Improvement of Photostability in Formulation: A Review

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In this review an improvement of photostability in formulation is discussed the issue of photostability in pharmaceutical dosage forms. This review deals with mechanism of photodegradation with examples, factors affecting photostability, formulation characteristics affecting photostability, ICH guidelines for testing photostability of new drug substances and products. Various reported formulation approaches which improved photostability have also been discussed.

Key Words: Photostability, Photodegradation, Liposomes, Microspheres, Cyclodextrins.

INTRODUCTION

Photostability deals with the effect of light on stability of pharmaceutical substances/products. Light can influence the active principle in a drug formulation, as well as the final product or package. In this manner, the photostability deals with the effect of the light (photons) on stability of pharmaceutical substances. Photodegradation may be observed as bleaching or as discolouration of products. The other effects include cloudy appearance of the product, a loss in viscosity of formulation, precipitation of active principle, alteration in dissolution rate, etc.1. Although many drugs are found to decompose when exposed to light, the practical consequences may not be the same for all these compounds2. Some compounds may decompose only to a smaller extent after several weeks exposure, while others like 1,4-dihydropyridine derivatives (nifedipine, nimodipine, etc.) have a photochemical half life of only a few minutes. All these drugs are sensitive to light but same precautions may not be necessary in all the cases.

Light sensitive drugs can be affected by sunlight (ultraviolet light) or by artificial light (like fluorescent light). 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 may further contribute to oxidative breakdown of

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drugs and ultimately toxicity to human tissues\textsuperscript{3,4}. A very severe exposure of photosensitive compounds to light is not necessarily required; even trace amount can also lead to significant problems. Clearly, the most important consequence of photodegradation is the loss of potency of the product.

Light in the form of energy can initiate and accelerate decomposition. It is essential to distinguish whether instability is due to light or heat, in order to determine whether a preparation must be stored below 20 °C or protected from light. Unfortunately, a discussion of photostability is not as straightforward as that of thermal stability due to complexity of the formulation design, reaction mechanisms and interpretations of results\textsuperscript{5}. Thus, to stabilize the formulation or compound sensitive to irradiation, necessary precautions should be taken to exclude or minimize the amount of light reaching the product, such as by placing it in protective package. The selection of protective packaging will be based on the knowledge about wavelength causing the instability. If the formulation has to be modified in order to improve the shelf life, the influence of the excipients and presentation of the product must be taken into account.

In most cases, packaging the product in suitable container can solve the problem, but this is not the only solution to protect the drugs from light. Plastic material is also sometimes used as packaging material, but data from various studies demonstrates that plastic material offers least protection towards radiation\textsuperscript{6}. The conditions leading to photodegradation may vary from solid to liquid preparation, type of packaging material, mode of administration and most importantly the environmental conditions in which it is stored. To stabilize the product sensitive to light, an insight to the nature and extent of photodegradation is required. This review will focus on the problems related to photostability in formulation and methods to overcome them.

PHOTODEGRADATION PROCESS AND MECHANISM

Photodegradation of drug substances strongly depends on the spectral properties of the drug and the spectral distribution of the light source\textsuperscript{6} \textit{viz.}, discoloration of sulpyrine is significant in the presence of a mercury lamp, which is a good source of UV energy; however little discoloration occurs in the presence of a fluorescent lamp, which radiates mainly visible light\textsuperscript{7}. The unit of radiant energy equivalent to one quantum is called the photon. The energy of the photon is directly proportional to the frequency and inversely proportional to the wavelength of the absorbed radiation. Thus, there is more energy in a photon of short wavelength (and high frequency) than in a photon of longer wavelength. Hence, photochemical destruction of pharmaceutical products is usually due to absorption of light of the visible blue, violet and ultraviolet wavelength (500 to 300 nm)\textsuperscript{5,6}.
A dilute solution of a photolabile drug may be completely inactivated when exposed to light, whereas more concentrated solution will be only partially destroyed under similar conditions. The energy imparted by the light excites vibrational motions in drug molecules, so changes in both lengths and angles of bonds takes place; energy requirements lie in the range 1000 to 36,000 cal/mol. Electronic transitions and cleavage of chemical bonds may occur.

Photochemical reaction is a complex process, which usually occurs in two stages. Primary reactions, due to direct absorption of light and secondary (thermal) reactions occurring from intermediates produced by the primary photochemical process (e.g., radicals, radical ions, etc.). The primary reaction does not depend on temperature for activation of the molecules while the intermediates in the secondary process can eventually react through ‘dark’ reaction to form the final, stable products. The drug molecules may be affected directly or indirectly by irradiation, depending on how the radiant energy is transferred to the substance. In direct photochemical reaction there is a certain overlap between the absorption of the molecule and the incident radiation while in an indirect or sensitize reaction the energy may be absorbed by a non-drug 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.

Presence of some molecular features may indicate susceptibility of drug molecule to photodegradation (Fig. 1). Presence of these chemical functions are expected to introduce photo reactivity in a molecule.

Some typical functions are as follows (Fig. 1): (a) The C=C double bond: Such molecule usually undergoes E/Z isomerization and may undergo polar addition or cyclo-addition quietly easily; (b) The C=O double bond: The carbonyl function behaves as an electrophillic radical in the excited state and is easily involved in inter- or intra-molecular hydrogen transfer processes or fragmentation reactions; (c) Among aromatics, nitro derivatives resemble ketones in their radical activity and chlorides often undergo hemolytic or heterolytic dechlorination; (d) Among heterocycles, five membered rings usually undergo easy rearrangements and N-oxides are involved in electrolytic reactions; (e) Products containing weak C-H bonds, such as α-C-H in amines, alcohols, ethers, sulphides may be involved in oxidative or degradative processes, often related to the activation of oxygen by photosensitization.

Some pharmaceutical examples of effects of light are as follows: (1) The introduction of a fluorine atom in drug design (e.g., fluoroquinolones,
Fig. 1. Presence of some molecular features responsible for susceptibility of drug molecule to photodegradation

an antibacterial agent) is often associated to improve the antibacterial efficacy while avoiding undesirable side effects because of great chemical inertness of the carbon-fluorine bond. However, this dose not holds in photochemical conditions, where it is the carbon-fluorine bond which is labilized\(^{11}\) (Fig. 2). Fluoroquinolones undergo photodegradation with formation of product that exhibit photomutagenic effect\(^{3,12}\) or loss of antibiotic activity such as ciprofloxacin\(^{13}\), on the contrary some photodegradation products of fluoroquinolones posses antimicrobial activity\(^{14}\). The recovery of ofloxacin, exposed to natural day light (240 h) and direct UV light (24 h) were 80 and 85 \%, respectively. The recovery of ofloxacin from powder of
ofloxacin tablets subjected to direct UV light (24 h) is 75 %. When ofloxacin (bulk drug) and powder of ofloxacin tablets subjected to UV light, there is decrease in stability of the ofloxacin in powder of ofloxacin tablets, inferring one or more of the excipients might be contributed to increase the degradation. (2) trans-Cinnamic acid isomerizes to its cis-isomer in the presence of light because the C-C π-electrons are excited into antibonding orbital (Fig. 3), which allow rotation. (3) Dehydro-halogenation of meclofenamic acid gives two products (Fig. 4A and B). (4) Amlodipine, belonging to the 1,4-dihydropyridine class of antihypertensive drugs, is photosensitive since light catalyzes its oxidation to pyridine derivatives (Fig. 5), lacking any therapeutic effect. Another 1,4-dihydropyridine compound, nifedipine, also undergoes extensive photodegradation (Fig. 6). Dilute aqueous solutions of antihypertensive drug diltiazem, when exposed to UV radiations, give diltiazem-S-oxide as the main photodegradation product, other product include desacetyl-diltiazem. (5) Triprolidine, E-isomer, which is therapeutically active form isomerizes to triprolidine, Z-isomer, a therapeutically inactive form (Fig. 7) in the presence of light. (6) Photoxidation is quite common with phenothiazines. Two solutions (5 %) of therapeutically useful phenothiazine salts, chlorpromazine hydrochloride and prochlorpromazine ethanesulfonate, were placed in a Warburg respirometer to permit measurement of oxygen uptake and were then exposed to sunlamp. The solutions became coloured shortly after the light was turned on and then they continued to darken.

![Fig. 2. Schematic presentation of defluorination of fluoroquinolones](image1)

![Fig. 3. Isomerization of trans-cinnamic acid to cis-cinnamic acid](image2)
Kinetics of photolysis: The rate of degradation in dilute solutions is faster, when compared with concentrated solutions. Dilute solutions approach approximately first order kinetics while, concentrated solution approach pseudo zero order kinetics. The change in reaction order results because the number of incident quanta of energy limits the reaction and because in concentrated solutions quenching of excited molecules becomes more efficient. Equation 1 and 2 defines an alternative process.

\[ B \rightarrow B^* \]  
\[ B^* + A \rightarrow A^* + B \]
Fig. 6. Chemical structure of nifedipine and photoproducts (A and B)

Fig. 7. Isomerization of triprolidine, E-isomer to Z-isomer in presence of light

Fig. 8. Schematic presentation of effect of pH on fluoroquinolones
In this case, molecule B is photosensitizer i.e. ‘A’ itself may not be capable of absorbing the radiation energy at frequency \( \nu \), but B can. B* then transfers the absorbed energy to A to produce A*.

**FACTORS INFLUENCING DRUG PHOTODEGRADATION AND PHOTOSTABILITY**

**Excipients and formulation:** The effect of excipients and frequently used stabilizers is often difficult to predict and photostability and hence, stability testing is often mandatory. The evaluation of interactions between drug and light should form an integral part of the research and development of new drug substances and products. Both excipient and type of formulation are likely to influence the photodecomposition of the active compound. Excipients can initiate, propagate or participate in photochemical reactions. For liquid preparations, the selection of buffer and pH will be determined from solution kinetics. Buffer may also effect the photodegradation reactions of riboflavin in aqueous solution. For parenterals, metal ions contamination and compatibility with packaging components (plastic plugs) are of importance, even though the drug molecule itself is non-light absorbing at wavelengths > 300 nm. The major contributors to the observed photosensitivity are the citrate buffer; parts per billion (ppb) levels of iron, oxygen and light exposure level. Chlorophenesine solutions undergo photodehalogenation with the formation of varying photodegradation products depending on the solvent used. Excipients in the drug preparations strongly influence the photodegradation kinetics and the chemical structure of photodegradation products.

Solid preparations contain a large number of excipients like lactose, di-calcium phosphate; corn starch, mannitol and sugar are used. Some diluents like mannitol, lactose, sugar, starches and polyvinyl pyrrolidone (PVP) are susceptible to free radical attack in that they have abstractable hydrogens. Therefore, they act as free radical transfer agents to inhibit the degradation of the drug substance. For emulsions of oral or topical, non-ionic surfactants which are susceptible to oxidation.

**Solid dosage forms:** The photostability of drug substances in solid preparations is poorly investigated. That is mainly due to the smaller extent of degradation of drugs in solid state when compared to solution. However, since 2002, ICH guidelines make it mandatory to include photostability testing as an integral part of stress testing (ICH Q1B, 2002) since then, new drugs are being added to the list of light sensitive drugs. In the solid state (e.g. tablets, capsules, powder), the photochemical process, takes place on the product surface while the interior is unaffected. The degradation rate in the surface layer of the solid dosage form is dependent on various factors. Based on extensive investigations on the various factors influencing
the photostability of tablets following parameters should be taken into consideration during the preparation of solid dosage forms (especially tablets) containing light sensitive drugs.\textsuperscript{22,23}

**Particle size:** As the particle size is decreased the rate of degradation increases because of increased surface area exposed to light. However, influence of particle size of drug powder will have no effect when incorporated into tablets.

**Drug content:** The rate of decomposition of drugs, in solution is decreased by higher drug concentrations. This phenomenon is due to light absorption by the drug substance itself, protecting the molecules in the inner area of the reaction volume but for the tablets photostability increases by increasing the drug content.

**Tablet geometry:** The diameter and size of the tablet depend on the drug content. By increasing the diameter the photostability of the drug was improved. Though the difference is low, it is of importance. Degradation in biconvex shaped tablets was higher when compared to biplanar tablets. However, the difference was little.

**Preparation method:** Tablets can be prepared by granulation or by direct compression. Granulation will decrease the photostability of tablets.\textsuperscript{2}

**Solutions**

**Concentration:** The rate of decomposition of drugs, in solution is decreased by higher drug concentrations. This phenomenon is due to light absorption by the drug substance itself, protecting the molecules in the inner area (inner filter effect). Most of the light will be absorbed close to the sample surface if a solution contains the drug substance in high concentration. Hence, a concentrated solution is likely to be more stable than the same product in a diluted form. Studies on diltiazem in dilute aqueous solutions (pH 4-7), was found to be more photolabile, giving diltiazem-S-oxide as the main photodegradation product.\textsuperscript{8,17}

**pH and Ionization:** pH will significantly affect the photodegradation process.\textsuperscript{24} Some drugs undergo degradation at lower pH while the others undergo at higher pH. Diltiazem undergoes slow degradation at pH 4.0 and 7.4 while at higher pH 9.0, there is a serious degradation.\textsuperscript{17} Fluoroquinolones are amino acids and thus are amphoteric substances. At neutral pH 5-5.5, it is a cation, over pH 9 is an anion. Thus photochemistry is expected to be pH dependent. The stability of gatifloxacin was found to be maximum at pH 4.5 degradation increased above pH 4.5.8 photodegradation process is also dependant on the ionized form of the molecule because most medicinal agents are salts. The influence of pH-modifying compounds can influence the stability. The phosphate buffer is known to influence the photochemical properties of compounds (e.g. tyrosine) by facilitating proton transfer from the excited state of the reacting species.\textsuperscript{2}
**Ionic strength:** Increase in the ionic strength is reported to have a photostabilizing effect on certain drugs by providing a protective film of solvated ions around the reacting molecule on the contrary a study on lomefloxacin reported that higher the ionic strength in lomefloxacin hydrochloride aqueous solution, the higher the photodegradation kinetic rate constant is. As the dielectric constant of solution increased, the photodegradation kinetic rate constant was also increased as more drug is in ionic form.

**Oxidation:** Oxygen plays an important role in many photochemical processes and thus a reduction in oxygen concentration would stabilize the product. The effect of antioxidants and chelating agents is unpredictable. The effect is strongly dependant on the environment and light conditions and must, therefore, be carefully evaluated. It is also known that Fe(III)-EDTA chelates are reduced by super oxide quite quickly and EDTA will, therefore, not inhibit photodegradation in such systems. Addition of coloured substances, which have same absorption wavelength as of drug molecule, showed to stabilize drugs in various preparations. Nifedipine has proved to improve photostability by various methods.  

**METHODS FOR STABILIZATION OF PHOTOLABILE DRUGS IN FORMULATION**

Photostabilization of a drug molecule in a formulation can be broadly classified as: (a) photostability achieved using conventional methods (b) photostability achieved using novel drug delivery system.

**Conventional approach:** Excluding light can easily prevent photolytic reactions. This can be done by placing the drug product in a package that drug product in containers that are protective or opaque or amber coloured containers, *i.e.* light is excluded or that filter out all the light of those wavelengths that catalyze the reaction. Various pharmacopoeias specify the light transmission limits of glass and plastic containers. The stabilizing effect of amber glass as only means of photo protection is not satisfactory.  

In cases where oxygen takes an active part in the degradation process, the use of an inert atmosphere should be considered. Quenchers or scavengers could also be used. Quenchers deactivate excited state (singlet oxygen) by energy transfer or charge transfer while scavengers react with free radicals. Antioxidants like ascorbic acid, BHT, α-tocopherol, L-histidine, β-keratin could be capable of reducing photodegradation. Incorporation of curcumin in soft gelatin capsule shells by making a curcumin-gelatin complex has reported to improve the photostability of photolabile drugs. When curcumin was incorporated in soft gelatin capsule shells, it resulted in 3-fold or more increase in the half-life of the test compounds. Similarly, a curcumin content of 0.02 % (w/w) resulted in 20 % increase of half-life for nifedipine.
Curcumin will absorb the light and prevent the direct contact of the light with the drug to large extent28.

**Formulation approach:** A different approach is to change the photoreactivity by complexation with suitable carriers. The extent of photodegradation has been reduced by inclusion complexation with cyclodextrins (CDs) for a number of drugs. CDs are cyclic oligosaccharides capable of forming non-covalent inclusion complexes with a large variety of agents. The interaction of CDs with labile compounds can retard drug degradation, accelerate degradation, or have no effect on molecules reactivity. By providing molecular shield, CD complexation encapsulates labile drug molecules at molecular level and thus insulates them against various degradation processes29. The protective effects of CDs against photodecomposition of some photosensitive compounds have been reported30. Drugs from the group of 1,4-dihydropyridine derivatives are characterized by high photosensitivity, the photodegradation of DHP in inclusion complex with β-CD is reported to be 200 times lower than the same compound in crystalline phase31. Isradipine another 1,4-dihydropyridine derivative, when complexed with methyl β-CD, increased photostability twice that of the drug32. The results suggest that fast dissolving tablets of nifedipine can be prepared with added advantage that these products require less light protection33. Photostability studies on another nicardipine-cyclodextrin complexes; showed a photo protective effect by β-CD, hydroxyl propyl β-CD (HP β-CD) and hydroxyl ethyl β-CD (HE β-CD) and a photo degradative effect by α-CD33. Triprolidine hydrochloride an antihistaminic is also reported to be photosensitive and requires storage in sealed (Fig. 7), light tight containers (British Pharmaceutical Codex) triprolidine has improved photostability with β-CD and the presence of β-CD as excipients in dosage forms33.

In some cases complexation with cyclodextrins can increase photodegradation. This would be happen if the guest molecule is partially included in the CD cavity with the lightsensitive group of the molecule exposed1.

Incorporation of photolabile drugs in to supramolecular self-assembling systems, such as liposomes is also demonstrated to improve the photostability. Liposomes are microscopic vesicles in which an aqueous volume is enclosed by lipid molecules. The drugs molecules can either be encapsulated in aqueous space or intercalated between individual phospholipid molecules making up the bilayers15. Incorporation of the drug, amlodipine, in liposomes, improves photostability16. A combination of CDs and liposomes is also demonstrated to improve drug photostability3. Data also indicate that optimal protection of riboflavin, a B-vitamin, was provided by liposomes containing the γ-CD inclusion complex of the vitamin within their aqueous phase and the light absorbers oil red oxybenzone and dioxybenzone.
together with antioxidant β-carotene in the lipid phase. Encapsulation of tretinoin, a vitamin A derivative, in liposomes protected against photodegradation. Degradation constants of tretinoin in liposomes were roughly 1.8 times lower than in castor oil as the liposomes encapsulated tretinoin is less accessible to light beams due to the light scattering by the surface of the vesicle. Microspheres and microcapsules have recently attracted the attention of researchers as encapsulation systems for controlled release studies and for the potential protection of photosensitive drugs. Microspheres containing amlodipine imparted high degree of protection from light and amlodipine degradation was significantly lower in microspheres than in CD or liposomes. When pantoprazole prepared as microcapsules, it demonstrated high quality and stability. Solid dispersion of pantoprazole with Eudragit E also demonstrated to protect pantoprazole from photodegradation.

Changing the salt form would change the physico-chemical properties. Complex formation with organic acids and salts also proved to improve the photostability of pharmaceuticals. A novel crystalline adipic salt form of amlodipine has superior photostability.

PHOTOSTABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS

Information on stability of the drug substance is an integral part of the systematic approach to stability evaluation. It is also important for ensuring good quality over the shelf-life of the product. Basic information for testing of new drug substances for the first submissions is described in the ICH (Q1B) guideline for photostability testing.

For drug substances, the photostability testing consists of two parts: forced degradation and confirmatory testing. Forced degradation studies is undertaken to evaluate the overall photosensitivity of the material for stability-indicating method development purposes, pathway elucidation and types of degradation products formed. The purpose of the confirmatory study is to estimate the photostability characteristics under standardized conditions.

To ensure formation of all possible degradation products including products formed in sensitized reactions, the sample must be irradiated at all absorbing wavelengths (i.e. a broad spectrum irradiation source should be applied). The intensity of the light source must be related to the actual intensity under real conditions in order to determine the accelerating effect. It is also recommended that the degradation studies be conducted with low concentration of the drug so that first order kinetics applies.
Although the proposed test is reasonably simple to conduct, special attention should be given to parameters like irradiation source, irradiance level and the temperature effects, calibration of lamps and presentation of samples. The ICH Guidelines gives two options for selection of irradiation source, however, it does not specify an irradiance level and only the overall illumination is mentioned. It is essential to calibrate the light source and periodically monitors its irradiance in order to obtain the predetermined exposure value. If irradiance drops; the lamp power is adjusted accordingly to keep the irradiance level constant. 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 that the sample thickness should not exceed 3 mm for solid drug substances.

Conclusion

Light-stability testing for pharmaceutical formulation should provide information related to the practical use of the product and the storage conditions. There is a growing interest in the development of drug delivery systems, which would offer photostability. Finally, the knowledge of drug-light interactions is a necessary prerequisite to the development of dosage forms that are stable and of good quality. There are various established drug delivery systems apart from cyclodextrins such as ion exchange resins, solid dispersions, microspheres that should be explored for their potential to offer protection against photodegradation of active pharmaceutical ingredient in formulation. It is hoped that this review provides some perspective of this important area of drug formulation and development.

REFERENCES
