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Enabling thermal processing of ritonavir–polyvinyl alcohol amorphous solid dispersions by KinetiSol® Dispersing

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ABSTRACT

Polyvinyl alcohol has received little attention as a matrix polymer in amorphous solid dispersions (ASDs) due to its thermal and rheological limitations in extrusion processing and limited organic solubility in spray drying applications. Additionally, in extrusion processing, the high temperatures required to process often exclude thermally labile APIs. The purpose of this study was to evaluate the feasibility of processing polyvinyl alcohol amorphous solid dispersions utilizing the model compound ritonavir with KinetiSol® Dispersing (KSD) technology. The effects of KSD rotor speed and ejection temperature on the physicochemical properties of the processed material were evaluated. Powder X-ray diffraction and modulated differential scanning calorimetry were used to confirm amorphous conversion. Liquid chromatography–mass spectroscopy was used to characterize and identify degradation pathways of ritonavir during KSD processing and ^{13}C nuclear magnetic resonance spectroscopy was used to investigate polymer stability. An optimal range of processing conditions was found that resulted in amorphous product and minimal to no drug and polymer degradation. Drug release of the ASD produced from the optimal processing conditions was evaluated using a non-sink, pH-shift dissolution test. The ability to process amorphous solid dispersions with polyvinyl alcohol as a matrix polymer will enable further investigations of the polymer's performance in amorphous systems for poorly water-soluble compounds.

1. Introduction

Thermal processing methods, such as hot-melt extrusion (HME), continue to be an active area of research and commercial interest in the pharmaceutical industry [1,2]. In particular, the range of amorphous solid dispersion (ASD) platforms driven by polymer carriers is expanding and continues to be optimized [3,4]. However, thermal processing of many compositions can be challenging due to thermal degradation, viscoelastic properties, or disparities between the active ingredient and excipient temperature processing windows [5]. This can lead to a compromise between manufacturing capability and selection of the optimal formulation composition. Given polymer carriers are often the driving force for determining the performance of an ASD to inhibit crystallization in the solid [6,7] and solution [8,9] states, as well as controlling the release properties to match the desired product profile [10,11], enabling processing of the widest range of carriers is desirable.

One such polymer that has been difficult to thermally process into an ASD while offering a diverse range of properties by grade is polyvinyl alcohol (PVA). PVA is typically a semi-crystalline polymer that is available in a range of grades that vary by the degree of hydrolysis, a measure of the ratio of polyvinyl alcohol to polyvinyl acetate groups, and degree of polymerization [12]. Only grades that contain a majority of polyvinyl acetate groups are fully amorphous. The ratio of alcohol groups to acetate groups, which affects the degree of crystallinity, greatly influences the solubility and swellability of the polymer [13], which in turn can impact the release properties when formulated into a drug product. For physical stabilization in ASDs, the ratio of alcohol to acetate groups dictates the number of hydrogen bond donor groups (hydroxyl) as well as the number of hydrophobic groups (acetate), which is important given various researchers have shown that both hydrogen bonding and hydrophobic interactions between drugs and polymers can impact physical stability in the solid and solution state [14,15].

The reason that PVA has been difficult to process by thermal methods such as HME is twofold. First, semicrystalline PVA remains solid-like below its melting point and is thus not extrud-

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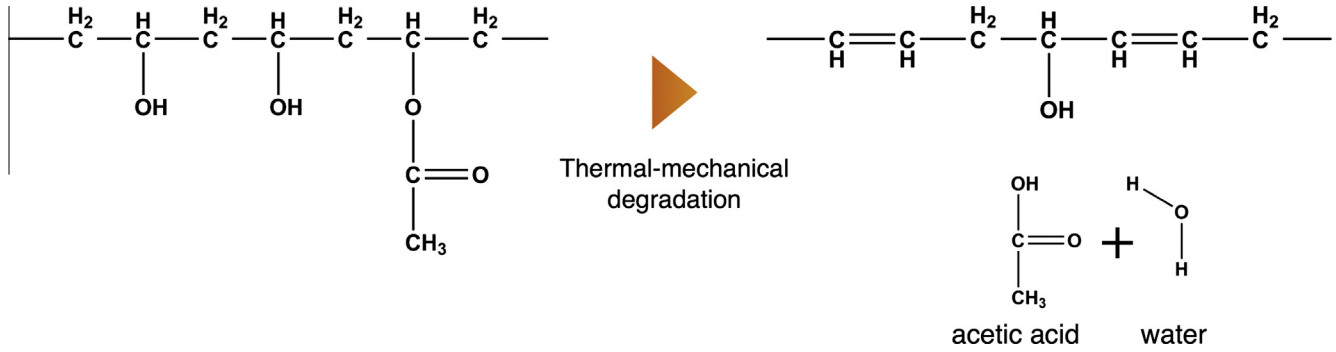

Scheme 1. Thermal degradation of polyvinyl alcohol by elimination of hydroxyl and acetate side groups results in the formation of acetic acid and water and double carbon–carbon bonds along the polymer backbone.

able below this temperature [16,17]. Second, PVA is thermally sensitive and degrades near its melting point through elimination of hydroxyl and acetate side groups, forming water and acetic acid as shown in Scheme 1, with acetic acid further catalyzing the degradation process [18,19]. Interestingly, a recent study evaluated PVA in extrusion processing, requiring processing temperatures at the melting point (~180 °C) for partially hydrolyzed PVA, but no evaluation of polymer degradation was performed [20], though the study did highlight the exclusion of APIs that are thermally labile below the processing temperature. Elimination of side groups is clearly undesirable given their impact on drug product properties as previously described. Attempts to process PVA by extrusion, film blowing, and injection molding have required the use of plasticizers or other additives to depress the melting point and melt viscosity of PVA [21,22], with such methods achieving limited success in fully eliminating polymer degradation [23]. The incorporation of additives may be undesirable in ASDs, however, due to potential impacts on physical stability and release properties [24,25].

KinetiSol® Dispersing (KSD) is an emerging thermal processing technology in the pharmaceutical industry [26]. The process consists of a chamber with a central rotating shaft containing a series of mixing blades. The shaft rotates at relatively high velocities (1000's of RPMs), imparting high frictional energy from particle impaction, which results in very rapid temperature increases with total processing times typically less than 20 s. Notably, no external heating is applied in the process. The process has enabled manufacturing of ASDs without the use of plasticizers [25], including non-thermoplastic polymers and thermally labile polymers [27]. Given the ability of KSD to process non-thermoplastic polymers with very short residence times, we hypothesized that this technology could be used to form amorphous solid dispersions of PVA at temperatures below its melting point with minimal or no side chain elimination. We have previously evaluated KSD processing of PVA with itraconazole [28], but several questions remain unanswered including a thorough understanding of the relative impact of KSD processing parameters on the physical and chemical stability of the drug and polymer. While size exclusion chromatography (SEC) was previously utilized to investigate the impact of processing on the apparent polymer molecular weight and no decrease in apparent molecular weight was observed [28], a deeper investigation of side chain elimination of PVA is warranted.

The aims of this study were to understand the impact of KSD processing parameters in order to produce an ASD with minimal to no degradation of the polymer and model API. Ritonavir was chosen as the model API as it is commercially processed as an ASD by HME in Kaletra®, Norvir®, and Viekirax® [29,30]. Additionally, ritonavir has been shown to be shear sensitive [31], thus representing a challenging model in the KSD process, which exhibits much higher shear rates compared to HME.

2. Materials and methods

2.1. Materials

Polyvinyl alcohol 4-88 (PVA 4-88, Art. No.141350, EMPROVE® exp Ph Eur, USP, JPE) was kindly donated by MilliporeSigma (MilliporeSigma is a business of Merck KGaA, Darmstadt, Germany). Kollidon PVP VA64 was kindly donated by BASF The Chemical Company (Florham Park, NJ, USA). Ritonavir (>98% purity) was purchased from Shengda Pharmaceutical Company Limited (Shenzhen, China). High performance liquid chromatography grade acetonitrile, methanol, and water were purchased from Fisher Scientific (Pittsburgh, PA, USA). Formic acid and deuterium oxide were also purchased from Fisher Scientific. SIF powder was purchased from biorelevant.com (Surrey, United Kingdom).

2.1.1. Thermogravimetric analysis

Thermogravimetric analysis (TGA) was performed on a TA Thermogravimetric Analyzer Q500 (New Castle, DE). Temperature ramp experiments were performed from 25 °C to 300 °C at a rate of 5 °C per minute with air purge at 60 ml/minute. TGA was performed for ritonavir, PVA 4-88, and a blended composition containing ritonavir:PVP VA64:PVA 4-88 in a 3:1:6 ratio.

2.2. Rheology

Rheology experiments were performed with a TA Discovery Hybrid Rheometer 3 (New Castle, DE). A sample preparation was previously described [32] where approximately 1 g of material was weighed and pressed into a slug using a 25 mm die using a hydraulic press with 5000 lb of force for 5 s. The sample was placed between two parallel 40 mm plates after zero gap calibration. Polymer samples were first conditioned at 150 °C for 1 min followed by an oscillation sweep between 0.1 rad/s and 500 rad/s at 10 °C increments from 150 °C to 100 °C. For samples containing drug, conditioning at 150 °C for 1 min was performed followed by an oscillation sweep between 0.1 rad/s and 500 rad/s at 10 °C increments from 100 °C to 150 °C. A strain of 0.1% was used along with an axial force control of 1 N ± 0.1 N. Rheology was performed for PVP 4-88 alone, a PVP VA64:PVA 4-88 blend in a 1:6 ratio, and ritonavir:PVP VA64:PVA 4-88 blend in a 3:1:6 ratio.

2.3. KinetiSol Dispersing

KSD processing was conducted with a compounder developed by DisperSol Technologies, L.L.C. (Georgetown, Texas). Physical mixtures of ritonavir, PVP VA64, and PVA 4-88 (3:1:6) were prepared by dispensing and weighing each component with a top-loading balance, followed by mixing with a mortar and pestle for 30 s. PVP VA64 was included in the composition as a binder and