Review article

The drug release of PLGA-based nanoparticles and their application in treatment of gastrointestinal cancers

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A B S T R A C T

The poly (lactic-co-glycolic acid) (PLGA) based nanoparticles have been applied for drug delivery due to their simple preparation, biodegradability, and ideal biocompatibility. In this study, the factors affecting the degradation of PLGA-based nanoparticles are reviewed, encompassing the ratio of PLA to PGA, relative molecular weight, crystallinity, and preparation process of PLGA nanoparticles. The drug release behavior of PLGA-based nanoparticles, such as the degradation environment, encapsulated drug properties of polymers, and drug loading rates, are also discussed. Since gastrointestinal cancer is one of the major global threats to human health, this paper comprehensively summarizes the application of PLGA nanoparticles in gastrointestinal cancers from diagnosis, chemotherapy, radiotherapy, and novel tumor treatment methods (immunotherapy, gene therapy, and photothermal therapy). Finally, the future application of PLGA-based drug delivery systems in treating gastrointestinal cancers is discussed. The bottleneck of application status and the prospect of PLGA-nanoparticles in gastrointestinal tumor application are presented. To truly realize the great and wide application of PLGA-based nanoparticles, collaborative progress in the field of nanomaterials and life sciences is needed.

1. Introduction

In China, gastrointestinal cancer ranks second among malignant tumors of the gastrointestinal tract and poses a major threat to public health [1]. Despite the possibility of a complete cure through early surgical treatment, most patients have insidious symptoms and seek medical attention only when the cancer has progressed to an advanced stage. Without chemotherapy, the probability of a complete cure through curative surgery is limited. However, due to the low blood drug concentration in the digestive and circulatory system, as well as tumor cell resistance to traditional chemotherapy drugs, conventional chemotherapy regimens are often limited by various toxic side effects [2]. Therefore, it is imperative to develop novel drug-delivery nanosystems and drug types to alleviate the toxic side effects of traditional chemotherapy drugs and improve the antitumor effect.

In the biomedical field, poly (lactic-co-glycolic acid) (PLGA) is the only biodegradable polymer approved by the US Food and Drug Administration (FDA) as well as the European Medicines Quality Agency (EMA) [3]. PLGA is a linear aliphatic polyester-based

copolymer formed by the polymerization of lactic acids and glycolic acids in a particular proportion (see Fig. 1). In addition to lipid nanoparticles, PLGA particles in the nano and micron range have emerged as the predominant drug carrier polymers extensively investigated for biomedical applications [4]. The US FDA has approved 12 PLGA-based nanoparticle drug products [5]. The biodegradable aliphatic amorphous polymer PLGA is formed from acetic acid and glycolic acid polymerization. The classical methods of PLGA synthesis are ring-opening polymerization addition and direct polycondensation reactions [3]. The emulsification-solvent evaporation technique is the most common method for preparing PLGA particle formulation. Other preparation methods encompass spray-drying, phase separation, microfluidics, and nanoprecipitation [6]. The PLGA nanoparticle has been developed for sustained release (from weeks to months) of different active pharmaceutical ingredients such as small molecules, peptides, and proteins. It overcomes the limitations of chemotherapeutic drug therapy to protect them from degradation in the gastrointestinal tract, achieve high load capacity, and provide a variety of surface modifications. A wide range of diverse biomedical applications involving PLGA-based drug delivery systems are being investigated in preclinical and clinical studies encompassing the treatment of cardiovascular and inflammatory diseases as well as wound healing and tissue regeneration [7].

Nevertheless, the development of new drug-delivery products poses significant challenges due to potential dose dumping and associated risks to patient safety arising from high drug loads intended for sustained release. Therefore, a comprehensive understanding of key parameters affecting the drug release behavior of PLGA-based nanoparticles is essential to ensure their performance and safety. This study summarizes information about drug-loaded PLGA-based nanoparticles, including factors affecting drug release and their applications in treating gastrointestinal cancers. This study aims to provide reference ideas for experts in the field of gastrointestinal cancer and to prospect the future application of PLGA-based nanoparticles in the clinical treatment of gastrointestinal cancers.

2. The drug release of PLGA-based nanoparticles

As a nano drug loaded nanoparticle carrier, the degradation behavior of PLGA polymer directly affects the release behavior of sustained-release preparations [8]. Therefore, by adjusting the relevant factors affecting the PLGA degradation behavior [9], the release degree of sustained-release drugs can be adjusted [10]. The factors affecting the PLGA degradation behavior include the ratio of PLA (polylactic acid) monomer to PGA (polyglycolic acid), relative molecular weight (M_w), crystallinity, degradation environment (pH value, temperature, etc.), drug type, and preparation type after matrix encapsulation of the drug.

2.1. Factors influencing the degradation of PLGA-based nanoparticles

2.1.1. Ratio of PLA to PGA
The PLGA composition is usually determined by the ratio of its monomer PLA to PGA. As known to all, the molar ratio of L-lactic acid (LA)/glycolic acid (GA) affects the PLGA crystallinity, thereby affecting the swelling and water absorptivity of the polymer. Specifically, the introduction of glycolic acid reduces the crystallinity of the polymer and accelerates the water absorption rate of the nanomaterial. Therefore, by changing the ratio of LA to GA in amorphous polymers, the degradation rate of PLGA can be adjusted. Research has proven that when the GA content is below 50 %, PLGA is more inclined to the properties of PLA as the GA content decreases, namely an enhanced hydrophobicity and reduced degradation rate. The higher the PGA content, the stronger the hydrophilicity, wettability, and amorphous nature of PLGA, and the faster the degradation rate, resulting in faster drug release [11]. PLGA copolymers undergo degradation in both in vivo and in vitro aquatic environments, and the degradation time of PLGA can vary from several months to years depending on the polymer composition and its relative molecular weight. Petposri et al. compared the degradation rates of PLGA polymer membranes with different compositions (PLA to PGA ratios of 10:90 and 70:30) and same relative molecular weight. As the PGA ratio decreased and the PLA ratio increased, the PLGA degradation rate decreased [12]. Essa et al. found that higher GA content and more amorphous regions in PLGA polymers resulted in faster degradation of PLGA polymers due to stronger hydrophilic [13]. Due to this property of PLGA, drug release can be flexibly regulated in the drug delivery systems.
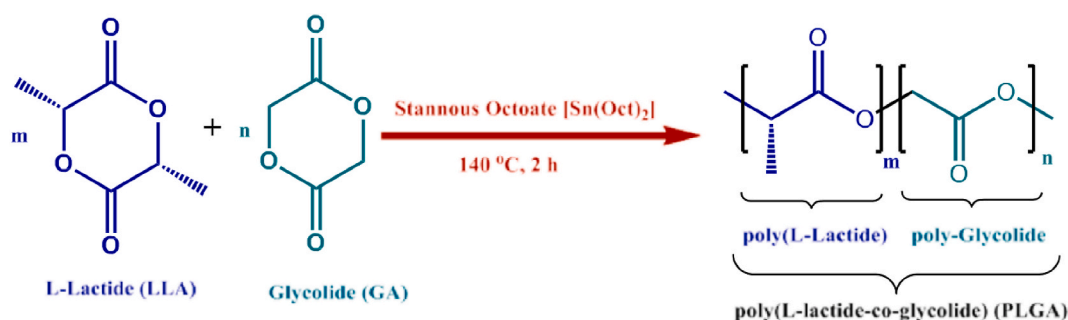

Fig. 1. Structure and synthesis of PLGA. Reprinted with permission [14].

2.1.2. Relative molecular weight

The molecular weight (M_w) and the distribution of polymerization degree (M_w/M_n, PDI) of PLGA are important factors affecting the PLGA degradation rate. With low polymer's M_w and a short PLGA chain, the content of terminal carboxylic groups is higher comparing to that of high M_w PLGA. Due to the fact that carboxylic groups can cause self-catalysis of polymers, the degradation rate of low M_w PLGA is faster [15]. Therefore, when low M_w PLGA is used to prepare drug loaded particles, the sustained release period of the delivery system is short. Brauner et al. investigated the release rates of low relative M_w PLGA 2300 and PLGA 503H. The results showed that low relative M_w PLGA can produce water-soluble oligomers more quickly than high relative M_w PLGA, ultimately releasing drugs faster [16]. Ochi et al. used leuprorelin acetate as the active carrier drug and increased the relative M_w of PLGA (75:25) from 6500 to 15400 [17]. They found that with the increase of the PLGA relative M_w, the particle size of the nanoparticles gradually increased, and the drug loading and release significantly decreased. The above research results indicate that as the relative M_w of PLGA decreases, both the polymer degradation and drug release rates will increase. The drug release of low M_w PLGA nanoparticles is usually regulated by drug diffusion, while the drug release of high molecular weight PLGA nanoparticles is usually controlled by both drug diffusion and polymer erosion [9].

2.1.3. Crystallinity

The crystallinity of PLGA polymers affects their mechanical strength, swelling behavior, biodegradation rate, and drug release behavior. The PLGA polymers crystallinity depends on the crystallinity of the units formed during the copolymerization process of glycolic acid (GA) and lactic acid (LA) [18]. Lactic acid is crystalline, while glycolic acid exhibits more amorphous characteristics. A higher content of GA will cause the proportion of crystalline and amorphous phases within PLGA particles to shift towards the amorphous region, resulting in faster hydrolysis of polymer particles. When the ratio of LA to GA is 50:50, the degradation rate is the fastest [6]. Therefore, the ratio of LA to GA can affect the crystallinity of PLGA copolymers. PLGA is generally an amorphous polymer. Studies have proven that the X-ray diffraction peak intensity of its crystalline phases gradually increases with the enhancement of LA content in the PLGA copolymer. When the amount of LA in the copolymer reaches or exceeds 90 %, the PLGA copolymer has a strong crystalline diffraction peak, and the increase of crystallinity reduces the degradation rate of PLGA. In addition, the reason why the degradation rate slows down with a higher PLA proportion may also be due to the presence of methyl groups in PLA, which increases the PLGA hydrophobicity and thus reduces its degradation rate [19]. Frank et al. [20] applied lidocaine as an active drug and PLGA as a highly crystalline form of L-lactic acid. When the crystallinity of PLGA increased from 40 % to 50 %, the diffusion coefficient of the drug reduced from 6.95×10^{-14} cm^2/s to 3.84×10^{-14} cm^2/s, leading to a decreased drug release rate.

2.1.4. Preparation process of PLGA nanoparticles

The preparation method, conditions, and nanoparticle properties of PLGA nanoparticles can all affect the burst release rate of drugs [9]. There are various preparation methods of PLGA nanoparticles, among which the emulsification-solvent evaporation method is the most simple. It can be divided into two parts: the emulsion preparation, and the solvent evaporation. Colostrum is the product of the emulsion preparation, and also an important intermediate during the nanoparticles preparation. The stability of colostrum is a significant prerequisite for ensuring the nanoparticles quality. Firstly, different emulsifiers applied in the emulsion preparation display different drug release behaviors. For example, the emulsifiers can be made into water-in-oil (W/O), oil-in-water (O/W), water-in-oil-in-water (W/O/W) or solid-in-oil (S/O) emulsion and so on. W/O/W double emulsion solvent evaporation method (i.e. double emulsification-solvent evaporation method) is usually used to prepare protein peptide drug loaded PLGA nanoparticles [21, 22]. Secondly, the drug release behavior of drug loaded PLGA nanoparticles varies with the emulsification conditions. Changing the shear force (e.g. using a homogenizer to prepare colostrum) or ultrasound intensity (e.g. using probe ultrasound to prepare colostrum) during the W/O colostrum preparation can finally result in the PLGA nanoparticles with different physicochemical properties and drug release behaviors. Qi et al. [23] prepared drug loaded PLGA nanoparticles by selecting exenatide, a type II diabetes treatment drug, as a model polypeptide. They found that the nanoparticles synthesized by ultrasonic emulsification method released slowly in vivo with a low hypoglycemic degree, while the nanoparticles prepared by homogenization method released rapidly in the first two weeks, leading to a better hypoglycemic effect. Thirdly, the stirring rate of colostrum during the emulsion preparation can affect the drug release behavior.

2.2. Factors influencing the drug release behavior of drug loaded PLGA nanoparticles

2.2.1. Degradation Environment

Environmental factors can also affect the degradation of PLGA polymers, thereby affecting drug release behavior. For example, high temperature can accelerate the drugs release controlled by nanoparticles corrosion via enhancing the hydration and degradation of PLGA polymers. High temperature can also increase the migration rate of PLGA polymers in the nanoparticles matrix, thus improve the polymers fluidity and the PLGA degradation rate, and finally accelerate drug diffusion effectively. Therefore, high temperature is also the most commonly used parameter in accelerating drug release experiments [24]. Generally speaking, PLGA nanoparticles can remain stable for 12 months below the glass transition temperature (T_g) [8]. At temperatures close to the glass transition temperature, the drug diffusion coefficient can increase by up to three orders of magnitude. Due to changes in the release mechanism at temperatures above T_g, it is recommended that the ambient temperature should not be higher than the T_g of the PLGA polymers. The plasticization of polymers at high temperatures can lead to changes in particle morphology (such as surface pore closure and particle aggregation), thereby reducing the drugs release rate [25]. Wang et al. [26] proposed that humid conditions and elevated temperatures can affect the mobility of PLGA polymer chains, leading to their T_g changes, furthermore resulting in undesirable PLGA degradation

and drug release behavior.

The pH value of the surrounding environment has a significant impact on the degradation rate, stability, and drug release of PLGA nanoparticles. The degradation of PLGA polymers is accelerated under both acidic and alkaline conditions, especially under alkaline conditions. This is because PLGA belongs to ester polymers, and its degradation mainly occurs through the hydrolysis of ester bonds. Under alkaline conditions, OH^- in the environment can attack ester bonds, causing them to break [27]. At the same time, excessive alkali will neutralize the acidic products produced by PLGA hydrolysis, producing salt substances that enhance the hydrophilic of the polymer and accelerate degradation [28]. In Xu's study [10], the degradation rate constant of PLGA nanoparticles with a relative M_w of 25000 at pH 2.4 was 1.63 times higher than that at pH 7.4. It takes 21 days to fully release the drug in a neutral environment with 7.4 pH level, while it only takes 2 days to release the entire drug in an alkaline environment with 10.8 pH level. This property of PLGA can help to construct pH-responsive drug delivery systems [29].

2.2.2. Drug types, drug distribution, and drug loading rates

The drug types affect the drug release behavior of drug loaded PLGA nanoparticles. This is because different physicochemical properties of drugs can affect the PLGA degradation rate and the release parameters of selected drug [30]. Due to the association between hydrophilic and drug release, it is necessary to explain the drug release mechanism based on drugs and polymer types [31]. The Naidu research group [32] investigated the effect of hydrophilic or hydrophobic drugs on the degradation rate and drug release of PLGA carriers. The results showed that hydrophilic drugs significantly accelerated the degradation rate of PLGA polymers, thereby accelerating drug release. It may be due to the high water solubility of hydrophilic drugs, leading to a great sustained driving force for drug diffusion and a high initial rupture degree of nanoparticles [33].

The drug distribution in PLGA polymer matrix can also affect the drug release performance. Under normal circumstances, the drug release in nanoparticles is from the surface to the inner layer, so the drug diffusion distance can significantly affect the drug release behavior from the inner nanoparticles. The uniform distribution of drugs in the carrier provides a sustained driving force for drug diffusion, which may lead to early burst release. Kakish et al. [34] regulated the drug concentration distribution in PLGA nanoparticles to form a gradient distribution with higher center drug concentration. This nanoparticle structure can reduce early burst release and enable drug release at a steady rate.

The drug loading rate of PLGA nanoparticles affects the burst release efficiency, thus the drug loading rate plays a vital role in the drug release process. The higher the drug loading rate of PLGA nanoparticles, the higher the concentration gradient of drug diffusion in the internal environment, and furthermore the higher the drug burst release rate. A low drug loading rate can lead to a decrease in drug burst release but requires a longer time to release the drug [30].

3. Application of PLGA nanoparticles in the treatment of gastrointestinal cancers

Gastrointestinal cancer is a major disease threatening human health worldwide. Surgery combined with radiotherapy and chemotherapy is still the most popular treatment for this disease [35–37]. In recent years, the advancing comprehension of malignant tumors has led to significant breakthroughs in novel treatment modalities within clinical practice, thereby enhancing patients' quality of life. Despite this, the overall prognosis of patients with gastrointestinal tumors is still unsatisfactory. For example, colon cancer is the third most common cancer and the fourth most common cause of death in the world [38,39], gastric cancer is the fifth most common cancer and the third most common cause of cancer death globally [40].

3.1. Chemotherapy

Chemotherapy inhibits tumor growth or eliminates tumor by systemic or local administration of chemotherapeutic drugs, which plays an irreplaceable role in the treatment of malignant tumors. There are primarily three ways of administration: intravenous injection, oral administration and local administration [41–43]. As a widely applied chemotherapeutic drug in the treatment of gastrointestinal cancer, 5-fluorouracil's (5-FU) side effects include the unspecific damage of normal cells, the short half-life and wide distribution [44].

To prolong its plasma circulation life and improve its therapeutic activity, a magnetic PLGA nanocapsule loaded with 5-FU was prepared and displayed great anticancer ability against colon cancer allografts in mice [45]. There was little difference in the drug release between in vitro and in vivo studies. The 5-Fu-loaded magnetic nanocapsules hindered tumor growth effectively at week 3, in accordance with sharply rising of the in vitro release plot from day 20. Intravenous injection of drugs loaded with magnetic PLGA nanocapsules supports the idea that magnetic drug targeting processes may be an effective delivery strategy. When the drug loaded PLGA nanoparticles are exploited as intravenous injection in the treatment of gastrointestinal cancers, the polymeric nanoparticles must avoid non-specific interactions with mononuclear phagocyte system and survive in circulation until reaching tumors [46]. Additionally, once polymeric nanoparticles reach the tumors, it is essential to establish interactions with tumor cells to avoid the nanoparticles drain from the tissues [47]. To improve PLGA nanoparticles retention in tumors, Park et al. [48] constructed PLGA nanoparticles coated with zwitterionic chitosans as the surface and dopamine as a mediator. Zwitterionic chitosans (ZWC) can change charges along with pH level and allow PLGA nanoparticles to interact with cells in acidic tumor microenvironment (TME) [49]. Magnetic resonance imaging showed that ZWC-coated PLGA nanoparticles were more persistent in tumors of bearing LS174T-xenografts mice than polyethylene glycol (PEG)-coated nanoparticles, in agreement with the in vitro results. The results demonstrate that zwitterionic chitosans coated PLGA nanoparticles exhibited pH-dependent cell interactions and longer retention in LS174T human colon tumors.

The advantage of oral drugs delivery over injection or infusion chemotherapy is that it can expose cancer cells to a relatively lower and safer concentrations of anticancer drugs for a long time, leaving tumor blood vessels little chance to grow [50,51]. Oral chemotherapy can finally provide an innovative concept of chemotherapy: "chemotherapy at home" [52,53]. In terms of oral drug delivery materials for treatment of gastrointestinal diseases, PLGA nanoparticles have been widely studied to improve the relative oral bioavailability of curcumin and other polyphenols drugs recently. Curcumin is a polyphenol compound extracted from the root of Curcuma longa. It's anti-inflammatory, antioxidant, antibacterial etc., and possesses large pharmacological potential. Nevertheless, due to its low intestine absorption capacity and its easy metabolism by the liver, the therapeutic application of curcumin has been widely limited. Shaikh et al. [54] uncovered that the oral bioavailability of curcumin was significantly improved after PLGA encapsulation via pharmacokinetic studies. And the curcumin concentration in plasma was maintained longer after oral administration of nanoparticles. These results indicate that curcumin can be constantly released from PLGA nanoparticles. In vitro drug release of PLGA nanoparticles occurs through diffusion and degradation. In this case, a biphasic release was observed, following the square root plot of Higuchi. It was observed from in vivo pharmacokinetic studies in rats that PLGA nanoparticles can improve the relative bioavailability of curcumin to 9.2 times, compared with piperine as an absorption enhancer for curcumin release. To boost the physical stabilization of nanoemulsions, Miele et al. proposed ionic amphiphilic chitosan derivative, chitosan oleate salt (CS-OA), to prepare curcumin loaded PLGA nanoparticles [55]. Previous tests validated the positive interaction between CS-OA coated PLGA nanoparticles and mucin, which helped to increase drugs absorption by prolonging the residence time of nanoparticles. Xie et al. [56] illustrated that one of the main reasons why PLGA nanoparticles can enhance the oral bioavailability in rats is that PLGA can prevent the curcumin efflux mediated by a biological transporter P-glycoprotein (P-gp). Vitamin E succinated polyethylene glycol 1000 (vitamin E TPGS) is an excellent emulsifier/solubilizer/absorption enhancer with great emulsification efficacy and cellular adhesion [57]. It can also be exploited as a reversal agent of P-gp mediated multidrug resistance and inhibit P-gp mediated drug transport [58]. It was shown that the curcumin was slowly released from the constructed curcumin (CUR)-PLGA nanoparticles in the artificial intestinal environment. Oral curcumin released from the CUR-PLGA nanoparticles reached the maximum concentration significantly longer compared with native CUR. Considering this, a fluorescent marker coumarin-6 encapsulated in PLGA nanoparticles manufactured by a modified solvent extraction/evaporation technique with vitamin E TPGS as emulsifier were prepared. The results of using Caco-2 cells as an in vitro model illustrated that vitamin E TPGS coated PLGA nanoparticles exhibited considerably higher cellular uptake compared with
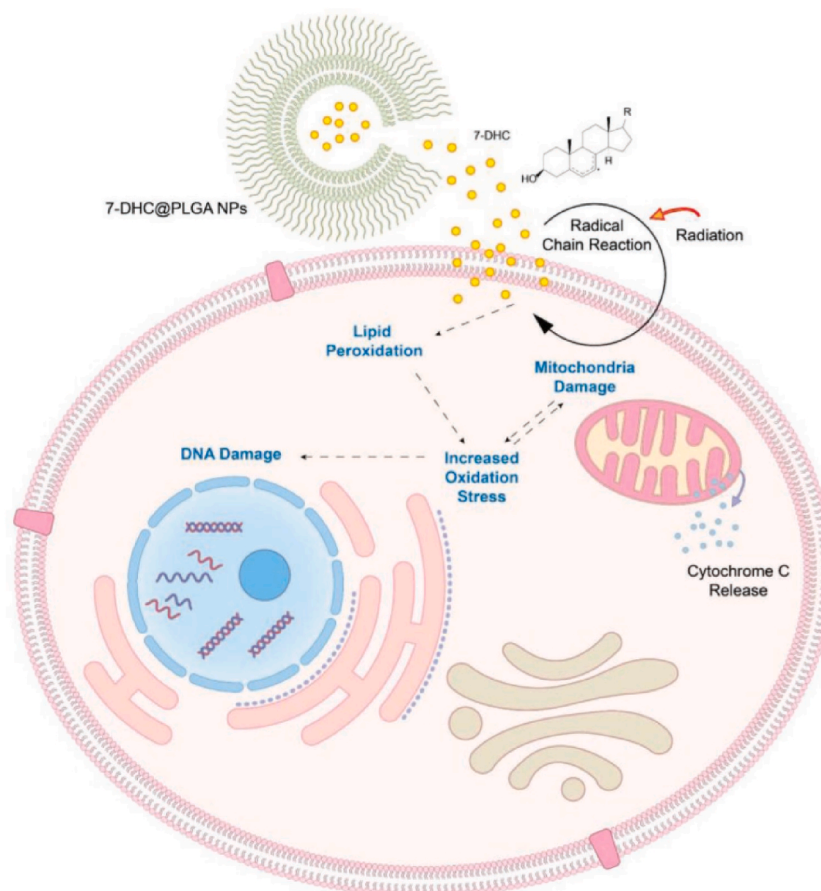

Fig. 2. Schematic illustration of radiosensitization with 7-DHC@PLGA-NPs. Reprinted with permission [75].

polystyrene nanoparticles and polyvinyl-alcohol-coated PLGA nanoparticles [59]. A Mucinous gastric carcinoma is known for its deeper invasion, more frequent lymph node metastasis, more progressive pathologic stage, and lower survival [60]. One uppermost reason is that therapeutic drugs can't penetrate the mucus barrier to reach the underlying epithelial cells [61]. It has been found that reducing hydrophobic and electrostatic interactions can minimize mucoadhesion [62]. In view of this, Lin et al. manufactured PEG-PLGA nanoparticles (PEG-PLGA-NPs) with hydrophilic and near-neutrally-charged surfaces. In their study, HGC-27 cells, a mucin-producing cell line derived from the metastatic lymph node of gastric tumor, took in 1.6- to 2.1-fold higher amount of PEG-PLGA-NPs than pure PLGA nanoparticles incubated for the same time [63]. It illustrated that with the help of a low M_w PEG and a high density of PEG-surface coverage, PEG-PLGA-NPs can quickly penetrate the mucus.

As to local administration materials for treatment of gastrointestinal cancers, Khalili et al. have modified the surfaces of PLGA-PEG nanoparticles with a low-density, second PEG layer (PLGA-TPEG-NPs-20) to decrease protein binding affinity, thus enhancing the delivery of therapeutics into dense mucinous cancer barriers [2]. Via in vitro, ex vivo, and in vivo LS174T murine xenograft subcutaneous cancer models, they showed that PLGA-TPEG-NPs-20 can effectively reduce nanocarrier entrapment and act as a possible platform for regional intraperitoneal chemotherapy. Local administration can attain high concentration of PLGA nanomaterials in the ideal position, while it is hard to touch many deep cancers, hence there are few application scenarios [64].

Different from traditional chemotherapy, target therapy targets to already defined oncogenic sites from cellular molecular level. It first emerged in the late 1990's, having a significant impact on the treatment of certain types of tumors. Small molecule targeted therapeutic agents can be taken orally and are often enzyme domain inhibitors of mutations, overexpression, or other key proteins within cancer cells. Jena et al. constructed capecitabine loaded Eudragit S100 and PLGA based nanoparticles [65]. The pH-sensitive polymer Eudragit S100 could prevent the release of capecitabine at the top of the gastrointestinal tract and can directly target the colon. In vivo pharmacokinetic studies applied a rabbit model, and in vivo study exhibited enhanced oral bioavailability. This better targeted PLGA based nanoparticles can improve the therapeutic effect of colorectal cancer.

3.2. Radiotherapy

Radiotherapy is still a typical treatment option for gastrointestinal cancer, and approximately 50 % patients have received radiotherapy at least once in the treatment process [66,67]. It may cause morbidities such as scars, rectal irritation and sexual issues, and its lifetime dose is limited to below 60 Gy [68]. Therefore, developing radiation-activatable radiosensitizing agents to improve the radiotherapy efficacy is extremely urgent. Inspired by the fact that the accumulation of low toxic 7-dehydrocholesterol (7-DHC) can cause a buildup of the cellular reactive oxygen species and lead to cholesterol-rich tissues damage [69–74], Delahunty et al. [75] explored 7-DHC as a radiosensitizer (Fig. 2). Poorly hydrosoluble 7-DHC was encapsulated into PLGA nanoparticles for efficient delivery [76]. 7-DHC@PLGA nanoparticles were intravenously injected into CT26 tumor bearing mice, followed by ionizing radiation. By the end of the study on Day 43, 60 % of the mice remained alive, half of which were tumor-free. It revealed that radiosensitizing effects of 7-DHC@PLGA nanoparticles accumulated in tumors through the enhanced permeability and retention effect and improved the radiotherapy efficacy [75].

Additionally, it has been found that tumor hypoxia and dysregulation of histone deacetylase (HDAC) in cancers are another two vital factors of radiation resistance [77,78]. Given these, Zhang et al. provided an alliance strategy to overcome radiation resistance through simultaneous hypoxia relief and chromatin remodeling. They established a multifunctional radiosensitizer CAT-SAHA@PLGA by the double emulsion method. The PLGA nanoparticles encapsulated catalase (a biological peroxidase) and SAHA (an US FDA approved HDAC inhibitor) with protective catalytic activity of catalase, and extended the pharmacokinetic exposure time of the HDAC inhibitor [79]. When combined with radiotherapy, the CAT-SAHA@PLGA treatment displayed obvious tumor inhibition in CT26-bearing mice, and there was no observable damage in the CAT-SAHA@PLGA group compared to other control groups in the presence of radiation. It confirmed that CAT-SAHA@PLGA combined with radiation displayed improved therapeutic efficiency in CT26 cells. The synergistic strategy has been proven obvious sensitization effect on tumor radiotherapy, which possesses great capability for further research in cancer treatment.

3.3. Novel tumor treatment methods

Classical chemotherapy and radiotherapy are prone to cause serious systemic adverse reactions, poor compliance, and tumor recurrence and metastasis. Therefore, the development of novel tumor treatment strategies has become a significant problem urging to be solved. With the in-depth understanding of tumor tissues, some new emerging tumor treatment methods such as immunotherapy [80], gene therapy [81], and photothermal therapy [82] have attracted more and more attention, and achieved good therapeutic effects.

Stimulating the host's immune system to attack cancer cells is called immunotherapy. It is a promising method to fight cancer and is considered to be one of the four pillars of tumor treatment [83]. Recent studies have illustrated that specific chemotherapeutic drugs such as doxorubicin (DOX) can cause immunogenic cell death (ICD) of cancer cells [84–86]. Yet, the short circulating half-life, low cancer accumulation and off-target toxicity of DOX lessened the ICD efficiency. In view of PLGA polymeric nanoparticles constricted by low drug loading ability, Zhang et al. prepared lipid/PLGA nanoparticles to deliver DOX and peptide-based programmed cell death ligand-1 (PD-L1) inhibitor P-12 concurrently for chemo-immunotherapy of tumor [87–89]. The optimal DOX and P-12 co-loaded nanocomposite exhibited improved tumor cellular uptake and effective ICD and PD-L1 blockade in in vitro CT26 tumor cells, and the in vivo anticancer effect was also verified by tumor-bearing mice model [90]. Lee et al. attached the Fc truncated F(ab) portion of α-PD-L1 monoclonal antibody (α-PD-L1 mAb) to a PEG-PLGA polymer [91]. They concluded that α-PD-L1 based nanoparticles has no

apparent toxicity in vitro or in vivo. There is no evidence of enhanced efficacy in mice treated with α-PD-L1 nanoparticles. Authors ascribed it to the insufficient immune activation to increase the regression of insensitive MC38 tumors. Given the restriction of local immunotherapy, systemic delivery of immune-activating combinations without systemic side effects is necessary [92]. To realize this, Kwon et al. developed adenosine triphosphate (ATP)-modified paclitaxel (PTX) loaded PLGA nanoparticles [93]. The designed PLGA nanoparticles could codeliver the ICD attractant (PTX) and the inducer of antigen-presenting cells (ATP) to solid tumors. By producing an immunoactive TME, the PTX-loaded NP_{pD}-ATP weakened CT26 growth, and the designed PLGA nanoparticles combined with anti-PD-1 antibody realized complete tumor regression and specific antitumor immune memory in 6 out of 8 mice [93]. Besides ICD, immune checkpoint blocking (ICB) therapy is also a broadly applied immunotherapy in the treatment of tumors [94,95]. Increasing evidence proves that cancer acidity can promote tumor immunosuppression meanwhile damaging the anticancer effects of cytotoxic $CD8^+$ T cells [96–98]. Considering this, Hao et al. reported that calcium carbonate encapsulated by PLGA and PLGA-PEG copolymers could function as a proton nanosponge to neutralize cancer acidity by reacting with protons after intravenous administration [99]. They demonstrated that $CaCO_3$@PLGA nanoparticles can enhance the therapeutic effect of ICB therapies on CT26 tumor xenografts by reinvigorating exhausted $CD8^+$ T cells and innate anticancer immunity. In recent years, with the extensive employment of ICB therapy in tumor, radiotherapy has been verified to promote anticancer immunity by adjusting the immune system [100]. Lu et al. assembled PLGA and R837 (Toll-like receptor 7 agonist) and then coated them with neutrophil membrane obtaining R837@PLGA@Neu nano-particle [101,102]. Results suggested that the nanoparticle owned strong uptake capacity, low cytotoxicity, and a high tumor targeting efficacy [103]. Combining with radiotherapy, it possessed an excellent effect in CT26-bearing mice through immune cell regulation, providing a promising strategy for colorectal tumor treatment.

Gene therapy targeting at the level of cellular gene expression provides another new route for gastrointestinal tumor treatment [104]. As reported, pigment epithelial-derived factor (PEDF) gene possessed excellent therapeutic effects on many tumors [105–109]. Based on the low-toxicity, biodegradability and biocompatibility of PLGA, Cui et al. loaded PEDF gene in PLGA nanoparticles and found that PEDF gene loaded in PLGA nanoparticles could efficiently impede CT26 cancer growth [110]. The hindering effect is related to CT26s apoptosis, and the inhibition of angiogenesis required for cancer growth. The animal results exhibited that the number of apoptotic CT26s from the PEDF-PLGA nanoparticles treated mice was apparently higher than that of normal saline (NS) treated group. Adopting PEDF gene and PLGA nanoparticles is an effective and safe gene delivery system for primary colorectal cancer treatment. Yet,
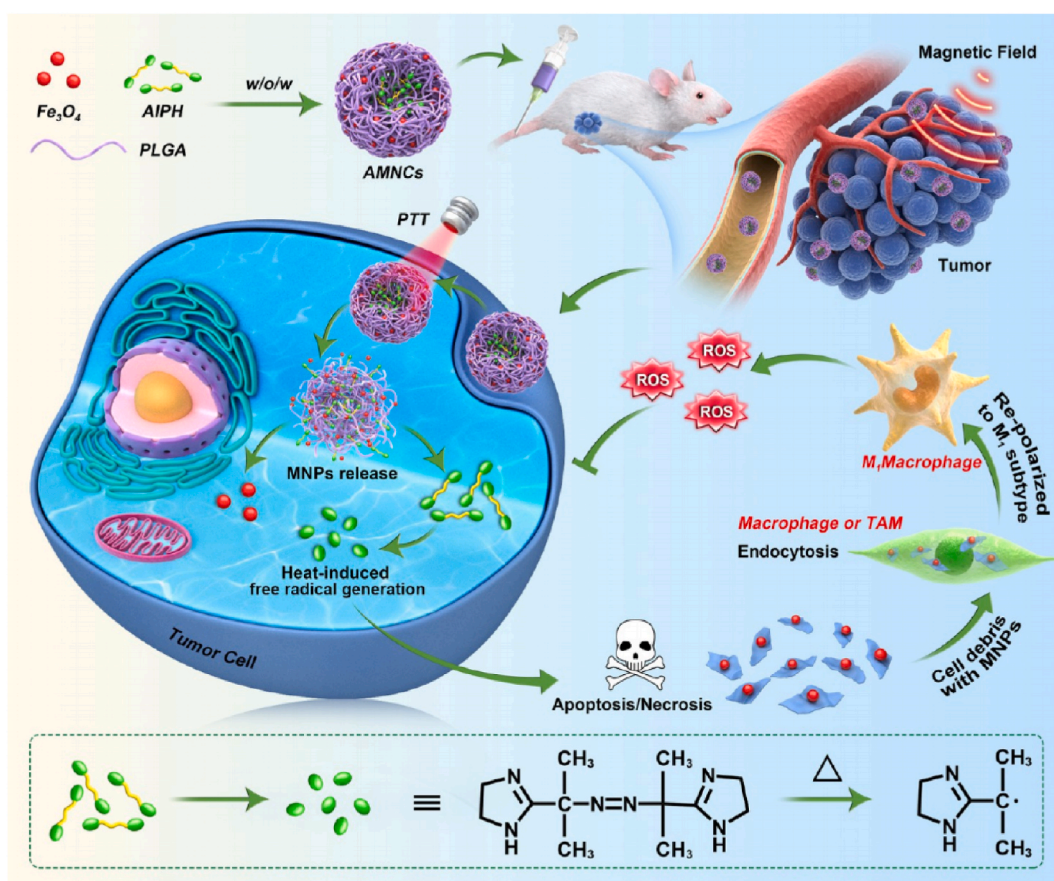
Fig. 3. Illustration of the AMNC-mediated free-radical cascade for enhancing MRI-guided chemo/thermodynamic hypoxic tumor therapy. Reprinted with permission [118].

its effect on late stage tumor growth and metastasis tumor are still unknown. Due to the high specificity of RNAi technology for target sequences, it possesses an ability to silence therapy-related genes in multiple cancer models. Moreover, evidence has accumulated over the years suggesting that the effector function of CD8$^+$ T cells can be improved by siRNA-mediated silencing of programmed cell death protein-1 (PD-1) or PD-L1. Based on this, Kwak et al. synthesized PLGA nanoparticles loaded with PD-1 and PD-L1 siRNA (i.e., siR-NA@PLGA NPs) [111]. Investigating by in vitro and in vivo colon cancer models, they found that in contrast to silencing PD-1 alone or PD-L1 alone, cosilencing of PD-1 and PD-L1 by siRNA@PLGA NPs more significantly encouraged the immune response of tumor-specific CD8$^+$ T cells. Furthermore, systemic administration of PD-1 and PD-L1 siRNA@PLGA NPs in MC38 tumor-bearing mice also led to a more pronounced antitumor effect. Moreover, synergistic therapy based on combination of gene and small-molecule chemotherapeutic medicine can be expected both high anticancer efficiency and low side effects [112]. Xu et al. fabricated a trun-cated basic fibroblast growth factor (tbFGF)-mediated targeting delivery system concurrently loaded with PEDF gene and PTX in PLGA nanoparticles (T-NPs) [113]. The improved anticancer capacity of T-NPs principally because the specific interaction between tbFGF on T-NPs and FGFR1 overexpressed on tumor cells and tumor neovascular endothelial cells elevated the nanoparticles distribution in tumor tissues [114]. The experiment results demonstrated that this combination therapy showed significantly improved anticancer effects in a C26 subcutaneous tumor model. It was also indicated that nanoparticle treated mice had no obvious side effects compared to the group treated by NS. Hence, T-NPs were safe formulations by systemic administration of intravenous injection.

Photothermal therapy (PTT) refers to the adopt of photothermal agents (PTAs) to eliminate cancer cells under laser irradiation. PTT is considered to be one of the most effective and hopeful clinical treatments for carcinoma owing to its noninvasive, controllable and repeatable character [115–117]. Thermodynamic therapy (TDT) is a novel type of dynamic therapy developed in recent years, characterized by applied of thermodynamic agents to produce oxygen-independent free radicals to kill tumors. At present, the main thermodynamic agent used is 2,2′-azobis[2-(2-imidazolin-2-yl) propane]-dihydrochloride (AIPH). The compound decomposes to release free radicals but is thermally unstable (half-life temperature is 44 °C), which generally needs to be loaded on the carrier and enters the body. Combined PTT, TDT and Fe$_3$O$_4$ magnetic nanoparticles mediated macrophage polarization strategies, Li et al. con-structed PLGA-based nanocomposites (AMNCs) that efficiently co-delivered AIPH and magnetic nanoparticles (MNPs) (Fig. 3). In the CT26 xenograft mouse model, AMNCs were highly gathered at the tumor site, and the encapsulated MNPs preserved their property as contrast agents for enhanced magnetic resonance imaging (MRI). Under near-infrared light irradiation, Fe$_3$O$_4$ and AIPH were released and produced oxygen-independent free radicals, which expediting the apoptosis and necrosis of cancer cells. Afterwards, fragments of tumor cells bond to undegraded Fe$_3$O$_4$ and were arrested by macrophages through endocytosis. At last, Fe$_3$O$_4$ induced macrophages to repolarize into pro-inflammatory subtypes, which further created free radicals, and thus improved the immune response to prevent cancer growth [118]. It offers an alternative strategy for MRI guided PTT/TDT combined therapy to produce oxygen-independent free-radical cascade. Scientists also adopt synergistic chemo-photothermal therapy for cancer treatment [119]. Banstola et al. re-ported on paclitaxel (PTX)-loaded PLGA microspheres coated with gold nanoparticles for pancreatic cancer treatment [120]. The developed nanosystem and NIR-treated Panc-1 cells displayed the highest cytotoxicity with meaningfully decreased viability compared with photothermal or chemotherapeutic agents alone. It suggested that PLGA microspheres coated with gold nanoparticles could provide synergistic chemical-PTT for cancer treatment of alimentary system.

Radiodynamic therapy (RDT), sometimes also referred to as X-photodynamic therapy (PDT), is a modification of conventional PDT in that the external activating light source is replaced by high-energy X-rays. Clement et al. designed a drug delivery system for RDT comprising a photosensitizer Verteporfin incorporated into PLGA nanoparticles that were surface-functionalized with a cell-penetrating HIV trans-activator of transcription (TAT) peptide [121]. Cytotoxicity tests in pancreatic cancer cells in vitro under 4 Gy X-ray exposure from a clinical 6 MV linear accelerator revealed that TAT targeting of the PLGA nanoparticles markedly increases the RDT effectiveness.

3.4. Diagnosis

Gastrointestinal cancer dose not exhibit obvious symptoms in the early stage, and vast majority of patients are in the middle and late stage at the first diagnosis. This is also the main reason for the low five-year survival rate of these patients. Hence, early diagnosis and timely treatment are crucial to improve the clinical prognosis of patients with gastrointestinal cancers. For gastrointestinal cancers, early screening and diagnosis are also very important [122–124]. Currently, clinical endoscopy primarily applies white light imaging technology, whose disadvantage is the high rate of missed detection, owing to the subtle lesions of many gastrointestinal diseases difficultly to recognize by naked eyes. To solve this problem, many studies have focused on new imaging technologies, such as fluorescence imaging [125–128] and magnetic resonance imaging [129].

Fluorescent labeled probes are employed to bind to receptors with specific molecular structures at the lesion site, and special light sources and camera systems are adopted for visualization, thus impressively improving diagnostic accuracy. As mentioned above, curcumin is anti-inflammatory, antioxidant, antibacterial. Moreover, curcumin can exhibit fluorescence spectra properties but poor photochemical stability in some solvents due to its hydrophobicity [130–132]. To improve its solubility and luminous property, Wang et al. encapsulated curcumin into PLGA nanoparticles (Cur@PLGA-NPs) as a novel aggregation-induced emission (AIE) formulation for cell bioimaging, in which curcumin plays two vital roles: AIE emission and drug [128]. The results indicated that Cur@PLGA-NPs had raised effectiveness on CT26 cancer cells compared with pure curcumin. Furthermore, Cur@PLGA-NPs can light up in cells via a concentration-dependent way, thus assisting the exploration of fluorescence probes for clinical gastrointestinal applications.

As to magnetic resonance imaging (MRI), Schleich et al. [129] have successfully co-encapsulated superparamagnetic iron oxide (SPIO, as MRI contrast agent) and PTX in PLGA based nanoparticles. The in vivo antitumor efficacy of the multifunctional PTX/SPIO loaded PLGA NPs was evaluated in CT26 tumor-bearing mice. Consistent with the in vitro cytotoxicity data, the PTX/SPIO loaded NPs

brought a higher delay of tumor growth than the other treatments. These PLGA NPs were proven to constrain the growth of CT26 colon carcinoma cells and simultaneously can be adopted as potential tumor targeted MRI contrast agents due to their high absorption by tumor cells and their magnetism. The PLGA based nanoparticles may become an encouraging candidate as an effective codelivery system for both the diagnosis and therapeutic applications for gastrointestinal diseases.

3.5. The clinical application of PLGA-based drug delivery systems

Currently, more than 20 PLGA particle-based formulations are approved for commercialization, and most of them are used as chemotherapeutic agents to treat malignancies [6]. Actually, there are two unavoidable problems in the way of clinical application of PLGA-based drug delivery systems [133]. The first problem is scale-up productions of PLGA-based systems. Although several well-established methods for producing PLGA nanoparticles on a laboratory-scale have been developed, it can induce changes in particle properties (e.g. drug release profiles) when the process is scaled up to industrial batch sizes. The second is the efficacy and safety assessment, which is the critical step during the ways of clinical translation. As summarized in Table 1, there are still works cited in this paper without animal experiments. And most of them conducted animal experiments on mice or rabbits rather than large animals. Pilot studies in large animal models are urgently needed, where protection and effectiveness can be investigated over long periods. Clinical trials enlisted in clinicaltrials.gov website for marketed PLGA-based therapeutics have been checked, and major tumor-related clinical trials focus on prostate cancer, oral cancer, breast cancer and so on. There are few clinical trials about advanced solid tumor, and none of them is investigating gastrointestinal cancers as to now [133]. Hence, a huge effort in investigating different PLGA platforms and evaluating their safety and efficacy on clinical trials of gastrointestinal cancers is really needed. Based on the generalization of studies in laboratories, we found that majority of them adopted the administration pathway of intravenous injection. More varied administration pathway may need to be investigated in the future. PLGA-based clinical probes are also needed to be noticed, since the small quantity of PLGA-based delivery systems for gastrointestinal cancers diagnosis [128,129].

4. Conclusions and perspectives

This study summarizes drug-loaded PLGA-based nanoparticles, elucidates the factors influencing drug release, and explores their application in treating gastrointestinal cancers. In the field of biomedicine, PLGA is the only biodegradable polymer approved by the US FDA. The drug release behavior is primarily affected by the degradation of PLGA-based nanoparticles, which is determined by various factors, including the ratio of PLA to PGA, M_w, crystallinity, and preparation process of PLGA nanoparticles. Moreover, the degradation environment and drug parameters, such as drug types, drug distribution, and drug loading rates, also significantly influence drug release behavior. Due to its facile functionalization, PLGA can potentially be applied in targeted drug delivery and diagnostic imaging for the treatment of gastrointestinal cancers. In chemotherapy of gastrointestinal cancers, PLGA nanoparticles are commonly employed as hydrophilic drug carriers to load chemotherapeutic drugs and subsequently functionalize with targeted ligands. The functionalized PLGA nanoparticles interact with tumor cells, enhancing their retention within tumors and ultimately increasing their therapeutic activity. In radiotherapy of gastrointestinal tumors, PLGA nanoparticles are designed to load various radiation-activatable radiosensizing agents to enhance the radiotherapy efficacy of the delivery system. As to novel tumor treatment methods (immunotherapy, gene therapy, or photothermal therapy), loading antibodies, genes, or thermodynamic agents on PLGA nanoparticles to construct delivery systems has become a general consensus. These novel drug delivery systems based on PLGA nanoparticles have also achieved satisfactory therapeutic effects in the clinical treatment of gastrointestinal cancer. When PLGA-based nanoparticles are exploited for gastrointestinal diagnostics, these particles are utilized for encapsulating or loading luminescent nanomaterials or magnetic Fe_3O_4 nanocrystal-based *T2* contrast agents.

However, due to the relative hydrophobicity of PLGA polymers, they cannot load hydrophilic drugs with higher encapsulation efficiencies [134]. The issue of burst release from PLGA nanoparticles arises due to the positioning of drugs on the surface or the formation of pores inside the particles [135,136]. In addition, using emulsion-based solvent evaporation technology to prepare hydrophilic drug-loaded nanoparticles exacerbates drug leaching in the water continuous phase during preparation, leading to low drug encapsulation efficiency [137]. These outstanding problems also directly impact the performance of PLGA polymer applications in the treatment of gastrointestinal cancers. Breaking through the above bottlenecks requires the design and modification of PLGA polymers from the perspective of microstructure. Moreover, the advantages of radiosensitizers largely depend on the radiation resistance mechanism behind them. Similarly, there are limitations in understanding the inherent mechanism of immunotherapy and gene therapy, making it difficult to develop innovative drug-loaded PLGA nanoparticles. Finally, the synergistic development of nanomaterials and life science fields is needed to realize the wide application of PLGA-based nanoparticles in the clinical treatment of gastrointestinal tumors.

This study provides a comprehensive overview of the application of drug-loaded PLGA-based nanoparticles in the treatment of gastrointestinal cancers. However, due to the limited availability of studies on drug loading polymeric nanoparticles specifically for gastrointestinal cancer treatment, a more extensive literature review comparing PLGA with other biodegradable polymers used in this context could not be included. Additionally, given the scarcity of research on different drug loading techniques employed with PLGA nanoparticles, a section discussing different drug loading techniques could not be incorporated.

Data availability statement

This is a review, and all of the data come from references.

Table 1

Comparisons of several PLGA-based nanoparticles for the treatment and diagnosis of gastrointestinal cancers. (Uploaded as a single file).

No.	Formulation	PLGA	Methods	Therapeutic agents	Loading techniques	Entrapment efficiency wt./%	Release rate/time	Treatments	Target tumor cell lines	Animals	Differences between in vitro and in vivo studies	References
1	5-Fu loaded magnetic PLGA nanocapsules	50:50, M_W 12000	w/o/w	5-fluorouracil (5-Fu)	Entrapped	63.8	100%-33 d	Chemotherapy	CT26	Mice	No	[45]
2	NP-pD-ZWC$_{0.1}$ (Zwitterionic chitosans coated PLGA NPs)	LA:GA = 85:15, 150 kDa	w/o/w	Hydrophobic iron oxide (IO) Indocyanine green (ICG)	Entrapped	–	90%-24 h (ICG)	Chemotherapy	LS174T 4T1 NIH/ 3T3	Mice	No	[48]
3	Curcumin loaded PLGA NPs	50:50, 0.41 dL/g	o/w	Curcumin	Entrapped	84.6	42%-20 d	Chemotherapy	–	Rats (oral)	–	[54]
4	Cur-CS-OA (Chitosan oleate) PLGA	Resomer RG 503H	w/o/w	Curcumin	Entrapped	68.8	–	Chemotherapy	Caco-2	–	–	[55]
5	CUR-PLGA-NPs	50:50, M_W 30000	s/o/w	Curcumin	Entrapped	92.0	77%-168 h (pH 7) 48%-168 h (pH 2)	Chemotherapy	–	Rats (oral)	–	[56]
6	Coumarin 6-loaded PLGA NPs coated with vitamin E TPGS	50:50, M_W 40000–75000	o/w	Coumarin-6	Entrapped	–	3.5%-24 h	Chemotherapy	Caco-2	–	–	[59]
7	10%-PEG$_{2000}$-PLGA-NPs	LA:GA = 75:25, 18 kDa	o/w	Coumarin-6	Entrapped	91.0	14%-24 h	Chemotherapy	HGC-27	–	–	[63]
8	PLGA-TPEG-NPs-20	M_W 5000–20000	Nanoprecipitation method	DiD (fluorochrome)	Entrapped	–	–	Chemotherapy	LS174T	Mice	No	[2]
9	Cap loaded PLGA based Nanoparticles	50:50, Sigma	–	Capecitabine	Entrapped	66.5	–	Target therapy	HT-29	Rabbits (oral)	–	[65]
10	7-DHC@PLGA NPs	–	Nanoprecipitation method	7-dehydrocholesterol (7-DHC)	Entrapped	21.9	35%-24 h (pH 6.5)	Radiotherapy	CT26	Mice	No	[75]
11	CAT-SAHA@PLGA	Sigma-Aldrich	w/o/w	Catalase SAHA (HDAC inhibitor)	Entrapped	66.9 (Catalase) 18.8 (SAHA)	40%-14 h (Catalase with H_2O_2) 40%-24 h (SAHA)	Radiotherapy	CT26	Mice	No	[79]
12	LPN-30-R8^{2K}@DP	50:50	w/o/w	Doxorubicin (DOX) P-12 (PD-L1 inhibitor)	Entrapped	–	35%-70 h (DOX) 72%-12 h (P-12)	Chemo-immunotherapy	CT26	Mice	No	[90]
13	α-PD-L1 NP	PEG-PLGA, M_W = 5 kDa	–	α-PD-L1 monoclonal antibodies	Attached	–	–	Immunotherapy	MC38	Mice	Yes	[91]
14	PTX@NPpD-ATP	LA:GA = 85:15, ester end, 0.55−0.75 dL/g	o/w	Paclitaxel (PTX)	Entrapped	3.4	70%-24 h 83%-96 h	Immunotherapy	CT26	Mice	No	[93]
15	CaCO$_3$@PLGA NPs	M_W 7000–17000	w/o/w	CaCO$_3$	Entrapped	15.5	–	Immunotherapy	CT26	Mice	No	[99]
16	R837@PLGA@Neu	PEG-PLGA 50:50 (w/ w), Mw~5000:10000 Da	o/w	R837 (Toll-like receptor 7 agonist)	Entrapped	–	41%-100 h	Radio-immunotherapy	CT26	Mice	No	[103]

Table 1 (*continued*)

No.	Formulation	PLGA	Methods	Therapeutic agents	Loading techniques	Entrapment efficiency wt./%	Release rate/time	Treatments	Target tumor cell lines	Animals	Differences between in vitro and in vivo studies	References
17	PEDF-PLGANPs	LA: GA = 75:25, M_W 15000 Da	w/o/w	PEDF gene	Entrapped	88.0	–	Genetherapy	CT26	Mice	No	[110]
18	siRNA@PLGA NPs	LA: GA = 75:25, M_W 20000 Da	w/o/w	PD-1 and PD-L1 siRNA	Entrapped	80.2	–	Genetherapy	MC38	Mice	No	[111]
19	T-NPs	PEG-PLGA M_W = 15 kDa; LA/GA = 75:25	w/o/w	Paclitaxel (PTX) PEDF gene	Entrapped	86.3 (PTX) 83.7 (PEDF)	65%-48 h (PTX) 95%-48 h (PEDF)	Gene-chemo-therapy	CT26 A549 LL2	Mice	No	[113]
20	AMNCs	Rui'xi Biotechnology Co. Ltd (Xi'an, China)	w/o/w	AIPH Fe_3O_4	Entrapped	–	95%-after laser 25 h (AIPH)	MRI guided PTT/TDT	CT26	Mice	No	[118]
21	GNPs-pD-PTX-PLGA-Ms	50:50 DLG 5 E from Lakeshore Biomaterials Inc. (Birmingham, AL, USA)	–	PTX	Entrapped	70.0	65%-24 d	Chemical-PTT	PANC-1	–	–	[120]
22	PLGA-VP-TAT NPs	50:50, M_W 38000–54000	w/o/w	Verteporfin	Entrapped	–	5%-30 h	RDT	PANC-1	–	–	[121]
23	Cur@PLGA-NPs	50:50, M_W 40000	w/o/w	Curcumin	Entrapped	70.0	–	Fluorescence probes	CT26	–	–	[128]
24	SPIO/PTX-NP	50:50, M_W 7000–17000	o/w	SPI (superparamagnetic iron oxide) PTX	Entrapped	24.8 (PTX)	–	MRI contrast agents	CT26	Mice	No	[129]

CRediT authorship contribution statement

Rui Sun: Writing – original draft, Visualization, Resources, Conceptualization. **Yanfei Chen:** Writing – review & editing, Visualization, Conceptualization. **Yanjiang Pei:** Writing – review & editing, Methodology, Conceptualization. **Wenbin Wang:** Resources, Conceptualization. **Zhi Zhu:** Visualization, Resources. **Zhaohua Zheng:** Resources, Conceptualization. **Limeng Yang:** Writing – original draft, Funding acquisition. **Li Sun:** Writing – review & editing, Resources, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Limeng Yang reports financial support was provided by Xi'an Polytechnic University. Limeng Yang reports a relationship with Xi'an Polytechnic University that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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