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Review

Drug Delivery Systems for Phthalocyanines for Photodynamic Therapy

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Abstract. *The focus of this review is to describe the state-of-art in the development of innovative drug delivery systems for phthalocyanines as photosensitizers for photodynamic therapy (PDT). PDT is a medical treatment combining photosensitizers (PSs) activated by visible light of a specific wavelength to selectively destroy targeted cells, tumor tissues and its surrounding vasculature. In the last decades, PDT has been under intense investigation, first as a promising alternative approach for improved cancer treatment, later against microbial infection and nowadays, mainly in aesthetic medicine, against age-related degeneration. The success of PDT is restricted because of difficulties with administration and skin permeation of PSs. As PDT importance raises, there is high interest for advanced formulations and delivery systems (DDS) for PS, especially formulations based on nanotechnology. Accordingly, this review deals with the innovations pertaining to DDS for PDT as disclosed in recent patents and literature.*

The photodynamic therapy (PDT) was originally developed as a tumor therapy with improved selectivity towards diseased tissues in comparison to conventional cancer treatments (surgery, chemo- or radiotherapy). In addition to its primary use to destroy tumors without causing damage to surrounding healthy tissue, PDT has been successfully employed for the photosterilization of the tumor bed after surgical resection of a large neoplasm to support surgical treatment (1-3). Although PDT has multiple clinical applications, it is mainly used in oncology for the treatment of various types of solid tumors. The benefits of treating superficial oncologic lesions (tumor thickness <2-3 mm) using PDT are the low level of invasiveness and the excellent cosmetic results after treatment (4, 5). In dermatology, topical PDT is effective for dermatooncological or precancerous skin conditions like squamous cell carcinoma (6, 7) and superficial basal cell carcinoma (8-10), actinic keratosis (11, 12), Bowen's disease (4, 5, 13-15), mycosis fungoides (an indolent subtype of cutaneous T cell lymphoma) (9, 16-19), Kaposi's sarcoma, extramammary Paget's disease, and cutaneous B cell lymphoma (20) as well as for other proliferative disorders, such as vascular malformations (21) or keloid scars (22-24). In aesthetic dermatology PDT is extensively used for the treatment of inflammatory dermatoses that have a high psychological impact, like localized scleroderma (25, 26), acne vulgaris (27-29), rosacea (30, 31) and granuloma annulare (32-34), as well as for aesthetic indications like photo aged skin or sebaceous gland hyperplasia (4, 35, 36). PDT is useful for the treatment of various viral diseases such as warts (human papilomavirus) (37-39) or viral skin lesions (molluscum contagiosum and herpes simplex) (4, 5, 40), various mycotic diseases (41-43) or parasite diseases such as leishmaniasis (44-46) or bovine trichomoniasis (47). Currently, PDT is successfully used in ophthalmology for the treatment of age-related macular degeneration (48, 49).

PDT is used mainly for dermatology, however, light sources such as lasers can be coupled with fibre optic systems allowing acces to inaccessible locations, such as urinary bladder, digestive tract, brain or deep-seated tumors (3). PDT can be used in association with other therapeutic techniques such as surgery or chemotherapy. In the case of surgery for tumour resection, PDT can be used to help to destroy any remaining cancer cells after surgery. In the case of chemotherapy, several trials have demonstrated synergistic effects of the combination of PDT with low doses of chemotherapeutic drugs. The combination destroys cancer cells more efficiently and also reduces the side-effects of chemotherapy, due to the lower doses of chemotherapeutic drugs required to obtain the desired effect (3, 50, 51).

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Photodynamic Therapy (PDT)

PDT uses visible light of a specific wavelength, for killing cells and tissues though activation of photosensitizers (PSs), that in the presence of molecular oxygen, generate reactive oxygen species (ROS) leading to oxidative cell damage and cell death (52, 53). Each component is harmless by itself, but, in combination they induce severe toxicity towards targeted cells and tissues. The mechanism of action of PDT is generally nonspecific, but there are two mechanisms leading to greater selectivity towards the selected targets. First, enhanced permeability and retention (EPR) effect causing preferential uptake and accumulation of PSs in rapidly dividing cells and diseased tissues. Second, restricted illumination to specific region/volume of tissue. Only cells that are exposed simultaneously to PS, light and oxygen are subjected to the cytotoxic ROS produced during PDT. Additionally, healthy cells are much more resistant against oxidative stress than cancerous cells. Combination of all the above allows destruction of tumor tissue while sparing surrounding healthy cells from damage. PDT usually damages surrounding blood vessels and thus prevents tumor from receiving nutrients, and may trigger an immune response towards cancer cells as well.

Basic Principles of PDT

The mechanism of PDT has been discussed in detail elsewhere (54-56). Briefly, when the drug (PS or its metabolic precursor) is administered (and metabolized to form PS in the case of the precursor), PS is activated by exposing the tissue that has accumulated PS to the light of a specific wavelength, usually in the maximum absorption band of the dye (1). The PS is excited from its ground state (54) (singlet state, no unpaired electron spins (57, 58)) and reaches a short-lived excited singlet state (54, 55). In a time-scale of nanoseconds, PS releases its excess of energy by emitting a photon (fluorescence) or by internal conversion of energy (heat) and decay back to the ground state. Another mechanism involves the conversion to the excited triplet state *via* intersystem crossing including inversion of the spin of one electron (59) which has longer lifetime due to higher stability than the excited singlet state. Decay from the excited triplet state to the ground state is possible by emitting a photon (phosphorescence) or by internal conversion of energy (heat) or by transfer of energy to surrounding molecules. Interactions with the surroundings can follow two pathways named Type I and Type II reactions (Figure 1).

In Type I, the PS in its excited triplet state interacts with an organic cellular substrate transferring or acquiring one electron/hydrogen *via* the radical mechanism. It generates free radicals and radical ions and thus initiates chain reactions. After interaction with oxygen, PS can produce highly reactive oxygen species (ROS), such as the superoxide anion O_2^-, hydrogen peroxide H_2O_2, peroxide anions and highly reactive hydroxyl radical $OH^\bullet$, which then attack cellular targets and damage various cellular components (56, 60-62). However, oxygen is not necessarily required because original free radicals can cause cellular damage directly.

In Type II, the PS in its excited triplet state transfers its energy directly to molecular oxygen in its triplet ground state through energy transfer and yields highly reactive and cytotoxic singlet oxygen (63). This phenomenon is called triplet–triplet annihilation. Singlet oxygen has a short lifetime in a time-scale of microseconds, but a sufficient concentration of highly cytotoxic singlet oxygen induces irreversible cell damage (54, 55).

Both types of reactions take place at the same time and balance between them depends on the PS itself, however, it is considered that the prevailing mechanism during PDT is a Type II process (54, 56, 60-62, 64-66). After generating of cytotoxic ROS the molecule of PS can be destroyed by photobleaching due to oxidation (67) or can return to its ground state without chemical alteration and prepared to repeat excitation-energy transfer process multiple times (1, 59, 68-70).

Mechanism of Action on Cells

Increased levels of ROS exert their affects only in a small area around the region where they were generated, reported radius of action ranging within a 20-200 nanometers (2, 3, 71, 72), and ultimately causes cell death *via* necrosis, apoptosis or autophagy (73-76). The predominant mechanism depends on PS and light dose, cell type, and subcellular localization (site where ROS is generated determines which subcellular target is attacked due to radii of action in the order of dozens nanometres compared to diameters of human cells ranging from 10 to 100 μm) (2, 77). PS usually act in the plasma membrane, mitochondria, endoplasmic reticulum, and lysosomes (3, 78-80). Produced ROS attack mainly DNA, protein thiol groups, and membrane lipids (3, 81).

Mechanism of Action on Tumor Tissues

The mechanisms of cell death caused by PDT are necrosis or apoptosis. The mechanism of tissue damage is more complex and depends on applied PS agent and treatment conditions. In general, molecules of certain sizes, especially lipophilic macromolecular drugs, as most PS agents, tend to selectively accumulate in tumor tissues. As tumor cells grow quickly, they stimulate the production of new blood vessels. These are usually abnormal in form and architecture, and they are formed by poorly aligned defective endothelial cells.

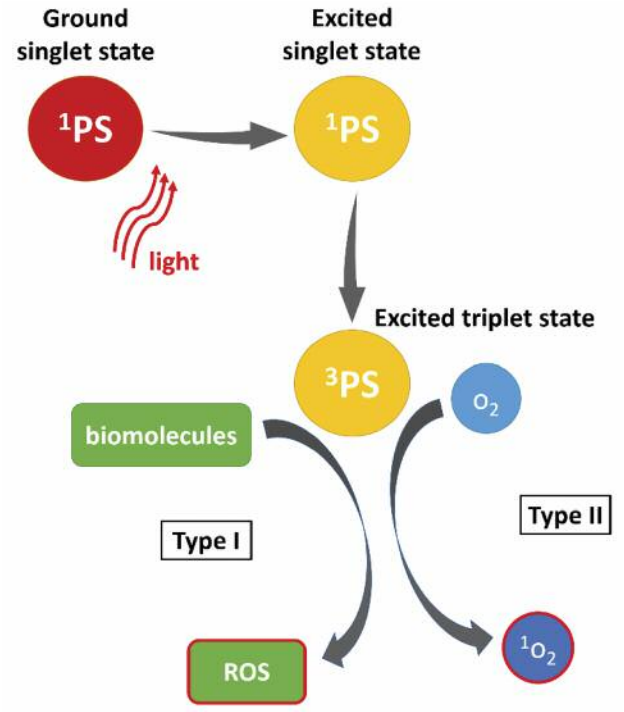

Figure 1. *The mechanism of action of photodynamic therapy.*

This leads to leaky vasculature. Other particular characteristics of tumors such as lack of effective lymphatic drainage, expression of specific enzymes and receptors, and pH variation play also role. All of these factors lead to accumulation of PS in tumor tissues and this phenomenon is called enhanced permeability and retention (EPR) effect. Disproportionately high numbers of low-density lipoprotein (LDL) receptors of tumour cell membranes and the fact that lipophilic PS agents are transported in the bloodstream bound to lipoproteins (such as LDLs) could enhance the accumulation of PS at close proximity to tumour cells (59, 82-84). PDT-induced changes in the vasculature may include vascular stasis, vascular leakage, or vessel collapse leading to ischaemic necrosis (3, 85-87).

Light Sources

PS is activated by exposing to the light of a specific wavelength, usually in the maximum absorption band of the PS (1). The stronger light absorption of PS at used wavelengths the higher quantum yields of excited states and potentially higher yields of ROS. However, for *in vivo* application PS requires a maximum of optical absorption at wavelengths higher than 650 nm due to strong absorption of endogenous pigments (such as hemoglobin, melanin). Absorption of endogenous pigments results in limited penetration depth (usually 1-3 mm) of light of wavelengths in the region of 400-600 nm (3, 87, 88). To enhance penetration into tissue to access deep-seated tumors, it is necessary to use high-energy light sources (lasers) that can easily burn surface tissues. With increasing wavelength, penetration depth increases as well. In the red visible region (650-780 nm) and near-infrared region (>780 nm) light of low intensity can be used to achieve depths of several centimeters without healthy tissue damage (3, 87). Energy of singlet oxygen corresponds to 1,270 nm, however, compounds able to absorb in the region higher than 800 nm are in fact extremely rare. For such high absorption wavelengths, it is necessary to conjugate dozens of aromatic bonds and/or incorporate some uncommon (bio-uncompatible) metal ions into the structure of the compound. Such compounds suffer of low solubility/bioavailability (unpolar structure) and toxicity (metal ions). Moreover light of these wavelengths tends to highly scatter in tissue (3). Practically, only the red region of the visible spectrum (650-780 nm) is available and is called “therapeutic transparency window” for PDT.

Porphyrin-based structures with extended aromatic systems such as phthalocyanines, naphthalocyanines, and benzoporphyrins have high absorption coefficients in the therapeutic transparency window and yield high levels of ROS. These, in combination with selective accumulation in tumor tissue (EPR effect), are the main advantages of these second-generation PSs.

Optionally lasers can be coupled with fiber optic systems allowing access to inaccessible locations, such as urinary bladder, digestive tract, brain or deep-seated tumors (3).

Photosensitizers

Although the first utilization of phototherapy for the treatment of diseases can be traced back over 4,000 years to the ancient Egyptians (89), contemporary PDT came first in the early twentieth century in the form of the first photosensitiser haematoporphyrin (Hp) which was isolated from blood and lately in the form of the purified haematoporphyrin derivative (HpD) used under the brand name Photofrin. The main disadvantages of this first-generation photosensitisers were weak absorption in the therapeutic transparency window and prolonged patient photosensitivity. This led to the development of improved PSs designed to minimize the drawbacks of the first generation PSs (90, 91).

Most of the second-generation PSs are porphyrin-like molecules (such as chlorins and bacteriochlorins), expanded porphyrins (such as texaphyrins), and structures with aromates fused to pyrrole rings (such as benzoporphyrins, phthalocyanines, and naphthalocyanines) or metabolic precursors of porphyrins (such as 5-aminolevulinic acid and

its esters). Although there exist numerous dyes and pigments displaying photosensitivity and effectively generate ROS, the PSs that are mostly used are only cyclic tetrapyrroles or structural derivatives of this chromophore. Cyclic tetrapyrrolic derivatives have little or no toxicity in the absence of light because of an inherent similarity to endogenous structures naturally occurring in human body. These compounds also display high absorption coefficients in the region of therapeutic transparency window, high yields in production of ROS, short serum half-life and selective tissue accumulation due to EPR effect (3, 92).

5-aminolevulinic acid (ALA) is not a photosensitizer by itself but is naturally occurring precursor in the biosynthetic pathway to photosensitive protoporphyrin IX (PpIX) (Figure 2). ALA is an endogenous metabolite that is synthesized usually in mitochondria from succinate-CoA and glycine. Conjugation of eight ALA molecules results of creation of PpIX which is subsequently metabolised and finally it results in formation of haem. Conversion of PpIX to its subsequent substrates requires activity of the enzyme ferrochelatase and this is the limiting factor concerning the rate of metabolism of ALA to haem. In case of external administration, the conversion of ALA to PpIX is quite fast but PpIX cannot be quickly converted by ferrochelatase to the final product haem and thus, PpIX accumulates in cells. Because PpIX is a strong photosensibilizer, this metabolic path has been frequently used in PDT. Kinetics of skin penetration and localisation can be modulated by using esters of ALA (such as methylester, hexylester or benzylester) which hydrolyze to form ALA and PpIX (93). This compound shows low toxicity and is rapidly cleared from the body by the existing clearance mechanism. In addition, PpIX-induced fluorescence can be visualized under blue light and can be employed in diagnosis (3, 94-98).

Porphyrins (Figure 3) are naturally-occurring intensely purple compounds with a porphine skeleton. Porphine frame consists of four pyrrolic sub-units linked on opposing sides through methine bridges resulting conjugated planar macrocycle. If substituted, compounds are known as porphyrins. The inner core can be deprotonated to form tetradentate dianionic chelators which can readily form complexes with most metal cations. Porphyrins display an intense absorption at around 400 nm (Soret band) followed by four weaker absorptions referred to as the Q bands (450-700 nm). Intensity of absorption in the region of the therapeutic transparency window can be modulated by exoskeleton substitution or by complexation with metal ligands into the centre of the macrocycle, however all porphyrins suffer relatively low extinction coefficients.

Porphyrins with reduced one exocyclic double bond are chlorins and after reduction of another exocyclic double bond bacteriochlorins are formed. Reduced bonds decrease the symmetry of the conjugated macrocycle which causes red-shift (650-680 nm for chlorins and 730-800 nm for bacteriochlorins) and 10-fold stronger absorption in the therapeutic transparency window for chlorins and 40-fold for bacteriochlorins. It is worth to mention that synthesis of them is difficult. Nowadays there are only representatives of chlorines (*e.g.* temoporfin under brand name Foscan, verteporfin under Visudyne and tin complex of etiopurpurin named Purlytin) commercially available or under clinical evaluation (91).

Expanded porphyrins with penta-aza core, called texaphyrins or motexafins, display strong absorption in the 730-770 nm region. These are usually in the form of metal complex with lutetium (motexafin lutetium known as texaphyrin, marketedas Lutex, Lutrin or Antrin) or gadolinium (motexafin gadolinium or gadolinium texaphyrin, marketed as Xcytrin) as potential radiosensitisers.

Porphyrin-like structures with aromates fused to pyrrole rings are mainly benzoporphyrins, phthalocyanines (PCs), and naphthalocyanines (NPCs) (Figure 3). PCs are synthetic macromolecules related to tetra-aza porphyrins (porphyrazines) with fused benzene ring to each of four pyrrole subunits, which are linked by four nitrogen atoms (like porphyrazines macrocycle) instead of four bridging carbon atoms in porphyrin macrocycle. NPCs are extended PC derivatives with naphthalene rings fused to pyrrole subunits instead of benzene rings. These modifications lead to highly conjugated skeleton of PCs and NPCs and subsequently to a red-shift (680-780 nm for PCs and 740-780 nm for NPCs) and very high extinction coefficients (significantly higher with respect to all PSs described above). Since PCs and NPCs absorb long-wavelength light strongly, they can be used in small doses. PCs and NPCs are usually prepared in the form of complexes with metal cations co-ordinated to the centre of macrocycle (Figure 4). This is due to the fact that during synthesis transition, metal cation helps to close the ring to easily form a macrocycle. The photophysical properties of PCs and NPCs are strongly influenced by the presence and nature of the central metal ion. Co-ordination of diamagnetic transition metal ions (such as zinc, aluminium, and gallium) usually results to metallo-phthalocyanines (MPCs) with high singlet oxygen quantum yields (99-105).

Strong absorption in the near infrared (NIR) region makes NPCs candidates for highly pigmented tumours, including melanomas, however, problems associated with lower stability (decomposition in the presence of light and oxygen) and a tendency to form photoinactive aggregates in solution prohibit their clinical use. Contrary, PCs are chemically stable, resistant to chemical and photochemical degradation and easy to prepare (1). Nowadays only members of MPCs family are on the list of drugs in clinical trials (a sulphonated aluminum PC derivative named Photosense, a liposomal formulation of zinc phthalocyanine CGP55847, and silicon

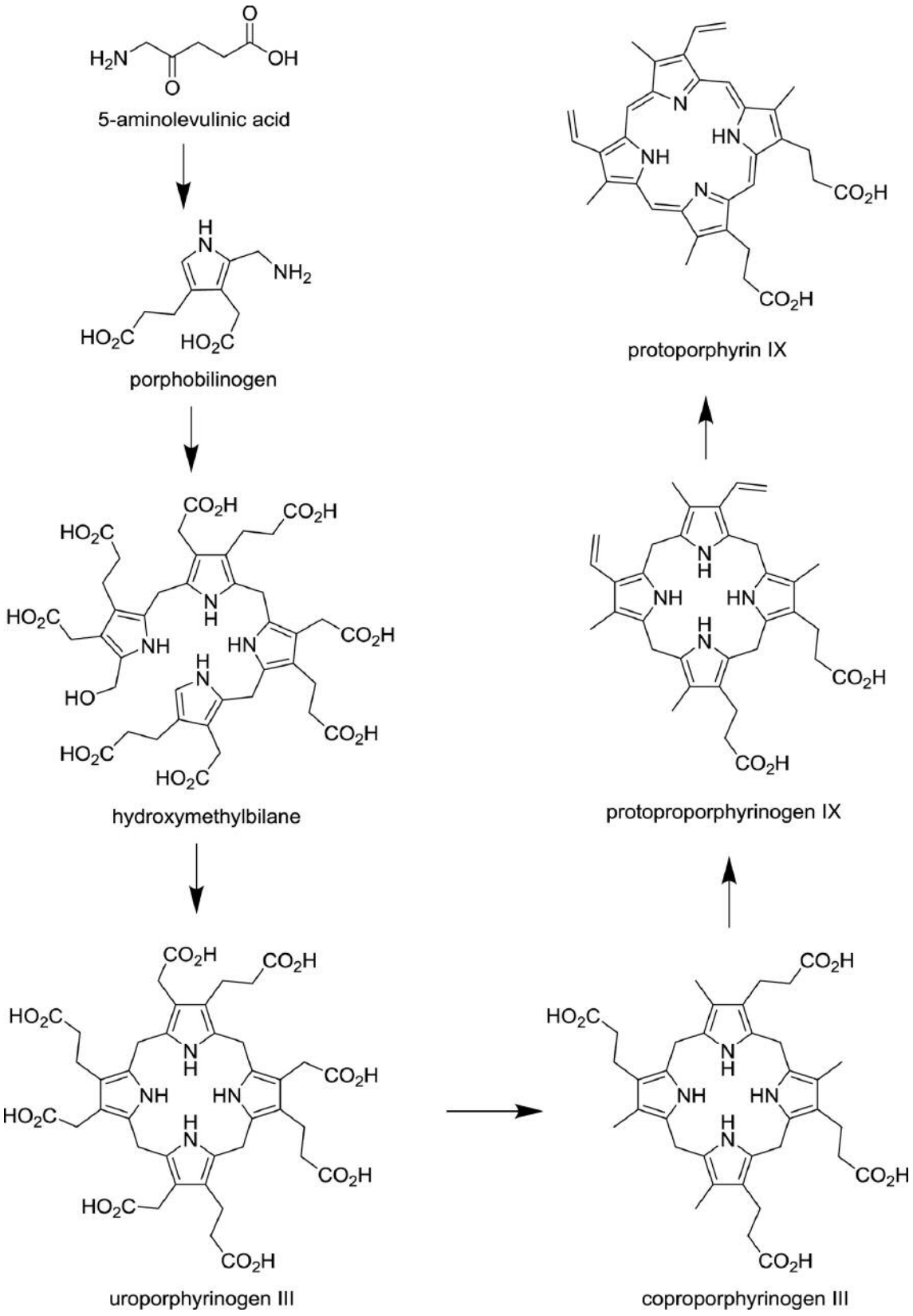

Figure 2. *Biosynthetic pathway from ALA to protoporphyrin IX*.

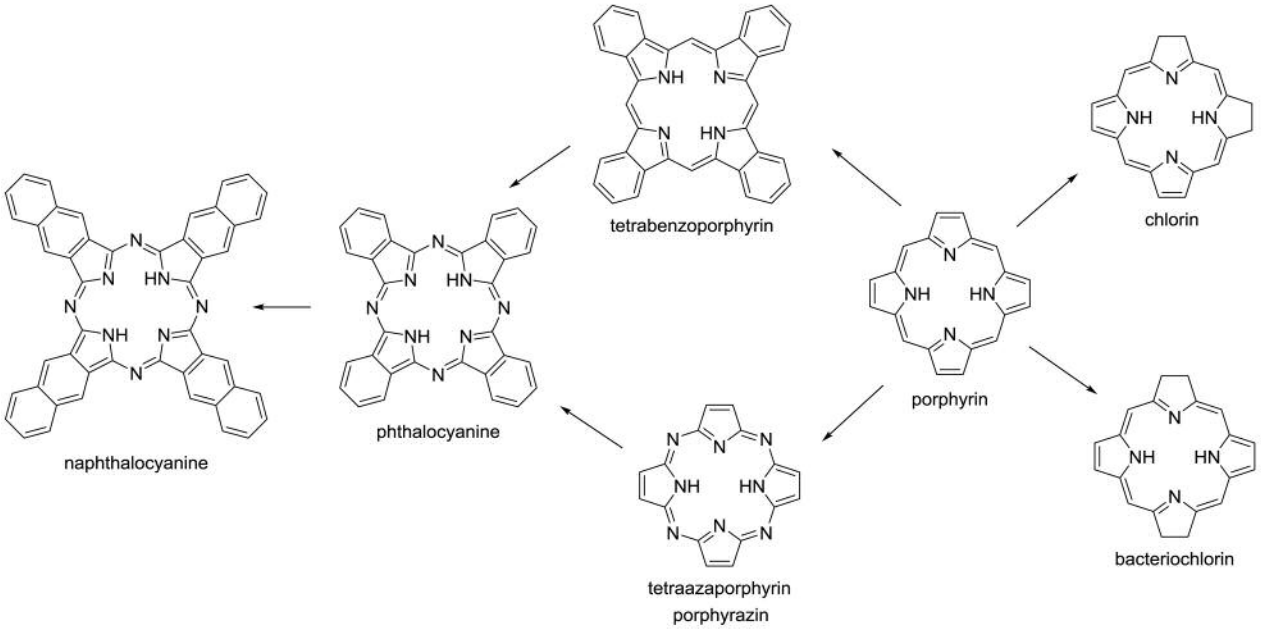

Figure 3. *Structures of porphyrin-like compounds (chlorin, bacrteriochlorin, porphyrin, tetraazaporphyrin, tetrabenzoporphyrin, phthalocyanine and naphthalocyanine).*

complex of PC known as PC4) but not PCs. General tendency of MPCs to aggregate in solution resulting in decrease of their bioavailability and photochemical activity can be overcome (minimized) using appropriate chemical modifications (sulphonated MPCs such as Photosense) or drug formulations (liposomal formulation of CGP55847).

Our interest and scope of this review is focused on the class of PCs and MPCs, their formulations and advanced drug delivery systems (DDSs).

Formulations and DDS of PCs and MPCs

PCs are composed of four isoindole units linked by nitrogen atoms forming a large planar aromatic system. They have the ability to form stable chelates with about sixty metal and metalloid ions inserted into central ring replacing two hydrogens of PC. The properties of these MPCs vary according to the nature of central ion and thus selection of central ion and synthetic modifications offer numerous options to control their physical properties. Closed shell diamagnetic PCs have higher yields and longer lifetimes of triplet states (such as Zn^{2+}, Al^{3+}, Ga^{3+}) in comparison to paramagnetic PCs and therefore, are more appropriate for PDT (99). The type of chelated central ion influences tumor retention as well. Some of the central ions are used for specific treatment such as copper and uranyl (brain tumor accumulation) or radioactive Technecium-99 (Tc-99) MPCs (1, 106-110).

Delocalization of the π-electrons gives them their characteristic intensive blue, cyan or greenish color. These metalocomplexes are valuable as colorants in ink jet printing (CI Pigment Blue 15), laser printing (titanyloxy-PC) (111, 112), color filters for LCD screens (111, 113), in catalysis, organic photovoltaic cells, as semiconductors, optical data storage materials and rewritable optical media (CD-RW) (87, 103).

Unsubstituted PCs and their metalocomplexes suffer poor solubility in water and thus introduction of various peripheral (macrocycle) and axial (coordination to central metal ion) substitutions have been applied to alter their properties, mainly to increase their solubility, and consequently hydrophilicity/lipophilicity (1, 114-118). Nevertheless, these PCs tend to dimerize and aggregate in aqueous media and thus lose their photoactivity in solution (only monomers are photoactive). If successfully administrated, PCs and MPCs bind to proteins and membranes and thus result in a complex photophysical behavior in the biological system (1). The advantage of solubilization through appropriate substitution allows direct biological administration without requiring an additional vehicle. In biological systems, PCs are diluted in the blood stream where they tend to disaggregate and bind to transport proteins (such as serum albumin) or lipoproteins (such as LDLs). Albumin has the ability to non-covalently bind molecules, not only to internal cavities, but also to the outer surface (119, 120) and thus albumin has physiological significance in the modulation of the activity of bounded

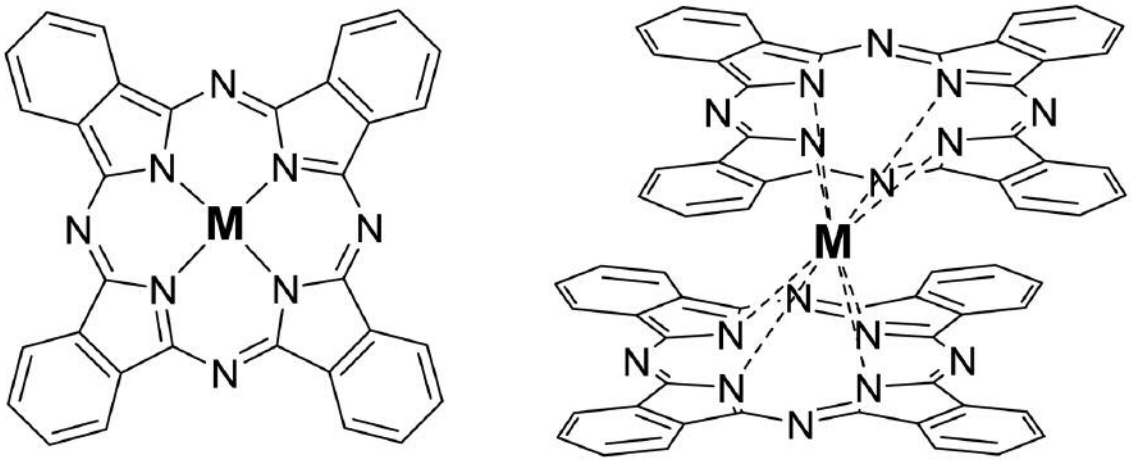

Figure 4. *Structures of metallophthalocyanines (MPCs).*

molecules and transport. Albumin delivers PCs to target tissue where they are absorbed using EPR effect (107). The high number of LDL receptors on tumour cell membranes enhance delivery efficacy to tumor tissue followed by the EPR effect (59, 82-84). Various MPCs non-covalently bound to albumin (121, 122) and LDL (122, 123) have been prepared. When one of these is administrated, redistribution of MPCs between albumin and LDL is expected. Covalent binding to albumin was described as well (124).

Typical peripheral substitutions leading to products with increased solubility and reduced tendency to aggregate are sulfonation, phosphonation (103, 125), glycosylation (68), carboxylation, or addition of other soluble substituents such as glucose, quarternary amino, hydroxyl or nitro groups to the periphery of macrocycle (1, 126). Sulfonation using fuming sulfuric acid leads to a mixture of many differently sulfonated PCs. The degree of sulfonation is inversely proportional to the degree of hydrophobicity and photodynamic activity of closed shell diamagnetic PCs (110, 127-131). Differently sulfonated aluminum complexes of PCs exhibit different subcellular localization (mono- and di- in cytoplasm while tri- and tetra-sulfonated in lysosomes) (132).

Axial substitution of central ion generally decrease tendency to aggregate due to sterical hindrance and also the nature of substitution modulates solubility and other properties. Suitable ions for this substitution are Al3+ with one or Si4+ and Ge4+, with two coordination sites. Note that opposite way unsubstituted MPCs with central ions such as silicon or iron tend to bind through oxo-bridges. Typical organic substituents are soluble polymers such as poly(ethylene glycol) or poly(vinyl alcohol). Shorter polymers tend to decrease the plasma half-life, but polymers with longer chains significantly prolong plasma half-life in comparison to unsubstituted metalophthalocyanine (133, 134).

Another option to increase solubility and bioavailability of hydrophobic PCs and their derivatives is their formulation using various Drug delivery systems. DDS can in principle provide enhanced efficacy and/or reduced toxicity of PS agents, deliver them to targeted tissues and allow their direct injection into the bloodstream. The most common and one of the simplest formulations is Cremophor oil emulsion and microemulsion. Cremophor formulations have been used for unsubstituted MPCs and MPCs with peripheral (fluorinated, hydroxylated) or axial substitutions (99).

More sofisticated colloidal carriers are micelles and liposomes. By chemical composition, liposomes are microscopic bilayer phospholipid vesicles similar to natural cell membranes separating an aqueous internal compartment from the bulk aqueous phase. When phospholipids dispersed in aqueous media unilamellar or multilamellar liposomes are spontaneously formed. Aqueous environment is an ideal medium for the existence of liposomes, rather than for microemulsions. Long circulating macromolecular carriers such as liposomes can exploit the EPR effect for preferential extravasation from tumor vessels (135). Their simple archetypal structures, facile preparation, controllable sizes and appropriate retention of PS incorporated into membranes explains why they are still popular as drug carriers. Examples of their utilization for MPCs include dipalmitoylphosphaditylcholine (DPPC), dipalmitoylphosphaditylglycerole (DPPG), 1-palmitoyl-2-oleoylphosphatidylcholine (POPC), 1,2-dioleoylphosphatidylserine (OOPS), DPPC/DPPG, DPPC/cholesterol and egg-yolk lecithin liposomes (136-143).

Basic liposomal DDS provide passive targeting only and suffer from undesirable interactions with plasma proteins and cell membranes. Thus, liposome constructs featuring direct molecular targeting of cancer cells *via* antibody-mediated or the ligand-mediated interactions have been developed. This

represents an integration of biological components capable of tumor recognition with delivery technologies (135, 144, 145). The immunoliposome approach, in which monoclonal antibody (mAb) fragments are conjugated to liposomes, offers greater capacity of liposomes to load thousands of PSs in contrast to PS immunoconjugates (limited number of PSs linked to mAb) (135). A similar strategy for molecularly targeted drug delivery uses tumor-targeting peptides. Though direct conjugation of MPCs to tumor-targeting peptides has been described (62, 146), incorporation into liposomes is widely used (142, 143, 147-150), and the immunoliposome approach has been used in the formulation of many other drugs, not many PCs or MPCs have been formulated this way yet (151). Another approach used for topical applications to improve delivery of liposomes into viable dermis and epidermis are stratum corneum lipid liposomes (SCLLs). SCLLs composed of stratum corneum lipids use similar mechanisms with human cell to enhance interaction with skin (62, 152).

Micelles are closed monolayered vesicles with a hydrophobic core and a polar surface, typically formed by lipids with a fatty acid core or by polymers. An advantage of polymer micelles is their tunability allowing them to covalently bind targeting moieties, and to prepare thermoresponsive and/or hydrolytically degradable micelles to form advanced DDS (153, 154).

Polymer nanoparticles (PNPs), compared to liposomes, have a higher stability and their adjustable size and uniformity prevents recognition by macrophages and extends their circulation time in the bloodstream. While PSs are protected against enzymatic degradation, PNPs are able to penetrate into cells and allow controlled release of PSs (62, 155-158). Their properties could be tuned by the composition of polymer and by coating. Mostly used biocompatible biodegradable polymers are polylactide (PLA), polyglycolide (PGA), their copolymer poly(D,L-lactide-co-glycolide) (PLGA), polycaprolactone (PCL), poly(ethylene glycol) (PEG), chitosan, gelatin, β-glucan, as well as crosslinked polymers such as dioctyl sulfosuccinate with alginate (159) or alginate with cholesteryl residues (160). Mostly used nonbiodegradable PNPs are made of polyacrylamide (PAA), N-(2-hydroxypropyl)methacrylamide (HPMA) or polyalkylcyanoacrylates (PAC) polymers and copolymers (62, 161, 162). The advantages of PAA and HPMA PNPs include ease of synthesis and functionalization, and robustness of structure integrity (158, 163). PEG is often used for coating of particle surface to reduce uptake by the reticuloendothelial system (RES) after intravenous administration (a major drawback of PNPs) and thus prolong the plasma residence time. PSs can be physically entrapped in the core of PNPs with a hydrophilic periphery for efficient delivery to tumor cells in an aqueous environment. After successful delivery of PNP to tumor cells, the entrapped PS can be released (typical mechanism for biodegradable particles) or the porous structure of PNP may allow permeation of ROS and interaction with the captured PS and thus maintaining their PDT performance in cells (158, 164). In case of drugs conjugated to polymer backbone, they can be cleaved enzymatically, hydrolytically or as a response of pH-sensitive bonds on change of pH (165). If targeting moieties such as oligopeptides are bound to the polymer, selective tumor uptake can be achieved (166). Examples of MPCs are PLA and PEG-coated-PLA PNPs containing perfluorinated MPCs (167) or poly(methyl vinyl ether-co-maleic anhydride) NPs which increased the singlet oxygen generation capacity of MPc by 10-fold compared to its free form (62, 168).

Other nanoparticle approaches include solid lipid nanoparticles (SLN), modified silica nanoparticles (SiNPs) (162) or metallic nanoparticles (MNPs). MNPs are functionalized mainly by gold (AuNPs) with covalently or non-covalently conjugated PSs (62, 169). These approaches have been described for MPCs, however, they are not widely used (170, 171). One specific type of extensively studied solid nanoparticles is upconversion nanoparticles (UCNPs).

UCNPs exhibit photon upconversion, which means that two or more incident photons of lower energy (typically in the infrared region) are absorbed and converted into one emitted photon with higher energy (typically in the visible or ultraviolet regions of the electromagnetic spectrum). Mostly used are fluorides of rare earths (group of elements consisting of Sc, Y, and the lanthanides) which are well known for their non-linear optical properties as downconversion or upconversion (172-175). Basically, the most of the rare earths have f-orbital partially filled with electrons and thus crystal structures of mixed rare earth fluorides (it means containing particular trivalent ions in various amounts in single crystal lattice) feature a wealth of electronic transitions within the 4f electron shells and transitions between closely matched intermediate-excited states of particular ions. Typically, compounds of general formula $AREF_4$ (A=alkali, RE=rear earth), *e.g.* NaYF4 doped with metals like Er or Yb, are used (176-182). These mixed rare earths nanofluorides can be prepared by the broad variety of methods (183-189). Low systemic toxicity and cytotoxicity and negligible solubility in aqueous media make these materials suitable for medical applications. Their use for advanced drug delivery systems in anticancer treatment (190, 191) and advanced photodynamic therapy is very promising (178, 192). To achieve biocompatibility and water dispersibility, they are commonly subjected to surface modification with silica, porous silica, biocompatible polymers or hydrophilic functional groups (193). The main advantages of these approaches are possibility to connect tumor-targeting biomolecules and covalently bind or encapsulate molecules of PS such as various PCs and NPCs (194, 195). After the delivery of nanoparticles into the cancer tissue, light with deep tissue penetration (such as infrared lasers) is applied. Upconverted light excites PS followed by ROS production and surrounding tissue damage.

Hydrogels are polymeric materials with hydrophilic structures capable of holding large amounts of water in their three-dimensional mesh structures with physical properties similar to those of living tissues (196, 197). These are widely used for the controlled release of hydrophilic drugs including water soluble PCs and MPCs (198-200). They can combine chemo-photodynamic therapy (201) or can be used for *in vivo* imaging (202).

Dendrimers are typical examples of bottom-up approach in preparation of vehicles for drug delivery as they are synthesized stepwise. They are repetitively branched polymers with a precisely defined diameter in the order of nanometers and typically symmetric around the core with a spherical three-dimensional morphology. Ability to control its size, number of functional groups available for modifications and predictability of the amount of incorporated drug makes them ideal DDS with reproducible pharmacokinetics (62, 203). PS can be trapped in the voids of a dendrimer, covalently bound to the dendrimer (204) or used as a scaffold to form a dendrimer (205). They can be conjugated with tumor-targeting peptides as well (204). PCs and MPCs can play the role of core of dendrimer with significantly improved ability to photosensitize singlet oxygen (206).

Natural cyclodextrins (CDs) are macrocyclic oligosaccharides shaped like the truncated cone with slightly hydrophobic central cavity and hydrophilic outer surface obtained by action of cyclodextrin-α-glycosyl transferase enzyme. They have six, seven, or eight α-1,4 linked α-D-(+)-glucopyranose units named α-, β-, and γ-CD, respectively,. Their shape and hydrophobicity of cavity allow formation of an inclusion complex with various lipophilic drugs. CDs can be modified to improve their properties, such as complexation of particular drug moiety (62, 207-210). In the literature, there have been described covalently bonded MPCs to natural CDs (211) or biodegradable nanoassemblies of modified CDs with MPC (212), both to overcome poor aqueous solubility of phthalocyanines.

Conclusion

PDT is generally known as an alternative approach for cancer treatment. However, its future lies in multimodal treatment, dermatology and aesthetic medicine. In cancer treatment, the major advantages compared to surgery, chemo- or radiotherapy include limited and more tolerable side-effects because ROS are generated only in areas with accumulated PS that are illuminated by sufficient doses of light of specific wavelength. The main disadvantage of the localized damage is recurrence due to metastases, as well as insufficient accumulation of the PS in the tumor area far from the vasculature. However optimal integration with other therapies leads to improved effectiveness (*e.g.* photosterilization of the tumor bed after surgical resection) and decreased side effects (lower doses of chemotherapeutics). The difficulties with administration and skin permeation and insufficient accumulation in targeted tissue can be overcome using appropriate drug delivery system with passive or active targeting. Limited tissue penetration of light commonly used to activate PSs to generate ROS can be overcome using photon upconverting nanoparticles with appropriate PSs, so far only phthalocyanines (PCs). The variability in metal cations coordinated to the centre and the peripheral substituents of the macrocycle results in many derivatives with tunable photophysical and photochemical properties. Their innovative formulations make them
Very powerful with immense promise in PDT.

Conflicts of Interest

There are no conflicts of interest regarding this study.

Authors' Contributions

JR, DV - literature search, defining the articles to be included in the systematic review, writing, drawing figures. JB, PP – review of the drafted manuscript.

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