The influence of spray drying parameters on particle composition, structure and *in vitro* release of injectable microspheres for controlled release

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ABSTRACT

This study shows how formulation (feed concentration) and process parameters (feed rate, inlet temperature and atomizing air pressure) can influence the characteristics of spray-dried microspheres. The microspheres consist of a double layered PLGA/PVP matrix containing a molecularly dispersed poorly soluble API. Differences were observed in component miscibility and phase heterogeneity of the samples, particle size and morphology as well as API surface coverage. Observed differences are likely due to changes in the droplet evaporation rate and thus particle formation process. However, varying particle characteristics did not influence the drug release behavior of the formulations studied, indicating the robustness of this approach to produce particles of consistent drug release characteristics. This is likely due to the fact that the first stage of release is dominated by diffusion from the PVP layer through pores and that observed differences in the PLGA surface layer have no influence in this stage of the release.

INTRODUCTION

In view of the increasing interest in injectable controlled release formulations for the treatment of chronic diseases, we aim to develop polymeric microspheres for intramuscular injection. The shell structured microspheres consist of two biocompatible polymers, particularly suitable for formulating poorly soluble drugs. In this model, the role of the poly(lactic-co-glycolic acid) (PLGA) is to form a phase separated surface layer so as to assure the required slow release characteristics of the formulation, whereas the underlying polyvinylpyrrolidone (PVP) phase will be used to increase the solubility/dissolution rate of a poorly soluble active pharmaceutical ingredient (API) by forming a solid dispersion.¹,²

A model formulation was prepared by spray drying. The resulting microspheres consisted of a ternary solid dispersion API/PLGA/PVP 30/25/45 wt%. The influence of various spray drying parameters (both process- and formulation) upon microspheres characteristics and *in vitro* release behavior was investigated. Feed concentration was selected as a formulation parameter, whereas feed rate, inlet temperature and atomizing air pressure were the process parameters tested. Resulting microspheres were investigated for particle size and morphology, miscibility and spatial API distribution.

EXPERIMENTAL METHODS

The model formulation, API/PLGA/PVP, 30/25/45 w%, was spray dried with varying formulation and process parameters. Each parameter studied was evaluated at a low and a high level and compared to a reference sample (middle level) (Table 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Inlet temp (°C)</th>
<th>Feed conc. (%)</th>
<th>Feed rate (ml/min)</th>
<th>Atomizing air (bar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low level</td>
<td>95</td>
<td>1</td>
<td>2</td>
<td>1.00</td>
</tr>
<tr>
<td>Middle level</td>
<td>115</td>
<td>5</td>
<td>6</td>
<td>1.25</td>
</tr>
<tr>
<td>High level</td>
<td>135</td>
<td>10</td>
<td>10</td>
<td>1.50</td>
</tr>
</tbody>
</table>

Table 1. Selected spray drying parameters

The miscibility of the spray-dried samples was characterized by modulated differential scanning calorimetry (MDSC). Scanning electron microscopy (SEM) provided insight into particle size and morphology. Time-of-flight secondary ion mass spectrometry (ToF-SIMS) was utilised for surface chemical analysis. Release experiments were performed in a surfactant containing phosphate buffer at pH 7. Samples were analyzed by high-performance liquid chromatography (HPLC) with UV detection.

RESULTS AND DISCUSSION

Morphological microsphere characterization

Particle size and morphology of the samples was evaluated by SEM and demonstrated to be comparable for all samples with the exception of those prepared from a feed concentration of 1% (Fig.1). The reduction in particle size may originate from a decreased viscosity of the feed solution as well as from a later solidification.

Figure 1. Scanning electron micrographs. Left: reference sample, right: sample with a feed concentration of 1%
Miscibility
MDSC indicated that changing spray drying parameters not only affects the glass transition temperature ($T_g$) but also the width of the $T_g$ range ($\Delta T_g$) and thus influences the miscibility of the samples at a molecular level (Fig.2).

**Figure 2. MDSC of selected formulations**

Spatial API distribution
API surface coverage of the samples was compared by ToF-SIMS (Fig. 3). It is clear that two sample types have a higher presence of API at the microsphere surface, namely those spray-dried with a low inlet temperature (95°C) and a low feed concentration (1%). Migration of the API to the sample surface might be more pronounced because of the slower droplet evaporation and hence particle formation.

**Figure 3. API surface intensity of the different formulations, obtained by ToF-SIMS (4mm x 4mm area scan)**

Release behavior
*In vitro* release testing showed that even when microsphere characteristics were influenced by varying the spray drying parameters, this was not reflected in significant differences in release profile (Fig. 4). Release profiles of samples were compared to those of three independently spray-dried reference samples.

**Proposed release mechanism**
In a previous study we described how the spray-dried polymeric matrix evolves upon exposure to increased humidity.² This knowledge combined with our current findings and additional release testing of binary API/PVP and API/PLGA formulations resulted in a hypothesis for the underlying release mechanism as depicted in Figure 5. It is postulated that in the investigated time frame (4hr) the release mechanism is dominated by fast PVP leach-out due to the high solubility of PVP. The resulting pores allow ingress of water and consequently a fast dissolution of the molecularly dispersed API. Hence observed differences in the PLGA surface layer, such as API surface enrichment, have no significant influence in this stage of the release.

**Figure 5. Hypothesized release mechanism. PLGA in green, PVP in red, API in yellow. Left: before exposure to release medium. Right: after exposure to release medium**

CONCLUSIONS
This study showed how formulation and process parameters can influence the characteristics of spray-dried microspheres. However, varying particle characteristics did not influence the release behavior of the formulation studied. This is likely due to the proposed release mechanism. Hence, for the timeframe tested, the developed formulation possesses robust release characteristics. It is expected that during a later stage of release differences in PLGA layer composition, such as API surface enrichment, will influence the release profile.

REFERENCES