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Solubility enhancement of desloratadine by solid dispersion in poloxamers

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ABSTRACT

The present study investigates the possibility of using poloxamers as solubility and dissolution rate enhancing agents of the poorly water soluble drug substance desloratadine that can be used for the preparation of immediate release tablet formulation. Two commercially available poloxamer grades (poloxamer P 188 and poloxamer P 407) were selected, and solid dispersions (SDs) containing different weight ratio of poloxamers and desloratadine were prepared by a low temperature melting method. All SDs were subjected to basic physicochemical characterization by thermal and vibrational spectroscopy methods in order to evaluate the efficiency of poloxamers as solubility enhancers. Immediate release tablets were prepared by direct compression of powdered solid dispersions according to a General Factorial Design, in order to evaluate the statistical significance of two formulation (X_1 – type of poloxamer in SD and X_2 – poloxamer ratio in SD) and one process variable (X_3 – compression force) on the drug dissolution rate. It was found that desloratadine in SDs existed in the amorphous state, and that can be largely responsible for the enhanced intrinsic solubility, which was more pronounced in SDs containing poloxamer 188. Statistical analysis of the factorial design revealed that both investigated formulation variables exert a significant effect on the drug dissolution rate. Increased poloxamer ratio in SDs resulted in increased drug dissolution rate, with poloxamer 188 contributing to a faster dissolution rate than poloxamer 407, in accordance with the results of intrinsic dissolution tests. Moreover, there is a significant interaction between poloxamer ratio in SD and compression force. Higher poloxamer ratio in SDs and higher compression force results in a significant decrease of the drug dissolution rate, which can be attributed to the lower porosity of the tablets and more pronounced bonding between poloxamer particles.

1. Introduction

Desloratadine (DSL), or 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6] cyclohepta[1,2-b] pyridine, is a new, selective H1-receptor antagonist. It inhibits important cytokines and cellular activity, suggesting an anti-allergic and anti-inflammatory profile (Sweetman, 2009). Desloratadine is commercially available as immediate release tablets and syrups. For adults and children aged 12 and over, the desloratadine dose is 5 mg. After oral administration desloratadine is rapidly absorbed and the maximum plasma concentration is reached after 3 h. One daily administration rapidly reduces the nasal and non nasal symptoms of seasonal allergic rhinitis, including congestion (Geha and Meltzer, 2001).

From a chemical viewpoint, DSL (Fig. 1) is a base whose non-protonated forms are poorly soluble in water (Popović et al., 2009), resulting in reduced drug dissolution rate in gastrointestinal fluid following oral administration, and consequently, reduced bioavailability. Various approaches can be followed for the enhancement of solubility and dissolution rate of poorly water soluble drugs like DSL, such as salt formation (Serajuddin, 2007), solubilization by cosolvents (Jeffrey et al., 2002), particle size reduction (Chaumeil, 1998), and inclusion in cyclodextrins (Ali et al., 2007) or preparation of solid dispersions (Chen et al., 2004; Gohel and Patel, 2003; Hang et al., 2007; Leuner and Dressman, 2000; Passerini et al., 2002, 2006; Yu et al., 2007). Solid dispersion techniques seem to be the most promising for solubility enhancement, as they overcome the limitations of previous approaches. When solid dispersions of microcrystalline drug particles, are exposed to aqueous media, the carrier dissolves and the drug is released as a fine colloidal dispersion, thus resulting in higher surface area and consequently,

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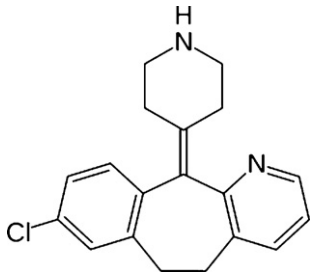

Fig. 1. Structural formula of DSL.

enhanced dissolution rate and bioavailability of poorly water soluble drugs (Craig, 2002; Patil and Naresh, 2009; Yoo et al., 2000). If an active substance is molecularly dispersed in the polymer matrix or exists in the amorphous state, solid dispersions offer the additional advantage that no energy is required to break up the crystal lattice of a drug during the dissolution process (Taylor and Zografi, 1997) and its solubility as well as wettability may be increased by surrounding hydrophilic carriers (Chutimaworapan et al., 2000).

Solid dispersions are usually prepared by melting or solvent methods, while combined melting solvent methods have also been employed. However, these methods have several drawbacks. High temperature, applied within melting as well as melting solvent methods, can induce chemical decomposition of the drugs, carriers or both (Narang and Shrivastava, 2002). Regarding solvent methods, it may not always be possible to find a common solvent for both hydrophobic drug and hydrophilic carrier, and large volumes of solvents and long duration of heating are required to enable complete dissolution of both components (Kim et al., 2006). Drying techniques used for the removal of organic solvents from solid dispersions make them more tedious and costly (Hu et al., 2004; Kai et al., 1996; Moneghini et al., 2001). Also, amounts of residual solvents may be present in SDs when various solvents, carriers or drying techniques are used, which could be toxic (Serajuddin, 1999).

Melt agglomeration, using a hot solution of low melting point hydrophilic carriers as a binding agent, is claimed to be an advantageous industrial scale alternative (Seo et al., 2003). According to this method, solid dispersions can be prepared by different ways: (a) by the addition of the molten binder containing the drug to the heated excipients, (b) by pouring of the molten binder to a heated mixture of drug and excipients or (c) by heating the mixture of the drug, binder and excipients to a temperature within or above the melting range of the binder (Breitenbach, 2002; Forster et al., 2001b; Kabanov et al., 2002; Newa et al., 2007). However, these approaches are also associated with many disadvantages. Separate melting of polymer with or without drug can be an extra step that makes the process complicated and costly, and the entire amount of drug used in the preparation is not always dissolved in a polymer solution or formulation mixture. Moreover, the yield of such a process in many cases is low because of the polymer/drug losses while pouring into the powder mix, thus making them relatively more expensive in terms of invested time and required technology (Newa et al., 2008).

In order to overcome the aforementioned disadvantages, in the present study we investigate the possibility of preparing solid dispersions (SDs) by a low temperature melting method using poloxamers in order to increase the solubility and dissolution rate of the poorly water soluble drug, DSL. Poloxamers are nonionic polyoxyethylene–polyoxypropylene copolymers available in different grades, differing in the relative amounts of propylene and ethylene oxides added during manufacture. They have been widely used primarily in pharmaceutical formulations as emulsifying or solubilizing agents (Collett, 2009) for many poorly water soluble drugs by various techniques including melting agglomeration and melting method (Kabanov et al., 2002; Newa et al., 2007). In order to investigate the influence of poloxamer grade on DSL dissolution rate, two common poloxamer grades were used, namely P 188(Lutrol® F68) and P 407 (Lutrol® F127), because of their low melting point, surfactant properties and oral safety. The physicochemical properties of the obtained SDs were characterized and immediate release tablets were prepared in order to evaluate their influence on the drug dissolution rate. Although XRPD is the preferred technology to understand and study the crystalline and amorphous nature in the solid state characterization in this study due to the unavailability of this equipment, for this purpose DSC and FTIR were used.

2. Materials and methods

2.1. Materials

DSL (Shenzhen Salubris Pharmaceuticals Co., Ltd., China), a model drug used in this study had the following characteristics: off-white powder; melting point 156–157 °C; loss on drying 0.1%; heavy metals 0.001%; poloxamers F-grades (Lutrol® F68 and Lutrol® F127, BASF Aktiengesellschaft, Germany) were used as solubilizing agents. They are white, coarse-grained powders with a waxy consistency and had the following characteristics: specific gravity, 1.06 and 1.05; melting point, 52 °C and 56 °C; HLB value, >24 and 18–23 for P 188 and P 407, respectively.

Other excipients used in this study were microcrystalline cellulose (Avicel® PH 101, FMC BioPolymer, Philadelphia), calcium hydrogen phosphate dehydrate (EMCOMPRESS®, JRS Pharma, GmbH & Co., KGA, USA), magnesium stearate (Mg-st, NOF Corp., Japan) and colloidal silicon dioxide (AEROSIL® 200, Evonik Degussa GmbH, Germany), all of pharmaceutical grade.

All other reagents purchased from commercial sources were of analytical grade.

2.2. Methods

2.2.1. Preparation of solid dispersion by melting method

DSL and poloxamers (P 188 and P 407) were mixed in 1:1, 1:2 and 1:3 weight ratios and melted in a glass evaporating dish immersed in a water bath at 70 °C with continuous stirring to obtain a homogeneous dispersion. The melted mixture was then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass was crushed, pulverized and sieved (400 μm).

2.2.2. SD characterization

The SDs were analyzed regarding particle size distribution, moisture content and intrinsic dissolution rate. Their physical state and potential interactions between their components were evaluated by DSC and FTIR.

2.2.2.1. Particle size analysis. The mean particle size and the particle size distribution of the prepared SD were analyzed by optical microscopy using a digital image processing and analysis system comprising an Olympus polarizing microscope BX41 (Olympus Europa GmbH, Germany) equipped with a Leica digital camera DFC 295 (LAS Leica Microsystems AG, Switzerland), operated through the Leica Application Suite image analysis software (LAS Leica Microsystems AG, Switzerland).

2.2.2.2. Moisture content. The moisture content of the SD particles was estimated on the basis of the mass loss, determined by thermogravimetric analysis using a Shimadzu TGA-50 (Shimadzu Scientific Instruments, USA) thermogravimetric analyzer. Approximately 5 mg of sample were placed into an aluminum sample