

CELLULOSE OXIDATION IN DENSIFIED CARBON DIOXIDE MEDIUM

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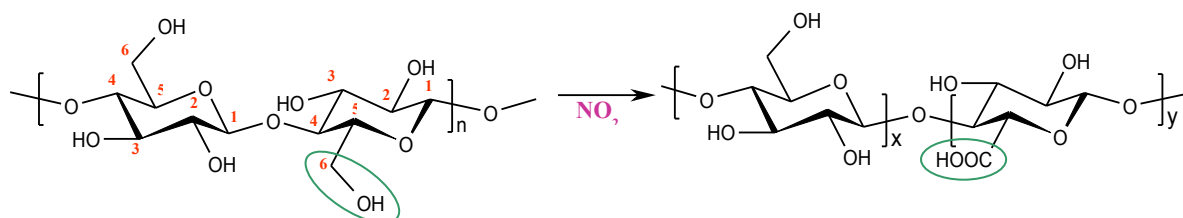
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Abstract

When oxidized in a selective way, cellulose becomes resorbable inside human body and, parallelly, develops hemostatic and antibacterial properties, thus leading to the manufacturing of medical devices such as absorbable hemostatics and adhesion barriers. Current industrial processes involve the reaction of cellulose with the oxidative nitrogen dioxide (NO₂), dissolved into chlorofluorocarbons or perfluorinated hydrocarbons, these solvents being chosen because of their inertness in respect to oxidation. We present here a new process, based on the use of supercritical carbon dioxide (SCCO₂) as a solvent for NO₂. This study addresses the influence of reaction time upon the degree of oxidation of the product. In this process, the oxidative reaction is typically performed at 100 bar and 40  C. This procedure yields a material with limited degradation products, a degree of oxidation of 0.6, and with good bioresorbability and mechanical properties.

Introduction

Oxidation of cellulose is performed through the selective oxidation of primary OH-groups, nitrogen dioxide being the oxidant. Heterogeneous fluid-solid oxidation, involving adsorption of the reactant onto cellulose fibres, and reaction with the primary hydroxyl groups of the cellulose is described on the following scheme:



The first industrial process was based on the use of gaseous nitrogen dioxide, where layers of fabrics were crossed by the gas. This process was abandoned because of the difficulty of handling a gas, as well as for mastering the exothermicity of the [gas process in gaseous state](#) in industrial conditions. As a consequence, solvent based processes were proposed, where nitrogen dioxide was dissolved in an organic solvent, and the oxidation took place in the liquid phase. Nevertheless, the oxidant could cause some damage to the solvent, and degradation products were often present. Therefore, the biomedical company Johnson & Johnson proposed the use of inert solvents, and patented the use of perfluorocarbons -as solvents for this reaction¹-([ref 1](#)).

We have proposed the use of an alternative solvent, supercritical carbon dioxide. Indeed, carbon dioxide can be considered as a [non-oxidizable solvent](#) in the sense that carbon [atom](#)

is at its maximum degree of oxidation. Furthermore, no problematic solvent residues will remain in the processed fabric, and ~~that~~ this is a great advantage considering the biomedical aspect of the product. More widely, carbon dioxide is considered as a green non expensive solvent, and, in this case, compares very favourably with perfluorocarbons. We will see here that nitrogen dioxide solubility is quite good in carbon dioxide, enabling the operation of a competitive “supercritical phase” process, which we recently patented² ([ref 2](#)).

Materials and methods

Chemicals

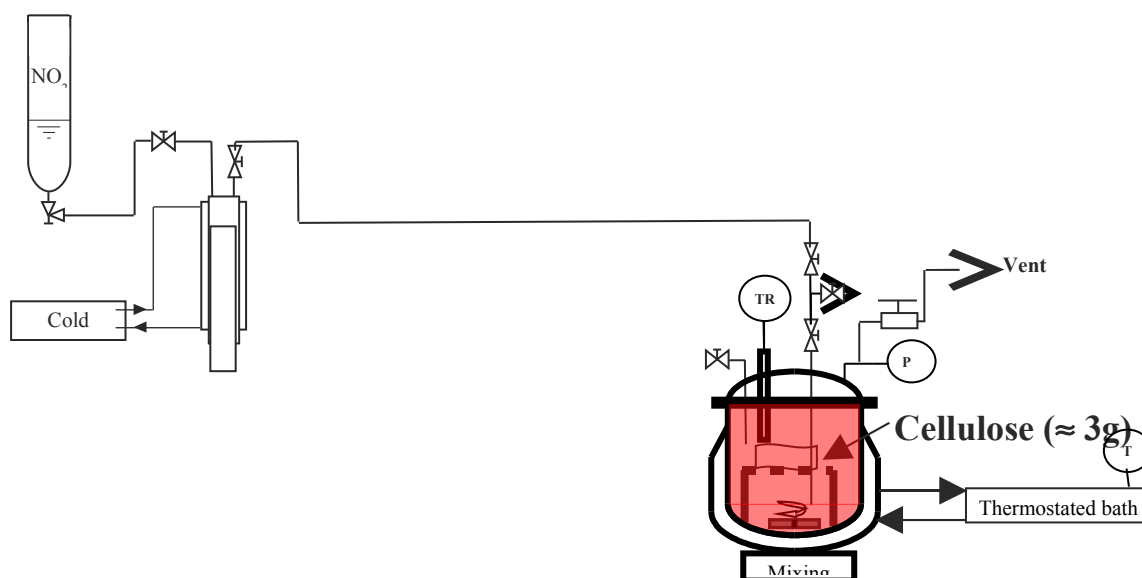
Cellulose is under the form of fabric pieces made of [Bemberg](#) Rayon, which is regenerated cellulose (cellulose II) ~~provided by Bemberg, and~~ made using the Cuprammonium process. NO₂ is provided by l’Air Liquide under the form of 6 kg bottles.

Experimental device

The experimental device is constituted of three parts: [i](#)) ~~the reactor itself,~~ [ii](#)) [the injection device for nitrogen dioxide,](#) [iii](#)) ~~the feeding system for pressurized carbon dioxide.~~

The reactor has been built by Parr Industry and has the capacity of 250 mL. It is equipped with two sapphire windows, enabling visual observation of the reacting mixture. A water jacket allows maintaining a constant temperature. A back pressure regulator (Tescom) is located on the venting, which allows constant pressure operation for the discharge procedure (see operation of the oxidation process paragraph).

The device can be seen on the Fig 1



[Fig. 1](#)-: scheme of experimental device

Carbon dioxide is fed into the reactor, thanks to a high pressure pneumatic piston pump (Top Industrie). Indeed, in this case, liquid carbon dioxide is pumped from a bottle equipped with a plunging tube. A mass flowmeter based on Coriolis effect (Micro Motion-~~????~~) allows measuring the quantity of carbon dioxide introduced into the reactor.

Injection of nitrogen dioxide is done into the carbon dioxide pressurized reactor, containing the fabric sample (~~around 1g a few grams~~) to be processed, placed on a specific perforated Teflon made support. This introduction is made using a high pressure pneumatic injection system, specifically manufactured by Top Industrie. Note that, because of the strong corrosivity of NO₂, all parts are made of 316 L stainless steel (~~???~~), and all gaskets in contact with the reacting mixture are made in Teflon. In addition, all the tubing is always previously flushed with dry nitrogen, to eliminate any trace of water, which may cause severe corrosion when contacting NO₂. More widely, use of NO₂ implies very careful handling, first for security reasons (NO₂ is very toxic), and also for its aggressiveness towards most of materials. Personal Protection Equipment, such as individual air fed masks, had to be available for interventions of the operators during NO₂ injection and for the discharge of the reactor. The whole system is placed under a ventilation hood.

Operation of the oxidation process

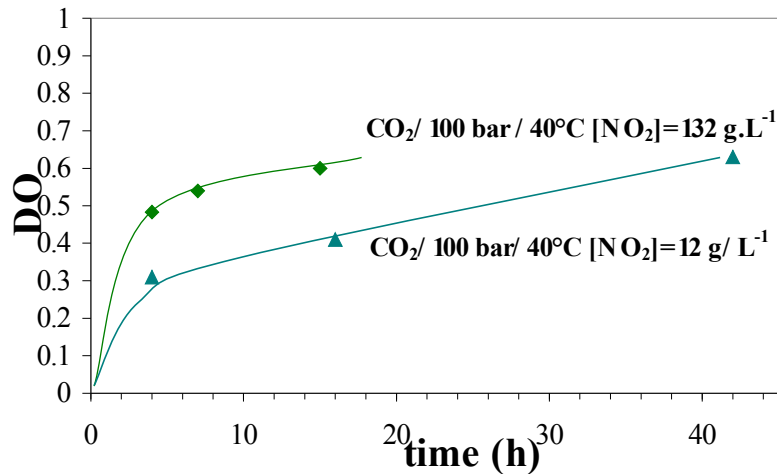
After pressurization with supercritical carbon dioxide, the nitrogen dioxide is injected in the vessel containing the cellulose sample and the reaction proceeds for durations from 1 hour up to 20 hours. At the end, the vessel is not ~~directly~~ immediately depressurized, as it is conventionally for batch reactions, because this could cause condensation of a liquid rich NO₂ phase, ~~which that~~ could react on the fabric in a non homogeneous way. So, a dilution discharge procedure is operated, where carbon dioxide is pumped into the vessel, while the back pressure regulator evacuates the reactional mixture to maintain a constant pressure. When the mixture exhibits only light red colour through the sapphire window, the dilution is assumed sufficient to allow depressurization of the vessel. Then the vessel is opened and the fabric is let to degas a few minutes before the washing procedure is undertaken. This washing procedure is taken from the Johnson~~& and~~ Johnson patent. This is done using a massic 50/50 mixture of isopropanol and water, up to the neutrality of the solution (assessed with a pH paper). Then, two washing sequences with pure isopropanol are done to eliminate the water. Finally the fabric sample is dried in an oven at 60°C during 24 hours. Note that the washing step has been shown to have a prominent influence upon the shell life of the product.

Analysis and characterization of the processed cellulose

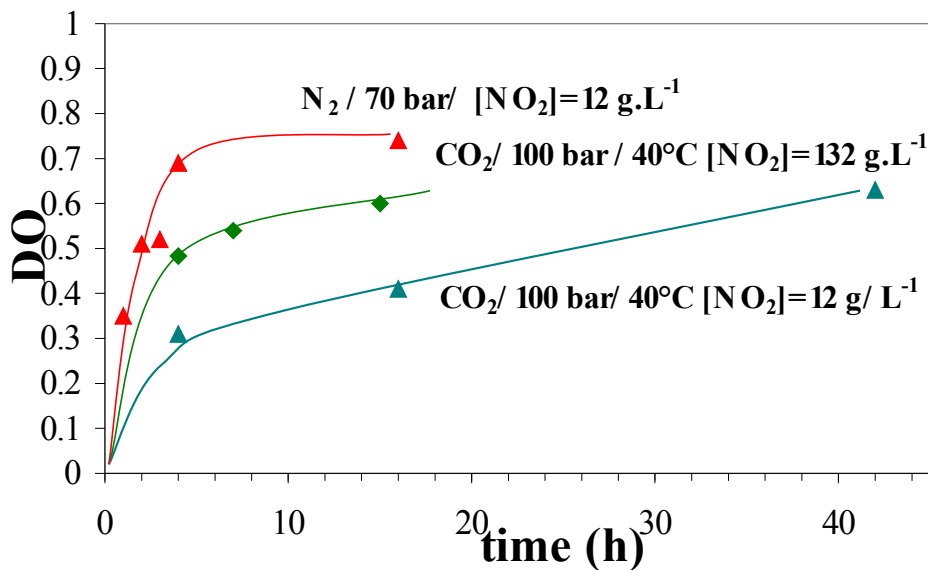
The main feature of the oxidized cellulose is its degree of oxidation, which is equal to 1 when all primary ~~hydroxyl~~ hydroxyl groups are oxidized, that corresponds to 25% of the total number of ~~hydroxyl~~ hydroxyl groups. Indeed, the degree of oxidation is related to the degree of bioresorbability of the final product, characterized by the *in vivo* time of degradation of a piece of fabric. The degree of oxidation can be very simply determined by the acidity titration of the acid groups resulting from the oxidation of the primary hydroxyl groups. ~~An~~ other important feature is the possible degradation of the product because of side reactions, or over oxidation of the product. This degradation is responsible of a loss of the mechanical properties of the processed fabric, which must be maintained to obtain an acceptable product for biomedical applications. This will not be considered in the study presented here.

Results and Discussion

Oxidation was performed at 100 bar and 40°C for two different initial concentrations of NO₂. Note that, even for the lowest concentration, NO₂ is in excess in respect to the mass of cellulose (which is 3g⁻²)- ~~A verifier!!!~~ Results are shown on [Fig. 2](#).



[Fig. 2](#): kinetics of oxidation of cellulose in scCO₂



~~il faut enlever la~~

~~courbe de l'azote !!~~

As expected, it is seen that initial kinetics are faster for the higher concentration of NO₂. Nevertheless both kinetics diminish and seem to tend to a plateau for a value around 0.7 for the degree of oxidation. This limiting value can be related to the degree of cristallinity of the cellulose, around 25%, indicating that the crystalline part is much harder to oxidize, probably for accessibility reasons.

Note that the concentrations given here assume that oxidizing reactant is under the form of NO₂ molecules. Indeed, NO₂ is in equilibrium with its dimmer N₂O₄^{-3(ref 3)}, and because the NO₂ molecule is supposed to be the only active species, this is of great importance for the

