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Phototoxic Antibiotics and Aspects of their Liposomal Encapsulation: A Mini-Review

Budai M[1*], Budai L[1], Wijesooriya C[2], Roy RJ[2] and Petrikovics I[2]

[1]Department of Pharmaceutics, Semmelweis University, Hőgyes E. u. 7. H-1092 Budapest, Hungary
[2]Department of Chemistry, Sam Houston State University, Huntsville, TX, 77341, USA

***Correspondence**: Marianna Budai, Department of Pharmaceutics, Semmelweis University, Hőgyes E. u. 7. Budapest, H-1092, Hungary, Tel: +36-1-459-1500/53056; Fax: +36-1-217-0914; E-mail: budai.marianna@pharma.semmelweis-univ.hu

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Abstract

The liposomal encapsulation of antibiotics offers advantages from the aspect of bioavailabilty and therapeutical efficacy. As among antibiotics many possess phototoxic properties, and during preparation (e.g. sterilization), storage or in case of topical application ultraviolet light exposure can be present, photodegradation of liposomal antibiotics should be taken into consideration. Thus, the examination of lipid-phototoxic drug interactions in the presence of ultraviolet light is of great importance. In some cases liposomal encapsulation can alter the ways and rates of photodegradation, leading to the formation of more or less (photo) toxic compounds. Through the examples of selected phototoxic antibiotics (nalidixic acid and lomefloxacin) we highlight the role of liposomal composition in altering the photodegradation process of drug molecules, - leading to possible changes either in the ways or in the rates of their photodegradation.

Keywords: Antibiotics, Liposomal encapsulation, Lomefloxacin, Nalidixic acid, Phototoxicity

Abbreviations: CPFX: Ciprofloxacin; DOPC: Dioleoyl-Phosphatidylcholine; DPPC: Dipalmitoyl-Phosphatidylcholine; DSC: Differential Scanning Calorimetry; ENOX: Enoxacin; EPR: Electron Paramagnetic Spectroscopy; FQ: Fluoroquinolone; LMFX: Lomefloxacin; MLV: Multilamellar Vesicle; MS: Mass Spectrometry; NANa: Nalidixic Acid; OFLX: Ofloxacin; PEFX: Pefloxacin; ROS: Reactive Oxygen Species; SL: Spin Labeled Stearic Acid; SUV: Small Unilamellar Vesicle; UV: Ultraviolet

Definition and Mechanisms of Drug-Induced Phototoxicity

Drug-induced phototoxicity, a non immunological event, refers to the development of skin reactions as a result of combined effects of a chemical substance and ultraviolet (UV) radiation. In vivo, phototoxicity is primarily due to UV-A (320-400 nm) light [1],[2]. The photoactive substances may enter into the skin by topical administration or they may reach the skin indirectly by the blood stream following ingestion or parenteral administration. Among drugs many antibiotics possess phototoxic potential (Table 1) [1],[2].

The electrons of photoactive compounds being localized in the skin can be excited by appropriate wavelengths of electromagnetic radiation penetrating through the skin and being absorbed in the phototoxic chemicals. This leads to the formation of unstable singlet or triplet states, and as a consequence of it, results in the generation of singlet oxygen species. As these molecules aim to achieve a more stable state, the transferred energy induces cellular damage and generates inflammatory mediators. While in some cases the photochemical activity of drugs is caused by the excited singlet form of oxygen, in other cases the photochemical activity is

driven by free radical formation [1],[2].

Table 1: Antibiotics possessing phototoxic potential

Ceftazidime
Clofazimine
Fluoroquinolones (e.g. ciprofloxacin, enoxacin, lomefloxacin, ofloxacin, pefloxacin)
Gentamicin
Isoniazid
Nalidixic acid
Nitrofurantoin
Sulfonamides (e.g. sulfathiazole, sulfamethazine, sulfamethoxazole)
Tetracyclines (e.g. doxycycline, oxytetracycline, tetracycline)

Some photoactive substances act on cellular DNA, while others on cellular membranes. Some drugs, e.g. fluoroquinolone (FQ) antibiotics may induce DNA breaks thus leading to cell death. Phototoxic reactions typically appear as an exaggerated sunburn or an increased skin fragility with blisters from trauma [1],[2].

Possibilities to Minimalize the Phototoxic Property of Drugs

As phototoxic reactions develop in most individuals if they are exposed to sufficient amounts of light and drug, the limitation of drug and/or light exposure can minimalize the risk of phototoxic reactions. In order to reduce the ultraviolet exposure, the use of physical and/or chemical photoprotection (e.g. sun protective clothing, sunscreens) can be advised [1],[2]. Aiming the reduction of administered drug dose, innovations of pharmaceutical technology – among them encapsulation techniques - can be applied, too [3].

Modern technologies aim to increase the bioavailability of drugs by means of nano-carriers e.g. cyclodextrins, micelles or liposomes. It seems clear that a well-designed carrier system allows increased drug concentrations at the sites of action, also in the inflamed tissues. Furthermore, carrier systems - due to targeting - make possible the use of lower drug doses and offer the reduced possibility of side effects. However, it does not automatically mean a reduction in the frequency of phototoxic reactions, too. As it is well known from the field of supramolecular chemistry, the host-guest relationships (e.g. cyclodextrin-drug) and other forms of molecular interactions (e.g. lipid-drug interactions in case of liposomes) can lead to altered ways and reaction rates of photochemical processes [3]. In special cases the molecular interactions can have a "negative" impact on the photodegradation process of the encapsulated phototoxic drug resulting in increased reactive oxygen species (ROS) production and/or more pronounced phototoxicity.

It is clear, that it is necessary to investigate the effects of carrier system not only on the therapeutic efficacy of the encapsulated drug, but also on the extent of ROS generation and photodegradation of the encapsulated drug, too.

In our earlier work we have designed liposomal carriers systems for phototoxic antibiotics. We aimed to improve the liposomal encapsulation of selected phototoxic drugs (e.g. nalidixic acid, lomefloxacin, ciprofloxacin, ofloxacin, ceftazidime, oxytetracycline, doxycycline) via altering the lipid composition, the lamellarity of liposomal vesicles or the pH of the hydrating systems [4],[5],[6],[7],[8]. As the liposomal carriers can interact with the encapsulated photoactive drugs, the examination of factors having a potential influence on the photostability of encapsulated antibiotics is of great importance [3],[4],[9].

In the present mini-review - through the selected examples of nalidixic acid (NANa) and lomefloxacin (LMFX) - we highlight the considerations of liposomal formulations in case of phototoxic antibiotics. We discuss some factors, among them lipid composition, lamellarity, that may have an impact on the routes and rates of photodegradation of encapsulated phototoxic antibiotics. However, the recommendations regarding the optimal method to reduce the phototoxicity of liposomal antibiotics are beyond the scope of this work.

Locatization of the Drug and the Free Radical Formation – Liposomal Nalidixic Acid

Nalidixic acid is a classical phototoxic drug, that has several structural features retained by many of the newer FQ compounds, and is based on a 4-oxo-1, 8-naphthyridin-3-carboxylic acid nucleus (Figure 1) [4].

For the encapsulation of NANa small unilamellar and multilamellar liposomes (SUVs and MLVs, respectively) were prepared from the most generally used lipid molecules - dipalmitoyl-phosphatidylcholine (DPPC) and dioleoyl-phosphatidylcholine (DOPC). The amount of DOPC was between 0 and 30 mol/mol%. The molecular interactions between NANa and the lipid molecules of the liposomal membrane in the presence and absence of

ultraviolet-B (UV-B) light were studied [4].

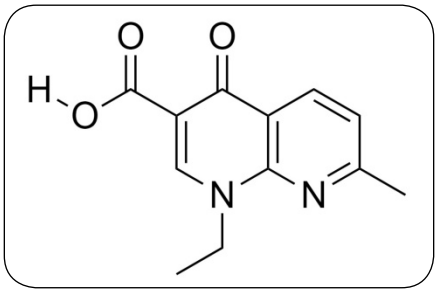

Figure 1: Chemical structure of nalidixic acid

Using differential scanning calorimetry (DSC), we observed the changes of the enthalpy and phase-transition temperatures for the pre- and main-transitions of the artificial membrane. With electron paramagnetic spectroscopy (EPR), we tried to localize the NANa in the liposomal membrane.

On the basis of DSC and EPR measurements, NANa mainly interacts with polar head groups of the lipid molecules – through weak interactions. This interaction increases the rigidity of the lipid bilayer at this depth of the membrane. The fluidity changes caused by the presence of NANa can only be detected close to the lipid head groups. This fact raises the question - whether the free radical formation due to UV-B radiation in the presence of NANa would also be limited close to the upper region of the bilayer? Or could it be detected further along the hydrocarbon chain, too?

Decay-kinetics of the spin labeled stearic acid (SL-5, SL-12 and SL-16) free radicals, incorporated into various depths (5, 12, 16th carbon atoms) of the membrane were studied in the presence of NANa and different doses of UV-B irradiation by EPR. Increased nitroxide reduction due to UV-B irradiation of the NANa-treated samples revealed the effect of the free radical production along the whole lipid chain. Interestingly, reduction rates almost coincide in different depths of liposomal membrane. At 10 kJ/m2 UV-B dose the reduction is almost complete for SL-5 and SL-16, and more than 80% of the incorporated SL-12 labels was reduced. It seems, that free radicals, produced in the upper regions of the membrane close to the NANa, can move down to the apolar region leading to the reduction of spin probes (SL-12, and SL-16) being present in this depth. This phenomenon can be explained by two possible pathways. One of them is the NANa mediated lipidperoxidation, which can occur also in case of saturated fatty-acid chains of DPPC. The other one is the known, increased lifetime of the generated free radicals in the apolar inter-space of the hydrocarbon chains [4].

In summary, the localization of a phototoxic drug in the liposomal membrane does not necessarily coincide with the localization of the free radicals detected in the membrane.

Altered Ways of Photodegradation– Liposomal Lomefloxacin

Fluoroquinolone antibiotics are one of the most important groups of pharmaceuticals. Among their side effects – in the presence of light – acute phototoxic reactions are by far the most common. Their phototoxicity order is reported as follows: lomefloxacin (LMFX), pefloxacin (PEFX) > ciprofloxacin (CPFX) > enoxacin (ENOX), ofloxacin (OFLX), while others report LMFX > OFLX > CPFX [4],[5],[9]. As not only ROS, but also photodegradation products of FQs can be responsible for the light induced adverse effects, it is necessary to evaluate the process of photodegradation in various media and carrier systems.

We address the question whether the presence of liposomes alters the extent and the ways of fluoroquinolone photodegradation and whether the liposome composition and structure (unilamellar versus multilamellar vesicles) influence the LMFX degradation (Figure 2).

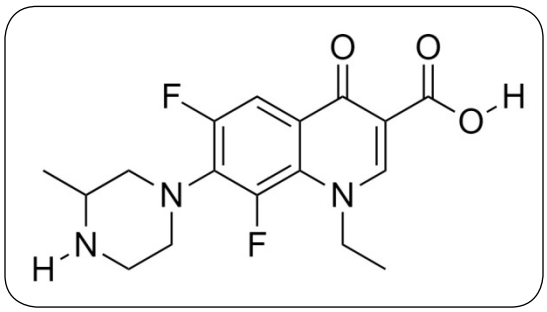

Figure 2: Chemical structure of lomefloxacin

LMFX containing SUVs and MLVs composed of pure DPPC or DPPC-DOPC mixture (70/30 mol/mol%) were studied by mass spectrometry (MS) [9].

For liposomal suspensions of LMFX the degradation rates do not seem to differ remarkably from each other. It seems that liposome composition and/lamellarity do not influence the rate of LMFX-photodegradation. Only 1–25% alteration can be found in the degradation rate values among the liposomal LMFX samples. However, the pathways of degradation and the photoproducts

strikingly differ in various media [9]. The presence of lipids does not accelerate the degradation process of LMFX, however, compared to aqueous phase it alters the ways of degradation leading to the formation of different photoproducts. In pure DPPC liposomes the double defluorination (m/z = 316) is a common and characteristic way of LMFX photodegradation in comparison to aqueous medium. While lamellarity of the DPPC vesicles does not influence the LMFX photodegradation, lipid composition has a significant impact on it: the presence of unsaturated fatty acid chains (DOPC) in the liposomal bilayer modifies the LMFX-photodegradation-ways, making the CO2 loss (m/z = 308 and 288) more common and increasing the frequency of dehydrogenation followed defluorination (Table 2) [9].

Table 2: Degradation products of LMFX in aqueous and liposomal media determined by MS – as a result of UV-B irradiation (3 kJ/m2). LMFX-concentration was 0,2 mM, for liposomal samples lipid concentration was 2 mg/ml

Medium	Characteristic photoproducts (m/z values)
Aqueous	350; 348; 336; 332; 316; 308; 288
DPPC SUV or DPPC MLV	350; 336; 332; 316; 308; 288
DPPC/DOPC (70/30) SUV	350; 336; 332; 308; 288; 153; 69

m/z = 352; LMFX
m/z = 350; LMFX-2H
m/z = 348; LMFX-4H
m/z = 336; LMFX-2H-CH_3
m/z = 332; LMFX-2H-F
m/z = 316; LMFX-2F
m/z = 308; LMFX-CO_2
m/z = 288; LMFX-CO_2-2H-F
m/z = 288; LMFX-2H-F-CO_2

It is not known which LMFX-photoproduct possesses higher or lower phototoxic potential. It would be important to identify the species being responsible for phototoxic effects. In the future this knowledge may lead to minimalization of phototoxic side effects in case of marketed products and to the design of new drug candidates with reduced phototoxic potential, such as delafloxacin [9],[10].

Conclusions

As in some cases liposomal encapsulation can alter the ways and rates of photodegradation, leading to the formation of more or less toxic compounds, the examination of lipid-phototoxic drug interactions in the presence of ultraviolet light is of great importance.

In case of phototoxic antibiotics during the design of novel drug delivery systems the potential impact of molecular interactions on the photostability of drug should also be taken into consideration.

Declarations

Conflict of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Authors' contributions

All authors contributed to the preparation of the manuscript.

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