PRODUCTION OF POLYMER MICROPARTICLES FOR PHARMACEUTICAL APPLICATIONS BY SUPERCRITICAL FLUID EXTRACTION OF EMULSIONS

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The biodegradable polymer PLGA is an interesting excipient for pharmaceutical purposes such as controlled drug release and drug targeting. Drug-entrapping micro-particles with a narrow particle size distribution are desired for such applications. In this work, we investigate a novel process for the production of such particles, namely supercritical fluid extraction of emulsions, and demonstrate its potential by producing spherical, submicron PLGA particles with a homogeneous size distribution.

INTRODUCTION

Poly-lactic-co-glycolic acid (PLGA) is a biocompatible and biodegradable polymer, and used as constituent for drug-polymer co-formulations serving specific pharmaceutical purposes such as controlled release and targeted drug delivery [1]. Since important characteristics of the particles, e.g. the kinetics of drug release from co-formulations, or their suitability for drug targeting, are influenced by particle size [2], narrow particle size distributions are desired for such applications [3]. There is a need for the development of processes that enable the production of such particles in the size range of a few micrometers, and at conditions that comply with the delicate nature of the materials involved.
Supercritical fluids, mostly supercritical CO_2, are applied in a number of different processes aiming at the production of particulate pharmaceuticals [4]. In all cases, the major advantage of these processes is that they allow the production of a pure and solvent-free product at comparably mild operating conditions. Supercritical fluid extraction of emulsions (SFEE) is a novel process characterized by advantages, namely good control over particle size [5, 6]. In this process, an organic solution of PLGA is dispersed in an oil-in-water emulsion and stabilized by a suitable surfactant. Then, the emulsion is mixed with supercritical CO_2 in order to extract the organic solvent from the emulsion droplets. Thereby, stable suspensions of solvent-free PLGA droplets in water are obtained, and solidified polymer particles may be recovered upon depressurization. The current study demonstrates the potential of the supercritical fluid extraction of emulsions process for the production of submicron, spherical particles of PLGA and drug-PLGA composites for pharmaceutical applications.

EXPERIMENTAL

Processing of PLGA by the SFEE process

A 1 %wt. solution of poly-vinyl alcohol (PVA; Mowiol 4-88, Sigma-Aldrich, Buchs, Switzerland) was prepared in water saturated with ethyl acetate, and 10%wt. PLGA (5050 DLG 5A, Lakeshore Biomaterials, Birmingham AL, USA) were dissolved in ethyl acetate saturated with water. At a ratio of 4:1, both solutions formed an (o/w) emulsion upon mixing with a Polytron mixing device (Kinematica AG, Luzern, Switzerland), applying a stirrer speed

of 30000 rpm for 150 s. At 45°C and 80 bar, a feed stream of 2 ml/min emulsion was continuously mixed with 80 g/min of supercritical CO_2 in a two-substance nozzle (Schlick, Untersiemau, Germany) in order to extract the solvent. The solvent-free suspension was collected in the bottom of a 900 ml reactor vessel (Premex, Lengnau, Switzerland), and withdrawn continuously during the process. PLGA particles were recovered from the suspension by centrifugation, washing and subsequent freeze-drying. Figure 1 shows a SEM micrograph of the recovered PLGA particles. It is worth noting the remarkably small size and uniformity of the produced particles.

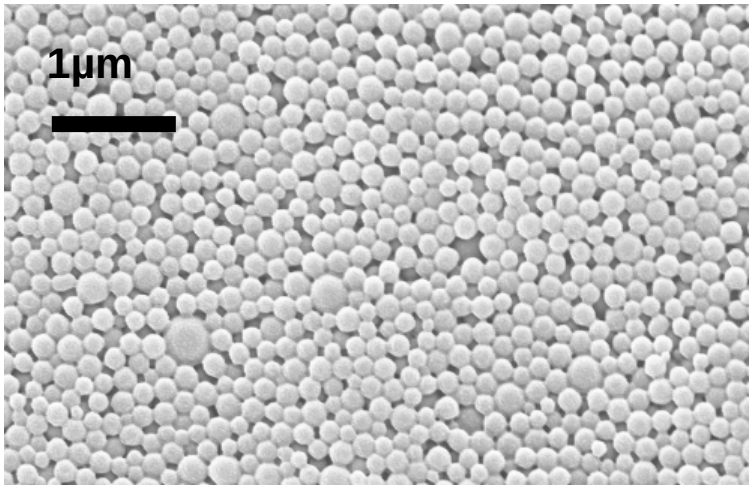

Figure 1:

SEM micograph of freeze-dried PLGA particles prepared by the SFEE process.

CONCLUSION

The SFEE process was successfully applied for the production of submicron spherical PLGA particles characterized by a very homogeneous particle size distribution. Ongoing investigations address whether and how the size of the particles may be influenced by operating conditions. A further aim of this study is to demonstrate the potential of the SFEE process for manufacturing co-formulations of PLGA with active pharmaceutical ingredients. This includes an investigation of methods for drug incorporation into PLGA particles, which is especially challenging for the case of water-soluble bio-molecules. As a next step, the kinetics of drug release from such co-formulations will be addressed.

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