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REVIEW

PEGylated polylactide (PLA) and poly (lactic-co-glycolic acid) (PLGA) copolymers for the design of drug delivery systems

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Abstract

Background PEGylated polylactide (PLA) and poly (lactic-co-glycolic acid) (PLGA) copolymers are biodegradable polyesters, widely employed in the last decades for the design of drug delivery systems such as polymeric hydrogels and nanocarriers (e.g. micelles and nanoparticles). The coupling with polyethylene glycol (PEG) offers some advantages with the respect to PLA and PLGA, including a higher hydrophilicity and a prolonged retention time for nanoparticulate systems, as well as the possibility of preparing thermoresponsive hydrogels. A large variety of pharmacologically active-compounds (small molecules, natural compounds or biomolecules such as proteins, peptides, oligonucleotides) has been formulated and delivered through PEGylated PLA or PLGA copolymers. Due to the high number of papers recently published about the use of these biodegradable copolymers in drug delivery, PEGylated PLA or PLGA copolymers are being still attractive. Their potential applications have been also broadened by the developing of ligand-functionalized copolymers, enabling an "active drug targeting" for nanoparticulate systems.

Area covered The present review summarizes the recent advances in drug delivery systems based on PEGylated PLA or PLGA copolymers, focusing on self-assembled micelles and thermoresponsive hydrogels as well as nanoparticles. A particular consideration has been given to functionalized PEGylated PLA/PLGA nanoparticles for active drug delivery.

Expert opinion Further advances in the design of PEGylated PLA/PLGA delivery systems will be beneficial for an improved drug release and targeting in the light of novel personalised therapeutic strategies.

Keywords Block copolymers · Nanosystems · Thermogels · Decorated nanoparticles · Stealth nanoparticles

Introduction

Polylactide (PLA) and Poly (lactic-co-glycolic acid) (PLGA) are biodegradable, aliphatic polyesters prepared by the condensation of biological monomers as lactic acid (i.e. PLA) or lactic acid and glycolic acid (i.e. PLGA). They possess favourable properties as a good degradability in the environment and biocompatibility, thanks to which these polymers have been approved by Food and Drug Administration (FDA) for application in the biomedical (e.g. tissue engineering, medical devices) and pharmaceutical field (e.g. drug delivery carriers) (Oh 2011; Makadia and Siegel 2011; Xu et al. 2017). In the pharmaceutical field, PLA and PLGA have been exploited in the last decades for the design of a large variety of drug delivery carriers as micro or nanoparticles, polymeric micelles, polymersomes (Cho et al. 2016; Mir et al. 2017; Swider et al. 2018). Particularly, biotherapeutics (as peptides, proteins or vaccines), synthetic drugs and natural bioactive compounds have been incorporated in PLA or PLGA based nanosystems with the aim of increasing the solubility, enhancing the chemical stability and, finally, improving the bioavailability (Ding and Zhu 2018) (Fig. 1).

Chemical and physical properties of PLA and PLGA can be changed as a function of their molecular weight, molecular weight distribution and composition (e.g. different ratios for monomers in the case of PLGA), thereby controlling the size, shape and biodegradability of the prepared nanocarriers, which, in turn, affect the pharmacokinetics of the encapsulated drug (Lee et al. 2016).

However, nanosystems based on PLA or PLGA display some limitations and drawbacks. The inherent hydrophobicity of these polymers (generally PLAs are more hydrophobic than PLGAs) confers a hydrophobic character to the

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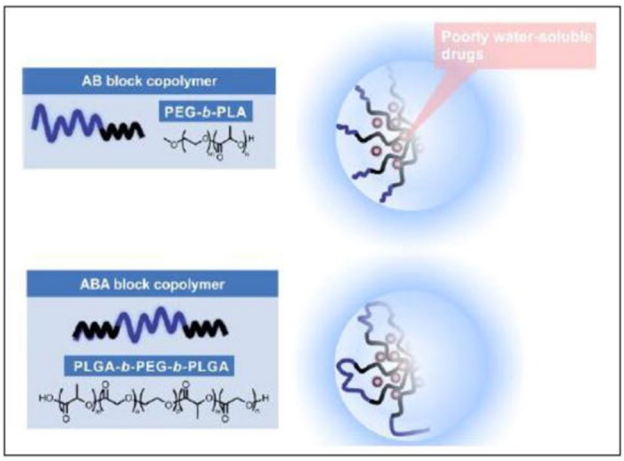

Fig. 1 Self-assembling of PEG-b-PLA and PLGA-b-PEG–PLGA block copolymers into micelles and hydrogels for drug delivery. The figure shows the amphiphilic structure of the PEGylated di- and triblock copolymer and how the hydrophilic (PEG) and hydrophobic (PLA or PLGA) self-organise into micelles and entrap poorly water soluble drugs (Cho et al. 2016)

nanosystem, resulting in a low ability to interact with biological structure (e.g. cell membrane, extracellular matrix) in vivo. The hydrophobic character of PLA/PLGA based nanocarriers is also responsible for the poor loading of hydrophilic drugs and long degradation time, which affects drug release, and, therefore, its bioavailability. Moreover, the high hydrophobicity determines a fast clearance of these nanocarriers in vivo by the reticuloendothelial system (RES).

Copolymerization of PLA/PLGA with hydrophilic monomers (e.g. polyethylene glycol, PEG) for different purposes have been employed to overcome these concerns (Zhang et al. 2014; Suk et al. 2016).

At this extent, the copolymerization with PEG offers some advantages, including the improvement of the hydrophilicity, resulting in a higher drug loading and a faster degradation rate (Perinelli et al. 2014). Moreover, the in vivo residence time of nanocarriers is prolonged since their resistance to the immunological recognition has improved by avoiding phagocytosis by macrophages (Zhang et al. 2018).

A further improvement is the use of PLA/PLGA-PEG block copolymer functionalized at the end groups with different ligands or to perform a PEG coating of the nanocarrier by grafting, tethering or adsorption (Martins et al. 2018).

These modifications are generally performed to improve the surface properties of the nanocarriers, in terms of biocompatibility and of preventing protein adsorption, platelet adhesion and macrophage attachment. Moreover, surface functionalization of the PLA/PLGA nanocarrier with selective ligands allows for active targeting at specific sites (e.g. solid tumors) (Sah et al. 2013; Pelaz et al. 2015).

The present review deals with the update regarding the design and formulation of PEGylated PLA/PLGA based drug delivery systems. Firstly, non-functionalised PEGylated PLA- or PLGA-based copolymers will be considered, which can be employed for the formulation of self-assembled systems as polymeric hydrogels and micelles as well as nanocarriers (e.g. nanoparticles). In the second part, the applications of functionalised PLA/PEG–PEG copolymers for the preparation of polymeric nanoparticles in terms of active targeting and adsorption are described.

Drug delivery systems based on PLA/PLGA-PEG block copolymers

PLA/PLGA micelles and hydrogels

In the last years, new injectable biodegradable and biocompatible polymers characterized by reverse gelation properties have been synthesized (Rathi et al. 1997; Cha et al. 1997). These polymers are composed of A-blocks and B-blocks arranged as ABA or BAB, where A is polyethylene glycol (PEG) and B can be the poly(dl-lactide, PLA) or the poly(dl-lactide-co-glycolide, PLGA). The final copolymers have the characteristics to be soluble in water at or below room temperature but become hydrogels at the injection site, forming depots that degrade over a period of 4–6 weeks (Jeong et al. 1999a).

PLA-PEG-PLA block copolymers characteristics (morphology, crystallinity, rate of biodegradation) can be modulated by adjusting the block copolymer segment sizes through variation of the polymerization parameters, in order to suit a particular application (Bonacucina et al. 2011). Mothé et al. described the preparation and the thermal properties evaluation of PLA-PEG-PLA prepared from two different PEG pre-polymers (Mn = 4000 or 600 g mol^{-1}) and various PLA segment sizes (Mothé et al. 2006). Lee and coworkers, instead, used a low molecular weight PEG (600 Da) and varied the total molecular weight of PEG/PLA multiblock copolymer to study the effect of this parameter on the sol–gel transition of the aqueous polymer solution (Lee et al. 2006).

Another example is the modification of the middle block composition, the block length, and the block ratio, to obtain a next generation of poly(ethylene glycol-b-L-lactic acid-co-glycolide-b-ethylene glycol) (PEG-PLGA-PEG) triblock copolymers. The resulting aqueous polymer solution was a free-flowing sol at room temperature that becomes a gel at body temperature (Jeong et al. 1999a). The sol–gel transition temperature and the critical gel concentration decreased with increasing hydrophobicity of the triblock copolymers (Jeong et al. 1999c). Thus, for the PEG-PLGA-PEG triblock copolymers, the sol–gel transition temperature can be

controlled by changing molecular parameters such as the PLGA length, the PEG length or LA to GA ratio of the middle block. An increasing hydrophobic block length brought to an increase of gel-to-sol transition temperature allowing to control the gel region by simply varying the PLGA length. Also the gel strength was mainly determined by the hydrophobic block; in fact increasing PEG length, the gel region remained almost constant (Jeong et al. 1999b). Also the presence of additives can influence the gelation temperature of PEG-PLGA-PEG copolymers: salting-out salt (NaCl, 1 wt%), decreased the sol–gel transition temperature by 5 °C, whereas a salting-in salt, i.e. NaSCN, increased the sol-to-gel transition temperature by 5 °C (Lee et al. 2001; Zentner et al. 2001).

Regarding the gelation mechanism, the polymer forms micelles where PLGA block are in the core and PEG forms the curved shells, but it may also give rise to bridging micelles at increasing concentration and temperature.

Poly(ethylene glycol)-block-poly(D,L-lactic acid) (PEG-b-PLA) micelles and poly(D,L-lactic-co-glycolic acid)-block-polyethylene glycol)-block-poly(D,L-lactic-co-glycolic acid) (PLGA-b-PEG-b-PLGA) sol–gels have been extensively researched for systemic and local drug delivery systems in form of polymeric micelles, nanoparticles, polymersomes, and sol–gels (Gaucher et al. 2010; Jeong et al. 2012). PEG-b-PLA micelles and PLGA-b-PEG-b-PLGA sol–gels have proven safety profiles and to be amendable to scale-up for human clinical trials (Peer et al. 2007). In addition, PEG-b-PLA micelles and PLGA-b-PEG-b-PLGA sol–gels could load poorly water-soluble anticancer agents, offering a new perspective on delivery of drug combination. Thus, these biodegradable in situ forming hydrogels represent promising delivery systems, particularly able in controlling drug release and increasing the performance of different drug. Genexol-PM® is an injectable formulation PEG-b-PLA micelles loaded with paclitaxel, that gained approval in several Asian countries (Yang et al. 2010; Stirland et al. 2013). Genexol-PM® does not increase the circulation time of paclitaxel but is less toxic than Taxol®, permitting dose escalation of paclitaxel in pre-clinical studies and demonstrating to be much more effective than Taxol® in ovarian and breast murine tumor models, justifying entry into human clinical trials (Kim et al. 2001). Genexol-PM has been approved for breast cancer treatment in South Korea (Deng et al. 2012). Furthermore, Genexol-PM® was licensed by a US company Sorrento Therapeutics Inc., and they changed the name to Cynviloq™. Cynviloq™ entered a phase 3 bioequivalence study versus nabpaclitaxel (Abraxane®) (ClinicalTrials.gov 2015). Another example is represented by BIND-014, a first "active" targeting micellar docetaxel formulation based on biodegradable PEG–PLA or PEG-b-poly(D,L-lactide-co-glycolide) (PEG–PLGA) copolymers, that has been approved for the phase I clinical trials in the treatment of advanced solid tumors and metastatic cancers (Hrkach et al. 2012). These micellar drug formulations have demonstrated to decrease side effects, improved pharmacological profiles, and drug tolerance over the current clinical approaches. Chen et al. successfully developed a formulation based on triblock co-polymer PLGA–PEG–PLGA micelles loaded with US597 for anti-cancer therapy by oral administration. The morphology, diameter, zeta potential, drug loading and encapsulation efficiency of US597 micelles were characterized and the cytotoxicity of US597 loaded into micelles over the US597 alone was demonstrated in various cell lines. The spherical shape of the micellar system containing US597 allowed a better extravasation of tumor microvasculature and tumor accumulation and the drug loading efficiency was much higher than conventional PLGA–PEG-PLGA micelles. Interestingly, US597 micelles demonstrated enhanced rapid cell uptake, growth inhibition and induction of apoptosis on HepG2 cancer cells. Furthermore, the improvements in absorption, metabolism and clearance of US597 micelles indicate that they posses a better bioavailability, pharmacokinetic profiles and enhanced anticancer properties in SD rats making possible their use for a chronic oral administration suitable for future clinical application (Chen et al. 2017).

Other examples are represented by PLGA–PEG–PLGA micelles loaded with 3b-acetoxy-urs-12-en-28-oic acid hexamethylenediamine investigated as a sustained oral formulation for cancer therapy, to improve the bioavailability and efficacy of this molecule (Chen et al. 2017) and by PLGA–PEG–PLGA hydrogels loaded with topotecan, a camptothecin-family drug, investigating the interactions between hydrogels and drug (Chang et al. 2011).

Irinotecan is another member of the camptothecin family and, under physiological conditions, the main form is inactive with a lower drug efficacy and higher toxicity. It was found that after being loaded in the hydrogel the active closed-ring form, the active one, was more than that in physiological conditions. (Liu et al. 2009). Even in this case, the amount of the active form increased by the addition of PLGA–PEG–PLGA hydrogel, leading to a reduced ionization of the active form. Yu et al. were the first to report the encapsulation of a PEGylated drug into these hydrogel demonstrating that their T gel was altered by encapsulating the PEGylated drug. To be more precise, it has been demonstrated that mPEG–camptothecin reduced the Tgel and increased the viscosity of the hydrogel significantly. This result could be explained by fact that the mPEG–camptothecin micelles act as a bridge by increasing intermicellar interactions and, therefore, causing a gelation at lower temperatures (Yu et al. 2008). It is also possible that the sol–gel transition disappeared due the interaction between copolymers and drugs. For example, Yang et al. mixed the PEGylated Taxol (2.0 wt%) with PLGA–PEG–PLGA

copolymers at 20 wt% concentration and although the Tgel of the copolymer solution at the same concentration was 28 °C, the thermosensitivity of the copolymer disappeared. This system called Janus nanogel was formed thanks to the interaction between the PEG chains present on the PEGylated Taxol and the copolymers showing a good stability due to the core–shell structure (Wei et al. 2013).

Asadi et al. prepared PLA-PEG-PLA hydrogels loaded with a hydrophobic narcotic antagonist, naltrexone (Asadi et al. 2011). A higher ratio of PLA/PEG blocks caused a greater naltrexone loading efficiency due to a greater core loading capacity for hydrophobic drugs. A different amount of ethylene glycol dimethacrylate, used as a crosslinker, modified the drug realese kinetics since the drug release profile relied on the dissociation of crosslinked polymers.

According to Jeong et al. PEG-PLGA-PEG copolymers formed micelles as temperature increased, since PEG segments interact with a PLGA core, forming a new intermixed phase between core and shell. Thus, due to an increased miscibility and interphase volume, the micelles start to contact, and the PEG chain in the corona interpenetrates between micelles. At the same time, the intermixed phase hydrophobically interacts with each other, leading to solid micelle packing and preventing the dissolution of the gel from dilution (Jeong et al. 1999c).

Thanks to these different processes, PEG-PLGA-PEG systems form gels that maintain their properties for more than 1 month, as demonstrated by subcutaneous injection of these triblock copolymers aqueous solutions in rats.

In addition, drug hydrophobicity can strongly affected release profile from a PEG-PLGA-PEG triblock copolymer hydrogels (Jeong et al. 2000).

For example, the more hydrophilic ketoprofen was released continuously over 2 weeks with a first order release profile, while the more hydrophobic spironolactone was released over two months with a S-shape release profile. This result is probably due to a different partition of the two drugs in the system: the more hydrophobic drug partitioned into the hydrophobic core and the release from the PLGA core depends on system degradation. Another very interesting system is represented by PLGA–PEG–PLGA triblock copolymers hydrogel (ReGel®). ReGel® is the trademark of the PLGA–PEG–PLGA copolymers, with a weight average molecular weight (Mw) of approximately 4200 and an Mw/Mn ratio of 1.3. ReGel® is a water soluble, biodegradable polymer at temperatures below gel transition temperature; but once injected, it forms a water-insoluble gel with a viscosity of four orders of magnitude greater than before. Thus, a drug controlled release system with delivery times ranging from 1 to 6 weeks was obtained. This copolymer showed the ability to solubilize and stabilize poorly soluble drugs. ReGel® entry into clinical trials, reaching phase 2b clinical trials for the local treatment of esophageal cancer. Kim et al. studied ReGel based systems (Oncogel™) loaded with paclitaxel that showed an excellent control of release for approximately 50 days. In a phase 2a multi-center clinical trial involving 11 patients, a study on Oncogel™ was carried out on patients with histologically confirmed adeno- or squamous cell carcinoma. Oncogel™ plus radiation treatment seemed to reduce tumor burden, without any improvement in dysphagia condition.

Zentner et al. showed a flexible approach of this copolymer based system for the delivery of protein and small molecule that was simple to process and administer (pGH, G-CSF, insulin, rHbsAg) (Zentner et al. 2001; Choi and Kim 2003). Other temperature-responsive PLGA–PEG–PLGA triblock copolymers, which have a different dl-lactide/glycolide molar ratio from ReGel® (ranging from 6/1 to 15/1) showed higher gelation temperature and longer period of drug release (Qiao et al. 2005). It has been demonstrated that as varying block lengths and concentrations of PLGA–PEG–PLGA triblock copolymers it is possible to deliver protein (i.e. lysozyme) in biologically active form for longer time (Chen et al. 2005). Yu and co-workers mixed an aqueous sol of a block copolymer with a precipitate of a similar copolymer with different block ratio and obtained a thermoreversible physical hydrogel. This study highlighted the importance of the balance of hydrophobicity and hydrophilicity for these amphiphilic copolymers. Then, lysozyme, chosen as model protein, was used to study the possibility to encapsulate and deliver biological substances such as proteins in a biologically active form, for long duration. This study demonstrated that the release rate could be adjusted by changing the ratio of copolymer mixtures, and an almost zero-order sustained release of lysozymes was achieved up to 50 days (Yu et al. 2009).

In another study, solutions of PLGA–PEG–PLGA containing calcitonin as model peptide showed a zero order release kinetics for up to 100 h without a significant burst release effect (Ghahremankhani et al. 2008). Moreover, the release kinetics, from a polymeric solutions at 25% w/w concentration could be controlled by adding different excipients such as sodium lauryl sulfate that showed to reduce drug release rate from the systems (Ghahremankhani et al. 2008).

Furthermore, PLGA–PEG–PLGA triblock copolymers were evaluated for sustained release of bee venom peptide over 40 days. The mechanism of release of bee venom peptide was firstly characterized by a Fickian diffusion during initial stage and, then, by a combination of diffusion and degradation, following the mechanism of degradation of the PLGA–PEG–PLGA copolymer-based hydrogel (Qiao et al. 2006). In another study, a temperature-sensitive triblock copolymer PEG–PLGA–PEG was blended with an oily phase (Lipiodol®) to obtain a thermogelling emulsion applied for both vascular embolization and sustained release of an antiangiogenic drug. The release kinetics of paclitaxel

in the hydrogel and emulsion formulations demonstrated the feasibility of the thermogelling emulsions (Kan et al. 2005).

PLGA–PEG–PLGA 20% (w/w) hydrogels with a low critical solution temperature of 32 °C, have also been studied for the ocular delivery of dexamethasone acetate. The gelation temperature closed to the surface temperature of the eye make it a potential thermosensitive gel-forming system able to improve the bioavailability of some eye drugs (Gao et al. 2010). Even PLA–PEG block copolymers have been tested as carrier for the peptide and protein delivery. A water soluble pentapeptide—TP5, taken as a model drug, was successfully incorporated into PLA–PEG–PLA hydrogels. Higher copolymer concentrations brought to a slower release rate with a less burst effect while higher molar mass of the copolymers disfavored the release of TP5 (Zhang et al. 2010).

Different anticancer agents [topoisomerase II, mammalian target of rapamycin (mTOR), heat shock protein 90 (Hsp90), androgen receptor (AR), X-chromosome-linked IAP (XIAP), histone deacetylase (HDAC), NAD(P)H dehydrogenase, quinone 1 (NQO1), heat shock protein 70 (Hsp70), and DNA polymerase] have been incorporated in PEG-b-PLA micelles (Gaucher et al. 2005, 2010).

Regarding the compatibility between PLA and a poorly water-soluble anticancer agent, it needs to consider its size, structural similarity, similarity in polarity, and then calculate solubility parameter values for anticancer agents comparing the values with PLA (Liu et al. 2004). Nevertheless PEG-b-PLA micelles are able to increase the water solubility of anticancer agents by two to three orders of magnitude.

A sustained co-delivery of PLK1shRNA/PEI-Lys complexes and doxorubicin (DOX) using the biodegradable PLGA–PEG–PLGA hydrogel for treatment of osteosarcoma in vitro and in vivo was developed by Ma and coworkers. The PLGA–PEG–PLGA hydrogel degraded gradually in the subcutaneous layer of rats up to 5 weeks, and showed good biocompatibility in vitro and in vivo. When incubated with osteosarcoma Saos-2 and MG-63 cells, the PLK1shRNA/PEI-Lys and DOX co-loaded hydrogel showed significant synergistic effect on tumor cell toxicity, making biodegradable PLGA–PEG–PLGA hydrogel a promising strategy for efficient clinical treatment of osteosarcoma (Ma et al. 2014) (Fig. 2).

Song et al. synthesized a poly (D,L-lactide-co-glycolide)-b-poly(ethylene glycol)-b-poly(D,L-lactide-co-glycolide) (PLGA–PEG–PLGA) to study the potential of these copolymer micelles to modify the pharmacokinetics and tissue distribution of Curcumin (CUR), a hydrophobic drug (Song et al. 2011). In this paper the physicochemical characteristics of CUR-loaded PLGA–PEG–PLGA micelles such as morphology, particle size, zeta potential and loading efficiency were investigated together with the evaluation of pharmacokinetics and biodistribution of CUR-loaded micelles in mice using CUR solution (CUR-solution) as control. The biodistribution study in mice showed that the micelles decreased drug uptake by liver and spleen and enhanced drug distribution in lung and brain.

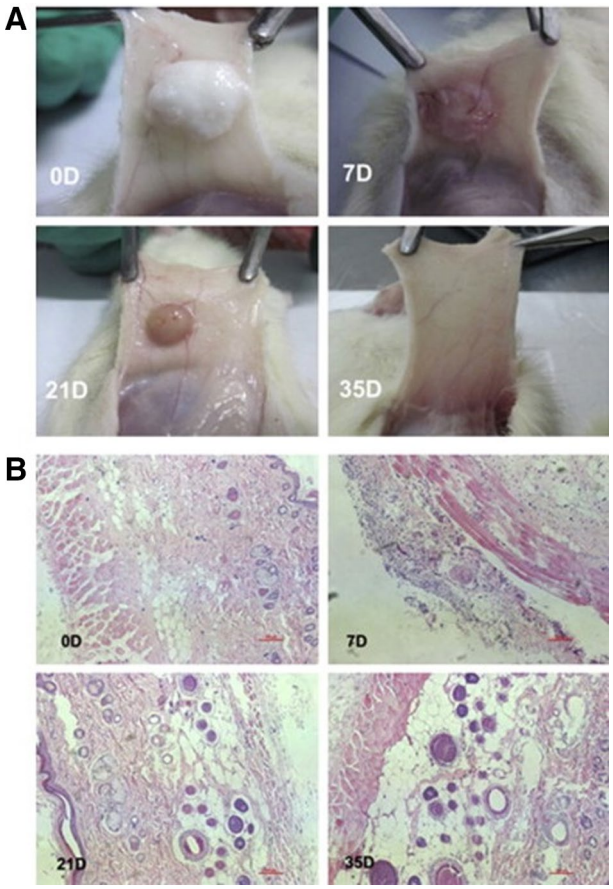

Fig. 2 Degradation of PLGA–PEG–PLGA hydrogel and its good biocompatibility in vivo up to 35 days. In vivo gel residence over time after injection into Wistar rats (**A**); Histological analyses assessing the tissue biocompatibility of the hydrogel over time (**B**) (Ma et al. 2014)

PLA/PLGA–PEG micro/nanoparticles (NPs)

Together with thermoreversible hydrogels and micelles structures, these copolymers could be used for the formulation of other long-term drug release carriers also for targeted drug delivery such as microspheres, nanoparticles, and liposomes.

PEG–PLGA micro/nanoparticles prepared from A–B and ABA structure polymers are commonly used for the delivery of protein drugs (Li et al. 2001; Moffatt and Cristiano 2006). There are two main preparation methods for nanoparticles. The traditional one is the nano-precipitation method. The entrapped drugs are usually hydrophobic due to the nature of PLGA and it is possible to achieve high encapsulation

efficiency. For example, co-delivery of paclitaxel and DOX by PEG–PLGA nanoparticles showed a high loading efficiency and an increased anti-tumor efficacy (Cai et al. 2010; Saadati et al. 2013).

Emulsification/solvent evaporation method was also used to produce triamcinolone acetonide-loaded mPEG-PLGA nanoparticles to create an effective formulation for treating uveitis. Triamcinolone acetonide-loaded mPEG-PLGA nanoparticles showed a well-defined spherical shape, small particle size, high entrapment rate and a good controlled-release profile in vitro and exerted anti-inflammatory effects on experimental autoimmune uveitis rats demonstrating to be a promising formulation for the treatment of uveitis (Guo et al. 2019). Another example of the use emulsion-solvent evaporation technique is the preparation of Bavachinin-loaded PEG5000-PLGA NPs. After oral administration, these NPs showed very good anti-asthma therapeutic effects in murine asthma model demonstrated to be a promising formulation for the oral delivery of bavachinin to treat asthma and the oral delivery of other drugs that have limited pharmacokinetic efficacy (Wang et al. 2018a).

A comparison of the effects of four different amphiphilic diblock copolymer (polystyrene-block-poly(ethylene glycol) (PS-b-PEG), polycaprolactone-block-poly(ethylene glycol) (PCL-b-PEG), polylactide-block-poly(ethylene glycol) PLA-b-PEG), and poly(lactic-co-glycolic acid) (PLGA-b-PEG)) on stabilizing hydrophobic drug nanoparticles formed by flash nanoprecipitation (FNP), have been performed by Zhu (2013). Thus, this study provided a guideline on choosing the suitable amphiphilic block copolymers for stabilizing hydrophobic drug nanosuspensions, choosing b-carotene as a model drug. PLGA-b-PEG demonstrated to be the most suitable copolymer, due to the biodegradability and noncrystallizable nature of the hydrophobic block as well as for the relatively high glass transition temperature and right solubility parameter Whereas, the molecular weight of PLGA block in the range 5–15 k showed an insignificant effect on controlling the particle size, an intersting result is the high drug loading of over 83 wt% achieved by using PLGA (10 k)-b-PEG (5 k). b-carotene nanoparticles were in amorphous state, hypothizing a higher dissolution rate and bioavailability of the encapsulated drug (Zhu 2013).

Hosseininasab et al. developed a formulation where insulin was encapsulated using variable compositions of PLGA–PEG nanoparticles. Insulin was encapsulated within nanoparticles made of PLGA–PEG copolymer, synthesized with two molecular weights of polyethylene glycol (PEG2000 and PEG4000), with the double emulsion method (w/o/w). The loading efficiency values achieved for insulin were different between PLGA–PEG nanoparticles, probably because of the presence of different molecular weights PEG in PLGA chains. In fact, compared with PLGA–PEG4000 nanoparticles, PLGA–PEG2000 and PLGA–PEG nanoparticles have been shown a marked decrease in encapsulation efficiency.

In addition, the insulin-loaded PLGA–PEG nanoparticles show a certain pH sensitivity; Iinsulin release from nanoparticles, at a pH condition similar to the intestine environment, showed a moderately fast release while PLGA–PEG hydrogels have fewer tendencies of insulin release in gastric environment. This demonstrated the ability of this copolymer to protect insulin from enzymes in the gastric environment (Hosseininasab et al. 2014).

In another study, membrane-assisted nanoprecipitation has been used for the production of Poly[(D,L-lactide-co-glycolide)-co-poly ethylene glycol] diblock) (PLGA–PEG) nanoparticles using a pulsed back-and-forward flow arrangement. Dexamethasone was successfully encapsulated in a continuous process, achieving an encapsulation efficiency and drug loading efficiency of 50% and 5%, respectively and a release kinetic from the nanoparticles followed Fickian kinetics (Albisa et al. 2017).

Dexamethasone was successfully encapsulated also in a novel PEG–PLGA NPs delivery system capable of delivering drugs into glomerular mesangium for the treatment of mesangial proliferative glomerulonephritis (MsPGN). Biodistribution experiments demonstrated that A-DEX NPs targeted the kidney and kidney cortex efficiently. The formulation showed also a sustained release pattern (Li et al. 2019). Wilkosz et al. analysed the interaction between itraconazole, a water-insoluble drug, and a polymer matrix formed by PEG–PLGA copolymer to create a model for other hydrophobic drugs interacting with the PLGA matrix and to find general rules on the base of the behavior of other small organic molecules, loaded in nanostructural polymer-based drug delivery systems. This study suggests that the model drug has a relatively good affinity for the PEG–PLGA nanoparticles probably due to its hydrophobic nature being the drugs accumulated only at the water–nanoparticle interface. This fact could be diminished by creating polymeric structures with a developed surface area or with the incorporation of additives that would increase a free volume of the PLGA core (an unoccupied volume enclosed in the hydrophobic core), thus reducing the high density of PEG–PLGA NPs (Wilkosz et al. 2018).

Farajzadeh et al. co-encapsulated curcumin (Cur) and metformin (Met) in PEGylated PLGA nanoparticles (NPs) prepared by a double emulsion method and evaluated their anticancer effect against human breast cancer cell line T47D. The nanoformulation containing the Met–Cur combination was able to kill breast cancer cells more rapidly than the treatment alone, indicating a synergistic effect with a potential reduction of cytotoxicity and patient side effects. This study provides the scientific foundation for future clinical trials of nanocombinational therapy using Met and Cur for breast cancer treatment (Farajzadeh et al. 2018).

Another example of use of PLGA/PEG–PLGA nanoparticles in cancer therapy is represented by the study of Haji Mansor et al. Chemokine stromal cell-derived factor-1α (SDF-1α) was encapsulated into nanoparticles composed of poly-(lactic-co-glycolic acid) (PLGA) and a polyethylene glycol (PEG)–PLGA co-polymer to achieve sustained release. Chemokines are known to stimulate directed migration of cancer cells and the strategy involving gradual chemokine release from polymeric vehicles for trapping cancer cells represents a very interesting strategy. SDF-1α was successfully loaded into these nanoparticles under mild formulation conditions and released in its bioactive conformation in a controlled rate. By changing the number of uncapped carboxylic acid groups in the PLGA core, it was possible to obtain nanoparticles with different physicochemical properties that influence encapsulation efficiencies and protein release (Haji Mansor et al. 2018).

Docetaxel is a highly potent anticancer drug for a wide spectrum of cancer types, but many concerns regard the drug's pharmacokinetics when loaded in conventional formulation. Thus, drug-loaded NPs were prepared and characterized by Rafiei and Haddadi as long-circulating sustained-release delivery systems. PLGA and PLGA–PEG NPs were then intravenously administered to animal model, to study the pharmacokinetic and biodistribution profiles of docetaxel. The obtained data confirmed the role of NP's average size in modifying the biodistribution proving the relationship between NPs' characteristics and their in vivo behaviors. These information can be very interesting to further modifications of PLGA nanoparticles for cancer chemotherapy (Rafiei and Haddadi 2017).

PLGA and PEG–PLGA carriers, were studied to load doxorubicin and sorafenib together in nanotherapeutics in order to obtain a synergistic effect. The results showed that the systems possessed promising physical and chemical properties; high drug encapsulation efficiency, and high drug loading with a doxorubicin released profile of 6 days, while the sorafenib was released quickly during 24 h. In an acidic tumor-simulated condition, the two agents presented opposing characteristics with accelerated doxorubicin and sustained sorafenib release. Another interesting result was that PEG-PLGA nanocomposites showed high cellular uptake (Babos et al. 2018).

β-Sitosterol (β-Sit) is a dietary phytosterol with anticancer activity, but its poor solubility in water limits its bioavailability and therapeutic efficacy. Thus, poly(lactide-co-glycolic acid) (PLGA) and block copolymers of poly(ethylene glycol)-block-poly(lactic acid) (PEG-PLA) were used to encapsulate β-Sit, to enhance its solubility in the aqueous phase. PLGA showed to be a better polymer for encapsulation of β-Sit compared to PEG-PLA since antiproliferative activity against MCF-7 and MDA-MB-231 cells resulted to be enhanced, making PLGA nanoparticles a promising strategy to increase β-Sit therapeutic efficacy against cancer (Andima et al. 2018).

Another example of the application of biodegradable nanoparticles is for the vehiculation of gentamicin. Gentamicin release from the NPs was biphasic with about 40% of drug released in the first hour and a general trend that showed a gentamicin release from NPs prolonged 20 times with respect to free gentamcin. The most important result is that Gentamicin sulfate loaded nanoparticles maintain the drug antimicrobial activity at the same levels of free gentamicin as proved by MIC and MBC values obtained (Dorati et al. 2018).

An important application of polylactic-co-glycolic (PLGA) nanoparticles is the possibility to load Memantine (MEM), the only drug approved both in Europe and in the United States for moderate and severe degrees of Alzheimer's disease. MEM–PEG–PLGA nanoparticles were aimed to target the blood–brain barrier (BBB) upon oral administration. The in vitro and in vivo results for brain drug levels showed clear evidence that the nanoparticulate systems provide a sustained delivery of the drug into the target tissue increasing the drug amount into the target organ. An important achievement was the possibility to reduce the administration frequency (on alternate days) that revealed to be effective to achieve brain therapeutic concentrations of drug. Thus, MEM–PEG–PLGA NPs, being able to provide a more effective treatment than free memantine, represent a promising alternative for better treatment of patients with Alzheimer's disease (Sánchez-López et al. 2018).

The recent works regarding drug loaded PEG–PLA and PEG–PLGA nanoparticles are reported in Table 1.

Drug delivery systems based on functionalized PLA/PLGA–PEG block copolymers

Functionalised PEGylated PLA/PLGA nanoparticles

In recent years, research has been devoted to the synthesis and characterization of functionalized PLA/PLGA–PEG copolymers in order to broaden their applications in different fields including pharmaceutics. In this context, functionalised PLA/PLGA and PLA/PLGA–PEG copolymers have been employed for the design of nanocarriers with improved characteristics in term of "active targeting", aimed to selectively deliver the drug at the site of action (especially for anticancer drugs). In functionalised copolymer, PEG acts as a spacer between the PLA/PLGA unit and the ligand. In this way, the hydrophobic PLA/PLGA forms the core of the nanocarrier, while PEG chains extend outside in the aqueous environment by exposing the ligand, which is able to interact with its biological target. At this extent, several

Table 1 Overview regarding the recent nanoparticles based on PEGylated PLGA/PLA block copolymers

Encapsulated compound	References
PEG-PLGA NPs	
Stromal cell-derived factor-1α SDF-1α	Haji Mansor et al. (2018)
Docetaxel	Rafiei and Haddadi (2017)
Sorafenib/doxorubicin	Babos et al. (2018)
Triamcinolone acetonide	Guo et al. (2019)
Gentamicin sulfate	Dorati et al. (2018)
Memantine	Sánchez-López et al. (2018)
Itraconazole	Wilkosz et al. (2018)
Dexametasone acetate	Li et al. (2019)
Bavachinin	Wang et al. (2018a)
Metformin-curcumin	Farajzadeh et al. (2018)
PEG-PLA NPs	
β-Sitosterol	Andima et al. 2018)
Human growth hormone	Ghasemi et al. (2018)
Galbanic acid	Afsharzadeh et al. (2019)
Auranofin	Valerio et al. (2019)
Phospho-sulindac	Wen et al. (2019)
Desogestrel	Lin et al. (2019)
Rosiglitazone	Giacalone et al. (2018)
Oxytocin peptide	Gourdon et al. (2018)
Quercetin	Onishi et al. (2018)
Leukemia inhibitory factor	Davis et al. (2018)

heterobifunctional PEGs have been synthesized, which display different functional groups at the two ends, allowing the coupling with PLA/PLGA at one end and the selective functionalization with the ligand at the other end. For these purposes, PEGs have been functionalised with vinyl-sulphone, amine or acetal groups (Arıcan et al. 2018; Bae et al. 2009). These functionalised PLA/PLGA-PEG copolymers have been used for the design of nanocarriers as micro/nanoparticles, micelles and dendrimers.

Functionalization with peptides

The coupling with peptides is one of the explored strategy to improve oral drug bioavailability or the therapeutic efficacy of anti-cancer agents thanks to a targeted delivery. Surface of nanoparticles were decorated with F3 peptide (CKDEPQRRSARLSAKPAPPKPEPKPKKAPAKK) to achieve an active targeting to glioma cells and endothelial cells of glioma angiogenic blood vessels and co-administered with the homing and penetrating peptide, tLyp-1 peptide. This strategy potentiated the paclitaxel delivery and internalization into glioma cells both in vitro and in vivo (Hu et al. 2013). In another study, PLGA-PEG nanoparticles conjugated with B6 peptide and loaded with curcumin were prepared for a potential application in Alzheimer disease. B6 peptide (CGHKAKGPRK) is a ligand for transferrin receptor, which is involved in the drug permeability of the blood–brain barrier. As such, these nanoparticles were applied to HT22 cells to study in vitro internalization, and were administered in APP/PS1 transgenic mice for in vivo studies. The functionalization with B6 peptide has increased the uptake inside the cells and improved the delivery of the drug into the brain, resulting in a reduced hippocampal amyloid beta peptides production and a decreased tau phosphorylation in APP/PS1 mice (Fan et al. 2018). PLA-PEG copolymer was functionalized with valine, glycylsarcosine, valine-Glycine, and tyrosine-Valine to target the intestinal transporter for peptide PepT1 with the aim of increasing the oral bioavailability of acyclovir. Valine-functionalized PLA-PEG nanoparticles showed the best-improved in vitro acyclovir permeability and in vivo plasma concentration and residence time (Gourdon et al. 2017). Cell penetrating peptides (CPP), such as penetratin, were proposed to improve the delivery of drugs in the brain. Xia et al. prepared PLA-PEG nanoparticles functionalised with the CCP penetratin, which showed a marked enhanced brain uptake via transcytosis and a reduced accumulation in the non-target tissues when compared with nanoparticles functionalised with low molecular weight protamine, a CPP with a high content of arginine. The better pharmacokinetic profile was explained by the lower content of basic amino acids in penetratin with the respect of protamine, thereby avoiding the aggregation probably due to the interaction between cationic surface of nanoparticles and negatively charged of plasmatic proteins, which enhances the elimination process. These results suggest that surface-charge modulation is a parameter important to be controlled for the design of brain-targeting delivery system (Xia et al. 2012).

Integrins are a family of proteins with a major role in cancer, including adhesion, cell mobility and signalling (Desgrosellier and Cheresh 2010). Different peptides are known to be ligands for integrin receptors, which can be exploited for a target delivery. One of the most common investigated are RGD peptides, which are able to target $\alpha_v\beta_3$ integrins. PEGylated PLGA nanoparticles conjugates with RGD peptide or RGD-peptidomimetic have been demonstrated to target the tumor endothelium and enhance the anticancer activity of paclitaxel in comparison to the non-functionalised nanoparticles (Danhier et al. 2009). RGD-targeted PLGA–PEG nanoparticles loaded with cisplatin showed an improved cytotoxicity in model cell lines of prostatic and breast cancer as well as in a human breast cancer xenograft in comparison to the drug alone and drug loaded in non-functionalised nanoparticles (Graf et al. 2012). cRGD-tagged PEG-PLGA nanoparticles were a successful vehicle for the intracellular delivery of functional microRNAs (antagomiR-21 and antagomiR-10b). This nanocarrier

has also increased the sensitivity glioblastoma cells to lower doses of temozolomide (Malhotra et al. 2018) (Fig. 3).

Functionalization with small molecules

Several ligands belonging to different class of compound have been linked to PLGA/PLA–PEG nanoparticles to improve drug targeting at tumor site, exploiting the ligand-receptor interaction. Folate receptor is overexpressed in several epithelial cancers, such as breast, ovarian, endometrial, colon and lung cancer, thus the conjugation of nanoparticles with folic acid has been explored as a possible therapeutic strategy for these cancers. In a first study, folate-conjugated PLGA–PEG nanoparticles loaded with paclitaxel were prepared to enhance the delivery of the drug to endometrial carcinoma. Folate-conjugated PLGA-PEG nanoparticles showed a higher cytotoxicity and an increased targeting efficiency and specificity as well as anticancer effect than no functionalised PLGA-PEG nanoparticles (Liang et al. 2011). Recently, particlesplexes formed by mPEG-PLA, folate-PEG-PLA and DOTAP have been loaded with the gene for the chemokine ligand 19 (CCLG 19). This nanosystem was able to transfect the gene in CT26 cells, as model for colon cancer. The expression of CCL19 activated the immune systems in vivo, inducing the antitumoral activity (Liu et al. 2019). Folate-PEG–PLGA/PLA nanoparticles were loaded with the microRNA miR-204-5p for a targeted colon cancer therapy. MicroRNAs can target multiple genes and simultaneously regulate different signalling pathways, which are altered in this malignancy. These functionalised nanoparticles can be taken up by HT-29 and HCT-116 cells and they exert an antitumoral activity in terms of tumor growth in a Luc-HT-29 xenograft model (Zheng et al. 2018).

Functionalization with aptamers

Another strategy to improve drug delivery is the functionalization with aptamers, which are single-stranded oligonucleotides able to selectively bind to receptor target on the cancer cells (Kim et al. 2018). One of the most used aptamer for conjugation is the anti-nucleolin aptamer AS1411. It is a 26-base guanine rich oligodeoxynucleotide, able to bind to nucleolin, a phosphoprotein overexpressed in many cancer cells, and to induce apoptosis (Reyes-Reyes et al. 2015). AS1411 aptamer surface-decorated PLGA-PEG nanoparticles were prepared to target the overexpression of nucleolin in non-small cell lung cancer. After conjugation, an enhanced cellular uptake and cytotoxicity in A549 cancer cells was observed, confirming the efficiency of the active targeting (Alibolandi et al. 2016). Superparamagnetic iron oxide nanoparticles (SPIO) and doxorubicin were co-loaded in PLGA-PEG nanoparticles conjugated with AS1411 aptamer as a dual diagnostic and therapeutic strategy for targeted anti-cancer activity. These nanoparticles showed and enhanced cellular uptake and cytotoxic effect of doxorubicin in C26 cancer cells and a higher tumor inhibition in vivo and prolonged survival in mice bearing C26 colon carcinoma xenografts. At the same time, the contrast of magnetic resonance images in tumor site was improved, confirming the diagnostic efficiency of the nanosystem (Mosafer et al. 2017a) (Fig. 4). The same authors have investigated the same nanosystem (SPIO and doxorubicin co-loaded PLGA-PEG nanoparticles) in high nucleolin-expressing C6 glioma cells in comparison to low nucleolin-expressing L929 cells, highlighting the AS1411 ability and specificity in targeting the cancerous cells expressing nucleolin (Mosafer et al. 2017b). AS1411 aptamer surface-decorated PLGA-PEG nanoparticles were also employed to target ovarian cancer (A2780

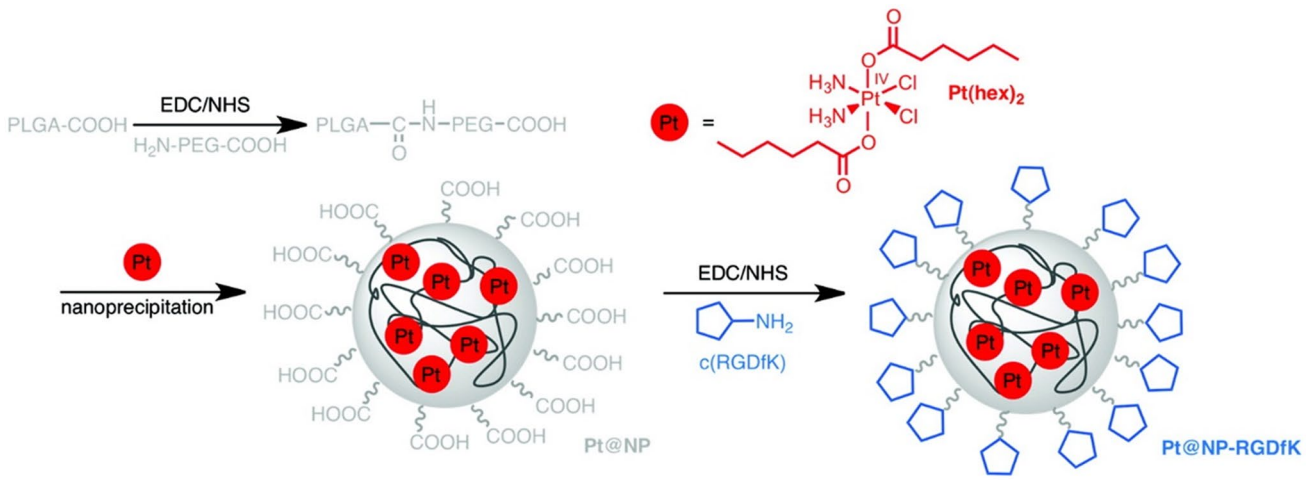

Fig. 3 Preparation of Platinum(IV)-encapsulated PLGA–PEG nanoparticles functionalised with the cyclic pentapeptide RGDfK for the targeting to $\alpha_v\beta_3$ integrins (Graf et al. 2012)

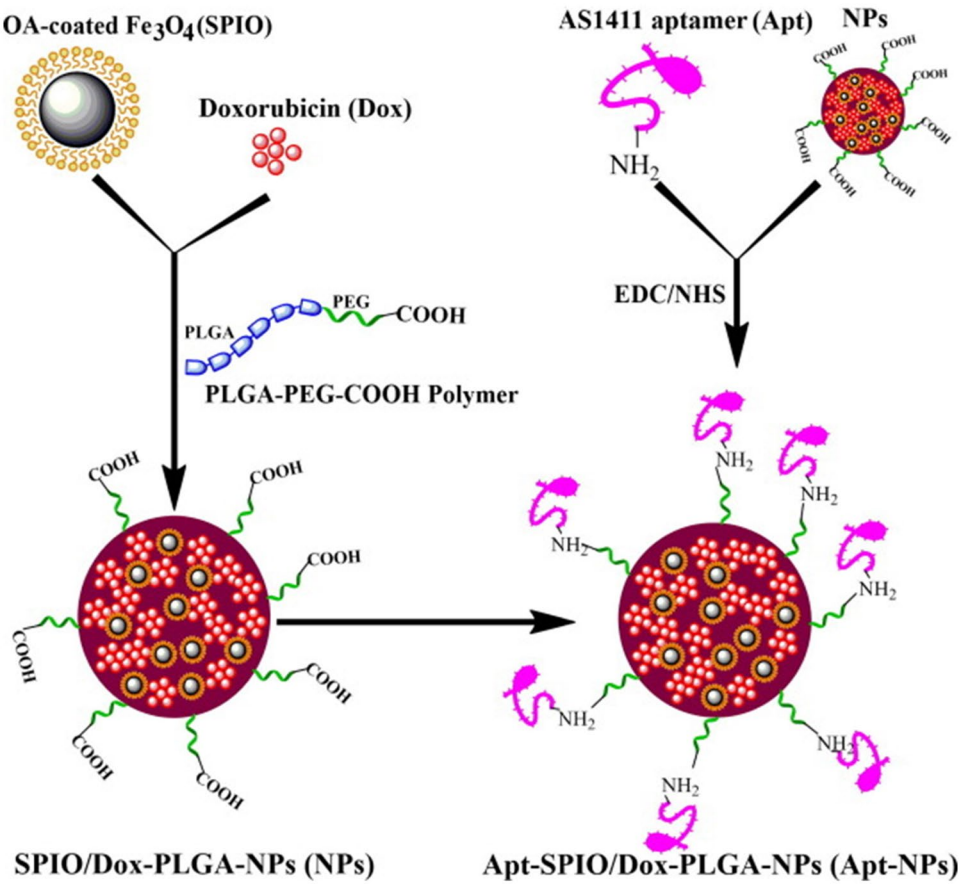

Fig. 4 Schematic representation for superparamagnetic iron oxide/doxorubicin PEG-PLGA based nanoparticles before and after functionalization with AS1411 aptamer (Mosafer et al. 2017a)

R cells). Indeed, the functionalised nanoparticles showed an improved delivery and a better anticancer activity of the loaded drug cisplatin and the anti-miR-21 toward A2780 R cells (Vandghanooni et al. 2018).

Functionalization with antibodies

Antibody-conjugated nanoparticles offer a great potential to deliver the therapeutic agent to the target site, thereby minimizing off-target side effects. Moreover, these functionalised nanoparticles can be efficiently internalized by receptor-mediated endocytosis and accumulate inside cell (Cardoso et al. 2012; Johnston and Scott 2018). Several cancers show an overexpression or modified forms of cell surface molecules (e.g. classification determinants, CD or receptor for growing factors), which can be targeted by antibody-functionalised nanoparticles. Spherical PEG-PLGA nanoparticles functionalised with human Fab that specifically target human CD44v6 (v6 Fab-PLGA NPs) were developed and it was demonstrated that these nanoparticles can effectively in vivo accumulate in carcinomas overexpressing CD44 (Kennedy et al. 2018). In another study, PEG-PLGA nanoparticles were conjugated to different amount of the marketed antibody Herceptin® in presence and in absence of PEG as linker, with the aim to target HER2-positive breast cancer cells. These functionalised nanoparticles were investigated in terms of cell uptake and immunogenic properties using murine macrophages and human dendritic cells. Results indicated that nanoparticles covered by a 50% PEG-modified Herceptin® showed the most reduced phagocytic uptake (Badkas et al. 2018). The delivery of chemotherapy in breast cancer can be also improved by targeting epithelial growth factor receptor (EGFR) with antibodies. As such, PEG–PLGA nanoparticles anti-EGFR anchored and loaded with paclitaxel were prepared. The functionalised nanoparticles showed a 93-fold higher paclitaxel accumulation in the tumor with the respect to non-functionalised nanoparticles and, therefore, a pronounced reduction of cancer cell viability (Venugopal et al. 2018). Duan and et al. prepared Fab' (antigen-binding fragments cut from TMAB)-modified mPEG–PLGA, mal-PEG–PLGA NPs (Fab'-NPs) loaded with curcumin in order to achieve an effective targeting of human epidermal growth factor receptor 2 (HER2/ErbB2/Neu), overexpressed on breast cancer cells. In vitro cellular uptake experiments showed that Fab′-NPs exhibited enhanced cellular accumulation and PK and BD experiments in vivo demonstrated that Fab′-NPs expressed

higher tumor permeability and longer blood circulation times. Thus, Fab′-modified nano-vector and intact antibody-modified nano-vector demonstrated that Fab′ fragment can overcome the disadvantages of intact antibody conjugation and achieve targeted drug delivery to tumors (Duan et al. 2018).

Recent nanoparticles formulation based on functionalised PEGylated PLGA/PLA block copolymers are reported in Table 2.

Conclusions

PEGylated PLGA and PLA copolymers offer a suitable platform for the development of drug delivery systems such as hydrogels and nanoparticles, as demonstrated by the large number of papers published in the last years. These copolymers are suitable for the formulation or encapsulation of a wide variety of pharmaceutically active

Table 2 Overview regarding the recent nanoparticles based on functionalised PEGylated PLGA/PLA block copolymers

Ligands on NPs	Target on cells	References
Peptides		
Cell penetrating peptide *Penetratin*	Ammonium transporter (AMT)	Xia et al. (2012)
B6 peptide (CGHKAKGPRK) T7 peptide (His-Ala-Ile-TyrPro-Arg-His)	Transferrin receptor	Fan et al. (2018), Bi et al. (2016)
Tumor homing peptide tLyp-1	Neuropilin-1	Hu et al. (2013)
Glycylsarcosine, Valine-Glycine, Tyrosine-Valine	Intestinal transporter Pep1	Gourdon et al. (2017)
RGD	$\alpha_v\beta_3$ integrin	Danhier et al. (2009), Valencia et al. (2011), Graf et al. (2012), Malhotra et al. (2018)
RVG29	Nicotinic acetylcholine receptor (nAchR)	Hua et al. (2018)
GE11	EGFR	Jin et al. (2017)
Protein		
Lactoferrin (Lf)	Lf receptor (LfR)	Li et al. (2018)
Antibodies		
Anti-CD24	CD24	Bharali et al. (2017)
Anti-CD133	CD133	Xin et al. (2018), Mi et al. (2018)
Anti-EGFR	EGFR	Patel et al. (2018), Venugopal et al. (2018)
Anti-CD 20 (rituximab)	CD20	Chen et al. (2018), Tang et al. (2018)
Anti-HER2 (trastuzumab)	HER2	Le et al. (2016), Badkas et al. (2018), Duan et al. (2018)
Anti-transferrin	Transferrin	Cui et al. (2018)
Fab-fragment AbD15179	CD44v6	Kennedy et al. (2018)
Anti-CEA (COL-1)	Carcinoembryonic antigen (CEA)	Pereira et al. (2018)
ITEM4	Fibroblast growth factor-inducible 14 (Fn14) receptor	Wadajkar et al. (2017)
Oligonucleotide		
AS1411 aptamer	Nucleolin	Guo et al. (2011), Zhou et al. (2014), Alibolandi et al. (2016), Mosafer et al. (2017a, b), Vandghanooni et al. (2018)
Anti-EpCAM aptamer	Epithelial cell-adhesion molecules (EpCAMs)	Alibolandi et al. (2015)
Prostate-specific membrane antigen (PSMA) aptamer	PSMA	Pan et al. (2017)
A15 aptamer	CD133	Guo et al. (2017)
A6 aptamer	Her-2 receptors	Powell et al. (2017)
Small molecules		
Folic acid	Folate receptor	Liang et al. (2011), Valencia et al. (2011), Zheng et al. (2018), Wang et al. (2018b), Liu et al. (2019)
Biotin	Biotin receptor	Mehdizadeh et al. (2017)
Hyaluronic acid	CD44	Saneja et al. (2017), Alam et al. (2017)
Retinoic acid	RA receptor alpha (RARα)	Emami et al. (2018)

substances as small molecules, natural compounds or biomolecules (such as proteins, peptides, oligonucleotides). PEGylated tri-block copolymers are generally employed for the formulation of polymeric hydrogels, able to modulate drug release. On the other side, PEGylated di-block copolymer are commonly used for the preparation of nanoparticles, as valuable carriers able to enhance drug solubility and stability, thus, increasing its bioavailability in vitro. Recently, the development of functionalized PLA/PLGA-PEG block copolymers have broaden the application of these nanoparticles in term of "active targeting", thanks to the selective interaction between the ligand on the surface of the carrier with its specific receptors on the biological target. Advances in this area will be beneficial for the design of new targeted or personalised therapeutic strategies, especially for cancer treatment.

Compliance with ethical standards

Conflict of interest All authors (D.R. Perinelli, M. Cespi, G. Bonacucina, G.F. Palmieri) declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human and animal subjects performed by any of the authors.

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