In vivo evaluation of various formulation strategies for controlled release injectables of poorly soluble drugs

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ABSTRACT SUMMARY

A formulation strategy based on the molecular dispersion of a poorly soluble drug into a biphasic PLGA/PVP matrix was evaluated. This strategy was compared towards other solubility enhancing approaches. A physicochemical and structural comparison of the formulations was performed. Additionally in vitro drug release behavior and in vivo exposure in dogs was compared. The addition of PVP in a PLGA matrix resulted in both a more sustained release as well as a higher extent of drug release from the polymeric matrix compared to the other formulation strategies assessed.

INTRODUCTION

Injectable controlled release formulations are gaining an increasing interest for the treatment of chronic diseases. In view of this, we recently reported on the development of spray-dried polymeric microspheres for intramuscular injection for the long-term treatment against the human immunodeficiency virus (HIV). Our formulation strategy was based on the solid dispersion of a poorly soluble active pharmaceutical ingredient (API) in a polymeric matrix consisting of a water soluble (PVP) and a water insoluble polymer (PLGA). This formulation strategy was evaluated and compared to other strategies. In total six model formulations were developed. These formulations differed mainly at the level of the polymeric matrix and can be divided in two groups: formulations based upon a binary PLGA/PVP matrix vs formulations with a PLGA matrix. Consequently the potential benefit of the inclusion of PVP was assessed. A microsuspension was developed as well, to compare the solid dispersion strategy with the strategy of particle size reduction.

Formulations were first physicochemically and structurally characterized and their in vitro release behavior was tested in a surfactant containing phosphate buffer at pH 7. A summary of these findings is provided as follows where PLGA is represented in green, PVP in red and API in yellow.

1. API/PLGA/PVP K30, 30/25/45 w%, spray-dried

These microspheres consist of a PLGA-rich surface layer with an underlying PVP-rich phase. The API is predominantly dispersed in the PVP phase

2. API/PLGA/PVP K30, 30/25/45 w%, spray-dried

An increased thickness of the PLGA layer, as a consequence of an increased amount of PLGA, results in a more sustained release in vitro.

3. API/PLGA/PVP K12, 30/45/25 w%, spray-dried

A change in molecular weight of PVP did not influence the observed in vitro release.

4. API/PLGA, 30/70 w%, spray-dried (SD)

A solid dispersion of the drug in a PLGA matrix results in vitro in a limited release (6% after 24 hours).

5. API/PLGA, 30/70 w%, emulsion method (EM)

This different manufacturing process leads to a threefold increase in the surface area to mass ratio compared to its spray-dried counterpart. This results in a significantly higher in vitro release.

6. API microsuspension, ball milled

Reducing the drug particle size resulted in immediate and complete dissolution of the drug in vitro.

The goal of this study was to evaluate the in vivo bioavailability of these formulations and to link these observations to their structural and physicochemical characteristics and observed in vitro release.
EXPERIMENTAL METHODS
The six formulations were intramuscularly injected in male Beagle dogs (n=4). The administered drug dose was 20 mg/kg. Prior to administration, microspheres were suspended in TPGS containing phosphate buffer of pH 7. Blood samples were collected at 0.5, 1, 2, 4, 6, 24, 55, 79, 223, 343, 511, and 679 hr. Plasma concentrations were determined by LC-MS/MS. For the resulting plasma concentration-time profiles various time slots were studied in detail. Linear regression was performed on the data within these time slots. The slopes of the best fitting curves as well as the AUCs of the plasma concentration-time profiles were compared via ANOVA. Observed plasma concentrations were used as a measure of the amount of API released, assuming linear pharmacokinetics.

RESULTS AND DISCUSSION

Plasma concentration-time profiles
The obtained profiles are depicted in Figure 1.

![Plasma concentration-time profiles](image1)

Figure 1. Plasma concentration-time profiles of the API up to 28 days after IM administration of the six formulations. Inset: 1-6 hours

Burst release
Possible burst release was studied based on the plasma concentrations obtained within 30 minutes after administration. The microsuspension and formulation API/PLGA 30/70 wt% (SD) showed a significantly higher burst release compared to the other formulations.

Sustained release
The inset of Figure 1 demonstrates the decreasing plasma concentration-time profiles of the microsuspension and the binary, PLGA-based formulations. This is in contrast to the more constant profiles of the PLGA/PVP based matrices and indicates that the latter are more suitable for sustained release.

Extent of release
The extent of drug release from the various formulations was evaluated by comparing the cumulative release based on the total AUC (0-∞) for the plasma concentration-time profiles. Formulation API/PLGA/PVP K30 30/45/25 w% showed the highest total release of API, followed by the microsuspension. Subsequently the other two ternary PLGA/PVP based formulations (API/PLGA/PVP K30, 30/25/45 w% and API/PLGA/PVP K12, 30/45/25 w%) released a similar amount of API. The two binary (PLGA-based) formulations had the lowest total release (Fig.2).

![Cumulative release](image2)

Figure 2. Cumulative release for the six formulations based on total plasma exposure of the API (AUC_{0,∞})

Comparison of the different formulation strategies
The microsuspension showed an immediate high release of the API, both in vitro and in vivo, and thus did not fulfil the requirements for controlled release. The two binary, PLGA-based formulations differed in that in vivo the spray-dried formulation showed a burst release, in contrast to the formulation prepared by the emulsion method. Both binary formulations showed a significantly lower bioavailability compared to the ternary formulations (Fig.2), indicating the advantage of inclusion of PVP in terms of the extent of drug released from these formulations. Moreover, the decrease in plasma concentration-time profiles for these formulations (Fig.1, inset) suggests that they are more suitable for immediate release. This is in contrast to the ternary formulations, where a more constant and prolonged release is observed.

CONCLUSIONS
In vivo evaluation of the different formulation strategies demonstrates the benefit of combining PVP and PLGA to develop controlled release formulations compared to the other formulation strategies assessed. The benefit is dual and comprises both a more sustained release as well as a higher extent of total drug release from the polymeric matrix.

REFERENCES