NOTE

A Novel Accelerated Oxidative Stability Screening Method for Pharmaceutical Solids

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ABSTRACT: Despite the fact that oxidation is the second most frequent degradation pathway for pharmaceuticals, means of evaluating the oxidative stability of pharmaceutical solids, especially effective stress testing, are still lacking. This paper describes a novel experimental method for peroxide-mediated oxidative stress testing on pharmaceutical solids. The method utilizes urea–hydrogen peroxide, a molecular complex that undergoes solid-state decomposition and releases hydrogen peroxide vapor at elevated temperatures (e.g., 30°C), as a source of peroxide. The experimental setting for this method is simple, convenient, and can be operated routinely in most laboratories. The fundamental parameter of the system, that is, hydrogen peroxide vapor pressure, was determined using a modified spectrophotometric method. The feasibility and utility of the proposed method in solid form selection have been demonstrated using various solid forms of ephedrine. No degradation was detected for ephedrine hydrochloride after exposure to the hydrogen peroxide vapor for 2 weeks, whereas both anhydrate and hemihydrate free base forms degraded rapidly under the test conditions. In addition, both the anhydrate and the hemihydrate free base degraded faster when exposed to hydrogen peroxide vapor at 30°C under dry condition than at 30°C/75% relative humidity (RH). A new degradation product was also observed under the drier condition. The proposed method provides more relevant screening conditions for solid dosage forms, and is useful in selecting optimal solid form(s), determining potential degradation products, and formulation screening during development. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:3529–3538, 2011
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INTRODUCTION

Because of the presence of ubiquitous oxygen and various known impurities, including peroxides, free radicals, and transition metals, drug products may frequently face the risk of being oxidized under storage or shipping conditions. Oxidation has been a major degradation route for pharmaceuticals, second only to hydrolysis.[1,2] The following primary oxidative degradation mechanisms have been known: autoxidation (free radical mediated), nucleophilic/electrophilic (peroxide mediated), electron transfer (transition metal catalysis), and photochemically-induced oxidation.[3–7] A variety of oxidative stress degradation studies have been designed accordingly to probe the susceptibility of the active pharmaceutical ingredients to these mechanisms, which is usually conducted during the transition period from discovery to early development in the pharmaceutical industry. The purposes of these studies are not limited to the elucidation of the intrinsic oxidative stability of drug candidates. They also provide important information regarding the major oxidative pathways and potential degradants in drug products, which is also useful for development and validation of analytical methods. A thorough understanding of the oxidative mechanisms behind the degradation of a drug candidate is important for pharmaceutical scientists to anticipate possible stability culprits and develop sensible mitigation strategies during solid form selection, formulation design, process development, and drug product manufacturing.

Although a large body of information on oxidative mechanisms and approaches to studying these

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mechanisms in solution is available in literature and/or has been utilized in the pharmaceutical industry,[6] to our best knowledge, means of evaluating oxidative stability of pharmaceutical solids are still lacking. Conventional methodologies for solution screening cannot be readily adapted to solid state. Because of the heterogeneity of solid–solid mixtures, reproducible results from solid-state screening are expected to be challenging. As a result, scientists often rely on the oxidative or other chemical stability of drug candidates in solution to speculate on their behavior in solid state, hoping that the molecules will behave consistently or similarly in these two distinct physical states. However, given the substantial difference in molecular environments between the solid and solution states, the complexity associated with solid-state forms such as polymorphism, hydrates, salts, and the potential of a chemical reaction modulated by topochemistry,[8,9] such a simple extrapolation may prove inadequate and even misleading at times. For a given drug candidate intended to be formulated as a solid dosage form, besides its physicochemical properties such as melting point, solubility, dissolution rate, hygroscopicity, and thermal stability (e.g. hydrolysis), oxidative stability is another important factor in the considerations when selecting an optimal solid form. The oxidative stability in solid state becomes even more important and relevant if the drug candidates consist of oxidatively susceptible functional groups such as amines and thiols.[10,11] In addition, topochemistry may dictate a different oxidation pathway and/or degradant in the solid state from that in solution. An early readout on this will certainly help the timely identification and quantification of degradants that are more relevant to drug products. Thus, it is desirable and valuable if a reliable and convenient screening method can be established and utilized early, allowing bench scientists to routinely evaluate the oxidative stability of pharmaceutical solids.

Common excipients such as polyglycols, ether-based surfactants, povidone, and crospovidone are considered as major sources of peroxide impurities that can cause oxidation in pharmaceuticals products.[12–15] Thus, the main aim of this paper is to propose and describe a new method of conducting peroxide-mediated oxidative stress testing on pharmaceutical solids, using the equilibrium between hydrogen peroxide and urea–hydrogen peroxide to provide a constant vapor pressure of peroxide. Urea–hydrogen peroxide is a molecular complex between urea and hydrogen peroxide. It is extensively used as an oxidizing agent in the chemical industry. When the vapor pressure of hydrogen peroxide is below a critical value (termed critical activity or critical vapor pressure), the solid complex quickly decomposes and releases hydrogen peroxide vapor. Decomposition will continue until the hydrogen peroxide vapor reaches a critical value. After this, the equilibrium will be maintained by further decomposition if hydrogen peroxide vapor is consumed or escaped from the system. This phenomenon is exploited in the proposed method for solid-state oxidative stability screening. The presence of hydrogen peroxide vapor as the oxidizing agent minimizes issues associated with the heterogeneous nature of solid –solid oxidative stability screening. The experimental setting is simple and can be operated routinely in most laboratories. We have focused our work and discussion on three main aspects: (a) experimental setting including reaction chamber design and sample preparation, (b) characterization of hydrogen peroxide vapor generated in the system, and (c) demonstration of its use in oxidative stability screening of model pharmaceutical solids.

Experimental

Materials

Urea–hydrogen peroxide, potassium titanium oxalate, sulfuric acid, and sodium hydrochloride were purchased from Aldrich Chemical Company (Milwaukee, Wisconsin). Hydrogen peroxide solution was purchased from J.T. Baker (Phillipsburg, New Jersey). (1S,2R)-(+)-Ephedrine hydrochloride, (1R,2S)-(–)-ephedrine anhydrous, and (1S,2R)-(+)-ephedrine hemihydrate, which are all highly crystalline solids and have similar particle size range (X-ray pattern and polarized light microscopic image shown in Fig. 1), were purchased from Sigma Company (St. Louis, Missouri). Benzoic acid and benzaldehyde were purchased from Sigma Company. Saturated sodium chloride solutions may be optionally used to control the relative humidity (RH). All other chemicals are high-performance liquid chromatography (HPLC) grade. All materials were used as received.

Reaction Chamber Assembling and Sample Preparation

The reaction chamber design (Fig. 2) consists of two HPLC vials and one 20-mL clear borosilicate glass vial with Teflon®/silicone septum in an open-top 24-414 polypropylene cap purchased from I-Chem, Brand Inc. (Rockwood, Tennessee). Prior to sample loading, disassemble caps from the vials and put them aside. Weigh out approximately 4 mg test sample and place in a HPLC vial; weigh out approximately 40 mg of urea–hydrogen peroxide addition compound and place in the other HPLC vial. In order to maintain the structural integrity of a hydrate or to study the impact of moisture on the oxidation stability of a solid form, a saturated salt solution, for example, NaCl salt solution, can be optionally loaded into the bottom of the 20-mL glass to control the chamber RH during the course of the experiment.

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