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Abstract

Interactions between medical device material and the drug itself have been evoked for polyurethane and may lead to underdosing. Polyurethane, sterilization mode and the crosslinking level of the polymer have an influence on sorption. The aim here is to evaluate the impact of polyurethane conservation time and conditions as well as sterilization mode.

Two polyurethane extension tubes were tested, one sterilized by ethylene oxide and the second by gamma radiation. Forced degradation experiments were performed. After 3 and 6 months of incubation, thermal properties, diazepam delivery and cytotoxicity of leachates were assessed.

Diazepam delivery differs significantly according to the version of polyurethane. Sterilization however has no impact on diazepam delivery. No cytotoxicity was observed whatever the infusion tube and the aging conditions. In conclusion, sterilization procedures do not induce polyurethane degradation, but high temperature/relative humidity/time storage conditions lead to a slight degradation in polyurethane.

Keywords: Biomedical Applications, Differential Scanning Calorimetry (DSC), Polyurethane Thermogravimetric Analysis (TGA).

Introduction

Infusion is defined as the administration of drugs, physiological solutes or products derived from blood intravenously and sometimes subcutaneously, arterially or intrathecally, at a regular rate over time for therapeutic or diagnostic purposes. Infusion is a common act in hospital. Indeed, the National Agency for the Safety of Medicines and Health Products (ANSM) in 2013 noted a 63% consumption of injectable forms, making this route of administration the most used. The efficacy of the infusion requires the use of a medical device adapted to the properties of the molecule to be infused.

Various materials are used for the manufacture of medical devices (MDs) for infusion. Extenders used for the administration of injectable drugs in children or adults are usually made of plasticized PolyVinylChloride (PVC), polyethylene (PE), polyurethane (PUR), Silicon, PE/PVC co-extrudate and Multilayer of PE/EthylVinylAcetate (EVA)/PVC [1]. One of the main criteria for choosing an infusion device is for the drug to be administered in a predictable and reproducible manner [1]. To assess the criterion of choice for the material, container-content interactions have to be taken into account. There are two types of container-content interaction: firstly the sorption of drugs on the MD and secondly the migration of molecules (plasticizers) initially contained in the material. These interactions vary according to the material used [2,3]: Neither of these interactions is noted for PE, PUR is subject to sorption and PVC is the most sensitive to them (sorption and migration). Among these materials, PE has a chemical inertia superior to the others [2]. For example, diazepam sorption was studied with three different materials: PVC, PE/PVC and PUR and was least adsorbed on PE/PVC (14.4% diazepam adsorbed at the end of the infusion). Plasticizers contained in PVC can migrate in contact with lipophilic drugs, blood or parenteral nutrition [4,5], these molecules being potentially toxic to humans [6]. Moreover, plasticizers have an impact on sorption [7,8]. the higher the plasticizer concentration in the PVC matrix, the greater the adsorption of diazepam. Differing plasticizers have similar behavior towards the sorption of diazepam and nitroglycerin, but it seems to be greater for PVC plasticized with 1,2-Cyclohexane dicarboxylic acid diisononyl ester (DINCH).

Various parameters influence drug/medical device interactions such as the lipophilic / hydrophilic character of the drug, the nature and surface of the material (hydrophilicity, roughness, positive or negative charges, etc..).. In our previous work, we observed that results for polyurethane were variable [2]. Some devices based on this material show a sorption level for some drugs higher than with plasticized PVC. Indeed, for two extension tubes in PUR the sorption of diazepam was approximately 50% while with PVC, it was about 40%. Others meanwhile show lower sorption levels, at about 20%. The hypotheses put forward to explain

these differences evoke the level of polymer crosslinking, the degree of polymerization and the sterilization method used, which alter the surface characteristics of materials and consequently drug sorption [2]. Another parameter, the aging of the device, appears relevant. Some authors have evaluated the evolution of the properties of infusion devices over time but focused mainly on the level of toxicity of extractives [9,10].

Different sterilization methods are used for MDs: ethylene oxide (EtO), electron beam irradiation, heat, hydrogen peroxide gas plasma or gamma radiations [11]. The two most common sterilization methods for infusion MDs are EtO and gamma rays. However, EtO is a substance classified as carcinogenic and mutagenic of category 1B and the permissible limits for EtO residues are specified in a standard (ISO 10993-7). Currently, other sterilization methods can be used, especially in pediatrics where exposure limits to ethylene oxide are rapidly exceeded…

Medical devices used in infusion can be stored for 3 years before use. It is therefore interesting to link the variables of time and storage conditions to the evolution in the properties of medical devices and in particular, their ability to interact with infused injectable drugs. This approach would raise professional awareness about the need to take these parameters into account rather than consider medical device materials as a homogeneous whole.

This is why our objective is to evaluate the impact of conservation time and conditions on polyurethane intended for medical infusion devices, by examining initial characteristics and in particular sterilization methods. This work will also be an opportunity to evaluate cytotoxicity evolution in extractables over time.

Materials and Methods

Infusion Tubes

Two PUR double-lumen extension tubes (Ref 841.264 and ref 5841.208, Vygon, Ecouen, France) available on the French market were analyzed (Table 1). The polyurethane used to manufacture the samples (PUR-264 and PUR-208) is a thermoplastic aromatic polyether urethane. The hard segment consists of methylene diisocyanate (MDI) and butanediol used as a chain extender. The soft segment is a linear polyol: polytetramethylene ether glycol (PTMEG).

Double-lumen extension tube	Manufacturer	Reference	Type of Plastic	Characteristics	Internal surface (mm²)	Type of sterilization
Octopus 2	Vygon	841.264	PUR	∅=1.50 x 2.50 mm, L=10cm	471	Gamma radiation
Octopus 2	Vygon	5841.208	PUR	∅=1.50 x 2.50 mm L=10cm	471	Ethylene oxide gas

Table 1. Characteristics of PUR double-lumen extension tubes

The Octopus 2 (Ref 841.264) will be named PUR-264 without sterilization and PUR-264R after sterilization. In the same way, the Octopus 2 (Ref 5841.208) will be named PUR-208 without sterilization and PUR-208EO after sterilization.

Forced degradation experiment

Samples were kept at room temperature (RT) or in an incubator (Binder GmbH, Binder, Germany) at 50°C with or without relative humidity (75% R.H.) for 3 and 6 months. At the end of incubation, samples were photographed. Thermal properties, wettability, diazepam delivery and cytotoxicity of leachates were determined.

Fourier Transform InfraRed spectroscopy

The chemical structure of virgin, sterilized and aged PUR samples was studied by Fourier Transform InfraRed spectroscopy (FTIR) using a Spectrum 100 spectrometer (Perkin Elmer, Zaventem, Belgium) equipped with an Attenuated Total Reflectance (ATR) accessory. Data were recorded at ambient temperature in the spectral range 4000-650 cm^{-1}, using 16 scans per sample at 4 cm^{-1} resolution.

ThermoGravimetric Analysis

Thermogravimetric analysis (TGA) was carried out using a TAQ50 apparatus (TA Instruments, Guyancourt, France) in order to observe the effect of aging on the degradation behavior of PUR. Virgin and artificially aged PUR samples were placed in an open platinum pan and

suspended on a microbalance at temperatures ranging from 30°C to 700°C with a heating rate of 10°C/min under N_2/O_2 (10/90 mL/min) flow delivered inside the oven.

Differential Scanning Calorimetry

Virgin, sterilized and artificially aged PUR samples were analyzed by Differential Scanning Calorimetry (DSC, Q100 apparatus, TA Instruments, Guyancourt, France) under nitrogen (50 mL/min). The following cycle was applied: heating at 10°C/min from 30°C up to 230°C, then cooling at 5°C/min down to -85°C and finally heating up to 230°C at 10°C/min. Glass transition and melting temperatures were taken at the onset of the second heating step after zooming with TA software (TA Universal V4.4A provided by TA Instruments).

Capillary test

4 cm of the tube was placed in ultrapure water for 30 seconds. The water level in tubes was measured. This test was repeated 3 times for PUR-208, PUR-208EO, PUR-264 and PUR-264R. An analysis using the Conover and Iman method with Bonferroni correction was used.

Scanning electron microscopy

Scanning electron microscopy (SEM) images were obtained on a Flexsem 1000 Hitachi, operating with an accelerating voltage of 5 kV and an emission current of 10 µA.

Cytotoxicity

In vitro cell culture was performed on samples with NIH3T3 mouse fibroblasts (ATCC CRL 1658) according to International and European Standards [13]. NIH3T3 were cultured in Dulbecco's minimum essential medium (DMEM Gibco), supplemented with 10% newborn calf serum (Eurobio). All media contained fungizon (25 mg/mL, Gibco BRL) and gentamicin (50 mg/mL, Panpharma). Cells were incubated at 37°C in 5% CO_2 atmosphere and 100% R.H. in a CO_2 incubator (CB 150/APT line/Binder). The samples were weighed and placed, for extraction purposes, in complete DMEM at a ratio of 200 mg/mL (24 h, 37°C, 80 rpm, Innova40, New Brunswick Scientific, France). Simultaneously, 4.0×10^3 NIH3T3 cells per well were seeded in a 96-well tissue culture plate containing 100 µL of DMEM per well. After 24 h, the extraction medium was collected and sterile-filtered (0.2 µm LPB Acrodisc®; PALL, France). The culture medium was removed from the cells and 100 µL/well of the filtrated extraction medium or DMEM (negative control), i.e. absence of cytotoxicity, was respectively added to the wells. After 24 h incubation, cell viability was measured by the AlamarBlue® assay

(ThermoFisher Scientific,France). The extraction medium was then removed from the cells and 200 µL/well of a 10% AlamarBlue® in DMEM solution was added to the wells and placed, away from light, in an incubator for 2 h. 150 µL of the AlamarBlue® solution was recovered from each well and transferred into a flat bottomed 96-well plate. Fluorescence was measured at an excitation wavelength of 530 nm and an emission wavelength of 590 nm, on a microplate fluorometer (TwinkleTMLB 970; Berthold Technologies GmbH & Co, Germany). Fluorescence readings were normalized relative to those of the negative controls. The experiments were performed in triplicate.

Drug Delivery

Diazepam solutions were prepared from the powder form of active pharmaceutical ingredients (vial of 25 g, Cooper, Melun, France). Briefly, diazepam (7.5 µg/mL) was prepared by dissolving in an isotonic saline solution (0.9% NaCl, 500 mL Viaflo1, Baxter, Maurepas, France) in a glass vial before using immediately. New syringes in polypropylene (20mL syringes, Becton Dickinson Plastipak, Le Pont de Claix, France) were prepared every day as reservoirs for the drug solutions and connected to extension lines in polyethylene (Lectro-cath, ref. 1155.10, Vygon, Écouen, France, L. 100 cm, Ø 1.0 x 2.0 mm, Vol. 1.1 mL) for which no sorption had been observed. Extension lines were purged with saline, using the automatic syringe pump function. According to clinical practices in adults, they were infused via syringe pumps (model Alaris1 CC, Carefusion, Voisins-le-Bretonneux, France) with a constant flow rate of 2.5 mL/h (n = 5 syringes per reference).

Diazepam concentrations in the prepared syringes and at the egress of extension tubes were determined over time by an analytical spectrophotometric UV-Vis method with a UV-Vis spectrophotometer (UV-2550 spectrophotometer, Shimadzu, Marne La Vallée, France) reading at λ = 235 nm to determine sorption kinetics. The catheter egress was connected to the 10-mm UV spectrophotometer quartz cell (ref. 178.710-QS, Suprasil, Hellma Analytics, Müllheim, Germany, V = 0.080 mL) through the inlet tube of the spectrophotometer flow cell (V = 0.137 mL) to measure drug concentrations continuously. Concentration values were recorded every minute over a total period of 150 minutes. The schematic of the device used for the absorption of diazepam is described in Figure 1. All data were collected with UVProbe software ver. 2.31 (Shimadzu Corporation, Kyoto, Japan). Initial diazepam concentrations in syringes were measured with the spectrophotometric UV-Vis method, which was validated with six concentrations of diazepam between 1 and 15 µg/mL, repeated six times by the same person. The limits of detection (LOD) and quantification (LOQ) were respectively 0.11 and 0.21 µg/mL.

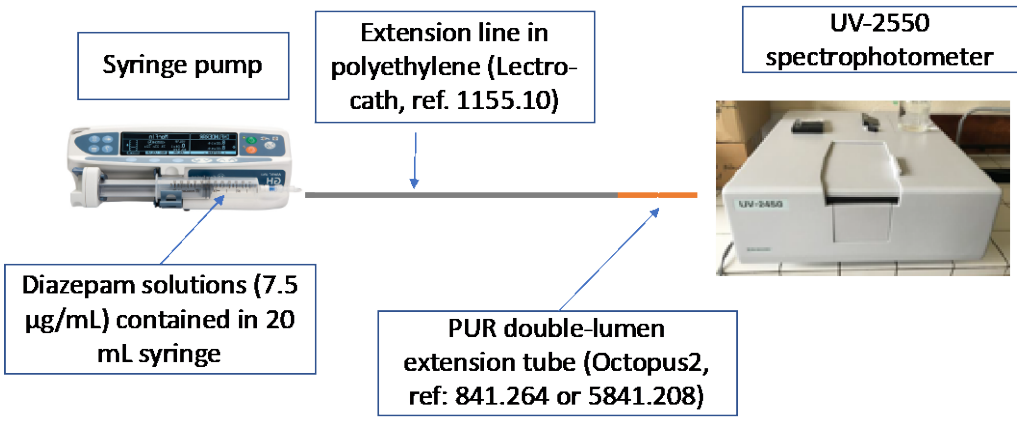

Figure 1. Schematic of set-up used for the absorption of Diazepam.

Statistics

The normality of all data collection was assessed by the Shapiro-Wilk test. The Student t test was used to compare the diazepam concentrations at the egress of extension tubes. Multiple comparisons were made using an analysis of variance (ANOVA). When this revealed a significant p value ($p < 0.05$), an analysis using Sidak's test was performed to detect significant differences between couples. All statistical tests were performed using GraphPad Prism version 7.0a for MacOS X (GraphPad Software, La Jolla California USA, www.graphpad.com). Data are presented as mean values and standard error. For all analyses, statistical significance was considered as a p-value <0.05.

Results and discussion

Chemical and thermal characterization of PUR tubes

PUR is a commonly-used material in infusion MDs as proven by the market study conducted by the National Agency for the Safety of Medicines and Health Products (ANSM) between 2014 and 2015 [14] which showed that out of 70 DMs analyzed, 57% were in PUR.

To evaluate the impact of sterilization procedures on the chemical structure of PUR tubes, two medical devices sterilized either by EtO (PUR-208) or gamma radiation (PUR-264) were studied by FTIR spectroscopy. Characteristic ATR-FTIR spectra were obtained for both non-sterile and sterile PUR (Figure 2A, PUR-208 and PUR-208EO): amide N-H stretching (3302 cm^{-1}), aliphatic CH_2 stretching (2918 cm^{-1}), non-hydrogen bonded (1730cm^{-1}) and hydrogen bonded (1701 cm^{-1}) urethane C=O stretching, urethane N-H bend and C-N stretching (1530

cm^{-1}), aliphatic α-CH_2 wagging (1368 cm^{-1}), C-N stretching (1220 cm^{-1}), ether band (1104 cm^{-1}), urethane group stretching (1077 cm^{-1}) and out of plane O-C=O bending (770 cm^{-1}). Similar spectra were obtained for PUR-264 and PUR-264R. Therefore, it can be assumed that neither ethylene oxide nor gamma radiation sterilization procedures induced PUR degradation [15].

Some changes in the intensities of several peaks could be noted on the IR spectrum of PUR aged for 6 months at 50°C and under 75%R.H. (Figure 2B, PUR-208EO). The decrease in the C-O-C band (1100 cm^{-1}) could be attributed to the scission of soft segments at the ether bond. This resulted in the formation of radicals and then oxidized species leading to an increase in the band at 3302 cm^{-1} which became sharper [16]. The decrease in the bands related to the urethane group at 1701, 1530, 1220, 1104 and 1077 cm^{-1} were attributed to the scission of the C-N bond. As a consequence, a new intense peak attributed to primary amines appeared at 1636 cm^{-1} as well as a lower one at 1563 cm^{-1}.

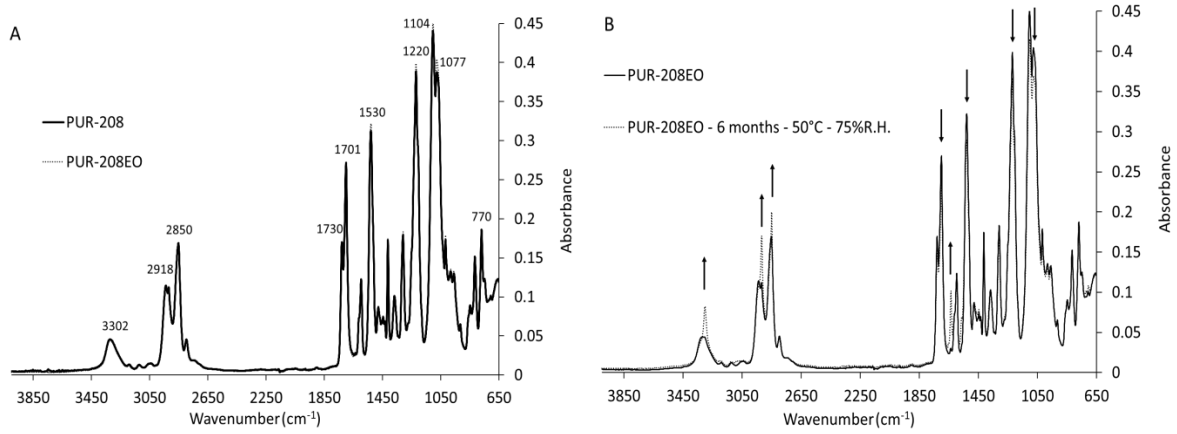

Figure 2. ATR-FTIR spectra of PUR-208 and PUR 208EO (A) and PUR-208EO before and after aging (50°C, 75% R.H., 6 months) (B).

To assess the effect of artificial aging on the bulk properties of PUR samples, a thermogravimetric analysis was performed on a non-sterile sample, a sterile sample and another was submitted to more severe aging conditions, i.e. 6 months at 50°C and 75% RH. This O2 flow value is the one recommended by the apparatus manufacturer (TA Instruments). As observed in Figure 3, similar degradation profiles were obtained. No significative difference was observed after sterilization. However, degradation occurred at a lower temperature for the artificially aged sample (starting at 225°C versus 245°C for aged and non-sterile PUR

respectively), indicating that high temperature/relative humidity/time storage conditions led to a slight degradation in PUR that weakened the PUR tube. This is consistent with the FTIR analysis. Similar results and findings were obtained for PUR-264 samples under the same conditions.

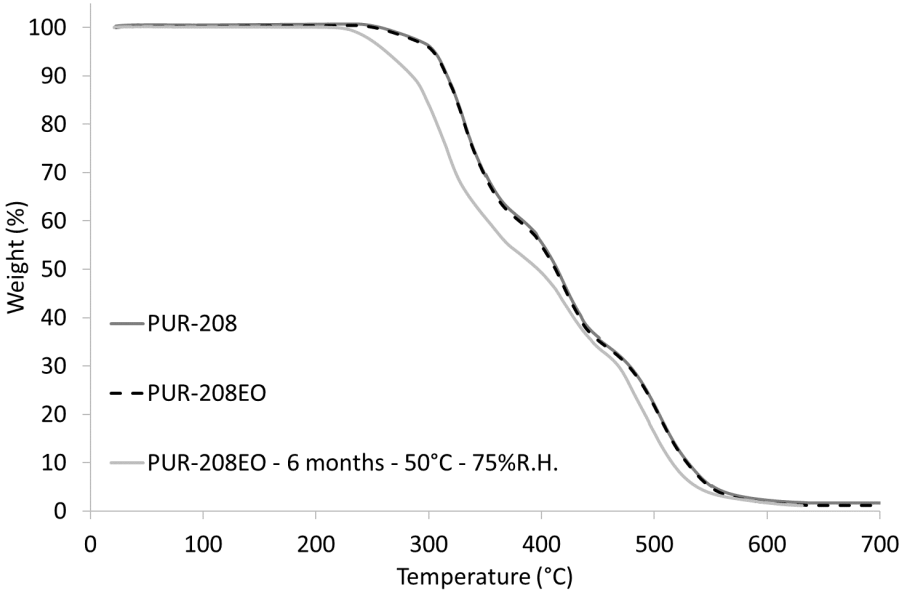

Figure 3. TGA curves of PUR-208, PUR-208EO before and after aging (50°C, 75% R.H., 6 months) under O_2/N_2 atmosphere.

As evidenced by FTIR results, the reorganization of molecular chains could modify chain mobility and consequently the crystallinity of PUR. The effect of sterilization and artificial aging was therefore studied through DSC analyses. Figure 4 presents the thermograms of non-sterile and sterile PUR-208 and PUR-264.

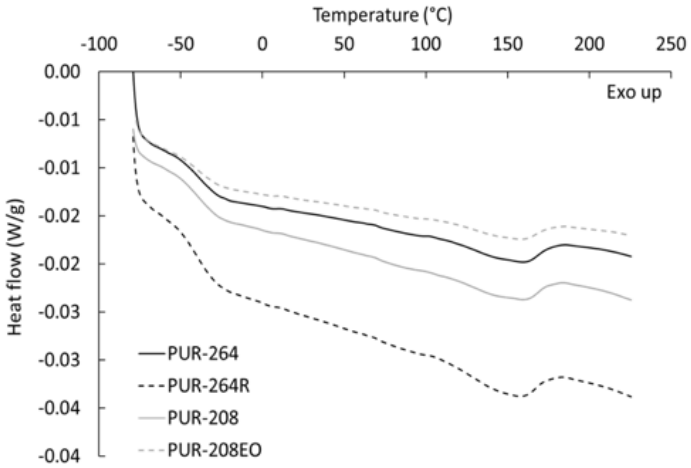

Figure 4. DSC thermograms of second heating step of non-sterile and sterile PUR-208 and PUR-264.

Glass transition (T_g) (characteristic of soft segments), melting point (T_m) and reaction heat (ΔH_m) (characteristic of hard segments) values for all samples are compiled in Table 2.

Storage conditions		PUR-208			PUR-264		
		T_g (°C)	T_m (°C)	ΔH_m (J/g)	T_g (°C)	T_m (°C)	ΔH_m (J/g)
Virgin	non-sterile	-40	109	9.0	-39	111	8.4
	sterile	-39	114	7.6	-39	109	8.3
3 months	25°C – 0%R.H.	-37	115	6.7	-36	110	6.7
	50°C – 0%R.H.	-35	107	6.4	-37	109	8.2
	50°C – 75%R.H.	-39	109	7.8	-42	112	7.4
6 months	25°C – 0%R.H.	-45	108	7.2	-40	109	6.3
	50°C – 0%R.H.	-40	110	6.4	-42	107	6.9
	50°C – 75%R.H.	-37	107	6.4	-41	107	7.1

Table 2. Results from the second heating of PUR-208 and PUR-264 samples for DSC analyses (non-sterile, sterile and aged). Tg and Tm were taken at the onset.

For PUR-208, no differences in glass transition temperatures were detected. A slight increase in T_m and decrease in ΔH_m after sterilization were observed, indicating that ethylene oxide sterilization provoked a very low scission of the chains or crosslinking that was not detected by FTIR. For PUR-264 on the other hand, no change was noted after sterilization by gamma radiation for either glass transition or melting phase.

After artificial aging (all conditions), the glass transition phenomenon was globally broader. Without humidity, after 3 months' storage, the glass transition temperature slightly increased. This can be explained by molecular recombination or a crosslinking mechanism after oxidation [17]. For 6 months' aging, the glass transition temperature decreased, indicating an increase in molecular mobility in soft segments caused by chain scissions occurring after a long storage time. When samples were stored in a high relative humidity environment, Tg values were lower than without humidity, which can be explained by the plasticizing effect of adsorbed water. As for the melting temperature related to hard segments, no significant trend was observed whatever the storage conditions. For all samples, the melting enthalpies for aged samples were lower than for virgin PURs. This indicates a decrease in crystallinity upon aging, which can be attributed to a degradation of the material at the crystal boundaries [16].

Drug Delivery

Diazepam, a drug belonging to the class of benzodiazepines, is a highly lipophilic molecule (Log P = 2.86) and therefore very prone to sorption. It is used in this study as a tracer [2,18,19].

Figure 5 shows the amount of diazepam delivered by the PUR tubes after 3 hours of infusion. Before sterilization, the amount of diazepam delivered was different from one device to the other (PUR-208 vs. PUR-264, 60.07% ± 1.41% vs. 50.64% ± 1.60%; p<0,0001) while the material was the same (PUR). Therefore, diazepam sorption is related to the wettability of the materials. As both references have the same composition, the observed difference in wettability could be accounted for by different parameters during the extrusion process. Indeed, Bovas et al. [20] showed that variations in melting temperature have a significant effect on catheter surface roughness and wettability characteristics. In particular, they showed that insufficient external heat could lead to the generation of an unmelted type of polymer mixture in the extruder, with higher shear stress at the exit of the die and therefore a less smooth and homogeneous catheter surface.

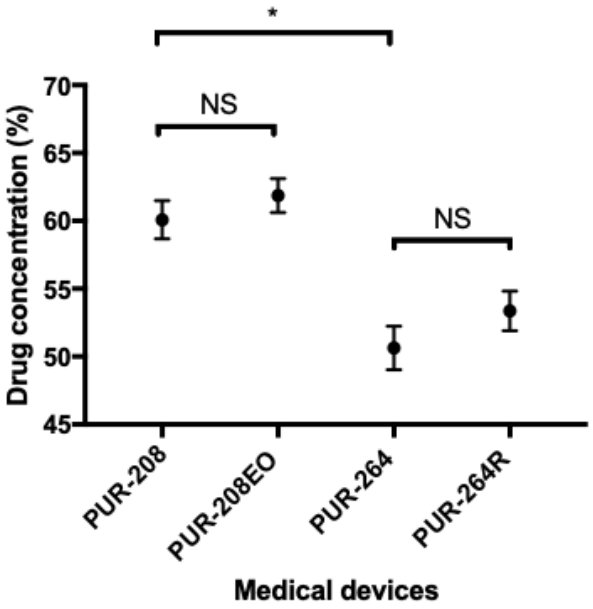

Figure 5. Drug concentration at the egress of the extension set at T0 (plots are means and SD).

The sterilization process had no impact on the delivery of diazepam (PUR-208 vs. PUR-208EO, 60.07% ± 1.41% vs. 61.87% ± 1.25%; NS and PUR-264 vs. PUR-264R, 50.64% ± 1.60% vs. 53.36% ± 1.45% ; NS) (Figure 5), which concords with the FTIR analysis. Nouman et al. clearly showed a morphological change on the surface of the PUR tubes after radiation; more particularly they observed an increase in surface roughness [21]. Nevertheless, in view of our results, this morphological change has no impact on the delivery of diazepam. Despite the different initial roughness highlighted for non-sterile catheters, the sterilization processes appeared to modify the surface sufficiently to erase this difference and resulted in a similar roughness.

After 6 months' natural aging (25°C, Figure 6A), accelerated (50°C, Figure 6B) or accelerated in wet conditions (50°C, 75% relative humidity, Figure 6C), differences in terms of diazepam sorption between the two references were not observed. Without humidity, the amount of delivered diazepam was still significantly different at 3 months between the two references (PUR-208EO vs. PUR-264R) when stored at 25°C (61.64% ± 2.69% vs. 52.56% ± 0.58%; $p<0.0001$). Nevertheless, when the storage temperature increased, aging accelerated and no significant difference was observed between the two references after 3 months (61.55% ± 2.08% vs. 61.83% ± 1.40%; NS). This suggests that the material had undergone a change, especially reference PUR-264R which could be explained by a rearrangement of the

macromolecular chains and a crosslinking mechanism shown by the DSC analysis. This rearrangement and crosslinking of PUR chains limited the adsorption or absorption of diazepam in/on the infusion tube. After 6 months' storage, the amount of diazepam delivered decreased to nearly 50% in both 25°C and 50°C storage. In the same way, this is explained by the properties of the material. DSC analysis clearly showed a decrease in Tg and therefore a mobility of macromolecular chains due to the progressive degradation of PUR. This led to an increase in the adsorption or absorption of diazepam. When tubes were stored at 50°C in the presence of humidity, the differences in terms of diazepam delivery were not observed after 6 months' storage. Under these conditions, the amount of diazepam delivered by PUR-264R increased from 53.36% on T0 to 71.00% at 3 months while it remained stable for PUR-208EO at around 62%. Surprisingly, the amount of diazepam delivered at 6 months remained stable at a high level for both references at over 65%. This is explained by the water intake of the tubes during storage and is proved by DSC analysis. Thus, the water trapped in the polymer network has not only a plasticizing effect but also a role in limiting the sorption of diazepam and consequently increasing the delivered dose significantly.

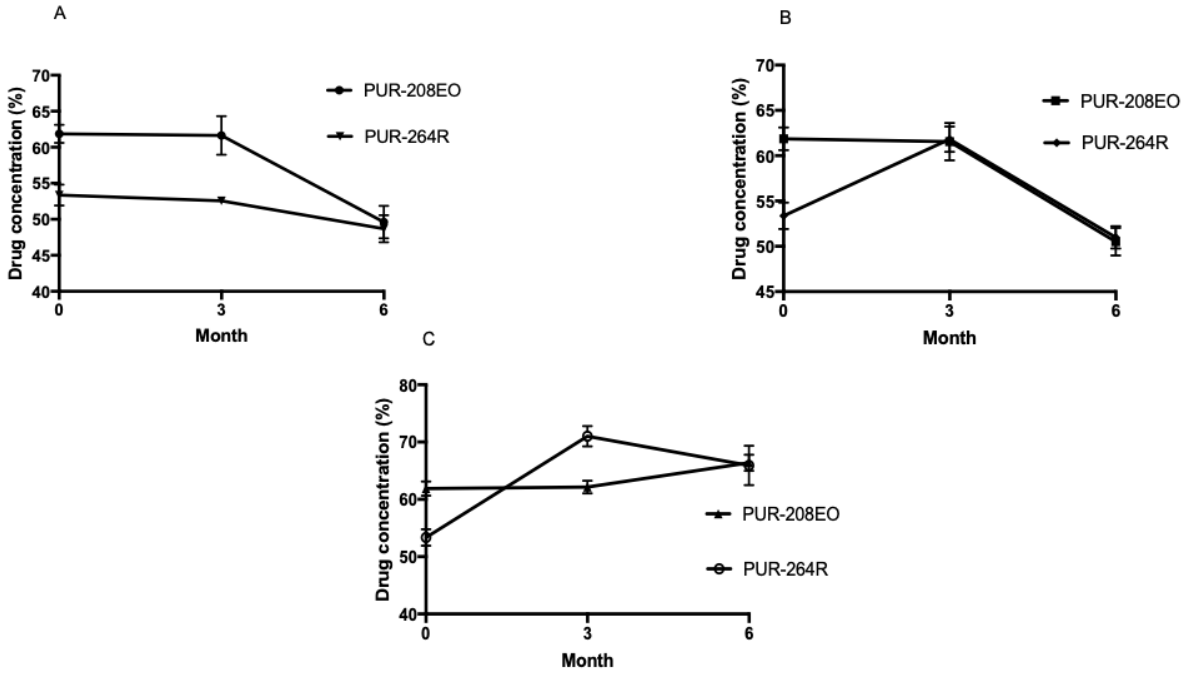

Figure 6. Drug concentration at the egress of the extension set after 3 and 6 months at 25°C without humidity (A), at 50°C without humidity (B) and at 50°C with 75% relative humidity (C) (plots are means and SD).

Figures 7A and 7B summarize the impact of storage conditions on the delivery of diazepam. The figures show that whatever the PUR tube reference, storage (25°C and 50°C) contributes to reducing the delivered dose of diazepam to the patient. Conversely, and very interestingly,

storage humidity helps to preserve or even substantially improve the delivered dose to the patient (66.63% and 65.91% after 6 months of storage for PUR-208EO and PUR-264R respectively).

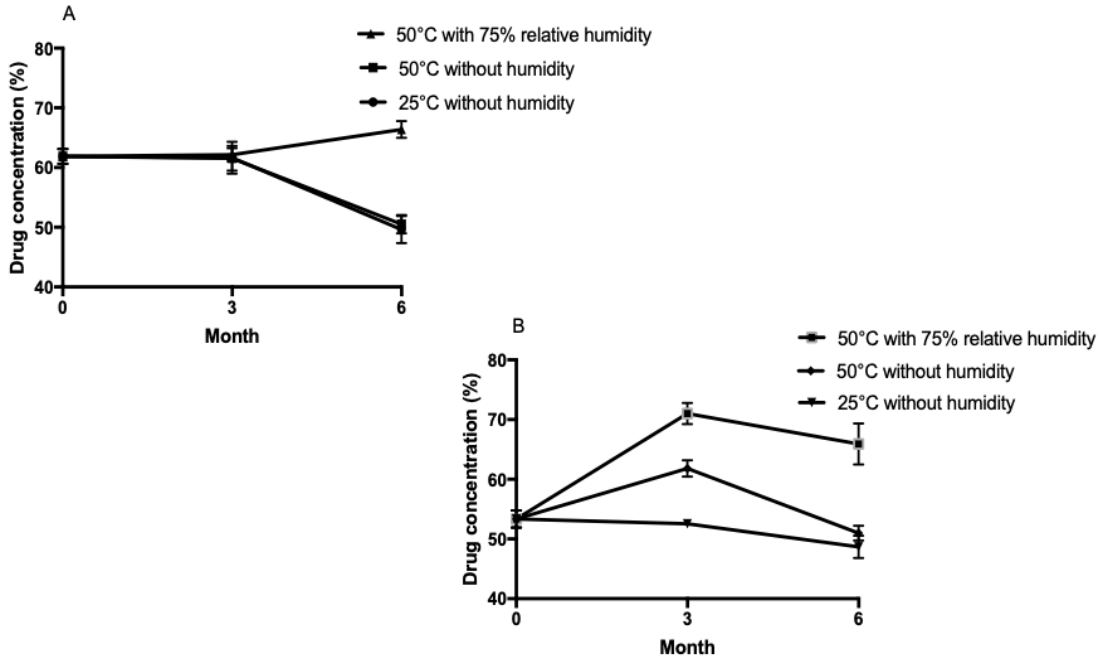

Figure 7. Drug concentration at the egress of the extension set after 3 and 6 months at 25°C without humidity, 50°C without humidity and at 50°C with 75% relative humidity: PUR-208EO (A) and PUR-264R (B) (plots are means and SD).

Capillary tests and a morphology study were carried out by SEM on the 4 samples, but no difference was found between the two references or the two sterilization modes (p. Bonferroni corrected = 0.0083).

Cytotoxicity

Cell vitality of fibroblasts (NIH3T3) was measured by an extraction test (24 hours) on the infusion tubes before and after 3 or 6 months of aging under different conditions (25°C, 50°C, 50°C-75%RH) (Figure 8). In general, no cytotoxicity was observed because cell viability was greater than 85%, whatever the infusion tube and the aging conditions. However, a decrease in cell viability could be noted when the samples were aged at 25°C and at 50°C without humidity, but remained insignificant. It can also be noted that the sterilization mode (radiation or EtO) had no impact on cell viability, which complements the data presented by Bertoldi et al on the impact of sterilization by plasma and ozone [22]. Indeed, the authors showed a degradation of the materials with no impact on cell viability. In agreement with USP82, the

infusion tubes showed no cytotoxicity whatever the type of sterilization, duration and storage conditions.

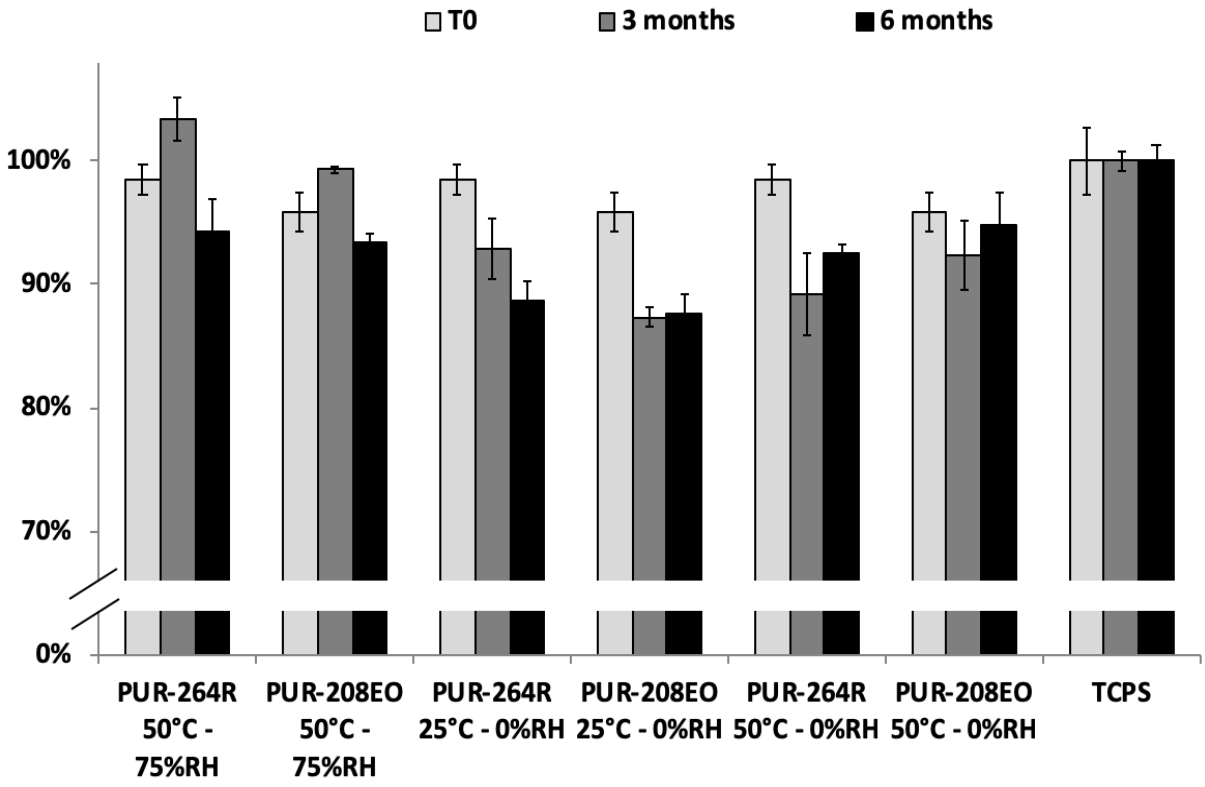

Figure 8. Assessment of viability by Alamar blue fluorescence of NIH3T3 fibroblasts on infusion tube at different times and conditions of aging.

Conclusion

This study shows that neither ethylene oxide nor gamma radiation sterilization procedures induced PUR degradation. The high temperature/relative humidity/time storage conditions led to a slight degradation of PUR. The rearrangement of the macromolecular chains and the crosslinking mechanism explain variations in drug sorption. In the studied conditions, the variability in the initial parameters of the material are erased with storage time. Health professionals choose medical devices based on their performance and material. They must be aware that PURs are not equivalent, especially where drug sorption is concerned. This phenomenon must be integrated into the studies of drug/medical device interactions. In addition, in these studies, storage conditions must be specified and standardized.

Finally, humidity, temperature and storage time have a role in the aging of these medical devices and must be also taken into account for storage conditions. These conditions must be controlled in industry and hospitals and should be included in manuals.

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References

1. Maiguy-Foinard, A.; Genay, S.; Lannoy, D.; Barthélémy, C.; Lebuffe, G.; Debaene, B.; Odou, P. and Décaudin, B. *Anaesth. Crit. Care Pain Med.* **2017**, *36*, 53-63.

2. Maiguy-Foinard, A.; Blanchemain, N.; Barthélémy, C.; Décaudin, B. and Odou, P. *PloS One* **2016**, *11*, e0154917.

3. Masse, M.; Maton, M.; Genay, S.; Blanchemain, N.; Barthélémy, C.; Décaudin, B. and Odou, P. *PloS One* **2018**, *13*, e0201623.

4. Faessler, D.; McCombie, G.; Biedermann, M.; Felder, F. and Subotic, U. *Int. J. Pharm.* **2017**, *520*, 119-125.

5. Bernard, L.; Cueff, R.; Breysse, C.; Décaudin, B. and Sautou, V. *Int. J. Pharm.* **2015**, *485*, 341-347.

6. Eljezi, T.; Pinta, P.; Richard, D.; Pinguet, J.; Chezal, J.-M.; Chagnon, M.-C.; Sautou, V.; Grimandi, G. and Moreau, E. *Chemosphere* **2017**, *173*, 452-459.

7. Treleano, A.; Wolz, G.; Brandsch, R. and Welle, F. *Int. J. Pharm.* **2009**, *369*, 30.

8. Al Salloum, H.; Saunier, J.; Aymes-Chodur, C.; Barakat, H. and Yagoubi, N. *Int. J. Pharm.* **2015**, *496*, 664-75.

9. Kozlovskaya, L. and Stepensky, D. *Int. J. Pharm.* **2015**, *478*, 693-701.

10. Kozlovskaya, L.; Popilski, H.; Gorenbein, P. and Stepensky, D. *Int. J. Pharm.* **2015**, *489*, 285-293.

11. Zhao, Y.; Zhu, B.; Wang, Y.; Liu, C. and Shen, C. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2019**, *105*.

12. ISO 10993-7: Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals.http://www.iso.org/cms/render/live/en/sites/isoorg/contents/data/standard/03/42/34213.html (accessed October 21, 2019).

13. ISO 10993-5: 2009 Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity. https://www.iso.org/standard/36406.html (accessed October 21, 2019).

14. Gimeno, P.; Auguste, M.-L.; Handlos, V.; Nielsen, A. M.; Schmidt, S.; Lassu, N.; Vogel, M.; Fischer, A.; Brenier, C. and Duperray, F. *J. Pharm. Biomed. Anal.* **2018**, *158*, 119-127.

15. Murray, K. A.; Kennedy, J. E.; McEvoy, B.; Vrain, O.; Ryan, D.; Cowman, R. and Higginbotham, C. L. *Eur. Polym. J.* **2013**, *49*, 1782-1795.

16. Adem, E.; Angulo-Cervera, E.; González-Jiménez, A.; Valentín, J. L. and Marcos-Fernández, A. *Radiat. Phys. Chem.* **2015**, *112*, 61-70.

17. Boubakri, A.; Guermazi, N.; Elleuch, K. and Ayedi, H. F. *Mater. Sci. Eng. A* **2010**, *527*, 1649-1654.

18. Jin, S.-E.; You, S.; Jeon, S. and Hwang, S.-J. *Int. J. Pharm.* **2016**, *506*, 414-9.

19. Al Salloum, H.; Saunier, J.; Aymes-Chodur, C.; Barakat, H. and Yagoubi, N. *Int. J. Pharm.* **2015**, *496*, 664-75.

20. Bovas, B. C.; Karunamoorthy, L. and Chuan, F. B. *Mater. Manuf. Process.* **2018**, *33*, 180-185.

21. Nouman, M.; Jubeli, E.; Saunier, J. and Yagoubi, N. *J. Biomed. Mater. Res. A* **2016**, *104*, 2954-2967.

22. Bertoldi, S.; Farè, S.; Haugen, H. J. and Tanzi, M. C. *J. Mater. Sci. Mater. Med.* **2015**, *26*, 182.