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Investigation and correlation of physical stability, dissolution behaviour and interaction parameter of amorphous solid dispersions of telmisartan: A drug development perspective

R. Dukeck, P. Sieger, P. Karmwar *

Department of Drug Discovery Support, Boehringer-Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss 88397, Germany

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ABSTRACT

The aim of this study was to investigate if amorphous solid dispersions of telmisartan, prepared in presence of different polymers, exhibit different structural and thermodynamic characteristics and whether these differences can be correlated to their physical stability (time to crystallisation) and dissolution behaviour. Amorphous samples were prepared by melt quenching. The resulting amorphous materials were characterised using X-ray diffraction, Raman spectroscopy and differential scanning calorimetry. All freshly prepared samples were completely X-ray amorphous (with a halo being the only feature in the diffractograms). The shape of the halos in the diffractograms varied suggesting structural variations in the near order of the molecules between the different amorphous solid dispersions (ASDs). Principal component analysis of the Raman spectra of the various ASD revealed that the samples clustered in the scores plot, again suggesting structural differences due to the presence of different drug–polymer interaction. The ranking of the samples with respect to physical stability and interaction parameter was: ASD of telmisartan:eudragit > ASD of telmisartan:soluplus > ASD of telmisartan:HPMC > ASD of telmisartan:PVP > amorphous telmisartan. The interaction parameter, calculated by using the Flory Huggins theory, showed a good correlation with the experimentally determined stability whereas a weak correlation was found with dissolution behaviour of different ASD. This study showed that correlation of physical stability and dissolution behaviour with calculated interaction parameter is possible for the same amorphous systems prepared by using different polymers. This could aid in selecting the most appropriate polymer for the development of optimised formulations containing amorphous drugs. It can be concluded that ASD prepared by using different polymers have different structural and thermal properties. These differences affect the physical stability and dissolution profiles of the amorphous solids. Thus, choosing the right polymer for preparing ASD is critical for producing materials with desired dissolution profiles and enhanced stability.

1. Introduction

Many new chemical entities coming out of pharmaceutical drug discovery exhibit low aqueous solubility and subsequently poor bioavailability after oral administration (BCS class 2 drugs) (Patterson et al., 2007). It is therefore often required to enhance dissolution rate and solubility of these compounds, to allow the further development of a drug into a medicine.

From a formulation point of view, particularly BCS Class II drugs with poor solubility but high permeability comprise an interesting development platform, since formulation strategies may be applied to improve the solubility (Chieng et al., 2009; Graeser et al., 2009; Heinz et al., 2007; Patterson et al., 2007). For example, the low solubility (and thus bioavailability) of BCS II compounds can be enhanced by solid-state transformations, such as the conversion of crystalline forms of drugs to the amorphous form (Haleblian, 1975). Another interesting aspect of transforming crystalline drugs into amorphous drugs is that the higher solubility often correlates with a faster dissolution rate of the drug (Karmwar et al., 2011b; Savolainen et al., 2009). The dissolution rate is also critical for the application of a drug, since adsorption via the oral route is only possible during gastro-intestinal passage of the drug. Examples of drugs for which the transformation into amorphous solids has improved their applicability in pharmaceutical industry, include indomethacin (Imaizumi et al., 1980), carbamazepine (Seefeldt et al., 2007), dipyridamole (Patterson et al., 2007), novobiocin (Mullin, 1961), itraconazole (Jung et al., 1999) and celecoxib (Gupta et al., 2004).

However, the amorphous form of drugs also encounters a major drawback: due to their high levels of energy (disorder), they are also inherently unstable, both physically and chemically. This is

* Corresponding author. Tel.: +49 7351 54 141973; fax: +49 7351 83 141972.
E-mail address: pranav.karmwar@boehringer-ingelheim.com (P. Karmwar).

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the reason, why traditionally crystalline forms of drugs are preferred in pharmaceutical formulations (Craig et al., 1999).

The physical stability of amorphous active pharmaceutical ingredient (API) can be increased by the use of miscible polymers. There has been much debate in the pharmaceutical literature about mechanisms involved in the physical stabilization of amorphous systems (Chieng et al., 2009; Karmwar et al., 2011a; Patterson et al., 2008; Sethia and Squillante, 2004; Taylor and Zografi, 1997; Van den Mooter et al., 2001). The formulation approach using drug–polymer blends has been used in the past in order to inhibit the crystallisation of the API in amorphous solid dispersions than the amorphous API alone. The aggregation/agglomeration of individual drug particles exhibiting a high solid–liquid surface tension is prevented by the presence of the carrier and it also creates a microenvironment, where the solubility of the drug is higher as compared to their crystalline counterparts (Six et al., 2004). The vast majority of drugs contain hydrogen-bonding sites. The presence or absence of intermolecular hydrogen bonds greatly influence properties such as cohesion and mixing of powders, adhesion and wetting (Castellanos, 2005; Li et al., 2011; Narang and Srivastava, 2002).

Drug–polymer systems (amorphous solid dispersions) lead to a promising approach for improving the oral bioavailability of poor water-soluble drugs, where a hydrophobic drug is dispersed within an inert matrix. Understanding the drug–polymer systems is of utmost significance to facilitate the optimisation of such formulations on the basis of structural variations, physical stability and dissolution. Trial and error experiments govern the screening process of polymeric excipients used in pharmaceutical formulations, with no systematic method available till date, to select a suitable functional polymer. The physicochemical properties of API are by large the major concern in the selection of a suitable polymer for solid dispersions. Whilst studies evaluating interaction affinity of API with individual polymers and the effect drug–polymer ratio on stability and dissolution have been conducted in the past (Chee, 1995; Marsac et al., 2009; Meaurio et al., 2005; Park et al., 2005; Vanhee et al., 2000), there has been comparatively little research into understanding the effect of drug–polymer interaction on the release of API from polymer matrix along with the degree of supersaturation as a function of time.

From a pharmaceutical industry perspective, the drug–polymer interaction governs the formulation selection for different stages of drug development. The formulation optimisation for early stage drug development is mainly C_{max} (concentration maximum) driven whereas the formulation for toxicological studies is *AUC* (area under the curve) driven.

The aim of this study was to investigate whether amorphous solid dispersions of telmisartan samples prepared (melt quenching) using different polymers, exhibit different structural characteristics (investigated by X-ray diffraction and Raman spectroscopy) along with different interaction affinity (calculated from differential scanning calorimetry measurements using the Flory–Huggins theory) and physical stability (time to crystallisation) and whether these can be correlated to the dissolution behaviour of the amorphous solid dispersions.

Telmisartan is an orally active, nonpeptide angiotensin II receptor antagonist. The renin–angiotensin system (RAS) plays an important role in the control of blood pressure and the regulation of volume and electrolyte homeostasis. It has a long duration of action and has the longest half-life of any angiotensin receptor blocker (Aoki et al., 2010; Kang et al., 1994; Ogihara et al., 1993). Since telmisartan is so effective, usage is increasing relative to those of other hypertension treatments. According to the biopharmaceutic classification system (BCS) (Löbenberg and Amidon, 2000), telmisartan is a class II drug with a log*P* value of 7.23, p*Ka* value of 3.5, 4 and 5.6 and poor water solubility of ≈1 μg ml^{-1}; however, it is freely soluble in highly alkalized solution. Telmisartan is a substituted benzimidazole derivative (Fig. 1). It has been proposed to have up to three different forms (two anhydrous forms, A and B, and a solvated form, C) (Dinnebier et al., 2000). The drug is marketed under the trade names Pritor™ and Micardis®.

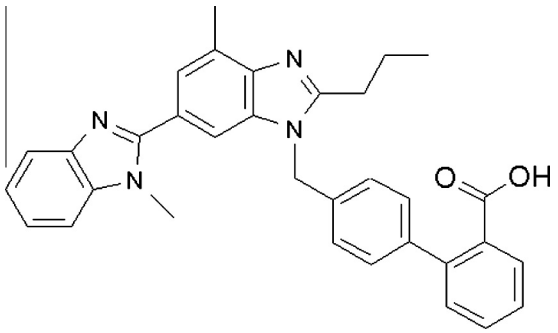

Fig. 1. Molecular structure of telmisartan.

2. Materials and methods

2.1. Materials

Telmisartan (>99% purity, form A) was synthesized in-house (Boehringer-Ingelheim Pharma, Germany). Soluplus and polyvinylpyrrolidone (PVP) K25 were obtained from BASF (Ludwigshafen, Germany), Hydroxypropyl methylcellulose (HPMC) E5 from Colorcon, Inc. (Pennsylvania, USA) and Eudragit E100 from Evonik industries (Krefeld, Germany). All materials were used as received.

2.2. Preparation of physical mixtures, amorphous samples and amorphous solid dispersions

2.2.1. Physical mixture

The drug and polymers were ground and sieved (separately) to obtain particles in the range 50–100 μm. Physical mixture of drug and polymer (7:3) was prepared using an oscillatory ball mill (Mixer Mill MM301, Retsch GmbH & Co., Haan, Germany). The powder sample was placed in 4 ml volume glass milling jar containing two 4 mm diameter glass beads. The samples were milled at 22 ± 2 °C with a frequency of 15 Hz for up to 2 min. Samples were prepared in triplicate.

2.2.2. Amorphous drug and amorphous solid dispersions

Telmisartan (form A) and physical mixtures thereof were melted in an aluminium cup at 275 °C and then cooled immediately using liquid nitrogen. The resulting amorphous solid was then warmed to room temperature over silica gel and then grounded and seived to obtain particles in the range of 50–100 μm. No chemical decomposition of telmisartan was observed for any of the samples in HPLC analysis. Samples were prepared in triplicate.

Amorphous telmisartan (pure drug) and amorphous solid dispersions (ASDs) of telmisartan will be referred to as amorphous samples and ASD of telmisartan with eudragit, soluplus, HPMC and PVP will be referred to as ASD of eudragit, soluplus, HPMC and PVP respectively in this manuscript.

2.2.3. Storage

A suspension of 100 mg ml^{-1} (equivalent to 70 mg ml^{-1} telmisartan) for all the freshly prepared amorphous samples was prepared (0.1 M McIlvaine buffer pH 4) and stored at room temperature (20 ± 1 °C) under continuous stirring until the onset of crystallisation was detected. The suspensions were collected