The Influence of Spray-Drying Parameters on Phase Behavior, Drug Distribution, and *In Vitro* Release of Injectable Microspheres for Sustained Release

JOKE MEEUS,[1] MAITÉ LENAERTS,[1] DAVID J. SCURR,[2] KATIE AMSSOMS,[3] MARTYN C. DAVIES,[2] CLIVE J. ROBERTS,[2] GUY VAN DEN MOOTER[1]

[1]Drug Delivery and Disposition, KU Leuven, Leuven, Belgium
[2]Laboratory of Biophysics and Surface Analysis, School of Pharmacy, The University of Nottingham, Nottingham NG7 2RD, United Kingdom
[3]Pharmaceutical Companies of Johnson and Johnson, Discovery Sciences, PD&S_PDM, Beerse, Belgium

Received 12 May 2014; revised 2 December 2014; accepted 9 December 2014

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24361

ABSTRACT: For ternary solid dispersions, it is indispensable to characterize their structure, phase behavior, and the spatial distribution of the dispersed drug as this might influence the release profile and/or stability of these formulations. This study shows how formulation (feed concentration) and process (feed rate, inlet air temperature, and atomizing air pressure) parameters can influence the characteristics of ternary spray-dried solid dispersions. The microspheres considered here consist of a poly(lactic-co-glycolic acid) (PLGA) surface layer and an underlying polyvinylpyrrolidone (PVP) phase. A poorly soluble active pharmaceutical ingredient (API) was molecularly dispersed in this matrix. Differences were observed in component miscibility, phase heterogeneity, particle size, morphology, as well as API surface coverage for selected spray-drying parameters. Observed differences are likely because of changes in the droplet generation, evaporation, and thus particle formation processes. However, varying particle characteristics did not influence the drug release of the formulations studied, indicating the robustness of this approach to produce particles of consistent drug release characteristics. This is likely because of the fact that the release is dominated by diffusion from the PVP layer through pores in the PLGA surface layer and that observed differences in the latter have no influence on the release.
Keywords: keywords spray drying; solid dispersion; controlled release; microspheres; injectables; PLGA; dissolution; polymeric drug delivery systems; calorimetry (DSC)

INTRODUCTION

Injectable sustained-release formulations offer multiple advantages for the treatment of chronic diseases. Side effects of drugs with a narrow therapeutic window can be limited and importantly the administration frequency can be reduced to significantly improve patient compliance. This is expedient in the treatment of chronic diseases and crucial for the therapy of viral infections like those with the human immunodeficiency virus (HIV). In this case controlled release of the drug assures minimal inhibitory drug concentrations and thereby avoids the development of viral resistance. Additionally, the sustained release of appropriate amounts of drug resulting in constant low drug plasma concentrations is sought-after for HIV pre-exposure prophylaxis. Different injectable sustained-release formulations are already marketed. For example, Trelstar® Depot (Debio RP),[1] Sandostatin LAR® (Novartis Pharmaceuticals),[2] and Risperdal® Consta® (Janssen),[3] which are based on the biodegradable polymer poly(lactic-co-glycolic acid) (PLGA) as a carrier.

We previously reported on the development of spray-dried polymeric microspheres for intramuscular injection for the long-term prophylaxis of infection with HIV.[4,5] These shell-structured microspheres consist of two biocompatible polymers, water-insoluble PLGA, and water-soluble polyvinylpyrrolidone (PVP). It was hypothesized that the function of the PLGA in the formulation is to form a phase-separated surface layer so as to provide the required slow release characteristics of the formulation. The underlying PVP phase was used to increase the solubility and dissolution rate of a poorly soluble active pharmaceutical ingredient (API) by forming a solid dispersion. A model formulation was prepared by spray drying where the resulting microspheres consisted of a ternary solid dispersion API/PLGA/PVP 30:25:45 wt %. The model drug used was a poorly soluble HIV protease inhibitor.

Various studies and reviews have already discussed the influence of spray-drying parameters on the resulting pharmaceutical product.[6–15] The majority of these studies describe how various spray-drying parameters influence particle size and morphology[6,9,10] and/or investigate binary systems.[11–15] In contrast to previous work, the present study focuses on how spray-drying parameters (both process and formulation) affect phase behavior and spatial drug distribution of ternary solid dispersions and the consequences for *in vitro* release behavior of these systems. Phase behavior and spatial drug distribution can be decisive for the release characteristics of a formulation. For example, phase behavior might influence the release, as

Correspondence to: Guy Van den Mooter (Telephone: +32016330304; Fax: +32016330305; E-mail: guy.vandenmooter@pharm.kuleuven.be)
This article contains supplementary material available from the authors upon request or via the Internet at http://wileylibrary.com.

Journal of Pharmaceutical Sciences

particles containing a poorly soluble drug in the form of amorphous precipitates in the polymeric matrix are likely to have a slower release compared with ideal glass solutions where the drug is molecularly dispersed within a matrix. Spatial drug distribution might also influence the observed release. For instance, when a drug-rich phase containing a poorly soluble drug is exposed to dissolution medium, the dissolution will be drug controlled, characterized by slow dissolving of the drug, compared with a faster dissolving polymer. In contrast, in a glass solution, the release will be controlled by the dissolution of the polymer.[8,16]

For the current study, feed concentration was selected as a formulation parameter, whereas feed rate, inlet air temperature, and atomizing air pressure were the process parameters tested. The particle size and morphology, phase behavior, and API surface coverage of the resulting microspheres were then characterized. The drug surface coverage is defined by the API distribution throughout the microspheres and hence can be used as an indicator for the latter.

In this study, a variety of complementary techniques were used to characterize the spray-dried samples. First, the phase behavior of three model formulations was studied by means of modulated differential scanning calorimetry (MDSC). Second, we examined the chemical composition of the sample surface by time-of-flight secondary ion mass spectrometry (ToF-SIMS). Other factors that might influence the release, such as particle size[17–19] and surface morphology (e.g., smoothness, porosity),[19] were studied via scanning electron microscopy (SEM). Release experiments were performed in a surfactant containing phosphate buffer at pH 7.

In these complex ternary systems (API/PLGA/PVP), it is indispensable to have an insight into the structure of the binary polymeric matrix and the spatial distribution of the API as this might influence the release profile and/or stability of these formulations. Additionally, the findings of the present study were used to elucidate the underlying release mechanism of these ternary API/PLGA/PVP microspheres.

EXPERIMENTAL

Materials

Poly(lactic-co-glycolic acid) (lactide–glycolide molar ratio of 75:25, inherent viscosity of 0.2 dL/g) was purchased from PURAC Biomaterials (Gorinchem, The Netherlands). PVP K30 (MW 44–54 kDa) was kindly donated by BASF (Ludwigshafen, Germany). The API was a poorly soluble investigational compound provided by Janssen (Beerse, Belgium). Disodium hydrogenphosphate dodecahydrate ($Na_2HPO_4{\cdot}12H_2O$) and formic acid were provided by Chemlab (Zedelgem, Belgium). Sodium dihydrogenphosphate monohydrate ($NaH_2PO_4{\cdot}H_2O$) was supplied by Merck (Darmstadt, Germany). Acros Organics (Geel, Belgium) supplied dimethylformamide (DMF) and ammonium formiate. Polysorbate 80 (Tween 80) was obtained from Alfa Aesar GmbH (Karlsruhe, Germany). Polyethyleneglycol 400 (PEG) was purchased from Fagron (Waregem, Belgium). Dichloromethane (DCM) and acetonitrile (ACN) were provided by Fisher Scientific (Leicestershire, United Kingdom). All solvents used were of high-performance liquid chromatography (HPLC) or analytical grade. Ultrapure water was produced with an Elga Maxima system (Elga Ltd., High Wycombe, Buckinghamshire, United Kingdom).

Table 1. Overview of the Spray-Drying Parameters Studied and the Levels at Which These Parameters Were Evaluated

Parameter	Inlet Air Temperature (°C)	Feed Concentration (%)	Feed Rate (mL/min)	Atomizing Air Pressure (bar)
Low level	95	1	2	1.00
Middle level	115	5	6	1.25
High level	135	10	10	1.50

Methods

Spray Drying

All samples were spray dried with a Micro Spray lab scale spray dryer (ProCepT, Zelzate, Belgium) starting from a feed solution in DCM and with a constant cocurrent drying air with a flow rate of 0.2 m^3/min.

The model formulation, API/PLGA/PVP 30:25:45 wt %, was spray dried with varying formulation and process parameters. Feed concentration was selected as a formulation parameter, whereas feed rate, inlet air temperature, and atomizing air pressure were the process parameters tested. Each parameter studied was evaluated at a low and a high level with all other parameters at the middle level (reference). Samples were compared with a reference sample (middle level) (Table 1). Three reference samples were independently spray dried (references A–C).

The binary samples API/PLGA and API/PVP were spray dried under the same conditions as the reference samples.

Physical Mixtures

Physical mixtures of amorphous spray-dried PVP K30 and API were prepared according to the rules of geometrical blending using a mortar and pestle.

In Vitro Drug Release

Release experiments were performed at room temperature in rotating test tubes (17 rpm) containing an amount of the spray-dried powders corresponding to an API dose of 0.6 mg in 40.0 mL release medium. In this way, sink conditions were assured throughout the experiment. The dissolution medium consisted of phosphate buffer at pH 7 containing 0.25% Tween 80 and 2.5% PEG 400. Samples were collected at 5, 15, 30, 60, and 240 min, filtered over a Chromafil RC-20/15 cellulose acetate filter with a pore size of 0.2 μm (Macherey-Nagel, Düren, Germany) and subsequently analyzed by HPLC with UV detection. Experiments were performed in triplicate.

Solubility Determination

The solubility of the API in an aqueous solution without PVP as well as in the presence of 0.5%, 1%, 2%, and 5% PVP K30 was determined. Therefore, 10 mL of the polymer solution were transferred into a test tube and an excess amount of API was added. These tests were performed at room temperature, and test tubes were rotated for 48 h at 17 rpm. Subsequently, these samples were filtered over a Chromafil RC-20/15 cellulose acetate filter with a pore size of 0.2 μm and analyzed by HPLC with UV detection. Experiments were performed in triplicate.