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Photostabilization of drugs in dosage forms without protection from packaging materials

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Summary

The number of new drugs sensitive to light has been steadily increasing during the course of the last two decades. When enwrapped by the packaging material, the pharmaceutical dosage form is normally well protected from the influence of photodegradation. However, the manufacturer must also take into consideration those periods of time when the dosage forms are not covered by packaging, i.e. both during the process of manufacturing itself and during handling by the consumer/patient on application at home or in hospital. In this respect, the kinetics of degradation are strongly dependent on light intensity and spectral distribution of the light source used; for example, nifedipine solutions undergo 3-fold faster degradation in 'normal' daylight than under exposure to a 40 W light bulb. The instability of nifedipinė corresponds absolutely with its absorption at about 450 nm and beyond. Stabilization with preselected colourants or other appropriate excipients has been successfully demonstrated. This mode of action applies to many drugs, e.g. daunorubicin, dihydroergotamine, haloperidol, furosemide (frusemide) and nitrofurazone, and it is not only feasible for drugs in solution, but also effective in other dosage forms such as tablets or topical preparations. The principle of photoprotection by spectral overlapping is described.

Introduction

Together with heat moisture and atmospheric oxygen, light is an important external factor in drug instability. Pharmacopoeias, e.g. USP XXII (1990), and licensing requirements take this into account by specifying appropriate storage instructions and packaging materials. However, the photostability of drugs is one of those areas largely ignored by pharmaceutical science, although the number of drugs known to be sensitive to light is on the increase (Thoma, 1978). Concerning such investigations (Klimek, 1978), an overview was reported by us in 1985 (Thoma, 1985).

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Materials and Methods

The following apparatus was used: Spectrotest, Original Hanau, Germany (light cabinet, no longer available on the market); Light-bulb: commercially available tungsten lamp (40 W); Acta III UV-Vis spectrophotometer, Beckman Instruments; 'Polarecord E 261 R' Polarographic assay unit Metrohm AG, Herisau, Switzerland.

All laboratory procedures, i.e. preparation of solutions, dilution of solutions, assay of actual drug content, etc., were conducted under red light (Fa. Philips TL 40/15, length 120 cm). All substances were taken into the tests as pharmacopoeial quality grade without any further pretreatment. For further details see the cited references.

Results and Discussion

In the following investigations the effects of photostabilization on dosage forms not protected by packaging materials are described, i.e. during their manufacture or use. As a prerequisite one must follow a stability-indicating analytical method (Thoma and Klimek, 1980).

The degradation kinetics of a photolabile drug show that they depend on both the intensity and spectral distribution of the light source used. In this case, the t_{90} of a nifedipine solution is reached 3-times faster in daylight than under exposure to a light bulb (Fig. 1) (Thoma and Klimek, 1985a). It is very often imagined that UV light in the energy-rich short-wavelength region is the cause of the degradation of drugs. However, a distinct spectral region of visible light is responsible for the photolysis of nifedipine:

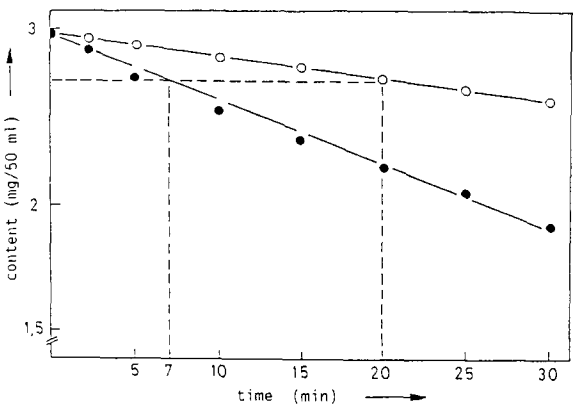

Fig. 1. Effects of light on the degradation kinetics of nifedipine ($c_0 = 1.73 \times 10^{-4}$ mol/l; solvent absolute alcohol). (●———●) Daylight, November $t_{90} = 7$ min; (○———○) light bulb, 40 W, 11 cm distance, $t_{90} = 20$ min.

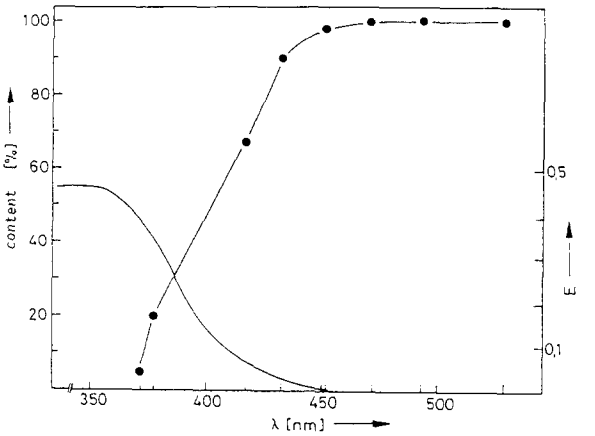

Fig. 2. Influence of the wavelength of the irradiation light on the photolability of nifedipine. (●———●) Dependence of the residual concentration on the wavelength of xenon radiation (left ordinate); (———) long-wavelength section of the nifedipine absorption spectrum (right ordinate).

The left-hand side of Fig. 2 shows the absorption spectrum of nifedipine in the long-wavelength region between about 350 and 450 nm. The right-hand curve compares the range of stability of the dissolved nifedipine with the irradiation wavelength. In each case, the points represent the lower limit of the wavelengths used. The graphs show that the solution is stable down to a wavelength of 475 nm. Photolysis starts exactly at the point where nifedipine absorption begins at 450 nm. Photolysis increases considerably up to about 400 nm. Nifedipine is thus completely degraded by light in the rather long-wavelength region within 10 min. If this wavelength region corresponds to the region of intrinsic instability, it ought to be possible to protect specifically the problem compound.

Fig. 3 demonstrates that by using the natural food colourant curcumin (a constituent of turmeric), the relevant long-wavelength region of nifedipine's spectrum between 300 and 450 nm is well covered. This does not apply to the short-wavelength region below 300 nm. Addition of curcumin in roughly equimolar proportions leads to remarkably good photostabilization by a factor of 60, relative to the half-life in daylight.

Other yellow food colourants can be used to produce similar stabilizing effects. The differences in the effects of stabilization are demonstrated in

Fig. 4. If one plots the decrease in content vs exposure time to daylight, then Fig. 4 clearly shows that three groups can be distinguished, with different stabilization effects:

The upper group demonstrates the influence of the yellow colourants, which covers the long-wavelength nifedipine peak very well or reasonably well.

The middle group consists of yellow and orange colourants which absorb daylight in this critical region only to a limited extent.

The line marked 9 is that obtained with the red colourant Ponceau 4R and Cochineal Red A, which, because it does not absorb at all, shows about the same instability values as those for line

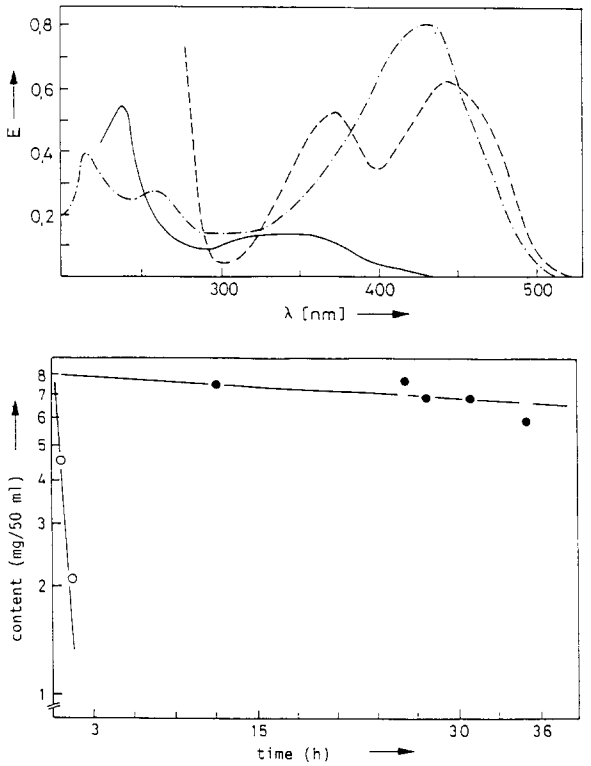

Fig. 3. Light absorption of curcumin (·–·–·) 0.7 mg% and riboflavine - 5′-phosphate Na (— — —) 2 mg%; nifedipine (———) 1 mg% (upper panel). Stabilization of nifedipine solutions with curcumin (E 100). (●———●) curcumin (3.2×10^{-4} mol/l), molar proportion 1 : 0.7; t'_{50} = 5.5 days; (○———○) without curcumin (lower panel).

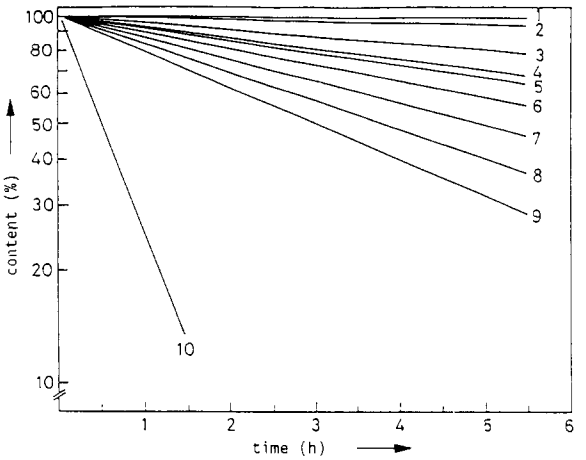

Fig. 4. Comparative investigation of the stabilization of nifedipine solutions with food colourants (radiation source: Spectrotest, $c_o = 4.6\times10^{-4}$ mol/l. (1) Curcumin (3.2×10^{-4} mol/l = 6 mg/50 ml); (2) Fast Yellow (2.9×10^{-4} mol/l = 6 mg/50 ml); (3) Chrysoine (3.7×10^{-4} mol/l = 6 mg/50 ml); (8) Apocarotinal (6 mg/50 ml); (9) Cochineal Red A (2.0×10^{-4} mol/l = 6 mg/50 ml); (10) nifedipine solution without additive.

10, i.e. the unprotected solution of nifedipine (Thoma and Klimek, 1990a).

To what extent can such a protection principle be applied to other drugs?

It is feasible to stabilize the highly light-sensitive, red-coloured cytostatic daunorubicin using red food colourants or other appropriate colourants (Thoma and Klimek, 1990b)

These absorption spectra clearly show that the intense red colour of daunorubicin is based on its light absorption in the region of 370–570 nm (Fig. 5). Fig. 5 also demonstrates that this absorption peak in the long-wavelength region is almost exactly overlapped by the food colourant Scarlet GN. The compounds Amaranth and particularly Ponceau leave the left flank of the peak partially unprotected.

Thus Scarlet GN should provide very good stabilization. With the other two food colourants, stabilization will be less reliable. Tartrazine, a yellow colourant that absorbs only in the short-wavelength region, was also included just for comparison.

Under the given irradiation conditions, the unprotected daunorubicin solution is quickly de-

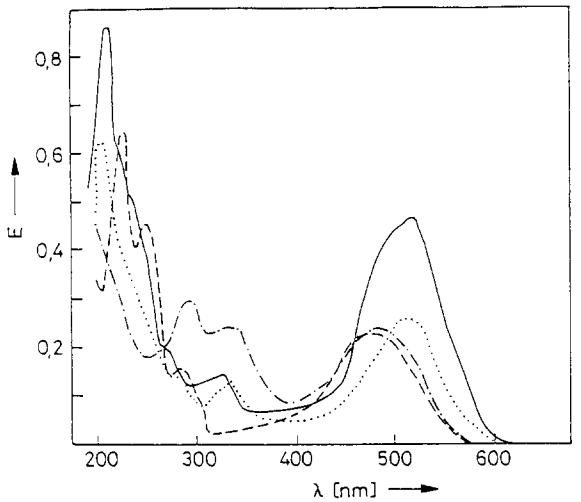

Fig. 5. Absorption properties of the stabilizers of daunorubicin ($c = 2$ mg/100 ml). (———) Amaranth (E 123); (·····) Ponceau 6 R (E 126); (·–·–·) Scarlet GN (E 125); (- - - - -) daunorubicin.

graded. The yellow colourant tartrazine prolongs the t_{90} to an insignificant degree. Ponceau and Amaranth produce better stabilization (Fig. 6). However, the half-life is doubled again to 20-times the initial value with the colouring agent Scarlet GN. This is the only colourant in this test that perfectly covers the crucial region of the daunorubicin spectrum.

How do the many photolabile colourless drugs behave in such investigations? This should be discussed using the photooxidizable dihydroergotamine as a model compound.

Under the influence of light, dihydroergotamine is broken down by photooxidation of the indole ring and other parts of the molecule to form an oxo derivative. Since this substance shows an absorption maximum between 250 and 320 nm, a protective effect should be achievable by using substances that absorb in this region (Thoma and Strittmatter 1990). This can be established for vanillin and methylgallate (Fig. 7).

As is clear from the left-hand section of Fig. 7, the concentration of a non-stabilized solution falls within 5 h by about 75%. Following stabilization with vanillin, only about 10% is degraded over the same period of time. Stabilization with methylgallate prolongs the t_{90} from 5 to over 100 h (Thoma and Strittmatter, 1990).

Addition of stabilizer to a commercial preparation increases the t_{90} from less than 5 to more than 70 h. With methylgallate, its properties as a redox stabilizer also play a role in addition to the

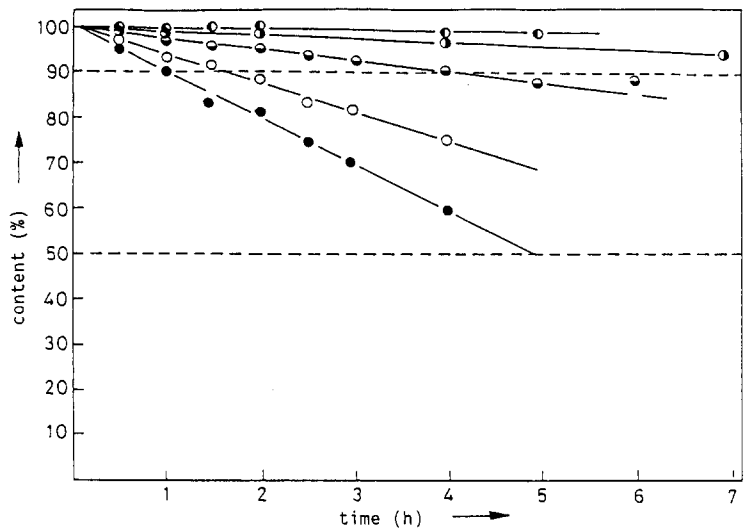

Fig. 6. Stabilization of daunorubicin by colourants (radiation source: Spectrotest, without filter = 700–290 nm; $c_o = 2$ mg/50 ml); (◐) Scarlet GN (E 125), $t_{90} = 19.5$ h; (◑) Amaranth (E 123), $t_{90} = 10.5$ h; (◒) Ponceau 6 R (E 126), $t_{90} = 4$ h; (○) Tartrazine (E 102), $t_{90} = 1.5$ h; (●) without colourant, $t_{90} = 1$ h.

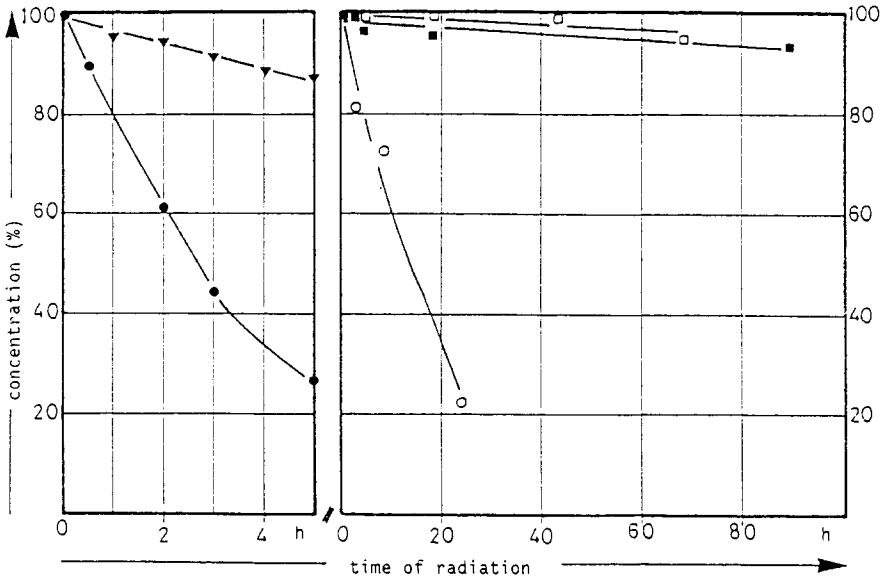

Fig. 7. Rate of degradation of stabilized dihydroergotamine solutions (light testing cupboard, filtered mercury high-pressure lamp). (●———●) Dihydroergotamine methanesulphonate 1 mg/ml in methanol (Stock solution); (▼———▼) stock solution with vanillin added (1 mg/ml); ■———■ stock solution with methylgallate added (1 mg/ml); (○———○) Dihydergot injection solution (1 mg/ml dihydroergotamine methanesulphonate); (□———□) Dihydergot injection solution with methylgallate added (1 mg/ml).

photoprotective action (Thoma and Strittmatter, 1990).

Further investigations have shown that mixtures of stabilizers can produce even greater photoprotection, if they thereby extend the absorption profile.

The three examples given in Table 1 concern proprietary medicinal products with nitrofura-

TABLE 1

Effects of photostabilizers and mixtures thereof on the t_{90} of drugs and proprietary medicinal products under light challenge-testing (mercury high-pressure lamp)

Drug	Photostabilizer	t_{90}	
		Unstabilized	Stabilized
Nitrofurazone 0.2% (ear drop preparation)	curcumin 0.05%	6 h	22 h
Furosemide 1% (injection)	vanillin 1.0%	1.5 h	~ 7 h
Haloperidol 0.5% (injection)	benzyl alcohol and vanillin (each 0.5%)	25 h	> 120 h
Thiothixene 0.2%	quinosol and vanillin (each 0.3%)	3 min	45 min

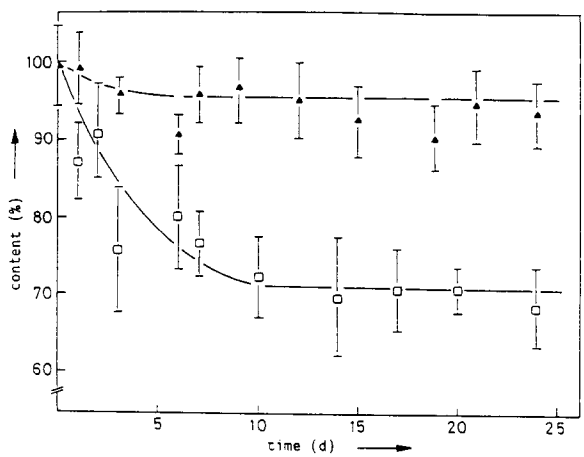

Fig. 8. Stabilization of nifedipine in tablets by Fast Yellow (E 105) (exposure in daylight; $c_0 = 4$ mg/tablet, plotted scatter: RSD; $n \geq 5$). ▲———▲ Colourant in granulate; (□———□) without colourant.

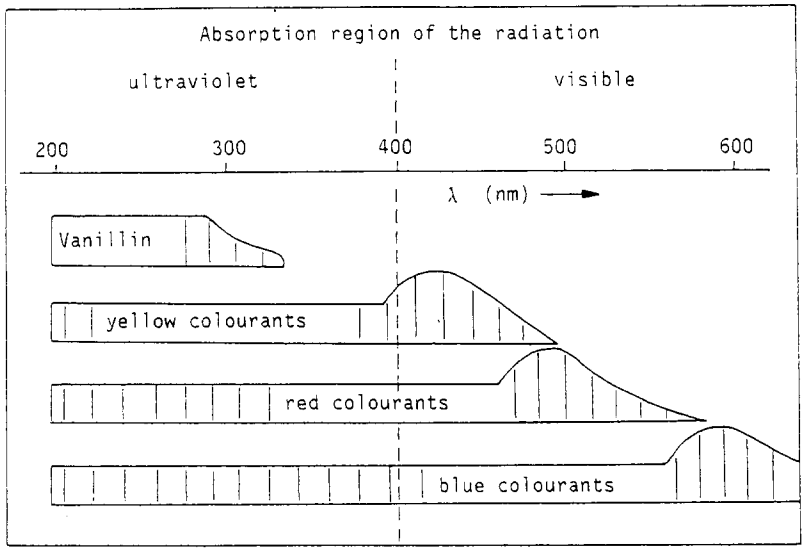

Fig. 9. Principle of photostabilization through spectral overlap with absorbing excipients.

zone, furosemide and haloperidol. The t_{90} of these agents is prolonged by a factor of 4 to 15.

With haloperidol and thiothixene, combinations of stabilizers give the best results (Thoma and Strittmatter, 1990). Such possibilities of stabilizing drugs exist not only for solutions, but also for other dosage forms, like tablets or topical products.

As shown in Fig. 8, through the granulation of nifedipine with Fast Yellow solution, stabilization of the tablets plateaus out at 95% of the content. Without stabilizer, the content falls to about 70% (Thoma and Klimek, 1990a).

As shown by a model experiment, it is also possible to stabilize photolabile gels in a suitable manner (polyacrylate gel with curcumin E100): The t_{90} of nifedipine is 12 min only, whereas with E100 one can work 5-times longer (= 60 min) on the safe side. Other excipients can also contribute to photoprotection according to the same principle. For example, this applies to Polysorbate 20 (Thoma and Klimek, 1985b).

Conclusions

The above-described technique of photoprotection for light-sensitive drugs is based on finding suitable stabilizers with absorption spectra that overlap that of the respective drug. In the ultraviolet region, these may be substances with benzene rings and suitable ligands; with yellow, red or blue drugs, suitable food colourants have proved effective (Fig. 9). (Thoma and Klimek, 1981).

If necessary, photoprotection of highly light-sensitive drugs can actually be incorporated into the dosage form, before further protection is given by packaging materials.

In order to carry out all these stability tests in a reproducible manner, one must pay attention to a number of essential light equipment parameters such as light intensity, wavelength region, influence of temperature, distance from sample to light source, starting concentration, geometric properties of the test flask, test flask material etc. (Thoma and Klimek, 1990c).

Acknowledgement

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