR-ATR spectroscopy before and after migration test.

Sorption Test

The drugs studied were the commercial products suitable for clinical use. They were chosen according to their known incompatibility with PVC. Isosorbide dinitrate (DNIS) used for treatment of left ventricular deficiency, particularly at the acute phase of heart attack and for the treatment of acute lung oedema or angina was the commercial formulation Risordan® 10 mg/mL intravenous injection (Sanofi-Aventis, France). Diazepam, a benzodiazepine anxiolytic drug, was provided by Roche Laboratories (Valium® 10 mg/2 mL). Stock solutions of DNIS at a concentration of 10 mg/mL and diazepam at 500 µg/mL were prepared and distributed under a volume of 6 mL in hemolysis tubes. Uncoated and coated Macoflex® PVC strips of 1 × 6 cm (used as positive references to assess drug sorption) and Ecoflac® ldPE strips of 1 × 6 cm (used as negative references) were put in contact with drug solutions during 30 min, 1, 3, 24, and 48 h. For each time, assays were performed in triplicate. After time contact, 1 mL of the drug solution was removed and remaining concentration of drug is determined by liquid chromatography. Furthermore, surface of material was monitored by SEM and FTIR-ATR spectroscopy.

Chromatography Analysis Method

Concentrations of DEHP, diazepam, and DNIS were determined by high performance liquid chromatography (HPLC). All assays

were performed isocratically at room temperature. Chromatographic analysis was performed using a LC-2012C integrated high performance liquid chromatographic system with a UV-Visible detector (Shimadzu). The separation was achieved using a 5 μm Lichrospher 100 RP 18 endcapped column (125 $\times$ 4.6 mm ID) (Macherey-Nagel)

The analysis of DEHP was performed using the method described and validated by Massard et al.[11] Due to the ubiquitous nature of DEHP, the experimental design of the study was conducted using disposable glass hemolysis tubes and disposable glass vials for HPLC analysis to minimize the risk of contamination by DEHP from laboratory equipment.

DNIS was quantified with an isocratic method using a mobile phase consisting of methanol and water (50/50, v/v) pumped at a flow rate of 1.2 mL/min. Twenty microliter samples were injected into the analytical column and the chromatographic separation was achieved with a detection set up at 220 nm. The chromatographic method is linear for concentrations ranging from 10 to 200 μg/mL. The mean linear regression equation obtained is $y = 11860x + 5586.9$ ($r^2 = 1$), where x is the DNIS concentration and y the surface area of the corresponding peak. This method has acceptable accuracy and precision with the intra-assay and inter-assay coefficients of variation all below 1.53%.

Diazepam analysis was performed at 254 nm with a mobile phase consisting of a mixture methanol-water (65/35 v/v) pumped at a flow rate of 1.5 mL/min. Two hundred and fifty-four nanometers is the wavelength recommended by the European Pharmacopea[13] and the one used by Kambia et al.[14] and Tada et al.[15] The injection volume was of 20 μL. Diazepam calibration curve was constructed at a concentration range of 10–200 μg/mL. A good linear response was found with a correlation coefficient better than 0.999. This method has acceptable accuracy and precision with the intra-assay and inter-assay coefficients of variation all below 5.55%.

For diazepam and DNIS, to exclude the sorption of the drugs, the experimental design of the study was set up using glass vials (not plastic bags) as reservoirs for drug stock solution.

The analysis of each sample was performed by HPLC after a suitable dilution in sodium chloride for diazepam to fit the calibration curve. At time zero, the initial concentrations of diazepam and DNIS were designated as 100% and all subsequent measured concentrations were expressed as percentages of the initial concentrations.

PVC Surface Characterization

Scanning Electron Microscopy. Morphology analysis of PVC surface samples (directly obtained from migration and sorption tests) was performed using a SEM JSM-6060LV (Jeol USA, Peabody) at 5 kV in high-vacuum mode. Samples were mounted on a metallic support with an adhesive carbon tab and then sputter-coated with gold-palladium (JFC-1300, Jeol).

FTIR-ATR Spectroscopy. FTIR spectra, performed on PVC surfaces before and after migration and sorption tests, were recorded by co-adding 40 scans at a resolution of 2 cm^{-1} using a single reflection diamond crystal in a Nicolet 6700 FTIR-ATR spectrometer. The migration of DEHP and the drug sorption phenomenon were followed by considering the evolution of four characteristic bands of the polymer (C—H stretching mode at 1426 cm^{-1}), the plasticizer (C—O—C stretching mode at 1463 cm^{-1}) and the drug solutions (C=O stretching mode at 1682 cm^{-1} for diazepam and NO_2 stretching mode at 1650 cm^{-1} for DNIS). Monitoring of plasticizer migration or drug sorption in the polymer was performed by rationing the absorbance intensities of bands at 1463, 1682, and 1650 cm^{-1} to that at 1426 cm^{-1}. Each different absorbance ratio, $A_{1463\,cm^{-1}}/A_{1426\,cm^{-1}}$, $A_{1682\,cm^{-1}}/A_{1426\,cm^{-1}}$, and $A_{1650\,cm^{-1}}/A_{1426\,cm^{-1}}$ is the average of 10 measurements performed on random spots of the surface of each sample.

Spectra were recorded by co-adding 40 scans at a resolution of 2 cm^{-1} using a single reflection diamond crystal in a Nicolet 6700 FTIR-ATR spectrometer.

Mechanical Properties. All the selected PVC samples tested exhibited the same geometry consisting in strips of 10 mm wide by 60 mm in length and 300 μm in thickness. They included uncoated and coated specimens, submitted or not to soaking test in ethanol and to sorption test in diazepam and DNIS. Tensile testing was performed in a MTS 20M model electromechanical testing machine. During the typical tensile experiment, the specimen was gripped at its two ends and pulled to elongate at a constant rate to its breakpoint. The testing machine included grips designed to minimize slippage, that means manual vise grips with rubber-coated inserts. Elongation of the samples subjected to the axial load has been calculated from crosshead displacement. The gauge length, constant for all specimens, was fixed at 40 mm.

To obtain accurate values of mechanical properties, a toe compensation was applied, that means the toe region of the strain–stress curves, which is artefact caused by a take-up of slack, alignment or seating of the specimens, was compensated to give the corrected zero point on the strain and extension axis. Each value of elongation at break and elastic modulus reported is the average of a minimum of three measurements.

RESULTS AND DISCUSSION

DEHP Migration

Figure 1 shows the concentrations of DEHP removed in ethanolic solutions after contact with uncoated PVC and PVC coated with the sol gel layer. The results highlight that the hybrid coating limits significantly the migration of the DEHP during a prolonged contact (more than 24 h). The mean protection given by the coating during the experiment is 80%, as shown in Figure 2. FTIR-ATR was also able to follow plasticizer migration from uncoated PVC. As reported in Figure 3, the decrease in the absorbance band ratios ($A_{1463\,cm^{-1}}/A_{1426\,cm^{-1}}$) with increasing contact time in ethanol undoubtedly confirms a drastic DEHP migration from the polymer, the releasing of DEHP being significant over the first hour of exposure. Because of the thickness of the hybrid coating, the FTIR spectra of the coated polymer before soaking in ethanol do not allow identification of the plasticizer or the PVC substrate. Even if the DEHP

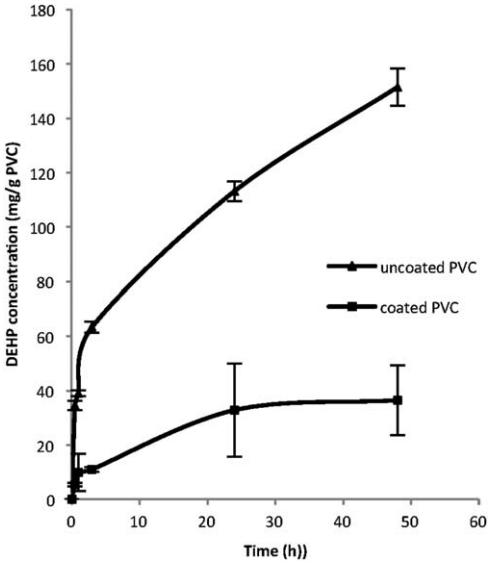

Figure 1. Concentration of DEHP released from uncoated (n = 15) and coated (n = 15) PVC in ethanol solution.

is no more detected in the coated polymer after plasticizer migration tests, it seems difficult in this configuration to consider the FTIR-ATR spectroscopy as being undoubtedly suited for monitoring the barrier effect of the hybrid sol-gel coating against DEHP migration.

The mechanical study confirms the results provided by the migration test. As shown in Figures 4 and 5, before soaking into ethanol (at T_0), the coated polymer shows a higher value of elastic modulus (around five times greater) and a lower value of elongation at break, reduced by a factor of 2.7 than the reference uncoated PVC. This is the direct result of the covering of a flexible plasticized polymer by a hybrid film, which presents a quite less ductile behavior than its substrate as shown by the authors.[11] The maintained value of elongation at break and the slight increase (without exceeding a raise of 50%) of elastic modulus during the 48 h period support the high efficiency of the barrier effect of the hybrid sol gel coating against the release

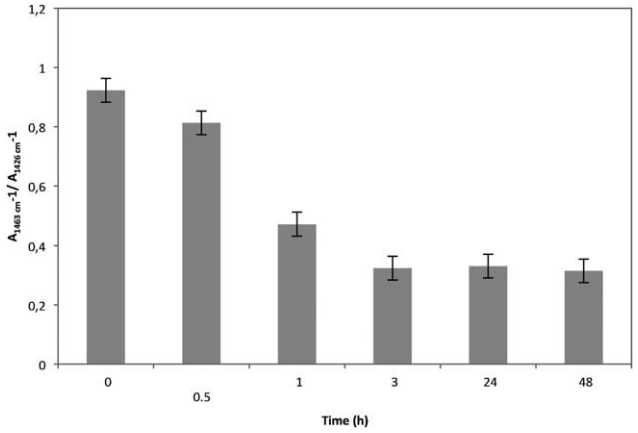

Figure 3. Absorbance ratio $A_{1463\,cm^{-1}}/A_{1426\,cm^{-1}}$ measured on uncoated PVC after ethanol exposure.

of the plasticizer, since it is suggested that the loss of additives such as plasticizers may alter the properties of the material, even it does not change the integrity of the polymer structure.[16]

However, it seems that ethanol plays a not inconsiderable role in the significant alteration of the mechanical properties of the polymer observed consecutively to ethanol exposure. It can be observed from curves presented in Figures 4 and 5 that the mechanical behavior of the uncoated polymer soaked in ethanol is radically different from that of the reference polymer (uncoated, before soaking into ethanol). The elastic modulus of the uncoated PVC in contact during 48 h is at least 15 times greater than that of the reference polymer. In the same time, the exposure of polymer in ethanol solution results in a decrease of the elongation at break, which is reduced by more than four times. This strong increase in the elastic modulus value combined with a reduction in the elongation at break reveals an important alteration of the mechanical behavior of the polymer consecutive to exposure in ethanol solution.

Although SEM images of uncoated PVC surface after DEHP migration tests show no cracks or plastic deformation throughout the 48 h study period, the mechanical properties of the

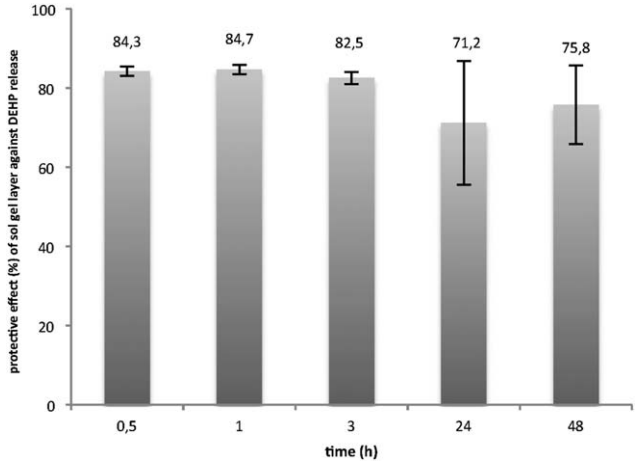

Figure 2. Barrier effect over time analysis of the hybrid sol gel coated on PVC samples.

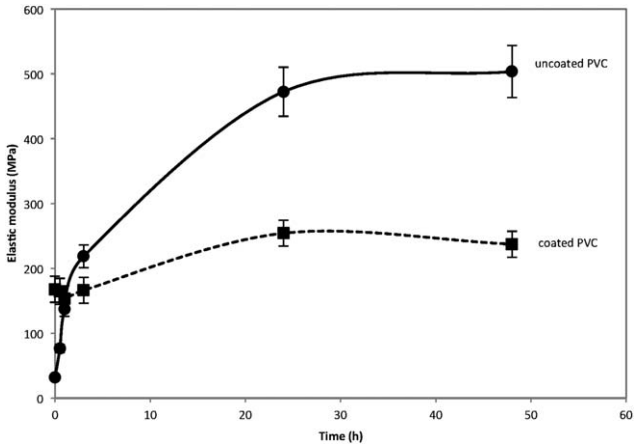

Figure 4. Effect of ethanol exposure on elastic modulus of uncoated PVC and coated PVC.

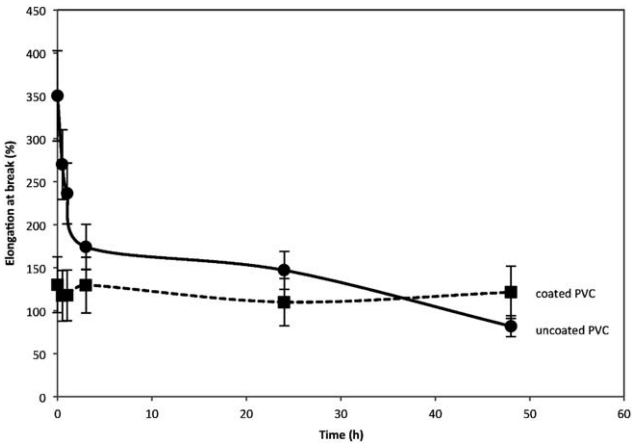

Figure 5. Effect of ethanol exposure on elongation at break of uncoated PVC and coated PVC.

uncoated polymer show strong alterations. The initially flexible polymer exhibits after ethanol exposure a stiffer and less ductile behavior. When subjecting uncoated PVC plasticized with DEHP to ethanol exposure, other authors also reported a significant continued alteration in the mechanical behavior of PVC.[16]

It has also been suggested that ethanol is capable of altering the hybrid coating. Indeed, the concentrations of DEHP leached from coated PVC at the end of the application time show an important variability. As shown in Figure 2, more than 30% of variability has been measured with coated PVC at long exposure times (24 and 48 h). These findings let us suppose the existence of an interaction between ethanol and the hybrid layer, which could explain the presence of typical fractures that appeared on SEM images, thus indicating a diffusion of the chemical into the organic/inorganic layer coated on PVC surface. Figure 6 is given as reference: it represents surfaces of uncoated (A) and coated (B) PVC before any soaking into ethanol or drug solution. The photographs show that the coating doesn't modify the PVC surface, which remains as smooth as the surface of uncoated PVC. Figure 7 shows SEM microphotographs of coated and uncoated PVC surfaces after contact with ethanol. For all DEHP migration times of analysis, uncoated PVC surfaces remained smooth, without any cluster or fracture or any swelling. Regarding coated PVC, changes can be observed on surface. After 30 min of contact with ethanol (A1 and B1), no significant change on surface is observed. Typical cracks appear from 60 min onwards on the PVC surface (A2 and B2), and seem to become numerous until 48 h, resulting in a disintegration of PVC surface. This might result in a time-related gradual swelling of the layer, which increases its strain and leads to these fractures. Moreover, the diffusion process of ethanol into the hybrid layer can be explained by its affinity for the propanol contained in the organic part of the layer. This creates a non-uniform distribution of these cracks on the coating, which can explain the variability and the lesser barrier effect at the end of the analysis when compared to the first time samples (30 and 60 min). It may also explain the increase of the elastic modulus shown over the 48 h period, which is probably higher than the decrease caused by a smaller covering of the polymer.

Diazepam and DNIS Sorption

Figures 8 and 9 show the behavior of diazepam and DNIS after contact with uncoated PVC, coated PVC, and ldPE. Non-PVC material (ldPE) shows, as expected, no sorption of both drugs into the strip: concentrations of diazepam and DNIS remained stable during 48 h.

Results obtained with sorption tests into PVC show interactions between drugs and uncoated PVC. Sorption of both diazepam and DNIS can be observed, resulting after 180 min of a respective loss of 77 and 52% of the original concentration. The FTIR study confirms the consequent sorption of both diazepam and DNIS in the uncoated polymer (as an example, Figure 10 presents FTIR spectra performed on PVC in contact with diazepam).The evolutions of the absorbance ratios $A_{1682\,cm^{-1}}/A_{1426\,cm^{-1}}$ and $A_{1650\,cm^{-1}}/A_{1426\,cm^{-1}}$ (Figure 11) suggest that this sorption effect is really effective after 3 h of contact and increases up to the maximum time exposure of 48 h.

These results with uncoated PVC are in compliance with migration theory, where the model for the sorption of these chemical compounds consists of both rapid adsorption onto surface of the plastic bag and a subsequent slower dissolution and migration of chemicals into the plastic matrix.[17] Loss of diazepam and DNIS obtained in our study confirmed that these drug solutions adsorbed quickly onto the PVC surface it is in contact with, affecting the response elicited in patients treated with an

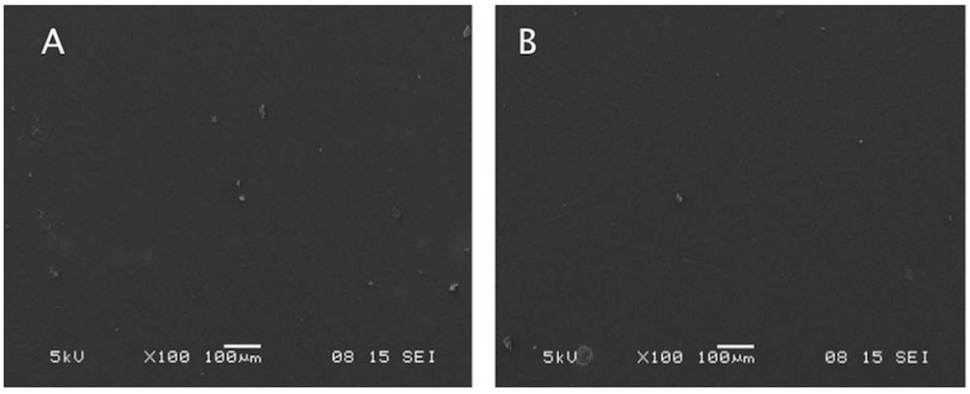

Figure 6. SEM micrographs (100x) of uncoated (A) and coated (B) PVC surfaces before any migration or sorption test.

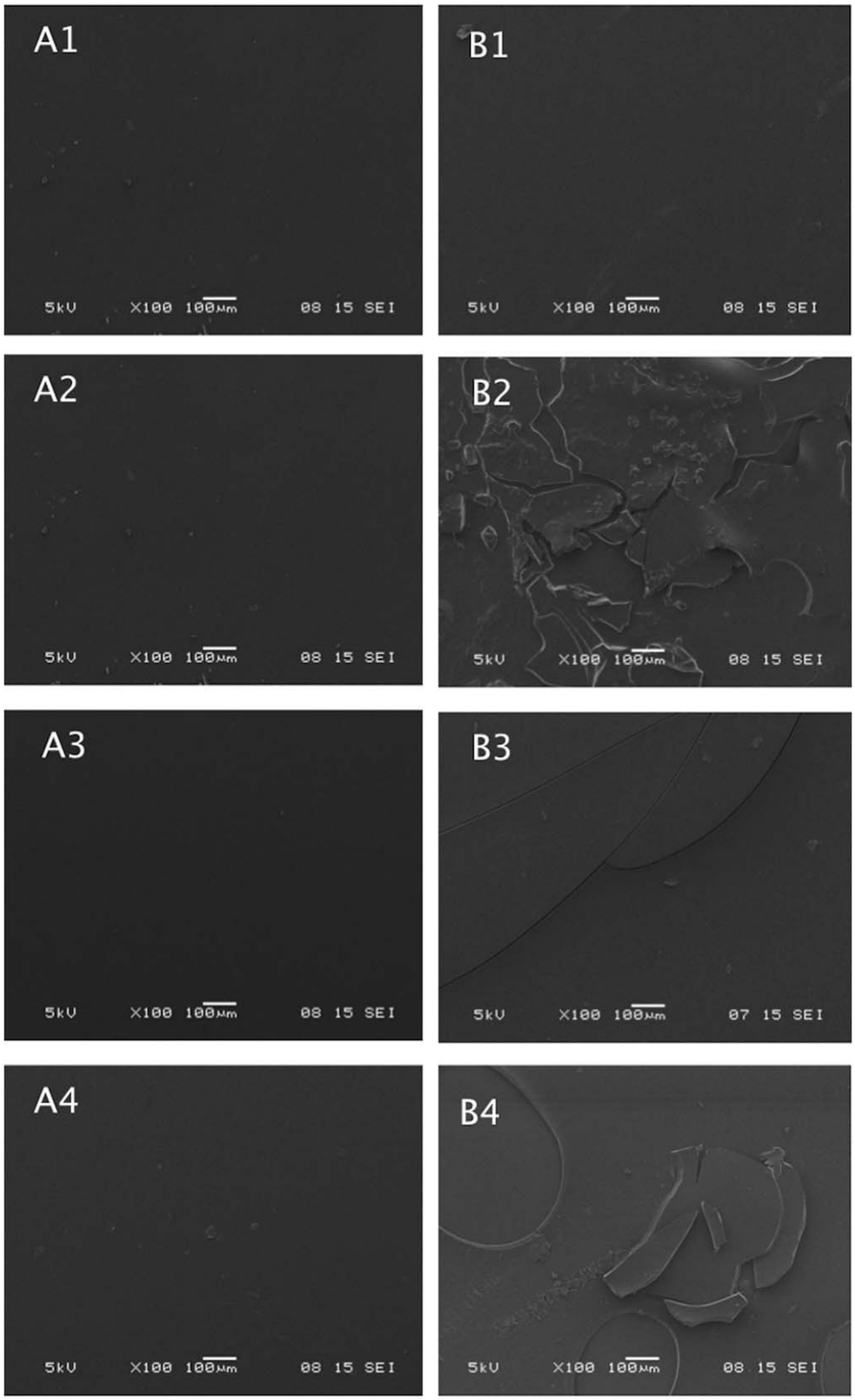

Figure 7. SEM micrographs (100x) of uncoated (A) and coated (B) PVC surfaces after DEHP migration test at different times: (1) t = 30 min, (2) t = 60 min, (3) t = 180 min, (4) t = 24 h.

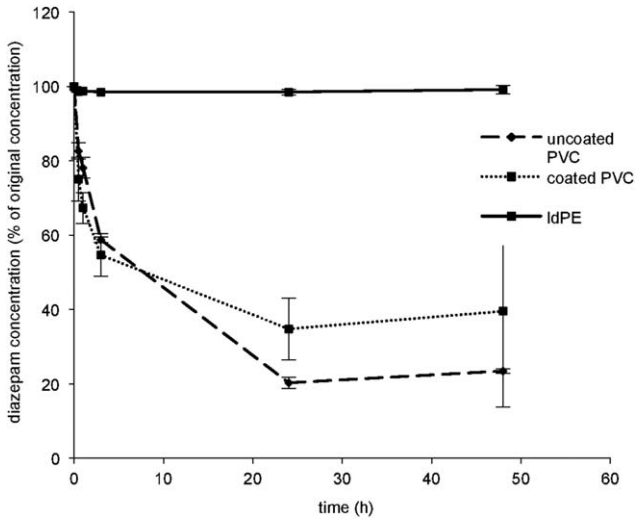

Figure 8. Remaining concentrations of diazepam after contact with uncoated PVC (n = 15), coated PVC (n = 15), and ldPE (n = 15).

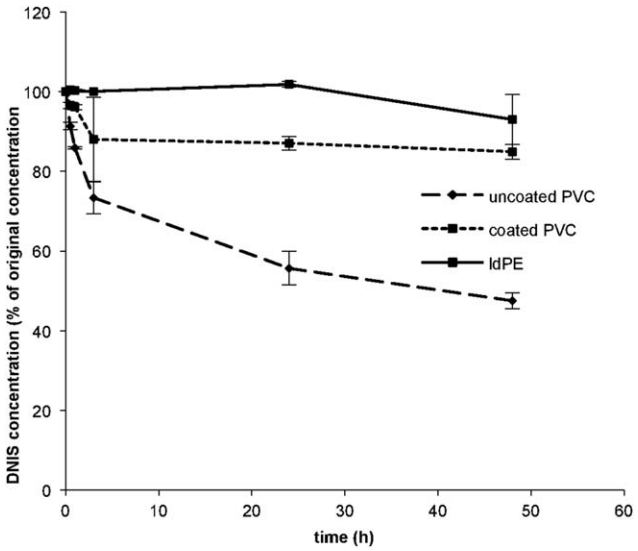

Figure 9. Remaining concentrations of DNIS after contact with uncoated PVC (n = 15), coated PVC (n = 15), and ldPE (n = 15).

I.V. diazepam or DNIS formulation. Differences in sorption rates are noticed between the two compounds. Diazepam is absorbed with a higher rate than DNIS, whatever kinetic time. Two phenomena can explain these findings. First, the main physicochemical determinant controlling sorption by the PVC material should be anticipated to be the PVC-water partition coefficient of the solute since this is a measure of the relative affinity of solute for the plastic.[18] Octanol-water partition coefficient of diazepam is two times higher than DNIS' (logP(diazepam) = 2.7; logP(DNIS) = 1.31), probably thanks to a typical benzodiazepine structure suitable for an interaction with plastic material, whereas DNIS is more water soluble than diazepam. The other phenomena taking part in the differences observed is the pH of the solution, which is directly responsible for the portion of the drug in its ionized form and the solubility of the unionized form. Indeed, for drugs that are weak acids or bases, solubility is a direct function of solution pH.[19,20] Diazepam, whose pKa is 3.3 (weak acid), gives a solution pH of 5.6 when diluted in sodium chloride. As the percentage of the drug present in its unionized form increases, so does the fractional sorption into PVC surface. With DNIS, PVC strips were immerged in the pure commercial solution, so no influence of pH occurred to increase the sorption process.

When PVC is coated with the sol gel layer, sorption of diazepam and DNIS is reduced. As shown in Figures 8 and 9, sorption of drugs is lower than the standard uncoated PVC, as a result of a similar barrier effect between the two drugs. Coating seems to have no effect on sorption in the first 3 h of contact, both for diazepam and only a low one for DNIS (reaching 16% at 180 min). However, sorption is reduced for both drugs by about 40% at further application times thanks to the hybrid layer,

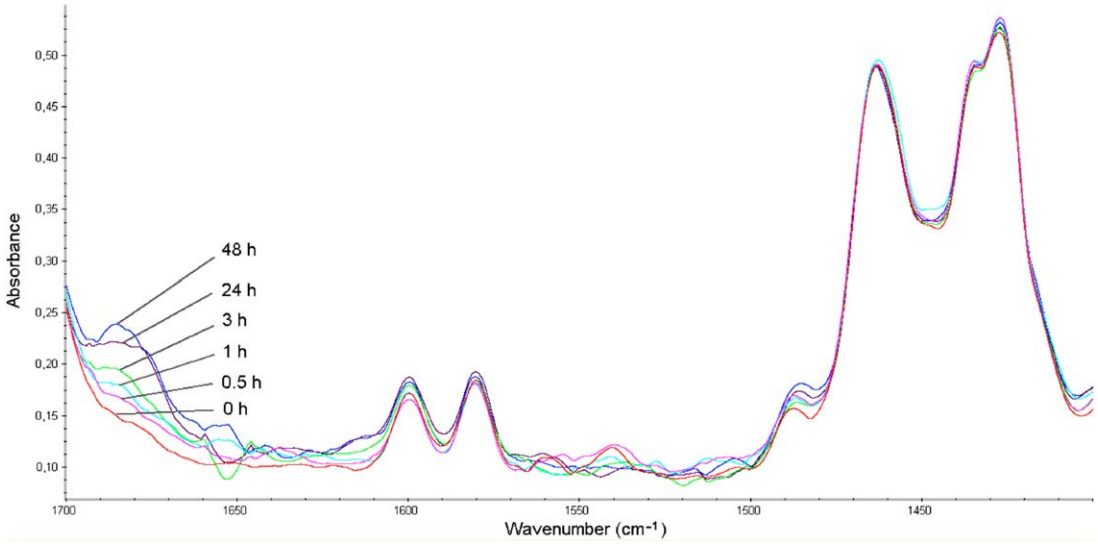

Figure 10. FTIR-ATR spectrum performed between 1700 cm^{-1} and 1400 cm^{-1} on uncoated PVC in contact with diazepam. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

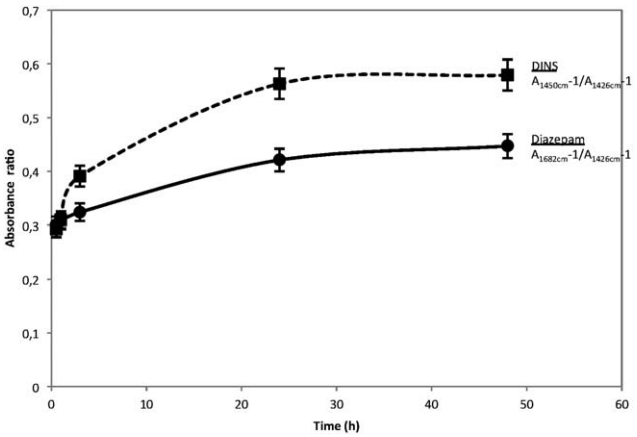

Figure 11. Effect of Diazepam and DNIS sorption tests with uncoated PVC on the absorbance ratio $A_{1682\,cm^{-1}}/A_{1426\,cm^{-1}}$ and $A_{1450\,cm^{-1}}/A_{1426\,cm^{-1}}$.

resulting in a smaller loss after 48 h than with the standard PVC, which is of 60% for diazepam and 15% for DNIS. This outcome can't be supported with certainty by FTIR results. Indeed, when the PVC is coated, the intense band of the hybrid sol-gel coating at 1715 cm^{-1} (carbonyl stretching region) covers the C=0 band of the diazepam at 1682 cm^{-1}; in the same way the C=C coating band located at 1636 cm^{-1} and the NO_2 band of the DNIS at 1650 cm^{-1} overlap each over. On that account, FTIR analysis cannot provide any undoubted information on the protection of the coating on sorption effect.

The results of the mechanical study reported in Tables I and II (see "mechanical properties" section for testing procedure) also show an absence of evolution of the characteristics of the polymer and the coated polymer upon time contact during diazepam or DNIS sorption. Neither the polymer nor the coating seems to be mechanically altered by drug sorption. The unchanged mechanical properties of uncoated PVC suggests that drug sorption does not affect DEHP migration.

This assertion is also supported by FTIR-ATR results, the absorbance ratio $A_{1463\,cm^{-1}}/A_{1426\,cm^{-1}}$ remaining invariant after drug sorption. The ratio value of 0.916 ± 0.006 measured after test sorption in Diazepam, or 0.917 ± 0.006 after test sorption in DNIS, is strongly similar to that observed in the reference uncoated PVC (0.923 ± 0.008).

The unchanged mechanical characteristics of the coated polymer after sorption tests also do not suggest any drastic coating degradation or significant interaction between diazepam or DNIS and the hybrid layer.

However that may be, issue could be found with the use of another migration simulant like olive oil, to avoid coating degradation. According to the European Regulation no 10/2011,[21] vegetable oils are the referent simulants assigned for fatty foods because they are able to extract lipophilic substances. The Regulation also allows their substitution by 95% ethanol, which doesn't require an extraction step.

Nevertheless, a strong variability has been found with sorption tests when using a diazepam solution (Figure 8) in the late application times, probably because of the drug formulation, which contains ethanol. Figure 12 shows SEM microphotographs of coated and uncoated PVC surfaces after contact with diazepam solution. Both PVC surfaces of uncoated and coated material don't remain smooth during analysis. From 30 min onwards, deposits of drug can be observed on the PVC surface (A1 and B1). These deposits seem slightly bigger and more numerous on the coated PVC than

Table I. Evolution of Mechanical Properties of Uncoated PVC Consecutive to Sorption Test with Diazepam and DNIS

	Contact with diazepam		Contact with DNIS	
Time contact (h)	Elastic modulus (MPa)	Elongation at break (%)	Elastic modulus (MPa)	Elongation at break (%)
0	31.7 ± 0.6	349.9 ± 55.5	31.7 ± 0.6	349.9 ± 55.5
0.5	35.9 ± 2.9	359.9 ± 60.3	35.7 ± 3.1	331.6 ± 43.2
1	34.1 ± 2.1	351.9 ± 34.4	33.1 ± 2.3	361.9 ± 48.6
3	33.3 ± 1.9	387.7 ± 47.8	36.8 ± 2.8	346.8 ± 51.8
24	32.3 ± 1.7	371.3 ± 51.2	33.4 ± 1.6	413.2 ± 54.2
48	32.5 ± 0.9	363.2 ± 39.5	34.3 ± 1.7	277.7 ± 68.4

Table II. Evolution of Mechanical Properties of Coated PVC Consecutive to Sorption Test with Diazepam and DNIS

	Contact with diazepam		Contact with DNIS	
Time contact (h)	Elastic modulus (MPa)	Elongation at break (%)	Elastic modulus (MPa)	Elongation at break (%)
0	167.8 ± 20.7	130.3 ± 43.9	167.8 ± 20.7	130.3 ± 43.9
0.5	145.3 ± 27.0	100.4 ± 30.3	168.7 ± 18.1	83.0 ± 28.2
1	158.4 ± 21.0	89.9 ± 34.4	163.6 ± 23.1	102.1 ± 28.6
3	151.5 ± 19.2	104.9 ± 29.8	171.4 ± 22.8	79.0 ± 31.8
24	151.1 ± 17.3	99.8 ± 31.2	163.7 ± 18.4	141.3 ± 44.2
48	164.3 ± 19.9	149.8 ± 39.5	148.9 ± 17.1	86.3 ± 28.4

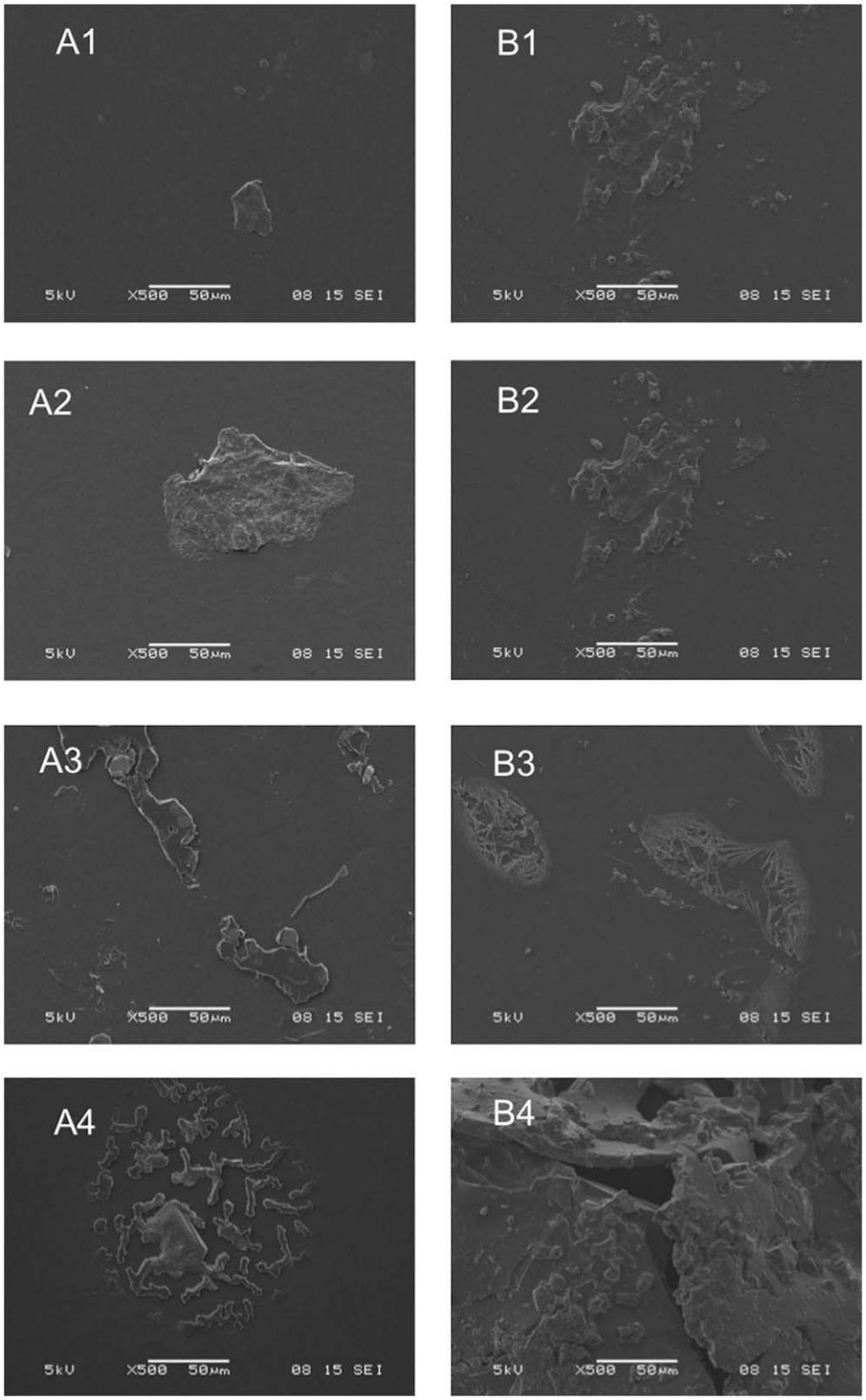

Figure 12. SEM micrographs (500x) of uncoated (A) and coated (B) PVC surfaces after diazepam sorption test at different times: (1) $t = 30$ min, (2) $t = 60$ min, (3) $t = 180$ min, (4) $t = 24$ h.

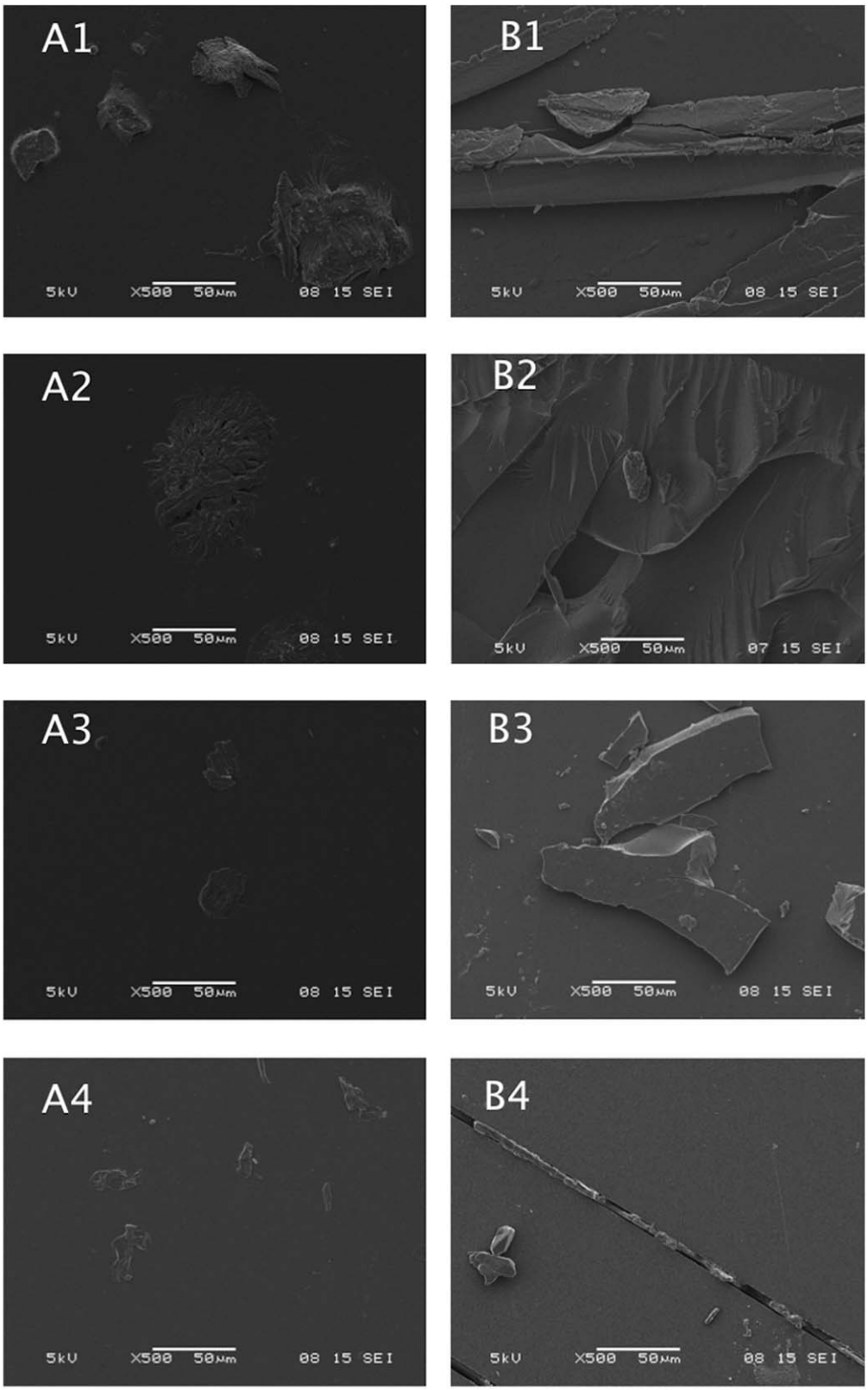

Figure 13. SEM micrographs (500x) of uncoated (A) and coated (B) PVC surfaces after DNIS sorption test at different times: (1) t = 30 min, (2) t = 60 min, (3) t = 180 min, (4) t = 24 h.

on the standard one. Up until 24 h, no cracks are visible on the polymer surface. Cracks appear on the 24 h' SEM micrograph of coated PVC surface only. At 24 h, coated PVC is covered with deposits of diazepam and we can observe typical evidence of some cracks, which are not present on the original PVC (A4 and B4). However, this apparent surface degradation didn't significantly impact the mechanical behavior of the coated PVC, as previously reported. In the same way, the mechanical study suggests that the presence of ethanol in the drug formulation of diazepam does not affect DEHP migration in the polymer.

For DNIS, PVC surface changes are observed from the beginning of the application to the end, as shown in Figure 13. For both types of PVC, no cracks appear on SEM images. But, DNIS deposits are present on PVC surface, not only on the original PVC surface but also on the hybrid one, and they take a shape of fine and long crystals.

All these results show that the protective effect of the layer is incomplete as drug loss is quantified. Although these findings are far from those theoretically expected, i.e., like those obtained with inert polyethylene (Figures 8 and 9), remaining concentrations of DNIS are close to the initial concentration. However loss into coated PVC remains important for diazepam. Overall, the hybrid layer allows a reduction of drug migration into PVC surface but isn't a satisfactory solution for the development of new technologies and devising infusion medical devices in collaboration with the concerned industries. The coating process has to be improved before to obtain a complete barrier against absorption. The composition of the sol gel needs to be adapted to provide a total protective effect against sorption of drugs, without adversely affect the efficiency regarding DEHP migration and also needs to be resistant against alcohol chemicals included in drugs' formulations.

CONCLUSIONS

The results of this study show that our hybrid sol gel coating provides a protection against the interactions on plasticized PVC surface. For long time exposures, as is the case for infusion procedure, DEHP release from PVC matrix is strongly reduced. These findings confirm our previous result, showing the efficiency of the layer against the release of the plasticizer during a contact of 1 h.[11] Our coated material also seems to be a promising way to prevent drug sorption. Diazepam and DNIS loss is generally reduced for a prolonged contact time. However, SEM microphotographs clearly indicate that the coating is affected by contact with simulant or drug injectable solutions, resulting in decrease of interaction protection.

Even though the results obtained are probably far from being optimised for manufacture and application to infusion medical devices, they give interesting indications of the promised role of the hybrid layer on two major interaction phenomena that always occur with plasticized PVC: plasticizer release and drug sorption. Furthermore improvements of the manufacturing process of the hybrid coating need to be made, like a suitable choice of reaction conditions or an accurate balancing of organic and inorganic phases content. Indeed, they probably control the adhesion and the barrier properties. Moreover, the coating also slightly modifies PVC transparency, which is one of the main relevant properties of the polymer material when used as a medical device. This opacity is induced by the presence of titane, whose components' release has also to be performed in further investigations. In the end, these changes and assessments might provide an efficient and safe barrier to advert risks impaired to PVC interactions, to provide safety for hospitalized patients.

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