Surface-Active Derivative of Inulin (Inutec® SP1) Is a Superior Carrier for Solid Dispersions with a High Drug Load

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ABSTRACT: The aim of this study was to compare the applicability of inulin, its surface-active derivative (Inutec® SP1), and polyvinylpyrrolidone (PVP) as carriers in high drug load solid dispersions (SDs) for improving the dissolution rate of a range of lipophilic drugs (diazepam, fenofibrate, ritonavir, and efavirenz). The SDs were prepared by spray freeze-drying. Scanning electron microscopy showed that the obtained samples were highly porous spherical particles. Modulated differential scanning calorimetry showed that the drugs incorporated in these carriers were fully or partially amorphous. The solubility of the drugs in solutions of the different carriers was increased in an order: inulin 2.3 kDa < PVP K30 ≪ Inutec® SP1. The dissolution behavior of SD tablets was evaluated. Inutec® SP1-based SD tablets showed the best performance followed by PVP- and inulin-based SD tablets. The superior dissolution behavior of the drugs from Inutec® SP1-based SDs could be ascribed to its surface-active nature. In addition, Inutec® SP1-based SD tablets gave good physical stability at 20°C/45% relative humidity (RH) and 40°C/75% RH for 3 months. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:2333–2342, 2011

Keywords: inulin; inulin derivative; Inutec® SP1; polyvinylpyrrolidone; surfactants; dissolution; amorphous; preformulation; solid dispersion; spray freeze-drying

INTRODUCTION

Increasing the dissolution rate of poorly water-soluble Biopharmaceutics Classification System class II drugs and thereby improving their bioavailability remains a challenging task for formulation scientists. Solid dispersions (SDs) offer an interesting option to deal with this challenge. The method of production, the type of carrier,[1–5] and formulation aspects such as incorporation of superdisintegrants,[6] surfactants,[7,8] or other excipients are only some of the parameters that may affect the performance of the SDs.

In a previous study, we showed that the dissolution of poorly water-soluble drugs from the inulin-based SD tablets was fast, except when the SDs contained a high drug load. At high drug loads, the drug concentration in the near vicinity of the dissolving tablets was too high. The high drug concentration resulted in uncontrolled crystallization and the formation of large crystals that subsequently dissolved slowly.[9] Recently, an inulin derivative, Inutec® SP1, was described as stabilizer for emulsions.[10] Inutec® SP1 consists of a hydrophilic inulin backbone to which lipophilic alkyl side chains are covalently linked. The chemical structures of inulin and Inutec® SP1 are shown in Figure 1. Inutec® SP1 can act as a surfactant due to the presence of both hydrophilic and lipophilic parts of the molecule. Because of its surface-active nature, it would be interesting to use Inutec® SP1 as a carrier for SDs. Previously, the application of an inulin derivative for SDs of itraconazole was described[11]; however, the carrier performance was not compared with other carriers nor was storage stability study of the SDs at high drug loads investigated.

The aim of this present study was to investigate the applicability of Inutec® SP1 as a carrier for SDs of various poorly water-soluble drugs at high drug loads, and to compare its behavior with native (non-surface active) inulin and polyvinylpyrrolidone (PVP). We speculate that compared with inulin-based SD

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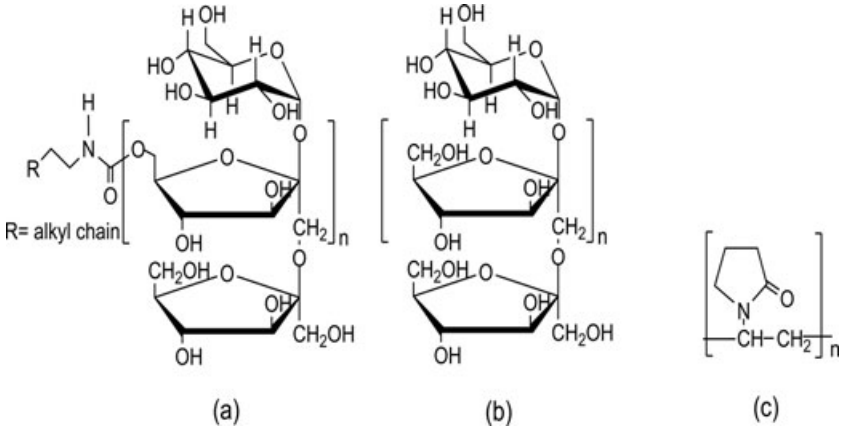

Figure 1. Chemical structures of (a) Inutec® SP1 (inulin lauryl carbamate), (b) native inulin, and (c) polyvinylpyrrolidone.

tablets, higher drug loads can be applied in Inutec® SP1-based SD tablets without the occurrence of crystallization of the drug during dissolution. The high drug load in the boundary layer around the dissolving tablets (or particles) will not result in crystallization due to the surface-active nature of the inulin derivative. To investigate this mechanism, Inutec® SP1 was compared with native inulin as a carrier for SDs. In addition, PVP was included in this study because it has been used as a successful carrier to produce amorphous SDs.[12–14] The chemical structure of PVP is also shown in Figure 1. SDs were prepared by spray freeze-drying using a water/tertiary butyl alcohol (TBA) mixture as a solvent. To investigate the versatility of Inutec® SP1 as a carrier for SDs, four different poorly water-soluble drugs were used as model drugs, that is, diazepam, fenofibrate, ritonavir, and efavirenz. The storage stability of Inutec® SP1-based SDs was also investigated.

MATERIAL AND METHODS

Materials

The following materials were used as received: Inutec® SP1 (generously provided by BENEO-Orafti, Tienen, Belgium), inulin 2.3 kDa (Sensus, Roosendaal, the Netherlands), PVP K30 and diazepam (BUFA B.V., Uitgeest, the Netherlands), TBA (Fluka Chemie GmbH, Steinheim, Germany), fenofibrate (Sigma–Aldrich Chemie GmbH, Steinheim, Germany), and ritonavir and efavirenz (generously provided by the Government Pharmaceutical Organization, Bangkok, Thailand).

Determination of Surface Tension

The surface tension of the aqueous solution at various Inutec® SP1, inulin 2.3 kDa, or PVP K30 concentrations was measured by a du Noüy ring-type tensiometer (Krüss Tensiometer K8, Hamburg, Germany) at $20 \pm 1^{\circ}$C. The carrier solutions at concentrations of 0.0005% to 0.08% (w/v) were prepared in demineralized water. The tensiometer was calibrated with demineralized water before use (surface tension $= 71.2 \pm 0.2$ mN/m). The surface tension measurement was performed in triplicate. The critical micelle concentration (CMC) was determined graphically from the slope changes in the surface tension versus logarithm of the carrier concentration plot.

Determination of Solubility

An excess amount of diazepam or fenofibrate was added to demineralized water, 5% (w/v) Inutec® SP1, inulin 2.3 kDa, or PVP K30 solutions. Efavirenz and ritonavir were treated similarly. Because the solubility of these drugs is pH-dependent, 0.05 M phosphate buffer solution (PBS; pH 6.8) was used instead of demineralized water. Samples of the drugs in demineralized water or PBS (pH 6.8) were used as controls. All samples were stirred at room temperature (20°C) and were analyzed after 24 h (control experiment revealed that equilibrium was reached within 24 h). Samples were filtered through 0.2-μm filter prior to analysis and then were diluted with mobile phase to obtain the suitable concentration. The samples were analyzed by high-performance liquid chromatography (HPLC). The HPLC system consisted of a pump (Model 510; Waters Associates, Milford, MA, USA), an autosampler (Model 717 plus autosampler; Waters Associates), ultraviolet (UV) detector (Applied Biosystems, Foster City, CA, USA; Model 783 Programmable Absorbance Detector), a C18, 5μm, 250 × 4.6 mm^2 column (Nucleosil®; Macherey-Nagel GmbH & CO. KG, Düren, Germany).

For diazepam, the HPLC analysis was performed according to US Pharmacopeia (USP)[15] with some modifications, the mobile phase consisted of milli-Q water, acetonitrile, and methanol (40:40:20, v/v/v), and at a flow rate of 1.0 mL/min. The detection wavelength was 254 nm. The retention time of