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Review article

Customizing poly(lactic-*co*-glycolic acid) particles for biomedical applications

Edyta Swider [a], Olga Koshkina [a], Jurjen Tel [a,d], Luis J. Cruz [b], I. Jolanda M. de Vries [a,c], Mangala Srinivas [a,*]

[a] Department of Tumor Immunology, Radboud Institute for Molecular Life Sciences, Nijmegen, Netherlands
[b] Department of Radiology, Leiden University Medical Center, Leiden, Netherlands
[c] Department of Medical Oncology, Radboud, Nijmegen, Netherlands
[d] Department of Biomedical Engineering, Laboratory of Immunoengineering, Eindhoven University of Technology, Eindhoven, Netherlands

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ABSTRACT

Nano- and microparticles have increasingly widespread applications in nanomedicine, ranging from drug delivery to imaging. Poly(lactic-*co*-glycolic acid) (PLGA) particles are the most widely-applied type of particles due to their biocompatibility and biodegradability. Here, we discuss the preparation of PLGA particles, and various modifications to tailor particles for applications in biological systems. We highlight new preparation approaches, including microfluidics and PRINT method, and modifications of PLGA particles resulting in novel or responsive properties, such as Janus or upconversion particles. Finally, we describe how the preparation methods can- and should-be adapted to tailor the properties of particles for the desired biomedical application. Our aim is to enable researchers who work with PLGA particles to better appreciate the effects of the selected preparation procedure on the final properties of the particles and its biological implications.

Statement of Significance

Nanoparticles are increasingly important in the field of biomedicine. Particles made of polymers are in the spotlight, due to their biodegradability, biocompatibility, versatility. In this review, we aim to discuss the range of formulation techniques, manipulations, and applications of poly(lactic-*co*-glycolic acid) (PLGA) particles, to enable a researcher to effectively select or design the optimal particles for their application. We describe the various techniques of PLGA particle synthesis and their impact on possible applications. We focus on recent developments in the field of PLGA particles, and new synthesis techniques that have emerged over the past years. Overall, we show how the chemistry of PLGA particles can be adapted to solve pressing biological needs.

Contents

* Corresponding author at Radboud University Medical Center (RadboudUMC), Department of Tumor Immunology, 278, Radboud Institute for Molecular Life Sciences (RIMLS), Nijmegen, Netherlands.
E-mail address: Mangala.Srinivas@radboudumc.nl (M. Srinivas).

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1. Introduction

The past decades have seen rapid development in the fields of nanotechnology and nanomedicine. Nanomedicine – a subset of nanotechnology – is described as the monitoring, repair, construction, and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures [1]. To be used in medicine, nanomaterials must have specific characteristics, such as a high surface-area-to-volume ratio, biocompatibility, and control of biodistribution and circulatory half-life. Furthermore, nanoparticles can be designed in different shapes and sizes and their surface can be modified to fulfill their biological need.

Polymer-based particles are now frequently studied and used as drug carriers in cancer and other pathologic conditions, as controlling their synthesis enables customizing their physicochemical properties. Thus, size distribution or side-chain composition of the polymer can be modified to improve delivery efficiency [2]. The "ideal" polymer for such particles must be biodegradable, with toxicologically safe *in vivo* degradation products, which can be easily eliminated by the metabolic pathways. Among various polymers, poly(lactic-*co*-glycolic acid) (PLGA) has received the highest attention because of its favorable degradation characteristics and biocompatibility. The application of PLGA as a biomaterial dates back to the 1970s, when it was developed as a material for biodegradable sutures, followed by its use in the production of devices such as implants, tissue grafts, prosthetic devices, and therapeutic devices. Now the technology has matured to the nanoscale. PLGA has been used for the encapsulation of various types of drugs, such as paclitaxel, doxorubicin, cisplatin, docetaxel, and curcumin [3]. Table 1 presents drug encapsulation where PLGA is used to control release, along with the encapsulation method used.

PLGA particles offer a number of advantages for biomedical applications: they can be targeted *in vivo* using antibodies, they protect DNA and other biomolecules from degradation, or, when modified with targeting ligands, they effectively enhance immune response [4]. Finally, aiming at clinical use, they can be stored for lengthy periods in a powder form. Current approved PLGA particles include, for example, Lupron Depot® (Abbott Laboratories, USA) and Trelstar® (Watson Pharmaceuticals, USA) for sustained release of leuprolide and triptorelin respectively, as well as several other formulations reviewed elsewhere [5–7]. PLGA has been used as a suture material since 1974 under the product name Vicryl® (Ethicon Inc, USA), a 10:90 PLGA braided construct (http://www.ethicon.com/). Other examples of currently available PLGA sutures include Polyglactin 910 (Dolphin Sutures®, Futura Surgicare Pvt Ltd, India) or Polysorb® (Syneture, USA). Additionally, there are several ongoing and recently completed clinical trials involving the use of PLGA as bioscaffolds, biodegradable polymer stents or bioabsorbable screws (https://clinicaltrials.gov/ct2/results?term=PLGA&Search=Search).

The properties of PLGA particles are strongly dependent on the preparation method. Specific applications, e.g. cell targeting, imaging, and therapeutic delivery, require particles with well-defined physicochemical properties. Due to its popularity, there have been several reviews published focusing on the formulation of PLGA particles. Sah et al. describe different well-established formulation techniques for PLGA particles and how to improve drug encapsulation efficiency [8]. In another review, Sharma et al. address the issues related to PLGA-based nanoparticles, like methods of preparation, characterization techniques, surface modification, and mechanism of drug release, as well as the drawbacks of using PLGA nanoparticles as drug delivery systems [9]. In this review, we highlight, how recent developments in the field of nanomedicine affect

Table 1
Table shows examples of drugs, which are encapsulated in PLGA.

Drug	Product	Application	Solubility in water	Encapsulation method	Ref.
Octreotide acetate	Sandostatin LAR® Depot	acromegaly, severe diarrhea, sudden reddening of the face and neck caused by carcinoid tumors	hydrophilic	coacervation	[134]
Leuprolide acetate	Lupron Depot®	advanced prostate cancer, endometriosis, uterine fibroids,	hydrophilic	w/o/w emulsion solvent evaporation	[134]
Buserelin acetate	Suprecur MP (Japan)	endometriosis, uterine myoma	hydrophilic	spray-drying	[134]
Vancomycin	Vancocin HCl Pulvules	bacterial infections	hydrophilic	nanoprecipitation-solvent evaporation	[135]
Phenobarbital	Solfoton	partial and generalized tonic-clonic seizures, epilepsy	hydrophilic	nanoprecipitation-solvent evaporation	[135]
Cucurbitacin I	N/A	inhibitor of STAT3/JAK2 signaling	hydrophobic	nanoprecipitation-solvent evaporation	[136]
Cyclosporin A	Gengraf, Neoral	organ transplantation for immune suppression	hydrophobic	nanoprecipitation-solvent evaporation	[135]
Valproic acid	Depakene, Depacon	seizures disorders, manic disorders	hydrophobic	nanoprecipitation-solvent evaporation	[135]

the design of PLGA particles, along with relevant modifications necessary. We emphasize both novel fabrication techniques, such as microfluidics or inkjet printing, and modifications of the PLGA polymer resulting in materials with smart properties, e.g. Janus nanoparticles, thermo- or pH-responsive particles, and upconversion nanoparticles. Finally, we discuss how the recent developments of PLGA particles can be applied in modern nanomedicine to improve the outcome of the treatment. For clarity, here we refer to particles under 1000 nm as nanoparticles, as those are often presented as nanoparticles in the literature, while larger particles are referred to as microparticles.

2. Physicochemical properties of PLGA

PLGA is a linear copolymer with lactic and glycolic acid repeat units, which can be organized as a block-*co*-polymer or statistical polymer (Scheme 1). The body can easily metabolize both monomers into carbon dioxide and water via the tricarboxylic acid cycle, resulting in minimal systemic toxicity [10]. PLGA can be synthesized by direct polycondensation of lactic and glycolic acid, which usually results in copolymers with a low molecular weight and broad molar mass distribution. Polymers with higher molecular weight and narrower molar mass distribution can be obtained by the ring-opening polymerization of cyclic dimers [11]. In general, the molecular weight of PLGA can be adjusted from 4 to 240 kDa by changing the polymerization conditions and the ratio of monomer to initiator [10]. The biodegradation rate of PLGA depends on several factors, e.g. the composition of the polymer [12] and its microstructure [13]. The degradation of PLGA is faster for polymers with the increased amount of glycolic acid units [12,14]. Polymers with a 50:50 ratio of lactic and glycolic acids have the fastest degradation rate and are therefore one of the most frequently used polymers in nanomedicine [12]. PLGA with the 50:50 ratio has the degradation rate of around two months *in vivo* and has the fastest release rate when compared to other ratios (Fig. 1) [10].

PLGA can be dissolved in a range of common organic solvents, depending on its composition. PLGA with a higher amount of lactic acid is dissolved by chlorinated solvents, such as dichloromethane or chloroform, and by water-miscible solvents, like acetone or tetrahydrofuran, while PLGA with a higher amount of glycolic acid is dissolved by fluorinated solvents, like hexafluoroisopropanol [15,16]. Finally, the glass transition temperature of PLGA can also be exploited; typically PLGA undergoes glass transition above body temperature, between 40 and 60 °C and this decreases with a decrease in the molecular weight and decrease of PLA content in the copolymer [10].

The physicochemical properties of PLGA particles primarily depend on properties of PLGA polymer used for synthesis, including the ratio of lactic acid to glycolic acid, molecular weight, and storage temperature [10,15,17]. However, most of the particle properties, for example, particle size and size distribution, are strongly dependent on the synthesis method in general and influenced by the synthesis parameters within the same method in particular, including the addition of encapsulated substance.

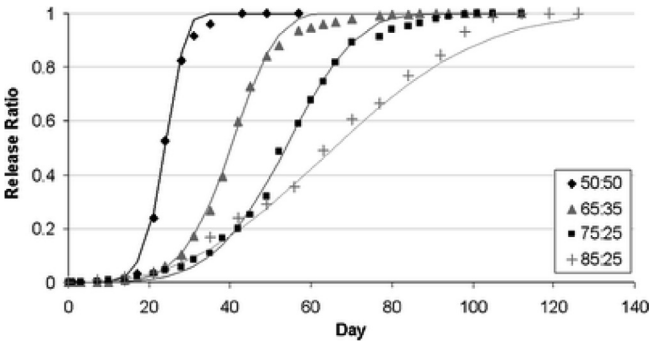
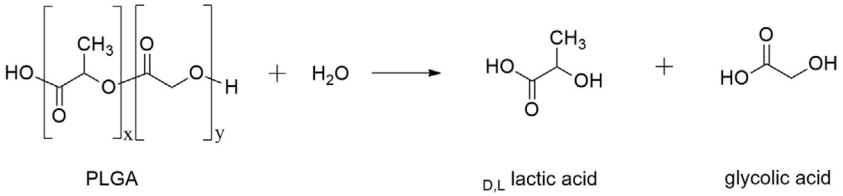


Fig. 1. The release profile from PLGA implants. Figure represents modeled *in vivo* release profiles of risperidone drug for 50:50, 65:35, 75:25 and 85:15 PLGA, where the first number represents the amount of lactic acid and second number the amount of glycolic acid (e.g. 85:15 means 85% lactic and 15% glycolic acid) [132]. Copyright (2010) Pharmaceutical Research.

PLGA particles can be functionalized with poly(ethylene glycol) (PEG) or other hydrophilic polymers resulting in particles with a "stealth" surface. These stealth particles become almost invisible to the reticulo-endothelial system, which is responsible for the clearance of particles from the blood stream, and have longer circulation (Table 2) [18,19]. Furthermore, the addition of coating materials may improve the production of particles with well-controlled and reproducible sustained-release profiles [20]. PEG is a water-soluble, non-ionic polymer, which has become a gold standard for the stealth modification of nanoparticles to increase their blood circulation time [21]. PEG has good synthesis flexibility and its end groups can be easily modified [21]. The addition of PEG layer can enhance particle hydrophilicity [15], resulting in reduced interactions with biomolecules, e.g. lipids or serum proteins, and therefore protect particles from elimination from the blood stream through the RES [22].

Some of the other commonly used surface-coating materials include PEG-containing block-*co*-polymers such as poloxamer or poloxamine, polysorbate 80 (TWEEN®-80) [23,24]. Poloxamer is (Poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*-poly (ethylene glycol)) block-co-polymer. Poloxamer is a coating material, which can enhance proapoptotic signaling and it can preferentially target cancer cells [25]. This coating material can be used during the encapsulation of hydrophobic drugs. Nevertheless, high doses of poloxamer can induce hyperlipidemia and hypercholesterolemia [25]. Poloxamine is an amphiphilic block-co-polymer formed by four arms of poly(ethylene oxide)-poly(propylene oxide) blocks, and it is useful in solubilization and stabilization of hydrophobic drugs, and it prolongs blood circulation half-life [26]. Polysorbate 80 is useful in improving the transport of drugs across the blood-brain barrier, however, it may cause severe non-immunologic anaphylactoid reactions [27]. Further advantages and downsides of these coating materials are described in Table 2.

Besides the modification of the particle surface, the PLGA polymer itself can be further modified by the linkage of PEG chains prior to particle synthesis, to form di-, tri-block copolymers [28].



Scheme 1. Hydrolysis of PLGA. PLGA hydrolysis leads to two monomers, lactic and glycolic acid- both familiar cell metabolites. These are metabolized via the tricarboxylic acid cycle, resulting in minimal systemic toxicity.

Table 2
Overview of materials used for coating the PLGA particles, with examples from the literature.

Coating material	Advantages	Disadvantages	Ref.
Polyethylene glycol (Poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*-poly(ethylene glycol)	low intrinsic toxicity prolonged blood circulation low toxicity timed release crosslink ability high binding efficiency	hypersensitivity non-biodegradability degradation under stress	[137–139]
Poloxamer	thermoreversible property, non-toxic non-irritant used with hydrophobic drugs	rapid erosion non-biodegradability	[25]
Poloxamine	self-assemble properties prolong blood circulation	N/A	[26]
Polysorbate 80	improved drug transport FDA approved	severe anaphylactoid reactions can cause infertility	[27,140]

When formulating the particles from PEG-PLGA copolymer, PEG chains align themselves in the direction of external aqueous phase. Triblock copolymers can be arranged in an ABA (PLGA-PEG-PLGA) or BAB (PEG-PLGA-PEG) manner, where the different blocks are coupled to each other via an ester linkage. There have been several studies using PEG-PLGA nanoparticles for various applications, with different methods for particle synthesis [29–31]. e.g. methoxy-PEG-PLGA (mPEG-PLGA) which was used to form core-shell nanoparticles via double emulsification for co-delivery of hydrophilic and hydrophobic drugs [32].

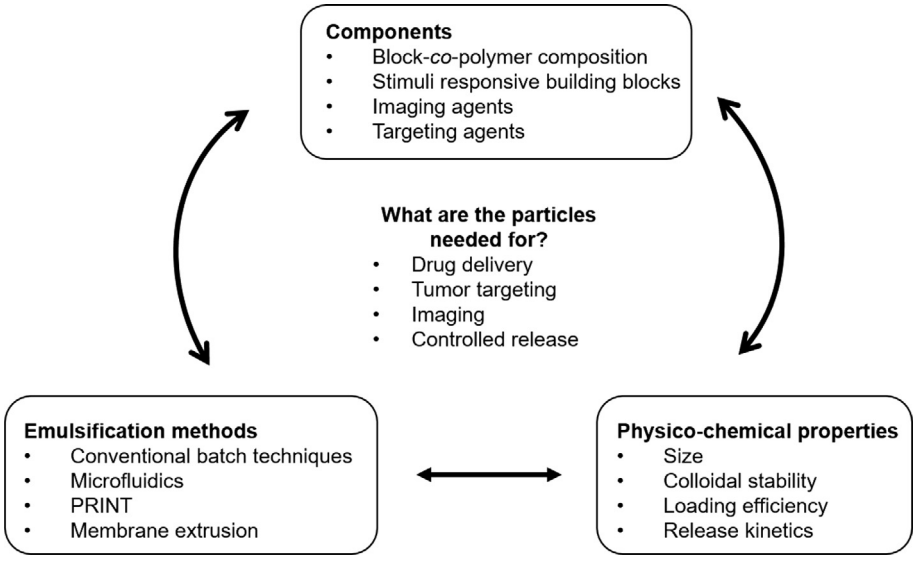
While PEGylation can shield nanoparticles from being recognized by the immune system, there have been reports, which suggest the formation of PEG-specific antibodies after the administration of PEG-coated liposomes [33]. The formation of such antibodies results not only in the early clearance of PEGylated particles from blood (Accelerated Blood Clearance or ABC effect) [34], but can also contribute to the change in pharmacokinetic profile of subsequent injected doses of the PEGylated compound. Other disadvantages of PEGylation include the degradation of PEG leading to production of toxic peroxides or the accumulation of PEG in organs by vacuolization [34,35]. This issue needs to be taken into account when considering the safety of nanoparticle-based therapeutics.

3. Preparation methods of PLGA nano- and microparticles

There are several methods of particle preparation from PLGA copolymers. To prepare particles with controlled properties, such as size or degradation rate, it is important to choose not only the right method, but also the right materials and synthesis parameters. For example, particle size can be affected by the amount of surfactant [36], polymer concentration, encapsulated compound, and the type and extent of energy input (e.g. sonication, homogenization or shear stirring) (Scheme 2).

The choice of preparation method is also important for the loading and release efficiency of any entrapped agents, which depends on both the specific properties of the agent and the eventual route of delivery of the particles. Furthermore, the preparation of particles of the desired size, surface charge, encapsulation efficiency, and release characteristics, requires precise control of specific parameters [23].

Before describing the new methods, we provide a brief summary of established techniques, with the key characteristics of obtained particles presented in Table 3 and Fig. 2. However, for more detailed information on the last, we highly recommend a review by Astete et al. [37].



Scheme 2. Aspects needed for the design of particles. Particle fabrication should be planned with the final application in mind. Several techniques, with many variable parameters, can be selected and optimized for an appropriate end product.

Table 3
Overview of PLGA particles synthesis methods.

Method	Diameter range	Mixing method	Solvent	Surfactant	Disadvantages	Advantages	Ref.
Double-emulsion solvent-evaporation	0.1–10 μm	Sonication	DCM Chloroform Ethyl acetate	PVA Pluronic F68 sodium cholate	shear stress size affected by cargo	suitable for hydrophilic compounds non-toxic solvents	[4,15]
Single-emulsion solvent-evaporation	~50–700 nm	Sonication Homogenization	DCM Ethyl acetate Chloroform	PVA Tween-80 Pluronic F68	size affected by cargo size affected by polymer concentration	suitable for lipophilic compounds solvent evaporation	[38,39]
Nanoprecipitation	~80–700 nm	N/A	Acetonitrile Acetone Ethanol	PVA poloxamer poloxamines Pluronic®F68	size affected by polymer concentration	low energy consumption no high share forces	[5,40–42]
Spray-drying	<10 μm	N/A	Acetone Chloroform Methanol Ethyl acetate	Tween-80 Pluronic®F68 Pluronic®F127 Polaxamer	diversity in particle shape adhesion of particles to the spray-dryer	high entrapment efficiency rapid process	[43–46]
Emulsification/salting-out method	100–500 nm	Homogenization	Acetone THF DMSO	PVA Poly(vinyl pyrrolidone)	poor encapsulation efficiency low yield high polydispersity	minimizes stress to protein cargo good for heat sensitive substances	[47–51]
Microfluidics	200–1000 nm; up to several μm	N/A	DMC DMSO DCM	PVA Tween-20/80	slow diffusive mixing	monodisperse droplets	[54,56–58,141]
Membrane extrusion emulsification	~200 nm up to 60 μm	Sonication Homogenization	DCM Ethyl acetate	PVA Tween 20/80 poloxamer Pluronic F68	low maximum disperse phase flux	controlled droplet sizes narrow size distribution less energy used	[66,68,69]
Particle replication in nonwetting template (PRINT)	10 nm–200 μm	N/A	Ethanol	Tween-20 PVA	multistep device preparation	control over shape, size and surface encapsulation of various cargos high drug loading	[70–72,142–144]

*DCM = dichloromethane, THF = tetrahydrofuran, DMSO = dimethyl sulfoxide, DMC = dimethyl carbonate, PVA = polyvinyl alcohol

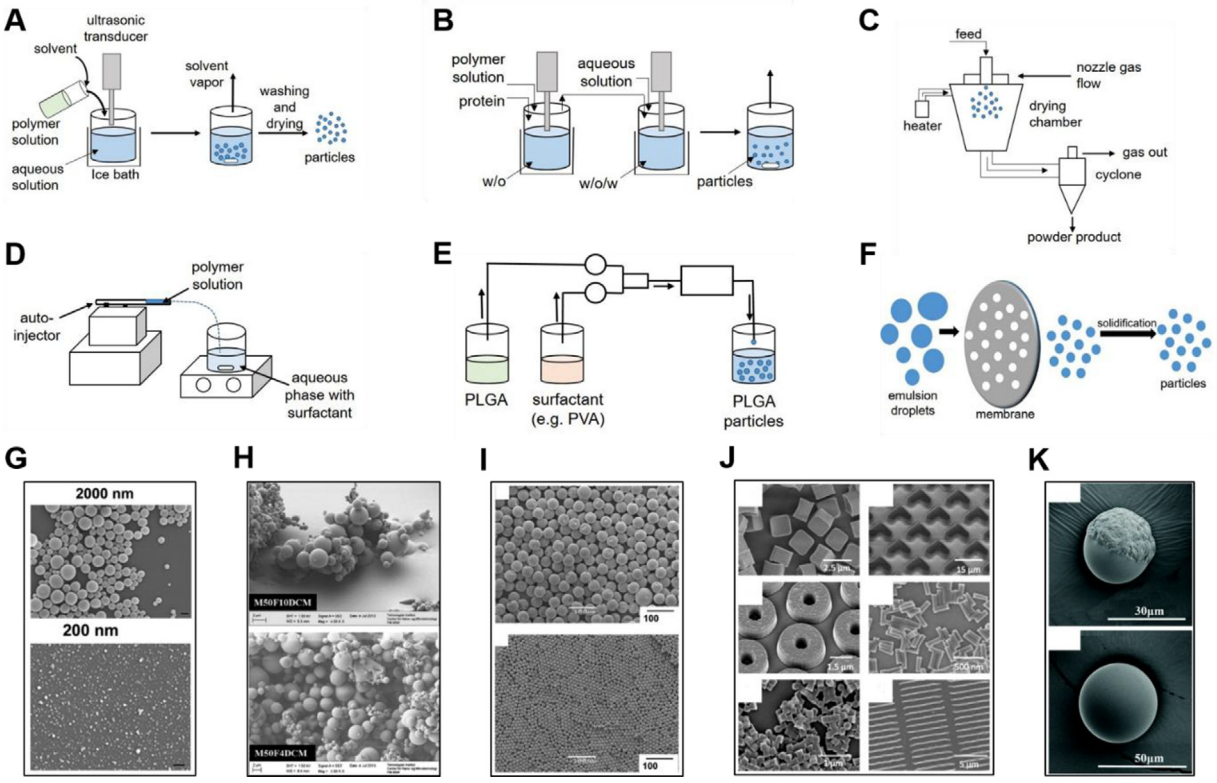


Fig. 2. Graphical representation of different preparation techniques of PLGA particles. PLGA particles can be formulated using various methods, including (A) single emulsion-solvent evaporation (B) encapsulation of a protein into PLGA nanoparticles using double emulsion solvent evaporation (C) spray-drying (D) nanoprecipitation (E) microfluidics, and (F) membrane extrusion emulsification. (w – water, w/o – water-in-oil, w/o/w – water-in-oil-in-water, PVA-polyvinyl alcohol). Scanning electron microscopy images represent particles prepared using: (G) emulsion solvent-evaporation–scale bar 1 μm [123] (Copyright (2010) Elsevier, Ltd.) (H) spray-drying [43] (Copyright (2014) Springer) (I) microfluidics [55] (Copyright (2009) John Wiley and Sons) (J) PRINT technique–particles of different shapes [70] (Copyright (2011) ACS Publications) (K) Janus particles made using a microfluidic system [89] (Published by The Royal Society of Chemistry (2015)).

3.1. Conventional preparation methods

3.1.1. Single and double emulsion–solvent evaporation method

Standard emulsification methods are based on the preparation of an oil-in-water (o/w) or water-in-oil-in-water (w/o/w) emulsion and are well-suited to encapsulate different types of lipophilic and hydrophilic drugs [38]. The emulsion consists of an oil phase with PLGA and the lipophilic agent (e.g. drug) in a non-polar organic solvent, and an aqueous phase with a surfactant. The organic phase is added to the aqueous phase under sonication or homogenization, followed by solvent evaporation and collection of particles (Fig. 2A,B) [39]. The final product is freeze-dried and can attain a shelf-life of several years. The single and double emulsion technique can be simply scaled up by adjusting the amount of polymer, type of solvents, addition of drugs, type of surfactant and sonication or homogenization [37]. The single-emulsion method is suitable for the encapsulation of hydrophobic compounds, while the double-emulsion method is used to encapsulate more hydrophilic cargo [38]. Both methods use high shear stress, which can be disadvantageous for the encapsulation of more fragile compounds, such as proteins.

3.1.2. Nanoprecipitation

Nanoprecipitation is especially useful for the synthesis of nanoparticles with size below 100 nm [5,40–42]. Here, polymer and drug are dissolved in a polar, water-miscible solvent and added in a controlled manner using an auto-injector, to an aqueous phase (Fig. 2D). Nanoprecipitation is typically used for the encapsulation of hydrophobic drugs, since the loading efficiency for hydrophilic compounds is low due to their poor interaction with the PLGA. This poor interaction leads to the diffusion of the hydrophilic drug during the solvent diffusion from the organic to aqueous phase [40]. Another disadvantage of this method is that nanoparticle size is affected by the polymer concentration, where lower polymer concentration results in smaller particles [37].

3.1.3. Spray-drying

Spray-drying is a rapid method with only a few processing parameters. It can be used to encapsulate both hydrophilic and lipophilic drugs, peptides, and proteins into a particle. Particles are prepared by spraying solid-in-oil (s/o) dispersion or w/o emulsion in a stream of heated air (Fig. 2C). Fig. 2H shows scanning electron microscopy (SEM) images of particles produced with the spray-drying method. The selection between s/o and w/o method depends on the properties of the encapsulated agents, particularly their hydrophilicity or hydrophobicity [43–45]. The main drawback of the conventional spray-drying approach is a significant loss of product caused by the agglomeration of particles or their adhesion to the walls of the spray-drying apparatus, which can be resolved with the use of an anti-adherent [46].

3.1.4. Emulsification/salting-out

The salting-out method is based on the separation of an aqueous phase from an organic phase via the addition of suitable electrolytes [47]. Particles form through controlled dilution of the electrolyte content, as the solvent diffuses from the organic droplets. Salting out is a robust technique, where size is not highly sensitive to increase in polymer concentration. Since the salting out agent is water soluble, this method is suitable for hydrophobic compounds. Downsides of the salting-out technique include low

yield, poor entrapment efficiency, and a high polydispersity index (PDI) [48–51]. However, the method is useful for the processing of heat sensitive substances and can easily be scaled up [47].

3.2. New design methods for PLGA particles

Conventional methods of particle synthesis frequently result in particles with a broad size distribution, leading to problems with control over reproducibility, biodistribution, drug loading, and encapsulation efficiency. Other issues facing current fabrication techniques for PLGA particles include a poor ability to tailor release kinetics and to co-deliver dual drugs with different solubility properties [52]. Recent developments in the formulation methods addressing these issues are described in the following sections.

3.2.1. Microfluidic platforms

Microfluidics is a new field which deals with the manipulation of fluids at the micro- and nanoscale. A classic microfluidic device includes a network of microchannels which are molded into a material forming a microfluidic-chip, inlets to inject fluids, micropumps and microvalves to manipulate fluids within the chip, outlets to remove fluids, and a detection system for analysis [53]. Microfluidic chips can be built using materials, such as glass, silicone or polymer (e.g. poly(dimethylsiloxane) (PDMS)), and formed into different geometries to control the droplet formation [54,55]. Microfluidics has different applications, one of them is a development of emulsions via droplet-based microfluidic systems.

Droplet-based microfluidic systems provide a new route to produce monodisperse and uniform droplet emulsions in a controlled way, with the use of various materials and reagents (Fig. 2E,I) [56–58]. For example, glass capillary devices consist of a set of glass capillaries which are chemically resistant and their geometry allows for controlled synthesis of multiple emulsions [59]. A major disadvantage of glass capillary devices is in upscaling production, as it is difficult to reproducibly construct more than one device at a time and have many identical devices [54]. A solution to this problem could be the use of PDMS microfluidic device. Here, a chip is built from PDMS bonded to a thin glass slide, which can also allow visualization of the sample and monitoring of the concentration of a drug at the same time [60]. These devices can be replicated and produced in big numbers, making them suitable for large-scale synthesis [54]. However, PDMS is less chemically inert, might become swollen with some solvents, and it can absorb small molecules, like biomolecules or drugs.

The formulation of droplets can be controlled by either passive or active techniques. In both active and passive mixing, the droplet diameter can be controlled by controlling the flow rates of the continuous and dispersed phases, the ratio between these liquid phases, and the geometries of the system [61]. In passive mixing, the mixing of organic and aqueous phases is affected only by the flow rate and the geometry of the microfluidic chip and thus no additional "active" energy input is present [62]. In active droplet production, the droplet diameter can be further tuned by additional energy input in the mixing part of the device by moving wall structures, integrating microheaters, and magnetically or pneumatically driven microvalves [62].

The most common geometries used for the formation of droplets are a T-shaped junction, a flow focusing (FF) system, and co-flowing streams (Fig. 3). T-junction geometry is the simplest geometry for producing and manipulating droplets. This type of geometry combines a horizontal and a perpendicular channel, resembling the two branches of a "T" [63]. During the droplet generation with T-junction, the continuous phase flows through the horizontal channel, while the dispersed phase comes through a channel perpendicular to it [64].

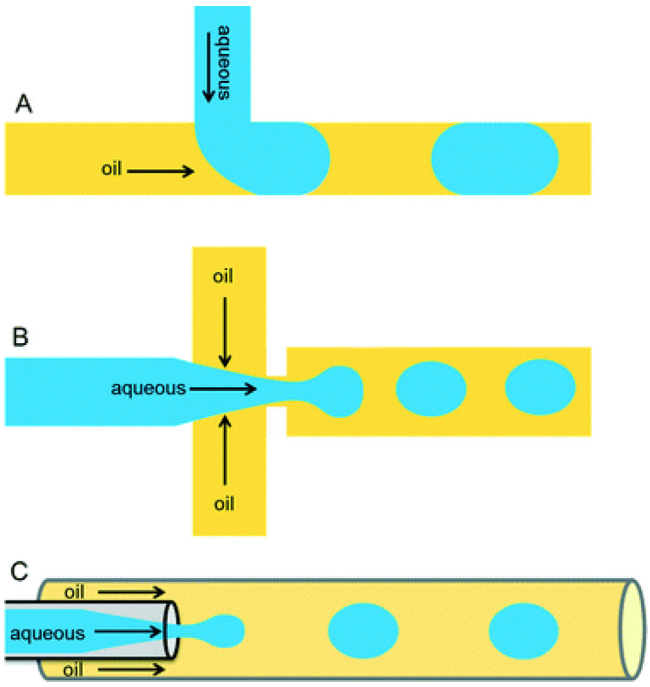


Fig. 3. Schematic view of droplet-based microfluidic geometries: (A) The T-junction geometry, the horizontal flow of the aqueous phase is sheared by oil and thereby generates droplets. (B) In the flow-focusing geometry, droplets are produced by shearing the aqueous stream from two directions. (C) The co-flow geometry, here the aqueous phase is forced through a capillary, which is placed coaxially inside a bigger capillary, through which an immiscible oil is pumped [133]. Published by The Royal Society of Chemistry (2016).

In the FF geometry, the dispersed phase flows inside the square capillary and the continuous phase flows from the two side channels. The dispersed phase is focused by the continuous phase through the narrow opening of the tapered round capillary, leading to the formation of emulsions in the collection capillary. Despite the diversity of the structures in the FF configuration, the mechanisms of droplet formation are similar to the T-junction configuration [63]. The set-up of the FF geometry uses symmetric shearing force by the continuous phase, resulting in a more stable and controllable formation of droplets [63]. Therefore, the FF system can be used for the production of smaller droplets, even if the opening of the channel has a larger size [62]. In the co-flow system, the dispersed phase flows inside the round capillary, while the continuous phase flows between the square and round capillaries. Here, both fluid phases flow in the same direction. These systems are used to form single emulsions [54]. To produce double emulsions a combination of FF and co-flow geometries can be used [54].

There are several distinct regimes of droplet formation in the geometries described above, e.g. dripping, squeezing, and jetting. The type of regime influences the size of generated droplets. For example, in the squeezing regime the size of droplet is described as a function of the ratio of the flow rates of the two liquid phases. Further details of different regimes have been described elsewhere [62].

The major advantage of a microfluidic platform is that it allows the selection of the chemical composition and structure of the particles needed for specific application [60]. With the microfluidic system, the physicochemical parameters of particles can be easily adjusted by the type of solvent and non-solvent, the solubility and type of encapsulated cargo, the concentrations of surfactant and polymer, and the presence of additional co-surfactant molecules [65]. In Table 3 we list further details about microfluidic systems regarding the size of particles produced and commonly used solvents.

3.2.2. Membrane extrusion emulsification

The membrane extrusion emulsification method forms emulsions with a narrow size distribution using membranes with defined pore sizes to form droplets from 200 nm up to 1–5 μm in size. Commonly used membranes include polycarbonate and poly (tetrafluoroethylene), and Shirasu Porous Glass® (SPG Technology Co. Ltd, Japan), although some other materials have also been studied [66]. Polycarbonate membranes are thin and, thus, they need to be additionally supported with drain discs or nylon meshes in order to protect the membrane from rupture. Polycarbonate membranes can easily be sterilized and can be used as a disposable, thus lowering any cross-contamination risk [67]. Generally, the membrane extrusion emulsification method involves the synthesis of single or double emulsion, which is further extruded through the membrane using high pressure (Fig. 2F) [66,68]. A major advantage of the membrane extrusion technique is that obtained particles are more homogenous when compared to solvent-evaporation methods. The membrane extrusion emulsification is one of the techniques, which allows the simultaneous encapsulation of hydrophilic or lipophilic therapeutics and an imaging agent, such as quantum dots, leading to the formation of multifunctional particles [69].

3.2.3. PRINT technique

The group of DeSimone described a novel Particle Replication In Nonwetting Templates (PRINT) technique for the synthesis of micro- and nanoparticles [70]. This method uses a mold made of a fluoropolymer to make the particles. The use of different templates for the production of these molds results in cavities with different shapes, for example, cubic particles used for the encapsulation of doxorubicin [70]. These cavities are then filled with PLGA solution. After solidification, the particles can be removed with a harvesting film. This technique allows for the production of particles in a size range of 10 nm to 200 μm (Table 2) [71,72]. PRINT allows for the synthesis of particles with a specific size and shape (Fig. 2J), as it has been shown that shape can have an important effect on the biological responses to nanoparticles [70]. Moreover, particles made using this technique can be loaded with fluorophores, MRI contrast agents, and both hydrophilic and hydrophobic chemotherapeutics. Along with the microfluidic platform and membrane extrusion techniques, the PRINT technique has an important advantage above other methods, as the resulting particles are homogenous with a low PDI. This is highly beneficial for applications, such as drug delivery, as monodisperse particles provide more equal and predictable distribution of drugs.

4. Smart PLGA based nanomaterials

Smart or stimuli-responsive polymeric systems can change their properties depending on the environment they are placed in. These systems can be sensitive to stimuli such as temperature, light intensity, magnetic field or pH [73]. In this section, we describe the modification of PLGA particles, which result in smart nanocarriers.

4.1. pH-responsive particles

Typical release profiles of PLGA particles consist of an initial burst phase, induction period, slow release phase, and a final release phase. One of the recent approaches to modify this release profile is the development of the pH-responsive particles. These particles contain a pH-responsive polymer in addition to PLGA. This type of particle will release their cargo only when the optimum pH window is reached [74], either in a specific organ, intracellular compartment, tumor microenvironment or inflammation

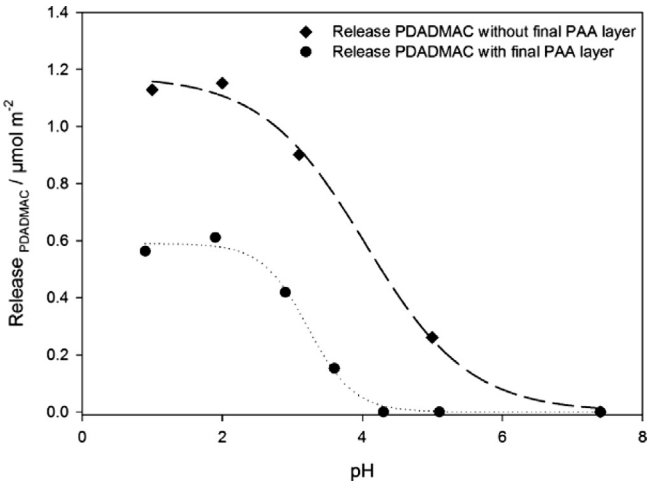


Fig. 4. Figure represents the released amount of PDADMAC per surface area in dependence of the pH [77]. Copyright (2015) *Beilstein* Journal of Nanotechnology.

[75]. There are several ways of developing pH-responsive particles, e.g. β-amino ester linkages within a polymer give pH sensitivity and make the polymer core soluble in water. Particles can be also designed to release their payload intracellularly. This release is achieved, for example, through the conjugation of a drug to the polymer backbone via an acid–responsive hydrazine bond or via a disulfide linker [76]. pH-sensitive particles can be also developed using the layer-by layer self-assembly technique, with poly(acrylic acid) as a pH-sensitive component and poly(diallyldimethylammonium chloride) (PDADMAC) as the releasable polycation [77]. Above modifications can also influence the release of encapsulated cargo as presented in Fig. 4. Furthermore, such modifications can trigger the release of drug within solid tumors, as they take advantage of tumor's acidic environment.

4.2. Thermo-sensitive particles

Another group of stimuli-responsive materials show Upper or Lower Critical Solution Temperature (UCST or LCST). Such materials are soluble in aqueous solution only above or below the critical temperature. Changes in temperature are relatively easy to control in both *in vitro* and *in vivo* settings, allowing the application of thermo-sensitive materials for biomedical applications. Thermosensitive nanocarriers should keep their load at body temperature (37 °C) and quickly deliver the therapeutic within a heated targeted area (~40–42 °C). Such nanocarriers can also react and release their cargo upon temperature decrease, e.g. during cryotherapy [75]. Poly(*N*-isopropylacrylamide) (pNIPAm) is perhaps the most intensively studied thermoresponsive polymer. PNiPAm undergoes the hydrophilic-hydrophobic phase transition at ~31–32 °C [78]. At temperatures below its LCST, pNiPAm nanoparticles are swollen and hydrophilic, while with the increase in temperature above the LCST they collapse as the polymer becomes hydrophobic [78]. An example of thermo-sensitive particles that use pNiPAm, are magnetic-based core-shell particles (MBCSPs), which were designed to target skin cancer and deliver chemotherapeutics in a controlled manner [79]. These particles have a thermo-responsive shell of poly(*N*-isopropylacrylamide-acrylamide-allylamine) and a core of PLGA embedded with magnetite nanoparticles. To target melanoma cancer cells, these particles were further conjugated with peptides that bind to specific receptors on melanoma cells. MBCSPs allow multifunctional delivery of therapeutics due to the degradation of PLGA core, controlled release via the temperature changes, and receptor-mediated

targeting. They can also serve as an imaging agents, as they produce regions of hypointensity in magnetic resonance imaging (MRI) [79]. Another example of the use of temperature-responsive polymers describes the encapsulation of naltrexone, a drug which stops the activity of opioids [80]. In their work, Salehi et al. studied the preparation of thermosensitive terpolymer poly (*N*-isopropylacrylamide-acrylamide-vinilpyrrolidone) and its blend with PLGA. They showed that the addition of PLGA to terpolymer leads to a lower burst effect and slower release rate of naltrexone at 37 °C [80].

4.3. Light-responsive particles

Particles made out of light-sensitive polymer alter their properties when exposed to light. Light irradiation can be used to activate the drug release from the polymeric carriers. This type of stimulus is of special interest, as its intensity is precisely tuned, it can be remotely used for a short period of time, and applied directly at the site of interest. One of the ways to increase the light sensitivity of polymers is the introduction of multiple light-sensitive triggering groups to the polymer chain [81]. The attachment of light-responsive groups to cyclizing side chains leads to the formation of polymers that can quickly degrade in response to UV light, and release encapsulated cargo [82]. One typical example is PLGA-based polymers containing pendant nucleophiles protected with a photocleavable o-nitrobenzyl (ONB) group, which degrades in response to UV light. Light irradiation makes the component polymers more hydrophilic, allowing water to infiltrate the particles and thus foster hydrolysis of the polymer backbone [82].

Park et al. developed doxorubicin-loaded PLGA-gold half-shell nanoparticles, where the gold films were placed on drug-loaded nanoparticles [83]. This approach combines photo- and thermal treatment. The gold surface absorbs light and converts it to cytotoxic heat, while the drug loaded into polymeric nanoparticles is released. In this study, the group showed that drug loaded in PLGA nanoparticles was released faster upon near-infrared (NIR) irradiation, as PLGA is degraded more rapidly at higher temperatures [83]. Thus, there is a possibility of controlling drug release by adjusting the intensity of NIR irradiation. However, when designing a light-responsive system, one should keep in mind the limited penetration depth of external light in biological tissue. Such limitations can be solved with the use of upconversion particles described in the next section.

4.4. Upconversion particles

Another system, which is used with the combination with light, are uponversion particles. Upconversion particles have the ability to convert NIR light (800, 915, 980 nm) to lower emission wavelengths at ultraviolet (UV), visible (VIS), or the NIR region by means of a low-power continuous-wave diode laser [84]. This characteristic is especially attractive, as NIR excitation permits deep tissue penetration, while the UV and VIS light emitted by upconversion particles allows for the photo-triggerable processes [85].

Upconversion particles can be created by the encapsulation of the sensitizer, e.g. Yb(III), and activators, e.g. Gd(III), Tm(III), within PLGA-PEG nanoparticles [85]. Such particles can further contain a photosensitizer, e.g. protoporphyrin IX, which is activated upon irradiation by absorbing UV or vis light, and results in the generation of reactive-oxygen species (ROS) [85]. The use of co-encapsulation of upconversion particles with protoporphyrin IX within PLGA-PEG lead to higher ROS production than when only protoporphyrin IX was encapsulated alone [85].

5. Janus particles

Janus particles are heterogenous particles consisting of two distinct hemispheres of different materials that bring different properties or functions to each hemisphere. Due to this characteristic, Janus particles recently received a lot of attention [86]. The term Janus is derived from the name of a two-headed god in ancient Roman mythology, as Janus particles have a similar structure with two distinct "heads" or hemispheres (Fig. 2K), making them suitable for many applications for which other types of particles are not always suitable, such as the delivery of two different drugs or the encapsulation of both a drug and an imaging agent [87,88]. Janus particles can be formulated using e.g. a fluidic nanoprecipitation system [88] or a droplet-based microfluidic platform [89]. In Janus particles, each side of the particle can be tailored for specific needs, i.e. co-delivery of drugs with different solubility. With the presence of both a hydrophilic and a hydrophobic sphere, these particles can stabilize both o/w and w/o single emulsions. Particles with two surfaces can be formulated using polymers with different end-groups and additionally coated with various chemical groups. Each surface can then be further modified with targeting ligands or imaging agents. Such modifications in Janus particles make them into bi- or multifunctional carriers [90], although it can be challenging to adjust the properties of one hemisphere without disturbing the other. There are a few ways of overcoming this issue, including transiently masking one side of the particle while modifying the other, or the micro-contact printing. These strategies are described in more detail elsewhere [90].

Janus particles can be synthesized by combining two polymers of distinct affinity for water, for example PLGA and polycaprolactone (PCL) [91]. The combination of two different polymers allows loading of hydrophilic and hydrophobic drugs, which will distribute unevenly in PLGA and PCL, which was shown by Li et al. [91]. In their work, they used a hydrophilic fluorescent dye, Rhodamine B, to stain Janus particles and they observed that the dye mainly stains PLGA, implying that Rhodamine B can selectively spread in different part of Janus particles. Furthermore, PLGA and PCL show distinct degradation rates, which gives the possibility for the delivery and controlled release of loaded drugs [91]. Another application of Janus particles includes the combination of drug delivery and imaging. Janus PLGA microspheres were synthesized with the magnetic Fe_3O_4 nanoparticles and the fluorescent-labeled drug EuLa3(Bim)12, resulting in microspheres which simultaneously had magnetic and fluorescent properties [92]. The EuLa3(Bim)12 and Fe_3O_4 particles were evenly distributed in separate spheres and Janus microspheres exhibited better fluorescent performance when compared to PLGA/EuLa3(Bim)12/Fe_3O_4 composite microspheres [92].

6. Therapeutic agents

6.1. Towards a perfect drug carrier

Particle size is a key parameter, which affects systemic distribution, cellular availability, uptake, and circulation lifetime [93]. For example, the solvent evaporation method gives low control over particle size distribution, while the spray-drying method requires a high temperature, which can destroy the polymer structure and damage the encapsulated cargo. The diameter of the particle can easily be affected by cargo, polymer concentration or energy input [37]. Extensive research has been carried over the past several years to overcome the limitations of the current systems as described in this review. One of the recent approaches to improve drug encapsulation and controlled release is the use of a continuous microfluidic FF method [94]. Xu et al. used this approach for

the encapsulation of two types of drugs, hydrophilic Doxorubicin and hydrophobic Tamoxifen in PLGA nanoparticles [94]. Here, they used a partially water-miscible mixture as a precursor for drug/polymer solution for nanoparticles nucleation, followed by the extrusion of the solvent solution to an aqueous medium. The group fabricated uniform PLGA nanoparticles with extremely high encapsulation efficiencies, as high as 88%, and longer sustained release [94].

Another important factor, next to the well-defined size and size distribution of particles, is the generation of drug carriers that can encapsulate two or more drugs, for release in a controlled manner. Controlled release of therapeutic drugs has a number of benefits for therapy: it eliminates the need for repetitive dosing to support the therapeutic effects, it provides better regulation and control over the drug release rate, it protects active drugs from degradation and loss of therapeutic activity prior to delivery and it reduces variability in drug-blood plasma concentrations which could lead to toxicity issues [95]. In recent years, controlled drug delivery synthesis and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. One can trigger the drug release by using stimuli responsive materials. Such materials can be sensitive to light, pH, temperature changes [76] or other physicochemical stimuli, like glucose concentration [96].

6.2. Sustained release

The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a consistently high blood level of the drug over a long period of time. With traditional tablets or injections, the drug level in the blood rises after each administration of the drug and then decreases until the next administration [97]. This level of the agent in the blood must remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective. However, the actual drug levels will fluctuate widely between these boundaries [97]. In controlled drug delivery systems designed for long-term administration, the drug level in the blood remains constant, between the desired maximum and minimum, for an extended period of time. Depending on the synthesis and the application, this time may vary between 24 h (Procardia XL®, Pfizer Inc., USA) to 1 month (Lupron Depot®, AbbVie Inc., USA).

In recent years, controlled drug delivery synthesis and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. For example, current controlled-release systems can respond to changes in the biological environment and deliver—or cease to deliver—drugs based on these changes. The common release mechanisms for PLGA particles are usually the diffusion of the drug, solvent penetration/device swelling, and degradation of the polymer matrix. A combination of these mechanisms can also take place at different time points [95].

Similar to the encapsulation of drugs, the release characteristics of polymeric particles can be tuned for specific applications by the synthesis method. The release of encapsulated drug depends on various properties of the particles, e.g. the size of particles and amount of loaded drug [15]. Typical PLGA release profiles consist of an initial burst phase, induction period, slow release phase, and final release phase. In the initial burst phase, around 30% of the entrapped agent can be released within a few days, which can hinder more specific control of release rates [15]. Such issues can be solved by adjusting the polymer ratio, particle size, drug content or the addition of coating to particles. Larger particles have a smaller initial burst and longer sustained release when compared to smaller particles [23]. When it comes to the amount of drug, the higher the drug loading the higher the burst and faster the release rate [23]. Blanco et al. developed PLGA nanoparticles designed for protein delivery for extended period of time using a modified double emulsion technique, and showed that the size of nanoparticles and the protein encapsulation efficiency together with release rate can be modulated by adjusting the synthesis conditions [98]. They used PLGA copolymers with free terminal carboxyl groups for particle synthesis, which resulted in improved protein encapsulation efficiency and decreased protein release rate [98].

There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion [15]. Drug release from PLGA can be controlled by the degradation rate of the PLGA copolymer. This can be achieved by the use of different molar ratios of the lactic and glycolic acids in the polymer chain, molecular weight of the polymer, and the degree of polymer crystallinity [94]. For a short-term release ($\leq$1 month) an amorphous polymer with higher hydrophilicity is suitable, while for long-term release (1–6 months) an amorphous polymer with high molecular weight is recommended. Release longer than 6 months typically requires polymer with a high degree of crystallinity [15]. Additionally, for the delivery of drugs or other agents, the chemical properties of encapsulated compound must be taken into account; Siegel et al. showed that the type of drug can influence the release and degradation rate of PLGA polymer [99]. They compared the rate of drug release through the degradation of 50:50 PLGA pellets for six different drugs: thiothixene, haloperidol, hydrochlorothiozide, corticosterone, ibuprofen, and aspirin. The authors used identical polymer matrices and drug loading, but the rate of polymer degradation and drug release still varied significantly between drugs, ranging from 13 days (aspirin) up to 38 days (haloperidol) Thus, the authors concluded that design of biodegradable polymeric drug carriers with high drug cargo must account for the effect of the drug on polymer degradation and drug release rate [99].

6.3. Targeted delivery

Targeted drug delivery aims to accumulate drug at the site of interest and could significantly lower side effects. Targeting the region of interest, e.g. tumors and organs, by the modification of the particle surface leads to an increase in selective cellular binding and particle internalization via receptor-mediated endocytosis [4]. Functionalization of particles with ligands directed against surface receptors of different cells can enhance the targeting of the immune system [4]. Sharma et al. described different targeting approaches in more details. Here, we give a few examples on the modifications of particles for targeting application.

A major advantage of PLGA particles is that their surface can be easily modified by the addition of targeting agents. A great number of ligands have been evaluated to functionalize particles, including peptides or proteins e.g. antibodies or lectins, glycoproteins, polysaccharides, and glycolipids [100] to target various tissues, for example brain, liver or tumors [101,102]. Typically, as shown in several studies [103,104], targeting ligands are conjugated at the particle surface through a PEG-linker. PLGA particles can be also coated with surfactants to enhance the targeting, e.g. polysorbate 80-coated nanoparticles were reported to cross the blood-brain barrier by mimicking the low density lipoproteins (LDL), enabling them to connect with the LDL receptor and being taken up by brain endothelial cells [105]. Another targeting approach involves developing biomimetic particles, where particle core is coated with the cell membranes, e.g. PLGA-indocyanine green particles were coated with cancer cell membrane, which resulted in a better adhesion of particles to cancer cells and accumulation in a tumor [106].

Tel et al. used PLGA nanoparticles (~250 nm) to investigate which plasmacytoid dendritic cell (pDC) receptors can be used to deliver antigens for antigen (cross-) presentation [107]. They encapsulated peptide antigens together with the Toll-like receptor 7 agonist R848 in PLGA nanoparticles, which was followed by coating particles with PEG and streptavidin, and coupling specific biotinylated antibodies, such as anti-DEC-205 or anti-CD32. The results showed that targeting nanoparticles to pDCs improved uptake, processing, and (cross-) presentation of encapsulated antigen to both $CD4^+$ and $CD8^+$ T cells. Other studies also showed enhanced immune response, when the antigens and adjuvants were delivered to DCs via nanoparticles [108,109].

Cheng et al. studied the functionalized PLGA-PEG nanoparticles for *in vivo* targeted drug delivery to prostate tumors. Here, PLGA-*b*-PEG copolymer was synthesized by the conjugation of amino-terminated-PEG to carboxy-terminated PLGA. They first synthesized drug-loaded nanoparticles via nanoprecipitation technique. These nanoparticles with desirable size and drug loading were then conjugated to the specific aptamer for targeting. The final results demonstrated enhanced nanoparticle delivery to prostate tumors as compared to non-targeted nanoparticles [30].

7. Theranostic agents

Theranostics is an emerging field which combines diagnostics and therapeutics into multifunction nanoparticle systems [110]. Drug delivery and cell fate can be monitored using noninvasive imaging techniques in order to optimize the route of delivery, migration, proliferation, localization, and other factors. A number of imaging modalities can be used for *in vivo* imaging, such as MRI and ultrasound or fluorescent imaging [111]. The performance of multimodal imaging can be improved by the intelligent design of contrast agents to label cells. PLGA particles can be modified for the use in diagnostic and therapeutic imaging by the addition of imaging agents during the particle synthesis. PLGA particles can be modified with the addition of different compounds, including MRI contrast agents, fluorescent dyes, quantum dots, superparamagnetic iron oxides (SPIO) or radiotracers such as technetium-99m [112–117].

There are several studies focusing on the development on PLGA particles for MRI [118–120], for example, an amphiphilic Gd(III) complex-loaded PLGA nanoparticles were formulated to provide highly sensitive MRI contrast for imaging guided drug delivery applications [121]. Our group demonstrated perfluorocarbon (PFC)-loaded PLGA particles, which are prepared with the single emulsion solvent evaporation method and can be used as imaging agents for ^{19}F MRI [122–126]. These particles can be customized for multimodal imaging by the addition of fluorescent dye or radioligand and also modified in terms of the particle diameter, and the type and amount of the encapsulated PFC [123,127]. The PFC-loaded PLGA particles were studied for *in vivo* imaging using both ^{19}F MRI and fluorescence, after the injection of particles or previously particle-labeled dendritic cells (DC) in mice [123]. Additionally, these particles can be used to encapsulate proteins or peptides, making them an interesting candidate for a theranostic agent. Alternatively, PLGA particles have also been loaded with other imaging agents, most often with fluorescent dyes (e.g. [128]), or MRI contrast agents as described previously.

In another study, anti-nucleolin-targeted magnetic PLGA nanoparticles loaded with doxorubicin were developed to enhance targeted cancer imaging and therapy [129]. SPIO/doxorubicin PLGA nanoparticles were synthesized using modified multiple emulsion solvent evaporation method and targeted with AS1411 aptamer (Apt) against murine C26 coon carcinoma cells. Obtained particles had doxorubicin loading of 3.0% and SPIO loading of 16%. As shown in the study, Apt conjugation to nanoparticles enhanced the cellular uptake of doxorubicin in C26 cancer cells. Apt-nanoparticles enhanced both the cytotoxicity effect of doxorubicin and the contrast of MR images in tumor site [129].

Wang et al. combined imaging and therapeutic application by synthesizing drug-encapsulating multifunctional nanoparticles for photoacoustic and fluorescent imaging [105]. Here, particles were prepared using double-emulsion solvent-evaporation method, with silica-coated gold nanoparticles loaded into the particle core, and the hydrophobic Paclitaxel (drug loading efficiency at 78.5%) and fluorescent dye encapsulation into the PLGA shell. Gold nanoparticles were used due to their high optical absorption and good photoacoustic signal. Synthesized nanoparticles were then loaded into cancer cells and exposed to laser pulses. The results show the decrease in cell viability due to the vaporization of the particles in and around the cells [105]. Furthermore, the studies in the phantoms and *in vitro* showed strong photoacoustic signals, which suggests the possible application of these nanoparticles as contrast agents for shallow tissue imaging. Overall, the study by Wang et al. indicates that the combination of laser activation and drug release could lead to better therapeutic outcome [105].

8. Conclusions and future perspective

Currently, the field of PLGA particles for medical applications is one that involves chemists, biologists, and clinicians, as well as academic and industrial groups. In the future, we expect new design techniques and functionalization with stimuli-sensitive "smart" building blocks further broaden the use of PLGA and to create efficient delivery systems, which will play a crucial role in personalized medicine. Current extensive preclinical [130] studies and ongoing clinical trials on biodegradable scaffolds (NCT01753089 and NCT03066245) or monitoring cellular therapeutics (NCT02574377) using PLGA demonstrate the continuing significance of this polymer [131], and show a great promise for further improvements in therapeutic, diagnostic, and theranostic agents. Multifunctional PLGA particles allow combining different applications for better therapeutic outcome. Another approach is to embed these multifunctional PLGA particles in various hydrogels or implants, which gives an interesting perspective for an application in the biomedical field for monitoring the implants and controlled release of active molecules.

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