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Physical stability of the amorphous state of loperamide and two fragment molecules in solid dispersions with the polymers PVP-K30 and PVP-VA64

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Abstract

The purpose of the present study was to investigate the impact of intermolecular forces on the stability of the amorphous state of loperamide and two of its fragment molecules (4-dimethylamino-*N*,*N*-dimethyl-2,2-diphenyl-butyramide (F1) and 4-(4-chlorophenyl)-4-piperidinol (F2)) in solid dispersions with PVP-K30 and PVP-VA64. The stability of originally homogeneous and amorphous dispersions was investigated under different storage conditions. The chemical stability of the compounds was evaluated with HPLC. TGA-analysis was used in order to assess the amount of water in the samples, whereas MT-DSC-measurements were performed to investigate changes in the physical state of the compounds caused by the storage procedure. TGA-analysis reveals a higher uptake of water in humid conditions of the dispersions with PVP-K30 in comparison to those with PVP-VA64, hereby reflecting the more hydrophilic nature of the former polymer. This water acts as a plasticizing agent resulting in an increased mobility and decreased glass transition temperature. Since the degree of supersaturation and the molecular mobility have an influence on the stability of the amourphous state, both parameters were assessed. With respect to the degree of supersaturation of the compounds in the dispersions, the materials seem to be very much alike. Therefore it was postulated that the induction of crystallization in the F1/polymer dispersions stored at high RH (52%) is due to higher molecular mobility of this compound in the dispersions in comparison to F2. The hydrogen bonds that are being formed between F2 and the polymers reduce its mobility and secure this compound from crystallization upon storage, thus indicating the importance of specific interactions with respect to stability issues of solid dispersions. No hydrogen bonds are formed between F1 and the polymers. As a result, the stability of the amorphous state of the compound is being compromised and crystallization takes place. Loperamide, that also does not form hydrogen bonds with the polymers, is less susceptible to crystallization due to its intrinsic good glass forming properties.

Keywords: Stability; Solid dispersions; Phase behaviour; Amorphous state; Crystallinity; Loperamide

1. Introduction

Formulation of solid dispersions is a promising approach to enhance the dissolution rate and solubility of drugs belonging to class II of the Biopharmaceutical Classification System (Chiou and Riegelman, 1971; Ford, 1986; Serajuddin, 1999; Leuner and Dressman, 2000; Kushida et al., 2002).

Often the amorphous state of the drug is preferred in solid dispersions, since it shows improved solubility and dissolution rate in comparison to the crystalline material. Glassy solutions, in which the drug is molecularly dispersed in the carrier, represent the highest level of particle size reduction.

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Furthermore, no energy is required to break up the crystalline structure of the drug upon dissolution (Taylor and Zografi, 1997).

However, one of the key limitations to the widespread commercial use of such dispersions include stability problems, which can lead to the reversion of the amorphous drug to the lower energy crystalline state (Serajuddin, 1999; Leuner and Dressman, 2000) and hence altered dissolution properties upon storage. The use of polymers with a high glass transition temperature for the formulation of solid dispersions is often sufficient to prevent crystallization. However, the basis for this stabilization on a molecular level is not yet clearly understood. Some authors state that the stabilization of the amorphous drug is mainly caused by the presence of specific drug–polymer interactions (Matsumoto and Zografi, 1999; Pignatello et al., 2004; Lin and Perng, 1993). On the other hand, Van den Mooter et al. (2001) clearly demonstrated that in dispersions of ketoconazole and PVP-K25, the antiplasticizing effect of the polymer was the only stabilizing factor.

The aim of the present study was, therefore, to investigate the physical state of three model compounds (loperamide and two of its molecular fragments, F1 and F2) in solid dispersions with PVP-K30 and PVP-VA64 in order to contribute to the understanding of the factors that determine the stability of the amorphous state in solid dispersions. The physicochemical characterization of the solid dispersions made up of the model compounds and PVP-K30 and PVP-VA64, immediately after preparation, was reported in a previous paper (Weuts et al., 2004). This investigation highlighted that loperamide and F1 did not form specific oriented interactions with both polymers, while F2 was clearly involved in hydrogen bonding.

However, all the dispersions of loperamide were amorphous while those of F1 and F2 were amorphous up to a certain concentration, indicating that the presence of specific drug–polymer interactions is no requirement to suppress crystallization of the drug during the preparation of the dispersions. The data also seem to point to the importance of the ease of vitrification of the amorphous state of the pure compounds. It had previously been shown that from the three molecules that were studied, loperamide was most easily obtained in the amorphous state and once in the amorphous state, was the most stable glass (Weuts et al., 2003). This was attributed to the fact that loperamide is the largest and most complex molecule of the three and crystallizes into a monohydrate.

2. Materials and methods

2.1. Materials

PVP-K30 and PVP-VA64 were obtained from BASF (Ludwigshafen, Germany). Their molecular structures are given in Fig. 1. Three low molecular weight compounds (LMWC) were used: loperamide and two fragments of this molecule. The molecular structures are also included in Fig. 1. Loperamide and F2 were available from Janssen Pharmaceutica (Beerse, Belgium) whereas F1 was synthesized (Weuts et al., 2004). The purity of the products was assessed by means of HPLC methods and was 99.8% (loperamide), 99.9% (F1) and 99.9% (F2).

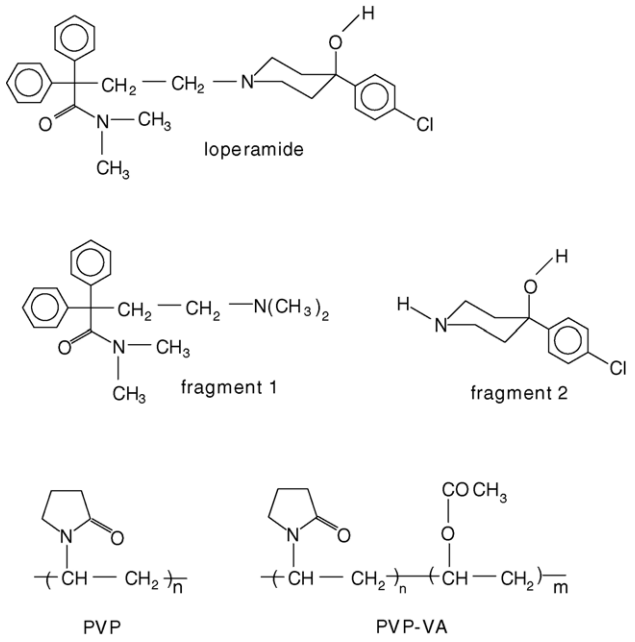

Fig. 1. Molecular structures of the compounds and polymers.

The preparation method for the solid dispersions was explained in a previous paper (Weuts et al., 2004). In this study, the stability of solid dispersions containing 20 and 60% (w/w) of loperamide, 20% (w/w) of F1 and 20% (w/w) of F2 were investigated.

2.2. Storage conditions

After preparation, the solid dispersions were stored under the following conditions: 4 °C/0% RH, 25 °C/52% RH and 40 °C/0% RH.

After 1 and 6 months the physicochemical characteristics of the samples were evaluated. In addition, solid dispersions of loperamide were also investigated after 12 months.

2.3. Methods

2.3.1. High performance liquid chromatography (HPLC)

The exact LMWC content of the dispersions was determined using appropriate HPLC methods. The solvents that were used were of HPLC-grade. All measurements were performed using a Merck Hitachi pump L7100, a Merck Hitachi autosampler L7200 and a Merck Hitachi UV-detector L7400 (Merck, Darmstadt, Germany). A Hypersil BDS-C18 (3 μm, 4.0 mm × 100 mm) column (Agilent, Palo Alto, CA, USA) was used. All measurements were performed at room