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Review Article

Soft versus hard nanoparticles in the delivery of aromatic macrocycles for photodynamic therapy of cancer

Alejandro Díaz-Moscoso

School of Chemistry, University of East Anglia, NR4 7TJ, Norwich Research Park Norwich, United Kingdom.

a.diaz-moscoso@uea.ac.uk

ABSTRACT

Background: Photodynamic therapy is a medical strategy to treat some types of cancer. It is based on the use of a photosensitiser, usually porphyrin or phthalocyanine derivatives, to generate toxic species in the cells upon light irradiation. **Aim:** An overview of the different types of nanoparticles already investigated to deliver the photosensitisers until its target is given in this review. **Materials and Methods:** Previous literature and various scientific search engines were used for the review. **Results:** A classification of the nanoparticles based on the nature of their components, 'hard'-inorganic and 'soft'-organic, is made and several advantages and disadvantages about their uses are pointed out. Also, a comparative summary is outlined. **Conclusion**: There are still some drawbacks that need to be sorted out for photodynamic therapy to become a generalised cancer treatment. These could be overcome by using nanoparticles as carriers for the photosensitisers.

Key words: Nanoparticles, photodynamic therapy, porphyrins, phthalocyanines, drug delivery, photosensitisers

INTRODUCTION

Photodynamic therapy (PDT), a clinical technique employed in the treatment of many types of cancer. After more than 30 years of recognised use, its efficacy as curative and palliative treatment is well documented. It has been shown to be very effective especially in small superficial tumours.[1]

The use of PDT has several advantages if compared with other usual treatments for cancer. Unlike surgery, it is a non-invasive treatment and healing occurs with minimal or no scarring, what makes the patients recover their normal life much easier. Besides, the treatment can be repeated without cumulative toxicity if recurrence occurs or a new tumour appears in a previously treated area (such possibility is very difficult for either radiotherapy or surgery, without the risk of severe damage to normal tissue. This treatment involves just two, quite simple, main steps: the administration of a photosensitive drug (typically by a single injection) and the irradiation of the tumour to activate the drug. PDT can even initiate an immune response against remaining malignant cells. Another advantage of PDT is that it does not need any large and expensive equipment.

For the irradiation, conventional broad-spectrum light sources could be used to activate the photosensitive drug. That means that even direct sun exposure could be used to treat some tumours. Nevertheless, it is usually preferable to control the dose of light used and avoid an excess of UV radiation that could cause additional damage. For these reasons, it usually employs LASER sources, which give a precise wavelength light beam that can be easily focused on the tumour. Some sources even incorporate an internal light dosimetric calculator and contain pre-set treatment

programs, what makes them more user-friendly. Light emitting diodes (LEDs) also can be used for PDT. These devices are cheaper, smaller and provide high power in a range of different wavelengths. In addition, the use of optical fibre technology makes the administration of the light an easy, very reliable and precise process.[2] Thus, PDT is cost-effective and it also increases life expectancy compared with other treatment modalities.[3,4]

Looking at these results, since PDT is efficacious with no documented long-term toxicity, and the fact that it was used for the treatment of cancer for the first time more than 100 years ago, one wonders why PDT has not yet become a paradigmatic therapy for the treatment of much types of cancer and is still overcome by surgery, radio- or chemotherapy in many cases. The fact is that there are still some problems that need to be solved for PDT to become a broad anticancer treatment. Some side effects have been reported when using inappropriate PDT schedules, especially in hollow organs such as the oesophagus[5] and bladder.[6] It can also cause temporary skin photosensitisation. Besides, the toxic species created after irradiation to kill the tumour cells are highly reactive and can only diffuse through tens of nanometres during their lifetime. At the time of illumination, the photosensitive drug must be close to the target. This makes PDT suitable only for localized and not systemic diseases. Finally, the wavelength of light used to excite currently approved drugs for PDT can penetrate in the organic tissues up to a maximum of 10 mm.[7] This can be seen as an advantage because this spares healthy tissue beneath the tumour from phototoxicity, but results useless for the direct irradiation of inner and/or bigger tumours.

Light-induced local production of toxic species is a mechanism for PDT. Singlet oxygen ($^1O_2$) is believed to be a major cytotoxic specie in this process, although other kinds of toxic radicals can be formed.[8] This molecular entity triggers peroxidative reactions that can cause direct damage in cells and lead to their death by inducing apoptosis and/or necrosis. Recent studies demonstrate that it also destroys the vessels of the tumour and the surrounding healthy vasculature, leading to hypoxia and starvation of the malignant cells.[9] The singlet oxygen is formed from natural (triplet) oxygen by the action of a photosensitiser, an entity able to absorb energy from light and transform it into chemical energy.

Many compounds have been used as photosensitisers, which include Rhodamine, fullerenes (C60), antraquinone, 5-aminolevulinic acid, and phenothiazinium,[10] but the use of those based on macrocyclic aromatic rings, like porphyrin and phthalocyanine derivatives (including chlorins), are by far the most studied and used. The structures of some of these photosensitisers are shown in Figure 1.

MACROCYCLIC AROMATIC PHOTOSENSITISERS

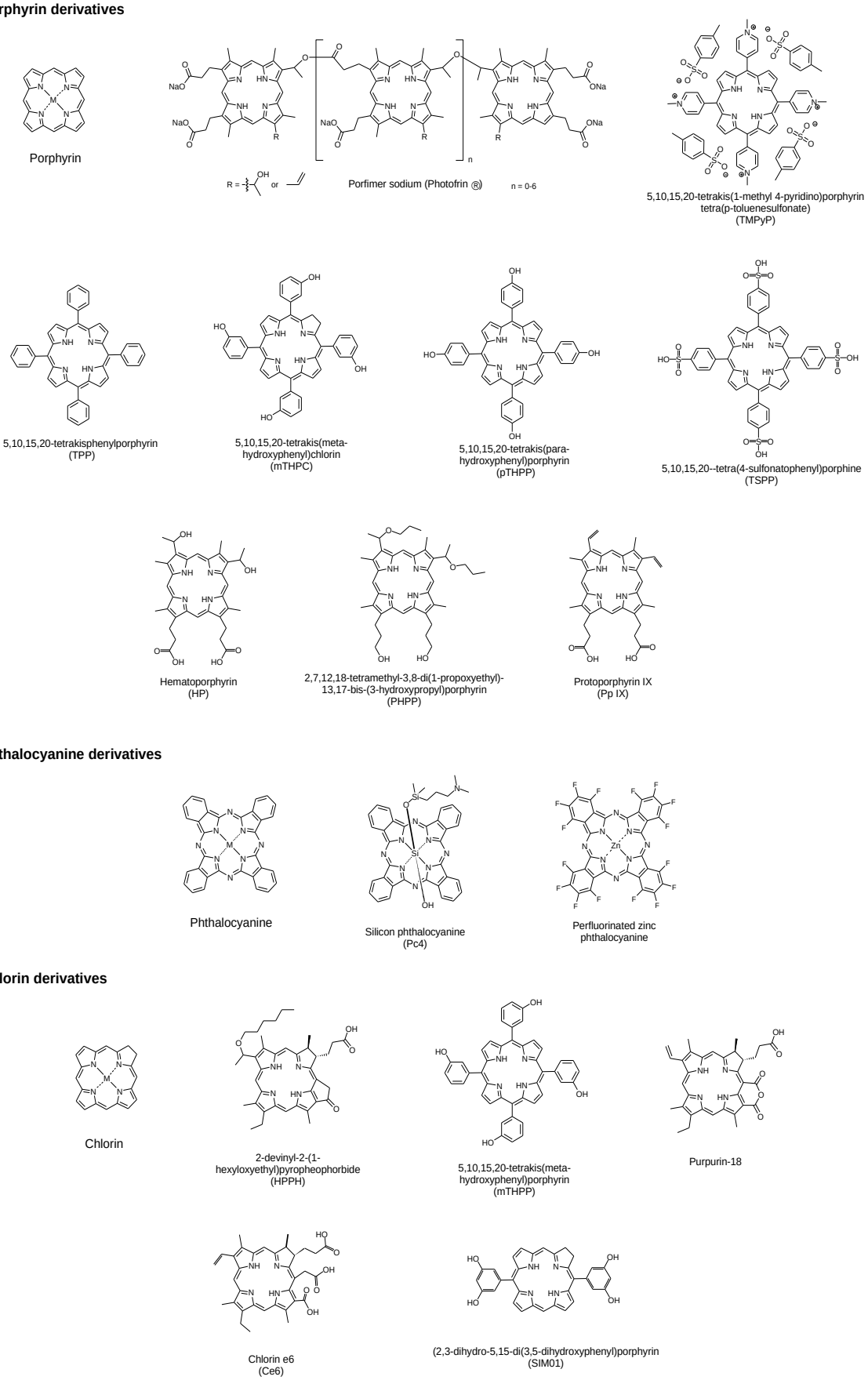
Porphyrins and phthalocyanines are heterocyclic aromatic macrocycles widely present in nature as the active core in molecules of vital importance as chlorophylls[11] or haemoglobin.[12] The natural importance of these compounds is closely related to their unique properties, given by the combination of a highly conjugated ring and their capacity of hosting metal cations. This combination makes them able to effectively harvest the sun light, giving them bright colours, and catch small molecules by co-ordination on the metal. These characteristics make them also very valuable compounds to use as molecular photosensitisers in PDT.

In fact, several PDT treatments using this kind of compounds have been approved during the last decades. In 1993, porfimer sodium (Photofrin ®; Axcan Pharma Inc., Mont-Saint-Hilaire, Canada) was used in the treatment of bladder carcinoma in Canada, and more recently, the *meta*-tetra-hydroxyphenyl-chlorin (mTHPC, temoporfin, Foscan®; Biolitec Pharma Ltd., Dublin, Ireland) (Figure 1).

An ideal photosensitiser should have a stable composition and be easily synthesised or readily available. It should be non-toxic in the absence of light (to avoid undesired side effects), photostable, and should have a low self-aggregation tendency. It should also absorb light in the red region of the spectrum (ideally in the near infrared, around 1000 nm wavelength, where the absorption by other components of biological tissues is minimal,[13] thus allowing a deeper light penetration and less phototoxicity) with high extinction molar coefficient (leading to excited states with relatively long lifetimes and with such energy levels that can convert light energy into chemical energy by generating radical species). It should be hydrophilic or be encapsulated inside appropriate carriers to allow a proper distribution trough the body aqueous media. It should be quickly cleared from the body after treatment and, when

possible, it should have target specificity.[14]

Porphyrin derivatives



Phthalocyanine derivatives

Chlorin derivatives

Figure 1. Molecular structures of porphyrin, phthalocyanine and chlorine cores and some related photosensitisers studied for PDT (M could be a metal or two hydrogen atoms).

Although, there is no such photosensitiser that fulfils all these ideal characteristics, porphyrin and phthalocyanines-related compounds have most of them. However, they also present some drawbacks to be used as photosensitisers such as poor water solubility or high aggregation of some derivatives (mainly in the case of phthalocyanines), and inadequate selectivity or low excitation wavelength (in the case of porphyrins).

These problems are being addresses with promising results. One way of improving the characteristics of these compounds is designing and synthesising new derivatives based on these macrocyclic molecules. A proof of the efforts in this sense can be seen on the great variety of structures studied as shown in Figure 1. Among these structures, we can find compounds with improved water solubility or with longer excitation wavelengths. Also, derivatives conjugated with other structures that provide them additional functionalities have been synthesised,[15] but the synthesis and purification of these derivatives is often quite challenging, what hampers their availability at big scale.

Other way to manipulate their properties is to use nanoparticles. Nanoparticles have become in the last years a very attractive way to deliver all kinds of therapeutic agents, from classical drugs[16] to genes.[17] These 'nanospheres', with typical diameters between 5 and 250 nm, can improve the bio-distribution, pharmacokinetics and targeting properties of other molecules embedded within them or covalently attached to them. PDT could not remain isolated of this treading topic. For example, silica nanoparticles have been described in which HPPH (a porphyrin based photosensitiser in phase I/II clinical trials for oesophageal cancer) has been mixed with an 'antenna compound' which enable its activation at higher wavelength (from 420 to 850 nm).[18]

NANOPARTICLES IN PDT

Nanoparticles can be designed to avoid enzymatic degradation, protecting the photosensitisers or even resist microbial attack. Nanoparticles with specific pore size can intake or release specific compounds like oxygen species without a direct interaction of the photosensitiser with the media. Nanoparticles can also penetrate deep into tissues through fine capillaries. Besides, nanoparticles do not trigger immune responses when introduced in the body. Nanoparticles are multifunctional platforms where several new elements can be attached to perform specific tasks to improve their performance depending on their goal; targeted delivery, stimuli response, imaging and treatment. The last one is probably the most appealing characteristic for scientists.

There have been several reports of nanoparticles as carriers for photosensitisers, even for non-anticancer therapies.[19] In this review, an overview of all kind of nanoparticles used for PDT of cancer using aromatic macrocycles as photosensitisers is given, trying to identify their advantages and drawbacks. With this goal, a classification is presented according to the nature of the nanoparticles, distinguishing them between 'Hard nanoparticles', including those particles made by inorganic materials that keep their original shape and size during all the process, and 'Soft nanoparticles', made by organic materials that are susceptible to size and shape change, to some extent, when facing different biological conditions such as pH, ionic strength, and pressure. Out of the scope of this review remains other nano-carriers used in PDT not considered as nanoparticles (even by the own authors in most cases) like carbon nanotubes or gold nanorods. An overview of the nanoparticles-photosensitiser complexes reviewed in this paper according to their disposition can be found on Figure 2.

HARD NANOPARTICLES

Silica nanoparticles

Silica nanoparticles (SiO_2) are chemically inert, thus avoiding interactions with other molecules in the body. Besides, a variety of well known and optimised methods are available for their synthesis, allowing precise control their particles size, shape, porosity and polydispersity during the preparation.[20] These particles allow to incorporate small molecules encapsulated within the own particle or covalently attached to the surface. These interesting properties have made silica nanoparticles the most studied nanoparticle-based PDT systems.

The delivery of photosensitisers embedded in porous silica nanoparticles has many advantages. First, almost any type of photosensitiser can be used. Second, the concentration of photosensitiser can be modulated as needed (increasing or decreasing it). Also, the silica surface offers the possibility for further functionalisation. One of the first papers reporting the use of these agents compare free m-THPC and m-THPC

embedded in silicon-based nanoparticles, showing a good spectral correspondence between them and an improved singlet oxygen production by the nanoparticles in comparison with free m-THPC.[21] Nowadays, almost all silica nanoparticles with embedded photosensitisers are prepared following the method designed by Prasad's group[22] which gives particles of 25-35 nm of diameter. This method has been used to encapsulate even highly hydrophobic photosensitisers like Pc4, improving the aqueous solubility, stability, delivery and PDT efficiency of the drug.[23]

In vivo studies have shown that silica nanoparticles with embedded photosensitiser PpIX accumulate in tumours better than the PpIX alone, but also accumulate in large amounts (even more than in tumours) in healthy tissues, specially into the liver.[24]

When the photosensitisers are incorporated onto silica nanoparticles trough covalent bonds, it is possible to avoid the eventual release of the compounds in the media, and the consequent lost of efficacy or the appearance of side effects. The main examples use PpIX covalently bonded through its acid groups to amino-functionalised silica nanoparticles,[25] showing no changes in the photosensitiser properties and even an improved integrity under laser irradiation.[26]

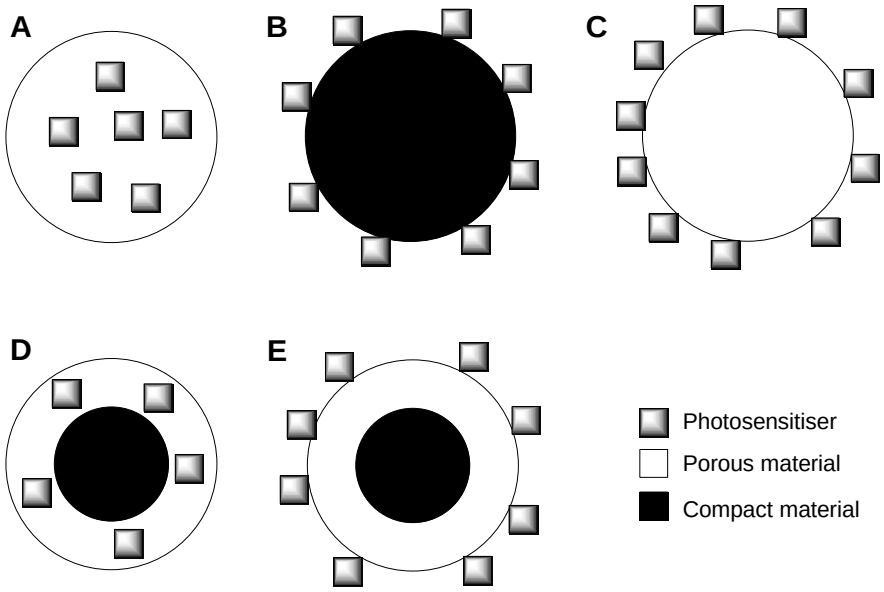


Figure 2. Schematic representation of the different kind of nanoparticles used as carriers for photosensitisers in PDT. A) Porous material with embedded photosensitiser (soft and silica nanoparticles). B) Compact material with photosensitisers covalently bonded (hard nanoparticles except silica). C) Porous materials with covalently bonded photosensitisers (soft and silica nanoparticles). D) Nanoparticles with compact core covered by a porous material with the photosensitisers embedded (hybrid nanoparticles and silica-coated hard nanoparticles). E) Nanoparticles with compact core covered by a porous material with the photosensitisers covalently bonded (hybrid nanoparticles and silica-coated hard nanoparticles).

The first attempt to target hard nanoparticles for PDT by incorporating recognition motifs was done with silica nanoparticles.[27] In this study, targeting breast cancer cells with mannose was necessary to get a high PDT efficacy. The involvement of mannose receptors in the active endocytosis of mannose-functionalized nanoparticles was demonstrated.

Finally, several of the hard nanoparticles that are presented ahead, have been coated with silica shells to take advantage of the properties already mention for this material, what makes them more versatile. These applications will be exposed in the corresponding section.

Gold nanoparticles

Several authors coupled molecular photosensitisers onto gold nanoparticles.[28] Different photosensitisers have been tested, but the most hydrophobic ones like phthalocyanines need to include a phase transfer reagent on the nanoparticle to be

dispersible in aqueous media.[29] In these systems, a definite rise in singlet oxygen quantum yield has been observed, which can be ascribed to an effect similar to metal enhanced fluorescence.[30,31]

Gold nanoparticles have been targeted to breast cancer cells by incorporating a primary antibody to their surface in addition to a zinc phthalocyanine photosensitiser and a bioavailability and solubility enhancer, with promising results.[32]

In this section can be included a new kind of composite nanoparticles consisting of a gold-silver nanocage core with a porous silica shell functionalized with an ytterbium (Yb) hematoporphyrin (HP) derivative.[33] These particles show an enhanced toxicity on HeLa cells and can also be used as monitoring agents thanks to the infrared emission originated from the Yb^{3+} ions.

An interesting feature of this method is that gold nanoparticles are non-toxic and already in use for other therapies.[34] Thus, it is expected that clinical approval and eventual application of these therapeutics will be easier to be achieved than with more unconventional systems.

Quantum dots

Nanoparticles based on semiconductor nanocrystals also known as Quantum Dots (QDs) can be used as photosensitiser themselves,[35] but that is beyond the scope of this review. On the other hand, it is interesting to note that these nanoparticles have been used as light antennas for molecular photosensitiser directly attached to them,[36] mainly using metalated phthalocyanines like Pc4.[37] This happens because QDs are down-converters, (they emit light of wavelengths longer than their excitation wavelength) with a high and broad light absorption[38] and a large particle surface, what allow them to absorb huge amounts of light and transfer it to the attached molecular photosensitisers, losing their own fluorescence.

The disadvantage of these nanoparticles is that patients might suffer from a heavy-metal poisoning due to the intrinsic components of QDs (Cd, Te, Se). So, it is questionable if a small increase of the efficiency of the photosensitisers compensates the potential risks of QDs.

Magnetic nanoparticles

Magnetic nanoparticles have also been used to deliver photosensitisers by attaching them to the surface of the iron oxide that typically forms these particles. Magnetic nanoparticles are very suitable to address one important challenge in nanomedicine such as integrating tumour targeting, imaging, and selective therapy functions into the same moieties. For example, chlorin e6 (Ce6) has been covalently anchored on the surface of magnetic nanoparticles retaining the spectroscopic and functional properties for both near-infrared fluorescence imaging and PDT.[39]

It is also possible to find examples where the magnetic nanoparticles are covered by a layer of silica,[40,41] what modify some of their external properties maintaining the unique and characteristic properties of the core. In these coated particles, the photosensitisers (purpurin-18, phthalocyanines or PHPP) seem to reduce their photosensitivity, but are still effective for potential PDT applications.[42]

Fe_3O_4-photosensitizer nanoparticles have an special interest because they could be used in combination treatment with both PDT and hyperthermia therapies.[43] Hyperthermia therapy is used to increase the efficacy of various cancer treatments and has been shown to increase the cellular uptake of oxygen molecules, what can increase the concentration of the toxic species (singlet oxygen) generated by the photosensitiser.

Up-converting material nanoparticles

$NaYF_4$ nanocrystals doped with trivalent erbium (Er^{3+}) and ytterbium (Yb^{3+}) are up-converting nanoparticles (emit light of a wavelength shorter than their excitation wavelength). Their advantage for PDT is that their use as delivery agents allows the molecular photosensitiser to be excited using infrared light. That is very convenient because infrared light can penetrate deeper in biological tissues than visible light or ultraviolet light and, besides, this is a softer radiation that would cause less damage in the tissue. The main problem is that their luminescence quantum yield is usually below 1%[44], and that would lead to a poor singlet oxygen production. They have been used to transport zinc phthalocyanine and, for this goal, they have been coated with silica,[45] what makes it possible to increase their bio-compatibility and to encapsulate the photosensitiser.

Luminescent nanoparticles

The scintillation nanoparticles have the characteristic of emitting persistent luminescence upon exposure to ionizing

radiation such as X-rays. This characteristic allows the simultaneous use of conventional radiation therapy and PDT. In this way PDT can augment the effectiveness of ionizing radiation and lead to the use of lower doses of radiation, reducing the damage to healthy cells and the costs of the therapy.

After the irradiation with X-rays, the nanoparticles emit luminescence for a prolonged period, this activates the photosensitisers attached producing singlet oxygen without using an external light sources. For this goal, porphyrins can be attached covalently to several doped nanoparticles ($LaF_3:Ce^{3+}$, $LuF_3:Ce^{3+}$, $CaF_2:Mn^{2+}$, $CaF_2:Eu^{2+}$, $BaFBr:Eu^{2+}$, $BaFBr:Mn^{2+}$, $CaPO_4:Mn^{2+}$) and semiconductor nanoparticles (ZnO, ZnS, TiO_2).[46]

SOFT NANOPARTICLE

Biodegradable polymers

Administration of drugs embedded into bio-degradable polymer nanoparticles is a technique that is rapidly emerging. This variation of drug delivery is based on the principle that the drug is released as the polymer particles degrade in the biological environment.[47] Although the biodegradability is not a requirement for the nanoparticles used for PDT, the biodegradation may enhance their bio-elimination rate. The capacity of the photosensitisers to induce phototoxicity depends on the nature of the polymer used; moreover, the polymer itself can also act as an impermeable barrier and prevent molecular oxygen from interacting with the photosensitiser.[48]

Poly(lactic-co-glycolic acid) (PLGA) has shown several advantages over other biodegradable polymers that are routinely used for photosensitiser delivery,[49] and has become the most popular polymer for PDT. It is a co-polymer of poly lactic acid (PLA) and poly glycolic acid (PGA). PLGA is biocompatible, exhibits a wide range of erosion times, has tuneable mechanical properties and is FDA approved.[50] The degradation of PLGA is affected by several factors and it is necessary to properly balance them during the design of the nanoparticles to get the best results during the whole process (encapsulation of the drug, transport and release).

It has been shown that the size of PLGA 50:50 nanoparticles with m-THPP as photosensitiser influences their photodynamic activity (bigger size, lower activity), but it also affects their interaction with the biological environment (protein absorption, cellular uptake or tissue distribution).[51]

The hydrophilic-hydrophobic balance is one of the most important characteristics of these kind of nanoparticles and it has been demonstrated to play an important role in the biodegradation rate.[52] The importance of the hydrophobicity of nanoparticle in pharmacokinetics and pharmacodynamics has been assessed by comparing the bio-distribution of a perfluorinated phthalocyanine incorporated into PLA nanoparticles coated with poly (ethyleneglycol) (PEG) or into non-coated PLA nanoparticles. PEG-coated nanoparticles exhibited a very different blood clearance, which reflected an extended circulation of the dye and reduced uptake by monocytes. As a consequence, the bioavailability of the photosensitiser was significantly enhanced.[53]

In other cases, there are third molecules playing an important role in the final performance of the nanoparticles. For example, the poly(vinyl alcohol) (PVAL), which is very often used as a stabilizing agent, was found to modify the surface characteristics of PLGA nanoparticles containing p-THPP. PVAL seems to have certain affinity for the photosensitiser, inducing the adsorption of PVAL onto the surface of the nanoparticle and leading to higher clearance of the complex.[47]

Non-biodegradable polymers

The use of non-biodegradable nanoparticles has some advantages with respect to their degradable counterparts. As the nanoparticle keeps its integrity, the photosensitiser has a permanent protection from the environment; besides, it is possible to use the nanoparticles as platforms to incorporate additional functionalities and they can be of smaller size.

Polyacrylamide polymers have been used to make non-degradable nanoparticles able to diagnose brain cancer due to the presence of a magnetic resonance imaging (MRI) contrast enhancer in addition to the photosensitiser (Photofrin), PEG to increase the biocompatibility and molecular targeting groups for specific cell targeting.[54] These nanoparticles kept their integrity over several months and were effective with just 5 minutes of irradiation.

5,10,15,20-tetrakis(1-methyl-4-pyridino)porphyrin tetra(*p*-toluenesulfonate) (TMPyP), has also been encapsulated in polyacrylamide-based nanoparticles. Its

phototoxicity with two photon IR radiation was demonstrated *in vitro* by modulating the time of exposure to light.[55]

Liposomes

Liposomes are artificial vesicles composed of a lipid bilayer usually used for the formulation and delivery of all kind of drugs. They have been also largely investigated as carries and enhancers for PDT using different strategies (basic or targeted liposomes or even with stimuli triggered effects).[56]

The benzoporphyrin derivative monoacid ring A (BPD-MA) has been used for antiangiogenic PDT encapsulated in polycationic liposomes modified with cetyl-polyethyleneimine. The encapsulated photosensitiser was better internalised by human umbilical vein endothelial cells and was found inside the nucleus and associated with mitochondria.[57] The commercial liposomal preparation of this same photosensitiser (Visudyne; Novartis) is active against tumours in sarcoma-bearing mice.[58]

Photofrin loaded into PEG modified liposomes presents enhanced phototoxicity compared to the free drug or when embedded in the same non-PEGylated liposomes.[59] Although the presence of the PEG inhibited the uptake of the nanoparticles by the tumour cells, it decreased the release of the photosensitiser from the liposome.

Another porphyrin derivative (2,3-dihydro-5,15-di(3,5-dihydroxyphenyl)porphyrin (SIM01)) in dimyristoylphosphatidylcholine liposomes also yields better results in PDT than the photosensitiser alone, mainly due to a major accumulation in the tumour cells (human adenocarcinoma in nude mice).[60]

Liposomal TPP is effective in PDT of human amelanotic melanoma in nude mice; after being intravenously administered, authors demonstrated that their use can totally disintegrate tumours.[61]

Cyclodextrin-based nanoparticles

Cyclodextrins are natural cyclic oligosaccharides with very attractive properties. They are highly symmetric, bio-compatible and non-immunogenic. Cyclodextrins present two faces with opposite orientation and an inner cavity with hydrophobic inclusion properties. Besides, they can be precisely modified by chemical reactions on both faces and are commercially available. All this have made them valuable molecules for medical, cosmetic and alimentary applications.[62]

Nanoparticles of cationic amphiphilic cyclodextrins encapsulating TPPS with molar ratios between 10:1 and 50:1 has been shown to maintain the photodynamic characteristics of the entrapped photosensitiser. The triplet state of TPPS is populated and as a result, able to generate singlet oxygen with quantum yield similar to the free TPPS. *In vitro* studies on tumour HeLa cells have proven the photodynamic efficacy of the carrier/sensitizer system.[63]

HYBRID NANOPARTICLES

Several authors have tried to get the advantages of both kinds of systems (hard and soft) creating hybrid nanoparticles. Typically, these systems contain a hard core surrounded by a layer of soft material, what enhances their biocompatibility and facilitate their further functionalisation, maintaining the unique properties of the inorganic core.

Silica nanoparticles have been coated with poly-(L-lysine) and hyaluronic acid by using the layer-by-layer method. Hyaluronic acid is able to target colorectal cancer cells.[64] In this case, the coating itself acts as targeting moiety for the particle with embedded TSPP as photosensitiser, demonstrating enhanced biocompatibility, efficacy and accumulation in tumours (allowing tumour regression) in preclinical studies.

Iron oxide nanoparticles has been coated with polyacrilamide to enhance their biocompatibility and provide a platform to easily bind PEG and targeting elements, obtaining versatile nanoparticles suitable for imaging and treatment (with Photofrin), with enhanced biodistribution.[65]

It is also possible to find examples where the magnetic nanoparticles are covered by a layer of other materials like chitosan, providing enhanced biocompatibility, biodegradability, non-toxicity and water solubility for PHPP without compromising their magnetic targeting.[66] These nanoparticles showed efficacy *in vitro* and *in vivo* with attenuated hepatotoxicity.

$NaYF_4$ nanocrystals have been coated with poly(ethylenimine) (PEI),[67] that allows the incorporation of folic acid as targeting moiety. Thus, colon cancer cells could be targeted for imaging and photodynamic treatment by irradiation of the zinc phthalocyanine

incorporated with infrared photons.

Also gold nanoparticles have been prepared with a PEI coating[68] in order to get positively charged nanoparticles able to absorb negatively charged PpIX and enhance their dispersion in water media. These coated gold nanoparticles shown to have a size dependent efficacy for PDT.

Other authors have covered gold nanoparticles with specifically modified amphiphilic cyclodextrins, forming water-soluble particles able to encapsulate photosensitiser for PDT within the coating layer.[69]

CONCLUSION

In summary, several nanoparticulated systems have been used during the past years to transport photosensitiser into tumour cells. Both inorganic and organic materials-based nanoparticles have shown specific and very interesting properties to improve the performance of the aromatic macrocyclic molecules used as photosensitisers. Silica based nanoparticles and liposomes seem to be at the forefront of this research.

Although, metal-based nanoparticles provide some attractive physical properties, their use could lead to intoxication by metals and, besides, their commercial availability could be a serious drawback for some applications including rare elements. In this sense, silica based nanoparticles seems to have a great advantage.

The use of organic materials lead to more biocompatible nanoparticles, usually with better pharmacokinetics and pharmacodynamics, but require a refined design of the systems to take all the possible factors that could modify their performance *in vivo* into account since they are more exposed to the biological conditions. Besides, it is difficult to predict an accurate release profile for the photosensitiser molecules from degradable systems.

The use of hybrid particles is emerging as a promising technique that, with a careful design, could merge the advantages of both kinds of systems.

On the other hand, during the last decades, medicine has been looking for inert materials to use in all kind of medical applications, what moved the PDT researchers to investigate particles made of inert materials, like silica and gold, that could be easily approved for their medical use. Nevertheless, the search for new medical materials is suffering a deep change in this sense, moving quickly from biologically inert materials to biologically interactive materials that could give a real-time response to the events occurring within the body. This idea, together with the fact that comparative studies with the same photosensitising phthalocyanines show better results *in vitro* for liposome carriers than for gold nanoparticles,[70] lead to think that the future research in the field of nanoparticles as carriers, not only for PDT but also for other therapies, will be dominated by the use of 'intelligent' organic materials.

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