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Functionalization and optimization of PLA with coumarin via click chemistry in supercritical CO_2

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ABSTRACT

For the first time the functionalization via click chemistry of polylactic acid (PLA) with coumarin in supercritical conditions CO_2 has been achieved. Click reaction was performed at atmospheric pressure and supercritical carbon dioxide ($scCO_2$) for comparison being observed that is possible to obtain similar yields, higher than 95% in both cases. Once click functionalization of PLA in $scCO_2$ was achieved the influence of operational conditions on the polymer characteristics and in the yield was studied to get an optimized functionalization process.

1. Introduction

The selection of the right solvent for the synthesis of pharmaceutical related products is critical. Beyond the obvious function of solvents to allow proper reactivity in solution, they should be easily separated from the Active Pharmaceutical Ingredient (API), reducing their economic and environmental impact on the product production [1]. The usage of harmful solvents also brings the disadvantage of solvent incorporation into the API. If they cannot be removed, the amount must be controlled or limited to levels safe to the patient [2].

Moreover, the presence of toxic residues related with raw materials excess, by-products or solvents from the production process or further manufacture is not acceptable in such medical related products [3]. Most of the drug related allergies is suspected that could be in relation with a deficient removal of synthesis and manufacture residues. This issue is even more critical in polymers destined to controlled drug delivery because the objective is that have a prolonged stay in the body until being biodegraded and bioabsorbed by the body [4]. By now, significant efforts in substitution of traditional organic solvents are focused on using green solvents to carry out environmental friendly processes which can eliminate this problem [5].

Supercritical fluids are finding application in the production of pharmaceutical related products due to their ability to solve difficult process, particulation and formulation problems [6,7]. Supercritical fluids exhibit a pressure-tuneable dissolving power with a liquid-like density and gas-like transport properties [8]. They possess the attractive property of easy separation from the substrate once the synthesis is complete, dragging with it most of the low molecular weight residues by simply and quickly venting [9].

In this context, the use of supercritical carbon dioxide ($scCO_2$) as solvent appears as a solution to carry out environmental and patient friendly processes due to its lack of reactivity, high diffusivity, zero surface tension, good transport properties and sterilization capacity [1,10]. In relation with polymeric materials, the employment of $scCO_2$ produces a significant reduction of the glass transition temperature (Tg) and polymer swelling that allows the proper and homogeneous diffusion and dispersion of molecules into the polymer network [11].

In order to get a polymer based material for controlled drug release there are two main alternatives: physical entrapping of the API (absorbed or encapsulated) or covalent bonding to the polymer backbone. Both have advantages and disadvantages, while the first one exhibits a prompt delivery of great part of the drug, the second one present a more time stable release linked with the polymer biodegradation.

Although the employment of $scCO_2$ as impregnation media and/or carrier for polymer-drug presentations (micro and nanocapsules, scaffolds, etc) has been widely described in literature, the functionalization of biopolymers in $scCO_2$ for medical application is a field waiting to be explored [11–15].

Among different techniques for polymer functionalization where toxic organic solvents are used, click chemistry has emerged as one of the most promising reactions because it is classified as a very specific, efficient and versatile reaction which allow to obtain high products yields [16]. Within the reactions included in the field of click chemistry, Huisgen 1,3-dipolar cycloaddition is the most employed in polymer chemistry. It consists on the reaction of an azido group to an alkyne

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Table 1
Temperature intervals in DSC analysis.

Polymer	Ramp (°C/min)	Temperature intervale (°C)
First heating	10	40–280
Cooling	10	280 to −50
Second heating	10	−50 to 280

group (AAC) catalyzed by copper (CuAAC) in organic media, where DFM or THF are the most common solvents used to achieve the functionalization of chemical product [17,18]. The employment of the "click" route to get functionalized polymers using $scCO_2$ as reaction media is almost unexplored and can open an absolutely green road to lots of pharmaceutical preparations. In fact, there are only three papers in the literature describing "click" reactions performed into $scCO_2$ and any of them describes polymer functionalization without the use of a ligand [19–21].

The polymer chosen to be functionalized in this work is Polylactic acid (PLA). PLA is an aliphatic polyester approved by the US Food and Drug Administration (FDA) for contact with biological fluids [22]. This polymer presents a big variety of properties including renewability, biocompatibility, processability and energy saving [23]. Among PLA properties, its bioresorbability and biocompatibility in the human body make this polymer an excellent candidate to be used in biomedical field as manufacture tissue engineering scaffolds, delivery system materials or different bioabsorbable medical implants [24–29].

The organic compound chosen for PLA functionalization in this work is the coumarin. This substance is a plant-derived natural product which consists of an aromatic ring fused to a condensed lactone ring [30]. Coumarin is well-known by its pharmacological properties such as anti-inflammatory where it is able to remove protein and oedema fluid from injured tissues, anticoagulant activity due to coumarin is vitamin K antagonist producing anticoagulant effect or antiviral activity because this compound is considered as anti-HIV agent [31].

In this work, the functionalization of polylactic acid (PLA) acetylene by click chemistry in supercritical carbon dioxide is studied for first time. The catalytic activity of the system and the purity of the products obtained is investigated to let clear the great advantages of using $scCO_2$ as reaction media for "click" functionalization.

2. Experimental

2.1. Materials

Sodium azide (> 99,5%, Sigma Aldrich), 4-Bromomethyl-7-methoxy-coumarin (97%, Sigma Aldrich), Copper(I) iodide (CuI) (> 99%, Sigma Aldrich), *N,N*-Diisopropylethylamine (DIPEA; > 99%, Sigma Aldrich), Polylactic Acid acetylene (98.3%, Specific polymers), Tetrahydrofuran (THF) (HPLC grade; SDS S.A., Spain) Copper(II) acetate monohydrate ($Cu(CO_2CH_3)_2{\cdot}H_2O$) (> 99%, Sigma Aldrich) and carbon dioxide (Carburos metálicos, S.A., Spain) with a purity of 99.5%. All other reagents and solvents used in the study were of analytical grade and used as delivered.

2.2. Synthesis of 4-azidomethyl-7-methoxycoumarin

The synthesis of this compound was carried out according to bibliography [32]. A mixture of NaN_3 (1,2 g) and 4-bromomethyl-7-methoxycoumarin (1 g) in acetone/acetonitrile (1:1, 120 ml) solution was added to a 250 ml flask. The mixture was stirred at 50 °C for 48 h. Then, solvents were removed under vacuum. The organic extracts were washed with water to precipitate the 4-bromomethyl-7-methoxycoumarin which did not react. Then, product was filtered and washed with heptane and dried under vacuum.

2.3. Synthesis of click product at atmospheric pressure

Click product at atmospheric pressure was synthetized using CuI as catalyst where DIPEA was used as nitrogen base.

PLA-coumarin click was synthetized as follows. A solution of 4-azidomethyl-7-methoxycoumarin (30 mg, 0.13 mmol) and PLA acetylene (258.31 mg, 0.13 mmol) in tetrahydrofuran (THF) (4,06 ml) was purged with nitrogen. Then, copper iodide (CuI) (6.19 mg, 0.032 mmol) and DIPEA (0.0057 ml, 0.032 mmol) were added under nitrogen atmosphere. Then reaction mixture was stirred for 24 h at 40 °C. After the reaction, the solvent was removed under vacuum, to obtain a click

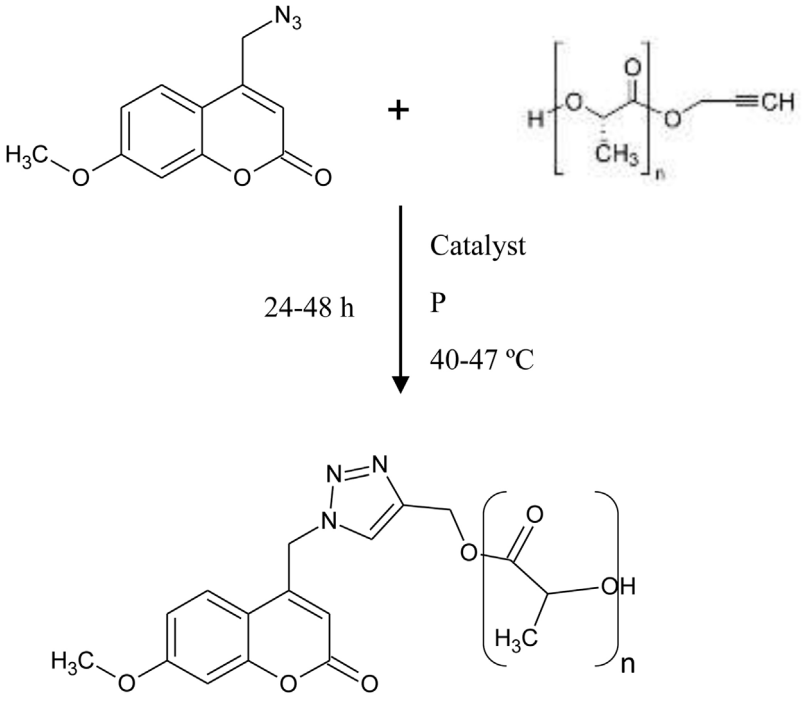

Fig. 1. Scheme of click reaction.