PERSPECTIVE

PLGA-based nanoparticles for the treatment of cancer: current strategies and perspectives

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Abstract

Research on cancer treatment is always of great importance because of the extensive and difficult treatment options and side effects of chemotherapeutic agents. Due to this, novel techniques for cancer treatment are the need of the day. Nowadays, nanotechnology is of great interest for its applications as diagnostic tools, theragnostic, contrasting agents, and vehicles for delivering drugs. Nanoparticles (NPs) are made up of biocompatible and biodegradable polymers that improve the pharmacokinetic and pharmacodynamic properties of drugs, reduce side effects, improve stability, prolong the release of drug, and reduce the dosing frequency. Poly (lactic-co-glycolic acid) (PLGA) is FDA-approved synthetic polymer which can be used to formulate NPs that can be targeted to a specific site for the safe and effective delivery of drugs. PLGA-based NPs can be used for a variety of cancer therapies including tumor-targeted drug delivery, gene therapy, hyperthermia, and photodynamic therapy. This article discusses the method of preparation, characterization, encapsulation of chemotherapeutic drugs, effect of physicochemical properties of PLGA- based NPs, and how we can exploit these aspects through various methods of preparation for drug loading, biodistribution, target specificity, and their use in cancer treatment. Along with these targeting strategies, gene therapy, cancer immunotherapy, and various applications have also been discussed. This article also aims to discuss the incorporation of diagnostic tools and therapeutic moiety in one versatile formulation of PLGA-NPs and the difficulties faced in translating this promising tool to clinical use.

Keywords: Poly (lactic-co-glycolic acid), Nanoparticles, Formulation techniques, Chemotherapeutic agents, Drug targeting

Introduction

Cancer treatment has always been an area of great research due to the difficult and extensive treatment options and severe side effects of chemotherapeutic drugs. In recent years, the use of nanotechnology has become an extremely intriguing subject for study, i.e., the use of nanoparticles as a tool for delivering medicine for the treatment and diagnosis of diseases. Among all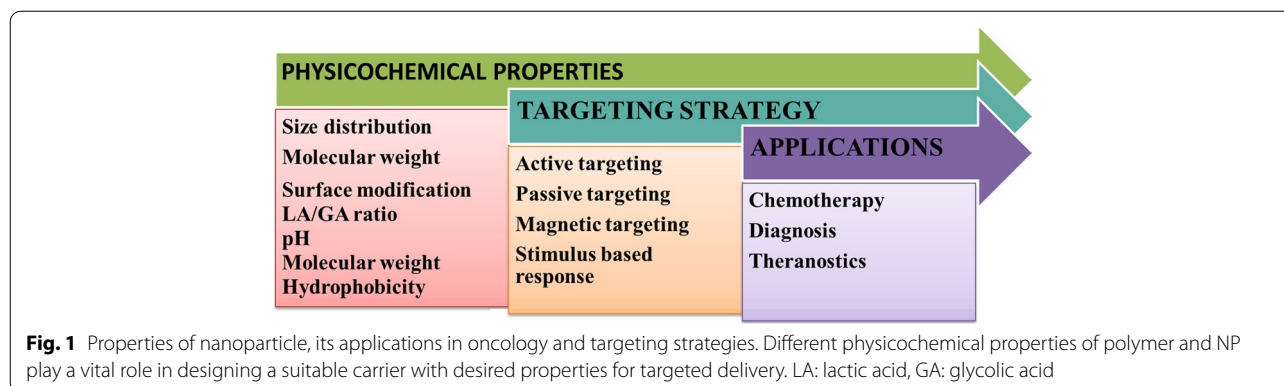 other applications, their use as strategic cancer treatment agents is of utmost importance. For this purpose, several submicron agents have been schemed, designed, formulated, and maneuvered. These applications involve the use of nanotechnology as diagnostic tools, theragnostic, contrasting agents, and vehicles for delivering drugs (Fig. 1). Nanoparticles are solid spherical vesicles ranging from 1 to 100 nanometers in size. Biocompatible and biodegradable polymers have been developed using natural and synthetic materials, but synthetic nanoparticles are more desirable for therapeutic uses as they can be modified to meet the desired properties needed for controlled and targeted drug release. Nanoparticles can be used to deliver a wide range of therapeutic agents including small hydrophobic and hydrophilic drugs as well as vaccines and

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Fig. 1 Properties of nanoparticle, its applications in oncology and targeting strategies. Different physicochemical properties of polymer and NP play a vital role in designing a suitable carrier with desired properties for targeted delivery. LA: lactic acid, GA: glycolic acid

macromolecules (Danhier et al. 2012). From a wide range of inspected nanoparticles, PLGA-based nanoparticles are of utmost interest for treating several diseases. The reason for their desirability as drug carriers is because upon hydrolysis in the body, PLGA metabolizes in endogenous monomer lactic acid and glycolic acid, thus ensuing minimal toxicity (Kumari et al. 2010).

PLGA-based nanoparticles have the potential to be used as drug delivery units for various therapeutic agents. Their use in oncology for targeted drug delivery is one such example. To have a tight control over pharmacological activity, drug release properties, target specificity and drug degradation, the particle size, surface charge, and other physicochemical properties must be in accordance with the intended use. This, however, is a very complex problem as changing a physicochemical activity say the nanoparticle's size which in turn depends on size, charge, coiling, and other such properties of polymers used, so optimizing one parameter of the NPs may compromise other parameters. Also changing the ratio of component polymers used (i.e., lactic acid and glycolic acid) may influence the hydrophobicity and crystallinity of the product. So, the polymer's properties and characteristics may force us to alter our targeting strategy and vice versa. Thus, designing a nanoparticle with optimum properties is like solving a complex puzzle where each block is connected to the other in such a way that removing or changing one block changes the whole dynamics of the puzzle. For instance, an external stimuli-based targeting strategy may enhance tumor retention but on the flip side, it may activate phagocytosis due to the increased size of nanoparticles.
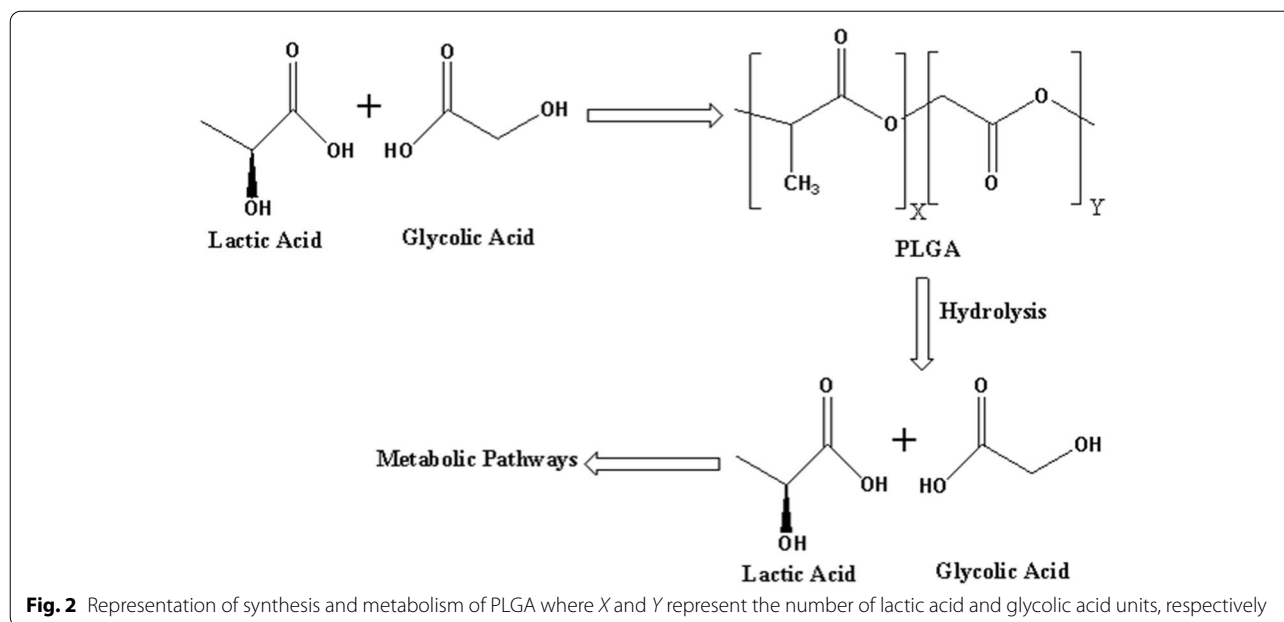
Thus, the scope of this review article is to focus on the different properties of PLGA- based nanoparticles and how we can exploit these aspects through various methods of preparation for target specificity and their use in cancer treatment.

Properties of PLGA

PLGA approved by both the FDA and the European Association of Medicine is an extensively used synthetic biodegradable polymer used for targeted drug delivery. It is a polymer made up of two different monomers (lactate and glycolate) which upon hydrolysis in the body metabolizes to its component monomers which are endogenous to the body, hence causing minimal toxicity as shown in Fig. 2 (Kumari et al. 2010; Kunjachan et al. 2014). Normally, PGLA is synthesized by a catalyst-mediated random ring-opening copolymerization of lactic acid and glycolic acid where both polymers link together through an ester linkage. Both component polymers are simply metabolized by the Krebs cycle and consequently converted to pyruvate.

Both monomers have different intrinsic properties which as a copolymer of these translate into PLGA, as a result, the properties of the polymer such as degradation rate depend on the ratio of monomers used. For example, by increasing LA/GA ratio, slower drug release rates are achieved due to increased hydrophobicity and lower degradation rate as PLA is hydrophobic while PGA is hydrophilic and easily degrades inside the body. Also, the polymer having a lower molecular weight will be more prone to both degradation and drug release (Engineer et al. 2011). The molecular weight also influences the size of NP produced. A lower range of nano-size particles is preferred despite the disadvantage of lower loading potential because it can better overcome the physiological roadblocks to reach the disease site. Commercially available polymers have different degradation times ranging from days to months and some even have degradation times of several years. Various ratios of monomers are used to formulate NP of desired properties, e.g., a 50:50 NP means both monomers (lactic and glycolic acid) are

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Fig. 2 Representation of synthesis and metabolism of PLGA where *X* and *Y* represent the number of lactic acid and glycolic acid units, respectively

present in equal quantity. LA/GA ratio is an efficacious tool for manipulating the degradation time and drug release rates. Faster degradation rates are observed with an increase in GA content (Xu et al. 2017). For prolonged drug release LA content is enhanced (LA/GA: 50/50, 75/25 resulted in faster drug release) (Horisawa et al. 2002). Hence, polymeric ratio, size, and molecular weight are essential in attuning the hydrophobicity, drug loading efficacy, and pharmacokinetic parameters of PLGA formulations.

For optimum cancer treatment, NPs must reach and enter the targeted cell and this internalization relies upon time and concentration-dependent endocytosis (Panyam and Labhasetwar 2003). PLGA-NPs enter the cell partly through fluid-phase pinocytosis, and the remainder enters the cell via clathrin-coated pits present in vascular smooth muscle cells (VSMCs). In in vitro cell culture studies, it was observed that NPs enter the cytoplasm within 10 min of incubation actively fleeing the endolysosomes.

The shape is another important factor to be considered when formulating NPs for cancer treatment. PLGA-NPs having different shapes are compared in terms of cellular uptake, cancer cell internalization, distribution, and blood half-life to conventional spherical nanoparticles. For instance, when tested in vitro needle-shaped nanoparticles appear more efficient in crossing the endothelial cell membrane and delivering small interfering RNA (siRNA) into the cellular cytoplasm as compared to their spherically shaped counterparts. A 150% higher internalization with a threefold increase in silencing efficacy

was observed (Kolhar et al. 2011). However, considerable cytotoxicity was associated with needle-shaped NPs. Needle-shaped particles induce cell apoptosis by staying in the lysosomes and damaging the lysosomal membrane consequently activating apoptosis signaling pathways (Zhang et al. 2017). Cylindrical PLGA-NPs loaded with docetaxel (DTX) showed less accretion in the liver, spleen, and lung when compared to free drug and DTX loaded spherical NPs (Chu et al. 2013).

Hydrophobic particles are recognized as foreign by the body. These are taken up in the bloodstream by the reticuloendothelial system (RES) and released in the liver or spleen. This essential biological process is a significant barrier in way of nanoparticle-based controlled drug delivery (Kumari et al. 2010).

Another factor that has an impact on the cellular uptake of NPs is surface charge (Danhier et al. 2012; Foged et al. 2005; Vasir and Labhasetwar 2008; Owens 3rd and Peppas 2006). For maximized interaction between the cells and NPs and optimum cell internalization, a positive surface charge is desirable (Kumari et al. 2010). PLGA-NPs are anionic but can be modified to neutral or cationic by coating the surface of polymer with PEG (PEGylation) or chitosan (Kumari et al. 2010; Vllasaliu et al. 2014).

The blood half-life of NPs can especially be increased by combining PLGA with other polymers like polyethylene glycol (PEG), polyvinyl alcohol (PVA), and D-α-tocopheryl PEG 1000 succinate (TPGS). Combining the polymer with PEG results in a stealth effect, preventing opsonization, NP escapes phagocytosis resulting in increased circulation time and a better pharmacokinetic

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profile (Turecek et al. 2016). On the downside, this may as well compromise the NPs uptake by the target cell. For example, research was conducted on PEGylated PLGA nanoparticles, PLGA nanoparticles, and free drugs (Rafiei and Haddadi 2017). PEGylated NPs showed a better pharmacokinetic profile, i.e., increased biological half-life and bioavailability. However, even with better pharmacokinetics, results showed a slightly faster drug release rate for PEG stealth NPs than PLGA-NPs. PEGylation also boosts the degradation of PLGA-NPs consequently accelerating drug payload release. This phenomenon can be explained by the hydrophilic nature of PEG chains which cause the decomposition of chains by absorbing water (Rafiei and Haddadi 2017). Thus, introducing a third component such as stealth polymer may further regulate the PLGA-NP properties. Concerning active targeting, the binding of NPs and targeting ligands, and targeting specificity may differ. Besides a multistep production process, their therapeutic effect is many times less than anticipated. A recent study conducted on PLA/PLGA-NPs loaded with DTX targeted on prostate-specific membrane antigen (PSMA) represented that active targeting was not as effective as expected (Hrkach et al. 2012). The hydrophilic nature of polymer can cover the ligand and hamper its binding to the targeted moiety. In addition, the size enlargement of NP can limit the ability to cross biological barriers and/or enhance uptake by phagocytes (Lammers et al. 2012).

Formulation techniques of PLGA-based NPs

Several techniques exist for the preparation of NPs, and the method used for preparation has a significant impact on the outcome of the NP such as its stability, shape, and size. These techniques include emulsification, spray drying, nanoprecipitation, and microfluidics. The advantages and disadvantages of these methods are described in Table 1. Some common techniques are discussed here.

Emulsion solvent evaporation technique

The most often used method for the formulation of PLGA-NPs is emulsification. The organic solvent is used to dissolve the drug which is then added to a large volume aqueous phase having a suitable emulsifier or surfactant (usually PVA). It is then continuously stirred till a homogenous emulsion is obtained. The organic solvent is evaporated to form the oil in the water emulsion. The particles thus obtained are washed and freeze-dried before the final formulation could be achieved. A single emulsion is not suitable in some cases so a double emulsion water/oil/water can be made in such cases, for example, hydrophilic drugs show higher encapsulation efficacy in the double emulsion as compared to the single-emulsion method (Ding and Zhu 2018; Kamaly et al. 2016; Masood 2016; Mendoza Muñoz et al. 2016). The size of NP is dependent on the polymeric concentration and evaporation step of the procedure. To achieve smaller particles, the concentration of polymer in the dispersed phase should be kept lower. Even after several times of washing, some residue of the stabilizer used may remain on the surface of particles which is major peril of this method (Ramazani et al. 2016).

Salting out/emulsification reverse salting out technique

The drug and polymer are added to a water soluble polar solvent, e.g., acetone, which is then added to another aqueous solution having a salt such as $MgCl_2$ or $CaCl_2$, and a stabilizing agent, like polyvinyl pyrrolidone, this mixture is stirred forcefully to form a homogenous emulsion. The resultant emulsion is diluted using an ample quantity of water, the organic solvent diffuses in water, and NPs are formed. This method is advantageous for thermolabile materials and preparations containing high polymer concentrations (Mirakabad et al. 2014). Removing the stabilizer involves extensive washing which consumes a lot of time and is only suitable for hydrophilic

Table 1 Advantages and disadvantages of different PLGA nanoparticle preparation techniques

Method of preparation	Advantages	Disadvantages
Emulsion evaporation	Both hydrophobic and hydrophilic drugs can be encapsulated by single and double or multiple emulsion methods respectively. High production rate at a industrial scale.	Difficult to remove residue of stabilizer and solvents. Heating is required for evaporation. W/o/w emulsions are unstable.
Microfluidics	Fewer amounts of drug and solution were used. Suitable for heat-labile products. The size and shape of the particles are well controlled. Reproducibility.	Microchannels might get clogged. Small production scale.
Salting out	Suitable for RNA, DNA, proteins, and amino acids. No requirement for heating.	Restricted up-scaling. The purification step is time consuming. Homogenization at a high scale is required.
Nanoprecipitation	Low energy requirement. Single step process. Reproducibility.	Uneven particle size distribution during mixing.

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drugs, this is a major drawback of this procedure (Dinarvand et al. 2011). A combination of both emulsification and salting out method to encapsulate meloxicam in PLGA (50:50 ratio) nanoparticles having different mol. Wt. (5–15 and 40–75 kDa) was used by Sengul et al. The results showed that higher molecular weight polymer produced more stable particles (Dinarvand et al. 2011).

Nanoprecipitation technique
A one-step method involves dropwise addition of a solution containing drug, polymer, and water miscible organic solvent into an aqueous solution containing stabilizer, precipitation occurs and NPs are formed at the end, and reduced pressure is applied to remove the solvent. The ratio of polymer used, the concentration of solvent, molecular weight of the polymer, and mixing force determine the properties of resultant particles. This method is equally efficient for incorporating hydrophobic and hydrophilic therapeutic moiety (Miladi et al. 2016).

Microfluidics technique
The microfluidic method is a rather sophisticated technique that produces controlled size NPs with a high reproducibility rate. In this system, microscale volumes (micro- or nano-liter) of liquids are processed in a microchannel. It has two types depending upon the type of reagent flow: (a) continuous phase flow, and (b) droplet phase flow in microfluidic systems. If micron-sized NPs are the requirement segmented or droplet phase flow system is used while the former produces nanoparticles. In a continuous flow system, a solution of the drug, polymer, and an organic solvent is made to flow through a microchannel in which an aqueous solution is running on both sides of tubes, thus precipitation occurs and NPs are made in the organic phase. The NPs thus made are firm in structure and closely packed which inhibit initial burst release. Moreover, this method has a higher reproducibility (Valencia et al. 2011; Li and Jiang 2018; Hasani-Sadrabadi et al. 2015).

Characterization of nanoparticles
Before developing the nanoparticles for pharmaceutical purposes, their characterization is necessary to fully understand the properties of nanoparticles. The efficacy of a therapeutic agent depends on the size of the nanoparticle in terms of cellular uptake and tissue penetration, and release profile and degradation kinetics are also contingent on the size of NPs (Dinarvand et al. 2011; Gaumet et al. 2008). Many methods including dynamic light scattering or photon correlation spectroscopy (Cheng et al. 2008; Govender et al. 1999; Fonseca et al. 2002), transmission electron microscopy (Song et al. 2008; Panyam et al. 2003; Yang et al. 2007), scanning

electron microscopy (Ricci-Júnior and Marchetti 2006; Esmaeili et al. 2008), and atomic force microscopy (Ravi Kumar et al. 2004a) are employed for the characterization of particle size, size distribution, and morphology of nanoparticles.

The size of the nanoparticle, encapsulation efficiency and degradation rate all are dependent on the molecular weight of the polymer (Dinarvand et al. 2011). The molecular weight and chain length of polymer are directly proportional to each other, polymers with longer chain lengths have higher molecular weight. Additionally, chain length is also indicative of hydrophilicity or lipophilicity of the polymer used. A longer chain length means increased lipophilicity of drug hence increased stability in vivo. Hence, the degradation and release kinetics of the drug can be controlled by manipulating the chain length or molecular weight of the polymer (Dinarvand et al. 2011; Mittal et al. 2007). Size exclusion chromatography can be used to determine the molecular weight of the polymer (Garinot et al. 2007).

Drug release kinetics is dependent on both the physical state of the drug and the polymer used. The mucoadhesion, consistency, and intracellular uptake of particles are reliant on zeta-potential as a function of pH. The lipophilicity of nanoparticles influences their distribution in the body. Lipophilic NPs tend to remain longer in the blood (Dinarvand et al. 2011; Astete and Sabliov 2006). Zetasizer is used to determine the zeta potential (Garinot et al. 2007). Based on the type of polymer used and the nature of the material used for surface modification, the zeta potential may be positive or negative. This method is extensively used for determining the surface charge of NPs (Soppimath et al. 2001; Ravi Kumar et al. 2004b). Water contact angle measurements are used to determine the lipophilicity or hydrophilicity while hydrophobic interactions are known using chromatography (Dinarvand et al. 2011).

Encapsulation of chemotherapeutic agents in PLGA nanoparticles
Paclitaxel
Paclitaxel is a chemotherapeutic agent used for the treatment of many cancer types including ovarian and breast cancer (brand Taxol®). It binds the β-subunit of tubulin, thus inhibiting the normal microtubule functionality. It causes polymerization of tubulin, disrupting the order of cell division, and resulting in cell death. Paclitaxel has poor solubility which limits its clinical use. PLGA nanoparticles modified with tocopheryl polyethylene glycol succinate (TPGS) and vitamin E prepared via solvent evaporation method have been used for paclitaxel encapsulation (in vitro controlled release). Mu and Feng fabricated a paclitaxel-loaded nanoparticle formulation using

α-tocopheryl polyethylene glycol l000 succinate as well as a matrix material with other biodegradable polymers. The study showed the value of vitamin E TPGS for preparing a controlled release formulation of PLGA either as an emulsifier or as matrix material mixed with PLGA (Dinarvand et al. 2011; Mo and Lim 2005).

Vincristine sulfate
Vincristine sulfate (VCR) is an important antineoplastic agent used to treat various types of cancer, but some cancerous cells are resistant to it. This resistance is attributed to mediated efflux pumps that export the drug out of the cell (Borst et al. 2006; Acharya and Sahoo 2011). These cell proteins pump out the drug when it is present in the cell membrane. As nanoparticles enter the endosomal complex after cell internalization, the drug encapsulated in NPs escapes the P-glycoprotein and associated proteins. Experiments showed that Vincristine containing PLGA-NPs with optimal properties could be prepared by a combination of two methods namely salting out and emulsion solvent evaporation technique. The study also concluded that a combination of vincristine and verapamil (enhances cellular internalization of vincristine by reducing the efflux rate) could be prepared by simultaneous encapsulation of both drugs in NPs 100 nm size with increased entrapment efficiency $69.47 \pm 5.34\%$ for verapamil and $55.35 \pm 4.22\%$ for Vincristine. PLGA nanoparticles containing a combination of antineoplastic agent and chemosensitizer might be the ultimate answer to cancers that have become resistant to traditional drug therapy (Song et al. 2008; Acharya and Sahoo 2011; Song et al. 2009).

Cisplatin
Cisplatin has been used for decades in cancer treatment. It causes cell death by binding to purine residue of tumor cell DNA hindering cell division and ultimately leading to cell death by apoptosis. Toxicity associated with this otherwise important chemotherapeutic agent limits its use to its full potential (Kumari et al. 2010; Rosenberg 1985). Targeted tumor cell delivery is desirable in this case. PLGA−mPEG nanoparticles formulated by the double emulsion technique have been used to encapsulate cisplatin (Kumari et al. 2010; Acharya and Sahoo 2011; Gryparis et al. 2007). When tested in mice with prostate tumors, cisplatin-containing PLGA methoxy polyethylene glycol (mPEG) nanoparticles had longer cisplatin blood circulation transit time (Kumari et al. 2010; Avgoustakis et al. 2002).

Etoposide
Etoposide is used for the treatment of a variety of cancers, including malignant lymphomas. This drug inhibits topoisomerase-II and creates derivatives that bind to DNA and cause DNA damage. Prolonged tumor exposure is required for fruitful chemotherapeutic results. Due to the short half-life of etoposide (3.6 h), tumor exposure time is shorter. Better results are anticipated by delivering etoposide to the peritoneal tumor through nanotechnology. Reddy et. al. formulated PLGA and Pluronic F68 NPs by using emulsion solvent evaporation and nanoprecipitation. The NPs so prepared had huge drug-loading efficiency of about 80% and a continuous drug release rate for up to 48 h (Acharya and Sahoo 2011; Reddy et al. 2004).

Nitrocamptothecin (9-NC)
9-Nitrocamptothecin is a camptothecin derivative and its other analogs belong to the fairly vital family of anticancer therapeutic agents with a unique mechanism of action. They target the topoisomerase-I enzyme. Structure of 9-nitrocamptothecin and the related analogs changes from closed ring lactone to inactive hydroxyl carboxylate by the process of rapid pH-dependent hydrolysis which leads to loss of anticancer activity. The drug has a low hydrophilic profile and is unstable at biological pH making delivery of lipophilic derivatives a challenge due to instability and its low water solubility. 9-Nitrocamptothecin has been effectively loaded in PLGA nanoparticles without disturbing lactone ring and biological activity. The nanoprecipitation method has a higher encapsulating (more than 30% EE) order while biological activity and lactone ring remain intact (Acharya and Sahoo 2011; Derakhshandeh et al. 2007).

Doxorubicin
Among anticancer agents, one of the most commonly used anthracycline agents is Doxorubicin because of its higher efficacy against tumor cells. Cardiotoxicity and myelosuppression side effects limit the therapeutics usage of doxorubicin (Acharya and Sahoo 2011; Misra and Sahoo 2010). The therapeutic efficacy of doxorubicin can be markedly improved with the formulated design of doxorubicin as PLGA nanoparticles. This controlled release pattern reduces the systemic toxicity of doxorubicin. Park et. al. studied the simultaneous effect of PLGA-based nanoparticles of doxorubicin and photothermal therapy on selected tumorigenic cells (Acharya and Sahoo 2011; Park et al. 2009).

Curcumin
The traditional use of Curcumin (Wojcieszyńska et al. 2012) as the antitumor agent has its fame in India and China for ages *(Acharya and Sahoo 2011; Shishodia et al. 2005).* Poor water solubility and reduced bioavailability at tumor-affected sites restrict the use of free curcumin

through the oral route of administration. The bioavailability and cellular uptake of curcumin can be enhanced by the novel design of curcumin, i.e., when curcumin is loaded in PLGA-based nanoparticles along with the admixture of PEG-500, PVA, and/or CTAB (cetyltrimethylammonium bromide) as a stabilizer. The emulsion diffusion evaporation method is used for this purpose. Formulated nanoparticle-based curcumin shows better in vitro bioactivity and in vivo bioavailability as compared to free curcumin. Curcumin-loaded PLGA-based nanoparticles are now used as adjuvant therapy in the treatment of prostate tumors (Acharya and Sahoo 2011; Mukerjee and Vishwanatha 2009).

Xanthones

Naturally occurring or semi-synthetic heterocyclic compounds like Xanthones produce a broad spectrum of antitumor compounds due to the substitution effect of different substituents on various carbons (Kumari et al. 2010; Pinto and Sousa 2003). They exert their inhibitory action on tumor cell lining by the production of nitric oxide in macrophages. The quality by design preparation of xanthone like PLA-based nanoparticle by solvent displacement method enhances the bioavailability and improved antitumor effects of xanthones (Kumari et al. 2010; Teixeira et al. 2005).

Triptorelin

Successive treatments of sex hormone-related tumors were carried out using a decapeptide analog of LHRH (luteinizing hormone releasing hormone) like triptorelin. It decreases the production and accumulation of testosterone in the tumor cells. This destroys tumor cells or prevents their growth because of the diminishing production of an LHRH which has a direct impact on the production of testosterone. The maintenance of steady-state plasma levels for a prolonged time is required in the treatment plan of tumor cells with triptorelin therapy. This is achieved when triptorelin is administered in the form of PLGA-based nanoparticles. The encapsulating efficiency varies from 4 to 83% when the triptorelin-loaded PLGA-based nanosphere was manufactured by a double emulsion solvent evaporation technique (Kumari et al. 2010; Nicoli et al. 2001).

Dexamethasone

In the treatment of bacterial meningitis, dexamethasone is injected before the antibiotics to reduce the inflammatory response of the body against the motile bacteria. At the site of inflammation, dexamethasone exerts its inhibitory action by preventing leukocyte accumulation, therefore improving prognosis. However, dexamethasone is weakly soluble in water which limits its usage, and the efficacy of dexamethasone can be improved when it is formulated by incorporating in PLGA-based nanoparticles by solvent evaporation methodology (Gómez-Gaete et al. 2007). Different formulations for a load of dexamethasone as PLGA (75:25)-based nanoparticles by using numerous solvents such as acetone dichloromethane 1:1 (v/v) are reported in the literature (Kumari et al. 2010).

Rapamycin

Rapamycin and analogs are currently used as an alternative therapy in the treatment of breast cancer. This drug is in the clinical trial phase, and the drug shows better stability and pharmacological properties as an antitumor agent for treating breast cancer (Acharya and Sahoo 2011; Hidalgo and Rowinsky 2000). Rapamycin and its analogs have poor water solubility (2.6 μg/ml) which affects the bioavailability of the drug at the site of action and ultimately affects the drug efficacy. The controlled release of drugs in the form of nanoparticles is used as a carrier system like PLGA-NPs for the introduction of smaller doses of rapamycin into the body to treat various diseases. They exert their regressive effect by alternating the maturation profile of dendritic cells (Simamora et al. 2001).

Hypericin

Hypericin is a naturally occurring photosensitizer. It is obtained by the extraction process from *Hypericum perforatum*. Hypericin is reported to act as an agent in the treatment of ovarian and other types of cancer. Hypericin is a hydrophobic agent which limits its therapeutic efficacy but the design of hypericin in PLGA-based nanoparticles improves its therapeutic effect in ovarian tumors (Zeisser-Labouèbe et al. 2006).

Different PLGA-based nanoparticles along with their targeting ligand, applications, and clinical status are described in Table 2.

Drug targeting

Generally, chemotherapeutic agents are administered into the body by oral or systemic (IV administration) route. Both routes have equal chances of serious side effects due to the non-specificity of the drug target. Drugs thus destroy normal healthy (actively dividing) cells along with malignant cells. This accounts for the limited use of some otherwise great antineoplastic agents in cancer treatment. The issue of off-targeting can be overcome by designing target-specific strategies for drug delivery. Some of these are discussed below.

Passive targeting

Increased permeability and retention of nanoparticles in the tumor cell are the primary parameter for tumor

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Table 2 PLGA-based nanoparticles with their targeting ligand and applications

Drug loaded	Targeting ligand	Main targets	NP size	Results	Application	Status	Ref.
Afatinib	None	Intracellular tyrosine kinase	180.2 ± 15.6 nm	Enhanced cytotoxicity KRAS-mutated NSCLC cell lines	Metastatic non-small cell lung cancer (NSCLC)	In vitro	(Elbatanony et al. 2021)
Docetaxel	Hyaluronic acid, disulfide-crosslinked star-PLGA	CD44-overexpressing A549 cells	105.5 ± 0.5 nm	Elimination half-life prolonged, better suppression of subcutaneous A549 lung tumor	Lung cancer cells	Preclinical	(Wang et al. 2021)
Chrysin	PEG	T47D & MCF7 breast cancer cell lines	70–300 nm	Higher absorption by breast cancer cell lines	It may be used in breast, ovarian, and prostate cancers	Preclinical	(Anari et al. 2016)
Trametinib	Melanoma-specific anti-gp100/HLA-A2 T-cell receptor (TCR) (Armenia Hamster IgG)	Melanoma cancer cells	193 ± 5.6 nm	In vitro: Excellent targeting and minimum toxicity and systemic clearance concerns In vivo: Intrinsic targeting, prolonged drug release, and therapeutic potential	Theragnostic carrier platform	Preclinical	(Yaman et al. 2020)
Pheophorbide	PEG and Folate	Human gastric cancer	200 nm	In vivo: Imaging showed high accumulation of FA-PLGA-Pba NPs in tumor site	Photodynamic chemo-therapy (PDT)	Preclinical	(Son et al. 2018)
Noscapine	None	4T1 breast cancer cell line	101±4.8nm	Antiangiogenic effect	Combination treatment Doxorubicin in breast cancer	Preclinical	(Esnaashari et al. 2020)
Indomycin green & Requisimide (dual-functional PLGA-ICG-R848 NPs	None	RM9 cells	157.7 nm	PTT with immunotherapy against PCa.	Low and/or intermediate risk prostate cancer	Preclinical	(Lin et al. 2021)
PRECIOUS-01 (NY-ESO-1 antigen coloaded with IMM60)	–	CD8+ T	Not available	Immunotherapy	Advanced solid tumor	Clinical trials phase 1	(Creemers et al. 2021)

accumulation of the drug. Pathophysiology of tumor cells results in enhanced permeability, i.e., a tumor with a leaky vasculature system combined with an inactive lymphatic drainage system makes the basis for enhanced accumulation of nanoformulation in the tumor cell (Maeda et al. 2001).

For the passive targeting technique, the high stability and regulated systemic circulation time of NPs are the important attributes to be used (Danhier et al. 2012; Wicki et al. 2015). Chemotherapeutic agent-loaded PLGA-based nanoparticles including doxorubicin (DOX) (Park et al. 2009), paclitaxel (PTX) (Danhier et al. 2009), cisplatin (Mattheolabakis et al. 2009; Moreno et al. 2010), and CUR (Mohanty and Sahoo 2010) are delivered through passive targeting for better antitumor activity and well-controlled pharmacokinetic parameters like enhanced stability and longer systemic circulation time. For instance, CUR has a short half-life to overcome this shortcoming PEGylated PLGA nanoparticles were prepared with castor oil core. These novel NPs resulted in prolonged blood circulation (Klippstein et al. 2015). Similarly, the case of DTX (docetaxel) PEGylated PLGA nanoparticles showed a 3.7 fold increase in elimination half-life as compared to traditionally administered free docetaxel (Rafiei and Haddadi 2017). In passive targeting as the phagocytosis of NPs decreases, the blood circulation time of the drug increases as the stealth NPs dodge the phagocyte cells and stay in systemic circulation for prolonged periods.

Parveen and Sahoo evaluated paclitaxel containing PLGA-NPs with different surface modifications where a constant concentration of chitosan (12%) was mixed with different ratios of PEG (5, 10, and 20%) and MWs (2, 6, and 10 kDa). The NPs with a combination of 12% chitosan and 10% PEG proved to be most productive in terms of longer circulation time (Parveen and Sahoo 2011). Drug side effects were also less when encapsulated in stealth polymers and delivered via passive targeting. When cisplatin-containing nanoparticles were tested in tumor-containing mice, no change was observed in body weight and blood urea nitrogen levels which indicates a decrease in side effects associated with the drug. Thus, when the chemotherapeutic agent is delivered as PLGA nanoparticles along with improved site specificity and antineoplastic activity, the occurrence of side effects is also significantly reduced (Moreno et al. 2010).

However, efficient passive targeting has its restraints. Questions about the effectiveness of this method were raised because it failed to overcome the tumor variances such as high interstitial pressure and changed permeability. The enhanced permeability and retention (EPR) effect is different among various tumor types and may change with time. These factors cannot be controlled by

modifying the PLGA characteristics only. These pitfalls however can be overcome by a detailed study of tumor pathophysiology. For instance, individual patients can be monitored for measuring the degree of EPR-dependent tumor targeting by using modern imaging techniques, the extent of nanomedicine accumulation can also be forecasted by using histopathological biomarkers (Lammers et al. 2012; Danhier and Preat 2015). For enhanced clinical use, and personalized cancer treatment with nanomedicine, it must have better tumor accumulation and effective EPR-based activity and this can be achieved by employing different pharmacological and physical techniques. The frontline in pharmacological modulation is a drug treatment that regulates vascular endothelial growth factor signaling which acts to increase local nitric oxide (NO) concentration and increases leakiness of endothelial vascular in TNF-α. Vessel induction is another pharmacological intervention for instance both cilengitide and recombinant human erythropoietin work increased tumor site drug delivery by promoting vessel density which in turn increases the concentration in relative blood volume (Bridges and Harris 2015; Doleschel et al. 2015; Nel et al. 2017; Wong et al. 2015). On other hand, suitable physical interventions like sonoporation, hyperthermia, or radiotherapy can also be used. Drug supply to the tumor site can be increased by enhancing vascular permeability by increasing tumor perfusion a phenomenon used by hyperthermia (Kong et al. 2001).

Radiotherapy after initially increasing vascular leakage tends to decrease tumor cell density which in turn leads to a decreased pressure of an interstitial fluid (Park et al. 2009). Site-specific drug delivery can also be achieved by employing sonoporation, and this technique uses microbubbles (ultrasound contrast agents) to enhance the permeability of the vessels consequently enhancing drug delivery to the site of interest.

Active targeting
Nanoparticles containing tumor-specific ligands are used to encapsulate the drug. These ligands bind to specific receptors present on tumor cells thus promoting target specificity and cellular uptake of NPs (Pérez-Herrero and Fernández-Medarde 2015). Some commonly used ligands used with PLGA-NPs include antibodies, aptamers, vitamin B7, folic acid, and peptides. For example, better tumor suppression was observed when the surface of DTX containing PLGA-NPs was modified with polydopamine (a hydrophilic neutral polymer) and tocopherol polyethylene glycol succinate (TPGS). DNA aptamer AS1411 was used for further functionalization where control groups contained saline, Taxotere(R)-treated NPs, and DTX containing poly (dopamine) NPs targeted using a passive targeting technique. One of the

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major drawbacks of active targeting is enhanced mononuclear phagocyte system (Hrkach et al. 2012) recognition and opsonization (Theek et al. 2014). Additionally, tumor receptor expression changes over time and receptors once present on the tumor might get replaced with substitute receptors (Rezvantalab et al. 2018). These facts vitalized the need to develop NPs with such surface modifications that targeted receptors that are abundantly expressed at different cancer cell differentiation states. For example, CD44 receptors are overexpressed in both regular cancerous cells as well as breast cancer stem cells, and these receptors are used for binding by DOX-containing NPs modified with hyaluronic acid and cyclopamine (hedgehog signaling pathway inhibitor). These showed better antineoplastic activity when used in combination while cancer cells proliferated after treatment with a single drug (Hu et al. 2015).

Magnetic targeting

Magnetic targeting of nanoparticles is another useful strategy for the deliverance of drugs to the tumor cell. When an external magnetic field is applied, there is an accumulation of magnetic nanoparticles at the tumor site. For example, the PTX chemotherapeutic agent when co-loaded with superparamagnetic iron oxide NPs (SPIONs) into a PLGA-based matrix along with arginine-glycine-aspartic acid (RGD) to α(v)β (Owens 3rd and Peppas 2006) integrin, caused the eightfold increase in accumulation of tumor as compared with passive targeting of nanoparticles which increases in survival time of colon carcinoma (CT26) xenografted mice. Schleich et. al. also observed that there is a marked reduction in tumor growth. There is no effect on the penetration and internalization of tumor cells by magnetic targeting; however, it causes an accumulation of nanoparticles at the site of the tumor cell. The EPR effect mediates this, and the conjugation of RGD mediating NPs binding to α(v)β (Owens 3rd and Peppas 2006) integrins on the tumor cell can increase the cellular uptake (Schleich et al. 2014).

Transferrin receptor targeting therapy when combined with magnetic field effects enhances the survival rate of treated animals. The expected pathway of transferrin-modified magnetic paclitaxel PLGA-NPs is shown in Fig. 3. However, magnetic targeting cannot focus magnetic field in deep body locations. This can be overcome by magnetic particle imaging. When the magnetic field is applied, the iron oxide nanoparticles are in line with the direction of the applied magnetic field. In this case, magnetic particle imaging (MPI) not only acts as a noninvasive imaging modality but can induce magnetic targeting and guide the SPIONs to target the tissue of interest. MPI can also be applied along with hyperthermia (Bauer et al. 2016).
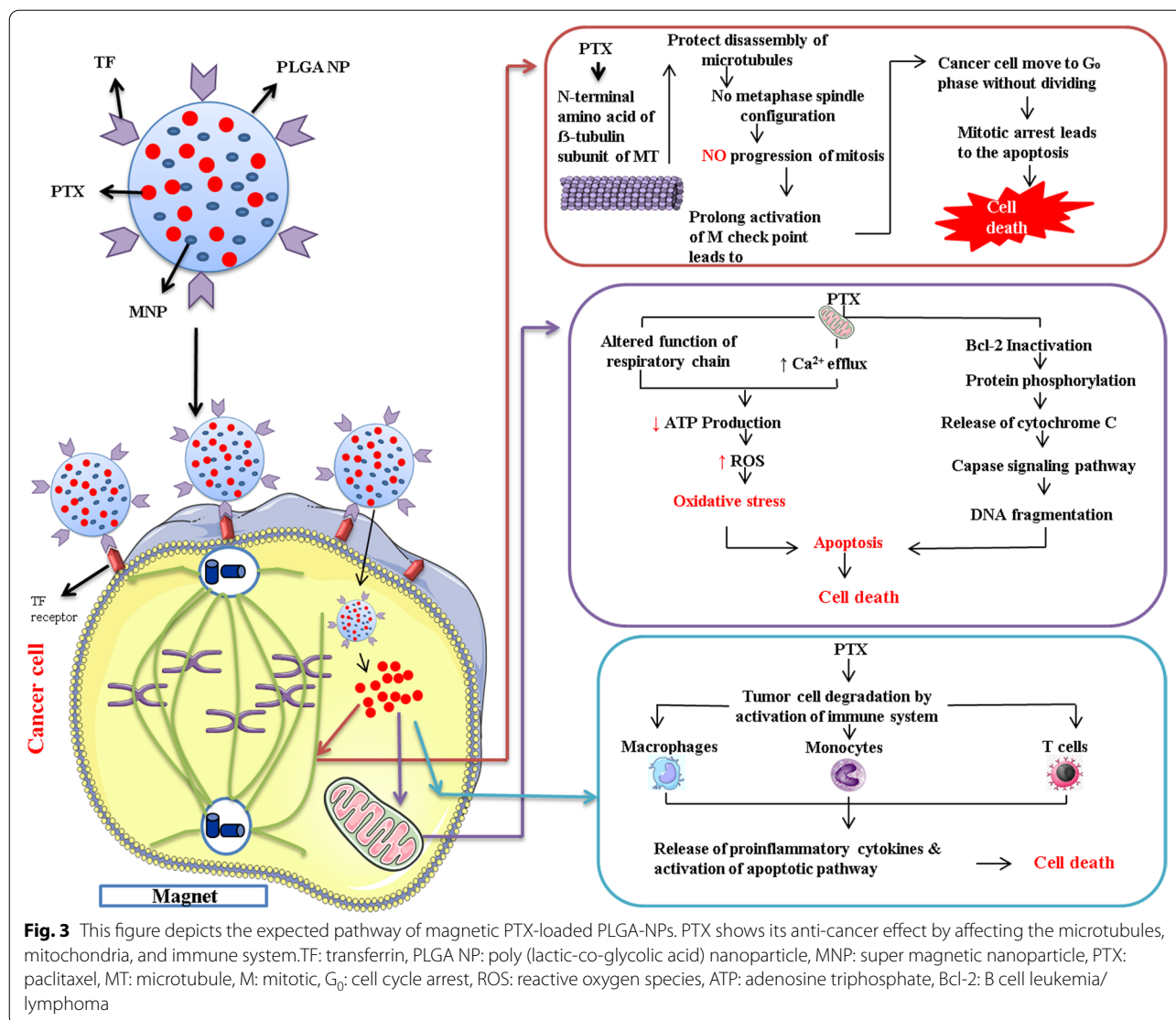
Magnetic hyperthermia

Tumor cell is impaired in case of hyperthermia, i.e., an increase in body temperature. Hyperthermia can be induced in the whole body or locally through high-intensity radio waves or microwaves, laser irradiation, or by any other means like changing the magnetic field when magnetic nanoparticles are loaded in a PLGA-based matrix and exert their chemotherapeutic effect. Sivakumar et. al. (2017) reported that the SPIONs become more stable when they are encapsulated in the PLGA matrix. The PLGA encapsulation process does not affect or change the photothermal character of nanocomposites of SPIONs. Through injecting magnetic nanoparticles or SPIONs, local hyperthermia can be induced by changing the magnetic field of tumor cells from 42 to 46 °C (Sivakumar et al. 2017). The ability of magnetic hyperthermia to produce the therapeutic effect is directly proportional to the size of the particles and applied magnetization. It is also dependent upon the maximum temperature that a particle attains. A combination therapy like chemotherapy or radiotherapy is usually planned with hyperthermia (Rao et al. 2010; Kaur et al. 2011). During in vitro study of colon cancer cell line HT29, Eynali et. al. (2017) reports that the use of 5-fluorouracil when encapsulated in 30–100 nm PLGA-based nanoparticles along with or without iron core markedly reduced the rate of proliferation of these cancer cell line in combination therapy of hyperthermia and chemotherapy (Eynali et al. 2017). A multimodal theranostic PLGA nanocomposite was formulated and characterized by Aravind et. al. in which the magnetic field produced by Fe_3O_4 is used for the introduction of hyperthermia and MRI imaging in a combination of PTX chemotherapeutic agent and Nile red fluorescent dye.

Cancer therapy using PLGA nanoparticles
Photodynamic and photothermal therapy (PTT)
Reactive oxygen species (ROS) can be generated by the process of photoexcitation of photosensitizing agents, which is used in photodynamic treatments (Calixto et al. 2016; Chatterjee et al. 2008). Most of the photosensitizing agents are water repellent, i.e., hydrophobic. Under laser irradiation, the photosensitizing agents give rapid decomposition; therefore, these agents are not accumulated well in the tumor. These agents show poor excitation in a near infrared range which is the prerequisite for reaching deeper tissues. These drawbacks can be minimized when they are formulated in nanocarriers like PLGA-NPs. (Paszko et al. 2011). Poly (aniline), indocyanine green (ICG), and zinc (Matsushita et al. 2004)-meso-tetraphenylporphyrin (ZnTPP) are the most commonly used photosensitizing agents which are loaded in nanocarrier PLGA nanoparticles.

Fig. 3 This figure depicts the expected pathway of magnetic PTX-loaded PLGA-NPs. PTX shows its anti-cancer effect by affecting the microtubules, mitochondria, and immune system.TF: transferrin, PLGA NP: poly (lactic-co-glycolic acid) nanoparticle, MNP: super magnetic nanoparticle, PTX: paclitaxel, MT: microtubule, M: mitotic, G_0: cell cycle arrest, ROS: reactive oxygen species, ATP: adenosine triphosphate, Bcl-2: B cell leukemia/ lymphoma

ICG is an effective photosensitizing and photothermal agent which is used in optical imaging. Chemo and photodynamic therapy can be co-administered in the form of lipid polymer hybrid nanoparticles (PLGA-lecithin-PEG) co-loaded with DOX and ICG. In this treatment, laser irradiation causes tumor growth inhibition which ultimately promotes cell death (Lee and Chang 2017).

Photon energy disrupts a cellular membrane which results in apoptosis and necrosis when a therapeutic agent absorbs it and dissipates it in the form of heat as in photothermal therapy. Photothermal therapy is most commonly used in combination with various organic nanomaterials like carbon, gold, or polymeric nanoparticles with near infrared absorbing agents. Vascular permeability and blood flow increase in photothermal therapy

consequently increasing the EPR effect and drug delivery at the site of a tumor (Yuan et al. 2016).

Gene therapy
Gene therapy is an emerging approach in the treatment of cancer. Affected genes can be replaced with a complete double-standard DNA or a single-standard DNA or gene silencing in response to small interfering RNA (Ibraheem et al. 2014). However, delivering negatively charged large and very fragile nucleic acid is problematic in gene therapy. This can be improved with PLGA-based carriers which protect and deliver nucleic acid at the desired target (Wang et al. 2016). The proliferation of breast cell cancer can be inhibited with calcium phosphate−pDNA complexes embedded in PLGA-NPs which induce apoptosis. This is reported by Tang et al. that in

clustered regularly interspaced short palindromic repeats (CRISPR) technology PLGA-based nanoparticles are used for gene editing (Hu et al. 2015).

Ultrasound-triggered cancer therapy

Ultrasound is a well-known, non-invasive technique in medicine with varied applications in diagnosis and treatment (Zhang et al. 2016). Ultrasound-triggered chemotherapy build on PLGA nanoparticles that include high-intensity-focused ultrasound (HIFU), ultrasound-mediated chemotherapeutic release, and ultrasound-enhanced gene transfection will be discussed here.

Since its introduction in the 1940s, high-intensity-focused ultrasound (HIFU) has become a more advanced and highly used technology (Manthe et al. 2010; Zhang et al. 2014). It has proved its effectiveness and feasibility as a non-intrusive option for the treatment of solid tumors. In their article on biomaterials, Sun et al. (2012) (Sun et al. 2012) loaded hydrophobic Fe_3O_4 in PLGA nanoparticles for enhanced efficiency of HIFU breast cancer treatment. The resultant Fe_3O_4/PLGA nanoparticles had a uniform spherical shape with a diameter of 885.6 nm. The extirpation outcome of HIFU on rabbits bearing breast cancer was evaluated. HIFU with 150 W of acoustic power for 5 s was used following percutaneous Fe_3O_4/PLGA injection while pure PLGA-NPs, and saline microcapsules were made control. After the experiment, Fe_3O_4/PLGA-treated group showed an increase in coagulative necrosis volume and a decreased proliferating cell nuclear antigen index of the removed tumor tissues as compared to the control group. The results indicated augmentation of the acoustic signal in the tumor region after introducing Fe_3O_4/PLGA nanospheres and exposure of the tumor to HIFU.

On-demand drug release from the PLGA-based DDSs at the tumor site using ultrasound (US) as the external trigger is another promising application. Niu et al. (2013) (Niu et al. 2013) designed multifaceted polymeric microbubbles (MPMBs) and co-encapsulated iron oxide nanoparticles and DOX for detecting and treating lymph node tumors. The controlled release of DOX was achieved through ultrasound sonication. The in vitro release profile of drugs with low-intensity sonication was recorded against the release profile without sonication. The ultrasound-triggered MPMBs showed ~90% DOX released while <75% drug was released after 48 h in MPMBs without US sonication. Results showed potential for controlled and target-specific drug release by using ultrasound imaging guidance. Various treatment groups were assessed in terms of cell proliferation in tumor lymph nodes using the immunohistochemical staining technique. The results displayed a substantial decrease in the proliferative index of tumor lymph nodes

in MPMBs triggered by the low frequency ultrasound sonication-treated group. However, the group treated with microbubbles (without loading iron oxide and DOX encapsulated nanoparticles) using low-intensity US radiations showed no significant difference from the saline-treated group. The results suggest that exposure to low-frequency ultrasound sonication can improve the therapeutic effect of microbubbles on tumor lymph nodes These results revealed that the developed MBMPs could remarkably improve the therapeutic efficacy against tumor lymph nodes when exposed to low-frequency US sonication, thus suggesting controllable drug release upon ultrasound irradiation (Niu et al. 2013).

Recently, the use of ultrasound has increased for gene delivery. Studies have confirmed that nanoparticle-based gene delivery may be enhanced to the targeted site when used in combination with ultrasound irradiation (Pitt et al. 2004; Zarnitsyn and Prausnitz 2004; Larina et al. 2005a; Larina et al. 2005b). The efficiency of the gene transfection can be improved with ultrasound and when manufactured in nanoparticles by using PLGA/PEI/DNA-based technology reported by Chumakova et al. in 2008 (Chumakova et al. 2008). In this, plasmids that contain ß-galactosidase was absorbed in polyethyleneimine (PEI) and loaded on PLGA nanoparticles. There are 8-fold increases in efficiency of ß-galactosidase expression when a combination of PLGA/PEI/DNA nanoparticles with ultrasound is used.

Cancer immunotherapy

Immunotherapy is a promising treatment option for cancer. Cytokine, cytokine receptors, cancer vaccines, checkpoint blockade, adoptive T cell transfer, and chimeric antigen receptor T (CAR-T) cell therapy are all types of cancer immunotherapy (Yoon et al. 2018). In this context, PLGA-NPs can act to protect the sensitive carriers (e.g., antigens, adjuvants) from degradation, facilitate active targeting, and encourage passive accumulation by enhanced permeability and retention effect via surface modification. In addition to tumor accumulation of immune cells, stimulation can also be used to elicit an immune response that recognizes and destroys malignant cells. The high affinity of NPs to MPS and enhanced uptake by macrophages can be used to elicit anticipated immune response (Jiang et al. 2017). Nanoparticles in this context can be introduced via the IV route for delivering immunogenic cell death (ICD) activators, vaccines, or immune checkpoint inhibitors. Zhao et al. (2016) prepared mPEG-PLGA oxaliplatin-loaded (ICD promoter) NPs. These showed a high response in mice with pancreatic cancer. PLGA-NPs loaded with chemotherapeutic gemcitabine used as control showed relatively low affectivity. Furthermore, the use of cells as vaccines for the

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generation of effective and adaptive immune responses is well established in cancer immunotherapy (Zhao et al. 2016). In 2017, Ahmed et al. prepared hybrid gamma-irradiated nonvital prostate cancer cells coupled with PLGA-NPs. These hybrid NPs contained either prostate or melanoma cancer cells or adjuvant Toll-like receptor activators. The resultant vaccine produced efficient results in a prostate cancer model, while melanoma cells containing hybrid NPs did not produce the same effects. The results settled the careful selection of tumor cells prerequisite to produce the desired effect (Ahmed et al. 2017).

Additionally, combining immunotherapy with other treatment options such as PTT may also prove an effective treatment option (Chen et al. 2016a). This can be explained when PEG-PLGA nanoparticles co-encapsulating imiquimod (R837) and ICG (PT\PS AGENT)-activated immune response just like vaccines. Further synergistic effect of inhibited metastasis growth and prevention of cancer recurrence was achieved by the addition of anti-cytotoxic T-lymphocyte antigen-4 checkpoint blockade therapy with this near IR heater-loaded PLGA-based nanovaccine.

A promising lead in the area of cancer immunotherapy is precious-01 (NCT04751786), a PLGA-based nanoimmunomodulating agent currently in phase 1 of clinical trials for advanced solid tumors. It contains the NY-ESO-1 antigen (New York Esophageal Squamous Cell Carcinoma-1) which is expressed in a variety of cancers including melanoma and ovarian, lung, and bladder cancers. NY-ESO-1 antigen is coloaded with IMM60 (α-Galactosylceramide a strong immunostimulant) an invariant natural killer T (iNKT) cell agonist.

PLGA-based cancer theranostics

In any case, patients are clinically diagnosed before starting any treatment, thus making diagnosis and treatment a lengthy process which sometimes may delay the treatment and miss the best time window for treatment (Wang et al. 2012). With rapidly evolving imaging technology, numerous studies have been done on several imaging modes for further advancement of diagnostic imaging. In this context, the development of an advanced multifaceted nanoformulation that combines diagnosis and therapeutic purposes is the future of nanomedicine (Song et al. 2017). With the implementation of such nanoformulation which combines diagnosis and treatment, the whole anticancer treatment can be done and scanned in real-time to monitor the effective delivery of a chemotherapeutic agent to the tumor site. Such technology also enables us to monitor the change in size, shape, and metastasis of the tumor to evaluate

the effectiveness of treatment given against cancer cells. Various drug delivery systems based on PLGA nanotechnology have been developed by researchers that can be used to accurately detect tumor cells using MRI, CT scan, fluorescence, ultrasound imaging, and photoacoustic (PA) imaging; meanwhile, pharmaceutical moieties can also be loaded on the PLGA-based systems such as small molecule inhibitors, antineoplastic agents, photosensitizer, and photothermal agents as well as siRNA (Menon et al. 2013). To reverse the drug resistance and enhanced activity of chemotherapeutic agents, Yang et al. (2018) prepared doxorubicin and P-gp short hairpin RNA (shRNA) coloaded PLGA-based ultrasound bubbles with charge reversal. The data obtained from in vitro and in vivo corroborated the use of PLGA-based nanobubbles containing the drug and gene as a theranostic agent for ultrasound image-guided treatment of multidrug resistance (Yang et al. 2018). Chen et al. (2016) prepared cancer cell membrane-coated PLGA nanoparticles for dual modal imaging-guided photothermal malignancy treatment. The core was made of the near IR light absorbing agent, ICG (indocyanine green), which was loaded into PLGA nanoparticles, and the surface was coated with cancer cell wall by simultaneous extrusion of cell membrane vesicles and ICG containing PLGA-NPs through a polycarbonate membrane having diameter 220 nm. The resultant ICG-loaded cancer cell membrane-coated PLGA-NPs had a positive photothermal effect and responded similarly in terms of cell model and animal testing in terms of targeting effect. ICG NPs showed significant accumulation in subcutaneous breast cancer tissues in tumor cells of (MCF-7) mice with target specificity and EPR effect, thus establishing its usefulness as the agent to exactly identify the tumor location. The animal model tests also established that PLGA-based NPs coated with cancer cell walls destroyed the tumor cells and prevented the recurrence when irradiated with a near IR source (Chen et al. 2016b). These results validated the prodigious potential of the PLGA-based ICNPs as multifaceted nanoformulation for targeted delivery of therapeutic agents and fluorescence/photoacoustic (PA) imaging. In another research, Gu et al. (2016) fabricated such versatile mPEG-modified PLGA-based nanocapsules encapsulating ICG and gold nanoclusters with bovine serum albumin capping (BSA). Amino groups present in RGD peptide formed amide linkage with the carboxyl group present on indocyanine green gold nanocages (ICG AuNCs) coloaded nanoparticles. The resultant AuNP-RGD nanocapsules explicitly targeted U87-MG cancer cells overexpressed integrin α(v)β (Owens 3rd and Peppas 2006) when studied through confocal laser scanning microscopy (CLSM) analysis. The potential of arginine-glycine-aspartic acid

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(AuNP-RGD) nanocapsules as theranostic agents was further validated by fluorescence imaging PTT of tumors (Gu et al. 2016).

Pitfalls in translating PLGA chemotherapeutic agents to clinical practice

PLGA is FDA-approved and highly promising polymer for targeting chemotherapeutic agents. Its various formulations are currently available in the market for different disease treatments including cancer. These formulations include Lupron Depot® (leuprolide) for treatment of prostate cancer and endometriosis and Trelstar® PLGA microsphere (Triptorelin pamoate) for prostate cancer. These are in the category of PLGA microspheres, and the only nanoformulation that was evaluated in clinical trials was made up of PLA-PEG (which did not contain glycolic acid). BIND 014(NCT02479178) was a targeted NP that showed increased anti-tumor activity by targeted DOX in comparison to regular DOX therapy. The formulation was evaluated as a potential treatment option in urothelial carcinoma, metastatic prostate cancer, and head and neck carcinoma. The drug was designed to target the neovasculature induced by cancer and PMSA over expressing cells, but the study was terminated in phase 2 due to low responsiveness. In terms of achieving high-response rates in novel drug development, researchers might benefit from focusing on improving the hydrophilicity of drugs, reducing the uptake by MPS, and enhancing tumor target specificity (Chidambaram et al. 2011).

Although PLGA-NPs possess high entrapment efficacies, the drug loading is usually poor which is a major pitfall in designing clinically important NPs with many chemotherapeutic agents. The burst release of drugs from the NP is another concern. As a result, the drug might not be able to reach the target tissue or cells, leading to a loss of efficacy. This initial burst release is usually caused by drug adsorption on the surface of the NP. Also, the acid production upon degradation of PLGA is a disadvantage when incorporating acid-sensitive drugs, thus inventing methods for stabilizing acid-sensitive drugs remains a subject of great research (Fredenberg et al. 2011; Houchin and Topp 2008). To translate the Novel DDSs to reality the nanocarriers must meet the required regulations on toxicology and efficacy in humans, while in vitro results may be encouraging but the in vivo studies must prove otherwise. Animal models used to evaluate preclinical safety are also not a true representation of how the drug will behave in humans. The difficulty in scale-up, reproducibility and associated cost are also hurdling the commercialization of chemotherapeutic PLGA-NPs (Danhier et al. 2012).

Conclusion

In this article, we have summarized the physicochemical properties, their preparation methods, targeting strategies, and various applications, while various PLGA-based therapeutics are commercially available but PLGA-based nanoformulations have not been translated to clinical use despite their encouraging performance in preclinical evaluation. Precious-01, an immunomodulating agent, is the only PLGA-based nanoformulation that is currently in phase 1 clinical trials for cancer treatment. Problems associated with reproducibility, size uniformity, industrial scale production, low drug loading, drug release, and biocompatibility all limit the use of nanoparticles for the commercial market. To overcome these challenges, concentrating on upscaling of formulation from the beginning of experimental design will be valuable.

Formulating targeted PLGA nanoparticles is a complex procedure. One must fully understand the hidden aspects of nanoparticle design. Having a thorough understanding of the pharmacokinetics and pharmacodynamics of both drugs and NPs is necessary to avoid the risk of off-target accumulation and side effects. When too large, NPs may miss its target and may not be able to bind to the cell which is a hindrance in the case of stealth NPs. Reduced cellular uptake thus results in therapeutic failure.

Due to the sophisticated nature of NPs, even a minute change during upscaling can alter the in vivo performance of the formulation. External stimuli-induced PLGA-NPs is a promising approach for targeted cancer treatment, but it also has its disadvantages such as when cancer is located at a deep site in the body (which is the case in most malignancies) increases the depth for irradiating light is a common problem with photo-triggered treatment options. Using near infrared spectroscopy (NIR) may prove helpful in this case owing to its ability to penetrate deep tissues. In the case of photodynamic targeting sufficient oxygen supply for photosensitizer poses a problem. Also, heterogenicity among different patients like EPR effect, biodistribution, and penetration limits the use of PLGA-based NPs in clinical practice. In conclusion, the researchers must reflect on ways to overcome the huge gap between in vitro and in vivo performance of PLGA nanoparticles to effectively translate the great potential afforded by PLGA-NPs in cancer immunotherapy, combination therapy, targeted drug delivery, and theragnostic. A versatile formulation that is minimally invasive and avoids the extensive side effects of traditional chemotherapeutic formulations may revolutionize cancer treatment forever.

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Abbreviations

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Authors' contributions
MSHA and KR presented the concept. AY, MA and MSHA wote the manuscript. MSHA, AY, MA and SMS did the literature search and editing of the draft. MSHA, KR, AY, MA and SMS read and approved the final manuscript.

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Declarations

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