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The influence of formulation and manufacturing process on the photostability of tablets

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Abstract

The formulation and the manufacturing process can significantly influence the photostability of tablets. Investigations of various formulation and manufacturing parameters were done with tablets containing nifedipine and molsidomine as highly light sensitive drugs. The effect of relevant formulation factors are stated. Whereas the particle size of the drug substance and the choice of the lubricant had no effect, the drug content, the compression diluent and geometric alterations significantly affected the photoinstability. Depending on the formulation drug losses varied between 30 and 55% after 12 h irradiation in a light testing cabinet (Suntest® CPS +). Manufacturing parameters like compression force and direct compression versus granulation showed less serious influences. Nevertheless, photostability changes up to 10% were registered.

Keywords: Photostability; Tablets; Nifedipine; Molsidomine; Formulation; Manufacturing process

1. Introduction

The light sensitivity of drug substances in solid preparations is poorly investigated. That is mainly due to the smaller extent of photodegradation of drugs in the solid state than in solution.

However, increasing interest in this matter is evident since the number of light sensitive drugs is growing and the ICH states that photostability testing should be an integral part of stress testing (ICH, 2002).

Some studies have been undertaken on the photostabilization of tablets by adding light absorbing substances (Thoma and Klimek, 1991; Thoma and Aman, 2002) or film coating (Teraoka et al., 1989; Matsuda et al., 1978), respectively. Curiously enough about the influence of formulation parameters like choice of excipients and the particle size of the drug substance no published work is known, although it is well known that the formulation is of great importance for the stability of drug products.

Therefore, it was the objective of this study to evaluate possible factors of tablet formulation and manufacturing process on the photostability of light sensitive drugs in tablets. The investigations were carried out with nifedipine and molsidomine tablets, since both substances reveal high light sensitivity even in the solid state.

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2. Materials and methods

2.1. Materials

Nifedipine Ph.Eur. (supplied by Stada, Bad Vilbel, Germany and Haupt-Pharma, Wolfratshausen, Germany), molsidomine Ph.Eur. (supplied by Haupt-Pharma, Wolfratshausen, Germany and Heumann, Nürnberg, Germany). Avicel® PH 101 (Lehmann und Voss, Hamburg, Germany), Lactose EP D 80 and Tablettose® (Meggle, Wasserburg, Germany), Starch® 1500 (Colorcon, Königswinter, Germany), corn starch (Cerestar, Krefeld, Germany), Aerosil® 200 (Degussa, Frankfurt, Germany), magnesium stearate and stearic acid (Caelo, Hilden, Germany), Precirol® Ato 5 (Gattefossé, Weil am Rhein, Germany).

2.2. Methods

2.2.1. Preparation of tablets

Nifedipine and molsidomine tablets were prepared according to the following basic formulae (Table 1).

Molsidomine tablets were also prepared using alternative excipients as diluents or lubricants, listed in Table 2. When testing different diluents, the compression diluent as well as the diluent were totally replaced. For this purpose directly compressible grades of diluents were used. Differences in the formula percentage for testing various lubricants were compensated by adjusting the diluent concentration.

Table 1
Basic formulae for nifedipine and molsidomine tablets

	Nifedipine tablets (20 mg)	Molsidomine tablets (4 mg)
Drug substance	9.0%	1.8%
Compression diluent	40.0%	40.0%
Diluent	44.5%	51.7%
Disintegrant	5.0%	5.0%
Flow promoter	0.5%	0.5%
Lubricant	1.0%	1.0%
Tablet weight	222 mg	222 mg

Table 2
Alternative excipients for the manufacture of molsidomine tablets

Function	Investigated excipients
Diluent	Avicel® PH 101; Tablettose®; Starch® 1500
Lubricant	Magnesium stearate; glycerolpalmitostaerate; stearic acid

For wet granulation of molsidomine tablets the formulae listed in Table 3 were used.

The tablets were biplanar and round with a diameter of 8 mm. They were pressed on 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 under red (long-wavelength) light to avoid photodegradation (European Pharmacopoeia, 2002).

Water content (Karl–Fischer method) of directly compressed molsidomine tablets was found to be 4.9%.

2.2.2. Irradiation of tablets

The tablets were irradiated in the light testing cabinet Suntest CPS+ (Atlas, Gelnhausen, Germany). UV special filter for nifedipine tablets or

Table 3
Formulae for the manufacture of molsidomine tablets by granulation

	Watery granulation	Alcoholic granulation
Molsidomine	1.8%	1.8%
Compression diluent	40.0%	40.0%
Diluent	52,2%	50.8%
Disintegrant	5.0%	5.0%
PVP	–	1.4%
Purified water	24.0%	–
Isopropanol	–	28.0%
Magnesium stearate	1.0%	1.0%
Tablet weight	222 mg	222 mg

window glass filter for molsidomine tablets, respectively, were installed to adapt the spectrum of the artificial light source to natural daylight.

Irradiance was set to 720 W/m^2 (nifedipine tablets) or 415 W/m^2 (molsidomine tablets), respectively.

The cooling aggregate VPC 075E WESTYone (White Westinghouse, Milan, Italy) was linked and kept the temperature below 25 °C. Control samples wrapped with aluminium foil were added to exclude thermal effects.

Tablets, six for each testing point, were placed in petri dishes. If the standard deviation was $> 3\%$, the whole testing was repeated. During irradiation the tablets were not turned. The petri dishes were lined with aluminium foil to avoid irradiation of the tablet underside by reflection of the bottom of the light testing cabinet.

2.2.3. HPLC analysis

2.2.3.1. Sample preparation. All steps of sample preparation were done under red light to avoid photodegradation (European Pharmacopoeia, 2002).

Nifedipine tablets. One tablet each was put into a 250 ml brown glass volumetric flask containing approximately 200 ml solvent. After 15 min of ultrasonic treatment and cooling to room temperature the volumetric flask was filled to 250 ml with the solvent. As solvent an ethanol–water mixture (1:1) was used. Samples were filtered prior to HPLC analysis. Drug recovery was found to be 100.1%.

Molsidomine tablets. One tablet each was put into a 100 ml brown glass volumetric flask containing approximately 80 ml solvent. After 15 min of ultrasonic treatment and cooling to room temperature the volumetric flask was filled to 100 ml with the solvent. As solvent an ethanol–water mixture (1:4) was used. Samples were filtered prior to HPLC analysis. Drug recovery was found to be 99.6%.

Powders. Drug powders were irradiated in tiny aluminium cups, like used for differential scanning calorimetry. For each testing 10 mg drug powder were analytically weighed into the cups, tapped for various times to result in a homogenous powder bed of 1 mm height. After irradiation the whole cup was put into a partly prefilled volumetric flask. Further sample preparation was the same as described for the tablets.

2.2.3.2. Analytical methods. 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).

3. Results

3.1. Influence of particle size

Nifedipine 20 mg and molsidomine 4 mg tablets were prepared by using two drug substance batches of different particle sizes. The mean diameter (Feret) of nifedipine particles was 25 or 220 μm, respectively, of molsidomine particles 100 or 180 μm, respectively.

Irradiation of 100% drug powders of different particle sizes revealed marked differences of the photostability. After 2 h irradiation drug losses were about 5–10% higher in the finer powders (Fig. 1A and Fig. 2A).

However, after incorporating drug powders into tablets no influence of the particle size on the photostability could be deduced from the results. Nevertheless, the photodegradation of nifedipine and molsidomine tablets was extraordinarilly high: more than 30% of the initial drug content were decomposed after 12 h light exposure (Fig. 1B and Fig. 2B).

3.2. Influence of drug content

The decomposition rates of nifedipine and molsidomine solutions are decreased by higher drug concentrations (Thoma and Klimek, 1985; Thoma and Kerker, 1992). This phenomenon is due to light absorption by the drug substance itself, protecting the molecules in the inner area of the reaction volume. No such investigations have been carried out for tablets.

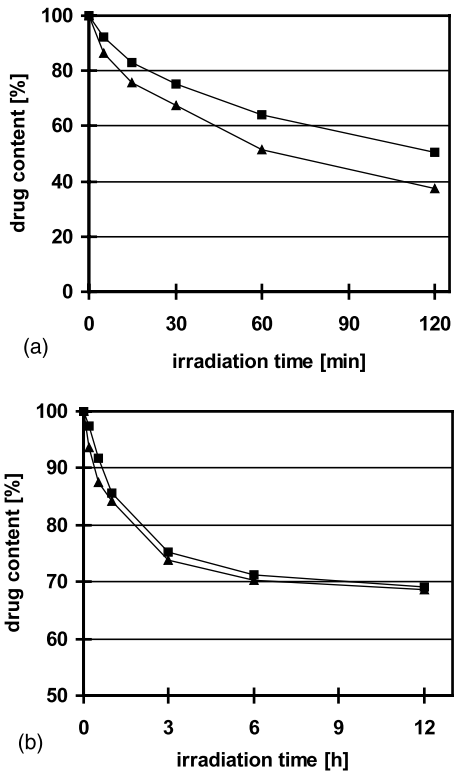

Fig. 1. Influence of particle size on the photostability of nifedipine preparations (Suntest CPS+, 720 W/m^2, UV special filter). A, nifedipine powder; B, nifedipine tablets 20 mg (biplanar, $d = 8$ mm); ■, 220 μm; ▲, 25 μm.

Nifedipine and molsidomine tablets with drug contents varying from 4 to 20 mg were prepared (neglecting the purity value). The volume and the weight of the tablet remained unchanged. Different amounts of drug substance were compensated by the diluent.

For both drugs similar results were obtained: comparably with solutions the photoinstability of nifedipine and molsidomine tablets decreases by increasing the drug content.

This effect is more pronounced for nifedipine tablets. After 12 h irradiation 54% of the drug were destroyed within the 4 mg tablets, 40% within the 10 mg tablets, and only 31% within the 20 mg tablets (Fig. 3A).

Drug losses of molsidomine tablets differed only by a maximum of 10%, depending on the drug content (Fig. 3B).

Regarding the drug degradation not relatively to the initial drug content, but as the absolute loss of drug amount, the result is twisted. The higher the drug content the higher was the absolute loss of drug amount (Fig. 3C, D). In nifedipine 20 mg tablets 6.3 mg, in molsidomine 20 mg tablets 4.6 mg of the drug substance were finally degraded, which is in each case more than the total available amount of the tablets with the lowest concentration (4 mg).

3.3. Influence of tableting excipients

3.3.1. Diluent

The compression diluent had the most noticeable effect on the photostability of the tablets, possibly due to to its high concentration in the tablet formulation.

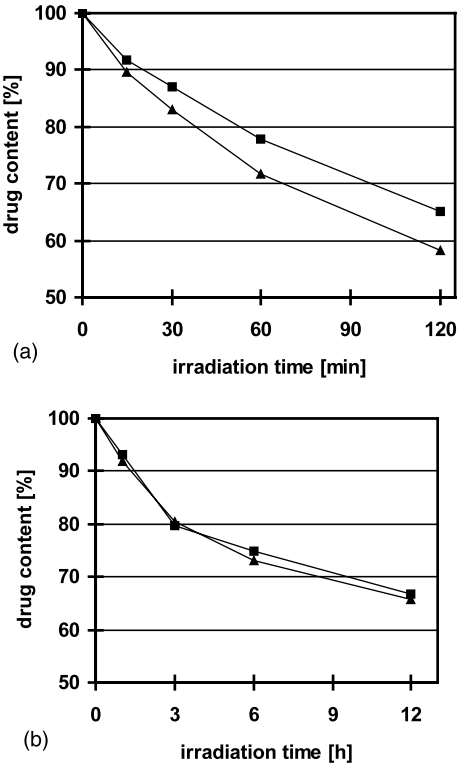

Fig. 2. Influence of particle size on the photostability of molsidomine preparations (Suntest CPS+, 415 W/m^2, window glass filter). A, molsidomine powder;B, molsidomine tablets 20 mg (biplanar, $d = 8$ mm); ■, 220 μm; ▲, 25 μm.

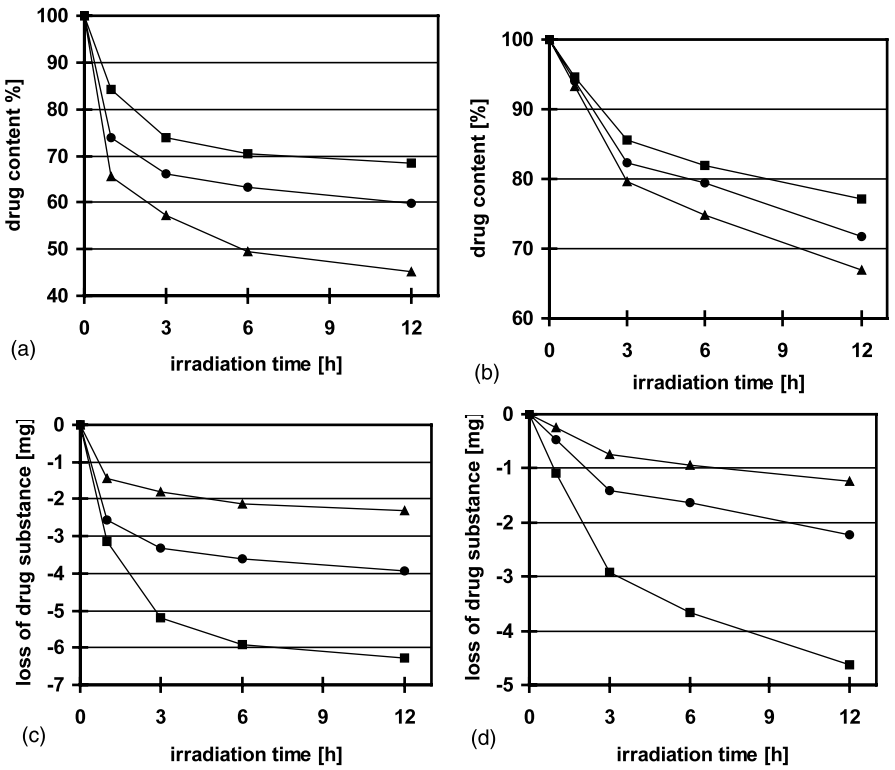

Fig. 3. Influence of the drug content on the photodegradation of tablets. A, B, relative drug loss;C, D, drug amount decomposed; A, C, nifedipine tablets (biplanar, $d = 8$ mm) (Suntest CPS +, 720 W/m^2, UV special filter); ■, 20 mg;●, 10 mg; ▲, 4 mg; B, D, molsidomine tablets (biplanar, $d = 8$ mm) (Suntest CPS +, 415 W/m^2, window glass filter); ■, 20 mg; ●, 10 mg;▲, 4 mg.

Molsidomine 4 mg tablets were prepared by using three different compression diluents: microcrystalline cellulose (Avicel® PH 101), lactose (Tablettose®) and modified starch (Starch® 1500). To avoid granulation directly compressible grades were used.

As can be seen from Fig. 4 the compression diluent had a significant effect on the photostability of molsidomine tablets. In tablets prepared with microcrystalline cellulose the residual amount of molsidomine was 68% after 12 h irradiation, whereas in lactose tablets only 61% of the drug substance remained intact. The lowest photostability was observerd with tablets made of modified starch. Only 50% of the initial molsidomine content was found after the same light exposure.

3.3.2. Lubricant

Magnesium stearate is one of the most common lubricants in tablet formulations. However, it is not suitable for each drug substance due to the potentially negative influence on drug stability, e.g. acetylsalicylic acid tablets should not be for-

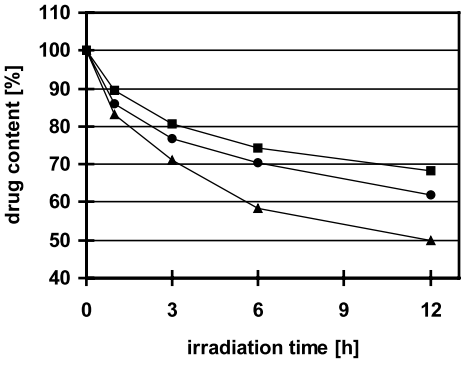

Fig. 4. Influence of the compression diluent on the photostability of molsidomine tablets 4 mg (biplanar, $d = 8$ mm) (Suntest CPS +, 415 W/m^2, window glass filter). ■, Microcrystalline cellulose; ●, lactose; ▲, modified starch.

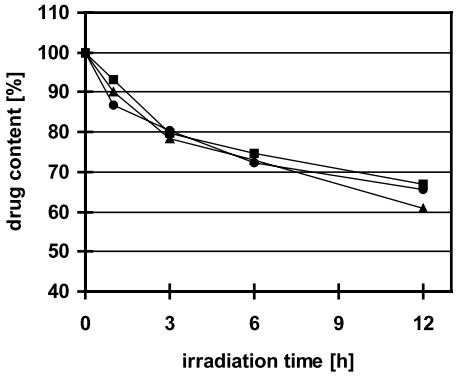

Fig. 5. Influence of the lubricant on the photostability of molsidomine tablets 4 mg (biplanar, $d = 8$ mm) (Suntest CPS+, 415 W/m^2, window glass filter). ■, Magnesium stearate; ●, glycerolpalmitostearate; ▲, stearic acid.

mulated with magnesium stearate because of the increased danger of hydrolysis (Haag, 2001).

Investigations of molsidomine solutions at different pH values showed a decreased photostability in acid solutions compared with neutral and alkaline solutions (Thoma and Klimek, 1985).

As lubricants for molsidomine tablets magnesium stearate, glycerolpalmitostearate and stearic acid were used, representing an alkaline, a neutral and an acidic substance. They had to be added at different concentrations since their lubricating efficacy is not the same: magnesium stearate 1%, glycerolpalmitostearate 2%, stearic acid 3%. The different amounts were compensated by adjusting the diluent.

The influence of the lubricant on the photostability of molsidomine tablets was not significant. Photodecomposition was similar with each formulation, resulting in a drug loss of 35–40% after 12 h light exposure (Fig. 5).

3.4. Influence of the tablet geometry

3.4.1. Diameter

Usually the diameter and size of tablets depend on the drug content. Since molsidomine is a low dosed drug, tablets of 5, 8 and 12 mm in diameter could be prepared. In each case biplanar round tablets containing 4 mg molsidomine were pressed. The tablet weight was adopted to its diameter (to 60 mg for the 5 mm tablets, and to 500 mg for the 12 mm tablets).

The relative composition of the tablet excipients remained the same.

By increasing the diameter the photostability of molsidomine tablets was improved. The effect was a minor one, but nevertheless significant. After 12 h irradiation 72% of the drug were undecomposed in 12 mm tablets, whereas the residual amount of 5 mm tablets was only 65% (Fig. 6).

3.4.2. Shape

Irradiation of biconvex tablets gives higher photodegradation than of biplanar tablets (both 8 mm in diameter). However, the difference was only 3% (Fig. 7).

3.5. Influence of compression force

The compression force determines the final volume and, therefore, the porosity of tablets (at constant tablet weight).

Molsidomine tablets were pressed at different compression forces. The porosity was calculated from the measured values of absolute density and apparent density (Eq. (1)).

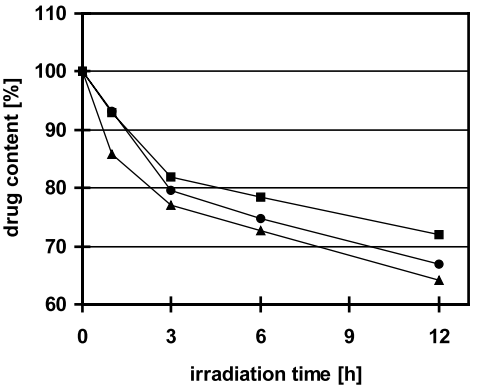

Fig. 6. Influence of the diameter on the photostability of molsidomine tablets 4 mg (biplanar) (Suntest CPS+, 415 W/m^2, window glass filter); ■, 12 mm (tablet thickness 3.7 mm); ●, 8 mm (tablet thickness 3.3 mm), ▲, 5 mm (tablet thickness 1.7 mm).

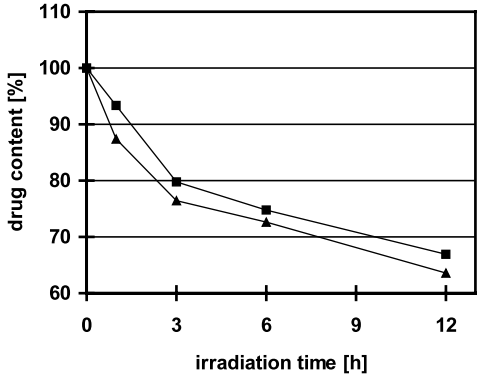

Fig. 7. Influence of the shape on the photostability of molsidomine tablets 4 mg (biplanar, $d = 8$ mm)) (Suntest CPS+, 415 W/m^2, window glass filter). ■, Biplanar; ▲, biconvex.

$$\text{Porosity [\%]} = (\text{Absolute Density} - \text{Apparent Density}) \times /\text{Absolute Density} \times 100 \quad (1)$$

The porosities of the tablets were 27.5% at a compression force 3.5 kN, 14.0% at 9.0 kN and 8.0% at 21.0 kN. With the compression force the tablet thickness was altered. It varied from 3.7 to 3.0 mm.

As the irradiation test revealed, the photostability of molsidomine tablets decreased with increasing compression force. After 3 h irradiation only 12% of the drug were destroyed when tablets were prepared at 3.5 kN, whereas more than 20% were degraded when compression forces of 9.0 and 21.0 kN were chosen (22 and 24%, respectively) (Fig. 8).

3.6. Preparation method

Molsidomine tablets can easily be prepared by direct compression. However, the influence of granulation on the photostability was investigated.

As granulation liquids purified water or a solution of polyvinylpyrollidone 5% in isopropyl alcohol, respectively, were used.

Water content was found to be 4.9% for directly compressed molsidomine tablets, 5.7% after watery granulation, and 4.8% after alcoholic granulation.

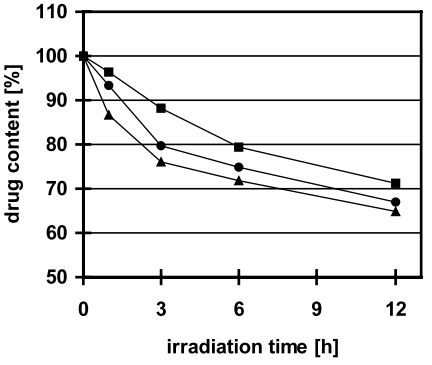

Fig. 8. Influence of the compression force on the photostability of molsidomine tablets 4 mg (biplanar, $d = 8$ mm) (Suntest CPS+, 415 W/m^2, window glass filter); ■, 3.5 kN (tablet thickness 3.7 mm); ●, 9.0 kN (tablet thickness 3.3 mm), ▲, 21.0 kN (tablet thickness 3.0 mm).

Granulation reduced the photostability of molsidomine tablets. Whatever the granulation liquid was, the drug loss was about 4% higher than in directly compressed tablets (Fig. 9).

4. Discussion

The particle size had significant influence on the photostability of the drug powders themselves, but not of the tablets. The incorporation of the low dosed drug substances like nifedipine and

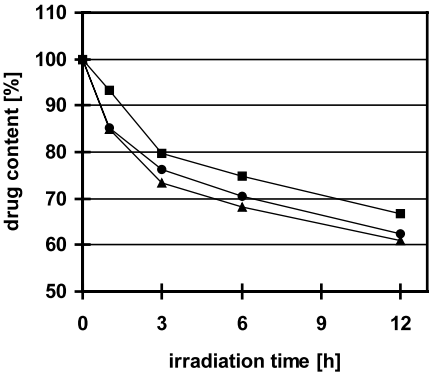

Fig. 9. Influence of the preparation method on the photostability of molsidomine tablets 4 mg (biplanar) (Suntest CPS+, 415 W/m^2, window glass filter). ■, Direct compression; ●, granulation with polyvinylpyrollidone in isopropyl alcohol; ▲, granulation with water.

molsidomine into the tablet matrix diminished the importance of the particle size by surrounding them with excipients. Additionally, the reflection of the smooth tablet surface may contribute to this effect. However, perhaps the particle size plays a role for high dosed drug substances, when the major part of the tablet consists of the active ingredient itself.

The reduced photodegradation of tablets with higher drug contents is only a relative effect. It should not seduce to regard this as a way of stabilization, because the absolute amount of drug loss and, therefore, the amount of degradation products would be higher. This fact has to be considered above all for substances, of which the degradation products hold toxicological risks. That is the case for molsidomine, decomposing to morpholine, which is potentially carcinogenic (Lijinsky et al., 1994).

The effect of drug content on the photostability is stronger for nifedipine tablets than for molsidomine tablets. The reason why is probably due to the light absorption properties of the degradation products. The degradation products of molsidomine do only absorb light below 280 nm (Asahi et al., 1971), which is of no importance for light induced degradation. Nifedipine partly decomposes to strongly colored substances having a photoprotective effect on the drug by absorbing light (Hayase et al., 1994).

As molsidomine test formulations with different tabletting excipients showed, of those excipients tested only the diluent seems to have an influence on the photostability. It is likely, that this influence is due to different refractive indices and not to different chemical properties. Therefore, the effect of an excipient will only be significant for tablets with low drug content and high amount of excipient (diluent). However, this can only be a clue but not a general rule and has to be verified for each drug substance.

The influence of the diameter, resulting in a weaker photodegradation taking place in larger tablets might be due to the increased relative amount of the diluent. Since light penetration in tablets is poor, higher tablet volumes represent a thicker and more effective barrier consisting of diluent.

The higher photodegradation of biconvex tablets compared with biplanar tablets accorded with our expectations. When irradiated, the underside of biconvex tablets is additionally affected by irradiation due to reflection from the bottom of the light testing cabinet.

Surprisingly, higher porosity, meaning more hollow spaces in the tablet, did not support photodegradation. The differences of photostability are probably geometrically reasoned, since the compression force altered the relation of tablet surface to drug content via the band height. By low porosities the drug content is relatively increased in the surface regions of the tablet, which can be reached by light. As a consequence more drug substance can be decomposed.

The diminished photostability of molsidomine tablets after granulation may be caused by the solubility of the drug substance in the granulation liquids. Since the water content was higher in the water granulated tablets (5.7% compared with 4.9%), residual amounts of granulation liquid could have lead to increased photoinstability by partly dissolving the drug. Granulation with a purely alcoholic solution of polyvinylpyrollidone did not significantly change the water content (4.8%), since no water was added. However, the drug activity could have been changed by dissolving and recrystallizing.

Concluding the results it is evident, that—besides of adding stabilizers and/or film coating—the formulation and the manufacturing process are of decisive importance for the photostability of tablets. Based on the results of this study the following parameters should be taken into consideration for the preparation of tablets containing light sensitive drugs: When feasible, the compression diluent should not only be chosen from a technological or commercial, but even from a stability point of view. If therapeutically possible and acceptable the preparation of biplanar tablets with big diameter should be preferred. High compression forces should be avoided. If the drug is soluble in the granulation liquid, tablets should be directly compressed.

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