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Particular features of photolabile substances in tablets

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Nifedipine and molsidomine tablets are extremely photolabile drug preparations, even at cool room light. Compared to solutions the light spectrum responsible for photodegradation is moved towards the long-wavelength range corresponding to the bathochromic shift of light absorption in the solid state. In the case of nifedipine tablets light up to 500 nm, especially the range between 400–420 nm, is degrading. Molsidomine tablets are affected only by ultraviolet light, but not by visible light. In both cases light penetrates less than 1 mm into the tablets. For nifedipine tablets the exact penetration depth could be determined due to the discolouration of the drug substance upon irradiation. It varied from 360 μm to 880 μm depending on the drug content. Since the decomposition products of nifedipine act as photostabilizers by spectral overlay, light penetration and photodegradation in nifedipine tablets are limited. The formation of gaseous and liquid decomposition products in molsidomine tablets enhances photodegradation. Changes of the tablet structure as well as dissolution and migration processes are discussed. Furthermore the degradation products do not photostabilize the drug substance due to the missing light absorption above 300 nm.

1. Introduction

The photostability of drug substances in the solid state is not much investigated. Probably the main reason is the reduced photoinstability of solid drugs compared to drug solutions. Reduced instability, reduced interest? One should be aware that tablets are the most important dosage form. As the number of publications is limited, many important particular characteristsics of drug decomposition in the solid state, especially after light exposure, are not fully investigated and cannot be explained up to now. Therefore it was aim of our studies to illuminate, what happens to drug substances when irradiated in the solid state, especially in tablets.

For various reasons nifedipine and molsidomine were chosen as model drug substances. First of all both substances are very light sensitive, even in the solid state [1, 2]. Secondly, both substances have different absorption characteristics, which helps us making more general statements. As a third criterion the substances were selected, because the extent of photodegradation differs significantly and the reasons why were not clear. These studies helped us to find out.

Another point was the dependency of photodegradation on the wavelength. To know, which part of the light is responsible for drug decomposition is basically important for specific stabilisation attempts.

Generally the lower photolability of drug substances in tablet formulations is referred to the low penetration depth of light into tablets. However, the concrete figures are not known. Methods for evaluating the penetration depths of light into tablets are presented.

2. Investigations and results

2.1. Photolability of nifedipine and molsidomine tablets

Intense day light was simulated by a xenon arc lamp, which is in accordance to the ICH guideline for photostability testing [3].

Generally marketed nifedipine tablets are light protected by red pigmented film coatings and/or red blister packages. Marketed molsidomine tablets are only protected by packaging. Figs. 1 and 2 show the high photosensitivity of both drug preparations and – in the case of nifedipine tablets – the effects of photostabilizing measures.

For our deepening studies similar nifedipine and molsidomine tablets were formulated and produced in the laboratory. Nifedipine tablets contained 20 mg drug substance, molsidomine tablets 4 mg drug substance. The comparability of their light sensitive properties to marketed products was proven.

Unprotected nifedipine tablets (study formulation) are rapidly destroyed by light, after 30 min. already more than 10% of the drug substance are last. The degradation slows down after 2 h and comes to an end after 12 h intense irradiation. The maximum degradation was 32% of the initial drug amount.

The photolabile properties of molsidomine tablets (study formulation) are somewhat different. Although the degradation was similar after 12 h (34%), it did not stop at this point. Decomposition ended after 48 h, reaching a maximum level of 42%.

As the xenon lamp simulates blazing sun light, more realistic tests with room light were carried out.

Even when exposed to room light, unprotected nifedipine tablets are very photolabile. After 3 h more than 10%, after 12 h more than 15% were decomposed.

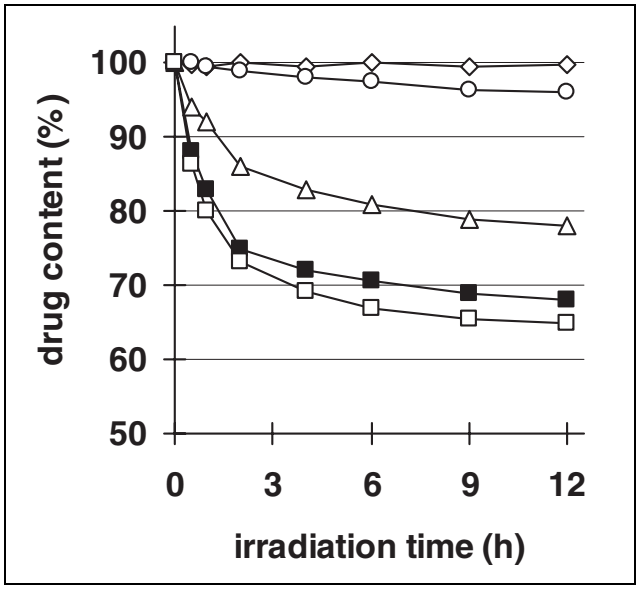

Fig. 1: Photodegration of nifedipine 20 mg tablets (Suntest CPS+, 720 W/m^2, UV filter), ◇ cooated tablets in the blister (marketed formulation), ○ coated tablets outside the blister (marketed formulation), △ uncoated tablets in the blister (cores of the marketed formulation), ■ uncoated tablets outside the blister (study formulation), □ uncoated tablets outside the blister (cores of the merketed formulation)

Unlike nifedipine tablets, the light sensitivity of molsidomine tablets was much more reduced by altering the light stress. Even after 6 h more than 95% of the drug remained unchanged (Fig. 3).

2.2. Wavelength dependency of the photodegradation

It is not the whole daylight range, which causes photodegradation. Only light which is absorbed by the drug product can induce degradation. Absorption spectra of the drug substances give a good idea, from which part of the light the drug preparation should be protected. However,

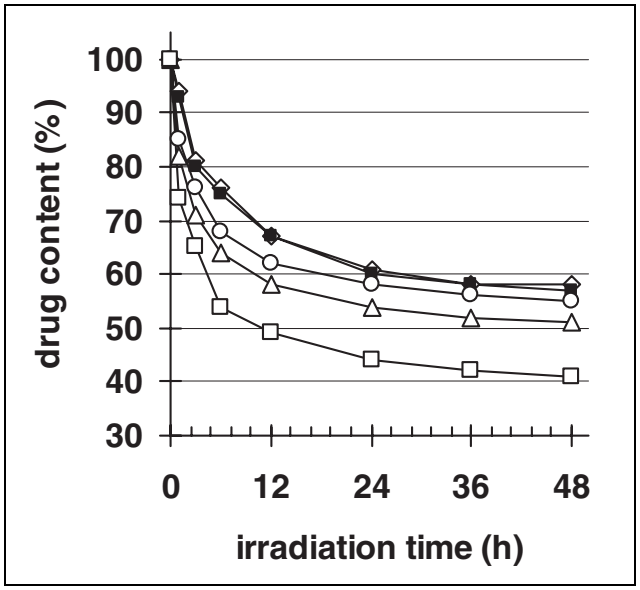

Fig. 2: Photodegration of molsidomine 4 mg tablets (Suntest CPS+, 415 W/m^2, window glass filter), ◇ marketed formulation 1, ■ study formulation, ○ marketed formulation 2, △ marked formulation 3, □ marked formulation 4

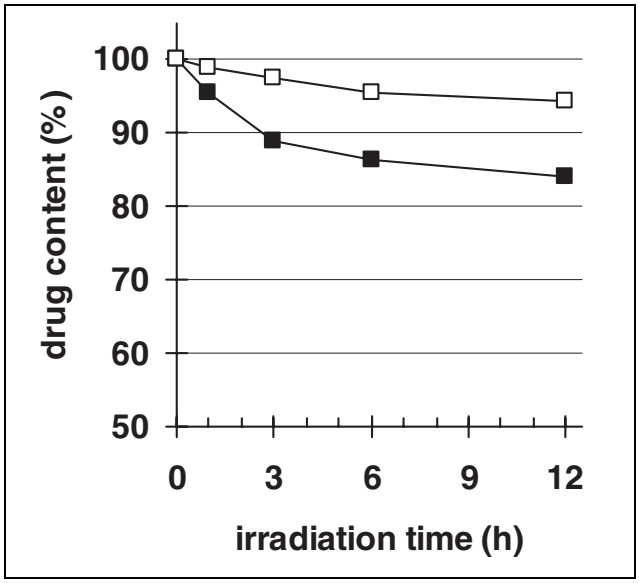

Fig. 3: Photodegration of nifedipine 20 mg tablets and molsidomine 4 mg talets at room light (light testing cabinet Thoma and Strittmatter), □ uncoated molsidomine 4 mg tablets, ■ uncoated nifedipine 20 mg tablets

knowledge of the absorption spectra of the drug substance may not suffice to predict the degrading wavelength range, since only certain parts of the absorbed light may induce photodecomposition.

Primarily the light absorbance by the drug substance itself is important. But even if light is absorbed by excipients only, drug decomposition may occur due to secondary reactions. Therefore it was interesting to study the wavelength dependency of the tablet formulation and not of the drug substance itself. All degrading effects of absorbed light, even photosensitization, were therefore included.

To assess the wavelength dependency of photodegradation the tablets were shielded by filters which eliminate light below certain wavelengths. The wavelength at which light transmission is 50% defines the filters. Fig. 4 compares

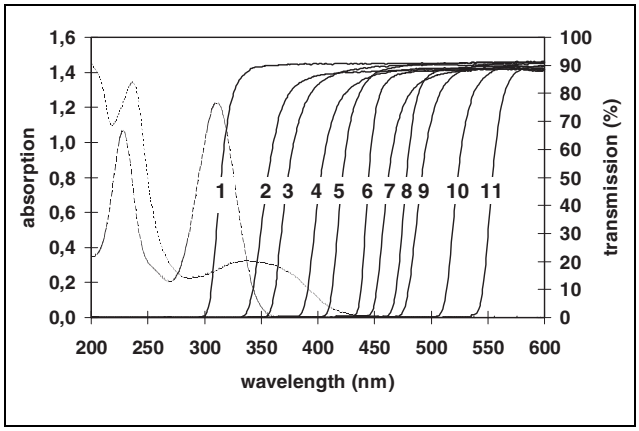

Fig. 4: Transmission spectra of light cutting filters (Schott glass factory) compared to absorption spectra of nifedipine and molsidomine solutions (c = 20 µg/ml), ... absorption spectrum of nifedipine, —·—·— absoption spectrum of molsidomine, ——— transmission spectra of lights cutting filters;
1: WG 320 (314 nm)
2: WG 345 (354 nm)
3: GG 375 (372 nm)
4: GG 400 (401 nm)
5: GG 420 (421 nm)
6: GG 435 (444 nm)
7: GG 455 (461 nm)
8: GG 475 (475 nm)
9: GG 495 (490 nm)
10: GG 515 (524 nm)
11: OG 550 (555 nm)

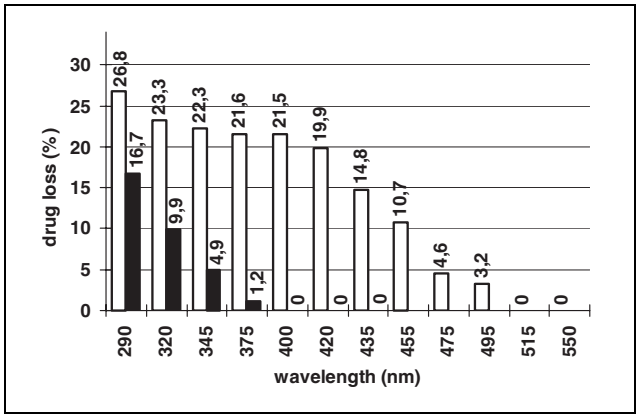

Fig. 5: Photodegradation of nifedipine taablets and molsidomine tablets depending on the wavelength of light, □ uncoated nifedipine 20 mg tablets (Suntest CPS+, 720 W/m^2, UV filter), ■ uncoated molsidomine 4 mg tablets (Suntest CPS+, 415 W/m^2, window glass filter)

the transmission spectra of the filters with the absorption spectra of the drugs. Nifedipine tablets were irradiated 2 h at 720 W/m^2, molsidomine tablets 3 h at 415 W/m^2. Test procedures remained the same except changing the light cutting filters.

No matter which part of the UV range (300 nm to 400 nm) excluded, the extent of photodegradation of nifedipine tablets remained relatively constant. It was only after removal of the violet part of the visible light, that photodegradation decreased. Light above 515 nm did not affect nifedipine tablets anymore (Fig. 5).

Photodegradation of molsidomine tablets decreased by eliminating short-wavelength light. After exclusion of ultraviolet light degradation was stopped (Fig. 5).

2.3. Penetration depth of light into tablets

Two methods are presented by which the penetration depth of light into tablets can be determined.

Tablets of low band height were produced. Those tablets were piled one tablet to another, surrounded by the die. The tablet pile was brought into the die in a way that the uppermost tablet closed the die surface smoothly. Irradiation of the tablets induced photodegradation. Since light could only get through the top tablets, the number of affected units gives the penetration depth (Fig. 6). Light affection was tested by HPLC detection of photodegradation products.

Bi-planar, round tablets, 8 mm diameter were manufactured. Band height was 1 mm. The results were the same for nifedipine tablets as for molsidomine tablets. After

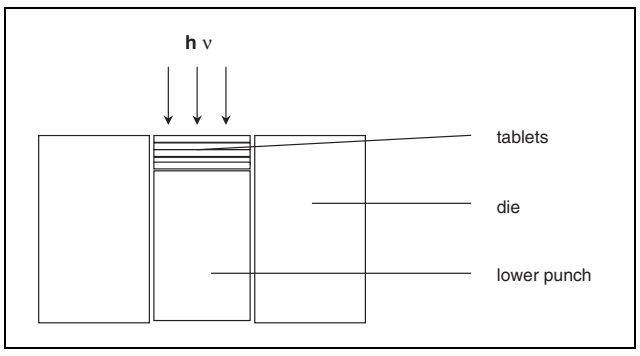

Fig. 6: Experimental design for determinig the penetration depth of light into tablets

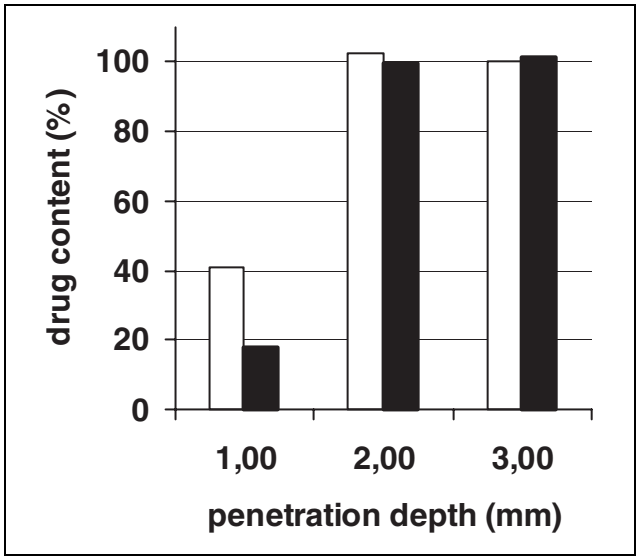

Fig. 7: Influence of the layer thickness (penetration depth) on the photodegration of nifedipine and molsidomine tablets, □ uncoated nifedipine tablets, band height 1 mm (Suntest CPS+, 12 h, 720 W/m^2, UV filter), ■ uncoated molsidomine tablets band height 1 mm (Suntest CPS+, 48 h, 415 W/m^2,window glass filter)

irradiation photodegradation was detected in the top tablet only. Lower tablets remained completely unaffected of the light stress, meaning that the penetration depth into tablets is below 1 mm. Differences were seen in the extent of photodegradation of the top tablets. More than 80% of the drug were degraded in molsidomine tablets, but only 60% in nifedipine tablets (Fig. 7).

Since the precision of the presented analytical method clearly depends on the band height (the lower the more precise) another method was developed for nifedipine tablets. Nifedipine products darken upon light stress due to the formation of a coloured degradation product [4]. Cross-sections of maximally degraded nifedipine tablets show a distinct discoloured exterior zone. The layer thickness of this zone was 360 μm for 20 mg nifedipine tablets and defined to be the penetration depth of light (Fig. 8).

Earlier studies revealed the influence of drug content on the rate of photodegradation [5]. The effect of drug content on the penetration depth was studied with nifedipine tablets of varying contents (4–20 mg). Table 1 summarizes the results. Lower nifedipine contents led to deeper penetration of light into the tablets.

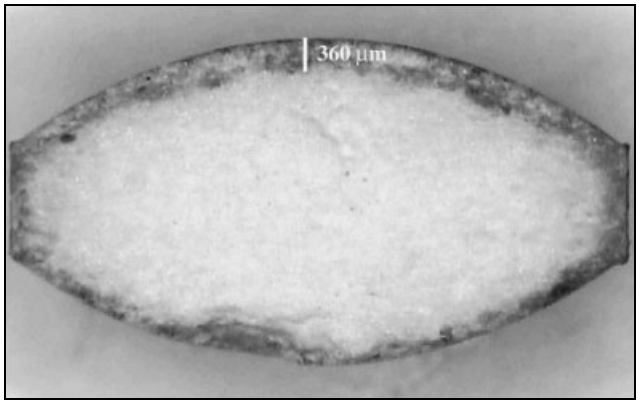

Fig. 8: Cross-section of an irradiated nifedipine 20 mg tablet (Suntest CPS+, 12 h, 720 W/m^2, UV filter)

Table 1: Influence of drug content on light penetration and drug loss in nifedipine tablets (Suntest CPS+, 12 h, 720 W/m^2, UV filter)

Drug content/tablet	Penetration depht of light	Drug loss
20 mg	360 µm	−32%
10 mg	670 µm	−40%
4 mg	880 µm	−55%

2.4. Particular photodegradation of molsidomine tablets

Irradiation of molsidomine tablets lasts longer and yields higher drug losses than in any other known tablet formulation, including highly light sensitive nifedipine tablets. This is amazing since for tablets the destructive influence of light should be restricted by the reflection and absorption of the excipients. Molsidomine is a low dosed drug and the relative content in the tablet formula was only 1.8%. This unique light sensitivity could therefore not be deduced from other data. It was assumed that probably the degradation products might be the reason for this phenomenon.

The mechanism of the photolytic degradation of molsidomine is not completely known. For solution gaseous degradation products like carbon dioxide and nitrogen are described [6]. There were no direct methods to detect the formation of those gaseous substances after irradiation of solid molsidomine. Other analytical ways were chosen.

Molsidomine substance was weighed into tiny aluminium pans and tapped to get a homogenous powder layer. After 12 h irradiation the pans were weighed again and the difference of weight recorded. For all trials weigth losses of about 7.5% were determined. An aluminium foil wrapped blank did not show any weight loss after irradiation.

Table 2: Elementary analysis of non irradiated and irradiated molsidomine substance (Suntest CPS+, 12 h, 415 W/m^2, window glass filter)

Element	Initial	Irradiated	Difference
Carbon	44.785%	45.108%	+ 0.323%
Hydrogen	5.832%	5.863%	+ 0.031%
Nitrogen	22.976%	19.561%	− 3.415%
Oxygen (calculated)	26.407%	29.468%	+ 3.061%

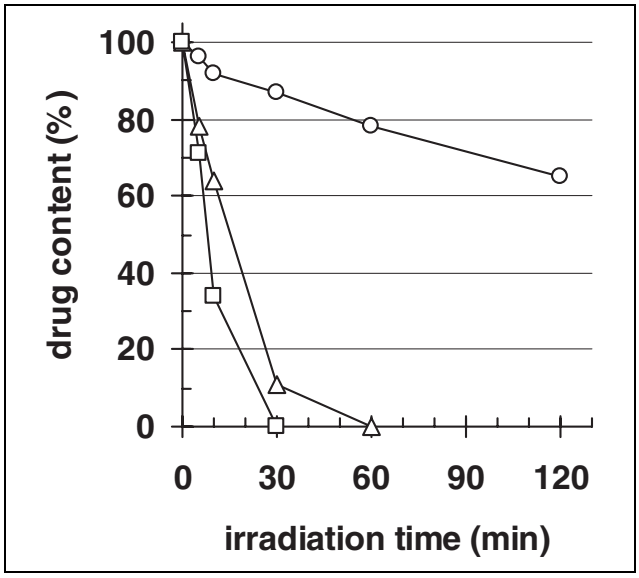

Fig. 9: Influence of solvents on the photodegration of molsidomine (Suntest CPS+, 415 W/m^2, window glass filter) ○ molsidomine substance, △ molsidomine ethanol solution (c = 2 mg/ml), □ molsidomine morpholine solution (c = 2 mg/ml)

CHN analysis revealed signifcant changes of non-irradiated and irradiated molsidomine substance. After light stress the nitrogen part was reduced by 3%, whereas the values for carbon and hydrogen remained the same (Table 2).

The formation of liquid photodegradation products like ethanol and morpholine is known, too [2, 6]. The drug substance is highly soluble in both liquids. It could be demonstrated that molsidomine dissolved in any of this solvents is much more photolabile than the solid (Fig. 9).

Lasting irradiation of molsidomine tablets results in visually noticeable changes of the tablet surface. The homogenous white area of intact molsidomine tablets is disturbed by yellowish stains having diameters of up to 350 µm (Fig. 10).

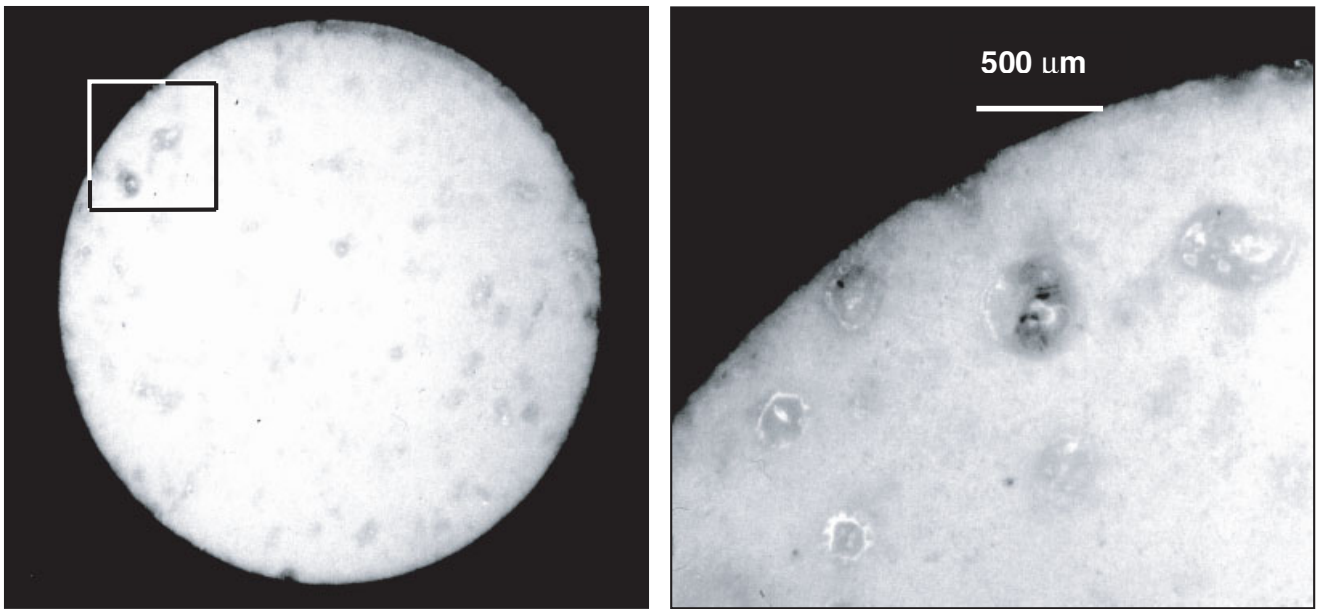

Fig. 10: Surface of irradiated molsidomine 4 mg tablet (Suntest CPS+, 12 h, 415 W/m^2, window glass filter)

3. Discussion

Nifedipine and molsidomine tablets are highly light sensitive drug products. 30 to 50% of the drug may be degraded after light exposure of unprotected tablets. Whereas nifedipine tablets are generally film coated only for this reason, the lack of light protective coating for molsidomine tablets is not understandable from a stability point of view. Complete photostabilisation outside the packaging is possible [7], but it must be attributed to registration hurdles that the authorisation holders do not want to change the formulation.

Especially in the case of molsidomine consequent light protection is essential, since not only the drug potency is reduced, but also a potentially toxic degradation product is formed. After irradiation morpholine was detected in molsidomine tablets [2]. In the acidic enviroment of the gastric liquid and in the presence of nitrite (which is found in food) N-nitroso-morpholine may be formed, which was shown to be cancerogenic in animal experiments [8].

For specific photostabilisation of drug products it is essential to know which part of the light is destructive. In the case of nifedipine tablets it was demonstrated that light up to 500 nm is responsible for photodegradation.

That is deviating from nifedipine solutions, where already light waves above 450 nm had no more harmful effect on the drug product. Those results were in good accordance to the absorption spectrum of the dissolved nifedipine [9].

This deviation can be explained by a bathochromic shift of the nifedipine absorption in the solid state. Absorption of longer waves results in photosensitivity to a wider light range, since light absorption is the prerequisite to photodegradation.

Especially the range between 400 and 420 nm is crucial for the photoinstability of nifedipine tablets. It is only after eliminating ligth below 420 nm that the degradation is reduced. Additional UV parts of the light below 400 nm did not increase photodegradation. These results are conforming to the outcomes of a Japanese working group, who noticed the highest light sensitivity of nifedipine tablets at 420 nm [10].

Corresponding to its absorption spectrum molsidomine is degraded by UV light only. Dissolved molsidomine absorbs light up to 360 nm. However, molsidomine tablets are degraded even by UV light of 375 to 400 nm. A bathochromic shift in the absorption properties of solid molsidomine needs to be postulated, too. The main destructive effect is exerted by light below 320 nm. Since window glass removes this part of light, consequences for photostability tests should be taken into account. The adjustment of artificial light sources to natural daylight spectrum is clearly demanded in the ICH guideline for photostability testing, the usage of a window glass filter eliminating light below 320 nm possible [3].

The penetration depth of light into tablets is restricted to the exterior zone due to absorption and reflection of the solid material. The drug substance is therefore only partly degraded by light. In general the tablet core remains unaffected. As well for nifedipine tablets as for molsidomine tablets the penetration depth is below 1 mm.

The discolouration of nifedipine upon irradiation enables the precise determination of light penetration into tablets. The penetration depth of 360 μm is equivalent to 33% of the tablet volume. This calculated value of maximum drug degradation corresponds quite well with the experimentally found 32% drug loss. This accordance proves that the discolouration is a reliable parameter for light penetration into nifedipine tablets.

The extent of light penetration depends not only on the absorption and reflection properties of the excipients, but also on the drug load. This has already been demonstrated for drug solutions [2, 11]. For tablets it is equally due to light absorption by the drug itself that the penetration depth of deteriorating light is reduced. In the case of nifedipine this effect is intensified by coloured light absorbing degradation products.

The extremely high photosensitivity of molsidomine tablets is partly due to its degradation products. The formation of gaseous substances upon irradiation is probable, the formation of liquids like morpholine was shown in earlier studies [2]. The loss of nitrogen in elementary analysis may be caused by the formation and the escape of nitrogen gas.

As gases escape from the tablet matrix, they change the structure. Porous "light channels" may be the consequence, giving the light a chance to penetrate deeper. A look on the irradiated tablet clearly shows the structural changes.

As ethanol and morpholine are not only degradation products, but also solvents of molsidomine, drug substance may be dissolved. We all know from chromatographic processes that a dissolved substance is mobile even in a solid matrix. Migration processes may transport drug substance from normally unaffected to irradiated areas of the tablet. Furthermore it was shown, that the photodegradation of molsidomine is much higher in solutions than in the solid state.

Another contrast to nifedipine tablets is the fact that the degradation products of molsidomine do not absorb light above 300 nm [6]. Therefore protection by spectral overlay, as it is the case for nifedipine products, cannot be expected for molsidomine preparations.

Xenon light irradiation represents massive light stress, which is unlikely to happen during practical usage. Tests with artificial room light are therefore nearer to practice and might be helpful for handling and storage recommendations to the customer.

Since unprotected nifedipine tablets are very sensitive even to room light, their storage outside of the packaging, e.g. in transparent boxes for facilitating multiple application of drugs, is not recommendable for stability reasons. One should keep in mind that there are uncoated nifedipine tablets on the market, which are light protected by an aluminium mono blister only.

Coated tablets must not be divided.

Molsidomine tablets are much less photolabile at room light than at daylight. The main reason is not only the lower irradiance, but also the low UV part of fluorescent lamps. However, photodegradation is still existing at room light and unprotected storage should be avoided.

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 (Lehmann und Voss, Hamburg, Germany) lactose (Meggle, Wasserburg, Germany), corn starch (Cerestar, 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 following formulae (Table 3):

Table 3: Composition of the tablets investigation

	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

Tablets were round with a diameter of 8 mm. They were pressed on a single punch eccentric tabletting 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 und red (long-wavelength) light to avoid photodegradation (European Phamacopoeia 2002).

4.2.2.1 Artificial daylight

The tablets 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 tablets or window glass filter for molsidomine tablets were installed to adapt the spectrum of the artificial light source to natural daylight.
Irradiance was set to 720 W/m^2 (nifedipine tablets) respectively 415 W/m^2 (molsidomine tablets).

4.2.2.2 Artificial room light

The tablets were irradiated in the light testing cabinet of Thoma and Strittmatter. The light source consisted of 6 fluorescent tubes Osram L 20 W daylight 5000 de Luxe. Irradiance was 12 W/m^2. Distance light source sample tray was 90 cm. A cooling fan kept the temperature below 25 °C.

4.2.3. HPLC

The HPLC system consisted of an 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 tablets

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 µ 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 tablets

The mobile phase was prepared by mixing 200 ml of acetonitrile with 800 ml of ammonium formiate buffer 20 mmol/l pH 6.7. A 250 × 4 mm 5 µ 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.

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