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Reactive impurities in large and small molecule pharmaceutical excipients – A review

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ABSTRACT

Reactive impurities in excipients can cause drug product degradation or protein modification even at trace levels, and thus impact drug stability and quality. It is critical to understand the potential impact of these impurities during development in order to ensure a robust clinical and commercial product. In this article, we review reactive impurities in pharmaceutical and biopharmaceutical excipients for both small molecule and large molecule drugs. The common reactive impurities in excipients, including peroxides, aldehydes, organic acids, reducing sugars and elemental impurities are reviewed. Sources of these impurities, reactions and impact, analytical methods, and control and risk mitigation strategies are also discussed.

1. Introduction

The vast majority of pharmaceutical products contain excipients in addition to the active pharmaceutical ingredient (API). These excipients enhance drug performance such as bioavailability and pharmacokinetic profile, accurate dosing, manufacturability, product uniformity and stability, and also help to improve patient compliance and acceptance (taste, appearance, etc.). Excipients typically constitute most of the total weight of drug products. Although most of the commonly used excipients are considered chemically inert, in reality, they often contain low levels of reactive impurities that can react with the API or with other excipients in the formulation [1–4].

These reactive impurities even at trace levels can cause degradation and stability issues, and thus impact product quality and patient safety. For example, providone (polyvinylpyrrolidone or PVP) is a binder, commonly used in many solid oral dosage formulations. It may contain peroxides and aldehydes, which may react with various functional groups in the API, resulting in loss of potency and forming degradation products, some of which could potentially be toxic. Polysorbate (also known by the trade name Tween®) is an excipient widely used for biological drugs to prevent protein adsorption on the surface of hydrophobic contacts and also to protect products from physical stresses during processing and storage. Polysorbate can contain multiple impurities such as peroxides, fatty acids, formaldehyde, metals, etc., either originated from polysorbate neat material or formed during manufacturing, shipping and storage (Fig. 1) [5]. Undesired effects of these impurities include protein oxidation and particulate formation.

Limits for reactive impurities are typically based on toxicology assessments, and often are higher than the levels that could pose a stability issue for a specific product. This is particularly true for impurities such as peroxides and metals that can propagate or catalyze reactions even at trace levels. Often, neither the source nor the levels of some reactive impurities can be accurately correlated to certain stability issues. The specifications for reactive impurities should be based on the specific drug substance and drug formulation. Further complicating product understanding, some impurities are not commonly tested for or controlled in excipients by suppliers. For instance, formaldehyde can be formed through polyethylene glycol (PEG) and polysorbate oxidation. It is commonly not tested in excipients, but it is known to cause protein cross linking and adducts.

The reactive impurities in excipients can add to the heterogeneity of biologics, especially for the protein related drugs [3]. Although many of the reactive impurities are similar in small molecule drugs and large molecule drugs or biologics in terms of type of chemical reactions, there are differences in the degradants formed and potential impacts, which we will address in this review.

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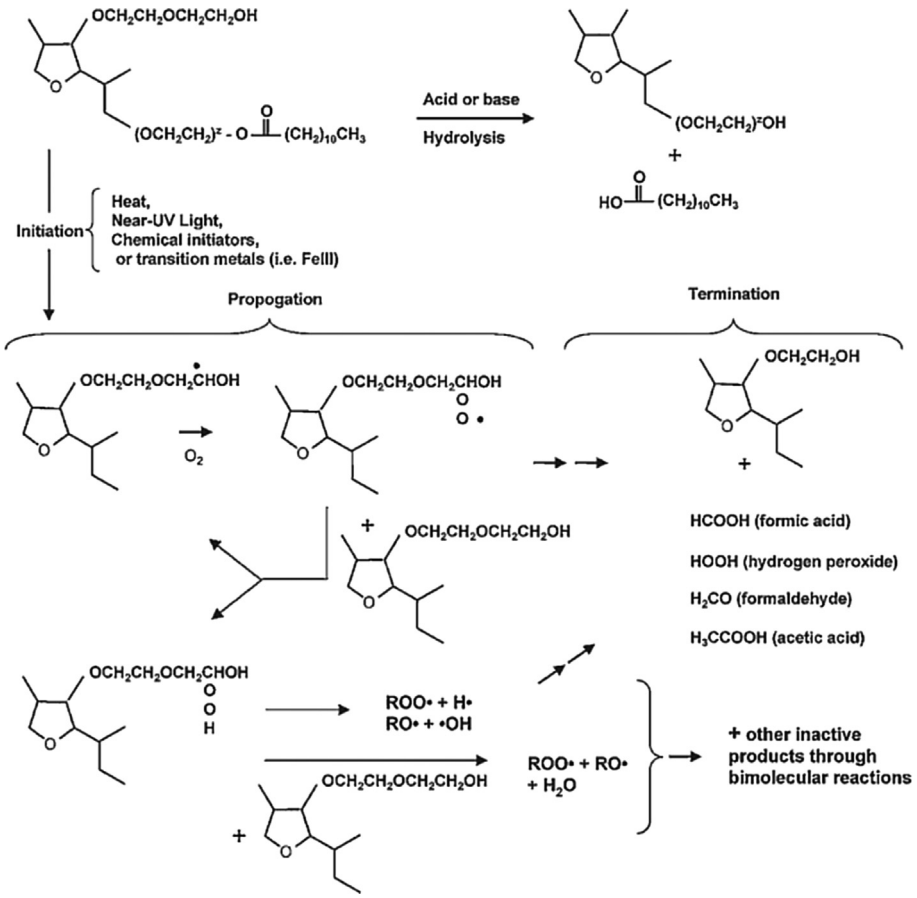

Fig. 1. Reaction scheme showing the generation of different impurities in polysorbate excipient [5].

Testing and control of the impurities in excipients is receiving increased attention from both industry and health authorities. For instance, some health authorities now require more stringent specifications for surfactants used in injectable products. Some of this increased attention is an attempt to better control source-to-source and lot-to-lot variability of excipients that might be used for a particular product. To decrease the risk of encountering stability issues caused by reactive impurities, a number of measures can be taken during product development and over the commercial lifecycle of product. These measures are aligned with "Quality by Design" (QbD) approaches to product development and include excipient compatibility studies during development [6], automation [7], accelerated stability studies, and supplier relationship management [8].

This review focuses on common reactive impurities in excipients for both solid and liquid dosage forms for small molecule and large molecule drugs. The types of reactive impurities including peroxides, aldehydes, organic acids, reducing sugars and elemental impurities, together with their analytical testing methods and control strategies are reviewed. Related reactions involving oxidation [9], reduction, hydrolysis [10], and catalyzed degradation are discussed. A key message is that selection of excipients should not only be based on excipient functionality, but also with consideration for compatibility with API and other excipients. Packaging is also an important component. Reactive impurities can be brought in through packaging components. Excipients could also degrade and sometimes interact with API or each other to form degradation products. The compatibility of specific excipients with a particular API is out of the scope in this review and readers can find information from some previous reviews [6,11]. An article published in 2011 by Wu et al. reviewed reactive impurities in ten commonly used solid dosage form excipients for small molecule drugs [1]. Readers can find more details of solid dosage form excipients related reactive impurities information published before 2011 in that review.

2. Reactive impurities in pharmaceutical and biopharmaceutical excipients

2.1. Peroxides

Peroxides in excipients are a major source of oxidation in drug formulation, especially for polymeric excipients, such as polysorbates, polyethylene glycol (PEG), povidone and crospovidone, and hydroxypropyl cellulose (HPC). Metals and aldehydes are also major contributors to oxidation, which will be discussed in the later sections in this review. Peroxides are generally present in excipients as hydrogen peroxide (H_2O_2), hydroperoxides (ROOH), or organoperoxides (ROOR′). Peroxides are commonly used in the manufacturing of polymers and bleaching cellulosic excipients and can be challenging to be completely removed during purification procedures. In addition, they can be generated during the course of polymer degradation. Different manufacturing conditions, purification processes and storage history can result in variation in peroxide levels between vendors and also between lots produced by a single vendor [12]. Peroxides can undergo three types of oxidative reactions with drug [9]: 1) nucleophilic addition, such as the Michael addition to an α, β-unsaturated ketone that results in