ABSTRACT
The drug camptothecin has a wide range of antitumor effects in cancers including gastric cancer, rectal and colon cancer, liver cancer, and lung cancer. Camptothecin-based drugs inhibit topoisomerase 1 (Topo 1), leading to destruction of DNA, and are currently being used as important chemotherapeutic agents in clinical antitumor treatment. However, the main obstacle associated with cancer therapy is represented by systemic toxicity of conventional anticancer drugs and their low accumulation at the tumor site. In addition, low bioavailability, poor water solubility, and other shortcomings hinder their anticancer activity. Different from traditional pharmaceutical preparations, nanotechnology-dependent nanopharmaceutical preparations have become one of the main strategies for different countries worldwide to overcome drug development problems. In this review, we summarized the current hotspots and discussed a variety of camptothecin-based nanodrugs for cancer therapy. We hope that through this review, more efficient drug delivery systems could be designed with potential applications in clinical cancer therapy.

KEYWORDS
Camptothecins; nanomedicine; cancer therapy; drug delivery system

Introduction
In 1966, Monroe E. Wall first isolated camptothecin (CPT) from the stem of Camptotheca, a plant genus endemic to China. He discovered that CPT had a number of effects on malignant tumors such as gastrointestinal cancer, liver cancer, and leukemia. Later, in 1985, Y. H. Hsiang found that CPT could block the synthesis of topoisomerase I (Topo 1), an enzyme closely related to cell division. Blockade of Topo 1 production by CPT prevents cancer cell growth, thus endowing this compound with unique anticancer properties. From this discovery, research on CPT entered a new stage. A large number of CPT derivatives and analogs emerged, among which irinotecan, topotecan, and 10-hydroxycamptothecin (HCPT) were approved for listing. Moreover, various active compounds are currently in the clinical stage. However, similar to most chemotherapeutic agents, application of CPT is limited by its inherent deficiencies such as poor water solubility, low biocompatibility, toxic side effects on healthy tissue, and a variety of complications.

In recent years, scientists have been trying to overcome these deficiencies. The emergence of nanotechnology provides possibilities to address chemotherapy-associated drawbacks such as toxic side effects of anticancer drugs as well as their low water solubility. Due to the unique features of nanoparticles, including nanoscale size, high specific surface area, and controllable physical and chemical properties, the water solubility and stability of drugs can be improved, resulting in desirable pharmacokinetics and other parameters. In addition, nanopharmaceuticals can accumulate at the tumor site and regulate drug distribution due to their enhanced permeability and retention effect (EPR). The key advantages of nanomedicines are as follows: (1) improved water solubility and biocompatibility of the drug, (2) prolongation of tolerance time for the anticancer drug in the body by surface-modified nanoparticles, (3) precise accumulation of chemotherapeutics at the tumor site by targeting strategy, (4) stimulus-responsive release of payloads, and (5) reduced toxic side effects against normal cells and tissues. In this regard, an effective combination of conventional chemotherapeutics with nanotechnology-based approaches to achieve efficient...
tumor treatment with low toxic side effects has become an important research area in cancer treatment and clinical application\textsuperscript{8-11}.

Onivyde, a nanoliposomal dosage form of irinotecan, was approved by the FDA for pancreatic cancer treatment in 2015, and is currently being tested clinically for other malignancies\textsuperscript{12,13}. In this manner, carrier-assisted CPT nanodrug delivery systems have been studied extensively. In addition, prodrug-coupled nanodrug delivery system is more suitable for effective transport and tracking of CPT-based drugs. Carrier-free, self-assembled pure nanodrug delivery systems provide more efficient drug doses for better therapeutic effects. In this review, we present all three nanodrug delivery systems based on CPTs (Figure 1).

**Carrier-aided nanodrug delivery system**

Normally, drugs undergo rapid metabolism in the body and lose their pharmacological activity. Therefore, it is important to improve their effective accumulation in the lesion. Based on the remarkable research achievements made in material science and pharmacy, nanomaterials with different sizes, structures, and surface properties have been developed including liposomes, polymeric nanoparticles, and inorganic nanomaterials such as iron oxide, carbon nanotubes, and silica\textsuperscript{14}. These carriers can be widely used for delivering CPT drugs in vivo. The therapeutic effect of the drug is improved by the systemic (intravenous) or in situ route of administration. In addition, existing surface modification techniques can also affect the pharmacokinetic behavior and biodistribution of nanoparticles. For example, PEGylation protects drug-loaded nanoparticles from adsorption in the bloodstream, thereby achieving a long circulation cycle in the body and resulting in enhanced delivery at the tumor site through the EPR effect. Furthermore, the nanoparticle surface can be modified with active ligands to target specific cells. At present, many nanocarriers of CPT drugs have been used in clinical trials (Table 1).

**Polymer-based nanocarriers for delivering CPTs**

Delivery systems for transporting CPT drugs based on polymers as building blocks can be divided into two groups: natural polymers (such as proteins, and polysaccharides), and synthetic polymers (such as PLGA-PEG and PCL-PEG). Due to its natural presence in humans as well as its unique shape and excellent biocompatibility, the transferrin nanocarrier has attracted substantial interest. Chen et al\textsuperscript{24} prepared surface-modified transferrin nanoparticles of irinotecan, containing the specific targeting polypeptide PROM1, to achieve targeted delivery in colorectal cancer. Min et al\textsuperscript{25} loaded CPT into glycol-modified chitosan to prepare a nanoscale drug delivery system that shows prolonged blood circulation time and tumor targeting ability, for use in the treatment of human breast cancer. In addition, human serum albumin (HSA) is a multi-gene family protein that exists in the circulatory system with an average molecular weight of 66 kDa and a blood concentration of 50 mg/mL. It has low toxicity, high biocompatibility, and suitable biodegradation rate, and has therefore been widely used in drug delivery systems. Wang et al\textsuperscript{26} prepared HSA-modified HCPT-containing nanoparticles, FA-HSA-nHCPT-NPs, in which the drug loading was 7.8%.

Owing to the diversity of chemical properties, synthetic polymer nanocarriers are a promising tool for nanotechnology-based therapy. Svenson et al\textsuperscript{27} prepared CPT nanoparticles CRLX101, based on cyclodextrin as a carrier. Preclinical data indicated that CRLX101 showed a complete tumor response of 55.6% at day 125 after treatment at a dose of 10 mg/kg,

![Figure 1](image-url)
whereas no complete tumor responses were observed in irinotecan-treated mice. Because of its antitumor properties such as inhibition of tumor cell proliferation and angiogenesis, CRLX101 has entered the clinical stage. Hamaguchi et al. have developed NK012 into clinical phase II. SN-38 was first connected to polyglutamate through an ester bond, and then assembled with polyethylene glycol as a shell to form nanopolymeric micelles. The size of the resulting nanoparticles was about 20 nm, even in different patients who have shown a stable effect. The copolymer was also considered a promising carrier. For example, Lee et al. loaded SN-38 onto poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) (Pluronic F-108) and poly(PEG-b-PCL) to form nanoparticles. The drug loading capacity was (20.73±0.66)% and good biodistribution was observed, which improved the drug's ability to kill tumor cells. Apart from these, PDMA-block-poly(ε-caprolactone) (PDMA-b-PCL), poly-lactide-co-glycolide-poly-Ethylene glycol-folate (PLGA-PEG-FOL) conjugate and other polymers have the potential to improve cell penetration and enhance the antitumor effect of CPT drugs.

**Lipid-based nanocarriers for delivering CPTs**

Liposomes are vesicles composed of a phospholipid bilayer with an aqueous phase as the core. This structure allows loading of therapeutic drugs either into the hydrophobic region of the liposome (the partition of the lipid layer) or in the hydrophilic part (the aqueous phase). This feature makes liposomes very promising nanocarriers. A new technique was first demonstrated for stabilizing the embedded drugs using liposomes by encapsulating irinotecan (CPT-11) into long-term circulating liposomal nanoparticles in 1999. After that the most critical achievement is that irinotecan nanoliposomes (Onivyde) was approved by the FDA for the treatment of metastatic pancreatic cancer in 2015. In addition, the presence of polyethylene glycol (PEG) on the nanocarrier surface can prevent absorption of liposomes by the vascular endothelial system (RES). Atyabi et al. found that the blood concentration of PEGylated nanoliposomes carrying SN-38 is nearly 50%, higher than that of non-PEGylated liposomes, and their accumulation in the liver, spleen, lungs, kidneys, and other organs is lower than that of non-PEGylated nanomicelles. Recently, Zhang et al. obtained (HCPT-Ch-LDH)@LS nanostructures by liposome surface modification through a co-assembling strategy, thus providing better water solubility and sustained release of HCPT compared to those of unmodified-liposome nanoparticles.

**Inorganic nanoparticles for delivering CPTs**

Inorganic nanoparticles are widely used in tumor imaging, radiotherapy, and drug delivery. Single-walled carbon nanotubes have low immunocompetence and show effective cell endocytosis, and were used by Lee et al. as carriers of...
SN-38 for targeted delivery and controlled drug release. Liu et al.\textsuperscript{41} developed a lipid carrier coated with mesoporous silica (LB-MSNP), which shows better biocompatibility and therapeutic effects than those shown by liposomes and free drugs, and is expected to be used as the first-line medication in the treatment of pancreatic duct cancer (PDAC). This group also attached the iRGD polypeptide to the liposome surface in order to enhance the efficacy of irinotecan and reduce tumor metastasis.\textsuperscript{42} In addition, Song et al.\textsuperscript{43} utilized PEG-modified hollow tantalum oxide with the payload SN-38 (H-TaOx-PEG@SN-38) for magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) multimodal imaging, as well as to achieve the combined effect of radiotherapy and chemotherapy. Muniesa et al.\textsuperscript{44} also designed a nanomaterial with CPT and mesoporous silica, thereby achieving a response in the glutathione environment.

**Prodrug-coupled nanodrug delivery systems**

At present, prodrug-coupled nanodrugs are one of the successful drug delivery systems in clinical treatment. A prodrug is a compound that is metabolized to a pharmacologically active drug after administration. Nanotherapeutics are designed by covalently linking prodrugs with nanosized carriers composed of antibody molecules, lipids, proteins, polysaccharides, polypeptides, or polymers, which can improve bioavailability when a drug itself is poorly absorbed, and thus reduce the severe unintended and undesirable side effects of the drug.\textsuperscript{45}

Only a few nanoparticles conjugated with CPT, such as N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers\textsuperscript{46,47}, polyglutamic acid (PGA), polyethylene glycol (PEG)\textsuperscript{48-50}, and carboxymethyldeextran polyalcohol polymer\textsuperscript{51,52} have entered clinical practice so far. Prodrug-coupled nanodrug delivery systems
systems have also been used in clinical trials (Table 2). These block copolymers are assembled to form micelles. Drug coupling to the polymer carrier can improve the water solubility of hydrophobic drugs, thus making it easier to inject them in patients. Although there are many polymers that can be used for drug delivery, only few of them can be used in the clinic due to their toxicity and immunogenicity, resulting in less effective drug delivery\textsuperscript{45}.

In addition, most nanoparticles conjugated with CPT using polymers show tumor targeting dependent on tumor vascular permeability (EPR effect\textsuperscript{53}). Han et al.\textsuperscript{54} connected herceptin (an antibody to HER2) to the surface of MAP-CPT nanoparticles via a boronic acid bond to achieve targeted combination therapy for HER2-overexpressing breast cancer. Peng et al.\textsuperscript{55} conjugated the anticancer drug CPT with a polypeptide that was self-assembled to form nanofibers that could release CPT by hydrolysis. Zhang et al.\textsuperscript{56} prepared a combination of irinotecan and fatty acids to achieve a high drug load with 77.2\% irinotecan content, high drug availability, and enrichment at the tumor site.

**Carrier-free pure nanodrug delivery systems**

While drug-loaded nanocarriers have many advantages, there are still some concerns regarding potential issues\textsuperscript{8,59,60} in the fields of environment, health, and safety\textsuperscript{61,62}. Furthermore, almost all carriers have no therapeutic efficacy by themselves\textsuperscript{63,64}. It is complicated to establish a proper manufacturing process\textsuperscript{65} for drug-loaded nanocarriers, and most of them demonstrate low drug-loading capacity\textsuperscript{66}. Even worse, many carriers may cause high toxicity and serious inflammation in the kidneys and other organs\textsuperscript{61,63,64}. Therefore, development of alternative targeted delivery strategies with minimum use of inert materials is highly desirable\textsuperscript{67}. There is no doubt that carrier-free pure nanodrugs will thus become candidates in the next generation of drugs\textsuperscript{63,68-71}.

Hitoshi Kasai\textsuperscript{68} proposed the use of CPT (SN-38) to form a dimer and first assembled it to form nanoparticles successfully. These nanoparticles showed reduced side effects due to the absence of other components, and the drug-loading capacity was nearly 100\%. Since then, pure drugs with the ability to self-assemble into nanodelivery systems have opened a new chapter in drug delivery. Subsequently, disulfide-linked CPT and irinotecan nanoparticles achieved a response to glutathione and drug release in a specified area\textsuperscript{72}. Improvement of the water solubility of CPT and multiple attacks against tumor cells could be achieved through co-assembly of CPT and other drug components. In a previous work, Chen et al.\textsuperscript{73} provided a new strategy for the combination of drugs by co-loading HCPT and doxorubicin (DOX)\textsuperscript{73,74}, which resulted in a synergistic effect in overcoming tumor drug resistance. Wen et al.\textsuperscript{75} combined HCPT with dihydraphorphyrin (C6). These two components co-formed a nanorod structure by π-π conjugation and hydrophobic interaction. This hybrid nanodrug not only circumvents the extreme hydrophobicity of HCPT (with a solubility at least 100-fold higher than that of free HCPT in water), but also integrates two tumor treatment modalities into one system. It provided a simple and green solution to develop pure carrier-free nanodrugs that combine two treatment modalities, chemotherapy and photodynamic therapy, into a single platform to circumvent the drawbacks.

**Table 2** Prodrug-coupled nanodrug delivery system for camptothecins nanomedicine in clinical trials. Alternative names for the products are given in brackets.

| Product [company]          | Platform                              | Drug                    | Indication                                  | Status | Ref. |
|----------------------------|---------------------------------------|-------------------------|---------------------------------------------|--------|------|
| CT-2106 [CTI Biopharma]    | Polylglutamic acid drug conjugate     | Camptothecin            | Colon cancer, ovarian cancer                | Phase 1/2 [57] |
| DE-310 [Daichi Pharmaceutical] | Carboxymethylidextran polyalcohol drug conjugate | DX-8951 (camptothecin derivate) | Solid tumors                                | Phase 1 [52] |
| Delimotecan (Men 4901/T-0128) | Carboxymethylidextran drug conjugate | T-2513 (camptothecin analogue) | Solid tumors                                | Phase 1 [51] |
| MAG-CPT (PNU166148/ Mureletecan) [Pfizer] | HPMA drug conjugate | Camptothecin            | Solid tumors                                | Phase 1 [47] |
| NKTR-102 (Etirinotecan pegol) [Nektar] | PEG drug conjugate | Irinotecan              | Breast cancer, ovarian cancer, colorectal cancer | Phase 3 [48] |
| Pegamotecan (EZ-246) [Enzon] | PEG drug conjugate | Camptothecin            | Gastric cancer                              | Phase 2 [50] |
| XMT-1001 [Mersana]         | Fleximer drug conjugate              | Camptothecin            | Gastric cancer, lung cancer                 | Phase 1 [58] |
of traditional small molecules and to achieve highly potent antitumor capacity, which could be easily expanded to other drugs and modalities. The rationale of this facile and green strategy for carrier-free pure nanodrugs might provide new opportunities for the development of combinatorial therapeutics for tumors.

Conclusions

Due to their unique physical and chemical properties, CPT drugs have received widespread attention in the field of pharmaceutical preparations. However, there are many obstacles for nanodrugs in their journey from the laboratory to the clinical stage. Although CPT drug delivery systems have been extensively studied, most nanodrug-dependent nanopharmaceuticals are limited by the potentially toxic side effects of nanomaterials and in vivo metabolism and controllable problems. Thus, nanodrugs that can be used without nanocarriers, relying on self-assembled drug molecules, are thought to be the new generation of pharmaceutical preparations of clinical value, but they still need to be tested. As a general rule, the simpler and easier the development of a system is, the better are its chances of reaching the clinic.

Conflict of interest statement

No potential conflicts of interest are disclosed.

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