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Effect of excipient properties, water activity, and water content on the disproportionation of a pharmaceutical salt

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ABSTRACT

Excipients are crucial components of most pharmaceutical formulations. In the case of a solid oral dosage formulation containing the salt form of a weakly ionizable drug, excipient selection is critical, as some excipients are known to cause salt disproportionation (conversion of salt to the free form). Therefore, robust formulation design necessitates an in-depth understanding of the factors impacting salt disproportionation during processing or storage as this can negatively impact product quality and performance. To date, there is an incomplete understanding of key excipient properties influencing salt disproportionation. Specifically, the potential roles of amorphous excipient glass transition temperature and excipient hygroscopicity, if any, on salt disproportionation are still not well understood. Furthermore, the relationship between the compression and the extent of salt disproportionation is an unknown factor. Herein, by utilizing various grades of polyvinylpyrrolidone (PVP), its copolymer, copovidone (PVPVA), and magnesium stearate, a systematic investigation of disproportionation was performed using pioglitazone HCl as a model salt of a weak base. It was observed that there was a poor correlation between excipient hygroscopicity and the rate and extent of disproportionation. However, powder compression into compacts enhanced the rate and extent of disproportionation. This work focused on disproportionation of the salt of a weak base, as basic drugs are more prevalent, however, salts of weak acids may have similar tendencies under relevant conditions. The knowledge gained from this study will help in understanding the role of various excipients with respect to salt disproportionation, paving the way for designing stable salt formulations.

1. Introduction

Excipients, vital for the successful design of pharmaceutical formulations, present a wide range of structural diversity. They can be either amorphous in nature, for example polymers such as polyvinylpyrrolidone (PVP) and croscarmellose sodium (CCS), or they can be present as crystalline forms such as mannitol, lactose, and magnesium stearate (Forster et al., 2001; Jivraj et al., 2000; Waterman and MacDonald, 2010). Major considerations for excipient selection include stability and interaction with the active pharmaceutical ingredient (API) (Chadha and Bhandari, 2014; Gao et al., 2015). For instance, amorphous excipients can be hygroscopic, increasing the water content of the formulation, and leading to undesirable effects for moisture sensitive APIs which can degrade or react with excipients in the presence of water (Rajabi-Siahboomi et al., 2015). Crystalline excipients tend to be less hygroscopic, but their partial amorphization during manufacturing can lead to variability in product performance (Pazesh et al., 2017; Priemel et al., 2016).

Acidic or basic excipients, when combined with the salt form of an API, can lead to ion-exchange reactions, known as salt disproportionation (Nie et al., 2017). Salt disproportionation, a type of acid-base reaction, is the conversion of the salt form of an API to its free form (Thakral and Kelly, 2017). These reactions can be considered as the reverse process of salt formation. For instance, during salt formation, the free base is reacted with an acid to form the salt, while, in the case of disproportionation, the salt of a weak base, when it comes in contact with a basic microenvironmental pH (as induced by a basic excipient), forms the free base (Hsieh and Taylor, 2015). In short, for the salt of a weak base, disproportionation involves the transfer of a proton from the drug to the excipient. Due to the ubiquitous nature of water, and its ability to act as a medium for proton transfer and salt disproportionation, water is expected to play a role in

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disproportionation (Guerrieri and Taylor, 2009).

Salt disproportionation results in formation of the unionized form of the API which is typically orders of magnitude less soluble than the corresponding ionic form (Thakral and Kelly, 2017). This may decrease API bioavailability, with a negative impact for the patient (Nie et al., 2017; Thakral and Kelly, 2017). Several instances of salt disproportionation have been reported, for example, miconazole mesylate and pioglitazone hydrochloride convert to free base in the presence of CCS and magnesium stearate (MS) (Guerrieri and Taylor, 2009; John et al., 2013; Nie et al., 2016b). In addition, partial disproportionation of prasugrel HCl during processing decreased bioavailability in patients with elevated gastric pH, as a result of the conversion to free base and the resultant decrease in solubility (Unger, 2009). There have been some attempts to deconvolute the various factors that govern salt disproportionation reactions. Although it has been established that certain physicochemical properties of excipients including particle size and basicity play a major role (Guerrieri and Taylor, 2009; Hsieh and Taylor, 2015), much of the work to date has focused on the link between disproportionation tendency and API properties. Thus, factors such as excipient mobility (i.e. the glass transition of amorphous excipients such as polymers), water content and/or water activity have not received attention.

The objective of this study was to understand the influence of excipient hygroscopicity and mobility on the salt disproportionation reaction occurring between the salt of a weakly basic drug and a basic excipient. Pioglitazone HCl (PIOH) was used as the model salt and MS was the basic agent; this system was previously shown to undergo disproportionation (John et al., 2013; Koranne et al., 2017; Nie et al., 2016b). Various grades of PVP and its copolymer, poly(1-vinylpyrrolidone-co-vinyl acetate) (PVPVA), were used to investigate the impact of water content and excipient glass transition temperature (Tg). Raman spectroscopy was used to monitor the progress of disproportionation. First, to determine the effect of the excipient Tg on salt disproportionation, PVP K12 and PVP K90 were used. These polymers have similar water content when stored at a given RH, but varying mobility (based on Tg), allowing the importance of polymer molecular mobility on salt disproportionation to be evaluated. Second, to probe the impact of excipient hygroscopicity on salt disproportionation, PVP and PVPVA were used. These polymers have similar mobility (based on Tg), but varying water content, allowing evaluation of the effect of water content on salt disproportionation. Control samples without hygroscopic excipients were also evaluated.

2. Experimental section

2.1. Materials

PIOH was obtained from the Tokyo Chemical Industry Co, Ltd. (Portland, OR). PVP K12, PVP K90, and PVPVA were generously provided by BASF (Florham Park, NJ). MS was supplied by Brand Nu Labs (Meriden, CT). Fumed silica (Aerosil® R 972, hydrophobic) and mannitol were purchased from Evonik Corporation (Parsippany, NJ) and Sigma-Aldrich (Saint Louis, MO), respectively. Sodium hydroxide (NaOH) and hydrochloric acid (HCl) were purchased from Fisher Scientific (Pittsburgh, PA). All the chemicals were greater than 99% of purity. The molecular structures of PIOH and the excipients are shown in Fig. 1. Pioglitazone (PIO) free base was obtained by slurrying an excess amount of PIOH in 1 M NaOH solution at 700 rpm for 3 h. The resultant solids were then vacuum filtered, washed with water, and air dried.

2.2. Methods

2.2.1. X-ray powder diffraction (XRPD)

A Rigaku SmartLab (XRD 6000) diffractometer (The Woodlands, TX) was used to collect diffraction patterns with Bragg–Brentano mode using CuKα radiation (λ = 0.15405 nm) as described previously (Patel et al., 2017d). About 40 mg of sample was placed onto a sample holder and the diffraction data were recorded (at room temperature) with a step size of 0.02° between 5° and 40° 2θ.

2.2.2. Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR)

A Bruker Vertex 70 spectrometer (Bruker Co., Billerica, MA) was used to generate ATR-FTIR spectra as described previously (Patel et al., 2017b, 2016). The instrument is equipped with a Golden Gate attenuated total reflectance (ATR) sampling accessory with a diamond crystal (Specac Ltd., Orpington, UK). Data collection and analysis were performed using the OPUS software (Bruker Co., Billerica, MA). A small quantity of sample was placed on to the diamond crystal of the ATR accessory and the FTIR spectra were generated at a resolution of 4 cm^{-1} by accumulating 64 scans between 650 cm^{-1} and 3950 cm^{-1}.

2.2.3. Differential scanning calorimetry (DSC)

A Q2000 DSC (TA instruments, New Castle, DE) was used to generate the thermal profiles of various samples as described previously (Kavuru et al., 2016). A refrigerated cooling accessory (RCS) (TA instruments, New Castle, DE) was used to cool the furnace and the instrument was purged with nitrogen gas continuously. A Tzero pan with a hermetic Tzero lid (TA instruments, New Castle, DE) was used and about 10 mg of each sample was heated at a rate of 10 °C/min. The TA Analysis software (TA instruments, New Castle, DE) was used to determine the midpoint Tg and the onset of melting temperature.

2.2.4. Thermogravimetric analysis (TGA)

A Q500 TGA (TA instruments, New Castle, DE) was used to generate the thermogravimetric profile of PIOH as described previously (Patel et al., 2017a). The instrument was purged with nitrogen gas continuously. A platinum pan (TA instruments, New Castle, DE) was used and the sample was heated to 500 °C with a heating rate of 10 °C/min. The TA Analysis software (TA instruments, New Castle, DE) was used for data analysis.

2.2.5. pH-solubility profile

The pH-solubility profile of PIO was obtained using the slurry method. An excess amount of PIO was allowed to slurry for 48 h in water with varying pH values ranging from 0.5 to 8 (adjusted using HCl). An Optima L-100 XP ultracentrifuge (Beckman Coulter, Inc., Brea, CA) was used to remove the excess solids (35,000 rpm for 30 min). An Agilent 1290 Infinity Series high performance liquid chromatography (HPLC) system (Agilent Technologies, Santa Clara, CA) was then used to determine the concentration in the supernatant. An Inertsil® ODS-3 C18 5 µm, 4.6 × 100 mm column (GL Sciences Inc., Rolling Hills Estates, CA) was used. Mobile phase with a flow rate of 1 mL/min consisted of a mixture of 0.1% trifluoroacetic acid in water (70%) and acetonitrile (30%). An injection volume of 30 µL was used for all samples. The elution of PIO was monitored at 210 nm using an ultraviolet detector. A calibration curve (R^2 value of 0.997) was used to determine the concentration of each sample. Dilution of the samples with the mobile phase was performed if necessary during the analysis.

2.2.6. pK_a determination

A Sirius inForm instrument (Sirius Analytical, Forest Row, U.K.) was used to experimentally determine the pK_a of PIO. An acid–base titration method coupled with UV spectroscopy was used as described previously (Indulkar et al., 2015). Briefly, a stock solution of PIO was prepared in 1 M HCl. A solution of 0.15 M NaCl in water was used as a titration medium along with 0.5 M HCl (acid) and 0.5 M NaOH (base) as titrant. The sample and solutions were placed in the sample holder of the Sirius inForm, from where the medium and the sample can be automatically dispensed and titrated with acid and base. The experiment was performed at 37 °C and UV spectra were collected simultaneously during