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Kinetics of solvent extraction/evaporation process for PLGA microparticle fabrication

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ABSTRACT

Organic solvent extraction/evaporation from an o/w-dispersion has been widely used for the fabrication of PLGA microparticles. The purpose of this work was to elucidate the kinetics of the solvent extraction/evaporation process. A mathematical diffusion model was developed and applied to predict the duration of the solvent extraction. As the diffusion coefficient, D_p, plays a major role in the modeled process, a new and experimentally simple method for estimating D_p was developed. Both the experimental method and the mathematical model were validated through PLGA microparticle fabrication experiments. For microparticles of mode diameters of 2 and 20 μm, the solvent was extracted in approximately 10 s. Sufficient hardening of the microparticles required, however, the evaporation of solvent from the extraction phase. Residual solvent in extraction phase exerted a strong effect on the morphology of the final product as demonstrated by scanning electron microscopy. Only if most solvent was removed from the aqueous extraction phase, a powdery product of individual microparticles was obtained. At residual organic solvent concentration of above 0.2% in the extraction phase, the microparticles strongly aggregated during collection on a membrane filter and final drying. The presented methods may be useful for better controlling microparticle fabrication processes by solvent extraction/evaporation.

1. Introduction

Biodegradable poly(lactide-co-glycolide) (PLGA) or poly(lactic acid) (PLA) microparticles for controlled drug delivery are frequently fabricated by organic solvent extraction from o/w- or w/o/w-emulsions. The performance and robustness of the fabrication processes have successfully been optimized by well-controlled emulsification techniques (Freitas et al., 2004, 2005; Berkland et al., 2001) and the composition of the o- and w-phases (solvents and other additives) (Zhang and Zhu, 2004; Graves et al., 2005; Chen et al., 2004). Various studies have also elucidated the most important physical chemical parameters controlling the solvent extraction process (Wang and Schwendeman, 1999; Li et al., 1995a,b; Maa and Hsu, 1996). Such parameters are critical for modeling the process steps, which in turn may be of general significance for, e.g. (i) fabrication of micro- and nanoparticles from different materials, (ii) scaling the process to pilot or production level, and (iii) introduction of automation technologies.

A review of the literature has revealed that the modalities and duration of solvent extraction and solvent evaporation from the process system still much depends on empirical know-how. To predict the duration of the solvent extraction, the diffusion coefficient of the solvent in polymer solution is an important parameter. To determine the solvent diffusion coefficient, experimentally developed equations like the Wilke–Chang equation (Wang and Schwendeman, 1999) and others (Li et al., 1995a) have been used. These equations require empirical parameters and approximations, which are strongly material dependent.

In addition to the solvent diffusibility in the polymer phase, the amount of solvent in the extraction phase is also a critical parameter. The solvent extracted from the o/w- or w/o/w-emulsions must eventually be removed from the extraction phase to obtain solid particles. We noticed that there is very little data and discussion on the relationship between the amount of residual solvent in the extraction phase and the quality of the final particulate product (micro- or nanoparticles).

In this work, we aimed at elucidating the kinetics of solvent extraction and evaporation from an o/w-dispersion. In particular, we developed a mathematical model describing the kinetics of solvent transport from the o-phase into the surrounding w-phase (extraction phase). Moreover, we investigated the influence of the amount of residual solvent in the extraction phase on the

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morphology of the final product. We expect that the model and derived knowledge will assist in future process design optimization (automation, up-scaling) and provide information on the conditions needed (fluid dynamics, process time) to obtain solid particles that can readily be separated from the processing liquid.

2. Model development

Fig. 1 illustrates the basic steps of commonly used solvent extraction/evaporation processes for PLGA micro- and nanoparticle fabrication. In Step 1, a solution of polymer in an organic solvent is emulsified into an aqueous extraction phase generating the initial stage of microparticle shaping. In Step 2, the organic solvent of the polymer phase droplets is extracted into the surrounding aqueous extraction phase; this process is governed by solvent diffusion along its concentration gradient between the two phases. In this step, the droplets transform into semi-solid or solid particles, which still contain residual organic solvent and water. In Step 3, the extracted organic solvent is evaporated to a sufficient extent from the aqueous extraction phase. At completion of this step, the slurry consists of polymeric particles and aqueous extraction phase with ideally minimal residual organic solvent. Commonly, the solid particles are separated from the slurry by collection on a membrane filter or by centrifugation (step 4) and dried (step 5).

In a typical particle fabrication process, Steps 2 and 3 occur simultaneously. Past endeavors to model the solvent extraction/evaporation process have indeed considered the simultaneous occurrence of Steps 2 and 3 (Wang and Schwendeman, 1999; Li et al., 1995a,b; Maa and Hsu, 1996). Nonetheless, the solvent extraction from the polymer phase droplets and the solvent evaporation from the extraction phase are different processes, which deserve individual consideration for better understanding their importance.

Of particular practical importance is the duration of Step 2, i.e., the time needed for solvent extraction. To elucidate the kinetics of solvent extraction, two mathematical models were developed. The first model was derived from a diffusion equation to calculate the solvent extraction time from polymer phase droplets (Step 2). The second model was developed to obtain valid solvent diffusion coefficient values in the polymer phase. The model was derived from experimental data on solvent evaporation from a polymer solution, as described in Section 3.3.

2.1. Model for solvent extraction from polymer phase droplets into surrounding aqueous phase

For the solvent extraction step, a diffusion equation for a single polymer solution droplet surrounded by aqueous extraction phase was defined. Assuming central symmetry, the solvent diffusion is expressed as

$$\frac{\partial c_\mathrm{d}}{\partial t} = \frac{D_\mathrm{p}}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c_\mathrm{d}}{\partial r}\right) \tag{1}$$

where c_d stands for solvent concentration, t for time, r for radial position, and D_p for the solvent diffusion coefficient in the polymer solution. Although the real diffusibility depends on the solvent concentration in the polymer phase, the diffusion coefficient was assumed to be constant. At the center of the droplet ($r=0$), the boundary condition can be defined as

$$\left.\frac{\partial c_\mathrm{d}}{\partial r}\right|_{r=0} = 0 \quad \text{at}\, r = 0 \tag{2}$$

At the droplet surface ($r=R$), where the solvent molecules pass from the inner to the outer side of the droplet, the boundary condition is defined as

$$D_\mathrm{p}\left.\frac{\partial c_\mathrm{d}}{\partial r}\right|_{r=R-0} = D_\mathrm{E}\left.\frac{\partial c_\mathrm{d}}{\partial r}\right|_{r=R+0} \quad \text{at}\, r = R \tag{3}$$

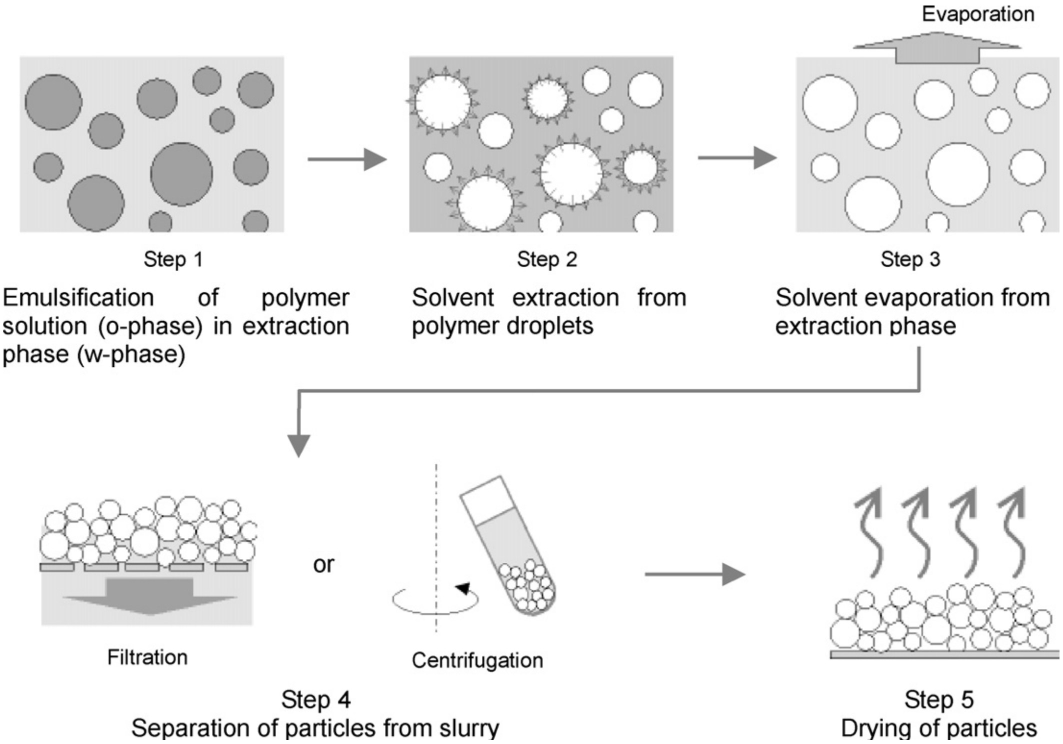

Fig. 1. Schematic illustration of the PLGA microparticle fabrication process by organic solvent extraction/evaporation from an o/w-emulsion.