

USING PHOTOSTABILITY TESTING CHAMBERS TO MEET THE REQUIREMENTS OF DRUG TESTING IN ACCORDANCE WITH ICH Q1B

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Abstract

For companies performing photostability testing in accordance with ICH guideline Q1B, CARON's 6540 series chambers overcome the challenges of lamp selection, light control, and other chamber design issues. By integrating technical requirements with practical solutions, CARON's Photostability Chambers enhance the testing process to ensure product quality and regulatory compliance.

INTRODUCTION TO PHOTOSTABILITY TESTING

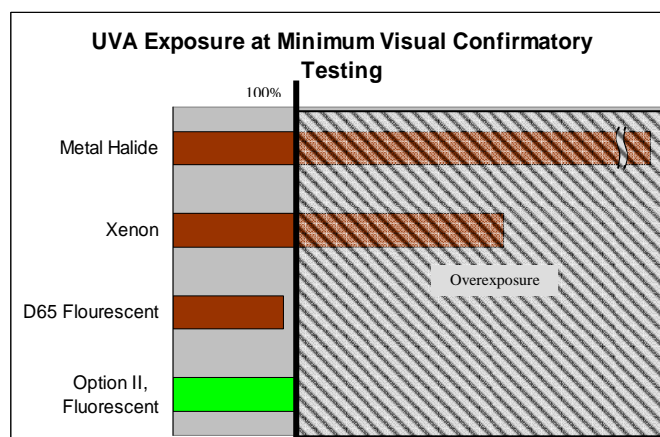
ICH Q1B guideline is the harmonized effort to standardize photostability testing on new pharmaceutical drug substances and drug products. For companies developing or manufacturing pharmaceutical drugs, a robust photostability testing process is essential to ensure product quality and regulatory compliance. Inadequate or substandard testing equipment can result in costly delays and lost revenue. Whether performing forced degradation or confirmatory studies, the solution is a carefully designed photostability testing chamber that creates environmental test conditions in accordance with ICH Q1B.

THE CHALLENGES OF PHOTOSTABILITY TESTING

Troublesome Lamp Selection

The first step in choosing a photostability chamber is to select the proper light source. ICH allows either single lamps (Option I: fluorescent D65, metal halide or xenon) or two lamps (Option II: fluorescent near-UV and cool white) to be used. Option I uses single lamps emitting both UVA and visual irradiance, thus the UVA to visual irradiance ratio is fixed. Since the exposure requirements for photopic and UVA levels are independent, this fixed ratio causes one of the dose levels to overexpose.

This fixed ratio varies according to lamp type. At the minimum confirmatory testing requirement, UVA overexposure is around 540 W-h/m² for xenon and 2500W-h/m² for metal halide.⁽¹⁾ This corresponds to 270% and 1250% overexposure respectively. Due to fluorescent D65 lamp's lower UVA irradiance, they overexpose in the visual region. Ideally, the illuminance and UVA irradiance would be controlled independently. This problem is only alleviated by using two different fluorescent lamps, Option II.



In addition to over-exposure, xenon and metal halide lamps produce significant amounts of heat. At elevated temperatures, dark controls are needed to segregate photochemical degradation from thermal degradation. Large internal cooling fans are necessary to dissipate

this heat and can pose presentation problems by blowing samples around. Sample color changes due to high temperatures can not easily be compensated for.⁽²⁾

Problems with xenon and metal halide are not limited to overexposure and excessive heat generation. Xenon and metal halide lamps have a short life span and need replaced every 750 to 1500 hours.⁽¹⁾ They require light filters to eliminate radiation below 320nm. Over time, the filters become solarized and the wavelength of the UV cutoff increases.⁽¹⁾ They also have a relatively small illumination area.

Irradiance Measurement Difficulty

While chemical actinometers can be used to measure sample dose, selecting a suitable chemical actinometer involves trade-offs. Each chemical actinometer used must be calibrated for the light source used.⁽³⁾ Absorption spectra of the test compound and actinometer should be similar.⁽⁴⁾ ICH describes the use of quinine hydrochloride dehydrate as an example of a chemical actinometer. Quinine has a 'dark reaction' where the reaction continues after it is used.⁽⁵⁾ Not only is quinine wavelength dependent, it is affected by temperature and pH variations.⁽¹⁾ Due to these characteristics, quinine has been shown to be inaccurate with lamps that produce significant amounts of heat, such as xenon lamps.⁽⁶⁾

Selecting the proper physical actinometer, such as a radiometer, to measure light is not trivial either. Irradiance measurements with instrumental radiometers have high margins of uncertainty; 10% is not uncommon.⁽⁷⁾ Spectral radiometers are expensive, cumbersome to use and awkward to integrate with photostability chamber lamp controls. Spherical light detectors are suited for free-floating applications that receive light from all directions. However, these detectors yield erroneously high light levels when intending to measure incident light on a surface, such as most photostability testing. While planar light detectors can precisely measure light falling on a surface, they must be cosine corrected to compensate for angled light.⁽⁸⁾ Unless using a spectral radiometer, two light detectors configured specifically for each wavelength region (UVA and visual) are required and should be calibrated or certified before use.

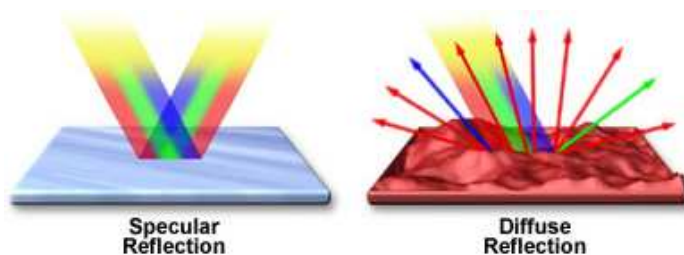
Test Completion Control Issues

Chemical actinometers are inherently limited with respect to a photostability chamber. They do not provide a mechanism to automatically turn the lamps off or alert the operator when the desired exposure level is reached. What if confirmatory testing completes while the

chamber is unattended? Chemical actinometers cannot record irradiance levels throughout the test.

Performing photostability studies based on time creates dose level uncertainty. As lamps age, their intensity decreases. This causes irradiance levels of full-power light sources to fluctuate over time. Because timed tests are unable to compensate for irradiance level changes, a timed test based on initial light intensity would terminate prematurely compared to the desired dose. This is particularly troublesome for confirmatory studies. Ideally, a radiometer with irradiance integration would continually monitor dose and control the photostability test duration accordingly.

Distorting the Spectral Power Distribution



Using a proper light source does not guarantee product samples will receive the correct light spectrum radiation as required by ICH guidelines. Interior chamber materials that reflect light onto samples should reflect/absorb radiation uniformly across the UVA and photopic spectrums. If not, samples will be subjected to light having a spectral power distribution different than that specified by ICH. This is especially true comparing reflective properties of UVA versus visual irradiance. Chamber interior materials such as mirrored stainless steel and white paint distort reflected light by absorbing different amounts of irradiance over the relevant spectrum.

Humidity Control Factor

While not required by ICH for confirmatory studies, the state of hydration affects the photostability of some samples.⁽²⁾ This means identical drug substances subjected to identical irradiance and temperature conditions can have very different results if exposed to different humidity levels. When product presentation is such that samples are exposed to ambient (chamber) air, the affects of humidity must be considered. Uncontrolled, humidity can alter photostability testing results and cloud their interpretation.

Controlling humidity in a photostability chamber requires proper equipment and associated controls. Using steam or vapor generators to raise the humidity level adds more heat into the chamber and requires long warm-up times. Atomizers respond quickly but inject larger particles (mean diameter of 30 microns or more) making uniform distribution more difficult. Ideally, humidification equipment would quickly reach equilibrium by dispersing fine droplets without introducing heat.

SOLUTIONS TO PHOTOSTABILITY TESTING CHALLENGES

A skillfully designed photostability chamber will address the challenges of photostability testing in accordance with ICH guidelines.

Prudent Lamp Selection

The advantages of cool white and near-UV fluorescent lighting (Option II of ICH guidelines) outshine other options. Independent control of illuminance and UVA irradiance eliminates overexposure for confirmatory tests and provides flexibility for forced degradation and research studies. Fluorescent lamps generate minimal heat and eliminate the need for expensive light filters and dark controls. Small internal fans can be employed to subtly maintain proper air temperature without disturbing sample presentation. Fluorescent lamps typically last over ten thousand hours, have low replacement costs, and provide a large illumination area.

Accurate Light Measurements

Accurate illuminance and UVA irradiance measurements can be achieved with a built-in radiometer and planar light detectors. Photopic detectors have a wide bandwidth and spectral response that closely follows the CIE photopic action spectrum. Near-UV irradiance is then measured by an independent UVA light detector. Detectors utilizing a Teflon hemisphere may result in an exceptionally good cosine response. Detectors should be both cosine corrected and calibrated to NIST or other traceable standards. It is best if radiometer displayed units for illuminance and UVA irradiance are consistent with ICH documentation.

Precise Test Completion Controls

An integrating radiometer combined with chamber controls should be used to ensure precise dose levels at test completion. Lamps can then be programmed to automatically shut-off based on an exposure level (dose). Advanced systems are capable of running based on exposure level or timed tests. Whether operating at full power or dimmed condition, the

programmable exposure level should automatically adjust testing time to compensate for influencing factors like lamp aging as well as pause testing for sample evaluation. During both exposure level and time based testing, the radiometer should show irradiance, test time remaining and accumulated dose levels.

Preserving the Spectral Power Distribution

The lamp's spectral power distribution is best preserved by using specular aluminum on interior reflective surfaces. Specular aluminum uniformly reflects light across both UVA and photopic spectrums. It is available with a 95% total reflection and only 0.01% diffuseness at 15°. Specular aluminum's superior reflective properties outshine mirrored stainless steel and white painted surfaces for not only illuminance reflection but also UVA irradiance.

Tight Humidity Control

Precise humidity control can be achieved by using state-of-the-art ultrasonic nebulizers. Nebulizers vaporize water droplets as small as a 3 micron mean diameter. This small particle size enhances uniform humidity distribution throughout the chamber without injecting additional unwanted heat--especially beneficial in a compact chamber. Employing solid state controls enables nearly instantaneous response, further facilitating tight humidity control. Dehumidification is often accomplished through mechanical refrigeration.

Value Added Features

Numerous photostability chamber features are available that enhance the end-user experience. Chambers should keep track of accumulated lamp hours and alert the operator when to replace the lamps. High and low process alarms should signal out-of-tolerance testing conditions. Validation is simple with pre-written IQ/OQ/PQ validation protocols and professional on-site validation services. Chart recorders assist in demonstrating regulatory compliance by permanently recording illuminance, UVA irradiance, temperature and humidity testing conditions. For temperature sensitive samples requiring photostability testing at refrigeration temperatures, modifications can be made to allow the chamber to maintain a 5°C air temperature with lights on. Sliding shelves, access ports and security lockouts are other features that can enhance ease of operation.

Global Solution, Local Response

As pharmaceutical companies and government regulations throughout the world adopt ICH guidelines, it becomes increasingly important that photostability

chambers accommodate the world-wide customer by tailoring each photostability chamber to regional utilities. Electrical power and water hook-ups should coincide with local standard facilities' resources and connections. Replacement parts such as lamps and ballasts should be available on the open market and from local suppliers. Lamps should not be of proprietary nature that limits the purchaser to the chamber manufacturer. Controls should be icon based and available in multiple languages.

THE CARON SOLUTION: 6540 SERIES CHAMBERS



The 6540 series chambers overcome the challenges of photostability testing. These chambers prudently utilize cool white and near-UV lamps. An integral radiometer accurately measures and controls lighting. Specular aluminum surfaces line the chamber interior maintaining proper spectral power distribution. Ultrasonic nebulizers are used for tight humidity control. All controls are programmed through an eye-level icon-based multi-language color touch screen interface that tracks lamp usage. Off-the-shelf components allow users to replace consumables locally.

For companies choosing a photostability chamber to perform photostability testing in accordance with ICH guideline Q1B, consider using CARON's 6540 series chambers which overcome the challenges of lamp selection, light control, and other chamber design issues. By integrating technical requirements with practical solutions, these photostability chambers enhance the testing process to ensure product quality and regulatory compliance.

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