Realistic Prediction of Solid Pharmaceutical Oxidation Products by Using a Novel Forced Oxidation System

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ABSTRACT: This study investigated a novel solid-state-based forced oxidation system to enable a realistic prediction of pharmaceutical product oxidation, a key consideration in drug development and manufacture. Polysorbate 80 and ferric(III) acetylacetonate were used as an organic hydroperoxide source and a transition metal catalyst, respectively. Homogeneous solutions of target compounds and these reagents were prepared in a mixed organic solvent. The organic solvent was removed rapidly under reduced pressure, and the oxidation of the resulting dried solid was investigated. Analysis of the oxidation products generated in test compounds by this proposed forced oxidation system using HPLC showed a high similarity with those generated during more prolonged naturalistic drug oxidation. The proposed system provided a better predictive performance in prediction of realistic oxidative degradants of the drugs tested than did other established methods. Another advantage of this system was that the generation of undesired products of hydrolysis, solvolysis, and thermolysis was prevented because efficient oxidation was achieved under mild conditions. The results of this study suggest that this system is suitable for a realistic prediction of oxidative degradation of solid pharmaceuticals. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1184–1193, 2014

Keywords: oxidation; stress testing; solid state; HPLC; X-ray diffractometry; degradation products; polysorbate; ferric(III) acetylacetonate

INTRODUCTION

Oxidation and hydrolysis are major pathways in drug degradation. Several types of oxidation mechanisms have been identified, including autoxidation (mediated by free radicals),[1,2] nucleophilic/electrophilic (mediated by peroxides),[3,4] electron transfer (mediated by transition metals),[5] and photochemically induced oxidation (singlet oxidation, and so on).[6,7] In some cases, an oxidation reaction is triggered by a trace level of impurity (peroxides or transition metals) contaminating the drug excipient[3–5] and/or by the direct oxidation of the excipients or active pharmaceutical ingredients (for example, autoxidation of polysorbates).[8,9] In general, these oxidation reactions have complicated mechanisms and sometimes generate unfavorable degradation products, such as hydroperoxide, aldehyde, and epoxide forms,[10,11] which show structural features that may be linked to mutagenicity or carcinogenicity.[12,13] For this reason, oxidation is associated with a high risk of generating potentially genotoxic impurities.

Many previous studies have described approaches for studying oxidative mechanisms, including autoxidation prediction using free radical initiators,[14–17] the use of *N*-methylpyrrolidone[18] and Tween80/Fe^{3+},[19] nucleophilic/electrophilic oxidation prediction with peroxides,[3,4,20,21] electron transfer oxidation prediction with transition metals,[5] electro-oxidation prediction with voltammetry,[22] and prediction of photochemically induced oxidation with a photosensitizer.[6] Indeed, these approaches have been used in the pharmaceutical industry, often producing useful information relating to oxidation susceptibility that has been helpful in pharmaceutical development. Furthermore, this information can help prevent or mitigate the risk of potential oxidation product formation, by including an appropriate antioxidant in the formulation, improving the manufacturing process, or modifying packaging. Many pharmaceutical companies have therefore developed and applied forced oxidation systems during drug development to facilitate the prediction of oxidation products.

As many of the forced oxidation systems are solution based, they may not adequately reflect the oxidation reactions that occur in a solid state. There are fewer methods available for the prediction of oxidation in solids. Previous studies have reported solid-state-based methods in which 2,2′-azobis(-amidinopropane) dihydrochloride was simply added to a mixture of a drug and excipients;[23] in which hydrogen peroxide (H_2O_2) was spiked into a mixture of a drug and excipients before tablet formation;[4] in which a drug was exposed to the vapor from H_2O_2 dissolved in water in a sealed container filled with oxygen;[21] and in which urea-H_2O_2 was used to expose a drug to H_2O_2 vapor.[24] The present study proposes and describes a novel solid-state-based forced oxidation system that can be used for a realistic prediction of oxidation products.

It is well known that transition metal ions, such as Fe^{3+}, catalyze the decomposition of H_2O_2 in dilute acid solutions.[25] In

Abbreviations used: PS-80, polysorbate 80; Fe^{3+}A, ferric(III) acetylacetonate; AIBN, 2,2′-azobisisobutyronitrile; XRD, X-ray diffraction; TP, triphenylphosphine; TPO, triphenylphosphine oxide; RH, relative humidity.

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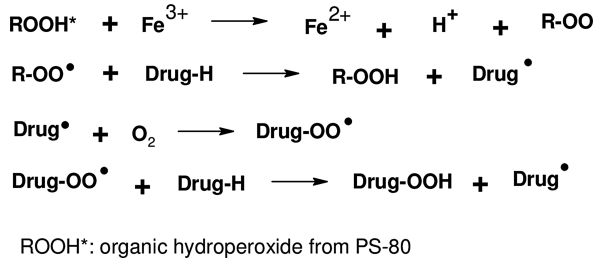


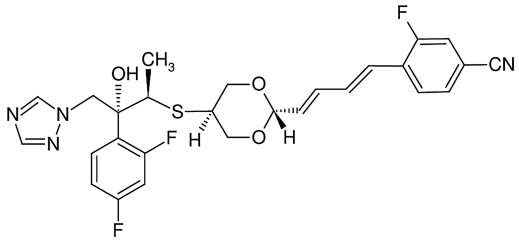
Figure 1. Drug oxidation pathway in the solid-state forced oxidation system.

addition, similar reactions have been reported in which H_2O_2 is replaced by hydroperoxide to yield ROO• instead of HOO•.[26] Harmon et al.[19] developed a unique forced oxidation system by utilizing a system generating peroxy radicals in 10% polysorbate 80 (PS-80) aqueous solution with $FeCl_3 \cdot 6H_2O$. Similarly, our forced oxidation system aims to generate reactive radical species such as ROO• or RO• (Fig. 1). The proposed system uses PS-80 as an organic hydroperoxide source, and ferric(III) acetylacetonate (Fe^{3+}A) as a transition metal catalyst (Fig. 2). Two significant changes distinguish this solid-state system from the solution-based system. Firstly, the use of PS-80/Fe^{3+}A facilitates preparation in an organic solvent, allowing subsequent rapid solvent removal under reduced pressure and the development of a homogeneous solid-state oxidative system. Secondly, PS-80/Fe^{3+}A is present at only 9% by weight, with the remaining 91% being the drug under investigation. This compact matrix of the drug, the hydroperoxide source, and the transition metal catalyst accelerated oxidation in the solid state, allowing rapid evaluation of solid-phase pharmaceutical oxidation. The present study describes the characteristics of this PS-80/Fe^{3+}A-based solid forced oxidation system.

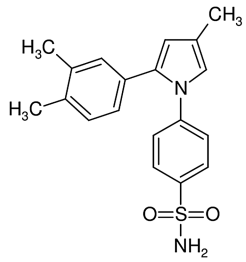
MATERIALS AND METHODS

Materials

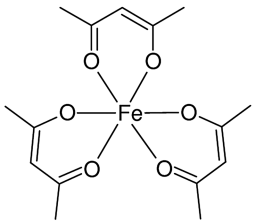
Several model drugs (Drugs A–H) were provided by Daiichi-Sankyo (Tokyo, Japan). The chemical structures of Drug-A, employed in the optimization of the forced oxidation system, and Drug-B are shown in Figure 2. Three grades of PS-80 (Sigma Ultra, nonanimal source, and for general use) were purchased from Sigma–Aldrich (St. Louis, Missouri); two grades of PS-80, which met Japanese Pharmacopoeia standards, were also purchased from Wako Pure Chemical (Osaka, Japan) and NOF (Tokyo Japan). Fe^{3+}A, 2,2′-azobisisobutyronitrile (AIBN), H_2O_2, and triphenylphosphine oxide (TPO) were obtained from Wako. Triphenylphosphine (TP) was purchased from Alfa Aesar (Ward Hill, Massachusetts). All other chemicals used were of analytical grade and obtained from commercial sources.



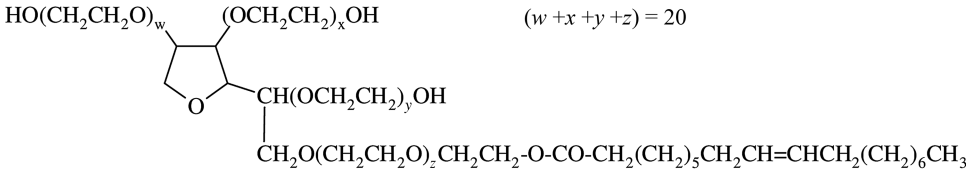
Drug-A (CS-758)



Drug-B



Fe^{3+}A



PS-80

Figure 2. Chemical structures of Drug-A, ferric(III) acetylacetonate (Fe^{3+}A), and polysorbate-80 (PS-80).