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Photoreactivity of drugs

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Abstract

A drug substance or drug product can be exposed to natural or artificial light during production, storage, administration and use. The great majority of drug substances and pharmaceutical excipients absorb UV and possibly visible radiation. Absorption is a first indication that a compound *may* participate in a photochemical process i.e. be photoreactive, which can result in its own decomposition or that of other components of the formulation *in vitro.* The photoreactivity may also give rise to adverse photosensitivity in patients, like phototoxic and photoallergic reactions. It is, however, possible to take advantage of the photoprocesses initiated by the drug substance *in vivo*. Drug photoreactivity is the basic principle in PUVA-therapy for treatment of psoriasis and photodynamic therapy (PDT) in the treatment of cancer. Photoactivated drug carrier systems and light activated prodrugs (caged compounds) are options in advanced drug delivery for controlled release and targeting of the active principle from a dosage form, which is important in order to optimize the medication and reduce side effects. Both negative and beneficial aspects of drug photoreactivity, therefore, may have great impact on product safety and efficacy. Recognizing that a drug substance or product is potentially photoreactive requires that the reaction pathway becomes sufficiently characterized and understood so that stability and toxicity assessments can be made. Photostability data are in most cases not available for preparations licensed before Jan 1 1998 or for drug products prepared *in situ*, which include preparations made for the individual patient at the hospitals.

Introduction

It is well known that optical radiation can change the properties of various materials and products. This is often manifested as discoloration of colorless (white or transparent) products or bleaching of colored compounds like paint and textiles. The number of drugs identified as photochemically unstable (i.e. photoreactive) is steadily increasing. It is important to emphasize that only the radiation absorbed by a drug substance or formulation excipient according to its spectral absorption characteristics may induce a photochemical process *in vitro* or *in vivo.* Most drug substances and formulation excipients do, however; absorb optical radiation in the UV or visible part of the spectrum, thereby having the potential of being photoreactive *in vitro* or *in vivo.*

Absorption of optical radiation may result in the formation of free radicals and / or reactive oxygen species (e.g. singlet oxygen) which are identified as the reactive species in the processes under discussion. The photoreactivity of a drug substance or drug product describes how efficiently and by which reaction pathway the compound or formulation responds to optical radiation. The optional initial processes are the same both *in vitro* and *in vivo* but might or might not take place, depending on the environment of the absorbing species. Basic knowledge on the reaction mechanisms for the individual drug substances and products is therefore required in order to ensure a safe handling, packaging and labeling of the products, to reduce the potential for adverse effects and to optimize drug therapy by e.g. developing new drug delivery systems or therapeutic regimes.

Photoreactivity of drugs *in vitro*

Let us first consider the reactions that may take place in a pharmaceutical preparation before it enters the body, i.e. during storage and use. Interactions between the drug substance and optical radiation can result in its own decomposition or that of other components in the formulation through indirect (sensitized) reactions. The most obvious result of the first process is a loss of potency of the product which will lead to a loss of therapeutic effect of the preparation and formation of (toxic) degradation products. Adverse effects due to the formation of minor degradation products during storage and administration have been reported (1). Sensitized decomposition of other formulation components may lead to a change in physicochemical properties of the drug product (e.g. viscosity, droplet and particle size and charge) which may have serious consequences, particularly if the product is intended for parenteral administration (2). Situations of major concern are

- Storage of drug preparations in hospital wards
- Long term infusion regimes
- *In situ* preparation of parenteral products

Drug products can be exposed to different types of optical radiation during storage and use, e.g. in a hospital setting. In most cases the drug product would mainly experience exposure to visible light (i.e. cool white fluorescent tubes) prior to distribution to the hospital pharmacy or –ward or to the home patient. It is, however, important to realize that all lamps, even incandescent ones, emit some radiation in the UVA- region of the spectrum. In a hospital setting, drugs are often stored in unit-dose containers on an open shelf, in a refrigerator with constant lighting or even in the window sill. In many cases, the protective market pack is removed; the inner container can be made of transparent plastic material or glass that offers little if any protection towards UV- and visible radiation (3, 4). The unprotected drug product can then be exposed to fluorescent tubes and/or glass-filtered daylight for several days or even weeks prior to administration to the patient (5). Photodecomposition of the drug substance can sometimes not be detected by visual inspection, although discoloration of tablets after light exposure is a fairly common observation. A change in colour is not necessarily correlated to the extent of chemical degradation of the drug substance, and it is obvious that tablets may be discarded even though they fulfil the specifications with respect to active substance (6). Furthermore, reactions in the solid state and in solution are often different, whether due to the constraint of the molecular movement imposed by the crystal lattice or because the reaction occurs only at the crystal surface.

Pharmaceutical products are frequently exposed to glass-filtered daylight or even direct sunlight during administration and use. Long-term infusion can lead to exposure for hours up to 2-3 days, while portable drug delivery devices allow the patient to bring the product outside the building. In our work we have detected infusions at the bedside containing less than 10% of active substance towards the end of the infusion time. It is easy to understand that in such a case the medical effect is reduced. A lack of therapeutic effect would normally result in an increase in the prescribed dose. The moment a new infusion bag with 100% intact drug is connected, the patient is at a risk of receiving an overdose.

Another setting that requires attention is intravenous medication of premature babies under treatment for hyperbilirubinemia. During infusion the drug can be exposed to radiation of high intensity, and protection of the infusion set may be required. The dimension of this problem has not been evaluated. Degradation also takes place in the plastic tubing. A relatively large surface -to- volume of the drug solution is exposed, compared to the situation in the infusion bag. The actual precaution to be taken in the case of parenteral products is to protect the preparation against exposure by use of an outer bag (e.g. protection of the infusion bag) or by wrapping the infusion set (including the tubing) in aluminum foil. Both alternatives are time and cost consuming. The required action will in each case depend on the photochemical half-life of the drug substance in the

formulation. Evaluation of *in vitro* photostability is therefore essential to ensure adequate quality over the entire life span of the drug. It is important to be aware that the photoreactivity of a drug substance is dependent on its concentration in the actual preparation and on the type of infusion medium or pharmaceutical formulation. It is therefore difficult to predict photostability from analogueous studies (7). A dilution step is often involved when preparations are made at the bedside and adjusted for the individual patient (*ex tempore* preparation). Dilution (e.g. change of medium and change in concentration) may lead to altered requirements with respect to protection of the infusion set.

The complexity of the problem can be illustrated by the following example. Epinephrine (adrenalin) is given as a long term infusion for epidural analgesia after major surgery. The compound does not absorb optical radiation above 300nm and is therefore expected to be photostabile under indoor conditions. The substance turns out to be photostabile in all commonly used infusion media except for sterile glucose solution (8). A pure glucose solution does not absorb radiation above 300 nm. Glucose infusion medium is, however, sterilized by heat prior to the addition of adrenalin or other drug substances. During the heat sterilization a degradation product of glucose is formed (5-hydroxymethyl-2-furaldehyde, 5-HMF). This degradation product has an absorption spectrum that extends above 300 nm, i.e. the compound is capable of absorbing glass-filtered daylight. 5-HMF is a very efficient source of singlet oxygen (9). Many drug substances, among them catecholamines, are susceptible to attack by singlet oxygen. This leads to the degradation of the drug substance. The concentration of 5-HMF allowed in sterile glucose infusion solutions exceeds by far the level needed to induce degradation of drugs present in the preparations (10). It is very difficult to avoid the formation of this product during the sterilization process. Every unit of glucose infusion medium thereby contains a source that can sensitize photoformation of singlet oxygen. Photosensitized degradation of drugs diluted in glucose solutions is therefore likely to occur, unless the units are protected against UVB-radiation. Nearly 500 000 units of sterile glucose solution are used in Norwegian hospitals annually (11).

The storage- and use conditions described above are valid for most European hospitals. It is, however, apparent that there are differences between the US, Europe and Japan concerning exposure to glass-filtered daylight. In the US and Japan exposure to glass-filtered daylight is believed to occur rarely in hospitals or pharmacies, although the trend is about to change. In the US new cancer hospitals are designed to provide convenience, comfort and tranquillity with an architecture with elements of natural light that ”brings the outside inside”. In the US, as well as in Europe, there is also a trend towards home treatment of elderly patients and patients diagnosed with a chronic illness. Home infusion therapy service now makes an important part of the clinically based care program offered in e.g. the US. Drug products are therefore more likely to be exposed to

glass-filtered daylight or even direct sunlight during storage and use in the future.

Since 1.1.1998 it has been mandatory to perform photostability testing of new drug substances and drug formulations according to the ICH Guideline on photostability testing (12). The official regulations do however, not cover drug products that were on the market before 1998, photostability of the preparations under “in use” conditions (e.g. during infusion) and preparations that have been made for the individual patient (*ex tempore* preparations). The present situation regarding drug photostability issues can be summarized as follows

- There is a lack of information on the photostability of products registered before 1998 and on parenterals made *ex tempore*.
- ” In use” conditions are not well characterized.
- There is an increasing demand for information from health personnel and regulating authorities on drug photostability issues.
- Information is important to secure safe and efficient medication and to reduce cost.
- Information is time-consuming to obtain because photostability is difficult to predict from analogue studies and the individual preparations have to be tested separately.
- An international expert group is working to establish an”*In use*” guideline for photostability testing.

Photoreactivity of drugs *in vivo*

Although a drug product is photochemically inert in the sense that it does not decompose during exposure to optical radiation, it can still act as a source of free radicals or form phototoxic metabolites *in vivo* (13). The drug will then be photoreactive after administration if the patient is exposed to light, causing photoinduced side-effects (photosensitivity). An increasing number of drug substances are reported to be photoreactive *in vivo*. This tendency is likely due to an increase in exposure to artificial light sources such as daylight lamps and solaria; a change in human leisure habits (i.e. more time spent outdoors) and a widespread use of drugs. The photosensitivity problem is getting much attention, particularly in the US, but still there are many uninvestigated compounds on the market. Several requirements are to be met if a drug is to cause a photosensitivity reaction. First, the drug substance or drug metabolite has to be distributed to tissues that are exposed to radiation, like the skin, eye and hair. Secondly, the absorption spectrum of the drug substance or metabolite must overlap the transmission spectrum of the actual tissue. A fraction of the optical radiation above 300 nm will penetrate sufficiently deep into Caucasian skin to react with substances circulating in the bloodstream or accumulated in the tissue. The undesired photosensitivity reactions will occur in some people who either

ingest the photosensitizing agents or apply them topically. The observed side-effects can be divided into phototoxic reactions, which are manifested on exposed areas (e.g. skin, eye), and photo-allergic reactions which are immune responses, and, therefore, can be manifested in both exposed and non-exposed tissue (14,15). A phototoxic reaction is essentially immediate in comparison to a photo-allergic reaction that has an immunological basis and requires previous exposure to the photosensitizing agent. Cutaneous phototoxicity is by far the most common of the drug-induced photosensitivity reactions. Major skin reactions are erythema, hyperpigmentation, exaggerated sunburn and blisters (14). Drug-induced photosensitivity can be anticipated among a wide range of therapeutic groups like e.g. antidepressives, antihistamines, antihypertensives, antimicrobials, antineoplastics, antipsychotics, diuretics, hypoglycemic agents and nonsteroidal anti-inflammatory drugs (NSAIDs) (16-18). Photosensitizing chemicals have usually a planar, tricyclic or polycyclic configuration and a molecular weight <500 Daltons (16). The photochemical and photobiological mechanisms are mainly free radical in nature, but reactive oxygen species are also involved (16, 19). The same drugs are generally innocuous to skin in the absence of exposure to optical radiation. The main protective actions to be taken by the patient are to avoid exposure to direct sun and solaria, to use broad-spectrum sunscreens and wear appropriate clothing and sunglasses, and to change medication if possible. Several photoreactive drugs can continue to cause light induced side-effects for up to one year after administration (14). Recent documents issued by FDA and EMEA provide guidance on how to address photosafety assessments and labeling requirements for potentially *in vivo* photoreactive substances (20, 21). These guidelines are most likely to be applied on new drug substances and not on products already on the market, but so far they are not mandatory.

Benefits from drug photoreactivity

In some cases a benefit can be gained from the photoreactivity of a drug substance or a pharmaceutical formulation. The dominant examples in regular use are the PUVA-therapy (combination of psoralens and UVA) as a treatment for psoriasis, application of blue light irradiation to counteract hyperbilirubinaemia or neonatal jaundice and photodynamic therapy (PDT) as a treatment for various cancers. In PDT a photosensitizing agent, usually a haematoporphyrin derivative is administered to the patient who is then irradiated selectively at the site of lesion. The sensitizers are taken up or retained in tumors with some selectivity compared to normal tissue. One of the disadvantages associated with the use of systemic photosensitizers is that the patient remains photosensitive until the sensitizer is eliminated from the body. Recently, ALA-PDT has become widely used in the treatment of skin tumors, particularly basal cell carcinomas. Aminolevulinic acid (ALA) is converted *in situ* into the

photosensitizer protoporphyrin IX which has some tumor selectivity. Depths of up to 2 mm can be reached and ALA-PDT gives very good cosmetic results (22). Oxygen is a crucial component in PDT, as the therapeutic effect is dependent on the formation of singlet oxygen. Singlet oxygen may induce a number of effects in cells and tissue, like destruction of the plasma membrane, lysosomes and tubuli, induction of apoptosis by oxidative stress and destruction of tumour blood vessels leading to tumour suffocation. Finding optimal sensitizers and drug delivery systems is crucial in improving the efficacy of PDT and reduce side effects. The commonly used porphyrins are not ideal and active research on new photosensitizer candidates is going on (23). Most of the candidates are porphyrin-like molecules (e.g. porphyrin derivatives, chlorines, bacteriocholins, phtalocyanins) and posses' physicochemical properties that make them difficult to handle in the compounding process. They are polycyclic, often heavily charged and in many cases present as zwitterions which makes them almost insoluble in both hydrophilic and lipophilic media. They are thereby difficult to incorporate in a simple emulsion or liposome preparation. In addition they frequently form inactive aggregates in the presence of aqueous media. Alternative formulation approaches may therefore be required for these photosensitizers (24). Drug targeting from parenteral administration of photosensitizers has been achieved by using liposomes, oil emulsions, microspheres, micellar nanoparticles, proteins and monoclonal antibodies but the ideal formulation has not yet been developed (25). Little effort is made to optimize the vehicle for topically administered sensitizers (e.g. dermal or to the oral cavity). A well-designed vehicle could allow topical administration of sensitizers to tumours located close to the skin surface and thus offer an alterative to systemic administration (26, 27). Application to the oral cavity and larynx would benefit from bioadhesive formulations to increase the contact time between sensitizer and tissue. The selection of vehicle also influences the localisation of sensitizer within the cells (28, 29).

Over the last years, photodynamic therapy has become increasingly regarded as a viable option for treatment of oesophageal carcinoma and Barrett's oesophagus as well as age-related macular degeneration (AMD), the most common cause of blindness in the Western population, and in the treatment of atherosclerotic plaques (30, 31). Another promising application of PDT is in the treatment of microbial infections (32-34). About 30% (i.e.15 million) of the deaths worldwide are caused by infections (35). Drug resistance is reported in tuberculosis, dysentery, typhoid fever, gonorrhoea and a number of hospital infections caused by Staphylococcus aureus, Enterococcus spp. and Klebsiella pseudomonas (36). PDT against microbial pathogens includes a broad spectrum of action because singlet oxygen has a number of targets within the cell. For the same reason it is unlikely that the bacteria will develop resistance towards PDT. It is known that gram-positive bacterial species are much more sensitive to photodynamic inactivation (PDI) than gram-negative species. Efforts have

therefore been made to design photosensitizers capable to attack the gram-negative strains (37, 38). Antimicrobial PDT is at an experimental stage at present, but is making rapid advances towards clinical applications within the field of oral candidacies, periodontal diseases, healing of infected wounds and treatment of Acne vulgaris (39-41). The first product to be applied in the oral cavity came on the market in Canada in 2005 (Periowave™, Ondine) and products for the treatment of infected wounds are under clinical trial (42). Antimicrobial PDT requires topical applications of photosensitizers which will be selective for the microorganism, without causing unacceptable damage to the host tissue (33). The possibility of adverse effects on host tissues has often been raised as a limitation of antimicrobial PDT. However, studies have shown that the photosensitizers are more toxic against microbial species than against mammalian cells, and that the concentration of photosensitizer and light energy dose necessary to kill the infecting organism has little effect on adjacent host tissues (43, 44). Photoactivated disinfection of blood samples and surfaces like benches and floors is also introduced as a promising application of antimicrobial PDT (45, 46).

One may take further advantage of the photoreactivity of a pharmaceutical compound or excipient in the development of new drug delivery principles and devices. Novel drug delivery systems are directed toward a controlled release rate, a sustained duration of therapeutic action, and/or a targeting of the delivery to specific tissue. Photoactivation is an attractive option for triggering drug delivery and includes different approaches. The method can be used to control the release rate of the active principle from a dosage form (i.e. a carrier system), to activate a drug molecule already present at the site of action in an inactive form (e.g. a photosensitizer or a prodrug), or to combine the two (i.e. photocontrolled drug release and drug activation). The application of photoactivated carrier systems offers an underdeveloped opportunity and includes systems like photosensitive hydrogels, microcapsules and liposomes (24). Recently, a novel technology named photochemical internalisation (PCI), for light-induced delivery of genes, proteins and many other classes of therapeutic molecules has been developed (47-49). Degradation of macromolecules in endocytic vesicles after uptake by endocytosis is a major intracellular barrier for the therapeutic application of macromolecules having intracellular targets of action. PCI is based on light activation of a photosensitizer localized in the endocytic vesicle membrane inducing a rupture of this membrane upon illumination. Thereby endocytosed molecules can be released to reach their target of action before lysosomal degradation takes place. More than a 100 fold increase in biological activity has been reported by use of this technique (46).

Conclusion

Evaluation of interactions between drugs and optical radiation now forms a natural part of the research and development work for new drug substances and products, while such information might be incomplete for drugs registered before 1998 and *ex tempore* preparations. Basic knowledge on the reaction mechanisms for the individual drug substances and products is required in order to ensure a safe handling, packaging and labelling of the products, to ensure safe and efficient medication and to reduce costs (e.g. in hospitals), to reduce the potential for adverse effects and to optimize drug therapy by e.g. developing new drug delivery systems or therapeutic regimes.
The combination of drugs and optical radiation has a great potential in cancer therapy and will find new applications in the near future (e.g. in the battle against resistant bacteria).

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