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# THE THERMAL AND PHOTOSTABILITY OF SOLID PHARMACEUTICALS
## A review

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## Abstract

Drugs degrade to different extents on separate exposure to heat, moisture, oxidation and light. Combination of these stresses causes very complex behaviour. Many studies have been reported of the thermal behaviour of drugs in the solid-state, but most of the information available on the photodegradation of drugs refers to reactions in solution, (usually aqueous) and photoreactions in the solid-state are even more complex. In drug formulations, the presence of excipients adds further complications because the excipients may increase, have no effect on, or decrease the inherent stabilities of the drug. The literature has been explored to review the thermal and photostabilities of solid pharmaceuticals.

**Keywords:** drugs, kinetic analysis, pharmaceuticals, photostability, thermal analysis, thermal stability

## Introduction

The stability of drugs towards heat, moisture, oxidation and exposure to light is a topic of great practical interest but of considerable complexity [1, 2]. Thermal stability is the simplest to assess, generally by use of the techniques of thermal analysis (TA) [3–5]. Comparison of TA experiments done using inert and oxidising atmospheres provides information on the susceptibility of the drug to oxidation. Addition of controlled amounts of water vapour to the purge gas allows a quantitative study of hydrolysis. TA methods may also be used to study possible drug-excipient interactions [6].

Because TA experiments are effectively accelerated testing methods, it is usually necessary to extrapolate the results obtained to the lower temperatures encountered in actual storage and use, if the behaviour of the drug is to be predicted. Such extrapolations require reliable kinetic information concerning the higher temperature reactions and knowledge of any intervening phase changes that could invalidate the predictions [7, 8]. In drug formulations, the presence of excipients further compli-

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cates thermal behaviour. New phases, including eutectics and solid solutions, may be formed on heating, while chemical interactions, including host-guest complexation [9] are also possible.

Some attempts have been made [10] to correlate the fragmentation patterns obtained using the pyrolysis probe of a mass spectrometer with the mechanism of thermal degradation, but the conditions existing are so different that such comparisons can only serve as a guide to the possibilities that exist. The problems of predicting the thermal behaviour of an untested compound from the existing information on related compounds have been discussed [11].

Photostability is usually tested using different, dedicated techniques, although differential photocalorimetry [5, 12] shows promise for the study of combined effects of heat and radiation.

The term 'photostability' includes not only the degradation caused by exposure to light, but also processes such as radical formation, energy transfer and luminescence [13]. Drugs can also be photoreactive after administration to a patient.

The photostability of a substance will depend upon the wavelength, the intensity and the time of exposure to the radiation, as well as a variety of physical factors such as the type, shape and orientation of the sample holder. These factors are all incorporated in the radiation dose, which is usually determined by actinometry using a standard sample [14, 15]. From a practical point-of-view, the conditions used for testing of photostability may be far removed from those to which a typical drug or drug formulation will be exposed. It can however be presumed, that if the substance is stable under the exaggerated conditions, it will not be affected by lesser stresses. Evidence for photodegradation under extreme conditions (forced degradation [16]) alerts a researcher to the need for additional testing under more realistic conditions, and can provide a basis for development of analytical methods for determining potential photodegradants. Such studies can also be of value in the interesting field of protecting drugs against photoreactions [17].

A related area of interest is the investigation of damage caused in solids in general and in solid drugs in particular, by a wider range of types of radiation, including γ- and X-rays. An example of such a study is that of El-Ries and Abou Sekkina [18] on the thermal stability of γ-irradiated tolbutamide.

Albini and Fasani [17] have listed the functional groups in drug molecules that are expected to introduce photoreactivity. They do warn, however, of the dependence on conditions. Greenhill and McLelland [19] have provided a comprehensive review of the photodecomposition of solutions of drugs and Greenhill [20] has discussed the prediction of photosensitivity for a wide range of drugs. There is not the same capacity for predicting thermal behaviour. Greenhill and McLelland [19] have also discussed the difficulties of classifying the large amount of information on the photoreactions of drugs. After considering the options of: (*i*) types of photoreaction; (*ii*) the therapeutic action of the drug; and (*iii*) the molecular type of the photoreactive compound, they used option (*iii*) but provided a table of the types of photodegradation covered. (Table 1 for the reaction types. Examples of each are given in the original reference.) Glass *et al.* [21] have explored the interesting general

question of whether a relationship exists between the photoreactivity and the therapeutic activity of a drug, by examining a group of related phenothiazines. These limited results suggested a correlation between photostability and the molecular structure and in this case the therapeutic activity.

**Table 1** Types of photoreactions of drugs [19]

| | |
|---|---|
| Cyclization | Hydroxylation |
| N-Dealkylation | Isomerization |
| Decarbonylation | Oxidation |
| Decarboxylation | Rearrangement |
| Dehalogenation | Reduction |
| Dehydroxylation | Ring dealkylation |
| Dimerization | Sensitization |
| Hydrolysis | |

Photodegradation in solution, particularly in aqueous solution, is likely to differ considerably from photodegradation in the solid-state. Secondary reactions of primary photoproducts with the solvent can result in the formation of species that are not possible in the solid-state. For solid samples, only a limited portion of a static sample will actually be exposed to the radiation, in contrast to the more uniform conditions existing during thermal treatments. Thoma [22] has given an excellent review of some of the special features of photodegradation of drug dosage forms in the solid-state. Particle size and surface area are important, as are colour and crystal structure. Amorphous forms often behave very differently from crystalline forms and different crystalline polymorphs can be expected to behave differently [23]. Photodimerization or isomerization are also possibilities. In a solid drug formulation, the amount of the actual drug exposed may be very small. Much depends upon the transparency of the photoproducts to the radiation being used [24]. If the photoproducts are strong absorbers, only limited overall reaction will occur. The radiation to which a sample is exposed may be reflected, scattered, transmitted or absorbed. Only the absorbed radiation participates in photodegradation. Because of the dilution and other possible shielding effects of excipients, the influence of the radiation is usually decreased in their presence, but enhanced degradation may occur in the presence of some excipients, which can act as photosensitizers by being better absorbers of radiation at the wavelength used. Such substances may transfer energy to the drug with or without undergoing degradation themselves. A quencher is a substance added to a formulation to react with any photochemical intermediates, ideally to produce harmless products. Thoma and Kerker [25] have studied the photostability of 60 commercial preparations of nifedipine. Different preparations showed different photostabilities. Stability was increased by protective measures such as storage of capsules or tablets in suitable blisters.

The formulation and the process for manufacturing tablets can have significant influences on the photostability of drugs [26] Aman and Thoma used tablets containing the highly light-sensitive drugs, nifedipine or molsidomine. The particle size has a considerable effect on the photostability of the drug powders themselves, but incorporation of low doses of the drugs in tablets led to such effects being undetected in the presence of the high proportions of excipients and the reflective tablet surfaces. Tablets can be photostabilized by addition of light-absorbing compounds or by film coating [27].

Absorption of radiation will usually lead to increases in surface temperatures. In extreme cases, thermal and photochemical processes may occur almost simultaneously in the surface region, with heat transfer producing some thermal degradation deeper in the sample. If very mobile photochemical intermediates are formed in the surface, they may diffuse inwards and react further. The overall photochemical process may also be sensitive to the presence of moisture and/or oxygen.

Moore [28] has listed the main considerations involved in photodegradation studies of drugs as: (*i*) whether the drug is stable in a particular formulation and container; (*ii*) whether degradation depends upon the wavelength range of the source; (*iii*) identification of the photodegradants, and (*iv*) the influences of factors such as oxygen, pH, additives and impurities upon the rate of photodegradation.

In assessing the possibility of photodegradation of a substance, it is useful to compare the extent of overlap of the emission spectrum of the light source with the absorption spectrum of the substance, modified by any intervening absorbing layer, such as glass [29]. Although photodegradation cannot occur without absorption of radiation, the outcome of such absorption need not be degradation.

The ICH guidelines on photostability are reproduced in [30] and discussed by Helboe [31]. These guidelines attempt to define the type of light source(s) to be used, the number of batches to be tested, the exposure to be used and means of measuring this exposure. Advice is also given on interpretation of results. Tests need to be carried out on the drug substance itself, the drug formulation and the product in its packaging. The sample temperature during exposure needs to be controlled or compensated for by including a dark control sample in the same environment. D65 is the internationally recognized standard light source for 'outdoor daylight' and ID65 the standard for 'indoor indirect daylight'. Depending on the results achieved from analysis of the drug substance in the formulation, intermediate pack and marketing pack, special labelling, repackaging or reformulation may be required.

## Kinetic aspects

*Rate equations*

Most kinetic studies of the thermal and the photodegradation of drugs have been carried out in solution. First- or zero-order rate equations have often been used to describe the results. If $\alpha$ is used to represent the fractional degradation of the drug, then an $n^{th}$ order rate equation is of the form:

$$\text{Rate} = v = -\mathrm{d}\alpha/\mathrm{d}t = k\,(1-\alpha)^n$$

where $k$ is the rate coefficient. In thermal studies $k$ is a function of temperature (usually the Arrhenius equation, see below, is used) and in photostudies $k$ may include a function of the intensity of the radiation. Logan [32] has shown how the rate of a photochemical reaction can appear to follow an apparent order of reaction model, where values of $n = 0$ or 1 result from differences in the experimental conditions used, and has suggested that the quantum yield (see below) is a more meaningful kinetic parameter than a rate coefficient based on an apparent order of reaction.

If $\alpha$ is small, $v \approx k$ (i.e. zero-order behaviour, with the initial approximately linear part of a deceleratory $\alpha$ – time curve giving an estimate of the rate coefficient, $k$). When, however, the $\alpha$ – time curve is s-shaped (sigmoid) rather than deceleratory, such an assumption does not hold. There are several interpretations of sigmoid curves, but, in solution, these curves are usually regarded as indicating autocatalysis by an intermediate or product. In the simplest form:

$$\text{Rate} = v = -\mathrm{d}\alpha/\mathrm{d}t = k\,\alpha\,(1-\alpha)$$

which can only apply once some product has formed, so an additional slow process is needed and is often represented by:

$$\text{Rate} = v = -\mathrm{d}\alpha/\mathrm{d}t = k_1\,(1-\alpha) + k_2\,\alpha\,(1-\alpha)$$

The concept of 'concentration' is not useful in describing the progress of reaction in a solid and is replaced by defining $\alpha$ as the fractional amount of reactant decomposed. For thermal decompositions of solids [33], either deceleratory or sigmoid curves are routinely obtained from experiments and several different rate equations, derived from a variety of models, have been developed for describing such results. The models are based on factors that are inapplicable in homogeneous reactions, such as geometry of the advancing reactant/product interface, diffusion through product layers of various geometries, and the formation and growth of product nuclei of various shapes. In thermal decompositions it is usually assumed that reaction will go to completion, but in the photolysis of solids, reaction may be limited to within a short distance inwards from the irradiated surfaces.

An alternative explanation for sigmoid curves is the Bawn model [34, 35] that involves melting of the decomposition product and partial dissolution of the remaining reactant in the melt. Decomposition then occurs concurrently in the solid-state and the melt, with reaction in the melt being more rapid.

The rate of photolysis in solution is determined by the number of photons absorbed by the sample in unit time, $N$, and the quantum yield of the reaction, $\varphi$,

$$\text{Rate} = v = N\,\varphi$$

where $\varphi$ is defined as the average number of molecules reacted per photon absorbed, per unit time and per unit volume of solution [36]. The effect of path length, $l$, of solution is introduced through the Beer-Lambert law. When the absorbance of the solution is so large that essentially all the photons are absorbed, the rate is determined by the intensity of the radiation and the reaction follows pseudo zero-order kinetics [32,

37]. When only a small amount (<10%) of the incident light is absorbed, the commonly observed first-order behaviour results:

$$\text{Rate} = k\, C/C_o = k\,(1 - \alpha)$$

where $C$ is the drug concentration, $C_o$ is the initial concentration and $k$ is an apparent rate coefficient that contains various factors that are approximately constant for the particular experimental system used. If other substances in the solution absorb light but do not participate further in the degradation of the drug, the incident light is effectively attenuated [36].

Sande [37] has developed a model for solid-state photochemical reactions, based on a powder bed of irradiated surface area, $S$ and depth, $B$. The bed is regarded as consisting of $n$ thin layers of thickness, $b$, so that a single layer will contain a fraction $b/B$ of the total amount of reactant. Assuming that the intensity of radiation, $I_n$, is uniform throughout each layer, the rate of reaction in layer $n$ will be:

$$\text{Rate} = v = -\mathrm{d}N_n/\mathrm{d}_t = \varphi\, I_{a,n}\, S$$

where $N_n$ is the number of reactant molecules photolysed. $I_{a,n}$ is the number of photons absorbed in the $n^{th}$ layer per unit time and will be given by the difference between the photon flux into ($I_{n,t}$) and out of the layer ($I_{n+1,\,t}$).

Division by Avogadro's constant, $L_A$, and the volume of the $n^{th}$ layer ( $= S\,b$) gives the rate in terms of concentration. Further division by the initial concentration, $C_o$ , converts to the dimensionless fractional reaction, $\alpha$.

$$\text{Rate} = v = -\mathrm{d}\alpha_n/\mathrm{d}t = \varphi\, I_{a,n}\, S/(L_A\, S\, b\, C_o) = \varphi\, I_{a,n}/(L_A\, b\, C_o)$$

Using the Beer-Lambert law:

$$I_{a,\,n} = I_{n,\,t}\,[1 - \exp(-\sigma_R\, b\, C_o\,(1 - \alpha_{n,\,t})]$$

where $\sigma_R$ is the molar Naperian absorption coefficient ($m^2\ mol^{-1}$) of the reactant, $C_o$ is the initial 'concentration' of the reactant ($mol\ m^{-3}$) and $\alpha_{n,\,t}$ is the contribution to the fractional degradation in the $n^{th}$ layer at time $t$, so that $1-\alpha_{n,\,t}$ is the fraction of drug remaining.

$$v = -\mathrm{d}\alpha_n/\mathrm{d}t = (\varphi / L_A\, b\, C_o)\, I_{n,\,t}\,[1 - \exp(-\sigma_R\, b\, C_o\,(1 - \alpha_{n,\,t})]$$

For infinitesimally thin layers, in which absorption by the reactant only is considered, the limit of $[1-\exp(-\sigma_R\, b\, C_o\,(1-\alpha_{n,\,t})]/b$ , as $b$ tends to zero, is $\sigma_R\, C_o\,(1-\alpha_{n,\,t})$, so:

$$v = -\mathrm{d}\alpha_n/\mathrm{d}t = (\varphi\, I_{n,\,t}/L_A\, C_o)\, \sigma_R\, C_o(1 - \alpha_{n,\,t}) = (\varphi\, I_{n,\,t}/L_A)\, \sigma_R\,(1-\alpha_{n,\,t})$$

Experimentally, the layers are not separable and the fractional degradations in each layer have to be averaged to give a value of $\alpha$ for the whole sample at time $t$:

$$\alpha_{tot,t} = \left(1/n\right)\sum_{1}^{n}\alpha_{n,t}$$

The depth, $B$, of the powder bed affects the photodegradation only by increasing the amount of material included in the averaging process described above, giving an

apparently slower degradation [37]. Increases in either or both the values of the quantum yield, φ, and the incident light intensity, $I_o$, increase the rate of degradation.

*The effect of temperature*

The temperature dependence of thermal processes is usually described by the Arrhenius equation [38] and the processes can be characterised by their Arrhenius parameters, the pre-exponential factor, $A$, and activation energy, $E_a$. In photochemical reactions, the energies of the photons involved are usually well in excess of the thermal activation energy [28, 36] so that the rates of true photochemical processes will usually be independent of temperature. The initial products of a photochemical process may, however, undergo secondary, thermally activated reactions.

*Kinetic analysis*

Determination of the rate equations that best describe the experimental results of thermal or photochemical experiments is not straightforward [33]. This is clearly illustrated by the papers that report on the outcome of the ICTAC kinetics project [39]. In this round-robin type of project, sets of numerical data (obtained from both isothermal and programmed-temperature experiments and simulations) were subjected to kinetic analysis by volunteer researchers, using methods of their own choice. The kinetic parameters obtained from these data sets showed more than the expected variation [40].

To describe a thermal reaction completely, it is necessary to specify the complete 'kinetic triplet': the conversion function, $f(\alpha)$ or $g(\alpha)$; the activation energy, $E$, and the pre-exponential factor, $A$. Quoting of activation energy values alone is misleading. It has been clearly shown that it is not possible to derive a unique kinetic triplet from the results of a single programmed-temperature experiment [41–43].

In pharmaceutical systems, most reported photolyses have been described by first-order kinetics [44]. It is even rarer for a reaction to show zero-order kinetics, except for some oxidations, e.g. the work by Asker *et al.* [45] and Asker and Larose [46].

## Literature selection

In reviewing the literature to obtain possible correlations between the results of thermal and photochemical studies on the same substances in the solid-state, one encounters several difficulties. There are many results for the photodegradation of substances in aqueous solution, but relatively few studies are done of photostability in the solid-state. Correlations between photochemical behaviour in solution and in the solid-state are not clearly established. In aqueous solution, the temperature range of thermal degradation studies is very limited and hydrolysis is likely to be a major competitive process. There are also many studies where drugs have been reported as being stable to both heat and light. For example, Suleiman *et al.* [47] reported that, in the solid-state, diltiazem is highly stable to high humidity even with added exposure to UV light, even though aqueous solutions hydrolyse relatively rapidly.

The criterion for literature selection has thus been that the study should report on the photostability of one or more of the solid forms of the substance. Behaviour is obviously complicated by the existence of several polymorphic forms. Where possible the photolytic behaviour has been compared with any thermal information. In some cases the photochemical behaviour in aqueous solution has provided additional insights.

There is a growing body of information on the changes in stability (both photo- and thermal) of drugs caused by the formation of inclusion complexes with cyclodextrins (CDs) [8, 48–50]. Some of the results reported are ambiguous in that it is necessary to provide some evidence for inclusion of the drug in the CD cavity before it can be concluded that changes in photostability are not simply caused by dilution in a physical mixture. In some cases complexation with cyclodextrins can increase photodegradation. This would be likely if the guest molecule was only partially included in the CD cavity with the photosensitive region of the molecule exposed. Such studies are also considered further below.

There are few studies on the photostabilities of excipients other than cyclodextrins and on the possible catalytic effects of excipients on the photodegradation of drugs. Nyqvist and co-workers [51, 52] have carried out extensive studies of the stability of drugs in tablets of various kinds on exposure to accelerated light, heat (25 to 60°C) and humidity (27 to 76%RH) conditions. Results for tablets of the pure drug (FLA 336) were compared with those containing several excipients (including lactose, cellulose and sodium carboxymethyl starch) and the light protection provided by film-coating with inorganic pigments was tested. Yellow iron oxide was found to be superior to titanium dioxide. From the range of results obtained, the shelf-lives under a variety of conditions could be predicted.

Tristimulus colorimetry has been defined, [53] as a quantitative means of simulating perception of color by humans in a production environment. Nyqvist *et al*. [51, 54] studied the light stability of excipients such as microcrystalline cellulose, magnesium stearate and lactose by accelerating the light exposure in a fadeometer with subsequent tristimulus colorimetry. In a study by *Lin et al*., [55] the effect of stabilizers on the coloration and physical stability of ascorbic acid creams was evaluated by tristimulus colorimetry. While coloration resulted in all creams exhibiting zero-order kinetics, not all of the group of stabilizers studied, which included dicarboxylic acids, amino acids, cyclodextrins, organic acids and organic salts, proved to be effective in decreasing the color change and enhancing the physical stability. Tristimulus reflectance spectrophotometry [56] was used to predict the stability of various nystatin dosage forms, including powders, ointments and creams. This proved to be useful because there is a relationship between the loss of microbial potency and a change in colour due to the thermal degradation.

## Behaviour of individual drugs

### *Carbamazepine*

The photostability of carbamazepine (1) polymorphs in solid dosage forms (tablets) was evaluated [57] using Fourier transform infrared reflection absorption spectrome-

try and colorimetric assessment of all three polymorphs (I, II, and III), after irradiation under a near-UV fluorescent lamp. The surface of the tablets discolored to yellow and then orange with results indicating polymorph II to be the least stable. The photodegradation followed first-order kinetics with the degradation rate constant for form II proving to be 1.5 times larger than for forms I and III. The resulting order of degradation was II > I > III.

*Cefuroxime*

The photoisomerization kinetics of cefuroxime acetil (2) revealed competition between the isomerization and photolysis of the β-lactam ring, with the two diastereoisomers reacting at different rates [58]. The fact that photoisomerisation occurs on exposure to UV radiation at 254 nm confirms the need for photoprotection from light.

*Chlorodiazepoxide (1,4-benzodiazepine)*

Reisch *et al*., [59] found that UV irradiation of chlorodiazepoxide (3) and its hydrochloride led to three photoproducts: 2-[(3-chlorophenyl) phenylmethylene] amino -N-methylacetamide (4) 1-benzoyl-7-chloro-1,2-dihydro-3-methylaminoquinoxaline (5) and 7-chloro-3,4-dihydro-2-methylamino-4-phenyl-5H-l,4-benzodiazepine- 5-one (6) as shown in Fig. 1.

In a study undertaken by Mhlongo *et al.*, [60] chlordiazepoxide in the solid-state was irradiated at 356 nm for a period of 2 months. DSC analysis revealed a broader and less intense endotherm for the parent drug at 229°C as opposed to 237°C. X-ray diffraction showed a decrease in the characteristic peaks and the appearance of a new peak at 2θ = 28.43°, confirming a decrease in the crystallinity after irradiation.

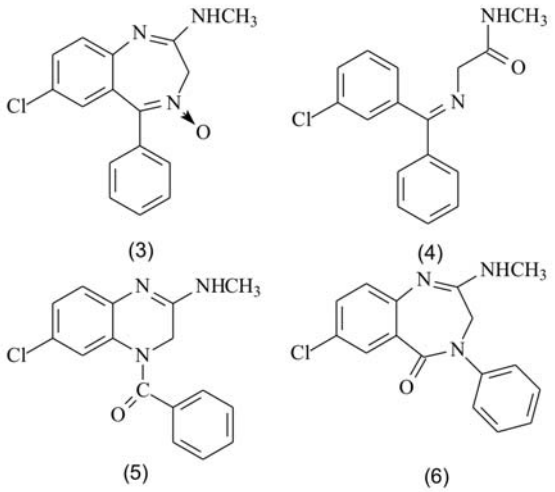



**Fig. 1** Chlorodiazepoxide (3) and three photoproducts (4, 5, 6)

LC-MS studies revealed that photodegradation in the solid-state to 7-chloro-3,4-dihydro-2-methylamino-4-phenyl-5H-l,4-benzodiazepine-5-one (6) had occurred via the formation of an oxaziridine, a reaction reversible under thermal conditions. This oxaziridine compound indicates the onset of a phototoxic effect due to the interaction of the epoxide with DNA and proteins.

*Chlorpromazine*

On irradiation, chlorpromazine (7), recognized as the prototype of many neuroleptic drugs in clinical use today, produces free radicals, as well as singlet oxygen, implying that both Type I and Type II photooxidation has occurred. Chlorpromazine has been demonstrated to act as a sensitizer for its own oxidation by the singlet oxygen mechanism. Reactions of the chlorpromazine cation radical with oxygen have been reported to lead to sulphoxide formation [61, 62]. Davies *et al.* [63] suggested that Type I and II mechanisms may relate to the photoallergic and phototoxic effects of a photosensitizing drug.

*Cianidanol*

Cianidanol (8) is used in the treatment of hepatitis. Seven crystal forms of the solid drug have been reported [64], together with their methods of preparation. These are: anhydrate I, II, III and IV; monohydrate I and II, and tetrahydrate I. Akimoto *et al.* [64] have studied the photostabilities of five of these forms. The anhydrates I and III were not included because they transformed too readily, under the experimental conditions needed, to the monohydrate I. Samples on glass slides, in Pyrex tubes over appropriate saturated salt solutions at 20°C, were irradiated with light from a high-pressure mercury lamp. The residual drug was determined using GLC. At 51–58% RH, the order of photostability was: monohydrate II > anhydrate IV ≈ anhydrate II > monohydrate I > tetrahydrate I. Tetrahydrate I was quite stable at 0% RH, presumably because of transformation to monohydrate I, but at over 60% RH it was unstable. The decreases in the photostability of monohydrate I and anhydrates II and IV at high RH were assumed to be due to partial transformation of these forms to the tetrahydrate I by absorption of water during the photostability test. Monohydrate II was stable, non-hygroscopic, and unaffected by humidity. Photo-decomposition is a light-induced autoxidation and differences in photostability of monohydrates I and II were attributed to the weaker binding of the water in monohydrate I aiding the penetration of oxygen into the crystals.

Akimoto *et al.* [65] have also compared the photostability of cianidanol in aqueous solution (at various pHs) with that in the solid-state. The role of oxygen in the surroundings was also examined. Cianidanol was found to be stable to light at wavelengths > 340 nm in aqueous solution and in the solid-state. In solution, photodegradation is accompanied by photo-induced oxidation, the extent of which increases markedly with increasing pH. In the solid-state, photodecomposition was inhibited by decreasing the concentration of oxygen in the surroundings to <0.1%.

Use of magnesium aluminium silicate as a solid excipient increased the photodegradation. The water content of the additive was important and magnesium ions were proposed to accelerate the photo-induced oxidation.

*Cyanocobalamin*

A study of the photolysis of cyanocobalamin (9) in the presence of visible light and at various pHs indicated a slow decrease in the rate at pH 1–3 and a fast decrease at pH 3–7, confirming the protonated form to be more susceptible to photolysis [66].

*Diltiazem*

The results of Suleiman *et al*., [67] for aqueous solutions of diltiazem (10) were similar to those for cyanocobalamin (above). In the solid-state, diltiazem was very photostable, even in the presence of high relative humidities.

*Fumagillin*

The antibiotic fumagillin (11), used in the treatment of AIDS patients with microsporidiosis, is extremely sensitive to heat, with degradation even occurring in the freezer [68]. This drug substance should therefore be stored at –60°C, and protected from light.

*Furosemide*

Furosemide (12) exists in the solid-state as at least three polymorphs, two solvates, an amorphous form and a high-temperature form (IV) [69]. A stability diagram has been given [69, 70]. DTA data for the polymorphic transitions were used to calculate apparent activation energies (using the Kissinger method of kinetic analysis). The values obtained are very large (250 to 2300 kJ $mol^{-1}$) compared to the measured enthalpies of transition (1.1 to 2.7 kJ $mol^{-1}$). No pre-exponential factors are given. Form I is the stable form at room temperature. The other forms are metastable. Photostability was tested by exposing surfaces of tablets to UV-light from a 400 W mercury-vapour lamp. Changes of colour, $\Delta E$, of the surfaces of the tablets and of a powder sample of form II were monitored with time by colorimetry. The darkening process followed a rate equation of the form:

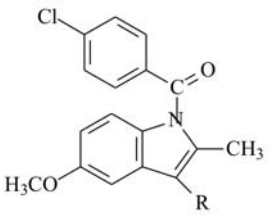
$$d\Delta E/dt = k\,(\Delta E)^n$$

Values of n for all the forms were similar (–1.2 to –1.6). Form I was the most stable.

The photostability [71] under air and nitrogen of polymorphic forms I and II of furosemide was investigated. The photodegradation followed first-order kinetics, with the photodegradation of form II occurring independently of oxygen. Both forms I and II gave rise to 4-chloro-5-sulphamoylanthranilic acid after exposure to sunlight

*Indomethacin*

UV-irradiation of indomethacin (13) for 72 h in the solid-state under nitrogen yields 5% of the decarboxylation product (14). In air, 7.5% degradation occurs under similar irradiation [72]. Indomethacin is thus reasonably photostable in the crystalline form. An impurity was identified as (15), the ethyl-ester of (13) as shown in Fig. 2.




(13) R = $CH_2COOH$

(14) R = $CH_3$

(15) R = $CH_2COOCH_2CH_3$

**Fig. 2** Indomethacin (13) its degradant (14) and an impurity (15)

Matsuda *et al.* [73] determined the photostability of indomethacin in gelatin capsules. A check was made that the gelatin films were not themselves photodegraded. The colour change of the indomethacin was measured. Unprotected indomethacin showed clearly visible changes after 120 min exposure to a 400 W mercury-vapour lamp. Less coloration was observed with increasing thickness of the gelatin film. Titanium dioxide was used to make the films more opaque to the radiation. The coloration of the drug decreased with concentration of $TiO_2$ in the film up to about 1%. There was a linear relationship between the extent of coloration and the square-root of the exposure time at all film thicknesses and concentrations of $TiO_2$. A film thickness of 80 mm and a concentration of 1% $TiO_2$ were regarded as providing adequate photoprotection.

*Levonorgestrel (16)*

UV-irradiation of levonorgestrel (16) (the proposed active form of the oral contraceptive) [74] in the crystalline state under a nitrogen atmosphere yielded its dimer (18) as the principal photoproduct, via an intermediate (17) in Fig. 3. X-ray crystallographic data for (16) supported the possibility of photochemical dimerisation.

The authors have also reported on the photochemical isomerisation of digitoxin [75] and, in a further paper [76], on the comparative photostability of solid-state digoxin and related compounds, including acetyldigoxin, which proved to be less stable than digoxin, while oubain exhibited greater photostability.

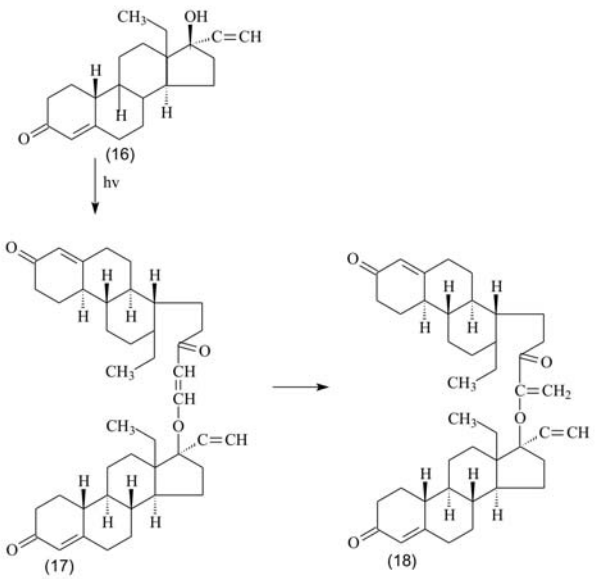



**Fig. 3** Dimerisation of levonorgestrel (16)

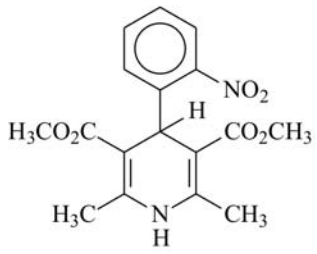
*Mefloquine hydrochloride (19)*

Different crystal structures of mefloquine hydrochloride were prepared [77] and studied by thermal analysis, IR spectroscopy and X-ray diffraction. Two forms were hydrates, two were polymorphs and two were solvates. Some transformed during long storage at room temperature, or on heating. The photosensitizing properties of mefloquine in aqueous solution are reported to occur through a triplet state energy transfer and in a pH range corresponding to physiological conditions [78]. The photo-instability of this and other antimalarials, including primaquine [79, 80] and chloroquine [81], is well documented.

*Nifedipine (20)*

Nifedipine (Fig. 4) is a highly photolabile, practically water-insoluble drug used therapeutically as a calcium channel antagonist for the treatment of various cardiovascular disorders.

Matsuda *et al*. [82] identified the major photodegradants in the solid-state as the nitroso and nitro derivatives. Maximum decomposition occurs at about 380 nm. Teraoka *et al.* [83] confirmed these findings using HPLC and FTIR-reflection absorption spectroscopy (RAS). The photodegradation of nifedipine powder followed first-order kinetics. The apparent rate constant increased with decreasing particle size in the range 324 to 127 μm. The amounts of drug remaining after 24 h exposure to a fluorescent lamp were 16.0% (127 μm) and 44.3% (324 μm). The photodegradation of the surface of nifedipine tablets (20 μm diam), based on the absorbance at 1682 $cm^{-1}$ attributable to the C=O




(20)

**Fig. 4** Chemical structure of nifedipine

stretching vibration, was studied using FTIR-RAS and also followed first-order kinetics and was independent of the particle size of the powder used.

The darkening process followed a rate equation of the form [82]:

$$d\Delta E/dt = k\,(\Delta E)^n$$

The amount of drug decomposed correlated well with the colour change, $\Delta E$, for the tablets. The rate of degradation of the drug in the surface of the tablets increased with increasing illuminance. Plots of ln (apparent rate constant) *vs.* the reciprocal of the illuminance (analogous in a way to Arrhenius plots) were approximately linear. Such plots thus permit extrapolation from accelerated tests to more normal illumination conditions.

Matsuo *et al.* [84] used the solid-state photodegradations of nifedipine and santonin to compare the efficacy of various light sources. Degradation products were determined by HPLC. Samples were spread in a glass dish to give an about 3 mm thick layer and covered with a transparent PVC film. A sample wrapped in aluminium foil served as a dark control.

Thoma and Kerker [85] have studied the photostability of 60 commercial preparations of nifedipine. Different preparations showed different photostabilities and stability was increased by protective measures such as storage of capsules or tablets in suitable blisters.

Aman and Thoma [86] used tablets containing the highly light-sensitive drugs, nifedipine or molsidomine, to investigate the influences of the formulation and tabletting processes on the photostability of drugs. The particle size had a considerable effect on the photostability of the drug powders themselves, but incorporation of low doses of the drugs in tablets led to such effects being undetected in the presence of the high proportions of excipients and the reflective tablet surfaces. Some of the photodegradants of nifedipine absorb visible light strongly and hence have a photoprotective effect on the drug. Less photodegradation occurs in larger diameter tablets. The larger surface area in biconvex tablets, compared to biplanar tablets, led to greater photodegradation. As the porosity of tablets decreased, the photodegradation increased as more drug was forced from the shelter of pores. Granulation before tabletting led to complications caused by dissolution of the drug in the granulation liquid. Depending upon the formulation, drug

losses ranged from 30 to 55% after 12 h irradiation in a Suntest cabinet. Tablets can be photostabilized by addition of light-absorbing compounds or by film coating [27]. Worthington *et al.* investigated the photostabilisation of nifedipine by preparation of nifedipine – cyclodextrin binary systems, using both natural cyclodextrins and cyclodextrin derivatives. However these cyclodextrins proved to be ineffective as single component photostabilizers of nifedipine in the solid-state [87].

Desai *et al.* [88] used iron oxides for photostabilization of sorivudine and nifedipine. Tablets of the drugs were made with and without iron oxides and some tablets were also coated with 'Opadry'. Under the same conditions, with turning of tablets every 24 h for 14 days, nifedipine tablets with iron oxide showed 25% degradation compared to 43% without iron oxides. The corresponding figures for sorvudine were <2% with and 6% without iron oxides.

In a recent study, Caira *et al.* reported on the single-crystal X-ray structure of the solvated species, nifedipine 1,4-dioxane. Desolvation produced a monoclinic polymorph (I), which, when exposed to water, transformed into the dihydrate. Amorphization resulted in a six-fold increase in the solubility; however, when suspended in water at pH 1, the amorphous form was converted to form I [89].

The photostability and photostabilization of nifedipine has and continues to receive considerable attention in the literature [90–98].

### *Nisoldipine*

Álvarez-Lueje *et al.*, [99] used electroanalytical methods (polarography and cyclic and differential pulse voltammetry) to study the photodegradation of nisoldipine (21), which belongs to the nitroaryl-l,4-dihydropyridine family and is a calcium channel antagonist. The main photodegradation products of nisoldipine (exposed to both UV and artificial daylight) as a powder and in an ethanol/aqueous buffer solution were the nitro and nitroso derivatives, as found for the photodegradation of nifedipine. Thus the different substituent in the 3-position of the dihydropyridine moiety did not affect the overall photochemical behaviour.

### *Phenazone derivatives*

Marciniec [100] has determined the rates of decomposition of phenazone, aminophenazone, 4-aminophenazone, aminoantipyrine, isopyrine, propylphenazone, morazone and nifenazone in the solid-state, in KBr disks, under the influence of 254 nm UV irradiation. Initial decompositions (determined from the IR spectra) followed approximately zero-order kinetics, but over longer times behaviour was approximately first-order. The reaction rate is dependent on the particle size and the thickness of the exposed layer. The order of photochemical stability was: aminophenazone < 4-aminophenazone < aminoantipyrine < isopyrine < propylphenazone < morazone.

Crystalline aminophenazone is liable to topochemical photo-oxidation, which is attributable to the small distance between the carbonyl oxygen in the one molecule and the hydrogen of the 5-ethyl group in the neighbouring molecule. After intermolecular hydro-

gen-atom abstraction by the activated CO group, the resulting radical takes up oxygen to form 4-dimethylamino'-5-formyl-l-methyl-2-phenyl-4-pyrazolin-3-one. A 'photosensitized' autoxidation (type-I photo-oxidation) underlies this reaction.

*St. John's wort*

The thermal and photostability of a commercial dried extract and capsules of St. John's wort (*Hypericum perforatum* L.) were evaluated by Bilia *et al.*, [101] under the ICH test conditions, including the use of capsules of different colours and amber containers. HPLC was used to determine the stability of the main constituents, (flavonols (12.7%), hyperforins (4.2%) and hypericins (0.32%)). All the constituents were photosensitive under the test conditions and their different photostabilities were influenced differently by the colour of the capsules or containers. Long-term thermal stability testing (3 months at 25°C with 60 to 65% RH) showed that, while the flavonol content was still 98%, the hyperforins had decreased to 90% and the hypericins to about 30%, even if ascorbic and citric acids were added to the formulation as antioxidants.

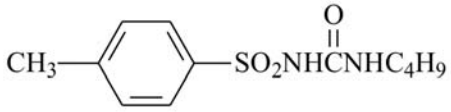
*Sulfisomidine*

Sulfisomidine (22) was investigated in the presence of oxybenzone, an UV absorber in the film coating used to stabilize this photosensitive dosage form. Results indicate that increasing film thickness and increased absorber concentration retard the photodegradation of sulfisomidine [102].

*Tolbutamide (23)*

El-Ries and Abou Sekkina [103] studied the thermal stability of γ-irradiated tolbutamide (23), an orally active hypoglycemic agent (Fig. 5).

Doses ranged from 0 to 8.8 kGy from a Cs-137 source. Before irradiation, the DTA curves for tolbutamide heated in air showed melting at 128°C followed by an endothermic polymorphic transformation at 255°C. There were two exotherms at 390 and 490°C associated with oxidative decomposition. After irradiation, the decomposition peaks were shifted to higher temperatures, suggesting that irradiation had caused some thermal stabilization. This stabilization appeared to increase with increasing dose.



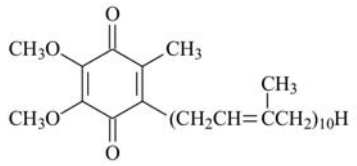

(23)

**Fig. 5** Chemical structure of tolbutamide

Bottari *et al.* presented a study on the thermal dissociation of tolbutamide which is shown to dissociate to either butylamine or *p*-toluene sulphonylisocyanate [104].

*Ubidecarenone (24)*

The photostability of ubidecarenone (24), 2,3-dimethoxy-5-methyl-6-decaprenylbenzoquinone, used in the treatment of angina, (Figure 6) was investigated by Matsuda and Masahara [105]. Stability was significantly affected by irradiation wavelength, with UV radiation causing the greatest changes. Degradation increased with the light absorption properties of the substrate. Photodegradation followed apparent first-order kinetics at all wavelengths. The rate of photodegradation increased at higher temperatures, but even at 60°C in the dark no thermal degradation occurred. An Arrhenius plot for the rate constants of the photodegradations gave an activation energy in the solid-state (28 kJ $mol^{-1}$) different from that in the liquid state (13 kJ $mol^{-1}$) with the intersection of the linear regions near the melting point of ubidecarenone at 46°C. These activation energies decreased linearly with increasing intensity of UV light, from a value of about 90 kJ $mol^{-1}$, typical of normal, thermally-activated processes, at very low doses to a constant value of about 30 kJ $mol^{-1}$ at the highest doses (about $10^{-6}$ ergs $cm^{-2}$).




(24)

**Fig. 6** Chemical structure of ubidecarenone

The drug is a yellow or orange crystalline powder and darkens on exposure to light. Tablets, granules, and hard or soft gelatin capsules are photo-protected with light-resistant packages. Formulation of ubidecarenone in a redispersible dry emulsion results in its photostability being improved due to being dissolved in an oily carrier and the presence of a colourant [106].

## Drug/cyclodextrin mixtures

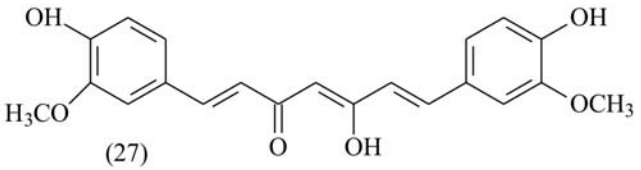
The photochemistry and photophysics within the cyclodextrin cavity involve features quite distinct from those of the uncomplexed substances since the interior of the cavity constitutes as isolated environment where the included species are usually present as single molecules restricting the photochemistry to intramolecular events.

As mentioned above, it is necessary to provide some evidence for inclusion of the drug in the CD cavity before it can be concluded that changes in photostability are not simply caused by dilution in a physical mixture. In some cases, complexation

with cyclodextrins may increase photodegradation. This would be likely if the guest molecule was only partially included in the CD cavity with the photosensitive region of the molecule exposed [107].

Uekama *et al., [108] prepared solid complexes of benzaldehyde (25) with* a-, β- and γ-cyclodextrins (ACD, BCD and GCD, respectively), from aqueous solutions, and characterized them using XRD and IR. The volatility of benzaldehyde was retarded by inclusion, oxidation (to benzoic acid) was completely inhibited and photo-oxidation was retarded. ACD gave the most protection because of the tight fit of the benzaldehyde molecule in its cavity. The poor solubility of molsidomine was however not improved by complexation with ACD and, in addition, GCD conferred no better photoprotection to molsidomine than lactose, mannitol or sodium chloride in the same mass ratios [109]. In a study on clofibrate (26), Uekama *et al.* [110] showed that the photostability of clofibrate was increased in the solid-state in the presence of BCD and GCD.

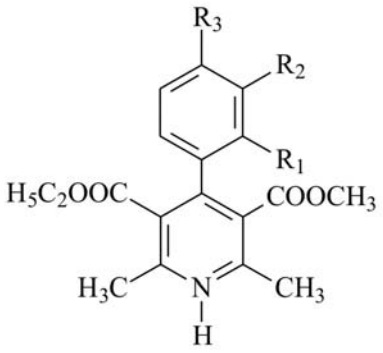
Curcumin (27) is a natural product used mainly for food colouring and as a pharmaceutical excipient [111]. Because of its light-absorbing properties it has potential for stabilizing photolabile drugs in solution and in gelatin capsules. At pHs above neutral, curcumin (Fig. 7) hydrolyses rapidly (half-life of a few minutes) giving feruloyl methane, ferulic acid and vanillin. In organic solvents, curcumin photodegrades. The photoproducts have been identified [112] and a mechanism proposed [113]. Tonnesen *et al.* [111] thus used a variety of cyclodextrins (hydroxypropyl-α-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, sulfobutylether-β-cyclodextrin, and hydroxytrimethyl-ammoniumpropyl -β-cyclodextrin) to attempt to prepare a more stable water-soluble curcumin complex at pHs where hydrolysis would not be significant. The observed increase in solubility was high and the protection against alkaline hydrolysis was significant. The formation of an inclusion complex, however, decreased the photostability of curcumin relative to its degradation in solution. The α- and γ-derivatives of the CDs had less of a destabilizing effect than the β-derivatives. These differences were ascribed to differences in the polarity inside the cavities and the orientations and hydrogen bonding of the guest molecule.




(27)

**Fig. 7** Chemical structure of curcumin

Mielcarek [114] studied the photodegradation of aqueous solutions of a range of derivatives of 1,4-dihydropyridine (NR) with various substituents (–$NO_2$, –Cl, –F and –$CF_3$) at different positions in the phenyl ring (Fig. 8). These compounds are used for investigating calcium channel structures and functions. They are poorly sol-




| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| (28) | $NO_2$ | H | H |
| (29) | H | $NO_2$ | H |
| (30) | $CF_3$ | H | H |
| (31) | H | H | Cl |
| (32) | H | H | F |
| (33) | H | CN | H |

**Fig. 8** Chemical structures of 1,4 dihydropyridine derivatives

uble in water and known to be photosensitive. The rates of photodegradation were determined in the absence of, and in the presence of, β-cyclodextrin. The behaviour of the two NR derivatives containing an $–NO_2$ group in the phenyl ring was very different: the *ortho* isomer degrades about ten times faster than the *meta*-isomer. Photodegradation of the *ortho*-isomer in the presence of β–cyclodextrin was reported to be 200 times slower than that of the compound in the crystal phase. For the halogeno- and cyanoderivatives, the presence of β-cyclodextrin caused a 4-fold increase in the photodegradation rate.

Metronidazole (34) benzoate dispersed in an aqueous medium turns yellow within 2–3 days of exposure to daylight as a result of photochemical surface oxidation of the crystals. However, suspensions of the BCD inclusion complex remain colorless and hence stable for more than 3 months [115].

## Discussion

The stability of drugs towards heat, moisture, oxidation and exposure to light is a topic of great practical interest and any degradation will usually adversely affect the therapeutic activity of the drug. Unless very special precautions are taken, most drugs will receive some exposure to light and will generally be expected to be able to tolerate room temperature. One of the interesting questions that arises in considering drug stability, and which is discussed here, is the possible correlation between thermal degradation and photodegradation. This general topic could be further subdivided

into examining correlations between photodegradation in solution (including the influences of the solvent) and in the solid-state. For example, Thoma and Kerker [116] have reported that the extent of photodegradation of molsidomine in solution increased as the solvent was changed from water to propylene glycol to ethanol to macrogol. Far more studies of photodegradation of drugs in aqueous solution have been carried out than of solid drugs or drug formulations in the solid-state, because of the experimental difficulties discussed above. Thermal degradation of drugs in solution (again including use of different solvents) [117] does not appear to have been as extensively studied as has the thermal behaviour of solid drugs and drug formulations. These latter thermal studies have been of particular value in revealing actual and potential drug-excipient interactions and are essential for obtaining information on the conditions for existence of drug polymorphs. In the solid-state, the temperatures required for thermal degradation at a measurable rate are generally far higher than the temperatures existing, even locally, during photolysis, so the mechanisms of thermal and photochemical degradation can be expected to differ.

Attention has been focused on the solubility of polymorphic active ingredients and the influence of polymorphism on dissolution kinetics and bioavailability [118]. Since most drugs exhibit polymorphism, it is the goal of the Pharmaceutical Manufacturer to develop the most thermodynamically stable polymorph to ensure the bioavailability of the product over its shelf-life [119]. However it is also their task to formulate a product which is physically and chemically stable and to this end the thermal and photostability of different polymorphic forms of drug substances is important. Although it is difficult to compare the thermal and photostability of drug substances in the solid-state, this study [57, 64, 69, 70, 77–80] highlights the fact that various crystal forms of drug substances, exhibit not only different thermal behaviour but also different photostability.

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