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PERSPECTIVE

Hydrogels: Soft Matters in Photomedicine

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Photodynamic therapy (PDT), a shining beacon in the realm of photomedicine, is a non-invasive technique that utilizes dye-based photosensitizers (PSs) in conjunction with light and oxygen to produce reactive oxygen species to combat malignant tissue and infectious microorganisms. Yet, for PDT to become a common, routine therapy, it is still necessary to overcome limitations such as photosensitizer solubility, long-term side effects (*e. g.*, photosensitivity) and to develop safe, biocompatible and target-specific formulations. Polymer based drug delivery platforms are an effective strategy for the delivery of PSs for PDT applications. Among them, hydrogels, 3D polymer scaffolds with the ability to swell in aqueous media have been deeply investigated. Particularly, hydrogels-based formulations present a real potential to fulfill all requirements of an ideal PDT platform by overcoming the solubility issues, while improving the selectivity and targeting drawbacks of the PSs alone. In this perspective, we summarize the use of hydrogels as carrier systems of PSs to enhance the effectiveness of PDT against infections and cancer. Their potential in environmental and biomedical applications, such as tissue engineering photoremediation and photochemistry, is also discussed.

1. Introduction

1.1 Photodynamic Therapy

Photodynamic therapy (PDT) is a minimally invasive therapeutic tool induced by light that potentially exerts a selective cytotoxic activity against malignant cells and tissue and has potential anti-microbial uses.[1] The historical development,[2] fundamental concepts[3] and potential of photomedicine are well described. Essentially, it relates to the use of photoactive dyes as theranostic agents for the identification and removal of malignant cells, tissue or microorganisms giving rise to clinical concepts such as photodynamic diagnosis (PDD),[4] photodynamic therapy (PDT),[5] photodynamic antimicrobial chemotherapy (PACT),[6] and photochemical internalization (PCI).[7] At its core is the use of a photosensitizer (PS), a light-activatable compound, which after absorption of light generates a long-lived triplet state that can transfer the excitation energy to another compound, such as triplet oxygen, ultimately forming reactive oxygen species (ROS).[8] Thus, the basis of PDT is formed by three elements: 1) a photosensitizer,[9] 2) a source of light,[10] and 3) molecular oxygen.[11]

The photophysical processes taking place in the course of PDT are illustrated in Figure 1.[12] The photosensitizer used in PDT is in ground electronic singlet state (S_0) and after irradiation with light of a suitable wavelength is excited to a short-lived singlet-state (S_1). The photosensitizer can return to the ground S_0-state, emitting the absorbed energy as fluorescence (used for diagnosis and imaging) or undergo intersystem crossing to the excited triplet state (T_1). This transition is generally spin-forbidden, indicating that suitable PSs must have a high triplet-state quantum yield. The T_1-state is sufficiently long-lived to take part in different chemical reactions or can return to the S_0-state *via* phosphorescence.

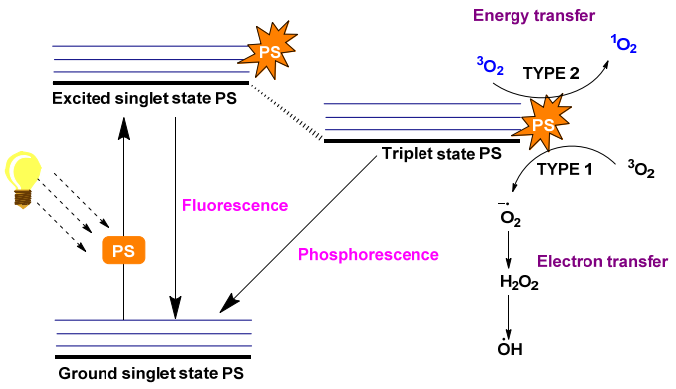

Figure 1 Schematic illustration of the main photophysical and photochemical processes involved in PDT.

Depending on the reactive species formed, PDT is classified into two types.[13,14] Type I relies on the interaction between the excited triplet state of photosensitizer (^{3}PS*) and substrates from the target tissue. New radicals generated from the reaction between photosensitizer and substrates interact with molecular oxygen and other molecules in the environment. In type II direct reaction of ^{3}PS*

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and molecular oxygen gives rise to singlet oxygen [$^1O_2$], a highly reactive form of oxygen. The two types differ in their requirement for molecular oxygen.[15,16]

1.2 Photosensitizers in PDT

A photosensitizer is a chromophore-based compound with the ability to absorb photons from the incident light, thus producing ROS that are highly active species.[17] To be of clinical use photosensitizers must possess distinctive properties[18] such as:

- chemical purity and ease of synthesis for commercial use;
- photostability;
- chemical stability for transportation, storage and reconstitution;
- good degree of tissue penetration, clinically useful half-life;
- rapid exclusion from target tissues to minimize any side effect, minimal photosensitivity towards the sub-cutaneous tissues, good pharmacokinetic activity;
- high quantum yield for ROS ($^1O_2$) generation;
- selective enrichment in target versus healthy tissue, particularly skin.

Typically, photosensitizers are excited within the red part of the visible range <650 nm of light (first generation) or closer to the near infra-red (second generation). First generation PSs are hampered by minimal tissue penetration of light. Second generation PSs, which absorb at longer wavelengths (>630 nm) where light penetrates tissue deeper without being impeded by other endogenous biomolecules, are found to have a better activity for PDT.[19,20] Likewise, more elaborate photosensitizers are under development with enhanced uptake, pharmacokinetics and better target specificity.[21,22]

A wide variety of chemical compound classes have been used in PDT-related studies.[2,8,20,23] These range from the classic examples of acridines **1**, hypericin **2**, anthraquinones **3**, psoralene **4**, phenothiazines **5** and others, to contemporary ones such as BODIPYs (boron-dipyrromethenes **8**) (Fig. 2).[24] However, the most studied PSs are porphyrinoid-based molecules such as porphyrins **9**, chlorins **10**, bacteriochlorins **11** or phthalocyanines **12,** which have been found effective in different therapeutic models. The possibility to easily modify the macrocycle at different loci, alterations of macrocyclic aromatic system, coordination of different metal ions and other chemical alterations also explains their extensive use in PDT.[25,26,27,28,29,30]

Notably, these macrocycles can absorb in the spectral range of 600-850 nm, allowing for excellent light tissue penetration. Yet, only a limited number of PSs have been used in clinical studies and found approval from the regulatory bodies. Some of the clinically accepted photosensitizers are: haematoporphyrin derivative (**14**, Porfimer sodium, Photofrin, Photogem), 5-aminolevulinic acid (**15**, ALA, Levulan), methyl aminolevulinate (**7** R^1 = Me, Metvixia), 5,10,15,20-tetrakis(*meta*-hydroxyphenyl)chlorin (**18**, Temoporfin, Foscan), benzoporphyrin derivative (**16**, Verteporfin, Visudyne) and *N*-aspartyl chlorin e_6 (**17**, NPe6, Talaporphin, Laserphyrin). Several others, such as Tookad and Redaporfin, are currently undergoing clinical trials (Fig. 3).[31]

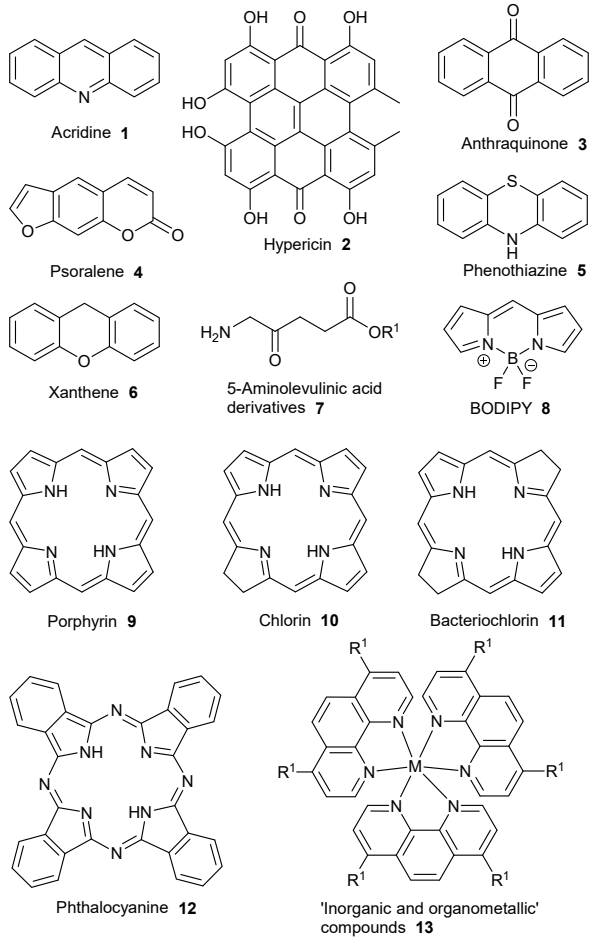


Figure 2 Classes of chemical compounds used as photosensitizers in PDT.

On-going work in the molecular engineering of new PSs targets many different aspects. New strategies range from dyes with improved photophysical properties (long-wavelength absorbing pigments with high absorption coefficients and larger triplet quantum yields),[27] synthesis of bioconjugates with suitable targeting groups (*e.g.*, peptides, carbohydrates, antibodies),[32,33] multi-modality compounds with covalently attached effector groups (*e.g.*, chemotherapeutics, anti-inflammatory residues),[34,35] complex super-structured singlet oxygen generating systems,[36] to the use of concepts such as photon–up-conversion for the design of suitable photoactive agents.[9,37,38] These organic synthetic strategies can be complemented by a multitude of drug delivery and formulation methods; for example, liposomes, dendrimers, nanoparticles, and nanocarriers.[39,40,41,42] In fact, the distinction between classic single molecule drugs, multimodality systems,[43] formulations, co-delivery systems, combination therapies,[44] and complex photoactive materials in the field of PDT becomes more and more blurry. With the explosive growth of new potential PDT 'drugs' the question may be asked, whether ever more complex systems are really necessary? To some extent, the development of new treatment modalities and the clinical success of PDT might be achieved faster through

improvements in the (light) treatment protocol and pharmacological/pharmacokinetics aspects rather than through the elaborate design/synthesis of new photosensitizers. An adequate PS pharmacokinetics/ biodistribution profile can be sometimes difficult to reach; in this regard, hydrogels offer a simple and versatile concept for the modulation of the pharmacokinetics properties of PS and as a new weapon in the PDT arsenal and will be discussed in detail in the following sections.

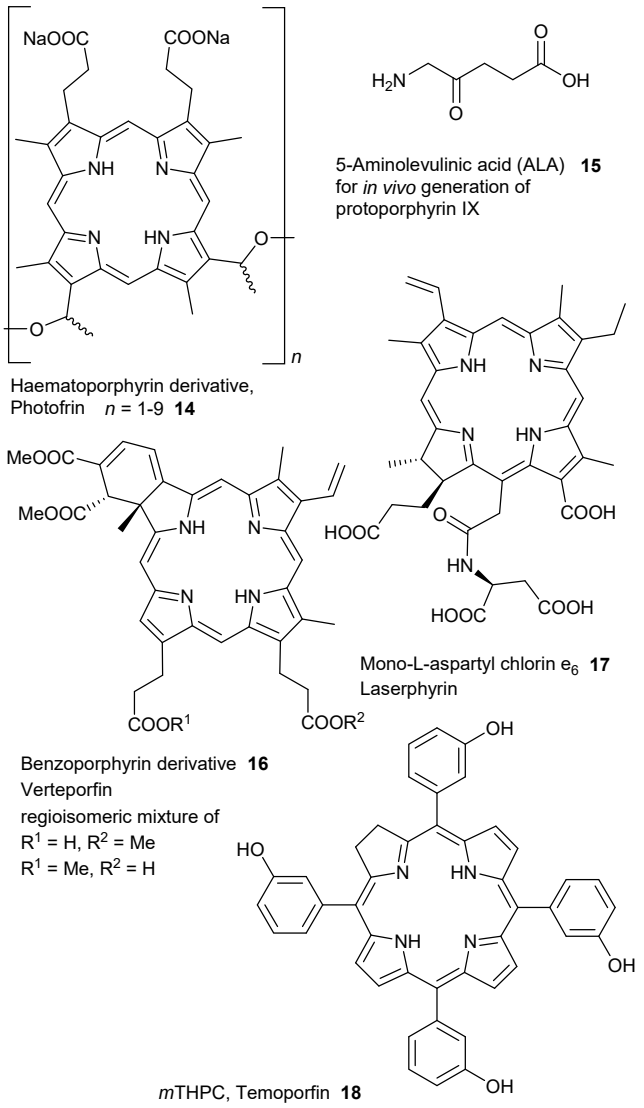


Figure 3 Selected porphyrin-related photosensitizers in clinical use.

1.3 Biomedical Applications of Photodynamic Therapy

Photodynamic concepts are used in many different areas of medicine. To briefly illustrate current clinical uses, we highlight cancer therapy, direct antimicrobial action, and applications in dermatology by providing a few selected examples.

1.3.1 Cancer Therapy. Cancer is still a major public health problem throughout the world and therefore new and more effective treatment options are required.[46] Clinical cancer treatments comprise conventional methods, which include surgical removal of tumors, chemotherapy or radiotherapy. Main problems consist of resistance to irradiation and chemotherapeutic agents, and the non-selective impact on healthy tissue that ends in significant side effects.[47] Many of these side effects are circumvented or alleviated with PDT. For cancer treatment, PDT involves the use of an effective drug delivery system, with the photosensitizer accumulating in the target tissue for a duration of time depending on the type of the PS being used. After accumulation, light is applied to the target tissue activating the photosensitizer and, through reaction with molecular oxygen, generates ROS. These damage vital structures and functions of the target cells, which results in abrasion of the tumor tissue.[48] PDT also exerts damage to the malignant tissue *via* targeting the tumor vasculature, thus inhibiting nutrients and oxygen supply.[49,50] An inflammatory and anti-tumor immune response is often also trigger by PDT, which contributes significantly for the long-term control of the diseased state.[45,51,52,53]

Naturally, tumor imaging is equally important. Safe, biocompatible and cancer-cell targeting formulations that will overcome the blood-brain-tumor barrier are especially needed.[54] For example, promising *in vitro* and *in vivo* results were reported by Nie *et al.* using a Coomassie Blue - polyacrylamide hydrogel for real time brain tumor imaging, which might allow for easier, cost and time-effective tumor surgery in the future.[55]

Photothermal therapy (PTT) has also emerged as an effective way to curb such issues. This modality employs light energy through laser-activated photon absorbers generating enough heat to cause cellular destruction *via* cell apoptosis, necrosis or necroptosis. PTT can result in well-controlled action against tumor-affected tissues with high efficiency, selectivity and with an advantage of low systemic toxicity.[56,57] Combinations of PTT and PDT have been recently applied, as both therapies complement each other and enhance the therapeutic effectiveness, leading to tumor removal being less painful and more successful.[58,59,60]

1.3.2 Photodynamic Antimicrobial Chemotherapy. Mortality rates are increasing due to microbial infections. Microbes are becoming more resistant against the clinically available medicines limiting effective treatments.[61,62] Photodynamic antimicrobial chemotherapy (PACT[63,64]) has emerged as a promising modality to treat a number of microbial infections, hence offering the possibility to combat this problem more effectively.[6,65] Similarly to PDT, PACT employs the use of a non-toxic compound (PS) and light to cause cell death. The infected tissue is pre-impregnated with a suitable PS which upon subsequent irradiation with a suitable source of light, causes ROS generation and the eventual removal or death of the microbial species.[66,67] In fact, this brings contemporary PDT research back to its historical beginnings.[63,68,69]

A typical example is the case of *Acinetobacter baumannii*, a Gram-negative bacterium often associated with hospital acquired infections. This species, which possesses multi-drug resistance, causes problems by triggering obstinate infections in wounds and burns, notably for people affected during military conflicts.[70,71] Other Gram-negative bacteria such as *Aggregatibacter sp.*, *Porphyromonas sp.* and *Fusobacterium sp.* and Gram-positive ones, such as

Staphylococcus sp. and *Steptococcus sp.,* lead to inflammation of tooth supporting tissue, a disease known as periodontitis, and are often associated with antibiotic resistance.[72,73] The number of examples of drug resistant bacteria is increasing significantly. In this regard, PACT offers promise to eliminate these species efficiently, cost effectively and more importantly, without associated mechanism of resistance.[74]

The two different strains of bacteria – Gram-positive and Gram-negative – respond very differently towards PACT, due to the complexity of their cell membrane and cell wall constitutions. This complicates the chemical design of PSs in terms of targeting the microbial cell (type)s selectively, without affecting the surrounding tissue. Herein, the PS charge and the solubility are important factors in determining the PDT effectiveness.[75,76,77] Gram-negative strains have an outer cell membrane, formed by phospholipids, lipoproteins and polysaccharides, making them difficult to interact and impregnate with anionic compounds. Positively charged molecules, such as the polymixin B nonapeptide, have been used to functionalize PSs for PACT applications by improving their internalization by different strains of Gram-negative bacteria.[78] Chlorin e_6 (**56**), a chlorophyll-derived tetrapyrrole, combined with the cationic polymer polyethylenimine (PEI) also showed PACT efficiency against some strains of Gram-negative bacteria.[79] Indeed, PSs possessing a positively charged molecular structure, such as tetracationic porphyrins, phthalocyanines and dyes such as toluidine blue O (**31**) or methylene blue (**30**), are the most suited to eliminate tough Gram-negative species of bacteria. The latter, in contrast to Gram-positive bacteria, are impermeable to many anionic and lipophilic molecules.[80]

A major concern of antimicrobial PDT is the unspecific PS accumulation into healthy tissue which might lead to cutaneous photosensitivity.[81] Here, an alternative approach, chemiluminescent photodynamic antimicrobial therapy (CPAT), uses chemiluminescence activation of the PS and can be effective against targets difficult to treat with traditional PACT.[82,83] Recently, antiviral PDT is gaining more traction again as well.[84] However, PDT used in extracorporeal applications, such as the disinfection of blood products, is one of the most successful stories of PDT/PACT. This has been also accepted as a disinfection treatment.[85,86,87,88]

1.3.3 PDT in Dermatology. Due to the ease of light application, PDT has found many applications in dermatology.[89,90,91] Next to the well-known PUVA therapy (psoralen and ultraviolet A)[92] one such example is the treatment of acne. Acne is a chronic inflammatory disease of the sebaceous glands affecting the cutaneous tissue lining.[93] Colonization of bacterial species such as *Propionibacterium acnes* is one cause of skin infestation which has been targeted by PDT.[94,95] Studies showed that aminolaevulinic acid-photodynamic therapy (ALA-PDT) can reduce the acne by targeting *P. acnes* having a specific effect on the sebum excretion as well.[96,97] ALA (**15**) is metabolized intracellularly *via* the haem synthesis pathway leading to the formation of protoporphyrin IX, a potent photosensitizer, which is then activated *via* photosensitization to destroy the affected cells. PDT, similar to other anti-acne treatments, is extensively used in trials against many other skin infections, for example, *Verruca vulgaris*, sarcoidosis, and *Condyloma acuminatum*.[98]

1.3.4 Limitations of PDT. Clearly, PDT has a great potential for applications in a wide area of medical problems, namely for the treatment of malignant diseases and to overcome the current antibiotic resistance problem. However, in clinical practice it is still limited to special cases, for instance the treatment of superficial lesions, and hampered by practical problems.[99] Bulky or deep-seated tumors are not effectively treated *via* the conventional PDT pathway.[100] Lack of structural knowledge of the tissue complexity and optical properties, which only give a crude idea about the measurements involved in the amount of the PS and the quantum yields of the singlet oxygen species, augments the application challenges. Thus, a more dynamic process is required to enhance the effectiveness of PDT for tissue abrasion.

One of the fundamental requirements of PDT is the presence of molecular (triplet) oxygen, which on illumination changes to singlet oxygen and leads to eventual cell death. However, the infected tumor tissue generally uses molecular oxygen for its cellular growth needs, depleting oxygen and resulting in tumor hypoxia.[101,102] Such cells remain relatively resistant towards PDT and the photodynamic action itself can cause acute hypoxia and limit treatment effectiveness.[103] The effectiveness of PDT also depends on the tissue penetration of the light.[104] Biomolecules such as haemoglobin, melanin, etc. are tissue chromophores which absorb light in the visible spectrum and thus, in addition to light scattering, the intensity of the incident light falls dramatically as the tissue penetration depth increases. Hence, new long-wavelength absorbing PSs using near infrared excitation have been developed to overcome this problem. Additionally, selective targeting of the affected target cells/tissue without impacting healthy surrounding tissue remains a challenge due to insufficient knowledge about drug and light doses.

As outlined, porphyrin derived PSs have been shown to be good PDT agents, but the efficacy of these derivatives has been undermined by the fact that they are poorly soluble in aqueous media, may lack photostability, can cause major skin photosensitization, and differ significantly in their pharmacological properties. As planar, aromatic compounds the PSs are prone to π-π stacking and hydrophobic interactions and they usually form aggregates in aqueous solution.[105] Thus, a PS must be formulated in a way to overcome the aggregation problem. In addition, it should be biodegradable, non-toxic in the absence of light, and deliver PSs in its monomeric form to the target tissue. Next, we briefly outline the fundamentals of hydrogels and their potential use in PDT.

2. Hydrogel Fundamentals

Hydrogels are described as a hydrophilic cross-linked three-dimensional polymeric network of 'soft and wet' material possessing water absorbing and retaining property.[106] They have found wide use as drug delivery systems, in tissue engineering and other areas.[107,108,109,110,111]

2.1 Brief History of Hydrogels

The term 'hydrogel' was used for the first time in the late 19th century by Van Bemmelen for colloidal mixtures of inorganic salts forming a gel.[112,113,114] Today's understanding of hydrogels as soft polymeric materials goes back to studies with poly(vinyl alcohol) (PVA) cross-linked with formaldehyde in the late 1940s;[115] this was used as biocompatible implants for humans and marketed as "Ivalon".[116] In 1958, Danno synthesized a polyvinyl alcohol polymer through the use of gamma-radiation, forming a cross-linked network of a hydrogel.[117] A key year was 1960, when Wichterle and Lim reported a hydrogel cross-linked system of macromolecules based on poly(2-hydroxyethyl methacrylate) (pHEMA). This material is in current use to manufacture soft contact lenses for eyes, making a first successful mass marketed cross-linked material, developed to use safely for humans (Fig. 4).[118,119]

Figure 4 Practical application of hydrogels – contact lenses.

The polymeric network of pHEMA fairly represents the characteristics of the modern-day hydrogels exhibiting swelling upon absorption of water without dissolution and retention of the shape of the cross-linked network. Thus, many hydrogels were prepared by polymerization of water-soluble monomeric units in the presence of a cross-linker, which connects the hydrophilic units forming a porous network.[120] First generation hydrogels were established by chemical modifications and linking of monomeric and polymeric units using initiator molecules with the aim to develop a cross-linked material with good swelling ratios and mechanical properties which enhances their water retaining capacities.[121] Most polymeric networks utilized for the formation of hydrogels are of pHEMA, PVA and poly(ethylene glycol) (PEG) type.[122,123,124] These polymeric platforms were established by polymerization of water-soluble monomers using chain-addition reaction mechanisms.

In the 1950s and 1960s Katchalsky worked extensively on polymeric networks and established the possibility to transfer chemical energy into mechanical strength.[125] This inspired in the early 1970s the development of stimuli specific second-generation hydrogel materials.[114] These materials showed stimuli-responsive activity for variables such as temperature, pH, and the concentration of molecules in solution, affecting the polymerization properties and the pore size of the hydrogels, thus potentiating drug-delivery activity. Temperature-sensitive hydrogels based on the polymeric networks of poly(isopropylacrylamide) (PNIPAAm), poly(*N*-(2-hydroxypropyl)methacrylamide)[126] (PHPMAm) and PEG-polyester block copolymers and the *in situ* formation of hydrogels based on stimuli such as pH were established. Later, in the mid-1990s, physical interactions were exploited to cross-link the polymers to form hydrogel networks, which enhanced the mechanical, degradation and thermal properties of the polymeric systems. Thus, third generation hydrogels were established; for example, *via* stereo-complexed materials by block-copolymers as reported by Kimura and coworkers,[127] or *via* forming an inclusion complex possessing metal-ligand coordination in addition to peptide cross-link interactions.[128] Hydrogels with incorporated metals are widely used for sensing applications, *e.g.*, by our colleague Prof. Gunnlaugsson utilizing photoluminescent hydrogels for pH sensing.[129]

The extensive research into the dynamics of the hydrogel formation has led to the development of so-called 'smart-gels'. These are polymeric cross-linked hydrophilic networks possessing tunable properties which can be triggered by varied stimuli-specific physiological responses.[130,131] These gel systems were established by *in situ* cross-linking of the hydrogels, radical polymerization, formation of double-network hydrogels, by combination of natural and synthetic polymeric materials, or by forming composite hydrogels using small inorganic molecules. This provides a platform for biological applications such as controlled drug delivery to the target site; *e.g.*, as potent photosensitizer carriers used in PDT, as discussed below.[132]

2.2 Classification of Hydrogels

Hydrogels are broadly classified into different subtypes based on origin, durability, response to external stimuli, charges on the polymeric configurations, structural details, and composition of the polymers.[133,134] Classification of the hydrogels on the above-mentioned characteristics is briefly summarized as follows:

Based on Hydrogel Origin: The polymeric material forming a hydrogel network can be originally derived from natural sources or can be synthetic or semi-synthetic. Naturally occurring systems are mainly based on polymeric materials of agarose, alginates, gelatin, fibrin, hyaluronic acid or collagen; for example, with applications in the differentiation of human embryonic stem cells.[135] Synthetic or man-made polymers, despite being more inert than the natural occurring polymeric materials, bear the advantage of longer shelf-life with a greater retention capacity and can easily be modified further.[136] This provides a better platform for the incorporation of drugs into hydrogel carriers or improvements in tissue engineering. Synthetic polymeric hydrogels systems often are derived from materials such as polyacrylamide or polyethylene glycol and are widely used as carrier hydrogels. In many cases the term 'nanogel' is used to indicate hydrophilic nanosized polymeric materials (see 4.2.1).[137]

Based on Hydrogel Durability: The durability of the hydrogel plays an important role in regulating the activity of the system designed. They have been sub-classified as durable (*e.g.*, polyacrylate-based) and biodegradable (*e.g.*, polysaccharide-based) and further depend on their synthetic or natural origin.[138,139] Biodegradable systems have important uses in both biomedical and materials sciences. One advantage is their possible elimination from the body or a system *via* a self-elimination degradation mechanism.[140]

Based on Structure of the Network: Physical configurations of the polymers and the chemical composition of the subunits play an important role in determining the structure of hydrogel networks; thus, further classifications are amorphous, semi-crystalline and crystalline systems.[141]

Based on Charge of the Hydrogel Network: Cross-linked polymeric networks might carry electrical charges which gives rise to a whole set of further sub-classifications:[142]

- *Nonionic or neutral hydrogels:* These networks respond to the change of external physical factors such as temperature, causing swelling and de-swelling, depending upon variation in the conditions. The permanent linkages in these networks are irreversible.
- *Ionic (anionic or cationic) hydrogels:* Ionization causes development of permanent charges on the hydrogel networks. The amount of absorbed solvent depends upon the electrostatic repulsions. For anionic cross-linked networks, the swelling of the network is enhanced at higher pH, due to an increase in electrostatic repulsion. For cationic networks, a lower pH enhances the swelling.
- *Ampholytic hydrogels:* Cross-linked networks carrying both acidic and basic monomers constitute an ampholytic hydrogel network and its activity is dependent upon the ionic groups present in the polymeric chains.
- *Zwitterionic hydrogels:* A hydrogel platform having both cationic and anionic monomeric groups, constitutes a zwitterionic system.

Based on response to stimuli: Physical or chemical stimuli induce a swelling or deswelling of the networks. Physical stimuli are, for example, temperature, electric field, magnetic field or light, while chemical stimuli typically include changes in the pH of the solvent systems, ionic strength, or solvent composition. This results in major changes in the network composition and their activity, both for smart and conventional network platforms.[143]

Based on hydrogel composition: When a single species of a monomer is employed for the formation of the network, it forms a homo-polymeric hydrogel while use of two or more different monomeric units, either of which is hydrophilic, results in randomly or alternatingly arranged co-polymeric hydrogels.[134]

Based on type of cross-linking: Cross-linking established by chemical interactions between hydrophobic groups eventually results in a chemical cross-linked mesh of polymers and entraps the co-effectors or the payload molecules.[144] When the polymeric structures are entangled *via* hydrophobic interactions between the constituent units or physical interactions *via* hydrogen or ionic bonds, it forms a physically cross-linked network, with relatively temporary and weak junctions[145] as opposed to chemically cross-linked networks, which yield permanently bonded networks.[146]

2.3 Design and Structural Modeling of Hydrogels

Hydrogel preparation requires the integral presence of three components: monomer, initiator, and the cross-linker as shown in Figure 5.[147] Diluents such as water are required to control the heat of polymerization and other properties of the hydrogels. In addition, to enhance the applicability of the hydrogels, it is necessary to reduce and remove side products of the reactions such as unreacted monomer, initiators, and cross-linkers.[148]

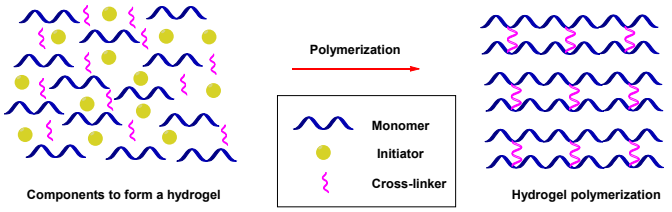


Figure 5 Components required for formation of hydrogels.

Hydrogels retain a substantial amount of water due to their porous network and extensive cross-linking. They possess hydrophilic groups or domains, which are hydrated when placed in an aqueous environment. In rheological terms, a hydrogel is characterized based on deformation of the network depending upon its viscosity change with variables, such as temperature, time or concentration possessing either Newtonian or non-Newtonian behavior.[149] Cross-linkers, which prevent the dissolution of the linked networks into an aqueous environment, can be incorporated into the mesh of these polymers by a variety of methods to yield cross-linked hydrogels.[150]

Cross-linking can be achieved either physically or chemically.

Physical cross-linking:[134]

- *Hydrogen bonding: E.g.*, polymeric materials based on PEG form hydrogels *via* hydrogen-bonding between the oxygen atom of the material and the hydrophilic group.
- *Ionic interactions:* Cross-linking in the polymeric material of the alginate can be achieved for example by incorporation of calcium ions at a certain pH.
- *Crystallization:* Polymeric material, *e.g.*, polyvinyl alcohol in aqueous solution, obtained *via* repeated freeze thaw cycles forms a tougher cross-linked network. This results in a higher crystalline nature of the gel as compared to the hydrogel obtained at room temperature conditions, conferring them enhanced mechanical strength and higher stability.[151]

Chemical cross-linking:

- *Chemical reactions:* Reactions of functional groups such as amine, carboxylic acid or aldehyde result in cross-linkage throughout the hydrogel network. For example, polymeric materials, such as chitosan and PVA, are cross-linked using glutaraldehyde. Chemical cross-linking is generally established by either addition reactions or condensation reactions of the cross-linkers with the polymeric hydrogel

materials.[152] A brief survey of cross-linking *via* chemical reactions of complimentary functional groups[153] is given in Table 1.

- *High energy electromagnetic radiation:* High-energy beams or gamma radiations can help generating cross-linked hydrogels for unsaturated molecules[154] and can achieve sterilization at the same time.[155]
- *Free-radical polymerization:* A suitable polymer such as poly(ethylene glycol) diacrylate (PEGDA, *e.g.*, **19**) and pentaerythritol triacrylate (PETA, **23**) is mixed with a photoinitiator molecule such as 2,2'-dimethoxy-2-phenyl-acetophenone (DMPA) and then subjected to UV illumination to cross-link the chains *via* free-radical reactions. For example, a highly reactive methyl radical **20** released by the photofragmented initiator molecule DMPA, initiates the polymerization by attacking the carbon-carbon double bonds present in the acrylate groups of the polymer as shown in Figure 6.[156] Applications include drug delivery systems and encapsulation of mammalian cells.[157,158,159,160,161]

Table 1 Chemical cross-linking of polymers to form hydrogels.

Hydrogel	Cross-linking agent
Polyvinyl alcohol	Sodium borate/boric acid, glyoxal
Gelatin	Glyoxal
Agarose	Oxidized dextrins
Chitosan	Glutaraldehyde
Agarose and chitosan	Dextrins[159]
Guar gum	Epichlorohydrin
Hydroxamated alginates	Zinc(II) and calcium(II)[160]
Alginate beads	Zinc(II) and iron(III)[161]
Poly(acrylic-co-vinylsulfonic)acid	Ethylene glycol dimethacrylate
Polyacrylamide	*N,N´*-methylenebisacrylamide
Chitosan-PVA	Glutaraldehyde
Albumin	Glutaraldehyde

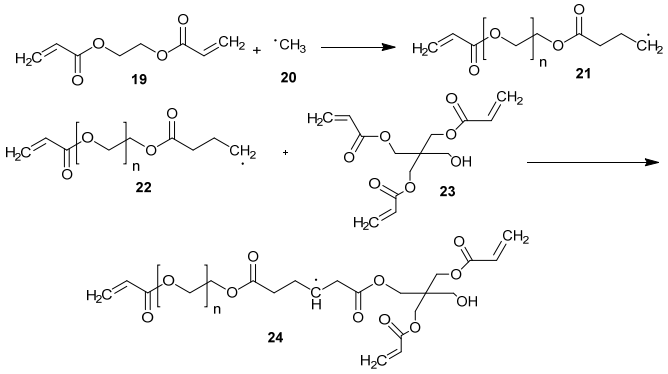


Figure 6 Schematic of free radical photopolymerization between PEGDA **19** and PETA **23**.

Polymerization techniques such as bulk polymerization can be used to establish the cross-linked networks whereby the reaction is initiated in the presence of external radiation[162,163] or in presence of a catalyst and the resultant hydrogels differs in their morphological characteristics. As the concentration of the monomers is very high, a homogenous network is produced, which is usually hard, but softens in presence of the aqueous medium and solution polymerization. In the synthesis of heterogeneous cross-linked hydrogels the solvent used acts as a heat sink. The hydrogel formed is then subjected to dialysis to remove unreacted mixture and impurities.[148]

2.4 Physical/Rheological Properties

The feasibility of using hydrogel platforms as delivery systems or as a therapeutic tool can be ascertained by analyzing their mechanical properties, which can be tailored to provide appropriate means, *e.g.*, for tissue engineering.[164,165] The mechanical properties of these materials are determined by analysis of the tensile strength, compression tests and dynamic mechanical analysis (DMA).[166] Mechanic features of the gels such as *Young's modulus*, which is defined as the ratio of the tensile stress to the tensile strain, and *compressive modulus*, which is defined as a ratio of the mechanical stress to strain in an elastic polymeric material under compression, can be determined using tensile testing. This gives an indication of the material's durability.[167] Compression testing measures the stiffness of the material, mirroring the resistance of this platform against the deflection of the force applied to the system.[168]

Furthermore, to understand the viscoelastic behavior of the gels, rheological studies are performed *via* DMA.[169] Rheology of matter is defined as the study of continuous flow and deformation under the influence of different external forces.[170] The flow properties of the hydrogels make them excellent candidates for therapeutic delivery across biological systems. Their ability to shear-thinning when under the influence of shear stress and the ability to self-heal enables payloads (like therapeutics) to remain entrapped in the gel against *in vivo* biological forces. [171] Thus, a fundamental understanding of the mechanisms involved in gelation unveils the optimum pathway to form a cross-linked network and enables further developments, *e.g.*, for tissue repair and localized drug delivery.[172]

The viscosity and elasticity also depend on the external experimental conditions, timescales and temperature.[173] Furthermore, small deformation rheology experiments, such as small amplitude oscillatory shear (SAOS), are used to determine critical hydrogel properties.[174] The applied shear stress (s*) is measured *via* the stress transducer, whereas g*, the stress induced in the sample, is measured *via* a strain transducer.[175] Furthermore, the complex modulus of the material is calculated using Equation 1.

Equation 1: $G^*(w) = s^*/g^* = G' + iG''$

G´ (shear storage modulus), which is used to measure the deformation energy stored during shear stress of the test material, G˝ (loss modulus), representing the energy dissipated during s and tan δ (loss factor), with respect to time, frequency and strain. Tan δ, the loss factor is defined as G˝/G´. If G˝>G´ (tan δ>1), the sample behaves like a viscous liquid and conversely, when G´>G˝ (tan δ<1), the sample behaves like an elastic solid material.[170]

Several non-invasive and non-destructive methods, which provide high spatial resolution, are used to enhance the mechanistic understanding of these scaffolds.[176] Atomic force microscopy (AFM) is utilized for the imaging of the topographic surface of the scaffolds and to measure forces such as *Young's modulus* on the materials.[177]

Magnetic resonance elastography (MRE) is a technique used to visualize the spatial changes in the mechanical properties of platforms.[178] This technique has emerged as an effective tool to determine the mechanical properties of soft tissues *in vivo,* providing a simple method to determine pathological changes and anomalies.[179] However, the use of AFM and MRE must be improved to allow for the systematic characterization of hydrogels in living tissues and for developments in tissue engineering through integration of their chemical, physical and topographical activity. For example, designing cell-biomaterial interactions in 3D hydrogel scaffolds[180] might contribute to understanding of the complex interdependency of substrate mechanics and cell-adhesiveness.[181]

2.5 Singlet Oxygen Determination

An important aspect related to the analysis of hydrogels in the context of PDT is the requirement to evaluate the ability of the embedded or linked PSs to produce singlet oxygen or other ROS. As hydrogels offer significant potential to reduce PS's limitations and hence increase their efficiency, it is highly desirable to obtain a direct, effective, inexpensive and efficient method to accurately quantify singlet oxygen/ROS production in aqueous media, allowing for evaluation for biological applications. For polymeric and porous materials this is not a trivial endeavor as most routine singlet oxygen measurements are based on simple colorimetric or fluorometric tests.[182]

Typically, methods for ROS quantification involve indirect chemical reactions between dyes and singlet oxygen, leading to endoperoxide formation. The main disadvantage of these methods is photobleaching of the probe decreasing the reliability of the received data. Chemical analysis of ROS is the most commonly used method, as it is convenient and highly sensitive in homogenous systems. Nevertheless, the choice of chemical probe must be considered for each system, bearing in mind the properties of the photosensitizer and polymer. Often, the sensor dyes used are not charge compatible with the hydrogel system and can interact with a polymeric surface or have solubility or reliability issues. Moreover, singlet oxygen's short lifetime and its possible reactivity with biomacromolecules or/and chemical probes decreases the utility of the probes in *in vivo* quantitative studies.[183,184]

The most widely used chemical dyes include 1,3-diphenylisobenzofuran (DPBF),[185] singlet oxygen sensor green,[186,187] 2,5-dimethylfuran,[188] and various anthracene derivatives, of which the most promising is anthracene-9,10-dipropionic acid[189] due to its solubility in aqueous media. In 2014, Craig *et al.* reported an improved method tailored to the analysis of porphyrin-hydrogels using anthracene-9,10-dipropionic acid, which undergoes photobleaching at the 378 nm absorption band *via* endoperoxide formation.[189,190] For hydrogels, this is compounded by the need to measure singlet oxygen generation (with its short lifetime) in an aqueous environment and to account for the possibility of the sensor migrating into the matrix. Electron paramagnetic resonance, microwave spectroscopy and mass spectrometry can be considered as direct methods that can be used for singlet oxygen determination in hydrogels. Nevertheless, the only method that is currently widely utilized is molecular emission spectroscopy at 1270 nm and involves direct detection of singlet oxygen, which can be improved by using D_2O to reduce the environmental quenching effect on the singlet oxygen's lifetime.[191] It is however, technically challenging owing to the low sensitivity of the detectors relative to singlet oxygen's emission efficiency and its short lifetime. To allow for more specific ROS quantification using emission spectroscopy, improvements focused mainly on the replacement of the light detection systems, *e.g.*, using an indium gallium arsenide detector[192] or near-infrared photomultiplier.[193] However, more specialized detectors are expensive, thus restricting their comprehensive utility.[192] For this reason, the majority of studies only uses indirect "biological measurements", *i.e*. the overall antimicrobial or photocytotoxic effect.

3. Hydrogels in Medicine

At time of writing (spring 2019), close to 50,000 papers have been published on hydrogels, with about one third of these relating to biomedical aspects.[194] This makes it impossible to give even a cursory overview of the use of hydrogels in medicine. To highlight the state-of-the-art, we again use selected classical and contemporary examples in the following sections.

3.1 Hydrogels as Drug Delivery Platforms

Conventional drug formulations face a backlash due to their inefficiency to deliver drugs adequately to the site of action at a predetermined rate and for a predefined period.[195] To mediate such temporal modulations, controlled site-specific targeting delivery platforms are required.[196] Hydrogels have been extensively investigated as effective, 'smart', and 'on-demand' drug delivery systems.[197,198] They offer an advantage of protecting encapsulated drugs against hostile environments, such as enzymatic degradation and physiological pH fluctuations in the body.[199] Depending on type of administration and material they also offer benefits in biocompatibility and modulation of pharmacokinetics and biodistribution.

Oral, intravenous, intramuscular or topical are the main routes of traditional drug administration, whereby the maximum dosage of the drug decreases rapidly with time.[200] However, hydrogels can act as intelligent drug carriers where there is an on-demand drug delivery over time[201] offering advantages in, *e.g*., transdermal drug delivery.[202] This controlled drug release allows for a safer, site-specific and better drug distribution in the body, efficiently reducing side-effects. Stimuli responsive hydrogels have been shown to modulate a controlled drug-release as a response to physiological fluctuations[203] or other stimuli, such as ultrasound.[204] Several of the stimuli-sensitive drug delivery systems have been designed based on the principle of hydrogel swelling under a specific physiological response.[205]

The responsive properties of these platforms to a broad spectrum of external environmental stimuli makes them an ideal system for controlled drug delivery.[206,207] Temperature sensitive

polymers are widely exploited due to their intrinsic phase transition properties, which enables changes in swelling kinetics and sol-gel phase transitions as a response to temperature changes.[208,209] Common examples of such polymeric systems are (poly(*N*-isopropylacrylamide) PNIPAAm,[210] poly(*N,N*-diethylacrylamide) (PDEAAm) or a copolymeric network of hydrophilic acrylamide (AAm) and hydrophobic butyl methacrylate (BMA) (NIPAAm-BMA) which have lower critical solution temperatures (LCST) in the range of the physiological body temperature. All these thermo-responsive platforms[211] undergo a negative thermosensitive drug release under swelling-shrinkage transition. Similar systems utilizing the same underlying principle are block copolymers derived from poly(ethylene oxide) (PEO) or poly(propylene oxide) (PPO).[212] Polymeric networks of poly(acrylic acid) (PAA), poly(acrylamide) (PAm) or a copolymer of polyacrylamide and butyl methacrylate (PAm-co-BMA) show a positive thermosensitive drug release to the temperature change.[133] *E.g.*, a PNIPAAm hydrogel was fabricated with bovine-haemoglobin as a novel oxygen carrier which exhibited temperature dependence.[213] Moreover, a PEG-peptide hydrogel with incorporated oligo(*p*-phenylenevinylene-co-benzothiazole) as PS, provided enzyme specific responses to matrix metalloproteinase (MMP), an enzyme responsible *i. a*. for tumor growth processes.[214] Recently, enzymatic responsive hydrogels were designed by Wang *et al*., which achieved sustained release of PS in the presence of MMP and antitumor activity against head and neck squamous cell carcinoma *in vitro* and *in vivo*.[215]

Furthermore, many pH sensitive polymeric materials are known. Polymeric networks of PAA undergo ionization at high pH, opposite to poly(*N,N'*-diethylaminoethyl methacrylate) (PDEAEM), that is charged at low pH.[216,217] In another example, the water-soluble anti-depressant drug venlafaxine was released upon a pH-dependent stimulus from a PVA-hydrogel.[218] Moreover, a copolymer of temperature-sensitive poly(*N*-isopropylacrylamide), vinyl terminated with poly(dimethylsiloxane) and acrylic acid (PNIPAAm-PDMS-co-AA) based hydrogel network showed a pH-dependent delivery of the anti-inflammatory drug indomethacin through the gastrointestinal tract.[219] Similarly, hydrogels based on poly(methyl acrylate) (PMA) and PEG exhibit unique pH-sensitive properties whereby at low pH, acidic protons of the carboxyl groups of PMA interact with the ether-functionalized moiety of PEG through H-bonding interactions, resulting in release of solutes.[220] Likewise, electricity and light-driven hydrogel matrices have been designed. For example, poly(2-acrylamido-2-methylpropane sulfonic acid-*n*-butylmethacrylate) is used as a drug delivery platform by varying the intensity of electrical stimulation.[221] Moreover, polymeric networks of PNIPAAm functionalized with spirobenzopyran undergo changes in swelling when irradiated with appropriate light.[222] Novel, dual responsive hydrogels were recently presented by Belali *et al.* who incorporated 5,10,15,20-tetrakis(4-*N*-carbonylacrylic aminophenyl)porphyrin into poly(*N*-isopropylacrylamide) hydrogels. These systems were simultaneously sensitive to temperature and pH changes.[223] Clearly, drug delivery from hydrogels can be affected by various factors such as diffusion, swelling or chemical influence.[224,225]

3.2 Hydrogels for Tissue Engineering and as Cell/Virus Mimics

Tissue or organ transplantation has emerged as an effective means to treat tissue or organ failure. One approach is to utilize a combination of patients' body cells with polymeric scaffolds that are analogue to the extracellular matrices (ECM) found in the target tissue.[226] ECM are composed of amino acids, polysaccharides, glycoproteins, collagen and other components that provide structural support and regulate the normal functioning of the cells.[227]

The hydrogels-based scaffolds deliver cells to the target site, provide potential space for the formation of new tissue, and help to control the structure and the functionalization of the newly bio-engineered tissue.[227]

Hence, hydrogels as 3D polymeric networks, whether derived synthetically or from natural materials, have been designed with suitable chemical, physical or mechanical properties, further incorporating growth factors[228] as matrices for tissue regeneration.[229] For example, collagen tissue-derived natural polymer has been used towards the development of hydrogel matrices that can be used as skin substitutes.[230] Similarly, natural polymers of hyaluronate, fibrin,[231] alginate,[232] agarose and chitosan[233] have been widely utilized for the formation of bioengineered scaffolds.[234] However, they often lack effective mechanical strength which limits their effectiveness. Thus, there is a need to synthesize polymeric systems with improved properties. These include resistance to degradation *via* hydrolysis and enzymes, higher mechanical strength, better cell adhesion properties and suited biocompatibility to avoid inflammatory responses. One possible approach is interpenetrating polymer network hydrogels.[235]

Furthermore, chitosan polymers and copolymers of PEO show a high biocompatibility and low toxicity and have therefore been used for surface modifications of biomaterials, biological conjugates, and to induce cell membrane fusion.[236] Polymeric scaffolds of PVA, polyphosphazene and polypeptides have also been proposed owing to their non-toxicity, high mechanical strength, and biocompatibility.[237] Hydrogels can also be used to model the 3D microenvironment of tumor vascularization,[238] potentially repair nerve system deficits,[239] and are transforming *in vitro* drug testing by allowing the development of 3D cell cultures.[180,240,241,242] Contemporary multicomponent systems are becoming even more complex for tailored applications.[243,244] Photocleavable hydrogels allow a direct control of the physicochemical properties, spatial arrangement, and cell development in 3D systems.[245,246] From the beginning, hydrogels have also been used as matrices for (other) nanomaterials[247] and feature prominently in the development of bioprinting for next generation tissue engineering.[248] Naturally, hydrogel-based 3D cell tissue models are also used for testing the PDT efficacy of standard PSs.[249]

Enhanced understanding of macromolecular interactions and advances in nanotechnology led to increased interest of engineers to combine the multi-tool properties of hydrogels with cell cultures or genetically modified artificial viruses to create platforms able to mimic various biological functions. However, previous studies with two-dimensional models revealed that the interactions with the

target cells are not specific and do not fully reproduce the biological mechanisms that occur *in vivo*.[181] As discussed above, while hydrogels have adequate properties to be used as an extracellular matrix, they still require improvements to recapitulate dynamic equity.[250,251] To obtain the desired hydrogels' chemical and physical properties and hence, target biological responses, various modifications of polymers are being investigated.[252,253]

Cell encapsulating hydrogels offers potential to be used in various biological applications, notably in tissue engineering and as diagnostics tools. For tissue engineering, regulation of cell proliferation is usually controlled *via* two main pathways - modifying cell-receptor adhesion[254,255] or by growth factor release.[256] Moreover, hydrogel cell cultures can be used in drug cytotoxicity studies. Sung and Shuler studied the anticancer activity of a chemotherapeutic drug (tegafur) using a microcell culture analog incorporated into hydrogels and placed in separate chambers. The system, connected to the flow that mimics human blood circulation, represented the liver, tumor, bone marrow compartments and was used as a physiologically-based pharmacokinetic model.[257] Specific cell interactions with environmental toxins raised interest to use cell-based hydrogels as biosensors. Desai *et al.* used collagen hydrogels to observe depolarization-induced differences in intracellular calcium of SH-SY5Y human neuroblastoma cells, which was not possible using a 2-D models.[258] Hydrogels have been used as cell patterning devices after incorporation of photoactive agents to regulate cell growth and migration.[259,260] Tam *et al.* investigated photosensitive agarose and hyaluronic acid hydrogels to study cell differentiation and migration. Incorporation of light responsive biomolecules allowed their immobilization under irradiation and to observe the impact of growth factors on endothelial cells and retinal stem cell interactions.[261] Furthermore, hydrogels found application in mimicking red blood cells[262] and heparin to improve bone morphogenetic protein activity.[263]

Hydrogel-based virus-like systems have the ability to transfer modified genetic information, which can be targeted to specific cells by using ligands. After gene expression, specific cell response, *e.g.*, differentiation[264] or lysis, is observed.[265,266,267] One example is Sitasuwan's *et al.*'s study on the regulation of bone marrow stromal cell differentiation. 2-D substrates covered with tobacco mosaic virus (TMV), resulted in enhanced bone morphogenetic protein-2 gene expression; nevertheless, cell aggregation due to cell-material interactions was a critical point for further investigation.[268] In a subsequent study, TMV was incorporated into alginate hydrogel structures, which resulted in improved cell attachment indicating potential for tissue engineering studies. Recently, Lauria *et al.* presented an engineered Potato Virus X for enhanced cell matrix mineralization and improved attachment to human mesenchymal stromal cells.[269] Contemporary studies aim to optimize the hydrogel's structural properties (*e.g.*, by PEG[270] or polyamidoamine dendrimer[271] attachment) in order to develop an injectable hydrogel for cartilage tissue regeneration.

With regard to PS delivery for virus like particles, Yang *et al.* developed a formulation that allows for controlled release of tetrasulfonated Zn(II)Pc.[272] They non-covalently cross-linked guest-modified cowpea chlorotic mottle virus particles and guest-modified hydroxylpropyl cellulose using cucurbit[8]uril for host-guest complex formation. The virus like particles could be loaded with the PS with a high loading efficiency, which allow to improve the solubility of the PS, and control the drug release (see S.I.).

Hydrogels have not only been used to bind and encapsulate cells, but to mimic their natural function as well.[273] For example, soft colloidal gels can mimic the size, deformability and shape of red blood cells.[262,274] This led to particles which were able to bypass certain organs and with prolonged circulation times.[262] *E.g.*, Merkel *et al.* studied the *in vivo* behavior of monodisperse hydrogels with different particle sizes. The material was prepared using the PRINT® (particle replication in non-wetting templates) method, which allows for accurate size and shape control of the microparticles. Hydrogels with a size and shape close to natural red blood cells exhibited extended circulation times and avoided clearance mechanisms.[275] Furthermore, hydrogel particles were loaded with non-human hemoglobin to mimic oxygen transport by red blood cells.[276]

Currently the most challenging aspect is to design hydrogels able to mimic the dynamic nature of the cell environment. Likewise, formulations able to respond to specific stimuli, such as photo-[259,277] or enzymatically[261] responsive hydrogels are desirable. For example, Lee *et al.* designed a virus-like shaped pH-responsive hydrogel for the encapsulation of the anti-cancer drug doxorubicin. The hydrogels with a hydrophobic core and hydrophilic coating bonded to cancer cells in a receptor-dependent manner and, after dug release, caused tumor cell death.[278]

4. Photobiological Applications of Hydrogels

Hydrogels constitute a potential platform for the delivery of various drugs, including photosensitizers.[42] This requires incorporation of the PS into the hydrogel network and its local administration to the target site. The controlled release of the photosensitizer then occurs under a stimulus such as illumination with light and/or changes of the physiological conditions. In the following sections, we describe the current status of the field and emerging trends on the combined use of PDT agents and hydrogels.

4.1 Photoactivity of Hydrogel Scaffolds

Light plays an important role in controlling the temporal and the spatial properties of the chemical transformations within the polymeric scaffold.[279] It can be utilized to control the cross-linking pattern of the hydrogel platforms, may alter the polymeric configuration and cause degradation and sensing of surfaces.[280] The activating processes are rapid and clean. A classic case is standard *cis/trans* isomerization. For example, azobenzene and its derivatives can uniquely undergo photo-controlled *cis/trans* isomerizations. When irradiated with a suitable wavelength of light, the azobenzene moiety undergoes a transformation from the more stable *trans* form to the less stable *cis* form.[281] This *trans-cis* isomerism can control the intrinsic properties of the sol-gel transformations (Fig. 7a, **25**). Earlier, the same feature was used to effect a light-controlled release of proteins from a dextran-based photo-responsive hydrogel.[282]

Notably, photo-isomerization of azobenzene has been used to photochemically drive small plastic-motors.[283]

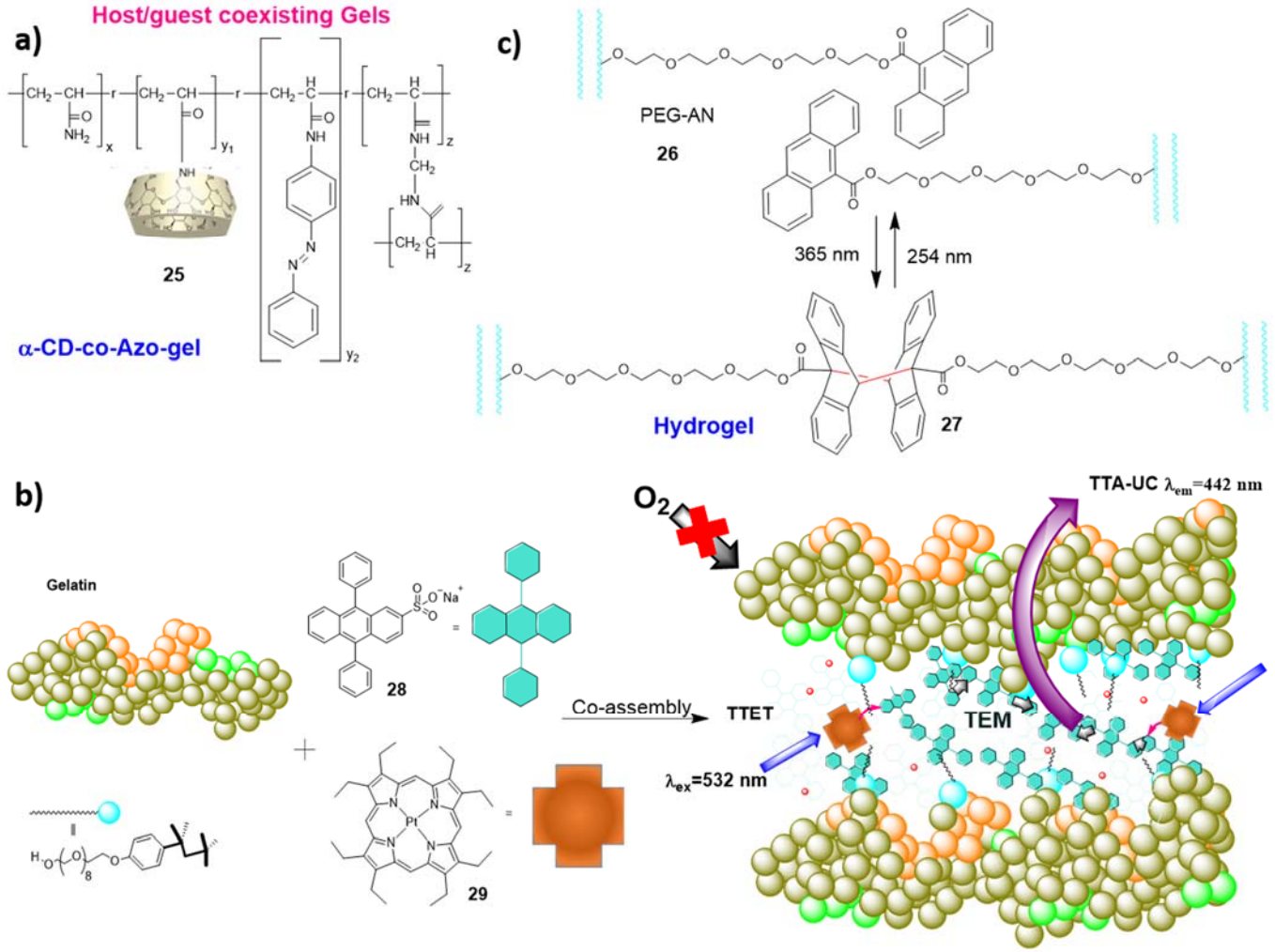


Figure 7 Selected examples of photochemistry used to a) impart function, b) control shape and structure and c) prepare hydrogels.

Recently, *o*-fluoroazobenzene has been used as a green/blue light activated switch in hydrogels allowing a reversible tuning of the elastic modulus.[284] Furthermore, free radical cross-linking techniques have been used for highly versatile and robust materials in soft imprinting lithography and nanoimprinting.[285]

In molecule-specific photochemistry a chromophore absorbs light at a specific wavelength and the polymeric material does not. This makes it possible to address functionalities within the polymeric networks and to selectively perform degradation, isomerization or cross-linking at a particular site within the material. Materials employed in this context are becoming even more complex. For example, a combination of a hydrogel consisting of gelatin, Triton X-100, a porphyrin triplet sensitizer (**29**), and anthracene-based emitter (**28**) allowed the generation of a triplet-triplet annihilation photon upconversion (TTA-UC) system in an aqueous environment (Fig. 7b).[286]

At the other end of the spectrum, photochemistry may be employed in the construction of the hydrogel backbone. *E.g.*, photo cross-linked polymeric PEG materials with terminal anthracene moieties (**26**) gave photochemically prepared hydrogels upon dimerization of the anthracene groups *via* a [4+4] cycloaddition (Fig. 7c, **27**).[287]

Light can also be used for site-specific degradation of cross-linked hydrogel matrices,[245,246] such as PEG.[288] Here, an intriguing example by Shin, Revzin and coworkers used an antibody-appended hydrogels to capture human CD4 or CD8 T-cells and then to release those cells upon UV-induced photodegradation of these "photogels".[288] Key step was the use of the photocleavable *ortho*-nitrobenzyl, which has also been used earlier for the release of porphyrin photosensitizers.[289]

Another photogel study used nitrobenzyl-protected cysteine residues in an agarose gel to produce spatially defined channels upon laser illumination where fibronection fragments could be bound selectively. These hydrogel-based particles guided neurite outgrowth, thus illustrating the level of directional control which can be obtained with photo-patterned hydrogels.[290] Earlier, photodegradable networks of poly(*tert*-butyl acrylate) have been synthesized using copper-catalyzed azide-alkyne cycloaddition

chemistry to give soluble products of a predefined size and structure.[291] Thiolene photopolymerization has also been used for biochemical 3D pattern of photoreactive polypeptides in hydrogels[292] and two-photon patterning of photodegradable hydrogels has recently been achieved as well.[293]

Near-IR irradiation was used to induce gel-sol transitions – in hydrogels containing core-shell upconversion nanoparticles ($NaYF_4$:TmYb) which result in the release of the encapsulated biomolecules. Similarly, a thermoresponsive PNIPAAm/acryclamide/PEG system was loaded with $NaYF_4:Yb^{3+}/Er^{3+}$ nanoparticles for upconversion labeling and NIR antenna effect, which upon illumination with 980 nm light could release entrapped lysozyme.[294] Thus, light is an effective tool to prepare functional and responsive materials by applying appropriate chromophores and polymeric materials that can be further used in tissue engineering or microelectronics.[245,295]

4.2 Hydrogels in PDT and PACT

Hydrogels have gained considerable importance in the development of new therapeutic systems underlined by their capability to hold a high water content and intrinsic hydrophilicity.[296,297] As we will outline in the following paragraph, they clearly present an emerging material to overcome drug delivery limitations of classical PSs. The use of these hydrogel-based platforms provides the advantage of having small size particles, allowing them to penetrate the tissue to reach the target sites. When the target disease is a solid tumor, hydrogel formulations in the nanoscale, can take advantage of the enhanced permeability and retention (EPR) effect (leaky tumor vasculature), which , facilitates the diffusion of the PSs and their retention within the tumor tissue.[40] Hydrogel scaffolds can help to prevent premature drug (PS) release, inactivation of these drugs (*e.g.*, curcumin)[298] *via* interaction with plasma components, and nonspecific site accumulation in healthy tissue , thus improving their effectiveness and sensitivity for photo-action.[299] PS hydrogel formulations can be modified by attaching functional moieties, making them target specific agents by improving their pharmacokinetics, cell uptake, and targeting ability.[300,301] This opens the way for combination therapies. For example, injectable hydrogels were designed to deliver anti-inflammatory therapeutics to injured kidneys with improvements in functional outcomes and reduced systemic inflammation.[302] Similarly, indocyanine green hydrogel formulations have been used for tumor indication.[303]

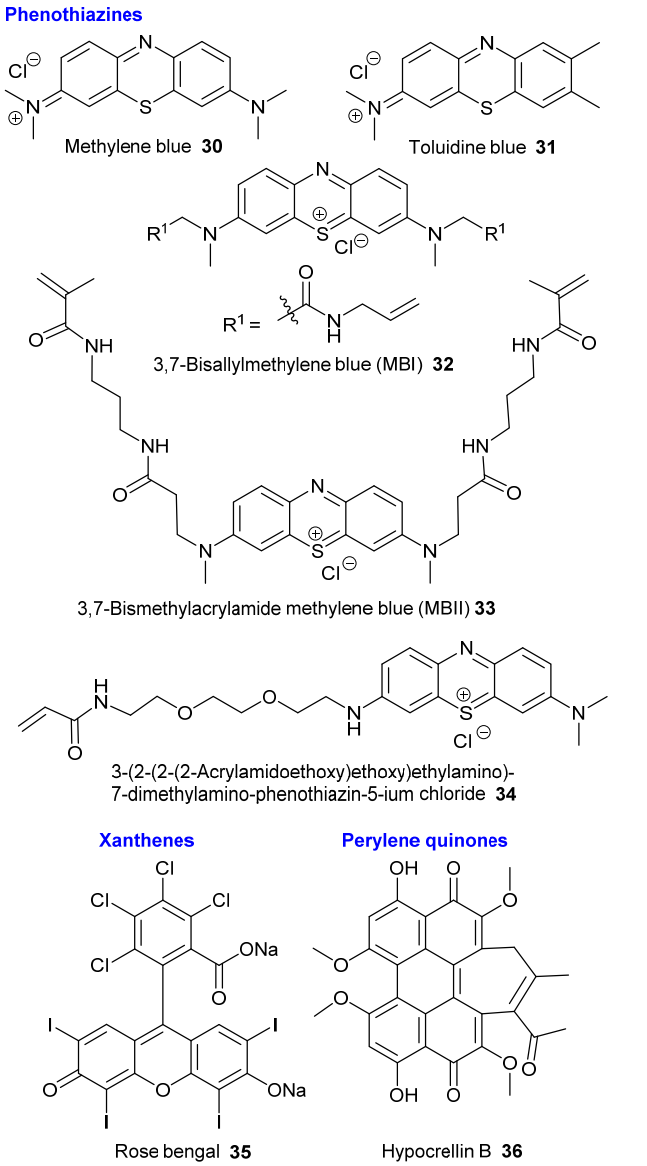
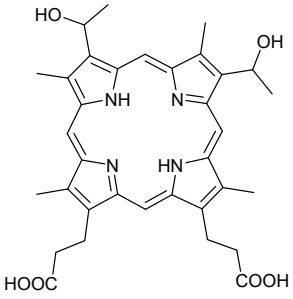
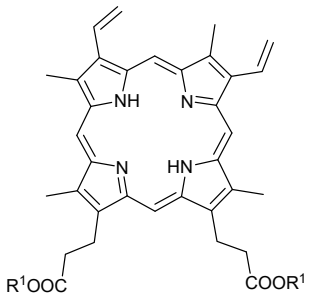


Figure 8 Non-porphyrin photosensitizers used in hydrogels. For details of the hydrogel types see S.I.

Porphyrins

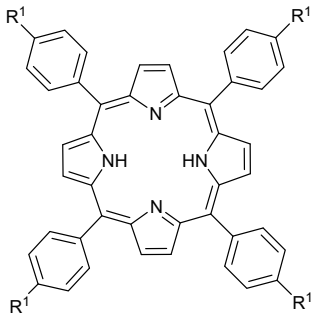


Haematoporphyrin **37**



Protoporphyrin IX (PPIX) **38** $R^1 = H$

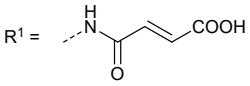
Protoporphyrin IX dimethyl ester (PPIX-DME) **39** $R^1 = CH_3$

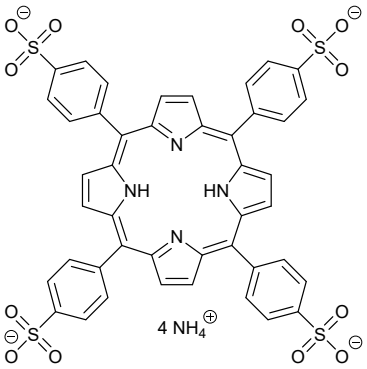


5,10,15,20-Tetrakis(4-(2-hydroxethoxy)phenyl)porphyrin **42** $R^1 = O\text{-}CH_2CH_2OH$

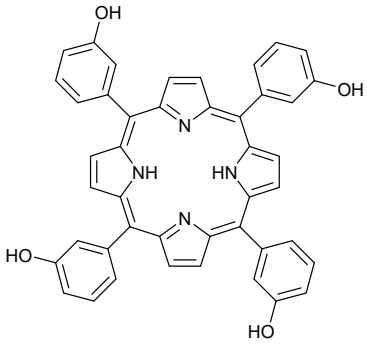
5,10,15,20-Tetrakis(4-aminophenyl)porphyrin (NH_2-TPP) **43** $R^1 = NH_2$

5,10,15,20-Tetrakis(4-*N*-carbonylacrylicamino-phenyl)porphyrin **44**





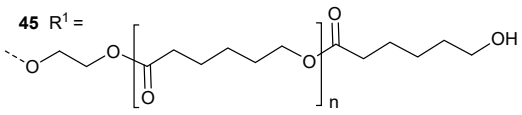
5,10,15,20-Tetrakis(4-sulfonatophenyl)porphyrin tetraamonium salt **40**

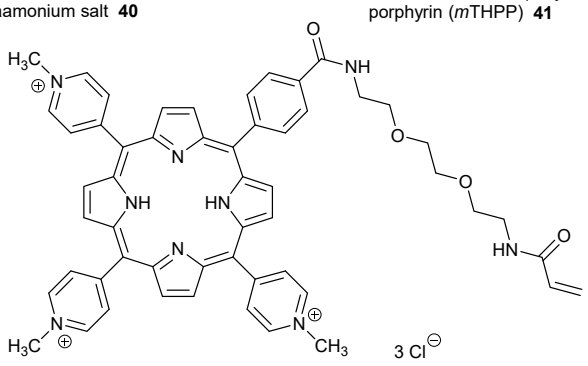


5,10,15,20-Tetrakis(3-hydroxyphenyl)-porphyrin (*m*THPP) **41**

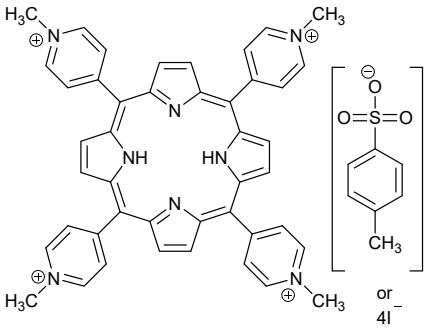
5,10,15,20-Tetrakis(4-O-phenyl)porphyrin-cored poly(ε-caprolactone)-block-PEG

45 $R^1 =$



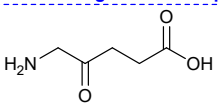


5-[4-2-(2-(2-acrylamidoethoxy)ethoxy)ethyl]carboxyphenyl-10,15,20-tris(4- *N*-methylpyridyl)porphyrin trichloride **46**

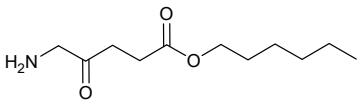


5,10,15,20-Tetrakis(*N*-methyl-4-pyridyl)porphyrin (TMPyP) tetratosylate **47**

Precursors for *in vivo* generation of porphyrin

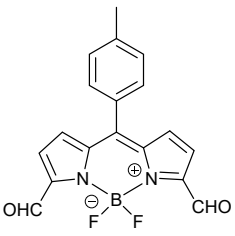


5-Aminolevulinic acid (ALA) **15**

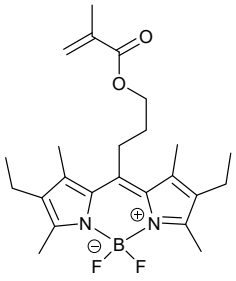


5-Aminolevulinic acid hexyl ester (HAL) **48**

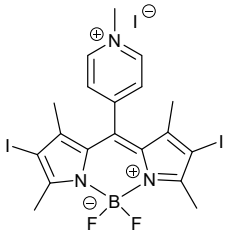
BODIPYs



'3,5-Diformyl-BODIPY' **49**



'BODIPY-MA' **50**



'BODIPY-NMe' **51**

Figure 9 Porphyrins and related compounds used in hydrogel formulations. For details of the hydrogel types see S.I.

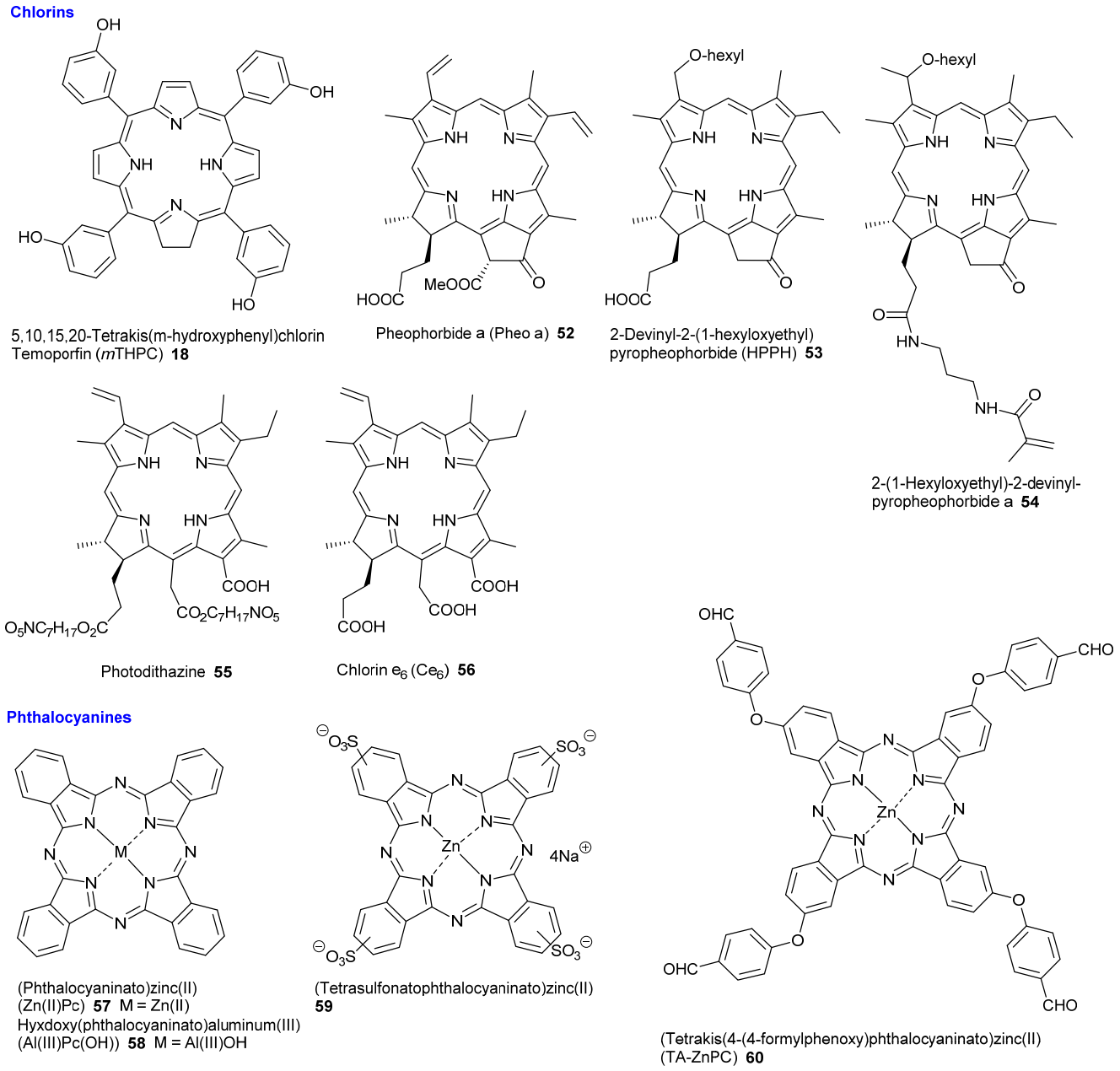


Figure 10 Chlorins and phthalocyanines employed in hydrogel systems.

4.2.1 Nano-Hydrogel Formulations in PDT. Nanogel platforms potentially enable the PS to effectively reach the target sites *via* the EPR effect,[40,304] facilitating accumulation in tumor tissue.[305] Numerous 'nano-'hydrogel formulations of PSs have been reported.[137] Note, that the use of nanogel versus hydrogel is not clearly defined in the literature and that many systems, while "nano-sized", fall outside of the clinically useful criteria with relation to the EPR effect.[197] Various hydrogel-based formulations used for PS delivery are compiled in Tables S1 and S2 (E.S.I.). For ease of comparison, hydrogel-PS formulations are grouped by photosensitizer type (see Fig. 2) and formulae of specific PSs are given in Figures 8, 9, 10 and 11. While we use the term 'formulation' loosely here, two distinct strategic approaches must be considered. The photosensitizer may be simply physically incorporated (encapsulated) in the hydrogel matrix or it may be used as a reactive component in the construction of the hydrogel system, i.e. as a chemical cross-linker (Fig. 12).

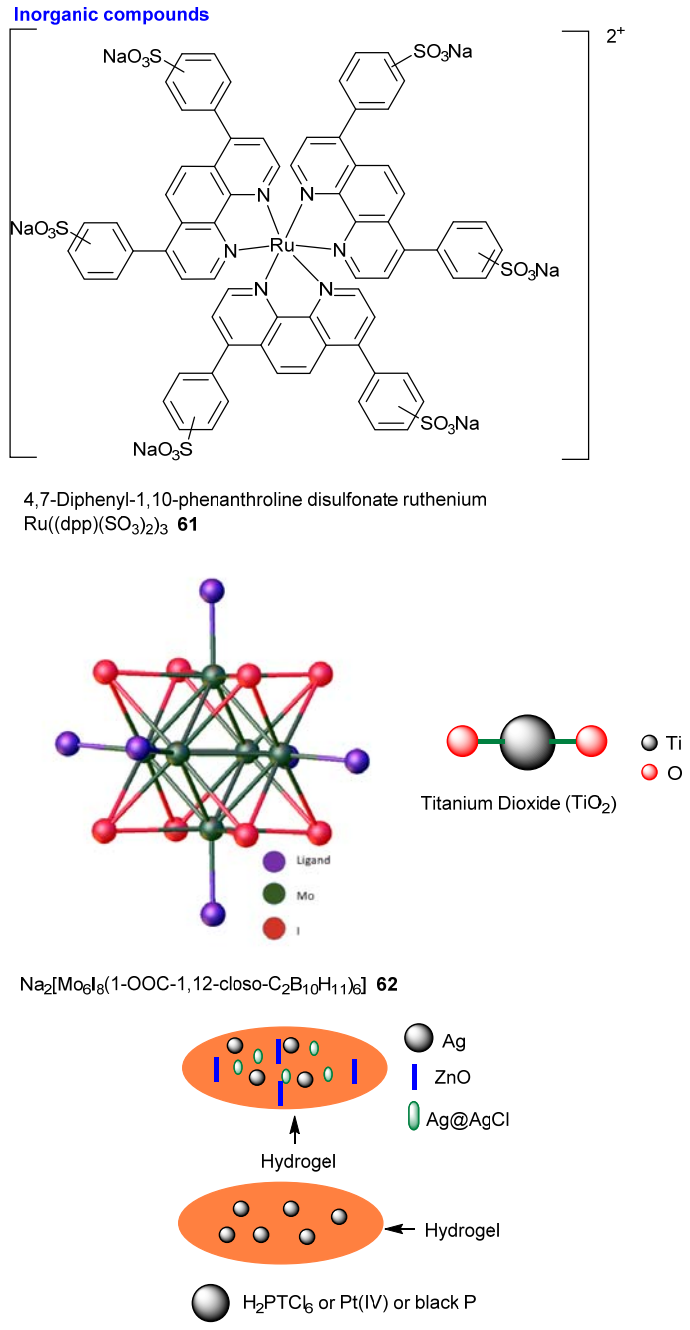


Figure 11 'Inorganic' photosensitizing materials used in hydrogel formulations.

4.2.1.1 Phenothiazines. Due to the relative ease of preparation, more photosensitizers have been used in encapsulation studies than as covalent components of hydrogels. A classic example of PS encapsulated in nanomaterials is methylene blue (MB, **30**).[306] MB typically has low efficacy after systemic administration due to conversion to the colorless leuko-MB form. This enzymatic inactivation can be prevented by encapsulation into PAA nanoparticles.[307] Subsequently, the PS was introduced by attaching methylene blue succinimidyl ester to *N*-(3-aminopropyl)methacrylamide to yield a PS-appended monomer. Introduction of the F3 peptide, a tumor-targeting ligand, resulted in PDT-active nanoparticles that significantly killed cancer cells in vitro.[308] This system proved to be superior to earlier formulations with encapsulated MB[306] and was later extended to other MB derivatives (*e.g.*, **32**, **33**).[309] MB has also been encapsulated into aerosol OT-alginate materials[310] and, in combination with co-delivery of doxorubicin, gave improved cytotoxicity in drug-resistant tumor cells.[311] An intriguing enzymatic approach to construct hydrogels[312] was used in the work from Jin *et al.* on a MB releasing system.[313] They prepared biodegradable chondroitin sulfate-tyramine conjugates through *in situ* tryrosinase mediated cross-linking under physiological conditions.

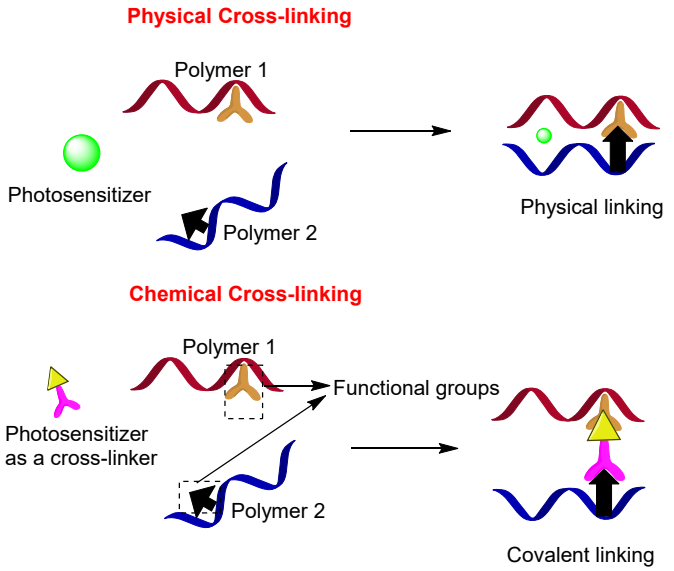


Figure 12 Different strategies for incorporating photosensitizers in hydrogels.

Liposomal MB formulations[314,315,316] were used in a PDT study of 20 patients with nodular and ulcerative basal cell carcinoma showed 11 patients to have complete response with good cosmetic outcome and minimal side effects after six months.[317] Toluidine blue (**31**) is another phenothiazine PS used in PDT for a long time.[318,319,320] Formulation in liposomes followed by incorporation into carboxymethylcellulose hydrogels (sometimes called a transferosome approach) and *in vivo* studies on subcutaneous Ehrlich tumor showed an increase in overall survival of mice when compared to treatment with free toluidine blue.[318]

4.2.1.2 Xanthenes. Rose bengal (**35**) has long been used for diagnostic purposes. In order to evaluate its potential use in dermatological applications, a safety study with green light tested/evaluate a range of topical formulations on murine and rabbit skin. Studies on pharmacokinetics, toxicity and photosensitization revealed only negligible side effects in healthy skin.[321] Multivesicular liposomal Rose bengal formulations in carboxymethylcellulose hydrogels also indicated good skin penetration.[322] A pilot, double-blind study also indicates the utility of topical rose bengal hydrogels for white hair removal.[323]

4.2.1.3 Perylene quinones. Hypocrellin B (**36**), a natural PS, was employed in a targeted, multicomponent system. Calcium-alginate-

based hydrogel microcapsules were prepared and loaded with doxorubicin. These were then coated with a folate-linked lipid mixture on the surface containing hypocrellin as PS (Fig. 13). This chemo- and phototherapeutic combination system was more effective against HeLa cells than either a chemotherapeutic or PDT approach alone.[324]

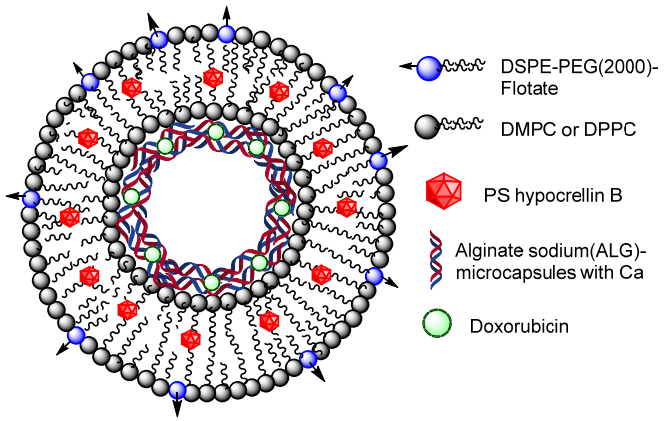


Figure 13 Calcium-alginate-based hydrogel microcapsules containing hypocrellin B and doxorubicin.

4.2.1.4 Porphyrins. Haematoporphyrin (**37**), a classic drug of PDT[325], was used in an early example as a covalently cross-linked PS. Janda and coworkers synthesized a cross-linked polyacrylamide hydrogel where the porphyrin could be covalently attached through the formation of amide bonds between the amino groups of the gel and the carboxylic acid group of the PS. The gel showed excellent swelling properties in both organic solvents and water, and singlet oxygen production was observed.[326]

Protoporphyrin IX (PPIX, **38**) and its biosynthetic precursor 5-aminolevulinic acid (ALA, **15**) are effective moieties for PDT.[327,328] Initial hydroxyethylcellulose hydrogel formulations of lipophilic ALA ester for treatment of cervical intraepithelial neoplasia (CIN) indicated better drug delivery compared to creams, but were plagued by short shelf-lives.[329] Better results were obtained with thermosetting gels which are a solid at body temperature and liquid at room temperature, aiding adhesion of ALA to the cervix uteri. Use of polyoxamer 407, consisting of PEO and PPO units, allowed for a more effective release of ALA-hexyl ester and generation of PPIX in nude mice skin.[329] Notably, ALA and hexaminolevulinate (HAL, **48**) formulations showed selectivity for CIN and were used for fluorescence diagnostic in female patients.[330,331]

Microneedle (MN) arrays,[332,333] first introduced in the late 1970s'[334] and successfully developed in the mid 1990ies,[335] play an important role in the field of advanced transdermal drug delivery systems. MNs are small (to 1000 µm height), needle-like structures, and can be made of different materials (*e.g.*, silicon,[336] metals,[337] polymers[338]). They offer significant potential as minimally invasive, painless and efficient drug delivery systems *via* microporation through the stratum corneum, which is the main barrier in transdermal drug administration.[339,340] Based on their design, they can be classified into five types: solid, coated, dissolving, hollow and hydrogel forming MNs.[341] General MN disadvantages, such as rapid drug release, required sterilization and their intact removal from skin, may be overcome by using hydrogel-forming microneedles. Advantages of these systems include their biodegradable properties, complete and painless removal and no sterilization requirement.[332] Upon contact with interstitial skin fluids, hydrogel forming microneedles swell and imitate drug reservoirs that allow sustained, continuous drug release depends on the cross-linked density of the hydrogel system.[342] Moreover, hydrogel forming MNs give the possibility to incorporate various active pharmaceutical ingredients, regardless of their different properties, such as solubility and molecular weight. This enabled the development of different therapeutic strategies by using a range of compounds including both macro- and micromolecules (insulin,[343] vaccines[344]) with potential for transdermal administration.

To enhance the activity of ALA, it has been introduced into hydrogel forming microneedle arrays, designed by the polymerization of the polymeric scaffolds of poly(methyl vinyl ether/maleic acid) (PVM/MA), cross-linked *via* esterification with glycerol.[332] This is introduced as skin patches into the physiological systems, enhancing the transdermal delivery of 5-ALA.

Protoporphyrin IX (**38**), as a natural compound, is a good PS candidate regarding its biocompatibility. Nevertheless, it has low solubility in aqueous media and tends to form aggregates. In order to also allow its direct use, we explored novel poly(*N*-isopropylacrylamide) (PNIPAM) hydrogels. Pheophorbide a (**52**), protoporphyrin IX (PpIX, **38**) and its dimethyl ester (PpIX-DME, **39**) derivative were covalently cross-linked with the polymer backbone. This allowed overcoming the aggregation problem, due to incorporation of the PS in a 'monomeric' manner, while at the same time improving its solubility in water. Moreover, incorporation into hydrogels did not affect the efficiency of ROS production, which makes them promising candidates as drug delivery platforms for PS.[185] Furthermore, Zampini *et al.* studied hydrogels with incorporated silica-PPIX samples in the presence of gold nanoparticles. This preliminary study showed enhanced ROS production and an improved excitation field due to plasmonic effect.[345]

Charged PSs such as 5,10,15,20-tetrakis(*N*-methyl-4-pyridyl)porphyrin tetratosylate (TMPyP, **47**) were encapsulated into chitosan/alginate nanogels.[346] Typically, these positively charged PS are highly hydrophilic, which hamper cellular uptake. Both nontargeted and targeted versions with anti-death receptor 5 (DR5) antibodies were prepared and tested against HCT116 colorectal cells. TMPyP injectable hydrogel formulations also showed enhanced fluorescence emission and in *in vivo* experiments improved tumor accumulation.[347] González-Delgado *et al.* prepared TMPyP-poly(lactic-co-glycolic acid) (PLGA) nanoparticles that were incorporated into Carbopol® hydrogels. Results demonstrated that such a formulation offers a significant potential for PDT application regarding its controlled drug release, good stability (6 months at 4 °C) and skin permeability.[348]

PVA polymeric platforms have been widely used for biomedical applications, due to their intrinsic advantage of having good

mechanical strength, enhanced water absorption, and swelling properties. AS example, the encapsulation of 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin salts into PVA-based hydrogels(**40**) resulted in enhanced uptake by endothelical HUVEC cells.[349] After intracellular release, the PS was found in the mitochondria.

Over the years, a range of neutral porphyrins have been incorporated into hydrogels and nanogels.[137b] For example, *m*THPP [5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin, **41**] was loaded into hydrogels derived from *N*-sulfonato-*N,O*-carboxymethylchitosan grafted with PMAA *via* free radical graft copolymerization.[350] It was also used in a study where carboxymethyl starch hydrogels were prepared with dextran sulfate to yield polyanionic polymers. The hydrogel-based mTHPP exhibited increased triplet state lifetimes compared to the non-encapsulated PS.[351] Recently, Belali *et al.* reported a pH-sensitive formulation of 5,10,15,20-tetrakis(4-aminophenyl)porphyrin (NH_2-TPP, **43**) and 2,4,6-tris(*p*-formylphenoxy)-1,3,5-triazine (TRIPOD) chemically cross-linked to a chitosan chain. The hydrogel was conjugated with folic acid moieties that allowed for specific tumor targeting resulting in high selectivity and cytotoxicity (over 80%) against human breast cancer MCF-7. Over 90% of drug release was attained in acidic pH, which is specific for extracellular environment of solid tumors.[352]

A combination of a covalent linking and a supramolecular chemistry approach was used in a study by Dai and coworkers.[353] Using a 5,10,15,20-tetrakis(4-(2-hydroxethoxy)phenyl)porphyrin (**42**) core they prepared star-shaped poly (ε-caprolactone)-b-poly(ethylene glycol) copolymers. Together with α-cyclodextrin these formed supramolecular hydrogels based on host-guest inclusion complexation. The system could be co-loaded with doxorubicin and upon light activation produced singlet oxygen.

4.2.1.5 Chlorins. Chorins derived from natural sources, such as chlorin e_6 derivatives, featured prominently in early advances to prepare targeted and water-soluble PS-polymer constructs.[126,354,355,356,357] HPPH (2-devinyl-2-(1-hexyloxyethyl) pyropheophorbide a, **53**), a promising drug candidate,[358] was incorporated into targeted amine functionalized polyacrylamide (AFPAA) gels using a HPPH-conjugated acryclamide derivative (**54**).[359] The structural design of these scaffolds involved make use ofbiodegradable cross-linkers during the polymerization process along with the introduction of photodynamic and fluorescence imaging agents into the polymeric matrix, similar to earlier studies with methylene blue.[308] Here, the added benefit is the ability to concomitantly use fluorescence imaging.

m-THPC, 5,10,15,20-tetrakis(*m*-hydroxyphenyl)chlorin (**18**), widely known as temoporfin, is one example of second generation photosensitizers,[21] discovered and characterized by Bonnet *et al.* more than three decades ago.[360] Today, as a successfully clinically tested PS it is a commercially available anti-cancer therapy drug with the tradename Foscan® (solution) and its liposomal formulations Foslip® and Fospeg®.[361,362] Nevertheless, further advances, with special focus on novel drug delivery systems, are being evaluated to reduce PS dosage and side effects during therapy.

The first temoporfin hydrogel formulation was prepared in 2007 by Kopelman's group.[363] They prepared polyacrylamide particles using acrylamide monomer and *N,N*-methylenebis(acrylamide) as cross-linker. Polymerization was initiated with ammonium persulfate and *N,N,N',N'*-tetramethylethylenediamine in the presence of *m*THPC to yield 2-3 nm sized nanoparticles. Aggregation of the PS was minimized with no significant leaching of the dye and photocytotoxicity of free and hydrogel-bound temoporfin were comparable, although in the latter care the PS was not internalized into the cell.

Carbomer hydrogel formulations of temoporfin loaded into liposomes have also been investigated in detail for their skin penetration properties. Various compositions of the hydrogels were tested, and the elasticity of the gels correlated inversely with the PS concentration. Gels containing 0.75% weight/weight, carbomer and lecithin with a high content of phosphatidylcholine were considered to be optimal.[364] In a follow-up study such materials were found to be stable at 4 and 23 °C for over six months storage.[368]

Chlorin e_6 (Ce_6, **56**), an unsymmetrical photosensitizer with three ionizable carboxylic groups in its structure, is commonly used as a drug in PDT, but tends to aggregate, especially in acidic conditions.[366] To overcome such limitations, various hydrogel formulations have been studied. Improved properties were achieved by Lim *et al.,* who prepared starch and PEG hydrogels with Ce_6. Formulation resulted in enhanced ROS generation and efficient cytotoxicity upon light irradiation.[367] Moreover, potential of Ce_6 incorporated hydrogels, was used to develop a platform for therapy of articular joints.[368] Injectable *N*-fluorenylmethoxycarbonyl diphenylalanine (Fmoc-FF)/poly-L-lysine (PLL) hydrogels with Ce_6 offer a significant potential for superficial tumor therapy. Research by Abbas *et al.* showed that intratumorally injected formulations allowed for local drug delivery and inhibited tumor growth without toxicity for healthy tissues.[369] Furthermore, combination of brachytherapy and photodynamic therapy with use of Ce_6 incorporated hydrogels has been proposed.[370]

In addition, a water-soluble glucosamine salt of Ce_6, Photodithazine® (**55**), was incorporated into Natrosol–based hydrogels. Carmello *et al.* tested its antimicrobial activity *in vitro* against mono and duo-species biofilms of *Candida albicans* and non-*albicans Candida*. Preliminary studies indicated antimicrobial PDT activity only for each species individually, but there was no reduction in total biomass of dual species biofilms.[371] Further improvements of the PDZ-Natrosol hydrogel formulation against *Candida spp.* were studied *in vitro* and *in vivo* (case study), showing potential for treatment of denture stomatitis.[372]

Pheophorbide a (Pheo a, **52**), a magnesium-free dephytylated derivative of chlorophyll a was used in 2012 in an intriguing study on how PS activity can be specifically activated *in vivo*. Bae and Na prepared pullulan (**63**, a fungal polysaccharide) hydrogels with cross-linked folate units (**64**) wherein Pheo a was covalently bound *via* ester linkages (Fig. 14).[373] The material **66** was photoactive in organic solvents but in water the PS exhibited self-quenching. However, after treatment with esterase or exposure to HeLa cells the photoactivity was restored. This indicated uptake by the cells *via* folate-receptor

medicated endocytosis, followed by intracellular enzymatic degradation, resulting in intracellular generation of a PS. The *in vitro* photocytotoxicity of free and the hydrogel-incorporated Pheo a was comparable (IC_{50} ~0.2 μg.mL-1); *in vivo* PS fluorescence reached levels comparable to free Pheo a after about 12 h.

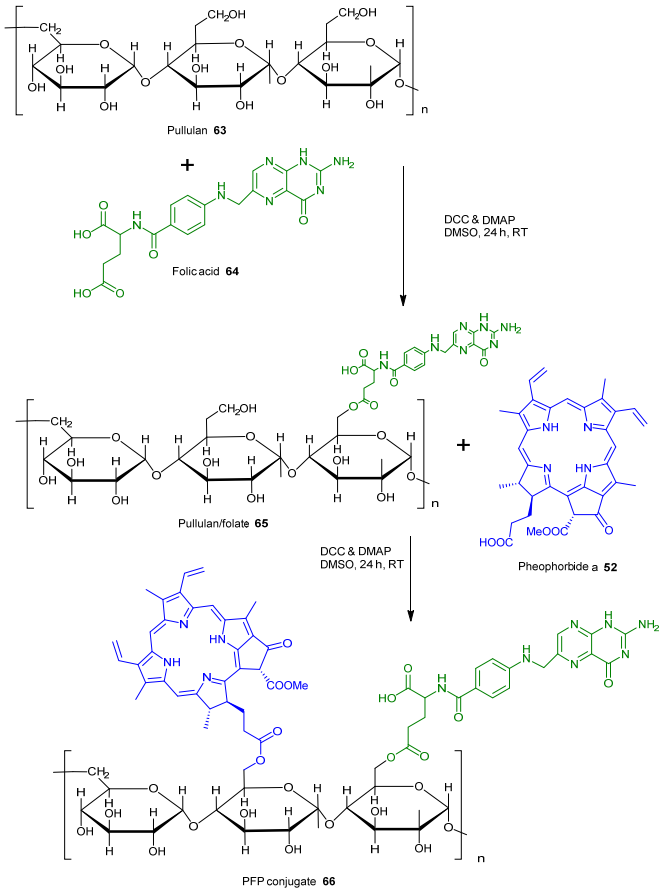


Figure 14 Synthesis of a Pheo hydrogel conjugate.[373]

Pheo a was also covalently linked to the hydrogel matrix of PNIPAM to yield a stable and water soluble nanohydrogel formulation.[185] This nanoporous 3D structure prevented the aggregation of the PS and enhanced the efficiency of singlet oxygen production. The photosensitizer also displayed an excellent *in vitro* PDT efficacy wherein Pheo a-PNIPAM formulation gave a LD_{90} of 9×10^{-5} as compared to Pheo a alone, which displayed a LD_{90} of 5×10^{-7} (HT-29 cancer cells).

To overcome costs and multi-step syntheses of photosensitizers, Pan *et al.* proposed using natural chlorins, *e.g.*, a chlorophyll rich *Spinacia oleracela* extract. A spinach extract–poly(ethylene glycol) double acrylate (PGDA) hydrogel was prepared *via in situ* photopolymerization and its PDT activity was studied *in vitro* against Hela cells and Chinese hamster ovary (CHO) cells. Efficient ROS generation, controlled drug release, and biocompatibility were noted indicating the possibility for green, cost-effective and photoactive hydrogel formulation development[374] using natural pigments as photosensitizers.[375]

4.2.1.6 Phthalocyanines. As industrially relevant dyes, phthalocyanines present a unique class of compounds to highlight the advantages of hydrogel formulations. Phthalocyanines are excellent dyes and PSs with high stability but are prone to aggregation. The approach taken by Karim *et al.* involved using the phthalocyanine as a cross-linker in the gel. This was achieved by preparing a Zn(II)Pc-tetraaldehyde (**60**) which was linked *via* Schiff-base formation with the amino groups of chitosan.[376] This self-healable and injectable hydrogel slowly released the PS in an acidic tumor cell environment and showed improved PDT activity compared to the free PS.

Another multi-component system used hybridized hydrogel platforms prepared from poly(ethylene glycol) diacrylate and PEG-400. (Phthalocyaninato)zinc(II) [Zn(II)Pc, **57**] and phosphotungstic acid were present in the preparation mixture and used for *in situ* photopolymerization to generate the hydrogel. Additionally, the Zn(II)Pc through incorporation into the hydrogel remained photochemically active and could be used for $^1O_2$ production for PDT.[377] Zn(II)Pc was also incorporated into a biocompatible *Aloe vera* gel/Pluronic F127 formulation.[378] Al(III)Pc(OH) (**58**) is currently under investigation for use as an antimicrobial agent as well.[379]

For substituted Pcs, a contemporary example utilized a combination of four components: poly-β-cyclodextrin, modified dextran, (tetrasulfonatophthalocyaninato)zinc(II) (**59**), and a nitric oxide photodonor.[380] In this supramolecular chemistry approach, the cyclodextrin polymer[381] served as host for the co-encapsulation of the two dyes and the dextran units, thus yielding a stable hydrogel where the two fluorogenic units remained photochemically isolated and could be used in conjunction. Thus, visible light excitation gave red and green fluorescence and resulted in $^1O_2$ and NO generation.

4.2.1.7 BODIPYs. The BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene, **8**) dye framework is an extensively versatile fluorescence moiety possessing intriguing properties such as large molar extinction coefficients, high quantum yields, low rates of intersystem crossing and an excellent photo-stability.[382,383] Thus, these dyes have practical uses in the fields of biochemical labelling, photonic molecular systems, laser dyes, organo-gelator, and light-emitting devices respectively.[384] However, problems are sometimes poor biocompatibility due to instability or toxicity, low water solubility, and aggregation in the aqueous biological medium with attendant reduction in fluorescence quantum yields. Again, covalent incorporation of BODIPY dyes into hydrogel platforms could overcome these issues.[385] For example, BODIPY dyes have found use as optical sensors for pH sensing. To overcome low water solubility and quenched fluorescence a polymeric polyurethane hydrogel film with an embedded BODIPY derivative was synthesized as a basic pH-sensitive fluorescence sensor. It overcame problems of traditional glass electrodes in the basic pH ranges and preserved the spectroscopic characteristics of the isolated BODIPY fluorophore.[386]

Furthermore, our group reported on the 3,5-diformyl-BODIPY **49** covalently linked to a self-healing chitosan hydrogel matrix (Fig. 15). The composite **67** displayed a dynamic fluorescence resonance energy transfer (FRET) process along with enhancement in solubility

in aqueous medium.[387] It displayed improved mechanical and photo-responsive characteristics; the fluorescence quantum yield of the BODIPY dye was enhanced 14.5-fold in the hydrogel matrix compared to the individual dye. First examples of combining, thermo-sensitivity and luminescence in a cross-linked network used 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA) covalently linked with BODIPY methacrylic monomer (BODIPY-MA, **50**).[388] These polymeric hydrogel platform exhibited a reversible change in the fluorescence intensity with temperature in addition to an increased thermal fluorescent response of BODIPY-MA.

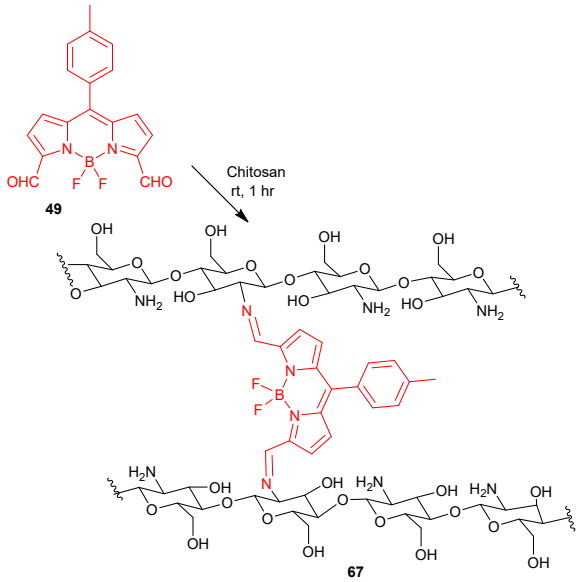


Figure 15 Synthesis of a covalently cross-linked chitosan-3,6-diformyl-BODIPY hydrogel conjugate.[387]

4.2.1.8 'Inorganic' Materials. 'Classic' inorganic PSs such as 4,7-diphenyl-1,10-phenanthroline disulfonate ruthenium $[Ru(dpp(SO_3)_2)_3]$ (**61**) were used early in the development of PDT-hydrogels. PAA hydrogels containing the complex, prepared by Kopelman's PEBBLES approach,[389] produced singlet oxygen.[390] A chemotherapeutic formulation, which includes a platinum(IV) complex-based polyprodrug incorporated into 2-methacryloyloxy ethyl phosphorylcholine hydrogel was studied by Guo *et al.* After irradiation, the platinum complexes undergo a reduction from Pt(IV) to Pt(II), yielding highly toxic species with the ability to generate ROS without oxygen consumption.[391] Ag/Ag@AgCl/ZnO nanostructures incorporated into a CMC hydrogel provided both antimicrobial activity (>95% cytotoxicity) and a pH-sensitive swelling–shrinking transition, which together are essential for wound healing materials.[392]

Certain inorganic materials such as molybdenum clusters also possess an intrinsic ability to produce ROS under light illumination and they can be used in hydrogel formulations. Thus, a luminescent octahedral molybdenum cluster complex of $Na_2[Mo_6I_8(1\text{-}OOC\text{-}1,7\text{-}closo\text{-}C_2B_{10}H_{11})_6]$ (**62**), having a very high photoluminescence quantum yield up to 93% and an efficient quantum yield of $^1O_2$ of about 70% was used for self-assembly with β-cyclodextrin polymer and formed monodisperse singlet oxygen generating hydrogel particles.[128]

TiO_2 nanoparticle semiconductors were employed in a PEG double acrylate (PEGDA) hybrid hydrogel. PEGDA was photopolymerized *in situ* in the presence of TiO_2 nanorods and this could even be achieved in the presence of HeLa cells, which became coated by the hydrogel shell. The near-IR irradiation used for the polymerization also resulted in $^1O_2$ generation and apoptotic cell death. Thus, TiO_2 fulfilled a dual role, both as polymerizing agent and as a photosensitizer.[393] A recent report by Glass *et al.* showed that simple TiO_2 (titania) can be used for the photoinitiation of PEGDA-based hydrogels. Notably, the TiO_2 remained in the hydrogel and stayed photoactive, capable of photodecomposition of MB.[394]

4.2.2 Hydrogels for Antimicrobial PDT. Increasing antibiotic resistance among pathogenic microbes and viruses is one of the most challenging issues in current medical research. The need for the development of new antimicrobial drugs, in addition to their recent excessive prescription for viral infections and patients' incompliance, spurred studies into strategies that will overcome raising antibacterial resistance.[395] Briefly, general microbes' resistance to antibiotics can occur through four main pathways: (i) drug inactivation, (ii) elimination from cells *via* active efflux, (iii) modification of the bacterial cell wall composition and permeability or (iv) acquired genetic information from other microbes that encode resistance.[396,397] To date, there is no report of bacterial resistance to reactive oxygen species (ROS), which highlights antimicrobial PDT as a promising method that can become a lead therapy in an antibiotic-sensitive and multi-resistant bacteria treatment.[397,398,399] As before, the mechanism of action of antimicrobial PDT combines a non-toxic photosensitizer, ground state oxygen and light to generate, in this case, a cytotoxic impact on the microbial stratum.[6,63,84,400]

Microbes grow as a biofilm, which is a non-homogenous organization of microbes and an extracellular polymer substrate (EPS) which in turn provides structural stability and protection against adverse environmental conditions.[401] Similar to PDT, current studies use PS-hydrogel combinations for PACT.[402] Additionally, hydrogels have been used as delivery systems for classic antimicrobial drugs or to prevent the growth of biofilms.[403]

Recent examples of related work in this area include a study by Risbud *et al.* who prepared a freeze-dried chitosan/polyvinyl pyrrolidone (PVP) hydrogel with the incorporated antibiotic drug amoxicillin; this was introduced as a pH-sensitive controlled release drug delivery system.[404] Furthermore, amphotericin B, a broad-spectrum chemotherapeutic drug, was integrated into carboxymethylcelullose-dextran hydrogel and displayed extended antifungal activity. Moreover, the gels were injectable and did not cause hemolysis or tissue injuries.[405] In 2010, Sung *et al.* combined antimicrobial polymers and chemotherapeutic potential *via* minocycline incorporation into PVA/chitosan hydrogels that significantly improved wound healing.[406] Recently, hydrogel implemented intraocular lenses with the tetracationic porphyrin TMPyP **47** were successfully used against Gram-positive and -negative bacteria and showed efficient ROS production.[407]

Moreover, Lie *et al.* published promising results of a hydrogel system that for the first time used electrochemiluminescence to provide an antimicrobial effect.[408]

Antibiotic resistance is a problem in dermatology.[66,409] Notably, after long-term antimicrobial therapy, skin microbiota might become resistant not only to the drug used during the treatment, but also to structurally different groups of chemotherapeutics.[395] The most challenging aspects in terms of increasing antibiotic resistance in dermatology concern wound infections, impetigo, atopic dermatitis, psoriasis and acne vulgaris diseases.[397] A recent study by Frade *et al.* used methylene blue (**30**) incorporated in a chitosan-based hydrogel as a formulation against *Propionibacterium acnes* which showed very promising results.[410]

Note, antimicrobial hydrogels are already in widespread use in the clinic, *e.g.*, in the form of bactericidal silver-hydrogels which are used as coatings for medical devices such as endotracheal tubes and catheders.[179] Hydrogels in general are also used as wound dressings to support wound healing.[411] A recent review on this area is available from Neves, Almeida and Faustino's group.[412]

Fadel *et al.* used liposomal MB, formulated in MB hydrogel and investigated it for acne treatment.[314] Thirteen patients with mild to moderate acne vulgaris were treated and after 12 weeks, 90% of the patients showed an improvement without serious side effects. After two treatment sessions, an 83% reduction in the number of inflammatory acne lesions and a 64% reduction in the number of non-inflammatory acne lesions was noted. A similar study was performed for truncal acne[315] and the same approach was evaluated in a study of 16 patients with resistant psoriatic plaque stage lesions which showed complete clearance of lesions.[316] The antibacterial activity of MB incorporated into PAA based hydrogel matrices proofed effective against bacterial suspensions and biofilms and was suggested for water-sterilization.[413]

Peng *et al.* proposed toluidine blue incorporated in chitosan hydrogels with an addition of hydroxypropyl methylcellulose (HPMC) to increase polymer mucoadhesiveness. The formulation showed a high PACT efficiency against periodontal biofilms.[319] Moreover, studies showed that toluidine blue containing hydrogels offer a potential for periodontitis treatment.[320]

Also, hydrogels based on HEMA incorporated with NO donor $[Mn[PaPy_3](NO)]ClO_4]$ exhibited an antimicrobial activity against bacterium *P. aeruginosa*.[414] Similarly, a PVA-borate hydrogel containing MB showed good efficiency against methicillin-resistant *Staphylococcus aureus* (MRSA), but was affected by the presence of newborn calf serum.[415] The same study also investigated TPyP (**47**) hydrogels, where the antibacterical effect was unaffected by calf serum; the material was also effective against biofilms. Toluidine blue O (**31**) has also been used in a chitosan hydrogel containing hydroxypropyl methylcellulose and chitosan for topical applications.[416]

Boyle's group reported on an easily prepared new covalently-linked phenothiazonium derivative (**34**) which could be used for immobilization in a polyacrylamide hydrogel and showed photodynamic activity against *Staphylococcus aureus* and *Escherichia coli*.[417] Subsequently, the same group studied the antimicrobial photodynamic activity of the cationic (5-[4-2-(2-(2-acrylamidoethoxy)ethoxy)ethyl]carboxyphenyl-10,15,20-tris(4-*N*-methylpyridyl)porphyrin trichloride (**46**) and its Pd(II) and Cu(II) complexes cross-linked with polyacrylamide. The cytotoxic effect on *Escherichia coli* suspensions of all PSs and its low dark toxicity indicates potential use in water disinfection.[418] Upconverting nanoparticles have also been applied in PDT studies. For example, a cationic (quaternized) chitosan hydrogel with encapsulated $NaYF_4$:Er/Yb/Mn methylene blue-doped silica has shown to effectively 'attract' the outer anionic part of microbes and was effective against Gram positive and negative bacteria.[419]

In more applied studies, a specific surface localization of TMPyP electrostatically bound in acrylate hydrogels was shown to prevent bacterial colonization and was suggested for use as intraocular lens biomaterials to prevent eye infections, endophthalmitis.[407] In an earlier study, Bell and McCoy's groups had comparatively investigated TMPyP (**47**) and $TPPS_4$ (**40**) copolymers of 2-hydroxyethyl methacrylate with either methacrylic acid or 2-(diethylamino)ethyl methacrylate as potential intraocular lens biomaterials.[192] Unexpectedly, $TPPS_4$ showed very low $^1O_2$ production in the hydrogel indicating that 'simple' characteristics such as the charge of the PS can have a profound effect on its utility in complex hydrogel materials. The TMPyP material, with the PS at the surface of the hydrogel, was able to significantly reduce *Staphylococcus epidermidis* adherence both in the light and in the dark.[420] Al(III)Pc(OH) (**58**) is currently under investigation for use in treating diabetic foot ulcers and leishmaniosis lesions.[379]

Additionally, photosensitizers based on the BODIPY dyes have been utilized effectively for the antimicrobial PDT (aPDT) against both gram strains of bacteria.[421] Linear polymeric amidoamines (PAAs) were used for the preparation of hydrogel matrices together with the BODIPY-NMe (**51**) dye. This association enhanced the killing efficacy of BODIPY upon irradiation within 480 to 580 nm range (λ_{max} = 525 nm) at BODIPY concentrations of 1.0 and 0.1 μM against *Escherichia coli* and *Staphylococcus aureus*, respectively.

An antimicrobial effect *in vitro* and *in vivo* was also achieved using black phosphorus sheet hybrid-hydrogels that were found to exhibit efficient ROS production and favorable photothermal properties. The black phosphorus sheets loaded into chitosan structures enhanced the wound healing processes due to stimulation of fibrinogen formation and cell proliferation and differentiation.[422] Future practical developments are indicated by anti-adherent hydrogel formulations composed of Poloxamer 188 and 2-hydroxyethyl methacrylate with incorporated ofloxacin as surface antibiotic coating of catheters to reduce device-associated infections.[423] A photoactive system was developed by Donnelly *et al.* using poly(2-methyoxyethyl acrylate) hydrogels with incorporated drug-3,5-dimethoxybenzoin conjugates.[424] Iontophoteric release of PSs from a polyelectrolyte hydrogel for potential wound healing was studied by the same group, who loaded a poly(methyl vinyl ether-co-maleic acid) gel with either MB or TPyP. Upon application of an electric current to the hydrogel films the PSs were released and induced complete kill of MRSA and *Burkholderia cepacia*.[425]

4.2.3 Hydrogels for Photothermal Therapy. Photothermal therapy (PTT) is a potential alternative to PDT. The mechanism of action concerns light absorption by the photothermal agent and subsequent electron excitation combined with non-radiative relaxation. The process results in increased kinetic energy and heat production in the local environment inducing necrosis and/or apoptosis.[391,426,427] One of the major advantages of PTT is the PTT agent's activation by NIR exposure, which has minimal interactions with water and biomacromolecules, and deep tissue penetration.[428,429] Hydrogels that undergo structural changes to stimuli including heat are favorable systems for PTT therapy.[430]

In a typical PTT treatment of the infected tissue, a photothermally active agent can selectively heat and kill off the abnormal cells or tissue.[431,432] A selection of photoactive materials used for PTT is compiled in Figure 16, while the respective hydrogel systems are listed in Table S4. In our context, one classic example from Kopelman's group is a hydrogel nanoparticle based on polymeric PAA with coomassie brilliant blue-G (**69**) as a conjugated photothermal agent (introduced as the crosslinker in form of a *N*-(3-aminopropyl) methacrylamide hydrochloride derivative) against the human cervical cancer cell line (HeLa) cells .[433]

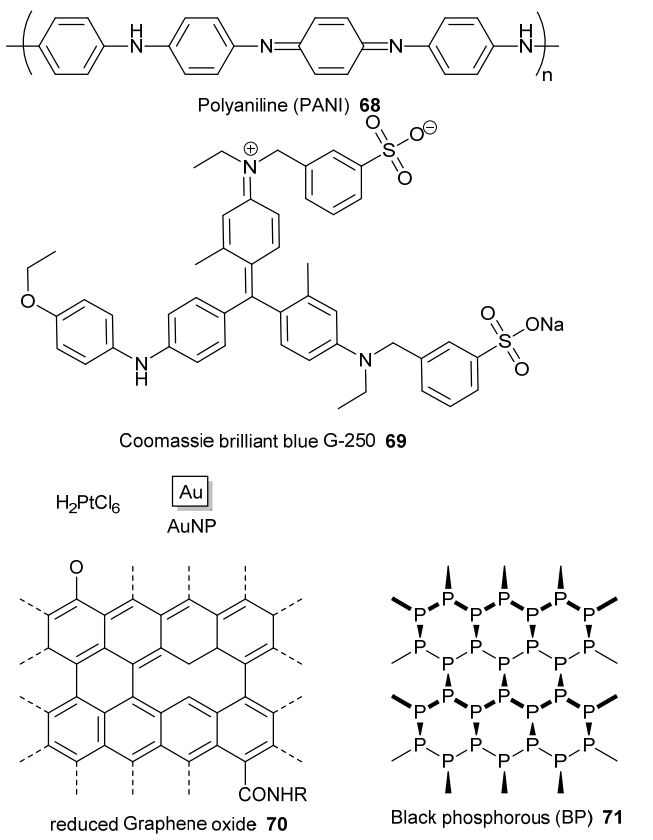


Figure 16 Photoactive materials used in photothermal therapy.

Chitosan derivatives possessing self-doped polyaniline (PANI, **68**) side chains self-assemble into micelles and transform into hydrogel scaffolds as a stimuli responsive system with a pH change.[434] The efficacy of these systems was tested in mouse models, enabling the selective killing of the cells in the light-illuminated areas. Similarly, alginate hydrogel matrices bearing dendrimer-encapsulated nanoparticles of platinum (DEPts) present excellent biocompatibility and degradation. These hydrogel/DEPts mediated PTT suppress tumor growth efficiency on repeated PTT and the scaffold can be degraded and eliminated *via* renal secretion out of the body.[435]

A notable development was recently reported by Qui *et al.*, who prepared black phosphorous (**71**) hydrogels by combining pegylated black phosphorous and low-melting agarose. Near-IR excitation allowed for controlled drug release (doxorubicin) depending on light intensity, duration, and hydrogel composition and gave very good tumor ablation in MDA-MB-231 tumor-bearing mice.[436]

4.2.4 Combination Therapy (PDT-PTT) with Hydrogels. Conventional PDT is a minimal invasive and efficient palliative cancer therapeutic technique with reduced side effects and improvised selectivity compared to traditional radiotherapy and chemotherapy.[437] In addition, imaging-guided PTT is a therapeutic method that could be efficiently used for eliminating residual tumor cells with precise guidance in the future.[438] Recent studies suggest that the combination of PDT and PTT could generate a synergistic therapeutic effect enhancing the efficacy of the overall treatment.[439] This synergism induces minor systematic toxicity, non-invasive characteristics and a higher selectivity, beyond the individual mode of treatments.[440]

The effectiveness of both treatment modalities against tumors relies on the fact that both, the photosensitizer and photothermal agents, co-accumulate in the same target region.[441] Especially gold nanoparticles (AuNPs) have emerged as a model of photothermal agents used in combination with different photosensitizers for synergistic PTT/PDT effect.[442,443] Recently, hydrogel formulations have attracted attention due to their intrinsic capability of good retention of the loaded drugs, as well as favorable responsiveness to environment stimuli.[444] For example, a composite hydrogel matrix containing gold nanorods (AuNRs), spinach extract, and poly(ethylene glycol) double acrylates (PEGDA) was formulated *via* one-step in *in situ* photopolymerization under non-invasive laser irradiation and tested for localized antitumor activity.[445] The spinach extract served dually as a photoinitiator and as photosensitizer for the generation of cytotoxic singlet oxygen species. Furthermore, a hydrogel matrix integrated with reduced graphene oxide (rGO, **70**), amaranth extract (AE) and AuNPs was used as a platform for PTT/PDT.[446] Irradiation of cells cultured with a precursor solution of rGO-AE-AuNPs induced hydrogel shell formation and showed remarkable synergistic antitumor effects. IR-spectroscopy indicated that the reduced graphene oxide after treatment had lost hydroxy-, epoxy- and alkoxy-groups and gained amide functionalities indicating covalent binding to amaranth components.

Similarly, spinach extract, reduced graphene oxide and gold nanocages have been combined in hydrogels loaded with fluorouracil and showed significant antitumor effects with HeLa cells.[447] Spinach extract has also been used as photoinitiator for the formation of PEGDA hydrogels loaded with Au nanorods upon illumination with 660 nm light. HeLa cells were effectively killed when exposed to the composite precursors through the synergistic

combination of photothermal heating, the photodynamic effect of spinach extract and the localized gelation.[445] Natural hydrogel forming materials such as *Brassica chinensis* extract, were also used in conjunction with fluorouracil and reduced graphene oxide to add a chemotherapeutic component to the PTT/PDT approach.[448]

In addition, TiO_2 and multi-walled carbon nanotubes were combined with PEG double acrylates as polymer matrix and doxorubicin was used as chemoactive drug. After injection of the precursor materials into a tumor, near-IR irradiation resulted in *in vivo* gelation *via* photo-induced cross-linking.[449] The *in situ* gelation effectively creates a slow release drug depot in the tumor, containing both the chemotherapeutic drug and materials suitable for PDT and PTT. *In vivo* studies with S180 tumor bearing mice showed that of all control groups the one with initial irradiation for gelation and then followed by irradiation every two days to created PTT/PDT effects exhibited the best effect. PVA hydrogels have also been used to embed AuNRs. Studies at the single nanoparticle level with near-IR fs pulses showed the formation of hydroxyl radicals through a plasmon-assisted multiphoton process. This indicates the possibility to use water instead of oxygen for ROS generation, *e.g.*, in hypoxic tissue.[450]

Conde *et al.* proposed triple-combination anticancer therapy using a hydrogel patch as a gene (siRNA) and drug delivery (bevacizumab) platform. The hydrogel scaffolds made of oxidized dextran and poly(amidoamine) G5 dendrimer increased the stability of incorporated molecules and provided photoresponsive properties due to incorporation of gold nanoparticles that can convert NIR irradiation into heat. These specifically designed platforms allowed for local chemotherapeutic release and enhanced antitumor activity.[451] Sun *et al.* studied collagen-gold hybrid hydrogels formed *via* a biomineralization process. TMPyP was incorporated into the hydrogel as PS giving a high cytotoxic effect in *in vivo* studies (up to 80% tumor reduction) indicating the potential of synergistic PDT/PTT therapies.[187,452] Moreover, Li *et al.* studied the combined PDT and PTT effect of mesoporous silica and modified CuS nanoparticles incorporated into hydrogel for wound healing. After irradiation, the generated heat provided an antimicrobial effect and stimulated fibroblasts proliferation and angiogenesis due to copper ion release.[453]

4.3 Other Uses of Hydrogels

4.3.1 Environmental Remediation. All applications of hydrogels highlighted here so far were based on the principle that the polymer material binds and/or stabilizes the photoactive compound for light-activated uses thereafter. However, there are also cases where binding of dyes by polymers can be used for environmental remediation. For example, organic dyes are used in the industrial processing of textiles, in print-media, leather processing, and more. They are found in industrial effluents and their removal poses an environmental challenge.[454] Among many possible approaches the use of hydrogels and related materials is currently under scrutiny for dye removal, much of which is based on using polysaccharides.[455]

This is not the place to review this field; hence, a few examples may serve to illustrate this approach. *E.g.*, cationic hydrogels derived from hydroxypropyl cellulose were used to absorb anionic dyes, such as acid orange 7 or acid red 18.[456] Likewise, a superabsorbent hydrogel of cellulose-grafted crylic acid polymers was efficient to remove MB dye particulates.[457] Composite hydrogels synthesized by homogenous acetylation of cellulose also had an enhanced adsorption capacity for MB.[458] Another form of composite material was a combination of hydroxypropyl cellulose with MoS_2 which, when introduced, improved the adsorption efficacy. In this case, presence of the photocatalytic MoS_2 allowed for photo-regeneration of the hydrogel after absorption of MB.[459] A haemin [chloro(protoporphyrinato)iron(III)] graphene hydrogel, easily prepared hydrothermally from the dye and graphene oxide, showed high absorption and photocatalytic destruction of MB.[460]

Further, an amphoteric hydrogel generated by photopolymerization of *N,N*-diallyl-carboxypiperidinium bromide, NIPPAAm and (3-acrylamidopropyl) trimethylammonium chloride was effective for the removal of industrial effluents such as reactive dyes (reactive red 195, reactive blue 222, reactive black 5).[461] Additionally, supramolecular hydrogels (xerogels) of chiral amphiphilic lithocholic acid and dodecyldimethylamine oxide as surfactant showed adsorption activity for several toxic dyes.[462]

Hydrogels have also been discussed in the context of waste water treatment and remediation,[463] *e.g.*, through photosensitized dichlorination reactions of pentachlorophenol.[464] Another example is a pH-sensitive (swelling in acidic water), electrospun TiO_2 PVA/poly(*N,N*-dimethylaminopropyl acrylamide hydrogel, which was highly efficient to degrade MB under UV irradiation.[465]

4.3.2 Hydrogel Formation, Sensing and Photochemistry. From the beginning of complex hydrogel preparation, PSs have been used as components for the photogelation of hydrogels and for the photoinitiation[466] of grafting onto films.[159,467] A non-exhaustive list of examples includes eosin Y,[468,469,470,471,472,473] erythrosine B,[474] 2,2-dimethoxy-2-phenylacetophenone,[475] thioxanthone,[476] benzophenone,[477] riboflavin for localized photodynamic cross-linking,[478,479,480] flavin mononucleotide,[481] camphorquinone,[482] anthraquinone,[483] cinnamate moieties,[484,485] polyoxazoline,[486] anthracene,[487] TiO_2,[394] and more. A careful selection of the respective PS is necessary if such methods are used for the construction of cell encapsulating systems[488] or for use in 3D-printing.[472,481,489]

Naturally, standard photocycloaddition reactions can also be applied to cross-link hydrogels, but this typically requires UV irradiation. Recently, Truong *et al.* utilized the 400-500 nm visible light [2+2] photocycloaddition of styrylpyrene to conjugate and cross-link PEG in water to hydrogels. Photoreversion of this reaction with UV irradiation (340 nm) was possible.[490]

Hydogels have also been employed as covers for glass slides to prepare porphyrin microarrays for binding studies with plasma proteins.[491] Another intriguing approach was the use of spiropyran **72** in polyurethane hydrogel films to act as photochromic pH sensor (Fig. 17).[492] A spiropyran was also used in a dynamic photoresponsive zwitterionic hydrogel constructed from a copolymer of zwitterionic monomer carboxybetaine acrylamide, photoswitchable monomer

spiropyran methacrylate and cross-linked with zwitterionic carboxybetaine dimethacrylate. This system was used to trigger and arrest stem cell differentiation processes through modification of nonspecific cell-hydrogel interactions.[493]

Quantum dots have also been employed in hydrogels as potential biosensors, *e.g.*, in CdTe quantum dots encapsulating tyrosinase for the detection of dopamine.[494] Moreover, hydrogels were introduced as oxygen-producing biomaterials to reduce the resistance against chemotherapeutics due to hypoxic tumor conditions.[495] Another promising area for hydrogels is in food safety applications. *E.g.*, antimicrobial hydrogel food coatings can increase food shelf-live and protect against cross-contamination and illnesses.[496]

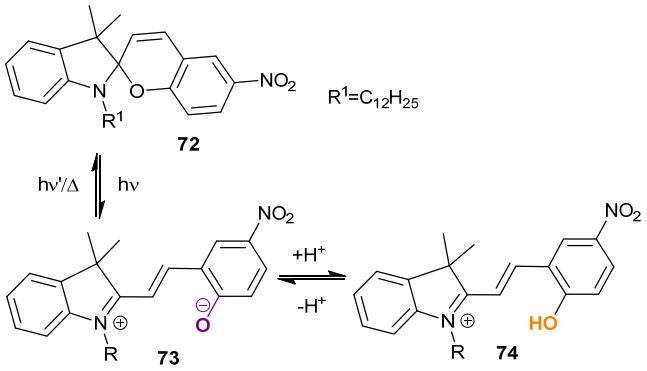


Figure 17 A hydrogel embedded spiropyran-merocyanine photoswitch for pH sensing.[492]

PS loaded hydrogels can also be used for photoredox chemistry[497] and synthetic photochemistry. Thus, one of the oldest studies used gelatin hydrogels incorporating tri(bipyridine)ruthenium(II) [Ru(bpy)$_3$] to facilitate a reversible redox reaction of a cobalt(III) chelate.[498] In terms of synthetic organic chemistry, the haematoporphyrin hydrogel mentioned earlier (**75**) was used as a catalyst for the photooxidation of anthracene (**76**) to the respective endoperoxide (**77**) (Fig. 18).[326]

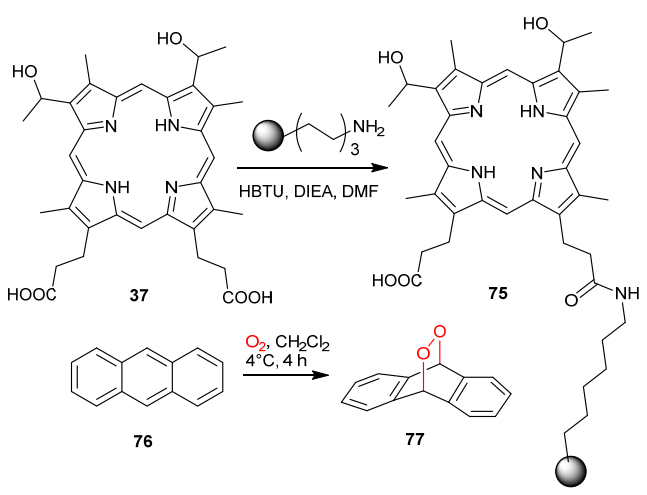


Figure 18 Hydrogel mediated photooxidation of anthracene.[326]

[Ru(bpy)$_3$] photosensitizers have also been used in artificial photosynthesis systems. For example, Okeyoshi and Yoshida reported on a material containing copolymerized poly(*N*-isopropylamide-co-Ru(bpy)$_3$) and Pt nanoparticles as immobilized catalysts (Fig. 19).[499] The system could convert light and water into H_2.

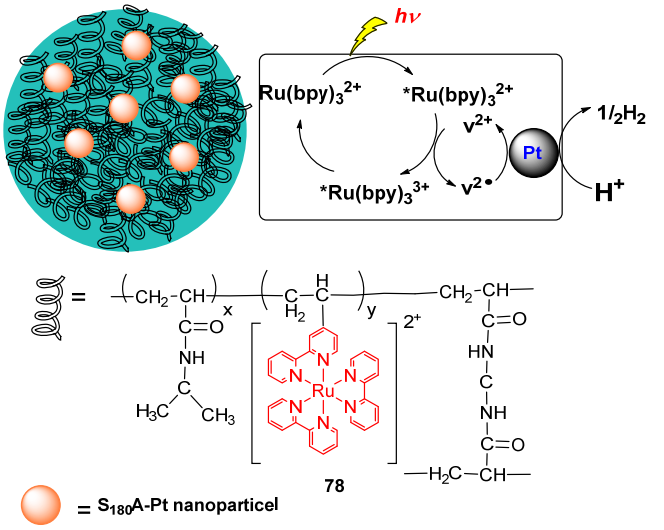


Figure 19 [Ru(bpy)$_3$] photosensitizers: copolymerized poly(*N*-isopropylamide-co-Ru(bpy)$_3$) and Pt nanoparticles for H_2 generation.[499]

5. Conclusions and Outlook

PDT is a promising therapeutic technique for tumor treatment and microbial infections but is only slowly gaining full traction. This is mainly due to scarcity of translations studies and shortcomings in the classical PS drugs. Hydrogels offer one additional tool to overcome some of the current drawbacks of PS formulations. They are easily prepared, allow room for inclusions of co-effectors and/or targeting units and can be used to either covalently or noncovalently bind drug/PS payloads. From an organic chemist's perspective, they offer a simple approach to solubilize water-insoluble PSs without having to 're-invent' the synthetic sequence for water-soluble derivatives.[28] They can also be used to improve the pharmacokinetics of hydrophilic PS-pro-drugs. Likewise, 'nano-sized' polymeric scaffolds of hydrogels can potentially transport a high payload to the target site *via* the enhanced permeability and retention effect if solid tumors are targeted. Surface modification and functionalization of hydrogels are facile means to increase the selective mode of action of photosensitizers and transport across biomembranes. Additionally, the photophysical properties of the PS formulated in hydrogels are often superior to those of the PS alone.[387] For example, the enhanced fluorescence intensity achieved with hydrogel formulations facilitates their use in imaging-guided PDT.[347]

Additional benefits arise from specific hydrogel properties (injectable, self-healing), the ability to pattern the gels,[293] control of the sol-gel transition,[500] and from advanced drug delivery techniques. For example, recently, the permeability and oral bioavailability of non-permeable drugs such as acyclovir was significantly enhanced by encapsulating the drug into the photo-cross-linked hydrogel matrix of PMMA in a microdevice.[501] The

recently developed hydrogel-forming microneedles offer a promising approach as minimally invasive and biocompatible transdermal drug delivery devices,[502] *e.g.*, for controlled drug delivery of metformin[503] and ALA.[332]

The range of possible medical applications of hydrogels constantly expands. This might be among other things due to the chemical, physical and biological flexibility of these systems, which makes them the material of choice for a broad range of applications. Hence, they have recently been used not just for drug delivery but also as artificial muscles, for wound dressings, wearable sensors, bioimaging, and for tissue engineering.[504] Another example are DNA nanohydrogels based on aptamers which are now developed for gene therapy,[505] virus-mimetic gels are used for specific drug delivery,[278] and hydrogels are suggested for use in immunotherapy.[506] Besides hydrogels which only carry one type of drug also multimodality systems can be obtained. Such systems often incorporate several different therapeutic methods. Hence the hydrogel could be loaded for instance with both drugs and photothermal agents, once again showcasing the enormous flexibility of hydrogels. Not all of this relates directly to PDT, but it indicates the multifaceted roles of hydrogels and their potential for the development of new therapeutic combination approaches in photomedicine. An interesting example is the report by Weber and coworkers from earlier this year describing the application of optogenetic with cyanobacterial phytochrome as photoreceptor for tuning the mechanical properties of hydrogels.[507] While applied to investigating mechanosignaling pathways in human mesenchymal stem cells, it also shines a light on possibilities for optically controlled drug depots.

In future, supramolecular chemistry will help to design gels with modifiable characteristics that can be synthesized in aqueous environments, thus having desirable characteristics and a predefined activity. One may even envisage biorthogonal approaches for photoactive systems. Clearly, the use of hydrogel-based PS systems is a promising and versatile approach for translational and technological advances in the PDT area and allied fields.

Conflicts of interest

There are no conflicts to declare.

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Abbreviations

AFM – Atomic force microscopy; AFPAA – amine functionalized polyacrylamide; ALA – δ-aminolaevulinic acid; ALA-PDT – aminolaevulinic acid-photodynamic therapy; AuNP – gold nanoparticles; BODIPY – boron-dipyrromethene; BODIPY-MA – BODIPY methacrylic monomer; BODIPY-NMe – 2,6-diiodo-1,3,5,7,-tetramethyl-8-(*N*-methyl-4-pyridyl)-BODIPY iodide; BP – black phosphorous; CIN – cervical intraepithelial neoplasia; CPAT – chemiluminescent photodynamic antimicrobial therapy; DPBF – 1,3-diphenylisobenzofuran; DMA – dynamic mechanical analysis; DMPA – 2,2'-dimethoxy-2-phenyl-acetophenone; ECM – extracellular matrices; FRET fluorescence resonance energy transfer; HAL – ALA hexyl ester; hexylaminolevulinate; HPMC – hydroxypropyl methylcellulose; HPPH – 2-devinyl-2-(1-hexyloxyethyl) pyropheophorbide; LCST – lower critical solution temperature; LED – light emitting diode; MB – methylene blue; MEO_2MA 2-(2-methoxyethoxy)ethyl methacrylate; MN – microneedle; MRE – magnetic resonance elastography; MRSA – methicillin-resistant *Staphylococcus aureus*; *m*THPP – 5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin; NH_2-TPP – 5,10,15,20-tetrakis(4-aminophenyl)porphyrin; NIR – near infrared; PAA – poly(acrylic acid); PACT – photodynamic antimicrobial chemotherapy; PAM – poly(acrylamide); P(Am-co-BMA) – poly(acrylamide and butyl methacrylate); Pc – phthalocyaninato; PCI – photochemical internalization; PDD – photodynamic diagnosis; PDEAAm – poly(*N,N*-diethylacrylamide); PDEAEM – poly(*N,N'*-diethylaminoethyl methacrylate); PDMS – poly(dimethyl siloxane); PDT – photodynamic therapy; PEG – poly(ethylene glycol); PEGDA – poly(ethylene glycol)-diacrylate; PEO – poly(ethylene oxide); PETA – pentaerythritol triacrylate; pHEMA – poly(2-hydroxyethyl methacrylate); PMA – poly(methyl acrylate); PMMA – poly(methyl methacrylate); PNIPAAm – poly(isopropylacrylamide); PPO – poly(ethylene oxide); PPIC – protoporphyrin IX; PS – photosensitizer; PTT – photothermal therapy; PUVA – psoralen and ultraviolet A; PVA – poly(vinyl alcohol); ROS – reactive oxygen species; SAOS – small amplitude oscillatory shear; TMPyP – 5,10,15,20-tetrakis(*N*-methyl-4-pyridyl)porphyrin tetra tosylate; $TPPS_4$ – 5,10,15,20-Tetrakis(4-sulfonatophenyl)porphyrin; TRIPOD – 2,4,6-tris(*p*-formylphenoxy)-1,3,5-triazine; TTA-UC – triplet-triplet annihilation photon upconversion.

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Bhavya Khurana, B.Sc. Life-science, completed undergraduate studies at Miranda House, University of Delhi, India (2015) and obtained a M. Sc. Chemistry from Thapar University, Patiala, India (2017). In 2017 she started postgraduate studies at Trinity College Dublin on the formulation of photosensitizers with polymeric hydrogel platforms. Currently, she is part of a collaborative H2020 Marie Skłodowska-Curie project ('POLYTHEA'). Supervised by Prof. Vincent Sol (U Limoges) and Prof. Dr. Mathias O. Senge she aims to synthesize biopolymeric or polymeric hydrogel formulations with different photosensitizers against the antimicrobial strata. Her interests are materials science, nanochemistry, synthetic organic chemistry, and photomedicine.

Piotr Gierlich

In 2018, Piotr Gierlich graduated from Poznan University of Medical Sciences with a master's degree in Pharmacy. His master project was performed in collaboration with the University of Southern Denmark, where he studied photosensitizer drug release from bifunctional liposomes. Currently, he is pursuing his Ph.D. studies as an Early Stage Researcher in the Marie Skłodowska Curie actions Horizon2020 ITN, 'POLYTHEA' programme, which targets the development of photodynamic therapy for anticancer and antimicrobial applications. While his background is in pharmaceutical sciences, his main interests are medicinal chemistry and all aspects of phototherapy.

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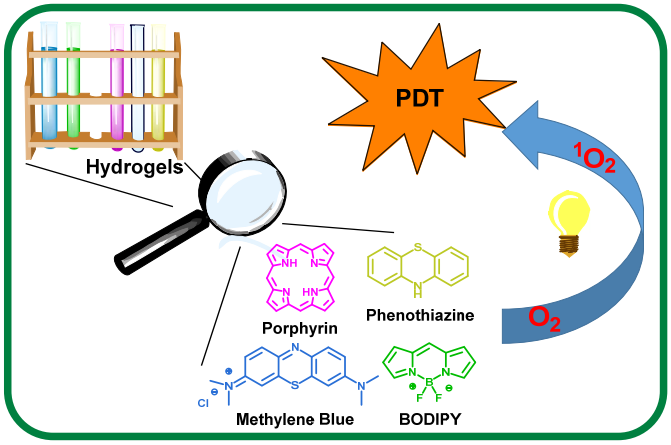
Alina Meindl

Alina Meindl studied technical chemistry (B.Sc. 2014) at the Vienna University of Technology. Her postgraduate studies in synthetic organic chemistry with Prof. Senge at Trinity College Dublin (Ph.D. 2018) focused on the functionalization of unsymmetrically substituted porphyrins as well as methods development for electron-transfer donor-acceptor compounds. She currently is a postdoctoral researcher in the Senge group, exploring long-wavelength absorbing π-extended porphyrins.

Mathias O. Senge

Mathias O. Senge, Dipl.-Chem., M.A., Dr rer. nat., F.T.C.D., studied chemistry and biochemistry in Freiburg, Amherst, Marburg, and Lincoln. After a Ph.D. from the Philipps Universität Marburg (1989) and postdoctoral studies with K. M. Smith at UC Davis he received his habilitation in Organic Chemistry in 1996 at the Freie Universität Berlin. From 1996 on he was a Heisenberg fellow at the Freie Universität Berlin and UC Davis and held visiting professorships at Greifswald, Potsdam, and TU Munich. In 2002 he was appointed Professor of Organic Chemistry at the Universität Potsdam and since 2005 holds the Chair of Organic Chemistry at Trinity College Dublin. He was the recipient of fellowships from the Studienstiftung des Deutschen Volkes, the Deutsche Forschungsgemeinschaft, and Science Foundation Ireland (Research Professor 2005–2009). His interests are synthetic organic chemistry, the (bio)chemistry of tetrapyrroles, photobiology and photomedicine, structural chemistry, and history of science and are reflected in over 340 publications.

ToC graphic



ToC text entry

Photodynamic therapy is a powerful and reliable tool in photomedicine. To bring this therapeutic technique to its full potential limitations such as drug solubility and targeting need to be overcome. Using hydrogels as carrier systems and formulations for photosensitizers offers significant potential for cancer treatment and combating infections and other areas in medicine where light is used to control molecular properties and therapeutic effects.