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REVIEW ARTICLE

Nanocarriers for Topical Psoralen Delivery

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Abbreviations:: UVA, ultraviolet A; UVB, ultraviolet B; PUVA, psoralen and ultraviolet A; PSs, photosensitizers; PDT, photodynamic therapy; Hp,Hematoporphyrin; PQPs, perylenequinone pigments; PUVB, psoralen and ultraviolet B; CTCL, cutaneous T-cell lymphoma; GvHD, graft-versus-host disease; ROS, reactive oxygen species; 8-MOP, methoxsalen; SLNs, Solid lipid nanoparticles; LNPs, Lipid nanoparticles; NLCs, nanostructured lipid carriers; PLA, polylactic acid; PLGA, poly lactic-co-glycolic acid; PAMAM, polyamidoamine.

Abstract

Light has proven itself as a promising treatment modality for skin diseases. Phototherapy is a simple technique based on the exposure to light without photosensitizers, while photochemotherapy is a combination of phototherapy and chemotherapy which involves systemic or topical delivery of a photosensitizer to a target tissue followed by selective irradiation of the affected lesions with a suitable light. Psoralens are photosensitizers known to induce phototoxic reactions when applied in conjunction with UVA or UVB light. Challenges in the topical delivery of psoralens led to the emergence of nanoparticles as suitable delivery vehicles for psoralens. The current review sheds the light on the most commonly used nanocarriers for delivery of psoralens.

Keywords: psoralen; PUVA; nanocarriers

1. Introduction

Light has been applied in the treatment of skin diseases since ancient times. Sunlight, either alone (known as heliotherapy or phototherapy) or in combination with certain plant extracts containing photosensitizers (PSs) has been widely used to provide therapeutic effects in ancient Egyptian, Indian, Greek and Chinese cultures for the treatment of various skin conditions such as lupus vulgaris, cutaneous tuberculosis, psoriasis and vitiligo.[1,2] Since then, several studies have focused on the therapeutic effects of light and its potential applications in skin diseases.

Phototherapy; a simple technique based on the exposure to light without the application of PSs, has been successfully employed for the treatment of neonatal jaundice, psoriasis, vitiligo, scleroderma and atopic eczema.[3] On the other hand, photochemotherapy which is a combination of phototherapy and chemotherapy involves systemic or topical delivery of a photosensitizer to a target tissue followed by selective irradiation of the affected lesions with a suitable light resulting in cell death via necrosis or apoptosis.[4] The photosensitizer used, either synthetic or natural is non-toxic in the dark but is active upon absorbing light at appropriate wavelength, typically ultra-violet, visible, or near infrared light.[2] The activation of the photosensitizer with appropriate light triggers a series of oxygen-dependent and/or oxygen-independent photochemical reactions in the affected tissues resulting in photodamage and subsequent cell death via apoptosis or necrosis.[5] In the oxygen-independent (Type III photochemical reactions) pathway, the photosensitizer can directly react with the pyrimidine and thymine bases of nucleic acids or unsaturated

fatty acids forming stable adducts which interfere with the cellular division. In the other set of oxygen-dependent (Type I and II) photoreactions, also known as photodynamic reactions (PDT), the photosensitizer can transfer its excess energy to molecular oxygen available in the target tissues, generating free radicals or highly reactive singlet oxygen able to damage the cellular membranes. The photosensitizers utilized in photochemotherapy can generally be classified as porphyrins or non-porphyrins [6] as shown in figure 1.

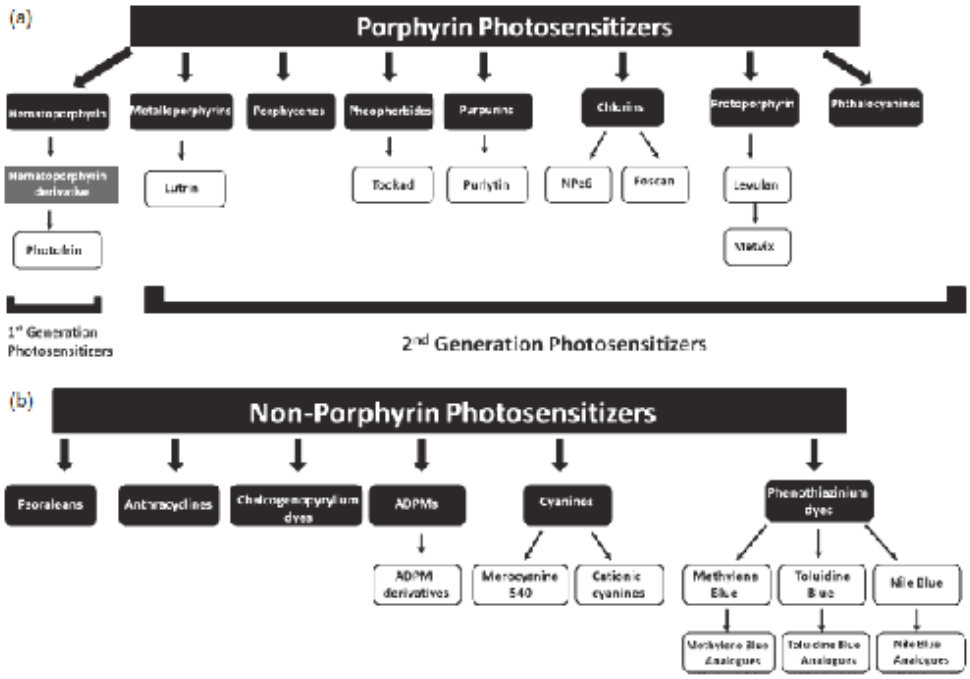

Figure 1: Classification of photosensitizers as (a) porphyrin-based or (b) non-porphyrin-based PSs. [6]

a) Porphyrin-based PSs

Porphyrins are a class of tetrapyrrole structures which make up the largest group of PSs that have been employed for photochemotherapy. Tetrapyrroles have been termed the 'pigments of life' since they occur naturally in several important biomolecules such as heme, chlorophyll and bacteriochlorophyll [7]. Porphyrin-based PSs are further classified as first, second and third generation drugs. Hematoporphyrin (Hp), isolated from hemoglobin in 1981 and its derivative, Photofrin® were the first utilized PSs for oncologic applications. However, the first generation PSs have several drawbacks which are:

1. they are not single compounds but they consist of mixtures of porphyrins with different properties, thus making it difficult to establish structure-activity relationships,
2. they are not very selective,
3. they lack long wavelength absorption, and
4. higher doses are required to achieve consistent photosensitizer uptake in tumors which result in prolonged patient photosensitization.[8,9]

Therefore, a number of second generation PSs such as protoporphyrins, phtalocyanines, naphthalocyanines, chlorins and bacteriochlorins have been developed to overcome the problems associated with first generation molecules. These PSs are chemically pure and have more intense long wavelength absorption (650-800 nm) with an optimal tissue penetration. Therefore, they induce lower toxicity and cause significantly less post-treatment skin photo-

sensitization compared to the first generation PSs. Second generation PSs conjugated to carriers such as antibodies and nanoparticles for selective accumulation within tumor tissue are referred to as third generation PS.[6]

b) Non-porphyrin-based PSs

Although Hp derivatives come from a natural source, they don't act as photosensitizing compounds in nature. There are many examples of natural non-porphyrin PSs which have evolved over millions of years mainly in plants for chemical defense against microbial or herbivorous attack.[10] The isolation and elaboration of compounds such as the perylenequinone pigments (PQPs) and the furanocoumarins represent a major advance in the field of photochemotherapy. Many synthetic non-porphyrin PSs have also been realized and studied for their photosensitizing activity such as Rose Bengal, methylene blue or toluidine blue.

Furocoumarins (psoralens) are a class of naturally occurring heterocyclic compounds with a known phototherapeutic activity that takes place via the previously described mechanisms. These compounds have been found to induce phototoxic reactions when applied in conjunction with UVA (320–400 nm) or UVB (290-320 nm) light exposure.[11,12] The therapeutic use of plants rich in psoralens was employed in ancient India and Egypt to treat certain skin disorders such as vitiligo and psoriasis.[5,13] The most frequently used plants belong to Apiaceae (Umbrelliferae) family such as celery and parsnip, Fabaceae such as Psoralea corylifolia L., Moraceae such as fig, and Rutaceae such as lemon and bergamot.[1,14] The current treatments involving psoralen plus either UVA (PUVA therapy) or UVB (PUVB therapy) light have provided successful clinical treatment against different diseases, from skin disorders like psoriasis or vitiligo to promising anticarcinogenic uses.[5,15] PUVA therapy involves topical application or oral administration of psoralens followed by total body exposure to UVA light. The radiation sources commonly used for PUVA are UVA fluorescent lamps with a fluorescence spectrum extending from about 320 to 400 nm, with a peak at around 352 nm. Recent studies have indicated that the shorter UVB wavelengths may have equal or greater therapeutic efficacy in combination with psoralens than the longer UVA wavelengths.[16,17] Therefore, PUVB therapy has been recently introduced in the clinical practice for treating different skin diseases with varying reports of success.[18] This technique combines the use of UVB fluorescent lamps emitting either broad band UVB (290–320 nm) or narrow band UVB (311-312 nm) together with psoralens. Several studies has proved that PUVB therapy had similar clinical efficacy to PUVA therapy, however it achieved earlier response and required lower dose of light compared to PUVA therapy.[18,19]

PUVA therapy has been reported to be important not only for its antiproliferative effects on skin cells, but also for its influence on the immune system regulation.[1] Accordingly, psoralens are not only considered as PSs, but also photochemoprotective agents against cancer and immune system disorders.[20] Therefore, many conditions, such as cutaneous T-cell lymphoma (CTCL), lichen planus, granuloma annulare, graft-versus-host disease (GvHD), Grover's disease and autoimmune diseases such as lupus erythematosus and progressive systemic sclerosis could be treated using psoralens.[1] The most commonly used psoralens

are 8-methoxypsoralen (8-MOP, methoxsalen), 5-methoxypsoralen (5-MOP, bergapten) and 4, 5', 8- trimethylpsoralen (TMP, trioxsalen).[12,21] The molecular structure of these psoralens is shown in figure 2.

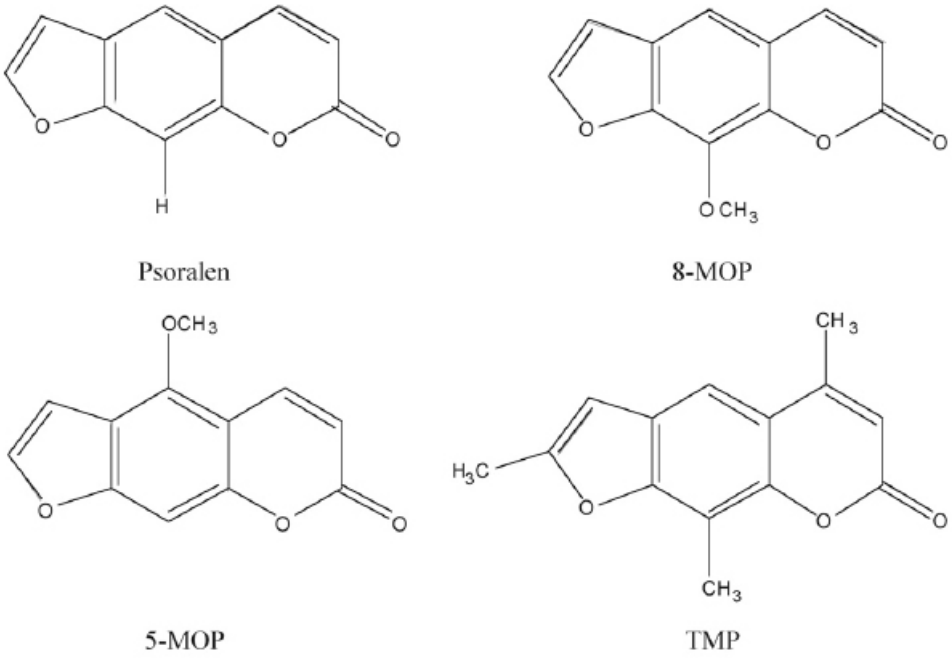

Figure 2: Structures of psoralen molecule and its derivatives: 8-MOP, 5-MOP and TMP.

The use of systemic PUVA therapy that involves oral administration of psoralens for the treatment of skin diseases has displayed several disadvantages with unsatisfactory cosmetic results.[22] Systemic psoralen absorption results in acute side effects such as headache, nausea, vomiting, hepatic and ocular toxicity as well as long term carcinogenic risks. Instead, topical PUVA has shown lower risk of side effects compared to oral PUVA since the systemic psoralen toxicity is avoided and the cumulative doses of both psoralens and light are reduced.[23] Moreover, topical PUVA is easy to handle and no protective glasses are needed because more limited areas can be treated, avoiding cumulative photodamage to the entire skin surface.[24] Unfortunately, most of psoralens are highly hydrophobic without specificity to the target site and their conventional topical formulations such as tinctures, lotions and ointments have poor percutaneous permeability and limited skin deposition, which leads to frequent psoralen administration and adverse reactions.[25] In addition, the direct contact of free psoralen with skin from these formulations lead to severe sunburn, blisters, abnormal dark pigmentation and increased risk of epithelial skin cancer due to uncontrolled reaction of psoralen with light.[26,27] To overcome these limitations, a considerable number of studies have been conducted on the synthesis or modification of psoralens as well as the development of nanocarriers for topical psoralen delivery.[28]

Nanotechnology has shown great promise in enhancing the efficacy and safety of topical PUVA therapy. The use of nanocarriers enables the control of the physicochemical properties of psoralens such as solubility, concentration, particle size and particle charge, thus enhancing drug delivery to diseased cells and avoiding collateral damage to healthy cells.[29,30] Additionally, the encapsulation of psoralens within nanocarriers modifies their photophysical properties. Nanocarriers have shown potential for protecting photosensitive drugs such as

psoralens against fast light degradation and ensuring the retention of adequate levels of psoralens within the targeted cells until light activation is done, which leads to increased production of reactive oxygen species (ROS), resulting in enhanced cellular photodamage.[31,32] This review article sheds the light on the most commonly used nanocarriers for topical delivery of psoralens.

2. Nanocarriers for topical psoralen delivery

A variety of delivery nanosystems have been used as psoralen nanocarriers targeted for topical delivery such as liposomes, niosomes, ethosomes, polymeric nanoparticles, lipid nanoparticles and dendrimers.

2.1. Vesicular delivery systems

Vesicular delivery systems such as liposomes and niosomes have been intensively studied as carrier systems for topical delivery of drugs and cosmetic agents. They have the potential to enhance the penetration of hydrophilic and hydrophobic drugs into the skin, increase physicochemical stability, reduce the serious side effects of skin irritation, and serve as a depot for sustained release of active components in the case of topical formulations.[33-35] Vesicular systems can be classified into two categories: conventional rigid vesicles such as liposomes and niosomes and novel elastic or ultra-deformable vesicles such as transfersomes and spanlastics. Conventional rigid vesicles were reported to be inefficient for transdermal drug delivery because they remain confined to the upper layer of the stratum corneum and do not deeply penetrate into skin.[36,37] However, they were suggested to enhance percutaneous drug penetration by acting as penetration enhancers through modifying the lipid bilayers of the stratum corenum rather than acting as carriers for drug across the skin.[38,39] Therefore, elastic vesicles were developed in order to deeply and easily penetrate through the skin and minimize the defective transdermal permeation of high and low molecular weight drugs.[40] Fluid vesicles such as ethosomes and invasomes are another form of highly deformable vesicles containing ethanol that even at low concentration bind to the lipid polar heads and increase the fluidity of the liquid crystalline state.[41] A wide variety of lipids and surfactants can be used to prepare vesicles: phospholipids (liposomes, transfersomes, menthosomes, ethosomes, transethosomes) or non-ionic surfactants (niosomes, elastic niosomes, invasomes, spanlastics).[41] Elastic vesicles are analogous to rigid vesicles in composition, with the difference that the former contain a surfactant (e.g. sodium cholate, sodium deoxycholate, different Spans and Tweens) that acts as an edge activator capable of destabilizing the lipid bilayer thus increasing its deformability.[42]

2.1.1. Liposomes

Charged liposomes were reported to enhance the topical delivery of psoralens since the inclusion of a charge inducer was reported to enhance the stability of vesicles by preventing their aggregation and enhance their cutaneous permeation.[26,32] In the study performed by Sinico et al. 2006, it was reported that the percutaneous permeation of 8-MOP from liposomes was higher than that obtained from the hydroalcoholic solution, which was attributed to the higher thermodynamic activity of drugs in vesicular systems and the action

of surfactants as penetration enhancers.[32] Also, it was reported that the negatively charged, unilammellar liposomes enhanced the penetration of psoralens through the skin whereas the positively charged unilamellar liposomes enhanced the psoralen accumulation in the epidermis. In another study conducted by Doppalapudi et al. 2017, it was reported that both cationic and anionic liposomal nanocarriers of psoralens were equally effective in improving the penetration and skin deposition of psoralens and thereby enhancing the efficacy of topical PUVA therapy in treating skin diseases such as psoriasis.[26] In addition, the results showed that the incorporation of psoralens in liposomes could possibly alleviate the adverse reactions caused by conventional vehicles because the sustained release of psoralens over prolonged time from liposomes would be beneficial in avoiding frequent administration of psoralens and the higher encapsulation of psoralens within liposomal nanocarriers together with their penetration to deeper skin layers could reduce the free drug availability on skin surface.

2.1.2. Ethosomes

Ethosomes represent a class of nanovesicles characterized by improved deformability, which enhances drug permeation and deep skin deposition. Ethosomes showed better percutaneous permeation and deposition of psoralens compared to conventional vehicles such as tinctures and conventional liposomes [25,43] which in turn may help reduce toxicity and improve the efficacy of long-term psoralen treatment. Furthermore, ethosomes were reported to be promising nanocarriers for enhanced topical delivery of 8-MOP in the treatment of vitiligo.[44] Ethosomal hydrogels of 8-MOP enhanced the permeation of 8-MOP into the deeper skin layers owing to the presence of ethanol on stratum corneum lipids by increasing vesicle fluidity, leading to superior delivery properties. Besides, they exhibited remarkably less phototoxicity on the skin owing to the presence of drug entrapped in the supramolecular vesicles, which tend to interact directly with the skin leading to higher concentration of drug in the inner microenvironment. The entrapped drug allowed slower and sustained delivery of 8-MOP to the targeted tissues, thus minimizing the inflammation and associated events causing changes in the skin physiology upon exposure to the UV radiation.

2.1.3. Niosomes

Compared to the phospholipids employed for the preparation of liposomes and ethosomes, non-ionic surfactants used for preparing niosomes are considered more chemically stable. Therefore, the higher stability as well as the ease of large scale production and storage have promoted niosomes as alternatives to the lipid-based vesicles for topical drug delivery. [36] Niosomes were reported to enhance skin permeation and deposition of 8-MOP and thus could be a promising vehicle for topical delivery of 8-MOP which may help in reducing toxicity and improving the efficacy of long-term PUVA therapy of various dermatological based diseases.[45] In another interesting study concerning niosomal systems, some authors successfully utilized niosomes for combined delivery of methotrexate and trioxysalen for topical treatment of psoriasis using PDT.[46] Authors suggested that this approach will offer selective and targeted therapy as well as satisfactory safety profile, enabling treatment of psoriasis for prolonged periods of time because the developed niosomal formulations improved the local concentration of both encapsulated drugs and reduced their systemic side

effects.

2.2. Lipid Nanoparticles (LNPs)

LNPs were developed as alternative carrier systems to emulsions, liposomes and polymeric nanoparticles. They offered several advantages as topical drug carriers, because of their biocompatibility and biodegradability through natural pathways, drug-solubility enhancement, and occlusive properties which enhance drug permeation through the skin. [47]

Solid lipid nanoparticles (SLNs) were introduced as the first generation of LNPs by replacing the oil of an o/w emulsion with lipid matrix that is solid at both room and body temperatures.[48] The use of solid lipid imparts advantages to the colloidal particles such as prevention of drug leakage, controlled and targeted drug release, enhanced stability of encapsulated drugs and colloidal carrier itself.[49] However, the sole use of solid lipids to form the nanoparticles resulted in perfect or highly ordered crystalline matrix leading to low drug loading capacity due to poor solubility of drug in solid lipid and drug expulsion during storage due to lipid polymorphism. Therefore, nanostructured lipid carriers (NLCs) were developed as the new, improved second generation of LNPs. NLCs are produced by using a blend of solid and liquid lipids (oil), in which this blend is also solid at body temperature.[50] As a result, a less ordered lipid matrix is formed with more imperfections in the crystal lattice that can accommodate the drugs.[49] Problems associated with the use of SLNs in drug delivery such as limited drug loading capacity, adjustment of drug release, and drug expulsion during storage are avoided by the use of NLCs.[28] SLNs and NLCs were formulated by Fang et al. 2008 for topical psoralens delivery targeted for psoriasis treatment.[28] Both nanoparticulate systems enhanced the bioavailability of psoralens penetrating the skin compared to their aqueous suspensions because their small particle size ensured close contact with the stratum corenum and offered better chance to adhere to the skin and to transport the drugs in a more controlled fashion. However, results of this study indicated that the NLCs could potentially be exploited as topical carriers with more enhanced psoralens permeation for psoriasis compared to SLNs.

2.3. Polymeric Nanoparticles

In the field of dermatology, increased attention has been given to polymeric nanoparticles to overcome the limitations associated with other lipid systems such as higher drug permeation, lower drug loading and phase stability.[51] Several non-toxic and biodegradable synthetic or semi-synthetic polymers, including polylactic acid (PLA), poly lactic-co-glycolic acid (PLGA), poly (e-caprolactone) and chitosan have shown promising results for topical drug delivery. The polymeric carriers can provide controlled and sustained release via modification of polymer composition and thus reducing irritation associated with direct contact of drug with skin. In recent published studies, PLGA-based nanoparticles and microparticles were chosen for the loading of benzopsoralen owing to a number of advantages including non-toxicity, biocompatibility and biodegradability through natural pathways.

[29] The results of these studies showed that the benzopsoralen (psoralen A)-loaded PLGA nanoparticles and microparticles were found promising for enhancing the efficacy and safety profile of PUVA therapy because the high levels of drug incorporation in the particles that were phagocyted by the target cells (macrophages), promoting efficient cellular photodamage after ultraviolet light application without chromatin condensation.

Another class of polymeric nanoparticles is dendrimers. Dendrimers are hyperbranched, monodisperse, three dimensional macromolecules with defined molecular weight and host-guest entrapment properties. They allow the precise control of size, shape, and placement of functional groups and combine typical characteristics of small organic molecules and polymers that result in special physical and chemical properties.[52] Polyamidoamine (PAMAM) dendrimers were shown to be effective enhancers of transdermal delivery of 8-MOP resulting in higher concentrations of 8-MOP in epidermis and dermis in relation to standard 8-MOP solution.[53,54]

3. Conclusions

Psoralens are an important class of natural and synthetic photosensitive compounds used for the PUVA therapy of numerous skin diseases characterized by either hyperproliferative nature or lack of skin pigmentation. Topical PUVA therapy emerged as a promising approach to minimize the systemic PUVA adverse effects. Unfortunately, the available topical formulations of psoralens such as emulsions, creams and solutions do not achieve good skin permeation and penetration of psoralens to deeper skin layers owing to the barrier functions of skin. To this end, several nanocarriers encountered in this review were highlighted, promoting safe and effective topical delivery of psoralens. The use of nanocarriers (either organic or inorganic) for delivery of psoralens is expected to replace other conventional therapies, leading to increased popularity of the topical route in phototherapy.

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Authorship (contribution or attribution)

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