PRODUCTION OF OXIDIZED CELLULOSE FOR BIOMEDICAL APPLICATION

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ABSTRACT

Fabrics made of oxidized cellulose are used for surgical applications because they are bioresorbable and hemostatic. Existing industrial process (Johnson and Johnson process) is using nitrogen dioxide dissolved in a perfluorinated solvent as the oxidant. Recently, from a 2005 CNRS patent, which more widely envisages oxidation of polysaccharides, supercritical CO_2 was proposed as an alternative greener solvent for this reaction. Preliminary lab tests were done at the Laboratoire de Génie Chimique (LGC) in collaboration with the Centre de Recherche sur les Macromolécules Végétales de Grenoble. In 2006, the patent was licensed to Covidien Company and a pilot plant was built and operated at LGC. Specific technological solutions, especially to insure homogeneous processing of the fabric, management of the exothermicity of the reaction and post-treatment washing, were validated. In synergy with another Covidien proprietary processing, a commercial product has been designed and registered in Europe (Veriset® hemostatic patch).

INTRODUCTION

Supercritical fluids have often been proposed as a medium to perform reactions [1]. In addition to be a green solvent, it has other advantages, as for instance the control of the selectivity of the reaction by adjusting pressure and temperature. Using supercritical CO_2 as the supercritical fluid provides a very specific advantage when oxidation reactions are considered: indeed CO_2 is totally inert in respect to the oxidant that makes it a solvent of choice for this type of reactions. Such an advantage is shared with other non oxidizable solvents like perfluorinated solvents.

Fabric made of oxidized cellulose is a very interesting material for biomedical applications because it is bioresorbable and also exhibits haemostatic and antibacterial properties [2]. Oxidized cellulose is thus used for medical devices such as adhesion barriers, , absorbable haemostats.

NO_2 has been chosen as the oxidant for its selectivity to oxidize mainly the primary hydroxyl group of the glucose monomer. This selective partial oxidation maintains the mechanical properties of the fabric while the property of bio-resorbability obtained is sufficient.

Initially, in the 40's, the manufacturing process by the Eastman Kodak company was using gaseous NO_2. In addition to practical difficulties (the boiling point of NO_2 is 21°C), the selectivity of the gaseous oxidant was difficult to control. This process was abandoned probably because good homogeneity of the final product was not achieved. Industrial production of this material is currently done using NO_2 as the oxidant dissolved in a perfluorinated solvent [3]. After reaction, oxidized products have to be washed to eliminate NO_2 residue and by-products of the reaction. This is done by using aqueous alcohol solutions.

The reaction scheme is given below in figure 1.

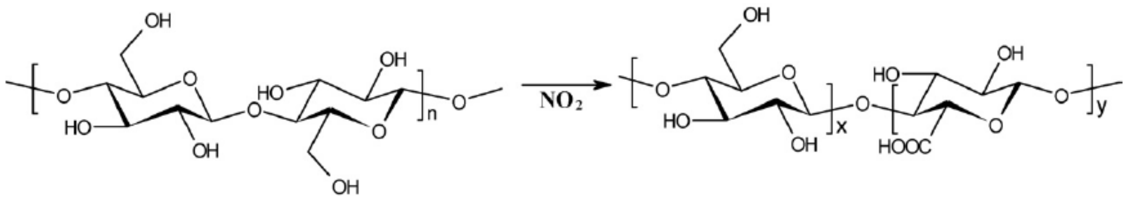

Figure 1: scheme of the oxidation reaction

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 associated to propose and test 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 done in a 200mL autoclave and made it possible 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 as a modulating solvent for the reaction. So variation of the operating pressure may provide a way to adjust the degree of oxidation, which in turn may allow adjusting the duration of bioresorption in the human body. Note also 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 done to determine the phase diagram in order to secure the choice of the operating conditions, especially in order to insure operation in a monophasic system to 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].

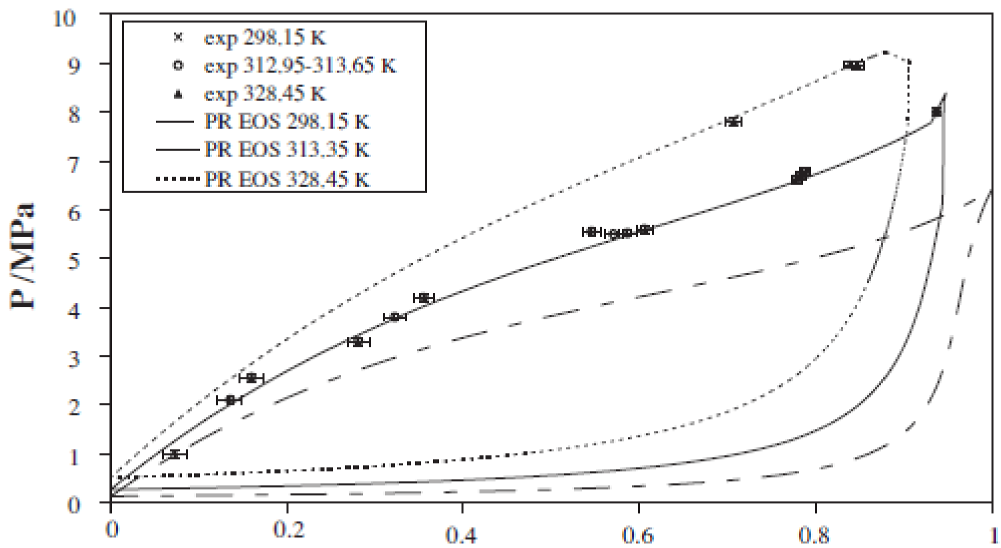

Figure 2: Phase diagram of the CO_2-NO_2 mixture (from [6])

Note that the thermodynamics of the system is rendered complex by the presence of a 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

The patent [4] was licensed in 2006 to the Sofradim company. This company belongs to the biomedical sector and is located in Trévoux (France). It is a subsidiary of the US company Covidien. In collaboration with this company, the Laboratoire de Génie Chimique proposed a design for a pilot scale installation to envisage the extrapolation to industrial scale (Figure 3).

Figure 3: Pilot installation for oxidation of cellulose

The main challenge was to design a reactor where the maximum of cellulose matter, in the form of rolls of fabric, could be processed. Indeed, the ratio mass of cellulose/reactor volume was rather small in the initial lab scale reactor. The increase of this ratio arises two kinds of problems:

- achieving a good distribution of the NO_2 reactant in the reactor
- managing the exothermicity of the oxidation reaction in an intensified configuration

The chosen technological solution was to implement a recirculation loop where different heat exchangers are located. The geometry of the reactor was specifically designed to insure homogeneous flow through the fabric in order to avoid hot points and to obtain a good homogeneity. Because the project is under high confidentiality, it is not possible to disclose further this specific information.

Also, the washing step using pure supercritical carbon dioxide and mixtures of supercritical carbon dioxide and ethanol were tested and the washing process was patented in 2010 [8]

All technological solutions were tested and validated on the pilot installation and a commercial product has been designed and registered in EU. This product, Veriset® hemostatic patch, associates oxidized cellulose fabric and a proprietary processing of Covidien to achieve hemostasis. Note that the final choice of the operating conditions had to take into account specific constraints for the final product, such as mechanical properties, minimization of geometrical restriction of the fabric resulting chemical properties of the processed cellulose. For the same reason, all this information cannot be disclosed here. From all information obtained from the pilot scale study, this process is being scaled-up.

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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