Drug Loading of Sutures by Supercritical CO_2 Impregnation: Effect of Polymer/Drug Interactions and Thermal Transitions[a]

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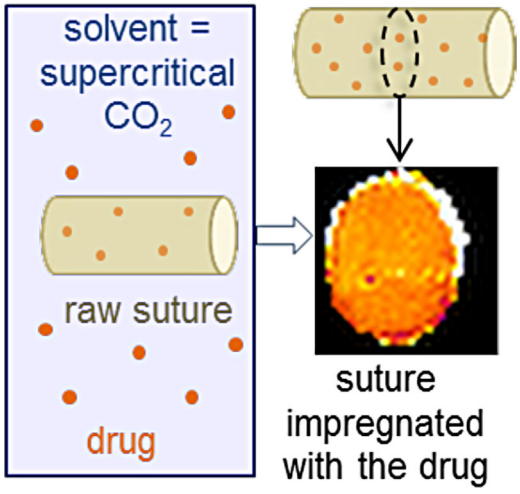
This paper aims at exploring the $scCO_2$ impregnation of three commonly implanted polymer sutures made of poly-L-lactide (PLLA), poly(ethylene terephthalate) (PET) and polypropylene (PP) with two anti-inflammatory drugs namely ketoprofen and aspirin. For all the investigated polymer/drug systems, the drug loading increases with temperature and pressure. It appears that two main criteria must be fulfilled by the polymer to achieve high drug loading: (i) a good affinity between the polymer and the drug and (ii) a high chain mobility to favor the diffusion of the drug into the matrix. As the investigated PLLA fulfills these two requirements, drug loading up to 32.5% with ketoprofen and 8.1% with aspirin has been achieved.



1. Introduction

Suture threads are widely used in surgery due to their ability either to close a wound or to immobilize prosthesis. In order to reduce the pain due to the inflammatory response after the surgery, the patient has to undergo a pain-relief treatment, the drug being generally administered via the oral route or injection. However, the oral administration way suffers from low drug bioavailability and a high amount of drug is generally required in oral or injection treatment to reach the therapeutic effect, which can entail side effects on untargeted tissues. A local drug delivery can limit these side effects and increase patient compliance.[1] This interesting delivery system can be achieved by loading an anti-inflammatory drug into the surgical suture.

Several strategies have been developed to process drug delivery sutures. Electrospinning or hot melt extrusion allows to incorporate drugs into the polymer matrix during the processing of the suture.[2,3] Other techniques enable to add the drug to an already commercialized suture by creating an erodible coating containing the drug, grafting species on the surface that can interact with the drug or soaking the suture into a drug solution.[4,5] Yet, these processes often require either high temperature that can degrade thermosensitive drugs or the use of toxic organic solvents that must be removed.

In this context, supercritical carbon dioxide ($scCO_2$) impregnation appears as an interesting alternative to load a drug into a preformed polymeric suture. Indeed, if very few polymers are soluble in this medium, CO_2 in supercritical conditions (i.e., above 31 °C and 73.8 bar) can be dissolved in

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[a]**Supporting Information** is available from the Wiley Online Library or from the author.

DOI: 10.1002/mame.201400369

a variety of polymers. $ScCO_2$ swells them and thus temporarily increases their free volume. Since $scCO_2$ can solubilize different active pharmaceutical ingredients (API) of interest, such as some anti-inflammatory drugs, it can carry them into the swollen polymer matrix. The high diffusivity of $scCO_2$ makes such impregnation process easy and fast. Being environment friendly, inert, non-flammable, inexpensive and easy to remove from the system by depressurization after treatment, $scCO_2$ offers several additional advantages as compared to conventional organic solvents.[6] Moreover, since the supercritical state of CO_2 can be reached at a reasonable temperature, this process remains compatible with thermosensitive API. $ScCO_2$ has been widely used to incorporate API into various polymer implants and medical devices, such as intraocular lenses,[7,8] contact lenses,[9–11] sutures,[12,13] and scaffolds for tissue engineering.[14–22]

Two mechanisms of $scCO_2$ impregnation are generally distinguished depending on the polymer/API interactions.[23] The first mechanism involves polymer/API systems that have low affinity. The drug is carried by the $scCO_2$ into the matrix during the impregnation process. Then, the depressurization conditions are determinant to allow the CO_2 molecules to leave the matrix while keeping the API trapped in the polymer matrix of low affinity. The second mechanism concerns polymer/API systems of high affinity. The driving force of the impregnation process is here the interactions between the matrix and the API, which lead to high drug loadings (DLs) and good dispersion of the API into the polymer matrix, the $scCO_2$ allowing to fasten the impregnation by swelling the polymer.

This project aims at exploring the $scCO_2$ impregnation of three commonly implanted polymer sutures made of poly-L-lactide (PLLA), poly(ethylene terephtalate) (PET) and polypropylene (PP) with two non-steroid anti-inflammatory drugs namely ketoprofen and aspirin (AA) that both bear a carboxylic acid function, at least an aromatic ring and a carbonyl group (Figure 1), which makes them both soluble in $scCO_2$.

The three polymers of the considered sutures are all semi-crystalline polymers as it is required to get fibers of relevant mechanical resistance but possess distinct physicochemical properties (Table 1), such as the thermal transition temperatures (glassy and melting temperatures) and the presence or not of ester groups able to interact by H-bonding with the acid group of the selected drugs.[24–26] The impact of these properties on the CO_2 sorption, the polymer swelling and ultimately on the DL could then be highlighted in this study. Moreover, the studies generally report the impregnation of a single polymer/API system. In the present work, the comparison of the DL of six polymer/API systems led to determine the criteria that must fulfill a polymer matrix to achieve high DL.

In the biomedical field, the temperatures investigated for the $scCO_2$ impregnation process range generally between 35 and 55 °C and the solute loadings are generally between 0.5 and 10%.[8,27,28] Surprisingly, Weinstein et al. achieved a much higher DL within PLGA braided suture using a similar process, but these values may result from the coating of the fibers instead of a bulk impregnation.[29] In contrast, the $scCO_2$ impregnation of dye within hydrophobic polymers, such as PET, is generally performed in a higher temperatures range between 60 and 150 °C.[30] For that account, we have chosen to cover a large range of temperatures between 40 to 140 °C to evidence how far the impregnation can be tuned by varying the operational conditions and relate more clearly the influence of the polymer properties on this process.

First, the effects of contact time, pressure, temperature and depressurization conditions on DL were evaluated. The evolution of DL was rationalized regarding the CO_2 sorption and the swelling of the matrices, as well as the changes in the polymer microstructure with the experimental conditions, especially with the temperature. The respective effects of CO_2 and API on the microstructure were determined by comparing the behavior of the impregnated fibers with the fibers only subjected to $scCO_2$. The tensile properties of the impregnated fibers have then been evaluated, since sufficient mechanical strength must be preserved to act as a suture.

Finally, the affinity of the drug with the matrices was explored.

2. Experimental Section

2.1. Materials

Carbon dioxide N45 (purity 99.95%) was supplied by Air Liquide. Ketoprofen and Acetylsalicylic Acid (i.e., AA) were purchased from Sigma-Aldrich. PET, PP and PLLA suture fibers were provided by Covidien. Phosphate buffer saline (PBS) was purchased from Lonza. Structures and properties of the fibers used in this study are displayed in Table 1.

The solubility of ketoprofen and aspirin in CO_2 has been measured as a function of pressure and temperature by Fourier transform infrared spectroscopy (FTIR) analysis. The solubility of the two drugs are in the same range, i.e., between $0.1 * 10^{-5}$ and $9.2 * 10^{-4}$ molar fraction for ketoprofen and between $0.8 * 10^{-5}$ and $9.5 * 10^{-4}$ molar fraction for aspirin.

2.2. Supercritical Impregnation Process

The impregnation of the fibers was performed in a batch process. A 40 mL stainless steel vessel was loaded with between 300 mg of API powder to ensure access of API, and with a stirrer bar. About 60 mg of each polymeric fiber was wind up and put together in a flask. The flask was placed above the stirrer bar to physically separate the polymers from the powder. Subsequently, the

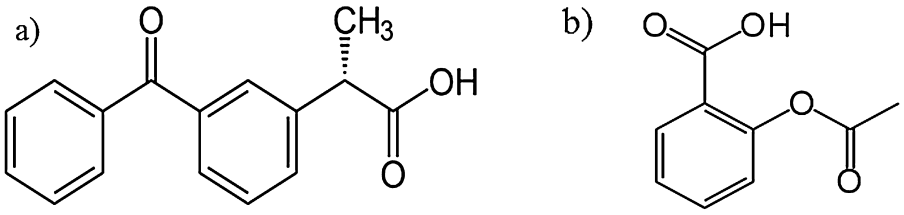


Figure 1. Chemical structure of a) ketoprofen and b) aspirin.

high-pressure reactor was placed into a thermostated bath heated up to the desired temperature. Then, CO_2 was introduced into the reactor by a syringe connected to a high-pressure liquid pump (model 26D from Teledyne Isco). When the required pressure was achieved, the system was kept at a given pressure and temperature, and the magnetic stirring was turned on (100 rpm). After the soaking time, the reactor was dipped immediately into an acetone/dry ice bath to quickly freeze the system and to avoid the removal of the drug during the following rapid depressurization (2 s) except for the samples used to study the influence of depressurization conditions, for which specific conditions were applied (see Section 3.2.3).

2.3. Characterization

2.3.1. Drug Loading

The DL is defined as the mass of API impregnated into the matrix per mass of polymer. Some fibers were covered by a coating made of API precipitated on the surface. Since the impregnation involves the drug only being loaded into the matrix, this coating was removed to determine the DL by gravimetry. Five minutes of dipping into PBS at 37 °C were sufficient to remove the coatings made of ketoprofen, whereas 5 s in dichloromethane were necessary to remove the coating of aspirin.

Practically, the fiber was weighted before and after impregnation (after removal of the coating) using a balance Mettler Toledo XS 204 (precision 10^{-4} g). The DL was calculated using Equation (1):

$$Drug\ loading\ (\%) = \frac{m_{fiber\ after\ impregnation} - m_{fiber\ before}}{m_{fiber\ before\ impregnation}} * 100 \quad (1)$$

2.3.2. Thermal Analysis

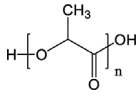
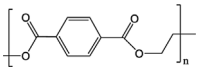
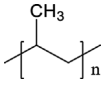
The differential scanning calorimetry (DSC) analysis was used to characterize the crystallinity of the samples and the impact of both CO_2 treatment and of the presence of drug, using the Instrument DSC Q100 from TA instrument. The fibers were cut in small pieces and 5 to 10 mg were placed in an aluminum pan, which was sealed. Then the pan was heated from 40 °C to 200 °C for PLLA and PP samples and to 300 °C for PET samples with a ramp of 10 °C/min, then cooled to −80 °C and heated again to 200 °C or 300 °C (named 2nd heating) at the same rate.

The crystallinity of the fibers was calculated using Equation (2):

$$\chi = \frac{\Delta H_f}{\Delta H_{f,100\%}} \times 100 \quad (2)$$

with ΔH_f being the experimental fusion enthalpy measured on the DSC thermogram, and $\Delta H_{f,100\%}$ the fusion enthalpy of 100%

Table 1. Physico-chemical properties of the starting polymer fibers as provided by Covidien

Polymer	Structure	Diameter[a] (μm)	Density[b] (g · cm^{-3})	Crystallinity[c] χ (%)	T_g[d] (°C)	T_m[e] (°C)
PLLA		150	1.25	52	61	168
PET		90	1.38	43	79	254
PP		150	0.91	41	−16	167

[a]The diameter was measured with a caliper. [b]The density was provided by Covidien for the three fibers. [c]The crystallinity was determined by Differential Scanning Calorimetry (DSC) analysis. [d]The glass transition temperature T_g was determined from the 2nd heating of DSC analysis with the tangent method, the four polymers being too crystalline to show a T_g transition during the 1st heating. [e]The melting temperature T_m was determined from the 1st heating of DSC analysis at the minimum of the melting peak.

crystalline polymer. The values of $\Delta H_{f,100\%}$ for PLLA, PP and PET are respectively 93.1 J/g; 207 J/g and 140 J/g.[31,32]

2.3.3. Tensile Test

The tensile properties of the fibers were measured with an electromechanical tensile tester (Instron model 5566, Elancourt, France). All samples were mounted between holders at a distance of 2 cm (Pneumatic Action grips, Elancourt, France). Tensile testing was conducted at room temperature, at a rate of 5 $mm \cdot min^{-1}$. Three replicates were performed for each condition.

The load is reported instead of stress since the diameter of the fiber is increased at the end of the treatment (up to 65%) due to the swelling and the presence of drug into the matrix.

2.3.4. API Distribution by Raman Imaging

The fibers were cut perpendicularly to their length. The API distribution was evaluated along a line on the cross section of the fiber by Raman imaging. A confocal Raman system ¨(Labram II £ (Horiba Jobin-Yvon), with a 633 nm excitation wavelength was used, with a 50x objective. A spectrum was recorded each 5 μm.

3. Results and Discussion

3.1. Drug Impregnation vs. Coating

In the investigated conditions, a coating appeared on the fibers (see Supporting Information) due to the precipitation of the drug on the surface during depressurization. In order to study the actual impregnation process and to determine the DL of the fibers, the coatings were removed by dipping the fibers in an adequately selected solvent that could dissolve the coating.

After removing this coating, the fibers were weighted to measure the DL. In order to confirm that the drugs are truly impregnated inside the fibers, Raman imaging have been performed on the cross-section of a PLLA fiber loaded with 18.3 wt% of ketoprofen. As shown in Figure 2, ketoprofen is homogeneously distributed along the cross-section of the suture, which underlines the ability of $scCO_2$ to carry the drug into the inner part of the fiber. The white periphery corresponds to the coating that was not removed in this case.

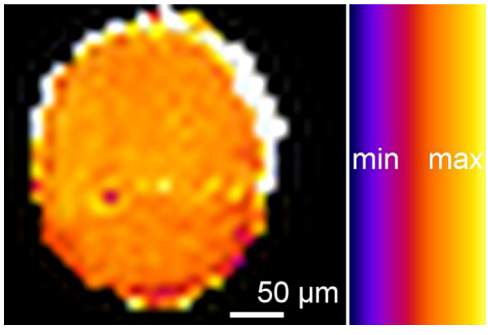


Figure 2. Raman imaging of the ketoprofen distribution along the cross-section of a PLLA fiber (drug loading = 18.3%).

3.2. Influence of Impregnation Operational Parameters on the Drug Loading

The impregnation process being driven by thermodynamics and mass transfer, the DL is highly dependent on the operational conditions, i.e., the contact time, temperature, pressure and depressurization. Indeed the mass transfer of the API from the CO_2-phase to the polymer matrix is driven by the diffusion and thus depends on the contact time, whereas both pressure and temperature can directly impact the solubility of the API into the CO_2-phase and the thermodynamic behavior of the polymer when subjected to CO_2 (CO_2 sorption and swelling). Indeed the higher CO_2 sorption and swelling, the higher can be the mass transfer since the diffusion of the API molecules into the polymer is facilitated. Moreover, the depressurization is a crucial step since it can impact the DL. The drug can be dragged with CO_2 during the venting or stay in the polymer, and it can influence the distribution of the API across the sample.

On that account, the influence of these different parameters (contact time, temperature, pressure and depressurization) on the DL has been investigated. The study concerning the influence of the contact time on the DL is reported in Supporting Information. It appeared that a time of 3 h was sufficient in all the studied conditions to reach the thermodynamic equilibrium and was then chosen to study the influence of the other parameters.

3.2.1. Pressure

The effect of pressure was investigated in the range of 100–350 bar at T = 80 °C for PLLA and T = 120 °C for PP and PET, for a contact time of 3 h (Figure 3 and Figure 4). The results are not presented for PP impregnated with ketoprofen since the DLs were too small (below 0.8%) to see any significant trend.

A clear increase of the DL with pressure has been observed in PLLA impregnated either with ketoprofen or aspirin. Remarkably, more than 30% of ketoprofen can be loaded by impregnation at 350 bar and 80 °C.

The effect of pressure on DL in PET and PP tends to show an optimal value at 300 bar (Figure 3b and Figure 4). The DL rises between 100 and 300 bar and levels up in PET, whereas it shows a slight decrease at 350 bar in PP.

Consequently, a common optimal pressure of 300 bar was selected for the study of the influence of temperature.

The influence of pressure on DL can be rationalized by the evolution of the drug solubility in $scCO_2$, the CO_2 sorption and the swelling of the matrix. Indeed, the solubility of ketoprofen and aspirin rises with pressure

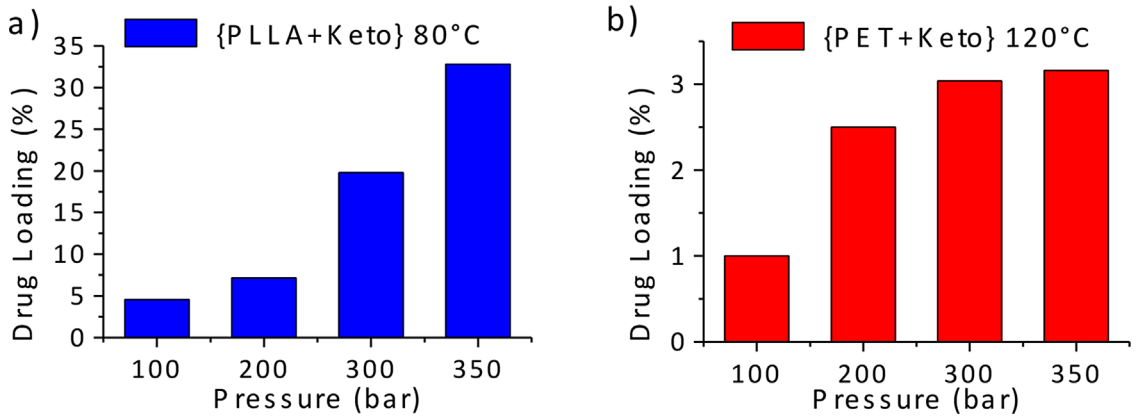


Figure 3. Effect of pressure on the drug loading of ketoprofen in a) PLLA impregnated at 80 °C and b) PET impregnated at 120 °C.

under isothermal conditions because the density of CO_2 increases which improves its solvating power.[33]

In parallel, CO_2 sorption increases with pressure until a plateau-like value is reached due to the limitation of polymer swelling according to our previously published results.[26] In some cases, a decrease of swelling and a CO_2 desorption have been observed in the literature when the pressure was even more increased, due to hydrostatic compression of CO_2 on the polymer,[34] which could be responsible for the decrease of the DL in PP at 350 bar.

In the case of PLLA, the impact of the drugs on the crystallinity of the polymer is another parameter that can explain the increase of DL with pressure at 80 °C, as it will be further demonstrated by DSC analysis.

The plateau-like value of the DL in PET reached at 300 bar, which has also been observed in dyeing of PET and has been explained by the total filling of the free volume of the matrix by the loaded drug.[35]

3.2.2. Temperature

The effect of the temperature on the DL was investigated in the range of 40 °C–140 °C at 300 bar and for a contact time of 3 h. The impregnation of PLLA, PP and PET with ketoprofen (Figure 5) and aspirin (Figure 6) was carried out. The studied temperature ranges for PLLA and PP were limited by their melting temperature when subjected to $scCO_2$. For example, the impregnated PLLA sample completely melted at 100 °C under 300 bar, whereas its melting temperature is 168 °C under atmospheric pressure. This CO_2-induced reduction of melting temperature of polymer has been widely reported in the literature for various semi-crystalline polymers.[24,36]

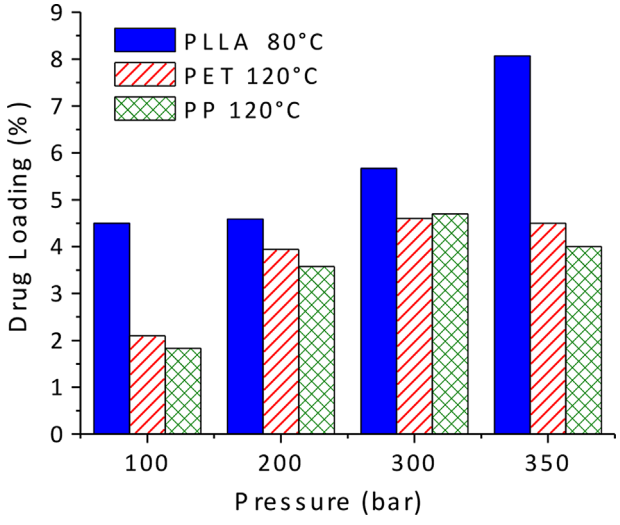


Figure 4. Effect of pressure on the drug loading of aspirin into PLLA impregnated at 80 °C; PET and PP impregnated at 120 °C.

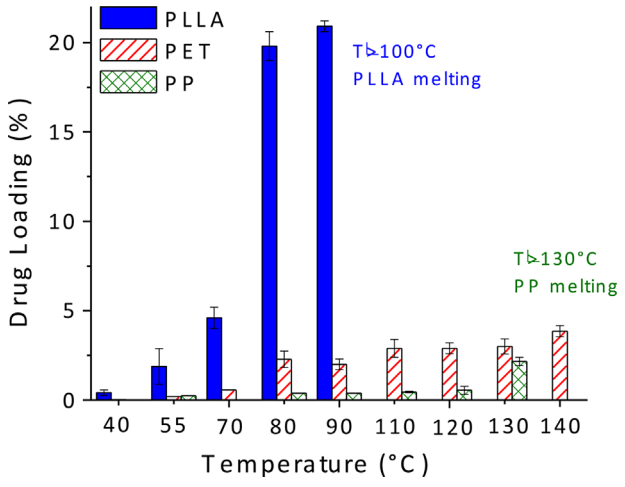


Figure 5. Effect of temperature on the drug loading of ketoprofen into PLLA; PET and PP at 300 bar, contact time = 3 h.

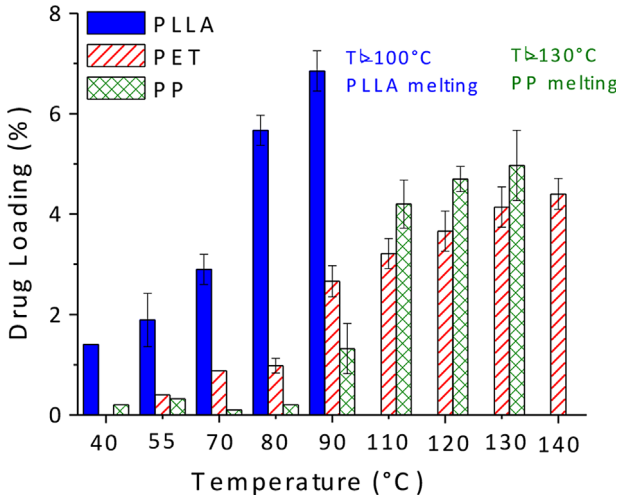


Figure 6. Effect of temperature on the drug loading of aspirin into PLLA; PET and PP at 300 bar, contact time = 3 h.

As shown in Figure 5 and 6, the increase of temperature globally results in the increase of DL for all the impregnation systems. The DL is highly dependent on the polymer matrix. Comparing the three polymers impregnated with the same drug in the same experimental conditions, the DL widely varies from one matrix to another. For instance, the DL of ketoprofen at 90 °C and 300 bar reaches 20.9% in PLLA, 2.0% in PET and only 0.3% in PP (Figure 5).

Furthermore, the DLs obtained with the two different drugs vary in a great extent in the same polymer matrix and in the same experimental conditions. The DL of ketoprofen in PP is inferior to 2.2%, whereas the DL is superior in the case of aspirin (5% at 130 °C). The reverse trend is observed in PLLA with a DL of ketoprofen (20.9%) highly superior to the one of aspirin (maximum value = 6.9% at 80 °C and 300 bar).

Similarly as for pressure, two effects of temperature must be considered in the impregnation process: The solubility of the API in CO_2; and the effect of the thermal transitions of the polymer matrices on the CO_2 sorption and swelling.

Concerning the influence of the temperature on the solubility of the API, it has opposite effects depending on the pressure. Below a pressure so-called crossover pressure, increasing the temperature has a negative impact on the solubility, whereas above this pressure increasing the temperature increases the solubility of the drug in CO_2.[37] The solubility of the two molecules has been measured at different temperatures and the crossover pressures of ketoprofen and aspirin were found at 170 bar and 150 bar respectively. Consequently, under the investigated pressure (300 bar), the solubility of the two drugs rises with temperature. The solubility of the two drugs are in the same range, i.e., between $0.1 * 10^{-5}$ and $9.2 * 10^{-4}$ molar fraction for ketoprofen and between $0.8 * 10^{-5}$ and $9.5 * 10^{-4}$ molar fraction for aspirin.

The amount of CO_2 sorbed in the matrix tends to decrease with temperature at fixed pressure since the density of CO_2 decreases but this parameter cannot account for the observed increase of DL.

Finally, the effect of the thermal transitions on the DL will be thoroughly discussed in the next section for each polymer matrices.

3.2.3. Depressurization Conditions

The impact of the conditions of depressurization on the DL has been explored on the system {PLLA + Ketoprofen} that achieved the highest DL among the investigated systems. In all the experiments, the PLLA fibers were impregnated at 80 °C and 300 bar during 3 h. Then, the three different conditions of depressurization that were carried out are summarized in Table 2, either the temperature of depressurization or the depressurization rate has been changed. The DL of each fibers is also reported in Table 2. Raman imaging was carried out to study the distribution of ketoprofen in PLLA fibers. The results are shown in Figure 7.

The samples A and C exhibit similar DLs, whereas sample B contains fewer drugs. This reveals that a loss of ketoprofen arises from a quick depressurization at high temperature, the drug being dragged out with CO_2. However, the drug is homogeneously dispersed along the cross section of this sample meaning that even some of the drug impregnated in the center of the sample has been dragged during the depressurization step (Figure 7). This observation can be accounted by the small dimensions of the fiber and we can suppose that a gradient could be created in bigger samples with a lower concentration close to the edges.

Table 2. Depressurization conditions that were carried out

Sample	Temperature of depressurization (°C)	Pressure before depressurization (bar)	Duration of the depressurization step	Estimated depressurization rate	Drug Loading (%)
A	−78 °C	≈ 5	5 s	1 bar/s	18.3
B	80 °C	300	5 s	60 bar/s	11.8
C	80 °C	300	5 h	0.6 bar/min	19.8

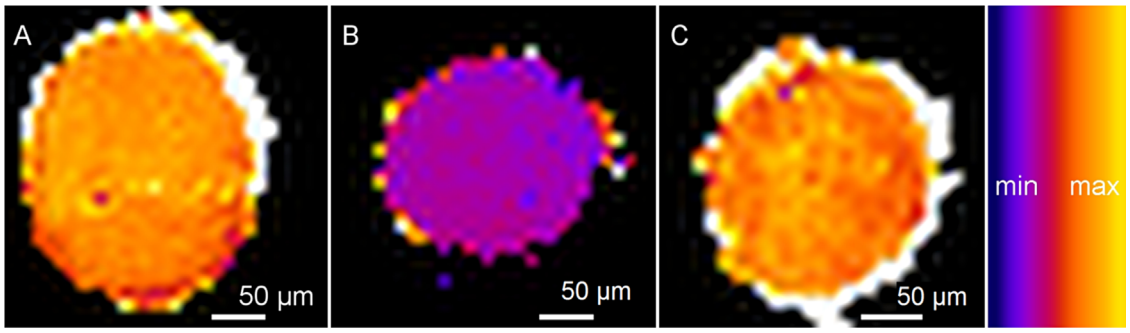


Figure 7. Distribution of ketoprofen on the cross-section of PLLA fibers impregnated at 80 °C and 300 bar and depressurized in different conditions a) sample A (–78 °C; 5 s); b) sample B (80 °C; 5 s) c) sample C (80 °C; 5 h).

A homogeneous distribution of ketoprofen is also found in samples A and C. It is important to note that the white edges appearing on the samples A and C correspond to the coating of ketoprofen. Surprisingly, a slow depressurization rate at 80 °C does not impact the DL. The affinity for the matrix is responsible for the partitioning of ketoprofen in favor to the polymer phase instead of being vented with CO_2. It confirms the observation of Braga et al. who impregnated acetazolamide into a silicone-based polymer. The authors evidenced that API/polymer systems that present a good affinity should be depressurized at low rate to avoid the venting of the drug and also to avoid the potential foaming of the polymer.[9]

3.3. Thermal and Mechanical Properties of Impregnated Fibers

The thermal transition of the polymer matrices will have a strong impact on the CO_2 sorption, on the polymer swelling and consequently on the DL. It is generally admitted that CO_2 sorbs only in the amorphous regions of semi-crystalline materials. In a previous study, we have identified that a polymer matrix must fulfill two criteria to sorb a high quantity of CO_2: high chain mobility in the amorphous regions and specific polymer-CO_2 interactions.[26] It can be reasonably considered that the polymer-CO_2 molecular interactions are slightly influenced by the operational conditions. However, the chain mobility can evolve with pressure and temperature especially around the glass transition temperature T_g and the melting temperature T_m of the polymer. When the operational temperature is below the T_g of the polymer, the chain mobility is restricted, which is detrimental for CO_2 sorption. Above the T_g, the CO_2 sorption starts to increase since the higher chain mobility allows the reorganization of the chain for the CO_2 to penetrate. Moreover, when the temperature becomes close to the melting temperature T_m of the polymer, the crystals can be partially melted, thus, increasing the proportion of amorphous regions and enhancing the swelling and the CO_2 sorption of the matrix. It is worth noting that T_g is decreased in $scCO_2$ because of its plasticizing effect[36,38] so as T_m due to cryoscopic effects of the dissolved CO_2 in the polymer. Nonetheless, these favorable effects of temperature on CO_2 sorption can be counterbalanced by the decrease of the CO_2 density with increasing the temperature under isobaric conditions.

In this section, we measured the effect of the impregnation process on the tensile properties of the fibers and particularly the impact of both the CO_2 pressurization/depressurization treatment and the impregnated drug. This point is particularly important since the impregnated fibers must keep sufficient mechanical properties to be used as suture.

3.3.1. Poly-L-Lactide

As shown above, PLLA can be impregnated by ketoprofen in a larger extent compared to PET and PP, since a maximal DL of 32.5% could be reached in the best conditions. Moreover, temperature has a pronounced impact on the DL.

Between 40 °C and 90 °C, the working temperature is above the glass transition T_g of the PLLA. As reported in Table 1, the T_g of PLLA is about 61 °C, but it can be decreased in $scCO_2$ conditions since CO_2 can plasticize glassy polymers.[36] Thus, the chains that are more mobile can rearrange to sorb more CO_2 and consequently facilitating the impregnation. However, the large crystallinity of the PLLA sample (52%) still restricts both CO_2 sorption and swelling to the amorphous phase, i.e., only 48% of the material.

First, the effect of CO_2 on the PLLA fiber thermal transitions was investigated by applying the typical impregnation process but without API to PLLA samples (the fibers were only subjected to $scCO_2$). Various temperatures and a CO_2 pressure of 300 bar have been used for these processes, and then the PLLA samples have been analyzed by DSC (Figure 8). The DSC traces show a sharper melting peak for PLLA after CO_2 treatment at 70 °C and higher temperature (Figure 8). As compared to raw PLLA, the melting peak appears at a little lower

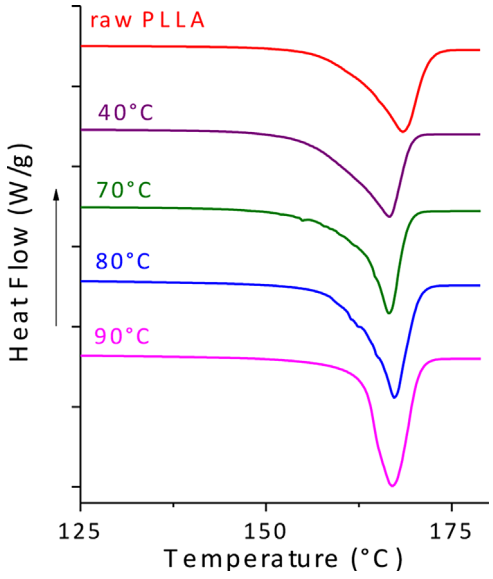


Figure 8. Comparison of DSC thermograms of raw PLLA fiber and PLLA subjected to $scCO_2$ (300 bar) at different temperatures.

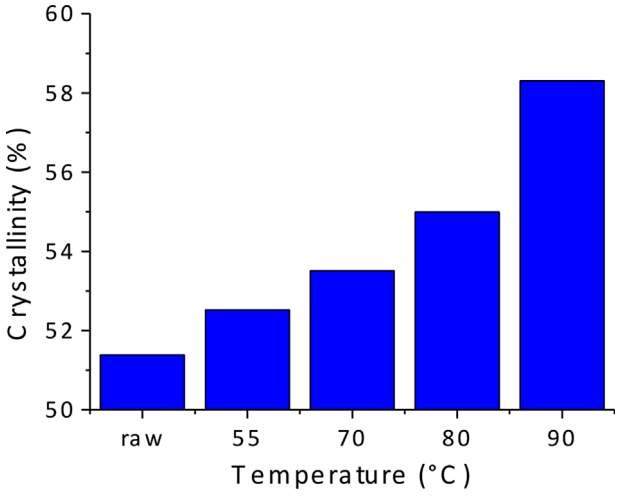


Figure 9. Crystallinity of PLLA fibers subjected to $scCO_2$ (300 bar) at various temperatures as measured from DSC thermograms.

temperature indicating the formation of less stable crystallites upon CO_2 treatment. During the process, the original PLLA crystals are partially melted and new ones are created either simultaneously during the CO_2 treatment and/or during the cooling/depressurization step. The melting of the crystals is certainly not complete between 70 °C and 90 °C since the PLLA fibers keep their original shape after the treatment. However, the process gives some mobility to chain segments that were initially part of semi-crystalline areas. The melting of crystals is possible even if the working temperature is lower than the melting temperature of the raw polymer owing to the decrease of the T_m of PLLA when subjected to $scCO_2$.[36,39] For instance, Lian et al. observed a decrease down to 55 °C at 276 bar.

The size of the crystals in the final impregnated PLLA become more homogeneous because the shape of the melting peak becomes sharper. Remarkably, the crystallinity of the PLLA fiber increases up to 59% when the temperature of the process is raised to 90 °C (Figure 9).

These experimental observations, thus, show that the process with pure CO_2 slightly affects the overall crystallinity of the samples recovered at the end of the treatment. Moreover, it evidences that processing at high temperature under CO_2 pressure allows giving chain mobility to segments of crystalline regions. If the first aspect (slight increase of the crystallinity) is not in favor of higher DL, the drug being located in the amorphous parts, the second one (mobility of the segments of crystalline regions) could explain a better diffusion of the {CO_2 + API} solution within the material under pressure at high temperature and thus leading to higher DL.

The effect of the impregnated drug on the polymer microstructure has been determined by measuring similar DSC thermograms with PLLA fibers impregnated with different DLs obtained by impregnation at different pressures (100, 200 and 300 bar). Under isothermal conditions (90 °C), the pressure is known to have little influence on the melting peak and crystallinity of PLLA[40] so that the observed differences can be mainly attributed to the presence of the drug.

Figure 10 shows the recorded DSC traces of PLLA fibers impregnated with ketoprofen and aspirin. The PLLA melting endotherm is clearly modified by the presence of the drug since the T_m of PLLA is largely decreased and the peak is broadened. A decrease of the melting temperature is generally a sign of the presence of smaller crystals. As previously observed, the crystals can partially melt under CO_2 and new ones are created during cooling and/or the depressurization process. The presence of drugs tends to intensify this phenomenon. The creation of smaller crystals can be explained by the heterogeneity induced by the presence of the API that can act as nucleating agent for the crystal growth. Nonetheless, even if the size of the crystals decreases, the overall crystallinity of the impregnated PLLA fibers after treatment is not impacted by the presence of the drugs (see supporting information Figure S5).

This hypothesis concerning the nucleating effect of the API is supported by the evolution of the crystallization peak during the 2nd heating in DSC analysis (Figure 10b). The crystallization peak tends to shift to lower temperature when PLLA is impregnated, which means that the molecules of API in PLLA facilitate the crystallization. The reduction of the size of the crystals in situ should enhance the polymer swelling and the diffusivity of the

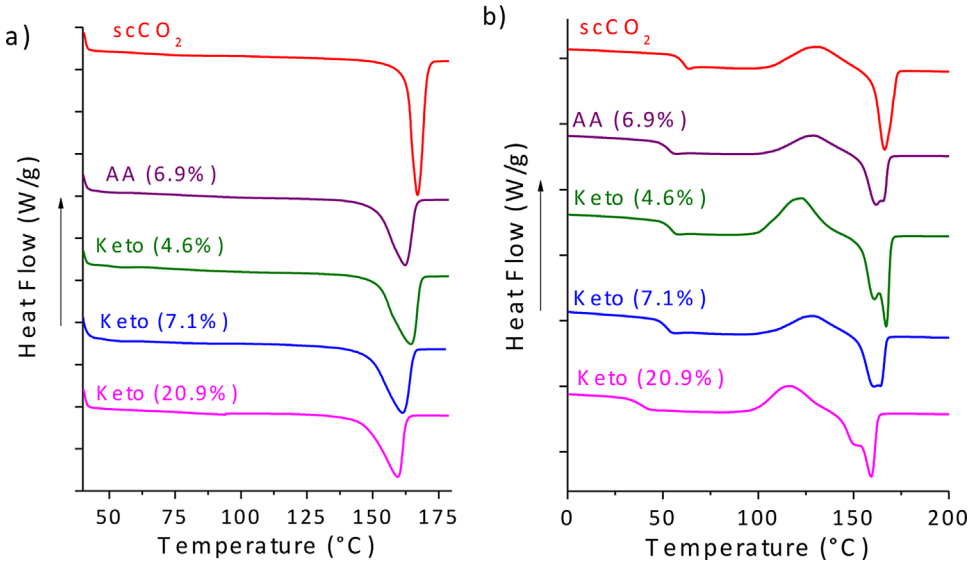


Figure 10. DSC thermograms of PLLA after CO_2-treatment (300 bar) and impregnation with AA (300 bar) and ketoprofin (100; 200 and 300 bar) at 90 °C a): 1st heating b) 2nd heating. The numbers in brackets are the drug loading of the fibers.

{$scCO_2$ + API} solution, thus explaining the high DLs achieved when partial melting of the polymer occurs.

In addition, the melting endotherm associated with crystalized API is not observed on Figure 10a, which supports a molecular dissolution of the drug within the polymer instead of the presence of drug crystallites. Accordingly, a clear plasticizing effect of both ketoprofen and aspirin is highlighted by the decrease of the T_g of PLLA observed during the second heating (Figure 10b). The T_g decreases linearly with the DL of the two API in the range of 0 to 20.9% emphasizing the good solubility of the API in the polymer (see supporting information Figure S6).

All these observations are, thus, in line with an increase of the DL with the temperature of the impregnation process thanks to the improved mobility of the chain segments at higher temperature and under $scCO_2$ pressure, offering higher diffusion to the {CO_2 + API} solution in the PLLA matrix.

The tensile properties of the suture are an important feature since it should be elongated only in its elastic domains for maintaining tissue approximation (in close contact) during the healing process. The suture is first implanted in swollen tissue surrounding the wound, but the swelling of these tissues will progressively decrease. The suture should be able to follow the movements of the tissue, i.e., to become tighter in order to continuously closely approximate the wound edges.[41]

As evidenced from DSC measurements, the microstructure of PLLA fibers evolves after CO_2-treatment and API impregnation depending on the process temperature. As demonstrated by the tensile curves of Figure 14, these changes in the microstructure greatly impact the tensile properties of the CO_2 processed (Figure 11) or API impregnated (Figure 12) PLLA fibers. Indeed, the PLLA fiber becomes more and more ductile when the temperature of the CO_2-treatment is increased in absence of API and especially when the temperature approaches the T_m (Figure 11). The ultimate elongation increases and the ultimate force decreases when the treatment temperature is increased. The tensile yield stress is decreased by 0.6 N after treatment at 70 °C but remains independent on the temperature up to 90 °C. The tensile curve of PLLA fiber annealed at 80 °C without $scCO_2$ is poorly impacted by the treatment showing that CO_2 is responsible for the change of the tensile behavior of the fiber. Interestingly, the slope of

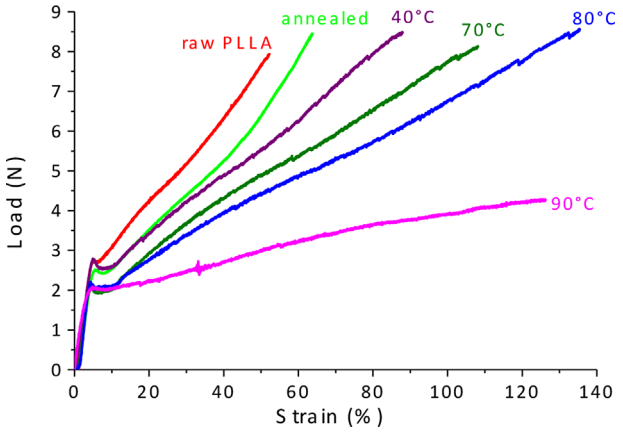


Figure 11. Comparison of the load-strain curves of raw PLLA fiber; PLLA fiber just annealed at 80 °C; and subjected to $scCO_2$ (300 bar) at different temperatures.

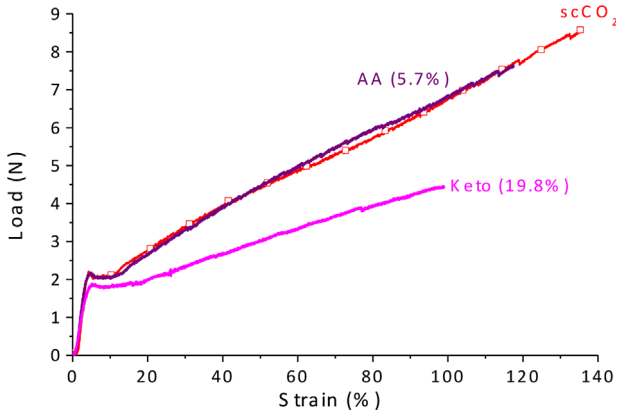


Figure 12. Comparison of the load-strain curves of PLLA fibers subjected to $scCO_2$ and impregnated with AA (DL = 5.7%) and ketoprofin (DL = 19.8%) at 80 °C and 300 bar.

the elastic domains is not significantly disturbed by the CO_2-treatment.

The presence of a plastisizing drug has also a significant impact on the PLLA tensile properties (Figure 12). Indeed, the tensile curve of PLLA impregnated with 5.7% of aspirin is not significantly different from the sample only subjected to CO_2 (Figure 12). In contrast, the plastification imparted by ketoprofen clearly affects the tensile curve. PLLA impregnated with 19.8% of ketoprofen has an ultimate load of 4.5 N (as compared to 8 N without drug) and an ultimate elongation of about 100% (as compared to 140% without drug).

However, the elastic domain is only slightly impacted by the treatment and/or the presence of drug. The ultimate charge is also high compared to other absorbable sutures which makes these impregnated PLLA fibers suitable for suture application.[42]

3.3.2. Polypropylene

The DL obtained in PP is lower than for PLLA sutures, and highly dependent on the impregnated drug. The DL of aspirin increases with temperature, especially for temperatures above 90 °C and reaches 5% at 130 °C. However, the DL of ketoprofen is inferior to 0.6% in all the temperature range, and increases suddenly at 130 °C (DL = 2.2%).

All the studied temperatures are above the T_g of PP (–16 °C under atmospheric pressure), which means that the amorphous chains should have enough mobility to rearrange during the impregnation process.

The impact of CO_2 treatment on the microstructure and on the tensile mechanical properties of PP was firstly investigated without drug. Similarly to PLLA, the DSC analysis shows an increase of the crystallinity from 41% up to 46% after treatment at 40 °C and 80 °C, and up to 49% at 130 °C (Figure 13). No significant change in the shape of the

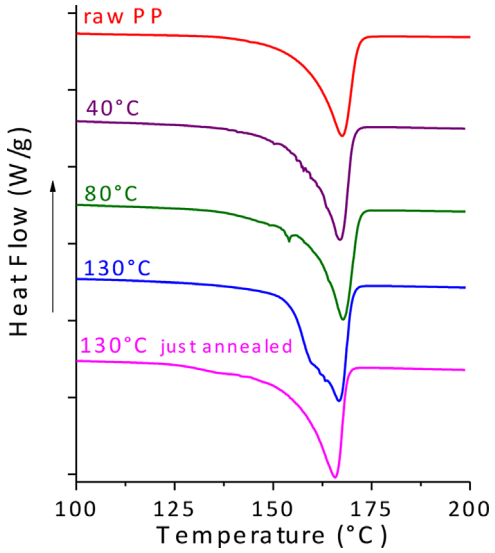


Figure 13. Comparison of DSC thermograms of a raw PP fiber, PP subjected to $scCO_2$ (300bar) at different temperatures, and a PP fiber just annealed at 130 °C.

melting peaks is observed with treatment at 40 °C or 80 °C, in contrast to 130 °C.

Accordingly, the tensile properties of PP subjected to CO_2 up to 80 °C are similar to the tensile properties of the raw PP sample, even if the crystallinity degree of these samples is slightly increased (Figure 14). However, the fibers become more ductile when the temperature is increased in the 120 °C–140 °C range as a consequence of the modified microstructure.

Similarly to PLLA, higher DLs can be obtained when the temperature approaches the T_m because of the partial melting of the crystals. Since the significant increase of DL of aspirin started at 90 °C, it can be reasonably supposed that the onset temperature of the melting peak is around this temperature at 300 bar in presence of this API.

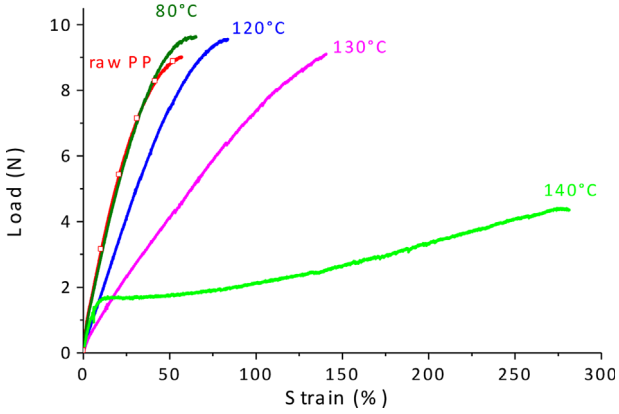


Figure 14. Comparison of the load-strain curves of a raw PP fiber; and PP fibers subjected to $scCO_2$ (300 bar) at different temperatures.

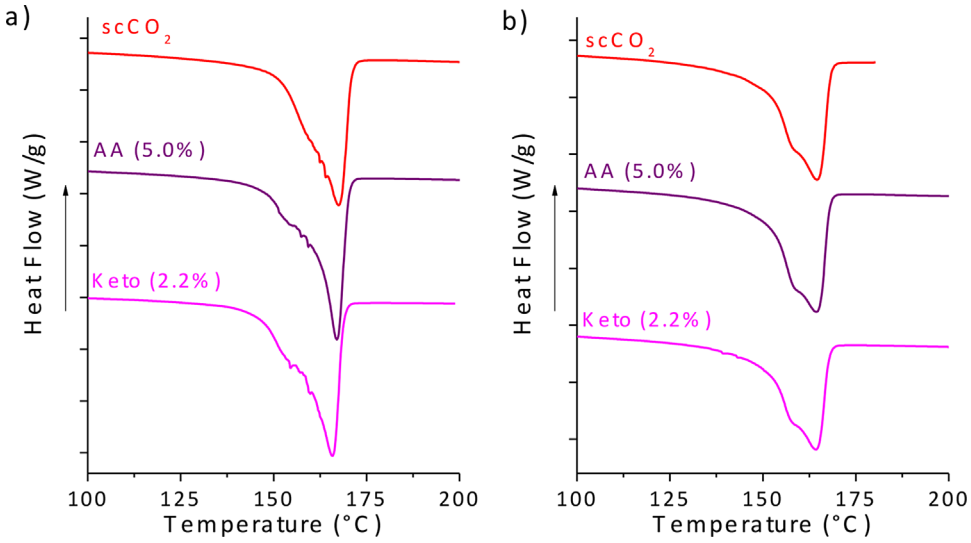


Figure 15. DSC thermograms of PP after CO_2-treatment and impregnation with AA (DL = 5.0%) and ketoprofin (DL = 2.2%) at 130 °C and 300 bar (a): 1st heating, (b) 2nd heating.

Figure 15 presents the DSC of PP subjected only to CO_2, and impregnated with ketoprofen and aspirin at 130 °C and 300 bar. No obvious difference can be observed between the three curves and the crystallinity of the final fibers was not significantly impacted by the presence of the drug, even by the presence of 5% of aspirin, whereas such a low DL was sufficient to impact the microstructure of PLLA. The DSC thermograms of the second heating confirm that the drugs do not significantly impact the microstructure of PP (Figure 15b).

The tensile properties of the different PP fibers are reported in Figure 16. The slope of the elastic domain is decreased by both the $scCO_2$ treatment and the presence of drugs. Interestingly, the presence of drugs tends to decrease the negative impact of the CO_2 treatment. Interestingly, the yield stress remains larger than the limit for suture application.

3.3.3. Poly(Ethylene Terephthalate)

The DSC thermograms of PET subjected only to $scCO_2$ at 40 °C, 80 °C and 140 °C are shown in Figure 17. Contrary to the literature, we did not observe any increase in crystallinity of PET with the $scCO_2$ treatment as all the samples have approximately the same crystallinity degree than the raw PET

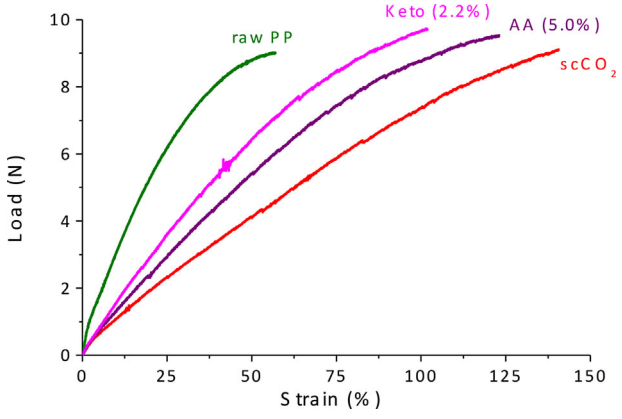


Figure 16. Load-strain curves of a raw PP fiber and PP fibers subjected to $scCO_2$ and impregnated with AA (DL = 5.0%) and ketoprofin (DL = 2.2%) at 130 °C and 300 bar.

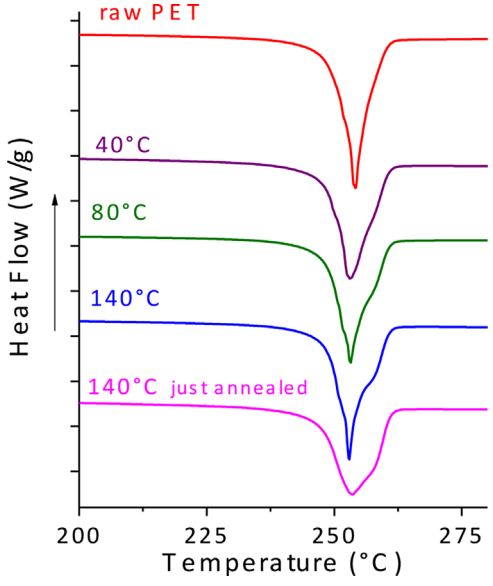


Figure 17. Comparison of DSC thermograms of raw PET fiber, PET subjected to $scCO_2$ (300 bar) at different temperatures, and a PET fiber just annealed at 140 °C.

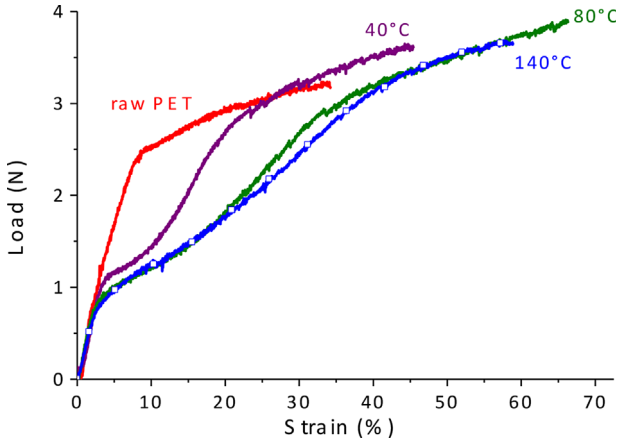


Figure 18. Comparison of the load-strain curves of a raw PET fiber; and PET fibers subjected to $scCO_2$ (300 bar) at different temperatures.

sample ($\chi = 40 \pm 2.1\%$). [43,44] However, the shape of the endotherm peaks starts to be significantly modified at 80 °C with the appearance of a shoulder at high temperature. This observation is a sign that this temperature is above the effective glass transition temperature in $scCO_2$, which entails a higher mobility of the chains that allows the formation of more stable crystallites. This increase in chain mobility also explains the significant enhancement of the DL observed at 70–80 °C (Figure 5 and 6).[25]

The tensile properties of PET are impacted by the CO_2-treatment, even at temperature below the T_g, the PET becoming more ductile (Figure 18). When subjected to $scCO_2$ at $T > T_g$, the tensile properties of PET are not impacted by a further increase of temperature. The tensile yield load is decreased, whereas the ultimate load and the ultimate elongation are increased. Even if the tensile yield load is strongly decreased from 2.5 N to 1 N, the fibers keep sufficient mechanical properties to be used as a suture.

The thermal and tensile properties of the impregnated PET samples do not significantly change compared to the sample subjected only to CO_2 (Figure 19 and Figure 20). However, some interesting features can be drawn from the analyses of the 2nd heating of DSC i.e. of the melt-quenched samples. Some significant data extracted from the DSC thermogram are summarized in Table 3. The raw PET sample cannot totally crystallize during the melt-quenching and a crystallization peak is observed upon 2nd heating above the T_g around 80 °C (Figure 19b). The sample impregnated with aspirin has a smaller crystallization peak while it totally disappears in presence of ketoprofen. The presence of drug favors then the cold crystallization of PET, acting probably as a nucleating agent. This strong impact of the API demonstrates that the drugs are dispersed within the polymer during the impregnation process.

3.4. Solubility Parameter Approach

Some results cannot be totally explained by the evolution of the thermodynamic parameters with pressure and temperature. For instance, PLLA is up to threefold more impregnated with ketoprofen than with aspirin in the same conditions, even if aspirin and ketoprofen have similar solubility in $scCO_2$. In contrast, PP is more impregnated with aspirin than with ketoprofen. In order to explain these

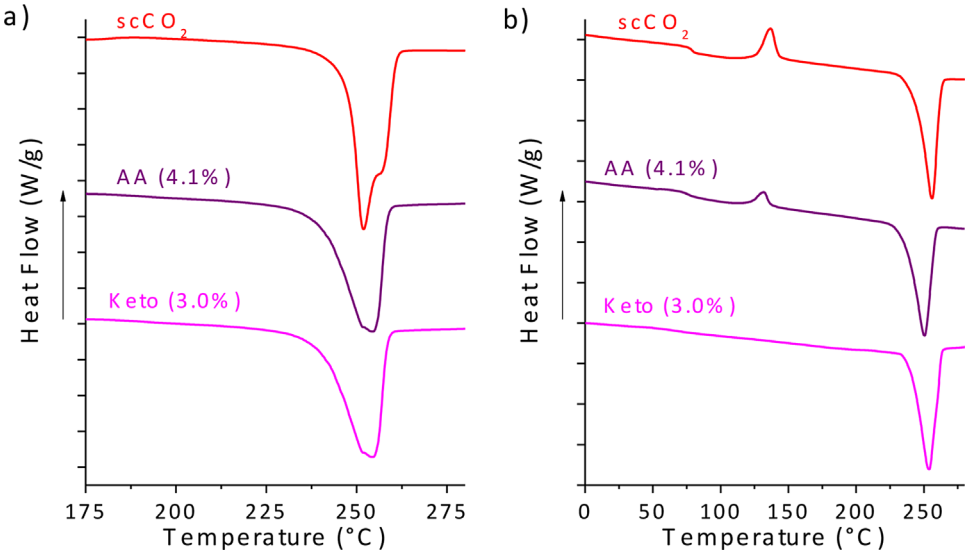


Figure 19. DSC thermograms of PET after CO_2-treatment and impregnation with AA (DL = 4.1%) and ketoprofen (DL = 3.0%) at 130 °C and 300 bar (a): 1st heating, (b) 2nd heating.

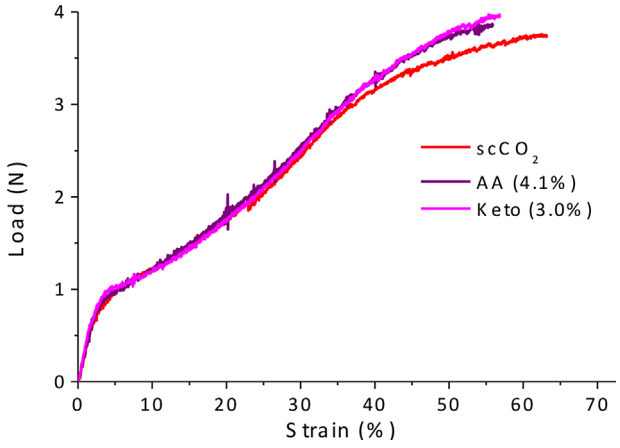


Figure 20. Comparison of the load-strain curves of PET fiber subjected to $scCO_2$ and impregnated with AA (DL = 4.1%) and ketoprofin (DL = 3.0%) at 130 °C and 300 bar.

observations, the solubility parameter approach has been used.

The dispersion of the drug into the polymer matrix depends on its miscibility with the polymer. The solubility parameter approach is widely used to predict the compatibility of polymer/drug binary systems in the pharmaceutical field.[45,46] This method derives from the Flory–Huggins equation for the calculation of free energy of mixing of a polymer-solvent system. In this theory, two organic compounds are miscible if their solubility parameters δ_t get closer.[47] The solubility parameter of a molecule is defined as the square root of its cohesive energy density. It can be expressed as the sum of three contributions accounting for Van der Waals dispersion forces δ_d, dipole–dipole interactions δ_p and hydrogen bonding δ_h.[48] The three contributions δ_d, δ_p and δ_h can be determined using the group contribution method, and the solubility parameter δ is calculated using the following Equation (3):

$$\delta_t = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} \quad (3)$$

The three contributions δ_d, δ_p and δ_h have been calculated using the Hoftyzer–Van Krevelen's method[49]

Table 4. Contributions parameters δ_d, δ_p and δ_h and total solubility parameters for the compounds calculated using the group contribution method (MPa $^{0.5}$)

Compound	δ_d	δ_p	δ_h	δ_t
PLLA	17.6	9.7	11.8	23.3
PP	15.8	0	0	15.8
PET	21.5	5.7	10.8	24.7
Ketoprofen	20.9	5.9	5.9	22.5
Aspirin	19.5	7.9	14.8	25.7

for ketoprofen, aspirin, PLLA, PP and PET. Table 4 summarizes the three contributions, as well as the overall δ_t solubility parameter of each compound. The difference between the solubility parameters of the polymers and the two drugs has been calculated and reported in Table 5. The data are given as an absolute value.

The predictions of the solubility parameters are concordant with the DLs in PLLA. Indeed, the solubility parameters of PLLA and ketoprofen are very close, which explains the high values of DL observed in this case, whereas the affinity between aspirin and the polymer is lower, so as the API impregnation in this case. A high affinity between aspirin and PET is also predicted. However, in this case, the DL is limited by the poor mobility of the chains. In contrast, the difference between the solubility parameter of PP and the two kinds of drugs is very high, and the low DL observed can be explained by this poor affinity. In this case, the lower DL obtained with ketoprofen (up 2.2%) compared to aspirin could be accounted by the higher molecular size of the molecules of ketoprofen that could prevent its good diffusivity into PP matrix.

In the light of these different results, we can conclude that two main parameters must be fulfilled to achieve a high DL: A high affinity between the drugs and the polymer and high chain mobility. These two requirements are only truly met for the couple PLLA/ketoprofen, especially around the melt temperature of the polymer where DLs up to 32.5% have been achieved.

Table 3. Different DSC data of the 2nd heating for PET fibers only subjected to $scCO_2$ and impregnated with aspirin and ketoprofen at 130 °C and 300 bar

Treatment	$\chi_{after\ cold\text{-}crystallization}$ (%)	$\chi_{recrystallization}$ (%)	χ_{total} (%)	T_g (°C)	T_c (°C)	T_m (°C)
$scCO_2$	22.6	8.5	31.1	78.7	137.7	255.4
AA DL=4.1%	31.4	2.6	34	76.7	134.1	250.6
Ketoprofin DL=3.0%	40.6	0	40.6	x	x	253.4

Table 5. Difference between the solubility parameters of the polymer matrices and the drugs $|\delta_{t\ polymer} - \delta_{t\ drug}|$ (MPa $^{0.5}$)

Polymer	$\lvert\delta_{t\ polymer} - \delta_{t\ ketoprofen}\rvert$	$\lvert\delta_{t\ polymer} - \delta_{t\ aspirin}\rvert$
PLLA	0.80	2.41
PP	6.66	9.87
PET	2.20	1.01

4. Conclusion

Using $scCO_2$ impregnation process, three commercial fibers made of PLLA, PP and PET were impregnated with two anti-inflammatory drugs namely ketoprofen and aspirin. The objective of the present study was (i) to evaluate the influence of pressure, temperature and depressurization conditions on the impregnation efficiency, i.e., on the DL; (ii) to understand the key parameters governing the $scCO_2$ impregnation process, and especially the criteria that must fulfill a polymer matrix to be efficiently impregnated with this process, and (iii) to evaluate the impact on the process on the tensile properties of the final impregnated fibers.

The DL increases with temperature and pressure for all the investigated systems. The influence of the depressurization step on the DL and on the distribution of the drug in the fiber was explored on the system {PLLA + Ketoprofin}. Ketoprofen and PLLA having a good affinity, the system can be depressurized at a temperature above the T_g of PLLA at low rate without removing the impregnated drug. On the contrary, fast depressurization entails a loss of drug that is vented with CO_2.

The DLs are highly different from one system to another. Regarding the thermal behavior of each polymer matrix and the affinity between the polymer and the drug, we concluded that a high DL could be obtained if the polymer fulfills two main criteria: high chain mobility and a good affinity with the drug.

High chain mobility favors the diffusion of the {CO_2 + API} solution into the matrix, increasing the CO_2 sorption and the swelling. The chain mobility is enhanced above the T_g but also when the temperature approaches the effective T_m of the polymer, taking into account that CO_2 induces a reduction of T_g and T_m. Above the T_g, the chain mobility increases with temperature in the amorphous regions, whereas a partial melting of the crystals is observed close to the T_m. However, it is worth noting that a part of the crystallinity must be preserved during the treatment to keep the shape of the polymer device.

A good affinity between the polymer and the drug must exist. For example, higher DL is observed when the solubility parameters of the two compounds are close to each other.

As the investigated PLLA fulfilled these two requirements, DL up to 32.5% with ketoprofen and 8.1% with aspirin is achieved when the temperature approaches its effective T_m. The impregnated drugs also help in modifying the microstructure to enhance the impregnation.

In contrast, PP and PET only meet one criterion, since PP cannot interact with the selected drugs and PET does not exhibit high chain mobility in the investigated operational conditions.

The tensile properties of the impregnated fibers were still suitable for being used as sutures since their elastic domains did not dramatically changed.

Acknowledgments: This work was funded by the "Conseil Régional Aquitaine" through the international doctoral school program "IDS-FunMat" supported by the European Community (ERASMUS MUNDUS Doctoral program). CERM is much indebted to IAP VII-05 "Functional Supramolecular Systems" (FS2). J-M. T. is Logistic Collaborator by the FRS-FNRS.

Received: October 20, 2014; Revised: December 22, 2014; Published online: February 6, 2015; DOI: 10.1002/mame.201400369

Keywords: anti-inflammatory drugs; drug loading; impregnation; mechanical properties; polymer sutures; supercritical carbon dioxide

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