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Bio-inspired drug carrier: An emerging size distribution and the potential role of mPEG-PLA structural features bearing site specific drug delivery

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Abstract

mPEG-PLA is a bio inspired drug carrier that shows a new horizon to improve the treatment of cancer therapy in modern science. mPEG-PLA-based nano drug delivery holds flexible size, modifiable character, safety, and treatment efficacy. It prolongs the systemic circulation of drugs, improves cellular uptake and thus prevents normal cellular cytotoxicity. mPEG-PLA characteristics diminish the toxicity of drugs and allows drugs to reach the destination without interfering the normal cells. The modifications of mPEG-PLA have been extensively studied in formulation, drug release profile, and prospective pharmaceutical application studied extensively. In this review, we will discuss the current understanding of this literature by providing the prominent features of self-assemble mPEG-PLA nano-formulation. Overall, advance nanotechnology, and the ongoing development of new targeted therapies have opened up a new opportunity to the development of mPEG-PLA.

Keywords: mPEG–PLA, Block copolymer, Characteristics, Particles size, Surface modification, Drug delivery systems, Application.

Introduction

Amphiphilic block copolymers could assemble by their own nature and formed the variety of nanoparticles like micelles, polymersomes, nanocapsules, nanosphere *etc*[1]. This copolymer was usually used as a drug vehicles that that held vast potential to prepared nanoparticles in biomaterials and pharmaceutical fields. It was known that the ring opening polymerization could synthesize effective amphiphilic block copolymers (di-block or triblock)via trans-esterification with poly lactic acid (PLA)[2]. PLA has both high strength and thermoplastic synthetic biodegradable properties [3, 4]. Therefore, It could be hydrolyzed through cleavage of ester bond and metabolized into water and CO_2 in the citric acid cycle[5]. However there were still some limitation like weak hydrophilicity, rigidity, and poor drug loading capacity of polar drugs in the application of PLA. Synthesis of amphiphilic block could resolve those problem. It can improve the physicochemical properties of drug delivery system like suitable

biodegradability, immunity, and inveterate mechanical strength [4, 6], that exhilarated the copolymerization of PLA with other hydrophilic block like Poly ethylene glycol(PEG)[7]. Polyethylene glycol (PEG) possessed stealth behavior, good hydrophilicity, flexibility, anti-phagocytosis against macrophages, non-toxic and non-immunogenic [8], anti-fouling [9], and high biocompatible pharmaceutical excipient. PEG-PLA nanoparticles could resist adsorption of proteins of the coagulation cascade and impede thrombosis[10] therefore achieving good interactions in blood components[11].After copolymerization with PEG and PLA could improve its characteristics such as hydrophilicity, degradation rate[12], crystallization, increase the drug loading and prolong the *in vivo* residence time of drugs, showed the great potential activity drug delivery. The aggregated hydrophobic blocks could form a core structure and hydrophilic block improved the nanoparticles (NPs) water soluble and influenced the drug release. PEG-PLA could support in the passive targeting of tumors by the enhanced permeability and retention (EPR) effect,[13] and meanwhile possess terminal ligands such as biotin[14] or antibodies[15] for active targeting. Besides the PEG-PLA fabricating NPs held higher therapeutic effects and much lower adverse effects than Taxols [16, 17]. In the description of our review, we would describe the synthesis of PEG-PLA block co-polymer, tunable particle size, and surface modified targeted therapy. It also indicated that the PEG-PLA could regulate the drug delivery in the different delivery system can regulate the drug delivery and gives the overview of the applications and treatments in pharmaceutical prospective.

1.Synthesis of mPEG-PLA block copolymer

1.1 Ring-opening polymerization

mPEG-PLA was synthesized by ring-opening polymerization between PEG or its end-group derivatives such as methoxy polyethylene glycol and lactide [18] (**Fig.1.A**).

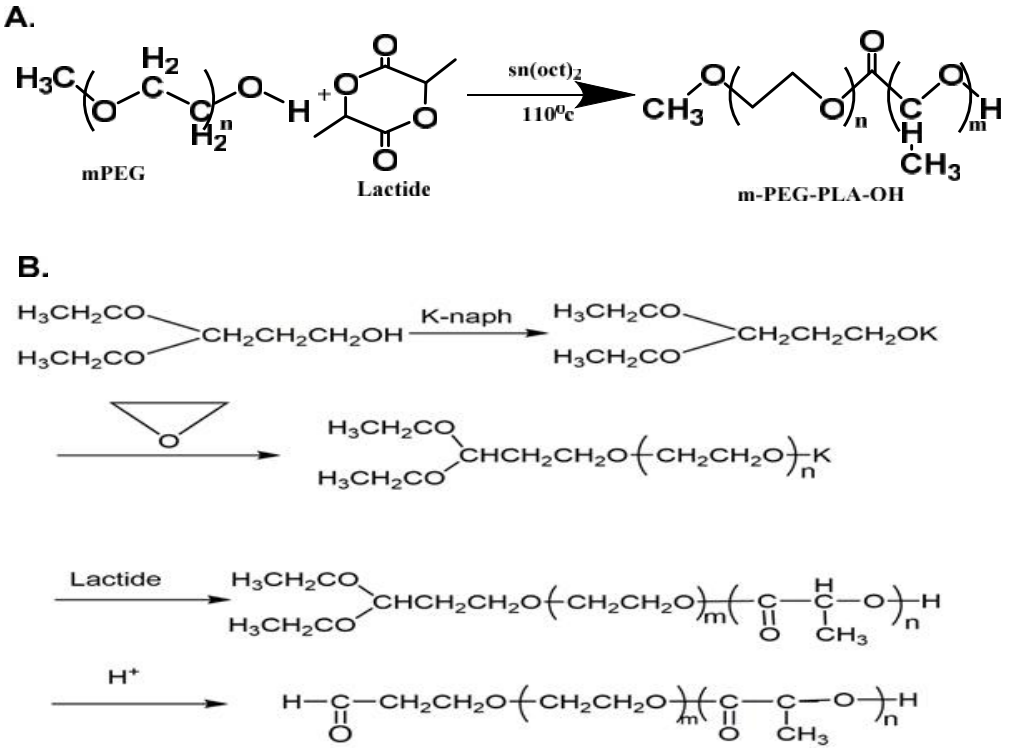

Fig.1 Synthesis of mPEG-PLA[21].

Tin salts were the commonly used as catalysts, especially stannous compounds with a higher catalytic efficiency. However, due to the toxicity of these heavy metal compounds, acetic acid bismuth was used as an initiator by Kricheldorf *et al.*[19] and found the copolymerization of L-lactide and PEG tetramer. Copolymers with different molecular structures could be synthesized, such as A-B stellate copolymer, A-B-A triblock copolymer, multiblock copolymer[20], and reticular copolymer. Obviously, the length of polymer

chain could be controlled by proportion of monomer and initiator. This synthesis method had several advantages like easy and faster method, minimizing deleterious transesterifiation reactions, different architectures, fix of PLA/PEG weight ratio and narrow molecular weight distribution etc.

1.2 Anionic ring-opening polymerization

Synthesized block copolymer mPEG-PLA are produced by an alternative anionic ring-opening polymerization, commonly used as potassium alkoxide,[22] sodium alkoxide, and butyl lithium as a catalyst (**Fig.1.B**). For example, Otsuka *et al.*[23] synthesized 3,3-diethoxy-potassium propanol with the initial reactants 3,3-diethoxy-propanol, potassium naphthalene and the solvent tetrahydrofuran (THF). Finally, α-acetal-PEG–PLA block copolymer was synthesized through anionic ring-opening polymerization with ethylene oxide and lactic acid (LA) as reactants and 3,3-diethoxy-potassium propanol as an initiator. Diblock copolymers composed of poly (oxy-ethylene) and poly (DL-lactic acid) segments were synthesized by anionic polymerization of D, L-lactide using the oxyanion formed by reaction of the monohydroxyl monomethoxy-poly(ethylene glycol) on sodium hydride. For comparison, a similar copolymer was possible to prepare by using tin octoate to catalyze the lactide polymerization [22].Although its serve few advantages of the techniques like precipitation recovered the copolymer in methyl alcohol, the unreacted Methoxy- PEG being soluble in this solvent, easy to modified, less toxic and long stability.

Overall study about the synthesis of mPEG-PLA and its modification would be used in the ring opening polymerization because of possessed several advantages contrast over the anionic polymerization such as easier, high efficacy and less time consuming process.

2. Self-assembly behavior of mPEG-PLA

Copolymerized PEG-PLAblock performed an amphiphilic nature in colloidal solution which composed the different structures by self-assembly with similar radii [24, 25]. Hydrophilic shell kept the stability by avoiding the direct contact of the hydrophobic PLA in aqueous solution, which could easily shape the self-assembled nanostructure. Although, self-assembling aggregation preeminently depended on the proportion of hydrophobic to hydrophilic segments of polymers [26].In other words, the amphiphilic copolymers possessed the ability to form the self-assemble complex in a selective solvent via a “bottom-up” route by building blocks with asymmetric structures [27] and designed for mPEG-PLA copolymers with different PEG blocks. mPEG-PLA had been broadly explored as the self-assembled for biomedical fields due to their exceptional biocompatibility and degradability[28, 29]. Polymersomes and micelles were self-assembly of this copolymer with a high fraction of hydrophobic blocks[30] in recent works using the mPEG-PLA. Also, *Wu et al.* confirmed another interesting investigation of PEG–PLA–PEG copolymers that had an instance tendency to the aqueous solution and asymmetric PEG blocks exhibited a more apropos morphology of aggregates after self-assembly, as compared to symmetric ones[29].Additionally, this strategy reported and dealt with the assessment of characteristics, advantages, and limitations of relevant bio-degradable drug delivery strategies.

3. Surface modification activity of mPEG-PLA

Surface modifying mPEG-PLA nanoparticle is one of most potent in nanoparticles due to the gentle size distribution and the overcome of targeting issues. In particular, PEG could conjugate with a single reactive group at the terminal end, and this facilitated site-specific conjugation to avoids protein cross-linking [8].This modification could be used to introduce targeting moiety and thus enhance target ability**.** This orientation of mPEG-PLA block copolymer could accomplish assorted special nanoparticles in order to expand the therapeutic effect of drugs, such as long-circulating nanoparticles, immune nanoparticles, thermosensitive nanoparticles, and pH-sensitive nanoparticles (**Fig.3**).Therefore, surface modification classified into three sorts (1) polysaccharides (cyclodextrin and chitosan) (2) Surfactants (polysorbate) (3) poloxamer and their targeting moiety. Another way, due to their immaculate structure, the surface of mPEG–PLA block copolymer nanoparticles (NPs) is often modified by targeting moiety like folic acid, peptide, lectin, and albumin [31, 32]. *Salem et al.*[14] is well-known as the pioneer for the synthesis of biotin-PEG linked with PLA, through the ring-opening polymerization. This modification could actively focus on targeting area with high drug efficacy and attenuate the drug toxicity in normal cells. Furthermore, coumarin-6-loaded mPEG-PLA nanoparticles surface-modified with lactoferrin for

brain-targeted drug delivery could improve the drug uptake and accumulation in the brain with significantly higher levels than the unconjugated nanoparticles in mice model[33].*Lu and his coworkers* designed a new kind of adjuvant with a longer hydrophilic synthesized chain of PEG2000-PLA (80/20) and found glycyrthetinic acid contained in mPEG-PLA modified liposomes was more stable in *in vivo* practically[34].In general, the immobilization of PEG on the hydrophobic surface of NPs composed on covalent grafting or adsorption of PEG-containing surfactants. Compared with the covalently attached PEG, physically adsorbed to the surface was unstable and easy to be replaced by plasma proteins[11]. Also, *Vonarbourg et al.*[35] have reported that the presence of terminal hydroxyl group(s) allowed functionalization of various species by covalent coupling to facilitate uptake of paclitaxel and promotethe anti-angiogenic activity, migration, and tube formation compared with cells treated with nanoparticles or commercial Taxol. mPEG-PLA modified with the folic acid or salts as target materials could accumulate (**Fig.2**) and increase drug concentration in cancer locations, and prolong the duration time[36]. *Tsai et al* [37] did the comparison study with a surface modifying folate-PEG-PLA micelles and found higher cellular uptake than non-folate micelles due to the folate-binding effect on the cell layer and exhibited effective inhibition against tumor growth. *Jain et al.*[38] improved the copolymerizing mPEG-PLA nanoformulation using the different block copolymers which encapsulated hepatitis B surface antigen to evaluate their adequacy as oral vaccine delivery. Overall these results prove that surface modified mPEG-PLA nanoparticles possessed tumor growth inhibition through the different delivery system.

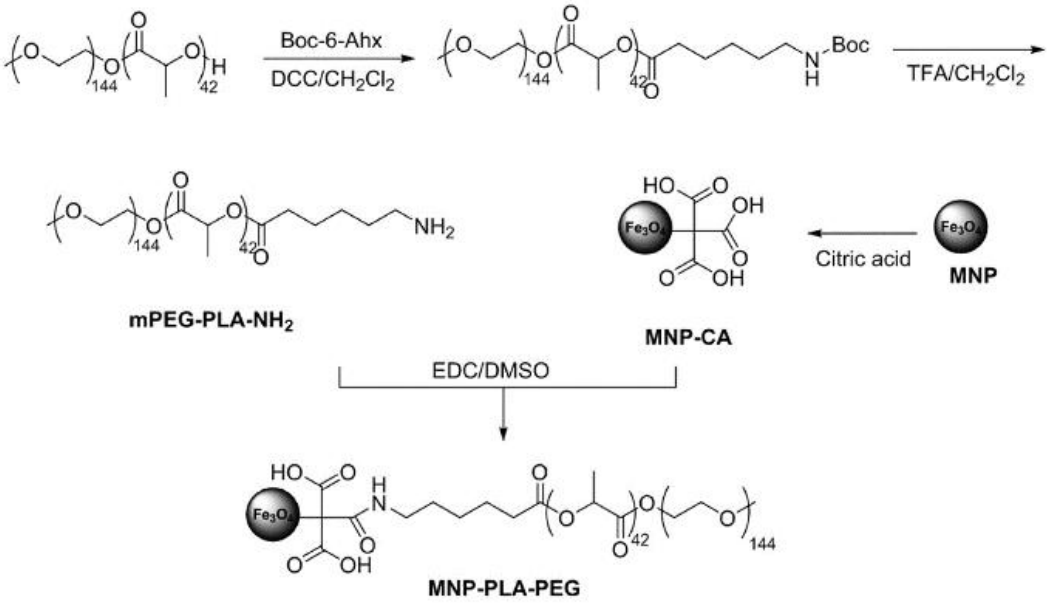

Fig. 2 Surface modifying pathway of mPEG-PLA witha targeting moiety.

4. Influencing factors on the particle size of mPEG-PLA block copolymer-based nanoparticles

The particle size is one of regulatory factors that influence the character of mPEG-PLA NPs in the blood circulation and its physical stability. Many reports had investigated the effects of individual parameters on the conduct of smaller particles in blood *in vitro* and *in vivo*. However, it is often difficult to control unintended changes to other physiochemical properties. PEG surface density and Molecular weight of PLA both could be DifferNP size[31, 32].Molecular weight (MW) or surface density might be impact in stability. Nevertheless, we summarized and discussed the reported key factors, including a block copolymer, Molecular weight, PEG surface density, mPEG-PLA rational and physicochemical properties that impacted circulation of NPs in the blood. This phenomena had been partially reviewed previously[35]and supported some additional recent works**.** The attempts to an ethical comprehension of different factors related to block copolymer composition and the methods of preparation that may influence the type of nanoparticles was discussed in depth below.

4.1 Block length dependent Particle size

In literature, hydrophilic and hydrophobic blocks variation is one a regulatory factor to prepare smaller nanoparticles formed by corresponding alteration[6].Generally, the micelle size depends on the balance of Hydrophilic lipophilic balance (HLB) as well as the block lengths of PLA and PEG[39, 40]. The multiblock copolymers bearing two to six blocks mean numbers of block directed to differences in micelle size, micelle structure, and aggregation number. The particle size of nanoparticles could be change using the PEG and PLA ratio adjustment [41]. Different sizes will lead to different degradation or diffusion rates of Nano matrix, resulting in tunable drug release[42].In another study of the shape dependent copolymers PEG-(PLA) n, (n = 2 or 4) parameters such as the length of hydrophobic blocks, and the tacticity of the PLA blocks were properly modulated with a moral control over the final architecture of $mPEG_{2000}$-$PLA_{2000.}$ The two-arm copolymers gave more stable micelles comparable with the linear ones. First order of magnitude lower than the corresponding four arms copolymers and discrete formation of mono micelle[43].

Separately, the chain length of PEG and PLA could be regulated by the molecular weight (MW) as the results influenced the nanoparticle size, drug loading, and kinetics. As the PLA content of mPEG–PLA copolymers increased, the amount of drug release will be extended and the copolymers of nanoparticles would be uniformed. It was found by *Yang et al.* [44]that the longer PLA chain length formed the high drug-loaded larger micelles and the greater interaction between PLA chain and the hydrophobic drug possibly reduced the drug release rate of micelles in *in vitro* study. The increase of PLA block in the copolymer would significantly reduce the stability of nanoparticles and can also be condensed to the solvent. *Yue et al.* reported the *in vivo* behavior of mPEG-PLA micelles with a size of 30 to 150 nm by changing the PLA block length. The number of micelles that accumulated in each organ depended on the micelle size, and the smaller particles were more effective in tumor-growth inhibition particle size and PDI depends on the different block were shown in **Table 1**.

4.2 Molecular weight dependent Particle size

The MW of PEG chains is proportional to the polymer chain length,this is considered to be an important determinant of effective surface shielding of nanoparticles. Low Mw of PEG are easily deformed due to the small molecular chain and low flexibility the more stable will they reform. Thus, above studies demonstrated an improvement in circulation time for PEGylated liposomes, but another study did not find additional improvements by increasing PEG MW, this may be related to physiochemical differences between the liposome formulations, including a core material and particle diameter. Detailed research performed by *Gref et al.* evaluated particles with different PEG molecular weight (Mw 2000–20,000 Da) copolymers and showed the greatest reduction of plasma protein absorption for the PEGMw of 5000 g/mol *in vitro*[45]. Bazile and associates additionally demonstrated that the half-life of ~150 nm mPEG-PLA NPs expanded as PEG MW increased [46].This study indicated that higher molecular weight mPEG 4000-PLA 2200 has a larger size than the lower molecular weight mPEG 2000-b-PLA 1800 (**Table 1**)[47].

Additionally, it had been exhibited that PEG MW of 2 kDa or higher was required to shield NP surfaces from protein adsorption and decrease recognition by the MPS [48]. *Cui and collaborators* found that increasing PEG MW from 10 to 40 kDa while keeping consistent particle size, reduced phagocytic blood cell association of PEGylated mesoporous silica NPs (MSN).Recently, *Yang and coworkers* reported that PEG with a MW as low as 559 Da could adequately shield surfaces of 100 nm polystyrene (PS) NPs due to the “high” grafting [49].However, higher MW PEG coating also increased at a higher density of nanoparticles, so it was hard to isolate the two impacts.

4.3 Mixed polymers can improve the Particle Size

The several attempts had been performed for spherical shape with small size at meanwhile PEG-PLA came to evolution with the new outline as migratory mixed micelles to overcome the MDR of tumor cells that knocked the Pharmaceutical science. The mPEG-PLA/TPGS mixed micelles possessed high drug-loading, high encapsulation efficiency, and small size [50]. Another Study clearly suggested that the mean diameters of the mPEG-PLA micelles and mixed micelles were 22.46±0.54 nm and 16.36±0.78 nm respectively, showed the size distributions due to their combine self-asseble behavior. The addition of VE-TPGS and mPEG-PLA developed there smaller mixed micelle than mPEG-PLA micelles [51] (**Table 1**).

Table 1. Block and molecular weight dependent Particle size

Sl.no	PEG-PLA	Formulation	Particle size(nm)	PDI	Refs.
1.	mPEG2-PLA1.8 mPEG4-PLA2.2	Micelles	18.05 34.09	0.079 0.137	[47]
2.	PLA mPEG-PLA mPEG-PLA-PEG PLA-PEG-PLA (Block dependent)	Micelles	167.2 132.8 109.2 215.6	0.247 0.148 0.113 0.183	[38]
3.	mPEG5k-PLA2.5k mPEG2k-PLA5k mPEG5k-PLA10k mPEG2k-PLA15k (Molecular weight dependent)	Micelles	50.51 66.75 82.51 91.55	0.131 0.141 0.123 0.127	[44]
4.	mPEG4.2kPLA2.1k/TPGS (Mixture design dependent)	Mixed micelles	58.9	0.12	[50]
5.	m-PEG2k-PLA3k-R15(polyarginine) (surface modified multi drug dependent)	Micelleplex	54.3	0.207	[39]

5. Therapeutic drug delivery using mPEG-PLA based nanosystems

Multiple applications of systemic delivery could improve efficacy while minimizing the side effects, but each mode of administration has associated barriers for effective delivery. mPEG-PLA NPs was employed to prolong circulation time, stability, reduce interactions with serum components and had more benefits with the various non-systemic mode of administration (**Fig.3**). Discussed in this section, PEG coatings could improve the penetration of "biological barriers", including reducing interactions with tissue extracellular matrix, cellular barriers, and biological fluids such as mucus, thereby leading to improved delivery. Here, we had discussed only molecular weight and surface density to demonstrate the multifunctional mPEG-PLA coated therapeutic smaller delivery.

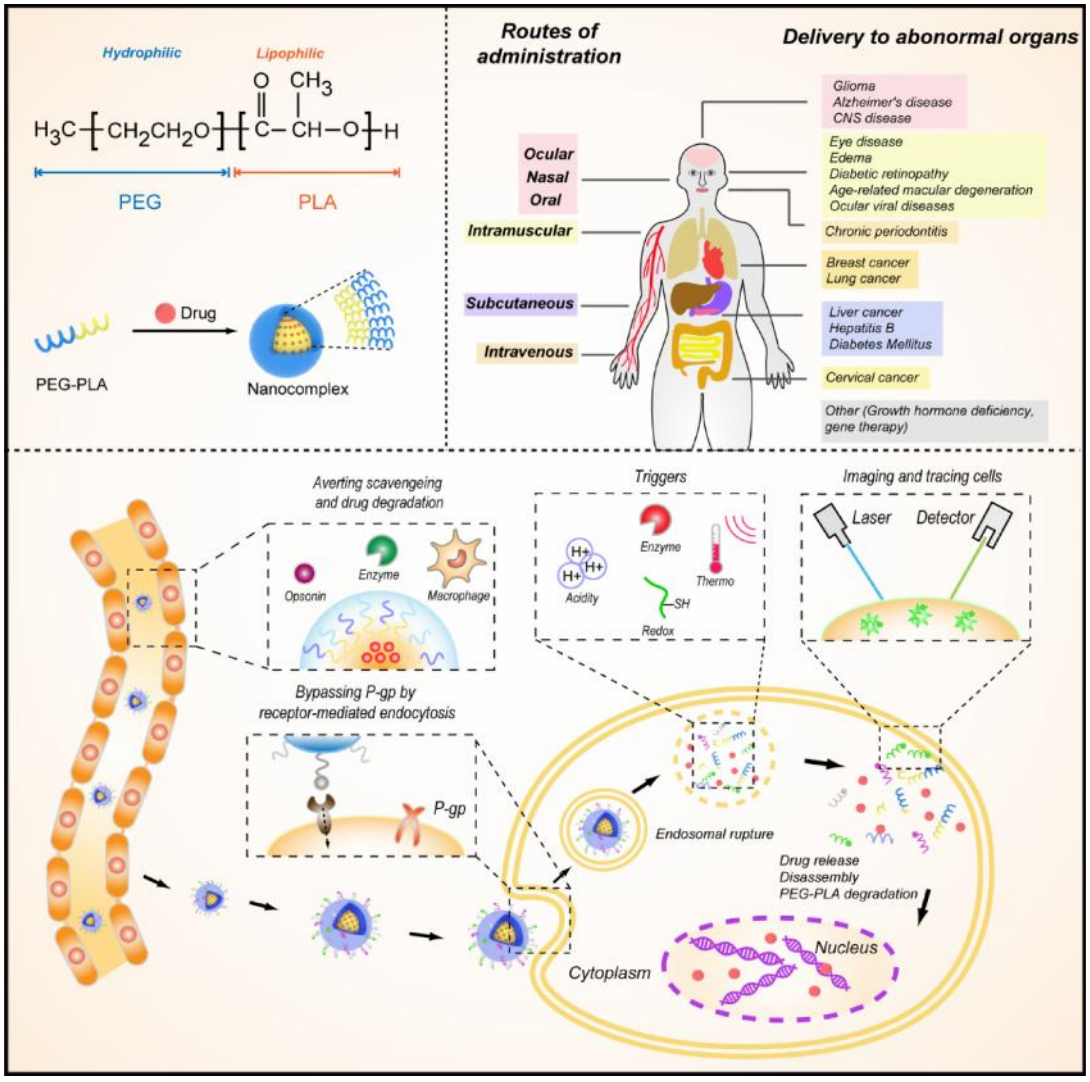

Fig.3 Schematic diagramed of the mPEG-PLA trigger the therapeutic effects.

5.1 Brain targeting drug delivery

Novel design of surface modified mPEG-PLA could be exploited to give the prospective benefits for brain drug delivery. However, this modified drug loaded NPs easily crossed the blood brain barrier (BBB). It administered directly to the brain by bolus injection or convection-enhanced delivery (CED), the tissue extracellular matrix (ECM) presents an additional barrier to reaching target cells. In a study we found that the viability of C6 and U251 cell lines in the smaller Cur/mPEG-PLA micelle decreased more significantly and speculated that the high drug uptake may contribute to anti-glioma activity *in vitro* and *in vivo*. Through the studies, the Physiological change of subcutaneous gliomas were more effectively inhibited in the Cur/mPEGPLA micelles better than free curcumin. It implied that mPEG-PLA micelles enhanced the anti-glioma activity of Curcumin at the same time and Cur-PEG-PLA was very simple and faster than Curcumin Poly (lactic-coglycolide) delivery[52]. *Zhongyang et al.* explored a B6 peptide conjugated mPEG-PLA NPs discovered by phase display as a substitute for transferrin, and enhanced the delivery of a neuroprotectivedrug across theBBB for the treatment of Alzheimer's disease in brain. It exhibited significantly higheraccumulation in capillary endothelial cells via lipid raft-mediated and clathrin-mediated endocytosis and promising DDS for facilitating the brain delivery of neuropeptides [53]. Optimizing CPPs-functionalized NPs for brain drug delivery, penetratin (CPP With the relatively low content of basic amino acids) was functionalized to mPEG-PLA NPs with pharmacokinetic and biodistribution profiles characterized and compared with that of low-molecular-weight protamine funtionalized nanoparticles. In contrast, penetratin-NPs exhibited a relative superiority in brain delivery

efficiency and were found the concentration were found 0.85-fold higher than LMWP- NP in the brain with in 15 mins, which was speculated to be ascribed to its relatively lower level of positive charge[54].

5.2 Ocular drug delivery

Eyes are rather accessible, numerous barrier to efficient drug delivery preclude effective treatment of the various blinding diseases that inflict the eye. It tends to the mode of administration is topical drops to the eye, unfortunately, it's frequently cited there is rapid clearance and poor absorption in intraocular tissues[55]. *Giannavola and coworkers* have explored as a way to ascend the prolongation and penetration of drugs administered to the ocular surface using them PEG-PLA as a mucoadhesive agents. It promoted the interactions and prepared the acyclovir-loaded NPs. mPEG-PLA increased the levels of acyclovir in the aqueous humor of rabbits after instillation into the conjunctival sac compared to PLA NPs or free drug. They attributed this decrease to the reduction of mucoadhesive forces between the mPEG-PLA NPs and the surface of the eye. Exception, mPEG–PLA microparticles showed great potential for sustained ocular drug delivery because of their high stability *in vitro* and *in vivo*, and their release profile. They allowed for targeted delivery to cells at the back of the retina (i.e. photoreceptor cells), which could prove operative treatment of blinding diseases caused by photoreceptor cell loss [31].

5.3 Oral nanoparticle delivery

We already discussed the efficacy of different block copolymers to stabilize the antigen during the release from noncomplex owing to the presence of PEG, which prevented the generation of acidic microenvironment resulting from the degradation of PLA to lactic acid provide efficient cellular uptake and elicit impressive immune response[56]. The gastrointestinal (GI) tract was a common target site for drug and gene delivery, asa simple and preferred oral mode of administration. However, there were numerous barriers to effective GI delivery, such as the harsh GI environment. The known stability enhancing properties of PEG coatings had also improved NP delivery to the GI tract. *Tobio and coworkers* demonstrated that mPEG-PLA NPs improved the stability in digestive fluids *in vitro*, which led to enhanced oral tetanus toxoid delivery in rats compared to uncoated PLA NPs. They observed 5-times higher radioactive tetanus toxoid levels in the blood after administration mPEG-PLA particles compared to PLA particles for up to 24 h, despite the belief that hydrophobic NPs were more favorably absorbed across the GI mucosa[57]. The stability of copolymerizing PLA with PEGNPs were improved using by different block copolymers encapsulating hepatitis B surface antigen (HBsAg) to evaluate their efficacy as oral vaccine delivery system that exhibited adroit levels of humoral immunity along with the mucosal (sIgA) and cellular immune response (TH1). The results demonstrated that depict enhanced mucosal uptake leading to effective immune response as compared to other polymeric nanoparticles both *in vitro* and *in vivo* studies [38].

Conclusions and prospects

In conclusion, Bio-inspired platforms directly derived from biological sources were becoming a rapidly emerging field in the development of upcoming anticancer therapeutics. As discussed in this review, synthesized mPEG-PLA block copolymers can be assembled into smaller nanoparticles of delivery systems exhibited unique mechanisms and interesting properties that are capable of achieving prolonged circulation and release capacity *in vivo* due to their modified character. It has attracted particular interest on different therapy and attention from researchers and manufacturers alike over the past decade. By adjusting the ratio of PLA and PEG and the block copolymers can escalation the drug loading and encapsulation efficiency of hydrophobic drugs, reduce particle sizes, avoid recognition by the reticuloendothelial system, and elevated the circulation time. However, the long circulating property and kinetics of mPEG-PLA block copolymer nanoparticles and the cristalinity were required to be developed additional. Moreover, due to small particle sizes and surface adsorption, the first-pass effect still existed, and blood clearance could also be accelerated. Otherwise, the synthesis of PEG-PLA block copolymer by the lactide ring-opening polymerization method was exclusive and not reproductive for large-scale production, whereas the polymer prepared by a direct method had a lower MW with a wider distribution. The current studies on mPEG-PLA nanoparticles are still performed in the laboratory practices, and there is a long way to go on how to promote large-scale production. mPEG-PLA nanoparticles can be probable to provide more tools and possibilities for the clinical tumor treatment with wide application prospects in pharmaceutical and biomedical field.

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