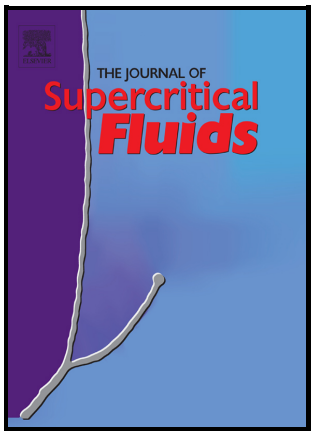

Supercritical CO_2-assisted Impregnation/Deposition of Polymeric Materials With Pharmaceutical, Nutraceutical, and Biomedical Applications: A Review (2015-2021)

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Supercritical CO_2-assisted impregnation/deposition of polymeric materials with pharmaceutical, nutraceutical, and biomedical applications: A review (2015-2021)

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ABSTRACT

The loading of polymeric carriers with active pharmaceutical and nutraceutical ingredients using supercritical CO_2 ($scCO_2$) as solvent and diffusion enhancer has received increasing attention as an alternative for the development of active materials and delivery systems. In this contribution, recent advances in $scCO_2$ impregnation/deposition in the pharmaceutical, biomedical, and nutraceutical fields are reviewed, covering the period 2015-2021. The main physicochemical phenomena underlying the impregnation/deposition process (phase equilibrium, diffusion, plasticization, sorption, adsorption, etc.) are briefly presented and discussed. Applications are reviewed including drug and botanical drug products, medical devices, and dietary supplements. The effects of different process variables on the impregnation efficiency and some relevant properties of the obtained materials are also critically discussed and compared.

Keywords:

Supercritical carbon dioxide, impregnation/deposition, drug delivery, medical devices, dietary supplements

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1. Introduction

Impregnation can be defined as the infusion of a substance into the bulk of a polymeric material, in order to modify some properties of the polymer or impart different types of activity. The incorporation of additives or active ingredients can be physical or chemical; in the first case, solute molecules are dispersed and not chemically bonded to the polymer structure, and therefore remain free to move and can be released at the polymer surface (by evaporation, or dissolution in a liquid environment), while the second case implies immobilization of solutes via covalent bonding with specific functional groups in the polymeric structure.

Conventionally, impregnation is performed by contacting the polymer with the solute in liquid or gas state, or more frequently with a solution of this solute in a suitable solvent. The main limitations of these processes are the usually long periods required to achieve a significant impregnation yield (unless only superficial impregnation is required), due to the very low diffusivity in most polymers, and/or the requirement of a subsequent drying step to remove the liquid solvent from the impregnated material. Diffusion rate can be enhanced by operating at higher temperatures, particularly above the glass transition temperature of the polymer, but this is not always practical or possible when thermosensitive drugs or natural compounds are used. High temperatures can also modify some properties of the polymer. On the other hand, the removal of liquid solvents is a more difficult problem to solve, because it usually involves high temperatures and/or significant energy consumption, with the subsequent economic and environmental impact. Besides, in the case of food and pharmaceutical products, regulations impose strict limits to the presence of solvent residues.

In this context, supercritical carbon dioxide ($scCO_2$)-assisted impregnation appears as an interesting and promising alternative to conventional impregnation for the preparation of active

polymeric materials. In this technology, the liquid solvent is replaced by $scCO_2$, which plays several simultaneous roles: it dissolves the solutes of interest, transfers them to the polymer surface, acts as a diffusion enhancer by temporarily modifying some polymer properties, and finally induces solute precipitation by depressurization, as explained in detail in Section 2. CO_2 is a gas at ambient conditions; therefore, it desorbs from the polymer and evaporates by simple depressurization, leaving a solvent-free product. The many interesting physicochemical properties of $scCO_2$, which are the basis for a broad range of supercritical technologies, have been extensively discussed. The most relevant properties are its "tunable" density and solvent power, which can be adjusted by temperature and/or pressure changes; gas-type diffusivity and viscosity; a very low surface tension; and a low critical temperature (31°C), which allows operation at relatively mild conditions. Moreover, $scCO_2$ is an inexpensive, nontoxic, and nonflammable solvent, which allows a safer operation. It is relatively inert, although it can react with some substances, like amines. It can be easily regenerated and recycled, minimizing emissions. Due to all these properties, $scCO_2$ is considered a "green" and multipurpose solvent. Nevertheless, $scCO_2$-assisted impregnation faces some limitations. One of them is the low solubility of many drugs of interest in $scCO_2$, even at high pressure conditions. Besides, the absorption of $scCO_2$ and its subsequent desorption can drastically modify some properties of the polymer, for example by inducing foaming, particle aggregation, changes in crystallinity, etc. From the economic point of view, large investments in high pressure equipment may be required.

It has to be noted that, along with impregnation, superficial loading of solutes frequently occurs during the high-pressure treatment and subsequent depressurization. In fact, solutes can be physically adsorbed or simply precipitate or crystallize on the polymer surface or in the bulk of porous materials. This is a different loading mechanism from impregnation, leading to heterogeneous products. Considering that in many cases both mechanisms contribute to the total loading, but not always the difference is clear from the data reported, in this review, we will frequently refer to this technology as "$scCO_2$-assisted impregnation/deposition".

Since early works, such as Berens et al. [1], proposed the use of $scCO_2$ as a coadjuvant for the enhanced incorporation of small penetrants in polymers, based on its plasticizing effect, this technology has experienced great development. Besides increasingly intensive research activity, some applications have been successfully applied at industrial scale, such as wood impregnation with antimould agents [2] or the water-free dyeing of textile fibers [3].

Figure 1 shows the number of publications with the keywords "supercritical" + "impregnation" in the title, abstract, and/or keywords that have appeared since 1992, after a search in Scopus, divided into periods of 5 years. Although this search criterion obviously may not account for some papers dealing with supercritical encapsulation, adsorption, dyeing, or other loading

techniques that can be broadly included in the category of impregnation, the observed trend gives a good idea of the growing activity in this field.

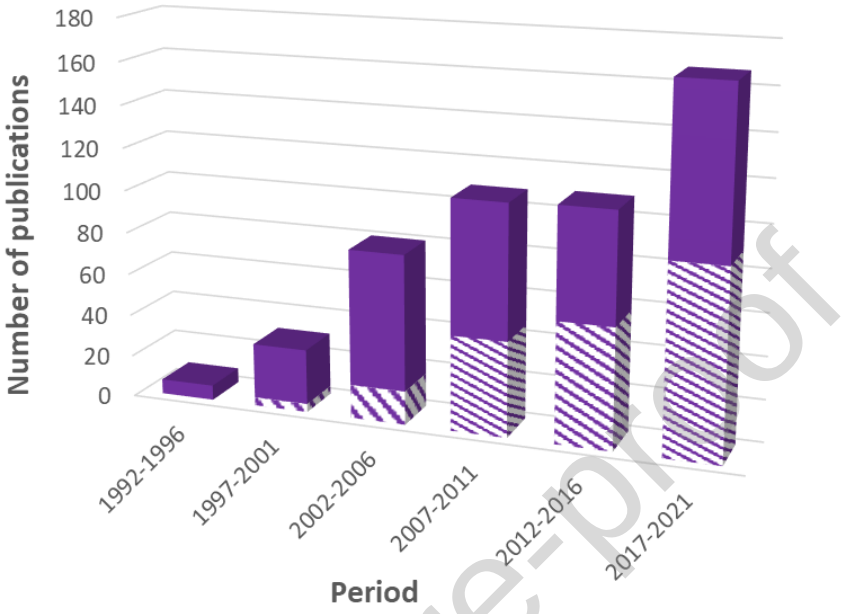

Fig. 1. Number of publications related to supercritical impregnation reported in the literature in the last decades (1992–2021). Stripped patterns represent the percentage of publications in the area reviewed here (pharmaceutical, nutraceutical, and biomedical applications).

Several authors have reviewed the advances and opportunities in $scCO_2$-assisted impregnation/deposition, some of them as a part of very comprehensive reviews on supercritical processing of polymers [4–6], or focused particularly on impregnation [7,8]. Some reviews on $scCO_2$-assisted impregnation applied to specific fields, such as wood protection [9], biomedical and tissue engineering [10], implants [11], textile dyeing [12], and food packaging [13], among others, have also been published in past years.

This review presents a survey of the advances in the field of $scCO_2$-assisted impregnation/deposition of bioactive compounds in polymeric materials in the 2015-2021 period. Two main research areas are covered in Section 3: drug delivery systems for pharmaceutical and biomedical applications, and nutraceuticals and food additive formulations. In each case, specific aspects of interest are discussed, related to the effect of different process variables on the loading performance, the properties and/or activity of the modified carrier materials, as well as the main trends and future challenges. Previously, the fundamentals and

physicochemical principles involved in $scCO_2$-assisted impregnation/deposition are presented and briefly discussed in Section 2.

2. Fundamentals and principles

2.1. The impregnation/deposition process

The $scCO_2$-assisted impregnation/deposition process can be described in terms of three main steps: (i) a first pressurization step, where the polymer is contacted with a solution of the active ingredient in $scCO_2$ and the temperature and pressure conditions are adjusted; (ii) a soaking or diffusion period, during which the system is kept at fixed conditions during a certain period; and (iii) a final depressurization step. The process can be conducted in batch or semi-batch mode. In the second case, a continuous flow of fluid mixture is fed to the impregnation chamber. Several physicochemical phenomena occur during the process, either sequentially or simultaneously, involving the polymer matrix, the supercritical solvent, and the solute to be incorporated. The loading yield at a given set of conditions, as well as other important properties of the impregnated polymeric material, ultimately depend on the interplay of these interactions, which are summarized in **Figure 2.**

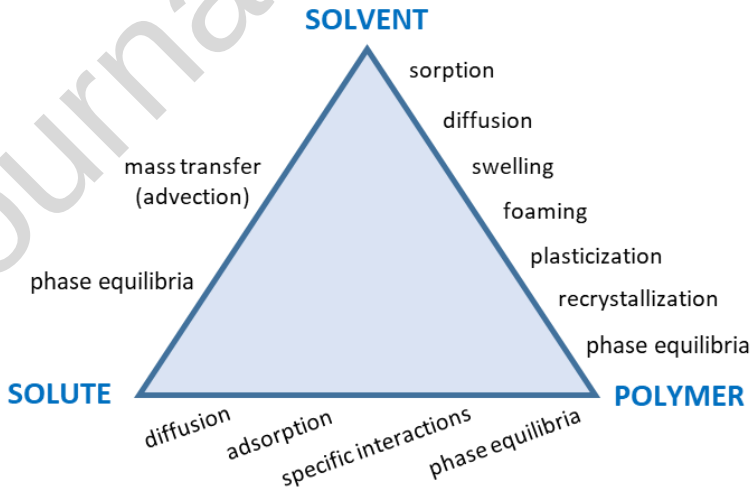

Fig. 2. Different interactions and related phenomena in the supercritical impregnation/deposition processing.

2.2. Solubility and phase equilibrium

As in every mass transfer process, the driving force for impregnation is the solute chemical potential difference between the supercritical fluid phase and the polymer phase. In practical terms, at a given temperature and pressure, impregnation will be faster if the fluid phase is more concentrated. The concentration of a given solute in $scCO_2$ is limited by its thermodynamic solubility at given temperature and pressure conditions. Solubility in $scCO_2$ has been the subject of intensive research, because it is a key aspect underlying all supercritical technologies, and therefore it will not be discussed in detail here [14]. In general terms, it depends on temperature, pressure, and the chemical nature of the solute [15]. $scCO_2$ density (and consequently its solvent power) increases with pressure, at a constant temperature, which is reflected in a nearly exponential increase in solubility. The effect of temperature is more complicated: on the one hand, $scCO_2$ density and solvent power decrease with temperature (at constant pressure); on the other hand, the solutes' vapor pressure increases with temperature. These opposite effects often lead to "crossover" phenomena, where the temperature-dependence of solubility inverts at a certain pressure level [16]. Finally, the chemical nature of the solute and the possible specific interactions with $scCO_2$ determine how much solute can be dissolved. $scCO_2$ behaves as a non-polar to weakly polar solvent and therefore dissolves easily non-polar and lipophilic substances of low to mid-molecular size (for example, terpenes, hydrocarbons, etc.). Polar substances and high molecular size compounds (like triglycerides and many pharmaceutical drugs) are poorly soluble in $scCO_2$, requiring very high pressures to achieve practical solubility values [17,18]. As mentioned above, this is one of the main drawbacks of this technology. In these cases, solubility can be significantly increased by the addition of small amounts of polar cosolvents (like water or alcohols), which modify the polarity of the fluid phase and enhance solvation [19].

The knowledge of the solubility behavior of the substance to be impregnated in a polymeric matrix is fundamental for the design of an impregnation process or experiment, and the modeling of the mass transfer phenomena [20]. Impregnation can be conducted under conditions of saturation (of the fluid phase) or under-saturation. In the first case, saturation is ensured by loading an excess of solute in the impregnation chamber, by constantly dosing the solute, or by recirculating the fluid phase through a pre-saturator column or vessel. This "saturated fluid" approach is the most frequently applied in experimental studies. Although it ensures the highest impregnation rate and yield at a given temperature and pressure condition, it complicates the analysis of the separate effect of these variables. In fact, when temperature or pressure are modified, also is solubility, and the effect of the solute concentration in the fluid phase is superimposed to the effect of the other variables. In this sense, the "under-saturated fluid" approach allows decoupling the effect of concentration, which becomes an independent variable, and therefore seems more adequate for screening purposes [21]. In this case, the fluid phase concentration can be kept constant by adding small amounts of solute; otherwise, it will decrease along the impregnation process as more solute is being transferred to the polymer. If

the sample to be impregnated is small compared to the impregnation chamber volume, or if the impregnated amount is a small fraction of the initially loaded mass of solute, the change in concentration during the experiment may be neglected. This last assumption often simplifies the modeling of the mass transfer process.

The impregnation process involves a ternary system (polymer + solute + $scCO_2$), or a multicomponent system, if a cosolvent is added or the solute to be impregnated is actually a mixture (for example, a natural extract or essential oil). The system can be biphasic (single fluid phase + polymer) if the solute is completely dissolved in the $scCO_2$, or triphasic, if there is an excess of solute, forming a third (solid or liquid) phase. At most practical temperature and pressure conditions, the polymer can be considered insoluble in the fluid phase. Therefore, there is a partition equilibrium that ultimately determines how much solute can be incorporated into the polymeric matrix at a given condition. If the polymer has a porous structure, an adsorption equilibrium may also be present. Binary [solute + $scCO_2$] equilibria have been studied for a wide range of substances, and data on new systems of interest are constantly being reported in the literature [14,22,23]. Binary [polymer + $scCO_2$] equilibrium data have also been reported and modeled for numerous polymers [24–26]. In contrast, systematic ternary [solute + $scCO_2$ + polymer] phase equilibria have been much less studied in the context of supercritical impregnation [27–29]. Reports usually present maximum loading values at given conditions, but equilibrium data (e.g., in terms of partition coefficients) and phase equilibrium modeling are scarce, which opens an interesting and fruitful field for future research.

2.3. CO_2 sorption and polymer plasticization

As previously stated, $scCO_2$-assisted impregnation is based on the ability of many polymers to absorb significant amounts of CO_2 under high pressure conditions, which in turn facilitates the diffusion of the active compound into the polymer. In general, the equilibrium sorption value increases when CO_2 molecules can interact with specific functional groups present in the polymer structure, for example, via acid-base mechanisms [30,31]. Thus, for instance, sorption tends to be higher for polyesters and polyamides than for polyolefins. For a given polymer, CO_2 sorption usually increases with pressure and decreases with temperature, in close correlation with the fluid density. CO_2 sorption isotherms and/or single equilibrium values have been reported for a wide range of polymers, above and below their melting point [24,25].

There are several effects connected with the sorption phenomenon. The interaction of CO_2 molecules with polymer residues weakens chain-chain interactions, allowing a higher chain and segment mobility. In this sense, $scCO_2$ has been considered a sort of “molecular lubricant” [4]. This effect can be considered analogous to thermal plasticization, with the advantage of occurring at lower temperatures [32]. The distance between polymer chains is also increased by

CO_2 sorption, resulting in an expansion or swelling of the polymeric matrix. The increase in free volume contributes to the enhanced diffusivity of small penetrant molecules. In this sense, a preliminary analysis of the CO_2 sorption and swelling behavior of a specific polymer usually provides relevant information about the way it will respond to the active ingredient diffusion, and therefore about the expected rate of the impregnation process and the conditions at which it may be accelerated. In the last years, several authors have reported this kind of data in the context of supercritical impregnation, including polymeric fibers [33], particles [34], films [35], wound dressings [36], and intraocular lenses, among others.

In glassy polymers, the enhanced chain mobility induced by CO_2 sorption leads to a decrease in the glass transition temperature (T_g), which can fall below the operating temperature as pressure is increased. CO_2-induced T_g depression has been studied for numerous polymers, including a typification of different observed behaviors [37], and it was a major motivation for early impregnation studies. Under $scCO_2$ pressure, glassy polymers can be plasticized and impregnated at lower temperatures, due to the enhanced mass transfer properties achieved in this way. Interesting images captured inside a high pressure cell, showing the advance of the plasticized/glassy boundary as a polymer (polymethylmethacrylate, PMMA) is progressively plasticized by $scCO_2$, have been reported by Üzer et al. [38]. However, excessive plasticization can be counterproductive, as it may lead to unwanted particle collapse and/or aggregation, as has been reported for PVP microparticles, for instance [39].

In semicrystalline polymers, which are usually depicted in terms of crystalline domains embedded in a continuous (glassy or rubbery) amorphous phase, it is usual to consider that sorption and diffusion take place mainly in the amorphous parts [24]. For practical purposes, crystalline regions are assumed impermeable. However, two specific effects can be pointed out. Firstly, the crystalline domains impose mechanical restrictions on the polymer swelling, which is usually lower than in a purely amorphous material. Secondly, recrystallization processes can be induced by $scCO_2$ sorption. Under the plasticizing effect of CO_2, polymer chains can be rearranged to a more ordered state, in a similar way as occurs in thermal annealing processes [32], or become more disorganized. As a consequence, polymer crystallinity can be increased or decreased by these effects, or different types of crystals can be induced, sometimes with a significant impact on the polymer mechanical, diffusional, and thermal properties. The absorption of $scCO_2$ can also induce a melting temperature (T_m) depression in semicrystalline polymers with respect with its value at ambient pressure, along with viscosity and surface tension changes, allowing for the low-temperature production of melts and foams [40,41]. T_m depression is the basis of the mixing-foaming process, where the active ingredient is dissolved in the molten polymer under $scCO_2$ pressure, and then a foam is obtained by depressurization. Depending on the envisaged application, $scCO_2$-induced recrystallization or foaming

phenomena can be advantageously exploited or represent a drawback, negatively affecting the desired properties of the material.

In porous structures (such as foams, aerogels, etc.), adsorption phenomena are also important. A significant amount of supercritical mixture can be filling the pores and adsorbed to their surface, rather than being dissolved in the polymer. In these cases, the adsorption equilibrium will depend on the availability of active sites at the polymer surface, capable of interacting with CO_2 and the solutes, in addition to the pressure and temperature conditions.

CO_2 sorption behavior in biopolymers is particularly relevant because many of the carrier materials reviewed here are polysaccharide- and protein-based. CO_2 sorption, as well as the relative proportion of CO_2 dissolved and adsorbed, depends on several features, such as the specific surface area and porosity, crystallinity degree, morphology, swelling ability, and water content, in addition to temperature and pressure. Hoshino et al. [42] have reported adsorption isotherms (at 40°C) for different polysaccharides (corn and potato starch, dextrin and cellulose), showing a typical adsorption peak near the critical point and a subsequent sharp decrease at higher pressure, stabilizing at approx. 2 wt.% for starch and dextrin, and between 3 and 4 wt.% for cellulose, in the range of 10-30 MPa. Nakamura et al. [43] have reported similar data for different proteins, observing almost constant adsorption values of 2-5 wt.% in the range of 10-30 MPa at 40°C (decreasing in the order: casein > gluten > gelatin > ovoalbumin), while CO_2 adsorption in soybean protein increased with pressure from 2 to 8 wt.% within the same range. Although CO_2 sorption is rather low in all these materials, results show that proteins are capable of more specific interactions with CO_2 than polysaccharides. More recently, Muljana et al. [44] have reported sorption data of CO_2 in native and acetylated potato starch, showing the enhancing effect of this chemical modification, by providing carbonyl groups that can interact with carbon dioxide. Sorption data were reported as “solubility”, although it is not clear how much of this is due to adsorption. While sorption in native starch showed a maximum of approx. 3% at 8 MPa (and 50°C) and decreased with pressure (<1% at 12 MPa), for the acetylated starch sorption increased up to approx. 5% in the same range. The predicted swelling degree was in the range of 1.0-2.8% for native starch and up to 4% for the modified starch. All these values are rather low compared to other semicrystalline polymers, showing that CO_2 has a limited ability for interacting with these materials and/or modifying their structure. Therefore, it is expectable that the predominant loading mechanism in these cases will be the deposition or crystallization on the porous surface rather than the molecular dispersion in the bulk of the polymer matrix.

Although CO_2 sorption and polymer plasticization are dynamic processes, limited by the diffusion rate of CO_2 in the polymeric matrix, they usually take place at a much higher rate than the active ingredient diffusion, which can be considered to occur in an already plasticized medium [35]. Nevertheless, polymeric substrates can be preconditioned (swollen) with pure CO_2 for some time before impregnation, to ensure their homogeneity and optimize their

properties for solute diffusion. For example, starch can be pregelatinized before impregnation, either by conventional methods or using $scCO_2$ pressure [45], in order to disrupt the granules structure and reduce their crystallinity, making starch more accessible for CO_2 and solutes sorption. In other cases, the polymeric carrier is pre-swollen in liquid solvents; for example, water soaking as a preliminary step for the impregnation of contact lenses [46].

2.4. Diffusion and mass transfer kinetics

The active ingredient diffusion through the $scCO_2$-swollen and plasticized polymer usually determines the impregnation global rate. The fluid phase is usually stirred or recirculated, and the diffusivity of the active ingredient in $scCO_2$ may be several orders of magnitude higher than in polymers (typically 10^{-8}–10^{-9} m^2 s^{-1} [47–49] vs. 10^{-10}–10^{-14} m^2 s^{-1} [50,51], respectively); therefore, the mass transfer resistance on the fluid side is often negligible compared to that on the polymer side. In this sense, the concentration profiles of the active ingredient near the fluid-polymer interface can be schematically depicted as in **Figure 3**, being uniform on the fluid side and dependent on time and position on the polymer side. At the interface, the concentrations are assumed to be in equilibrium.

Diffusivity in $scCO_2$-swollen polymers can be several orders of magnitude higher than in the same polymers at ambient conditions. For example, it has been observed that the diffusivity of carvone in LDPE under $scCO_2$ pressure is in the range of $(0.6–8.5)\times10^{-10}$ m^2 s^{-1} (at 35–60°C and 7.5–9.7 MPa), while it is $\sim3\times10^{-14}$ m^2 s^{-1} for the same system at atmospheric pressure [52]. The knowledge of the diffusivity behavior for each particular system, as well as its dependence on temperature, pressure, and composition, is of great importance for the modeling, simulation, and design of impregnation processes, because it provides information about the expected rate at which impregnation will proceed, the impregnation degree achieved for a certain time interval, or, inversely, the time required for a given penetration level.

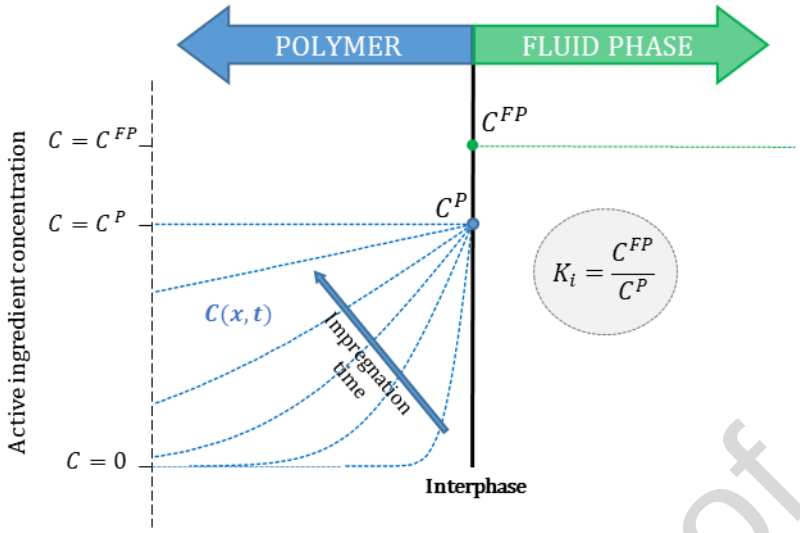

Fig. 3. Schematic diagram of the active compound penetration process: concentration profiles and equilibrium conditions in the polymer/fluid phase interphase. C^P: concentration in the polymer; C^{FP}: concentration in the fluid phase; K_i: partition coefficient.

Diffusion in glassy polymers often presents different types of "anomalous" behavior, related to the limited relaxation rate, which may be comparable to the penetrant diffusion rate [53]. However, if the polymer is completely plasticized due to CO_2 sorption (rubbery state), the polymer chains can rapidly respond to the diffusion of other molecules. In these cases, diffusion of active ingredients can be described by Fick's laws in terms of a single diffusion coefficient [51], generally dependent on temperature and concentration, but also on pressure, due to its influence on CO_2 sorption and polymer swelling. In many cases, CO_2 plasticization of glassy polymers can lead to semicrystalline states, by inducing a T_g depression below ambient temperatures. In semicrystalline polymers, mass transfer is assumed to occur only in the amorphous phase. According to the crystallinity degree, the diffusion of penetrant molecules will be more or less restricted by the crystalline domains embedded in the amorphous parts, following a tortuous path [54]. In these cases, diffusion is usually described in terms of Fick's laws using an "apparent" or "effective" diffusion coefficient which includes the tortuosity effects. The crystallinity degree of the polymer, as well as the distribution and size of the crystallites, may significantly affect the observed diffusivity.

Diffusion coefficients of active ingredients in $scCO_2$-swollen polymers are most often estimated from impregnation kinetics data, by correlating the total amount of active ingredient loaded into the polymer along time with a suitable solution of Fick's laws. Quantification can be performed *in situ*, using a microbalance or by spectroscopic analysis, or after depressurization, assuming that CO_2 desorption is much faster than solute desorption, and therefore the depressurization step does not significantly affect the equilibrium loading value. In this way, impregnation

kinetics has been studied for several systems within the reviewed period, including different morphologies, such as mango polyphenols in cotton fabrics [55], eugenol in PA fibers [35], thymol in cellulose acetate particles [56], and polyamide nanofibers [57], and mesoglycan in calcium alginate aerogel [58], among other examples. On the other hand, penetration methods are based on the correlation of concentration profiles inside the impregnated polymer (for a given time) with a suitable solution of Fick's laws. Although these methods allow the estimation of the diffusion coefficient from a single impregnation experiment, they are limited to samples of practical size and simple geometry, where concentration profiles can be determined without much difficulty. In the case of thin films, the "film roll" method is a simple and effective way of obtaining such profiles; for instance, it has been applied to synthetic dyes in PET [59] and carvone in LDPE films [52] under $scCO_2$ pressure. Nevertheless, diffusivity data of active ingredients of interest in $scCO_2$-swollen polymers are still scarce, which represents an open field for future research.

2.5. Depressurization

The final step in a $scCO_2$-assisted impregnation process involves the depressurization of the system, from the operating pressure down to atmospheric conditions, by the release of the fluid phase. As pressure decreases, so does the solubility of the active compounds, which precipitate or condense in the polymeric matrix bulk or surface. The compounds which remain dissolved in the fluid phase are partly extracted by the CO_2 flow and partly precipitate or condense inside the vessel. In this sense, the partition (or adsorption) equilibrium is modified by pressure reduction in favor of the polymer phase. At the same time, CO_2 is desorbed from the polymer, carrying away solute molecules. Morphological changes that occurred under CO_2 pressure (for example, polymer plasticization) may be totally or partially reversed. If the depressurization rate is low enough compared to the polymer relaxation rate, the swollen polymer tends to recover its original dimensions. However, if the plasticized polymer becomes glassy during this step, this process will be interrupted, and the polymer will remain totally or partially swollen [5,6]. Foaming can also occur due to the entrapment of CO_2 bubbles. The final amount of solute retained in the polymer after depressurization results from the complex interplay of all these processes, which are simultaneous but occur at different rates.

Depressurization is generally recognized as an important parameter, due to its effects on impregnation yield as well as on polymer morphology. Therefore, the conditions (namely, rate and temperature) under which it is performed should be investigated and optimized for each particular system. The impregnation chamber can be depressurized at a constant pressure rate or a constant flow rate, which involves some control of the expansion valve opening to compensate for the density variation as pressure decreases. In the reviewed literature, the constant pressure

rate approach was mostly applied, as it is easier to measure and control. However, some authors report depressurization at constant mass flow rate [60,61]. Temperature can be kept constant at the same impregnation value during depressurization, set to a different (higher or lower) specific value, or allowed to decrease naturally with CO_2 expansion (by Joule-Thomson effect). Cooling the impregnation system before decompression may induce precipitation or insolubilization of compounds, with a subsequent release of CO_2 almost free of solutes. This strategy intends to enhance the precipitation of solutes inside the polymeric matrix, but care has to be taken regarding the possible formation of a liquid-CO_2 phase enriched in solute compounds [62], or polymer damage due to excessive brittleness. Finally, depressurization rate can also affect the amount of loaded solute. A fast depressurization usually induces excessive solute losses, especially if the drug-polymer affinity is low. In this sense, most of the reviewed works have selected low decompression rates (of the order of 0.1-1.0 MPa min^{-1}).

3. Recent applications

3.1. Overview

Within the reviewed period (2015-2021), the supercritical impregnation/deposition of poorly water-soluble drugs and/or natural compounds into polymeric materials has been studied with the major purpose of analyzing the effect of process variables on the drug loading and the physico-chemical properties of the obtained products or devices, including in many cases morphological aspects and drug release behavior. The utilization of polymeric carriers to protect and release the impregnated drugs or active principles in a controlled manner has been explored as an alternative solution in two wide areas: on one hand, in the pharmaceutical field for the treatment or prevention of diseases, and on the other hand, in the conservation and/or the improvement of the nutritional quality of food products.

According to FDA, a human drug is defined as *"a substance recognized by an official pharmacopoeia or formulary intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. A substance (other than food) intended to affect the structure or any function of the body, intended for use as a component of a medicine but not a device or a component, part or accessory of a device"* [63]. In the reviewed literature, non-steroidal anti-inflammatory compounds are the most frequently studied drugs for $scCO_2$-assisted impregnation/deposition, including ibuprofen [64–68], ketoprofen [60,69–72], diclofenac [70,73], acetylsalicylic acid [69,74,75], flurbiprofen [76,77], and indomethacin [78], either as model drugs or for specific applications. In general, these drugs are poorly water-soluble molecules and may have unwanted side effects via oral delivery. Other anti-inflammatory drugs

have been explored to a lesser extent, belonging to glucocorticoids [61,79–81] and cyclooxygenase-2 (COX-2) selective families [70]. A few reports have proposed the impregnation of other drugs for attending specific pathologies, such as high blood pressure [82–84], symptoms of bacterial infections [79,80], excessive excretion of stomach acid [85,86], cancer [87–89], epilepsy and its symptoms [90], vascular disorders [58,67], and skin affections [91,92]. Finally, some articles reported the use of compounds with claimed medicinal or bioactive properties that are not registered in the US Pharmacopeia nor approved by FDA.

As a general trend, the impregnation of polymeric carriers with natural bioactive compounds obtained from plants has received increased attention in recent years. According to FDA, a botanical drug consists of "*vegetable materials, which may include plant materials, algae, microscopies fungi, or combinations thereof that is used as a drug"* [93,94]. Although their therapeutic use in pharmaceutical formulations has not yet been approved by the FDA, numerous publications propose using essential oil components or plant extracts for treating or preventing diseases. Essential oils are volatile extracts composed of secondary metabolites (mostly terpenes) biosynthesized by aromatic plants. Some of these oils present bioactive properties *in vitro* which may be of medicinal interest, such as antioxidant, anti-inflammatory, and biocidal activity. The $scCO_2$-assisted impregnation of essential oils or isolated compounds in polymeric carriers has been studied by several authors in the reviewed period, based on the high solubility of terpenes in $scCO_2$. For example, thymol is a natural phenol found in essential oils of thyme and oregano [95] with reported antibacterial, antifungal, antiseptic, anesthetic, and anti-inflammatory activities. The impregnation of this phenol has been studied in different polymers [56,96–100]. Carvacrol (a structural isomer of thymol) [82,101,102] and carvone [69] are also essential oil components that have been proposed as active compounds for impregnation. The reviewed literature also includes the impregnation of other multicomponent plant extracts, such as mango leaves extract (rich in gallic acid, iriflophenone derivatives, and mangiferin) [103–106], *Clinacanthus nutants* Lindau extract (rich in phytol) [107,108], and *Helichrysum italicum* extract (rich in pyrogallol, chlorogenic and gentisic acids) [109,110], among others, in different polymers.

The $scCO_2$-assisted impregnation/deposition of vitamins has also received attention. Fat-soluble vitamins E (α-tocopherol) and A (β-carotene) have been used as active pharmaceutical ingredients in the production of drug delivery systems [98,111–113], while vitamins D (cholecalciferol) and K (menadione) were intended for dietary supplement ingredients [111,114,115]. FDA defines a dietary supplement ingredient as "*a vitamin, mineral, herb or other botanical, amino acids, dietary substance for use by humans to supplement the diet by increasing the dietary intake. Unlike drugs, supplements are not intended to treat, diagnose, prevent, or cure diseases*" [116]. Some articles using natural extracts that are registered by US Pharmacopeia (Dietary Supplements section), such as chia [117] and fish oils [118], among

others [119,120], have been also reported in the literature, as well as others employing compounds not registered for this purpose [36,109,121–125].

In this review, the analyzed papers have been organized according to their specific applications in the pharmaceutical field (drug and botanical drug products, medical devices, and combination products) and as dietary supplement products, following the FDA classification.

3.2. Drug and botanical drug products

FDA defines a drug product as "*the finished dosage form (the physical form in which a drug is produced and dispensed) that contains a drug substance, generally, but not necessarily, in association with other active or inactive ingredients"* [126]. As inactive ingredients, carrier materials based on cellulose and other polysaccharides, natural proteins, PLA, and other polymers, have been employed as matrices for $scCO_2$-assisted impregnation/deposition, their main purpose being to provide support and to control the release rate of the impregnated drug.

3.2.1. Cellulosic-based drug products

Microcrystalline cellulose (MCC) is widely used in drug products as a binder and/or diluent in oral tablets and capsule formulations, as well as lubricant and disintegrant, being listed in the FDA Inactive Ingredients Database [127]. In contrast with its extensive use in the pharmaceutical industry, the supercritical impregnation of this polymer has hardly been explored in the reviewed period, due to its high crystallinity and the strong intra- and inter-molecular H-bonds that restrict chain mobility and limit the penetration of hydrophobic compounds [128,129]. The reviewed papers, along with the employed materials, process conditions, and loading results, are summarized in **Table 1.**

For example, MCC obtained from wheat straw was employed for the $scCO_2$-assisted impregnation/deposition of ibuprofen [130]. The authors evaluated the effect of impregnation temperature, pressure, and time on drug loadings. Increasing pressure in the range of 10–25 MPa and contact time from 2 to 24 h favored ibuprofen loading into MCC, while temperature changes (40–60°C) had a negligible influence. The highest impregnation yield (9.43%) was achieved at 25 MPa and 40°C, corresponding to the highest drug solubility in the supercritical fluid phase (13.98 mg/mL) and the highest CO_2 density, and after 24 h of contact. In this article, the applied pharmaceutical forms (powder and tablets) were considered to evaluate the effect of the carrier form on the *in vitro* drug release profiles. From the powdered forms, ibuprofen was rapidly released (80% after 5 min) at pH 6.8 and 37°C, indicating that the loading mechanism is a combination of superficial impregnation and deposition. In contrast, the drug release was

considerably retarded (80% after 400 min) from the tablets prepared with the impregnated cellulose. The application of this oral delivery system would be suitable for low-dose active substances.

The change in cellulose morphology from compact particles to aerogels is an interesting strategy for enhancing its drug loading capacity by increasing its porosity and surface area. In this way, Lopes et al. studied the $scCO_2$-assisted impregnation/deposition of phytol (a major bioactive compound from *Clinacanthus nutans* Lindau extract) in cellulose aerogels at 10 MPa and 40°C for 24 h [108]. Cellulose aerogels were prepared using different alkylmethylimidazolium-based ionic liquid solutions and dried with $scCO_2$. The achieved drug loadings were up to 50 wt%, even higher than for other aerogels (silica and alginate), explained in terms of the higher surface area (2-fold) and pore volume (3-fold) of the cellulose aerogel obtained from ionic liquids solutions [107]. This suggests a prevalence of superficial deposition on the loading mechanism. In fact, no swelling or morphological changes were observed in the cellulose fibrils after the supercritical treatment.

Cellulose acetate (CA) is the cellulose-derived material mostly employed in supercritical impregnation. The presence of the acetyl moieties increases the interaction with CO_2 via carbonyl groups and therefore enhances its swelling ability and impregnability. This polymer has been used in the form of films, beads, and membranes. For instance, CA films were employed for the supercritical impregnation of thymol [99] and carvacrol [101], two natural compounds with antibacterial activity. These compounds are prone to degradation and rapid evaporation, hence the authors proposed impregnation as a suitable technique to prolong their activity. Similar loading results (~30 wt%) were achieved for both bioactive compounds, operating at 15.5 MPa and 35°C for thymol, and 21 MPa and 50°C for carvacrol, with a contact time of 2 h, followed by decompression at 1.4 MPa min^{-1}. The similar loading of both compounds is probably the result of their comparable chemical structure (structural isomers), resulting in similar $scCO_2$ solubilities and equivalent interactions with the polymer via hydrogen bonding between hydroxyl and carbonyl groups. It is important to mention that the high loading induced a strong plasticizing effect on CA films, decreasing the T_g value from 221°C to approximately 30°C and 35°C for thymol and carvacrol, respectively. Adamovic et al. observed an increase in carvacrol loading with contact time (from 0.5 to 2 h), suggesting a diffusion-controlled bulk impregnation as the main loading mechanism. A negative effect of depressurization rate (from 0.3 to 36 MPa min^{-1}) was also reported [101]. The release behavior of the impregnated compounds from the films was also similar. Almost 85% and 90% of carvacrol and thymol were released, respectively, within 360 min in physiological saline solution at 37°C, by a mechanism governed by diffusion, supporting the hypothesis of bulk impregnation. Thymol-impregnated CA films showed antibacterial *in vitro* activity against

Pseudomona aeruginosa and *Staphylococcus aureus*, avoiding bacterial attachment and biofilm formation.

Milovanovic et al. have reported the synthesis of two formulations with strong antibacterial and antifungal activity based on the $scCO_2$-assisted impregnation of thymol into CA beads for topical application [56] and oral delivery [96], achieving loading values up to about 70 wt%. The authors report impregnation kinetics data at different pressure (10-20 MPa) and temperature (35-50°C) conditions, observing a faster impregnation at higher pressure (**Figure 4**). This behavior can be explained both in terms of the increase in thymol solubility and CO_2-induced polymer plasticization, and it is consistent with the hypothesis of a diffusion-controlled impregnation.

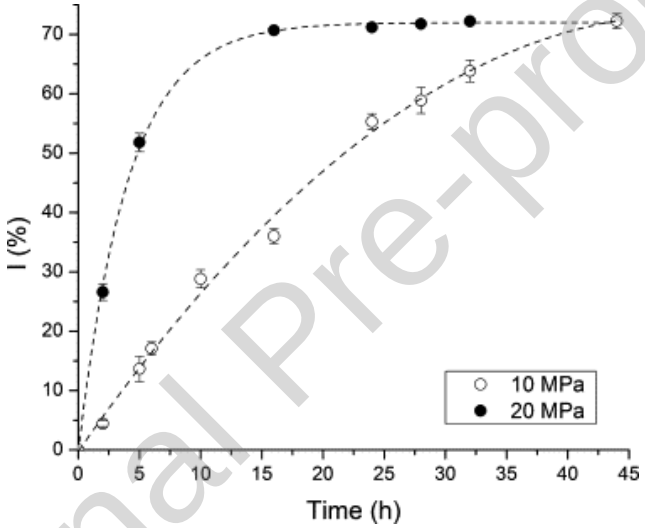

Fig. 4. Impregnation kinetics of thymol in CA beads, at *T*=35°C and *P*=10 and 20 MPa. Adapted from [56], with permission. Copyright, Elsevier.

An analysis of the microstructure of the polymer revealed a progressive modification of the particle morphology with the thymol loading (or the impregnation time), with an increasingly smoother surface and a loss of internal porosity. Experiments performed with pure $scCO_2$ suggest that these changes are induced by the plasticizing effect of thymol. Additionally, the release rate of thymol from the impregnated beads depended on the drug loading and the pH of the release medium. Overall, higher loading led to a somewhat more prolonged release in distilled water (60% vs 70% released in 2 days from the high-loaded and low-loaded samples, respectively) [56,96], whereas at simulated gastric conditions thymol was completely released from the beads in 2 days, regardless of the initial drug loading. In the former case, the loss of internal porosity may lead to a more retarded release, while in the latter case it may be related to the higher solubility of thymol at acidic pH, since CA is stable and insoluble under these

conditions [96]. In this way, the authors claim that materials with various release rates can be obtained for different purposes, like prolonged or short treatments.

Finally, CA membranes have been also proposed as carrier materials for impregnation. Polymeric membranes represent an interesting alternative to other drug delivery systems, based on some important characteristics such as the pore size, pore interconnectivity, surface area, mechanical properties, and biodegradability. They are generally obtained using a phase inversion technique where the polymer-rich phase of a highly concentrated polymeric solution solidifies to create a polymeric matrix. The phase inversion can be carried out using an antisolvent, such as $scCO_2$. The advantage of using supercritical fluids for this procedure relies on the shorter production time (2–6 h), in contrast with conventional techniques that may require days [131,132]. In this way, Baldino et al. [133] have prepared CA membranes loaded with quercetin (as antifungal agent) for tissue engineering applications, by performing simultaneously the impregnation and the formation of the polymer porous structure. Quercetin-loaded membranes were prepared at 20 MPa and 45°C for 4 h, with a fixed concentration of drug (10 wt%) and different polymer concentrations. As shown in **Figure 5**, three different membrane morphologies were obtained depending on the polymer concentration: particle-like (**Fig. 5a**), finger-like (**Fig. 5b**), and cellular structure (**Fig. 5c**).

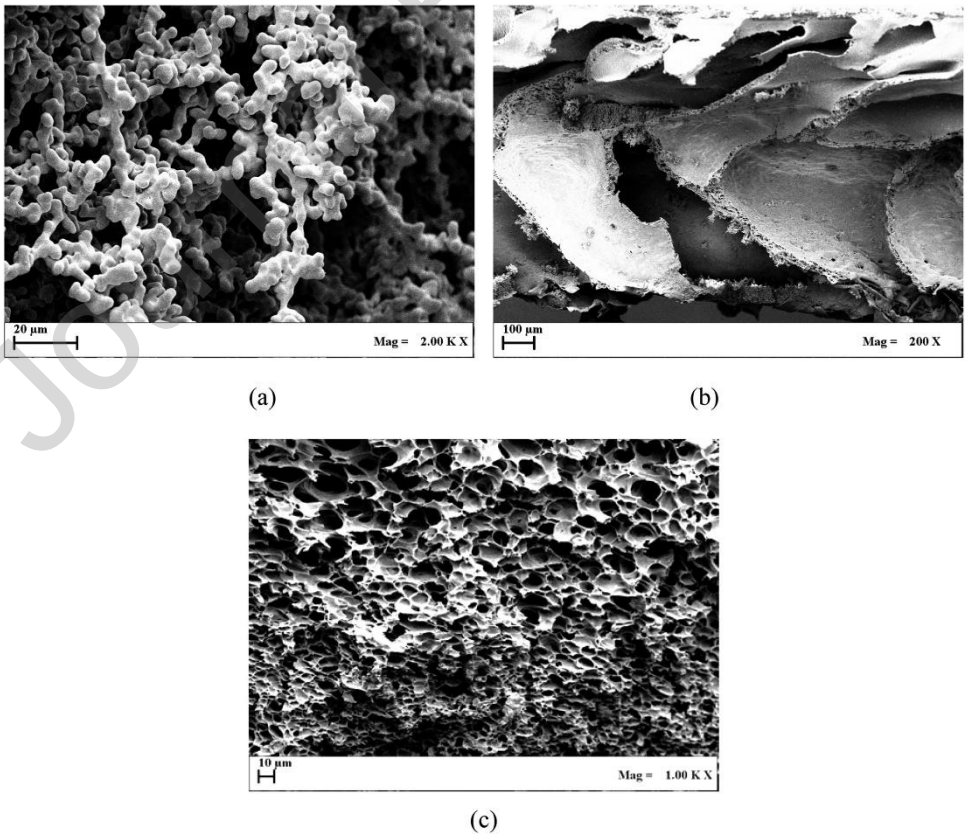

Fig. 5. SEM images of CA membranes loaded with quercetin at 20 MPa and 45°C: (a) 5 wt% CA, (b) 10 wt% CA, (c) 15 wt% CA. Adapted from [133], with permission. Copyright, Elsevier.

The most suitable membranes for the proposed application were those obtained with 15 wt% CA, with cellular structure and 6.05 μm of mean pore size. An important approach of this work is the evaluation of the quercetin release in simulated physiological conditions in relation with the membrane morphology. The complete drug release was faster (200 min) from membranes with finger-like morphology (with macrovoids), whereas a prolonged release was observed in the cellular structure membranes (1 day), due to the lower mass transfer resistance involved in the first structure. Results revealed that impregnation did not affect the drug fungistatic properties (against *Kluyveromyces lactis* and *Yarrowia lipolitica)*, with a reduction of survival percentage up to 20% in 10 h, the membrane morphology being irrelevant for the antifungal power. In this way, the supercritical phase inversion process appears as a versatile tool to prepare loaded polymeric membranes in short times with controlled and reproducible morphologies for particular biomedical applications.

In conclusion, although cellulose is widely applied in pharmaceutical formulations and has many attractive properties, its use in native form as carrier for the impregnation of drugs is quite limited due to its strong hydrophilic nature, high crystallinity, and resistance to CO_2-induced plasticization. Nevertheless, cellulose aerogels provide an interesting platform for CO_2-assisted drug deposition and/or adsorption, based on their high surface area and porosity, which notably increase the loading capacity. In turn, CA appears as an attractive material, with a better interaction with $scCO_2$, morphology versatility (porous and continuous structures), and higher plasticization ability. However, it can undergo significant morphological changes due to the supercritical treatment, an aspect that must be kept in mind when developing specific applications.

Table 1. Cellulosic-based drug products obtained by $scCO_2$-assisted impregnation/deposition.

Polymer-based matrix	Active ingredient, or mixture of active ingredients/extract	Morphology	Process conditions						Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent	wt% drug loading	
Microcrystalline cellulose	Ibuprofen	Particles	10–25	40–60	2–24	*n.i.*	-	9.43	[130]
HPMC	Carvedilol	Particles	30	100	2	1.5	-	*n.i.*	[134]
Cellulose	Phytol	Aerogels	10	40	24	0.2	-	50	[108]
Cellulose acetate	Carvacrol	Films	21	50	0.5–2	0.3–36	-	31.4	[101]
Cellulose aceate	Quercetin	Membranes	20	45	4	*n.i.*	-	5–15	[133]
Cellulose acetate	Thymol	Beads	10–20	35–50	2–32	0.3	-	4.4–72.2	[56]
Cellulose acetate	Thymol	Beads	10	35	2–32	*n.i.*	-	4.5–63.8	[96]
Cellulose acetate	Thymol	Films	15.5	35	2–32	1.4	-	26–30	[99]

3.2.2. Non-cellulosic polysaccharide-based drug products

In the reviewed period, some advances have been reported regarding the $scCO_2$-assisted impregnation/deposition of drugs in starch, alginates, pectin, β-glucans, and chitosan as carrier materials (**Table 2**). The biocompatibility, low toxicity, and relatively low cost of most of these natural polymers make them suitable and attractive for health and medical applications [135]. The most common approach has been their impregnation/deposition in the form of aerogels, for the same reasons mentioned above in relation with cellulose. The high surface area and porosity of polysaccharide aerogels allow higher loading degrees (mainly by adsorption and deposition) than their native forms.

Starch and alginate have been mainly studied for the preparation of drug-loaded aerogels by $scCO_2$-assisted impregnation/deposition. Starch is composed by two polymers: amylose and amylopectine, forming semicrystalline granules. The overall crystallinity degree depends on the relative proportion of both polymers [136]. Main starch sources are wheat, maize, cassava, and potato. Alginate is an anionic polysaccharide made from guluronic acid and mannuronic acid. Both materials are employed in the pharmaceutical industry as gelling and stabilizing agents, binders, and diluents. Aerogel particles based on maize starch (as hydrophilic carrier) and calcium alginate (as hydrophobic carrier) have been employed for the supercritical adsorption/deposition of anti-inflammatory drugs (ketoprofen, diclofenac sodium, and nimesulide) to formulate tablets for oral delivery [70]. The authors reported adsorption isotherms (at 18 MPa and 40-60°C) and adsorption kinetic data for each drug/polymer combination. In the first case, calcium alginate aerogels showed higher loading values than starch aerogels, which is explained in terms of the higher surface area and hydrophobicity of the former material. As for the adsorption kinetics, the analysis performed by the authors provides useful insight regarding the loading mechanism, concluding that in a first step adsorption is controlled by film diffusion and occurs rapidly at the outer particle surface, followed by a slower process governed by intraparticle diffusion. Finally, the release behavior in PBS (pH=7.4) was also different for each material, being faster for starch aerogel. The authors confirmed that the drug concentrations in the loaded polymers were suitable to perform a therapeutic effect. Besides, the different release mechanisms of each aerogel may be suitable for a particular therapy. For example, starch aerogels loaded with diclofenac sodium (63 wt% drug loading) may be applicable to toothache or headache conditions, since they promote a fast release (90% in 1.2 h). On the contrary, the same drug within calcium alginate aerogels (100 wt% drug loading) may be suitable for rheumatoid arthritis treatment since tablets with slow dissolution rates can be prepared (90% in 7 h).

The incorporation of natural compounds in alginate aerogels has also been explored. For example, in a comparative study, phytol (a hydrophobic compound) and a hydrophilic extract of

Clinacanthus nutans (rich in flavonoids, phenols, and chlorophyll) have been loaded in monolithic calcium alginate aerogels using two methods: $scCO_2$-assisted impregnation/deposition of dry aerogels, and "wet impregnation" [107]. In the latter process, the solute is incorporated in the last solvent exchange step (dissolved in the liquid solvent), and its impregnation/deposition occurs simultaneously with the $scCO_2$-drying. Interestingly, results showed that "dry impregnation" led to higher loading values than "wet impregnation", presumably due to the increased affinity of the solutes to the $scCO_2$ phase when ethanol is present. In addition, loading values in alginate aerogels (19-22 wt% for phytol) were comparable to those obtained in silica aerogel, despite the lower specific surface area of the biopolymeric material (126 vs 881 m^2 g^{-1}). This seems to be related to the higher ability of alginate to absorb CO_2 and become partially plasticized, inducing some degree of molecular dispersion besides simple deposition.

The topical application of alginate aerogels appears as an attractive strategy for wound healing, by providing a moist environment around the wound, removing exudates, and restricting the colonization of microorganisms [137]. The incorporation of a drug may provide additional therapeutic effects. In this context, drug-loaded alginate aerogels obtained by $scCO_2$-assisted impregnation/deposition have been developed for attending two different stages: inflammation [66] and re-epithelization [58]. These articles belong to the few ones where the therapeutic effects of the proposed drug products are confirmed via *in vivo* assays. In the first case, Johnson et al. have incorporated ibuprofen in alginate hydrogel scaffolds for accelerated burn wound healing by combining the pressurized gas expanded technology (PGX) and supercritical impregnation (or "adsorptive precipitation") as a viable method for the obtention of hydrophilic materials loaded with hydrophobic compounds [66]. This technology uses PGX in a single phase which contains $scCO_2$ and up to 80 wt% of ethanol. With this method, PGX–alginate scaffolds were obtained with a 320-fold increase in surface area compared to unprocessed alginate. Consequently, 9 wt% of ibuprofen was loaded by $scCO_2$-assisted impregnation/deposition (at 15 MPa and 50°C for 1 h), while the unprocessed material did not incorporate any amount of drug. Then, the hydrogel formation was performed after the addition of an appropriate $CaCO_3$ and glucono-δ-lactone concentration for improving its mechanical properties (crosslinking). Therefore, this hydrogel was stronger compared to the obtained with the unprocessed material because of the higher interconnectivity of its network. In addition, these hydrogels were easy to handle, and they properly retained their shape. The hydrophilic matrix was able to release ibuprofen rapidly, 70% within the first 10 h, which represents a dose of ~800 μg per disk. In this sense, the authors ensured that a single disk of hydrogel contained a high and safe ibuprofen concentration. On the other hand, *in vivo* wound healing using induced burn murine assay showed an accelerated healing process, achieving complete healing within 21 days [66].

Mesoglycan-loaded calcium alginate aerogels have been developed for accelerating wound healing in the re-epithelialization stage [58]. Mesoglycan is a mixture of glycosaminoglycans that induces the migration of keratinocytes and early differentiation [138]. In this work, the authors reported global solubility values of mesoglycan in $scCO_2$ at different temperatures (40 and 60°C), observing a crossover pressure at 15.6 MPa, with an increase in solubility with temperature at higher pressures. This helps explain the enhancing effect of temperature on drug loading observed at the tested pressure (18 MPa). Loading kinetic curves are also reported, which indicate that equilibrium is achieved after approx. 15 h of contact (at 18 MPa and both temperatures), as shown in **Figure 6(a)**. The analysis of the kinetic data indicated that the diffusion of the solute to the outer surface of the material (film diffusion) was the rate-limiting step of the impregnation/deposition process. SEM analysis of the loaded aerogel confirmed that the drug is mainly deposited onto the porous structure, as can be seen in **Figure 6(b).**

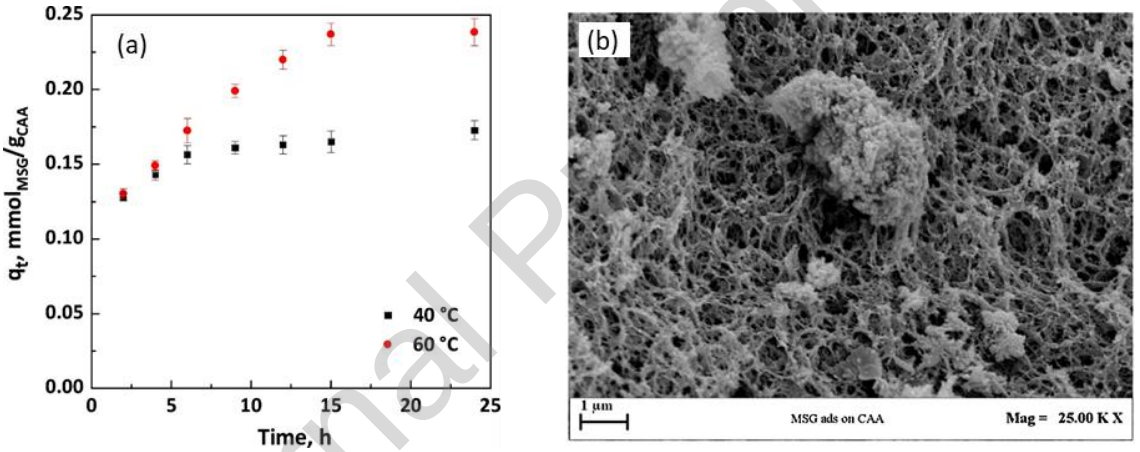

Fig. 6. (a) Kinetic curves for the $scCO_2$-assisted impregnation/deposition of mesoglycan on calcium alginate aerogel (at 18 MPa and 40-60°C). (b) SEM analysis of mesoglycan-loaded aerogel. Adapted from [58], with permission. Copyright, Elsevier.

The structural complexity of mesoglycan in comparison with ibuprofen [66] may explain the more severe impregnation conditions required, such as the prolonged contact time (1 h for ibuprofen vs 15–24 h for mesoglycan), possibly related to the slower diffusion of mesoglycan, which has a significantly higher size than ibuprofen, inside the polymer, although the diffusion coefficients were not measured. At these conditions, the maximum amount of mesoglycan loaded into the alginate aerogels was 0.24 mmol g^{-1} at 60°C without affecting the nanoporous structure of the aerogels. Regarding the mesoglycan release, it was fast and complete after 3 h in PBS at pH=7.4. This result is relevant because a direct and immediate action of mesoglycan is necessary for the re-epithelialization step. This effect was confirmed using *in vivo* experiments with cell lines involved in the skin wound healing process. An increase in human immortalized

keratinocytes (HaCaT) motility compared with non-treated cells in 24 h was observed. Thus, the authors demonstrated that this system is suitable for application in skin regeneration and wound protection [58].

Other polysaccharides barely explored are β-glucans, which are formed by D-glucose monomers linked by β-glucosidic bonds. They are obtained from cereals, algae, yeasts, or bacteria, showing different structures and characteristics. These polysaccharides have protective effects in oral delivery, either on the stomach (from ulcers formation derived from intake of some drugs), or on the bioactive compounds (from acidic gastric conditions) [139,140]. Barley and yeast β-glucan aerogels have been proposed as polymeric matrices for the $scCO_2$-assisted impregnation/deposition of acetylsalicylic acid, as novel biocompatible carriers for oral delivery [74]. In this work, the drug loading was carried out during the drying of the alcogels, which was performed using a [$scCO_2$ + drug] mixture instead of pure $scCO_2$. Drug loading was 8–15 wt%, depending on the operation conditions (8–20 MPa, at 35, 40, and 50°C) and the type of β-glucan aerogel (barley or yeast). Thus, drug loading on barley aerogels was only limited by the drug solubility in $scCO_2$, which increased with gas density. However, in the case of yeast aerogels, loading was limited by the diffusion of CO_2 into the polymeric matrix, which showed lower surface area, pore volume, and pore sizes compared to barley aerogels. Both aerogels showed a fast drug release in PBS solution at 37°C, although a different behavior was observed (**Figure 7**). Barley aerogel showed an initial lag time of 3 h, followed by a fast release step, whereas yeast aerogel showed a fast release rate in the first 2 h, and a subsequent slower and sustained release for 25 h. Based on these results, the proposed aerogels have promising properties for oral delivery, especially the barley aerogels which showed a lag time: in this way, drugs can be released in the intestinal tract avoiding the gastric medium. However, the behavior of these loaded aerogels in simulated gastrointestinal conditions should be studied for more specific conclusions.

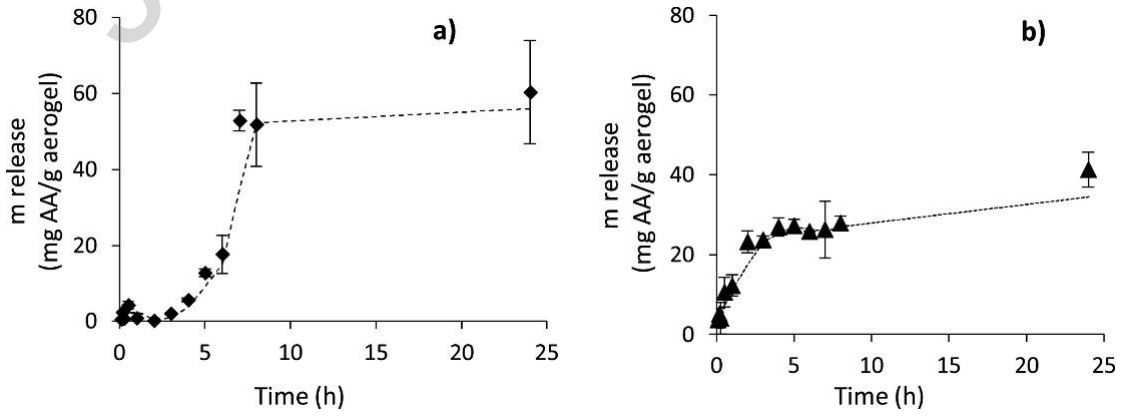

Fig. 7. Cumulative release of acetylsalicylic acid per mass of aerogel: (a) 4% barley, and (b) 2.5% yeast β-glucans. Adapted from [74], with permission. Copyright, Elsevier.

Finally, combinations of different polysaccharides have also been proposed as a strategy for developing drug-loaded materials with enhanced performance, compared to the individual components. For example, the anionic nature of alginate enables the formation of a polyelectrolyte complex with chitosan, a cationic amino polysaccharide. Chitosan is a biopolymer composed of varying amounts of glucosamine and *N*-acetyl-glucosamine residues. As a pharmaceutical excipient, this polymer can be used as coating agent, disintegrant, mucoadhesive tablet binder, among others [127]. In this way, the complexation of these two macromolecules by multiple and strong amine-carboxyl electrostatic interactions, as well as by hydrogen bond interactions, could result in a better performance of the final product [141]. Pires et al. have reported the simultaneous impregnation of thymol and β-carotene in chitosan/alginate films modified with poly(dimethyl siloxane) (PDMS) for the treatment of skin lesions [98]. These authors employed the strategy of improving the mechanical properties by incorporating synthetic polymers. The impregnation was performed with ethanol as cosolvent due to the limited solubility of β-carotene in CO_2. The vitamin was efficiently impregnated (42%) at 25 MPa and 45°C for 14 h, and loading was mainly affected by the depressurization rate since it was not detected in the material when the system was expanded at low rates (0.5 MPa min^{-1}). Nevertheless, thymol impregnation loading was considerably lower (0.28 wt%), being affected by the presence of β-carotene as well as ethanol. In addition, the difference in the impregnation loading of these bioactive compounds could be a consequence of the favorable hydrogen bond interaction between β-carotene and the polymer matrix, and the higher vapor pressure and $scCO_2$ solubility of thymol. In comparison with previously mentioned works [56,96,97,99], the incorporation of thymol into modified chitosan/alginate films was significantly lower, even though the supercritical process was performed at higher pressure, temperature, and contact time. Hence, the addition of a cosolvent to promote the β-carotene loading limited the impregnation of thymol. Pires et al. also evaluated conventional thymol and β-carotene impregnation in ethanol solution, for comparison purposes. Although the incorporation efficiency of thymol was similar in both methods, β-carotene loading was considerably higher when supercritical impregnation was used. Indeed, the incorporation efficiency of this vitamin using conventional impregnation was lower than 0.1% [98]. It should be noticed that there is a limited number of reports focusing on the development of materials with synergistic properties, such as the last one, which combined two compounds with complementary biological functions offering a more complete therapeutic effect, opening an interesting field for future research.

able 2. Non-cellulosic polysaccharide-based drug products obtained by $scCO_2$-assisted impregnation/deposition.

Polymer-based matrix	Active ingredient, or mixture of active ingredients/extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
Starch	α-tocopherol (vitamin E)	Aerogels	15	40 – 60	1 – 48	1	-	95 – 98	[142]
Starch	Thymol	Xerogels, aerogels	15.5	35	24	0.3	-	Xerogel: 1.8–4.0; aerogel: 0.6–3.3	[100]
Starch, calcium alginate	Diclofenac sodium	Aerogels	18	40–60	2–72	1	–	Starch: 63; calcium alginate: 100	[70]
Starch, calcium alginate	Ketoprofen	Aerogels	18	40–60	2–72	1	-	Starch: 13; calcium alginate: 29	[70]
Starch, calcium alginate	Nimesulide	Aerogels	18	40–60	2–72	1	-	Starch: 2; calcium alginate: 5	[70]
Starch/PCL	Ketoprofen	Scaffold/ Aerogels	15	40	11	*n.i.*	-	0.8	[60]
Calcium alginate	Mesoglycan	Aerogels	18	40–60	2–24	1	-	0.24 mmol/g aerogel	[58]
Sodium alginate	Ibuprofen	Hydrogels	15	50	1	*n.i.*	–	8.6	[66]
Sodium alginate	Phytol	Aerogels	20	40	-	0.2	-	20	[107]

Polymer-based matrix	Active ingredient, or mixture of active ingredients/extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
PDMS/ Chitosan/ alginate	Thymol	Films	25	45	14	0.5–1.0	1.3 v% ethanol	0.3	[98]
PDMS/Chitosan/ Alginate	β-carotene (vitamin A)	Films	25	45	14	5 – 10	1.3 v% ethanol	42	[98]
Silica/Sodium alginate	*Clinacanthus nutans* extract (rich in phytol)	Aerogels	15	40	24	2	10 wt% ethanol	13	[107]
Alginate, Chitosan, Pectin, Pectin/ Chitosan, Alginate/ Chitosan	Esomeprazole	Aerogels	11	35	24	0.3	–	Alginate: 10; Chitosan: 15.5; Pectin: 16.5; Pectin/chitosan: 2.5; Alginate/ chitosan: 9	[85]
PVA/ Chitosan	Ibuprofen	Membranes	25	40	20	*n.i.*	–	*n.i.*	[65]
High-methoxyl pectin	Nifedipine	Aerogels	20	60	24	*n.i.*	-	13	[83]
Barley, yeast β-glucans	Acetylsalicylic acid	Aerogels	8 – 20	35 – 50	1.5	*n.i.*	-	8 – 15	[74]
Barley, yeast β-glucans	Dexamethasone	Hydrogel/ Scaffo	8 – 20	37	1.5	*n.i.*	-	5 – 10	[81]

Polymer-based matrix	Active ingredient, or mixture of active ingredients/extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
		lds							

3.2.3. Protein-based drug products

Natural proteins are attractive carrier materials for $scCO_2$-assisted impregnation/deposition, not only for their abundance and biodegradability but also for the presence of a variety of functional groups able to interact with CO_2 and drugs, which may result in higher CO_2 sorption than other biopolymers (like starches) and in loading and release mechanisms based on specific interactions. However, in the reviewed period only a few works have been reported exploring the use of natural animal proteins (gelatin and silk fibroin) for the development of potential drug products, based on the approach of producing drug-loaded aerogels. Materials, process conditions, and achieved loading values are summarized in **Table 3.** As will be seen, this approach has received more attention in the case of dietary supplement products (Section 3.4).

Veres et al. designed new hybrid organic/inorganic aerogels composed of silica and modified gelatin for the impregnation of ibuprofen, ketoprofen, and triflusal [67]. Drug loadings in aerogel particles were 25–29 wt% for triflusal (at 12 MPa and 45°C for 6 h), 19–24 wt% for ibuprofen, and 11–15 wt% for ketoprofen (both at 20 MPa and 45°C for 6 h). Interestingly, XRD and DSC analysis indicated the absence of drug crystallization in the aerogel pores after the supercritical treatment, suggesting that the drugs were most likely dispersed or adsorbed in the polymer at a molecular level. The loading values obtained were related to the drug solubility in $scCO_2$: ketoprofen has the lowest solubility due to its higher molecular weight [18], while triflusal is the most soluble because of the presence of the hydrophobic trifluoromethyl group [143]. The drug release was immediate or semi-retarded, according to the specific interactions between the aerogel matrix (-OH and -NH groups) and the drug at the pH of the medium. Hence, the release of the studied drugs was faster in basic medium than at pH=2.0, where the active compounds are protonated and can interact strongly via hydrogen bonds with the hydroxylated matrix surface. An important factor to be analyzed is the drug susceptibility to degradation in aqueous medium that may affect its therapeutic effect. In this work, the aerogel matrix showed a protective effect against the hydrolysis of triflusal, with a low conversion (10 mol%). Thus, hybrid aerogels can modify not only the drug dissolution profile but also their stability, contributing to ensure the desired therapeutic effect.

Silk fibroin aerogels were combined with poly(ε-caprolactone) scaffolds and impregnated with dexamethasone (a synthetic anti-inflammatory glucocorticoid and an osteogenic differentiation agent) intended for bone tissue healing [61]. The porous structure of aerogels is interesting in this respect because it can simulate the extracellular microenvironment, facilitating cell distribution, integration with the host tissue, and capillary ingrowth [144]. In addition, it enables the loading of drugs that can induce osteogenesis, such as dexamethasone. Goimil et al. achieved considerably high dexamethasone loadings (85–100%) at 14 MPa and 37°C for 1 h into this hybrid matrix [61]. Scaffolds were cylindrical and presented high porosity. The

presence of the aerogel in the scaffolds increased the micropore size (150–400 μm) and the superficial roughness. The pore size was also increased by the dexamethasone loading, possibly due to its plasticizing effect on the polymeric matrix. Thus, the prepared material showed an optimal pore size range for cell ingrowth and suitable for angiogenesis, with a superficial roughness favorable for cell attachment and proliferation. In fact, *in vivo* tests were performed with dexamethasone salt at 0.1 wt% and the results showed excellent biocompatibility of the material and accelerated tissue reparation, with repair percentages of 39% for 14 weeks post implantation. The drug release in PBS at pH=7.4 depended on the drug chemical state. Salt (ionic) dexamethasone was burst released in the first hour and afterward a sustained release was observed for three weeks, while basic dexamethasone showed a sustained release along this period. These differences were associated with the different solubility in aqueous medium and the interactions with the polymeric matrix. The release mechanism was governed by the drug diffusion from the porous material, which showed slow degradation and erosion rates. Bone regeneration was remarkably improved due to this release profile, since high doses were quickly reached, and then, these levels were maintained for weeks with a sustained release.

Table 3. Natural proteins-based drug products

Polymer-based matrix	Active ingredient, or mixture of active ingredients/extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
Silk fibroin/ PCL	Dexamethasone	Aerogel/ Scaffolds	14	37	1	*n.i.*	-	85 – 100	[61]
Gelatin/ Silica	Ibuprofen	Aerogels	20	45	6	0.2 – 0.3	-	19 – 24	[67]
Gelatin/ Silica	Ketoprofen	Aerogels	20	45	6	0.2 – 0.3	-	11 – 15	[67]
Gelatin/ Silica	Triflusal	Aerogels	12	45	6	02 – 0.3	-	25 – 29	[67]

3.2.4. PLA-based drug products

Poly-lactic acid (PLA) is a biodegradable synthetic polyester included in the FDA Inactive Ingredients Database [127] and is currently used in pharmaceutical formulations and technology, oral solid dispersions, and drug delivery systems. In the recent literature, PLA-based carriers have been most extensively explored for supercritical impregnation/deposition of drugs. PLA has good CO_2 sorption, plasticization, and swelling properties under high pressure conditions, as reported by several authors [145,146], which facilitate the incorporation of drugs and other solutes. This behavior is explained in terms of the strong interaction between the carbonyl groups present in the polyester and the electron-deficient carbon atom of CO_2 via Lewis acid-base interactions [147,148]. Reports using PLA-based carriers in the reviewed period are summarized in **Table 4**. The main innovations include the simultaneous impregnation of two or more drugs (as model multicomponent systems); the impregnation of novel devices, such as 3D printable filaments; and the production of drug-loaded foams.

The simultaneous impregnation of different drugs has been studied by Coutinho and Champeau [69] to evaluate possible synergistic or antagonistic effects compared to the impregnation of each one separately. The authors selected ketoprofen, acetylsalicylic acid, and carvone as model drugs (with different physicochemical properties), and PLLA and LDPE films as model carrier. Synergistic effects were observed only in PLLA: ketoprofen increased the loading of acetylsalicylic acid from 3.4 to 16.9 wt%, and carvone increased the loading of ketoprofen from 13.9 to 18.4 wt% (at 80°C and 30 MPa). The combination of carvone and acetylsalicylic acid did not show differences in comparison with the single-compound loading (**Figure 8**). According to the authors, the occurrence of synergistic effects in PLLA depends on two factors: a high chain mobility (induced by high temperature and CO_2 sorption) and a good drug-polymer affinity. In this way, the strong plasticizing and cryogenic effect of a drug with high polymer affinity (i.e., the ability to reduce the polymer T_g and T_m, allowing the melting and recrystallization *in situ*) can enhance the diffusion and penetration of other drugs compared to their individual impregnation. These observations are useful for the understanding and optimization of the impregnation of mixtures, in cases where synergy can be exploited, or others where selectivity effects should be avoided (for example, in the impregnation of natural extracts whose bioactivity depends on the specific composition).

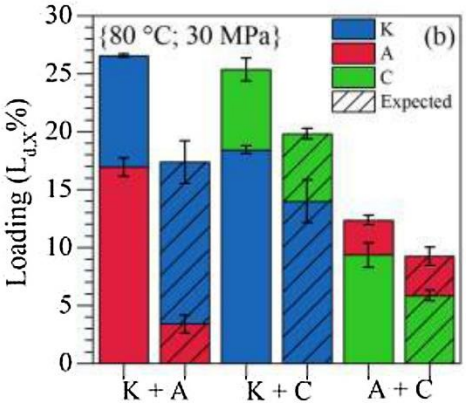

Fig. 8. Drug loading in the double $scCO_2$-assisted impregnation of LDPE ($L_{d,X}$ %) at 80°C and 30 MPa, compared to the expected (single) loading ($L_{s,X}$ %). A: aspirin, C: carvone, and K: ketoprofen. Adapted from [69], with permission. Copyright, Elsevier.

In a later work, the same authors employed PLLA films to compare the loading of acetylsalicylic acid by supercritical impregnation and by conventional liquid soaking [75]. Supercritical impregnation was performed at 30 MPa and 80°C for 3 h, while the soaking method was carried out by immersing the film in an acetylsalicylic acid ethanolic solution for 10 days. The results showed higher loadings (3.4 vs. 1.3 wt%) in shorter times (3 h vs 10 days) using the supercritical process compared to soaking, attributed to the higher swelling ability of $scCO_2$ which facilitates the drug diffusion into the matrix. Besides, the resulting systems were free of solvent residues. The release of acetylsalicylic acid in PBS solution at 37°C was also dependent on the loading method. A burst release was only observed in the soaked-PLLA samples because of the dissolution of drug crystals present on the film surface. Moreover, the release of drug from soaked-PLLA was faster compared to the $scCO_2$-treated samples, since a completed release was reached after 60 days for the conventionally prepared ones, whereas approx. 60% of drug was released after 74 days for $scCO_2$-PLLA. In this way, the authors confirmed that $scCO_2$ impregnation presents several advantages over conventional loading methods, like higher loadings, faster processing, and more sustained release.

Other authors explored the impregnation of 3D-printable PLA filaments. This recent technology is an innovative and auspicious strategy for biomaterials fabrication in the biomedical and pharmaceutical fields and can provide new forms of drug administration [149]. Verano-Naranjo et al. studied the supercritical impregnation of ketoprofen in PLA filaments for biomedical applications [71,72]. The authors evaluated the influence of pressure and temperature on the polymer swelling, the drug loading, and the drug release kinetics. Results showed an increase in the swelling degree (5-25%) at higher pressure (from 10 to 40 MPa) and temperature (from 35 to 75°C). Both variables favor the sorption of $scCO_2$ into the polymer samples and their plasticization and swelling. On one hand, when the temperature increases, the $scCO_2$ density is

reduced and its diffusivity increases, while the polymer plasticization degree also increases with temperature. Besides, the solubility of $scCO_2$ in PLA also increases with pressure. Regarding the swelling of PLA filaments, Rosales et al. evaluated the influence of ethanol as cosolvent on this property [105]. They observed that swelling was double at the highest pressure (40 MPa, at 55°C), reaching 50% in the presence of 3 v% of ethanol. Ethanol may promote plasticization by increasing the mobility of the internal chains, thus inducing a larger swelling. Regarding the drug loading, Verano-Naranjo et al. observed that the amount of impregnated drug increased with pressure, which was related to a higher ketoprofen solubility [72]. Another interesting result of this work is the quantification of the amount of ketoprofen superficially loaded onto the polymer, which decreased as either temperature or pressure increased, indicating a deeper impregnation and a more homogeneous drug distribution (**Figure 9**). Considering the maximum loading and minimum swelling effect, the best conditions were 75°C and 20 MPa for 2 h, with a total drug loading of 8.48%, 9.25% swelling degree, and 1.45% of superficial drug loading.

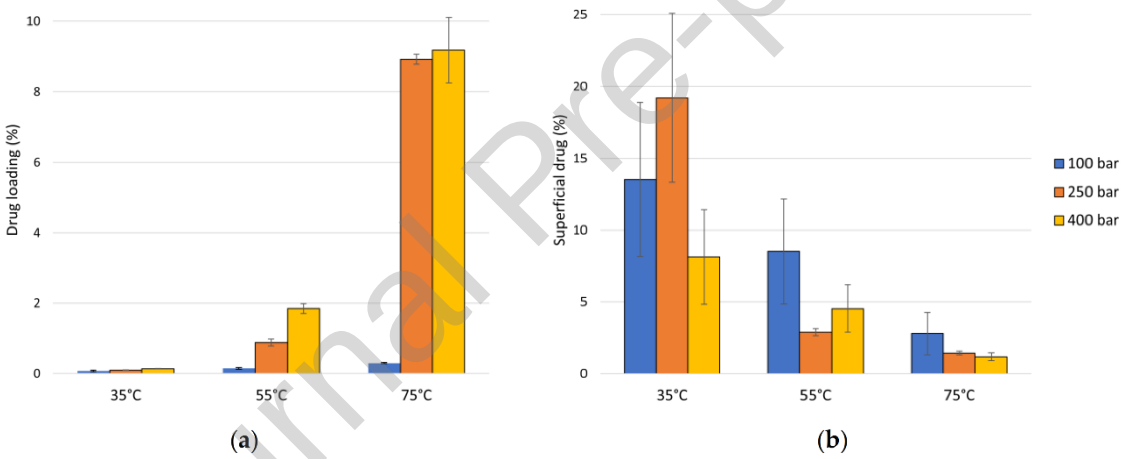

Fig. 9. Ketoprofen loading by $scCO_2$-assisted impregnation of PLA filaments: (a) total drug loading, (b) percentage of superficial drug with respect to total drug loading. Adapted from [72], with permission. Copyright, Elsevier.

The authors also showed that the processing variables not only determined the drug loading but also the permanent degree of swelling, and therefore, the kinetic release behavior of the impregnated filaments. The samples were subjected to release experiments at pH=7.4 and 37°C, and the experimental results were fitted with a multiphasic power-law model including four diffusion phases (I, II, III, and IV) [72]. The release profiles are shown in **Figure 10**. Phase I is the burst release, where the release kinetics is governed by diffusion. Phase II is a slow-release period, where the polymer hydration occurs, and degradation starts. Here, the porosity degree and the pore configuration achieved during the supercritical process are crucial. Phase III is fast since the scission of the polymer chains becomes the dominant driving force. Finally, phase IV

is slow, and it is only observed at the very end of a regular tri-phasic release profile. The hydration and degradation are relevant for a polymer like PLA which is biodegradable. Based on these results, during phases I and II, samples impregnated at 40 MPa allowed a more rapid drug release (more than 50%) in comparison with the other samples (about 10%) after 10 days, due to the high superficial drug loading as well as the presence of pores of larger size and a greater number of interconnections between them. Phase III (polymer degradation) was slower for the samples impregnated under mild conditions than for those obtained under extreme conditions due to the lower porosity level. Phase IV was only observed when phase II was very short, that is, in the sample impregnated at 40 MPa.

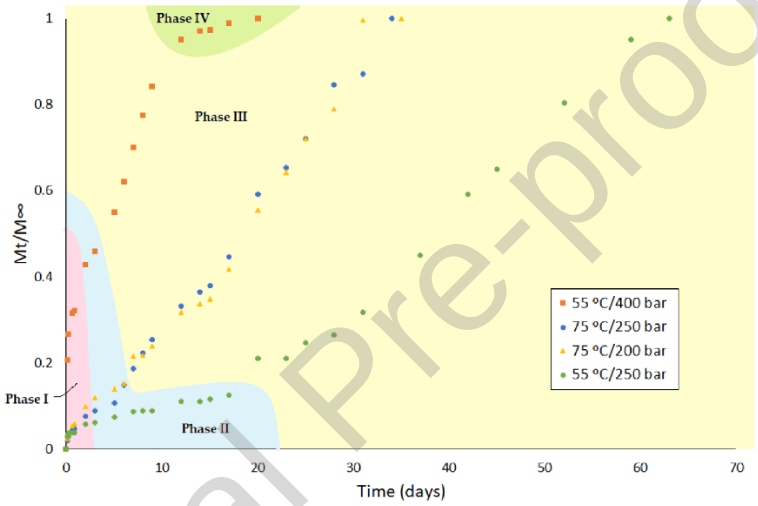

Fig. 10. Release profiles including the different phases of the release process from the PLA filaments impregnated with ketoprofen under different conditions. Adapted from [72], with permission. Copyright, Elsevier.

These kinds of studies are interesting if the PLA filaments are considered as a model polymeric carrier. However, it is likely that the release behavior, together with the polymer morphology and the drug distribution, will be affected by the printing process, where the filament is melted and injected. Future studies should focus on this aspect in order to assess the advantages (or not) of loading 3D-printable filaments by $scCO_2$-assisted impregnation.

Due to its high CO_2 sorption and plasticization ability, PLA appears as a good polymer substrate for preparing drug-loaded foams, by combining supercritical foaming and impregnation. In this way, Milovanovic et al. have developed PLA and PLGA foams loaded with thymol, as a natural therapeutic agent, for oral or topical delivery [97]. Foaming and impregnation were performed in a single step, varying pressure (7.5, 10, and 15 MPa), temperature (25–50°C), and contact time (2–24 h). Thymol loading was higher for PLA than for PLGA foams (5% vs. 3%, respectively), under the same conditions (10 MPa, 40°C, and 4 h). This phenomenon was

attributed to the more favorable interactions between thymol and the hydrophobic PLA. Regarding the foam structure, contact time had a considerable effect, since prolonged times had a negative impact on the foam expansion. The foam physical stability is a critical factor for the bioactive release, as well as its solubility in the release medium. Thymol release depended on the pH of the surrounding medium, the pore diameter and cell density of the foam, its loading capacity, and the swelling, water uptake and sink properties of the polymer. PLA and PLGA foams showed prolonged thymol release over 6 weeks, being faster for PLGA than for PLA (86% vs 40% release, respectively) under the same conditions, which was attributed to the hydrophilic glycolide content in the polymer. A complete analysis was performed regarding the estimation of the theoretical thymol concentration in the release medium. The authors claimed that it was sufficient for performing anesthetic, anticancer, antifungal, and antibacterial activity. In addition, all formulations were expected to be safe for the proposed applications, considering the thymol daily dosage according to the European Chemicals Agency.

The same foaming+impregnation approach was evaluated for developing PLGA foams loaded with gemcitabine, a highly hydrophilic anticancer drug [150]. In this work, ethyl lactate was used as cosolvent due to the very low solubility of gemcitabine in CO_2. A prolonged contact time (24 h) was favorable for high impregnation loadings without modification of the foam structure, achieving 99.44% of drug impregnation efficiency (with respect to the initial amount of drug added to the high pressure vessel) at 12 MPa and 25°C after 24 h of contact time and a PLA:PLGA ratio of 75:25. The impregnation yield was affected by the drug/polymer ratio, PLA:PLGA copolymer ratio, pressure, and temperature. In the same way, the drug release depended on the polymer composition and the drug loading. A remarkable point of this work is the detailed analysis of the release mechanism of gemcitabine from the foam. The authors proposed a theoretical mechanism of three steps that considers the foam structure and the drug distribution inside it. The first step is the release of the most accessible drug by external diffusion, which was affected by the initial gemcitabine concentration and the content of glycolide in the polymer. The increase of both factors induced a faster drug release. The second step is the release of the most inaccessible drug by internal mass transfer, although the theoretical model did not fit adequately the experimental data, which makes further analyses necessary for an acceptable adjustment. Finally, the third step is the degradation of the polymer and the release of the remaining drug, which was altered in this case by the glycolide content in the polymer.

Briefly, PLGA-based foams [120,150] were more appropriate for hydrophilic drugs, while PLA for hydrophobic ones [97,151]. However, all foams enabled a prolonged release.

The combination of PLA with other polymers in an amphiphilic matrix (PLLA/PEG/PLLA) was also proposed as a strategy to enhance the impregnation of polar drugs, for example, nitrendipine [84]. Although the drug loading was lower (10.5 wt%) than for caffeine, even using

ethanol as cosolvent (3 mol%), the impregnation was performed at shorter times (2 h vs 40 h) and considerably lower $scCO_2$ density (526 vs 834 kg m^{-3}). Moreover, a more prolonged release was obtained with these composite microparticles since the complete release of nitrendipine was achieved after almost 6 days using PBS solution as release medium.

Finally, the modification of PLA with a copolymer and an inorganic salt has been proposed for the preparation of films with foam structure and enhanced properties. Liparoti et al. designed topical anti-cellulite porous films composed of polylactide/poly(butylene adipate-co-terephthalate)/calcium carbonate (PLA/PBAT/$CaCO_3$) loaded with caffeine (a polar drug) [152]. The addition of PBAT and $CaCO_3$ to PLA was previously studied and the resulting blend showed enhanced cell uniformity and increased cell density [153]. The polymer foaming and the impregnation of caffeine were performed in a one-step process at 17 MPa and 35°C. At these conditions, large film pore sizes were obtained (25.6 ± 0.5 μm) and the caffeine solubility in $scCO_2$ was high. The maximum loading of caffeine was 23 wt% after 40 h of contact time, higher than the available in commercial products (3 wt%). However, the prolonged contact time required (40 h) represents a limitation, requiring further optimization studies. The incorporation of caffeine in this carrier showed a significant reduction in its release and dissolution rate in PBS (1-2 days), in comparison with pure caffeine crystals which dissolved in approx. 30 min (**Figure 11**).

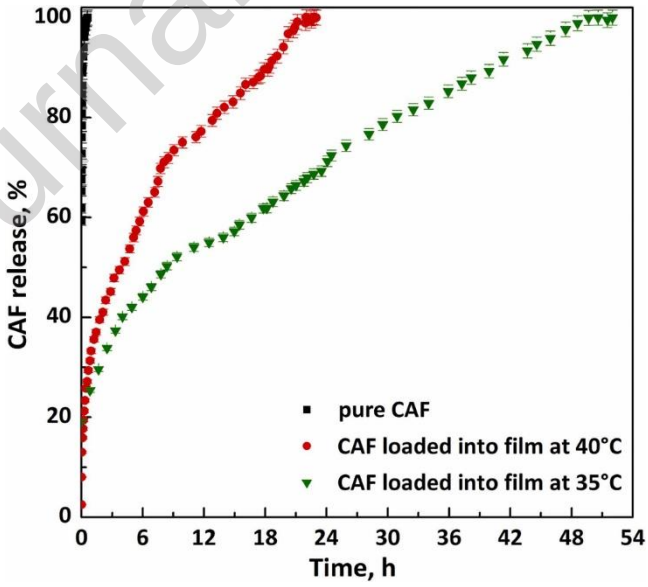

Fig. 11. Dissolution profiles of caffeine at pH 7.4 and 37°C (pure crystals and from loaded porous films). Adapted from [152], with permission. Copyright, Elsevier.

Table 4. Polylactic acid-based drug products

Polymer-based matrix	Active ingredient, or mixture of active ingredients/ extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
PDLLA	α-tocopheryl succinate	Particles	10	40	2	*n.i.*	-	11	[73]
PLLA	Acetylsalicylic acid	Films	30	80	3	*n.i.*	-	3.4	[75]
PLLA	Acetylsalicylic acid	Films	9 – 30	60 – 80	3	*n.i.*	-	1.3 – 3.4	[69]
PLLA	Acetylsalicylic acid + carvone	Films	9 – 30	60 – 80	3	*n.i.*	-	Acetylsalicylic acid: 0.8 – 3; Carvone: 6.4 – 9.4	[69]
PLA/ PBAT/ $CaCO_3$	Caffeine	Films	17	35	40	*n.i.*	-	23	[152]
PLLA	Carvone	Films	9 – 30	60 – 80	3	*n.i.*	-	5.1 – 5.8	[69]
PDLLA	Diclofenac	Particles	10	40	2	*n.i.*	-	13	[73]
PDLLA	Dihydroquercetin	Particles	10	40	2	*n.i.*	-	1	[73]
PLGA	Gemcitabine	Foams	12 – 20	25 – 40	24	*n.i.*	-	91 – 99	[150]
PLA	Ketoprofen	Filaments	25 – 40	55 – 75	2	*n.i.*	-	1.8 – 9	[71]

Polymer-based matrix	Active ingredient, or mixture of active ingredients/ extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
PLA	Ketoprofen	Filaments	20	75	2	0.1	-	9	[72]
PLLA	Ketoprofen	Films	9 – 30	60 – 80	3	*n.i.*	-	1.4 – 13.9	[69]
PLLA	Ketoprofen + acetylsalicylic acid	Films	9 – 30	60 – 80	3	*n.i.*	-	Ketoprofen: 0.1 – 9.6; Acetylsalicylic acid: 1 – 16.9	[69]
PLLA	Ketoprofen + carvone	Films	9 – 30	60 – 80	3	*n.i.*	-	Ketoprofen: 0.5 – 18.4; Carvone: 7	[69]
PLA	Mango leaf extract (rich in gallic acid, iriflophenone derivatives, and mangiferin)	Filaments	10	39	24	0.3	1 – 3 v% ethanol	1.5 – 8.5	[105]
PLLA/ PEG/ PLLA	Nitrendipine	Particles	13	55	2	*n.i.*	3 mol % ethanol	10.5	[84]
PLGA	Rutin	Foams	0.8 – 20	35 – 55	2	0.5 – 10	-	28 – 75	[120]
PLA	Thymol	Foams	20 – 30	100 – 120	2 – 24	*n.i.*	-	4.7 – 19.8	[151]

Polymer-based matrix	Active ingredient, or mixture of active ingredients/ extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
PLA, PLGA	Thymol	Foams	7.5 – 15	25 – 50	2 – 24	0.5	-	PLA: 4.9; PLGA: 6.6	[97]

3.2.5. Other polymer-based drug products

In the reviewed literature, drug products obtained by $scCO_2$-assisted impregnation/deposition in other synthetic polymeric carriers, such as poly(*N*-vinyl-2-pyrrolidone) (PVP), low density polyethylene (LDPE), polymethylmethacrylate (PMMA), and polycaprolactone (PCL), have been also reported, mainly for hydrophobic drugs (**Table 5**).

PVP is a linear hydrophilic polymer included in the FDA Inactive Ingredients Database and widely used in a variety of pharmaceutical formulations as suspending agent, tablet binder, etc. [127]. Ameri et al. [86] have reported the $scCO_2$-assisted impregnation of lansoprazole (a highly hydrophobic molecule, belonging to the gastric proton pump inhibitors drug class) into PVP particles. They obtained size-uniform particles with an average diameter of 200 nm. Besides, the drug loadings achieved at the optimal conditions were up to 1.16% (at 25 MPa and 55°C for 180 min). Furthermore, the authors observed a positive effect of temperature, pressure, and contact time on the impregnation yield, explained in terms of a higher CO_2 sorption and swelling, as well as a higher drug solubility in $scCO_2$. The effect of time indicates an increased in-depth diffusion of the drug in the swollen polymer [86]. However, neither the drug stability (in gastrointestinal conditions) nor the ability of the delivery system to perform an appropriate medicinal effect was studied.

PVP was also selected as carrier for the impregnation of ketoprofen, partially confined into microcontainers of epoxy resin for its oral delivery [39]. The authors defined a microcontainer as a reservoir with micrometer dimensions, composed of a non-permeable shell and a cavity for the drug formulation, open on one side from which the drug is released unidirectionally (**Figure 12**). In this work, the drug loading ranged between 10 and 33 wt% and it was affected by pressure, temperature, and impregnation time. In general, higher loadings were obtained at higher pressures under isothermal conditions because of the high drug solubility and fluid density. The effect of temperature on impregnation yield depended on the pressure. At lower

pressures (10 MPa), the drug impregnation decreased when the temperature raised from 40 to 60°C, due to a decrease in $scCO_2$ drug solubility. On the contrary, the drug loading increased with temperature at higher pressures (20 MPa), due to the swelling of the polymer that facilitated the drug diffusivity. The impregnation equilibrium was achieved in a relatively short time (4 h).

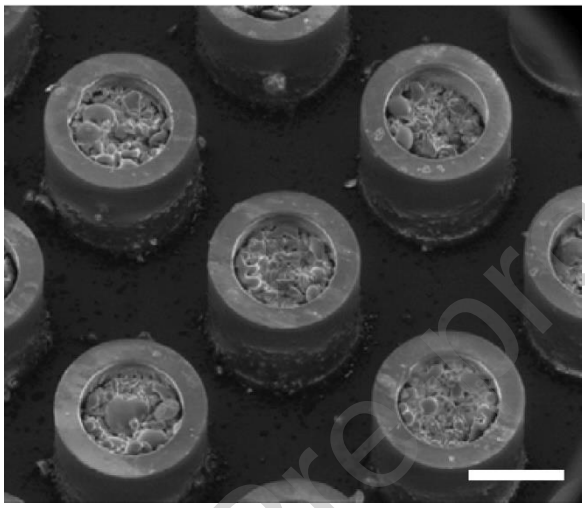

Fig. 12. SEM images of microcontainers filled with PVP (before ketoprofen loading). The scale bar represents 300 μm. Adapted from [39], with permission. Copyright, Elsevier.

The impregnation of ketoprofen in PVP was considerably higher compared to lansoprazole at the best observed conditions (33% vs 1.16%), which were 20 MPa/60°C/4 h, and 25 MPa/55°C/3 h, respectively. Although both drugs have similar molecular weights, ketoprofen solubility in $scCO_2$ (14.1 g kg^{-1} [39]) is higher than for lansoprazole under these conditions (4.49 g kg^{-1} [154]). The addition of a cosolvent like ethanol during the supercritical impregnation could enhance the lansoprazole solubility in $scCO_2$ as well as improve polymer-fluid interactions to obtain higher impregnation yields in PVP. In general, ketoprofen impregnation yield depended mainly on its $scCO_2$ solubility, while lansoprazole loading was mainly affected by the swelling of PVP at the impregnation conditions. Both authors found a positive impact of pressure on drug loading, attributed to a higher solubility for ketoprofen and other more complex phenomena in the case of lansoprazole impregnation. However, the effect of temperature was different. Ameri et al. observed higher lansoprazole loading at higher temperature, but the effect of this variable was more complex for the ketoprofen impregnation. This phenomenon was attributed to a crossover pressure in the solubility isotherms between 16 and 18 MPa. In this way, ketoprofen solubility decreases with temperature at 10 MPa but the opposite effect is observed at 20 MPa.

LDPE, PMMA, and PCL are currently employed in the pharmaceutical industry and approved by the FDA. LDPE is a low-cost material extensively used for packaging applications in food, drug, and cosmetic products [155]. However, its biodegradability resistance is one of its major drawbacks. PMMA is mainly used in the tissue engineering field, for example as denture bases and as a cement for dental prostheses [127], while PCL is applied in the area of medical devices [156]. Recently, linear LDPE has been employed as model hydrophobic polymer for studying the $scCO_2$-assisted impregnation of some drugs. Coutinho et al. evaluated possible synergistic effects in the drug loading of more than one drug in LLDPE [69]. Ketoprofen, acetylsalicylic acid, and carvone (alone or combined) were impregnated into LLDPE particles at 9 MPa and 60°C for 3 h. Low loadings were obtained (< 4 wt%) in the single compound impregnation, being highest for carvone (3.2%) and lowest for acetylsalicylic acid (0.3%). These results were explained in terms of drug-polymer affinity, estimated from solubility parameters calculated using the Hoftyzer Van-Krevelen´s method. According to this theory, the closer are the solubility parameters of two substances, the higher is their miscibility. In this way, solubility parameter analysis can be a good approach to assess or predict the feasibility of the impregnation [1]. For these drug-polymer systems, solubility parameters were very close for LDPE and carvone (17.6 vs 17.0 $MPa^{0.5}$), while the difference was higher for LDPE and acetylsalicylic acid (17.6 vs 25.7 $MPa^{0.5}$). Besides, the absence of polar groups in the chemical structure of LDPE able to interact with CO_2 via Lewis acid/base interactions resulted in a low CO_2 sorption. In this way, the impregnation yield that can be achieved in this polymer is limited. The simultaneous impregnation of both compounds did not show synergistic nor antagonistic effects, with loading values similar to those obtained in the impregnation of each individual compound. These results confirm the importance of the polymer/CO_2 interactions and polymer/drug affinity to obtain high loadings. In any case, the loading of multicomponent systems using LDPE might be estimated by simply adding the impregnation yields of the individual compounds from the literature.

In a later work, the authors evaluated the supercritical impregnation of acetylsalicylic acid into LDPE in comparison with a conventional liquid soaking method using isopropanol [75]. Similar loading values were obtained using both methods: 0.4 ± 0.5 wt% with $scCO_2$ and 0.6 ± 0.5 wt% with the liquid soaking method. However, the required time was considerably longer for the conventional method in comparison with the supercritical impregnation (10 days vs. 3 h), clearly showing the role of diffusion enhancer of $scCO_2$. Besides, further steps were needed in the conventional method, such as the film drying at 80°C for 3 h. The authors found almost 10 wt% of residual solvent in the sample impregnated by soaking, although this value is within the FDA accepted limits. In this way, the $scCO_2$ impregnation method represents an advantageous alternative to conventional soaking since it leads to samples free of residual solvent.

Despite the great potential of PMMA and PCL in biomedical applications [156], few studies have been reported in the last years using these polymers as carriers for the $scCO_2$-assisted loading of drugs [78,87,90,157]. Oparin et al. studied the morphology of carbamazepine (used in the treatment of epilepsy and trigeminal neuralgia) impregnated in PMMA (as model polymer) using $scCO_2$ [90,157]. The impregnation was performed at two different temperatures (75 and 105°C) and constant CO_2 density (corresponding to pressures of 19.3 and 27.6 MPa, respectively) [90]. The XRD and Raman spectra analysis showed that no drug crystallization or thermal degradation occur. A higher drug loading was obtained by increasing temperature, explained in terms of the changes in the polymer structure. Open pores were obtained at 75°C, while closed or sealed porous structures were formed at 105°C, entrapping the drug inside the polymer matrix. Besides, the conformational state of the carbamazepine molecules in the polymer matrix also depended on the impregnation process temperature. Another relevant result was the determination of the maximum drug concentration in the external PMMA surface, which was in direct contact with the CO_2 phase during the impregnation process, being 1.5 times higher than in the polymer bulk. This work demonstrated that by changing the process parameters, such as temperature, it is possible to control the drug morphology as well as the polymer structure. However, release experiments and the study of the interconversion between the conformers (i.e., stability) of the impregnated samples were not performed.

Salerno et al. prepared PCL scaffolds combining $scCO_2$ foaming and impregnation to improve the therapy with 5-fluorouacil (an hydrophilic anticancer agent) [87]. The low melting point of PCL (~60°C) makes it suitable for foaming induced by $scCO_2$. Due to the very low solubility of the drug in $scCO_2$, the composite components (drug and polymer) were premixed before foaming (at 20 MPa for 1 h). The results showed that the initial amount of drug in the composite (4.8–9.1 wt%), the process temperature (45–50 °C), and the depressurization rate (6–120 MPa min^{-1}) affected the mean pore size and distribution, and the drug release in acidic media (to avoid drug degradation). The optimal preparation (using 4.8 wt% of drug initial concentration, 45°C, and 0.1 MPa s^{-1}) were those with the highest porosities and the slowest release with a burst release of less than 2% at 2 h followed by a sustained release (60% after 6 days). From the pharmaceutical point of view, the procedure proposed resulted in an attractive strategy to prepare sustained drug delivery systems using hydrophilic drugs and hydrophobic polymer matrices. However, more analyses are necessary to confirm the effective drug loading after foaming and if this amount is enough to perform its anticancer activity.

Other porous materials that have received increased attention for drug delivery are the metal-organic frameworks (MOFs) [82,91,158]. They consist of crystalline porous materials built from metal centers connected by polytopic organic linkers. Besides, they present a high surface area with pore sizes in the micropore range and can be categorized as rigid or flexible. Rigid MOFs have permanent porosity and robust porous frameworks similar to inorganic materials. In

contrast, flexible MOFs are dynamic and respond to external factors, such as temperature, pressure, and light. Due to the ability to adapt their porosity to the shape of the guest molecule and adjust the framework functional group, flexible MOFs are very attractive for enhanced drug delivery [159,160]. An interesting strategy was proposed by Kubovics et al., who used $scCO_2$ technology for the preparation of a cutaneous polymeric formulation based on MOFs loaded with azelaic acid, which has antibacterial and anti-inflammatory activity for skin disorders (**Figure 13**) [91].

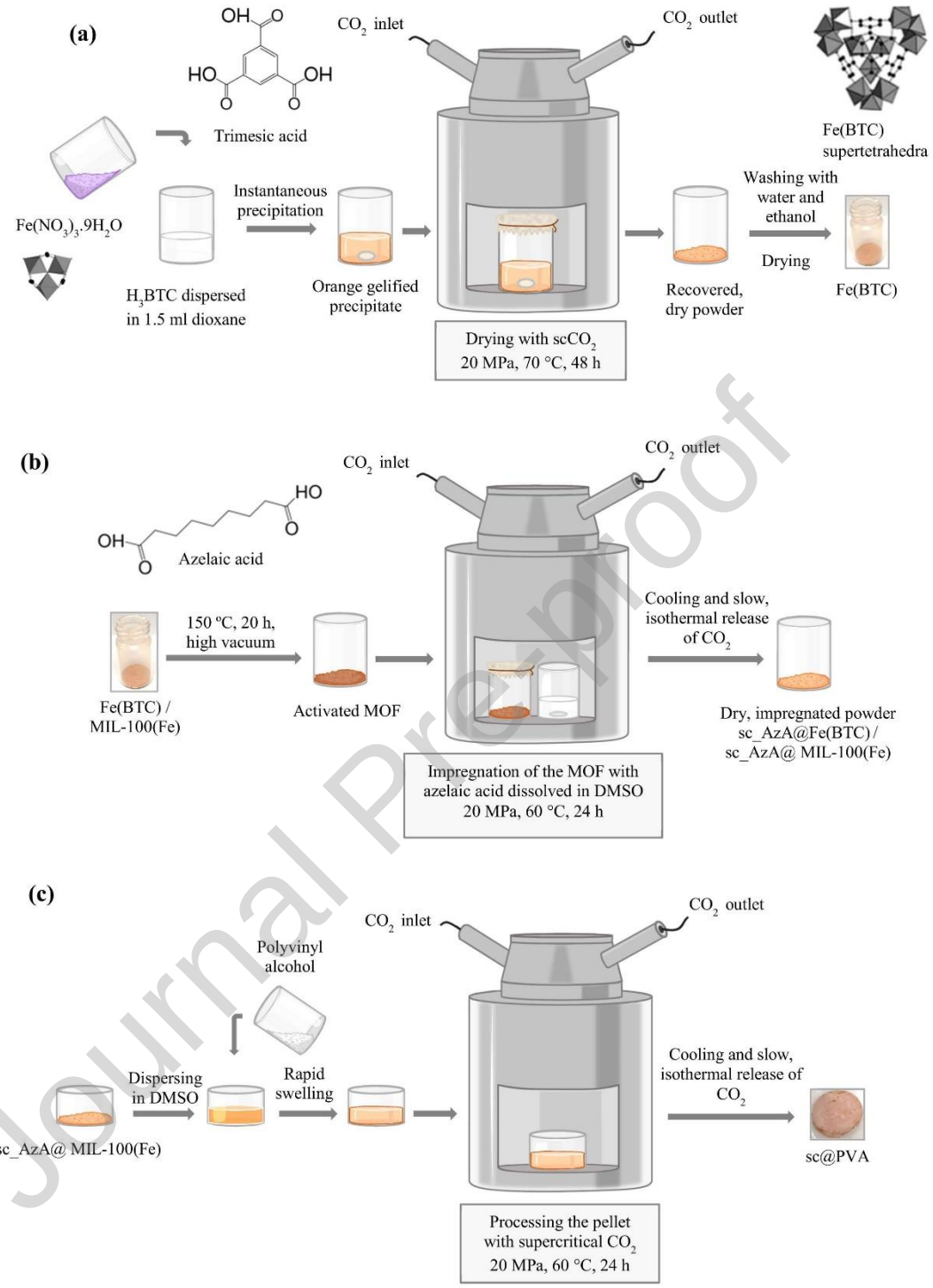

Fig. 13. Schematic representation of the $scCO_2$ method used for: (a) the synthesis of Fe(BTC) nanoparticles, (b) their impregnation, and (c) PVA pellets preparation intended for patches. Adapted from [91], with permission. Copyright, Elsevier.

Due to the poor drug solubility in $scCO_2$, 0.2 v% DMSO was added as cosolvent. The main novelty of this work was the use of $scCO_2$ in all the processing steps, i.e., in the synthesis of the porous MOF, the drug impregnation, and the patches composing and foaming. The cutaneous

patches were made of poly(vinyl-alcohol) (PVA) due to its suitable topical properties, such as biocompatibility, prophylaxis against infections, lubricity, etc. [161]. Besides, conventional synthesis methods were also applied in each step for comparison purposes. The authors employed two MOFs belonging to the trimesate MIL-100 family, the crystalline MIL-100(Fe) and its semi-amorphous analogue Fe(BTC). The first one was prepared using a conventional (hydrothermal) method, and the second one using $scCO_2$. The prepared materials differed not only in their structure but also in the mean particle size. MIL-100(Fe) were octahedral crystals with a particle size between 300 and 700 nm and a surface area of 1542 $m^2 g^{-1}$, while Fe(BTC) were small near-spherical nanoparticles of 10–20 nm and agglomerates of 100-300 nm, which slightly reduced the surface area to 1290 $m^2 g^{-1}$. In this way, similar results were obtained with $scCO_2$ minimizing the need for additives, the addition of organic solvents, or further cleaning steps.

The drug loading into the MOFs was performed using $scCO_2$-impregnation/deposition and water soaking as a conventional method. Remarkably, the azelaic acid loading using $scCO_2$ (at 20 MPa/60°C/12 h) was twice the values reached using conventional liquid impregnation, being 17.0 vs 7.9 wt% for Fe(BTC), and 15.0 vs 8.9 wt% for MIL-100(Fe), respectively. The authors assigned these results to the high water affinity of the substrate sorption, which competes with the drug molecules. This competition is removed when $scCO_2$ is used, since it is not adsorbed in those sites. The composite patches containing drug-loaded MOFs were prepared with PVA using $scCO_2$ foaming and a press-molding method. *Ex vivo* permeation assays using porcine skin at pH=7.4 were carried out to determine the drug release from the patches prepared by the different methods. No considerable differences were observed in the drug bypass through the porcine skin from both patches after 8 h (7.5% and 6% for supercritical and press-molded samples, respectively); however, it was superior to other commercial products (~4% in 24 h). On the other hand, the presence of MOF in the formulation controlled the drug release rate, since the diffusion flux was 1.2 and 3 times slower from patches prepared by the supercritical and the conventional method, respectively, than from the control (loaded-PVA without MOF). Although no differences were found between the preparation methods, the resulting patches showed superior performance to the available commercial ones. However, the stability of the MOFs in biological solutions and their imparted toxicity could be potential issues for future research.

Table 5. Other polymer-based drug products obtained by $scCO_2$-assisted impregnation/deposition.

Polymer-based matrix	Active ingredient, or mixture of active ingredients /extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
LLDPE	Acetylsalicylic acid	Films	30	80	3	*n.i.*	-	0.4	[75]
LLDPE	Acetylsalicylic acid	Particles	9 – 30	60 – 80	3	*n.i.*	-	0.3 – 0.4	[69]
LLDPE	Acetylsalicylic acid + carvone	Particles	9 – 30	60 – 80	3	*n.i.*	-	Acetylsalicylic acid: 0.2 – 0.4; Carvone: 0.8 – 1.1	[69]
LLDPE	Carvone	Particles	9 – 30	60 – 80	3	*n.i.*	-	0.5 – 3.2	[69]
LLDPE	Ketoprofen	Particles	9 – 30	60 – 80	3	*n.i.*	-	0.4 – 0.6	[69]
LLDPE	Ketoprofen + acetylsalycilic acid	Particles	9 – 30	60 – 80	3	*n.i.*	-	Ketoprofen: 0.6; Acetylsalicylic acid: 0.2	[69]
LLDPE	Ketoprofen + carvone	Particles	9 – 30	60 – 80	3	*n.i.*	-	Ketoprofen: 0.4; Carvone: 1.3 – 2.8	[69]
PMMA	Carbamazepine	Powder	19.3 – 27.6	75 – 105	-	*n.i.*	-	-	[90]
PCL	5-fluorouraci	Foams	20	45 – 50	1	6 – 120	-	1.21 - 7.34	[87]

Polymer-based matrix	Active ingredient, or mixture of active ingredients /extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
	l								
PVP	Ketoprofen	Microcontainers	10 – 20	40 – 60	1-4	*n.i.*	-	33	[39]
PVP, HPMC	Carvedilol	Particles	30	100	2	1.5	-	-	[134]
PVP, PCL-co-PVAc-co-PEG	Indomethacin	Particles	15	60 – 70	2	*n.i.*	-	10 – 50	[78]
HPMC, PVP	Lansoprazole	Particles	15 – 25	35 – 55	1 – 3	0.5	-	HPMC: 0.6 – 1.3; PVP: 0.6 – 1.2	[86]
MIL-100(Fe), Fe(BTC)/PVA	Azelaic acid	MOFs/ Patches	20	60	~12	*n.i.*	0.2 v% DMSO	MIL-100(Fe): 15; Fe(BTC):17	[91]
MIL-53-(Al), Mg-MOF-74	Caffeine	MOFs	10	40	2 – 24	0.2	-	MIL-53-(Al): 6.2 – 32.1; Mg-MOF-74: 2.8 – 24.3	[82]
MIL-53-(Al), Mg-MOF-74	Carvacrol	MOFs	10	40	2 – 24	0.2	-	MIL-53-(Al): 26.5-34; Mg-MOF-74:	[82]

Polymer-based matrix	Active ingredient, or mixture of active ingredients /extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
PMMA/β-tricalcium phosphate biocomposites	Flurbiprofen	Particles	0.85 – 11.5	40 – 50	24	*n.i.*	-	12.7-30.1 26	[76]
Medium-chain-length Polyhydroxylalkanoates	Ibuprofen	Particles	15 – 20	40	0.5 – 3	*n.i.*	-	9	[68]
Potassium/γ-cyclodextrin	Honokiol	Inclusion complex	20	50	2	*n.i.*	-	40.8	[158]

3.3. Medical devices and combination products

As shown in **Table 6**, $scCO_2$-assisted impregnation/deposition has proven useful for the incorporation of drugs and active ingredients in different biomedical devices and materials, providing solvent-free products in an inert processing atmosphere. FDA defines a medical device as an "*instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related articles, including a component part or accessory which is recognized in the official National Formulary, or the US Pharmacopeia, intended for use in the diagnosis of disease, the cure, mitigation, treatment or prevention of disease…*" [162]. Recent examples reviewed here include contact lenses, functional fibers, and tissues, catheters, sutures, dental care products, etc.

The development of ophthalmic drug delivery systems via $scCO_2$-assisted impregnation has received great attention [163]. These implants are able to extend the effect of the drug in the aqueous humor, favoring its absorption and biocompatibility during treatment [164]. Several authors have reported the successful impregnation of different materials, including polymeric blends, commercial soft contact lenses (SCLs), and intraocular lenses (IOLs), with ophthalmic drugs (such as cefuroxime sodium [165], acetazolamide, and timolol maleate [166], ibuprofen and flurbiprofen [167], ciprofloxacin and dexamethasone 21-phosphate disodium [79,80], and methotrexate [89]) without modifying their main properties, such as oxygen permeability, wettability, and transparency. These properties can be affected by several factors, such as the gas sorption in the polymer and its swelling degree, as well as by the drug loading. In this sense, different strategies have been explored to preserve the final properties of the product, including the use of cosolvents and low pressurization and depressurization rates. For example, Bouledjouidja et al. [79] applied $scCO_2$-assisted impregnation to incorporate ciprofloxacin (CIP) and dexamethasone phosphate disodium (DXP) into foldable IOLs made of poly-2-hydroxyethyl methacrylate (P-HEMA) for cataract post-operative treatment. IOLs and the drug were exposed to $scCO_2$ and ethanol (5 mol%) as cosolvent, at pressures of 8 and 20 MPa and a temperature of 35°C during 30–240 min, followed by a slow depressurization (0.2 MPa min^{-1}). Impregnation yields were up to 3.83 μg/mg for CIP and 14.53 μg/mg for DXP. Results showed an increase in loading yield with pressure, along with an increase in drug solubility. Interestingly, the authors also observed the effect of pressurization rate on the optical properties of the IOLs, reporting the occurrence of foaming as it is performed faster (**Figure 14**).

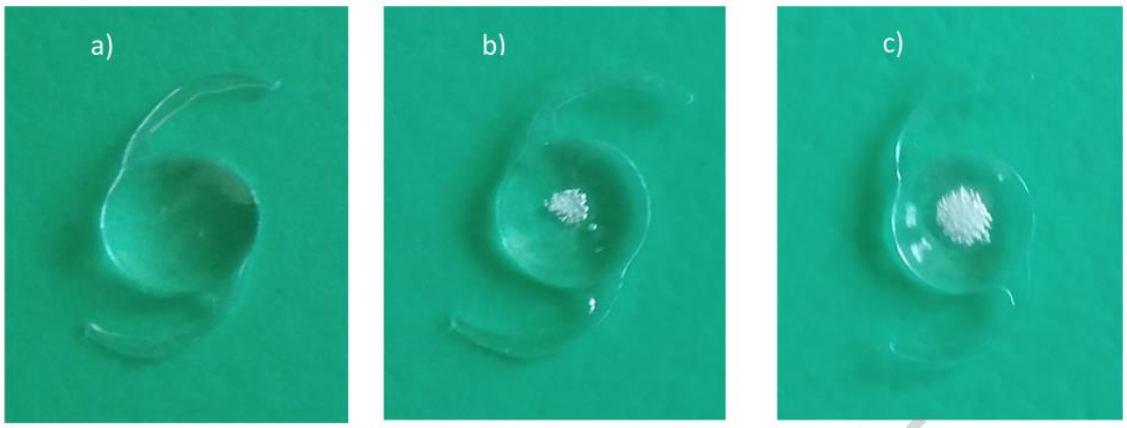

Fig. 14. Influence of pressurization rate on the optical properties of P-HEMA intraocular lenses: (a) non treated; (b) pressurized at 650 g h^{-1}; (c) pressurized at 900 g h^{-1} (35°C, up to 200 MPa, for 2 h, followed by slow depressurization at 0.7 MPa min^{-1}). Adapted from [79], with permission. Copyright, Elsevier.

The higher loading values obtained for DXP suggest a higher affinity for P-HEMA than CIP, as the former molecule has more H-bond sites in its structure. Additionally, the release profile of CIP and DXP into simulated aqueous humor from impregnated IOLs (obtained with and without cosolvent) revealed that IOLs with higher loading values released the drug for longer periods (40–45 days). In contrast, Ongkasin et al. [89] obtained lower impregnation values (0.43–0.75 μg/mg) when incorporating methotrexate in IOLs made of P-HEMA and PMMA blends under similar operation conditions (8 and 25 MPa, 35°C, depressurization rate of 0.2 MPa min^{-1}) and exposure time (30–240 min). Contrary to expectations, the presence of cosolvent (ethanol 5 mol%) did not significantly influence the impregnation yield and in some cases was unfavorable. Moreover, at the longest impregnation time (240 min), pressure negatively affected the impregnation yield, leading to a 43% reduction in drug loading and a decrease in the release time (from 117 to 87 days). A possible explanation for this might be that, when $scCO_2$ density increases, the polymer swelling is enhanced by CO_2 sorption, and the solute can be more easily dragged out during the decompression step. Consequently, it seems that $scCO_2$/drug interactions prevail over polymer/drug interactions in this case. This finding is contrary to that of Bouledjouidja et al. [80], who in a later work studied the impregnation of the same IOLs (P-HEMA and PMMA blend) with CIP and DXP at similar conditions (8 and 20 MPa, 35°C, depressurization rate of 0.2 MPa min^{-1}). In this case, impregnation was more favorable at higher pressures and in absence of cosolvent for both drugs. When ethanol was used as cosolvent (5 mol%), impregnation loadings were similar at both pressures for CIP, whereas for DXP the impregnation was unfavorable. A higher drug/polymer affinity was observed for the system DXP/IOLs, with impregnation yields up to 23.7 μg/mg for DXP vs 8.6 μg/mg for CIP. In

addition, the release kinetics of CIP and DXP from impregnated IOLs into simulated aqueous humor showed a sustained drug delivery during approx. 10 days for all impregnated samples.

Yokozaki et al. [92] have recently studied the $scCO_2$-assisted impregnation of salicylic acid (SA) into commercial SCLs (Hilaficon b), evaluating the effect of pressure (9–15 MPa), temperature (35–45°C), and depressurization rate (0.06–0.18 MPa min^{-1}) on the impregnation efficiency (29.6–54.5 wt%), as well as the release kinetics of SA from impregnated contact lenses in an aqueous solution. Results indicated that the total amount of SA increases with pressure and decreases with temperature, while at slower depressurization the impregnation loadings were higher than those obtained at faster decompression. Furthermore, the authors observed that using a combination of low pressure, high temperature, and slow depressurization, it is possible to obtain a slow release rate (103 min) of SA from contact lenses.

The development of functional tissues capable of providing a controlled release of therapeutic substances for the treatment of different diseases is another application that has received some attention. For instance, commercial wound dressings based on collagen and cellulose (Spongostan® and Promogran®, respectively) were loaded with copaiba oil via $scCO_2$ impregnation/deposition for topical antileishmanial treatment [168]. In this study, Pascoal et al. focused on the effect of $scCO_2$ density (700–900 kg m^{-3}) as a process variable. Loading values in the range of 0.53–1.50% for Promogran® and 0.54–2.07% for Espongostan® were obtained after 3 h of treatment. The loading of copaiba oil increased with CO_2 density for both dressings. The authors explain the observed results in terms of the hydrophilic/hydrophobic nature of both materials and the $scCO_2$/solute/polymer interactions. Thus, copaiba oil/$scCO_2$ interactions were predominant during the impregnation of Promogran® (more hydrophobic), whereas copaiba oil/polymer interactions prevailed for Spongostan® (more hydrophilic). In the same way, Silva et al. [36] applied $scCO_2$-assisted impregnation/deposition to load the same wound dressing (Promogran®) with a spilanthol-enriched extract obtained from jambu (*Spilanthes acmella*) flowers to produce a dressing with anesthetic, analgesic, and anti-inflammatory properties. Loading yield showed a slight increase with CO_2 density, ranging from 2.4 to 6.4 wt%, and it was improved 2.5 times by the addition of ethanol as cosolvent (5 mol%). As mentioned, Promogran® presented a high level of hydrophobicity, possibly due to the presence of collagen type I, which increased with the incorporation of jambu extract as a consequence of the hydrophobic nature of the active compounds. No changes in the permeability of the dressing were observed after the high-pressure treatment. Due to the poor CO_2 sorption and swelling ability of cellulose and collagen, discussed in other previous examples, it is likely that the main loading mechanism in these cases is the deposition onto the surface of the fibers.

Similarly, Marković et al. applied $scCO_2$ impregnation/deposition to incorporate thymol into electrospun polyamide nanofibers (PA NFs) for the preparation of a potentially antimicrobial dressing [57]. Results indicated a fast impregnation process of thymol in PA NFs. For example,

after 30 min of impregnation time, loading values of 6.5, 23, and 32 wt% were achieved at 7, 10, and 20 MPa, respectively. Overall, impregnation yield varied up to 60 wt% (at 7–20 MPa and 25–35°C). The impregnation was favored by pressure and contact time. This behavior was attributed to the high thymol solubility in $scCO_2$ and the increased diffusivity of CO_2 in the solid matrix. In addition, a remarkable swelling of PA NFs after treatment was observed, which suggests a strong plasticizing effect of thymol along with CO_2. All these results indicate that loading is achieved mainly by bulk impregnation. In a similar study, Pajnik et al. [169] obtained lower thymol loadings (3.9–5.6% at 35°C, 10 MPa, 1–5 h) in the $scCO_2$ impregnation of PLGA/PCL/CSL-based sutures (Poly-sorb™). The impregnated suture showed antibacterial activity against *E. coli* and *S. aureus*. Additionally, in vitro release experiments in PBS at 37°C indicated that the treated material gradually released thymol for up to 6 days.

Functionalized dressings with antioxidant, antidiabetic, and antimicrobial activity based on calcium-sodium alginate loaded with mango leaf extract (MLE) rich in polyphenols by $scCO_2$-assisted impregnation/deposition were developed by Fernández-Ponce et al. [103]. These authors evaluated the effect of pressure (20–40 MPa) and temperature (35–55°C) on loading yield. Pressure and temperature negatively affected impregnation, obtaining the highest value at 20 MPa, 35°C, and a depressurization rate of 10 MPa min^{-1} (0.39 wt%). In another study by the same authors, high impregnation MLE loading (up to 55.8 wt%) in polyester fibers at similar conditions was obtained [106]. The impregnated alginate dressing also showed considerable ability to inhibit both the α-glucosidase enzyme and the growth of *S. aureus*, which confirms it as a potential transdermal drug delivery system for antidiabetic applications. On the contrary, pressure showed a positive effect on impregnation yield in the same temperature range when this extract was incorporated into calcium-sodium alginate wound dressings [104]. In this case, Valor et al. evaluated two impregnation methods: batch and semi-continuous, reporting that the highest loading values of the major polyphenolic compounds (0.42 wt%) and strong antioxidant activity were achieved in batch mode at higher pressure, lower temperature, and a slow depressurization (30 MPa, 35°C, 0.1 MPa min^{-1}) after 3 h of treatment. In the same sense, Jia et al. [123] obtained an antimicrobial PVA/chitosan nanocomposite film loaded with patchouli essential oil (PEO) as a potential wound dressing material via supercritical impregnation. The PEO loading in the nanocomposite was up to 42.8% at 15 MPa and 40°C after 90 min of impregnation. The impregnated dressing showed a slow PEO release during 5 days and exhibited a strong inhibition effect against *S. aureus.* Mallepally et al. [170] proposed the impregnation of hydrogen peroxide (H_2O_2) into cellulose acetate (CA) mats via sub- and supercritical CO_2 to obtain a potential oxygen delivery system for wound healing. These authors evaluated the effect of temperature on the impregnation efficiency at mild processing conditions (25–45°C and 8.23 MPa). Maximum H_2O_2 loading of 25% into CA mats was achieved at the lowest temperature. Results suggest that at low temperatures, the displacement of H_2O_2

partition toward the polymer phase is favored, probably due to the strong interactions between the polar functional groups of AC and H_2O_2. Shelf-life studies determined that H_2O_2-loaded CA mats stored at 2–8°C could retain more than 50 wt% of the impregnated H_2O_2. In addition, no effect on the CA mat morphology was observed after the high-pressure treatment.

In a recent study, Champeau et al. [171] demonstrated the suitability of $scCO_2$-assisted impregnation for the preparation of ketoprofen-loaded poly(L-lactic acid) (PLLA) sutures. In this study, the degradation of the treated PLLA, as well as the possibility to tune the drug release from the impregnated suture by changing the operational conditions, were investigated. The amount of ketoprofen loaded into the PLLA sutures was relatively high (up to 19.8 wt%) at 30 MPa, 80°C, and a depressurization rate of 0.06 MPa min^{-1}, and the release of ketoprofen from impregnated sutures in phosphate buffer solution (PBS) varied from 3 days to 3 months, depending on the impregnation and/or depressurization conditions. Moreover, it was observed that the release behavior of ketoprofen was influenced by the PLLA degradation rate, which increases with the drug content and the free volume of the material.

$scCO_2$-assisted impregnation has been successfully applied to fabricate other medical implants. Various patents have reported the use of $scCO_2$ impregnation for the fabrication of catheters and ureteral stents (made of silicone and polyurethane) with antimicrobial and antifungal drugs to reduce the risk of infection [172–174]. Barros et al. [175] have impregnated up to 25% ketoprofen into biodegradable alginate-based and gellan gum-based ureteral stents using $scCO_2$ at relatively mild operating conditions (10 MPa and 40°C). For both stents, the authors found that temperature has a significant effect on impregnation loading. Furthermore, the gellan gum-based stents showed higher impregnation yields. Release kinetics experiments showed that the system was capable to release ketoprofen in artificial urine during the first 72 h. The ability of the impregnated stents to locally and fastly deliver the active compound confirms the potentiality of this device for the envisaged application.

Nowak et al. [102] loaded carvacrol in polyamide microfiltration membranes by $scCO_2$-assisted impregnation aiming to obtain functionalized membranes to prevent perioperative contamination of open surgical wounds. They found that it is possible to impregnate carvacrol up to 43 wt% (at 20 MPa, 40°C, and 6 h), while the mechanical properties of the material were not significantly affected by the high-pressure treatment. According to the open thoracic cavity model applied, membranes loaded with 30–34 wt% carvacrol showed a 27% reduction in contamination levels compared to the standard membranes used for this purpose.

Another recent application is the $scCO_2$ impregnation of a commercial dental floss made of polyamide 6 (PA6) with eugenol for obtaining a functional dental floss for dental care applications [176]. Floss samples were impregnated at 60°C and different pressure levels (8–12 MPa) and depressurization rates (0.5 and 5 MPa min^{-1}) to evaluate the effect of these variables on the impregnation efficiency and the floss mechanical properties. Eugenol loadings up to 15

wt% were obtained, and the mechanical properties (tensile strength, elongation at break, and Young modulus) were not significantly affected by the high-pressure treatment. The release kinetics of eugenol from impregnated fibers to air and artificial saliva were also investigated and modeled. Results showed that the apparent diffusion coefficient values were in the range of $(1.70–2.55)\times10^{-14}$ m^2 s^{-1} in air, and $(1.0–2.0)\times10^{-14}$ m^2 s^{-1} in simulated saliva solution. Finally, the impregnated floss showed high antimicrobial activity against *E. coli* and *S. aureus.*

In a more recent contribution, Mosquera et al. [35] studied the mass transfer kinetics of CO_2 and eugenol into PA6 fibers under supercritical conditions (10 and 12 MPa, 40 and 60°C, 0.5–6.0 h). CO_2 and eugenol sorption in PA6 followed a Fickian-type behavior. Pressure and temperature did not have a significant effect on the maximum CO_2 sorption degree (~3 wt%) for all conditions. Nonetheless, the sorption of eugenol was enhanced mainly by temperature and moderately by pressure, obtaining loading values ranging between 3 and 16 wt%. Diffusive data revealed that there is a 4-order-of-magnitude difference between the apparent diffusion coefficient of CO_2 (10^{-10} m^2 s^{-1}) and eugenol (10^{-14} m^2 s^{-1}) under high pressure conditions, suggesting that in a first step the fiber is quickly saturated and swollen by $scCO_2$ and consequently eugenol diffusion occurs in the already plasticized polymer.

Table 6. Medical devices and combination products obtained by $scCO_2$-assisted impregnation/deposition.

Polymer-based matrix	Active ingredient, or mixture of active ingredients/extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
Acrylic-based (P-HEMA)	Ciprofloxacin	Lenses	8 – 20	35	0.5 – 4	0.2	5 mol % ethanol	0.09 – 0.41	[79]
Acrylic-based (P-HEMA)	Dexamethasone	Lenses	8 – 20	35	0.5 – 4	0.2	5 mol % ethanol	0.85 – 1.45	[79]
Acrylic-based (P-HEMA/PMMA)	Ciprofloxacin	Lenses	8 – 20	35	2	0.2	5 mol % ethanol	0.18 – 0.86	[80]
Acrylic-based (P-HEMA/PMMA)	Dexamethasone	Lenses	8 – 20	35	2	0.2	5 mol % ethanol	0.57 – 2.37	[80]
Acrylic-based (Hilaficon b)	Salicylic acid	Lenses	9 – 15	35 – 45	2	0.06 – 0.18	-	29.6 – 54.5	[92]
Acrylic-based (PMMA)	Methotrexate	Lenses	8 – 25	35	0.5 – 4	0.2	5 mol % ethanol	0.04 – 0.07	[89]
Acrylic-based **(**Clear Resin v4)	Flurbiprofen	Films	15 – 48	40 – 50	4 – 24	*n.i.*	-	14.7 – 23	[77]

Polymer-based matrix	Active ingredient, or mixture of active ingredients/extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
Collagen/cellulose-based	Copaiba oil	Wound dressings	13.2 – 31.7	45	3	0.5	-	0.5 – 2	[168]
Collagen/cellulose-based	Spilanthol-enriched extract	Wound dressings	8.9 – 18.3	35	4	0.5 – 1	5 mol% ethanol	2.2 – 6.4	[36]
Cellulose	Thymol	Nanofibrils	10	40	1	0.8	-	0.8 – 1.9 mol	[177]
Cellulose acetate	Hydrogen peroxide	Mats	8.3	25 – 45	1	*n.i.*	50 wt% Water	25	[170]
Cotton, PP	*H. italicum* extract (rich in pyrogallol, chlorogenic, and gentisic acids)	Gauze/Fabrics	15	35	5	3.5	10 wt% ethanol	Cotton:7.2; PP: 4.8	[110]
PLA	Cinnamaldehyde	Mats	12	40	3	1		3.3	[178]
PLLA	Ketoprofen	Sutures	8 – 9	30 – 35	3	Fast (~2 s) – 0.6	-	11.8 – 23.4	[171]
PLLA, PET, PP	Acetylsalicylic acid	Fibers	8 – 35	40 – 140	3	3.6 – 360	-	PLLA: 8.1; PET: 4.7; PP:5	[179]

Polymer-based matrix	Active ingredient, or mixture of active ingredients/extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
PLLA, PET, PP	Ketoprofen	Fibers	8 – 35	40 – 140	3	3.6 – 360	-	PLLA:32.5; PET: 3.2; PP: 2.2	[179]
PLGA/ PCL/ CSL	Thymol	Sutures	10	35	1 – 24	1	-	3.9 – 5.6	[169]
L-PCL, H-PCL	Nimesulide	Patches	15 – 20	40	1 – 48	Slow	-	L-PCL: 1; H-PCL: 35	[180]
Polyester	Mango leaf extract (rich in gallic acid, iriflophenone derivatives, and mangiferin)	Textiles	40 – 50	30 – 55	22	0.06 – 2.5	5 v% methanol	20.4 – 55.8	[106]
Polyamide	Carvacrol	Membranes	10 – 20	40	1 – 6	0.15		10 – 43	[102]
Polyamide	Eugenol	Fibers	8 – 12	60	2	0.5 – 5	-	8 – 15	[176]
Polyamide	Eugenol	Fibers	8 – 12	60	0.5 – 4	0.5	-	3 – 16%	[35]
Polyamide	Thymol	Nanofibers	7 – 20	35	0.5 – 4	1.4	-	6 – 50	[57]
Alginate/ Gelatin, Gellan	Ketoprofen	Stents	10	35 – 50	2	*n.i.*	-	Alginate / gelatin: 3.3 –	[175]

Polymer-based matrix	Active ingredient, or mixture of active ingredients/extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
gum/ Gelatin								8.7; Gellan gum/ gelatin: 4.8 – 16.6	
Alginate	Mango leaf extract (rich in gallic acid, iriflophenone derivatives, and mangiferin)	Wound dressings	20 – 40	35 – 55	2	10	-	0.1 – 0.35	[103]
Calcium/sodium alginate	Mango leaf extract (rich in gallic acid, iriflophenone derivatives, and mangiferin)	Wound dressings	10 – 30	35 – 55	3	0.1 – 10	-	0.1 – 0.4	[104]

3.4. Dietary supplement products

The $scCO_2$-assisted impregnation of biopolymeric materials as carriers for nutraceuticals and other food additives and ingredients, such as aromas, colorants, antioxidants, etc., has been developed as a strategy for enriching food products, as well as facilitating the handling and dosage of liquid compounds and/or preserving sensitive bioactive ingredients [181]. Impregnation of liquid compounds into solid particles yields powder formulations easier to manipulate and store and which may enhance their interaction with the other ingredients. In this sense, it appears as an alternative to spray-drying encapsulation, with the advantage of using lower temperatures (because there is no need for evaporating water or other solvents). On the other hand, the carrier material may protect against oxidation or other degradation agents, enhancing the stability of additives in food products and therefore their activity or bioavailability. Impregnation can also modify the phase state of the additive, or its size, thus changing its dissolution behavior and bioincorporation. Finally, the carrier can modulate the release rate and/or behavior of active ingredients by a combination of diffusion, swelling, erosion, and/or physicochemical stimuli, like pH. Many different polymeric materials have been studied as carriers, including native and modified starch, vegetable and animal proteins, alginates, biodegradable polymers (like PLA), or silica. In many cases, biopolymers are impregnated in the form of xerogels and aerogels. The high surface area and porosity of these materials, as well as their very low densities, make them excellent carriers. In this way, the combination of supercritical drying of aerogels with impregnation has opened very interesting possibilities for process intensification. The different compounds that have been proposed and studied in connection with $scCO_2$-assisted impregnation within the studied period are summarized in **Table 7** and can be broadly classified into two groups: lipophilic and hydrophilic. Each group has its own particularities and poses different problems, frequently leading to specific process solutions.

3.4.1. Lipophilic compounds

The impregnation of lipophilic compounds usually aims at enhancing solubility properties (e.g., liposoluble vitamins, phytosterols, lycopene) or preserving from oxidation (e.g., polyunsaturated fatty acids, vitamins). The poor solubility of crystalline lipids in aqueous media (such as gastrointestinal fluids) may dramatically reduce their bioavailability. In this sense, the impregnation of lipidic additives in aerogels has been proposed as a strategy for reducing and/or controlling the size of lipid crystals or particles, allowing a higher or faster dissolution. Ubeyitogullari et al. [121,122] have studied the supercritical impregnation of crude phytosterols in nanoporous starch aerogels in a semi-static process, where phytosterols are first dissolved in

$scCO_2$ in a separate chamber, and then the mixture flows through a bed of aerogel particles, achieving 5.5 to 9.9 wt% impregnation yields at 45 MPa and different temperatures (from 70 to 120°C). High pressure and temperature conditions were necessary due to the low $scCO_2$ solubility of this type of compound. The authors propose a mechanism in which the aerogel pores serve as "molds" where colloidal (nanosize) phytosterol particles are formed after depressurization, limiting the aggregation and formation of larger particles, and reducing the phytosterol crystallinity. The observed solubility (or dispersibility) in water of the impregnated phytosterols was almost 40 times higher than for the crude crystalline lipids (11.2 vs 0.3 mg L^{-1}). The dissolution in simulated gastric and intestinal fluids was also faster for the impregnated compounds than for the pure form. The release was faster in the gastric medium, due to the acidic conditions that favor both the dissolution and the hydrolysis of the aerogel matrix [122]. In their second study, the authors evaluated the effect of a cooling step (natural or accelerated) prior to depressurization on the size of phytosterol particles, but the results were not conclusive. Apparently, nucleation was favored by fast cooling, yielding more isolated particles [121].

Using a similar approach, Pantic et al. [114,115] studied the incorporation of liposoluble vitamins D_3 and K_3 in alginate aerogel particles. Interestingly, assays were performed not only at supercritical conditions, but also at subcritical temperatures (5, 15, and 25°C), due to the thermal sensitivity of these vitamins and the prolonged impregnation times (up to 24 h). The authors observed that impregnation yield was higher and faster at near- and supercritical conditions, but the vitamin stability was higher when using liquid CO_2. This was deduced from the impregnation kinetic curves (**Figure 15**), which presented a maximum loading at intermediate times in the first case, and a subsequent decrease due to vitamin decomposition, not observed for liquid CO_2 impregnation [114]. In this sense, temperature accelerates the vitamin decomposition, but at the same time enhances its solubility in CO_2, yielding higher loadings. Release kinetics in a simulated lower gastrointestinal medium was studied for vitamin D_3 and compared with the pure crystalline form, showing a gradual and complete release after 5–6 h for the impregnated samples, while the crystalline vitamin was practically insoluble. The mainly amorphous state of the impregnated vitamin, confirmed by XRD analysis, explains this behavior. On the other hand, impregnation also contributed to stabilizing the vitamin under storage conditions (2–8°C): around 75–85% of the loaded vitamin was preserved after 4 weeks, with slightly better results for the samples impregnated at 5°C. Vitamin adsorption isotherms were also studied [115], showing that impregnation loading increases with the vitamin concentration in the fluid phase, but pressure does not have a significant effect.

More recently, Aredo et al. [119] have proposed the impregnation of lycopene, a carotenoid compound with antioxidant properties, in hydrolyzed collagen particles as a strategy for stabilizing it and enhancing its solubility in aqueous media. The chosen carrier is of proteic nature and has its own beneficial properties. In this work, the influence of the impregnation

conditions (50 and 60°C, 15 and 25 MPa) on the structural properties of the biopolymer carrier is illustrated.

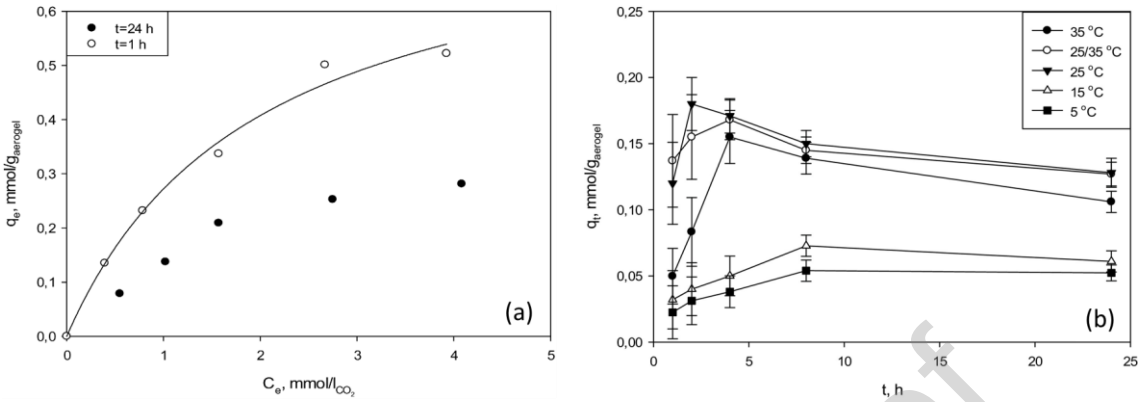

Fig. 15. (a) Adsorption isotherms for vitamin D_3 in alginate aerogel particles at 15 MPa and 40 °C with different contact times (line corresponds to Langmuir model fitting). (b) Impregnation kinetics of vitamin D_3 in alginate aerogel particles at 8 MPa and various temperatures. Adapted from [114,115], with permission. Copyright, Elsevier

When impregnation was performed at 50°C, loaded particles were obtained with no significant changes in size or morphology. However, at 60°C a semi-solid mass was obtained, which is attributed to the plasticizing effect of $scCO_2$ and indicates that the impregnation process was carried out above the glass transition temperature of the protein carrier, as confirmed by DSC analysis. Although the authors did not evaluate systematically the release rate of lycopene, they observed that the dispersion of the impregnated particles in water immediately produced two phases: an oily phase with most of the lycopene on the top, and an aqueous phase containing the particles and residual lycopene, suggesting that the release in this type of medium is very fast. Therefore, they suggest its applications in semisolid preparations, such as dairy products, where lipid and aqueous phases are well dispersed. It should be noted that lycopene was not used in pure form, but as a 20% solution in sunflower oil, which explains the appearance of the oily phase. Ethanol was used as cosolvent, due to the poor solubility of lycopene in $scCO_2$ at tested conditions.

Supercritical impregnation in biopolymeric carriers has also been studied as a way to protect some edible oils containing valuable nutraceutical compounds (such as polyunsaturated fatty acids, PUFA) which are sensitive to oxidation and/or elevated temperatures. Different carriers have been proposed. Gañán et al. [117] studied the impregnation of chia oil in soy protein isolate (SPI) microparticles, as an alternative to conventional spray-drying. This oil, obtained from chia seeds, is a natural source of linolenic acid (omega-3), among other PUFAs. In this work, the authors evaluated the effect of temperature (40–60°C) and pressure (10–16 MPa), as well as the use of ethanol as cosolvent, on the retention and encapsulation efficiency, operating

in batch mode. Up to 25% of the available oil was loaded into the particles, and results showed that pressure and presence of cosolvent (at 0.1 ethanol/CO_2 mass ratio) enhanced oil retention, which can be explained in terms of the increase of oil solubility in the CO_2 phase, or even a change of phase scenario (from partial to complete miscibility). The stability of the impregnated oil over time under storage conditions was evaluated via the hydroperoxyde value (HPV) and the fatty oil composition. Results confirmed the protective effect of the carrier: after 120 days of storage, HPV was 4.3 meq kg^{-1}-oil for the impregnated oil against 33.6 for free oil; the loss of omega-3 also showed an important reduction. Release tests in simulated salivary, gastric and intestinal fluids showed that most of the oil is delivered in the intestinal tract.

Aerogels have also been proposed as carriers for the protection of PUFAs and other valuable lipid compounds. Kleeman et al. [118] have evaluated the supercritical impregnation of fish oil in three protein-based aerogels: whey protein, egg white protein, and sodium caseinate aerogel microparticles. Impregnation yields (at 40°C and 18 MPa) were 33.1–51.1%, 44.3–63.6%, and 16.6%, respectively, depending on the pH of gel formation, which affected the aerogel structure. The aerogel swelling behavior and the release of oil in simulated salivary, gastric, and intestinal media were studied. All three protein-based aerogels did not disintegrate in aqueous solution, an advantage compared to polysaccharide-based aerogels. Moreover, they resisted gastric (peptic) digestion and released most of the oil in the simulated intestinal fluid, except the egg white protein aerogel, which was also resistant to tryptic digestion. Nevertheless, starch-based aerogels have also shown protective action against oxidative degradation of unsaturated lipids, as reported by Santos et al. [125]. These authors studied the supercritical impregnation of shark liver oil rich in squalene (a polyunsaturated triterpene with antioxidant and antitumor activity) in modified starch aerogel microparticles. Aerogels were obtained from two commercial octenylsuccinic anhydride (OSA)-modified starches, and they were impregnated with shark liver oil at 40–60°C and 12 MPa, using ethanol as cosolvent to increase the oil solubility. The microparticles were physically mixed with the oil, and the mixture was pressurized with CO_2 in batch mode for 40 min, followed by a fast depressurization. Penetration of the oil in the inner parts of the particles was observed, and impregnation yields of 17–19 wt% were obtained, independent of the operation temperature, representing retention of 74 to 82% of the oil present in the original physical mixture. This high retention efficiency may be due to the interactions between the lipids and the hydrophobic parts of the OSA-modified starch.

Starch-based aerogels and xerogels have also been proposed for protecting thymol, a monoterpene naturally present in several plant essential oils with aromatic and bioactive properties, from environmental degradation. In this sense, Milovanovic et al. [100] have studied the effect of the starch origin (corn and tapioca) and gelification temperature (T_{gel}, 70–100°C) on the impregnation yield of thymol using a view cell in batch mode, at 35°C and 15.5 MPa for 24 h, followed by decompression at 0.3 MPa min^{-1}. Air-dried xerogels and $scCO_2$-dried aerogels

were compared. Interestingly, the authors found a close correlation between T_{gel} and thymol loading, which was in the range of 0.58–4.02 wt%. In turn, xerogels showed a higher loading capacity than aerogels, which can be related to their quite different surface area (4.25–5.52 $m^2 g^{-1}$ vs. 0.019–0.035 $m^2 g^{-1}$), suggesting that the $scCO_2$-drying procedure should be further optimized for preserving the gel porous structure.

The dissolution behavior of a lipid compound can strongly depend on the type of carrier where it is impregnated. For instance, Scognamiglio and De Marco [113] have studied the release of α-tocopherol in an aqueous medium from two different aerogels after supercritical impregnation: inorganic silica and maize starch microparticles. Impregnation was performed at similar conditions (40°C, 11 MPa, in batch mode, with a depressurization rate of 1 MPa min^{-1}) for both systems, and the impregnation kinetics was determined up to 48 h. Impregnation yield was higher for the silica aerogel (30 wt% vs. 13 wt%), which may be related to the higher porosity and surface area of this material. The release behavior was qualitatively different: for the maize starch aerogel was very fast (100% released after 75 min, 16 times faster than for the pure tocopherol or its physical mixture with the particles), while the tocopherol loaded into silica aerogel was released at a much slower and sustained rate (approx. 4 times slower than the pure compound). This difference suggests a faster response to water absorption, swelling, and erosion for starch aerogel.

3.4.2. Hydrophilic compounds

In the case of hydrophilic compounds with poor $scCO_2$-solubility, such as polyphenols, the "wet impregnation" strategy has been explored by different authors for loading aerogels or other porous matrices. This approach consists in the incorporation of the active compound during the hydrogel or alcogel formation step, and its subsequent precipitation into the porous structure during the supercritical drying stage, where the liquid solvent is removed. In this way, Viganó et al. [124] have obtained alginate aerogel microparticles loaded with passion fruit bagasse extract (PFBE, previously obtained by supercritical CO_2 extraction) rich in bioactive polyphenols, such as piceatannol. An ethanolic solution of the extract was added in the last solvent exchange step (instead of pure ethanol), obtaining a PFBE-loaded alcogel, which was afterward dried with a continuous $scCO_2$ flow at 40°C, 12 MPa and a flow rate of 10 g min^{-1}, followed by depressurization at a rate of 1.5 MPa min^{-1} at a constant temperature. The total extract loading in the dried particles was 0.62 g g^{-1}-raw aerogel, while for total phenolics and piceatannol it was 10.77 mgGAE g^{-1} and 741.85 μg g^{-1}, respectively. However, the authors observed a loading efficiency of 47.1% for total phenolics and 34.7% for piceatannol, indicating that an important part of the extract is lost during the drying step. Therefore, an optimization of the drying

conditions, based on a deeper knowledge of the phase behavior of the [polyphenols+ethanol+CO_2] system, appears crucial for reducing excessive losses.

Using a similar approach, Dos Santos et al. [182] have explored the incorporation of trans-resveratrol, a bioactive polyphenol commonly administered in dietary supplements, in alginate aerogel particles. During the solvent exchange process, ethanolic solutions of resveratrol with different concentrations (1, 5, and 10 wt%) were added, and then the alcogels were dried at 40°C and 11 MPa with a continuous CO_2 flow rate of 4.16 g min^{-1}. In this case, resveratrol loading values were in the range of 6.7–63.7 wt% (by HPLC analysis), increasing with the concentration of the ethanolic solution. XRD analysis revealed that the supercritical process did not affect the amorphous structure of the alginate aerogel nor the crystalline nature of resveratrol. These works demonstrate that the combination of wet impregnation and supercritical drying is a suitable and convenient approach to obtaining aerogels loaded with hydrophilic active compounds in a relatively short time, although more research is needed to evaluate the effect of different process variables on the impregnation performance and final properties of the loaded materials.

Finally, the combination of supercritical CO_2 extraction and online impregnation opens an interesting field for the revalorization of bioactive natural extracts as well as process intensification. In this sense, the tunable properties of $scCO_2$ can be modified to adjust its solvent power and selectivity towards desirable compounds or families. Maksimovic et al. [183] have studied an integrated $scCO_2$ extraction+impregnation approach for the incorporation of a *Helichrysum italicum* extract in corn starch xerogels, obtained by air-drying of alcogels and acetogels. The aim was to obtain a formulation suitable for oral delivery of bioactive compounds with antioxidant activity and effective for treating digestive disorders. In this case, the plant material was extracted at 40°C and 35 MPa, with a flow rate of 0.19 kg h^{-1}, either with pure $scCO_2$ or adding 10 wt% ethanol to the extraction bed, and this mixture was continually fed to an adsorption column filled with the xerogel particles, operating at the same temperature and pressure conditions, for 5–8 h, followed by a final depressurization at 3.5 MPa min^{-1}. This study illustrates how the process parameters can affect differently the performance of each integrated operation. For instance, the authors observed an increase in extraction yield (more than 2-fold) when ethanol is used as cosolvent. However, in that case, the impregnation yield decreased by almost 50% (compared to extraction using pure $scCO_2$), which can be explained in terms of a higher affinity of the extracted compounds for the fluid phase when ethanol is present, leading to a higher fluid–polymer partition coefficient. Furthermore, a decrease in impregnation yield was also observed with time (from 5 to 8 h), which may indicate the exhaustion of the plant material: in that case, almost no extract was fed to the impregnation column after ~5 h, with $scCO_2$ acting rather as a desorber of already loaded compounds. In these cases, an overall process optimization approach seems essential.

Table 7. Dietary supplement products obtained by $scCO_2$-assisted impregnation/deposition.

Polymer-based matrix	Active ingredient, or mixture of active ingredients /extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
Starch	α-tocopherol (vitamin E)	Aerogels	15	60	1 – 48	1	-	13 (vs. silica aerogel: 30)	[113]
Starch	Menadione (vitamin K_3)	Aerogels	15	40 – 60	1 – 48	1	-	95 – 98	[111]
Starch	Thymol	Xerogels, aerogels	15.5	35	24	0.3	-	Xerogel: 1.8 – 4.0; aerogel: 0.6 – 3.3	[100]
Starch	*H. italicum* extract (rich in pyrogallol, chlorogenic, and gentisic acids)	Xerogels	35	40	5 – 8	3.5	10 wt% ethanol	0.5 – 1.26	[183]
Nanoporous starch	Crude phytosterols (beta-sitosterol + stigmasterol + campesterol)	Aerogels	45	70 – 95	3	1 L min^{-1} (NPT)	-	5.5	[122]
Nanoporous starch	Crude phytosterols (beta-sitosterol + stigmasterol + campestero	Aerogels	45	70 – 120	3	1 L min^{-1} (NPT, fast or slow cooling)	-	5.5 – 9.9	[121]

Polymer-based matrix	Active ingredient, or mixture of active ingredients /extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
	l)								
Modified starch	Shark liver oil (rich in squalene)	Particles	12	40 – 60	0.67	12	ethanol (% *n.i.*)	17 – 19	[125]
Alginate	Cholecalciferol (vitamin D_3)	Aerogels	8	5 – 35	1 – 24	0.3	-	0.77 – 6.53	[114]
Alginate	Cholecalciferol (vitamin D_3)	Aerogels	15 – 20	40	1 – 24	0.3	-	8 – 11	[115]
Alginate	Menadione (vitamin K_3)	Aerogels	15 – 20	40	1 – 24	0.3	-	6 – 7	[115]
Alginate	Trans-resveratrol	Aerogels	11	40	0.17 – 2	2 L min^{-1} (NPT)	ethanol (% *n.i.*)	6.7 – 77.1	[182]
Sodium alginate/ silica	*Phytol - Clinacanthus nutans* extract (rich in phytol)	Aerogels	15	40	24	2	10 wt% ethanol	13	[107]
Calcium alginate	Passion fruit bagasse extract (rich in piceatannol)	Aerogels	12	40	*n.i.*	1.5	-	62	[124]

Polymer-based matrix	Active ingredient, or mixture of active ingredients /extract	Morphology	Process conditions					wt% drug loading	Ref.
			Pressure (MPa)	Temperature (°C)	Contact time (h)	Depressurization rate (MPa min^{-1})	Co-solvent		
Soy protein isolate	Chia oil	Particles	10 – 16	40 – 60	2	0.6	0.1 – 0.1 wt% ethanol	2.1 – 12.5	[117]
Whey protein, egg white protein, or sodium caseinate	Fish oil	Aerogels	18	40	72	< 0.1	-	WPI: 33.1-51.1; EWP: 44.3 – 63.6; NaCaS: 16.6	[118]
Hydrolyzed collagen	Lycopene	Particles	15 – 25	50 – 60	0.75	Slow (~15 min)	4 wt% ethanol	8.4 – 9.4	[119]
PLA/ Lignin nanoparticles	Cinnamaldehyde	Films	12	40	3	1	-	10.8	[184]

4. Process and scale-up aspects

A $scCO_2$-assisted impregnation/deposition unit consists basically of two elements: 1) the impregnation or loading chamber, i.e., a high pressure vessel where the polymeric carrier is contacted with the supercritical solvent + active ingredient mixture; and 2) a system for handling and conditioning the supercritical solvent. The development of an impregnation/deposition process involves the progressive scaling up of this scheme, from laboratory scale to pilot plant and industrial units. At each step, the size of the loading chamber increases several orders of magnitude, from less than 1 liter in most lab-scale units to several tens or hundreds. Scaling up usually also involves changes in the overall process configuration. Most laboratory-scale schemes reviewed here operate in batch mode, i.e., the polymeric carrier and the active ingredients to be impregnated (and eventually the cosolvent) are loaded together in a high-pressure vessel, which is subsequently pressurized with CO_2. The system is kept at fixed temperature, pressure, and agitation conditions for a period of time, and then it is depressurized. However, some units operate in semicontinuous mode [104]; in this configuration, the polymeric carrier is loaded in the impregnation/deposition vessel or column and a continuous stream of [$scCO_2$ + active ingredient] mixture is continuously fed at a fixed flow rate. This mixture is synthesized in a separate vessel or in a presaturator, where the CO_2 stream dissolves the active ingredient prior to entering the impregnation column. Cosolvents can be added to the mixture or fed using a separate pump. In other cases, a combination of both schemes is employed; for example, Ubeyitogullari et al. [121] report the impregnation/deposition of phytosterols in starch aerogel particles using a semicontinuous process but in a single vessel, where the phytosterols and the particle bed are separate by a glass wool filter; the CO_2 enters continuously from the bottom, dissolves the phytosterols, and then flows through the particle bed. Semicontinuous operation is also applied in the "wet impregnation" process, where aerogel drying and impregnation are performed in a single step [124,182].

$scCO_2$-assisted impregnation/deposition processes are more easily scalable than other supercritical-based technologies. In many respects, impregnation/deposition is similar to an extraction process, although the mass transfer mechanisms are inversed. The problem of extract separation is replaced by the problem of synthesizing the [CO_2 + active ingredient] mixture.

As previously mentioned, two main applications have successfully reached the industrial scale: wood impregnation with antimould agents [2] and water-free textile dyeing [3]. Although these cases are out of the scope of this review, they can provide useful information for the design of impregnation/deposition processes of interest for the pharmaceutical industry.

At industrial scale, a system for the regeneration and recycling of CO_2 is mandatory due to economic reasons. As has been pointed out, the solubility of many drugs and other active ingredients in $scCO_2$ is usually very low, requiring significant amounts of CO_2 for achieving practical loading values. This is solved by operating in a closed CO_2-cycle, where a high pressure pump is used for pressurizing the

system at the desired value, and afterward, a secondary pump recirculates the fluid through the impregnation vessel and the presaturator, compensating for pressure losses in the circuit [3]. Different devices for purifying the CO_2 stream and separating the residual active ingredient without significant pressure loss (such as adsorption beds or membranes) can be added. This closed loop is operated for a certain period until the desired loading level, and subsequently, the system is depressurized and CO_2 is purified, cooled, and returned to the storage tank.

An efficient scale-up procedure involves the optimization of some process variables (pressure, temperature) in a lab-scale screening unit, and a subsequent study of geometrical, fluid dynamics, and mass transfer aspects in larger pilot plant units. The obtained experimental information can provide the basis for the development or adjustment of mathematical models which can be very useful tools for process design and optimization at industrial scale, along with the calculation of energy consumption and operation costs. Mathematical models have been developed, including mass and energy balances, phase equilibrium calculations, and suitable models for the mass transfer in the fluid phase and the polymer [20]. Different approaches, based on diffusion models or mass transfer coefficients, have been proposed. However, in the case of the impregnation/deposition processes analyzed in this review, the simulation and optimization of large scale processes, as well as the economic analysis, are still largely unexplored. In the reviewed period, only one paper has reported a life cycle assessment for the evaluation of the environmental impacts of the $scCO_2$-assisted impregnation/deposition of α-tocopherol in starch aerogel, from corn cultivation [185]. This analysis allowed to improve the original process, demonstrating that a 30% reduction of the global impact could be achieved by recycling the ethanol used in the alcogel formation and modifying the conditions of CO_2 condensation.

Moreover, the integration of $scCO_2$-assisted impregnation/deposition with other supercritical-based technologies may be a promising field for research. The coupling of extraction and impregnation makes use of the tunable properties of $scCO_2$ for obtaining active principles/extracts from natural sources and loading them into polymeric carriers in a single semicontinuous process; for instance, it has been proposed for the development of scaffolds with antimicrobial activity [186]. The integration of drying and impregnation has already been mentioned as a strategy for obtaining active aerogels. Finally, the combination of impregnation/deposition with other supercritical-based particle formation processes is particularly relevant and promising for the production of pharmaceutical and nutraceutical materials with specifically targeted functionalities [181].

Furthermore, industrial-scale high pressure equipment and accessories are currently available, mainly for $scCO_2$-based extraction, dyeing, and sterilization processing, with several companies in the market like *NovaSterilis*, *Superex*, *Lewa*, *Careddi Technology Co.*, *Kisko Ltd.*, *Natex*, among others. In particular, *ExtracteX* offers a *"supercritical fluid powder formation system for the pharmaceutical, food and cosmetics industries"* [187], suitable for different $scCO_2$ processes. Nevertheless, the open information on industrial processes and commercially available products for drug delivery, medical

devices, and dietary supplements based on supercritical impregnation/deposition is still scarce. Only two companies were found using $scCO_2$-assisted impregnation without mentioning any particular commercial product: HydrUStent SA (Portugal), which offers an innovative impregnation process for medical devices development using $scCO_2$ in a clean room (ISO 6) [188], and Pierre Fabre Laboratories (France), which patented FORMULPLEX [189], a process that improves the bioavailability of poorly-soluble active ingredients via complexation with cyclodextrin in $scCO_2$. Moreover, this laboratory offers to scale-up other $scCO_2$-assisted processes via good manufacturing practices (GMP) unit.

Finally, although the activity related to $scCO_2$-assisted impregnation/deposition in the pharmaceutical, biomedical, and nutraceutical fields has been mostly limited to lab-scale research during the last years, it is likely that some applications will reach industrial scale in the near future, based on the promising results obtained in some cases, as well as the know-how already developed in the successfully scaled-up processes [8].

5. Conclusions and perspectives

A good deal of work at lab-scale has shown the technical feasibility of loading drugs and other active ingredients in polymeric carriers by $scCO_2$-assisted impregnation with an efficiency comparable to (or even superior to) other conventional technologies. As can be seen, it has been an active field of research in the last years. In particular, the possibility of using commercial and/or pre-specified polymeric materials with definite properties as impregnation carriers, as well as the solvent-free and inert medium provided by this technology, allows for an optimistic view of the industrial development of $scCO_2$-assisted impregnation processes in the pharmaceutical, biomedical, and nutraceutical fields. This is, for example, the case of drug-loaded intraocular and contact lenses, where a carefully controlled supercritical treatment can provide a good drug dispersion while preserving desired properties (e.g., transparency). Nevertheless, in many cases, some operating aspects should be deeper studied and discussed in order to compare to other conventional technologies and evaluate the industrial viability of the proposed processes. Particularly, the control of the polymer morphology changes induced by the supercritical treatment is a critical aspect for the development of efficient products. It has to be noted that most of the work reviewed here is preliminary, and the relationship between process conditions and final properties has not yet been fully understood in many cases.

The incorporation of plant extracts and other botanical products with claimed bioactive or therapeutic properties in polymeric carriers is currently an attractive trend. However, many of these products are not yet approved for medicinal use by national agencies or pharmacopoeias, therefore limiting their possibility to reach the market. In this sense, more research to confirm the claimed therapeutic activity of botanical drug-based products is required.

Due to the great variety of systems reviewed here, it is difficult to systematize processing conditions that may guarantee a successful loading. However, some general conclusions can be formulated. Conditions that enhance drug solubility in $scCO_2$ (namely, higher CO_2 density) usually lead to higher loading yields if a good drug/polymer affinity exists; if not, the equilibrium partition will favor the fluid phase, and/or a significant amount of drug will be removed during depressurization. CO_2 sorption is also favored under these conditions, inducing a higher polymer plasticization; this can be an advantage, by enhancing the drug diffusion, but in some cases, it can lead to polymer melting, recrystallization, and/or foaming. If these morphology changes are to be avoided, a trade-off exists limiting the highest possible pressure and temperature conditions.

The loading mechanism is an important aspect regarding the subsequent product behavior, for example, in terms of drug release. Although there is always a certain amount of drug superficially deposited or adsorbed to the polymer (as shown in several cases), molecular dispersion (bulk impregnation) will be increasingly important as the polymer becomes more swollen and plasticized by CO_2. The diffusional behavior in both cases may be very different.

In the field of dietary supplements and active food ingredients, $scCO_2$-assisted impregnation/deposition has proven useful for preserving valuable compounds in particulate and/or porous carriers, either from environmental deterioration agents or from digestive processes, thus improving their bioavailability. However, the resistance to thermal degradation of the impregnated systems has not received much attention, although thermal treatments are usually common in food industries. The incorporation of impregnated particles in real food products, and the assessment of their organoleptic and textural properties in comparison with conventionally loaded carriers, is another interesting research area towards the application of this technology.

Finally, the combination of different $scCO_2$-based operations to intensify manufacturing processes is gaining increasing attention. The coupled extraction and impregnation of active natural extracts, the combination of drying and impregnation (“wet impregnation”) of aerogels, and the simultaneous foaming and impregnation of polymers are some challenging examples that illustrate the potential of supercritical technologies in this field.

Nevertheless, according to the open information, commercial products obtained by $scCO_2$-assisted impregnation/deposition for drug delivery, medical devices, or dietary supplements are not yet available on the market, even though some products have already been registered as patented inventions. In this sense, the normally long time needed from the research and development steps to the product commercialization in the pharmaceutical/medical/food fields, mainly due to regulatory aspects, may be delaying the appearance of commercial products. Furthermore, the selection of raw materials with the appropriate quality and approved for the intended use, as well as the conditioning of equipment and facilities under GMP regulations, seem crucial to shortening the path between laboratory scale and commercialization. Another possible limitation is the lack of available economic studies to confirm the feasibility and competitiveness compared to conventional processes. Finally, in

the same way as $scCO_2$-based extraction, dyeing and sterilization have reached the market after a certain period, it is expected that impregnation/deposition processes also reach some growth in the upcoming years.

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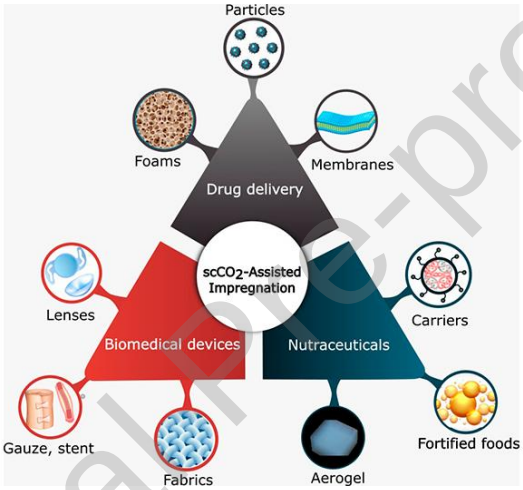
Declaration of Competing Interest

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:



Graphical abstract

HIGHLIGHTS

- Advances in scCO2 impregnation in pharmaceutical, biomedical, and nutraceutical fields are reviewed.
- The period 2015-2021 was included and critically discussed.
- Delivery systems have been mainly focused on enhancing or adjusting the drug solubility.
- scCO2-assisted impregnation results useful for preserving valuable food ingredients.
- Combined scCO2-based operations to improve manufacturing processes are gaining increasing attention.