Phototherapeutic Agents for Fabricating High Drug-Loading Nanomedicines

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The key requirement of the chemo–photo combination therapy is the high drug-loading nanomedicines, which can load either chemotherapy drugs or phototherapy agents at the same nanomedicines and simultaneously deliver them to tumors, and play a multimode therapeutic role for tumor treatment. Many kinds of photothermal materials or photosensitizers have been used as carrier materials to construct high drug-loading nanomedicines for tumor combination therapy.

Keywords: high drug-loading nanomedicines ; chemotherapy ; phototherapy ; combination therapy

1. Introduction

On the premise of a stable system, the lesser amount of carrier material and the higher drug-loading ratio are pursued to prepare the high drug-loading nanomedicines. For tumor chemo–photo combination therapy, chemotherapeutic drugs and phototherapeutic agents (photothermal agents and photosensitizers) are equally important in the nanomedicines, and their proportion determines the final therapeutic effect on tumor to a certain extent. However, the construction of nanomedicines to realize the high loading of chemotherapeutic drugs and ensure the effective dose of phototherapeutic agents in the same nanomedicine is a challenge. After long-term exploration, researchers have found that using a phototherapeutic agent as a carrier to load chemotherapeutic drugs is an effective method of realizing high drug-loading for chemo–photo combination therapy. Now, many kinds of photothermal materials or photosensitizers (PSs) have been used as carrier materials to construct high drug-loading nanomedicines for tumor combination therapy of chemo-PDT (photodynamic therapy), chemo-PTT (photothermal therapy), and chemo-PDT-PTT.

2. Photothermal Agents as Carriers for Fabricating High Drug-Loading Nanomedicines

Photothermal agents absorb the energy of near-infrared (NIR) light and convert it into heat. Consequently, local tumors are induced to generate high temperatures, leading to their thermal ablation or thermal damage, thereby killing tumor cells with less harm to healthy tissues. At present, many photothermal agents, especially nanomaterials with strong absorption capacity and high photothermal-conversion efficiency in the NIR, have been widely studied and explored with some already undergoing clinical trials [1]. These photothermal agents can be primarily divided into inorganic and organic materials. Inorganic materials also include noble-metal nanomaterials, transition-metal chalcogenides and oxides, and carbon-based materials. Numerous studies have shown that nanomedicines prepared using a photothermal agent as a nanocarrier loaded with chemotherapy drugs have high drug-loading and high combination efficiency of chemotherapy-PTT [2]. In this section, chemo-PTT combination therapy with common photothermal agents used as carrier materials are summarized in **Table 1**.

Table 1. A summary of photothermal agents as carriers for high drug-loading nanomedicines.

Photoabsobers	Photothermal Agents	Chemotherapeutic Drug	Main Drug-Loading Mechanism	Drug-Loading Efficiency (wt%)	Ref.
Noble metal–based materials	AuNPs	Methotrexate	Electrostatic interactions	36.2%	[3]
	AuNRs	Doxorubicin	Electrostatic interactions	76.0%	[4]
	AuNBs	Doxorubicin	Electrostatic interactions	70.0%	[5]
	AuNFs	Doxorubicin	Electrostatic interactions	78.9%	[6]
	Au@Pt NPs	Doxorubicin	Electrostatic interactions	32.3%	[7]
	$Pd@MnO_2$	Doxorubicin	Electrostatic interactions	58.0%	[8]
Transition metal–based materials	CuS NPs	Doxorubicin	Electrostatic interactions	55.5%	[9]
	MoS_2	Doxorubicin	Electrostatic interactions	95.7%	[10]
	CoS, PDA	Doxorubicin	Electrostatic, π-π stacking	44.6%	[11]
	WS_2 nanosheets	Doxorubicin	Electrostatic, π-π stacking	95.0%	[12]
	MoO_x nanosheets	Doxorubicin	Electrostatic, π-π stacking	65.0%	[13]
Carbon-based material	Nano-GO	Dacarbazine	π–π stacking	80.0%	[14]
	GDYO	Doxorubicin, cisplatin, methotrexate	Amide reaction, π-π stacking, electrostatic interactions	40.3% of Doxorubicin	[15]
	MCNs	Doxorubicin	Electrostatic, π-π stacking	69.2%	[16]
	CNTs	Doxorubicin	Electrostatic, π-π stacking	50.0%	[17]
	GQDs	Doxorubicin	Der Waals interaction, π-π stacking	96.6%	[18]
	SWNHs	Cisplatin and doxorubicin	Hydrophobic-hydrophobic, interactions and π-π stacking	52.4%	[19]
	mCNFs	5-Fluorouracil	electrostatic adsorption	31.0%	[20]
Organic nanomaterial	IR783	Camptothecin	Electrostatic, π-π stacking and hydrophobic interactions	62.0%	[21]
	ICG	Doxorubicin	Electrostatic, π-π stacking	58.2%	[22]
	IR1061	Paclitaxel	Electrostatic adsorption	59.3%	[23]
	PDA NPs	Doxorubicin	Coordinate bond, electrostatic adsorption	80.0%	[24]
	HMPAn NPs	Doxorubicin	Noncovalent electrostatic	37.5%	[25]
	PPY NPs	Doxorubicin	electrostatic adsorption	43.3%	[26]
Others	Iron oxide NPs	Curcumin	electrostatic adsorption	93.0%	[27]
	Ti-WC nanowires	Doxorubicin	π-π stacking	69.2%	[28]
	HM-Bi	Doxorubicin	electrostatic adsorption	78.0%	[29]

Abbreviations: AuNPs, gold nanoparticles; AuNRs, gold nanorods; AuNBs, gold nanobones, AuNFs, gold nanoframeworks; GO, graphene oxide; GDYO, graphdiyne oxide; MCN, mesoporous carbon nanospheres; CNTs, carbon nanotubes; GQDs, graphene quantum dots; SWNHs, single walled carbon nanohorns; mCNFs, mesoporous carbon nanoframes; HMPAn NPs, hollow mesoporous polyaniline nanoparticles; PPY, Poly(pyrrole-3-COOH); HM-Bi, hollow mesoporous bismuth nanoshells.

2.1. Inorganic Materials

Noble-metal-based materials (Au, Ag, and Pb) are extensively used in tumor imaging and PTT due to their strong localized surface plasmon resonance (LSPR) and enhanced photothermal-conversion efficiency in the NIR-light region [30]. Among them, gold (Au)-based nanomaterials have excellent performance for clinical translation owing to their high X-ray attenuation coefficient, excellent biocompatibility, and bio-inertness. Accordingly, the preparation of high drug-loading

nanomedicines with Au-based materials such as gold NPs (Au NPs) [31][32][33], Au nanorods (Au NRs) [34][35], and Au nanocages (Au NCs) [36][37], Au nanoflowers (Au NFs) [38][39], and Au nanoclusters (Au NCSs) [40][41] are attracting extensive attention for chemo–photo combination tumor therapy. Huang et al. used crystalline zeolitic imidazolate framework-8 (ZIF-8) to grow on Au NRs and prepare biocompatible and biodegradable metal–organic frameworks (MOFs), i.e., Au@ZIF-8 [42]. Due to the large surface area and guest-matching pore size of ZIF-8, DOX is successfully loaded into Au@ZIF-8 with a high drug load efficiency of ~37%. Au@ZIF-8 shows a high photothermal effect upon NIR irradiation, and the ZIF-8 layer quickly degrades with laser irradiation, resulting in on-demand drug release at the tumor site. Furthermore, in vivo therapeutic results confirm that the combination of chemo–photothermal with Au@ZIF-8/DOX + NIR achieves much higher treatment efficacy than that of PTT with Au@ZIF-8 + NIR or chemotherapy with DOX only, even resulting in complete tumor elimination without obvious adverse effect. Xu et al. fabricated PDA-coated Au nanobone (NB) nanocomplexes (AuNBs@PDA) through the in situ polymerization of dopamine on the surface of Au NBs. The DOX is loaded through π-π stacking and hydrogen-binding interactions with PDA [5]. The AuNBs@PDA nanocomplexes exhibit higher photothermal-conversion efficiency (75.48%) than Au NBs alone, which is beneficial to photoacoustic imaging and PTT.

Moreover, the load efficiency (LE) of DOX by AuNBs@PDA nanomedicines could reach up to about 70%, showing significant cytotoxicity and antitumor effect. He et al. prepared metal@MOFs (Au@$Cu_3(BTC)_2$NPs) with a core–shell structure by assembling $Cu_3(BTC)_2$ on Au NPs with 4-mercaptobenzoic acid (4-MBA) as bridging molecule [43]. The $Cu_3(BTC)_2$ shell can provide sites for aptamer functionalization and drug loading. The Au@$Cu_3(BTC)_2$NPs exhibit high drug-loading efficiency (57%) and good photothermal-conversion efficiency.

Carbon nanomaterials primarily include the zero-dimensional (0D) fullerenes, the one-dimensional (1D) carbon nanotubes (CNTs), and the two-dimensional (2D) graphene [1]. Given the high NIR absorption coefficient (6.2×10^6 M^{-1} cm^{-1}) and ultra-high specific surface area of CNTs and graphene, the preparation of high drug-loading nanomedicines based on these materials for tumor chemo–photothermal combination therapy is attracting considerable attention [44][45]. However, CNTs and graphene without appropriate surface functionalization cause toxicity and side effects because of the poor dispersibility and stability of carbon-based materials in physiological solutions. Accordingly, researchers have developed various surface-functionalized CNTs or graphene nanocarriers to load chemotherapeutic drugs and prepared high drug-loading nanomedicines for tumor chemo–photothermal combination therapy. Xing et al. synthesized a three-dimensional framework with good stability and large specific surface area through the amide reaction of graphdiyne oxide (GDYO) and cisplatin (CDDP) and then loaded DOX by π-π stacking [15]. Self-assembly is then performed with the targeting group DSPE-PEG2000-methotrexate (MTX) and GDYO-CDDP to obtain multifunctional nanomedicines of GDYO-CDDP/DOX@DSPE-PEG-MTX (GCDM) for diagnosis and targeted cancer chemo–photothermal combination therapy. In this nanomedicines, three traditional anticancer drugs (CDDP, DOX, and MTX) play new roles and can reduce multidrug resistance through combined antitumor effects. Although only 40.3% of DOX is given, the load efficiency of the three chemotherapy drugs is actually higher. Wang et al. modified the surface of graphene oxide (GO) nanosheets with PEG derivatives and lactobionic acid (LA), and then loaded curcumin (CUR) on graphene nanosheets by π-π stacking to prepare GO-PEG/LA-CUR composite nanomedicines with a drug-loading efficiency of 56.8% [46]. In vivo experiments show that tumor growth is significantly inhibited in subcutaneous hepatocellular carcinoma tumor-bearing mice treated with GO-PEG/LA-CUR after NIR irradiation with a tumor inhibition rate of 86%, demonstrating the higher efficacy of the chemo-PTT combination therapy. Yang et al. designed a highly potent chemo–photothermal theragnostic system by sequentially loading DOX and CDDP onto dual polymer-modified single-wall carbon nanohorns (SWNHs) [19]. SWNHs are first modified simultaneously with poly(maleic anhydride-alt-1-octadecene) (C18PMH) and methoxyPEG-b-poly-D,L-lactide (mPEG-PLA) through hydrophobic–hydrophobic interactions and π-π stacking. Among various carbonaceous materials, SWNHs are advantageous for drug loading and have strong potential for chemo–photothermal combination therapy owing to their unique structure with a horn shape. This closed-tip nanotube possesses large inner voids and can be filled with suitable drugs ranging from small molecules to proteins. In this nanomedicines, the drug-loading efficiency of DOX and CDDP is 44% and 66%, respectively. In vivo treatment results show that SWNHs/C18PMH/MPEG-PLA-DOX-Pt-mediated chemo–photothermal combination therapy with the guidance of photoacoustic imaging completely eliminates the primary breast tumor and inhibits its lung metastasis.

A wide variety of transition-metal compound nanomaterials have opened up a new regime in PTT owing to their excellent NIR absorption and efficient heat-generation abilities. These nanomaterials primarily contain transition-metal chalcogenides (e.g., Cu_xS_y [9][47][48], $Cu_{2-x}Se$ [49], CoS [11], MoS_2 [50], WS_2 [51], $FeSe_2$ [52], FeS [53], and TiS_2 [54]) and oxides (e.g., MoO_x [55], W_xO_y [56], and Ti_8O_{15} [57]) with different structures of nanosheets, nanodots, and nanoparticles. Among them, copper chalcogenide semiconductors characterized by low cost and toxicity are new kinds of promising photothermal agents. Wu et al. synthesized hollow copper sulfide NPs (HCuSNP) loaded with DOX and a photothermal agent (ICG). They coated the surface of B16 membrane to prepare HCuSNP-ICG-DOX@B16F10 (ID-HCuSNP@B16F10)

nanomedicines, which serve as a biomimetic platform for in vivo chemo–photothermal combination therapy of tumors [58]. The hollow mesoporous structure of HCuSNPs makes them an ideal drug carrier. The loading efficiency of ICG and DOX can reach 98% and 85%, respectively. ID-HCuSNP@B16F10 exhibits an excellent photothermal effect in melanoma animal models and achieves a high tumor-ablation rate. As an emerging two-dimensional nanomaterial, MXenes have a large specific surface area and various surface groups, which enable them to have high drug-loading efficiency and the possibility of surface functionalization. Some recent reports have also confirmed the high photothermal-conversion performance of MXenes in NIR PTT. Li et al. developed multifunctional Ti_2N MXene-based nanomedicines (Ti_2N@oSi) for chemo–photothermal combination anticancer therapy [59]. Ti_2N nanosheets are stabilized with soybean phospholipids and loaded with DOX, followed by coating with biodegradable silica shells to prevent drug leakage, and finally loading with the second drug (CDDP) and the target agent (bombesin) in the outer layer. The unique structure of Ti_2N nanosheets endows the drug carriers with an ultrahigh drug-loading efficiency of 88.8% and an excellent NIR photothermal-conversion efficiency of 41.6% for chemo–photothermal combination therapy. Although inorganic nanomaterials have been developed for the PTT treatment of tumors, most of the inorganic photothermal agents currently used are nonbiodegradable and have potential long-term toxicity, hindering their further application in clinical tumor therapy.

2.2. Organic Materials

Organic photothermal agents have excellent biodegradability and biocompatibility. Compared with inorganic photothermal agents, organic agents have fewer safety problems. Thus, the development and application of organic photothermal agents have also been extensively studied for many years.

Common organic photothermal agents include NIR-absorbing dye containing nanocomplexes, NIR-absorbing conjugated polymers, and melanin-based photothermal materials. Small-molecule organic dyes such as ICG, IR780, and IR808 are difficult to be loaded with drugs as nanomedicines owing to some of their physicochemical characteristics, such as concentration-dependent aggregation and poor aqueous stability. Accordingly, other carrier materials are often needed. Lu et al. designed two-component NPs by π-π stacking and hydrophobic interactions between amino acid-conjugated camptothecin (CPT-RT) and canine dyes (IR-783) [21]. Then, the positively charged Angiopep-2-modified PEGlyated poly-l-lysine (Ang-PEG-g-PLL) is coated onto the negatively charged two-component NPs by electrostatic interaction to form the three-component nanomedicines Ang-PEG-g-PLL@CPT-RT@IR783 (APCI) for synergistic chemo–photothermal anti-glioma therapy. The drug-loading efficiency of APCI reaches about 62%. In vivo results reveal that the nanomedicines mediated by chemo–photothermal combination therapy achieve a better therapeutic effect, longer survival time, and minimal toxic side effects in orthotopic glioblastoma tumor-bearing nude mice.

Compared with NIR dyes, conductive polymers such as polypyrrole and polyaniline have better photothermal stability, are not easy to photobleach and have a longer circulation time in vivo [25]. Thus, as a photothermal agent, the conductive polymer is also an ideal drug-delivery platform. Liu et al. fabricated poly(acrylic acid) (PAA)-stabilized poly(pyrrole-3-COOH) NPs (PAA@PPyCOOH NPs) as nanomedicines loaded with DOX for chemo–photothermal combination therapy [26]. The PAA@PPyCOOH NPs are found to be ideal nanomedicines with good dispersity, excellent biocompatibility, high drug-loading efficiency (43.3%), and photothermal-conversion efficiency (56%). In vivo experiments demonstrate that the PAA@PPyCOOH@DOX nanomedicines can be specifically degraded by excess H_2O_2 in the tumor, and the tumor growth of 4T1 breast-cancer model is drastically inhibited by chemo-PTT.

PDA is a kind of melanin-like polymer that has been developed for photothermal agents and nanocarriers because of its excellent biocompatibility, biodegradability, simple preparation conditions, and high photothermal-conversion efficiency. PDA has many functional groups such as benzene ring, catechol group, and quinone group, enabling it to load a large number of antitumor drugs through π-π stacking or hydrogen bonding. In previous work, researchers have developed lollipop-like dual-drug-loaded NPs (DOX–PDA–gossypol NPs) based on the self-assembly of gossypol, DOX, and PDA through π-π stacking [60]. The DOX–PDA–gossypol NPs have a high drug-loading efficiency of 91%. In vivo antitumor experiments show that the TIRs of DOX-PDA-gossypol NPs are more than 90% at both low doses, which is beneficial for widening the drug therapeutic window. In another study, the researchers used PDA as a carrier for loaded hemoglobin and Ce6 to construct small NPs (PHC NPs; about 10 nm) for combined PTT/PDT [61]. The PHC NPs were encapsulated into the micelles formed by aldehyde-modified PEG and polyethyleneimine through benzoic-imine bonds, and the surface was modified with hyaluronic acid to form larger-size composite NPs ([PHC]PP@HA NPs; about 140 nm). The photothermal-conversion efficiency of [PHC]PP@HA NPs is 47.09%, and the load contents of Ce6 and Hb in PHC NPs were 27.3% and 54.8%, respectively. In vivo PTT/PDT experiments show that the TIR in mice is close to 100% within 30 days, and the tumor-recurrence rate is only 8.3% within 60 days.

In addition to the common nanomaterials mentioned above, researchers have developed photothermal agents such as mesoporous Prussian blue NPs [62][63], Mo-based polyoxometalate clusters [10][64], PbS/CdS/ZnS quantum dots [8][65], and so on. To prepare multifunctional nanomedicines with good biocompatibility, high stability, high drug load, degradability in vivo, nontoxic side effects, and high photothermal-conversion efficiency, it is a popular trend to hybridize inorganic and organic materials [66]. However, developing the perfect photothermal agent mentioned above for nanomedicines, and in vivo toxicity and photothermal-conversion efficiency are the most important issues.

3. Photosensitizers as Carriers for Fabricating High Drug-Loading Nanomedicine

PDT has become an important method in preclinical research and clinical practice in tumor treatment because of its minimally invasive and local tumor-killing ability without damaging surrounding healthy tissues and cells. The laser, PS, and oxygen are three indispensable elements in PDT. An ideal PS has high absorption coefficient in the 650–850 nm region, high $^1O_2$ yield, solubility under physiological conditions, high tumor selectivity, low damage to healthy tissues, and few side effects. However, the PSs developed at present have some disadvantages. Hematoporphyrin isolated from hemoglobin is the first-generation PS, which has obvious toxicity. The second-generation PSs such as Ce6 and methylene blue are mostly hydrophobic drugs, which easily aggregate in the aqueous medium, and have no tumor selectivity and poor bioavailability. Therefore, the third-generation PS combining PS with a nanosized delivery system or nanomedicines has been developed. Those nanoformulated PSs are also called smart PSs because of their specificity and good therapeutic effects [67][68]. **Table 2** summarizes the different photosensitizers as carriers for fabricating high drug-loading nanomedicines.

3.1. Inorganic Materials

In recent years, the development of inorganic material synthesis technology has been booming. Naturally, different kinds of inorganic materials with appropriate sizes and surface properties have been prepared and used as photosensitizers in the field of PDT. At present, the reported inorganic materials that can be equipped with chemotherapeutic drugs and enhanced PDT include CdSe/ZnS quantum dots [69], gold nanorods [70], reduced graphene oxide [71], and black phosphorus [72]. Those inorganic nanomedicines can not only directly generate singlet oxygen, but also change the microenvironment of tumor cells and promote the PDT effect.

Wang et al. constructed novel stimulation-responsive multifunctional nanomedicines by inserting folate-linked $ZnPcG_4$ molecules ($ZnPcG_4$-FA) into layered dihydroxide (LDH) via a simple coprecipitate method [73]. Chemotherapy drugs (DOX) are loaded on the surface of LDH, and the loading efficiency of DOX was calculated to be 41.7%. In the acidic tumor microenvironment, the release of DOX can be controlled with the degradation of LDH. The LDH is an interesting series of layered inorganic materials with the chemical formula as $[M^{2+}_{-x}M^{3+}_x(OH)_2]_x{}^+ A^{n-}_{x/n}{\cdot}uH_2O$, where M^{2+}, M^{3+} and A^{n-} represent divalent, trivalent metal ions and charge-balancing interlayer anion. Due to the special structure and pH response performance, LDH has been used as a carrier in drug delivery. Upon the 650 nm laser irradiation, the nanomedicines demonstrated excellent anticancer efficiency in vitro and in vivo because of the chemo–photodynamic combination therapy derived from the released DOX and $ZnPcG_4$ photosensitizer.

Table 2. A summary of different PSs as carriers for fabricating high drug-loading nanomedicines.

Classes	Photosensitizer	Chemotherapeutic Drug	Nanoformulation	Drug-Loading Content (wt%)	Ref.
Inorganic	BODIPY	Doxorubicin	BODIPY-derivate MOFs	49.7%	[74]
	Si-Pc	Doxorubicin	Hybrid mesoporous NPs	DOX: 34.5%, Si-Pc: 51.2%	[75]
	PPa	Doxorubicin	UCNP@SiO_2/PPa&DOX	DOX:72.8%	[76]
	Ir(III) complex	Cisplatin	Pt&Ir@polymer NPs	Pt: 38.9%, Ir(III): 12.9%	[77]
	Porphyrin	Doxorubicin	AuNP@dsDNA/Porphyrin	DOX: 75.0%	[78]
	PpIX	Doxorubicin	ZiF-67/8@DOX-PpIX NPs	DOX: 12.5% PpIX: 25.3%,	[79]
	UCNPs, Eosin Y	Camptothecin	UCNPs@CPT NPs	CPT: 53.7%	[80]
	Chlorin e6	Doxorubicin	rGO-DOX-Ce6 NPs	DOX: 82.3%	[81]
	TCPP	Doxorubicin	porphyrin MOFs	DOX: 52.2%	[82]

Classes	Photosensitizer	Chemotherapeutic Drug	Nanoformulation	Drug-Loading Content (wt%)	Ref.
Organic	Chlorin e6	GA	GA-Ce6-FA NPs	Ce6 48.5%, GA 47.79%, FA 3.71%	[83]
	Chlorin e6	Cabazitaxel	LNA-CTX-Ce6 NPs	Cabazitaxel: 98.87%	[84]
	VPF	Doxorubicin	VPF-FRRG-DOX NPs	>70.0%	[85]
	Zn-TPPS	Doxorubicin	Zn-TPPS-HDP NPs	Zn-TPPS: 17.0%, DOX: 31.5%	[86]
	Zn-TPPS	Doxorubicin	H_2TPPS@DOX NPs	DOX 42.4%	[87]
	TPCI	Paclitaxel	TPCI-PTX liposomes	PTX: 75.0%	[88]
	HPPH	Camptothecin	CPT-HPPH NPs	CPT: 55.0%, HPPH: 76.0%	[89]
	PpIX	Doxorubicin	DOX@PpIX-RGD NPs	DOX: 34.5%	[90]
	ALA	Doxorubicin	HA-chitosan@DOX-ALA NPs	DOX: 29.4% ALA: 11.5%	[91]
	PPA	Paclitaxel	PTX-PPA NPs	PTX: 44.2 %, PPA: 27.6 %	[92]
	PPA	Mitoxantrone	MTX-PPA NPs	MTX: 43.5%, PPA: 56.5%	[93]
	Chlorine e6	Doxorubicin	PEG-PBC-TKDOX@Ce6 NPs	DOX: 41.9%	[94]
	Chlorine e6	Paclitaxel	Ce6-PEG@PTX micelles	PTX: 90.1%	[95]
	TCPP	Doxorubicin	PEP FA@TCPP nanotubes	DOX: 30.5%	[96]
	Chlorine e6	Doxorubicin	DOX-NPs/Ce6-MBs NPs	DOX: 18.5%,Ce6: 67.1%	[97]
	TPC	Paclitaxel	RBC(M(TPC-PTX)) NPs	PTX: 38.0%, TPC: 13.0%	[98]

Abbreviations: BODIPY, dipyrromethene boron difluoride; PPa, Pyropheophorbide-a; PpIX, protoporphyrin IX; UCNPs, upconversion nanoparticles; CPT, camptothecin; rGO, reduced graphene oxide; TCPP, mesotetrakis(4-carboxyl)-21H,23H-porphine; GA, Gambogic acid; LNA, α-linolenic acid; VPF, Verteporfin; Zn-TPPS, tetra sodium meso-tetra (sulfonatophenyl)-porphyrin zinc (II); PTX, Paclitaxel; HPPH, photosensitizer 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a; TPCI, dual-functional theranostic PS; ALA, 5-aminolevulinic acid; PPA, pyropheophorbide a; MTX, mitoxantrone; PEP, peptide; TPC, 5,10,15,20-tetraphenylchlorin.

Recently, dipyrromethene boron difluoride (BODIPY) has been widely employed as an ideal photosensitizer for PDT, which is attributed to its strong absorption coefficient, significant photostability and high ROS yield. Meng et al. synthesized a novel two-fold interpenetration pillar-layered metal–organic framework (MOF) material (BBP-MOFs) using BODIPY-derivate bipyridine as a linker and photosensitizer, biphenyl-4,4′-dicarboxylic acid (BPDC), and Cd $(NO_3)_2$ [74]. BBP-MOFs are not only photodynamic agents that generate singlet oxygen ($^1O_2$) to perform PDT under 660 nm light irradiation, but also are drug carriers by loading DOX for chemotherapy. The results showed that BBP-MOFs exhibited high drug-loading efficiency of 49.7% as well as controlled drug release and ideal biocompatibility.

Zou et al. designed and constructed multifunctional hybrid mesoporous nanomedicines (HMNPs) that integrate near-infrared persistent luminescence nanoparticle, magnetic nanoparticles (Gd_2O_3), and radionuclides (^{68}Ga) via a large-pore (mesoporous silica nanoparticle) MSN-templated strategy [75]. The prepared HMNPs not only have good morphology, mesoporous structure, and surface properties, but also can load a variety of therapeutic agents at the same time. In the nanomedicines, the loading efficiency of DOX and photosensitizer (Si-Pc) were 34.5% and 51.2%, respectively. The studies on mice tumor models demonstrate that the DOX/Si-Pc-loaded HMNPs possess excellent cancer-cell-killing ability and an outstanding tumor suppression effect without systemic toxicity.

In addition to a variety of inorganic materials mentioned above, metal nanoparticles can be used in photodynamic therapy by conjugation or loading photosensitizer on their surfaces. For example, it is possible to modify the Au NPs either covalently or noncovalently with photosensitizer molecules [78][99]. Magnetic nanoparticles (MNPs) are one of the few inorganic materials approved by the FDA for therapeutic or imaging use in vivo. Photosensitizer molecules could be conjugated to MNPs for simultaneous magnetic resonance imaging and PDT [100][101]. Other carbon nanomaterials, including CNTs, graphene, and carbon dots, have also been used as carriers in PDT [102][103][104]. Moreover, upconversion nanoparticles (UCNPs) can emit high-energy light words under lower energy radiation, which has the advantages of better

tissue penetration depth and higher photochemical stability. Therefore, nanomedicines of photosensitizer materials based on UCNPs have been gradually developed for photodynamic therapy [105][106][107].

3.2. Organic Materials

Biodegradable organic-based nanomedicines have been widely used in drug delivery, including photosensitizers loaded with organic materials for photodynamic tumor therapy. For example, coupling or loading photosensitizer with poly(ethylene glycol) (PEG) [86][108], amphiphilic block polymers [94][109], polysaccharides [91][110], folic acid [93], peptides [90][95], liposomes [88][97], and polystyrene [104] have been studied. Phycocyanin (PC) is considered to be an effective natural photosensitizer, but it has not been well utilized due to its low biostability and intracellular accumulation. In order to overcome these limitations, nanosized PC particles (LAPC/DOX) were prepared by grafting lactonic acid (LA) and loading adriamycin (DOX). Compared with PC solution, the storage stability and photostability of PC particles are significantly improved, and the formation of nanomedicines further improves their biological stability [111]. Zhang et al. synthesized pH/reactive ROS dual-responsive PEG-DOX conjugate (labeled TPD) through acyl alkynylamine click reaction by PEG dipropiolate (PEGB), amine-terminated thioketal (TKL), and DOX [108]. The prepared amphiphilic TPD not only has high drug-loading efficiency for photosensitizer chlorine e6 (Ce6), but is also sensitive to acidic tumor microenvironment (TME) and ROS. Under laser irradiation, Ce6 produces abundant singlet oxygen ($^1O_2$), enabling programmable accelerated release of DOX and more Ce6 at tumor sites. Luo et al. prepared a prodrug nanoparticle (CDC NPs) by co-encapsulation of single thioether-linked dihydroartemisinin (DHA) dimer and Ce6, then stabilized by albumin-capturing maleimide- and hypoxia-sensitive 2-nitroimidazole-modified carboxymethyl chitosan [110]. DHA-S-DHA served as a ROS-responsive carrier for Ce6 and a chemotherapeutic drug. Upon laser irradiation, Ce6 could generate reactive oxygen species (ROS), which not only exerted the effect of the PDT but also broke the ROS-sensitive single thioether bridge in the dimeric prodrug DHA-S-DHA, thus accelerating the disassembly of the nanomedicines. Moreover, some researchers attempted to functionalize Ce6 with amino acid [112] and poly (amido amine) generation dendrimer [113] for better therapeutic effect.

The carrier-free nanomedicines, made up of photosensitizers and antitumor drug molecules, have become a kind of common nanomedicines for chemo–photodynamic combination therapy. Liu et al. fabricated porphyrin-based drug self-framed delivery systems without any carrier materials, in which water-soluble photosensitizer (tetra sodium mesotetra (sulfonatophenyl)-porphyrin, H2TPPS) and DOX could self-assemble to form H_2TPPS@DOX nanomedicines by supramolecular interaction such as hydrophobic, electrostatic and π-π stacking interactions [87]. Owing to the higher drug-loading efficiency of 42.4%, the H2TPPS@DOX could effectively generate singlet oxygen to obviously block DOX efflux and ultimately induce apoptosis to effectively reverse multidrug resistance of tumor cells under light irradiation.

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