Development of injectable microspheres for controlled release: Rationalization of the release behavior by structure elucidation

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ABSTRACT SUMMARY

Three model spray-dried formulations with varying ratios API/PLGA/PVP were developed and their drug release was studied. Differences in release profile could be rationalized based upon a comprehensive structure elucidation of the formulations, including chemical depth profiling. It could be concluded that the distribution of the API throughout the microspheres, which consist of a PLGA surface layer and an underlying PVP phase, was the release determining factor. Moreover, its influence was greater than that of the thickness of the rate controlling PLGA surface layer.

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 or subcutaneous injection. The shell structured microspheres consist of two biocompatible polymers, particularly suitable for formulating poorly soluble drugs. In this model, the role of the PLGA is to form a phase separated surface layer so as to assure the required slow release characteristics of the formulation, whereas the underlying PVP phase will be used to increase the solubility/dissolution rate of a poorly soluble active pharmaceutical ingredient (API) by forming a solid dispersion.

Three model formulations with varying ratios API/PLGA/PVP were developed, which demonstrated different release behavior. This study specifically aimed to elucidate the structure of each formulation, allowing rationalization of the observed release behavior.

EXPERIMENTAL METHODS

Three model formulations with the following API/PLGA/PVP (w/w/w) ratios were prepared by spray drying: 10/75/15, 20/50/30 and 30/25/45. The miscibility of the spray-dried samples was characterized by modulated differential scanning calorimetry (MDSC). Scanning electron microscopy (SEM) provided insight in particle size and morphology. Time-of-flight secondary ion mass spectrometry (ToF-SIMS) was utilised for surface chemical analysis and quantification. An insight in the in-depth sample composition was gained by ToF-SIMS depth profiling. 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

Release behavior

Figure 1 reveals that formulation 30/25/45 API/PLGA/PVP (w/w/w) shows the slowest release profile, followed by the formulations containing respectively 10/75/15 and 20/50/30 API/PLGA/PVP (w/w/w). This demonstrates that the amount of PLGA in the sample, and hence the thickness of the PLGA surface layer¹, is not the determining factor to control the release profile of these formulations.

Morphological microsphere characterization

SEM showed that there are no meaningful differences regarding particle size and morphology when comparing the three model formulations, indicating that these factors are not responsible for the observed differences in the release behavior.

Thermal characterization and phase behavior

MDSC was used to determine the glass transition temperatures (T_g) of the pure compounds, which are 38°C for PLGA, 56°C for the API and 174°C for PVP under the given experimental conditions. The phase behavior of the model formulations was examined and the resulting thermograms are displayed in Figure 2. This
shows two mixing Tgs for each sample, evincing that the API is present as a solid dispersion in a phase separated system with a PLGA-rich phase and a PVP-rich phase. However, these data do not reveal in which of these phases the API is predominantly present, demonstrating the need for a characterization technique based upon chemical identification of the different compounds.

Figure 2: MDSC of the model formulations. From top to bottom reversing heat flow with following API/PLGA/PVP (w/w/w) ratios: 10/75/15, 20/50/30 and 30/25/45

Structure elucidation

Surface characterization

ToF-SIMS was used to chemically analyze the microsphere surfaces. Figure 3 illustrates that the appearance of API at the particle surface is not in agreement with the total amount of API present in the microparticules. E.g. formulation 30/25/45 API/PLGA/PVP (w/w/w) has the highest bulk concentration of API (30%) but shows the lowest surface coverage compared to the other model formulations. This inconsistency between API bulk concentration and surface coverage might lie at the origin of the observed differences in release behavior between the three model formulations and indicates that an in-depth structure study is required.

Figure 3: API surface intensity of the model formulations obtained by ToF-SIMS

Bulk characterization

Insight into chemical sample composition with depth from the surface was gained by ToF-SIMS depth profiles of the model formulations. Figure 4 revealed that depending upon the API/PLGA/PVP ratio, the drug was predominantly present in the PLGA surface layer or in the underlying PVP phase: Figures 4a and 4b demonstrate that for both 10/75/15 and 20/50/30 API/PLGA/PVP (w/w/w) formulations the drug intensity followed the same decreasing tendency as the PLGA intensity. Hence for these formulations the drug is predominantly present in the PLGA surface layer of the microspheres.

In contrast, in formulation 30/25/45 API/PLGA/PVP (w/w/w) the drug was present, as a solid dispersion, in the PVP layer (Fig. 4c). This allowed the surrounding PLGA layer to assure the desired controlled release. When looking at the release data, it was indeed observed that this formulation showed the slowest release behavior. The other two formulations showed a faster release due to the presence of the drug in the PLGA surface layer of the microspheres.

CONCLUSIONS

The release behavior of the three model formulations could be rationalized based on their structure. This insight should result in the development of a drug matrix with desired and tuneable characteristics in terms of drug release profile in future stages of this research.

REFERENCES