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Review Article

PHOTOSTABILITY TESTING OF PHARMACEUTICAL PRODUCTS

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ABSTRACT
Stability testing is a key aspect while formulating any pharmaceutical product. The photostability studies are conducted with main objective that appropriate light exposure does not leads to unacceptable changes in dosage form. Photo degradation leads to changes in Physical appearance as well as chemical composition of dosage form. The objective of the present study is to describe the approaches for the photostability studies on pharmaceutical Products. Also this review deals with the factors affecting the photostability of pharmaceutical products as well as certain examples of photostability studies on pharmaceutical products are also described.
Keywords: Photosensitivity, Degradation, Light source, Test conditions, Drug substance, Drug product.

INTRODUCTION

Stability is officially defined as time period in which the drug product retains the same properties and characteristics that it possessed it at the time of its manufacturing. The stability of drug product is always expressed in terms of its shelf life. Expiration period is valuable quality attribute for all dosage forms. A Manufacturer is always obliged to indicate shelf life of a drug on its label unless it is greater than 3 years no product may be sold after 5 years. Stability studies are necessary for following reasons:

- Product instability may lead to under medication due to lowering of active drug concentration in dosage form.
- Drug decomposition leads to formation of toxic products.
- Instability leads to changes in physical appearance[11].

The Photostability studies are carried out to demonstrate that the appropriate light exposure does not results into unacceptable changes in dosage form. 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 discoloration 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, Although many drugs are found to decompose when exposed to light[1]. Some compounds may decompose only to a smaller extent after several weeks' exposure, while others like 1, 4-dihydropyridine derivatives (Nifedipine) 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 drugs and ultimately toxicity to human tissues clearly, the most important consequence of photodegradation is the loss of potency of the product. Light energy like heat activates molecules and enhance rate of reaction. The drug which undergo light induce degradation are called as photolabile drugs ex. Chlorpromazine, tetracycline. Colour development colour fading are also examples of Photo degradation. Such Photo degradation reactions are complex and proceed in several steps. These reactions usually follows zero order kinetics but some are exceptions the drugs like Adriamycin nefiipine also have first order photokinetics[11].

Pharmaceutical product photosensitivity classification system

A pharmaceutical product photosensitivity classification system is a potentially useful for understanding and managing the implications of product photosensitivity during manufacturing, packaging, shelf storage, testing, and administration. Such a classification system offers a means to establish a common understanding that can be applied across a particular category of photosensitive products. Class II and III products are those that photodegrade or otherwise exhibit significant change upon direct-light exposure. The difference between Class II and Class III products is that although Class II products are fully protected from photo-driven change when placed into an appropriately protecting immediate package, Class III products may be adversely affected by light even when housed in an immediate package. Class III products thus require protection from light with an additional packaging layer (e.g., a cardboard carton). The photostability implications for Class II and Class III products necessitate different approaches. Class II and Class III products both require carefully designed photostability studies to support effective decision making for product protection in each of the key areas of product development[8].

Photostability testing

USA FDA in 1996 issued ICH guidance for industry and stated 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 unacceptable change". In this photostability testing is recommended to be carried out on a single batch of

material; however these studies should be repeated if certain variations and changes are made to the product (e.g., formulation, packaging). The guidelines which are given addresses primarily generation of photostability information for submission in registration applications for new molecular entities and associated drug products. The guideline does not cover the photostability of drugs after administration (i.e., under conditions of use) and those applications not covered by the parent guideline. A systematic approach to photostability testing is recommended covering, as appropriate, studies such as[10,6,9]:

- Tests on the drug substance.
- Tests on the exposed drug product outside of the immediate pack.
- Tests on the drug product in the immediate pack; and if necessary.
- Tests on the drug product in the marketing pack.

Light Source

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[6,10].

- Artificial daylight tubes: The visible output will provide a reasonable simulation of natural daylight and should also provide a reasonable simulation of natural UV light. Fluorescent tubes they are suited because they provide illumination over wider area and also they have low cost and high popularity.
- Xenon lamps: It is well known that xenon lamps provide the closest simulation of sunlight of all artificial sources and can give a total irradiance (W m-‘) similar to that of natural sunlight over a small area Their selection by a number of pharmaceutical laboratories indicates that these laboratories wish to reproduce natural light as closely as possible.
- Tungsten-mercury lamps: These provide a high level of visible light with a small or very small UV component, depending on the specification. Laboratory light. The use of laboratory light (typically 400-800 lx), as opposed to natural daylight or more intense artificial sources, provides a “low light” condition which is of value in investigating the sensitivity to photo degradation of products containing drug substances known to be very susceptible to such degradation. However its use is less relevant in routine product testing.
- Natural Light: The spectral distribution as well as the intensity of daylight varies not only with the time of day, weather conditions and atmospheric pollution, but also with the time of year Thus along with that U.V. component also varies and this makes the natural light not suitable for the testing.
- Other: A cool white fluorescent lamp designed to produce an output similar to that specified in ISO 10977 (1993); and A near UV fluorescent lamp having a spectral distribution from 320 nm to 400 nm with a maximum energy emission between 350 nm and 370 nm; a significant proportion of UV should be in both bands of 320 to 360 nm and 360 to 400 nm.

Defining the Test Conditions

In order to fully define the test conditions during photostability testing it is necessary to measure not only the visible light (illuminance) to which products are exposed but also the UV content (irradiance) since many drugs absorb little or no visible light but absorb in the UV range present in natural light (290-400 nm). Data on UV irradiance are not necessary for sources which are known to provide good simulation of sunlight (e.g. xenon lamps) in order to predict product behavior in natural light. However, for other sources of light, such a prediction cannot be made without knowledge of their UV irradiance[6].

Presentation of Samples

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account and efforts should be made, such as cooling and/or placing the samples in sealed containers, to ensure that the effects of the changes in physical states such as sublimation, evaporation, or melting are minimized. For solid drug substances they should be placed in glass or plastic dishes and covered with a suitable transparent cover Solid drug substances should be spread across the dish to give a thickness of typically not more than 3 Millimeters. Drug substances that are liquids should be exposed in chemically inert and transparent containers. For the drug products when the testing is done outside the primary pack they 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, should be spread in a single layer. If direct exposure is not practical (e.g., due to oxidation of a product), the sample should be placed in a suitable protective inert transparent container (e.g., quartz). 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 (e.g., dispensing packs)[6].

Analysis of Samples

At the end of the exposure period, the samples should be examined for any changes in physical properties like appearance clarity, color of solution and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes. The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark control if these are used in the test. For the drug product sampling considerations like homogenization solubilization of the entire sample, apply to other materials that may not be homogeneous after exposure (e.g., creams, ointments, suspensions)[6].

Judgment 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 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 time of use[6].

A factor that influences the photostability

In Solid dosage form: - Here the parameters for tablet dosage form are considered[2].

Particle size

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

In the case of solution dosage forms: - The following parameters are considered.

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.

pH and Ionization

pH will significantly affect the photodegradation process. Some drugs undergo degradation at lower pH while the others undergo at higher pH. 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.

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 drugs are 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 colored 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.

Some typical examples of Photostability studies of drugs

- Carbamazepine: The photostability of carbamazepine poly morphs in solid dosage forms (tablets) was evaluated using Fourier transform infrared reflection absorption spectrometry and colorimetric assessment of all three polymorphs (I, II, and III), after irradiation under a near-UV fluorescent lamp. The surface of the tab lets discolored to yellow and then orange with results indicating polymorph II to be the least stable. The photo degradation followed first-order kinetics with the degradation rate constant for form II proving to be 1.5 times larger than for forms I and III. The resulting order of degradation was II > I > III.
- Cyanocobalamin: A study of the photolysis of cyanocobalamin in the presence of visible light and at various pH indicated a slow de crease in the rate at pH 1–3 and a fast de crease at pH 3–7, confirming the protonated form to be more susceptible to photolysis.
- Fumagillin: The antibiotic fumagillin, used in the treatment of AIDS patients with microsporidiosis, is extremely sensitive to heat with degradation even occur ring in the freezer. This drug substance should therefore be stored at –60°C, and protected from light.
- Furosemide: Furosemide exists in the solid-state as at least three polymorphs, two solvates, an amorphous form and a high-temperature form (IV) The photostability under air and nitrogen of polymorphic forms I and II of furosemide was investigated. The photo degradation followed first-order kinetics, with the photo degradation of form II occur ring in dependently of oxygen. Both forms I and II gave rise to 4-chloro-5-sulphamoylanthranilic acid after exposure to sunlight[7].

Tests to determine stable/unstable classification

Exposure (klx days)	Maximum permitted level of degradation (%)
Liquids	
8	0.5–1
<180	0.1–0.5
45–180	0.5–1
Solids	
<360	0.5–1
360–1080	0.5–1
180–1260	0.5–1

Figure 1: Showing Max. Permitted level of degradation upon exposure to light

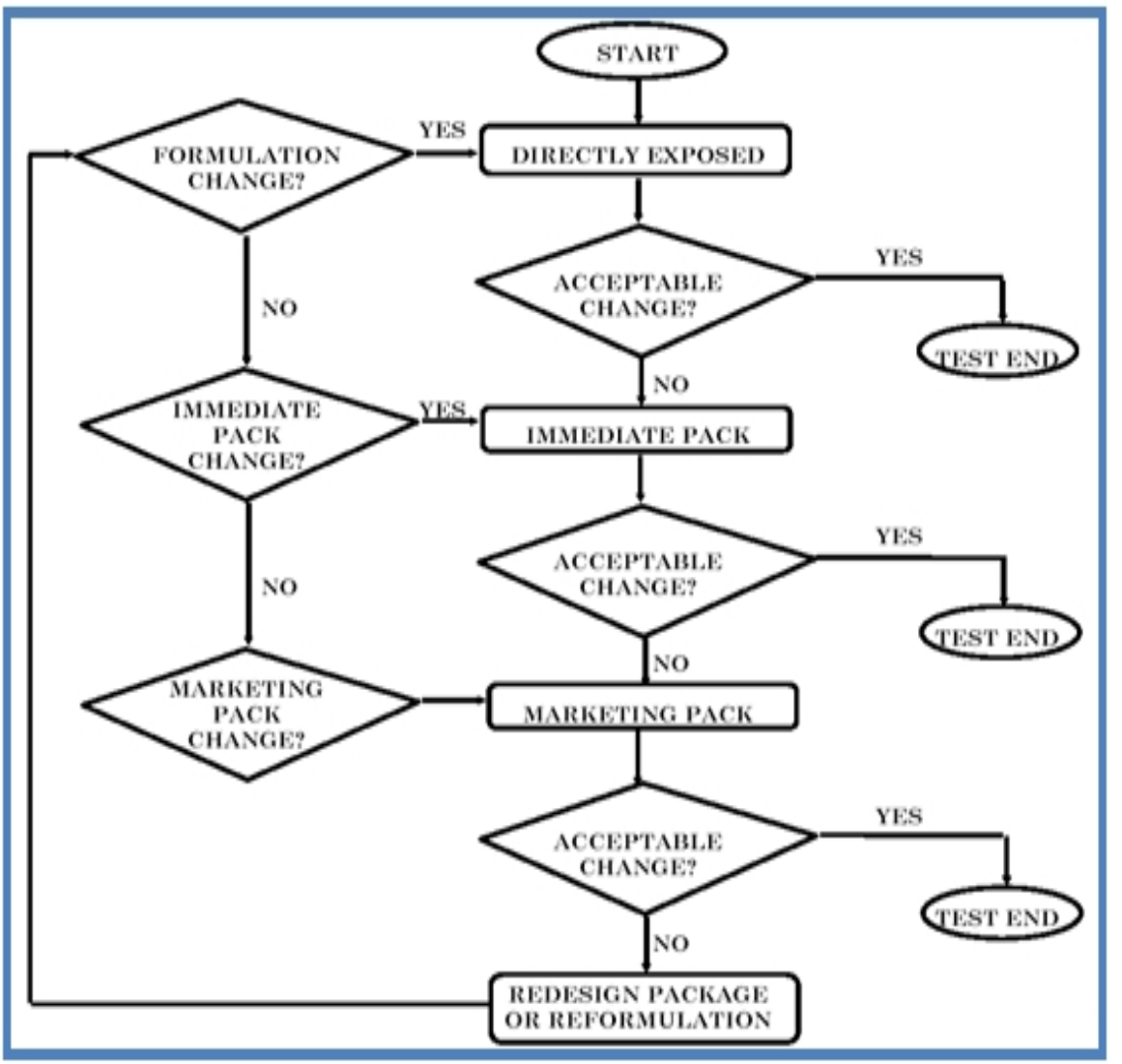

Figure 2: Protocol for Photostability Studies of Pharmaceutical products

CONCLUSION

Photo stability data is as important as other stability indicating data for pharmaceutical dosage form hence its requirement for the complete stability studies for most of the pharmaceuticals dosage form as well as drug substance is a priority. With an advent of Guidelines give by US-FDA and ICH Guidelines the above testing protocols were ascertained for the photo stability of pharmaceutical dosage form and drug substances. The various factors affecting the photo stability of dosage form should be clearly indicated so as to prevent their interference with the testing and the stability of dosage form.

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