Superkriticni CO₂, čistejša alternativa tradicionalnim metodam procesiranja polimernih biomaterialov

Supercritical CO₂, a clean alternative to traditional methods of processing polymeric biomaterials

Abstract

A wide variety of natural and synthetic polymers have applications in biomedical devices. They are usually processed by melting or by using organic solvents, but these methods may affect the efficiency of incorporating delicate bioactive compounds, such as drugs and proteins, during polymer processing. These shortcomings can be avoided by using supercritical fluids as processing solvents or plasticizers. Supercritical carbon dioxide (scCO₂) has attracted attention for its potential as a plasticizer in polymer processing. It is used for obtaining microspheres, microcapsules, foams, membranes and polymer/drug composites. The method offers important advantages over other techniques, including the absence of harmful organic solvents, the mild processing conditions, and the ready control of particle and foam morphology simply by varying...
minjanjem tlaka in temperature. \( \text{ScCO}_2 \) hkrati predstavlja tudi alternativo običajnim postopkom sterilizacije medicinskih pripomočkov. Zahteve na področju biomaterialov so specifične in postajajo s časom vedno strožje, zato predstavlja tehnika procesiranja polimerov s \( \text{scCO}_2 \) obetavno alternativo klasičnim metodam tkivnega inženiringa ter metodam za pridobivanje nosilev, ki omogočajo kontroliранo sproščanje zdravil itor replikacije Pseudorabies virusa v okuženih celicah.

**INTRODUCTION**

Polymers are the most widely used materials in biomedical applications. They offer advantages (highly versatile, easily obtained and processed, similar to natural compounds) which recommend them for applications in all domains of medicine, such as implants, grafts, medical equipment, drug delivery systems and tissue engineering scaffolds.

**MATERIAL & METHODS**

A wide variety of natural and synthetic polymers has been investigated for drug targeting and release or resorbable or non-resorbable implants, including protein-based polymers, polysaccharides, polyesters, polyanhydrides, polyamides, silicones, acrylic polymers, polyorthoesters, polyurethanes, polyacetals, homopolymers, copolymers and blends [1-4]. A few examples of the synthetic polymers used as biomaterials are presented in Figure 1.

**RESULTS**

Processing of polymeric biomaterials.

The traditional methods for polymer processing involve either high temperatures, necessary for melting or viscosity reduction, or hazardous volatile organic solvents (VOCs) and chlorofluorocarbons (CFCs). These methods may affect the incorporation of delicate bioactive compounds during processing, since denaturation may occur upon exposure to solvents, high temperature or shear stresses [5]. Therefore, extensive research is focussing on seeking new and cleaner methods for processing polymeric biomaterials.

One such method is the use of supercritical fluids as processing solvents or plasticizers. A supercritical fluid is a substance for which both pressure and temperature are above the critical values [6]. The critical state denotes the conditions at which the phase boundary between liquid and gas ceases to exist. The special combination of gas-like viscosity and diffusivity, and liquid-like density and solvating properties, of a supercritical fluid makes it an excellent solvent for various applications [5].

Supercritical carbon dioxide (sc\( \text{CO}_2 \)) is the preferred choice for these applications. It is a clean, versatile solvent and a promising alternative to organic solvents and chlorofluorocarbons. It is non-toxic, non-flammable, chemically inert, environmentally safe and inexpensive. Its supercritical conditions (\( T_c = 304.1 \text{ K}, P_c = 7.38 \text{ MPa} \)) are easily attained and it can be removed from a system by simple depressurization [5, 6].

Sc\( \text{CO}_2 \) is a good solvent for many low molecular weight compounds and a few polymers, but it is generally a very poor solvent for high molecular weight polymers. However, its solubility in many polymers is substantial, being influenced by temperature, pressure and, sometimes, by weak interactions with the groups in the polymer.

Dissolved \( \text{CO}_2 \) causes a reduction in the viscosity of the polymers by increasing their free volume. Thus
the polymers are plasticized, allowing processing at lower temperatures. The plasticization is confirmed by a decrease in the glass transition and melting temperature of the polymer [6]. The supercritical fluid also alters the physical properties of the polymers, such as density, diffusivity and swollen volume. 

ScCO₂ has been used successfully in polymer synthesis and (as a solvent, an antisolvent or plasticizer) in polymer processing for microcellular foaming, particle production, impregnation of polymers, obtaining polymer composites and solvent extraction.

**ScCO₂ as the polymerization environment**

Polymerization with scCO₂ has been studied for the production of polycarbonates [6] and polyesters [7-12], among other things. The main advantage of using CO₂ is the reduced viscosity of the polymer during synthesis, which decreases the mass transfer resistance, leading to an increased conversion and molecular weight [6].

**Porous materials**

In the domain of polymeric foams, scCO₂ has found an application as a blowing agent for obtaining polymeric devices with controlled porosity [5, 13-24]. The replacement of traditional blowing agents, such as CFCs, VOCs and hydrochlorofluorocarbons (HCFCs), with CO₂ has proven beneficial for the biocompatibility of the final medical devices. Moreover, supercritical fluids offer the possibility of controlling the size and distribution of the pores by simple variation of the processing parameters (pressure, temperature and depressurization rate) [5]. However, despite the obvious advantages, there are some limitations. The control over the internal scaffold architecture cannot approach that offered by 3D printing techniques, and this indicates the need for further process optimization [5].

**Microparticles**

Extensive research has focused on the use of scCO₂ for obtaining particles for drug delivery applications. For this purpose, pharmaceuticals alone [22, 25-29] and in combination with polymeric supports [10, 30-36] have been processed.

When compared to the traditional methods for obtaining particles – oil-in-water (o/w), water-oil-water (w/o/w) double emulsion, hydrous water-oil-oil, water-oil-oil-oil (w/o/o/o), solid-oil-water (s/o/w), anhydrous solid-oil-oil-oil (s/o/o/o), spray drying – particle production using scCO₂ as a solvent or an antisolvent offers two major advantages. The first advantage is better control of particle size, particle size distribution and morphology. This can be achieved by tuning process parameters such as the amount of dissolved CO₂, temperature, pressure, nozzle diameter and depressurization rate. Control over drug or delivery system particle size is essential for good targeting and for the efficacy of the active compound [22].

The second advantage is not needing an organic solvent or to efficiently remove and recover a solvent. Supercritical fluids provide a clean alternative to traditional techniques that employ toxic organic solvents or elevated temperatures. This has allowed sensitive bioactive molecules, such as proteins, drugs, and nucleic acids, to be introduced during the polymer processing stage [22].

Existing methods that use scCO₂ as a solvent or an antisolvent to obtain drug or polymer-drug particles...
over, neither the polymer nor the reinforcing agent need to be soluble in scCO2. One can also control the morphology of the final product (filler distribution, pore size and distribution) and obtain high loadings of reinforcing agent [23].

**DISCUSSION.**

Supercritical carbon dioxide has attracted particular attention due to its tremendous potential as a plasticizer in polymer processing. Of particular interest is the use of supercritical fluids for processing polymers destined for biomedical applications (as microspheres, microcapsules, foams, membranes and polymer/drug composites). The method offers important advantages over other techniques in terms of the absence of harmful organic solvents or, when necessary, the efficient extraction of solvents and impurities; the mild processing conditions, which do not alter the active compound; and easy control of particle and foam morphology by simply varying the pressure and temperature. Because of the highly specific and increasing requirements of the field of biomaterials, these techniques may represent a promising alternative to classical methods of obtaining controlled delivery systems and tissue engineering scaffolds.

**Table 1. Comparison of supercritical processes for microparticle formation**; RESS, rapid expansion of supercritical solutions; GAS, gas antisolvent crystallization; SAS, supercritical antisolvent precipitation; PCA, precipitation by compressed antisolvent; SEDS, solution enhanced dispersion by supercritical fluid; ASES, aerosol solvent extraction system; SAA, supercritical assisted atomization; PGSS, particles from gas-saturated solutions; SCF, supercritical fluid.

<table>
<thead>
<tr>
<th>Process</th>
<th>RESS</th>
<th>GAS/SAS/PCA</th>
<th>SEDS/ASES/SAA</th>
<th>PGSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>The substrate is dissolved in the SCF; the solution is subjected to rapid expansion through a nozzle, which causes supersaturation and particle precipitation.</td>
<td></td>
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<tr>
<td>The substrate is dissolved in an appropriate solvent; SCF (antisolvent) is added under high pressure; the depressurization causes supersaturation of the solution and solute precipitation.</td>
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<tr>
<td>The substrate, dissolved in an appropriate solvent, is introduced through a nozzle into the SCF antisolvent; the solvent is extracted and the substrate precipitates as droplets.</td>
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<tr>
<td>The SCF is dissolved in the melted substrate, resulting in viscosity reduction; the gas-saturated solution is expanded through a nozzle, to induce particle precipitation.</td>
<td></td>
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</tr>
<tr>
<td>Gas quantity</td>
<td>High</td>
<td>Medium</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Organic solvent</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Pressure</td>
<td>High</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td>Separation of gas</td>
<td>Easy</td>
<td>Easy</td>
<td>Easy</td>
<td>Easy</td>
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REFERENCES:


