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The use of microviscometry to study polymer dissolution from solid dispersion drug delivery systems

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Abstract

Solid dispersions can be used to improve dissolution of poorly soluble drugs and PVP is a common polymeric carrier in such systems. The mechanisms controlling release of drug from solid dispersions are not fully understood and proposed theories are dependent on an understanding of the dissolution behaviour of both components of the dispersion. This study uses microviscometry to measure small changes in the viscosity of the dissolution medium as the polymer dissolves from ibuprofen–PVP solid dispersions. The microviscometer determines the dynamic and kinematic viscosity of liquids based on the rolling/falling ball principle. Using a standard USP dissolution apparatus, the dissolution of the polymer from the solid dispersion was easily measured alongside drug release. Drug release was found to closely follow polymer dissolution at the molecular weights and ratios used. The combination of sensitivity and ease of use make microviscometry a valuable technique for the elucidation of mechanisms governing drug release from polymeric delivery systems.

Keywords: Solid dispersion; Microviscometry; Polymer dissolution; Ibuprofen; Polyvinylpyrrolidone

1. Introduction

Solid dispersions describe the dispersion of one or more active ingredients in an inert carrier matrix at solid state. Various grades of polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) have emerged as the most widely used carriers. They can be prepared by a number of methods including melt-fusion and solvent evaporation. Development has been limited due to problems with preparation, reproducibility, formulation development, scale-up and stability (Serajuddin, 1999) and the solid-state structure, stability and mechanism for dissolution enhancement are poorly understood in the majority of cases (Craig, 2002).

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Theories proposed for the mechanisms governing drug release from solid dispersions are dependent on an understanding of the dissolution behaviour of both components. Some systems exhibit carrier-controlled release with the rate of release being determined by the dissolution of the polymer and independent of the drug loaded (Corrigan, 1985; Dubois and Ford, 1985) while others have shown that release is dependent on the properties of the drug (Sjökvist and Nyström, 1988).

Although many articles have been published detailing the dissolution of the drug, few studies are reported examining the dissolution of the polymer. Various techniques have been used to study polymer dissolution and are discussed in a recent review (Miller-Chou and Koenig, 2003). The use of differential refractometry, optical microscopy, interferometry, ellipsometry, gravimetry, NMR and FT-IR imaging to study polymer dissolution are described and the relative benefits of the techniques discussed. For example, FT-IR imaging, using spatially embedded spectral features, has been proposed to study the quantification of drug release alongside polymer dissolution (Coutts-Lendon et al., 2003).

Quantification of drug-release rates along with a simple technique for measuring polymer dissolution is advantageous when the amount of drug released depends on the dissolution rate of the polymer. The dissolution of polyethylene glycol (PEG) from solid dispersions was determined using a colorimetric assay involving addition of a number of reagents, even in a simplified method (Corrigan et al., 1979). The dissolution of the drug in the polymer and dissolution of the polymer itself were equivalent, confirming that the mechanism was carrier-controlled in this example (Corrigan, 1986). Thus, the development of a simple method to study polymer dissolution is of importance when attempting to ascertain the mechanisms governing dissolution from solid dispersions and other polymer-controlled drug delivery formulations. This study uses microviscometry to measure the dissolution of PVP from ibuprofen–PVP solid dispersions. The microviscometer in this method uses Stokes law to determine viscosity by measuring the rolling ball time over a fixed distance. The variable inclination angle of the thermostatically controlled capillary allows shear stress/shear rate variation.

2. Materials and methods

Ibuprofen was a gift from GSK Consumer Healthcare and polyvinylpyrrolidine was purchased from Sigma (UK) (PVP-40; intrinsic viscosity 26–35K, PVP-360; intrinsic viscosity 80-100K). All other reagents were purchased from Fisher Scientific and were of HPLC or analytical grade as appropriate.

Ibuprofen and PVP were dissolved in ethanol at ratios of 1:2 and 1:4 and the solid dispersions were obtained by spray-drying (Buchi Mini Spray Drier 191). The operating parameters were: inlet temperature, 75 °C; feed rate, 15 ml/min; airflow, 400 and aspiration at 100%. The solid dispersions were fully dried and stored at room temperature and desiccated until use. In vitro dissolution studies were carried out using USP dissolution apparatus 2 (Hanson Research, SR6, USA) at 37 °C and 50 rpm. Either 200 mg of drug, or an amount of solid dispersion equivalent to 200 mg of drug, was added to 1000 ml of phosphate buffer (pH 6.8). Samples were collected up to 60 min, filtered and assayed for ibuprofen by reversed-phase HPLC. The chromatographic HPLC system (Shimadzu, C-R4AX Chromatopac, Japan) used UV detection at 225 nm. The analytical column was Symmetry C18, 5 μm (ODS-2), 4.6 × 150 mm (Waters). The mobile phase was a mixture of acetonitrile:water:*ortho*-phosphoric acid (500:500:10), flow rate was 1 ml/min and the volume of injection was 20 μl. An internal standard, fenoprofen, was used in all determinations.

PVP dissolution was measured using microviscometry (Automated Micro Viscometer, AMVn, Anton Paar) using a 1.6-mm capillary tube at 20 °C.

3. Results and discussion

Standard polymer solutions were prepared in phosphate buffer (pH 6.8) and calibration curves for PVP of two viscosities are illustrated in Fig. 1.The viscosity of the buffer alone was subtracted from each reading. The coefficient of correlation was 0.990 for PVP-40 and 0.9965 for PVP-360 proving both were linear over the concentration range in these experiments. The viscosity of dissolution medium containing ibuprofen alone (mean = 1.0231 mPa s) was not found to be significantly different to the viscosity of the buffer control

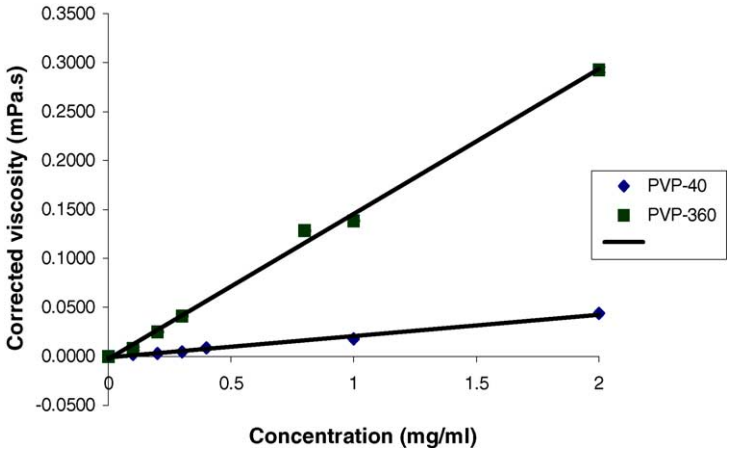

Fig. 1. Viscosity of PVP standard solutions in phosphate buffer ($n = 3$; mean ± S.D.).

(mean = 1.0209 mPa s) over the whole time course of the experiment.

Ibuprofen dissolution was greatly enhanced by the formation of a solid dispersion (1:4 ratio) with 100% of the drug dissolving within 60 min for both PVP polymers used (Fig. 2). Spray-drying of ibuprofen–PVP ethanolic solutions can result in the successful formation of solid dispersions. Decreasing the content of polymer to a ratio of 1:2 resulted in decreased release from both formulations (results not shown). Release from the dispersion using the higher molecular weight polymer (PVP-360) was slower in this case than from its lower molecular weight formulation, although release was more variable using PVP-40.

PVP dissolution within the same samples was measured using microviscometry for all samples at all time points. Dissolution of the drug was found to follow dissolution of the polymer from the dispersion at all ratios and molecular weights used. The dissolution of PVP-40 from a solid dispersion (ratio 1:4) and PVP-360 from a dispersion of 1:2 ratio are illustrated in Figs. 3 and 4. It has been proposed that different mechanisms governing dissolution may dominate at different ratios. For high-molecular-weight PVP, it is reported that dissolution of the solid dispersion is mainly diffusion-controlled whereas decreased particle size, increased

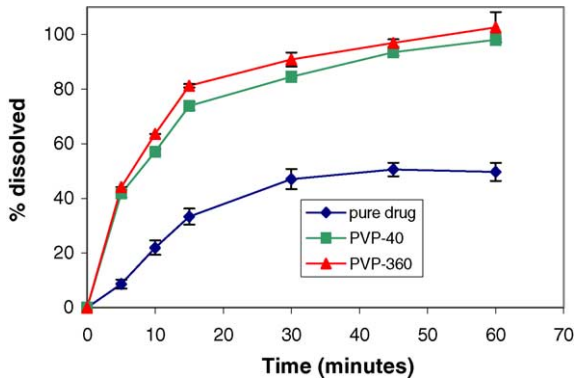

Fig. 2. Dissolution of ibuprofen from ibuprofen–PVP solid dispersions (1:4 ratio) compared with dissolution of pure drug ($n = 3$ for dispersions; $n = 6$ for pure drug; mean ± S.D.).

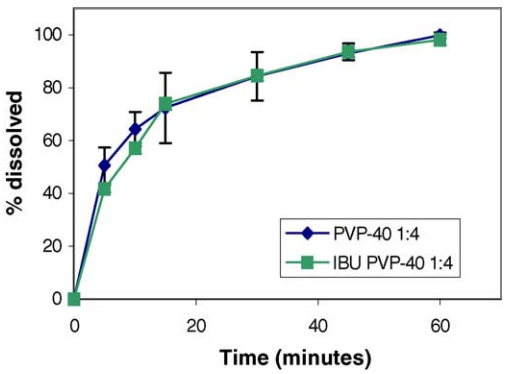

Fig. 3. Dissolution of PVP-40 and ibuprofen (IBU PVP-40) from a 1:4 solid dispersion ($n = 3$; mean ± S.D.).

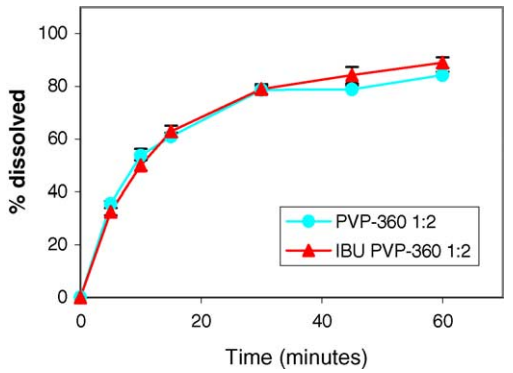

Fig. 4. Dissolution of PVP-360 and ibuprofen (IBU PVP-360) from a 1:2 solid dispersion ($n = 3$; mean ± S.D.).

wettability and prevention of aggregation may be more significant for solid dispersions of lower molecular weight (Tantishaiyakul et al., 1999). In this study, by measuring the dissolution of the polymer alongside the drug, it is possible to say that polymer dissolution is the main mechanism governing dissolution of the drug and the release of drug is controlled by the dissolution of the polymer and the proportion of incorporated drug. The implications are that altering the physical properties of the drug should not have an effect on dissolution and dosage form design should concentrate on the properties of the polymer for this formulation.

Microviscometry to study dissolution of polymers from solid dispersions can be easily carried out in conjunction with drug-release studies. The technique can be used to study dissolution in dilute solutions where the only contributing factor to changing viscosity is the dissolution of the polymer.

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