

Review Article

Photostability and Photostabilization of Drugs and Drug Products

Iqbal Ahmad,¹ Sofia Ahmed,¹ Zubair Anwar,¹ Muhammad Ali Sheraz,¹ and Marek Sikorski²

¹Baqai Institute of Pharmaceutical Sciences, Baqai Medical University, Toll Plaza, Super Highway, Gadap Road, Karachi 74600, Pakistan

²Faculty of Chemistry, Adam Mickiewicz University in Poznan, Umultowska 89b, 61-64 Poznan, Poland

Correspondence should be addressed to Iqbal Ahmad; iqbal.ahmed@baqai.edu.pk and Muhammad Ali Sheraz; ali_sheraz80@hotmail.com

Received 27 October 2015; Accepted 29 February 2016

Academic Editor: Adel A. Ismail

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Photostability studies of drugs and drug products are an integral part of the product development process in the pharmaceutical industry. These studies are carried out to ensure quality, efficacy, and safety of the formulated products during manufacture, storage, and use. This review deals with the concept of photostability and related aspects and the literature available in the field. It highlights the role of the photochemistry in the photostability studies, describes the functional groups important for the photoreactivity of drugs, explains photophysical processes, and deals with the kinetics of photochemical reactions. The various modes of photodegradation of drugs with examples of selected compounds are presented. The biological consequences of the effect of light on the drug degradation are described. The photostability testing of drugs and drug products and the requirements under ICH guideline are discussed. Some information on the packaging requirements for the formulated products is provided. The various methods used for the photostabilization of solid and liquid dosage forms are also discussed.

1. Introduction

A large number of drugs are sensitive to light [1, 2] and therefore their formulated products may degrade during manufacturing, storage, and administration. This may result in potency loss, altered efficacy, and adverse biological effects. The European Pharmacopoeia [3] prescribes light protection for more than 250 drugs and adjuvants. Knowledge of the photochemical behavior of drugs can provide guidance for handling, packaging, and labeling of drug products. The use of the appropriate containers and packaging material can protect the products from the deleterious effects of light. The sensitivity of a drug to a particular spectral region of light may vary with its chemical structure, photoreactivity, and nature of the dosage form. The rate of a photochemical reaction may be influenced by the intensity/wavelengths of the radiation source and the transmission characteristics of the container. The study of the photochemical reactions may

provide information on the mode of stabilization of the active ingredients in a product. These reactions are often complex and involve free radical species that form photoproducts [4–6]. Photosensitized reactions may also lead to the degradation of the drug substances [6]. The photoproducts of a drug may be harmful and cause phototoxic, photoallergic, or photosensitization reactions upon administration [7–9]. These reactions may also be initiated by the interaction of a drug with endogenous substances in the body in the presence of light. The evaluation of the photochemical stability of drugs and drug products is an essential component of the formulation development process in the pharmaceutical industry. Several monographs [10–12], details [13–23], and reviews [24–29] have been published on the photochemistry, photostability, and related aspects of the drugs and drug products. Information on the photosensitivity, photostability, and storage of pharmaceuticals is also provided in the pharmacopoeias [1–3] and other literature [14, 30, 31].

2. Photostability

The photostability of a drug substance may be defined as the response of the drug or drug product to the exposure to solar, UV, and visible light in the solid, semisolid, or liquid state that leads to a physical or chemical change.

The response of the drug to light absorption and excitation can be considered in terms of photodegradation (photolysis) reactions through the formation of free radicals or photosensitization reactions by intermolecular energy transfer. These reactions involve primary (photochemical) and secondary (chemical) reactions that give the final products.

2.1. Objectives of the Photostability Studies. In view of the photosensitivity and photoinstability of drugs and adjuvants, knowledge of the photostability of these substances and their formulated products is necessary to evaluate the following:

- (i) The intrinsic photostability characteristics.
- (ii) The physical and chemical changes upon the exposure to light.
- (iii) The photodegradation pathways and mechanisms.
- (iv) The shelf life of the products.
- (v) The efficacy of the stabilizing agents in photostabilization.
- (vi) The need for modification of the formulation parameters.
- (vii) The need for the measures to overcome the effects of the light exposure during manufacturing, packaging, labeling, transportation, and storage.
- (viii) The light-induced biological effects.
- (ix) The primary and secondary package design.

2.2. Requirements for the Photostability Studies. Consider the following:

- (i) The solubility of the drug and choice of reaction medium.
- (ii) The spectral characteristics of the drug molecule.
- (iii) The sensitivity of the drug molecule to the solar, UV, and visible light.
- (iv) The reaction vessel and the radiation source appropriate for the spectral characteristics of the drug molecule.
- (v) The knowledge of the photodegradation mode and the nature of the photoproducts from the preliminary studies.
- (vi) A validated stability-indicating assay method to determine the intact drug and the photoproducts in the degraded material.

3. Photochemical Reactions

The photochemistry of the organic compounds has been studied for a long time [32–36] and an advanced treatment

of this subject is available [6, 37]. The study of the photochemistry provides a basis for the understanding of the photochemical reactions of the drug substances that affect their stability and efficacy.

Photochemical reactions may lead to the degradation of the drug substances by one or more pathways to form different products. The elucidation of the mechanisms of these pathways requires a thorough understanding of the nature and type of the photochemical reactions involved. These would largely depend on the presence of certain functional groups, physical characteristics (light absorption, pK_a s, solubility, etc.), and the degradation mode of the compound. The assessment of the photostability of the drug substances is based on the study of all those factors that determine the rates and mechanisms of the underlying photochemical reactions.

3.1. Spectral Regions of the UV, Visible, and Solar Radiation. The spectral regions of the UV, visible, and solar light involved in the photochemical reactions are as follows:

UVA: 320–400 nm.

UVB: 290–320 nm.

UVC: 200–290 nm.

Visible: 400–700 nm.

Solar: including UVA, UVB, and visible ranges.

The majority of the photochemical reactions occur with the help of the UVA, UVB, or visible light.

3.2. Chemical Groups Important for the Photoreactivity of the Drug Molecules. The presence of the following chemical functional groups in the drug molecules [10] is usually necessary for the occurrence of photochemical reactions:

- (i) Double bond, C=C (oxidation/isomerization).
- (ii) Carbonyl group, C=O group (reduction/fragmentation).
- (iii) Aryl chloride, $C_6H_4Cl_2$ (homolytic/heterolytic dechlorination).
- (iv) Nitroaromatic group, $-C_6H_4NO_2$ (hydrogen abstraction/nitrite ester rearrangement).
- (v) A weak C–H bond (photoinduced fragmentation via hydrogen atom transfer or electron-proton transfer).
- (vi) Sulfides, alkenes, polyenes, and phenols (highly reactive with singlet oxygen, photochemically formed from the ground-state triplet oxygen).

3.3. Photophysical Processes. It is necessary to understand the various photophysical processes involved in the absorption and dissipation of the light energy (see (1)–(7)) that have been described by Moore [38]. These may be followed by additional reactions forming free radicals and subsequently the final products (see (8)–(11)), as a result of the photodegradation of the drug substances.

(i) Absorption:



(ii) Internal conversion:



(iii) Fluorescence:



(iv) Photoionization:



(v) Intersystem crossing:



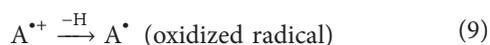
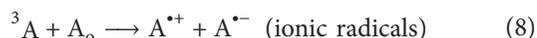
(vi) Internal conversion:



(vii) Phosphorescence:



(viii) Radical formation:



(ix) Final products:



Upon the absorption of a photon at a specific wavelength in the UV or visible range, a molecule in the ground state (A_0) is promoted to the singlet excited state (1A), with the electron spins remaining antiparallel (see (1)). The molecule in the singlet excited state may dissipate its energy within nanoseconds by different physical process and thus get deactivated. This may happen by internal conversion (IC) (see (2)), a nonradiative transition to the ground state, or photon emission (fluorescence) leading back to the ground state (see (3)). The excess energy in the excited state may also be dissipated as heat on collision with neighboring molecules by vibrational relaxation (VR). Since the ionization potential of the molecule is lower in the singlet excited state, it is easier to remove an electron from an excited rather than from the ground state. This occurs in the presence of an electron acceptor as a result of photoionization (see (4)), particularly in molecules having an anionic state. Another process that can occur from the singlet excited state is the intersystem crossing (ISC) to a metastable triplet excited state (3A) with parallel electron spins (see (5)). The ISC is highly efficient for the photochemically active molecules. The triplet excited state with its lifetime in the microsecond to second range has a greater probability for the reaction with other molecules. Alternatively, it can return back to the ground state by another ISC (see (6)) or by phosphorescence emission (see

(7)). Further photochemical processes involving the triplet excited state may lead to the formation of cationic and anionic radicals (see (8)) and neutral (oxidized) (see (9)) and reduced free radicals (see (10)). The reduced free radicals may react to form the final products (see (11)). The triplet excited state is a more powerful electron donor or acceptor than the ground state of a molecule. All these processes occur mostly within nanosecond to seconds after the excitation and may be studied by laser flash photolysis, time-resolved spectroscopy, and other techniques [39].

3.4. Kinetics of the Photochemical Reactions. The preformulation studies in the drug development also include the photostability testing of the drug substances. This is necessary to evaluate their overall photosensitivity and to ascertain the rate at which they degrade under specific experimental conditions. These aspects involve the study of the kinetics of the photodegradation reactions. The rate of a photochemical reaction depends on the number N of photons absorbed per second and the quantum yield of the reaction Φ . Moore [40] has presented the following kinetic treatment for the photochemical reactions that can be applied to the degradation of the drug molecules.

The rate of a photochemical reaction may be expressed as

$$\begin{aligned} \text{Rate} &= \text{number of molecules transformed per second} \quad (12) \\ &= N\Phi. \end{aligned}$$

The value of N at a particular wavelength λ is given by

$$N_\lambda = I_\lambda - I_t = I_\lambda (1 - 10^{-A}), \quad (13)$$

where I_λ and I_t are the incident and the transmitted light intensities, respectively, and A is the absorbance of the sample at the irradiation wavelength.

N is directly proportional to the concentration at low absorbance values ($A < 0.02$), provided that the substance follows Beer's law relation between the absorbance and the concentration:

$$N_\lambda = 2.303I_\lambda A = 2.303I_\lambda \epsilon_\lambda bC, \quad (14)$$

where ϵ_λ is the molar absorptivity at the wavelength λ , C is the molar concentration of the absorbing species, and b is the optical path length of the reaction vessel. Since I_λ and ϵ_λ vary with the wavelength, (14) integrated over the relevant wavelength range gives

$$\begin{aligned} N &= 2.303bC \int (I_\lambda \epsilon_\lambda) d\lambda \text{ integrated from } \lambda_1 \text{ and } \lambda_2, \quad (15) \\ \text{Rate} &= 2.303bC\Phi \int (I_\lambda \epsilon_\lambda) d\lambda. \end{aligned}$$

The overlap integral $\int I_\lambda \epsilon_\lambda d\lambda$ is a constant for a particular combination of the photon source and the absorbing substance; b is obtained from the reaction vessel used; and Φ is

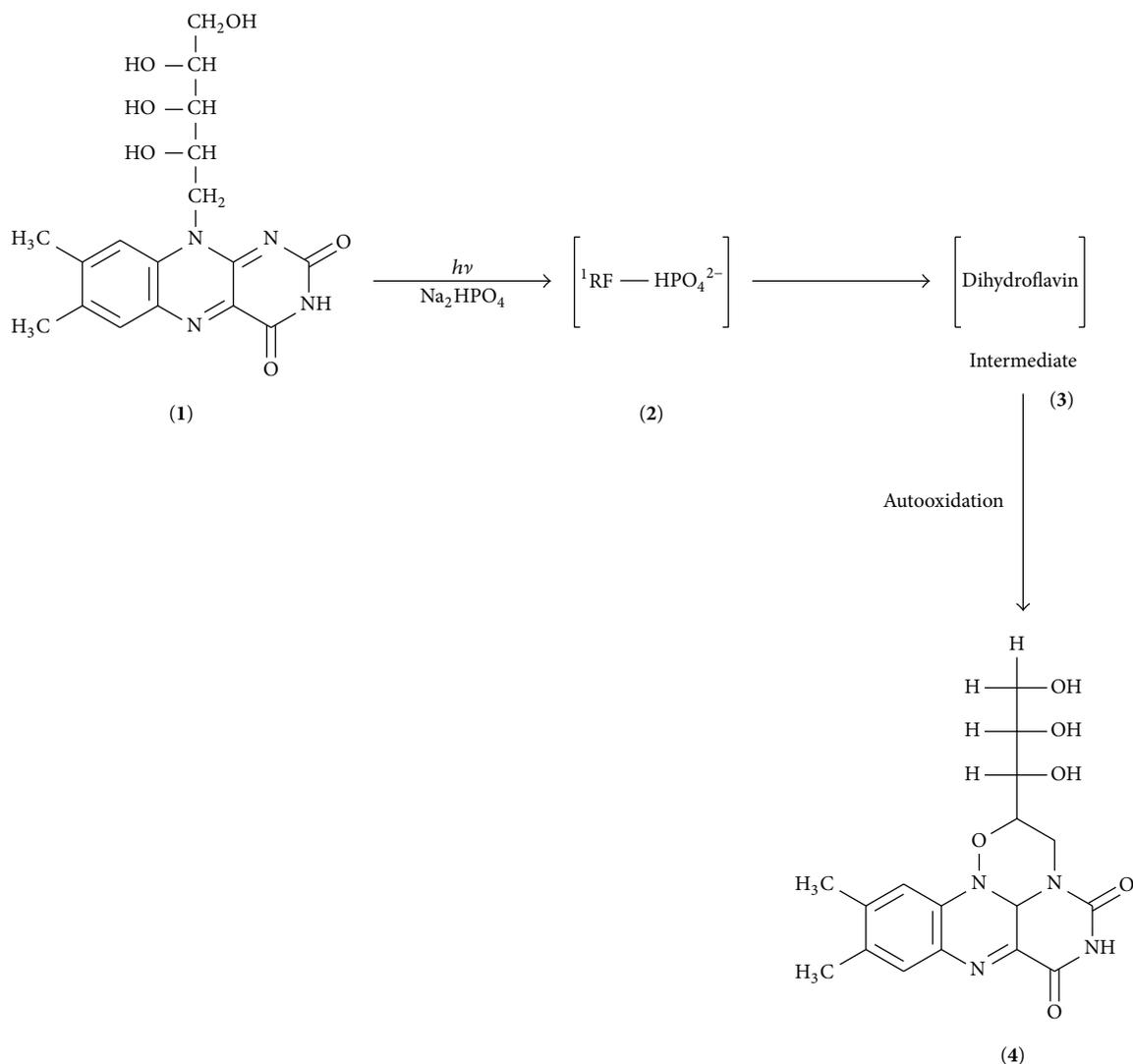


FIGURE 1: Photoaddition reactions of riboflavin.

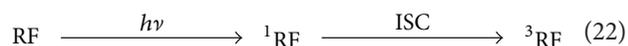
CN^- group is removed with its full complement of electrons and is replaced by a water molecule without any change in the oxidation state of cobalt. This reaction takes place by the absorption of light to cause a $\pi\text{-}\pi^*$ transition in the corrin ring. The $[\text{Co}^{3+} \text{OH}]$ molecule may be oxidized to corrin ring cleavage products (21). The photodegradation reaction of B_{12} is pH dependent, as B_{12} is a polyacidic base with six weakly basic amide groups and has pK_a of 3.3 [47]. In the acidic pH range, the molecule exists as a cation $[\text{B}_{12} \text{H}^+]$ due to the ionization of the 5,6-dimethylbenzimidazole moiety. The rates of the photodegradation reactions depend on the ionization state of the molecule in the pH 1–12 range [45].

4.3. Photocyclization Reactions: Meclofenamic Acid. Exposure of aqueous solutions of meclofenamic acid (5) (*N*-(2,6-dichloro-*m*-tolyl)anthranilic acid) to UV or visible light results in the dehydrohalogenation and cyclization

to form approximately equimolar amounts of 8-chloro-5-methylcarbazole-1-carboxylic acid (6) and 8-chloro-7-methylcarbazole-1-carboxylic acid (7) [48] [Figure 2].

4.4. Photodealkylation Reaction: Chloroquine. Chloroquine (8) undergoes photochemical degradation in aqueous solutions (pH 7.4) on irradiation with 240–600 nm light. The major reaction leads to *N*-dealkylation to give several products including (9)–(11), which have been identified by MS and NMR spectrometry [49]. Some of the dealkylation reactions are shown in Figure 3.

4.5. Photodecarboxylation Reactions: Amino Acids. Aliphatic amino acids undergo decarboxylation to produce carbon dioxide and an aldehyde by riboflavin (RF) sensitized photooxidation [50]:



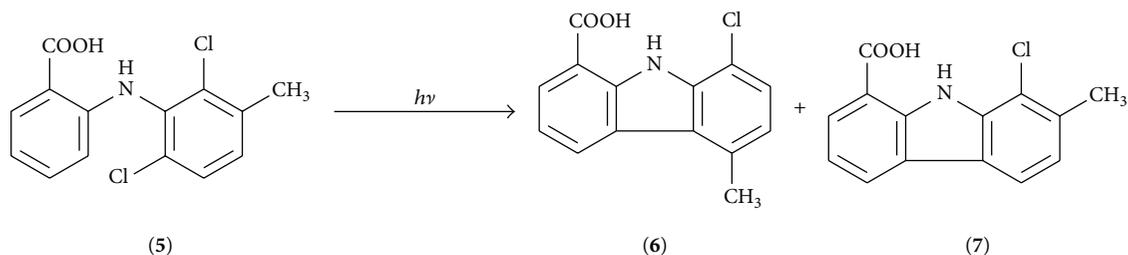


FIGURE 2: Photocyclization reactions of meclufenamic acid.

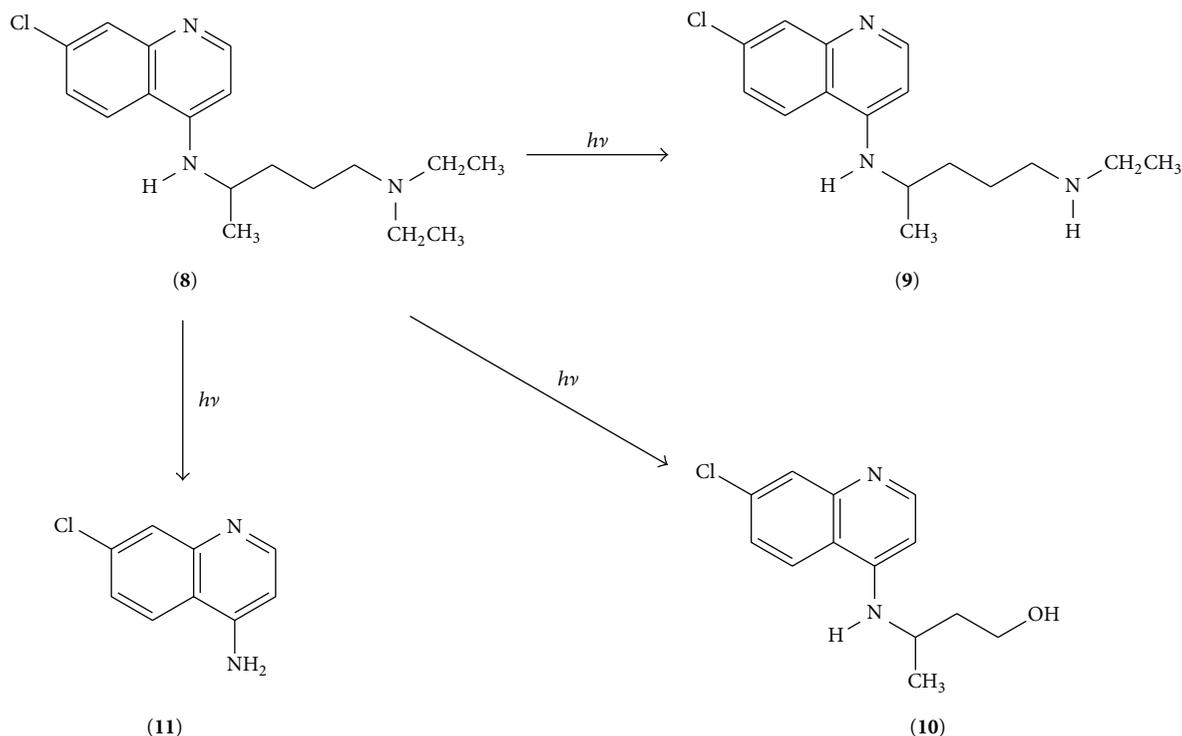


FIGURE 3: Photodealkylation reactions of chloroquine.



RF on light absorption is excited to the singlet state [${}^1\text{RF}$] which may be converted to the triplet excited state [${}^3\text{RF}$] by intersystem crossing (ISC). [${}^3\text{RF}$] reacts with the amino acids and causes their oxidation according to the reactions expressed by (22) and (23).

4.6. Photodehalogenation Reactions: Norfloxacin. Fluoroquinolones contain at least one fluorine atom and undergo defluorination in neutral solutions [51]. Norfloxacin (12) on irradiation in aqueous solutions (pH 7.2) is degraded slowly by defluorination ($\phi = 0.06$). The process involves solvolysis at position 6 (13) [52] [Figure 4].

4.7. Photodehydrogenation Reactions: Nifedipine. Visible irradiation of nifedipine (14) in 95% ethanol results in the dehydrogenation of the molecule. The degradation is fastest in aqueous solutions at pH 2.0 [53]. The degradation products have been identified by ${}^1\text{H}$ - and ${}^{13}\text{C}$ - NMR studies as 4-(2-nitrosophenyl)pyridine (15) and its oxidation product 4-(2-nitrophenyl)pyridine (16) derivatives [54] [Figure 5].

4.8. Photodimerization Reactions: Primaquine. The photochemical stability of primaquine (17) has been studied by irradiating the aqueous solutions of primaquine diphosphate (pH 7.4) with a 120 W high-pressure mercury lamp (emission at 320–600 nm). It gives numerous products including the dimer (18) that has been identified by GC/MS and NMR spectrometry [55]. The dimerization reaction is shown in Figure 6.

4.9. Photoelimination Reactions: Mefloquine. Mefloquine (19) in aqueous solutions undergoes photoelimination to

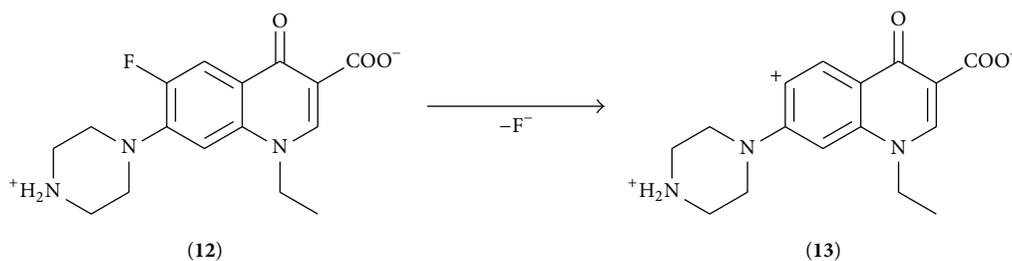


FIGURE 4: Photodehalogenation reaction of norfloxacin.

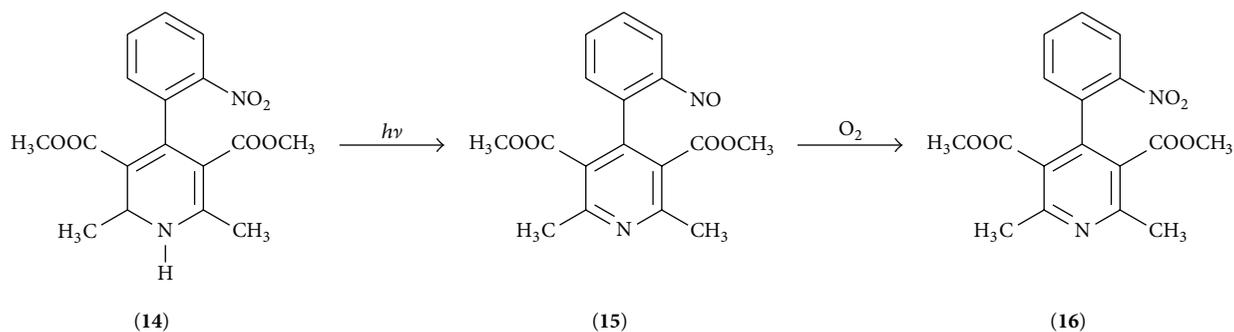


FIGURE 5: Photodehydrogenation reactions of nifedipine.

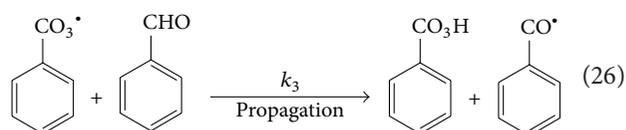
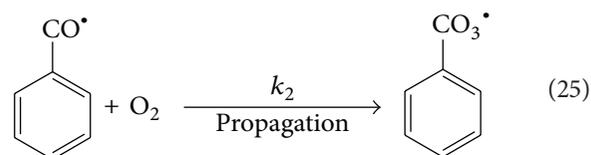
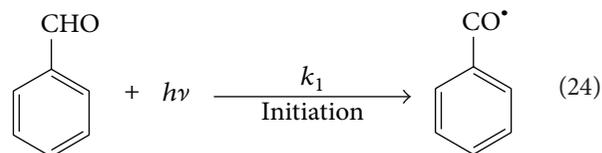
form 2,8-bis(trifluoromethyl)-4-hydroxyquinoline (**20**) [56] [Figure 7].

4.10. Photoinduced Hydrolysis Reactions: Sulfacetamide. Sulfacetamide (**21**) on UV irradiation in aqueous solutions is hydrolyzed to sulfanilamide (**22**) [57] [Figure 8].

4.11. Photoisomerization Reactions: Aztreonam. Aqueous solutions (pH 5.0) of aztreonam (**23**) (a third-generation cephalosporin) undergo syn-anti-isomerization (**24**) on UV irradiation involving the alkoxyimino group in the side chain [58] [Figure 9].

4.12. Photooxidation Reactions

4.12.1. Photooxidation of Benzaldehyde. The photooxidation of drugs by UV radiations usually involves a free radical mechanism, as reported for benzaldehyde [59]. In the free radical chain process, a sensitizer abstracts a hydrogen atom from the drug molecule (see (24)). The free radical of the drug next reacts with molecular oxygen to form a hydroperoxide radical (see (25)). The chain reaction is propagated by removing hydrogen atom from another molecule of the oxidant (see (26)). The hydroperoxide radicals then react further to form inert products (see (27)). The following equations show initiation, propagation, and termination steps in the chain reaction involved in the photooxidation of benzaldehyde:



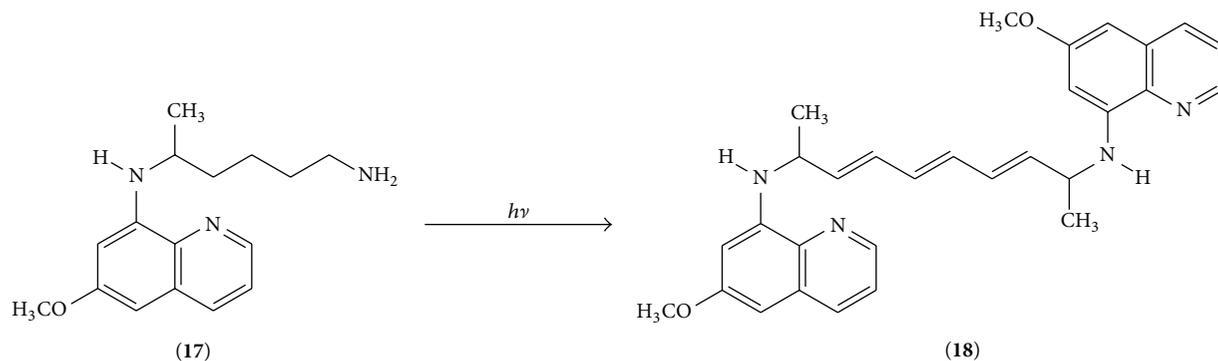


FIGURE 6: Photodimerization reaction of primaquine.

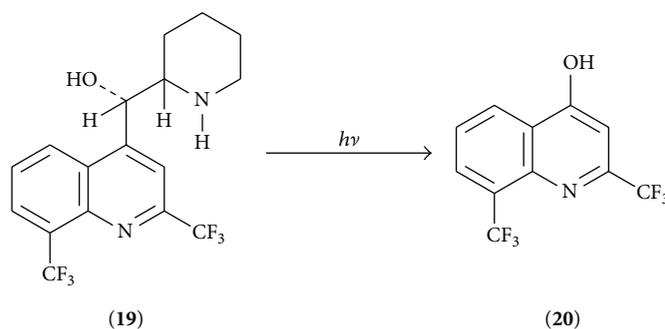
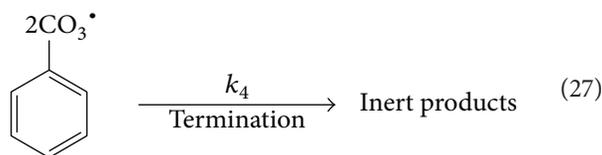


FIGURE 7: Photoelimination reaction of mefloquine.



4.12.2. *Photooxidation of Menadione.* Menadione (vitamin K_3) (25) is oxidized in aqueous solutions (pH 6–12) on UV irradiation to give 2-methyl-2,3-epoxy-1,4-naphthoquinone (26) [60] [Figure 10].

4.13. *Photoinduced Rearrangement Reactions: Benzydamine.* Benzydamine (27) on UV irradiation in aqueous solutions undergoes rearrangement to give product (28) [61] [Figure 11].

4.14. *Photoreduction Reactions: Riboflavin.* A detailed study of the photoreduction reaction of riboflavin (RF) (1) in aqueous and organic solvents has been made [62–74].

A reaction scheme for the photodegradation of RF by the photoreduction pathway is shown in Figure 12. RF on light absorption is promoted to the singlet excited state [^1RF] which may be converted to the triplet excited state [^3RF] (29). The [^3RF] abstracts a hydrogen atom by intramolecular transfer from the C-2' atom of the ribityl side chain to N-1 of the isoalloxazine ring leading to the formation of the biradical (30), earlier suggested by Brdička [75] in

the photolysis of RF through polarographic studies. The biradical is oxidized to form formylmethylflavin [FMF] (31), an intermediate product isolated by Smith and Metzler [76]. FMF is hydrolyzed to lumichrome [LC] (32) in acid solutions and LC and lumiflavin [LF] (33) in alkaline solutions [77–79]. It is also oxidized to carboxymethylflavin [CMF] (34) in aqueous solutions [79, 80]. The rate-pH profile indicates a greater susceptibility of RF to photodegradation in the alkaline solutions as a result of the sensitivity of [^3RF] to alkaline hydrolysis [81].

4.15. *Photoinduced Ring Cleavage Reactions: Norfloxacin.* Norfloxacin (12) on UV irradiation in aqueous solutions undergoes piperazine ring cleavage to give product (35) [51] [Figure 13].

5. Biological Effects of the Photoinstability

The biological consequences of the action of light on drugs undergoing photodegradation are important. These include several adverse biological reactions involving phototoxicity, photoallergy, photosensitization, and others [7–9, 82–87]. UV radiation present in the sunlight is usually classified into different spectral ranges including UVA (320–400 nm), UVB (290–320 nm), and UVC (270–290 nm). UVC radiation is absorbed by ozone and is thus absent at the sea level. UVA radiations involve longer wavelengths than those of UVB and are less harmful. UVB radiations may affect human skin and can produce erythema, edema, and pigmentation

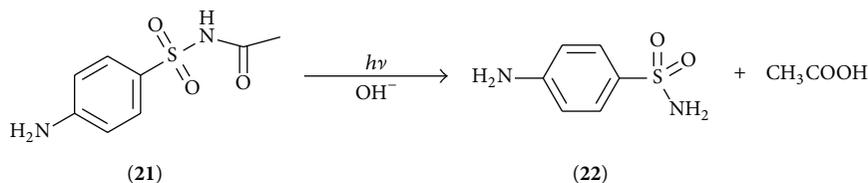


FIGURE 8: Photoinduced hydrolysis reaction of sulfacetamide.

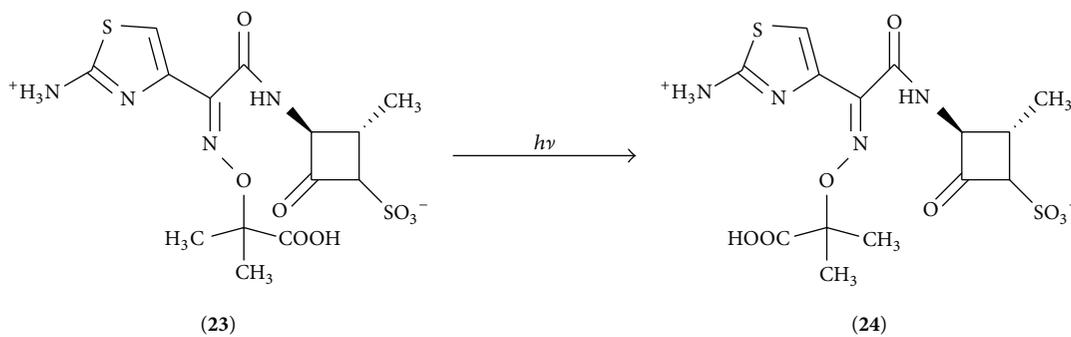


FIGURE 9: Photoisomerization reaction of aztreonam.

[88]. UVB may also cause photoaging, immunosuppression, and photocarcinogenesis [85, 89]. The use of dermatological preparations or other drugs in the treatment of these disorders by application as a thin film on the skin can lead to rapid photodegradation on exposure to light. This may make them ineffective or form toxic photodegradation products affecting the skin. The list of some drugs causing adverse biological reactions [8, 84] is given in Table 1.

Kullavanijaya and Lim [9] have suggested the use of the sunscreen agents containing UV light filters for the photoprotection of the human skin. An ideal sunscreen agent should be photochemically stable and dissolve in a suitable vehicle. The photostability of the product depends on the nature of the UV filter. One of the first widely used sunscreen filters is para-aminobenzoic acid (PABA) ($\lambda_{\max} = 283$ nm). It is soluble in water and is very effective against UVB radiations at 5% concentration in 50–60% alcohol base [90]. However, PABA causes photoallergy and is a potent carcinogen; therefore, its use in sunscreen products is limited [91]. The commonly used UV filters nowadays include avobenzone, octinoxate, and octyl dimethyl PABA. These compounds are photolabile, being rapidly destroyed on exposure to UV light [92–94]. Some of the photostable filters include terephthalylidene dicamphor sulfonic acid (Mexoryl SX), drometrisole trisiloxane (Mexoryl XL), methylene-bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M), and bis-ethylhexyloxyphenol methoxyphenol triazine (Tinosorb S) [92]. ZnO, TiO₂, octocrylene, salicylates, and methylbenzylidene camphor have been found to increase the photostability of the sunscreen products [9]. The organic sunscreen agents may interact with the skin on exposure to light and induce adverse biological reactions resulting in photoallergy, phototoxicity, and photosensitivity [95–101]. Therefore, care should be exercised in the selection of the sunscreen agents by consultation with a dermatologist. The Food and Drug

Administration, USA, has provided a list of 16 agents for use as sunscreens including UVA and UVB filters [101]. A list of common UV filters approved in Australia, Europe, Japan, and the United States is also available [102].

6. Packaging Requirements

The light sensitivity of the drug substances requires the use of an effective packaging system to protect them from photochemical damage. The pharmacopoeias [1–3] prescribe conditions for containers (e.g., light-resistant) and storage (e.g., protected from light) for the light-sensitive drugs and formulated products. The requirements for a packaging system for pharmaceuticals differ from product to product, that is, solid or liquid dosage form. There is a greater chance of interaction between a liquid dosage form and the container than that of the solid dosage form. The efficacy of a packaging system for a particular drug or product may be evaluated by performing photostability studies. Protection of a product from light can be achieved by the use of an opaque or amber-colored container. Amber glass is suitable for drugs absorbing in the UV region as it transmits light above about 470 nm. An opaque secondary package may also be used for this purpose.

Light transmission tests may be applied to evaluate the light transmission characteristics of containers to be used for photosensitive drugs [2]. Templeton et al. [28] have discussed the implications of photostability on the manufacturing, packaging, and storage of formulated products, emphasizing the need for appropriate measures to protect photosensitive products during these processes.

7. Photostability Testing

Photostability testing of drug substances and formulated products is an integral part of the development process

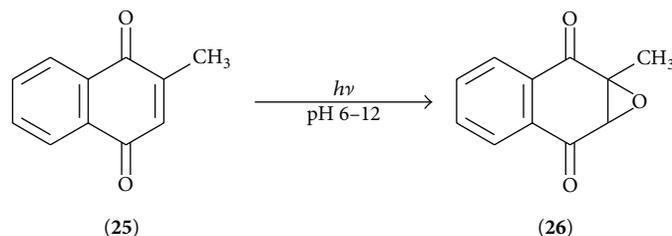


FIGURE 10: Photooxidation of menadione.

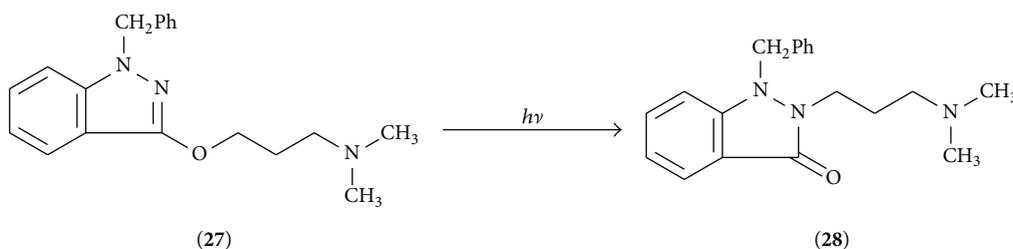


FIGURE 11: Photoinduced rearrangement reaction of benzydamine.

in industry to ensure their quality during the shelf life period. It is carried out under standardized conditions to determine the extent to which the drug or the product undergoes an undesirable chemical change. Photostability testing is undertaken to evaluate the overall photosensitivity of the pharmaceuticals for the development and validation purposes and to provide information necessary for handling, packaging, and labeling [11]. "ICH Harmonized Tripartite Guideline for Photostability Testing of New Drug Substances and Products" [103] has stated the importance of light testing as an integral part of stress testing. It is necessary to determine the intrinsic photostability characteristics of the new drug substances and products during the development process and to demonstrate that light exposure does not result in an unacceptable change. Another objective of this study is to demonstrate whether precautionary measures in manufacturing, packaging, and labeling of the products are needed to overcome changes due to light exposure [104].

Photostability testing of drug substances and products is conducted according to ICH Q1B guideline [103], with the choice of an appropriate light source being an important consideration for the uniformity of the results. The photodegradation of a drug in a product is a function of the spectral distribution and the intensity of the light source. Therefore, the use of specific light sources is necessary to achieve harmony in the evaluation of photostability. ICH guideline specifies the use of an artificial daylight fluorescent lamp, a xenon lamp, or a metal halide lamp emitting in the UV and visible region with an output similar to that of the standard daylight lamp D65/ID65. Any radiation emitted below 320 nm should be eliminated by the use of an appropriate filter. Alternatively, a cool white fluorescent lamp (emission ~320–800 nm) or a near UV lamp (emission 320–400 nm) with the maximum emission between 350 and 370 nm should be used. The details of the photostability

testing procedures for the drug substances and drug products are stated in the ICH guideline [103].

Several publications have dealt with the light sources, their spectral distribution and use [20, 40, 105–111], photostability chambers [104, 112, 113], and experimental conditions [28, 108, 114–117] for the photostability testing.

Various aspects of the photostability testing in relation to the application of the ICH guidelines have been discussed [17, 20, 25, 118–123] and there is a need to improve the guideline in the light of these studies. The application of the photostability testing in the pharmaceutical industry is necessary to ensure the potency, the efficacy, and the safety of the manufactured products in their clinical use.

8. Photostabilization

The photosensitivity of the drug substances and the solid and liquid dosage forms makes it necessary to adopt appropriate measures for their stabilization during manufacturing, compounding, and storage. The common approach to afford photostabilization of pharmaceuticals is to protect them from light by using suitable primary and secondary packaging. The various methods of photostabilization [12, 27, 124, 125] and photoprotection [9, 20] have already been reviewed and are briefly presented in the following sections.

8.1. Spectral Overlay. The photosensitive drugs or products can be protected by reducing the amount of the undesirable light impinging on the material. This can be achieved by the application of the principle of the spectral overlay to the pharmaceutical formulations [126]. It is based on the use of excipients that exhibit the absorption spectra similar to that of the drug. This results in the absorption of light by the excipients at the expense of the drug and thus protecting it from photodegradation. Molsidomine tablets have been stabilized

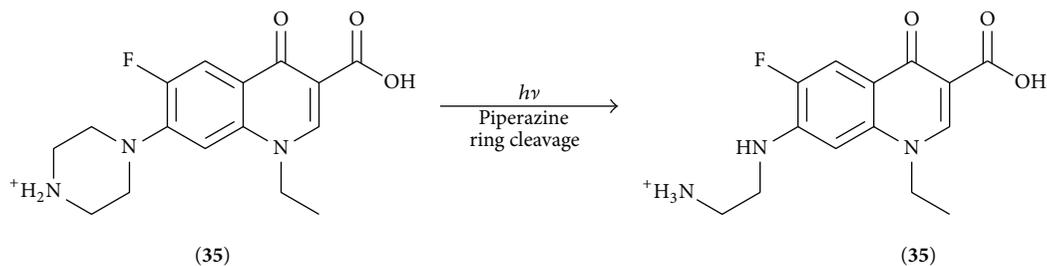


FIGURE 13: Photoinduced ring cleavage reaction of norfloxacin.

TABLE 1: Drugs causing adverse biological reactions.

Phototoxicity	Photoallergy	Photosensitivity
Acridine	Aminobenzoic acid derivatives	2-Benzyl-4,6-dichlorophenol
Aminobenzoic acid derivatives	Bithionol	Chlorophenols
Anthraquinone dyes	Chlorpromazine	Ethanol
Anthracene	Chlorpropamide	Hexachlorobenzene
Chlorpromazine	Fentichlor	Oestrogens
Nalidixic acid	6-Methylcoumarin	
Phenothiazine	Promethazine	
Protriptyline	Salicylanilides	
Psoralens	Sulfanilamide	
Pyrene	Thiazides	
Sulfanilamide		
Tetracycline		

Another method of photostabilization of the tablet formulations involves film coating with agents possessing light absorption or reflection properties. The protective effect of the film coating depends on its absorption, which is related to the film thickness and concentration of the absorbing/reflecting excipient [127]. Film coatings have been used for the photoprotection of sulfisomidine [137], nifedipine [135, 138], and other drugs [139].

8.3. Complex Formation. Complex formation between photosensitive drugs and complexing agents is among the earlier methods for the stabilization of drugs. Caffeine has been employed as a complexing agent for the photostabilization of riboflavin, a highly photosensitive drug. It is most stable in the complex form in aqueous solution, being suitable for pharmaceutical formulations [140]. Caffeine complexation has been reported by several workers and occurs by the formation of stacking complexes [141–144]. Riboflavin also forms a complex between the ribityl side chain and boric acid resulting in the photostabilization of the vitamin [145, 146].

8.4. Cyclodextrin Complexation. The photostabilization of drugs by the cyclodextrin inclusion complexation has been discussed by Thoma [124], Yoshioka and Stella [18], and Sheraz et al. [29]. Cyclodextrins are nonreducing cyclic oligosaccharides that consist of six (α -CD), seven (β -CD), or eight (γ -CD) dextrose units. Internally these

molecules are relatively hydrophobic, while externally relatively hydrophilic. This structure imparts to them the capability of forming inclusion complexes with the drug molecules and thus provides photoprotection for the latter [18].

Numerous examples of the photostabilization of drugs by cyclodextrin complexation have been reported. These include the complexation of clofibrate with β - and γ -CD in the solid state [147], nifedipine, pyridoxine HCl, and retinol acetate with β -CD in aqueous solutions and in the solid state [148], doxorubicin with γ -CD in aqueous solutions [149], daunorubicin with octakis (2,6-di-*o*-methyl)- γ -CD in acidic solutions [150], mitomycin C with γ -CD in aqueous solutions [151], riboflavin with α -, β -, and γ -CD in aqueous solutions [152–158], diphenylhydramine with β -CD in aqueous solutions [159], isradipine with methyl β -CD [160], triprolidine HCl with β -CD [161], and other photosensitive drugs with different CDs [162].

8.5. Liposome Formation. Liposomes are microscopic and submicroscopic phospholipid vesicles with a bilayered membrane structure. Photostabilization of the drug substances by entrapment into liposomes is an effective method to improve their photostability. Examples of stabilization of the photosensitive drugs in liposomal formulations include riboflavin [163–167], doxorubicin [168], vitamin A palmitate [169], fluoroquinolones [170, 171], rose Bengal [172], amlodipine [173], tretinoin [174], 2,7-dichlorodihydrofluorescein [175], *o*-palmitoyl amylopectin [176], and zinc phthalocyanine and

chloroaluminium phthalocyanine [177]. The entrapment efficiency of the liposomes facilitates the enhancement of the photostability of the drugs [164, 165, 174, 178]. Barnidipine in cyclodextrin-in-liposomes matrices has shown increased photostability with a value close to that of the solid formulations [174]. The photostability of drugs in liposomal formulations may be affected by the composition of the liposomes, the entrapment efficiency, and the drug-phospholipid interaction [179].

8.6. Use of Stabilizers. A careful consideration of the factors that promote the photodegradation of drugs and their control may improve photostability. Some factors that adversely affect the photostability of drugs include oxygen, oxidizing agents, and metal ions. Photooxidation of drugs is among the most commonly occurring modes of their degradation. Oxygen present in a formulation may be removed by purging with nitrogen or by the addition of a suitable antioxidant depending on the susceptibility of the drug to photooxidation. The selection of an antioxidant may be made on the basis of the difference in the redox potential between the drug and the oxidant. The effectiveness of an antioxidant is determined by studying the pharmaceutical system under standard oxidation conditions and assaying the drug content periodically [180]. The drug substances that may be significantly affected by the oxidation-reduction reactions leading to photodegradation include ascorbic acid, riboflavin, cyanocobalamin, menadione, α -tocopherol, and chlorpromazine [14]. Some of the commonly used antioxidants are ascorbic acid, α -tocopherol, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), L-histidine, propyl gallate, and sulfur compounds. Ascorbic acid, α -tocopherol, β -carotene, and BHT act as free radical scavengers and singlet oxygen quenchers and thus inhibit the photosensitization reactions. If a drug substance acts as a photosensitizer and initiates a chain reaction in the drug product, some of the excipients may be oxidized, while the drug may be protected from photodegradation [38].

Examples of the photostabilization of drugs by the use of an antioxidant and other agents include ascorbic acid, stabilized by α -tocopherol [181], doxorubicin HCl by sodium thiosulphate [182], mitomycin and porfiromycin [183], sulfacetamide and sulphanilamide by sulfur compounds [184], vitamin A by propyl gallate, citric acid, and BHT [185], cholecalciferol by α -tocopherol and ascorbic acid [186], cianidanol by an oxygen adsorbent [187], and riboflavin by EDTA, thiourea, DL-methionine, and sodium thiosulfate [188].

8.7. Choice of Solvent. Solvents can exert considerable influence on the stability of the photosensitive drugs in the pharmaceutical formulations. The photodegradation rates may be affected by the polarity and viscosity of the medium. The choice of an appropriate solvent or a solvent combination may improve the photostability of a particular drug. In particular, the effect of the dielectric constant on the kinetics of the photodegradation of 10-methylisoalloxazine [62], formylmethylflavin [65], riboflavin [72, 189–193], moxifloxacin [194], and norfloxacin [195, 196] in aqueous and

organic solvents has been studied. The reaction rates of these compounds are a linear function of the solvent dielectric constant. This may imply the involvement of a polar intermediate in the reaction pathway [62].

The photodegradation rate of a drug may also be influenced by the solvent viscosity. In the case of the above-mentioned flavins [62, 65, 192] and fluoroquinolones [193–195], the reaction rates are a reciprocal function of the solvent viscosity. Thus, an increase in the medium viscosity leads to a decrease in the reaction rate. This could result from the inhibition of the solute diffusion into the solvent [6]. For example, the photodegradation of cyanocobalamin (vitamin B₁₂) in aqueous solutions is suppressed by the addition of glycerol due to an increase in the medium viscosity [197]. These studies indicate that the solvent characteristics such as dielectric constant and viscosity should be given due consideration in the formulation of drugs to achieve photostabilization.

8.8. Choice of pH. The pH of a solution is an important factor in the stabilization of the drug substances. A drug may be more stable in its ionized or nonionized form and may undergo specific acid-base catalysis in aqueous solutions. However, it would depend on the reactivity of the excited state of the molecule in the particular pH range. The oxidation of many drugs is affected by pH; for example, ascorbic acid ($pK_a = 4.17$) undergoes rapid photooxidation in the neutral and alkaline pH range and is stable in the acid pH range [197]. Several studies have been conducted to evaluate the effect of pH on the stability of the drug substances [14, 198] and to assess the optimum pH from the rate-pH relationships to achieve stabilization [14, 45, 194, 195, 199]. The buffer species present in a solution may be involved in the general acid-base catalysis [18] and should be carefully selected to avoid this effect.

9. Conclusions

The photostability evaluation and the photostability testing of the drugs and drug products are an important part of the formulation studies, providing information on their intrinsic photostability characteristics and enabling the development of stable, safe, and effective products. The knowledge of the photostability of drugs and their mode of degradation helps to guide the formulator in the assessment of the product and thus make modifications necessary to prolong its shelf life under the proposed storage conditions. The use of various photostabilization techniques may further enhance the stability of the products. The objective of these studies is to ensure product quality along with all of the necessary attributes during their storage and use.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

The authors are very grateful to Professor Dr. S. Fazal Hussain of the Baqai Institute of Pharmaceutical Sciences for his kind help in the preparation of this paper. The study was partly supported by the research Grant DEC–2012/05/B/ST4/01207 to Marek Sikorski from the National Science Centre of Poland (NCN).

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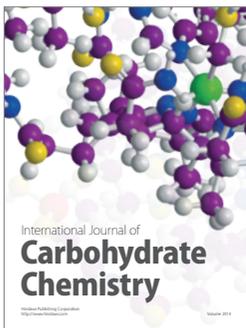
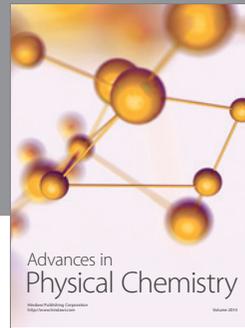
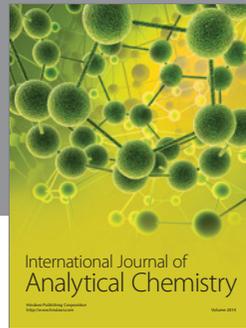
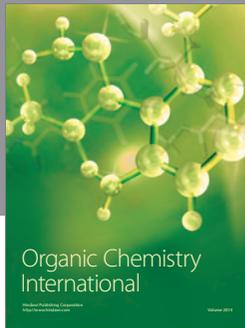
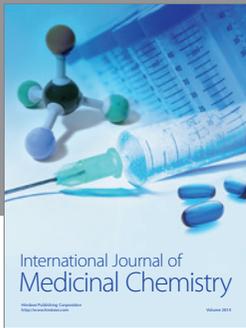
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