Treatment of medical devices using supercritical processes

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1. Introduction

In cardiology, stenosis is a narrowing of arteries due to fatty deposits on their wall (Plaque) that impede blood flow. Angioplasty using stents or vascular balloons to dilate the blocked artery (Fig. 1), is a dominant non-invasive solution to avoid fatal complications. Over the last decade, these medical devices have been considerably improved especially with the emergence of active stents and balloons, that have the particularity of releasing an anti-proliferative agent (e.g., Sirolimus), often via a polymeric layer, to avoid re-stenosis after implantation, and to promote healing of the artery. The elaboration of these medical devices involves the use of organic solvents during the polymer coating and drug loading steps. The process of removing the residual solvent from the finished coating below regulated thresholds is often long, and increasing time to market. In order to design a rapid, compact and ecological process, we are exploring the use of supercritical CO_2 ($scCO_2$) for the removal of residual solvent (chloroform) from finished stents, replacing conventional drying methods (50°C/48 hours to reach < 60 ppm). As regards vascular balloons, we are exploring the drug loading of the very balloon material directly by impregnation via $scCO_2$, thus removing the need to make coatings, and simplifying the manufacturing process. Indeed, the specific properties of $scCO_2$ allow a fast and homogeneous impregnation into a variety of polymeric materials: its good transfer properties resulting from its low viscosity, low surface tension as well as a rather high diffusivity, makes it a good impregnation carrier, especially with the possibility to recover a final product free of any solvent residue.

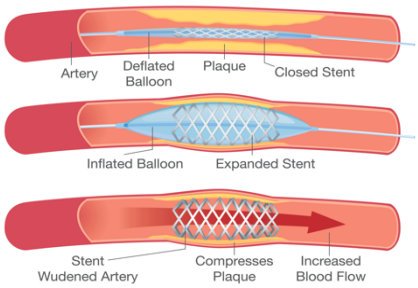

Fig. 1 Balloons and stent angioplasty

2. Materials and Methods for the solvent removal using $scCO_2$

a) Materials

Solvent removal using $scCO_2$ is tested on the HT Supreme® stent from Sinomed, which are coated with a layer of a biodegradable PLGA poly (lactic-co-glycolic acid) containing Sirolimus. They are supplied by Sinomed with a known residual concentration of chloroform after drying. Carbon dioxide (purity > 99.7%) is supplied by Air Liquide (France).

b) Experimental set-up for the supercritical solvent removal

Solvent removal using $scCO_2$ diagram is shown in Fig. 2. It is mainly composed of a 125 cm^3 high pressure cell (Top Industrie S.A., France) where the stents are introduced. The cell is placed in a thermostatic bath under a magnetic stirring. It is performed in semi-continuous mode, the autoclave is fed with CO_2 by a high-pressure pump (Milton Roy, France). After reaching the desired pressure and temperature conditions, a constant and continuous flow of CO_2 sweeps through the autoclave. After a predetermined treatment time, the cell is depressurized at a controlled rate of 2 bar/min. The choice of temperature and pressure parameters is made taking into account the fluid phase diagram of the binary CO_2/chloroform mixture presented by Im *et al* [1], as well as the solubility of sirolimus in $scCO_2$ measured by Chen *et al* [2]. Solvent removal using $scCO_2$ was performed under conditions of temperature and pressure ranging from 35°C to 55 °C and from 80 bar to 200 bar respectively, for 30 min and 2 hours.

Quantifications of residual chloroform and the drug release profile are carried out according to a well-defined protocol.

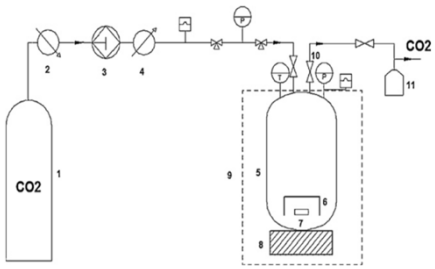

Fig. 2 Solvent removal and impregnation bench using $scCO_2$

(1) CO_2 bottle, (2) cooling bath, (3) liquid pump, (4) heating bath, (5) high pressure cell, (6) support, (7) magnetic bar, (8) magnetic stirrer, (9) thermostatic bath, (10) depressurization valve, (11) solvent trap.

c) Solvent removal results and discussion

The objective was to remove chloroform without extracting sirolimus. Solvent removal using $scCO_2$ showed excellent results, between 92% and 95% of the chloroform extracted under the experimental conditions for which quantification was performed, but the drug release profiles were altered for some stents, which may be due to the detachment of the polymer layer of the stent observed by SEM. However, the release profile of the stents treated under milder conditions was still acceptable, eg., Fig. 3.

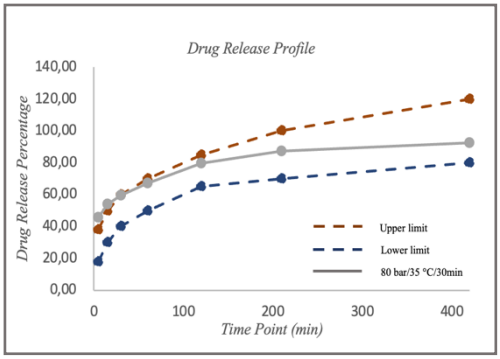

Fig. 3 Treated stent drug release profile

2. Materials and Methods for the supercritical impregnation

a) Materials

Supercritical impregnation is attempted on angioplasty balloons supplied by Sinomed made from Pebax (Poly-Ether-Block-Amide) polymer, either raw or further coated with PVP (Polyvinylpyrrolidone). Sirolimus is supplied by AlchiMedics.

b) Experimental set-up for the supercritical impregnation

The supercritical impregnation diagram is presented in Fig. 2. The bench used is the same than the one used for solvent removal. The impregnation experiments are performed in a batch mode. The balloons are introduced into the cell with the drug under magnetic stirring. The autoclave is supplied with fresh CO_2 using the high-pressure pump (Milton Roy, France) until the desired pressure is reached and is then isolated. After a predetermined contact time, the cell is depressurized at a controlled rate of 2 bar/min. Temperature and pressure parameters for impregnation are chosen taking into account sirolimus solubility in $scCO_2$ measured by Chen *et al* [2]. The supercritical impregnation was performed under conditions of temperature and pressure ranging from 35° C to 55 °C and 80 bar, for 30 min and 4 hours.

c) Quantification of the drug loading after the supercritical impregnation

The quantification of the drug loading by UV spectroscopy are carried out using PhotoLab 6600 UV-VIS series spectrometer, only for the balloons treated at 80 bar, 35°C for 4 hours (most relevant results).

d) The supercritical impregnation Results and discussion

Drug loadings of the Pebax and Pebax + PVP balloons treated at 80 bar 35°C for 4 hours are shown in the Table.1. The results demonstrate the feasibility of supercritical impregnations. The impregnation yields are high and close to the target (1.2 µg/mm^2) when the balloons contain a layer of PVP.

Table 1 Drug loading results after $scCO_2$ impregnation of the balloons at 80 bar, 35°C for 4 hours

Balloons	Sirolimus mass (µg)	Drug loading (µg/mm^2)
Pebax	119.7	0.22
Pebax +PVP	127.8	1.36

3. Conclusions

This project is part of an effort to evaluate the potential of $scCO_2$ in the design simplification and improvement of the manufacturing process of drug eluting devices used in interventional cardiology. Very encouraging results were achieved for the solvent removal using $scCO_2$, by lowering residual chloroform from finished stents by a factor of 10, below regulatory threshold. Further tuning is needed to secure that drug release profiles are within regulatory boundaries. This study also demonstrated that $scCO_2$ can achieve a quantitative loading of bare angioplasty balloons by direct impregnation. Further studies are underway to explore the drug release capabilities of such $scCO_2$ impregnated balloons and test their behaviors in animal models.

References

(1) Im, J.; Shin, H. Y.; Kim, H. Measurement and Correlation of Vapor-Liquid Equilibria of the Binary Carbon Dioxide-Chloroform Mixture System. *Korean J. Chem. Eng.* **2005**, *22* (3), 470–473. https://doi.org/10.1007/BF02719428.

(2) Chen, T.; Liu, L.; Zhang, L.; Lu, T.; Matos, R. L.; Jiang, C.; Lin, Y.; Yuan, T.; Ma, Z.; He, H.; Zhuang, X.; Li, Q. Optimization of the Supercritical Fluidized Bed Process for Sirolimus Coating and Drug Release. *Int. J. Pharm.* **2020**, *589*, 119809. https://doi.org/10.1016/j.ijpharm.2020.119809.