Printed in the Republic of Korea
ANALYTICAL SCIENCE & TECHNOLOGY
Vol. 37 No. 6, 347-353, 2024
https://doi.org/10.5806/AST.2024.37.6.347

Photostability considerations in preclinical studies: Mini-Review

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(Received November 28, 2024; Revised December 10, 2024; Accepted December 10, 2024)

Abstract: Photostability is a critical parameter influencing the stability and efficacy of pharmaceuticals and other scientific materials when exposed to light. In preclinical pharmacokinetic studies, photostability is often overlooked, leading to inaccurate data and potential challenges in drug development. This mini-review explores key considerations for photostability during dosing, administration, sample collection, storage, preparation, and analysis in preclinical studies. Factors such as solution concentration, pH, and light exposure are discussed, along with strategies to mitigate photodegradation risks, such as using UV-shielded materials and optimizing sample handling procedures. Additionally, the review highlights advancements in photostability enhancement, including encapsulation techniques, antioxidants, and the use of LED light sources. The integration of artificial intelligence (AI) in photostability research is also examined, showcasing its potential to predict photoreactive properties, optimize molecular stability, and improve drug development efficiency. Ensuring photostability throughout preclinical studies is essential to maintain data reliability, reduce development costs, and enhance the overall success of therapeutic products.

Key words: photostability, pharmacokinetics, drug development, photodegradation, artificial intelligence (AI)

1. Introduction

Photostability refers to the stability of a substance when exposed to light. It is a critical parameter in various scientific and industrial domains, as light-induced degradation can lead to significant alterations in chemical, physical, or biological properties.[1] This phenomenon holds particular importance in pharmaceuticals, where photodegradation can reduce drug efficacy, generate harmful by-products, and compromise patient safety. Regulatory agencies, including the International Council for Harmonisation (ICH), emphasize the necessity of photostability testing to ensure drug quality and compliance.[2]

Beyond pharmaceuticals, photostability is pivotal in the field of cosmetics.[3,4] Many active ingredients, such as UV filters in sunscreens, are designed to protect the skin from harmful radiation. However, if these ingredients degrade under sunlight, their protective function diminishes, potentially leading to adverse effects.[5] Similarly, in the food and beverage industry, photostability ensures the preservation of sensory qualities, such as flavor and color, and prevents the formation of toxic degradation products during storage

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and exposure.[6-9]

In material science, photostability is a key concern in the development of dyes, pigments, and polymers, where prolonged exposure to light can cause fading, discoloration, or structural breakdown.[10,11] This is especially relevant for applications in coatings, textiles, and advanced electronic devices, such as organic photovoltaics[12] and light-emitting diodes (LEDs).[13] Furthermore, in environmental studies, understanding photostability helps assess the fate and transformation of pollutants, contributing to risk evaluation and mitigation strategies.[14-16]

Given its broad applicability, photostability considerations are often overlooked in preclinical studies. These studies are crucial for evaluating drug behavior before human trials, but failing to address photostability can lead to significant discrepancies in the observed data. Especially in pharmacokinetic studies, drugs that degrade under light exposure can yield inaccurate pharmacokinetic data, which may result in misleading conclusions about drug safety, efficacy, or dosage requirements. The ICH Harmonised Tripartite Guideline Q1B provides guidance on photostability testing for new drug substances and products. However, it explicitly states that it does not address the photostability of drugs after administration. According to the guideline, "The guideline does not cover the photostability of drugs after administration (i.e., under conditions of use) and those applications not covered by the Parent Guideline."[2] In this review, we aim to explore several examples of issues arising from overlooked photostability concerns during various stages of pharmacokinetic studies. Furthermore, we will summarize the efforts and strategies undertaken to address these challenges, emphasizing the importance of integrating photostability assessments into drug development protocols.

2. Dosing and Administration

The dosing and administration of photosensitive drugs are critical stages where photostability can have a significant impact on pharmacokinetics. When administering drugs, particular attention must be paid to photosensitivity, which can manifest in two key forms: photodegradation in the solid state and photodegradation that occurs when the drug is dissolved in a vehicle.

Glass *et al.*[17] have provided a comprehensive overview of photostability in the solid state, highlighting the photostability properties of approximately 20 different drugs. They emphasize that photostability in the solid state is influenced by various physicochemical properties, particularly polymorphism and particle size. Generally, drug degradation due to photodegradation in the solid state is not considered a significant issue under normal conditions. However, they note that exposure to intense radiation could pose potential risks, warranting further consideration.[17]

1,4-dihydropyridines, calcium channel antagonists, are highly susceptible to photodegradation, which can reduce its therapeutic efficacy if exposed to light in solid state.[18] Photodegradation of nifedipine was significant, with over 10 % degradation observed within 5 – 10 minutes for methanolic solutions. In contrast, pure powder samples showed a slower degradation rate, under 24 hours of artificial sunlight exposure.[19]

As demonstrated in the example of nifedipine, drugs are generally more susceptible to photodegradation in solution form than in the solid state. This increased vulnerability has also been reported for other drugs such as diltiazem and cyanocobalamin.[20,21] For drug administration in small animal studies, water-soluble vehicles are typically used, which significantly increases the likelihood of photodegradation such as labetalol, folic acid and riboflavin.[22-24]

Photolysis kinetics vary with solution concentration. Dilute solutions degrade faster and follow first-order kinetics, while concentrated solutions degrade more slowly and exhibit pseudo-zero-order kinetics.[25] This difference arises due to limited incident energy and more effective quenching of excited molecules in concentrated solutions.[26,27] Tønnesen emphasizes that diluted solutions in infusion therapy are prone to photodegradation due to low concentrations and high surface-to-volume ratios, while high-concentration solutions are more stable due to the inner filter effect.[27]

In preclinical pharmacokinetic studies, intravenous (IV) infusion is often used for poorly soluble or toxic drugs when using iv bolus administration. If the infusion time is extended, measures should be taken to shield the infusion components from light exposure to prevent photodegradation.

Elste *et al.* recently updated and listed over 300 injectable drugs that are sensitive to light. This paper categorizes and organizes the necessity of light protection during storage, reconstitution, dilution, and administration, with additional comments provided for areas requiring special attention.[28] Light protection is essential for storing the drugs included in this list. Additionally, it specifies that amphotericin B, doxycycline, epoprostenol, micafungin, nitroprusside, phytonadione, and thiotepa require light protection during administration as well. Furthermore, a significant number of these drugs also necessitate light protection during reconstitution and dilution, making it a critical consideration in the preparation process for drug administration in preclinical studies. A similar listing of over 300 light-sensitive oral medications, including both oral solid and oral liquid products, has also been published.[29]

Therefore, special caution is required to mitigate these risks during such experiments. For new drugs with unverified photostability, it is essential to adhere to the principle of immediate preparation prior to administration and to implement methods that provide maximum light protection during the process.

3. Sample Collection, Storage and Transportation

A critical aspect of pharmacokinetic studies following drug administration is the collection of biological samples for specific drug analysis. These samples typically include whole blood, plasma, serum, urine, and various tissues. The stability of drugs in biological samples is influenced by a greater number of factors including metabolic instability compared to their stability in standard aqueous solutions.[30] In addition, plasma or serum samples, which are commonly used in pharmacokinetic studies, undergo multiple processes before drug analysis.[31] These include blood collection, plasma or serum separation, aliquoting, storage, freezing, and thawing. During these processes, the instability of the drug can lead to errors in drug concentration measurements, compromising the accuracy of the analysis.

Photostability tests in aqueous solutions or mixed aqueous-organic solvent systems have been relatively well-documented,[1,14,16,32] whereas photostability tests in biological samples remain comparatively limited. This could be attributed to several factors, including the complex matrix effects caused by biomolecules in biological samples, which can alter photo-reactivity. Additionally, enzymatic and metabolic degradation pathways often dominate over photodegradation in biological environments. Components such as hemoglobin and albumin further complicate the process by absorbing or scattering light, reducing its availability for photoreactions. Moreover, limited light penetration in biological matrices prevents uniform photoreactions, and environmental factors like pH, ion concentrations, and temperature introduce further variability, making photostability analysis in biological samples more challenging.

Even though, some drugs were reported vulnerable to light-induced degradation in biological samples. For instance, nifedipine has been reported to degrade upon light exposure in plasma,[33] and the same has been observed for omeprazole and furosemide.[34,35] These photostability issues in biological samples, which can also affect drug concentration analysis, have been studied in connection with photosensitivity or phototoxicity. In the case of furosemide[36] and well-known phototoxic tetracyclines,[37] it has been reported that photodegradation by-products form covalent bonds with albumin. Similarly, non-steroidal anti-inflammatory drugs such as suprofen,[38] ketoprofen,[39] and naproxen[40] have also been reported.

4. Sample Preparation and Chromatography Analysis

Sample preparation for drug analysis in biological matrices is a critical step to ensure accurate and reliable

results. Protein precipitation, liquid-liquid extraction, or solid-phase extraction are commonly employed techniques to isolate the drug and remove impurities.[39] Comprehensive reviews on sample preparation techniques for drug analysis in biological matrices highlight advancements in methods such as solid-phase extraction and solid-phase microextraction, focusing on innovative strategies like the use of molecularly imprinted polymers to enhance specificity and efficiency.[42,43]

The potential for drug photodegradation can vary significantly depending on the solvents used during sample preparation, including organic solvents such as acetonitrile and methanol, as well as aqueous and buffer solutions. Notably, photodegradation risks are often higher during the preparation process than when the drug is dissolved within biological matrices, as the latter may provide some degree of natural protection against light-induced degradation. Also, processes such as solvent evaporation using nitrogen gas and subsequent reconstitution can pose significant risks of photodegradation just before chromatographic analysis.

Therefore, particular cautions must be exercised to mitigate photodegradation during these steps, as it can impact the integrity and accuracy of analytical results. Proper handling, including minimizing light exposure and using appropriate storage conditions, is essential to ensure the reliability of the analysis.

5. Approaches to Enhancing Photostability

Photodegradation poses significant challenges in pharmaceutical development, particularly for photosensitive drugs. Exposure to light can lead to the loss of drug potency, formation of harmful degradation products, and reduced shelf-life. To address these issues, several strategies have been developed to enhance drug photostability.[1,44-47]

Coelho et al. provides an excellent summary of various studies aimed at improving photostability. The research is categorized into three main strategies: encapsulation techniques, antioxidants, and solar filters. Among these, encapsulation using liposomes and lipid nanoparticles were reported to be the most effective in enhancing photostability.[46] However, these approaches to improving drug photostability are primarily designed to ensure stability before drug use and may not fully address the photostability challenges that arise during sample collection, sample storage, preparation and analysis in pharmacokinetic studies.

Using antioxidants or solar filters alongside sample collection can help maintain photostability when samples are exposed to subsequent light exposure. However, these additives may interfere with various analytical methods, potentially affecting the accuracy of the results. Furthermore, if these additives are entirely removed during sample preparation to avoid such interference, the samples are no longer protected against photodegradation, which raises concerns about the reliability of the analysis.

To address these challenges, analytical methods should be optimized to minimize interference caused by additives while ensuring accurate results. Retaining a suitable amount of stabilizers during sample preparation can help maintain photostability without compromising analytical integrity. Additionally, alternative protective measures, such as using UV-shielded containers, can be explored to reduce reliance on stabilizing additives. Balancing these factors is essential to ensure both the reliability of the analysis and the photostability of the sample.

Dried blood spot (DBS) sampling is a minimally invasive method where a small blood sample is applied to filter paper for drying and storage.[48-50] It is cost-effective, easy to transport, and ideal for remote settings, requiring only minimal blood volume. Recent advancements, such as integration with LC-MS/MS and microfluidic technologies, have expanded DBS applications to matrices like plasma and urine and extended its use to proteomic approaches.[51,52] There have been reports indicating that the use of the DBS technique reduced the photodegradation of nifedipine and omeprazole,[53] which aligns with the concept that photostability tends to improve in the solid phase, making this a promising approach.

There are also reports suggesting that changing the light source can influence photostability.[54] Considering

environmental and economic factors, the use of light-emitting diode (LED) light sources in laboratories and various institutions is seen as a promising approach to enhancing photostability.[55] LEDs offer greater control over light intensity and wavelength, providing an efficient and sustainable solution for experiments involving photosensitive compounds.

6. Photostability Prediction using Machine Learning and Artificial Intelligence

Artificial Intelligence (AI) is transforming drug development by streamlining processes and reducing costs.[56,57] In drug discovery, AI analyzes large datasets to identify potential drug candidates and predict molecular interactions, accelerating lead compound optimization.[58] During preclinical development, AI predicts pharmacokinetics and toxicity, helping to select safer and more effective compounds.[59] In clinical trials, AI facilitates patient recruitment, optimizes trial design, and monitors data in real-time to detect adverse effects.[60] Overall, AI integration is enabling faster and more efficient drug development, improving patient outcomes.

AI-driven research on photostability focuses on improving the understanding and optimization of molecular stability under light exposure. By leveraging machine learning algorithms, researchers can analyze large datasets to predict photoreactive potential based on molecular structures and UV-Vis absorption spectra.[61] Techniques like random forest and neural networks have been used to identify key molecular features, such as aromaticity, conjugation, and the presence of heteroatoms, which influence photostability.[62] Hofmann and Agivetov used AI models (logistic regression, XGBoost, and deep learning) to predict photosensitizing effects of drugs using a dataset of 2,200 compounds, identifying 205 as photosensi-tizers, and highlighted key molecular features linked to photosensitivity, including fluoroquinolones.[63] Moreover, AI models integrated with closed-loop experimentation and physics-based features help uncover general design principles, which traditional methods have struggled to achieve.[64] Delmar *et al.* developed random forest models using LC-MS/MS datasets to predict photooxidation of methionine and tryptophan in therapeutic proteins, which could help optimize drug development by reducing costly remediation and improving stability, quality, and clinical success rates.[65]

7. Conclusions

Ensuring photostability is a key factor in maintaining the reliability of preclinical studies using drug analysis. From dosing and administration to sample collection, storage, preparation, and analysis, each step requires careful handling to mitigate the risks of light-induced degradation. In preclinical studies involving animals, the lack of attention to photostability can result in misleading data, which ultimately affects the success of drug development. Utilizing light-protective materials, maintaining samples in dim conditions, and considering the impact of photodegradation during data validation are essential to ensure accurate and reproducible data. By enhancing photostability prediction and control, researchers can develop more robust and effective products, ensuring improved patient outcomes, reduced development costs, and increased sustainability in pharmaceutical and material science industries.

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