INFLUENCE OF NANOPARTICLES AS DELIVERY AGENTS IN PHOTODYNAMIC THERAPY

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ABSTRACT

This paper presents the influence of nanoparticles as the delivery agents in photodynamic therapy for clinical application to overcome variety of cutaneous and sub-cutaneous diseases including cancer due to their less toxicity, super paramagnetic behavior, high magnetization saturation, surface chemistry, stability, size and biocompatibility. Nanoparticles principles and molecular mechanism of action when incorporated with Photosensitizer (PS) has been discussed, whereby introducing the nanoparticles enhance effective treatment in PDT by targeting the cell membrane and deliver the singlet oxygen; which is a powerful oxidant that can react with several kinds of biomolecules, as well as prevent the PS from moving out of the cell by resistive multidrug mechanisms.

Keywords: Photodynamic therapy, Nanoparticles, Drug Delivery.

1. INTRODUCTION

Photodynamic therapy (PDT) is a modern approved treatment modality of many cancers that is believed to operate through cytotoxic singlet oxygen production when light is absorbed by a photosensitizer (PS) and transfer this energy to ground state oxygen from its excited triplet state. The production rate of singlet oxygen solemnly depends on PS absorption, fluence rate, PS concentration and triplet oxygen availability in the tissue. Moreover, high fluence rate accelerates photochemical conversion of triplet to singlet state depletion thereby regulating photodynamic process and tumor control [1].

Photodynamic therapy is of advantage to both the patient and the physician. The need for delicate surgery and lengthy recuperation periods is minimized, along with minimal formation of scar tissue and disfigurement. PDT uses selective irradiation in therapeutic treatment which does not damage tissues that are healthy. This mode of

treating cancer is very fast, easy and causes no pain to the person under cure with least effect. It develops no resistance in case of repeated treatment. It can also be used to treat cancers that are resistance to other medication and heal very fast as the collagen contain in the tissue is not affected by photodynamic damage [2]. Base on these, photodynamic therapy appeared to be a promising way of transforming many of the existing problems in definitive cancer therapies with least effect. In PDT, light photosensitizing drug (photosensitizer), oxygen, and light are combined to have therapeutic effect. The activation of the photosensitizer by exposure to a carefully regulated dose of light of appropriate wavelength for a specified length of time elicits a cytotoxic action resulting in cell death [3].

However, for more effective treatment, Nanoparticles provide new interaction with biomolecules on cutaneous and sub-cutaneous tissues which may raise cancer treatment and diagnostic when used in photodynamic therapy. Nanoparticles are been recognized as a drug transporting system, drug targeting, cell isolation and cell sorting because of their ability to concentrate the photosensitizer (PS) on the wall of cells and result to the activation of the PS to increase deadly destruction on the cell [4].

2. MECHANISM OF PDT

The working principle of photodynamic process is triggered by irradiation of certain PS with light of specific wavelength to produce reactive oxygen species which are the effectors to the antimicrobial activity in the therapy. During photoactivation of the PS, photon of an electromagnetic radiation is absorbs in the form of light energy in which an electron is promoted into a higher energy molecular orbit by elevating the chromophore from the ground state (PS_0) into a short lived electronically excited state (PS_n) composed of a number of vibrational sub levels (PS_n*) [5]. The chromophore can return to the (PS_0) state by either emitting the absorbed energy as fluorescence or by internal conversion indicated in Jablonski Diagram [6], Figure 1.

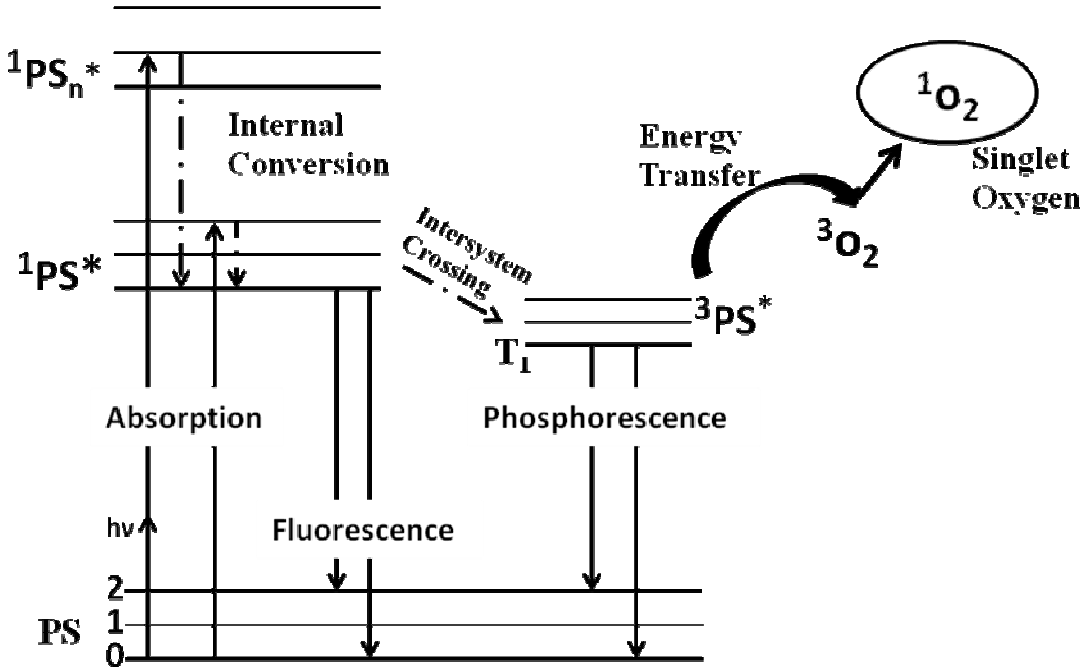

Figure 1. Jablonski Diagram

Alternatively, an excited singlet state electron *(*PS_1*)* undergoes spin inversion and populates the first lower energy excited triplet state (T_1) via intersystem crossing. This transition is spin forbidden, since the spin of the electron is no longer conserved [5]. The T_1 chromophore can return to the (PS_0) state via phosphorescence emission. This T1state is sufficiently long lived to take part in chemical reaction, and therefore the photodynamic action is mostly mediated by the T1 state. The T1 state can undergo two kinds of reactions, *Type I* and *Type II* as presented in Figure 2.

A *Type I* reaction is basically a redox or radical reaction in which an electron or a hydrogen atom from a neighboring substrate molecule reacts with the excited triplet state photosensitizer (P_{sen}) producing a radical anion P^- or cation P^+. This radical anion goes on to react instantly with oxygen to produce superoxide radical anion O_2^- which goes on to generate a highly reactive hydroxyl radical, initiating a cascade of oxygenated products. Triplet excited state photosensitizer can also take part in *type I* reaction whereby Hydrogen atom move to triplet excited state photosensitizer (P_{sen}*) to produce free radicals whose are liable to react with oxygen molecule ($^3O_2$) [6].

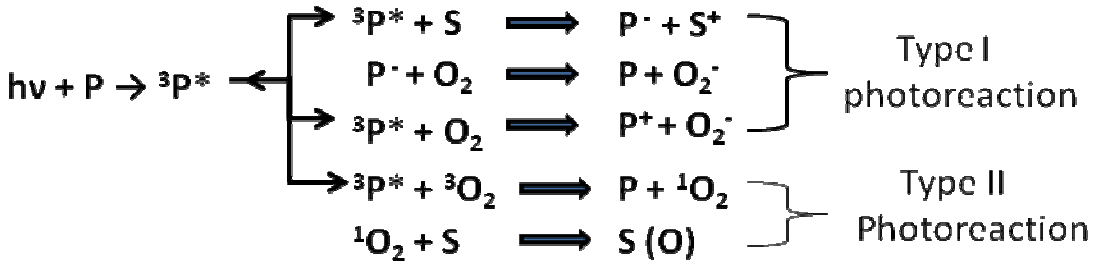

Figure 2. Type I and Type II Photoreactions

In a Type II reaction, which is mostly common, involves the direct transfer of energy from the triplet state photosensitizer to ground state molecular oxygen thereby generating cytotoxic first excited singlet state oxygen. The Singlet-oxygen is a powerful oxidant which can react with several kinds of biomolecules. The existence of the highly reactive oxygen (O) in a cellular environment is short and therefore it reacts at the instance of formation [7].

3. THE NANOPARTICLES

Nanotechnology is now widely applying research and development to medicine, pharmaceutical industry, tissue engineering, electronics, robotics and engineering particle for cell targeting within an organism for either therapeutic or diagnostic purposes. Nanoparticles are applied to target tissue to deliver drugs and enhance stability against degeneration by enzymes [8].

A nanoparticle is a colloidal solid particle sized form 1 to 1000nm. In medicine, nanoparticle can be used to tissue or surfaces that are altered deliberately at nano meter scale sequel to new properties. Shape and chemical composition are also factors that distinguished nanoparticles because (1) many nanoparticles are prepared as colloidal dispersion in biomedicine and (2) their physical properties that differentiate them from atoms and bulk materials. Moreover, Sara and Gregor [9] came along with chemical compounds and shapes of nanoparticles and indicate how they are distinguished besides their size in delivery system. It was also shown that, magnetic and gold nanoparticles are the most widely used nanoparticles in biomedical application as shadowed (Table 1).

3.1. MAGNETIC NANOPARTICLES

Magnetic carriers base on their unique microscopic chemical, physical, mechanical and thermal properties are widely use to drug targeting [10], enzyme immobilization [11], cell sorting and isolation [12], tissue repair [13], tumor hyperthermia [14], cellular therapy [15], magnetofection [16], magnetic field as carrier for radioactive therapies or localizing drug [17] and magnetic resonance imaging, MRI [18] in fields of biomedicine and biotechnology. The iron oxides due to their less toxicity, super paramagnetic behavior, high magnetization saturation and biocompatibility are the most extensively applied magnetic nanoparticles in biomedical application. Magnetic nanoparticles usage in biomedicine is greatly achieved by coating their surfaces with inorganic metals, oxide materials or organic polymers which are biocompatible coating materials that protect the magnetic core and enhance surface functionalization [19].

The effectiveness of cancer therapy can be attributed to the use of magnetic nanoparticles for gene or drug delivery system in many ways; (1) Magnetic behavior determine bio-distribution quantity by MRI which enhance optimal cancer dosing in therapy. (2) Using magnetic nanoparticles to target tumors supplement the difficulty of some therapeutic modality in transporting into the tumor for cancer therapy. (3) Magnetic nanoparticles selectively targeted tumor site for treatment to protect normal cells, reduce side effects and as well minimize cost of treatment. (4) The use of magnetic field as particles driving force to contained the particles in tumor site or target tissue suggests that it is a non-invasive treatment approach [9].

Magnetic nanoparticles are required to bind to drugs, enzymes, nucleotides, proteins or antibodies which were to be directed to tumor, tissue or an organ using an external magnetic field which might also be heated for use in hyperthermia [8].

Table 1. Classification of nanoparticles sized delivery modality by their shape and chemical compounds. The shadowed nanoparticles (Magnetic and Gold) are often used in biomedical application

CHEMICAL COMPOUNDS				SHAPE
ORGANIC	NATURAL	LIPIDS	Egg phosphatidylcholine (EPC), egg phosphatidyl glycerol (EPG)	Liposomes
		PROTEINS	Human serum albumin (HSA), gelatin	Nanoparticles*
		CARBON HYDRATES	Chitosan, alginate	Nanoparticles*
	SYNTHETIC	LIPIDS	Dipalmitoyl phosphatidylcholine (DPPC), dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG), dipalmitoyl phosphatidic acid (DPPA), distearoyl phosphatidylcholine, cholesterol (Ch)	Liposomes
			Tricaprin, trilaurin, trimylistin, tripalmitin with gliceryl monostearate, cetyl palmitate, stearic acid	Solid lipid nanoparticles
		POLYMERS	**Homopolymers**: Poly(alkylcyanoacrylate) (PACA), poly(2-hydroxyethyl methacrylate) (pHEMA), poly(N-(2-hydroxypropyl)methacrylamide (pHPMA), polyvinylpyrrolidone (PVP), poly(methyl methacrylate) (PMMA), polyorthoesters, polycaprolactone (PCL), poly(vinyl alcohol) (PVA), poly(acrylic acid) (PAA), polylactides (PLA) **Copolymers**: Poly(alkylcyanoacrylate)-*co*-poly(ethylene glycol), poly(lactid acid)-*co*-poly(glycolic acid) (PLGA), poly(L,L-lactide-*co*-Laspartic acid), poly(ethylene-*co*-vinyl acetate) (PEVA)	Dendrimers Nanoparicles* Nanocomposites Nanobrushes Nanotubes Micelles Nanogels
		SURFACTANTS	**Cationic**: Sodium dodecyl sulfate (SDS) **Anionic**: Cetyl trimethylammonium bromide (CTAB) **Non-ionic**: Copolymers of poly(ethylene oxide) and poly(propylene oxide)	Micelles
ORGANIC & INORGANIC		LIPIDS	DPPC/Ch/γ-Fe_2O_3, Fe_3O_4	Magnetic liposomes
INORGANIC	MAGNETIC	POLYMERS	Ni-Zn-ferrite/SiO_2, Fe-Ni/polymer, Co/polymer, PMMA/α-Fe_2O_3	Nanocomposites
		COMPOUNDS	Ni-Fe/SiO_2, Co/SiO_2, Fe-Co/SiO_2, Fe/Ni-ferrite, Ni-Zn-ferrite/SiO_2	Nanocomposites
		COMPOUNDS	**Iron:** **γ-Fe_2O_3, Fe_3O_4**	**Nanoparticles***
			$MgFe_2O_4$, $MnFe_2O_4$, FePt, $NiFe_2O_4$	Nanoparticles* Nanorods
			Nickel: NiO, $NiFe_2O_4$	
			Cobalt: Co_3O_4, $CoFe_2O_4$	
			Manganese: Mn_3O_4, MnO_2	
	NON-MAGNETIC		CdSe/ZnS	Nanocrystals
			ZnO, Ag, Au, Cu, CdSe/ZnS, GaN, TiO_2, TiC, VO_2, V_2O_5, PbS, CdS, SiC, $BiPO_4$, AOB	Nanorods Nanoparticles*
			Au	**Nanoparticles***
			Calcium phosphate	Nanocomposites
		ELEMENTS	C	Fullerenes Nanotubes

* Nanoparticles include nanocapsules and/or nanospheres

3.2. GOLD NANOPARTICLES

Gold nanoparticles (GNPs) have surfaced as a wide drug delivery modality. They became known by their surface chemistry, stability, size, biocompatibility and minimal toxicity. Considering biomolecules high binding ability, gold nanoparticles can be applied to transport proteins, nucleic acid and peptides for gene therapy. It can as well be applied as carrier of antibodies, anti-tumor drugs, antibiotics and some variety drugs to selective killing of microbes and diseased cells [20].

Gold nanoparticles strategies for clinical intervention include chemotherapy, radiation therapy and surgery due to their unique properties. In clinical settings, most especially cancer therapy that photothermal is employ to tumor tissue and cancer cell destruction, the irradiated light targeted nanorods, nanospheres, nanocages and nanoshells to kill those tissues or cells [21].

Gold nanoparticle coated with polyethylene glycol (PEG) was developed to increase tumor damage and the reduction of systematic toxicity in drug delivery system [21]. The coated GNP surface gives an amphiphilic room for lipophilic PDT drugs and this drug can be physically ejected until the nanoparticle is released from the drug. The main advantage of this GNP coated PEG is its water solubility, minimal absorption of any protein and can prevent and/or enhance rapid clearance from reticular-endothelium system (RES), as such, drugs on GNP carriers can provide prolong blood circulation time [22].

Gold nanoparticles can be more useful in drug delivery system and some biomedical application both therapy and imaging, if they are specifically and effectively directed to the desired organ or diseased location without any obstruction [21].

4. NANOPARTICLES BIOCOMPATIBILITY

Biocompatibility of nanoparticles is highly required and considered for nanoparticles to be applying in biology. Biocompatible is the ability of materials usually medical, to perform its function without any systematic or undesired local effects. Nanoparticles take part in some domain as proteins because of their size dependent, physical and chemical

properties which make them suitable for labeling and tagging. However, the size of single DNA strain is as 2.5nm wide and that of proteins is 1-20nm in diameter, this size is a characteristic needed by nanoparticle to engage a successful moiety in biology.

Moreover, for nanoparticle to interact effectively with biological target, a molecular biological coating is attached to the nanoparticles which serve as bio-inorganic interface as such antibodies, monolayer peptides or biopolymers (collagen) can act as the bio-inorganic interface [23].

5. DEGRADATION OF NANOPARTICLES

5.1. BIODEGRADABLE NANOPARTICLES

Biodegradable nanoparticles are formed by polymers that undergo degradation in a biological environment and then eject the photosensitizer. Generally, it is believe that the degradation mechanism of aliphatic polyester nanoparticles like poly (DL-lactide-co-glycolide) (PLGA) nanoparticles is comprised of hydrolytic process by considering the possibility of enzyme-catalyzed degradation.

In the research taken by Grizzi et al [24] on hydrolytic degradation nanoparticles size dependence on polymers, heterogeneous degradation assembly of particles (0.5-1m) range were observed in *in vivo* and *in vitro* which were shown to be characterized by degradation greatly at the core than at surface which result to more outer layer formation. In contrast, homogeneous degradation pattern is observed with particles that are less than 300µm in diameter and shows characterization at the core similar to that of the surface.

5.2. NON-BIODEGRADABLE NANOPARTICLES

In non-biodegradation of nanoparticle, time is not needed because the environment protects the photosensitizer and the nanoparticle can be of smaller size which serves as platform for multifunctional settings. Polymers like polyacrylamide can be apply for non-degradable nanoparticles synthesis but mostly, non-degradable nanoparticles are either metallic or ceramic based (i.e. made of silica).

The use of ceramic nanoparticles captured the attention of many researchers in PDT as the cell death is attributed to introducing new nanoparticle by which the photosensitizers are attached covalently to the silica matrix. This result shows that, the singlet oxygen $^1O_2$ was mainly deactivated outside the nanoparticles. In contrast, the metallic nanoparticles are composed of an extremely wide surface area that large amount of photosensitizer molecules are attached to the surface, unlike the silica based nanoparticles that are attached to the core that result to increased singlet oxygen $^1O_2$ diffusion.

Non-Biodegradable nanoparticles show stable fluctuation in pH and temperature as the peptide shape, size, mono-dispersibility and porosity during their preparation can be controlled because they are not liable to microbial attack. Moreso, the small spores in ceramic particles are small enough to enable passage of the drug through the matrix but large enough to allow efficient diffusion of oxygen in and out of the particles [25].

5.3. PHOTO-DEGRADATION

In the presence of oxygen or air, the irradiated nanoparticles, NPs are capable of damaging several organic contaminants. The activation of the nanoparticles by light produces pairs of electron-hole which are to be powerful oxidizing and reducing agents [26].

$$NP + h\nu \rightarrow h^+ + e^- \quad \text{..... Eq. 1}$$

The expression of the oxidative and reductive reaction is as;

$$OH^- + h^+ \rightarrow OH \quad \text{..... Eq. 2}$$

$$O_2 + e^- \rightarrow O_2^- \quad \text{..... Eq. 3}$$

6. PHOTODYNAMIC THERAPY WITH NANOPARTICLES

Nanotechnology is a discipline that has many reputations in cancer detection and accurate diagnosis [27][28][29]. Considering nanoparticles, NPs, are typically very small in size (<1µm size) compared to receptors, enzymes and antibodies of biomolecules as such they can give exceptional interaction with biomolecules both in *in vivo* and *in vitro* which may change the diagnosis of cancer and treatment [29].

Photodynamic therapy, PDT, is now considered as a modality for the treatment of many superficial tumors and localized cancerous cells. It was believe that, the action of PDT results in formation of singlet oxygen ($^1O_2$) which is the main medium for cell intoxication. Therefore, the efficiency of PDT can be traced to the production of singlet oxygen by following two methods using nanoparticles. The first is biodegradable nanoparticles; where the released PS from the NPs carrier are irradiated to produce $^1O_2$ and the second is non-biodegradable nanoparticles; where the oxygen can move freely in and out of the nanoparticles without releasing the PS out of nanoparticle carriers.

But, this modality has one shortcoming of low absorbance in optical opening for photosensitizer excitation which reduces the production of singlet oxygen [25]. However, for more effective treatment, Nanoparticles provide new interaction with biomolecules on cutaneous and sub-cutaneous tissues which may raise cancer treatment and diagnostic when used in photodynamic therapy (PDT). Nanoparticles are been recognized as a drug transporting system because of their ability to concentrate the photosensitizer (PS) on the wall of cells and result to the activation of the PS to increase deadly destruction on the cell [29]. Therefore, nanoparticles are introduced in PDT to target the cell membrane and deliver only the $^1O_2$ rather than the photosensitizer and prevent the photosensitizer from moving out of the cell by resistance multidrug mechanisms [30].

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