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REVIEW

Advances in Antitumor Nano-Drug Delivery Systems of 10-Hydroxycamptothecin

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Abstract: 10-Hydroxycamptothecin (HCPT) is a natural plant alkaloid from Camptotheca that shows potent antitumor activity by targeting intracellular topoisomerase I. However, factors such as instability of the lactone ring and insolubility in water have limited the clinical application of this drug. In recent years, unprecedented advances in biomedical nanotechnology have facilitated the development of nano drug delivery systems. It has been found that nanomedicine can significantly improve the stability and water solubility of HCPT. NanoMedicines with different diagnostic and therapeutic functions have been developed to significantly improve the anticancer effect of HCPT. In this paper, we collected reports on HCPT nanomedicines against tumors in the past decade. Based on current research advances, we dissected the current status and limitations of HCPT nanomedicines development and looked forward to future research directions.

Keywords: 10-hydroxycamptothecin, antitumor, nanomedicine, nano-drug delivery systems

Background

A series of multiple processes, including the rapid spread and uncontrollable multiplication of abnormal cells, lead to the formation of malignant tumors with the potential for metastasis.[1] There are many different approaches to cancer treatment, such as conventional radiotherapy, chemotherapy, etc. However, some therapies are not as effective and some have side effects.[2] Natural compounds are a valuable resource for discovering and developing novel drugs, primarily for cancer treatment, that can serve as safe alternatives to the various synthetic drugs used in existing clinical therapies.[3,4] Evidence suggests that alkaloids are essential for the development of antitumor botanicals. Alkaloids are commonly found in plants, and new alkaloids have been found to have potent apoptotic and antitumor abilities against various cancer cells during the screening process of new drugs.[5,6] HCPT, a natural alkaloid, is the most potent anticancer compound among more than 20 monomers isolated from Camptotheca, with an anticancer activity equivalent to 30 times that of Camptothecin (CPT).[7] Numerous studies have shown that HCPT has the advantages of high efficiency, low toxicity and broad anticancer spectrum and is clinically used to treat colorectal cancer, liver cancer, gastric cancer, ovarian cancer, leukemia, head and neck tumors, etc.[8–11] However, its clinical application is limited by poor water solubility and low bioavailability. Current formulation research is focused on improving the solubility of lactone HCPT in water and improving the slow and controlled release of the drug to enhance its clinical application.[12] One promising approach to overcome these challenges is the incorporation of HCPT into different nano-sized delivery vehicles.[13] The use of nano-drug delivery systems for tumor-targeted therapy is an effective way to overcome the lack of specificity of conventional chemotherapeutic agents and the shortcomings of clinical treatment of tumors.[14,15] Nano-drug delivery systems can effectively enhance the in vivo distribution of chemotherapeutic drugs after systemic administration and improve the balance of efficacy and toxicity in systemic chemotherapeutic interventions.[16,17] Nanomedicines show potential therapeutic advantages over free drugs in vitro and in vivo.[18,19] However, although HCPT nanomedicines

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have been very much researched, there has not been significant progress in the clinical application of HCPT nanomedicines so far.[20] Studies have shown that inefficient accumulation and penetration in human tumors is the main reason for the poor clinical translation of most nanomedicines.[21] For this reason, many strategies, including enhancement of vascular permeability and optimization of nanoparticles, have been investigated. However, the results have been unsatisfactory.[22,23] A comprehensive overview of recent research advances in HCPT nanomedicines is essential to study this dilemma. However, although some studies on HCPT nanomedicines in cancer have been reported, these literatures have never provided a comprehensive review of the anti-tumor capacity of HCPT nanomedicines. On this basis, this paper classifies HCPT nanomedicines into organic nanoparticles (NPs), inorganic NPs and carrier-free NPs according to the material composition of HCPT nanocarriers (Figure 1). The research progress of the HCPT drug delivery system is critically reviewed and discussed, while the limitations and future directions of nanomedicine enhanced permeability and retention (EPR) effects are explored. We hope to provide a scientific basis and reference for HCPT nanomedicines research and clinical translation.

Organic NPs

Organic NPs such as polyethylene glycol (PEG), poly (lactic-co-glycolic acid) (PLGA), poly (D, L-lactic acid) (PLA), proteins, lipid, gels, peptides, dendrimer, cyclodextrins, electrospun fiber, polysaccharide and cell membrane, etc. can be physically encapsulated or loaded by conjugation of molecules at the core or surface functionalization and thus show great potential in biomedical applications. Due to their specific properties, such as high cellular uptake, high biodegradability and high loading efficiency, they have been widely used in cancer therapy.[24,25]

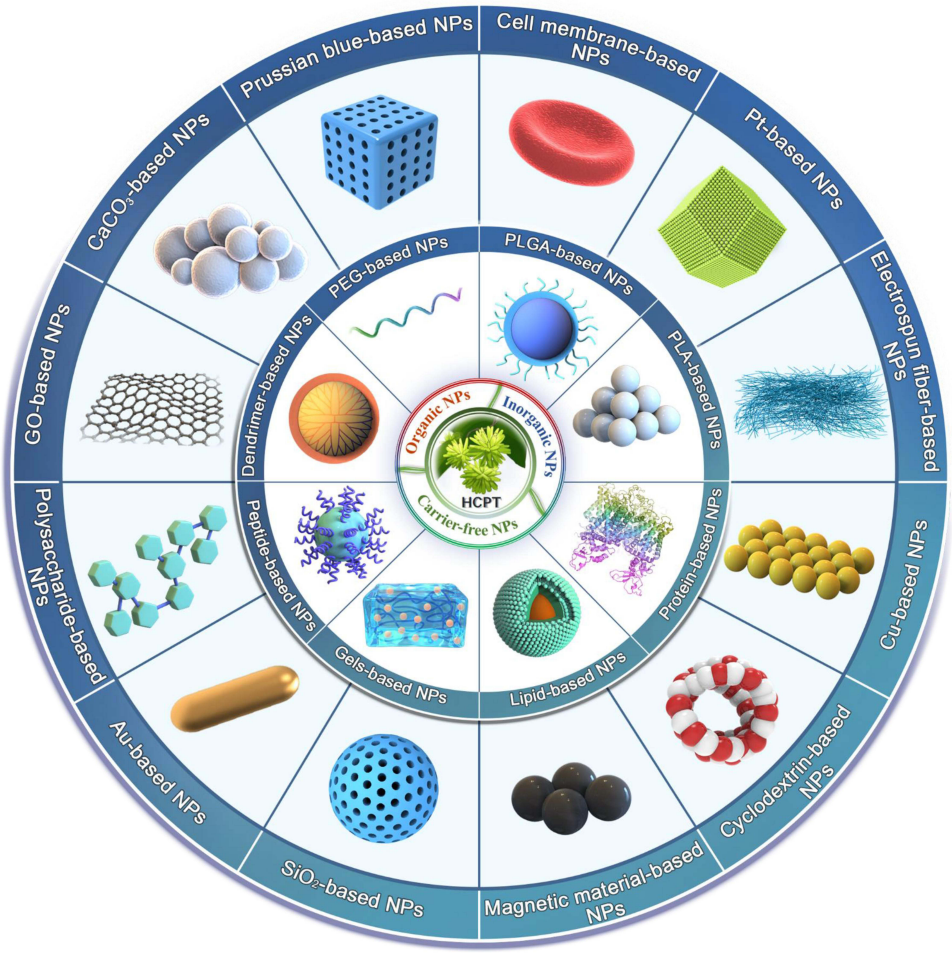

Figure 1 Schematic diagram of the classification of HCPT nano-drug delivery systems.

PEG-Based NPs

PEG is one of the most commonly used polymers for encapsulating nanocarriers to enhance biocompatibility, hydrophilicity, stability and biodegradability.[26] PEGylation increases the cycle time of nanocarriers by avoiding the absorption of the reticuloendothelial system (RES), and this Food and Drug Administration (FDA)-approved polymer is popular for its modifiable properties and well-established safety profile.[27] Combination therapy has been shown to be an effective strategy for improving treatment outcomes and reducing tumor resistance.[28] Diosgenin and HCPT are two typical natural anticancer drugs. Li et al prepared NPs loaded with 8armPEGylated diosgenin and HCPT. Studies have shown that NPs exhibit better tumor growth inhibition compared to free drugs.[29] It has been shown that the anticancer drug methotrexate (MTX) has a targeting effect and that MTX loaded in pellets can act not only as a drug but also as a potential targeting ligand.[30,31] Li et al synthesized PEG NPs loaded with HCPT and MTX. The NPs can target tumors while breaking down in the acidic microenvironment of the tumor with synergistic therapeutic effects.[32,33] Dexamethasone (DEX) is a hormone drug commonly used in clinical practice.[34] Meng et al reported that novel NPs consisting of HCPT and DEX could further increase the level of reactive oxygen species (ROS) in tumor cells and promote the normalization of blood vessels at tumor sites and reducing inflammation (Figure 2).[35] The synergistic application of chemotherapeutic drugs and small interfering RNA (siRNA) has emerged as an innovative approach for the treatment of cancer.[36] siRNA can suppress tumors by silencing oncogenes on the one hand, and improve the sensitivity of tumors to chemotherapy on the other.[37,38] Li et al synthesized NPs with poly-HCPT and siBcl-2 as the core, amphiphilic lipid-PEG as the shell, and lactic acid (LA) decoration. Through the specific binding between LA and asialoglycoprotein (ASGP) receptors, the NPs can accumulate and target in tumor tissues, exerting excellent synergistic tumor suppression effects.[39] Antibody-drug conjugates show great potential in cancer immunotherapy.[40] Liu et al fabricated an HCPT-based PEG amphiphilic antibody-drug coupling. The NPs have active tumor targeting through a specific interaction between anti-CD20 antibody and antigen.[41] The effect of linear/branched PEG chains in nanocarriers on antitumor efficacy is a little reported. Guo et al prepared HCPT NPs using the linear PEG_{45}, brush oligo (triethylene glycol) (TEG_{10}), and oligo (ethylene glycol) dendron (G2) as nanocarriers. All these NPs showed similar drug loading. The resultant proven in vitro

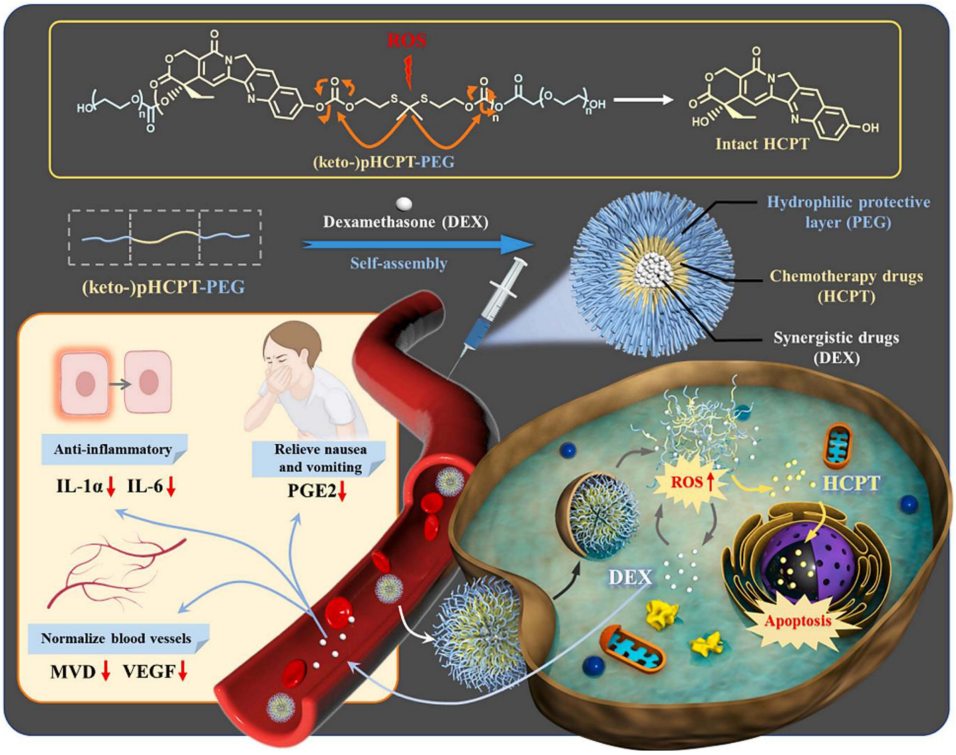

Figure 2 Schematic diagram of (keto-)pHCPT-PEG NPs synthesis and treatment of tumors.
Notes: Reprinted from Journal of Controlled release, 340, Meng Q, Hu H, Jing X, et al. A modular ROS-responsive platform co-delivered by 10-hydroxycamptothecin and dexamethasone for cancer treatment. J Control Release. 2021;102–113, with permission from Elsevier.[35]

and in vivo antitumor effects depended on the degree of nanocarrier branching, with G2 NPs showing the best antitumor effect compared to PEG_{45} NPs and TEG_{10} NPs.[42] iRGD as a tumor-targeting and tumor penetrating agent could enhance drug penetration through specific receptor binding affinity for αvβ3 and NRP-1.[43,44] Li et al prepared PEG and iRGD modified NPs. Compared with non-targeting NPs, iRGD-modified NPs significantly improved tumor therapeutic efficacy.[45] Nanosuspensions are drug delivery systems formed by mixing pure drug NPs in a solvent, generally with a surfactant to improve their stability and have a high drug loading capacity.[46] Researchers synthesized PEG-modified HCPT nanosuspensions have similar properties and show superior antitumor effects.[47,48] Due to its excellent biocompatibility and water solubility, mPEG is commonly used to encapsulate hydrophobic drugs to increase their circulation time in vivo.[49] Lv et al prepared novel prodrug micelles using water-soluble mPEG and HCPT as side chains. The prodrug micelles exhibited effective tumor cell internalization and excellent anticancer efficacy.[50] Compared with conventional chemotherapy, photodynamic therapy (PDT) is considered an advanced non-invasive approach in anti-cancer treatment.[51,52] Studies have shown that HCPT and photosensitizer loaded PEG NPs showed excellent anticancer efficiency under laser irradiation.[53,54] In addition to light triggering, the development of photosensitizers activated by specific triggers such as enzyme-activated has received much attention.[55,56] Lu et al synthesized a cathepsin B-activated photosensitizer, further PEGylated and modified with tumor cell-targeting peptide cRGD and used as a nanocarrier to load HCPT. The NPs showed cathepsin B-activated PDT and strong synergistic inhibitory effects on 4T1 cells.[57] It has been shown that NPs with positively charged surfaces have a short blood circulation half-life.[58] In contrast, the negatively charged NPs have a longer blood circulation time.[59] TAT peptide is a positively charged cell-penetrating peptide. Jing et al prepared negatively charged TAT peptide modified PEG nanomicelles that can undergo charge inversion in the acidic environment of tumor tissue, exposing positively charged TAT peptides to promote cellular internalization and subsequent nuclear targeting, showing efficient antitumor efficacy and inhibition of lung metastasis.[60] Folic acid (FA) has a high affinity for folate receptor (FR), which is overexpressed on the surface of tumor cells, thus targeting tumor cells.[61] It was shown that FA-modified HCPT-loaded PEG NPs enhanced cellular uptake via FR-mediated endocytosis and exhibited higher cytotoxic and tumor suppressive effects.[62,63] Recent observations suggest that physicochemical properties such as the shape of the nanocarrier can significantly affect its anticancer activity.[64] Zhou et al compared the shape-regulated anticancer activity of HCPT-loaded PEG nanorods (NRs) and NPs. It was shown that NRs exhibited better anticancer efficiency than NPs in 4T1 and MCF-7 cells.[65] It has been reported that shorter nanocrystals (NCs) with a high aspect ratio (AR) generally exhibit better drug delivery efficiency, but how AR will affect cellular uptake rates and biocompatibility remains unknown.[66] Tian et al developed HCPT-loaded PEG NCs with four different ARs. Studies have shown that shorter NCs with AR=1 are more readily captured by the liver and have less tumor uptake than longer NCs and higher NCs.[67] Similarly, Wu et al demonstrated that nanoneedle with high ARs exhibited strong shape-dependent effects on cell internalization.[68] The study of pH-responsive nanomedicines has become a hotspot in the field of drug delivery.[69] Researchers prepared HCPT-loaded pH-responsive PEG NPs exhibited greater tumor growth inhibition.[70–72] Furthermore, Researchers have developed HCPT-loaded PEG NPs with redox-responsive[73,74] and glutathione (GSH)-sensitive release.[75,76] Several studies have also demonstrated that HCPT-loaded PEG NPs exhibit significant liver targeting,[77] increase the rate of dissolution,[78] improve endocytosis[79] and enhance anti-tumor effect.[80]

PLGA-Based NPs

PLGA is an excellent biodegradable polymer. It has been approved by the FDA to use in drug delivery systems due to its controlled and sustained-release properties, low toxicity, and biocompatibility with tissue and cells.[81] Low-intensity focused ultrasound (LIFU) has been intensively studied for tumor treatment and diagnostic imaging as a non-invasive means of focusing energy on specific sites with considerable tissue penetration, which can significantly improve the efficacy of chemotherapy while preventing damage to surrounding tissues.[82,83] Wang et al synthesized cetuximab (C225) and HCPT-loaded PLGA NPs. The NPs can be triggered by LIFU and exhibit epidermal growth factor (EGFR) targeting and LIFU response properties in ultrasonography and synergistic chemotherapy of anaplastic thyroid carcinoma.[84] Yang et al demonstrated that dual drug PLGA nanoneedles loaded with MTX and HCPT are characterized by effective targeting, high drug loading and longer drug release, and easier access to HeLa cells.[85] Some excipients can enhance the cytotoxicity and chemosensitivity of NPs by overcoming drug efflux or maximizing the internalization of cancer cells.[86] Zaki showed HCPT-loaded PLGA NPs containing D-a-tocopheryl PEG 1000 succinate (TPGS 1000), pluronic P85 or

chitosan were more cytotoxic to cancer cells.[87] Arsenic trioxide (As_2O_3), commonly known as arsenic, is a highly toxic substance that can kill tumor cells.[88] Wu et al prepared PLGA microspheres loaded HCPT and As_2O_3 using multiple emulsion solvent evaporation method. The microspheres acted on vascular-associated cells and inhibited the formation of new blood vessels, thereby suppressed tumor growth.[89] Triphenylphosphonium (TPP) is a highly lipophilic polar cation that can penetrate the mitochondrial membrane.[90] Li et al showed that TPP-modified PLGA NPs could target mitochondria and nuclei, deliver more ring-closed form of HCPT to tumor tissues, and significantly enhance anti-tumor activity.[91] Furthermore, Ma et al demonstrated HCPT-loaded PLGA NPs with promising controlled release behavior, well stability and excellent tumor inhibition.[92]

PLA-Based NPs

PLA is widely used in various biomedical applications due to its biocompatible and non-toxic properties. Various methods, such as emulsion, salting and precipitation, have been used to fabricate better PLA NPs widely used as controlled drug delivery systems for therapeutic molecules.[93] Hou et al fabricated HCPT-loaded PLA microbubbles by a double emulsion-solvent evaporation method for use as an ultrasound-triggered drug delivery system. The PLA microbubbles had a smooth, spherical surface and the drug was amorphously dispersed within the shell. Nearly 20% of the HCPT was released after 10 min of exposure to diagnostic ultrasound at 3.5 MHz. Cytotoxicity tests on BEL-7402 cells showed that PLA microvesicles combined with ultrasound exposure showed more cytotoxicity than microvesicles alone.[94] Yang et al used a dialysis technique to prepare HCPT NPs using PEG-b-PLA and PLA, respectively. The results showed that although both exhibited slow and prolonged release profiles, the PEG-b-PLA NPs exhibited smaller particle size, faster drug release and higher cytotoxicity compared to the PLA NPs.[95]

Protein-Based NPs

Protein-based nanocarriers meet the requirements of low cytotoxicity, abundant renewable resources, high drug binding capacity and remarkable uptake into target cells. They are promising candidates for efficient drug and gene delivery.[96]

Albumin-Based NPs

Albumin is the most abundant protein in plasma and has high biocompatibility, biodegradability, non-immunogenicity and safety for clinical applications.[97] Also, the chemical structure and conformation of albumin allow interaction with many different drugs, thus potentially protecting them from in vivo elimination and metabolism, with the potential to facilitate half-life extension and targeted drug delivery.[98] Yang et al prepared HCPT-human serum albumin (HSA) NPs by a liquid composite method, which is relatively simple compared to the supercritical antisolvent process of emulsification and albumin coating method, which has the advantages of low toxicity, high step continuity, and less batch feeding, and the NPs can significantly inhibit tumor growth compared to free HCPT.[99] Glycyrrhetinic acid (GA) is commonly used in clinical practice for the treatment of chronic hepatitis.[100] Zu et al showed HCPT-GA-conjugated bovine serum albumin (BSA) NPs have hepatocyte targeting properties.[101] Wang et al similarly demonstrated the tumor targeting properties of FA-modified HSA NPs.[102]

Other Protein-Based NPs

High-density lipoproteins (HDL) are of great interest in drug delivery due to their relatively long half-life in the circulation, small particle size, and lipid core.[103] Yuan et al developed HCPT-loaded HDL NPs. Cytotoxicity studies in HT29 colon cancer cells showed that the IC50 of the NPs was approximately 3-fold lower than that of free HCPT.[104] Cui et al constructed T7 and dA7R peptide dual modified ligands HCPT-loaded HDL NPs. The dual modified NPs were found to show higher glioma localization than the single ligand modified NPs or free HCPT.[105] Casein (CA) is the main component of milk, and hollow casein nanospheres have the extraordinary ability to penetrate cell membranes, making them an ideal carrier.[106] Gao et al demonstrated that menthol-modified casein NPs loaded with HCPT can cross the blood-brain barrier and target gliomas.[107]

Lipid-Based NPs

Lipid-based NPs show great potential for drug delivery by offering excellent biocompatibility while improving drug solubility, encapsulating drugs in lipid membranes to achieve desired bioavailability and mitigating adverse drug reactions. Lipid-based NPs such as liposomes, solid lipid NPs, nanostructured lipid carriers, lipid nanoemulsion and lipid-polymer hybrid NPs, have promising applications in drug delivery and tumor therapy.[108–110]

Liposomes

Liposomes are the most successful nanocarriers for clinical applications. The bilayer structure of liposomes can be composed of natural phospholipids, cholesterol, etc., making them ideal carriers for different drugs with different solubilities, as hydrophilic molecules can be incorporated into the core. In contrast, hydrophobic drugs can be accommodated within the lipid membrane.[111] Thus, liposomes can carry water-soluble and insoluble drugs to the target site. In addition, they have low immunogenicity, toxicity and high pharmacoprotective effects.[112]

Li et al synthesized cell-penetrating peptide modified phase-transformation lipid NPs loaded with HCPT by thin film hydration method and phacoemulsification method. The NPs with ultrasound/PA dual-modality imaging capability could penetrate deeply into the tumor and release the drug under LIFU irradiation.[113] Stearyl glycyrrhetinate (SG) is a derivative of GA. It has been demonstrated that GA and its derivatives may be used as ligands targeting the liver.[114] It was shown that GA/SG-modified HCPT lipid NPs enhanced accumulated in liver tumors.[115,116] NK4 protein is a specific hepatocyte growth factor (HGF) antagonist that can act as a liver-targeting ligand, actively recognizing and binding to hepatocytes.[117] Zhou et al prepared NK4-HCPT liposomal NPs had excellent liver-targeting properties that could enhance the therapeutic effect of the HCPT for the treatment of hepatocellular carcinoma.[118] Compared to PDT, sonodynamic therapy (SDT) has been widely explored for cancer treatment because of its superior tissue penetration, lower cost, and higher safety profile.[119] Xiao et al prepared cationic HCPT liposomes by thin film method, combined with 5-aminolevulinic acid (5-ALA) by endotracheal administration for the chemotherapy and SDT treatment of metastatic lung cancer (Figure 3). The NPs showed higher anticancer effects in treating metastatic lung cancer mice.[120] Chen et al prepared HCPT-encapsulated liposomes by the thin film evaporation method. It was found that because this nanoparticle could continuously release the drug, it had a strong inhibitory effect on HepG-2, A549 and SGC-7901 cancer cells.[121]

Solid Lipid NPs (SLNs)

SLNs are colloidal drug carriers with superior biocompatibility, and their main components are solid at room temperature. The main advantages of SLNs over conventional drug carriers are their controlled and sustained drug release capability and excellent stability.[122,123] Xyloglcan (XG) is a natural polysaccharide with excellent biocompatibility and biodegradability to target drugs for hepatocellular carcinoma.[124] Liu et al prepared HCPT-loaded SLNs, which were coated with XG. This nanoparticle was specifically recognized by ASGPR on the surface of HepG2 cell membranes, thus

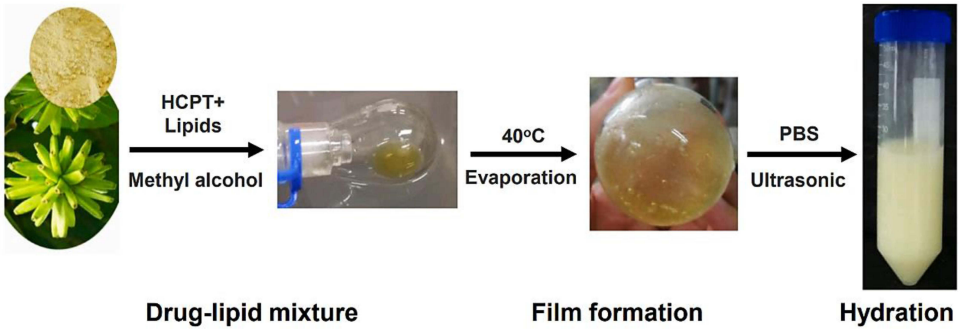

Figure 3 Schematic diagram of the preparation of HCPT liposomes.
Notes: Reprinted from International Journal of Pharmaceutics, 601:120572, Xiao Z, Zhuang B, Zhang G, Li M, Jin Y. Pulmonary delivery of cationic liposomal hydroxycamptothecin and 5-aminolevulinic acid for chemo-sonodynamic therapy of metastatic lung cancer. Int J Pharm. 2021, with permission from Elsevier.[120]

enabling targeting of hepatocellular carcinoma cells and accumulation of higher drug content, exhibiting superior antitumor effects.[125]

Nanostructured Lipid Carriers (NLCs)

NLCs are modified and improved forms of SLNs, in which lipid phase contains both solid and liquid lipids. Due to the nature of nanostructures, NLCs enhance their loading and stability to drugs.[126,127] Sun et al prepared N-Arginine-N-octyl chitosan (AOCS)-modified pH-sensitive NLCs. The in vitro and in vivo antitumor activities showed that such HCPT-loaded NLCs had better therapeutic effects than free HCPT. Under physiological conditions, the nanocarriers have a negative surface charge. They are safe in normal tissues, and when in an acidic environment, they can effectively disrupt lysosomes and disassembled drugs entrapped into cytoplasm efficiently.[128] Su et al prepared NLCs loaded with HCPT by the solvent evaporation method. The NLCs modified with octreotide-PEG (100) monostearate exhibited better-sustained release, the most efficient cellular uptake and cytotoxicity in SMMC-7721 overexpressed ligands of a growth inhibitor receptor (SSTR).[129]

Lipid Nanoemulsion

Lipid nanoemulsions are considered very attractive nanocarriers, increasing the solubility and bioavailability of drugs. They are capable of simultaneous sustained drug release while reducing drug toxicity.[130] Zhao et al prepared HCPT-loaded lipid emulsions, which were found to improve the therapeutic efficiency of HCPT by comparing it with HCPT injections and the inhibition of tumor growth in mice was stronger.[131]

Lipid-Polymer Hybrid NPs (LPHs)

LPHs exhibit characteristics of liposomal and polymeric NPs and are ideal nanocarriers. With advantages such as simple fabrication process, tunable size and surface charge, high loading capacity of low water-soluble drugs, and sustained and controlled drug release.[132,133] Yang et al synthesized HCPT-loaded LPHs by a modified emulsification technique. The LPHs consisted of a monolayer of lipid and a PEG shell with a hydrophobic polymer core. It was found that the LPHs improved cellular uptake efficiency and increased the cytotoxicity of HCPT on MDA-MB-435s cells.[134]

Other Lipid-Based NPs

Lipid-based NPs are widely used in drug delivery due to their unique advantages, and there are some other lipid-based NPs besides the classification mentioned above. Li et al developed a lipid microbubble carrying HCPT with high drug encapsulation and loading content while maintaining the acoustic properties as an ultrasound contrast agent. The combination of microbubbles with ultrasound exhibited significant drug accumulation and superior antitumor effects compared to microbubbles alone or HCPT injection.[135] Zhao et al prepared peptide-modified lipid NPs, which could penetrate the extracellular matrix, cell membrane, and even enter the nucleus under the induction of the novel cysteine-flanked cell-penetrating peptide CG-TAT-GC. Triggered by LIFU, the NPs can also improve drug release and enhance imaging of tumor sites.[136] Wang et al proposed lipid NPs loaded with HCPT and photosensitizer. The nanoparticle combined LIFU and laser with enhanced imaging, targeting and ovarian cancer treatment.[137] Some HCPT-loaded lipid NPs also showed excellent targeting. MTX-functionalized NPs enhance cellular uptake.[138,139] Several studies have shown that cellular sensitivity to anti-cancer drugs or radiation is significantly correlated with circadian rhythms and that the role of circadian clock genes is crucial in cancer therapy.[140,141] Hou et al found that when tumor suppressor period circadian regulator 2 (PER2) overexpression combined with HCPT-loaded lipid NPs can significantly enhance the anti-tumor effect.[142] Zhong et al prepared HCPT-loaded lipid nanocochleates, which can effectively improve the bioavailability of drugs. In addition, it can open cellular tight junctions and paracellular routes and showed more pronounced inhibition of tumor growth compared to normal saline, HCPT suspensions and HCPT-loaded liposomes.[143] Berberine hydrochloride (BBR), a class of drugs that regulate intestinal flora, has shown strong antitumor activity, reduces HIF-1a levels and induces apoptosis.[144] Qi et al prepared a novel lipid microsphere loaded with 10-HCPT-BBR that could significantly slow down tumor drug resistance.[145]

Gels-Based NPs

Nanogels and hydrogels have emerged as promising materials for biomedical applications due to their large surface area and tunable mechanical and chemical properties.[146] Their large surface area is well suited for biocoupling, while the internal porous network can be used to transport valuable biomolecules. The use of biocompatible hydrogels and nanogels avoids undesirable side effects within biological systems and preserves the excellent water content, thus creating an environment very similar to that of the extracellular matrix.[147,148]

Nanogel-Based NPs

Nanogels carriers are rapidly becoming a significant delivery strategy in biology and medicine due to their small particle size, excellent solubility, high loading capacity, and controlled release.[149] Studies showed positively charged nanogels with high HCPT loading efficiency, extended residence time, improved tissue penetration.[150] Positively charged disulfide-bonded nanogels that can specifically release cargo in cancer cells triggered by intracellular reduction micro-environment. Avoids the potential risk of HCPT resistance associated with high-dose chemotherapy.[151] Prolonged the retention period of HCPT in the rat bladder wall and enhanced tissue permeability.[152] Similarly, Qin et al demonstrated that HCPT-loaded phytanetriol cubic phase gel solutions, exhibited significant cytotoxic and anticancer activities against HepG2 and SMMC7721 cells.[153]

Hydrogel-Based NPs

Hydrogel-based therapies are a promising option for cancer treatment because of their controllability, biocompatibility, high drug loading capacity, extended drug release time, and specific stimulus sensitivity.[154] Several studies have revealed hydrogels maintain long-term sustained release of HCPT at a high accumulation rate, with optimized anticancer efficacy, satisfactory stability, injectability and recyclability.[155–158] Liu et al synthesized a novel octapeptide (1-YSV) to enable its co-assembly with HCPT to obtain supramolecular hydrogels with excellent viscoelasticity and increased the water stability of HCPT (Figure 4).[159] Guo et al prepared a supramolecular hydrogel composed of a self-assembling peptide, HCPT and macrocyclic polyamine cyclen can depleting cellular ATP and reversing ATP-dependent drug efflux, greatly improving cellular uptake and nuclear aggregation of HCPT.[160]

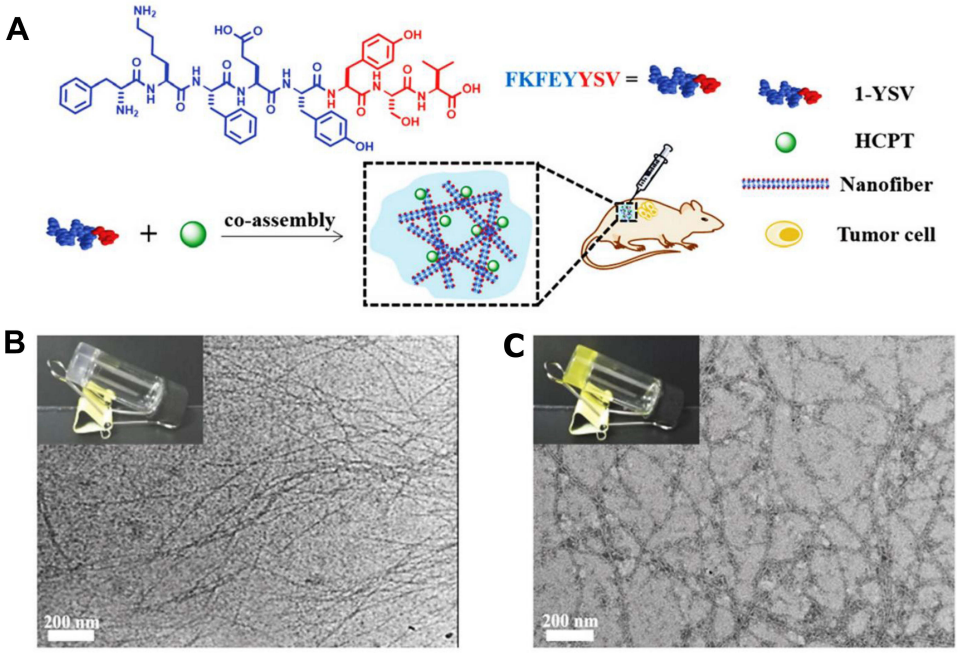

Figure 4 (**A**) Schematic illustration of co-assembly of tyroservatide-derived octapeptide (1-YSV) and HCPT for cancer therapy; (**B**) TEM micrograph of the 1-YSV hydrogel; and (**C**) TEM micrograph of the 1-YSV/HCPT hydrogel.

Notes: Used with permission of Nanoscale, from Molecular self-assembly of a tyroservatide-derived octapeptide and hydroxycamptothecin for enhanced therapeutic efficacy. Liu J, Wu C, Dai G, et al. Nanoscale. 2021;13(9):5094–5102. Permission conveyed through Copyright Clearance Center, INC.[159]

Peptide-Based NPs

Peptides are sequences of approximately 2–50 amino acids that have gained significant interest in therapeutic diagnostic applications in cancer research due to their better biosafety, customizability, ease of synthesis process, ability to target biological receptors by recognizing them on cancer cells.[161] D-peptides consist of D-amino acids that are resistant to endogenous peptidase-catalyzed hydrolysis and are very promising nanocarriers.[162] Liu et al developed D-peptide nanofibers for the controlled delivery of HCPT. The results showed that D-peptide nanofibers could improve the aqueous solubility of HCPT and exhibit better long-term stability and better cancer cell selectivity.[163] Zeng et al constructed a bladder tumor-specific peptide prodrug by enzyme-assisted assembly. The prodrugs can target bladder tumors through the specific binding ability of the YSA peptide to the membrane protein EphA2. Catalyzed by the enzyme cathepsin B, they could induce small molecule prodrugs to form nanostructures, which prolong the retention time of the HCPT, thereby reducing HCPT side effects.[164] The tLyP-1 peptide-modified NPs are targeted and penetrating, increasing tumor accumulation and penetrating deeply into extravascular tumor tissue.[165] Zhu et al developed phase change NPs modified by tLyP-1 peptide with loaded HCPT. In combination with LIFU, NPs can phase transform into microvesicles and enhance tumor ultrasound molecular imaging for tumor diagnosis while releasing drugs.[166] In addition, some experiments have shown that peptide-based NPs enhance the cellular uptake and aggregation of HCPT in the nucleus, improving the anti-tumor activity and anti-metastatic efficacy of HCPT.[167–171]

Dendrimer-Based NPs

Dendrimers are chemically synthesized, highly branched polymers with a highly symmetric spherical shape. They are typically made from natural or synthetic components, including sugars, nucleotides and amino acids.[172] Drugs can be trapped in the core of a dendrimer through hydrogen bonding, and electrostatic or hydrophobic interactions. Hydrophobic or hydrophilic anticancer drugs can also be covalently attached to the surface of the dendrimer.[173] Dendrimers are easily functionalized and have the unique advantages of high stability, excellent water solubility, low immunogenicity, and high antigenicity, making them attractive drug delivery vehicles.[174] Kong et al prepared novel multifunctional dendrimer NPs, which tightly encapsulated HCPT by simple complexation. The NPs could selectively target the drug to cancer cells overexpressing integrin avb3 through high affinity interactions and shown to exhibit significantly high cytotoxicity.[175] Zhang et al synthesized dendritic polymers loaded with doxorubicin (DOX) and HCPT. Studies of drug release and cellular uptake showed that the NPs were released in a pH-dependent manner and efficiently taken up by MCF-7 cells in anticancer cell therapy exhibited enhanced anticancer effects.[176] Guo et al prepared HCPT-loaded NRs using fluorescently labeled low-PEG co-dendrimers (POC) as carriers and showed higher internalization of HCPT NRs in HepG2 and 4T1 cells and higher cytotoxicity compared to HCPT injections.[177] Guo et al synthesized OEG dendrimer conjugated with octadecylamine (G2-C18) and further used as nanocarriers to prepare HCPT nanospheres and NRs by inverse solvent precipitation method. The NRs were shown to have significantly enhanced cytotoxicity compared to nanospheres and exhibited significantly higher antitumor activity in vivo.[178]

Cyclodextrin-Based NPs

Cyclodextrins are a family of cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity that have the unique ability to form inclusion complexes with a variety of organic and inorganic lipophilic molecules.[179] Used primarily as complexing agents to increase the aqueous solubility of insoluble drugs and to enhance their bioavailability and stability, cyclodextrins hold promise in a wide range of areas such as drug delivery, cancer therapy, gene delivery, and biosensing.[180] Lignin is an amorphous polyphenol with properties such as non-cytotoxicity.[181] Zhou et al grafted β-cyclodextrin (β-CD) with a hollow ring structure onto enzymatically hydrolyzed lignin to form NPs encapsulating HCPT. The results showed that the HCPT NPs were effective in inhibiting tumor cell growth, exhibiting higher specific surface area and porosity as well as better encapsulation and retarded release.[182] The supramolecular assembly of cyclodextrin-based polyrotaxane is also attracting more and more researchers. Zhang et al prepared HCPT-loaded cyclodextrin polyrotaxanes NPs and found that the NPs were more readily taken up by tumor cells and could effectively inhibit tumor growth and prolong the survival time of tumor-bearing mice.[183]

Electrospun Fiber -Based NPs

Electrostatic spinning is an effective and versatile method for the preparation of continuous polymer nanofibers, electrospun fibers due to their high loading capacity and encapsulation efficiency, surface area and porosity, and modification potential. They have promising applications in cancer diagnosis and treatment and are treated as promising candidates for drug delivery.[184] Wang et al developed HCPT-loaded fiber membranes by electrostatic spinning. They found that drug release from HCPT-loaded fiber membranes lasted for approximately seven days and well inhibited the growth of rabbit subcutaneous VX2 tumors.[185] Luo et al emulsion prepared core-sheath structured fibers with core-loaded HCPT by electrostatic spinning. In vitro and in vivo antitumor efficacy assays showed that HCPT-loaded fibers showed superior in vivo antitumor activity and fewer side effects than free HCPT.[186] Wei et al constructed fragmented fibers of negative HCPT by freeze-cutting neatly aligned electrospun fibers. The results showed that longer length fragment fibers indicated higher accumulation in the tumor and better retention at the injection site, and the HCPT-loaded fiber fragments showed superior in vivo antitumor activity and fewer side effects.[187] Luo et al prepared electrospun fibers loaded with HCPT, which can degrade in an acidic environment and release the drug. Cytotoxicity assays showed that the electrospun fibers showed 6-fold higher inhibitory activity against HepG2 cells after incubation in pH 6.8 medium compared to pH 7.4.[188] Combretastatin A-4 (CA4), a commonly used clinical vascular disruptor, inhibits the growth and metastasis of various tumors.[189] Luo et al prepared electrostatic spun fibers loaded with combretastatin A-4 (CA4) and HCPT. In situ breast tumor model, fibers loaded with CA4 and HCPT showed superior antitumor efficacy and higher survival rates than fibers loaded with individual drugs.[190] Phenolic derivatives, especially tea polyphenols (TP), showed significant ROS inhibitory properties.[191] Li et al developed an electrospun polymer patch from an emulsion to make nanofibers loaded with HCPT and hydrophilic TP. The nanofibers were shown to significantly synergistic tumor suppression.[192]

Polysaccharide-Based NPs

Polysaccharide-based biomaterials (chitosan, hyaluronic acid (HA), starch, pectin, cellulose, etc.) have received significant attention in the pharmaceutical field due to their excellent biodegradability and biocompatibility, while being easily modified chemically or physically, especially in the delivery of drugs for oncology treatment.[193]

Chitosan-Based NPs

Chitosan is a naturally occurring linear polysaccharide cationic hydrophilic polymer produced by the alkaline decomposition of chitin.[194] Chitosan and its derivatives are widely used in various biomedical applications due to their unique biocompatibility, mucosal adhesion, non-toxicity and gel-forming ability.[195,196] Studies have shown that chitosan NPs prolong the duration of HCPT administration, improve oral bioavailability, and improve antitumor effects while reducing side effects.[197–199] Positively charged chitosan NPs exhibited slow-release behavior, ensuring higher intracellular drug concentrations and more significant cytotoxicity.[200] FA-modified chitosan nanoneedles (Figure 5) and micelles exhibit significantly enhanced cellular uptake, higher cytotoxicity against folate-receptor-positive tumor cells.[201,202] Loaded with HCPT and MTX-dual drug chitosan NPs that exhibit sustained and prolonged drug release properties, as well as effective cellular internalization and enhanced cytotoxicity.[203] Studies have shown that nitric oxide (NO) is an endogenous gas transmitter can overcome multidrug resistance (MDR) by making nitrification of certain tyrosine residue of P-glycoprotein (Pgp) to inhibit the pumping function.[204] Niu et al formulated chitosan NPs loaded with HCPT by ionic gel binding and chemical cross-linking methods. The NPs possessed GSH-responsive NO donor release and pH-sensitive charge reversal ability, significantly enhanced cellular uptake at pH 6.5, and improved anti-tumor ability against drug-resistant tumors.[205]

HA-Based NPs

HA is a naturally occurring linear polysaccharide with excellent hydrophilicity, biocompatibility, biodegradability and low immunogenicity, making it one of the most attractive biopolymers for biomedical research and applications.[206] Due to its intrinsic affinity for CD44 (a receptor highly expressed on various cancer cells), HA has been widely designed for targeted anti-tumor drug-loaded NPs.[207] Chen et al developed a polymeric nanocomplex targeting CD44 by

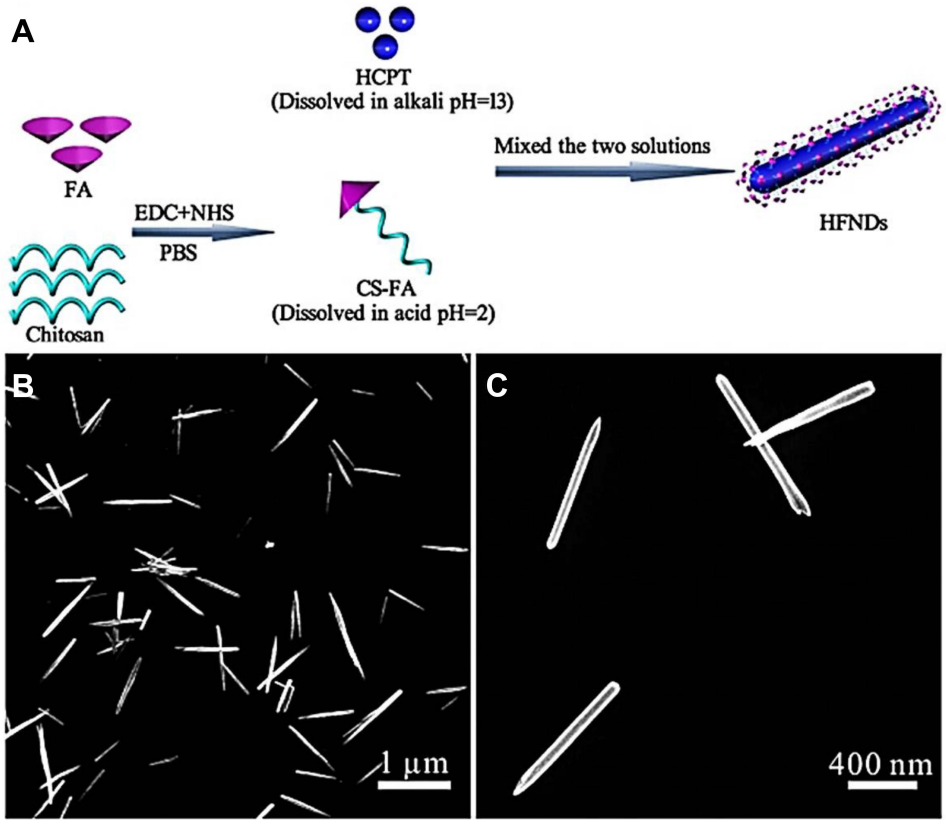

Figure 5 (**A**) Illustration of the completely green method of preparing chitosan nanoneedles. (**B** and **C**) The SEM images of chitosan nanoneedles.
Notes: Reproduced from Wu S, Yang X, Zou M, Hou Z, Yan J. A New Method Without Organic Solvent to Targeted Nanodrug for Enhanced Anticancer Efficacy. Nanoscale research letters. 2017;12(1):416.[201]

encapsulating HCPT into HA NPs. Compared with free HCPT, the NPs exhibited excellent biocompatibility, tumor cell targeting and specificity.[208] Li et al developed HA-modified NPs based on loaded HCPT and MTX. In vivo near-infrared fluorescence and photoacoustic (PA) bimodal imaging demonstrated effective aggregation of NPs at tumor sites through passive plus active targeting, producing highly synergistic tumor cell killing and tumor growth inhibitory effects.[209]

Starch-Based NPs

Starch is one of the most abundant biopolymers in nature and is usually isolated from plants in the form of micro-granules. Since starch is environmentally friendly, starch NPs are considered a promising biomaterial and are widely used as binders, disintegrants and fillers in drug delivery systems.[210] Amphiphilic α-tocopherol branched chain starch NPs, proved to be more cytotoxic than free HCPT.[211] Some experiments have also demonstrated that hydroxyethyl starch NPs loaded with HCPT have superior tumor suppressive effects and lower side effects.[212,213] Li et al prepared pH/reduction/α-amylase multisensitive hydroxyethyl starch micelles for amino acid transport proteins overexpressed on the surface of hepatocellular carcinoma cells. This micelle has a regular structure, suitable particle size and excellent drug release performance, and has better in vitro anti-proliferative ability and in vivo anti-tumor effect on human hepatocellular carcinoma HepG2 cells compared with conventional micelles and HCPT injection.[214]

Pectin-Based NPs

Pectin is one of the few polysaccharides with biomedical activity. The prevalence of hydroxyl and carboxyl groups in pectin contributes to their hydrophilicity and therefore excellent biocompatibility, low toxicity and biodegradability, making it an essential candidate for biomedical and drug delivery applications.[215] The galactose residue of the pectin molecule can be recognized by the asialoglycoprotein receptor on the surface of the liver cancer cell, promoting the rapid penetration and release of the HCPT.[216] Multi-drug combinations play an important role in tumor treatment. Research

reports ursolic acid (UA)-HCPT loaded pectin NPs[217,218] and dihydroartemisinin (DHA)-HCPT pectin NPs[219] both exhibited significant synergistic effects and enhanced antitumor effects.

Cellulose-Based NPs

As a biopolymer with relatively low cost, fine cross-section, excellent hydrophilicity, biocompatibility, high strength, processability, volumetric stability and durability, cellulose is playing an increasing role as a carrier material in the biomedical field.[220] Studies showed carboxymethylcellulose NPs have attractive properties, including easy preparation, suitable size, high HCPT loading capacity, well stability, rapid uptake by tumor cells, high synergistic effect and few side effects.[221] With a rapid HCPT release in response to acidic intracellular stimuli while maintaining sufficient stability under normal physiological conditions.[222]

Other Polysaccharide-Based NPs

Ganoderma lucidum polysaccharide (GLP), as the main bioactive components of Ganoderma lucidum, are natural polysaccharides with medicinal value, safe and non-toxic, and are widely used in drug delivery.[223] Zheng et al synthesized MTX and HCPT loaded GLP NPs. The NPs are irregularly spherical with uniform particle size, have high drug loading capacity and excellent biocompatibility, and can be rapidly released in the acidic microenvironment of tumor cells.[224] As a natural and renewable biomolecule, dextran is not only biodegradable but also has excellent biocompatibility.[225] Zhao et al constructed HCPT-loaded cinnamaldehyde (CA)-dextran polymers. The NPs not only induce cancer cell death by generating ROS, but also promote drug uptake, effectively prolonging drug circulation and increasing drug accumulation at tumor sites.[226] Xylan is the main component of hemicellulose, an important polysaccharide.[227] It has been shown that xylan modified NPs could be specifically recognized by ASGPR on the membrane surface of tumor cells, thus allowing the HCPT NPs to target hepatocellular carcinoma cells.[125] It has excellent cytotoxic and apoptosis-inducing effects on HepG2 cells.[228]

Cell Membrane-Based NPs

Cell membrane-based NPs, a new class of bio-NPs, are widely used for drug delivery because of their cell-specific targeting, biocompatibility, biodegradability and long circulating half-life.[229,230] Fan et al prepared a C6 cell membrane-encapsulated NPs using the ultrasonic encapsulation method. The NPs were spherical in shape, with core-shell structure, homologous cancer cell membrane-targeting mechanism and immune escape ability.[231] Ye et al developed and prepared red blood cell (RBC) membrane -camouflaged NPs loaded with HCPT and indocyanine green (ICG). Stimulated by near-infrared (NIR) laser and acidic stimulation, the NPs can rapidly disintegrate and accelerate drug release. The dual stimulation of NPs achieved efficient apoptosis in cancer cells by chemotherapy and photothermal therapy (PTT) compared to treatment alone.[232] Zhang et al synthesized NCs with high loading of HCPT by a mild nanoprecipitation process. Camouflaged cancer cell membranes (CMs) composed of a large number of membrane proteins conferred homotypic targeting ability of NCs at tumor sites. The photosensitizer ICG not only converts light energy into heat for PTT, but also promotes the breakdown of NCs, achieving high-performance tumor suppression in a triple-negative breast cancer model.[233]

Other Organic NPs

In addition to the above mentioned involved nanocarriers, there are some other organic carriers. Zwitterionic materials such as betaine are a class of superhydrophilic biomaterials that are expected to be an ideal substitute for PEG.[234] Li et al designed a zwitterionic sulfobetaine surfactant TSSB as a novel surface modifier for NRs loaded with HCPT. The TSSB-modified NRs were found to have higher cellular uptake efficiency and exhibit higher cytotoxicity through caveolin-mediated endocytosis.[235] Sun et al chemically synthesized NRs with 5-fluorouracil, HCPT and valine-citrulline mono-methyl auristatinE (vcMMAE) primers. The NRs showed high specific affinity and improved internalization with enhanced antitumor efficacy.[236] Luo et al encapsulated HCPT into matrix polymers containing acid unstable chain segments and galactose fraction by electrospray technique. Compared with other NPs preparation methods, electro-sprayed NPs demonstrated improved drug delivery efficiency and prolonged HCPT release. Facilitated uptake of

PGBELA NPs into HepG2 cells and accumulation in tumors of H22 tumor-bearing mice demonstrated the targeting ability of the galactose fraction.[237] Chen et al synthesized novel diblock copolymers loaded with HCPT, which have a relatively high drug loading capacity, significant stability, longer blood retention time and better therapeutic efficacy compared to free HCPT.[238] Sun et al developed a novel multipolyprodrug-arm hyperbranched amphiphiles (hPCM) that were efficiently internalized by MCF-7 cells and exhibited comparable cytotoxicity compared to free HCPT.[239]

Inorganic NPs

Compared with organic NPs, inorganic NPs such as silicon dioxide (SiO_2), gold (Au), magnetic nanomaterials, graphene oxide (GO), copper (Cu), Prussian blue, platinum (Pt) and calcium carbonate ($CaCO_3$) exhibit intrinsic structural robustness and relatively low manufacturing costs, and have great potential for cancer therapy.[240]

SiO_2-Based NPs

Mesoporous SiO_2 NPs have large specific surface area, large pore capacity, uniform and adjustable pore size, and stable skeleton, which has led to the widespread use of SiO_2-based materials and their oxides for drug delivery.[241] Fan et al prepared SiO_2@Au NPs loaded with HCPT and DOX. The results showed that the NPs could specifically target tumor cells and rapidly internalize them, which enhanced their sensitivity to the drug.[242] As a monocarboxylate transporter (MCT), MCT-4 allows lactate efflux to maintain intracellular pH stability and induces weakly acidic TME.[243] Silencing the expression of MCT-4 increases the intracellular lactate content of tumor cells and induces apoptosis. Li et al prepared hollow mesoporous SiO_2 NPs loaded with HCPT and siMCT-4 (Figure 6). The NPs could respond to weakly acidic TME and high levels of GSH in tumor cells. Combining inhibition of lactate efflux and chemotherapy effectively removed immunosuppressive TME, inhibited tumor growth, and suppressed lung metastasis from B16F10 cells and 4T1 cells.[244]

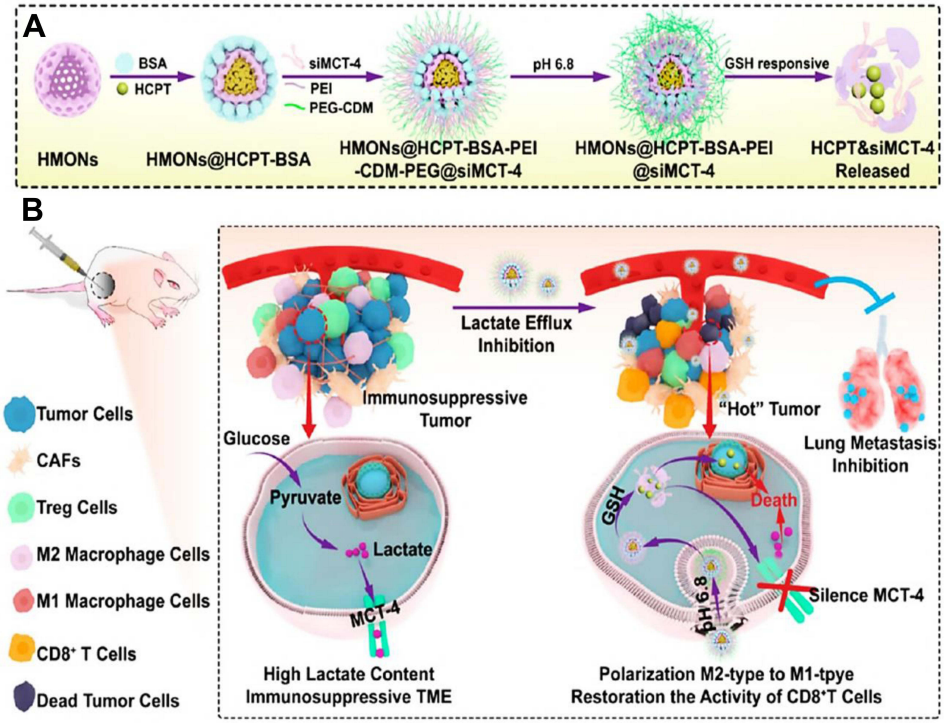

Figure 6 (**A**) Synthesis of SiO_2 NPs and stimuli-responsive degradation. (**B**) The SiO_2 NPs directly induces tumor cell apoptosis though HCPT and the increased intracellular lactate.

Notes: Reprinted with permission from Li K, Lin C, He Y, et al. Engineering of Cascade-Responsive Nanoplatform to Inhibit Lactate Efflux for Enhanced Tumor Chemo-Immunotherapy. ACS Nano. 2020;14(10):14164–14180. Copyright 2020 American Chemical Society.[244]

Magnetic Material-Based NPs

Magnetic nanomaterials can be loaded with drugs into NPs by electrostatic adsorption, encapsulation, and covalent binding and selectively transferred to focal sites by external magnetic field guidance.[245] Due to their superparamagnetic properties, targeting, biocompatibility, and ease of surface modification have been widely used in biomedical applications, especially for drug delivery for cancer therapy.[246] Liu et al developed a phase-change FA-targeted perfluoropentane (PFP) nanodrop containing HCPT and superparamagnetic Fe_3O_4. After intravenous administration to nude mice bearing SKOV3 ovarian cancer, the nanodrops exhibited enhanced magnetic resonance (MR) and PA imaging.[247] The key role of integrin αVβ3 in tumor angiogenesis and metastasis has been identified as an ideal therapeutic target for tumor chemotherapy.[248] Ding constructed arginine-glycine-aspartic acid-cysteine (RGDC) tetrapeptide functionalized and HCPT-encapsulated magnetic NPs for integrin αVβ3-targeted drug delivery. The NPs exhibit superior anti-cell migration activity with significantly enhanced cytotoxicity against A549 cells overexpressing αVβ3 compared to free HCPT and non-targeted micelles.[249] Studies showed that the HCPT-encapsulated magnetic NPs exhibited enhanced activity in inhibiting tumor cells migration and could be rapidly and efficiently internalized into cells at the target site under external magnetic guidance, thereby selectively killing cells in the region.[250,251] Yang et al fabricated HCPT-loaded iron oxide NRs having a drug loading capacity of up to 72%. In vitro studies have shown that the NRs have imaging capabilities and excellent chemical-photothermal synergistic effects for tumor ablation. More importantly, 100% in vivo tumor elimination was achieved at low laser power density with no weight loss and tumor recurrence.[252] Wang et al constructed novel magnetic NPs of HA-bound iron oxide nanoparticle (IONP). Dopamine can form a stable and strong shell on the surface of the NPs, which results in excellent biocompatibility, biostability and tumor targeting of the NPs. The NPs have triple tumor targeting ability through magnetic targeting, CD44 molecular targeting and passive EPR targeting.[253] Qu et al prepared HCPT-loaded chitosan-coated Fe_3O_4 NPs. Cytotoxicity experiments showed that the NPs showed significantly increased antitumor activity against HepG2 cells compared to free HCPT. The NPs also produced a local thermotherapeutic (42–45°C) effect on cancer when an external local alternating magnetic field was added.[254]

Cu-Based NPs

Cu NPs have attracted increasing interest in biomedical applications.[255] Metal organic backbones (MOFs) are widely used for drug delivery due to their porous structure as well as their large specific surface area and simple synthesis process, especially in cancer therapy.[256] Shi et al synthesized a hydrophilic Cu organic backbone with an amphiphilic carboxylic acid ligand as a connector, improved the solubility of HCPT in water. Cytotoxicity tests showed excellent solubilization, slow release and excellent biocompatibility of hydrophilic NPs.[257]

Au-Based NPs

Au NPs are increasingly used in drug delivery due to their unique physicochemical and optical properties and low toxicity.[258] Compared with organic nanocarriers used for therapeutic agents, Au NPs exhibit superior properties as drug delivery carriers, including inertness, proven synthesis strategies, adjustable size, and flexible and easy surface modification with various chemical and biological molecules.[259] Li et al prepared Au NPs loaded with HCPT by electrostatic deposition (Figure 7). The NPs can release drugs on demand in the NIR while exerting photothermal effects. 100% in vivo tumor elimination was achieved at a low laser irradiation power density of 1 $W \cdot cm^{-2}$ with no weight loss or tumor recurrence.[260] Bao et al prepared a series of HCPT-Au NPs of different sizes and compared their cytotoxic effects in vitro and antitumor effects in vivo. Transmission electron micrographs showed that the NPs were round and regular in shape with an average diameter of about 10, 25 and 50 nm. It was found that NPs with an average diameter of 50 nm showed the strongest oncogenic activity against mouse MDA-MB-231 tumors.[261] Wang et al prepared NPs with Au NPs as the core and FA-conjugated amphiphilic Zein-polydopamine (PDA) as the shell. The surface modification of FA conjugated PDA made the NPs more stable and also promoted the selective cellular internalization and enhanced endocytosis of the NPs. NPs exert superior tumor suppressive ability and low side effects compared to free HCPT and its non-targeted equivalents due to their active and passive targeted delivery in vitro and in vivo.[262] Evans Blue (EB) is a non-toxic dye that is widely used because of its excellent human serum albumin (HSA) binding affinity and excellent hydrophilicity.[263]

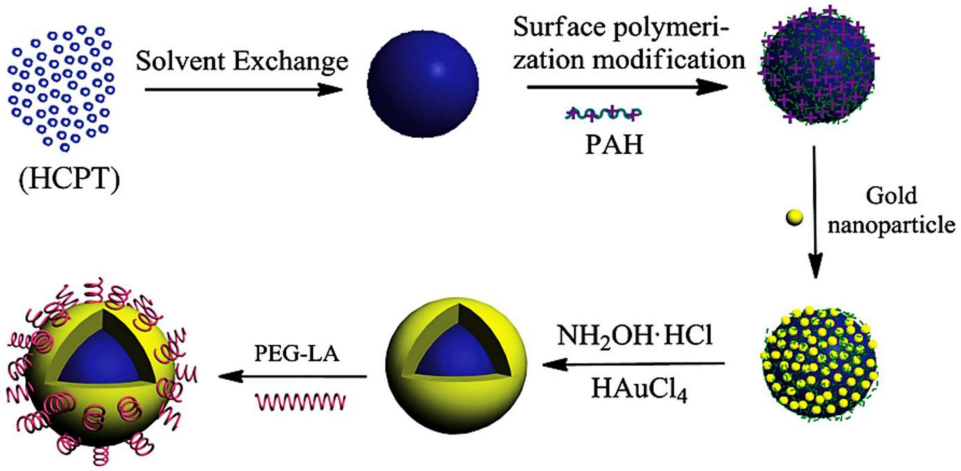

Figure 7 Schematic diagram of the preparation of Au NPs loaded with HCPT.
Notes: Reproduced from Li W, Zhang X, Zhou M, et al. Functional core/shell drug nanoparticles for highly effective synergistic cancer therapy. Adv Healthc Mater. 2014;3 (9):1475–1485. © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[260]

Wang et al constructed truncated Evans Blue (tEB)-modified Au NRs for better tumor treatment. HSA/HCPT was further complexed with Au NRs through the high binding affinity of tEB with albumin. In vitro and in vivo studies confirmed that the resulting the NRs have excellent tumor targeting, photothermal conversion efficiency and biostability.[264]

GO-Based NPs

GO is widely studied as a drug nanocarrier due to its high surface area, photothermal properties, high loading capacity and efficient cellular uptake.[265] Liu et al prepared starch-functionalized graphene nanosheets loaded with HCPT by the physical adsorption method. The nanosheets exhibited excellent biocompatibility and high drug loading capacity. The nanosheets exhibited high toxicity to SW-620 cells under the dual action of the acidic microenvironment and SW-620 cell amylase.[266] Huang et al prepared HCPT NPs using carboxymethyl chitosan and GO modified with HA as carriers. The NPs could target human hepatocellular carcinoma cells, improve drug uptake, and enhance the efficacy of HCPT in vitro and in vivo.[267]

Prussian Blue-Based NPs

Prussian blue NPs have attracted increasing research interest in bioimaging, drug delivery and applications as therapeutic agents due to their large inner pore size, tunable dimensions, ease of synthesis and surface modification, excellent thermal stability and excellent biocompatibility.[268] Jing et al reported hollow Prussian blue NPs loaded with HCPT and modified by HA-grafted PEG. The NPs were found to have excellent colloidal stability, prolonged circulation time, and the ability to target Hela cells overexpressing CD44 receptor. The NPs exhibited excellent photothermal efficiency and light-triggered drug release under NIR irradiation and showed significant inhibitory effects on cancer cells.[269]

Pt-Based NPs

Pt NPs have superior physicochemical properties and great potential in biomedical applications.[270] The combination of PDT with chemotherapy is of increasing interest, and the hypoxic nature of tumors greatly hinders the efficiency of PDT.[271] Fu et al prepared porous shuttle-shaped platinum methylene blue coordination polymer NPs loaded with HCPT. The NPs have a spatiotemporally controlled O_2 self-supply, self-administration of singly linear oxygen ($^1O2$) and excellent photothermal effects. Once they are taken up by tumor cells, the NPs acting as cascade catalysts can effectively catalyze the degradation of endogenous hydrogen peroxide (H_2O_2) into O_2 to alleviate tumor hypoxia. Subsequently, stimulated by external NIR irradiation and internal lysosomal acidity, the NPs can achieve on-demand release of HCPT to increase in situ mitochondrial ROS and efficient tumor ablation by phototherapy.[272]

$CaCO_3$-Based NPs

In recent years, the applications of $CaCO_3$ NPs have gained extensive interest as targeted drug/gene delivery systems to cancerous tissues and cells due to their accessibility, low cost, safety, biocompatibility, pH-sensitivity, and slow biodegradability.[273] Immunogenic cell death (ICD) can reinforce tumor immunotherapy by stimulating the auto-immune system through secreting associated signals. Qiu et al prepared pH-responsive NPs based on amorphous calcium carbonate loaded with HCPT and the photosensitizer Chlorin e6 (Ce6). Chemodynamic therapy (CDT)/PDT triggered immunogenic death for tumor eradication was achieved.[274]

Carrier-Free NPs

Carrier-free NPs are nanomedicine made from pure drug molecules without any organic and inorganic carriers involved or using only small amounts of organic molecules as surfactants to stabilize the nanomedicine or modulate the physical/chemical properties of the drug molecule so that it can self-assemble into it.[275] Synthetic carrier-free NPs, can be formulated from one or more drugs or coupled with functional organic molecules such as photosensitizers using covalent bonding and physical methods. Carrier-free NPs have attracted increasing interest in cancer therapy because of their improved pharmacodynamics/pharmacokinetics, reduced toxicity, and high drug loading capacity.[276,277] Some researchers have assembled HCPT and the photosensitizer Ce6 into stable NRs. These NRs not only circumvent the extreme hydrophobicity of HCPT, but also integrate two tumor treatment modalities into one. In vitro and in vivo antitumor studies have shown that NRs-mediated chemophotodynamic combination therapies exhibit superior antitumor efficacy compared to single chemotherapy or single PDT.[278,279] Wei Li et al chose HCPT as a model hydrophobic drug and then used FA for surface functionalization. The FA-modified NPs were found to exhibit higher cytotoxicity due to enhanced cellular uptake of HCPT via folate receptor (FR)-mediated targeted delivery.[280] Zhou et al prepared three widely used hydrophobic drugs MTX, HCPT, and paclitaxel (PTX) into a single NRs, which was then conjugated with PEG to improve its water dispersibility and bioenvironmental stability. It was shown that the NRs showed significantly higher cytotoxicity than the same dose of individual drugs and inhibited the resistance of MCF-7/ADR tumor cells to PTX.[281] Zhao et al used a convenient self-assembly method was used to formulate carrier-free NPs, which improved the water solubility of HCPT. The NPs improved the retention of drug in drug-resistant MCF-7R cancer cells, effectively enhancing the cytotoxicity.[282] Chen et al developed HCPT and DOX carrier-free NPs (Figure 8). When HCPT and DOX are assembled, they form small spherical drug NPs with a positive surface charge. The cellular uptake of HCPT was improved compared to HCPT alone, which exhibited enhanced synergistic cytotoxicity against breast cancer cells in vitro.[283] Han et al prepared stable HCPT nanosuspensions with small and narrow size distribution using a precipitation-ultrasonication method. Compared with HCPT injection, the nanosuspension showed better anticancer effects than injection in H22-tumor bearing mice.[284] Yang et al prepared NCs of HCPT using a modified acid-base micro-precipitation combined with a high-pressure homogenization technique. The NCs showed a sustained release pattern and were

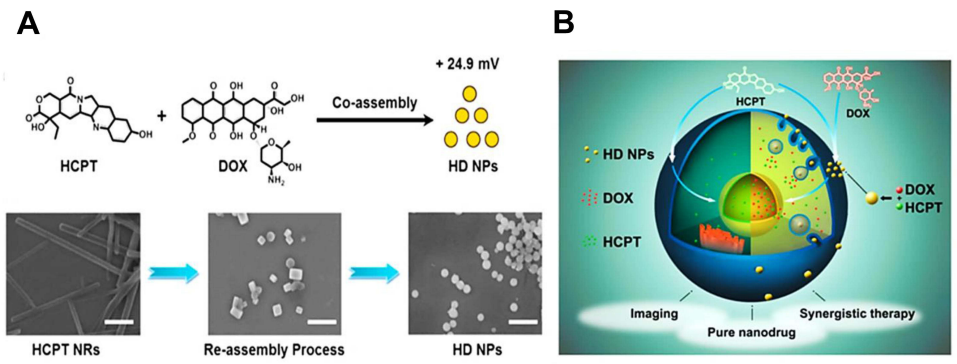

Figure 8 (**A**) Schematic illustration (top) and SEM images (bottom) of the co-assembly of HCPT and DOX molecules into carrier-free NPs. The bar is 1 μm. (**B**) Schematic diagram showing the different intracellular drug accumulation of free HCPT and carrier-free NPs.

Notes: Reprinted with permission from Chen F, Zhao Y, Pan Y, et al. Synergistically Enhanced Therapeutic Effect of a Carrier-Free HCPT/DOX Nanodrug on Breast Cancer Cells through Improved Cellular Drug Accumulation. Molecular pharmaceutics. 2015;12(7):2237–2244. Copyright 2015 American Chemical Society.[283]

shown to have higher cellular uptake and antiproliferative activity than HCPT injection.[285] Wang et al found tumor suppression by NPs with shape and polycrystal type dependence, needle-like NPs with longer blood retention time and more effective cellular uptake and higher cytotoxicity.[286]

Discussion

The introduction of nanocarriers as drug delivery systems can be traced back to a long time ago, and in recent years people have reported different functions and shapes of NPs through diffusion effect,[244] nanoprecipitation method,[221] self-assembly method,[198] dialysis method,[202] film dispersion method,[116] emulsion solvent evaporation method,[89] water/oil/water double emulsion process,[84] high-pressure homogenization,[47] solvent-exchange method[252] and other methods were used to prepare HCPT-loaded NPs with different functions and shapes. To ensure the stability of nanoparticles, various modifications have been performed on the surface of the particles. From the results, most HCPT-loaded NPs have excellent water dispersion and favorable bioenvironmental stability to release in the acidic tumor microenvironment. Depending on the type of material, HCPT-loaded NPs are classified differently and have different advantages and disadvantages (Table 1). For example, PEG, PLGA and PLA-based NPs are used as HCPT carriers for tumor therapy because of their excellent biocompatibility, stability and biodegradability. However, PEG-based NPs may limit the drug uptake by tumor cells although they prolong the circulation time of the drug in vivo. The release of PLGA-based NPs is not controlled during the initial drug delivery phase, and the same problem exists for PLA-based NPs.[287–289] Similarly, although protein-based NPs have the advantages of low cytotoxicity, reproducibility, and high drug binding capacity, they suffer from weak targeting and uncontrolled drug release.[290] As the most FDA-approved nanomedicine type, lipid-based NPs are known for their excellent non-toxicity, flexibility, and high drug-to-lipid ratio. However, when applied to deliver drugs, it is also found to suffer from instability, short half-life in vivo, and membrane leakage before reaching tumor sites.[291] To prolong the half-life of drugs, dendrimer-based NPs were chosen but were found to be time-consuming to produce, potentially cytotoxic and non-degradable.[292] When encountering insoluble drugs such as HCPT, cyclodextrins have often been chosen to increase the solubility of the drug, but cyclodextrin-based NPs were found to be easily and rapidly cleared in circulation.[293] Nanogels and hydrogels are favored for their excellent biocompatibility, large surface area and adjustable properties, but also have the problem of being easily cleared.[294] Electrospun fibers are increasingly used as drug delivery due to their high drug loading capacity, large surface area, high porosity and modification potential, however this it is also plagued by the problems of small pore size and lack of proper cellular infiltration inside the fiber.[295] Peptide-based NPs are easy to synthesize, customizable, have better biosafety, and can recognize bioreceptors on the surface of cancer cells for targeting, but they also suffer from unstable physicochemical properties, susceptible to oxidative hydrolysis, prone to agglomeration, short half-life and does not easily cross cell membranes.[296] Similar to peptides, polysaccharide-based NPs have excellent biocompatibility and degradability, and they are also readily available and easily modified, however, when they are used in practice, they are also found to have problems of easy swelling and premature disintegration.[297] Cell membrane-based NPs have attracted much attention because of their cell-specific targeting, long circulating half-life and immune escape function, but it is difficult to ensure that the cell membrane can be completely coated on the drug surface when they are prepared, and it is also difficult to control the inner and outer surfaces of the cell membrane.[298]

In addition to organic nanomaterials, inorganic nanomaterials are also the focus of research on HCPT carriers. Mesoporous SiO_2-based NPs are often used as nanocarriers for HCPT because of their large surface area, large pore capacity, controllable pore size adjustment and stable backbone structure, however, such carriers also have the problem of easy agglomeration.[241] $CaCO_3$-based NPs are widely used for drug delivery due to their availability, low cost, safety, biocompatibility, and pH sensitivity, but they also have the same problem of agglomeration as SiO_2.[299] Au-based NPs have long been used for drug delivery in HCPT due to their high surface area, tunable size, high stability, and high photothermal properties. However, they are susceptible to removal in circulation, potential biotoxicity, and non-degradability.[300] Magnetic materials-based NPs have received much attention for their excellent magnetic, imaging, and photothermal conversion capabilities, however it also suffers from easy scavenging.[301] GO-based NPs is of interest due to its superior properties such as high surface area, photothermal properties, high drug loading, and efficient cellular uptake, however, it is limited due to the fact that large-scale production of graphene is very difficult and expensive and

Table 1 Summary of Advantages, Disadvantages and Research Stages of Different Nanocarriers of HCPT

Materials	Nanocarriers	Advantages	Disadvantages	Clinical /Preclinical	References
Organic Materials	PEG-based NPs	Excellent biocompatibility, hydrophilicity, stability, biodegradability and extended internal circulation	May affect the cellular uptake rate	Preclinical	[26,27,287]
	PLGA-based NPs	Low toxicity, excellent biocompatibility, controlled and sustained drug release	Initial uncontrolled outbreak of the drug	Preclinical	[81,288]
	PLA-based NPs	Low toxicity, excellent biocompatibility, controlled and sustained drug release	Slow degradation speed	Preclinical	[93,289]
	Protein-based NPs	Regenerative, low cytotoxicity, high drug binding capacity	Weak tumor targeting and uncontrolled drug release	Preclinical	[96,97,103,290]
	Lipid-based NPs	Biocompatible, biodegradable, non-toxic, flexible and with high ratio of drug to lipid	Unstable, with a short half-life in the body and membrane leakage.	Preclinical	[108–110,291]
	Gels-based NPs	Large surface area and modifiable properties	Easily cleared in the loop	Preclinical	[146–148,294]
	Peptide-based NPs	Better biosafety, customizability, simplicity of synthesis process	Unstable physicochemical properties, easily oxidized and hydrolyzed, easily agglomerated, short half-life	Preclinical	[161,296]
	Dendrimer-based NPs	Long cycle time, not easily identified and cleared, easy surface modification for targeted delivery	Time consuming to manufacture, poor biodegradability	Preclinical	[172–174,292]
	Cyclodextrin-based NPs	Increase the water solubility of insoluble drugs to improve bioavailability and stability	Easily cleared in the loop	Preclinical	[179,180,293]
	Electrospun fiber-based NPs	High loading capacity and encapsulation efficiency, high specific surface area, high porosity and adjustable porosity	Small pore size and lack of proper cellular penetration inside the fiber.	Preclinical	[184,295]
	Polysaccharide-based NPs	Readily available, non-toxic, biocompatible, biodegradable, easily modified	Easy expansion and early disintegration	Preclinical	[193,297]
	Cell membrane-based NPs	Homologous targeting, biocompatibility, biodegradability and long circulating half-life, immune escapability	The orientation of the cell membrane is difficult to ensure when wrapping, and complete coverage cannot be guaranteed	Preclinical	[229,230,298]

Inorganic Materials	SiO_2-based NPs	Mesoporous SiO_2 NPs have large specific surface area, large pore capacity, uniform and adjustable pore size, and stable skeleton	Easy Reunion	Preclinical	[241]
	Magnetic material-based NPs	Excellent biocompatibility, magnetic properties, imaging	Easily cleared in the loop	Preclinical	[245,301]
	Cu-based NPs	Hollow Cu NPs have a porous structure as well as a large specific surface area and a simple synthesis process	Potential cytotoxicity	Preclinical	[255,256,303]
	Au-based NPs	High surface area-to-volume ratio, size tunability, high stability, high drug loading capacity, and high photothermal performance.	Easily cleared in the loop, potential cytotoxicity, poor biodegradable	Preclinical	[258,259,300]
	GO-based NPs	High surface area, photothermal properties, high loading capacity and efficient cellular uptake.	Large-scale production of graphene is very difficult and expensive, and may have toxicity risks	Preclinical	[265,302]
	Prussian blue-based NPs	Hollow Prussian blue with large pore size, adjustable size, easy synthesis and surface modification, good thermal stability and biocompatibility	Reproducibility and controllability are not satisfactory	Preclinical	[268,304,305]
	Pt-based NPs	Controlled release	Potential cytotoxicity	Preclinical	[270]
	$CaCO_3$-based NPs	Low cost, safety, biocompatibility, pH sensitivity	Poor affinity with polymers, easy agglomeration and adhesion	Preclinical	[273,299]
Carrier-free		High drug loading capacity	The self-assembly process is unpredictable and uncontrollable, unstable, prone to precipitation and aggregation	Preclinical	[275–277]

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may have toxicity risks.[302] Cu and Pt-based NPs, one in mesoporous form with large specific surface area and simple synthesis process, and one with controlled release of drugs, are thus attracting increasing interest, yet both share a common problem of possible toxicity risk.[303] Prussian blue is famous for its use as a dye, and mesoporous Prussian blue-based NPs are widely used for drug delivery due to their large internal pore size, tunable size, ease of synthesis and surface modification, excellent photothermal properties and biocompatibility, but their reproducibility and controllability are not satisfactory.[304,305] In addition to the above organic and inorganic nanocarriers, there is another type of HCPT nano drug delivery system that does not require any carrier, called "carrier-free NPs". Compared with carrier-based nano-delivery systems, carrier-free can greatly improve the drug efficacy and pharmacokinetics, reduce toxicity, and have high drug loading capacity, which is of great interest. However, they also have the defects that the self-assembly process is difficult to predict and control, easily unstable, and prone to precipitation and aggregation.[276] To date, most of the reported HCPT NPs, whether organic, inorganic or carrier-free, have shown superior antitumor effects compared to free HCPT. These NPs show promise in improving the aqueous solubility of drugs, enhancing cellular uptake and cytotoxicity, enhancing tumor targeting, and achieving a combination of diagnostic and therapeutic functions. These results suggest that nano-delivery systems are now a promising approach to improve the anti-tumor efficacy of HCPT and play a unique role in tumor therapy. Currently HCPT NPs are mainly used to kill tumor cells by chemotherapy or in combination with PTT or PDT, and not many are used in combination with other innovative therapies (Table 2). Meanwhile, unfortunately none of the HCPT nanomedicines have been approved by FDA for clinical use, which overshadows the development of nanocarriers for HCPT.

The main potential mechanism for nanomedicine design is the enhanced permeability and retention (EPR) effect, an approach known as passive targeting approach.[306] The EPR effect was first identified and named by Maeda et al in 1986 in solid tumors of mice.[307] The EPR effect has been well documented in small animal models, the number of related articles have grown exponentially, and scientists have made great efforts to develop and create nanomedicines that present a variety of shapes, sizes, therapeutic and imaging functions.[308] But this creative boom has failed to translate into better clinical outcomes. The number of anticancer nanomedicines currently in clinical trials has just broken into the single digits, and the vast majority are liposomal formulations, with no major innovative nanomedicines available.[309] More strikingly, even at the clinical stage nanomedicines have shown very limited improvement in the therapeutic effect of tumors.[310] The EPR effect as a mechanism of nanoparticle therapy for tumors has been increasingly challenged.[311] The low tumor penetration rate of nanomedicines is considered the most important reason for clinical translation failure.[312] Studies showed that mouse tumor models differ significantly from human cancers in many ways, including rate of progression, metabolic rate, and tumor-to-body weight ratio.[313] There is heterogeneity in the EPR effect because tumors vary greatly in blood flow and vascular permeability, and nanomedicines typically exhibit a more uniform EPR effect in small tumors and a less pronounced one in large, advanced tumors.[312,314]

If not the EPR effect, then what is the pathway of nanomedicines entry into tumors? Studies suggest that transcytosis, rather than the classical EPR effect, is the primary mechanism of NPs entry into tumors.[315,316] When there is simply not enough endothelial space in the vessel wall to support effective NPs extravasation and accumulation, active transcytosis of endothelial cells (involving active uptake, intracellular transport, and exocytosis) to be much more effective for in vivo nanoparticle delivery to solid tumors.[317] Active transcytosis allows rapid delivery of macromolecules and NPs into solid tumors, not only through alveolar epithelial cells but also across the blood-brain barrier.[318] Active transcytosis creating new hope for in vivo nanomedicines delivery and tumor penetration.[319]

Furthermore, there is research that in addition to transcytosis, nano-enhanced immunotherapy could offer a completely different approach to cancer nanomedicine.[320] Rather than designing NPs to overcome the vascular endothelial barrier, it would be more effective to use immune cells to destroy tumors. This approach bypasses the long-standing problem of in vivo delivery by formulating NPs that specifically stimulate the immune system and can effectively penetrate solid tumors.[321] It has also been found that after a specific dose threshold is breached, the hepatic clearance of NPs decreases and the circulation time is prolonged, which can effectively improve the drug delivery efficiency.[322] Others believe that nanomedicines can also be used for oncology applications that do not require EPR effects: reducing the toxicity of chemotherapeutic agents, local delivery of anticancer drugs, and as a tool for imaging.[309] In conclusion, the development of nanomedicines still has much to offer for deeper reflection and innovation, and we should reconsider

Table 2 Classification and Primary Treatment Strategy of the HCPT Nano-Drug Delivery System

Materials	Nanocarriers	Therapy Modality	In vitro/In vivo	References
Organic Materials	PEG-based NPs	Chemotherapy	In vitro	[33,50,68,75,77–80]
		Chemotherapy	In vitro and In vivo	[29,32,35,42,45,47,48,59,63,65,67,70–74,76]
		Chemotherapy combined with PDT	In vitro	[57]
		Chemotherapy combined with PDT	In vitro and In vivo	[53,54]
		Chemotherapy combined with radiotherapy	In vitro and In vivo	[62]
		Chemotherapy combined with siRNA	In vitro and In vivo	[39]
		Chemotherapy combined with antibody therapy	In vitro and In vivo	[41]
	PLGA-based NPs	Chemotherapy	In vitro	[87]
		Chemotherapy	In vivo	[89]
		Chemotherapy	In vitro and In vivo	[84,85,91,92]
	PLA-based NPs	Chemotherapy	In vitro	[94,95]
	Protein-based (Albumin) NPs	Chemotherapy	In vitro	[101,102]
		Chemotherapy	In vitro and In vivo	[99]
	Protein-based (Other) NPs	Chemotherapy	In vitro	[104]
		Chemotherapy	In vitro and In vivo	[105,107]
	Lipid-based (Liposomes) NPs	Chemotherapy	In vitro and In vivo	[113,115]
		Chemotherapy	In vitro	[116,118,121]
		Chemotherapy combined with SDT	In vitro and In vivo	[120]
	Lipid-based (SLN) NPs	Chemotherapy	In vitro and In vivo	[125]
	Lipid-based (NCL) NPs	Chemotherapy	In vitro and In vivo	[128,129]
	Lipid-based (Nanoemulsion) NPs	Chemotherapy	In vivo	[131]
	Lipid-based (LPH) NPs	Chemotherapy	In vitro	[134]
	Lipid-based (Other) NPs	Chemotherapy	In vitro	[138]
		Chemotherapy	In vivo	[135]
		Chemotherapy	In vitro and In vivo	[136,139,142,143,145]
		Chemotherapy combined with PDT	In vitro and In vivo	[137]
	Gels-based (Nanogels) NPs	Chemotherapy	In vitro	[153]
		Chemotherapy	In vitro and In vivo	[150–152]
	Gels-based (Hydrogels) NPs	Chemotherapy	In vitro	[155,157]
		Chemotherapy	In vitro and In vivo	[156,158–160]
	Peptide-based NPs	Chemotherapy	In vitro	[168]
		Chemotherapy	In vitro and In vivo	[163,164,166,167,169–171]
	Dendrimers-based NPs	Chemotherapy	In vitro	[175,176]
		Chemotherapy	In vitro and In vivo	[177,178]
	Cyclodextrins-based NPs	Chemotherapy	In vitro	[182]

(*Continued*)

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Table 2 (Continued).

Materials	Nanocarriers	Therapy Modality	In vitro/In vivo	References
		Chemotherapy	In vitro and In vivo	[183]
	Electrospun fibers-based NPs	Chemotherapy	In vivo	[185,192]
		Chemotherapy	In vitro and In vivo	[186–188,190]
	Polysaccharide-based (Chitosan) NPs	Chemotherapy	In vitro	[197,199]
		Chemotherapy	In vitro and In vivo	[198,201–203]
		Chemotherapycombined with Gas Therapy	In vitro and In vivo	[205]
	Polysaccharide-based (HA) NPs	Chemotherapy	In vitro and In vivo	[208,209]
	Polysaccharide-based (Starch) NPs	Chemotherapy	In vitro	[211]
		Chemotherapy	In vitro and In vivo	[212–214]
	Polysaccharide-based (Pectin) NPs	Chemotherapy	In vitro and In vivo	[216–218]
	Polysaccharide-based (Cellulose) NPs	Chemotherapy	In vitro and In vivo	[221,222]
	Polysaccharide-based (Other) NPs	Chemotherapy	In vitro	[228]
		Chemotherapy	In vitro and In vivo	[224,226]
	Cell membrane-based NPs	Chemotherapy	In vitro and In vivo	[231]
		Chemotherapy combined with PTT	In vitro and In vivo	[232,233]
	Other organic NPs	Chemotherapy	In vitro	[236]
		Chemotherapy	In vitro and In vivo	[235,237–239]
Inorganic Materials	SiO_2-based NPs	Chemotherapy	In vitro and In vivo	[242]
		Chemotherapy combined with immunotherapy	In vitro and In vivo	[244]
	Magnetic material-based NPs	Chemotherapy	In vitro	[249,250,254]
		Chemotherapy	In vitro and In vivo	[247,251–253]
	Cu-based NPs	Chemotherapy	In vitro	[257]
	Au-based NPs	Chemotherapy	In vitro and In vivo	[261,262]
		Chemotherapy combined with PTT	In vitro and In vivo	[260,263]
	GO-based NPs	Chemotherapy	In vitro	[266]
		Chemotherapy	In vitro and In vivo	[267]
	Prussian blue-based NPs	Chemotherapy combined with PTT	In vitro and In vivo	[269]
	Pt-based NPs	Chemotherapy combined with PDT	In vitro and In vivo	[272]
	$CaCO_3$-basedNPs	CDT combined with PDT	In vitro and In vivo	[274]
Carrier-free		Chemotherapy	In vitro	[280,283]
		Chemotherapy	In vivo	[284]
		Chemotherapy	In vitro and In vivo	[281,282,285,286]
		Chemotherapy combined with PDT	In vitro and In vivo	[278,279]

our strategies and gain a deeper understanding of nanomedicine action and tumor properties with the aim of developing nanomedicines with higher clinical translation rates.

Conclusion and Outlook

This article reviews the latest research advances of HCPT nano delivery systems for antitumor. It is found that there have been many studies related to HCPT-loaded NPs, and different types of NPs with various functions have been developed. The only troubling thing is that most of the studies on HCPT nanomedicines have remained in the papers and have not been used in the clinical setting for the treatment of tumors. This may be due to various objective conditions on the one hand, and the mechanism of nanomedicines for tumor treatment other than the EPR effect, on the other hand, is still unclear. As a promising development direction to overcome tumors, nanomedicines are regarded with high expectations. In the future, in addition to the innovation related to nanomedicine carriers and functions based on the original research, we should pay more attention to the study of the mechanism by which nanomedicine exerts anti-tumor effects. It is confident that in the near future, HCPT nanomedicines with high clinical translation rate will be developed to bring the dawn for tumor treatment.

Abbreviations

HCPT, 10-Hydroxycamptothecin; CPT, Camptothecin; EPR, Enhanced permeability and retention; NPs, Nanoparticles; NRs, Nanorods; NCs, Nanocrystals; PEG, Polyethylene glycol; PLGA, Poly (lactic-co-glycolic acid); PLA, poly (D, L-lactic acid); RES, Reticuloendothelial system; FDA, Food and Drug Administration; MTX, Methotrexate; DEX, Dexamethasone; ROS, Reactive oxygen species; siRNA, Small interfering RNA; ASGP, Asialoglycoprotein; FA, Folic acid; FR, Folate receptor; AR, Aspect ratio; GSH, Glutathione; LIFU, Low-intensity focused ultrasound (LIFU); EGFR, Epidermal growth factor; TPP, Triphenylphosphonium; HAS, Human serum albumin (HSA); BSA, Bovine serum albumin; GA, Glycyrrhetinic acid; HDL, High-density lipoproteins; CA, Casein; SDT, Sonodynamic therapy; 5-ALA, 5-Aminolevulinic acid; BBR, Berberine hydrochloride (BBR); SG, Stearyl glycyrrhetinate; HGF, Hepatocyte growth factor; β-CD, β-cyclodextrin; CA4, Combretastatin A-4; TP, Tea polyphenols; HA, Hyaluronic acid; NO, Nitric oxide; MDR, Multidrug resistance; Pgp, P-glycoprotein; PA, Photoacoustic; UA, Ursolic acid; DHA, Dihydroartemisinin; GLP, Ganoderma lucidum polysaccharide; RBC, Red blood cell; ICG, Indocyanine green; NIR, Near-infrared; CMs, Cancer cell membranes; vcMMAE, Valine-citrulline monomethyl auristatinE; SiO_2, Silicon dioxide; Au, gold; GO, Graphene oxide; Cu, Copper; Pt, Platinum; $CaCO_3$, Calcium carbonate; PFP, Perfluoropentane; MR, Magnetic resonance; MOFs, Metal organic backbones; PDA, Polydopamine; EB, Evans Blue; $^1O2$, Singly linear oxygen; H_2O_2, Hydrogen peroxide; ICD, Immunogenic cell death; CDT, Chemodynamic therapy; PTX, Paclitaxel; PTT, Photothermal therapy; PDT, Photodynamic therapy.

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Disclosure

The authors declare that they have no competing interests.

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