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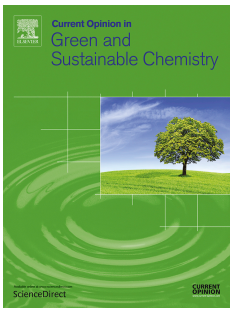

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Green solvents for enhanced impregnation processes in biomedicine

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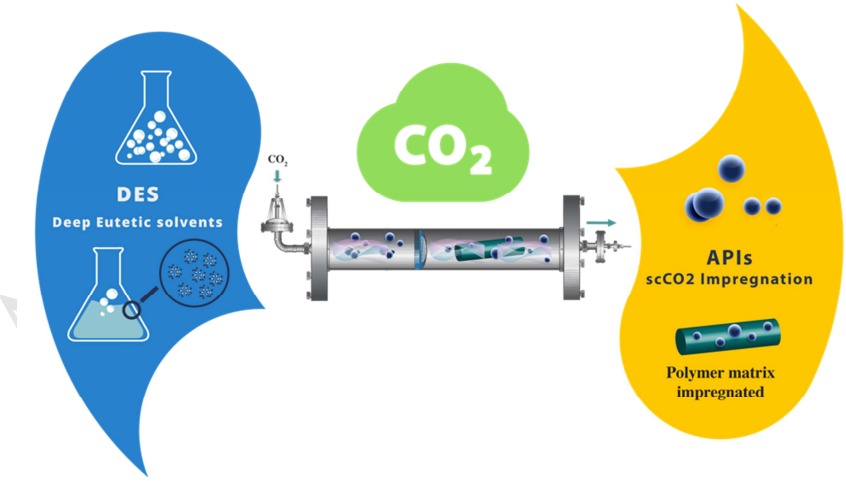
ABSTRACT

Supercritical carbon dioxide has been used as a green solvent due to their well-known potential in biomaterials impregnation. The versatility of this technique enables the loading of implants with Active Pharmaceutical Ingredients which present several benefits when compared with traditional techniques to impregnate active compounds. In this review, we have summarized the recent progresses achieved in supercritical CO_2 assisted impregnation of active compounds and therapeutic deep eutectic systems for biomedical applications.



KEYWORDS

Drug delivery systems, $scCO_2$ assisted impregnation, THEDES, green chemistry; APIs;

INTRODUCTION

Supercritical CO_2 ($scCO_2$) assisted impregnation has been used for loading active pharmaceuticals ingredients (APIs) in order to developed drug-eluting devices.

The preparation of drug-release products using an impregnation process demands the use of a mobile phase dissolve and transport the APIs, which at the same time should be able to swell the polymeric matrix, allowing the diffusion of the drug into the polymer bulk, increasing the impregnation rate (1). Typically, the preparation of drug-release systems requires three steps: solubilization of the APIs in an adequate solvent, APIs diffusion through the polymer matrix and removal of the residual solvent (2). In **Fig.1** the schematic representation of the three phases of the impregnation process is presented.

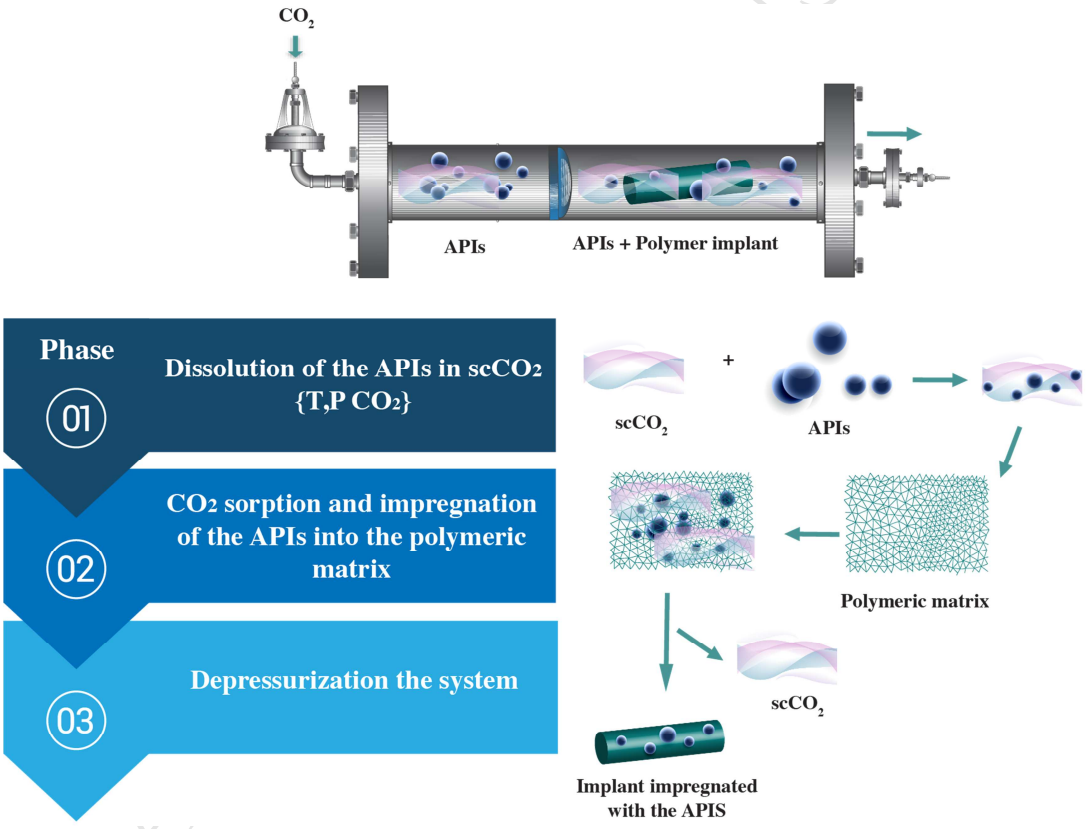


Figure1. Schematic representation of the three phases of the impregnation process.

In this sense, $scCO_2$ assisted impregnation has proven to be feasible when the pharmaceutical compound is soluble in carbon dioxide and the polymer can be swollen by the supercritical fluid.

Different yields of impregnation can be obtained by $scCO_2$ assisted impregnation. The most relevant factors that affect the yield directly are the operating pressure and temperature of the system, due to their influence on density and solvent power of CO_2 but also on the diffusivity of the fluid phase. According to Kazarian et al.(3, 4) there are mainly two mechanisms which describe $scCO_2$ assisted impregnation. One is highly dependent on the swelling ability of the polymeric matrix, when in contact of the $scCO_2$ the drug is solubilized in CO_2 and is placed in contact with the polymer, upon depressurization, the CO_2 rapidly leaves the polymer matrix, the solubilized drug precipitates and is deposited within the polymeric matrix. The second mechanism is more dependent on the affinity of the CO_2 with the drug and the drug towards the polymeric matrix. One of the major advances of this impregnation process is the fact that after impregnation, the drug-eluting device can be recovered free of any solvent residue and that the impregnation is carried under mild temperature and pressure conditions, which enables the impregnation of thermosensitive APIs (5, 6). In the last decades $scCO_2$ has been claimed as a good candidate to replace conventional organic solvents in order to develop a sustainable chemical process and to meet the regulatory requirements (6, 7). Furthermore, it is non-flammable, non-toxic, highly abundant and low cost solvent. CO_2 can be easily separated from other compounds such as APIs and/or co-solvent, recovered and recycled (5).

Due to the advantages of this process it has been applied in different fields from food to textile industries (5, 8, 9). Nowadays, $scCO_2$ assisted impregnation process is commercially used to dye textiles (9) and to impregnate fungicide in wood (2, 10). In the last years, the higher number of publications suggest a growing interest on $scCO_2$ assisted impregnation in biomedical and pharmaceutical fields, particularly in the processing of polymer-based systems for tissue engineering (7, 11-15) and drug delivery (1, 6, 16-18). In this review, we highlight the most recent advances and give some perspectives on what could be seen as the next big steps in the field.

IMPREGNATION OF ACTIVE COMPOUNDS FOR BIOMEDICAL APPLICATIONS

The interest and advantages of using $scCO_2$ assisted impregnation process in the biomedical field are notorious. The process has been essentially used to disperse APIs into a polymeric matrix, but at the same time it favors the crystallization of the API in the amorphous form. Not only the impregnation in polymeric matrixes has been described in the literature but also the creation of

drug-eluting devices through the impregnation of the APIs in a preexistent polymer-based device is a very ingenious way to prepare new therapeutic delivery devices (5). Different studies suggest the advantage of this process compared with other methods, in different areas such as oral drug delivery, ophthalmic (lenses and subconjunctival implants) and tissue engineering (sutures and scaffolds) (5, 16, 17). In which concerns oral drug delivery this has been by far the most studied area. $scCO_2$ assisted impregnation process has been intensively applied to prepare new drug loaded micro- or nanoparticles. This technique has not only improved the efficiency of drug loading but also it has enabled to improve the solubility and the dissolution rate of poorly water soluble drugs such as crystalline drugs (8, 19). García-González *et al.* (18) used $scCO_2$ assisted impregnation process to impregnate ketoprofen, an anti-inflammatory agent in polysaccharide-based aerogels in the form of microspheres, which may be used as carriers of poorly water soluble drugs for oral administration. The authors suggest the possibility of tuning drug loading and release by carefully choosing the polysaccharide used to prepare the aerogels. Another recent example. that can be found in literature are the use of $scCO_2$ for impregnation to create microcontainers with APIs for oral drug delivery (1).

Another interesting field in which $scCO_2$ impregnation process has been applied, is in ophthalmic drug delivery. These systems aim at the increase in the contact time of the drugs in the aqueous humor which enhances their efficacy and their biocompatibility (20). Different studies show the successful impregnation of different drugs (acetazolamide (21-23), timolol maleate (21), flurbiprofen (24, 25), ciprofloxacin and dexamethasone 21-phosphate disodium (20)) in soft contact lens without modifying their important characteristics such as oxygen permeability, wettability and transparency. This would not be possible by any other means of impregnation, due to the low drug solubility in aqueous solutions and the strict limitations in the use of organic solvents.

In the tissue engineering field, several studies demonstrate the advantage to use $scCO_2$ impregnation process in comparison with traditional processes for impregnation of antibacterial and anti-inflammatory compounds into commercial hydrogels, scaffolds and films, based on chitosan, collagen/cellulose, agarose and hyaluronic acid (25-27). In particular, the results of this studies suggest that using $scCO_2$ impregnation was observed higher drug loadings and a more efficient drug release (25-27).

Biodegradable and non-degradable sutures fibers have been also impregnated by $scCO_2$. The impregnation time to reach the maximal loading drug is relatively low, around one hour (2, 28, 29). Champeau *et al.* in a recent study, studied the influence of $scCO_2$ impregnation process in the tensile properties of the sutures made of poly-l-lactide (PLLA), poly (ethylene terephthalate) (PET) and polypropylene (PP) with two anti-inflammatory drugs namely ketoprofen and aspirin (2, 30).

$scCO_2$ assisted impregnation process has been a valuable tool in the development of other medical devices. Different commercial catheters and stents (from silicone and/or polyurethane) have been successfully impregnated with antibacterial, antimicrobial and antifungal drugs with the objective to decrease the risk of infection upon implantation (31-33). Various patents claim the use of this process for impregnation for example, for up to 25% of benzocaine into polyurethane-based catheter, under mild conditions (40°C; 80 bar) (31) and triclosan into silicone-based stent (33). On the same field, Barros *et al.* (17) developed of a ketoprofen-eluting biodegradable ureteral stent. The study involved a variety of biodegradable natural polymers in different concentrations and the results demonstrated that in fact different polymer matrixes render different impregnation yields at the same operating conditions. These systems have also shown to be effective carriers for the delivery of anti-cancer drugs targeting upper urinary tract urothelial tumors (16). To avoid the problems of the conventional method of drug administration via drug instillation, the authors proposed the use of biodegradable ureteral stents impregnated by $scCO_2$ with four different anti-cancer drugs (paclitaxel, doxorubicin, epirubicin and gemcitabine). The anti-cancer drugs eluted by the degradable stent showed to be able to reduce 75% of urothelial cancer cell (T24) after 72 hours, *in vitro*, with no toxicity observed in the non-cancer cells (HUVEC cells), which was used as a control.

A new trend in which concerns supercritical impregnation has to do with the coupling and integration of processes. Namely, the extraction of natural active compounds from plants followed by their impregnation in suitable polymeric matrices is becoming a focus of attention for scientist in the field. For example, Fanovich *et al.* investigated an integrated supercritical fluid extraction and impregnation process in order to fabricate microporous polycaprolactone-hydroxyapatite (PCL-HA) scaffolds with antibacterial activity after impregnation with Usnea *lethariiformis* extract (34). The authors obtained a PCL–HA scaffolds with Usnea extract with a yield of impregnation up to 5.9 wt.%, and the antibacterial activity of scaffolds was confirmed.

The use of natural extracts rather than synthetic antibacterial molecules may render products with an enhanced biocompatibility.

Industrial implementation of supercritical fluid impregnation has been validated for wood treatment and textile dyeing. In our opinion, $scCO_2$ assisted impregnation processes should soon start to be scaled-up in other fields, but especially for biomedical applications as the high added value of the products is indisputable the translation of the processes from bench to industrial scale urges. The recent studies clearly demonstrate that new processes using CO_2 around and below critical point, coupled with semi-finished medical devices aiming new applications may see interesting breakthroughs in the coming years.

IMPREGNATION OF THERAPEUTIC DEEP EUTECTIC SYSTEMS

Deep eutectic solvents (DES) appear as a new class of solvents that can be simply obtained via mixing of two or more components, which at a certain molar ratio interact through hydrogen bonding and lead to a decrease in the overall melting temperature of the system when compared to the individual components.(35-37) This family of solvents presents several advantages that turn them into promising alternative **solvents**, such as their low cost, both in which concerns production and raw materials, ease of preparation, negligible vapor pressure and non-flammability.(36-39) Thus, DES are generally called tailored made solvents due to the wide variety of compounds available coupled with the different arrangements of molecules that can be done and which may lead to up to 10^6 combinations.(36, 40, 41)

Among the compounds that can be used to form DES appear the ones that are involved in metabolic pathways. This subclass of DES has been termed natural deep eutectic solvents (NADES) and include the primary metabolites, such as organic acids, amino acids and sugars (e.g., choline chloride, citric acid, ascorbic acid, sucrose, tartaric acid, glucose, sucrose and xylose". (35-37) Later on, Stott and co-workers, introduced the use of DES in transdermal devices, being nowadays well-stablished the potential of these solvents to dissolve model drugs, by increasing their solubility, permeation and absorption.(36, 42-44) These can hence be called therapeutic deep eutectic systems (THEDES), since the eutectic system contain an active pharmaceutical ingredient (API's) as one of the DES components. The development of innovative, more effective and specialized release dosage is an emergent need to improve the poor drug solubility and bioavailability, avoiding high dosage

concentrations which inherently lead to severe side effects. THEDES have been attracting significant attention due to their high stabilization and solubilization power strength of a wide range of compounds such as the ones poorly water soluble.(36, 42, 43, 45) Up to now, several compounds have been reported to be successful included in DES which is an invaluable challenge in healthcare worldwide, as they increase the bioavailability of API's. The API's can be included in DES either by solubilizing them in the eutectic mixture either by using them as part of the mixture, i.e. being an eutectic component.(36, 42, 43)

There is always, however, the need to develop delivery systems and new carriers for drug delivery. The coupling of THEDES with polymeric material has been recently reported and brings new exciting possibilities for the production of suitable pharmaceutical systems. By doping polymers with THEDES and subjecting the mixture to $scCO_2$, a foaming/sintering process takes place due to the plasticizing properties of THEDES, rendering polymeric matrices with enhanced porosity being a viable alternative for drug delivery systems.(36, 42, 44) **Subcritical fluid sintering is a process which takes place at subcritical conditions and it is based on the slight plasticization of the polymeric particles which are fused together, creating a 3D architecture.** Recent results show that it is possible to solubilize dexamethasone in a DES based on choline chloride:ascorbic acid. This system is particularly relevant in the case of bone tissue engineering as ascorbic acid and dexamethasone are known to act on the differentiation of stem cells in the osteogenic lineage. A controlled delivery system based on a starch polymer blend was impregnated with the THEDES choline chloride:ascorbic acid: dexamethasone by supercritical fluid sintering (Figure 2). The results obtained corroborated the previous one and suggested the plasticization effect of THEDES as well as an increase on the porosity and surface area of the final construct.(42, 44)

Impregnation of drugs in polymeric matrices using supercritical CO_2 is a well described and studied method, with many examples using ibuprofen as a model nonsteroidal anti-inflammatory drug (NSAID)(46, 47). On the other hand, the impregnation of therapeutic DES in polymers using $scCO_2$ is still an area under development, particularly due to the lack of solubility measurements on the binary systems THEDES + CO_2. In a preliminary work we have evaluated the possibility to incorporate a THEDES system composed of menthol:ibuprofen 3:1 in alginate sponges prepared by freeze drying. The dissociation/precipitation of THEDES in its components

was never observed throughout the work, which means that THEDES and CO_2 behave as a pseudo-binary mixture.

VLE experiments were carried out at two different pressures, at 10 MPa and 15 MPa, bellow and above the supercritical region of THEDES respectively. At 15 MPa, the mixture THEDES/CO_2 presents only one phase, meaning that a high amount of THEDES is available for impregnation, thus increasing diffusion driving force. In Figure 3 it is observed the release profile of ibuprofen from alginate sponges in a PBS solution for different impregnation times at 15 MPa. As expected impregnation time influences the maximum amount of THEDES impregnated in the alginate sponges. The maximum impregnation **amount** is achieved at 3h with a value of 148 $mg_{Ibuprofen}/g_{Alginate}$ for 15 MPa. Further studies will be necessary to carry out a thorough characterization of the systems. Nonetheless, we can envisage that the possibility of coupling these new therapeutic agents with a technology that presents significant advantages in comparison with traditional impregnation techniques may open in the near future new opportunities for the preparation of enhanced drug delivery systems.

Seeking of new delivery systems based on polymeric matrices loaded with DES is hence attracting widespread and technological interests. The invaluable potential and high flexibility of the systems render them a guarantee of success that will surely find its way for a strong appearance in biomaterials science for different applications depending on the DES properties.

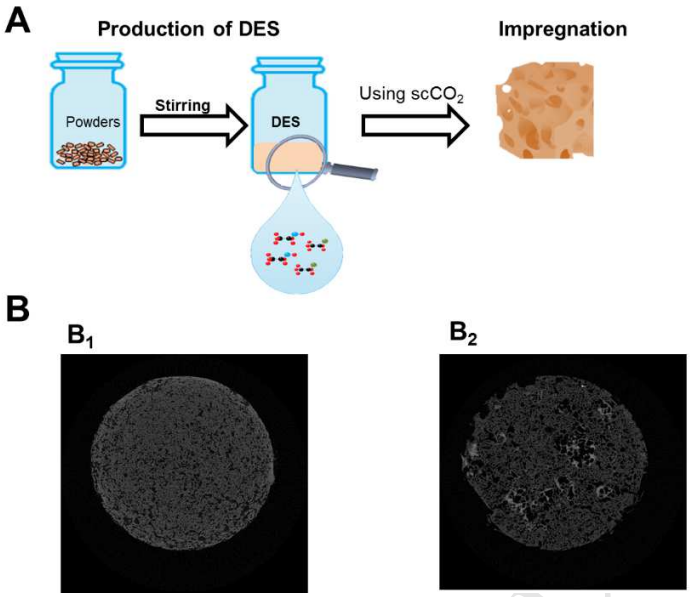


Figure 2. (A) Schematic representation of the preparation of DES and its respective impregnation in polymeric matrix. (B) Micro-computed tomography cross-section of SPCL (B1), SPCL + choline chloride:ascorbic acid: dexamethasone (B2).

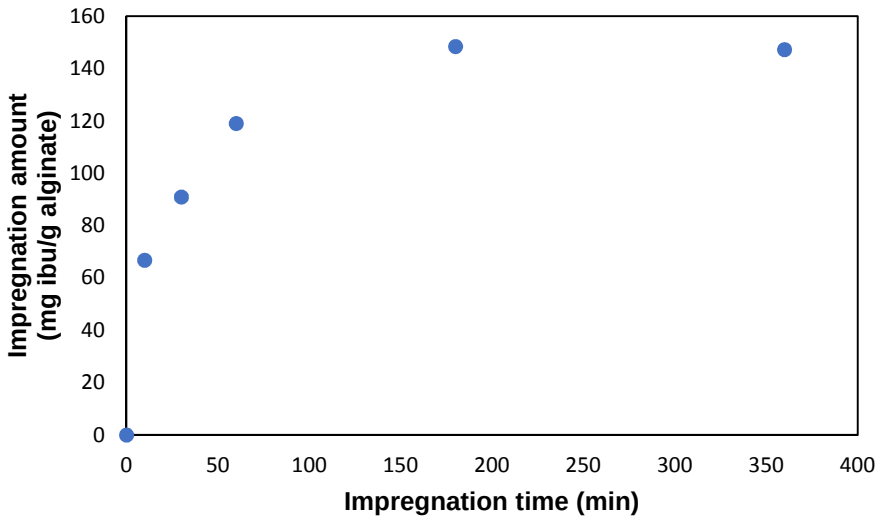


Figure 3. Impregnation **amount** of ibuprofen, from alginate hydrogels impregnated with THEDES at 15 MPa during different periods of time (10, 30, 60, 180 and 360 minutes). Values were obtained through release tests of the impregnated alginate sponges in PBS medium and ibuprofen concentration was obtained by measuring UV absorbance (at 265 nm) of aliquots taken at different time intervals.

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Papers of particular interest, published within the annual period of review, have been highlighted as: ◆ of special interest ◆◆of outstanding interest:

◆ – 1. This is a recent and complete review about supercritical carbon dioxide (scCO2) impregnation process and their applications.

◆◆ – 16. This is the first description of a drug-eluting degradable ureteral stent for cancer treatment combined supercritical carbon dioxide (scCO2) drying and impregnation process.

◆ – 29. This is an important article highlighting how antibacterial activity can be insert in scaffold by an integrated supercritical extraction and impregnation process.

◆ - 42. This paper is an updated review about deep eutectic solvents and their different applications.

◆◆ - 47. This paper brings insights on the design of new functional controlled release systems combining therapeutic deep eutectic solvents and supercritical technology.

◆◆ - 49. This paper reports for the first time the combination of deep eutectic solvents and supercritical technology.

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