ABSTRACT

Controlled release systems for therapeutic drugs have received extensive attention in recent years, due to their great clinical potential. Biodegradable microspheres are well-recognized systems to control the release rate of a drug out of a pharmaceutical dosage form; they are able to protect these agents against rapid degradation and clearance and release them in the body with a desired controlled rate and amount. Particularly, biopolymer microspheres are attracting increasing attention as drug carriers for injectable controlled release formulations.

Biopolymer microspheres for controlled drug delivery can be conventionally prepared by solvent evaporation/extraction of emulsions, but this technique shows many drawbacks (high temperature, long processing times, large polidispersity, high residual solvents, lower encapsulation efficiency). To overcome the limits of the traditional process, in recent years, Supercritical Emulsion Extraction (SEE) has been proposed for the production of drug/polymer microspheres with controlled size and distribution, starting from *oil-in-water (o-w)* and *water-in-oil-in-water (w-o-w)* emulsions. This process uses supercritical carbon dioxide (SC-CO_2) to extract the "oil" phase of emulsions, leading to near solvent-free microparticles. SEE offers the advantage of being a one-step process and is superior to other conventional techniques for the better particle size control, higher product purity and shorter processing times; but, as traditional processes, it shows problems related to batch-to-batch reproducibility and reduction of the process yield, due to the intrinsically discontinuous operation.

In the present work, a novel SEE configuration is proposed in a continuous operation layout (*Continuous Supercritical Emulsion Extraction, SEE-C*) using a countercurrent packed tower, for the production of controlled-size biopolymer microparticles in a robust and reproducible mode. Particularly, the purpose of this thesis is the optimization and characterization of the SEE-C process to investigate its capabilities and performances in the production of poly-lactic-*co*-glycolic acid (PLGA) microparticles with an engineered size and distribution and charged with different active principles (APs).

Before to investigate the possibility to produce AP/PLGA microspheres, an optimization of the process has been performed. Indeed, the thermodynamics of the selected system (ethyl acetate+CO_2) has been studied, together with the analysis of the process operating parameters. Moreover, a fluidodynamic characterization of the packed tower has been carried out to identify the best condition of operation, below the flooding point. The capacity limits for the packing material have been evaluated and, then, directly measured in terms of flooding point at different operating conditions.

Afterwards, firstly blank (drug-free) PLGA microparticles have been successfully produced, starting from single and double emulsions. Secondly, anti-inflammatory drugs (such as Piroxicam and Diclofenac Sodium), corticosteroids (such as Hydrocortisone acetate) and proteins (such as Insulin) have been chosen as model compounds to be entrapped within PLGA microspheres.

All the emulsions produced were stable with non-coalescing droplets. The corresponding microspheres obtained were spherical in shape and well-defined with narrow size distributions, due to the short processing time that prevents aggregation phenomena typically occurring during conventional solvent evaporation process.

The influence of some emulsion formulation parameters (such as polymer concentration and emulsion stirring rate) on particle size has been investigated, showing that the droplet formation step determines size and size distribution of the resulting microspheres; particularly, a significant increase in particle size with the increase of polymer concentration or the decrease of emulsion stirring rate has been observed. Moreover, the effect of kind and formulation of emulsion on the microsphere characteristics has also been investigated, demonstrating that the choice of the encapsulation approach and the emulsion composition have a considerable influence on the attainable drug encapsulation efficiency.

The produced microspheres have been characterized by X-ray, DSC, HPLC and UV-vis analysis. DSC and X-ray analyses confirmed that the microspheres were formed by an AP/PLGA solid solution and the active principle was entrapped in an amorphous state into the polymeric matrix. HPLC analysis revealed that good encapsulation efficiencies have been obtained in the products obtained. Release studies showed uniform drug concentration profiles, confirming a good dispersion of the drug into the polymer particles. The obtained AP/PLGA microspheres can degrade and release the encapsulated active principle slowly with a specific release profile. Active principle loading, particle size and emulsion kind revealed to be the controlling parameters for drug release. A study of PLGA microparticles degradation has also been carried out to monitor any morphological difference in time of the biodegradable devices produced by SEE-C.

Moreover, a comparative study between the characteristics of the PLGA microspheres obtained by SEE-C and the ones produced by the corresponding batch operating mode process (SEE) and conventional evaporation technology (SE) has been performed. PLGA microparticles produced by SEE-C showed a mean particle size always smaller than that associated with particles produced by SEE and SE; physico-chemical properties showed no morphological and structural differences between the processes. Compared with conventional technologies for the preparation of drug delivery systems, e.g. solvent evaporation emulsion techniques, the novel process is environmentally superior and suitable for scaling up to industrial dimensions. Moreover, the higher degree of control, as indicated by the high reproducibility, makes validation of the process very simple.

In conclusion, the SEE-C process has shown to be an attractive way of incorporating active principles into biodegradable microparticles for controlled release formulations. Greater product uniformity, higher throughput with smaller plant volumes and elimination of batch-to-batch repeatability problems are the significant advantages observed.