Journal of Controlled Release 351 (2022) 164–173

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review article

Nanoemulsion applications in photodynamic therapy

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ARTICLE INFO

Keywords:
Photodynamic therapy
Nanoemulsion
Nanoparticle
Photosensitizer
Nanomedicine

ABSTRACT

Nanoemulsion, or nanoscaled-size emulsions, is a thermodynamically stable system formed by blending two immiscible liquids, blended with an emulsifying agent to produce a single phase. Nanoemulsion science has advanced rapidly in recent years, and it has opened up new opportunities in a variety of fields, including pharmaceuticals, biotechnology, food, and cosmetics. Nanoemulsion has been recognized as a potential drug delivery technology for various drugs, such as photosensitizing agents (PS). In photodynamic therapy (PDT), PSs produce cytotoxic reactive oxygen species under specific light irradiation, which oxidize the surrounding tissues. Over the past decades, the idea of PS-loaded nanoemulsions has received researchers' attention due to their ability to overcome several limitations of common PSs, such as limited permeability, non-specific phototoxicity, hydrophobicity, low bioavailability, and self-aggregation tendency. This review aims to provide fundamental knowledge of nanoemulsion formulations and the principles of PDT. It also discusses nanoemulsion-based PDT strategies and examines nanoemulsion advantages for PDT, highlighting future possibilities for nanoemulsion use.

1. Introduction

The exponential interest in nanotechnology has fueled the emergence of the multidisciplinary nanomedicine field, which has been increasingly explored to develop new strategies to diagnose, treat, and prevent disease, alleviate pain, and maintain and enhance human health [1,2]. In the last decades, the innovative applications of drug delivery and controlled release systems in nanomedicine have significantly broadened research and development in this field, sparking numerous applications of nanomaterials in different scientific disciplines [3,4]. In this context, the most common drug delivery systems are nanoparticles, which can be classified based on their components into two groups: (i) organic nanoparticles, such as nanovesicles, nanocapsules, and micelles, and (ii) inorganic nanoparticles, such as metallic nanoparticles, carbon nanotubes, and silica nanoparticles [5]. Nanoemulsion is one of the most popular organic nanoparticles, which includes nano-scaled droplets stabilized by emulsifiers. Nanoemulsions have attracted researchers' attention due to their numerous advantages, such as high kinetic stability, prolonged release profile, improved treatment efficiency, and good dermis permeation [6–8]. Their characteristics are greatly influenced by their two primary ingredients: (i) amphiphilic molecules, as surfactants for lowering interfacial tension, and (ii) lipid/oil, as the hydrophobic phase. For instance, one of the most effective parameters affecting the size of nanoemulsion is the amphiphile molecular size and structure and it has been reported that small surfactants molecule are more adept in preparing smaller emulsions [9,10].

Nanoemulsions have been used in various imaging and therapeutic applications, including photodynamic therapy (PDT) [11]. PDT is a clinical ablation technique to treat malignancies and involves photosensitizing agents (PS) administration, followed by light irradiation [12–14]. Indeed, nanoemulsions can be used for PS encapsulation, as these molecules tend to self-aggregate, decreasing efficiency [15–17]. This strategy improves not only PS penetration into the target tissue but also minimizes phototoxic side effects and increases PS bioavailability and stability, resulting in superior PDT efficiency [6,18].

In this review, we provide a brief introduction to nanoemulsions, PDT principles, and the most recent application of photosensitizer-loaded nanoemulsions in cancer therapy. Then, we discuss the impact of nanoencapsulation and highlight the future possibilities of this approach.

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https://doi.org/10.1016/j.jconrel.2022.09.035
Received 14 August 2022; Received in revised form 14 September 2022; Accepted 15 September 2022

2. Nanomedicine

Over the past decades, nanomedicine has shown great potential in the treatment improvement of various cancers, such as leukemia, hepatoma, breast cancer, and skin melanoma [19–25]. Nanomaterials have unique physicochemical properties that distinguish them from bulk materials, resulting in new properties. For cancer therapy applications, the nanoscale size for drug delivery systems has several advantages, such as (i) increasing permeability and retention (EPR) effect, allowing the drug to diffuse and remain in tumor tissue [26,27]; (ii) enhancing the surface-area-to-volume ratio (SA/V), which would increase the tumor site uptake [28–30]; (iii) being applicable for different types of surface modification [31–33]; (iv) improving intracellular uptake and prolonging drug retention period, boosting pharmaceutical potential [34–36]; (v) improving biodistribution, tissue penetration and pharmacokinetics of therapeutic agents [37–40]; (vi) being possible to design approaches with multifunctional features, like combining photodynamic therapy with chemotherapy or optical imaging [41–44].

Generally, there are two strategies for nanomaterials preparation: (i) the top-down, which breaks down materials using techniques pioneered by solid-state physicists, and (ii) the bottom-up nanochemistry that lays the groundwork for the creation of nanostructures and nanomaterials by utilizing supramolecular and biomimetic materials [45,46]. While nanoparticles can be prepared using both strategies, the bottom-up approach, such as self-assembly and chemical synthesis, offers benefits in particle morphology and size and can lead to the best surface structure. Smaller particles with smoother surface morphology promote bioactive substances to work more efficiently when administered [47–49]. Here it is worth mentioning that depending on the nanoparticle loading type and degradation rate, the loaded drug can be released by a combination of deterioration and diffusion processes [50–52]. Therefore, it is conceivable to have sustained delivery and control of the release profile of chemotherapeutic agents by adjusting the biodegradability and biodistribution of nanoparticles [53–55].

3. Nanoemulsion

Nanoemulsions are biphasic dispersion of two immiscible liquid droplets stabilized by an interfacial layer of emulsifiers, like amphiphilic surfactants. They usually have nanodroplets with uniform size distribution (20–500 nm) [7,9] and are also known as sub-micron [56,57], mini- [58], and ultra-fine grain emulsions [59]. They are biomedical and pharmaceutical emulsions applied in cosmetics, cancer therapy, gene therapy, diagnostics, and biotechnologies [60,61], being rendered into several dosage forms, like liquids [62], creams [63], sprays [64], gels [65], and aerosols [66]. Compared to traditional emulsions, they have numerous benefits, including greater interfacial area, quicker absorption, and the possibility to improve drug solubility and, therefore, bioavailability [7]. They also have remarkable kinetic stability due to their small size, which removes the thermodynamic constraints that limit the composition space of microemulsions, allowing nanoemulsions to be functionalized with a broader range of additives [67].

3.1. Nanoemulsion components

Generally, nanoemulsion contains two main constituents: lipid/oil, as its hydrophobic phase, and surfactants and cosurfactants, amphiphilic compounds that reduce the interfacial tension and inhibit droplet aggregation [9]. The final characteristics of nanoemulsions highly depend on the components. Therefore, desirable formulation qualities can be acquired by carefully selecting components and varying the amount and weight ratio of oil and surfactants. An oil's aqueous phase solubility decreases linearly with its molar volume (V_m); therefore, oils with a lower V_m are preferred because they generally result in better drug solubilization [10,68,69]. Moreover, the oil's viscosity is another vital parameter for nanoemulsion formation and size. For instance, low-viscosity oils, such as silicone or n-alkane oils, were used to create nanoemulsions with diameters ranging from 50 to 100 nm [70,71]. On the other hand, nanoemulsions generated with high-viscosity oils, like long-chain triglycerides, were much larger than their counterparts made with low-viscosity oils, such as hexadecane [10].

3.2. Types of nanoemulsions

Nanoemulsions can be categorized into biphasic and multiple nanoemulsions based on their components and relative distribution of the internal phases. While biphasic ones consist of two phases, i.e., water in oil (W/O) or oil in water (O/W), multiple nanoemulsions are more complex systems, like water in oil in water (W/O/W), which in the inner water phase is disseminated in an oil phase that is then distributed inside a single system's bulk aqueous phase (Fig. 1) [72,73]. The components interaction that composes the nanoemulsions can be evaluated to predict their generated type. O/W emulsification is favored if the principal surfactant is water soluble, and W/O emulsification is favored if the chief surfactant is oil soluble [9]. Hydrophilic/lipophilic balance value, solubility, and emulsification ability are the three main factors for emulsifier selection [7]. Hydrophilic/lipophilic balance is a dimensionless parameter of emulsifiers that affects nanoparticle characteristics and can be used as a guide for selecting emulsifiers. Their values between 3 and 8 are usually related to W/O emulsifiers, whereas values between 8 and 18 refer to O/W ones [46,74].

3.3. Advantages of nanoemulsions

Nanoemulsion drug delivery systems have numerous advantages, such as long-term stability, easy methods of preparation, and high solubilization of drug molecules [68]. They also showed an improvement in the stability, solubility, and bioavailability of drugs for oral administration [75–78]. Nanoemulsions have a versatile potential in cancer therapy, particularly for dermal or transdermal routes of administration, due to better penetration across the stratum corneum and deeper diffusion into the dermis [79–82]. Moreover, studies show that nanoemulsions are suitable to be employed for different biological environments, like nasal [64,83,84], ocular [85–87], vaginal [88–90], pulmonary [91–93], and parenteral [94–96].

3.4. Nanoemulsion applications

Recently, there has been a boost in the investigation of nanoemulsions for various treatment and imaging applications. Nanoemulsions are widely applicable for chemotherapy, for instance, co-administration of cisplatin and gemcitabine for bladder cancer [97] and doxorubicin/simvastatin-loaded nanoemulsions for Ehrlich ascites carcinoma treatment [98]. They can also be utilized for gene delivery, e.g., CD73-siRNA-loaded nanoemulsions for glioblastoma treatment [99] and pIDUA/nanoemulsion complex to treat mucopolysaccharidosis type I [100]. They are employed to transport biopharmaceuticals like vaccines, DNA-encoded medicines, and antibiotics [101,102].

As a novel clinically authorized nanoemulsion, Cationorm®, a preservative-free therapy option for mild to severe dry eyes, has some advantages over traditional artificial tears, including a more extended residence period on the ocular surface and beneficial moisturizing and lubricating effects [103]. In clinical trials, A new topical nanoemulsion, called NB-001 (Nanobio Corporation), is undergoing phase III clinical trials for recurring cold sores and Herpes labialis. While current topical treatments for cold sores are only marginally effective due to inadequate skin penetration, NB-001 has been reported to be more effective and safe, with high tissue bioavailability [104]. Further examples of clinically approved nanoemulsions and those under clinical trials are shown in Table 1.

One of the most successful nanoemulsion applications is for the encapsulation of photodynamic agents. Here, we present a brief

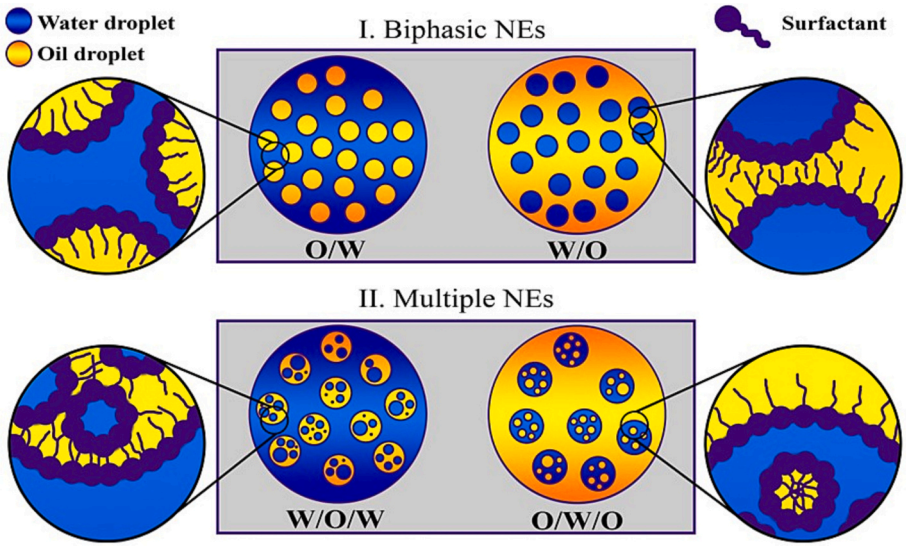

Fig. 1. Schematic illustration of nanoemulsion structure, including the biphasic systems (O/W or W/O), in which an appropriate volume of the internal oil phase is disseminated in the bulk aqueous solution or vice versa; and the multiple systems (W/O/W or O/W/O), within a single system, the inner water phase is dispersed in an oil phase, which is then dispersed in a bulk aqueous phase or vice versa.

Table 1
Current clinically approved nanoemulsions and under clinical trials reported by the national library of medicine in the USA.

Route	Condition	Drug	Product	Phase	Sponsor	Trial Identifier
Ocular	Dry eye	Medical device, MAF1217	Cationorm®	IV	VISUfarma SpA	NCT03833882
		Cyporin	Cyclosporine	III	Taejoon Pharmaceutical Co.	NCT02461719
		Brimonidine Tartrate	OCU-310	III	Ocugen	NCT03785340
	Cataract	Difluprednate	Tolf®	IV	Laboratorios Poen	NCT04631315
		Clobetasol propionate	SVT-15473	III	Salvat	NCT04246801
	Graft Versus Host Disease	Brimonidine Tartrate	OCU-310	III	Ocugen	NCT03591874
	Ataxia with ocular apraxia type 1	Dietary supplement: Coenzyme Q10	–	III	Assistance Publique - Hôpitaux de Paris	NCT02333305
Transdermal	Tinea Versicolor	Itraconazole nanoemulsion gel	–	II	Sara Botros	NCT04110834
	Menopause	Transdermal testosterone nanoemulsion	–	II	University Potiguar	NCT02445716
Topical	Knee Osteoarthritis	Diclofenac-Nanoemulsion cream	–	II	Pharmos	NCT00484120
	Herpes Labialis	Polysorbate/ cetylpyridinium chloride nanoemulsion	NB-001	III	NanoBio Corporation	NCT01695187
Nasal	Anthrax	recombinant protein nanoemulsion spray	BW-1010	I	BlueWillow Biologics	NCT04148118

introduction to PDT principles and how nanoemulsion could improve this strategy.

4. Nanoemulsion and PDT

PDT is a multidisciplinary area integrating photochemistry and photophysics sciences and has received attention due to the development of non-invasive cancer therapy and its relatively selective treatment [14,15]. In the 1970s and early 1980s, the first significant series of patients effectively treated with PDT utilizing hematoporphyrin derivatives (HpD) or porfimer sodium (Photofrin®), which included porphyrin monomers, dimers, and oligomers, was described by Dougherty et al. [105]. Up to now, early lung cancer, Barrett's esophageal cancer, bladder cancer, mesothelioma, intraperitoneal disseminated carcinoma, and head and neck malignancies have all responded well to PDT. Moreover, it has been the most effective therapy for skin cancer for the past three decades [106–110].

In a typical PDT process, a photosensitizing chemical compound is accumulated actively or passively within a tumor location and activated by light at a suitable wavelength. After exposure, the PS transitions from its low-energy ground state to a short-lived singlet-excited state, followed by the production of triplet-excited PS with a lower energy level and more prolonged duration due to an intersystem crossover. Once activated, PS transmits absorbed energy from their triplet-excited states to molecular oxygen, producing reactive oxygen species (ROS), such as hydrogen peroxides, superoxide anion, and hydroxyl radicals, or singlet-excited state of oxygen (singlet oxygen, $^1O_2$). PDT can cause cancer cell death through three different pathways (Fig. 2): (I) inducing necrosis, apoptosis, and autophagy, (II) causing vascular damage and, therefore, tumor ischemia, or (III) activating the host immune system against tumor antigens [16,111–114]. The PDT efficiency depends on PS's physicochemical features, such as $^1O_2$ quantum yield, hydrophobicity, charged groups, charge-to-mass ratio, ring type/number, intracellular localization [115–118], oxygen concentration surrounding the target cell/tissue, and the light conditions, like wavelength, energy or power density, and exposure time [119,120].

Despite its numerous advantages, traditional PDT has some drawbacks. The PS hydrophobicity is the main reason for its easy aggregation in water-based media, poor biodistribution, and low bioavailability, which seriously limits the effect of photodynamic therapy [17,121–124]. There are three generations of PSs, according to their evolution. The main aim of developing the second and third generation of PSs is to enhance the $^1O_2$ quantum yield, phototoxicity, uptake efficiency, and specificity [125–127]. In the last generation, PSs can be chemically modified using peptides and antibodies or encapsulated or conjugated with nanoparticles to increase bioavailability and improve their affinity and absorption in the targeted tissue while avoiding phototoxic side effects [16,128]. The best nanoparticles for PDT are

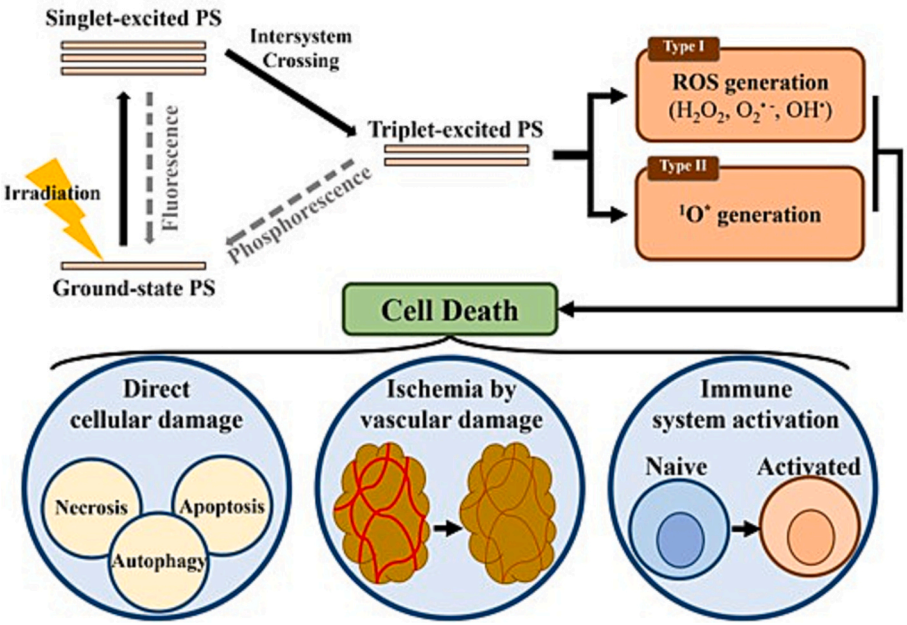

Fig. 2. PDT mechanism and cell death types caused by ROS or $^1O_2$ generation.

biodegradable, biocompatible carriers with low immunogenicity that can deliver PS in its monomeric state, minimizing the likelihood of aggregation, and selectively, with little absorption by non-target cells [129,130]. The most common nanoparticle types for PDT include gold [131–133], silica [134–136], PLGA (Poly(D,L-lactide-*co*-glycolide)) [137–139], TiO_2 (Titanium dioxide) [140–142], micelles [143–145] and liposomes [146–148].

4.1. Nanoemulsions' application in PDT

Among different nanoparticles for PDT application, O/W nanoemulsion fabrication, a common method for dispersing hydrophobic compounds in aqueous solutions, can overcome the PS drawbacks, including self-aggregation and low bioavailability. Up to now, only one PS, 5-aminolevulinic acid (ALA), has been approved for clinical trials (Table 2). ALA-loaded nanoemulsion gel formulation, also called BF-200, has been patented to overcome several drawbacks of ALA, such as low skin penetration and instability [6,18]. Szeimies et al. [149] studied the PDT for a total of 122 patients suffering from actinic keratosis using BF-200 with an irradiance of 630 nm and an energy density of 37 J/cm^2. Their results showed that the complete clearance rate of the lesion was 81%, which was higher than the placebo's rate (22%) (Fig. 3a) [149]. Using the same approach, Dirschka et al. compared the patient clearance rate with Methyl-5-aminolevulinate (MAL), and the results demonstrated the significant superiority of BF-200 ALA over the MAL cream [150]. These findings revealed that PDT based on ALA-loaded nanoemulsion is an effective actinic keratosis treatment. In other studies, ALA-loaded nanoemulsion, which could enhance epidermal penetration (Fig. 3b1-2) and tumor cell specificity, has shown a higher chance of complete eradication of basal cell carcinoma, compared with other existing PDT-based treatments, including free ALA and MAL [151,152]. Recently, Navarro-Triviño et al. studied the superficial basal cell carcinoma treatment by BF-200 ALA for a total of 31 patients with a median age of 63.74 years, reporting that 74.19% of patients were complete responders three months after two BF-200 ALA PDT sessions (Fig. 3c) [153].

Table 2
ALA-loaded nanoemulsions undergoing clinical trials reported in the USA national library of medicine.

Condition	Phase	Route	Sponsor	Trial Identifier
Lentigo Maligna	IV	Topical	Päijät-Häme Social and Health Care	NCT02685592
Basal Cell Carcinoma	II	Topical		NCT02367547
Actinic Keratosis	III	Topical	Biofrontera Bioscience GmbH	NCT01966120

4.2. Nanoemulsions' advantages in PDT

The advantages of nanoemulsion formulations in PDT have attracted intensive researchers' attention. Table 3 shows the last-decade studies on PS-loaded nanoemulsions and their advantages compared to traditionally used PSs. Indeed, the nanoemulsion offers several benefits to PDT, such as increased PS bioavailability and permeability, improved PDT efficiency and PS stability, and the ability to combine PDT with other types of treatments.

4.2.1. Nanoemulsion formulations increase PS bioavailability

A critical disadvantage of first/s-generation PSs is their weak bioavailability due to their hydrophobicity. This leads to self-aggregation, affecting the PDT efficiency [15]. The structure of O/W nanoemulsions aids PS hemogenic dispersion in aqueous solutions and biological environments and can be therefore employed to minimize self-aggregation, increase bioavailability, and enhance PDT efficiency [154]. Ma et al. studied Hypericin-loaded O/W nanoemulsions prepared using biocompatible oils (oleic acid or medium-chain triglycerides) and surfactants (Tween 80 or Kolliphor EL) to improve PS aqueous solubility and bioavailability [155]. Recently, Monge-Fuentes et al. studied the PDT application for non-metastatic melanotic melanoma using acai oil/Tween 80 nanoemulsions to change the PS solubility and enhance its bioavailability [156]. In another study, O/W nanoemulsions were used to improve the aqueous solubility of IR-780, a hydrophobic second-generation PS [157].

Moreover, another reason for the low bioavailability of first/s-generation PSs is their poor permeability across tissues and biological membranes, and due to the presence of surfactants and cosurfactants, nanoemulsions can increase the membrane permeability, which is highly desirable for topical PDT on corneal, ocular, and transdermal structures [158,159]. Using citrate-coated cobalt ferrite-based Zn(II)

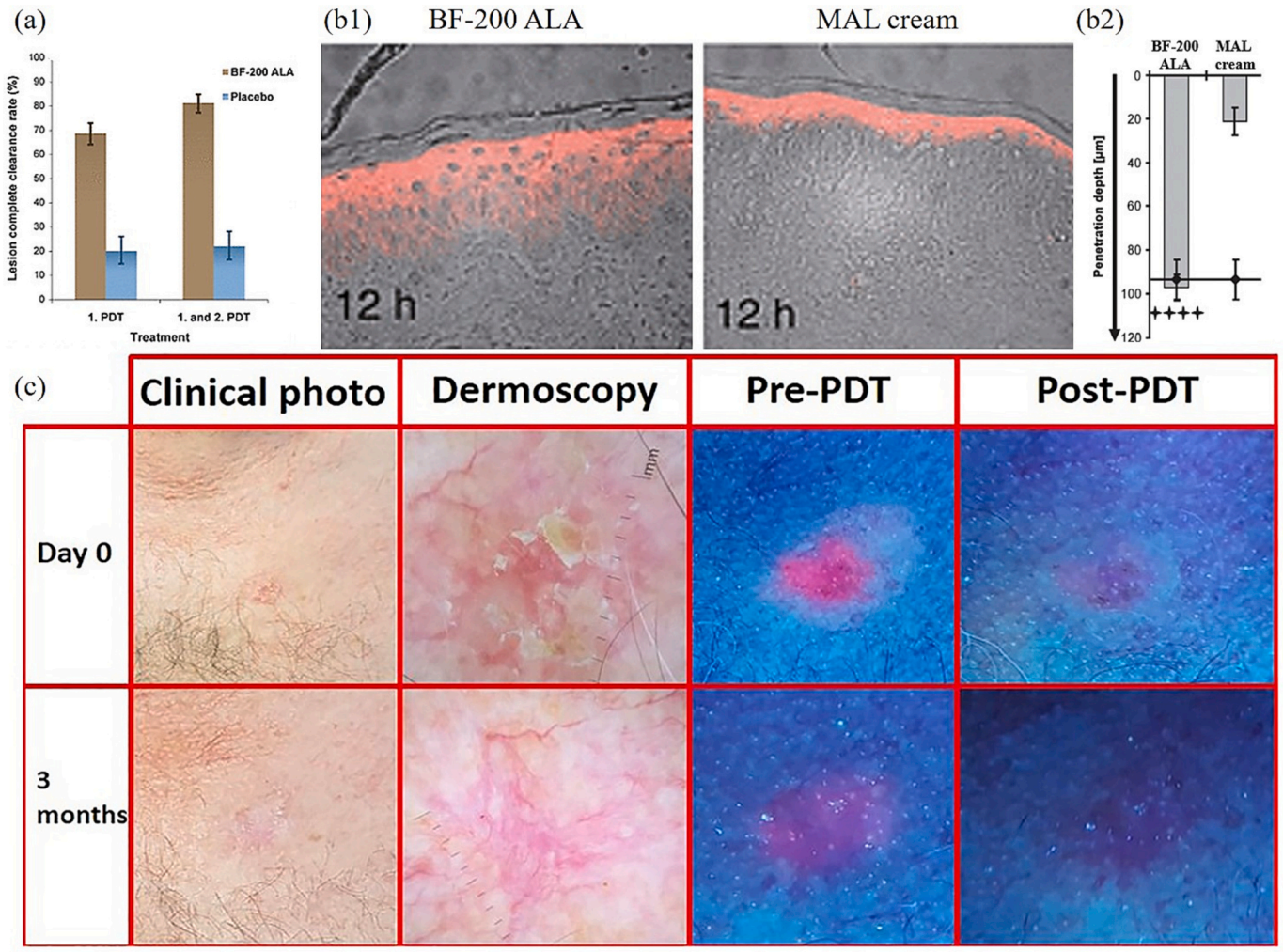

Fig. 3. (a) Actinic keratosis lesion complete clearance rates after PDT based on BF-200 ALA (Reprinted and adapted with permission from Szeimies et al. [149] © Wiley (2022)); (b1) Induction of PpIX fluorescence by BF-200 ALA or MAL cream in an ex vivo porcine skin model, and (b2) its graph of depth penetration (Reprinted and adapted with permission from Maisch et al. [152] © Wiley (2022)); (c) clinical assessment of the treated region at day 0 and 3 months after two BF-200 ALA PDT sessions (Reprinted and adapted with permission from Navarro-Triviño et al. [153] © Wiley (2022)).

phthalocyanine (ZnPc)-loaded magnetic nanoemulsions [160] or soy phosphatidylcholine Epikuron 170/Tween 80 and nonionic surfactants Poloxamer 188/Span® 80 nanoemulsions loading Foscan® (*meta*-tetrahydroxyphenyl chlorin, *m*THPC) (Scotia Pharmaceuticals Ltd., Guilford, Surrey, UK) [161] to treat skin cancer, Primo et al. reported that the topical administration of both approaches could increase the drug release on the deeper skin layers. In another study, zinc phthalocyanine tetrasulfonate ($ZnPcSO_4$)-loaded microemulsions prepared by surfactants (Span® 80/Tween® 80), canola oil, and a propylene glycol/water mixture (3:1) were developed to increase the skin penetration of $ZnPcSO_4$ while avoiding its aggregation [162].

4.2.2. Nanoemulsion formulations improve PDT efficiency

Several studies reported that nanoemulsions could improve PDT efficiency. For instance, *m*THPC-encapsulated nanoemulsion was more effective than free *m*THPC in eliminating tumors [163]. Additionally, nanoemulsions can decrease or avoid the side effects of some drugs, which also counts for PDT efficiency. Ma et al. reported that while the cytotoxicity of hypericin-loaded nanoemulsions was significantly higher than unencapsulated hypericin, the IC_{50} value was statistically inferior [155]. It is also important to highlight that in a hypoxic tumor environment, PDT efficiency is limited, and the use of oxygen-generating Chlorin e6 nanoemulsions can overcome this limitation aiding in the control of tumor hypoxia through releasing oxygen [164]. Hong et al. demonstrated the IR780- PFPE-in-water nanoemulsion's fascinating potential for reducing tumor hypoxia and improving the efficacy of oxygen-dependent treatments, including PDT, sonodynamic therapy, and radiation [157].

4.2.3. Nanoemulsion formulations improve PS stability

Nanoemulsions have been shown to improve drug physical and chemical stability with smaller droplet sizes and a more uniform size distribution retaining a higher level of stability [6,7,165]. Monitoring the zeta potential of nanoemulsions is one of the most common ways to examine kinetic stability, with nanoemulsions having a zeta potential of greater than 30 mV or lower than −30 mV providing excellent stability [7,166]. In a recent study, aluminum phthalocyanine (AlPc)-loaded nanoemulsions, which have shown mean size and zeta potential of 127 nm and −29 mV, remained stable for 17 months at 25 °C [167]. In another study, the colloidal and photophysical stability of AlPc-loaded nanoemulsions did not significantly vary over 365 days [168]. Similar exciting results have been observed in Rodrigues et al. study, which evaluated the hydrodynamic diameter, polydispersity index, fluorescence spectrum, and ROS production of AlPc-loaded Kolliphor® ELP/castor oil nanoemulsions, and reported that the physical and photophysical parameters were stable for at least four years at room temperature [169]. Evaluating the storage stability of Astaxanthin-loaded nanoemulsions over three months, Affandi et al. showed no significant

Table 3
Representative PSs-loaded nanoemulsions applied the recent studies and their advantages compared to traditionally used PSs.

Loaded PS	Emulsifier	Zeta potential (mV)	Hydrodynamic diameter (nm)	Irradiation characteristics	Application	Reasons for using nanoemulsions	Ref.
Ce6	PFPE	−0.02 ± 0.03	150.1 ± 5.1	633 nm, 50 mW/cm^2, 30 or 45 s	Eliminate the shortcomings of current PDT and SDT for cancer therapeutic applications	More accumulation into the tumor by passive targeting through the EPR effect and higher PDT efficiency	[164]
	PEG-b-PCL	−0.56	~ 220.3	671 nm	Drug delivery to metastatic mammary carcinoma tumors	To prolong blood circulation and increase tumor accumulation	[171]
	Cholesteryl oleate, egg phosphatidylcholine	−30.2 ± 3.0	153 ± 26	660 nm, 1 J/cm^2	To treat cancer selectively by combining hyperthermia and photodynamic therapy	Multifunctional features ability and also allow targeted therapeutic agent delivery to the tumor cells	[175]
AlPc	Cholesteryl oleate, egg phosphatidylcholine	−29.4 ± 3.4	127.5 ± 5.8	630 nm, 0.1–1.0 J/cm^2	Brain diseases like glioblastoma	Using 1.0 J/cm^2, nanoemulsions could increase the PDT activity by 55% compared with free AlPc	[167]
	Poloxamer 188	−56 mV	~ 200	670 nm, 700 mJ/cm^2	Combined treatment of HPT and PDT for brain cancer intervention, such as glioblastoma	To combine HPT and PDT, as one of the multifunctional nanoemulsion ability	[178]
	Kolliphor ELP®	−4.63 ± 2.34	25.00 ± 1.23	660 nm, 25.9 J/cm^2	Eliminating breast tumors and preventing the formation of metastasis in the lungs	The approach showed rapid internalization and complete eradication of tumors	[169]
ZnPc	Pluronic® F-127	–	30.19 ± 0.22	660 nm, 27.86 J/cm^2	PDT against Leishmania amazonensis and infantum	To improve the PS stability in an aqueous medium and its photobiological activity	[172]
	Poloxamer 188	−54.47 ± 1.50	200 ± 15.2	–	Designing a magnetic PS-loaded nanoemulsion system skin layers	To increase the drug penetration in the deeper layers of skin	[160]
IR-780	PFPE	−0.68 ± 1.15	205.81 ± 2.25	808 nm, 2 W/cm^2, 20 s	Mitigating tumor hypoxia and enhancing the PDT efficiency	To improve aqueous solubility and stability of IR780; to boost ROS generation	[157]
IR-786	D_2GHA-12 C_{12}(TAPAMS)$_2$	35 ± 5 42 ± 7	108–141	775 nm, 100 mW/cm^2	Assaying the anticancer efficiency of PS-loaded nanoemulsions with layer-by-layer adsorption of oppositely charged polyelectrolytes for breast carcinoma	To change the PS solubility and thereby improve the bioavailability, also to increase cellular uptake	[179]
Curcumin	Poloxamer 188	−46.3	199 ± 0.2	440 nm, 80 J/cm^2	PDT in an in vitro breast cancer model	To increase PDT efficiency	[180]
Sinoporphyrin sodium	HSA-PFTBA	−14.5	~ 150	635 nm, 200 mW/cm^2, 30 min	Photodynamic immunotherapy on breast cancer by integrating PD-1 protein with PS in nanoemulsions	The biomimetic nanoemulsion enhances the tumor accumulation of PD-1 protein via the EPR effect	[177]
Fluorous porphyrin	Pluronic® F-68	–	~ 175	420 nm, 8.5 mW/cm^2	Simultaneous delivery of singlet oxygen and photosensitizer	To minimize the aggregation and enhance the PDT efficiency	[154]
Acai oil	Tween 80	−0.53	117.5 ± 2.44	660 nm, 12.9, 25.9, and 51.8 J/cm^2	PDT treatment for non-metastatic melanotic melanoma	To change the solubility of the PS and increase the bioavailability	[156]
Hypericin	Kolliphor ELP® TWEEN 80	− 6.3 ± 0.8 − 10.5 ± 0.6	32.05 ± 0.07 18.92 ± 0.03	590 ± 10 nm, 8.4 mW/cm^2	PDT against breast cancer	To improve PDT efficacy of hypericin	[155]
Berberine	Poloxamer 188	−64	~ 220	447 nm, 80 J/cm^2	PDT-based treatment for cervical carcinoma	To improve bioavailability, efficacy, and pharmacological activity	[181]

Abbreviations: PFPE: perfluoropolyether, Ce6: chlorin e6, PEG-b-PCL: poly(ethylene glycol)-*block*-polycaprolactone, AlPc: aluminum phthalocyanine, ZnPc: zinc phthalocyanine, EPR: enhanced permeability and retention, HPT: hyperthermia, D_2GHA-12: 2-(dodecyldimethylammonio)ethylglucoheptonamide bromide, C_{12}(TAPAMS)$_2$: *N*,*N*-bis[3,3′(trimethylammonio)propyl] dodecanamide dimethylsulfate, PD-1: monoclonal programmed death 1, PFTBA: perfluoro- tributylamine, HSA: human serum aslbumin.

change in particle size or PS content during storage at 5 °C ± 3 °C, 25 °C ± 2 °C/60% ± 5%, and 40 °C ± 2 °C/75% ± 5% relative humidity [170]. Moreover, PS-loaded nanoemulsion can yield higher stability and thereby prolong blood circulation and tumor accumulation [171]. Siqueira et al. used PDT in the treatment of cutaneous leishmaniasis and reported that encapsulation of ZnPc in nanoemulsions made by clove oil and Pluronic® F-127 improved the stability and photobiological activity compared to free ZnPc [172].

4.2.4. Nanoemulsion formulations can combine PDT with other types of treatments

One of the most exciting advantages of nanoemulsions is their multifunctional feature ability. For instance, Chang et al. studied porphyrin-lipid nanoemulsions with paclitaxel loaded in the oil core as a novel platform for the combination of PDT and chemotherapy, reporting the potential to improve anti-tumor effectiveness and minimize the side effects associated with mono-chemotherapy [173]. In another study,

nanoemulsions containing PSs and chemotherapeutic agents significantly slow the progression of tumors in the breast, providing a better prognosis than current treatments [174].

Using nanoemulsions, the PDT combination with hyperthermia is also possible. Pellosi et al. increased anticancer functionality using a magnetic nanoemulsion combining magnetic hyperthermia and PDT to accelerate tumor destruction after small heat dissipation and visible light photosensitization doses, respectively [175]. Another study employed magnetic AlPc-loaded nanoemulsions as a combined PDT/hyperthermia strategy to increase the anti-tumor efficiency [176]. In another study, the synergistic effect of PDT and immunotherapy against hypoxic breast cancers, which was restricted by the adverse effects of the antibodies, and the hypoxic condition of solid tumors is also achieved by co-delivering a PS and the monoclonal programmed death 1 (PD-1) protein. The perfluorocarbon in the nanoemulsion core could serve as a source of oxygen for PDT against hypoxic cancers. Primary and distant subcutaneous 4 T1 cancers were totally suppressed by synergistic photodynamic and immunotherapy, which worked by promoting dendritic cell maturation and cytotoxic T lymphocyte infiltration of the tumor [177].

5. Conclusion and perspectives

Nanostructured emulsions have attracted scientific attention in various sectors, including diagnostics, pharmaceutics, and biotechnology. Nanoemulsions can enhance the functionality of chemical ingredients and improve their stability, solubility, polarity, and bioavailability. They exhibit excellent application potential in the PDT field, increasing PS diffusion rate into biological tissues, making them ideal for designing a new PS generation for topical and transdermal application. Due to their ability to improve membrane permeability, nanoemulsions make a unique impact in topical PS administration and imply the potential advantages of applying this vehicle in future preclinical and clinical research using PDT to treat noncancerous/cancerous corneal, ocular, and skin conditions. They can be effectively targeted by targeting agents thanks to their submicron size and functional groups on the surfactant hydrophilic head. In addition, nanoemulsions can protect unstable PSs, which can increase their stability and extend the duration of the medication's activity. Therefore, the higher stability, prolonged circulation, and the ability to be targeted can open up new possibilities for delivering PSs to the tumor location.

In conclusion, the features and benefits of nanoparticle droplets provide unique functional material capabilities. As consumers, scientists, and businesses envisage new concepts and products; this advantage ensures that nanoemulsions will occupy an important niche. It is anticipated that interest in PS-loaded nanoemulsions will grow as more people learn about their valuable features, improve their manufacture and stability, and discover new applications. Therefore, we expect exponential growth in the research and development for clinical deployment of PS-loaded nanoemulsions delivery.

Data availability

No data was used for the research described in the article.

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