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PHOTOCHEMICAL FATE OF PHARMACEUTICALS: AN UPDATED REVIEW

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Abstract: Photostability plays a vital role in the drug development process. It deals with the effect of light on stability of API & plays an important role to decide the recommended storage conditions for formulated product during its life history. The purpose of photostability testing is to provide evidence on how the quality of the product varies with time under the influence of light. Many regulatory bodies throughout the world like ICH, WHO, USFDA, EMEA etc. have issued various guidelines regarding the drug photostability testing and procedures for performing the photostability testing. The present study reviews mechanisms of photo degradation of pharmaceuticals, factors affecting photostability, formulation characteristics affecting photostability, various guidelines for testing Photostability of new drug substances and products throughout the globe. In addition to these various reported formulation approaches which improved Photostability have also been discussed. This review summarizes the current knowledge of the photochemical behaviour of pharmaceuticals and highlights the use of the fundamental photochemistry and photo toxicity literature to help understand and predict the photochemical fate of pharmaceuticals.

Keywords: Photostability, ICH, WHO, EMEA, Photodegradation.



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INTRODUCTION

The stability of a drug is defined as the capacity of a drug substance or the drug product to remain within the established specifications to maintain its identity, strength, purity, quality and efficacy throughout the retest or within expiration dating periods^{1, 2}. The purpose of Photostability study is to show how the quality of the formulation varies under influence of light or to demonstrate that appropriate light exposure does not result in unacceptable change. Photostability testing of the drug substance is undertaken to evaluate the overall photosensitivity of the material for development and validation purposes and to provide information necessary for handling, packaging and labelling. Photostability is used to describe how a drug molecule responds to light exposure and includes not only degradation reactions but other processes such as the formation of radicals, energy transfer and luminescence. A large number of pharmaceutical compounds undergo degradation on exposure to light (see table no. 1). Some photosensitive drugs are rapidly affected either by natural light (particularly ultraviolet) or by artificial light (e.g., fluorescent light). This may lead to a change in the physicochemical properties of the product resulting in photodegradation of the active ingredient. Drugs with absorption maxima greater than 280 nm may decompose in sunlight. However, instability due to light will probably only be a

Table 1: Photosensitive Drugs

1	Anticancer Drugs	Mehotrexate, Cisplatin, Danuorubicin, Dacarbazine, Vincristine, Carmustine, Bleomycin, Toposides, 5-Fluorouracil
2	Calcium channel blockers	Nifedipine, Verapamil, Nicardipine, Amlodipine
3	Chemotherapeutics	Sulphadiazine, Sulfamethazine, Sulfamethoxazole
4	Diuretics	Furosemide, Amilroide, Dilitiazem
5	Psychopharmacological Agents	Prochlorperazine, Haloperidol Perphenazine, Trifluoperazine, Fluphenazine
6	Antibiotics	Cholramphenicol, Tetracyclines, Rifampicin, Doxycycline
7	NSAIDs	Sulindac, Naproxen, Ketoprofen, Flurbiprofen, Indomethacin
8	Anti Hypertensive's	Ramipril, Lacidipine, Valsartan
9	H ₂ Blockers	Famotidine, Ranitidine, Cimetidine
10	Miscellaneous	Ubidecarenone, Emetine, Colchicine, Curcumin, Rutin, Quercitin, Riboflavin

Problem if the drug significantly absorbs light with a wavelength greater than 330 nm and, even then, only if the reaction proceeds at a significant rate³ (Albini and Fasani 1998). Light instability is a problem in both the solid and solution state, and formulations therefore need to be designed to protect the compound from its deleterious effects⁴. The most obvious effect of

drug photodegradation is a loss of potency of the product that becomes therapeutically inactive. Although many drugs are found to decompose when exposed to light, the practical consequences may not be the same for all these compounds. The study of photodegradation of drugs is important because the photodegradation products may be inactive or toxic. Such products may also develop by the action of sunlight on the epidermal layers of the skin or in the eye of the patient receiving the drug and may thereby cause photosensitivity reactions^{5,6}.

Photodegradation Process and Mechanism

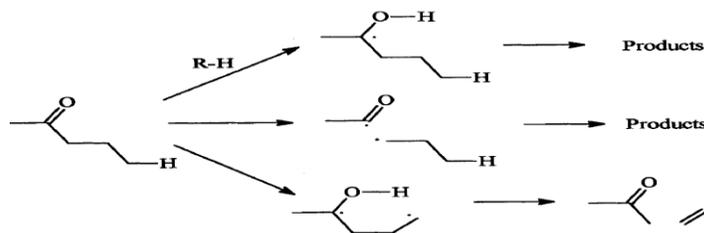
The number of compounds showing photo instability is very large. Photo degradation of drug substances mainly depends on the spectral properties of the drug and the spectral distribution of the light source⁹. Photochemical destruction of pharmaceutical products is usually due to absorption of light of the mainly visible violet, blue and ultraviolet light^{10, 11}. Photochemical reactions involve electronically excited states that are formed through the absorption of ultraviolet or visible light by molecules. A photon corresponding to the ultraviolet wavelength 300 nm has the energy equivalent to 400 kJ mol^{-1} , which is of comparable magnitude to the bonding energy of organic compounds¹². The fact that a drug absorbs radiation in the ultraviolet or visible region of the electromagnetic spectrum means that it is absorbing the energy that is sufficient to break a bond in the molecule. Thus the property of absorption is a first indication that the drug may be capable of participating in a photochemical process leading to its own decomposition or that of other components of the formulation. It is possible to indicate some molecular features that are likely to make a molecule liable to photodecomposition, even if it is difficult to predict the exact photochemical behaviour of a specific molecule¹³. There are a number of chemical groups that might be expected to give rise photo decomposition. These include the carbonyl group, the nitroaromatic group, the *N*-oxide group, the C=C bond, the aryl chloride group, groups with a weak C-H bond, sulphides, alkenes, polyenes and phenols^{9,13}.

At any rate, several above mentioned chemical functional groups are expected to introduce photoreactivity (Scheme 1). These are:

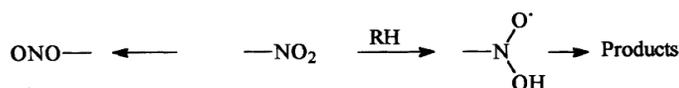
a. The carbonyl group-This behaves as an electrophilic radical in the $n\pi^*$ excited state.

Typical reactions are reduction via intermolecular hydrogen abstraction and fragmentation

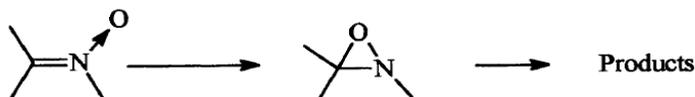
either via α -cleavage or via intramolecular gamma -hydrogen abstraction followed by $C\alpha$ - $C\beta$ cleavage .carbonyl group is present in many drugs such as naproxen .



b. The nitroaromatic group, also behaving as a radical, and undergoing intermolecular hydrogen abstraction or rearrangement to a nitrite ester.



c. The N-oxide function. This rearranges easily to an oxaziridine and the final products often result from further reaction of this intermediate.



d. The C=C double bond, liable to *EIZ* isomerisation as well as oxidation.

e. The aryl chloride, liable to homolytic and/or to heterolytic dechlorination



So it becomes very important to pay attention to existing and added wider knowledge of photochemistry in the literature to predict the photo activity of new drugs. On the basis of the literature available, it is certainly possible to predict photolability of a given molecule and to guess possible reaction paths.

Formulation Factors & Dosage Forms Characteristics Affecting Drug Photostability And Photodegraton

Photochemical reactivity of drug formulations is an important aspect to consider during development, production, storage, and use of pharmaceutical preparations. Photodecomposition and stabilization of compounds in dosage forms are increasingly gaining significance. Important formulation factors that may influence the photostability of drugs in solution include drug concentration, solvent system, pH, buffer salt (type, concentration), ionic strength, metal ions, chelating agents, complexing agents, antioxidants, preservatives, colours etc¹⁴.

Effect of 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 excipients and type of formulation are likely to influence the photodecomposition of the active compound¹⁵. Excipients can initiate, propagate or participate in photochemical reactions. For liquid preparations, the selection of buffer and pH will be determined from solution kinetics. The buffer may also affect the photodegradation reactions of riboflavin in aqueous solution¹⁶. 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 level¹⁷. For example Chlorphenesine 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 products¹⁸. 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^{19, 20}

Photodecomposition in the solid dosage forms

In the solid state (*e.g.* tablets, capsules, powder), the photochemical process, take place on the product surface while the interior is unaffected. Photodegradation of solid drugs depends on whether the state is crystalline or amorphous. Another factor influencing photodegradation is polymorphism. Furosemide and carbamazepin, for example, showed different rates of photodecomposition depending upon their polymorphous modification^{20, 21}. Investigations of the Photostability of ubidecarenone in the solid state show the degree of degradation as a function of the light-absorption properties of the yellow coloured substrate²¹.

Photodegradation in liquid dosage forms

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. Various factors affect Photodegradation in liquid dosage forms such as concentration ionization & pH. 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-Soxide as the main photodegradation product²². pH will significantly affect the photodegradation process. 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 degradation²².

Approaches to stabilization of formulations against photodegradation:

In principle, formulations containing drugs susceptible to photoreactions should be clearly marked and stored appropriately. However, in some situations the ideals are not maintained, and it is worth considering whether special procedures or additives should be included. Photostabilization of a drug molecule in a formulation can be broadly classified in photostability achieved using conventional methods and photostability achieved using novel drug delivery system. In cases where oxygen takes an active part in the degradation process, the use of an inert atmosphere should be considered. For example the oxidative cleavage of the double bond in D-9(11)-dehydroestrone methyl ether degradation can be prevented by removal of oxygen. 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. The major contenders would be substances such as ascorbic acid, α -tocopherol, and BHT, which are capable of acting as free radical scavengers and weak singlet oxygen quenchers.

Table no. 2 Photostabilization of Drugs in Dosage Forms

Stabilizing Approach	Examples of Excipients
Colouring of tablet core; tablet coating; gelatin capsule shell	Food colorants; flavonoids; yellowcolored Vitamins
Pigmentation of tablet core; tablet coating; gelatin capsule shell	Iron oxides; titanium dioxide
Remove oxygen	Inert atmosphere (nitrogen)
Addition of UV absorbers	Benzophenones; camphor derivatives; <i>p</i> -amino benzoic acid; vanillin
Addition of scavengers; quenchers; antioxidants	Mannitol; glutathione; beta carotene; ascorbic acid

Cyclodextrin is cyclic oligosaccharides capable of forming non-covalent inclusion complexes with a large variety of agents. The interaction of Cyclodextrin with labile compounds can retard drug degradation, accelerate degradation, or have no effect on molecule reactivity. By providing a molecular shield, cyclodextrin complexation encapsulates labile drug molecules at the molecular level and thus insulates them against various degradation processes²³. The stabilizing effect of cyclodextrins depends on the nature and effect of the included functional group on drug stability and vehicle²⁴. The protective effects of Cyclodextrin against photodecomposition of some photosensitive compounds have been reported²⁵. Drugs from the group of 1,4-dihydropyridine derivatives are characterized by high photosensitivity, the photodegradation of DHP in inclusion complex with β -cyclodextrin is reported to be 200 times lower than the same compound in crystal phase²⁶. Isradipine another 1,4-dihydropyridine derivative, when complexed with methyl β -cyclodextrin, increased photostability twice that of the drug²⁷. Photostability studies on another nicardipine-cyclodextrin complexes; showed a photo protective effect by β -cyclodextrin, hydroxyl propyl (HP β -cyclodextrin) and hydroxyl ethyl β -cyclodextrin (HE β -cyclodextrin) and a photo degradative effect by α -CYCLODEXTRIN²⁸. The cyclodextrins were reported to have improved the photostability of trimeprazine and promethazine^{29, 30}. Isotretinoin, a highly lipophilic and photolabile drug, is known to be hazardous and hence frequently raises formulation problems. In an effort to simultaneously improve the dissolution profile, photostability and safe handling of the drug was appreciably improved with co-inclusion compounds when the drug was co-included with rapidly adductible endocyte in a urea host lattice³¹. Liposphere formulation is an aqueous micro dispersion of solid water insoluble spherical micro particles of particle size between 0.01 and 100 μm in diameter. The lipospheres are made of solid hydrophobic triglycerides with a monolayer of phospholipids embedded on the surface of the particle³². Encapsulation of melatonin into lipid microparticles i.e. in lipospheres could be considered an effective carrier system to improve the photostability of melatonin³³. 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 cyclodextrin or liposomes³⁴. When pantoprazole prepared as microcapsules, it demonstrated high quality and stability. Solid dispersion of pantoprazole with Eudragit E also demonstrated to protect pantoprazole from photodegradation³⁵. 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 photostability³⁶.

Photostability testing:

Drug Photostability constitutes an important current subject of investigation because the photodegradation process can result in a loss of the potency of the drug and also in adverse effects due to the formation of minor toxic degradation products³⁷. As a consequence, various pharmacopoeias prescribe light protection for a number of drugs and adjuvants during storage. Knowledge of the photochemical and photophysical properties of drugs is essential to ensure adequate product quality and also for predicting drug phototoxicity. It is extremely difficult to establish the actual exposure of pharmaceutical products during practical usage. ICH issued guideline on photostability testing of new drug substances and products in November 1996 stating that the intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in an unacceptable change in composition. These guidelines are adopted by the EMEA in December 1996, Ministry of Health, Labour and Welfare of JAPAN in May 1997, USFDA in May 1997, ASEAN countries and GCC countries. Since January 1, 1998 it has been mandatory to provide photostability data for all new drug license applications to the markets in the U.S., Canada Union, Japan, and the European. In these parent guidelines it is recommended to be carried out on a single batch of material however under some circumstances these should be repeated if certain variations are made to the product i.e. change in formulation or packaging. The guideline primarily concerned with generation of photostability data for submission in Registration Applications for new molecular entities and associated drug products. However this guideline does not include the consequences of the Photostability of drugs after administration³⁸⁻⁴¹.

A systematic approach to photostability testing is recommended covering, as appropriate, studies such as⁴²⁻⁴⁴:

- ❖ Tests on the drug substance
- ❖ Tests on the exposed drug product outside of the immediate package
- ❖ Tests on the drug product in the immediate package
- ❖ Tests on the drug product in the marketing package

The extent of drug product testing should be estimated by determining whether or not an acceptable change has occurred at the end of the light exposure testing as described in the parent guidelines. Acceptable change is change within limits justified and it does not affect the quality, safety & efficacy characteristics of the product.

LIGHT SOURCE:**B. Light Sources**

The light sources described below may be used for photostability testing. The applicant should either maintain an appropriate control of temperature to minimize the effect of localized temperature changes or include a dark control in the same environment unless otherwise justified.

Option 1:

Any light source which is shaving output similar to D65 i.e. an international standard for outdoor daylight or ID65 i.e. equivalent indoor indirect daylight standard. For a light source emitting significant radiation below 320 nm, an appropriate filter(s) may be fitted to filter out it.

Option II: Exposure to two lamps that combined cover the requisite exposure wavelengths: a cool white fluorescent lamp conforming to ISO 10977 and a near UV fluorescent lamp with output from 320 to 400 nm and having an emission maximum in the 350–370 nm range.

C. Procedure

For confirmatory studies, samples should be exposed to light source providing an overall illumination of not less than 1.2 million lux hours. In addition to this an integrated near ultraviolet energy of not less than 200 watt hours/square meter for allow direct comparisons to be made between the drug substance and drug product. A validated chemical actinometric system for sample to expose it side by side to ensure the specified light exposure is obtained.

2. DRUG SUBSTANCE

Drug substance is defined as the unformulated substance which subsequently formulated to produce the suitable dosage form. For drug substances, photo stability testing consists of forced degradation testing followed by confirmatory testing. The main aim of forced degradation testing studies is to access the overall photosensitivity of the material for method development purposes and for degradation pathway explication. Testing involves the drug substance alone or in simple solutions/suspensions to confirm & validate the analytical procedures. The samples should be placed in a transparent and chemically inert container for these studies. Forced degradation studies involve a variety of exposure conditions are used which depend on the intensity of the light sources used the photosensitivity of the drug substance involved. Forced degradation studies provide more information about the decomposition products that are unlikely to be obtained under in confirmatory studies. This is

followed by Confirmatory studies which provide the necessary information for handling, packaging, and labelling.

Initially testing of single batch of drug substance is required and if the results of the confirmatory study are misleading then testing of up to two additional batches is required.

A. Presentation of Samples

Great Care is required to control the environmental conditions so that samples under test to remain unaffected by environmental changes. All such precautionary measure is required to minimize exposure of samples under test to adverse conditions which may affect the outcome. There must be no interaction between sample material & material used for container for obtaining robust data. . Liquid Drug substances should be exposed in transparent containers and chemically inert. The Major challenge for samples of solid drug substances, an appropriate amount of sample should be taken and placed in a suitable glass or plastic dish and protected with a suitable transparent cover if considered necessary. Solid drug substances are required to spread across the container so as to obtain a thickness of not more than 3 millimetres.

B. Analysis of Samples

After completion of exposure period, the samples are examined for any changes in physical properties such as appearance, colour of solution, clarity, assay and decomposition by a method suitably validated for products likely to arise from photochemical degradation processes. In testing of solid drug substance samples sampling should ensure a representative portion is used in individual tests. The analysis of the exposed sample should be performed simultaneously with that of any protected samples used as dark controls if these are used in the test.

Flowchart for Photo stability testing of pharmaceutical products

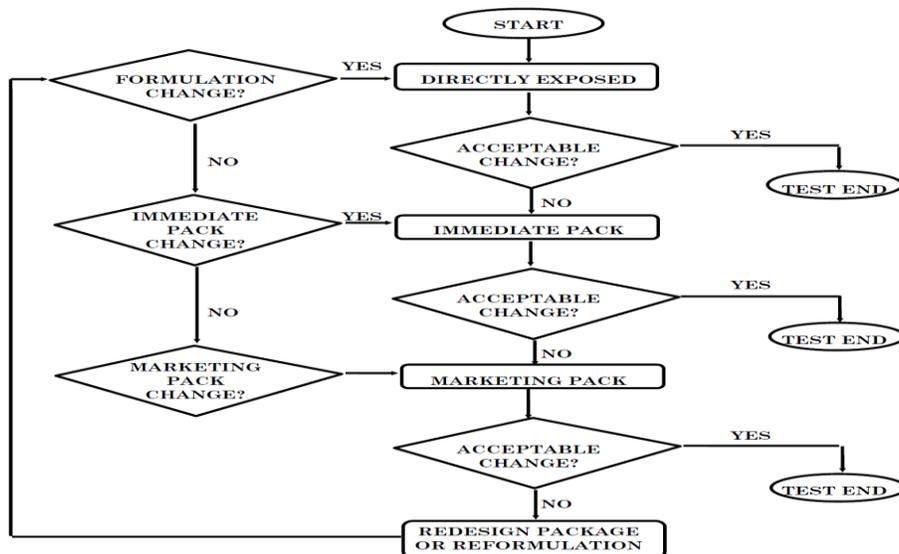


Fig1-Protocol for Photostability studies of pharmaceuticals

C. Judgement of Results

The forced degradation studies should be designed to provide suitable information to develop and validate test methods for the confirmatory studies. These test methods should be capable of resolving and detecting photolytic degradants that appear during the confirmatory studies. When evaluating the results of these studies, it is important to recognize that they form part of the stress testing and are not therefore designed to establish qualitative or quantitative limits for a change. The confirmatory studies should identify precautionary measures needed in manufacturing or in formulation of the drug product, and if light resistant packaging is needed. When evaluating the results of confirmatory studies to determine whether change due to exposure to light is acceptable, it is important to consider the results from other formal stability studies in order to assure that the drug will be within justified limits at the time of use.

➤ DRUG PRODUCT

Normally, the studies on drug products should be carried out in a sequential manner starting with testing the fully exposed product then progressing as necessary to the product in the immediate pack and then in the marketing pack. Testing should progress until the results demonstrate that the drug product is adequately protected from exposure to light. The drug product should be exposed to the light conditions described under the procedure in section I.C.

Normally, only one batch of drug product is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the Parent Guideline if the product is clearly photostable or photolabile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted.

For some products where it has been demonstrated that the immediate pack is completely impenetrable to light, such as aluminium tubes or cans, testing should normally only be conducted on directly exposed drug product.

It may be appropriate to test certain products such as infusion liquids, dermal creams, etc., to support their photostability in-use. The extent of this testing should depend on and relate to the directions for use, and is left to the applicant's discretion.

The analytical procedures used should be suitably validated.

➤ Presentation of Samples

environmental conditions must be monitored so as to minimize interference with the irradiation of sample under test. there should be no interaction between sample and material used for containers; if so eliminated with proper substitution. Where practicable when testing samples of the drug product outside of the primary pack, these should be presented in a way similar to the conditions mentioned for the drug substance. The samples should be positioned to provide maximum area of exposure to the light source. For example, tablets, capsules, etc., should be spread in a single layer. If testing of the drug product in the immediate container or as marketed is needed, the samples should be placed horizontally or transversely with respect to the light source, whichever provides for the most uniform exposure of the samples. Some adjustment of testing conditions may have to be made when testing large volume containers.

➤ Analysis of Samples

On completion of light exposure period, the samples should be examined for any changes in physical properties such as appearance, clarity or color of solution, dissolution/disintegration for dosage forms such as capsules, etc. and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes. When powder samples are involved, sampling should ensure that a representative portion is used in individual tests. For solid oral dosage form products, testing should be conducted on an appropriately sized composite of, for example, 20 tablets or capsules. Similar sampling considerations, such as homogenization or solubilization of the entire sample, apply to other materials that may not be homogeneous after exposure (e.g., creams, ointments, suspensions, etc.). The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark controls if these are used in the test.

➤ Judgement of Results

Depending on the extent of change in the drug substance special labeling & packaging is needed to extenuate the undesirable consequences of light exposure. When evaluating the results of photostability studies to determine whether change due to exposure to light is acceptable, it is important to consider the results obtained from other formal stability studies in order to assure that the product will be within proposed specifications during the shelf life.

Inconsistencies in current ICH guidelines

The ICH Harmonized Tripartite Guideline on Stability Testing of New Drug Substances and Products (Q1B) does not specifically address other photostability studies that may be needed to support, for example, the photostability of a product under in-use conditions or the photostability of analytical samples. The photochemical reaction is a very complex process which depends on many variables such light source, intensity, and wavelength of the light, size, shape, composition, and colour of the container. For properly accessing the effects of light on the quality of a drug substance or drug product, there must be a standard light-stability testing which considers all of the abovementioned variables.

CONCLUSION

Photo instability of pharmaceuticals has been long known twentieth century . As an example, Pasteur noticed the photolability of quinine in 1846 and industry-sponsored studies on the photochemistry of drugs were already systematically carried out in the twenties. However, until recently the matter has received only limited attention, mainly on the assumption that by using the appropriate opaque container . As a result, the available knowledge is quite sparse. All Pharmacopoeias mention that some drugs have to be protected from light, but one cannot rely upon such qualitative (and incomplete) information. The number of reports in specialised journals is growing, but remains low. The situation has changed recently, however, and this is due to several causes. The development of a new drug is very expensive and this calls for more attention to the photochemical properties of a molecule early in the development, or for a way to predict the photostability of a new molecule. So there is a need for a close collaboration between different areas such as industries, regulatory agencies and from different disciplines such as pharmaceutical techniques, pharmaceutical chemistry, photochemistry, photophysics, biology, and toxicology has been recognised.

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