Ph.D. course in INDUSTRIAL ENGINEERING,
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"Production of polymer/active compound composites by supercritical CO_2 assisted processes"

Abstract of the thesis

The interest in the production of novel polymer/active compound composites has increased over time as a response to the main issues encountered in the pharmaceutical field. Nowadays, polymeric carriers are employed to prepare composite systems with several aims, including the protection or stabilization of an active compound, as well as masking its unpleasant taste or odor. However, the main challenge is to reach a control of the drug release rate from innovative pharmaceutical forms, overcoming the drawbacks associated to the use of conventional formulations. The latter ones often provide uncontrolled drug release, sometimes out of the therapeutic range; as a consequence, high and repeated drug dosages are necessary, leading to serious side effects on the patient's health. Different formulations can be fabricated as drug delivery systems, such as granulates, tablets or topical patches. However, the technologies generally used to produce composites suffer from some drawbacks, including the possible degradation of the active compound due to the high operating temperature, or multistage processing required to remove organic solvents, whose residues are often not negligible in the final composites. Supercritical carbon dioxide ($scCO_2$) assisted techniques are considered a good alternative to overcome all the main limits involved in the use of traditional processes.

In this Ph.D. work, two $scCO_2$ assisted processes are proposed to produce different polymer/active compound composites:

- Supercritical AntiSolvent (SAS) technique, to produce composite powder with a microparticle-like morphology;
- supercritical impregnation, to obtain orally disintegrating tablets (ODTs) or topical patches.

The main goal is to accelerate or to slow down the dissolution rate of the active principle contained in the composites, depending on the therapeutic effect required by a specific application. In this way, the drug doses or the frequency of administration, as well as side effects, can be reduced,

improving the patient's compliance. For this purpose, different polymer/drug systems were studied. Both in case of the microspheres' production by SAS and the drug impregnation into supports, the selection of a proper polymeric carrier according to the desired drug release is particularly important. Specifically, when a hydrophilic carrier is employed, a fast dissolution rate of the active principle is reached. This option is promising to enhance the bioavailability of poorly-water soluble compounds, such as non-steroidal anti-inflammatory drugs (NSAIDs) prescribed for minor inflammations, or natural compounds (e.g., flavonoids) with numerous benefits for human health. On the other hand, the use of hydrophobic polymers promoted a prolonged drug release. This kind of carriers can be combined with drugs that are highly-water soluble or prescribed for chronic diseases, such as antibiotics, NSAIDs, antihistamines, bronchodilators or anticoagulant drugs.
Regarding SAS technique, the polymer/drug coprecipitation mechanisms in correspondence of different morphologies were also postulated by means of dissolution studies, demonstrating that SAS coprecipitation was fully achieved when microspheres are produced. Until now, one of the weaknesses of the SAS technique was that the coprecipitation had been actually achieved only with a limited number of polymers; i.e., polylactic acid (PLA), poly (L-lactic acid) (PLLA) and polyvinylpyrrolidone (PVP). In this work, the effectiveness of other carriers, namely zein, Eudragit L100-55 and β-cyclodextrin (β-CD), was successfully asserted, optimizing the process conditions to assure an effective coprecipitation in form of composite microparticles. It was proved that both microspheres and guest/host inclusion complexes can be produced by SAS, using a generic polymer or β-CD as oligosaccharides, respectively. The results of dissolution tests highlighted that zein and Eudragit L100-55 tend to prolong the release of the drug embedded into the microspheres. It has to be consider that Eudragit and zein are low cost polymers with respect to lactic acid-based polymers proposed so far to obtain SAS particles that promote a prolonged drug release. Conversely, the preparation of β-CD based complexes allowed to enhance the dissolution rate of active compounds. The use of β-CD also appears to be promising in reducing the amount of carrier in SAS-coprecipitated powders, which is a considerable milestone from a pharmaceutical point of view.
Topical patches and ODTs were prepared by the versatile supercritical impregnation, incorporating different drugs into thin films or aerogels. ODTs both for a rapid or prolonged release of NSAIDs were produced by selecting maize starch aerogel (MSA) and calcium alginate aerogel (CAA), respectively. Peppas mathematical model (Ritger and Peppas, 1987) was applied to identify the dominant factor in the drug release behavior, which is often a combination of solvent diffusion and polymer chain relaxation. In order to produce medicated patches for the wound healing, a single step consisting of the polymer foaming and the drug impregnation into the foam was proposed. The drug release from foamed polycaprolactone (PCL) was significantly prolonged, promoting a proper tissue regeneration. The supercritical impregnation of drugs into polymeric films was suggested for the first time for pharmaceutical applications. The study of the impregnation mechanisms of drugs into all the supports proved that, in general, the impregnation using $scCO_2$ is first governed by the film diffusion, thus the drug is impregnated on the outer surface of the matrix. Then, the impregnation is controlled by pore diffusion, so the drug is also loaded onto the inner pores of the support.
In conclusion, the $scCO_2$ assisted techniques are very versatile and promising to produce different pharmaceutical forms that offer different drug release kinetics, depending on the specific application.