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General Commentary

Implications of In-Use Photostability: Proposed Guidance for Photostability Testing and Labeling to Support the Administration of Photosensitive Pharmaceutical Products Part 3. Oral Drug Products

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ABSTRACT

The ICH Q1B guidance and additional clarifying manuscripts provide the essential information needed to conduct photostability testing for pharmaceutical drug products in the context of manufacturing, packaging, and storage. As the previous 2 papers in this series highlight for drug products administered by injection (part 1) and drug products administered via topical application (part 2), there remains a paucity of guidance and methodological approaches to conducting photostability testing to ensure effective product administration. Part 3 in the series is presented here to provide a similar approach and commentary for photostability testing for oral drug products. The approach taken, as was done previously, is to examine "worst case" photoexposure scenarios in combination with ICH-defined light sources to derive a set of practical experimental approaches to support the safe and effective administration of photosensitive oral drug products.

Introduction

Parts 1 and 2 of this series of commentary papers[1,2] have outlined the importance of photostability testing to support in-use handling and administration of pharmaceutical products intended for injection and for topical administration using a common approach, namely the following:

- Evaluate and establish realistic light exposure scenarios;
- Use of this information to develop a photostability testing plan; and
- Generate and interpret the necessary data to support safe and effective product administration.

These papers provide the necessary background and foundation for how to approach in-use photostability testing, including discussions on relevant light sources, supply chain considerations, and recommended photostability testing strategies. As a result, these topics will not be addressed in this study except as needed to address the topic of in-use photostability testing for oral drug products. This article applies these previously elaborated principles to the photostability testing of pharmaceutical products administered orally and is important for several key reasons:

(1) Liquid and solid oral products can be sensitive to photodegradation.
(2) Few examples in the literature discuss the photostability testing needed to support the administration of pharmaceutical products.
(3) It is clear that light exposure during handling and use can adversely impact the efficacy and safety of a pharmaceutical product.

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(4) Oral drug products represent the largest proportion of pharmaceutical products on the market (by prescription volume) because they provide a convenient and commercially favorable route of administration. Moreover, there are many oral drug products that have specific label language requiring protection from light.
(5) Oral drug products are often repackaged by pharmacists, other healthcare practitioners,[3] or patients into a substantial variety of packaging configurations and types, often without consideration of the light protective properties of the new package. Repackaging from light protective packaging to less protective packaging has obvious potential implications for the stability of the product. Results from some experimental studies examining the results of repacking of drugs are presented below.
(6) Owing to their widespread use, oral drug products are often stored and administered in a great variety of indoor and outdoor settings.
(7) Stimulating increased dialogue in the scientific community on the topic will lead to improved testing approaches, more effective labeling, better patient and practitioner education, and hence ultimately improved health outcomes.

Globally, the label language for protecting products from light during handling and use is often sparse, inconsistent, or not present for oral drug products. Our analysis of solid oral products in the United States Pharmacopeial Convention (USP)[4] showed that 285 of the 969 products listed (29%) have monograph language that indicates storage in light-resistant packaging is required; however, no information about the liability to in-use light exposure, or further guidance, is present. A similar proportion of oral products in Europe have language indicating the need to protect from light. Interestingly, the proportion of injectable,[1] topical,[2] and oral products that have USP monograph language suggesting they are photosensitive is very similar. Anecdotally the importance of light protective packaging does not figure highly when some community pharmacies consider the overall stability of the product, reinforcing the need to provide clearer guidance for practitioners, pharmacists, and patients.

Scope

The present work seeks to address the key gaps in guidance as described above and does not address the topic of photostability testing as intended by the ICH Q1B[5]; interested readers should refer to the previous body of literature on the topic.[6-13] Drug products intended for oral administration comprise a wide range of dosage forms including tablets, capsules, specialty tablets (e.g., buccal or sublingual delivery), thin films, solutions or suspensions, oral emulsions, oral gels, sprays, powders, granules, and pastes. As the majority of oral dosage forms are various formulations of tablets and capsules, this current work will focus on these 2 types of products. For other oral dosage forms guidance provided in the previous papers in this series may be more relevant.

Even within this somewhat narrower scope, there are a wide range of oral product formulation types with a large variation in excipient content and utilized manufacturing process. As a result, the first section of this commentary will describe key principles of relevance to the vast majority of situations, with subsequent sections that cover photostability testing considerations and the implications of photostability as it pertains to the handling and administration of the product. Formulation compositions can have a significant impact on the overall photostability of the drug product. Formulation studies should consider not only the effect of light exposure on the chemical stability of the active pharmaceutical ingredient (API) but all other aspects of tablet performance such as appearance, hardness, friability, dissolution, and so on.

All oral dosage forms are meant to deliver the active drug substance either locally in the oral cavity/throat or deliver their payload in the gastrointestinal tract for systemic absorption. We will not touch on the testing required to understand the interaction of the product with light postadministration, as this is really a photosafety issue and thus falls beyond the scope of photostability testing. It should be noted however that the API, metabolites, and degradation products can interact with light postabsorption, for example, in the skin and eye (especially the cornea and lens), and lead to adverse events such as phototoxicity. This area was covered in more detail in part 2 of this commentary series.

General Considerations

Background

As noted, there are many different types of products intended for oral administration. Excipients are added to aid absorption, stability, and/or processability and can range widely in proportions relative to one another and the API. Each excipient has its own purpose within the formulation and set of organic and inorganic impurities that it brings to the drug product matrix. Some of these components, including the coating, can serve to block and/or scatter light and thereby improve photostability. The reader is referred to specific literature in the field,[14-18] but it should be noted that compositional adjustments to the drug product during development can be used to control, minimize, or even eliminate drug product photostability concerns. If the drug product photostability is built into the product by the formulation then manufacturing, in use, and packaging issues become less relevant.[19]

Even when the absorbance of the API is apparently extremely low, photoreactions can occur, for example, the photodiscoloration of methimazole (Tapazole) tablets and API under fluorescent light.[20] It is also possible for formulation excipients and/or the impurities present within them to give rise to photoreactions that are not seen with the API. Discoloration or fading of tablet cores and/or film coats[21,22] along with fading of capsule colors and/or printing is quite common. These color changes can then impact on the further photodegradation of the product. If bleaching occurs, light may penetrate further into the tablet, whereas if the colored species are strongly absorbing they may shield the core from further reactions. Conversely, in some cases, depending on the mechanism of further degradation of the colored product, they may provide a source of reactive oxygen species leading to significant additional degradation.[23] Marked appearance changes can often occur even when there is an undetectable chemical change in the bulk. A range of other physical changes can be induced by light such as changes in the hardness of tablets or the brittleness of capsule shells. Thus the totality of the product performance needs to be considered, not just the chemical stability of the API. Repeat testing may be advisable following any significant formulation changes. A decision whether to test or not should be based on risk assessment derived from a knowledge of the product.

As a general rule-of-thumb, API in the solid state is less photoreactive than the same API that has been solubilized. Hence, oral drug products such as capsules and tablets with solid API forms in general have improved photostability relative to solution or suspensions, with the added characteristic that the photochemistry is limited to surface and light penetration depths which depend on product composition, light exposure wavelengths, as well as light intensity.[24] Typically for a “white” tablet, ultraviolet (UV) wavelengths (approximately 290-400 nm) are substantially scattered at