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Crystalline solid dispersion-a strategy to slowdown salt disproportionation in solid state formulations during storage and wet granulation

Haichen Nie[a,b], Wei Xu[c,*], Lynne S. Taylor[a], Patrick J. Marsac[d], Stephen R. Byrn[a,*]

[a] Department of Industrial and Physical Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN, 47907, United States
[b] Formulation Sciences, Teva Pharmaceuticals, 145 Brandywine Parkway, West Chester, PA, 19380, United States
[c] Preformulation Sciences, Merck & Co., Inc., 770 Sumneytown Pike, West Point, PA, 19486, United States
[d] Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, 789 South Limestone Street, Lexington, KY, 40536, United States

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ABSTRACT

Salt disproportionation (a conversion from the ionized to the neutral state) in solid formulations is a potential concern during manufacturing or storage of products containing a salt of the active pharmaceutical ingredient (API) due to the negative ramifications on product performance. However, it is challenging to find an effective approach to prevent or mitigate this undesirable reaction in formulations. Hence, the overall objective of this study is to explore novel formulation strategies to reduce the risk of salt disproportionation in pharmaceutical products. Crystals of pioglitazone hydrochloride salt were dispersed into polymeric matrices as a means of preventing the pharmaceutical salt from direct contact with problematic excipients. It was found that the level of salt disproportionation could be successfully reduced during storage or wet granulation by embedding a crystalline salt into a polymeric carrier. Furthermore, the impact of different polymers on the disproportionation process of a salt of a weakly basic API was investigated herein. Disproportionation of pioglitazone hydrochloride salt was found to be significantly affected by the physicochemical properties of different polymers including hygroscopicity and acidity of substituents. These findings provide an improved understanding of the role of polymeric carriers on the stability of a salt in solid formulations. Moreover, we also found that introducing acidifiers into granulation fluid can bring additional benefits to retard the disproportionation of pioglitazone HCl during the wet granulation process. These interesting discoveries offer new approaches to mitigate disproportionation of API salt during storage or processing, which allow pharmaceutical scientists to develop appropriate formulations with improved drug stability.

1. Introduction

Salt formation is a critical method to increase the bioavailability of ionizable APIs with poor aqueous solubility, and to improve the stability and manufacturability of APIs by changing their solid-state properties. (Berge et al., 1977; Nelson, 1957, 1958; Saal and Becker, 2013; Zhang et al., 2004) However, the ionized form of drug substances can be metastable and have a propensity of converting to the neutral form. This unwanted conversion of a drug salt to its neutral form is termed salt disproportionation which has been reported to negatively influence the performance of pharmaceutical products. (Christensen et al., 2012; Guerrieri et al., 2009; Mathias et al., 2013; Skrdla and Zhang, 2014; Stephenson et al., 2011; Unger, 2009) Therefore, it is imperative to develop formulation approaches to prevent or, at minimum, slow down salt disproportionation to ensure that robust formulations are produced.

In order to effectively inhibit salt disproportionation, it is a prerequisite to understand the following three key factors influencing the disproportionation process. The first of these factors is the presence of water, since salt disproportionation is reported to be a solution mediated reaction. (Guerrieri et al. 2016; Rohrs et al., 1999; Zannou et al., 2007) For solid dosage forms, the presence of residual water from manufacturing or after moisture sorption from the atmosphere is almost inevitable, and even a slight amount of water is sufficient to form a microscopic aqueous

* Corresponding authors.
E-mail addresses: wei_xu@merck.com (W. Xu), sbyrn@purdue.edu (S.R. Byrn).

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layer on the solid surface, which can mediate disproportionation. (Serajuddin, 2007) Second, microenvironmental pH, affected by the acidity/alkalinity of the excipient used in the formulation, is another important factor impacting salt stability. (Govindarajan et al., 2006; Kumar et al., 2013; Scheef et al., 1998; Serajuddin and Jarowski, 1985) For a salt of a weak base, salt disproportionation can potentially occur when the pH of the microenvironment surpasses the pH of maximum solubility (pH_{max}). (Hsieh et al., 2015; Madhu Pudipeddi and David Grant Heinrich Stahl, 2011; Serajuddin and Jarowski, 1985; Serajuddin and Rosoff, 1984) Hence, modifying the microenvironmental pH is a feasible approach to reduce the risk of salt disproportionation. For instance, microenvironmental pH can be decreased by avoiding alkaline excipients such as metallic stearates or croscarmellose sodium. (Merritt et al., 2013; Nie et al., 2016c; Serajuddin et al., 2013) Moreover, pH modifers, such as maleic acid or tartaric acid, can be added into solid formulations to further adjust the pH value of the microenvironment. (John and Harmon, 2014; Zannou et al., 2007) Third, the greater area of contact between the drug salt and problematic excipients was reported to significantly accelerate the disproportionation reaction (e.g. for miconazole and benzocaine salt). (Hsieh and Taylor, 2014) Therefore, reducing the exposure of the salt surface to the surface of the problematic excipient potentially can be used as a means to decrease the extent of salt conversion.

In the present study, the overall aim was to develop effective formulation approaches to slow down salt disproportionation in a solid formulation during storage and manufacturing. Pioglitazone

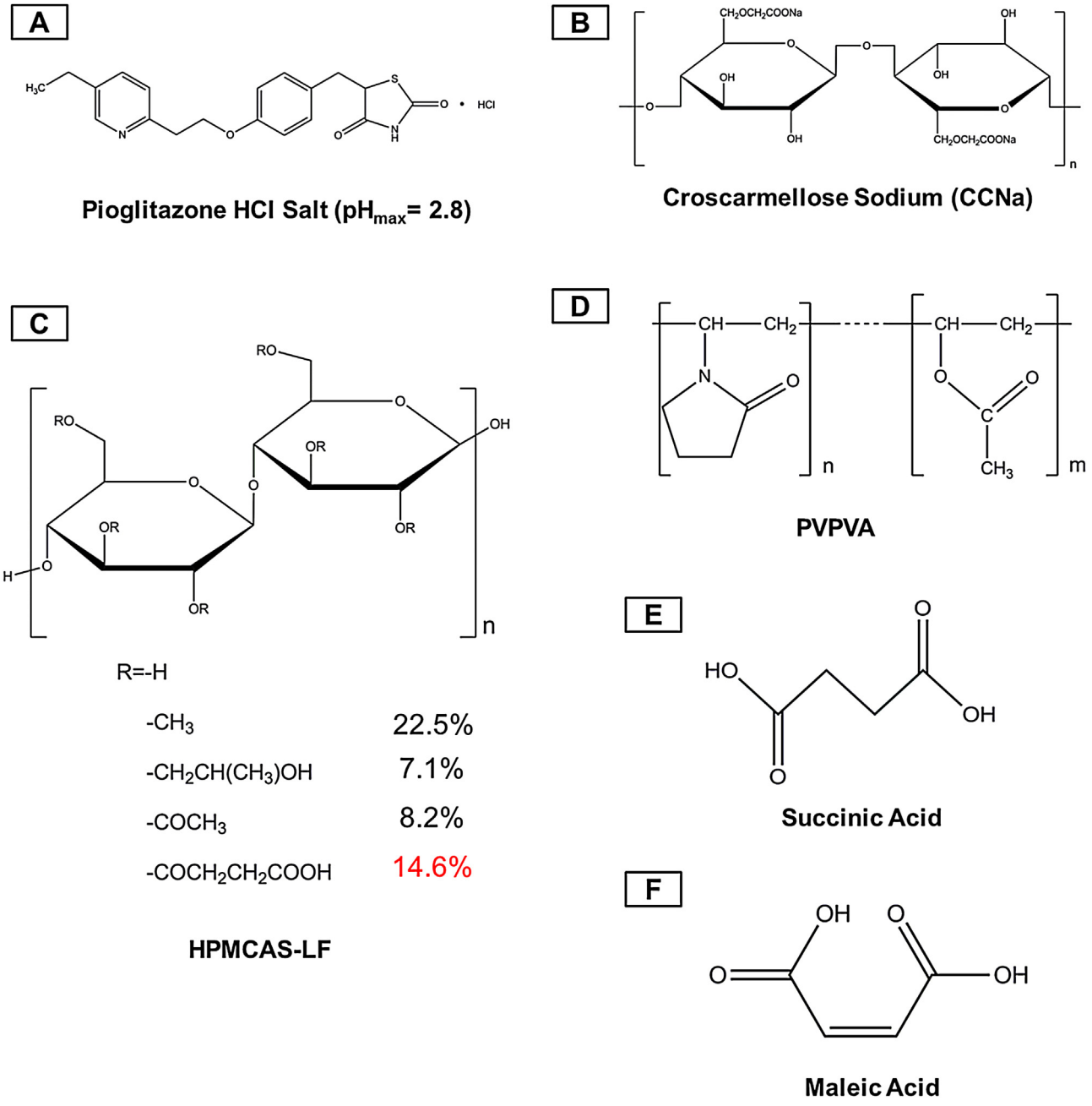

Fig. 1. Chemical structure of pioglitazone HCl salt (A); croscarmellose sodium (B); HPMCAS whereby the weight percentage of substituents are listed (C); PVPVA (D); succinic acid (E); maleic acid (F).