Photostability tests applied on commercial specialties for topical use have demonstrated a greater vulnerability of several drugs, due to greater exposure to light than other pharmaceutical forms. Photodegradation of a drug can considerably modify its pharmacokinetic behavior by varying the therapeutic index. The evaluation of the degradation profile of a drug, according to the ICH rules, is of primary importance in developing an appropriate topical formulation. Advanced strategies have been proposed to increase the protection from the light of the photolabile drugs. Supramolecular systems have been investigated to improve both pharmacokinetic profile and photostability. In this review, the more recent stability-monitoring methods for the analysis of drugs in topical formulations are collected and the main approaches for the drug photostabilization are discussed.

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**Keywords:** cyclodextrins • drug stability • niosomes • photodegradation • photoprotection • topical formulation

The interaction of a large number of drugs with light is not yet known despite this aspect could greatly affect the pharmacological profile. However, in the last years, a list of photosensitive drugs has been updated, suggesting the most appropriate storage conditions. For a long time, the most common strategy for protecting drugs from light has been the adoption of dark containers, but new and interesting light-protection approaches are emerging [1–4].

A high number of photosensitive drugs are used for topical use, applied directly to the skin or mucous membranes (oral, nasal, rectal, vaginal, conjunctival) to exert a local effect, and toxic effects due to photodegradation products of some of them are described in various papers [5–15].

For example, nonsteroidal anti-inflamatory drugs (NSAIDs) are the most commonly marketed drugs as topical preparations for the treatment of rheumatic diseases [7–10]. Stability studies applied on diclofenac and ketoprofen in gel formulations have shown the formation of several potential impurities [10–12]. Benzocaine is commercially available as cream, ointment and topical solution but the US Pharmacopoeia prescribes the preservation in tight containers, protected from light, avoiding prolonged exposure to temperatures exceeding 30°C, in consideration of its sensitivity to light [1,2]. The photodecomposition of nitrofurazone in ointment and topical solution showed a very complex degradation pattern with the formation of a high number of impurities [13,14]. Photolability of corticosteroid drugs is equally well known. Betamethasone, in cream and solution formulations for parenteral use, decomposes rapidly under light, even when combined with UV absorbing agents [15].

Table 1 lists the most important classes of light-sensitive drugs, their topical formulations commercially available and the
Table 1. The classes of light-sensitive drugs, the relative topical formulations commercially available and references.

<table>
<thead>
<tr>
<th>Drug classes</th>
<th>Photosensitive drug</th>
<th>Topical formulation</th>
<th>Study</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
<td>Ophthalmic solution</td>
<td>Degradation of chloramphenicol in water</td>
<td>[16]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Role of 1[O₂] in chlorotetracycline degradation</td>
<td>[17,18]</td>
</tr>
<tr>
<td></td>
<td>Chlortetracycline</td>
<td>Ophthalmic ointment</td>
<td>Photolysis of chlorotetracycline in aqueous solution</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>Cream ointment</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>Neomycin</td>
<td>Cream lotion ointment</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>Nitrofurazone</td>
<td>Ointment topical solution</td>
<td>Aquatic photochemistry of nitrofuran antibiotics</td>
<td>[13,14]</td>
</tr>
<tr>
<td></td>
<td>Oxytetracycline</td>
<td>Ointment ophthalmic ointment</td>
<td>Photodegradation of oxytetracycline hydrochloride in aqueous medium</td>
<td>[19]</td>
</tr>
<tr>
<td><strong>Anticholinergic agents</strong></td>
<td>Atropine</td>
<td>Ophtalmic solution</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td><strong>Antihypertensives</strong></td>
<td>Minoxidil</td>
<td>Topical solution</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td>Ointment</td>
<td>Photodegradation of nifedipine in tablets. Modeling of nifedipine photodegradation</td>
<td>[20,22]</td>
</tr>
<tr>
<td></td>
<td>Pilocarpine</td>
<td>Ophtalmic solution</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td><strong>Antimycotics</strong></td>
<td>Ciclopirox</td>
<td>Topical solution</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>Climbazole</td>
<td>Cream topical solution</td>
<td>Photodegradation of theazole fungicide climbazole by ultraviolet irradiation</td>
<td>[22]</td>
</tr>
<tr>
<td></td>
<td>Miconazole</td>
<td>Cream powder for aerosol</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td><strong>Antipsoriatrics</strong></td>
<td>Anthralin</td>
<td>Cream ointment</td>
<td>Photostability of dithranol</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>Calcipotriol</td>
<td>Gel</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td>Epinastine</td>
<td>Ophthalmic solution</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td><strong>Antiparasitic</strong></td>
<td>Crotamiton</td>
<td>Cream</td>
<td>Photocatalytic decomposition of crotamiton</td>
<td>[24]</td>
</tr>
<tr>
<td><strong>β-blockers</strong></td>
<td>Betaxolol</td>
<td>Ophtalmic solution</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>Timolol</td>
<td>Gel opthalmic solution</td>
<td>Photodegradation kinetics of timolol under simulated sunlight</td>
<td>[25]</td>
</tr>
<tr>
<td><strong>Disinfectants</strong></td>
<td>Benzethonium</td>
<td>Tincture topical solution</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>Chlorhexidine</td>
<td>Topical solution mouthwash</td>
<td>Photocatalytic degradation of chlorhexidine</td>
<td>[26]</td>
</tr>
<tr>
<td></td>
<td>Hydrogen peroxide</td>
<td>Topical solution</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td><strong>Local anesthetics</strong></td>
<td>Benzocaine</td>
<td>Cream ointment</td>
<td>Photostability test on topical drug product</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>Cocaine</td>
<td>Topical solution</td>
<td>Degradation products of cocaine in the aquatic environment</td>
<td>[27]</td>
</tr>
<tr>
<td><strong>Nonsteroidal anti-inflammatory drugs</strong></td>
<td>Ketoprofen</td>
<td>Gel</td>
<td>Photostabilization of ketoprofen</td>
<td>[15]</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>Gel</td>
<td>Photodegradation of ibuprofen in aqueous environments</td>
<td>[28,29]</td>
</tr>
</tbody>
</table>

DFT: Density functional theory; PABA: Aminobenzoic acid.
When applied on the skin or mucosa, a drug is more exposed to light respect to the other formulations, and then is susceptible of degradation before explaining the therapeutic effect. This problem is amplified in transdermal application, when the drugs are not easily absorbed and then the exposure time is sensitively prolonged [41]. It is necessary to always keep in mind that the stability of a drug can affect its bioavailability leading to a variation of its therapeutic index. For these reasons, in formulating a topical pharmaceutical preparation, it is necessary to ensure good light stability so that appropriate drug concentration reaches the site of action.

Novel advanced strategies to increase the light-stability of the drugs have been extensively investigated. The latest topical drug delivery systems, able of trapping the drug leading to greater stability and simultaneously improving pharmacokinetics, are reported and discussed in this review. Among these new formulations, vesicular systems (i.e., liposomes and niosomes), solid lipid nanoparticles, cyclodextrins and microemulsions (MEs) have been widely studied because of their many advantages. Besides effectively protecting drugs from photodegradation, they also provide enhanced permeation across the skin, resulting in favorable systems for topical applications. Conversely, although polymeric nanoparticles (nanospheres and nanocapsules) have been reported as drugs photoprotection systems, they do not provide comparable performance in terms of transdermal delivery.

Given the considerable interest generated by the photodegradation problems, various stability indicating methods have been proposed to monitor the photodegradation experiments. The most widely used references relative to the respective photodegradation studies.

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Given the considerable interest generated by the photodegradation problems, various stability indicating methods have been proposed to monitor the photodegradation experiments. The most widely used
techniques include spectrophotometric and chromatographic methods. In recent years, the analytical procedures have been supported by multivariate analysis that can handle the high number of analytical data provided by instrumental computerization. The adoption of these data processing techniques allows to estimate with great speed and accuracy the structural characteristics and the concentration profiles of the components involved in the degradation processes.

**Stability indicating methods for drugs in topical preparation**

**Photodegradation test**

The application of the photodegradation test on a drug is described in the ICH Guideline [42]. According to these rules, all laboratory procedures have to be realized in a dark room equipped with a red lamp to minimize the degradation of the drugs. The light sensitivity has to be tested on pure drug, on its pharmaceutical formulations and in the immediate and marketing pack. The photostability test can be conducted by means of two different light sources: an artificial daylight fluorescent lamp or a cool white fluorescent combined with a near ultraviolet lamp (320–400 nm). The irradiation instrument must be equipped with a refrigerator to guarantee an appropriate control of the temperature.

The irradiation power can be varied, depending on the sensitivity of the drug tested. The effect of this parameter on the degradation rate could be studied more in-depth as it may affect the degradation kinetics [42,43]. A high value of irradiation power applied on a very light-sensitive drug could produce the fast formation of a single photoproduct, masking the formation of secondary photoproducts [22,44].

**Sample preparation procedures**

A topical application involves the use of formulations with very different characteristics. The topical solutions show low viscosity and can be prepared using water or alcohol in the base matrix, lotions are usually made up of oil mixed with water and many of them also contain alcohol [12]. Many formulations are semisolid preparations as creams, ointments and gels, in which the content of hydrophobic and/or hydrophilic components can vary considerably.

Because of the wide variety of formulations, sample preparation in a quality-control method of a topical formulation is never a standardized procedure. In the case of topical solutions with a simple composition, a chromatographic determination could be applied directly to the solution without any pretreatment. An extraction step becomes necessary if the formulations have a high number of components or these are very different from each other. The extraction capability must be carefully verified and the whole procedure optimized to increase the value of this parameter.

In a conventional extraction method, the choice of the solvent, the sonication time and the centrifugation parameters are very important and usually carefully screened [12,45]. The microwave-assisted step in an extraction procedure has been recently proposed. This procedure can reduce the heating time in the pretreatment of the sample and at the same time increase the extraction capability of the procedure [46,47].

**Analytical methodologies**

In a photodegradation test, drug concentration should be determined immediately after preparation of the sample and at different exposure times. The time intervals and the overall time of irradiation depend on the photodegradation mechanism of the drug and its rate of degradation. The choice of the analytical technique that can effectively dose both the drug and its products of degradation is usually a very hard step and depends on several aspects. A spectrophotometric procedure can be usually applied when the analytical matrix is simple and the photodegradation products are in limited number. When the byproducts are seriously overlapping the spectrum of the drug, derivative transformation of the spectral data has proved very advantageous in many cases. When the complexity of the matrices increases, due to a high number of components or to the presence of interferences from extraction procedure, HPLC represents the most widely used approach.

The light exposure of nifedipine, a well-known calcium channel blocker topically applied in the treatment of chronic anal fissure, causes a rapid degradation process with the formation of the pyridine oxidation product [20]. This photoproduct has no significant absorption in correspondence of the main peak of nifedipine, whose absorbance can be used for the direct determination of the drug concentration in different formulations [21]. When two or more photoproducts are formed from nifedipine congeners, as nisoldipine and lacidipine, the derivative elaboration of the spectral data allowed to determine all the components without any preventive separation [48]. An ecofriendly, rapid and sensitive spectrofluorimetric method was performed to investigate the stability of two anticancer drugs, doxorubicin and epirubicin, in pure form, pharmaceutical preparations and biological fluids [49].

An HPLC method has been adopted in a very high number of works and different detectors have been used. An isocratic HPLC procedure coupled with UV detector was used to monitor the stability of ketoprofen in gel formulation [50] in presence of excipients and...
potential degradants. The presence of ketoprofen and diclofenac was investigated in wastewater by HPLC-diode array detection (DAD) [51]. An RP-HPLC-UV method, was developed to separate nepafenac and six potential impurities [52]. The stability of the antiviral daclatasvir dihydrochloride was investigated after forced hydrolysis, oxidation and thermal degradation and an HPLC-DAD method was applied to the analysis of the drug in the pharmaceutical forms [53]. Liquid chromatography was also proposed for the identification of ibuprofen derivatives from exposure to 500 W mercury lamp as a light source, under acid or neutral or alkaline conditions [28].

Ultrafast liquid chromatography coupled with mass spectrometry was recently developed for the quantification of isoflavones in topical delivery systems with antiherpetic activity. The isoflavone aglycones, as daidzein, glycitein, and genistein, were determined in soybean acid extract, nanoemulsions and topical hydrogels. The stability of the formulations was verified under acidic, alkaline, oxidative and thermal stress conditions [54].

Proton nuclear magnetic resonance (NMR) spectroscopy, coupled with MS analysis, was used to identify the degradation products of a new antineoplastic and anti-inflammatory compound, 4-(3,5-bis(2-chlorobenzylidene)-4-oxo-piperidine-1-yl)-4-oxo-2-butenic acid, exposed to stressed conditions as acid/base, light, oxidant and high temperature [55]. Nuclear magnetic resonance analysis was also adopted to study the degradation profile of naproxen [31].

Currently, the data from most of analytical techniques above reported are elaborated by chemometric analysis, in order to select the more useful information from the analytical signals [56,57]. These modern processing techniques are able to handle a very high number of data and to obtain results that were impossible with the use of traditional techniques. A multivariate method decomposes the data matrix collected from the degradation process into the contributions of the single components. This matrix is decomposed into the product of two smaller factor matrices corresponding to the concentration matrix of \( n \) components involved in the process and to the spectral matrix of the pure components [58]. The algorithm Multivariate Curve Resolution-Alternating Least Squares is a recent chemometric technique applied for the resolution of complex multicomponent mixtures. This procedure was directly applied to the analysis of the spectral and chromatographic data collected from photodegradation experiments applied to diclofenac, estrogens and 5-fluorouracil. The data were treated without any previous separation of the analytes [11,59,60].

**Strategies for drug photostabilization**

The design of light-stable drug formulations to avoid or at least minimize photodegradation [3,4] represents one challenge for pharmaceutical industry. Different approaches, such as packaging materials, light-absorbing excipients or novel drug delivery systems (DDS), have been proposed to overcome the conditions that induce photodegradation. In the last decades, DDS have been reported as the most versatile strategy to improve significantly drug photostability, so as to direct the interest of the scientific community towards this research field.

Several DDS are currently under development with the aim to both minimize drug photodegradation and provide continuous drug release over a prolonged period of time, so to assure a higher storage and pharmaceutical efficacy [5,6]. Among the most studied systems, the vesicular matrices (i.e., liposomes and niosomes), the lipid soluble nanoparticles, cyclodextrins and emulsions have shown the best results.

Below, this review lists an exhaustive collection of the most used approaches or representative investigations in packaging and novel delivery devices for light-sensitive drugs to be potentially used in topical formulations. Table 2 summarizes the nanocarriers approaches, some light-sensitive drugs entrapped in these systems, their topical formulations commercially available and the relative references.

**Containers**

In the research phase and the development of a drug formulation, the control of the stability of the active principles and their compatibility with the container are the first step in defining the primary packaging [3]. The use of light-protective containers represents the method most commonly used by the pharmaceutical industry to prepare formulations containing photosensitive drugs.

Glass containers are usually the first choice for liquid pharmaceutical forms (e.g., lotions, injectables, drops, etc.). Different types of glass can be used [4]. A good protection from UV irradiance is obtained by using colored yellow–green glass or amber glass. However, the adoption of these containers makes difficult the inspection of its contents [73]. The metal containers are preferred for topical application for being strong, impermeable to gases and shatterproof. Tubes or packs made from foil or blisters, cans, aerosol and gas cylinders are the most used. Aluminum and stainless are used in most cases for both primary and secondary packaging [74].

Any drug solutions are also packaged in plastic containers because these are unbreakable, collapsible and light [74]. Recently, the photoprotective potential of
### Table 2. Nanocarriers’ approaches for light-sensitive drugs and references.

<table>
<thead>
<tr>
<th>Nanocarriers</th>
<th>Photosensitive drug</th>
<th>Topical formulation</th>
<th>Study</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liposomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Cream</td>
<td>Photodegradation of piroxicam in nanoemulsions</td>
<td>[61]</td>
<td></td>
</tr>
<tr>
<td>Tretinoin</td>
<td>Cream gel topical solution</td>
<td>Tretinoin photostability in nanosuspension Nanostructured lipid carriers for the topical delivery of tretinoin</td>
<td>[62,63]</td>
<td></td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Hydrogels</td>
<td>Photostability of vitamin A palmitate</td>
<td>[64]</td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Gel</td>
<td>Photostability and ex vivo permeation studies Photodegradation of diclofenac</td>
<td>[10,11]</td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Ophthalmic solution</td>
<td>Naltrexone in niosomes for ocular formulations in the treatment of conjunctivitis</td>
<td>[65]</td>
<td></td>
</tr>
<tr>
<td><strong>Solid lipid nanoparticles</strong></td>
<td></td>
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<tr>
<td>Dithranol</td>
<td>Emulsion</td>
<td>Photostability of dithranol in solid lipid nanoparticles</td>
<td>[23]</td>
<td></td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Gel</td>
<td>Isotretinoin in solid lipid nanoparticles</td>
<td>[66]</td>
<td></td>
</tr>
<tr>
<td><strong>Microemulsion</strong></td>
<td></td>
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<tr>
<td>Isotretinoin</td>
<td>Microemulsion</td>
<td>Photostability of isotretinoin in microemulsion</td>
<td>[67]</td>
<td></td>
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<tr>
<td><strong>Cyclodextrin matrices</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Diclofenac</td>
<td>Gel</td>
<td>Photostability of diclofenac in cyclodextrins</td>
<td>[12]</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Cream</td>
<td>Doxycycline photodegradation in ophthalmic preparations Doxycycline photostability by complexation with β-cyclodextrin</td>
<td>[68,69]</td>
<td></td>
</tr>
<tr>
<td>Nootkatone</td>
<td>Topical solution</td>
<td>Nootkatone encapsulation by cyclodextrins</td>
<td>[70]</td>
<td></td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Topical solution</td>
<td>Strategies to improve the stability of stilbene</td>
<td>[71]</td>
<td></td>
</tr>
<tr>
<td><strong>Cyclodextrins in vesicles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riboflavin</td>
<td>Topical solution</td>
<td>Photostability of riboflavin in cyclodextrin in liposomes</td>
<td>[72]</td>
<td></td>
</tr>
</tbody>
</table>

Polymer bottles for drug solutions has been tested. Despite the great use of amber glass containers, De Luca et al. [75] demonstrated the ability of transparent polyethylene terephthalate containers to protect from light some drugs much better than the amber glass bottle.

**Addition of excipients**

When the use of the containers fails to protect the drugs from light, another strategy consists of the addition of light-absorbing agents in the formulation. In a recent study, cream containing three sunscreens, benzophenone-3, ethylhexyl methoxycinnamate and titanium dioxide at different amounts have demonstrated good microbiological and physical stability, showing good attitudes to be proposed as a safe and stable emulsion delivery system [76]. The sunscreens when used as excipients absorb visible and/or UV sun radiations, partially or wholly, providing to the photoprotection of the drug by overlapping its absorption spectrum [12,76]. However, the use of the light-absorbing agents in a drug formulation is strictly controlled by the EU, in accordance with the pharmaceutical and toxicological behavior of these compounds, and the permitted concentration is usually very low [77]. Derivatives of 2-hydroxybenzophenone, as 2-hydroxy-4-methoxybenzophenone-5-sulphonic acid and 2-hydroxy-4-methoxybenzophenone, have been used as UV filters in sunscreens with concentration values limited to 5 and 10%, respectively [78]. Photoprotection by adding UV-absorbing excipients is in most cases applied in topical preparations containing anti-inflammatory drugs. Light-stability of diclofenac has been investigated in new gel formulations by adding octisilate, octyl methoxycinnamate or a combination of them [12]. Also, methoxy dibenzoylemethane has been added in the ketoprofen topical formulations with satisfactory results [12,77].

**Drug-entrapping in colloidal matrices**

### Liposomes & niosomes

Niosomic and liposomal vesicles have received great attention in recent years for their use as DDS. Both systems have a two-layer structure consisting of amphiphilic molecules and an aqueous compartment, but differ chemically in their structural units. These vesicular systems are very versatile: they can entrap hydrophilic drugs in the aqueous core and lipophilic drugs by partitioning them into the bilayer domains.
Unlike liposomes, which are made up of natural phospholipids, niosomes are based on the use of surfactants, resulting in greater stability, low production cost and toxicity [79]. The most widely used niosomes are single chain, synthetic, nonionic surfactants, belonging to the class of alkyl ethers (e.g., Brij®), alkyl esters (e.g., Span® Tween®) and Pluronics type triblock copolymers (e.g., L64® P105®), as well as fatty acid and amino acid compounds [80]. Gentle agitation or sonication of an aqueous solution of phospholipid/surfactant and drug mixtures (at a temperature above the gel/liquid transition temperature of the lipid) are generally required for vesicles formation, while exhaustive dialysis, ultracentrifugation or low-pressure gel filtration chromatography are used to purify the system from the unentrapped drug [81]. Figure 1 shows the different approaches during the incorporation of a drug in a niosomal matrix.

Liposomes and niosomes have similar applications in pharmaceutical and cosmetic field, acting as targeted and sustained drug-delivery carriers. Recently, these matrices have been proposed as entrapping systems capable of improving the stability of photosensitive drugs, alternative to the traditional liquid and semisolid formulations [9].

Tretinoin (or retinoic acid [RA]) is used in the topical treatment of skin disorders, such as acne, photoaged skin and psoriasis. Unfortunately, RA is very unstable to light, whereby its incorporation in liposomes or niosomes has been reported in various papers to strongly protect the drug against photodegradation. Promising results have been achieved by Manconi et al. [82], which compared the chemical stability of methanol solutions of RA with liposomal and niosomal suspensions of the drug, after exposition of the samples to UV and artificial light. The preparation technique was optimized by using a film-hydration method, through extrusion or sonication. RA degraded very quickly in methanol, while vesicles offered high photoprotection. Moreover, the drug was found to be more stable in unilamellar vesicles than the multilamellar ones. The best results were obtained by including RA in P90H liposomes or Trito® CG110 niosomes, demonstrating the high potential of these vesicular matrices to assure a significant drug stability.

More recently, nanosuspension formulations were proposed by Lai et al. [62] to improve cutaneous targeting and photostability of tretinoin. The stability of the matrix was compared with an oil-in-water nanoemulsion and a methanolic solution of the drug. HPLC analysis showed that after 1 h of UV irradiation, 83, 52 and 27%, respectively, of the initial RA concentration was still present in the matrices above reported. Furthermore, permeation studies demonstrated that nanoemulsions enhanced the drug transdermal delivery, while nanosuspensions were able to localize the drug into the pig skin, acting as drug reservoir. In 2016, Ghate et al. [63] developed nanosized lipid carriers, as topical device, for the vehiculation and protection of RA.
Carlotti et al. have presented an interesting and exhaustive study on the photostability of vitamin A retinyl palmitate [64]. Photostability of the compound was tested in hydroxy ethyl cellulose hydrogels at different pH alone and with the addition of sunscreens or antioxidants. In addition, drug-loaded liposomes, poly-methylmethacrylate microcapsules, and double-coated nanocapsules were incorporated in hydroxyl-ethyl cellulose gel and in oil/water emulsion. Additional protection obtained by further incorporation of sunscreens and antiradical scavenger in the formulations was also evaluated. Drug protection obtained with traditional phosphatidylcholine liposomes and lipotec nanocapsules resulted more efficient than that obtained with lipotec liposomes and microcapsules. The bad results of these matrices were attributed to the loss of drug encapsulated in the multilamellar structures or to the possible depolymerization of polyacrylate due to radiation. Hydroxy ethyl cellulose hydrogels showed less protection than emulsions, while the best performance were obtained in the gels at pH 5.6 and 7.0. The presence of antioxidants increased the drug photostability over time.

In 2011, Fadel et al. [83] has designed Rose Bengala (RB)-loaded liposomes to enhance photostability of this compound and cytophototoxic activity in anticancer therapy. Nanosized RB showed a tenfold slower rate of photodegradation than the RB buffer solution. At the same time, cell mortality showed an increase of 1.6- to 2.5-times.

The formulation of naltrexone hydrochloride (NH) in niosomes and discosomes has been proposed as an ocular delivery system, because of their enhancing effect on the corneal penetration. The vesicular matrices showed potential protective effect against oxidation and photoinduced degradation of NH [65]. The results revealed that vesicles protected NH after exposure to \( H_2O_2 \) and daylight. The addition of antioxidants and metal chelators improved synergistically the potential of these formulations, showing protection capability for 24 h against photo-oxidation.

Recently, Ioele and collaborators [11] have designed niosomal gel formulations containing diclofenac (DC) for topical application. After confirming the high sensitivity of this drug to light, the authors demonstrated that its loading in niosomes in the presence of antioxidants and the simultaneous incorporation into topical gel was very effective in reducing photodegradation of the drug. Additionally, this work represents the first example of DC-containing niosomal gel that can strongly promote skin permeation. In fact, \textit{ex vivo} permeation experiments applied on rabbit ear skin, demonstrated the improvement of drug bioavailability from niosomes. After topical application, this system promotes the material exchange between vesicles and intercellular lipids in order to accelerate the diffusion of the drug.

**Solid lipid nanoparticles**

Solid lipid nanoparticles (SLN) have emerged as an alternative to liposomes for improving photostability of active pharmaceutical ingredients. SLN are colloidal drug carriers possessing a solid lipid core able to solubilize lipophilic molecules. However, depending on the preparation method, SLN can be used for both hydrophilic and hydrophobic drugs. The lipids used in the preparation of SLN include fatty acids, monoglycerides, diglycerides, triglycerides, waxes and steroids [84].

Since 1990, SLN have been proposed to replace liposomes due to the many advantages presented. Among these, the preparation in the absence of organic solvent, low cost, good physical stability, large-scale production, no toxicity and high biodegradability [85].

Gamblire and collaborators [23] have obtained SLN by pre-emulsion followed by ultrasonication technique to improve the stability of dithranol, an effective drug for topical treatment of psoriasis. The amount of drug retained after 30-min exposure to UV light as determined spectrophotometrically. The results of this study showed that inclusion of dithranol in nanoparticles decreased the drug degradation from 5.2 to 1.8%.

Thus, dithranol is usually applied in short contact therapy, SLN may represent a promising vehicle to optimize efficiency of this drug for the treatment of psoriasis.

More recently, new SLN containing isotretinoin were developed to improve photostability of the drug and reduce the irritating effects from exposure to sunlight [66]. Results demonstrated that the entrapment of isotretinoin into SLN strongly reduced the drug photodegradation.

**Drug-entraping in ME**

MEs are clear, stable, isotropic mixtures of oil, water and surfactant that are of interest in the pharmaceutical technology field because of their versatility and attractive advantages [86]. The main difference between the classical emulsions and MEs refers to the size and shape of the particles dispersed in the continuous phase. In the case of ME, drop dimensions ranged between 10 and 200 nm, smaller than those of conventional emulsions (1–20 \( \mu \)m). Additionally, MEs constantly change from droplet-like swollen micelles to bicontinuous structures, whereby the usual ‘oil in water’ and ‘water in oil’ distinction is often useless [87].

The first study on the inclusion of photolabile drugs in ME has been published by Patel and collaborators [67] in 2011, to evaluate the potential of ME in
improving drug photostability. Authors compared the stability of isotretinoin in methanolic solution and in ME after direct exposure to sunlight. Inclusion in ME showed an optimal drug photoprotection: drug solutions were degraded almost 100% after about 240 min, while only 25% of drug was degraded after the same time in the ME matrix.

**Drug-entrapping in cyclodextrin matrices**

Cyclodextrins (CDs) are oligosaccharides derived from starch, consisting of units of α-D-glucopyranose joined by α,1–4 bonds, forming structures similar to a truncated cone. CDs have shown particular propensity to incorporate molecules, including drugs. In an entrapping-complex, the drug is part of the cavity of the cone. CDs are the most used devices able to give significant reduction in drugs photodegradation [88]. Several studies have been focused on this matter, comprising the photoprotection of chemotherapics, anti-inflammatory and antihypertensive drugs [88]. Figure 2 shows the entrapping of a drug in a cyclodextrin matrix.

In 2016, Kfourya et al. [70] demonstrated that the nookatone inclusion in cyclodextrins permitted to overcome some problems like low aqueous solubility and poor photo- and thermal stability of this drug, enlarging its use in foods, cosmetics, pharmaceuticals and agrochemicals preparations.

Recently Riva-Granizo and collaborators [89] developed complex of the histamine antagonist loratadine in α-, β- and γ-CD to reduce the photodegradation of the drug. α- and γ-CD resulted the best formulations to considerably improve the photostability of the drug.

In 2014, Ioele et al. [12] conducted an in-depth study on the photodegradation of diclofenac through drug entrapment in CD or incorporation in gel in presence of UV-absorbers. Drug methanol solution, standard gels and two commercial formulations 1 and 2% were used as control samples. An impressive increase of six times of photoprotection was obtained when DC was incorporated in β-CD. Addition of UV absorbers contributed to further improving the photostability of the drug.

Doxycycline (DX) is a broad-spectrum antibiotic of the tetracycline class, but its highly light sensitivity has limited the use of the corresponding dosage forms. Several Authors have studied the possible inclusion of DX in β-CD, carrying out promising results for the development of new formulations for ophthalmic delivery [68]. Recently, Kogawa et al. [69] designed and characterized inclusion complexes of DX with β-CD, studying the influence on the antimicrobial activity and the drug stability when exposed to UV light for 6 h. A recovery rate of 97% was measured for the inclusion complex, compared with the 68% value for the reference solution, also recording a significant increase in antimicrobial activity.

Recently, Silva et al. [71] demonstrated that cyclodextrins increased stilbenes (resveratrol, pterostilbene and pinosylvin) aqueous solubility and photostability at 4°C, and proposed their incorporation in several materials for the food and pharmaceutical fields.

**Combination of cyclodextrins & vesicles**

Combination of CD and liposomes has demonstrated great ability in improving drug photostability [90]. This multifunctional system allows to incorporate water-soluble drugs in the liposomes or in the aqueous core or CD complex. Figure 3 shows the mechanism of the incorporation of a drug in cyclodextrin-in-niosomes.

A pioneering but very comprehensive study was conducted by Loukas et al. [72] in 1995, with the aim to protect riboflavin, because of its rapid degradation under UV light. Riboflavin loaded β- or γ-CD complexes were incorporated into the aqueous core of traditional liposomes, in presence or UV absorbers and the antioxidant β-carotene with the purpose of obtaining maximum protection through a combined synergistic strategy. The γ-CD complex, in presence of lipid-soluble light absorbers and β-carotene, resulted the best formulation, increasing 266-fold the half-life of the vitamin.

**Conclusion**

The review summarizes the studies on the photodegradation of drugs for topical use and the most recent...
approaches to improve their photostability. The drug extraction procedures from the topical formulations and the analytical methods to determine the drugs in presence of the respective photoproducts have been detailed. The approaches to protect the photolabile drugs in the pharmaceutical formulations have been also described. The most modern and advanced strategies to define the pharmacokinetic profile of the drugs have been detailed and increase their photostability. Nevertheless, a critical discussion is reported on the use of the traditional light protection techniques, such as shielding containers or addition of light-absorbent excipients. A special attention has been reserved to the supramolecular delivery systems, as niosomes, cyclodextrins and combination of them, as they have demonstrated great potential in ensuring light-stability of the drugs in the topical pharmaceutical formulations.

**Future perspective**

Sensitivity to light of a large number of drugs is almost well known and also the commercial formulations may degrade during manufacturing, storage and administration. For the pharmaceutical companies, the photostability study of a new drug and drug preparations is part of the product development process, realized according to the requirements under ICH Guideline. These studies must ensure quality, efficacy and safety of the drug formulations and, in some cases, the results from these tests prevent their realization. The problem of light protection is particularly important for the topical drugs as they are directly exposed to light. In addition, the preparation of topical formulations could suffer from the presence of photoproducts. These problems can be associated with a potential toxicity of the byproducts or with a lower absorption after transdermal application. For these reasons, many studies are currently proposed to prepare light-stable formulations for topical use. In the future, these studies can lead to the design of pharmaceutical preparations assuring high reliability in terms of both therapeutic and toxicological characteristics.

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Executive summary

Photodegradation study
- The procedures applied on drugs and drug formulations according the requirements from ICH rules have been described.
- Several options and methodologies have been proposed in consideration of the characteristics of the drugs.

Analytical procedures
- Sample preparation has been explained for the most of topical formulations commercially available.
- According to the complexity of the matrices, the selection of the determination method represents an important step to realize a successful analytical procedure.

Traditional photostabilization approaches
- The use of appropriate containers is the common approach to ensure quality and safety of a drug formulation.
- The use of light-protective containers is suggested in EU Pharmacopoeia.
- The presence of the UV-absorbing agents in the formulation can be considered to protect the drugs.

Photostabilization in supramolecular matrices
- The entrapping of the drugs in supramolecular systems has demonstrated ability in improving light stability and pharmacokinetic behavior of a drug.
- Currently, particular attention is given to liposomes, niosomes or cyclodextrin-in-niosomes formulations that have demonstrated high performance in reducing the drug photodegradation and increasing its permeability through the skin.

References
Papers of special note have been highlighted as:
• of interest; •• of considerable interest

** Reports an updated guide for photostable topical drugs.
**•• Reports novel approaches for the photostabilization of a photosensitive drug in topical formulations.
20 Dinakaran SK, Alluri B, Annareddy KR et al. Spectrophotometric method development and validation for


45. • Reports a novel and rapid quality-control method for the determination of the photosensitive drugs and their photodegradation products.


Light-sensitive drugs in topical formulations: stability indicating methods & photostabilization strategies


- **Reports a novel quality-control method for the studies of photosensitive drugs.**


- **Describe the use of the cyclodextrins as light-stabilizing matrices.**


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- Describe the use of the combined approaches in the stabilization of photosensitive drugs.