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Review

Drug loading of polymer implants by supercritical CO_2 assisted impregnation: A review

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ABSTRACT

Drug loaded implants also called drug-eluting implants have proven their benefits over simple implants. Among the developed manufacturing processes, the supercritical CO_2 ($scCO_2$) assisted impregnation has attracted growing attention to load Active Pharmaceutical Ingredients into polymer implants since it enables to recover a final implant free of any solvent residue and to operate under mild temperature which is suitable for processing with thermosensitive drugs.

This paper is a review of the state-of-the-art and the application of the $scCO_2$ assisted impregnation process to prepare drug-eluting implants. It introduces the process and presents its advantages for biomedical applications. The influences of the characteristics of the implied binary systems and of the experimental conditions on the drug loading are described. Then, the various current applications of this process for manufacturing drug-eluting implants are reviewed. Finally, the new emerging variations of this process are described.

Contents

Abbreviations: BEM, 2-butoxyethyl methacrylate; CBC, N-carboxybutyl chitosan; EGDMA, ethyleneglycoldimethacrylate; EHA, ethylhexylacrylate; HEMA, 2-hydroxyethyl methacrylate; P(D,L)LA, poly(D,L) lactide; PCL, poly(ε-caprolactone); PDMS, polydimethylsiloxane; PET, poly(ethylene terephtalate); PEVA, poly(ethylene-co-vinyl acetate); PLGA, poly(lactic-co-glycolic acid); PLLA, poly-L-lactide; PMMA, poly(methyl methacrylate); POE, polyoxyethylene; PP, polypropylene; PU, polyurethane; PVP, polyvinylpyrrolidone; UHMW-PE, ultra-high molecular weight polyethylene.

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1. Introduction

After implantation of a medical device, the patient generally undergoes a pharmaceutical treatment to either reduce the postoperative discomfort, to inhibit bacterial infections or to improve the action of the implant on the surrounding tissues. The current trend is to deliver the Active Pharmaceutical Ingredient (API) locally in a controlled manner in order to enhance patient compliance and to avoid the drawbacks of oral and injection administration routes. Indeed, the limitation of oral administration is the poor drug bioavailability whereas the drug administered via either oral or injection treatment reaches the systemic circulation so it can induce side effects on untargeted organs.

An interesting alternative to traditional API uptake can be to incorporate the drug to the implant, thus transforming it into a drug-eluting implant able to deliver the drug in its vicinity [1–4].

Several manufacturing processes have been developed to produce drug-eluting polymer implants and to control the release of the API, such as hot melt extrusion [5,6], solvent-casting, the creation of a coating containing the API on the surface of an already manufactured implant [7,8] or by soaking it into an API solution [9,10].

However, these traditional processes generally suffer either from high processing temperatures that can deteriorate thermosensitive APIs or from the use of organic solvents that must then be removed through numerous purification steps to respect FDA's requirements.

To tackle these two recurrent drawbacks, the supercritical CO_2 ($scCO_2$) assisted impregnation process has been developed and has attracted growing interest [11]. This process allows loading an API into an already manufactured implant. CO_2 in its supercritical state (above 31 °C and 73.8 bar) possesses a good solubility in numerous polymers so it can temporally swell them. $ScCO_2$ can also solubilize many APIs and carry them into the polymer matrices. Moreover, $scCO_2$ is inexpensive, environment friendly, it has low critical coordinates which allows to process with thermosensitive APIs and it enables to recover a final impregnated implant free of any solvent residue just by depressurization after impregnation.

The $scCO_2$ assisted impregnation has been applied in various fields [12]. Bach et al. and more recently Banchero reviewed the studies applying the $scCO_2$ impregnation process to the dyeing of synthetic and natural textiles [13,14]. The reviews mainly focus on the dyeing of PET and give an interesting overview of the phenomena occurring during this process. However, the $scCO_2$ dyeing process differs from the $scCO_2$ assisted impregnation of API in the experimental conditions and in the kind of impregnated materials. The typical investigated temperature and pressure ranges are 35–55 °C and 90–200 bar respectively in biomedical applications whereas textile dyeing is carried out between 60 and 150 °C and up to 350 bar.

The present paper is a review of the state-of-the-art and the application of the $scCO_2$ assisted impregnation process to prepare drug-eluting implants.

First, the properties of $scCO_2$ are introduced as well as the principles of the process and its advantages for the preparation of drug-eluting implants. Then, the influences of the characteristics of the implied binary systems and of the experimental conditions on the drug loading are described. Then, the current applications of this process and the major results in the biomedical field are reviewed. Finally, the emerging variations of this process are presented.

2. Supercritical carbon dioxide assisted impregnation process

Nowadays, the development of sustained chemical processes has become a priority for the chemical industry because of environmental concerns and of stricter legislation. In this context and since several decades, supercritical carbon dioxide ($scCO_2$) has appeared to be a good candidate to replace conventional organic solvents due to several criteria. For example, it is inexpensive, non-flammable, nontoxic, relatively chemically inert and available in a large quantity and high purity.

$scCO_2$ is particularly attractive in the synthesis and processing of polymer systems dedicated to tissue engineering and drug delivery [15,16]. It has also been largely used in the food and beverage industry to extract aromas or oils from natural products, for the decaffeination of green coffee beans or to remove contaminants [17,18]. Currently, many plants are using $scCO_2$ in the food industry. The $scCO_2$ assisted impregnation process is currently commercially used to impregnate fungicide in wood [19] and to dye textiles [20].

One of the major advantages is the possibility to recover a final product dry and free of any solvent residue since CO_2 can be easily removed by depressurization. This property is interesting from an economical point of view since it avoids the many purification steps that are usually performed after processing with toxic organic solvents. Moreover, the recovered CO_2 can be easily separated from other compounds such as Active Pharmaceutical Ingredients (APIs) and/or co-solvent and recycled.

Finally, both the diffusivity and the density of $scCO_2$ can be tuned by pressure and temperature control thus making $scCO_2$ a versatile medium.

2.1. Supercritical carbon dioxide

2.1.1. Generalities and phase diagram

The different phases of carbon dioxide can be represented in a pressure–temperature phase diagram in two dimensions (Fig. 1). Depending on the external conditions, CO_2 exists under solid, liquid or gaseous phase. Change of state can occur by varying pressure and temperature and the phase transition are represented by the phase boundary on the phase diagram.

If one follows the liquid–gas phase boundary with increasing pressure and temperature, the density of the liquid phase decreases and the density of the vapor increases. When the two densities become equal, the liquid and vapor phases merge into one phase. This phenomenon appears at a point named "critical point" defined by a critical temperature (T_c) and critical pressure (P_c).

The critical point of CO_2 is defined by a critical temperature T_c of 31.1 °C and a critical pressure P_c of 73.8 bar. Above the critical point, CO_2 is considered to be in its supercritical state. Compared to other pure compounds, the critical point of CO_2 is low and easily reachable. For example, the critical point of water is $T_c = 374.2$ °C and $P_c = 220.5$ bar.

2.1.2. Properties of supercritical carbon dioxide

The physico-chemical properties of supercritical CO_2 (density, diffusivity, viscosity) are intermediate between those of the gas and those of the liquid. Indeed, above the critical point, there is a continuity of the

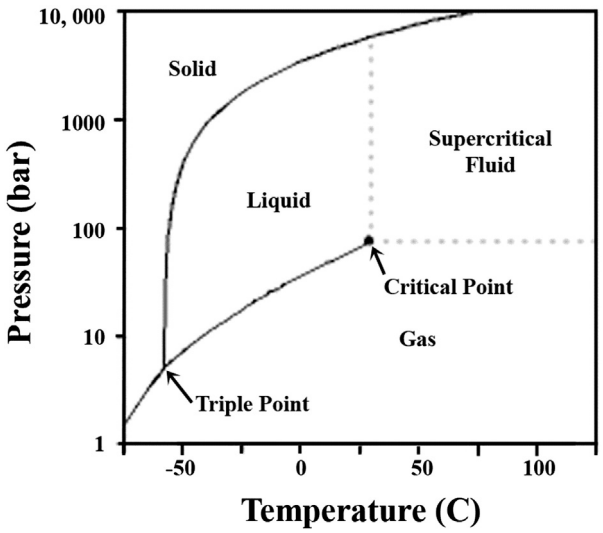

Fig. 1. Phase diagram of carbon dioxide.