Nanoscale Surface Characterization and Miscibility Study of a Spray-Dried Injectable Polymeric Matrix Consisting of Poly(lactic-co-glycolic acid) and Polyvinylpyrrolidone

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ABSTRACT: Injectable controlled-release formulations are of increasing interest for the treatment of chronic diseases. This study aims to develop and characterize a polymeric matrix for intramuscular or subcutaneous injection, consisting of two biocompatible polymers, particularly suitable for formulating poorly soluble drugs. For this matrix, the water-insoluble polymer poly(lactic-co-glycolic acid) (PLGA) is combined with the water-soluble polymer polyvinylpyrrolidone (PVP). Microparticles of these two polymers were prepared by spray drying. The phase behavior of the samples was studied by means of modulated differential scanning calorimetry and the results showed that phase separation occurred in the bulk sample through evidence of two mixed amorphous phases, namely, a PLGA-rich phase and a PVP-rich phase. Characterization of the samples by scanning electron microscopy demonstrated that the spray-dried particles were hollow with a thin shell. Because of the importance in relation to stability and drug release, information about the surface of the microparticles was collected by different complementary surface analysis techniques. Atomic force microscopy gathered information about the morphology and phase behavior of the microparticle surface. Time-of-flight secondary ion mass spectrometry analysis of the particles revealed that the surface consisted mainly of the PLGA-rich phase. This was confirmed by X-ray photoelectron spectroscopy at an increased sampling depth (~10 nm). Nanothermal analysis proved to be an innovative way to thermally detect the presence of the PLGA-dominated surface layer and the underlying PVP phase. Taken together, this information provides a rational basis for predicting the likely drug release behavior this formulation will display. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:3473–3485, 2012

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INTRODUCTION

The number of poorly soluble drugs that require formulation into effective medicines has increased steadily during the past two decades. This obviously poses problems not only for oral delivery, but also for the development of injectable formulations, especially in the case of prolonged-release preparations. Baert et al.[1] recently proposed the use of injectable nanosuspensions to sustain the delivery of the anti-HIV drug rilpivirine over several weeks. Despite the success of this strategy, the drawback of this formulation approach is its compound specificity, requiring the need to develop and optimize a formulation for each new

Additional Supporting Information may be found in the online version of this article. Supporting Information

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chemical entity. Hence, there is a clear need for a more universally applicable delivery platform that enables prolonged release of poorly soluble compounds and would require minimal optimization for different compounds. An ideal drug delivery system should significantly increase effective drug solubility while providing controlled release over an extended period of time (weeks). This study addresses these two hurdles by proposing a novel formulation strategy based on a matrix consisting of the water-insoluble polymer poly(lactic-co-glycolic acid) (PLGA) in combination with the water-soluble polymer polyvinylpyrrolidone (PVP). Each of these polymers has its own function in the formulation. PVP can improve the active pharmaceutical ingredient (API) solubility by facilitating the processing of the API in an amorphous solid dispersion.[2–5] To achieve a meaningful drug load, the miscibility between PVP and the selected API needs to be sufficiently high. The second polymer, PLGA, provides for controlled-release characteristics of the formulation.[6] These characteristics can be influenced by changing the amount of PLGA present in the formulation and/or by adapting the molecular weight of the polymer and/or by using a different ratio of lactic acid to glycolic acid.[7,8] A low miscibility between the PLGA and the selected API as well as a low miscibility between the two polymers is necessary for optimal drug release characteristics. Hence, miscibility behavior, including phase behavior as well as phase distribution, of the different compounds is a key characteristic and justification for the study presented in this paper.

The two polymers were selected based upon their differences in solubility and their biocompatibility, a characteristic which only applies to a limited number of polymers. Both PLGA and PVP are already used individually as a matrix material in commercial drug products. Examples include Cesamet® (Valeant Pharmaceuticals Inc. Costa Mesa, California) and Rezulin® (Warner-Lambert Co. Morris Plains, New Jersey), using PVP as a carrier,[2,4] and Trelstar® Depot (Debio RP, Martigny, Switzerland),[9] Sandostatin LAR® (Novartis Pharmaceuticals, East Hanover, New Jersey),[10] and Risperdal® Consta® (Janssen Pharmaceutica, Beerse, Belgium),[11] using PLGA as a carrier. A combination of these polymers has not been reported, indicating the novelty and scope of the present study.

The combined PLGA–PVP microparticles were prepared by spray drying and investigated in terms of polymer mixing behavior and surface characteristics, as well as the influence of the ratio of PLGA–PVP on these characteristics. A combination of several complementary solid-state characterization techniques was applied. Modulated differential scanning calorimetry (MDSC) was used to study whether PLGA and PVP showed the desirable phase behavior, that is, immiscibility. Nanoscale surface characteristics of the microparticles were analyzed using atomic force microscopy (AFM)[12–14] for studying the morphology and phase behavior, time-of-flight secondary ion mass spectrometry (ToF-SIMS)[15,16] and X-ray photoelectron spectroscopy (XPS)[12,15] for surface chemical quantification, and nanothermal analysis (nanoTA)[14,17,18] for local thermal surface characterization. NanoTA on binary polymeric particles has not been reported yet, and the results obtained in this study demonstrate the applicability of this technique for this type of sample geometry.

An understanding of the surface behavior will form the basis for the rational development of a drug matrix with desired and tuneable characteristics in terms of drug solubility enhancement and drug release profile in a later stage of research. The outcome of this study will have implications for the development of the polymeric drug matrix to deliver the optimum-release properties for poorly soluble drugs in future studies.

EXPERIMENTAL SECTION

Materials

Polyvinylpyrrolidone K30 (PVP K30) (molecular weight 44–54 kDa) was kindly donated by BASF (Ludwigshafen, Germany). PLGA (lactide–glycolide molar ratio of 75:25, inherent viscosity of 0.2 dL/g) was purchased from PURAC Biomaterials (Gorinchem, The Netherlands).

Methods

Spray Drying

Spray-dried samples were prepared with a Micro Spray laboratory-scale spray dryer (ProCepT, Zelzate, Belgium). A 15% feed solution of the polymers in dichloromethane was used. The inlet temperature was set to 95°C and the feed rate was 6 mL/min. The cocurrent drying air had a flow rate of 0.2 m^3/min, and the atomizing air was supplied with a pressure of 5 bar.

Physical Mixtures

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

Modulated Differential Scanning Calorimetry

Bulk miscibility of the samples was analyzed by MDSC (Q2000; TA Instruments, Leatherhead, UK). The data obtained were analyzed with the Thermal Analysis Software (version 4.4A) (TA Instruments, Leatherhead, UK). Crimped aluminum pans (TA Instruments, Brussels, Belgium) were used for the