

ICH guideline for photostability testing: aspects and directions for use

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*For the memory of Prof. Dr. K. Thoma who died December 2002**Received March 25, 2003, accepted May 26, 2003**Dr. Wolfgang Aman, Lindenweg 8, A-6300 Wörgl, Austria**Pharmazie 58: 877–880 (2003)*

The ICH guideline Q1B for photostability testing gives guidance on the basic testing protocol required to evaluate the light sensitivity and stability of new drugs and products. The choice of the irradiation method, although complying with the guideline demands, may effect test results. High irradiances may shorten testing times, but can lead to enforcement of photodegradation, which was demonstrated for molsidomine tablets. The exposure to an artificial light source (xenon lamp) was compared and correlated to natural daylight. Suitable testing methods for nifedipine and molsidomine tablets were developed. Deviating from the guideline recommendations, the presentation of powder samples should be done in tiny aluminium pans, facilitating the test procedure, minimising the risk of falsified test results due to improper sampling and improving reproducibility. When using glass dishes for the presentation of tablets to photostability testing, they should be lined by e. g. aluminium foil to avoid influences of light reflected from the sample tray.

1. Introduction

After decades of vagueness the ICH guideline for photostability testing [1] finally established the standards for light testing. It is now an integral part of stability testing for new drug substances and drug products. Although the guideline primarily addresses the generation of photostability information for submission in registration applications, all new photostability data should be created according to its instructions or set in comparison to them. This also applies to academic working groups.

The guideline gives a lot of helpful instructions to the applicant. Probably the most important issue is its demand for a certain amount of light energy to be emitted: overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/m. The guideline itself offers two options for irradiation testing. Nevertheless it is up to the applicant to develop proper methods which comply with the ICH guideline. It was the aim of the work to point out some practical aspects of light testing and give helpful directions to the user.

2. Investigations and results

2.1. Choice of irradiation method

Uncoated 20 mg nifedipine tablets and uncoated 4 mg molsidomine tablets were used as model drug products to investigate the influence of irradiation methods on the outcomes of photostability testing. Both drug substances are known to be very light sensitive, even in the solid state [2, 3].

Using a xenon lamp (according to option 1 of the guideline) irradiance may be set to different levels. Various irra-

diances of this artificial light source were compared to natural daylight. On a sunny day natural irradiance fluctuates between 380 and 500 W/m², on a cloudy day between 50 and 120 W/m². Maximum irradiance for bright sunlight in Central Europe may exceed 700 W/m² (Personal information from the Meteorological Institute of the University of Munich 1997). However, as the results with nifedipine and molsidomine tablets reveal, the best corre-

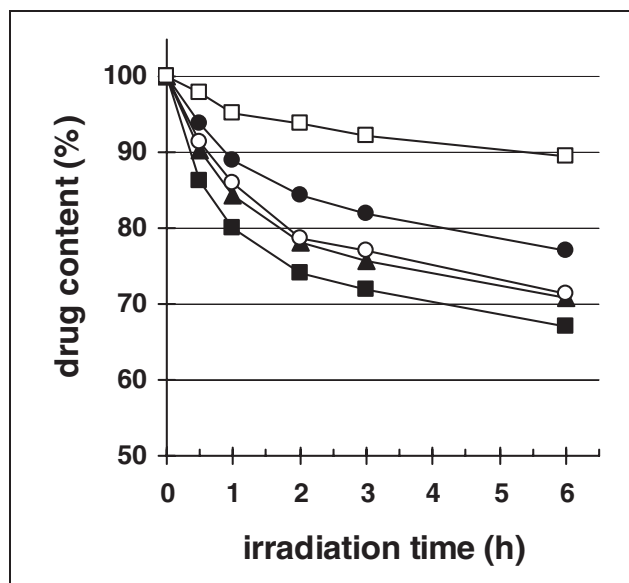


Fig. 1: Influence of light source and irradiance on the photostability of nifedipine 20 mg tablets. □ natural daylight, cloudy day (Central Europe, June); ○ natural daylight, sunny day (Central Europe, June); ● xenon lamp, UV filter, 250 W/m²; ▲ xenon lamp, UV filter, 415 W/m²; ■ xenon lamp, UV filter, 720 W/m²

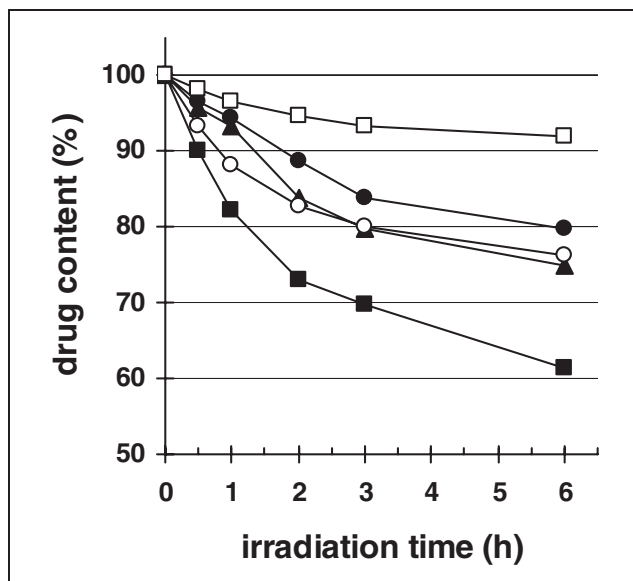


Fig. 2: Influence of light source and irradiance on the photostability of molsidomine 4 mg tablets. □ natural daylight behind window glass, cloudy day (Central Europe, June); ○ natural daylight behind window glass, sunny day (Central Europe, June); ● xenon lamp, window glass filter, 250 W/m²; ▲ xenon lamp, window glass filter, 415 W/m²; ■ xenon lamp, window glass filter, 720 W/m²

Table 1: Irradiation time in Suntest CPS+ to fulfil criteria of ICH Guideline Q1B at certain irradiances

Irradiance	Time to fulfill criteria of ICH Q1B	
	UV 200 W h/m ²	Illumination 1.2 mio lux h
250 W/m ²	8.9 h	21.8 h
415 W/m ²	5.4 h	13.0 h
720 W/m ²	3.1 h	7.5 h

lation of the light testing cabinet with natural sunlight was given at 415 W/m² (Figs. 1 and 2).

The ICH guideline does not demand a certain irradiance or irradiation time but light energy. Depending on the irradiance the time of light exposure needs to be adjusted. As Table 1 shows, testing time can be reduced from 21.8 h to 7.5 h by intensifying irradiance from 250 W/m² to 720 W/m².

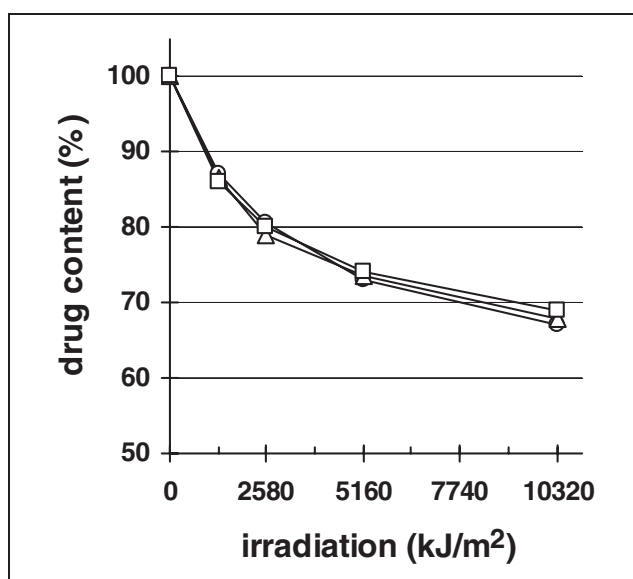


Fig. 3: Influence of irradiance on the photostability of nifedipine 20 mg tablets. ○ 250 W/m²; △ 415 W/m²; □ 720 W/m²

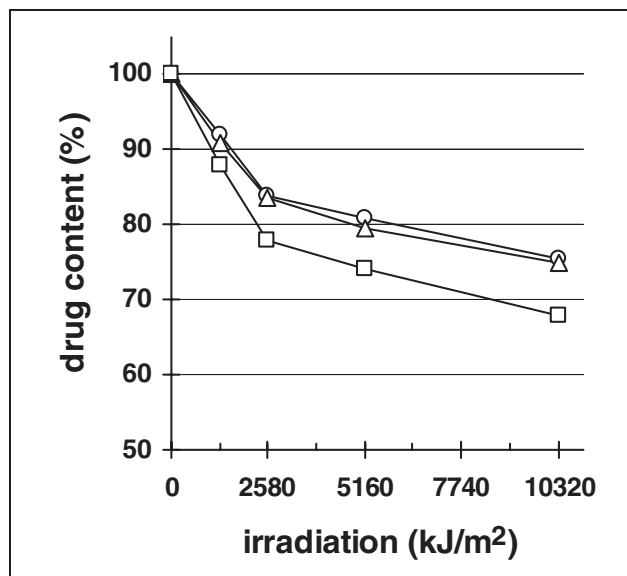


Fig. 4: Influence of irradiance on the photostability of molsidomine 4 mg tablets. ○ 250 W/m²; △ 415 W/m²; □ 720 W/m²

Uncoated nifedipine tablets and molsidomine tablets were therefore tested at different irradiances until certain illumination energies were reached. To exclude temperature effects, the sample tray was kept at 20 °C at each irradiance.

The photodegradation of nifedipine tablets depended only on the emitted light energy, but not on the irradiance (Fig. 3).

Deviating from the results obtained with nifedipine tablets photodecomposition of molsidomine tablets was higher at 720 W/m² than at 415 W/m², although the samples were exposed to the same light energy. Between 415 W/m² and 250 W/m² no significant change of photodegradation was observed (Fig. 4).

2.2. Presentation of samples

Two methods of sample presentation were tested. In the first case solid drug substances (nifedipine and molsidomine) were irradiated in glass dishes with 5 cm diameter. The *powders* were carefully spread to give a layer as homogenous as possible with a thickness below 3 mm. After irradiation samples for analysis were taken. About 50 mg of the drug powder was removed from the glass dish to determine the extent of photodegradation. 10 samples from the same dish were analysed without preceding homogenisation. Extreme deviations were found. Relative standard deviation of the test results were enormous (42.1% and 18.5%, resp.).

Another method was tested. Aluminium pans like those common for DSC analysis were used. Drug powder was analytically weighed into the pans (around 10 mg portions in 40 µl pans), than the pans were tapped to give a homogenous and reproducible layer of constant thickness (typically below 3 mm). After irradiation the whole pan was used for sample preparation. The test results corresponded well. Relative standard deviation was below 1.5% for both drug substances.

Also the mean values of remaining drug content differed highly depending on the method of sample preparation (Table 2).

Tablets were presented to light testing in glass dishes. The bottom of the glass dish produces a narrow, light permeable gap between the bottom of the tablet and the light reflecting sample tray. The influence of light reflected to

Table 2: Reproducibility of photostability testing results of nifedipine and molsidomine substance depending on the method of sample presentation

Sample no.	Residual nifedipine after 1 h illumination		Residual molsidomine after 1 h illumination	
	Glass dish	Aluminium pan	Glass dish	Aluminium pan
1	45.3%	63.0%	65.4%	78.3%
2	19.7%	64.2%	70.2%	77.6%
3	29.6%	64.1%	73.7%	79.4%
4	30.3%	64.5%	40.7%	76.2%
5	14.3%	63.8%	63.5%	80.2%
6	38.1%	64.7%	55.2%	78.2%
7	18.5%	63.0%	71.3%	79.0%
8	34.7%	65.1%	53.1%	77.9%
9	56.2%	64.6%	62.1%	78.5%
10	23.2%	63.9%	45.8%	78.7%
Mean	31.0%	64.1%	60.1%	78.4%
Rel. stand. dev.	42.07%	1.08%	18.48%	1.38%

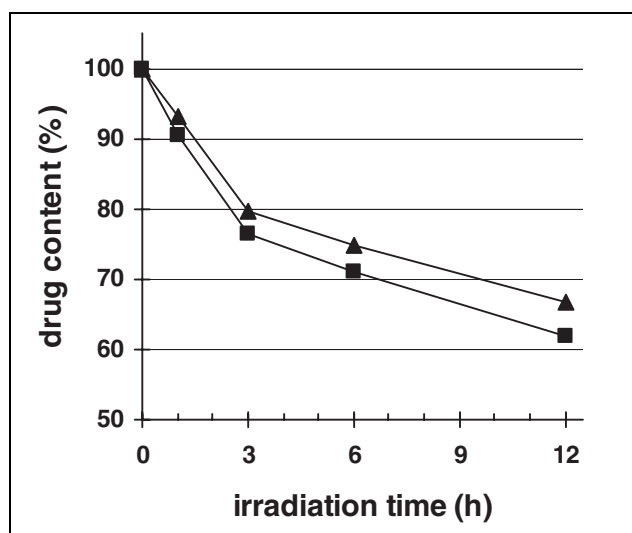


Fig. 5: Influence of sample presentation on the photostability of molsidomine 4 mg tablets. ▲ glass dish lined with aluminium foil (no reflected light); ■ glass dish without aluminium foil (additionally affected by reflected light)

the bottom of tablets was tested by comparing it to samples which were presented in glass dishes lined with aluminium foil. The tests were carried out with uncoated 4 mg molsidomine tablets.

Tablets presented in unlined glass dishes degraded to a higher extent. Drug loss was increased by 3% to 5% (Fig. 5).

3. Discussion

Although the ICH guideline for photostability testing presents quiet clear instructions, it is nevertheless up to the applicant to develop proper methods which comply with the guideline. The test design is crucial because it may change the results.

Light testing cabinets with xenon lamps or metal halide lamps produce an output similar to the D65/ID65 emission standard covering the visible and UV part of light (like described in Option 1 of the ICH guideline). As well the demands for overall illumination as for ultraviolet energy can be fulfilled by one test only. However, it has to be considered that, in the case of the xenon lamp, for providing the overall illumination an about 2.4 fold

amount of the demanded ultraviolet energy was emitted. This stress is not demanded by the ICH guideline and can be avoided by using Option 2.

Even if the samples are exposed to the same overall light energy, the test results may differ depending on the irradiation method selected.

In the case of molsidomine tablets irradiance of 415 W/m² is recommended for photostability testing. This value gives a good correlation with natural sunlight in Central Europe, which is helpful for the interpretation of the test results concerning the practical use of the drug product.

Additionally the xenon light should be filtered through a window glass and not a UV filter. Window glass eliminates light below 320 nm, UV filter below 290 nm. Since this part of light (290–320 nm) is deteriorating the photostability of molsidomine [4, 5]. The usage of the window glass is in accordance to the ICH guideline.

For nifedipine tablets it was demonstrated that the UV part of 290–320 nm does not affect the photodegradation [4, 5]. The choice for UV or window glass filter does not influence the test results in this case. Furthermore it could be demonstrated for nifedipine tablets that the irradiance has no effect on the test result. The photodegradation just depends on the emitted light energy. Therefore high irradiance should be preferred to keep irradiation time short. Testing time can be reduced from 21.8 h to 7.5 h by intensifying irradiance from 250 W/m² to 720 W/m².

The presentation of samples may also influence the test results. The ICH guideline states, that the presentation of solid powder samples, e. g. drug substances, should be done in suitable glass or plastic dishes and spread across the container to give a thickness of typically not more than 3 mm. However, we do not recommend the use of glass dishes for powder samples. In glass dishes sampling after irradiation is crucial and difficult, since it is mostly the upper part of the powder layer which is affected by light. Furthermore the sample tray reflects light to the bottom of the glass dish, since the glass layer enables the reflected light to irradiate the powder sample from beneath. How can you guarantee a representative and reproducible sampling? How much of the powder is from the top layers, how much from the bottom layers? As our results clearly reveal, homogenisation of samples exposed in glass dishes is absolutely necessary. Alternatively the whole dish could be taken, but would result in high amounts of solvents for analytical sample preparation. To solve all these problems, we recommend the use of aluminium pans like those common in DSC analysis instead of glass or plastic dishes. Since the whole unit of the sample is analysed, no homogenisation is necessary. No problems of inhomogeneity are to be expected. According to our experiences this method of powder presentation is an easy way to avoid problems due to non-reproducible sampling, inhomogeneous layers and varying light reflection from the bottom.

For presentation of unpackaged tablets to light testing, glass or plastic dishes lined with aluminium foil were suitable. When placed directly on the sample tray, tablets were moved and sometimes turned upside down by the cooling air current. The placing into a dish sufficiently protected the tablets from the current. Aluminium foil is necessary to avoid irradiation of the tablet bottom by reflected light.

4. Experimental

4.1. Materials

Nifedipine (kindly supplied by Stada, Bad Vilbel, Germany and Haupt Pharma, Wolfratshausen, Germany), molsidomine (kindly supplied by Haupt Pharma, Wolfratshausen, Germany), microcrystalline cellulose (Leh-

Table 3: Formulae of the tested nifedipine and molsidomine samples

	Nifedipine 20 mg	Molsidomine 4 mg
Drug substance	9.0%	1.8%
Microcrystalline cellulose	40.0%	40.0%
Lactose	44.5%	51.7%
Corn starch	5.0%	5.0%
Colloidal silica	0.5%	0.5%
Magnesium stearate	1.0%	1.0%
Target weight/tablet	222 mg	222 mg

mann und Voss, Hamburg, Germany), lactose (Meggler, Wasserburg, Germany), corn starch (Ceresstar, Krefeld, Germany), colloidal silica (Degussa, Frankfurt, Germany), magnesium stearate (Caelo, Hilden, Germany).

4.2. Methods

4.2.1. Preparation of tablets

Nifedipine 20 mg and molsidomine 4 mg tablets were produced according to the formulae presented in Table 3.

Tablets were round with a diameter of 8 mm. They were pressed on a single punch eccentric tableting machine EK 0 (Korsch, Berlin, Germany) with strain gauge on the upper punch. Compression force was set to 9.0 kN, and machine speed to 2500 tablets per h. Tablet hardness was 60–80 N.

Each step of the manufacturing process was done under red (long-wavelength) light to avoid photodegradation (European Pharmacopoeia 2002).

4.2.2. Irradiation of tablets

4.2.2.1 Artificial daylight

The tablets and powders were irradiated in the light testing cabinet Suntest CPS+ (Atlas, Gelnhausen, Germany) with a xenon arc lamp as light source and cooling aggregate. UV special filter for nifedipine preparations or window glass filter for molsidomine preparations were installed to adapt the spectrum of the artificial light source to natural daylight.

Dark controls were added to control temperature effects.

4.2.2.2. Natural daylight

The samples were irradiated on the roof of university building in Munich. Only results from constant weather conditions were selected. Irradiance fluctuated between 380 and 500 W/m² on a sunny day, between 50 and 120 W/m² on a cloudy day.

Dark controls were added to control temperature effects.

4.2.3. HPLC analysis

The HPLC system consisted of isocratic pump ConstaMetric[®], autosampler SpectraSeries[®] AS 100 and spectrophotometric detector SpectraSystem[®] UV 6000 LP connected to a computer-based software system PC 1000, version 3.5 (all by Thermoquest, Darmstadt, Germany).

4.2.3.1. Nifedipine preparations

The mobile phase was prepared by mixing 530 g of methanol with 470 g of phosphate buffer 10 mmol/l pH 6.0. A 125 × 4 mm 5 µm C18 column (LiChrospher[®] RP-18, Merck, Germany) was used. For detection the wavelength was set to 230 nm. The flow rate was controlled at 0.8 ml/min with a run time of 10 min. The linearity of the standard curve was > 0.9999.

4.2.3.2. Molsidomine preparations

The mobile phase was prepared by mixing 200 ml of acetonitrile with 800 ml of ammonium formate buffer 20 mmol/l pH 6.7. A 250 × 4 mm 5 µm C18 column (LiChrospher[®] RP-18e, Merck, Germany) was used. For quantitative determination of molsidomine the wavelength was set to 312 nm, for detection of degradation products the wavelength was set to 254 nm. The flow rate was controlled at 0.9 ml/min with a run time of 15 min. The linearity of the standard curve was > 0.9999.

References

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