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REVIEW ON PHOTOSTABILITY STUDIES OF FORMULATION

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ABSTRACT

This article tries to provide a fabulous journey of various studies that have been takes place in photostability evaluation and development of photostable formulations. This article includes photodegradation process, factors affecting process, various ways to tackle with photostability problem and regulatory aspects for photostability studies. The ways which are being used to tackle photostability problem include light resistant container, antioxidants, light absorber or pigments, light resistant coating, inclusion complexation with cyclodextrins, liposomes, microspheres, microcapsules and ion-exchange resins. The recent works show that the ion-exchange resins and complexation with cyclodextrins are being effective and can be used commercially for manufacturing of photostable formulations of photosensitive drugs.

KEYWORDS: Photostability, Inclusion complexation, Ion-exchange resins.

INTRODUCTION

Recently photostability of drugs and pharmaceuticals are gaining much more attention of researchers in this field. There are several reasons for this just like the photosensitive drugs undergo important chemical changes, accompanied by alternation in their activities and in some cases total loss of their therapeutic activity, adverse effect of photoreactive product, poor storage conditions may potentially decrease clinical efficacy of photosensitive products. There are number of drugs which are light sensitive nature and sensitivity differs among them.[1] They include 1, 4-dihydropyridine derivatives (nifedipine, nimodipine),

benzodiazepine derivative (midazolam, diazepam), proton pump inhibitors (pantoprazole, omeprazole) and leukotriene antagonist (montelukast) etc. These drugs are undergoes changes in chemical, physical and therapeutic properties on exposure of light radiation. Manufacturers of such products use light resistant coating or packing to minimize their photo degradation. Along with this they require special storage conditions, generally cannot be provided by patients. The light radiations causing degradation of these photosensitive drugs include sunlight, artificial day, ultraviolet and fluorescent light. Light can influence the active principle in a drug formulation as well as the final product or package. There are differences in the effectiveness of artificial light and natural indirect sunlight sources in photodegradation of various drugs like nifedipine. Nifedipine undergoes faster degradation in normal sunlight than under exposure to a light bulb or artificial light.[2] The effect of photodegradation causes drugs to discolor or change in colour. Sometimes cloudy appearance of the product, precipitation of active principle, loss in viscosity of formulation may be observed. Nifedipine is highly sensitive to photo-oxidation, changing in color from yellow to brown upon exposure to light.[3]

Photodegradation Process

Photodegradation process is takes place in two ways;

1) Direct reaction.
2) Indirect reaction.

The photodegradation is takes place when absorption spectrum of drug matches with that of source or incident radiation.[4] The absorption spectrum of nifedipine in the long-wavelength region is between about 350 and 450 nm.[5] The direct reaction occurs when these substances absorb light energy directly which will lead to intermediate products and these intermediates are converted to stable molecules by indirect reaction. The basic thing behind these reactions is to convert these substances into stable molecules (stable to light radiation which is absorbed by photolabile drug or pharmaceuticals). The indirect reactions or sensitizing reaction, the light energy may be absorbed by excipients; intermediates which further imparted to drug and leads to further degradation. The direct reaction does not depend on temperature for activation of the molecules while the intermediates in the indirect process can eventually react through ‘dark’ reaction to form the final, stable products. Various reactions which can take place in photochemical process include oxidation, hydrolysis, hydroxylation, isomerization, decarbonylation, decarboxylation and N-dealkylation. The chemical species

which absorb light energy and undergo photodegradation include some important functional groups such as carbonyl group, carbon–carbon double bond, and C-H bond in alcohols amines sulphides may be involved in some photosensitization reactions. Among aromatics nitro group and among heterocyclic compounds five membered rings may lead to photosensitization. The rate of degradation of compounds depends on the concentration of these species present in molecule and also on concentration of solutions.[6]

Factors Affecting Process

A. Experimental factors

- Wavelength of radiation.
- Intensity of radiation.
- Time of exposure of sample to radiation.
- Dimensions of sample holder.

B. Dosage form related factors

- Type of dosage form.
- Particle size.
- Tablet geometry.
- pH.
- Ionic strength.
- Concentration of solutes.
- Pharmaceutical excipients.

Photodegradation is depends on certain experimental factors like wavelength of radiation, intensity and time of exposure of sample to radiation and dimensions of sample holder. As small wavelength has great energy, it will degrade drug easily. Intensity, the term related to energy is directly proportional to photodegradation and similar relation with time of exposure. Photostability means the effect of light on stability of pharmaceutical substances or products. Pharmaceutical excipients are one of the important aspects regarding photochemical process as these acts as sensitizers in indirect reaction and it became necessary to establish data on compatibility studies between drug and excipients before formulation.[7] The effects of buffer on photostability of riboflavin in aqueous solution have been already explained by Iqbal Ahmad et al 2005.[8] Various excipients are causing photodegradation includes binding agents (povidone), disintegrants (crospovidone), viscosity modifying agents

(alginate), lactose, lipid excipients and polyethylene glycol.[9] Dosage form is another important factor which affects photostability. Solid dosage forms photodegradation occurs only on surface while in solutions interior part is affected depending on concentration of solutes. Concentrated solutions undergo less photodegradation as compared with dilute solutions. The rate of photodegradation was found to be inversely proportional to phenobarbital concentration, especially below 8×10^{-4} M.[10, 11] There are other factors related to dosage forms which affect photostability include particle size, drug content, tablet geometry, pH, and ionic strength.[12, 13] The influence of certain pharmaceutical adjuvants on the photostabilizing effect of dimethyl sulfoxide for a buffered solution of sodium nitroprusside was investigated by Ahmed F. Asker and Dorothy Canady in 1984.[14] Dimethyl sulfoxide in a concentration of 10% v/v was found to exercise its effect as a photo protective agent in the presence of methylparaben, sodium sulfite, sodium chloride, dextrose, PEG 300, tween 80, citric acid and sodium edetate. In the absence of dimethyl sulfoxide, sodium sulfite produced the most deleterious effect on the photostability of sodium nitroprusside solution. The photo protective action of dimethyl sulfoxide appeared to be slightly enhanced by the presence of sodium edetate, methylparaben, sodium chloride or citric acid.[14] The role of excipients and package components in the photostability of liquid formulations was also studied in 2003 and it was found that the major contributors to the observed photosensitivity are the citrate buffer, parts per billion levels of iron, oxygen, and light exposure level. The generation of the primary photodegradation was found to be directly proportional with the light exposure for a fixed concentration of iron present in the formulation. Conversely, the amount of photodegradation was also nearly linear with iron concentration (through 200 ppb levels) for a fixed amount of light exposure.[10]

Improvement of Photostability in Formulation

There have been used various ways to deal with the problem of photostability as early said light resistant coating.

A. Conventional Approaches

- Light resistant container
- Antioxidants (ascorbic acid, BHT, a- tocopherol, L- histidine, and β-keratin)
- Light absorber or pigments (curcumin).

B. Formulation Approaches

- Light resistant coating

- Inclusion complexation with cyclodextrins
- Liposomes
- Microspheres
- Microcapsules
- Ion exchange resins

The incorporation of photo stabilizers such as light absorber or pigments into the tablets considerably improved the photostability.[15] Photo protection for light-sensitive drugs is based on finding suitable stabilizers with absorption spectra that overlap that of the respective drug.[9] Selection of ingredients within the dosage form such as antioxidants like ascorbic acid, BHT, α- tocopherol, L-histidine and β-keratin and dimethyl sulfoxide are also improves photostability. Some sweetening agents are also found to be effective. Aqueous solutions of l-ascorbic acid were irradiated with simulated sunlight in the presence of dextrose, mannitol, sorbitol, sucrose and canderel; and the residual *l*-ascorbic acid was measured spectroscopically. The photostability of *l*-ascorbic acid was enhanced by all of the sweetening agents at 5% w/v concentration.[16] If these found to be ineffective some novel formulation approaches are being used like inclusion complexation with cyclodextrins for a number of drugs, supramolecular self-assembling systems, such as liposomes, microspheres and microcapsules.

Natural food colorant curcumin (a constituent of turmeric) have potential to provide photostability in the relevant long-wavelength region of nifedipine spectrum between 300 and 450 nm. It was also stated that yellow colour of this colorant gives more effect to nifedipine.[5,17] Vanillin, quinosol and azorubine have stabilizing effect on molsidomine. Uncoated tablets of nifedipine and sorivudine containing 0.2% w/w of yellow iron oxide were found to be light stable than those without it. Furthermore, inclusion of a combination of 0.05% w/w red and 0.04% w/w yellow iron oxides into uncoated tablets gave them more light protection than the inclusion of either 0.2% w/w yellow or red iron oxide alone.[18] Now a days, the researches in these studies are going to utilize some ion-exchange resins to enhance photostability and make photostable formulations.[19,20]

Regulatory Aspects

As per consideration stability affects safety and efficacy of formulation, this become necessary to regulate stability and studies relating to stability evaluation. The ICH harmonized tripartite guideline on stability testing of new drug substances and products were

issued on October 27, 1993. This document is an annex to the ICH parent stability guideline and addresses the recommendations on what should be submitted regarding stability of new dosage forms by the owner of the original application, after the original submission for new drug substances and products.[21] Following ICH guideline should be considered;

ICH Q1B: "Photostability Testing of New Drug Substances and Products"

ICH Q1C: "Stability Testing of New Dosage Forms"

ICH Q3A: "Impurities in New Drug Substances"

ICH Q3B: "Impurities in New Drug Products"

ICH Q 1B guideline states 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. There are two options to use light sources for study either any light source that is designed to produce an output similar to the D65/ID65 emission standard such as an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs, xenon, or metal halide lamp or 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 and a cool white fluorescent lamp designed to produce an output similar to that specified in ISO 10977.[21] According to this draft of guidelines for confirmatory studies, samples should be exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter to allow direct comparisons to be made between the drug substance and drug product (Fig.1).

Fig.1: Photostability Chamber meets requirements of ICH Q1B

Research Works

This article tried to provide a fabulous journey of various studies that have been takes place in photostability evaluation and development of photostable formulations with an aim to be updated in research related this topic. Earlier in 1989 analytical study of nifedipine and its photo-oxidized forms have been carried out and a direct and simple spectroscopic method for determination of both nifedipine as well as its photo-oxidized degradation products was developed.[22] Certain types of studies have been carried out in Canada and in Iran on different formulations of nifedipine available in local market and found very interesting result about efficacy of natural indirect sunlight in photodecomposition of nifedipine which is more than artificial light in Iran and it could be due to the fact that the intensity of natural light in Iran is more than Canada.[2, 23] Similarly, photostability of nifedipine for its dosage form (Cordaflex) was studied in Hungary, the efficiency of the used primary and secondary light protection implemented for the Cordaflex retard 20 mg tablet were studied using 48 months long term stability trials. The dissolution profiles and impurity levels (HPLC) obtained during the whole trial period met the strictest compendial requirements for this dosage form.[24] Recently, photo degradation of nifedipine, acetylsalicylic acid, acetaminophen, cetirizine and pantoprazole were studied with UV irradiation and differential scanning calorimetry (DSC). *In-situ* was used to evaluate changes in thermo physical behavior of the drugs and possible formation of new phases. The lowest degree of photostabilit**y** was shown for nifedipine and the highest for acetaminophen.[1] The effect of light and heat on the stability of montelukast in solution and in its solid state has been studied. The rate of photodegradation of montelukast in solution exposed to various light sources was found to be in the order of; sodium < neon < tungsten < daylight <UV (254 nm). The decrease in potency of montelukast (about 20%) after exposure to daylight for 1 week was found to be significant. Also unpacked montelukast chewable tablets, exposed to daylight for 2 weeks, showed a decrease of about 10% with the formation of monte *S*-oxide as a major photoproduct.[21,25] A number of riboflavin formulations were tested in 1995 for their effectiveness in protecting the vitamin against UV light and it was found that entrapment of riboflavin into dehydration-rehydration vesicles (liposomes) modestly increases its half-life. However, half-life was increased substantially when oil red O was also present in the bilayers and further increase in the half-life was found when oil red O in the bilayers was supplemented with oxybenzone and dioxybenzone.[26,27] Photo stabilization of drugs in dosage forms without protection from packaging materials were studied and another important ways for stabilization of photolabile drugs like use of curcumin, scarlet GN, tartrazine, methylgallate and certain combinations

have been proved effective.[16,22] In 1999, complexes of isradipine with methyl-ß cyclodextrins were found to be photostable and this lead to increasing use of cyclodextrins for complexing various photolabile drugs and make them photostable. The effect of inclusion complexation with cyclodextrins on photostability of nifedipine in solid state was studied later and it found more photostable to fluorescent light than to indirect sun light.[22, 28] In one study related to use of pigments and UV absorbers it was found that pigments are superior to colorants or ultraviolet absorbers and surface-treated titanium dioxide with reduced photo catalytic activity was less suitable than untreated. This study was also stated use of other substances for photo stabilization of molsidomine such as [4-(t-butyl-40-methoxydibenzoyl)-methane], [3-(4-methylbenzyliden)-camphora, vanillin, azorubine and iron oxide.[23, 28] The effect of microencapsulation on nifedipine photo-stability was conducted in Iran and it was found that microspheres prepared with pectin and ethyl cellulose containing titanium oxide protected nifedipine from photo-degradation for up to 6 days of light exposure.[24] Protection of 10^{-4} M daunorubicin hydrochloride (DNRUB) solutions against photolytic degradation was investigated using sodium sulfite photostability of DNRUB solutions was enhanced with an increase in sodium sulfate concentration in pH 6.5 citrate buffer (0.1 M). Sodium sulfite was found to significantly diminish the catalyzing effect of all the buffers.[27,28] Photo stabilizers used to stabilize the drugs is depicted in Table 1 and techniques used for photostabilization is given in table 2.

Table 1: Photo stabilizers used to stabilize the drugs

Sr. No	Drug	Photo stabilizer	Researcher
1	Isradipine	Methyl β cyclodextrins	Jadwiga Miecarek, (1999)
2	Nifedipine	Curcumin	K. Thoma and R. Klimek ,(1991)
3	Daunorubicin	Scarlet GN	K. Thoma and R. Klimek, (1991)
4	Dihydroergotamine	Vanillin and Methyl Gallate	K. Thoma and R. Klimek, (1991)
5	Nitrofurazone	Curcumin	K. Thoma and R. Klimek, (1991)
6	Furosamide	Vanillin	K. Thoma and R. Klimek, (1991)
7	Haloperidol	Benzyl alcohol and Vanillin	K. Thoma and R. Klimek, (1991)
8	Thiothexen	Quinosol and Vanillin	K. Thoma and R. Klimek, (1991)
9	Meslodamine	Curcumin and Azorubine	W. Aman et al, (2003)
10	Meslodamine	Iron Oxide	W. Aman et al, (2003)
11	Nicardipine	Cyclodextrin	Jadwiga Miecarek, (1997)
12	Nicardipine	Hydroxypropyl β-CD	Jadwiga Miecarek, (1997)
13	Nicardipine	Hydroxyethyl β-CD	Jadwiga Miecarek ,(1997)
14	Triprolidine	B-Cyclodextrin	R. Pomponio, (2004)
15	Amlodipine	γ-Cyclodextrin	G. Rango et al, (2003)
16	Nifedipine	B-Cyclodextrin	Mohsen A. Bayomi et al, (2002)
17	Nifedipine	Indion 204, Indion 264	M. A. Shende et al, (2010)
18	Nifedipine	Accurel MP 1000	Atmaram P. Pawar, (2012)

An important attempt has been made to improve the physiochemical stability of nifedipine by complexation using weak cation-exchange resins, indion 204 and indion 264 to eliminate light decomposition tendency of drug and indion 204 was found to be better complexing agent for reducing the photosensitivity and to design photostable nifedipine tablets.[19]

Table 2: Techniques used for photostabilization

Sr. No.	Drug	Techniques Used	Researchers
1	Amlodipine	Microspheres	G. Rango et al (2003)
2	Nifedipine	Microspheres	Rassoul Dinarvand et al (2006)
3	Nicardipine	Complexation	Jadwiga Miecarek et al (1997)
4	Nicardipine	Complexation	Jadwiga Miecarek et al (1997)
5	Nicardipine	Complexation	Jadwiga Miecarek et al (1997)
6	Triprolidine	Complexation	R. Pomponio (2004)
7	Amlodipine	Complexation	G. Rango et al (2003)
8	Nifedipine	Complexation	Mohsen A. Bayomi et al (2002)

Recently photostable gastro retentive formulation for nifedipine loading into low-density polypropylene microporous particles (Accurel MP 1000) by a solvent evaporation technique was developed and indicated remarkable improved photostability.[20]

CONCLUSION

Light-stability testing for pharmaceutical formulation should provide information related to the practical use of the product and the storage conditions. Photosensitive drugs are undergoes chemical changes, accompanied by alternation in their activities and in some cases total loss of their therapeutic activity and adverse effect of photoreactive product, Various factors affecting process include wavelength of radiation, intensity of radiation, time of exposure of sample to radiation, ionic strength, concentration of solutes and pharmaceutical excipients. The ways which are being used to tackle photostability problem include light resistant container, antioxidants, light absorber or pigments, light resistant coating, inclusion complexation with cyclodextrins, liposomes, microspheres, microcapsules and ion-exchange resins. The recent works show that the ion-exchange resins and complexation with cyclodextrins are being effective and can be used commercially for manufacturing of photostable formulations of photosensitive drugs.

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