Selection and Characterization of Suitable Lipid Excipients for use in the Manufacture of Didanosine-Loaded Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

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ABSTRACT: This research aimed to evaluate the suitability of lipids for the manufacture of solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) loaded with the hydrophilic drug, didanosine (DDI). The crystalline state and polymorphism of lipids with the best-solubulizing potential for DDI was investigated using differential scanning calorimetry (DSC) and wide-angle X-ray scattering (WAXS). DSC and WAXS were also used to determine potential interactions between the bulk lipids and DDI. Precirol® ATO 5 and Transcutol® HP showed the best-solubilizing potential for DDI. Precirol® ATO 5 exists in the β-modification before heating; however, a mixture of both α- and β-modifications were detected following heating. Addition of Transcutol® HP to Precirol® ATO 5 changes the polymorphism of the latter from the β-modification to a form that exhibits coexistence of the α- and β-modifications. DDI exists in a crystalline state when dispersed at 5% (w/w) in Precirol® ATO 5 or in a Precirol® ATO 5/Transcutol® HP mixture. DSC and WAXS profiles of DDI/bulk lipids mixture obtained before and after exposure to heat revealed no interactions between DDI and the lipids. Precirol® ATO 5 and a mixture of Precirol® ATO 5 and Transcutol® HP may be used to manufacture DDI-loaded SLN and NLC, respectively. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:5185–5196, 2011

Keywords: Didanosine; Precirol® ATO 5; Transcutol® HP; Preformulation; Polymorphism; Crystallinity; Calorimetry (DSC); X-ray diffractometry; Solid lipid nanoparticles (SLNs); Nanostructured lipid carriers (NLCs)

INTRODUCTION

The United Nations Children's Fund and the World Health Organization estimate that 13% of the people infected with the human immunodeficiency virus (HIV) in 2003 were children and that at least 300,000 new pediatric infections are likely to occur each year.[1] Approximately 40% of child mortality in countries where HIV is endemic is associated with acquired immunodeficiency syndrome (AIDS). This alarming trend is linked in part to the inaccessibility of antiretroviral (ARV) treatment for children, due to lack of availability of ARV medicines in appropriate pediatric formulations.[1]

Didanosine (DDI) is a hydrophilic nucleotide reverse transcriptase inhibitor approved by the US Food and Drug Administration for the management of advanced HIV infection in children.[2,3] DDI may be administered alone or in combination with other ARV agents as an important component of triple combination HIV treatment regimens.[4,5] A major hindrance to the use of DDI is the susceptibility of the molecule to hydrolytic cleavage in the acidic environment of the stomach, following oral administration with conventional formulations.[3,6] In reality, DDI has a t_{90} of less than 2 min in a solution of pH 3.0 at 37°C.[3,7] Consequently, there is a reduction in the bioavailability and *in vivo* activity of the molecule.[3,6,8]

In order to improve the acid stability and bioavailability of DDI, the drug is usually formulated as buffered chewable or dispersible tablets in addition to buffered or nonbuffered pediatric powders for

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reconstitution as an oral solution.[3,6,8,9] The nonbuffered pediatric powders are usually mixed with antacids following reconstitution, prior to oral administration to pediatric patients.[10] Despite these formulation strategies, the bioavailability of DDI in children with HIV infection remains highly variable and may range between 13% and 29%.[5,11] Furthermore, DDI-buffered formulations are unpalatable[6,9] and the presence of buffers and/or antacids in these formulations have been reported to cause diarrhoea, nausea, vomiting,[6,9] and abdominal discomfort.[4,5,9] The presentation of these side effects in addition to pancreatitis and peripheral neuropathy, which can be directly attributed to DDI,[4,5] may have a negative outcome on the quality of life of pediatric patients. Therefore, adherence of patients to chronic DDI therapy may be negatively affected, further hindering the management of HIV/AIDS in children.

In order to overcome the challenges associated with the use of buffered DDI formulations, an encapsulated enteric-coated bead formulation of DDI has been developed and is commercially available as Videx® EC.[12] Videx® EC eliminates the concomitant use of buffers and/or antacids to ensure DDI bioavailability and therefore may be a better dosage form for the oral administration of DDI.[13] However, Videx® EC capsules must only be swallowed whole.[12] Although children older than 3 years may be switched from a liquid to a solid oral dosage form in certain conditions, relatively young pediatric patients must continue to use DDI formulations that contain buffers or antacids.[10,14] Therefore, it is vital that research into the development of novel nonbuffered and nonmonolithic pediatric formulations that are able to protect DDI from acid-catalyzed degradation and improve its bioavailability in children is conducted as a matter of urgency.

The successful incorporation of DDI into innovative colloidal drug delivery systems such as solid lipid nanoparticles (SLNs) and/or nanostructured lipid carriers (NLCs) may have the potential to enhance the acid stability of DDI. SLNs[15] and NLCs[16] are lipid nanoparticles that consist of a lipid matrix that is solid at both room and body temperatures. SLNs and NLCs are prepared in a similar manner to an oil-in-water (o/w) emulsion except that the oil phase of the emulsion is replaced by a lipid phase that solidifies after production.[17] SLNs are prepared using solid lipids with a similar molecular structure,[17] whereas NLCs are manufactured by controlled mixing of solid lipids with suitable liquid lipids.[16,18] The addition of liquid oil to a solid lipid creates a less-ordered crystal lattice with an increased number of imperfections, which can accommodate drug clusters.[16,19] Therefore, the loading capacity of NLCs for drug molecules is higher than that of SLNs. In addition, drug expulsion during prolonged storage is less likely to occur from NLCs compared with SLNs.[16] A major advantage of using SLNs and NLCs is that these carriers are prepared using excipients with generally regarded as safe status, which minimizes the risk of acute and/or chronic toxicity during *in vivo* use.[20,21] Therefore, the objective of this research was to identify, select, and characterize lipid excipients that would be suitable for use in the manufacture of DDI-loaded SLNs and/or NLCs, which could potentially be used as a platform to manufacture a pediatric formulation.

MATERIALS AND METHODS

Materials

Didanosine was donated by Aspen Pharmacare Holdings Limited (Port Elizabeth, Eastern Cape, South Africa), Precirol® ATO 5 (glyceryl palmitostearate), Compritol® 888 ATO (glyceryl behenate), Labrafil® M 2130 CS [lauroyl macrogolglycerides (polyoxylglycerides)], Gelucire® 50/13 [lauroyl macrogolglycerides (polyoxylglycerides)] and Gelucire® 44/14 [lauroyl macrogolglycerides (polyoxylglycerides)], Transcutol® HP (diethylene glycol monoethyl ether), Labrafac Lipophile® WL 1349 (medium-chain triglycerides), Labrafac® PG (propylene glycol dicaprylocaprate), Lauroglycol® FCC (propylene glycol laurate), and Capryol® 90 (propylene glycol monocaprylate) were donated by Gattefossé SAS (Saint-Priest Cedex, France). Dynasan® 116 (triacylglycerol of palmitic acid) and Dynasan® 118 (triacylglycerol of stearic acid) were received from Condea Chemie GmbH (Witten, Germany). Cutina® CP (cetyl palmitate) was purchased from Cognis Deutschland GmbH (Düsseldorf, Germany). Imwitor® 312 (glyceryl monolaurate), Imwitor® 900 (glyceryl stearate), and Imwitor® 960 K (glyceryl stearate SE) were kindly donated by Sasol Germany GmbH (Witten, Germany). Miglyol® 812 (medium-chain triacylglycerols) was received from Caelo GmbH (Hilden, Germany). High-pressure liquid chromatography (HPLC)-grade water was prepared using a Milli Q Plus water purification system (Millipore, Schwalbach, Germany). HPLC-grade methanol was purchased from Mallinckrodt Baker (Deventer, the Netherlands).

Screening of Lipid Excipients

Selection of Solid Lipids

Because of the hydrophilic nature of DDI, an evaluation of the solubility of the drug in solid lipids was initiated by mixing 0.005% (w/w) of DDI with a solid lipid. The solid lipid–DDI mixture was then melted at 85°C and agitated at 100 rpm using a Model 4230 Innova refrigerated incubator shaker (New Brunswick Scientific, Edison, New Jersey) for 24 h. The solubility of DDI in the molten lipid was assessed visually. Following dissolution of the initial amount of DDI