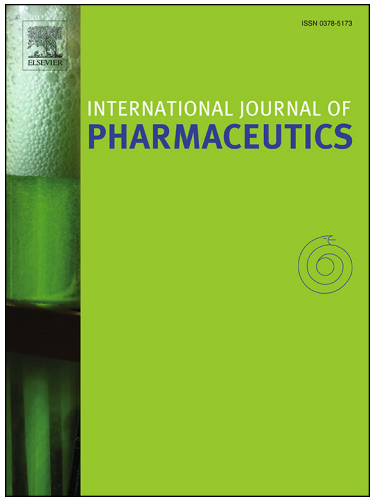

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The relevance of shear, sedimentation and diffusion during spin freezing, as potential first step of a continuous freeze-drying process for unit doses

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Abstract

Recently, a continuous freeze-drying process for the production of unit doses was presented and evaluated. In this concept, the freezing step is modified compared to traditional batch freeze-drying, as glass vials filled with a liquid formulation, are rotated around their longitudinal axis while cooled and frozen with a cold, sterile and inert gas (i.e. spin freezing). Finally, a thin frozen product layer spread over the entire vial wall is achieved. The aim of this paper is twofold: firstly, the relation between the rotation velocity and the relative difference between top and bottom of the frozen product layer thickness was determined for different vial types. Secondly, the impact of shear and centrifugal forces generated during spinning was examined, to find out whether they might cause pharmaceutical instability and sedimentation, respectively. Mechanistic and experimental evaluation showed that shear has no effect on proteins. Calculations showed that the sedimentation and diffusion velocity is too low to cause inhomogeneity in the product layer. In addition, Global Sensitivity Analysis (GSA) and Uncertainty Analysis (UA) were performed in order to account for the uncertainty of the used mechanistic model.

Keywords: freeze-drying, shear, sedimentation, diffusion, global sensitivity analysis, uncertainty analysis

1. Introduction

The pharmaceutical industry is 35 years after the approval of the first biopharmaceutical drug (i.e. recombinant human insulin) still confronted with several challenges during the development and manufacturing of biopharmaceuticals [1, 2]. One of the main challenges is the successful formulation of biopharmaceuticals (e.g. proteins), since biopharmaceuticals encounter stability issues when formulated as an aqueous solution [2–4]. Freeze-drying or lyophilisation is a low temperature drying process employed to convert these (heat-)labile solutions into solids of sufficient stability [4]. Glass vials, filled with an aqueous formulation, are placed on temperature controlled shelves. The temperature of these shelves is lowered to induce the

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