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Industrialization of a supercritical CO_2 process for oxidation of cellulose

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ABSTRACT

Surgical patches made with oxidized cellulose are used because this material is bioresorbable and hemostatic. The current industrial process (Johnson and Johnson process) uses nitrogen dioxide as oxidant, dissolved in a perfluorinated solvent, to process pure regenerated cellulose. A CNRS patent for the oxidation of polysaccharides has suggested supercritical CO_2 as an alternative solvent for this reaction, mainly because CO_2, like perfluorocarbon solvents, is chemically inert with respect to oxidants. Also, the products obtained with such a new process are free of organic solvents. Preliminary laboratory tests were successfully conducted at the Laboratoire de Génie Chimique (LGC) in Toulouse, France, in collaboration with the Centre de Recherche sur les Macromolécules Végétales (CERMAV) in Grenoble, France. The patent was then licensed to Medtronic company and the scaling up was developed at LGC by the operation of a 5L reactor pilot process, in collaboration with this company. On this pilot, specific procedures have been validated to insure homogeneous oxidation of tissues, mastering of the exothermicity of the reaction and to operate a *in situ* post-reactional washing. In synergy with another patented Medtronic coating process, the Veriset™ hemostatic patch was industrially produced in a new industrial unit in Trevoux (France) and commercially launched in December 2015.

INTRODUCTION

In addition to be a “green” solvent for conventional uses in separation processes, like vegetal extraction, supercritical CO_2 can be proposed as a “green” medium to perform reactions [1]. In this case, its variable solvent power may allow controlling the selectivity of the reaction by adjusting pressure and temperature. Also, CO_2 has a specific very useful feature when oxidation reactions are considered: CO_2 is totally inert with respect to the oxidant and this makes it a solvent of choice for this kind of reactions. Such an advantage is uncommon except for non oxidizable solvents like perfluorinated solvents.

Material made of oxidized cellulose is a very interesting material for biomedical applications as it is bioresorbable, *i.e.*, it degrades inside the human body. It also exhibits interesting haemostatic properties, *i.e.*, it can stop bleeding [2]. These two characteristics make this material very useful for surgical applications, as for instance emergency compresses allowing the surgeon to deal with uncontrolled bleeding.

For these uses, fabrics made of oxidized cellulose must be only partially and selectively oxidized in order to maintain their mechanical properties. NO_2 has been chosen as the oxidant because of its selectivity to oxidize mainly the primary hydroxyl group of the glucose monomer. This selective partial oxidation by NO_2 maintains the mechanical properties of the fabric while conferring it bioresorption properties.
Industrial production of such surgical products is currently performed using NO_2 as the oxidant, dissolved in a perfluorinated solvent (Johnson and Johnson process) [3]. After reaction, oxidized products have to be thoroughly washed to eliminate NO_2 residues and by-products of the reaction. This is done using aqueous alcohol solutions.

The reaction scheme is given below in figure 1.

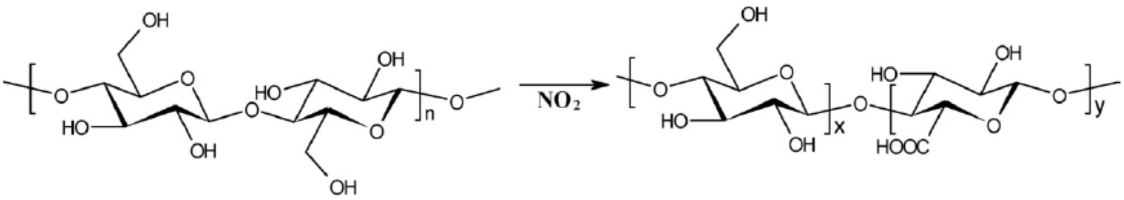

Figure 1: scheme of the oxidation reaction

CO_2 AS A SOLVENT FOR NO_2

In 2004, two academic laboratories, the Laboratoire de Génie Chimique (LGC) in Toulouse and the Centre de Recherches sur les Macromolécules Végétales (CERMAV) in Grenoble suggested and tested the use of supercritical CO_2 as an alternative solvent for this reaction. CERMAV is a reference laboratory in Europe for fundamental research upon cellulose. The LGC develops the use of the supercritical technology, especially for applications in reaction engineering.
First tests were performed in a 200mL autoclave and allowed to file a patent [4]. Detailed description of these experiments can be found in [5]. Because of its interaction with NO_2, CO_2 was found to be a modulating solvent for the reaction. Indeed, variation of the operating pressure may provide a way to adjust the degree of oxidation, which in turn may allow adjusting the duration of the bioresorption in physiological conditions. It was also noted that initial moisture content of the cellulose has a significant influence on the kinetics of the reaction. In parallel, a thermodynamic study of the mixture was performed to determine the phase diagram in order to secure the choice of operating conditions, especially in order to ensure operation in a monophasic system and avoid heterogeneities of the oxidized fabric. The phase diagram is given below (Figure 2) and shows the different domains. More information about the experimental device used and the proposed thermodynamic modelling can be found in [6].

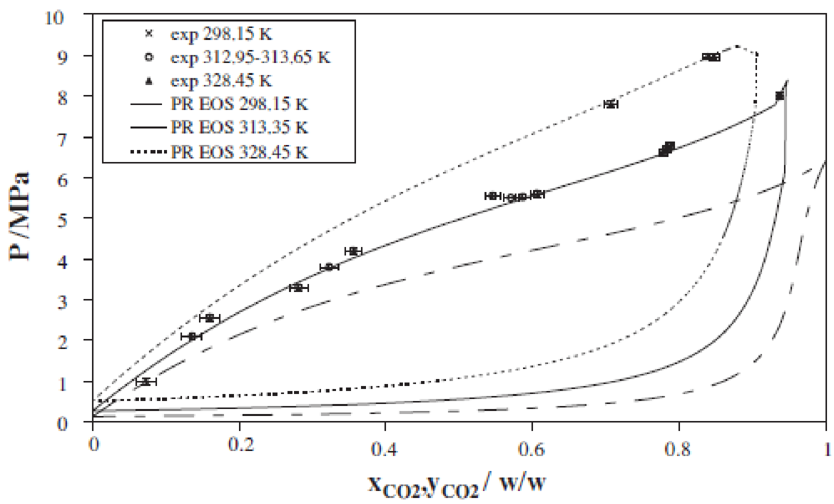

Figure 2: Phase diagram of the CO_2-NO_2 mixture (from [6])

Note that the thermodynamics of the system is rendered complex by the presence of dimerisation equilibrium between NO_2 and N_2O_4. Indeed, it is suspected that only the NO_2 form has an oxidative action. Modelling including this chemical equilibrium has been proposed using the soft-SAFT equation of state [7].

STUDY AT PILOT SCALE

Subsequently to the filing of a patent, an industrialist of the biomedical domain established a collaboration with LGC to industrialize this totally new process (design of the pre-industrial prototype, specifications for the building of the industrial unit, monitoring of the process...). This patent [4] was thus licensed in 2006 to the Sofradim company with an exclusive application in the biomedical sector. This company located in Trévoux (France) is a subsidiary of the US company Medtronic. In collaboration with this company, the Laboratoire de Génie Chimique proposed a design for a 4 liter pilot scale installation to consider the extrapolation to industrial scale.
In 2008, the pre-industrial prototype implemented at LGC allowed confirming the technological solutions envisaged for large-scale extrapolation. Different challenges were faced: an exothermic reaction in a high pressure reactor had to be managed and the reactor hydrodynamics should guarantee the homogeneity of the oxidation for each cm^2 of treated fabric rolls. For obvious confidentiality reasons, operating conditions of the reactor cannot be disclosed in the current document.

In 2009, the prototype was transferred to the Sofradim factory in Trévoux (France) to produce oxidized cellulose dedicated to manufacturing of Veriset™ lots as part of CE marking and clinical studies associated. Design and construction of the industrial unit were started. The industrial unit was operational in November 2014 and intensively tested to ascertain the robustness of the process, while fulfilling the very stringent standards of the biomedical sector. In 2013, parallel to the construction of the industrial unit, a small scale production was started using the pre-industrial unit to manufacture oxidized cellulose for Veriset™. The product was launched in Europe at the end of 2015.

THE COMMERCIAL PRODUCT

Veriset™ Hemostatic Patch is a resorbable topical hemostatic device for use in surgical procedures as an adjunct to hemostasis when conventional methods are ineffective or impractical [9].

Veriset™ is made of oxidized cellulose coated with polyethylene glycol (PEG) and impregnated with trilysine. When placed in a bleeding site, oxidized cellulose absorbs blood while PEG and trilysine cross-link to form a barrier that rapidly and actively stops bleeding.

This product is a patented combination of PEG and oxidized cellulose which exhibits strong advantages such as rapid time to hemostasis [10], full absorbability, efficacy in cases of inhibited coagulation and which is totally free of human or animal components [9].

CONCLUSION

This collaborative work between two academic laboratories and an industrial partner is a very good example of an efficient synergy of competences: academic knowledge upon the cellulose product, specific chemical engineering know-how upon the use of supercritical technology and the driving incentive of an industrial partner which has the opportunity to bring a very innovative product in its sector of activity, manufactured with a patented innovative process. This is also a good example of a process where CO_2 is used as a mono-solvent, for the reaction step and the purification step.

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