Reactive Components in Pharmaceutical Excipients

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Introduction

Similar to the degradation an active pharmaceutical ingredient (API) may undergo on storage, an excipient may also undergo degradation over the duration of its shelf life. Excipient degradation products may interact with an API and thus may impact the stability, safety and bioavailability of the drug product. There are also residual components such as process aids and intermediates from the excipient manufacturing process that may be carried over to the finished products. These residual components do not usually change on storage or upon incorporation into a formulation, but they may react with the API and each other and thus may compromise the stability and performance of the drug product. Excipient degradation products and residual components from excipient manufacturing processes which react with the API are termed '**reactive components**' in excipients. Understanding the nature and extent of the excipient degradation, and the excipient manufacturing process helps pharmaceutical scientists to design a drug product formulation with suitable and predictable stability and quality.

Common Reactive Components

Common excipient-related reactive components include peroxides, aldehydes, organic acids, and trace metals. Peroxides, aldehydes and organic acids may not only be carried over from the original excipient manufacturing process, but also potentially form when an excipient ages on storage. There are other kinds of reactive and nonreactive residual components which may exist in excipients, such as monomers and process aids that are used in manufacturing of many polymeric excipients.

Peroxides

Peroxides are very reactive and usually transient species in excipients or formulation solid matrices. They are an excipient-related reactive component that can play a major role in drug degradation.[1] Oxidative degradation of the drug substance may be caused by the formation and reaction of peroxy and alkoxy radicals, or by direct reaction of peroxides with nucleophilic groups on the API.[2] For example, the direct reaction of peroxide components in povidone and crospovidone with raloxifene hydrochloride in tablets has been reported.[2] Formation of the N-oxide derivative of raloxifene was an order of magnitude higher in the presence of povidone or crospovidone in comparison to other excipients investigated, and a strong correlation was observed between the total peroxide level and the quantity of the N-oxide formed upon accelerated storage. In addition, reactive peroxides are commonly associated with polymeric ether based excipients such as polyethylene glycol, polyethylene oxide, and polysorbate, while other cellulose based polymeric excipients such hydroxypropyl cellulose and microcrystalline cellulose may also have trace levels of peroxides.[3]

The most important source of peroxide generation in excipients and drug formulations is through oxidation of the excipients, for example the oxidation of polyethylene oxide derivatives, povidones, other polyols or cellulose-based excipients. This can occur during the manufacture and/or storage of excipients, or after they have been formulated into a drug product. Peroxides can be formed via *autoxidation*, which is known to occur with polyethylene glycol, a commonly used excipient in film coatings and other solid formulations. Autoxidation is an oxidation process that occurs in the presence of oxygen and forms 'organic' hydroperoxides (ROOH, sometimes also called alkyl hydroperoxides) and hydrogen peroxide (H_2O_2, sometimes also called hydroperoxide). Autoxidation is a free radical chain process involving three stages (*see* Figure 1): initiation (step a), propagation (steps b to d), and termination (steps e and f).[4]

Initiation involves generation of radicals in a so-called 'induction' period. Chain-initiating radicals may be generated through exposure of the system to light, heat, or catalytic levels of redox-active transition metals. Therefore, the induction period can vary significantly depending on the exposure condition, oxygen concentration, metal impurities in the excipient, and trace amount of existing peroxides. Once a radical is formed (step a), a chain reaction occurs (steps b to d) to form an alkyl hydroperoxide or a hydroperoxide. The chain reaction is terminated (steps e and f) when two radicals combine their extra electrons to form a new bond.

Peroxides can also be introduced into a drug product formulation from the raw materials and/or manufacturing process of an excipient. Examples include lower molecular weight polyethylene oxide which is often made by oxidizing a high molecular weight material using an oxidizing agent, and a synthetic polymeric excipient such as povidone which is often made with peroxide to initiate polymerization. In both cases, it is very difficult to completely eliminate the residual oxidizing agents. Thus, residual trace amounts of peroxides may be carried over to the final excipients.[1]

Analysis of trace level of peroxides in excipients and pharmaceutical formulations

Analysis of peroxides in excipients and formulations is challenging. Compendial methods for determining relatively concentrated levels of hydrogen peroxide in solutions include colorimetric determination and iodide titration.[5,6] Several more sensitive analytical techniques have been developed for analyzing trace levels of peroxides in various sample matrices, including the so-called Fox2 method[7] which analyzes total peroxides and can differentiate 'organic' hydroperoxides and hydrogen peroxide by use of catalase, as catalase reacts with hydrogen peroxide but not 'organic' hydroperoxides. Another method uses a different derivatization mechanism involving triphenylphosphine (TPP) and thus can serve as a complementary method to validate the results from the Fox2 method.[3]

Hydrogen peroxide levels have also been measured by high performance liquid chromatography (HPLC) with coulometric electrochemical detection,[8] and HPLC coupled with amperometric electrochemical detection.[9] A further method for hydrogen peroxide quantitation after derivatization uses a highly sensitive microplate-based fluorescence assay, although the relationship between the fluorescence signal and the hydrogen peroxide concentration is not linear and several interferences have been observed, which can complicate the assay design and data interpretation.[10]