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Research Paper

Polymer incorporation method affects the physical stability of amorphous indomethacin in aqueous suspension

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ABSTRACT

This study reports the potential of different polymers and polymer incorporation methods to inhibit crystallisation and maintain supersaturation of amorphous indomethacin (IND) in aqueous suspensions during storage. Three different polymers (poly(vinyl pyrrolidone) (PVP), hydroxypropyl methyl cellulose (HPMC) and Soluplus® (SP)) were used and included in the suspensions either as a solid dispersion (SD) with IND or dissolved in the suspension medium prior to the addition of amorphous IND. The total concentrations of both IND and the polymer in the suspensions were kept the same for both methods of polymer incorporation. All the polymers (with both incorporation methods) inhibited crystallisation of the amorphous IND. The SDs were better than the predissolved polymer solutions at inhibiting crystallisation. The SDs were also better at maintaining drug supersaturation. SP showed a higher IND crystallisation inhibition and supersaturation potential than the other polymers. However, this depended on the method of addition. IND in SD with SP did not crystallise, nor did the SD generate any drug supersaturation, whereas IND in the corresponding predissolved SP solution crystallised (into the recently characterised η polymorphic form of the drug) but also led to a more than 20-fold higher IND solution concentration than that observed for crystalline IND. The ranking of the polymers with respect to crystallisation inhibition potential in SDs was SP ≫ PVP > HPMC. Overall, this study showed that both polymer type and polymer incorporation method strongly impact amorphous form stability and drug supersaturation in aqueous suspensions.

1. Introduction

Increasingly, new drug molecules have very poor aqueous solubility, which causes challenges during different phases of drug development [22]. In particular, this is problematic during preclinical toxicology studies when higher systemic exposures are required to understand any dose-related adverse effects of drug molecules [18]. The formulations traditionally used for oral administration during preclinical toxicology studies are simple solutions and aqueous suspensions with crystalline drug, but these are not always acceptable for poorly water soluble drugs. The crystalline drug in suspension may not dissolve sufficiently or the excipients used to solubilise the drug may exert their own biological actions [14].

The amorphous form, which exhibits a higher apparent solubility and associated dissolution rate compared to crystalline forms, is potentially a feasible formulation approach for the administration of poorly water soluble drug molecules [26,43]. Since suspensions are recommended formulations for preclinical toxicology studies, formulating the suspension with the drug in the amorphous, instead of crystalline, form is an attractive approach, with potentially both the drug concentration in solution [16,9,5,25], and the dissolution rate of remaining solid drug after administration, being higher than for suspensions with crystalline solid.

However, the amorphous form is thermodynamically unstable and liable to recrystallisation, which leads to the loss of the desired solubility and dissolution rate advantages. Hence, it is important to develop strategies to suppress crystallisation of the drug in suspension for the period the formulation is expected to be stored and used [8]. In aqueous suspension, crystallisation is normally accelerated compared to that in dry or humid conditions, with amorphous solids able to crystallise via both the solid–solid and solution-mediated routes. Solid–solid phase transformations in

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suspension are accelerated compared to dry or humid conditions in air because the higher surrounding water concentration leads to higher water absorption and greater plasticisation of the solid [7,34]. Solution mediated crystallisation occurs when the supersaturated solution concentration generated (with respect to the crystalline drug) by the amorphous form leads to crystallisation from solution until the solubility of the crystalline material is reached [27]. In order to maintain the amorphous advantage (i.e. higher apparent solubility and dissolution rate) from aqueous suspensions, it is important to stabilise it against both solid–solid and solution-mediated crystallisation [8].

Amorphous solid dispersions (SDs) with polymers (most commonly where the drug is molecularly dispersed as a glass solution) have been used to improve the physical stability of the amorphous form in dry and humid conditions. In these systems, crystallisation inhibition is attributed to two main mechanisms: (i) the antiplasticising effect of the polymers, and (ii) specific bonding interactions (e.g. H-bonding) between drug and polymer [6,23,29]. These mechanisms are also relevant to SDs in suspension.

Polymers dissolved in the solvent may also inhibit crystallisation of amorphous solids [35,30,44,25]. In this situation, the inhibition of crystallisation of amorphous solid can be due to several mechanisms: (i) co-solvency effect of the predissolved polymer, which reduces the degree of supersaturation and hence the thermodynamic driving force for the solution-mediated crystallisation, (ii) adsorption of the polymer onto growing crystal faces, which inhibits the interaction of drug molecules with the crystal faces, and, (iii) formation of a thin polymer film around the amorphous particles, which inhibits nucleation on the particle surface [41,19]. These different mechanisms suggest that when using polymers to stabilise aqueous suspensions with solid amorphous drug, not only the polymer type, but also the method of polymer incorporation (used either in SD with the drug or introduced as a predissolved polymer solution) should be considered. The aim of this study was to investigate the effect of polymer type and polymer incorporation method on the crystallisation behaviour of amorphous drug in suspension. Their effects on the concentration of dissolved drug in the aqueous phase were also of interest. To the best of our knowledge the effect of polymer incorporation method on the physical stability of amorphous drugs in aqueous suspension has not been systematically investigated.

Indomethacin (IND) was selected as a model drug since the physical stability of its amorphous form during storage in dry and humid conditions [17,3,4] and, to some extent, during dissolution [34,2,15] has been well studied. Poly(vinyl pyrrolidone) (PVP), hydroxypropyl methyl cellulose (HPMC), and Soluplus® (SP) (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer) were chosen as model polymers. These polymers are described as biologically inert [31,1]. PVP and HPMC have been used widely for amorphous form stabilisation, either in solid dispersions or pre-dissolved in the dissolution medium [17,38,30,44]. SP is a relatively recent graft co-polymer which has been found to be promising in stabilising the amorphous form of many drugs in solid dispersions [1]. The polymers were incorporated either as SDs with the IND (as a glass solution) or as predissolved polymer solution.

2. Materials and methods

IND (1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid, >98% purity) was purchased from Chemie Brunschwig AG (Basel, Switzerland). PVP K 25 (average molecular weight (avg. MW) 24,000) was purchased from BDH Chemical Ltd. (Poole, England). HPMC 2910 (avg. MW 21,000) was obtained from Synopharm (Darmstadt, Germany). SP (avg. MW 118,000) was a gift from BASF (Ludwigshafen, Germany). Ethanol (analytical grade) and phosphorus pentoxide were obtained from Merck (Darmstadt, Germany).

2.1. Preparation and characterisation of the study samples

IND was supplied in the crystalline γ form. The α form of IND was prepared by the addition of Milli-Q water (antisolvent) to a saturated solution of the γ form in ethanol at 80 °C. The precipitated crystals were removed by filtration and then dried under vacuum at room temperature [33]. Pure amorphous IND was prepared by heating the γ form at 165 °C and quench cooling with liquid nitrogen. The δ, ε, ζ, and η forms were prepared as previously described [37]. Briefly, the ε, ζ and η forms were obtained by the crystallisation of amorphous IND in aqueous suspensions at 5 °C and pH 1.2 and the δ form was prepared by desolvation of a methanolic solution of IND. All the IND solid state forms were ground gently in a mortar and the fractions that passed through a 125 μm sieve and were retained on a 75 μm sieve were used.

The polymers (PVP, HPMC and SP) were sieved separately to the same size fraction. For the SD preparation, physical mixtures (10 g) of γ form and polymer were prepared at a 1:1 drug:polymer ratio (w/w) by gently mixing accurately weighed quantities of drug and polymer in a mortar and pestle. The mixtures were then melted and cooled using the same procedure as described for pure IND.

All forms of the drug and SDs were characterised using modulated temperature differential scanning calorimetry (MTDSC), X-ray powder diffraction (XRPD), attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy and polarised light microscopy (PLM).

2.2. Crystallisation and solution concentration profile in suspension

Suspensions were prepared in pH 5.5 phosphate buffer (200 mM). At this pH, differences in the solution concentration and changes in drug concentration were easily detected, and gelling of the drug, previously observed at pH 6.8, was avoided [37]. The use of buffer also prevented changes in pH occurring due to drug dissolution and crystallisation, simplifying interpretation of the data. Amorphous suspensions were prepared in 20 ml scintillation vials by either adding the SDs to the buffer solution (20 mg/ml, equivalent to 10 mg/ml of pure drug and 10 mg/ml or polymer), or by adding pure amorphous IND (10 mg/ml) into buffer solution containing predissolved polymer at a concentration of 10 mg/ml (resulting in the same total drug and polymer concentrations as with the SDs). Reference suspensions were also prepared to help interpret the crystallisation and solution data. These contained (i) pure amorphous IND (10 mg/ml) without any polymer addition, (ii) pure α form of IND (10 mg/ml) without polymer, (iii) pure α form of IND (10 mg/ml) with predissolved polymer (10 mg/ml), and (iv) pure α form of IND (10 mg/ml) in a physical mixture with polymer (10 mg/ml) corresponding to a 1:1 ratio. Suspensions were prepared and analysed in triplicate.

Each suspension was continuously stirred with a magnetic stirrer at 250 rpm and 25 °C. Solid-state behaviour and dissolved IND concentration in the aqueous phase were analysed at different time points up to 24 h or until crystallisation was complete (according to ATR-FTIR spectroscopy, detailed below). At each time point 400 μl of suspension was pipetted from the centre of the vial. Each sample was immediately centrifuged for 2 min at 14,000 rpm. The clear supernatant obtained was diluted with pH 5.5 phosphate buffer, vortexed and analysed by UV spectroscopy at a wavelength of 320 nm. The remaining solid was analysed by ATR-FTIR spectroscopy to study the solid-state behaviour.

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