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Analytical Survey

Photostability testing of drug substances and drug products in UK pharmaceutical laboratories

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Abstract: Results of a survey on photostability testing of drug substances and products by UK pharmaceutical laboratories are presented. The results indicate diverse practices in the form of presentation of the product and particularly in exposure to light (as measured in lx days), although there was more consistency in analytical methods and in the analytical criteria used to classify products as stable or unstable for those laboratories adopting this type of classification. A majority of laboratories use daylight in addition to artificial light sources for tests on drug substances and products. Artificial daylight fluorescent tubes and xenon lamps are the most widely used sources of artificial light and both should provide a reasonable simulation of natural light. All laboratories intend their photostability tests to represent light exposure which exceeds that expected to occur in practice but the tests actually applied vary widely in severity as shown in the wide range in light exposure (8–4500 klx days). Therefore the classification of products as stable or unstable needs to be considered carefully in relation to the severity of the test used.

Testing procedures for drug substances are broadly similar to those used for drug products. It is concluded that the variation in testing procedure is the result of differing perceptions regarding product exposure in practical usage and the absence of regulatory guidelines.

Keywords: *Drug substances; pharmaceutical products; photostability; light testing; photochemical degradation.*

Introduction

During the course of drug development, investigations are made of the stability of drug substances and products to a range of stress factors such as heat, pH, oxidizing conditions and light [1, 2]. In addition to meeting regulatory requirements, these investigations provide valuable information which may aid the selection of formulation, product–pack combinations or the recommended storage conditions. Regulatory authorities usually require a statement on the photostability of products and the means of protection, if required, but in product licence applications, no specific testing requirements are stipulated by any of the major regulatory agencies. In the course of reviewing photostability testing in the Sterling Research Group it was decided to undertake a survey of current practice within the UK pharmaceutical industry and the results of this survey are reported.

Scope of Survey

A questionnaire was sent to 23 laboratories including all the major UK centres of pharmaceutical research and development in 1989. Responses were received from 16 laboratories including the authors' own and two from each of three companies, where photostability testing was conducted at more than one site. The survey comprised separate sections covering drug substances and drug products. One responding laboratory did not test drug substances. Questions covered the form of presentation of drug substances and dosage forms, the type and output of light source used, times used for tests, analysis and interpretation of results and the underlying philosophy of testing.

Results of Survey

The answers given to the questions in the survey are presented in Tables 1–10.

In answer to a question on classification of results, seven of the laboratories classified drug substances and products as stable or unstable depending on whether degradation exceeded a defined level in a standard test. These levels ranged from <0.1 to 1%.

Eight laboratories isolated and identified photodegradation products from drug sub-

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Table 1
Form of presentation of drug substances and products in solution

	Number of responses	
	Drug substance	Oral–parenteral product
In clear glass	8	—
In clear and amber glass	5	5*
In clear, amber glass and PVC bags	—	6†
In primary pack only	—	3‡
Not tested	2	1

*Of these laboratories one used definitive labels. The following additional containers were also used by individual laboratories: pre-filled syringes, plastic bottles and primary pack.

†Of these laboratories two also used primary packs and two laboratories occasionally tested secondary packs.

‡One additional laboratory occasionally tested secondary packs.

Table 2
Form of presentation of solid drug substances and products

		Number of responses	
		Drug substance	Drug product
(A)	Open dish	2	—
(B)	Under clear glass/in clear glass container	5*	
(C)	Thin film in open dish	—	—
(D)	Thin film under glass	1	—
(E)	Under clear plastic (Petri dish)	1	1
(F)	In primary pack	—	4
	A + B	3	2†
	A + B + F	—	3‡
	A + F	—	2
	B + D	1	—
	B + C + D	1	—
	B + F	—	1
	A + B + C + D	1	—
	E + F	—	1
	No fixed procedure	—	2

*UV transparent glass was used by one laboratory.

†One laboratory also used aluminium foil.

‡Two laboratories also used amber glass. One laboratory occasionally tested secondary packs.

Table 3
Type of light source used for testing drug substances and products

	Combination of sources used*						
Daylight filtered through window glass	×	×	×	×	×		
Artificial daylight fluorescent tubes	×			×		×	
Xenon lamp		×			×		×
Mercury–tungsten lamp			×				
Mercury vapour lamp†				×	×		
Number of laboratories using combination for drug substance	2	3‡	2	2	1	4§	1
Number of laboratories using combination for drug product	4‡	5‡	2	—	1	4§	—

*Each column represents a different combination, denoted by × against the appropriate sources.

†254–366 nm; Various combinations of wavelengths achieved by use of a monochromator or filters.

‡Two laboratories also used laboratory light.

§One laboratory also used laboratory light.

Table 4
Numbers and illuminance of light sources used for testing drug substances and products

	Not available	<2 klx	5–12 klx	>50 klx
Artificial daylight	2	2(2)*	2(10,12)‡	—
Fluorescent tubes†	—	1(1.4)	1(6)	—
	—	—	1(5)	—
Xenon lamp	—	1(2)§	—	2(180)
	—	—	—	2(150)
Mercury–tungsten lamp	1	—	—	1(50)
Mercury vapour lamp	3	—	—	—

*Figures in parentheses give illuminance.
†One laboratory used two different sources (2 and 5 klx).
‡The irradiance of the 10 klx source in the UV-B (310 nm) band was reported as 0.5 W cm^{-2} and UV-A band (365 nm) as 2.5 W cm^{-2}.
§Low-power xenon lamp.

Table 5
Exposure times for drug substances as solid

Source illuminance (klx)	Exposure time* (days)	Total exposure (klx days)
2	30–180	60–360
5	<180	<900
6	30	<180
10–12	7–30	70–300
150	1–30	150–4500
180	0.7–8	126–1440

*Maximum and minimum values; intermediate times were also used. Exposure was terminated in many cases when degradation was detected.

Table 6
Exposure times for drug substances in solution

Source illuminance (klx)	Exposure time* (days)	Total exposure (klx days)
2	4–180	8–360
5	up to 180	<900
10–12	30–90	300–1080
150	1–30	150–4500
180	<1	<180

*Maximum and minimum values; intermediate times were also used. Exposure was terminated in many cases when degradation was detected.

stances and drug products as a matter of course when the total amount of degradation was greater than a fixed level. In the case of drug substances, four laboratories identified degradation products present at levels >0.1%, three at levels >0.5% and one at levels >1%. Identification was normally attempted following isolation. In the case of drug dosage forms, two laboratories identified and attempted to isolate degradation products formed at levels of <0.2% and six at levels of 0.2–1%. Five other laboratories also identified and isolated photodegradation products but did not follow any fixed procedure. Three laboratories did not normally isolate degradants from drug dosage forms but relied on modified packs to prevent degradation.

Analytical methods were required to detect photodegradation at the following levels: 0.1% (eight laboratories), 0.2% (two laboratories), 0.1–1% (one laboratory) and 1% (one laboratory). One laboratory had no fixed level and one did not determine the sensitivity of analytical methods.

Discussion

In a photostability test on a drug product, it is desirable to use a greater exposure to light than is likely to occur under the most adverse conditions of practical usage. In practical terms this is likely to be the exposure resulting from products being removed from their outer carton and left on a sunny window sill. Coloured product components and coloured outer packs may be degraded by visible light but most drug substances are colourless and therefore only susceptible to degradation by UV light. Although window glass, particularly double glazing, will remove much of the incident UV light, a small portion is transmitted and, because of the high energy in UV light, this can be important in the degradation of drug substances and products. For example, the levels of UV irradiance transmitted through 6-mm glass recorded in mid-summer at Alnwick, Northumberland, using a broad-band UV photometer were 126 and 1040 μW cm^{-2} for the UV-B (310 nm) and UV-A (365 nm) bands, respectively. Recognizing the importance of degradation by UV light, all the laboratories responding to the survey used either natural daylight and/or an artificial light source including a UV component for tests with drug products.

Table 7
Exposure times for drug products

Number of labs	Source illuminance (klx)	Exposure time (days)	Total exposure (klx days)
1	1.4	30–365	42–511
3	2	4–180	8–360
1	5	180	900
1	6	30 (90 for HDPE* bottles)	180 (540 for HDPE bottles)
1	10	30	300
1	12	30–90	360–1080
1	50	No fixed time	—
2	{150	<1–30 (liquids)	150–4500
	{150	<7–30 (solids)	1050–4500
1	150	Used for product trouble-shooting	—
2	{180	0.25–2 days (liquids)	45–360
	{180	1–14 days (solids)	180–2520

*HDPE = high density polyethylene.

Table 8
Daylight exposure of drug products

Exposure time	Number of responses
<1 month	3
<3 months	1
6 months	2
<12 months	1
12–60 months	1

Light sources

Artificial light.

Artificial daylight tubes. The visible output will provide a reasonable simulation of natural daylight and should also provide a reasonable simulation of natural UV light if the tubes conform to British Standard 950, part 1 [3]. Fluorescent tubes are ideally suited to providing even illumination over a large area and this, combined with their low cost, probably accounts for their popularity.

Xenon lamps. It is well known that xenon lamps provide the closest simulation of sunlight of all artificial sources and can give a total irradiance (W m^{-2}) similar to that of natural sunlight over a small area [4]. Their selection by a number of pharmaceutical laboratories indicates that these laboratories wish to reproduce natural light as closely as possible.

Tungsten–mercury lamps. These provide a high level of visible light with a small or very small UV component, depending on the specification [4]. They are used to test light fastness of textiles.

Laboratory light. The use of laboratory light (typically 400–800 lx), as opposed to natural daylight or more intense artificial sources, provides a "low light" condition which is of value in investigating the sensitivity to photodegradation of products containing drug substances known to be very susceptible to such degradation. However its use is less relevant in routine product testing.

Natural light. Midday summer daylight in southern England has been reported to be approximately 30 klx [5]. An illuminance of 94 klx was recorded behind window glass at Sterling's research laboratory in Rensselaer, near Albany (NY, USA) during August 1990. The spectral distribution as well as the intensity of daylight varies not only with the time of day, weather conditions and atmospheric pollution, but also with the time of year [6, 7]. Thus the UV component is up to 1000 times less in winter than summer at 50° latitude (private communication, M. Hibbert). This variability

Table 9
Classification of objectives of product tests and actual exposure

	Responses	Exposure (klux days)
Test simulating practical exposure	0	—
Significantly greater than practical exposure	9	8–4500
Very severe test	5	60–2520

Table 10
Tests to determine stable/unstable classification

Exposure (klx days)	Maximum permitted level of degradation (%)
Liquids	
8	0.5–1
<180	0.1–0.5
45–180	0.5–1
Solids	
<360	0.5–1
360–1080	0.5–1
180–1260	0.5–1

makes natural light not well suited to quantitative experiments unless its spectral irradiance is recorded during the course of the experiment.

Definition of test conditions

In order to fully define the test conditions during photostability testing it is necessary to measure not only the visible light (illuminance) to which products are exposed but also the UV content (irradiance) since many drugs absorb little or no visible light but absorb in the UV range present in natural light (290–400 nm). Data on the illuminance (lx) of sources (Table 4) were supplied by the lamp manufacturers in most cases (11 laboratories). Data on UV irradiance are not necessary for sources which are known to provide good simulation of sunlight (e.g. xenon lamps) in order to predict product behaviour in natural light. However, for other sources of light, such a prediction cannot be made without knowledge of their UV irradiance; such data, although normally available from the manufacturer, were provided by only three laboratories. No laboratory reported the monitoring of light levels during tests with natural light.

Stability tests on drug substances

Pharmaceutical companies investigate the photochemical stability of drug substances for a number of reasons. Since photochemical reactions are often complex and result in the formation of a number of products, it is likely to be easier to analyse products from the degradation of the pure drug substance than those formed by degradation of the drug dosage form (drug product) which is itself a mixture of components. In addition, photochemical tests on the drug substance can aid in the development and validation of stability-indicating methods.

The responses given in the survey indicate that a wide variety of experimental conditions were used in experiments with drug substances particularly in respect of the illuminance of the light sources (Table 4) and the time of exposure (Table 5). This is not particularly surprising given that a range of objectives is encompassed in experiments on the drug substance.

The popularity of presentation of the drug substance as a solution in clear glass (13 laboratories) is to be expected since this approach is convenient and will maximize degradation. All laboratories used a solid presentation; this suggests that experiments with the drug substance are used as a simple model of a solid drug dosage form. The thin film used by four laboratories is a stressful form of presentation providing a high ratio of surface area to mass.

The range of light sources used is the same as that reported for drug products, again indicating that most laboratories use data obtained from the drug substance to help in predicting potential problems with the product. The mercury vapour lamp used by three laboratories represents a convenient form of UV irradiation. Exposure times also are similar to those used for drug products and extend up to 6 months. The use of a more intense light source for a shorter time period would give results of equivalent value. The total exposure (illuminance × time) shows the same wide range as used in drug product experiments and this aspect is discussed further below.

Interpretation of results. In interpreting results, five of the seven laboratories using a stable/unstable classification indicated that a low or very low level of degradation would result in classification as unstable. However, the actual total exposure (klx days) used in the standard test varied considerably (Table 10), with the most stringent test using up to 1260 klx days, as compared with 8 klx days for the least stringent test. This wide variation indicates that there is no common well-defined quantitative objective underlying these tests and that the classification as stable or unstable needs to be considered in relation to the severity of the test applied.

Stability tests on drug products

Three laboratories tested solution products and four tested solid products only in the

primary pack (Tables 1 and 2). This will provide an assurance that the product is stable in the pack. Three laboratories also conducted occasional tests on secondary packs to confirm that the packs protect unstable products from degradation. Seven laboratories tested solid products both with and without the pack, to investigate the intrinsic stability of the product and the protection afforded by the pack. No details of packs were requested in the survey.

A number of laboratories exposed solution products in amber glass as well as in clear glass. This is an important test for products with poor intrinsic photostability since although amber glass transmits less than 10% of incident light, it will not afford complete protection.

The response to the question on the choice of exposure for product testing indicated that laboratories intend products to be exposed to light conditions significantly greater or much greater than those likely to be encountered in practical product use. Different laboratories probably have different views on the light conditions encountered in use but the widespread use of natural light (12 laboratories) suggested that many laboratories wish to determine the stability of drug products left on windowsills without an outer protective pack. However, the actual daylight exposure times used ranged from 1 to 60 months (Table 8) and a similarly wide range of exposures was employed with artificial light sources (Tables 5–7). This wide range is almost certainly related to the lack of data on how drug products are used or abused in practice, and the absence of any pharmacopoeial, regulatory or industry guidelines.

Comparison of the stated objective of product testing with the actual exposure used (Table 9) again confirms the conclusion that laboratories have widely differing views on what constitutes normal exposure of products in practice. Thirty days exposure at 12 h day^{-1} to midday UK summer daylight (sun + skylight) approximates to 450 klx days, as compared with the 8–4500 klx days used in the different tests.

Exposure times were also affected by the basic approach of laboratories to product testing. From answers provided to questions and from additional comments made, it appears that nine laboratories used a defined exposure in conducting tests, whereas three laboratories continued exposure until some degradation was observed and a further three continued exposure until a predetermined level (e.g. 10%) of degradation of product occurred. Similar differences of approach also apply to the testing of drug substances.

Interpretation of results. Seven of the 15 laboratories involved in product testing consider it appropriate to use a simple stable/unstable classification although it is interesting that only five of these laboratories used predefined tests rather than a flexible approach to testing. The actual exposures and degradation criteria used in defining products as stable or unstable are summarized in Table 10, from which it can be seen that the degree of exposure which "stable" products are required to withstand varies considerably.

The levels at which photodegradation products were isolated and identified are within the range (0.2–1%) typically applied for the analysis of impurities and degradation products. Where no fixed level is used, a range of other criteria may be applied. Of the three laboratories which did not normally isolate photodegradants from drug products, one conducted isolation and identification experiments on the drug substance and two altered the product pack design to prevent degradation. Here, too, is a clear difference in philosophy. One matter on which there is, however, close agreement is on the detection limits for photodegradation products in analytical methods.

Conclusions

The diverse approaches taken to the photostability testing of drug substances and products are almost certainly related to the absence of regulatory guidelines; it is of note that the Japanese pharmaceutical industry has recently published its own guidelines [8, 9]. An additional factor contributing to this diversity is that the perception of what represents a moderately stressful or stressful test also varies considerably. Presumably this is the result of the absence of data on the use or abuse of pharmaceutical products and differing views of what may occur in practice.

The use of a range of lamp sources was to be expected since all have limitations. However, it was surprising that most laboratories did not supply data on the UV irradiance of sources

since UV irradiation is likely to be the cause of much product instability; such data are needed to predict product stability in natural light and to compare results from tests using different sources.

Standards of analysis were high and similar between laboratories, reflecting those expected by the regulatory agencies. A discussion between representatives of most of the laboratories participating in the survey indicated that many are reviewing their current approaches to photostability testing. This is likely to result in the use of more fully defined test conditions and the re-evaluation of the objectives of the tests.

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