

Review

Formulation and stability testing of photolabile drugs

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Abstract

Exposure of a drug to irradiation can influence the stability of the formulation, leading to changes in the physicochemical properties of the product. The influence of excipients of frequently used stabilizers is often difficult to predict and, therefore, stability testing of the final preparation is important. The selection of a protective packaging must be based on knowledge about the wavelength causing the instability. Details on drug photoreactivity will also be helpful in order to minimize side-effects and/or optimize drug targeting by developing photoresponsive drug delivery systems. This review focuses on practical problems related to formulation and stability testing of photolabile drugs. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Light can have effects on the active principle in a drug formulation, as well as on the final product or packaging. This may be observed as bleaching of colored compounds or a discoloration of colorless products. The European pharmacopoeia prescribes light protection for a number of medical drugs and excipients. New compounds are frequently added to the list of photolabile drugs, although the justification of light protection requirements for certain compounds has been ques-

tioned (Reisch and Zappel, 1993; Hung, 1996). Although many drugs are found to decompose under exposure to light the practical consequences may not necessarily be the same for all these compounds. Some drugs will decompose by only a small percentage after several weeks exposure, while other substances like derivatives of the drug nifedipine have a photochemical half-life of only a few minutes. They are all 'sensitive to light' but the same precautions will not be required in the handling of these products. In any case, light-sensitive drug substances frequently raise formulation problems. It should be established at a fairly early stage that a compound is susceptible to photodecomposition. This knowledge requires the development function to consider several approaches

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to assessing and solving the problem. In many cases, a suitable packaging provides a good solution. If the problem can not be resolved in this way, modifications of the formulation must be considered. In order to stabilize the product, there is a need for good understanding of the nature and extent of photodecomposition, the mechanisms of the degradation reaction and the wavelength causing the instability. The conditions that a product will be submitted to in use will clearly vary as a result of product type (solid preparation or solution), protection by the packaging, the mode of administration and the local conditions of the clinic or in the pharmacy.

The most obvious result of drug photodecomposition is a loss of potency of the product. In the final consequence, this can lead to a drug preparation, which is therapeutically inactive. Although this is not often the case, even less severe degradation can lead to problems. Trace amounts of photodecomposition products formed in the formulation during storage and administration may lead to adverse effects (de Vries et al., 1984). Light-sensitive drugs can be affected either by sunlight (especially ultraviolet irradiation) or artificial light sources (e.g. fluorescent light). This may not only lead to photodegradation of the active principle but also to a change in the physico-chemical properties of the product, e.g. the product becomes discolored or cloudy in appearance, a loss in viscosity or a change in dissolution rate is observed or a precipitate is formed. Modern pharmaceutical practice limits the use of light-protective packing materials, i.e. the traditional brown medicinal flask or white pill-box. Intravenous solutions must be stored in transparent infusion bags or bottles. During long-term infusion, the formulation can be exposed to irradiation for hours or days. This is also a problem with portable drug delivery devices as the drug reservoir of such pumps are made of transparent plastic materials. Radiation of high intensity can be experienced by drug formulations used for intravenous medication of premature babies, which are under treatment for hyperbilirubinemia. In the case of solid dosage forms the outer container, which in most cases is non-transparent to light, will often be removed leaving the tablet or

capsule in a unit-dose container made of transparent plastic material. The plastic material offers little protection towards radiation. Data from a number of Norwegian hospitals/hospital pharmacies showed that the drug product was likely to be exposed to filtered daylight (i.e. sunlight through a window) for 1 day or more and that the exposure to fluorescent light was likely to exceed 1 week (Tønnesen and Karlsen, 1995). This was valid both for solid and liquid preparations. After the drugs were delivered to a local medical center outside the hospital, the products could be further exposed for at least one week. This emphasizes that although great effort should be taken to stabilize the formulation itself in such a way that the shelf-life becomes independent on the storage conditions, it might still be necessary to take precautions to exclude or minimize the amount of irradiation reaching the product. Data on in-use stability (e.g. the stability of products administered through an intravenous drip or reconstituted lyophilized products) should, therefore, be provided for a number of preparations.

A drug which displays photochemical reactivity *in vitro* may also give rise to adverse photosensitivity effects in patients after administration. Sunlight penetrates the skin to a sufficient depth to reach drug molecules circulating in the surface capillaries or it can react with compounds accumulated for instance in the eye. In any case, sunlight may induce interactions between the drug molecule and endogenous substrates, convert the drug into a toxic decomposition product or induce the formation of reactive oxygen species, which are toxic to human tissues. In this context it should be mentioned that a combination of drugs and light also can be beneficial such as in the treatment of vitiligo, psoriasis or cancer and in the development of site specific drug delivery systems (Karlsen, 1996; Beijersbergen van Henegouwen, 1997).

Basic information about the photoreactivity of the compounds is needed to provide information for handling, packaging, labeling and use of the drug substance or drug product. Unfortunately, a discussion of photostability is not as straight forward as that of thermal stability due to the complexity of the experimental design, reaction

mechanisms and interpretation of results. This review will focus on practical problems related to formulation and stability testing of photolabile drugs.

2. Photochemical processes

Only radiation that is absorbed by the reacting system can be effective in producing chemical changes. The photochemical reaction is a complex process, which usually occurs in two stages. The primary reaction is the reaction, which is directly due to the absorption of a photon, i.e. involves the excited state of the molecule. This reaction does not depend on temperature for activation of the molecules. The primary photochemical reaction will, however, often be followed by secondary (thermal) reactions occurring from the intermediates produced by the primary photochemical process (e.g. radicals, radical ions). These intermediates can eventually react through 'dark' reactions to form the final, stable products. A large number of different reaction types can be initiated photochemically, e.g. reduction, *N*-dealkylation, hydrolysis, oxidation, isomerization, ring alteration, polymerization or removal of various substituents like halogens or carboxyl groups (Fig. 1). In some cases, the final products may resemble the products of the purely thermal reaction (dark reaction from the molecular ground state), but this similarity is coincidental.

Knowledge about the mechanism by which the photodegradation occurs is of importance in stabilizing the product. The drug molecules may be affected directly or indirectly by irradiation, depending on how the radiant energy is transferred to the substance. Direct photochemical reactions as described above occur when the drug molecule itself absorbs energy, i.e. there is a certain overlap between the absorption spectrum of the molecule and the incident radiation. In an indirect or sensitized reaction, the energy may be absorbed by a nondrug molecule (e.g. excipient, impurity, degradation product) in the formulation. The energy is imparted to the active ingredient, which subsequently degrades. The absorbing component, in this case, is called a photosensitizer. The sensitizer

can transfer the absorbed energy completely and not be altered itself in the process, but in many cases it will undergo some degradation. One consequence of a sensitized reaction is that a drug substance with an absorption spectrum that does not overlap with the photon source still can photodecompose in a formulated product. Oxygen can strongly influence the degradation product profile as this molecule can participate both in a direct and a sensitized reaction. Oxygen in the ground state can add to a photoexcited molecule leading to oxidation products of this substance (e.g. drug). Alternatively, a photoexcited molecule (e.g. drug) can transfer its energy to ground state oxygen leading to the formation of singlet oxygen. Oxygen in this form is highly reactive towards oxidable molecules (e.g. drug substance, excipients) and the result is a photosensitized oxidation reaction. In some cases the excited drug molecule acts as a sensitizer for the formation of singlet oxygen while the drug molecule in the ground state acts as the oxidisable acceptor of singlet oxygen (self-sensitized reaction).

Any overlap of the product absorption spectrum with the photon source impinging upon it has the potential to cause a photochemical change. Photochemical stability of a drug compound in a formulation can, therefore, not be predicted simply from the absorption spectrum or stability studies of the drug in a pure solvent. Data must also be obtained for the drug in the final preparation. Many drug substances are white and hence the degradation depends mostly on the amount of ultraviolet (UV) radiation absorbed by the material. Degradation products formed during the shelf-life can, however, be colored and thereby change the over-all absorption characteristics of the formulation. Colored substances absorb light in the visible region of the spectrum. Stability studies of the drug substance in the final preparation should, therefore, always include exposure to both UV- and visible radiation to cover all possible degradation reactions.

The overlap integral between the absorption spectrum of a molecule and the incident radiation strongly influences the photodegradation rate. The rate of a photochemical reaction is in general

dependent upon the rate at which light is absorbed by the system (i.e. the number of photons absorbed per second) and the efficiency of the photochemical process (i.e. the quantum yield for

the reaction). The quantum yield is usually independent of wavelength. A primary photochemical reaction follows first order kinetics in a formulation which contains the drug substance in a low

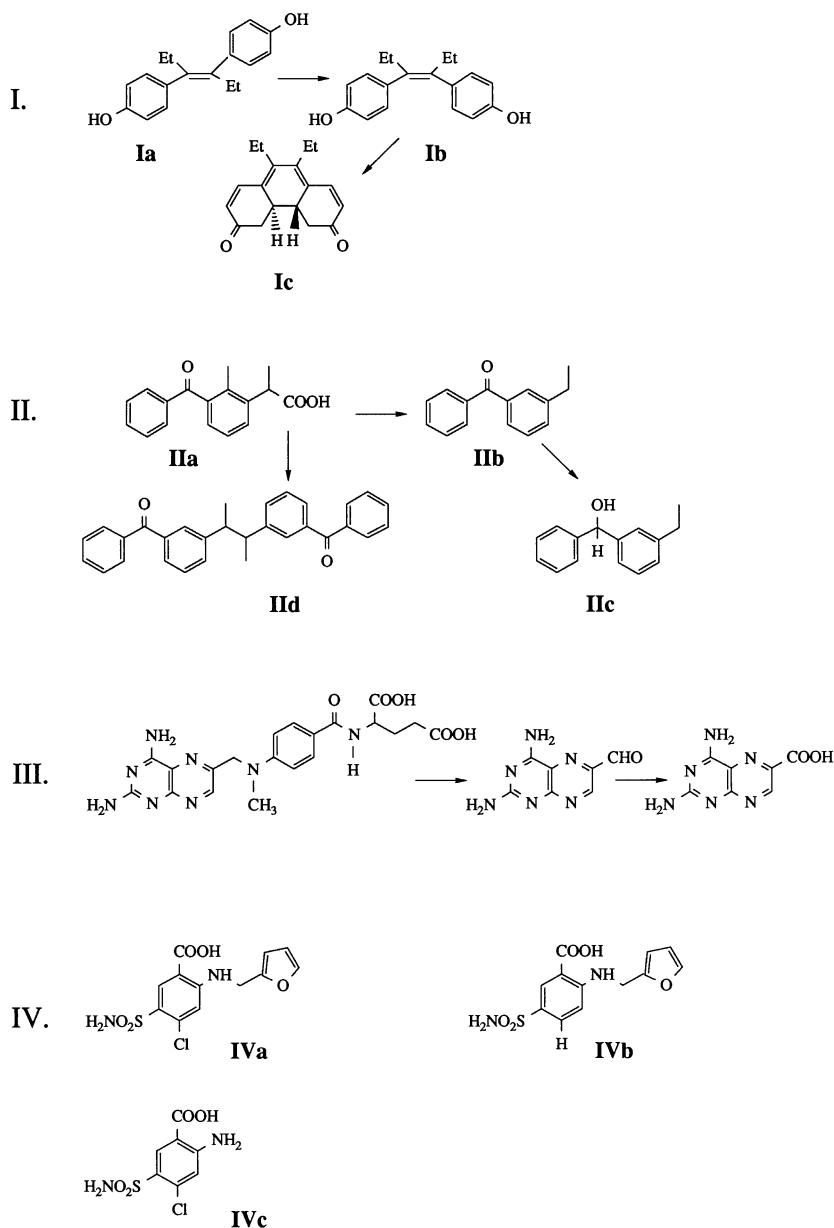


Fig. 1. Examples of photoinduced reactions in drug molecules. (I) Photoinduced isomerization (Ib), cyclization and enol–keto isomerization (Ic) of stilboestrol (Ia). (II) Photoinduced reactions of ketoprofen (IIa) and its degradation product (IIb); decarboxylation (IIb), reduction (IIc) and dimerization (IIc) products of the drug. (III) *N*-dealkylation of methotrexate followed by oxidation. (IV) Dehalogenation (IVb) and photohydrolysis (IVc) of frusemide (IVa)

concentration or where the overlap integral is small. The kinetics is more complicated at higher concentrations, in sensitized reactions or in the solid state (Tonnesen, 1991; Sande, 1996; Moore, 1996a). The value of the photodegradation rate constant depends strongly on the experimental set-up (Moore, 2001 in press). Determination of relative rate constants is useful for comparative studies using the same experimental design.

A relationship between structure and photoreactivity can be difficult to predict although certain structural types are known to have a high possibility for photodecomposition. During the last decade, a body of data relating to photolabile drug substances and degradation pathways has been accumulated and is recently presented (Greenhill and McLelland, 1990; Editorial, 1996; Greenhill, 1996; Albin and Fasani, 1998).

3. Influence of formulation factors on drug photostability

3.1. Excipients

Most photochemical reactions are affected by the medium. As a result, both the excipients and the type of preparation are likely to influence the photodecomposition of the active compound (Kerker, 1991; Thoma and Kübler, 1997). The compatibility of the drug with the excipients in the given formulation must be determined early in the formulation process. Excipients can initiate, propagate or participate in photochemical reactions. This can result in degradation of the active ingredient or formation of degradation products that may compromise safety and tolerance. For liquid preparations, the choice of buffer and pH is likely to be determined from solution kinetic studies. The formulations will often contain phosphate salts as a component of the buffer system. For parenterals, metal ion contamination and compatibility with packaging components (plastics, plugs) are also of importance. The situation is probably more complex in the case of solid preparations as a large number of excipients may be included in the formulation. For example, a tablet formulation can contain lactose, dicalcium phos-

phate, corn starch, mannitol and sugar. Photochemically induced interactions in tablets almost always lead to discoloration even when chemical transformation is modest or undetectable. Theoretically, many adjuvants can be expected to inhibit a photochemical reaction. Mannitol, lactose, sugar, starches and polyvinylpyrrolidone (PVP), the latter frequently used in containers, are all susceptible to free radical attack in that they have abstractable hydrogens. They would thereby act as free radical transfer agents to inhibit the degradation of the drug substance. Their effectiveness will, however, strongly depend on the overall composition of the formulation and in many cases, a destabilizing rather than a stabilizing effect is observed. Excipients, like drug substances, are not exquisitely pure. Low levels of residue can have a great impact on photostability. Phenols in tablet binding agents (e.g. povidone), disintegrants (e.g. crospovidone) or viscosity modifying agents (e.g. alginate) can participate in free radical reactions (Smidsrød et al., 1963). Aldehydes formed during spray-drying or autoclaving of lactose can undergo addition reactions with primary amino groups, resulting in colored products that change the absorption characteristics of the preparation (Janicki and Almond, 1974; Buxton et al., 1994). Lipid excipients often contain peroxides that decompose under the influence of light leading to formation of free radicals. Peroxides are also found in polyethylene glycol. Non-ionic surfactants cover a broad area of application and would often be found in emulsions for oral or topical use or as solubilizers and stabilizers in biotechnology products. These compounds are susceptible to oxidation (Donbrow et al., 1978; Rieger-Martin, 1975). Their influence on drug photostability is further discussed below. The possibility for light induced reactions involving excipients makes photostability testing of the final product mandatory.

3.2. Solid dosage forms

In the solid state (e.g. tablets, capsules, powder) the photochemical process takes place on the product surface. In most cases the interior of the preparation will be unaffected independent of ex-

posure time. A practical consequence is that the change in total drug concentration measured as a function of irradiation time does not necessarily follow any particular reaction order model although first order decay has been reported (Carstensen, 1974; Marciniec and Rychik, 1994; Sande, 1996). The degradation rate in the surface layer is not only dependant on the excipients as discussed above, but also on factors that will influence the depth of light penetration, i.e. change the absorption and reflection at the surface (e.g. particle size, crystal modification, color, thickness of powder bed and coating of the individual particles or the dosage form). For example, a capsule and a tablet have different light scattering characteristics and different ratios of surface area to volume leading to a variation in the photodegradation of the active principle (Thoma and Kerker, 1992a). Mefloquine, chloroquine, carbamazepine and furosemide are examples of drug substances that show different decomposition rates dependent on their polymorphous modification (Fig. 2) (de Villiers et al., 1992; Matsuda et al., 1994; Nord et al., 1997a; Tønnesen et al., 1997).

3.3. Solutions and topical preparations

Most of the light will be absorbed close to the sample surface if a solution contains the drug substance in a high concentration. The drug molecules inside the volume becomes protected from irradiation (inner filter effect). A concentrated solution is thereby likely to be more stable than the same product in a diluted form. This may cause severe problems in infusion therapy. In many cases, parenteral solutions assure high light impingement on the drug molecules due to a low drug concentration and a large surface to volume ratio. Protection of the infusion set by a colored or non-transparent outer package should always be considered, especially in the case of long term infusion regimes. Cosolvents and surfactants can have a photo-stabilizing or -destabilizing effect on the product as demonstrated for phenobarbital and nitrofurazone, respectively (Asker and Islam, 1994; Shahjahan and Enever, 1996). This may be ascribed to a change in the polarity and in some

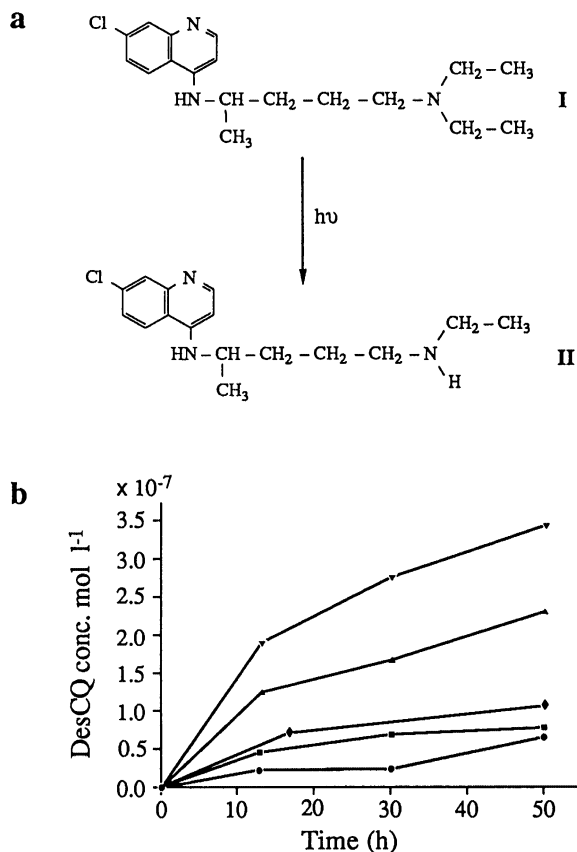


Fig. 2. (a) Desethylchloroquine (II) is the main decomposition product of chloroquine (I). (b) The formation of desethylchloroquine is strongly dependent on the polymorphic form of chloroquine in the solid state. The figure shows the formation of the degradation product as a function of irradiation time for a number of polymorphic forms of chloroquine.

cases the viscosity of the medium, or to a change in sample absorbance due to an increase in solubility and dissolution of particle aggregates.

Most medicinal agents are salts of organic acids or bases. For many drug substances, the photodegradation process is strongly dependent on the ionization form of the molecule (Fig. 3) (e.g. ciprofloxacin, midazolam, chloroquine, mefloquine) (Andersin and Tammilehto, 1995; Torniaainen et al., 1996; Nord et al., 1997a,b; Tønnesen, 1999). The presence of pH-modifying compounds can influence the stability. Various types of buffer salts exert different effects on the photodegradation process as demonstrated for the

drugs daunorubicin and mefloquine (Islam and Asker, 1995; Tønnesen, 1999). The phosphate ion is known to influence the photochemical

properties of compounds (e.g. tyrosine) by facilitating proton transfer from the excited state of the reacting species (Lakowicz, 1983). Buffer salts like citrate can change the absorption characteristics of the formulation by forming complexes with other components present, leading to products that absorb in the visible part of the spectrum. An increase in ionic strength is reported to have a photostabilizing effect on certain drugs by providing a protective film of solvated ions around the reacting molecule (Chinnian and Asker, 1996). This effect is not observed in the case of mefloquine (Tønnesen, 1999).

Oxygen plays an important role in many photochemical reactions as described above. One should, therefore, expect that a product would be stabilized by a reduction in oxygen concentration. This is, however, not always the case. Purging the solution and headspace with an inert gas may cause photochemical destabilization of the drug substance as demonstrated for nitrazepam and various aminoquinolines (Fig. 3) (Cornelissen and Beijersbergen van Henegouwen, 1979; Nord et al., 1997b; Kristensen et al., 1998; Tønnesen, 1999). The effect of antioxidants and chelating agents on drug photostability is also quite unpredictable. The effect is strongly dependent on the environment and light conditions and must, therefore, be carefully evaluated (Asker and Habib, 1991). A significant photodestabilizing effect on epinephrine in the presence of bisulfite has been demonstrated (Brustugun et al., 2000) while sulfite under other conditions has shown a photoprotective effect (Islam and Asker, 1995). It is also known that Fe(III)-EDTA chelates are reduced by superoxide quite quickly. EDTA will, therefore, not inhibit photodegradation of drugs in systems, where the iron-catalyzed Haber–Weiss reaction plays an important role. Other excipients like tonicity adjusters and sweetening agents could further influence the photoreactivity of the drug substance (Asker and Colbert, 1982; Asker and Canady, 1984; Asker and Harris, 1988; Ho et al., 1994). Addition of colors is shown to stabilize drugs in various preparations (Tønnesen and Karlsen, 1987; Takeuchi et al., 1992; Thoma,

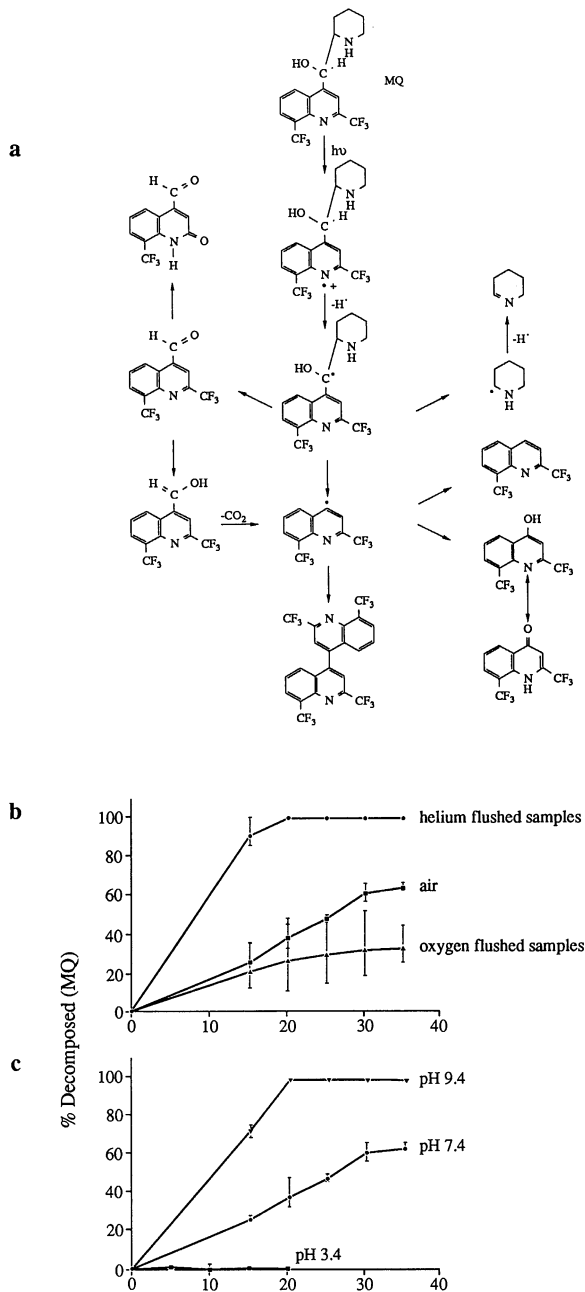


Fig. 3. (a) Degradation of mefloquine in aqueous solution. (b) Degradation rate as a function of oxygen concentration. (c) Degradation rate as a function of pH.

1996). A mixture of colors or pigments can, however, undergo catalytic fading (Kuramoto and Kitao, 1980) or induce degradation of other components in the formulations by radical formation (Skowronski et al., 1984; Sidhu and Sugden, 1992; Konaka et al., 1999).

The active compound of a topical preparation represents a situation part way between the solution and the solid state. The type of formulation (e.g. solution, emulsion, suspension) affects the light absorption characteristics of the product as well as the polarity of the reaction medium. A dependence of the light stability on the nature of the salt form and of the particle size of a drug in an ointment has been reported (Merrifield et al., 1996). At present, there are few studies on photodecomposition of drugs in topical preparations although photodegradation of UV-filters in sun-protective formulations is known (Marti-Mestres et al., 1997). There are also examples of photodecomposition of drug substances in liposome or hydrogel formulations after application to the skin (Schaefer and Zesch, 1975; Thoma and Kerker, 1992b).

4. Stabilization of light sensitive formulations

Photoprotection by spectral overlay with suitable excipients or coating of solid dosage forms by use of opaque films can stabilize various drugs and preparations (Tønnesen and Karlsen, 1987; Thoma and Klimek, 1991; Béchard et al., 1992; Desai et al., 1994; Thoma, 1996). However, the method most commonly used to protect photosensitive drugs is to place the preparation in a protective market pack or a colored or amber immediate container. During storage and use, the protective market pack may be removed as discussed earlier. Transparent glass or plastic material offers little protection towards radiation (Moore, 1996b). The stabilizing effect of amber glass as only means of photoprotection is not satisfactory for highly photolabile drugs like molsidomine (Thoma and Kübler, 1996). Even brown glass can offer inadequate protection as demonstrated for drugs like epinephrine, isoprenaline and levarterenol (Woll-

mann and Grünert, 1984). The destabilizing effect of the container was attributed to release of alkali and traces of heavy metal ions that import color to the glass.

In cases where oxygen takes an active part in the degradation process the use of an inert atmosphere should be considered. A full study of the role of oxygen in the photoreaction of the particular formulation must be carried out before an inert atmosphere is applied. The possibility of adding quenchers or scavengers to the product should also be evaluated. Quenchers deactivate excited states (e.g. singlet oxygen) by energy-transfer or charge-transfer while scavengers reacts with free radicals. If such compounds can be demonstrated to be non-toxic and therapeutically inert this is perhaps an option. The major possibilities are substances such as α -tocopherol, ascorbic acid and BHT. These substances are capable of acting as free radical scavengers, as well as weak singlet oxygen quenchers and they are already accepted as food additives. L-Histidine is a more efficient singlet oxygen quencher but may disturb a patient's amino acid balance. β -Carotene is useful in lipid preparations but adds a strong yellow color to the formulation.

A different approach is to change the drug photoreactivity by complexation with suitable carriers. The extent of photodegradation of a number of drugs has been reduced by inclusion complexation with cyclodextrins (Thoma and Kübler, 1997; Sortino et al., 1999; Ammar and El-Nahhas, 1995; Lin et al., 2000; Sur et al., 2000). There are, however, marked differences in stabilizing effect between the various cyclodextrins and in some cases the complex formation has a catalyzing rather than a stabilizing effect on the photodegradation process (Mielcarek, 1996; Jiménez et al., 1997; Sortino et al., 1998; Lutka, 2000; Sortino et al., 2001). A combination of cyclodextrines and liposomes or pure liposome preparations are also demonstrated to improve drug photostability (Habib and Asker, 1991; Loukas et al., 1995). Complex formation with organic acids and salts can have a stabilizing effect on some substances (Habib and Asker, 1989).

5. Photoresponsive drug delivery systems

The topic of photoresponsive drug delivery systems deserves a separate review and will only be mentioned briefly here.

Molecules which can change their structure in response to light may be a useful tool in the development of new drug delivery systems. The term caged compounds is given to synthetic molecules whose conversion from inactive to active form is controlled by light. The caged compounds are commonly designed by modifying the desired bioactive molecule with a suitable photoremovable protecting group (e.g. light activated prodrugs). The term caged is based upon an early concept that small biologically active molecules can be trapped inside a large matrix that could be opened upon illumination. In almost all caged compounds so far, photochemical cleavage of a covalent bond releases the active substance, i.e. photocleavage of a prodrug (Hagen et al., 1998). The active substance can be conjugated to macromolecules (Hasan, 1992; Jori, 1992) There exists a large number of groups used for photoactivation of biomolecules, and several drugs are available on the market as caged compounds (Karlsen, 1996). Molecules which can isomerize reversibly in response to light have potential uses in photochromic switching release systems such as light activated liposomes or photoresponsive hydrogels. A number of photoresponsive compounds and systems have been studied (Fig. 4) (Morgan, 1989; Tomer and Florence, 1993; Yui et al., 1993; Srinath and Jain, 1994; Morgan et al., 1995; Kinoshita, 1998; Ohya et al., 1998; Bisby et al., 1999, 2000) Light can further be used to improve the mechanical strength of membranes in capsules and coatings (Chang et al., 1999; Lu et al., 2000).

6. Photostability testing of drug formulations

Testing of the photostability of a drug substance and of the final dosage form is important to ensure good quality over the entire lifespan of the product. A basic protocol for testing of new drug substances and products for first submissions is described in the ICH Guideline for photostabil-

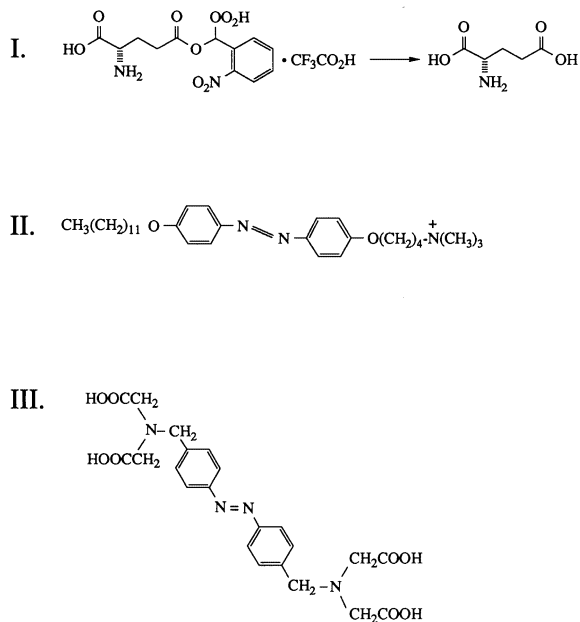


Fig. 4. Examples of photoactivated drugs (I) photoactivated prodrug. On photolysis, the protective group is detached and the active principle is released (II). Photoisomerization of a lipid. Only the *trans* form will form a lipid vesicle (III) Photosensitive chelator. Only the *cis* form can bind Zn^{2+} ions.

ity testing which have been implemented since January 1998 (Guideline ICH, 1997a). The Guideline notes that photostability testing should be an integral part of stress testing. For drug substances the photostability testing consists of two parts; forced degradation testing (stress testing) and confirmatory testing. Forced degradation testing is undertaken to evaluate the overall photosensitivity of the material for method development purposes and /or pathway elucidation. The design of stress testing experiments is left to the applicant's discretion and may involve a variety of exposure conditions. The reaction medium and photon source must be selected with care in order to get a realistic description of the photoreactivity of a certain drug. Valuable information can be lost if experiments are carried out only in one medium, i.e. organic solvents can not differentiate between various protonation forms of the molecule. To ensure the formation of all possible degradation products including products formed in sensitized reactions, the sample must be irradi-

ated at all absorbing wavelengths (i.e. a broad-spectrum irradiation source should be applied). The 'in-use' decomposition rate can be estimated by using a light source simulating indirect or direct sunlight. The intensity of the light source must be related to the actual intensity under 'real conditions' in order to determine the accelerating effect. An estimate of 'real conditions' can be based on a defined value for the irradiance of sunlight at a specific location or as a global average (Tønnesen and Moore, 1993). Pre-formulation kinetic studies often involve the drug substance in solutions or simple formulations (e.g. suspensions). In order to compare the degradation rate in the various preparations, the relative number of absorbed photons must be calculated as a double integral of absorbance over wavelength and irradiation time. It is recommended that the degradation studies are conducted with low concentration of the drug so that first order kinetics apply. Otherwise, the reaction rate is limited by the light intensity rather than the number of drug molecules. Solutions should be effectively stirred to maintain homogeneity, and the removal of samples should not affect the volume being irradiated (Moore, 2001 in press).

The formal test for product photostability (i.e. confirmatory testing) is based on the assumption that products will be exposed to a mixture of glass-filtered natural light and indoor light. The purpose of the confirmatory study is to estimate photostability characteristics under standardized conditions and this will normally be carried out as late as possible in the product development process. The aim is to determine the appropriate package/labeling combination needed in manufacturing, handling and packaging to ensure satisfactory product quality. The results obtained by use of the photostability guideline should be regarded essentially qualitative rather than quantitative, i.e. this is equivalent to a limit test. Although the proposed test is reasonable simple to conduct, special attention should be given to parameters like irradiation source, irradiance level and temperature effects, calibration of lamps and presentation of samples. A thorough discussion of the experimental design of the test is presented elsewhere (Tønnesen, 2001 in press). The ICH guide-

line gives two options for the selection of irradiation source. From a scientific viewpoint the various alternatives described in the two options are not equivalent since both the irradiance level and the spectral distribution of the lamps are different. For the purpose of a confirmatory study the options could, however, be regarded as equivalent, assumed that the results are combined with knowledge about the compound or product from earlier tests performed during the preformulation work. The ICH guideline does not specify an irradiance level, only the overall illumination. The user may, therefore, adjust the irradiance level according to the individual requirements. The use of a very high irradiance level compared with the 'real' conditions tends to decrease the correlation of test results. The temperature will increase as the irradiance is increased which can influence the overall degradation. At a high irradiance level the mechanisms of sample degradation may also change even when the spectral distribution of the lamp is kept constant. Tests conducted at significantly different irradiance levels should not be compared unless correlation has been established. It is essential to calibrate the light source and periodically monitor its irradiance in order to obtain the predetermined exposure value. Some light cabinets will have a build-in sensor for calibration. If the irradiance intensity drops, the lamp power is adjusted accordingly to keep the irradiance level constant. For instrumentation without a build-in sensor calibration can be performed manually by the use of a UV filter-radiometer, a lux-meter, a thermopile or a chemical actinometer. With the exception of the chemical actinometer these devices can not be used for an absolute measurement of irradiance or to compare irradiance between sources unless they are calibrated specifically for each source (Tønnesen and Karlsen, 1997).

Drug substance and drug products should be presented in a way to provide maximum area of exposure to the light source. Containers used to hold the sample should be specified in terms of their transmittance characteristics.

Preparations like tablets or capsules should be spread in a single layer. It is recommended in the ICH guideline that the sample thickness should

not exceed 3 mm for solid drug substances. The main disadvantage by using a protective container is that a significant increase in temperature can be expected. The temperature inside a covered glass dish can easily reach 40 °C although the temperature in the chamber outside the dish is kept close to room temperature. Some test chambers have an option for a water cooling system but in some cases this makes the interior surface of the chamber 'too cold' leading to the condensation of water droplets inside the protective container.

Photostability testing according to the ICH guideline will give an indication as to whether photochemical degradation of the drug substance or drug product is likely to occur during the shelf-life. The term 'acceptable change' is not defined in the guideline. Justification of impurity limits should be based on the ICH Drug Substance and Product Impurity (Guideline ICH, 1996, 1997b). If there is any risk to the product undergoing photodegradation, it should be labeled 'protect from light'.

7. Conclusions

Light sensitive drug substances frequently raise formulation problems. Photochemical reactions are complex and a good understanding of the photodecomposition process is needed in order to optimize the product stability. In fact, the study of the degradation of drug substances or products under the action of UV/visible light exposure is relevant to the process of drug development for a number of reasons. First of all, exposure to irradiation can influence the stability of the formulation, leading to changes in the physico-chemical properties of the product. The selection of a protective packaging will be based on knowledge about the wavelength causing the instability. If the formulation has to be modified in order to improve the shelf-life, the influence of the excipients and the physical state and presentation of the product must be taken into account. The effect of excipients or frequently used stabilizers is often difficult to predict and stability testing of the final preparation is mandatory. Another aspect of drug–light interactions is that inappropriate ex-

posure of the raw materials or the final preparation also can cause formation of toxic degradation products. For many drugs there seem to be a relation between photoinstability *in vitro* and adverse biological effects of the compound. Details on photoreactivity will then be helpful for advising the patient to avoid direct sun, wear sunglasses or use sun protective creams in order to minimize side-effects.

The combination of drug delivery systems and light seems to offer a great potential in drug targeting. There is a growing interest in the development of a new generation of drug delivery systems where the activation of the formulation or drug compound is based on a photochemical reaction taking place. Independent of what we are concerned about; *in vitro* stability or *in vivo* effects, the evaluation of interactions between drug and light should form a natural part of the research and development of new drug substances and drug products. Light-stability testing for pharmaceutical formulations should provide information related to the practical use of the product. Photostability testing according to the ICH guideline will give an indication as to whether photochemical degradation of the drug substance or drug product is likely to occur during the shelf-life. The results are used to make labeling decisions. Based on data related to sunlight conditions, it is also possible to make recommendations on how the product should be handled in use (e.g. at a hospital ward).

In summary, knowledge of drug–light interactions is a necessary prerequisite to the development of dosage forms that are stable, of good quality and have a potential in drug targeting. It is hoped that this review provides some perspective of this important area of drug formulation.

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