Journal of Controlled Release xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Real time Raman imaging to understand dissolution performance of amorphous solid dispersions

Francesco Tres [a], Kevin Treacher [b], Jonathan Booth [b], Les P. Hughes [b], Stephen A.C. Wren [b], Jonathan W. Aylott [a], Jonathan C. Burley [a,*]

[a] School of Pharmacy, Boots Science Building, University of Nottingham, Nottingham NG7 2RD, United Kingdom
[b] Pharmaceutical Development, AstraZeneca, Macclesfield, SK10 2NA, United Kingdom

ARTICLE INFO

Article history:
Received 28 March 2014
Accepted 30 May 2014
Available online xxxx

Keywords:
Poorly soluble drugs
Amorphous solid dispersions
Solid-state transformations
Raman imaging
Intrinsic dissolution rate
Multi-variate curve resolution (MCR)

ABSTRACT

We have employed for the first time Raman spectroscopic imaging along with multi-variate curve resolution (MCR) analysis to investigate in real time and *in-situ* the dissolution mechanisms that underpin amorphous solid dispersions, with data being collected directly from the dosage form itself. We have also employed a novel rotating disk dissolution rate (RDDR) methodology to track, through the use of high-performance liquid chromatography (HPLC), the dissolution trends of both drug and polymer simultaneously in multi-component systems. Two formulations of poorly water-soluble felodipine in a polymeric matrix of copovidone VA64 which have different drug loadings of 5% and 50% w/w were used as models with the aim of studying the effects of increasing the amount of active ingredient on the dissolution performance. It was found that felodipine and copovidone in the 5% dispersion dissolve with the same dissolution rate and that no Raman spectral changes accompanied the dissolution, indicating that the two components dissolve as single entity, whose behaviour is dominated by water-soluble copovidone. For the 50% drug-loaded dispersion, partial RDDR values of both felodipine and copovidone were found to be extremely low. MCR Raman maps along with classical Raman/X-ray powder diffraction (XRPD) characterisation revealed that after an initial loss of copovidone from the extrudate the drug re-crystallises, pointing to a release dynamics dependent on the low water solubility and high hydrophobicity of felodipine. Raman imaging revealed different rates of transition from amorphous to crystalline felodipine at different locations within the dosage form.

1. Introduction

A high number of new chemical entities emerging from the drug development process show pharmacological activity, but at the same time are characterised by poor dissolution and solubility profiles [1]. As a result, there is a strong push to develop innovative formulations for the delivery of such compounds so that the desired oral bioavailability and pharmacological effects are achieved. An increasingly popular class of formulation is represented by amorphous solid dispersions, which are prepared by co-processing the drug and a water-soluble or water-swellable polymeric carrier, commonly *via* spray drying or hot melt extrusion [2,3]. The resultant dispersion, as widely demonstrated for several poorly soluble compounds, has an improved dissolution profile and consequently bioavailability compared to the pure drug [4]. This is attributed to the fact that the drug within the dispersion exists in the amorphous form, which gives a higher dissolution rate than the corresponding crystalline form, and also due to the presence of the water-soluble polymer [5,6].

One of the key challenges for deploying amorphous solid dispersions in real-world formulations is the understanding of the dissolution performance. Although this is very relevant, due to the fact that the dissolution performance limits the *in vivo* efficacy, relatively few studies have been conducted to investigate the dissolution mechanisms that underpin these systems. As reported by Craig, [7] the dissolution mechanism of amorphous solid dispersions is characterised by a number of critical processes, which primarily depend on the chemical nature of the components and on the drug-to-polymer ratio. In relation to these parameters, Craig classified the drug release from amorphous solid dispersions as polymer-controlled or drug-controlled. It has been demonstrated that the re-crystallisation of the drug either in the solid state or after precipitation in solution, [8,9] the formation of nano- and micro-particles during the dissolution [10] and also the behaviour of the polymer itself, [11] strongly contribute to the final dissolution performance. Amorphous solid dispersion dissolution mechanisms are extremely difficult to de-convolute due to several processes occurring simultaneously.

* Corresponding author.
E-mail address: jonathan.burley@nottingham.ac.uk (J.C. Burley).

http://dx.doi.org/10.1016/j.jconrel.2014.05.061
0168-3659/

Classical methods of investigating drug release such as the use of USP dissolution apparatuses [12] do not offer any chemical or spatially-resolved information on potential changes of the solid form (*e.g.* from amorphous to crystalline, polymorphic transformations or formation of hydrate states) during the dissolution, since the data are collected from the solution, rather than directly from the solid dosage form itself. Given the limitations of the conventional dissolution apparatuses, innovative methods have been developed in an attempt to provide a more complete picture of the drug release. Such methods have included mid-IR, [13,14] near-IR [15,16] and magnetic resonance imaging (MRI) [8,17]. Mid-IR and near-IR provide chemical information, but also have a significant drawback; they are very sensitive to water which clearly limits the use of these techniques in aqueous environments. MRI is attractive as it can offer three-dimensional information, however it provides little chemical specificity.

Raman spectroscopy, theoretically, offers advantages/complementarities compared to these techniques. It provides chemically detailed and two-dimensional spatial information ('hyper-spectral data', one spectrum per pixel) and is able to readily differentiate between amorphous and crystalline solid forms [18,19]. These properties are significant since the chemical and physical forms of the drug can change during the course of the dissolution test [8,9,14]. Moreover, with respect to mid-IR and near-IR, Raman spectroscopy is relatively insensitive to water [20]. Raman spectroscopy is therefore an appropriate technique to investigate how the solid state properties of the drug affect its release and for this reason was employed in this work to understand the performance of amorphous solid dispersions during dissolution in aqueous media.

An amorphous solid dispersion of felodipine, the active ingredient, in a polymeric matrix of copovidone VA64, was used as model formulation. Felodipine is an antihypertensive drug, characterised by high permeability and low water solubility (lower than 0.5 mg/lt) [21]. Copovidone VA64 is a highly water-soluble polymer (solubility higher than 100 mg/lt), [22] recognised as a chemical analogue of polyvinylpyrrolidone (PVP). In previous studies, PVP and copovidone VA64 have been successfully used to prepare one-phase amorphous felodipine binary mixtures over a range of composition (0–70% drug loading), showing the ability to inhibit re-crystallisation and to increase the dissolution rate of poorly soluble felodipine [23–27]. The physical mixture of crystalline felodipine and copovidone VA64 has been shown instead to have a small increase in dissolution rate when compared to pure crystalline felodipine, further demonstrating how the physical state of the active ingredient (*e.g.* amorphous *vs.* crystalline) affects the whole dissolution performance regardless the presence or absence of the polymer in the formulation [8]. This work follows on from the recent paper by Langham et al., where the use of a combined spectrophotometric and magnetic resonance imaging technique to investigate the dissolution mechanisms of felodipine–copovidone spray-dried amorphous solid dispersions was described [8]. It was found that the dissolution behaviour of the high drug-loaded amorphous solid dispersions is governed by the low aqueous solubility of felodipine and by the re-crystallisation (confirmed by off-line XRPD) of the drug.

In the present work, we investigated formulations which have different drug loadings (5% and 50% w/w), with the aim of studying the effects of increasing the amount of active ingredient on the dissolution performance. Two different approaches were employed to probe the dissolution performance of amorphous solid dispersions. The first used Raman spectroscopy and the second uses a rotating disk dissolution rate (RDDR) test. Our RDDR method, with respect to conventional intrinsic dissolution rate (IDR) test described in the USP and in the European Pharmacopoeia, [12,28] employs HPLC to separate the drug from the polymer and ultimately allows us to measure the performance in aqueous media of multi-component systems.

The aim of this work is to investigate whether Raman spectroscopy provides additional chemical and spatial information regarding the dissolution mechanisms that underpin amorphous solid dispersions, used in conjunction with RDDR dissolution test.

2. Materials and methods

2.1. Preparation of amorphous felodipine and extrudate solid dispersions

The amorphous form of felodipine was obtained by heating the drug as received (AstraZeneca, Macclesfield, United Kingdom) in the oven to 160 °C and, after melting, cooling back to room temperature. Visual inspection and Raman spectroscopy confirmed the formation of the amorphous form and the absence of crystalline material within the detection limits (*ca.* 0.5% or better). 5% and 50% drug-loaded amorphous solid dispersions of felodipine in copovidone (BASF, Ludwigshafen, Germany) were prepared using a co-rotating twin-screw extruder (Thermo Scientific HAAKE MiniLab II). Felodipine and copovidone were pre-mixed for 20 min in a Turbula T2F mixer (Willy A. Bachofen AG Mashinefabrik). The extruder was manually fed with the physical mixture. The screw speed was set to 150 rpm and the temperature to 160 °C. The extrudates with spaghetti shape were then collected, cooled to room temperature and manually milled to fine powder. X-ray powder diffraction confirmed the formation of the amorphous solid dispersion and the absence of crystalline material (Figure S1).

2.2. X-ray powder diffraction (XRPD)

XRPD patterns were obtained using a PANalytical CubiX PRO diffractometer. Samples were exposed to Cu-Kα radiation at a voltage of 45 kV and a current of 40 mA. After being smeared onto the holder, samples were scanned from 2° to 40° 2θ, with a step size of 0.02° 2θ.

2.3. Rotating disk dissolution rate (RDDR)

RDDR testing was carried on using the rotating disk system, also known as 'Woods apparatus'. The die cavity has a diameter of 8 mm with subsequent exposed sample surface area of 0.5 cm^2. About 250 mg of extrudate powder was compressed under a compression force of 2000 kg using a manual IR press (Specac). The experiment was performed in a Sotax AT7 semi-automated dissolution bath equipped with an automated sample collector. Compressed discs were immersed in 500 ml of deionised water at 37 °C (±0.5), at 100 rpm rotational speed. The automated sample collector removed aliquots of sample from the dissolution medium at regular time intervals over 120 min. The samples were then analysed by reverse phase high performance liquid chromatography (RP-HPLC). Both the experiments for 5 and 50% extrudates were performed in triplicate. HPLC analysis was carried out using a Agilent 1100 with UV detection at 210 nm, equipped with an Agilent PLRP-S 300 Å 3 μm 50 mm column (polystyrene/divinylbenzene stationary phase). The flow rate was set to 1.0 ml/min and the temperature of the column was kept at 40 °C. A linear gradient elution was used starting at 40% acetonitrile/60% deionised water and ending at 90% acetonitrile/10% deionised water after 3.5 min, with chromatograms collected up to 5 min. A series of standard solutions of felodipine and copovidone were prepared to generate a calibration curve covering the concentration range of dissolved sample. The partial RDDR of both drug and polymer was calculated using linear regression analysis [12,28]. The partial RDDR of the substance tested was determined from the slope of the regression line.

2.4. Raman spectroscopy

We investigated the dissolution performance of compressed extrudate powder. Spherical compacts with a diameter of 5 mm and a weight of 50 mg were prepared with a manual IR press (Specac) using a compression force of *ca.* 20 kN. The dissolution test was performed in a flow cell, which is illustrated in Figure S2. Deionised water was

Please cite this article as: F. Tres, et al., Real time Raman imaging to understand dissolution performance of amorphous solid dispersions, J. Control. Release (2014), http://dx.doi.org/10.1016/j.jconrel.2014.05.061