Nanobiomaterials in Drug Delivery: Designing Strategies and Critical Concepts for Their Potential Clinical Applications

13

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Abstract

Nowadays nanotechnology has found extensive application in drug delivery. To design efficient nano-based systems as drug vehicles, the selection of appropriate materials as the carrier is of special importance. Owing to their biodegradability, biocompatibility, being renewable and presenting low toxicity, a myriad of biomaterials have been extensively used in the fields of biomedicine and tissue regeneration. Moreover, the use of biomaterials into nano-based drug delivery shows tremendous attraction. Regarding the design of ideal nanotechnology based drug delivery system, the selection of nanocarrier depends not only on the physicochemical features of drugs and materials, but also the administration route. Thus, in this chapter, first of all, commonly used biomaterials for nanocarrier design, including both natural and synthesized polymers, were introduced and their physicochemical properties were summarized. Thereafter the latest advances in drug delivery by using varied biomaterials as the nanocarriers for different administration routes, including parenteral drug delivery by preparing liposomes, micelles, nanoparticles, and mucosal drug delivery with either mucus bioadhesion or mucus penetration nanoparticles, were presented with related designing strategies covered. Finally, challenges and prospective in applying nanobiomaterials based drug delivery systems were discussed.

Keywords

Nanotechnology · Nanocarrier-based drug delivery systems · Nanobiomaterials · Nanoparticles · Route of drug administration

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13.1 Introduction

Nowadays nanotechnology is an emerging and rapidly evolving field, which has found extensive application in drug delivery. Compared with pure molecular therapeutics, nanocarrier-based drug delivery systems have numerous advantages, for example, it can protect drugs against enzymatic and hydrolytic degradation, providing the possibility of targeting for site-specific drug delivery, with controlled release of drugs leading to immense success. Since the 1990s, FDA-approved nanotechnology-based drug products and clinical trials have galloped ahead (Fig. 13.1a). Among them, nanoparticles (NPs) based on various materials as

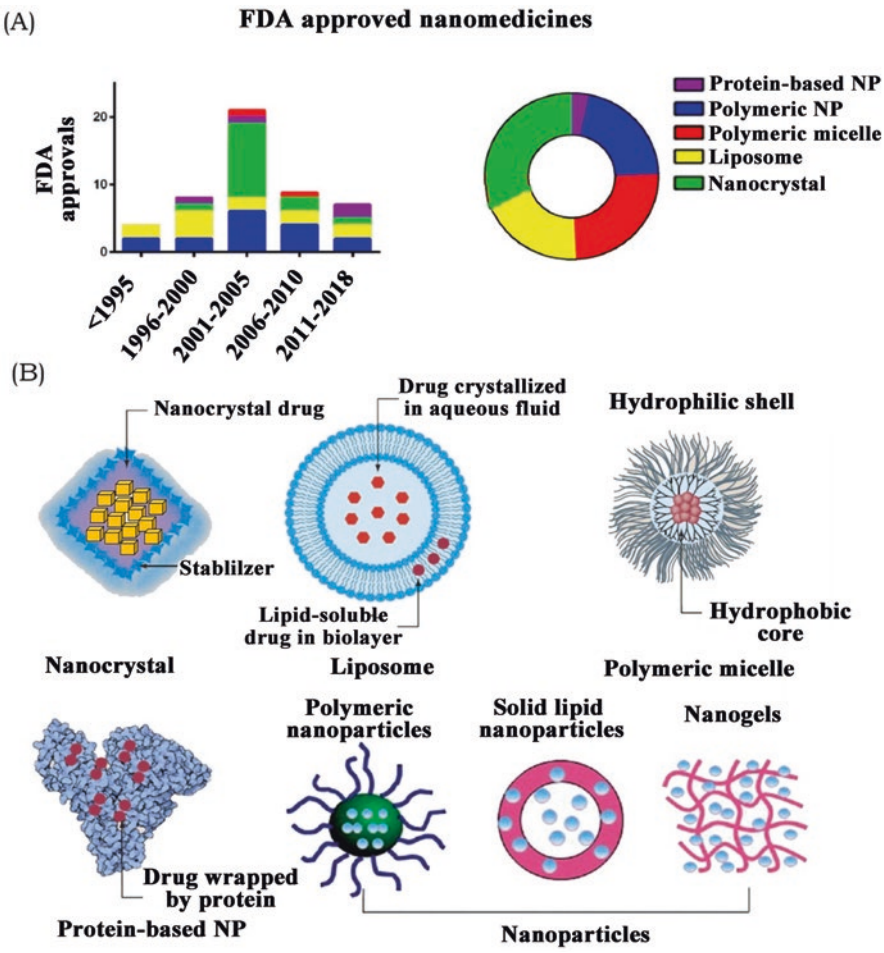

Fig. 13.1 (**a**) Trends in the development of FDA-approved nanomedicines classified by category; (**b**) diagrammatic representation of various types of nanocarriers. (Reproduced from Bobo et al. (2016) with copyright permission)

carriers have been widely explored, with the unique advantages such as the ease of synthesis, biocompatibility, and customizability. Nanocarriers, defined as a carrier with sizes ranging between 1 and 1000 nm, are excellent candidates for drug delivery based on their sub-micrometer size and high surface area to volume ratio. Quite frequently, Doxil® and Abraxane® have been used as examples of nanocarrier-based drug delivery systems. To design efficient nano-based systems for drug delivery, for example, the preparation of nanocrystals, liposomes, polymeric micelles, protein-based NPs, polymeric or lipid-based NPs, nanogels, or any other self-assembled nanosized system for drug delivery (Fig. 13.1b), the selection of appropriate material as the carrier is of special importance.

Owing to their biodegradability, biocompatibility, being renewable, and presenting low toxicity, a myriad of biomaterials have been extensively used in the fields of biomedicine and tissue regeneration. Moreover, the use of biomaterials into nano-based drug delivery shows tremendous attraction. So far, among these nanomaterials that are in phase study, 18 are directed to chemotherapeutics, 15 are intended for antimicrobial agents, 28 are for psychological diseases and autoimmune conditions, and 30 are aimed for nucleic acid-based therapies (Bobo et al. 2016; Bosselmann and Williams 2012).

Regarding the design of ideal nanotechnology-based drug delivery system, the selection of the nanocarrier depends not only on the physicochemical features of drugs and materials but also on the administration route. Thus, in this chapter, first of all, polymeric materials were introduced, and the physicochemical properties of these materials from natural and chemical sources were elaborately introduced. Meanwhile, commonly used materials for nanocarrier design were presented, with a focus on biomaterials. Thereafter the latest advances in drug delivery by using varied nanobiomaterials via different administration routes and related designing strategies were covered. Finally, challenges and prospective in applying nanobiomaterial-based drug delivery systems were discussed.

13.2 Commonly Used Biomaterials for Nanocarrier Design

Nanomaterials can be classified into different types based on their shape, composition, and dimension. Here, the utility of biomaterials for drug delivery was specifically highlighted due to their long history of safe use in humans and unique advantages for fabrication of nanocarriers for drug delivery (Hallan et al. 2016). In terms of polymeric nanomedicine, it consists of two categories: (a) polymer-drug conjugates for prolonged drug half-life and enhanced bioavailability and (b) preparations of NPs for drug delivery based on degradable polymers (Song et al. 2018). Based on their sources, polymeric materials can be classified into natural materials and synthesized ones.

13.2.1 Natural Polymer-Based Biomaterials

Natural polymers, classified as environmentally friendly materials, are a renewable resource considered to be safe in vivo. Commonly used natural polymers include chitosan (CS), alginate, cellulose, hyaluronic acid (HA), carrageenan, chondroitin sulfate, albumin, phospholipid, etc., which are being widely investigated as drug delivery carriers (Han et al. 2018). Among them, CS, HA, albumin, and phospholipid are extensively used.

As the most widely employed natural polysaccharide, CS is a cationic polysaccharide of copolymers glucosamine and N-acetyl glucosamine linked in a β(1–4) manner, prepared by the partial N-deacetylation of crustacean derived from natural biopolymer chitin (Mao et al. 2010). Also, it is naturally found in the fungal cell walls. Deacetylation of chitin renders CS some unique properties, such as bearing positive charge and consequently possesses the capacity to form polyelectrolyte complexes with negatively charged compounds. CS is soluble at acidic pH (pH <5) but precipitates as the physiological pH (pH 7.4) is restored. Besides, due to protonation of the $–NH_2$ group of the D-glucosamine repeating unit, CS is soluble at acetic acid media. The molecular weight and degree of deacetylation of CS can influence its solubility. When the degree of dissociation (α) in solution increases, the role of the cationicity of the amine groups, which depends on the degree of acetylation, plays a more important role in enhancing solubility. Also, the solubility of CS can be increased by decreasing its molecular weight or introducing some hydrophilic groups to the structure of CS. Moreover, a deacetylation of 85% or higher of CS is preferred due to its stronger mucoadhesive properties and biocompatibility. It is also found that CS can increase trans- and paracellular permeability in a reversible, dose-dependent manner (Elgadir et al. 2015). These properties make CS-based materials as an ideal candidate for drug delivery with enhanced mucoadhesion and permeation enhancing properties. CS derivatives, obtained via modification of amino and hydroxyl groups on the CS side chain through acylation, sulfation, hydroxylation, and quaternization, also show immense potential application in biomedical and drug delivery field (Kausar 2017; Wu et al. 2017).

Next to CS, another natural polymeric material HA is a biocompatible, linear glycosaminoglycan, composed of alternating units of N-acetyl-d-glucosamine and glucuronic acid linked together through alternating β-1,3 and β-1,4 glycosidic bonds (Rao et al. 2016; Yadav et al. 2008). Since the pKa value of the carboxyl groups of HA is 3–4, these functional groups are predominantly ionized at pH 7.4, and, therefore, under physiological conditions, HA bear negative charge. Naturally, HA could be found in extracellular matrix, vitreous humor, and synovial fluid of vertebrates, ranging in molecular weight from 5000 to 20,000,000 daltons. Traditionally extracted from rooster combs, HA is now increasingly produced through microbial fermentation. In solution, the chains of HA is highly hydrophilic and surrounded by water molecules linked through hydrogen bonds. Under these conditions, HA adopts random-coil conformation, resulting in forming a very viscous and elastic solution. Thus, HA has been expansively scrutinized for its potential use in biomedical field for visco-supplementation, drug delivery, eye surgery, tissue

regeneration, and embryo protection (Jiao et al. 2016; Ossipov 2010). Most notably, due to its ability to specifically bind to various cancer cells which overexpress the CD44 receptor, HA-based NPs have attracted extensive attention in tumor-targeted delivery and imaging (Yu et al. 2013).

With a molecular weight of 66.5 kDa and a diameter of ~10 nm, albumin is regard as the most abundant plasma protein naturally found in blood (Larsen et al. 2016). Under physiological conditions, about 10–15 g of albumin were produced in liver by hepatocytes and released into the vascular space daily. Usually, the circulation time of albumin in the blood proceeds for approximately 20 days (Mariam et al. 2016). This long half-life is thought mainly facilitated by neonatal Fc receptor (FcRn)-mediated recycling and the megalin-cubilin receptor-mediated renal rescue. Possessing multiple ligand binding sites with cellular receptors is in favor of albumin's recycling and cellular transcytosis. Furthermore, the surface of albumin is negatively charged making it highly water-soluble. Benefiting from its physiological transport mechanisms, charge, and solubility, it is regarded as a highly attractive drug carrier for both half-life extension and targeted intracellular delivery (Mariam et al. 2016). Albumin appears as brownish amorphous lumps, scales, or a powder, consisting of a single polypeptide chain of 585 amino acids. Structurally, albumin consists of three repeated homologue domains (sites I, II, and III). Each domain comprises two separate sub-domains (A and B), each of which contains four and six α-helices, respectively (Elzoghby et al. 2012). Besides, 35 cysteine residues were found in albumin domains, of which 34 form disulfide bridges internally in the structure contributed to high stability of albumin. A free cysteine residue at position 34 located on the outer surface of albumin provides a free thiol group (−SH) accounting for 80% of thiol in the plasma (An and Zhang 2017). Therefore, the major role of albumin in serum is mainly focus on covalent conjugation with drugs. Being one of the multifunctional abundant proteins in plasma, it can also play crucial physiological roles in free radical scavenging and maintaining osmotic pressure (Sleep 2015). Besides, being a nonimmunogenic and nontoxic protein, it is readily available and highly soluble and can be modified and manipulated depending on the proposed application.

Phospholipids are also well-established excipients for various applications, such as function as emulsifier, wetting agent, solubilizer, and liposome former. All lipids that contain phosphorus are called phospholipids, which comprise a polar head group and a lipophilic tail. Phospholipids are functional components of all cell membranes and can also be isolated from natural sources such as soybean, rapeseed, and sunflower seed. Moreover, properties of the phospholipids show some differences depending on their natural sources. For example, phosphatidylcholine obtained from egg yolk has a lower content of polyunsaturated fatty acids compared to phosphatidylcholine from soybean (Otto et al. 2018). Structurally, the phospholipid molecule consists of a glycerol backbone, which is esterified in position 1 and 2 with fatty acids and in position 3 with phosphate. Moreover, the phosphate group can be further esterified with an additional alcohol, for instance, in phosphatidylcholine (PC) with choline, in phosphatidylethanolamine (PE) with ethanolamine, and in phosphatidylglycerol (PG) with glycerol (van Hoogevest 2017). In typical

membrane phospholipids, most of them have neutral (PC, PE) or negative charge (PG, PS, PI, PA). Positively charged phospholipids rarely exist in nature. An example of a positively charged phospholipid is lysyl-phosphatidylglycerol. Until now, the most common nature phospholipid is PC, which is also the main component of lecithin. On the other hand, the fatty acids esterified to the glycerol backbone of the phospholipid molecule could be saturated (e.g., palmitic acid) or monounsaturated (e.g., oleic acid) or polyunsaturated (e.g., arachidonic acid). The resulting phospholipids are called DPPC, where two palmitic acids are esterified.

13.2.2 Synthetic Polymer-Based Biomaterials

Despite the advantages of naturally available biodegradable materials, limitations and concerns still remain with regard to the use of nature polymers, for example, quality inconsistency, the difficulty to control the mechanical properties and degradation rates, and the potential to elicit an immune response or carry microbes or viruses. In contrast, synthetic polymers are more homogenous in composition and therefore have a higher purity than natural polymers, making the preparation of NPs more reproducible. Furthermore, taking the biocompatibility and immunogenicity into consideration, in the current stage of nanomedicine development, only biodegradable polymers such as polylactide (PLA), polyglycolide (PGA), polylactide-co-glycolide (PLGA), and poly (glutamic acid) have been approved by the US FDA for parenteral use (Guo and Ma 2014).

As a widely reported biodegradable polymer, PLGA are made from a copolymer of PLA and PGA polymers. PLGA can be synthesized by random melting copolymerization of lactic and glycolic acid or their cyclic diesters, lactide, and glycolide, respectively. PLGA copolymers are amorphous in nature with glass transition temperature between 45 and 55 °C. The copolymer is more stable against hydrolytic cleavage than each of the polymers alone and the hydrolysis of PLGA results in lactic and glycolic acids which are natural metabolites found in the body. Depending on their molecular weight, inherent viscosity and ratio of lactic acid to glycolic acid, PLGA is commercially available from different companies and with different composition. The physical-chemical properties of PLGA depend mainly on LA:GA ratio. For example, the solubility of PLGA is closely correlated with its LA:GA proportion. Unlike LA and GA, PLGA is soluble in a wide range of solvents, including dichloromethane, tetrahydrofuran, chloroform, and acetone, ethyl acetate, and benzyl alcohol. The solubility decreases with increasing GA content (Makadia and Siegel 2011; Pandita et al. 2015). Likewise, the degradation rate of PLGA is also LA:GA ratio dependent, and this is mainly due to the different hydrophilic profile of each monomer (Xu et al. 2017). Owing to the absence of methyl side groups, GA is more hydrophilic than LA, and in vivo resorption period of PGA (100% GA) is only 6–12 months, whereas it is between 12 and 24 months for PLA (100% LA). Consequently, PLGA with higher proportion of GA is more hydrophilic and can be degraded faster in vivo (Zhang et al. 2014). At 50:50 LA:GA ratio, PLGA copolymers have high degradation rate, which slows down as the proportion of LA

increases from 50 to 100, with GA ratio reducing from 50 to 0. Benefiting from the versatile degradation profile of PLGA, it can be used in biomedical applications, such as surgical implants for controlled drug release. Besides, PLGA is also widely used in the preparation of microspheres, microcapsules, NPs, pellets, implants, and films (Kapoor et al. 2015; Makadia and Siegel 2011).

Poly (glutamic acid) can be achieved by microbial fermentation, which is water-soluble, nontoxic, and completely biodegradable. The molecular weight of poly (glutamic acid) ranges from 100,000 to over 1,000,000, which are largely dependent on the fermentation time. Owing to the presence of a polyglutamyl hydrolase enzyme which can catalyze the hydrolytic breakdown of poly (glutamic acid), their molecular weight decreases as the fermentation time increases (Jeon et al. 2016). Different from traditional proteins structure, poly (glutamic acid), made up of repeating units of L-glutamic acid, D-glutamic acid, or both, is defined as a pseudo-poly (amino acid) linked between the α-amino and γ-carboxylic acid functional groups (Ogunleye et al. 2015). Based on the attachment of the carboxyl group (α and γ, respectively), poly (glutamic acid) can be differentiated into two isoforms, α-poly (glutamic acid) and γ- poly (glutamic acid). α-Poly (glutamic acid) is synthesized chemically by nucleophile-initiated polymerization of the γ-protected N-carboxyanhydride of L-glutamic acid. Microbial production of α-poly (glutamic acid) is difficult, and the polymer can only be produced by recombinant technology. γ-Poly (glutamic acid) has been produced extensively using bacteria, especially those of *Bacillus* species (Ogunleye et al. 2015). So far, it is well known that utility of γ-poly (glutamic acid) plays several advantages over α-poly (glutamic acid) utility. Pure γ-poly (glutamic acid) can be readily obtained in large quantities without any chemical modification step. It is not susceptible to proteases and hence could provide better sustained delivery of conjugated drugs in the body (Shi et al. 2016b).

13.3 Biomaterial-Based Nanocarriers for Drug Delivery

13.3.1 Parenteral Drug Delivery

Compared to conventional injectable solution, injection of nanocarrier-based drug delivery systems offers several advantages, such as controlled drug release and/or selective cell targeting, enhanced cellular uptake, or prolonged circulation time, leading to the potential to maximize the therapeutic effect. However, adverse side effects associated with nanocarrier injection are also noticed, such as undesirable protein adsorption, cell adhesion, as well as inflammation and cytotoxicity. Thus, during the design of nanocarriers for parenteral administration, selection of biodegradable polymers with desirable surface properties is preferred. As shown in Table 13.1, currently marketed nanocarriers used for parenteral drug delivery mainly include liposomes, polymeric micelles, NPs, and polymeric materials stabilized nanosuspension. The materials used for specific nanocarrier design is NPs' type dependent, as described in the following parts.

Table 13.1 List of nanotherapeutics approved by FDA that utilized nanotechnologies for parenteral drug delivery

Formulation	Product	Drug loaded	Carrier materials used	Advantage	Year approved
Liposomes	Doxil	Doxorubicin	Cholesterol, fully hydrogenated soy phosphatidylcholine (HSPC); N-(carbonyl-methoxypolyethylene glycol 2000)-1, 2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (mPEG-DSPE) coating	Improved delivery to the site of disease; decreased systemic toxicity of free drugs	1995
	Abelcet	Amphotericin B	l-α-dimyristoylphosphatidylcholine (DMPC) and l-α-dimyristoylphosphatidylglycerol (DMPG)	Reduced toxicity	1995
	DaunoXome	Daunorubicin	Distearoylphosphatidylcholine and cholesterol	Increased delivery to tumor site; lower systemic toxicity	1996
	AmBisome	Amphotericin B	Egg phosphatidylcholine and cholesterol	Reduced nephrotoxicity	1997
	DepoCyt	Cytarabine	Cholesterol; dioleoylphosphatidylcholine (DOPC); and dipalmitoylphosphatidylglycerol (DPPG)	Increased delivery to tumor site; lower systemic toxicity	1997
	Visudyne	Verteporfin	Lactose, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine	Increased delivery to diseased vessels; photosensitive release	2000
	DepoDur	Morphine sulfate	1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC); cholesterol; 1,2-dipalmitoyl-sn-glycero-3-phospho-rac-(1-glycerol) (DPPG); tricaprylin; and triolein	Extended release	2004
	Marqibo	Vincristine	Sphingomyelin/cholesterol	Increased delivery to tumor site; lower systemic toxicity	2012
	Onivyde	Irinotecan	1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidyl ethanolamine (mPEG-2000-DSPE)	Increased delivery to tumor site; lower systemic toxicity	2015
	Vyxeos	Combination of daunorubicin and cytarabine	Distearoylphosphatidylcholine (DSPC), distearoylphosphatidylglycerol (DSPG), and cholesterol	Sustained release of the molecules and co-loading two molecules with synergistic antitumor activity	2017

Nanoparticles	Feridex/ Endorem	Ferumoxides	Superparamagnetic iron oxide associated with dextran	Superparamagnetic character	1996/2008
	Abraxane	Paclitaxel	Human albumin (containing sodium caprylate and sodium acetyltryptophanate)	Improved solubility; improved delivery to tumor	2007
Nano suspension	Invega Sustenna	Paliperidone palmitate	Polysorbate 20, polyethylene glycol 4000	Allows slow release of injectable low-solubility drugs	2009/2014
	Ryanodex	Dantrolene sodium	Mannitol, polysorbate 80, povidone K12	Faster administration at higher doses	2014
Polymeric micelle	Genexol-PM	Paclitaxel	Methoxy poly(ethylene glycol)-poly (lactide) (mPEG-PLA)	The ability to freely circulate throughout the vasculature to avoid being taken up by reticuloendothelial system (RES)	Phase II: IIa IIb approved (South Korea)

13.3.1.1 Nanomaterials as the Carrier of Liposomes

Liposomes, composed of a lipid or phospholipid, have spherical bilayer nanostructures with both hydrophilic and hydrophobic region. With good biocompatibility, low toxicity, and high safety, many hundreds of drugs, such as anticancer and antimicrobial agents, peptide hormones, vaccines, genetic materials, enzymes, and proteins, have been incorporated into the aqueous or lipid phases of liposomes aimed to deliver therapeutic drug at a sufficient concentration to the target tissues for in vivo absorption. In the development of nanomedicine, liposomes are the first nanomedicine transited from concept to clinical application. Early starting with the approval of liposomal formulations Doxil® in 1965, there have been a growing number of trials and approvals using liposome as the nanocarrier for drug delivery. And other liposomal drugs by intravenous administration are in various stages of clinical development.

The ability of liposomes to deliver a range of therapeutic drugs depends on a diverse toolbox of lipids with well-characterized biophysical behavior. Lipids in this toolbox can be naturally occurring or rationally designed using a variety of hydrophilic head groups, linkers, and hydrophobic moieties. The selection of each lipid is closely related to its phase transition temperature, chemical structure, and whether the lipid is unsaturated or not, as well as its charge. Characteristics of lipid affect the capacity of the membrane to accommodate the drug. For instance, unsaturated phosphatidylcholine species from natural sources (i.e., egg or soybean phosphatidylcholine) form much more permeable and less stable bilayer, whereas the saturated phospholipids, with long acryl chains (i.e., dipalmitoylphosphatidylcholine), form a rigid, rather impermeable bilayer structure (Sakai-Kato et al. 2015).

To create liposomes for intravenous administration, naturally occurring lipids are preferred. For example, fully hydrogenated soy phosphatidylcholine (HSPC) and 2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (mPEG-DSPE) coating are firstly used in Doxil® approved by FDA. Besides, AmBisome® and DepoCyt®, which used naturally occurring lipids, such as dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylglycerol (DPPG), and egg phosphatidylcholine, have also been approved by FDA. Further, to fulfill multiple functions of liposomes in vivo, synthetic phospholipids are widely used. An example of such a lipid, with extended circulation time, is PEGylated phospholipid such as mPEG-DSPE (methoxypolyethylene glycol-distearoyl phosphatidylethanolamine) (Doxil®). By forming a steric barrier around the liposome, PEG-modified lipids embedded in a lipid bilayer decrease interaction with serum opsonins, cellular ligands, and other pre-existing serum factors meanwhile reducing adhesion to other membrane surfaces (Jia et al. 2017). Also, in order to prolong circulation half-life, other synthetic polymer-modified lipids are also designed, such as HPMA (poly (N-(2-hydroxypropyl) methacrylamide)), PVP (poly (vinylpyrrolidone)), PMOX (poly (2-methyl-2-oxazoline)), and PVA (poly (vinylalcohol) (Kocisova et al. 2013; Zhang et al. 2016; Zylberberg and Matosevic 2017).

Properties of liposomes can also be modified via changing surface charge of materials used. For example, cationic liposomal formulation has been designed to selectively target tumor vasculature. DOTAP (1, 2 dioleoyl-3-trimethylammonium-

propane) is a cationic synthetic lipid, which comprises one positive charge at the head group. EndoTAG-1, the first formulation of cationic liposomes carrying paclitaxel in clinical trial, is prepared by DOTAP, DOPC, and paclitaxel in 50:47:3 molar ratio (Chang and Yeh 2012). Table 13.2 lists some liposomes in clinical trial and their lipid composition.

13.3.1.2 Nanomaterials as the Carrier of Micelles

In addition to liposomes, polymer micelles are another promising nanocarrier for delivering various drugs, such as cytostatic agents, nucleic acids via parenteral delivery, with better stability and stronger mechanical strength. Polymeric micelles can be formed through self-assembly of amphiphilic block copolymers with sizes ranging between 20 and 200 nm (Ohya et al. 2011). The inner hydrophobic core of polymeric micelles acts as a suitable microenvironment for hydrophobic bioactives, while the outer hydrophilic shell provides required colloidal stability. Table 13.3 lists the micellar-based injectable formulations under different phases of clinical study, and there are a large amount of polymeric micelles based formulations still under preclinical investigation. Genexol®-PM injection (paclitaxel), the only polymeric micellar NP-based formulation that has been approved in Bulgaria, Hungary, and South Korea, is being evaluated in Phase II trials in the USA. The formulation consists of 20–50 nm PEG-PLA micelles loaded with PTX, exhibiting superior cytotoxic activity against various human cancer cells, e.g., breast, colon, ovarian, and non-small cell lung cancer compared to Taxol® (Park et al. 2010).

Physical and biological properties of polymeric micelles are of special importance, which depend on the characters of materials used for micelle preparation. The selection of polymeric materials influences many important properties of micelles such as toxicity, bio-distribution, pharmacokinetics, and clinical compatibility. Many amphiphilic copolymers can be used as the carrier of polymeric micelles, which is mainly composed of hydrophilic part and hydrophobic part (Pepic et al. 2013; Qiu et al. 2007). A wealth number of hydrophilic polymers with a flexible nature can be selected as the hydrophilic part of amphiphilic copolymers, such as PEG, poly (ethylene oxide) (PEO), poly (acryloylmorpholine), and poly (vinylpyrrolidone). Sometimes the hydrophilic part is made up of a mixture of polymers like PEO and polyelectrolyte. Especially, PEG has been widely used in the outer layer of the polymeric micelles to block interparticle aggregation (Shiraishi et al. 2013). As for hydrophobic blocks, polyesters, poly (amino acid)s (PAAs), and polyether derivatives are often used as the hydrophobic segments of the copolymers. Polyesters, such as PLA and PCL (Poly (ε-caprolactone)), are biocompatible and biodegradable and have been approved by the FDA for biomedical applications in humans (Janas et al. 2016). PAAs, such as poly (aspartic acid) (P (Asp)) and poly (glutamic acid) (P (Glu)), are biodegradable, and their multiple carboxyl/amine functional groups enable in combination with drugs and formation of complexes with various metals or can be modified to optimize the core-drug compatibility, thus increasing drug loading and formulation stability (Jones 2015; Qiu et al. 2007). Polyethers of pharmaceutical interest are copolymers of PEG-block-poly-(propylene oxide)-block-PEG (PEG-b-PPO-bPEG), known as poloxamers (Pluronic), F68, has

Table 13.2 Liposome-based drugs in clinical trials via injectable route

Product	Drug	Lipid composition	Approved indication	Trial phase
LEP-ETU (powder/12 months) (Zhang et al. 2005)	Paclitaxel	1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), cholesterol, and cardiolipin (90:5:5 molar ratio)	Ovarian, breast, and lung cancers	Phase I/II
EndoTAG-1 (powder/24 months) (Dandamudi and Campbell 2007)	Paclitaxel	1,2 dioleoyl-3-trimethylammonium-propane (DOTAP), DOPC, and paclitaxel (50:47:3 molar ratio)	Breast cancer, pancreatic cancer	Phase II
Marqibo (Immordino et al. 2006)	Vincristine	Cholesterol and egg sphingomyelin (45:55 molar ratio)	Metastatic malignant uveal melanoma	Phase III
ThermoDox (Yarmolenko et al. 2010)	Doxorubicin	Dipalmitoylphosphatidylcholine (DPPC), monostearoylphosphatidylcholine (MSPC), and polyethylene glycol-distearoylphosphatidylethanolamine (PEG 2000-DSPE) (90:10:4 molar ratio)	Non-resectable hepatocellular carcinoma	Phase III
S-CKD602 (Immordino et al. 2006)	Camptothecin analog	Distearoylphosphatidylcholine (DSPC) and DSPE-PEG (95:5 molar ratio)	Recurrent or progressive carcinoma of the uterine cervix	Phase I/II
OSI-211 (Tomkinson et al. 2003)	Lurtotecan	Fully hydrogenated soy phosphatidylcholine (HSPC) and cholesterol (2:1 molar ratio)	Ovarian cancer, head and neck cancer	Phase II
INX-0125 (Immordino et al. 2006)	Vinorelbine	Cholesterol and egg sphingomyelin (45:55 molar ratio)	Advanced solid tumors	Phase I

Table 13.3 Current clinical status of polymeric micelle-based formulations for injection

Type of micelles	Product name	Copolymer composition	Drug	Purpose	Treatment	Clinical status
	Genexol®-PM (Cabral and Kataoka 2014)	mPEG-PDLLA	Paclitaxel	Solubilization	Breast and lung cancer	Phase IV/ approved in Korea
	NK105 (Aziz et al. 2017)	PEG-b-poly(α,β-aspartic acid)	Paclitaxel	Solubilization	Breast and gastric cancer	Phase III
	NK911 (Tagami and Ozeki 2017)	PEG-P (Asp)-DOX	Doxorubicin	Targeting	Solid tumors	Phase II
	NC-6300 (Cabral and Kataoka 2014)	PEG-b-poly(aspartatehydrazone)	Epirubicin	Targeting	Breast and liver tumors	Phase I
Single	NC-4016 (Aziz et al. 2017)	PEG-b-poly(L-glutamic acid)	Oxaliplatin	Targeting	Solid tumors	Phase I
	NK012 (Tagami and Ozeki 2017)	PEG-b-poly(L-glutamic acid) (SN 38)	SN-38	Solubilization	Triple negative breast cancer and small lung cancer	Phase II
	NC-6004 (Cabral and Kataoka 2014)	PEG-b-poly(L-glutamic acid) (cisplatin)	Cisplatin	Targeting	Pancreatic cancer	Phase III
	siRNA micelles (Tagami and Ozeki 2017)	cRGD-PEG-b-PAsp(TEP)-Chol/siRNA	siRNA	Targeting	Lung tumor	Preclinical/phase I
Mixed	SP1049C (Valle et al. 2011)	Pluronic L61 and F127	Doxorubicin	Anti-MDR	Adenocarcinoma of the esophagus and gastro esophageal junction	Phase III

been approved by the FDA for parenteral use. F68 is nonbiodegradable, but the individual polymer chains with a size of <50Kda can be excreted by the kidneys (Akbar et al. 2018).

However, one of the main shortcomings for micelles based on single amphiphilic copolymer is their inherent instability upon dilution after their administration, leading to premature release of encapsulated drug before reaching the targeted tissues. Aimed at efficiently improve micellar stability, tremendous researches have focused on mixed micelles by combining two or more dissimilar block copolymers to form micelles. At present, a mixed micelle-based formulation (SP1049C) composed of Pluronic L61 and F127 has reached clinical phase III studies (Valle et al. 2011). Pluronic® L61 copolymer was selected, because it induced a 7.2-fold higher drug uptake in Chinese hamster ovary CHRC5 (resistant) cells, while F127 granted physicochemical stability to the formulation, as it prevented liquid phase separation and preserved the effective size of the micelles below 30 nm, without significantly affecting cytotoxicity of the micelle system.

13.3.1.3 Nanomaterials as the Carrier of Nanoparticles

Similarly, to overcome several inherent problems of liposomes, such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components, and poor storage stability, biodegradable polymeric NPs have attracted considerable attention in view of their ability to target particular organs/tissues, as carriers of DNA/siRNA in gene therapy with improved stability. FDA approved the first "nano" particle-based delivery system, a 130 nm albumin-bound paclitaxel NP (Abraxane®), in January 2005 for the treatment of breast cancer. Augmented albumin uptake in tumors is attributed to the interaction of albumin with albondin, a 60-kda glycoprotein (gp60) receptor and SPARC (Secreted Protein, Acidic and Rich in Cysteine), an extracellular matrix glycoprotein which is over expressed in cancer cells (Socinski 2006). Besides, BIND-014, a tumor prostate-specific membrane antigen (PSMA)-targeted NPs (containing docetaxel) formulation, has also garnered attention in the field of cancer therapy. The results of phase I trial of BIND-014 support its further investigation in phase II studies, which are currently ongoing (Autio et al. 2016).

For the design of polymeric NPs, both natural and synthetic polymeric materials can be used, where polymer-drug compatibility is the main criteria for determining drug loading amount in the NPs (Shi et al. 2016a). Among the naturally available materials, CS, HA, gelatin, sodium alginate, and some other biodegradable polymers have gained a lot of attention as nanocarriers (Dong et al. 2018; Guan et al. 2018; Wang et al. 2018). Especially, it was found that CS-based NPs were widely applied not only in the delivery of anticancer agents, proteins, and peptides but also as the nanocarrier for gene therapy (Li et al. 2015; Zhang et al. 2018). Moreover, several CS derivatives, such as trimethyled chitosan (TMC) and hydrophobic groups modified CS, have also been widely evaluated as nanocarriers with additional functions, such as improved mucoadhesive and intestinal permeation capabilities (Liu et al. 2019). Commonly used synthesized polymeric nanomaterials include PLA (poly (D, L-lactide)), PLG (poly (lactide-co-glycolide)), PLGA, and poly

(cyanoacrylate) (PCA). It has been reported that the distribution of drugs encapsulated into PLGA NPs increased in the tumor site, with reduced systemic adverse reaction (Xu et al. 2017). However, it should be noted that the acidic nature of PLGA monomers is not suitable for acid sensitive bioactives. Thus, to overcome these problems, PLGA-based NPs can be prepared by blending with other materials, such as alginate, CS, pectin, poly (propylenefumarate), and polyvinylacohol (Bose et al. 2016).

13.3.2 Mucosal Drug Delivery

In addition to the outstanding performance of biomaterial-based nanocarriers in parenteral drug delivery, these nanocarriers have also been found to have extensive applications in mucosal drug delivery, including oral, pulmonary, intranasal, ocular, vaginal, or rectal drug delivery, with improved dissolution of hydrophobic drugs, enhanced cellular uptake, or site-directed drug targeting. However, the existence of the vicious and elastic mucus layer, which covers the gastrointestinal (GI) tract, lung airways, female reproductive tract, nose, and eye, performs an important role as a diffusion barrier for various nutrients, foreign particles, and hydrophobic drugs (das Neves and Sarmento 2018). Typically, the limited permeability of conventional particle-based drug delivery systems leads to their clearance from the mucosal tissue within seconds to a few hours, thereby limiting the duration of sustained drug delivery locally. In order to overcome these challenges, mucoadhesive nanoparticulate delivery systems can be designed, which are expected to remain at mucosal membranes for a longer period of time with prolonged and enhanced drug absorption.

Date back to 1947, mucoadhesive polymers have been developed in order to prolong drug residence time on mucosal surfaces (Wu et al. 2018; Zhang et al. 2018). With the rapid development of nanotechnology, mucoadhesive biomaterials from both natural and synthesized sources are extensively explored (Table 13.4) and used to prepare NPs in order to increase residence time of the particles at the mucus layer, leading to enhanced drug uptake at the site of absorption. Mucus can potentially bind to NPs via various physicochemical mechanisms, such as hydrophobic interaction, electrostatic interaction, and hydrogen binding (Zahir-Jouzdani et al. 2018). Figure 13.2 schemically presented the polymers commonly used for mucoadhesive NPs design and the related mechanism of binding. Anionic nanocarriers are characterized by the presence of carboxyl and sulfate functional groups that give rise to a net overall negative charge at pH values exceeding the pKa of the polymer. Among them, polycarbophil and carbomer, PAA derivatives have been studied extensively as mucoadhesive nanomaterials for drug delivery (Andrews et al. 2009; Makhlof et al. 2008). Notably, PAA, generally recognized as safe (GRAS) for oral use by the FDA, are widely used as mucoadhesive nanomaterials due to their nonirritant, nontoxic properties. Of the cationic polymers, undoubtedly CS is the most extensively investigated one. Whereas PAAs bind to mucus via hydrogen bonds, CS has been reported to bind via ionic interactions between primary amino functional

Table 13.4 Different mucoadhesive nanoparticle systems and their applications

Mucosa targeting	Carrier	Drug	Properties
Buccal mucosa	Thiolated CS/polyvinyl alcohol (Samprasit et al. 2015)	Garcinia mangostana extract	To maintain oral hygiene by reducing the bacterial growth that causes the dental caries
	Polyvinyl alcohol (Singh et al. 2015)	Docetaxel	Enhanced local absorption of anticancer drugs
	Gelatin and photoreactive polyethylene glycol diacrylate (Inoo et al. 2018)	Insulin	Significant reduction of blood glucose level
GI mucosa	Alginate/ wheat germ agglutinin (Dodov et al. 2009)	Insulin	Significant reduction of blood glucose level
	PAA-cysteine/PVP (Dodov et al. 2009)	Insulin	Significant reduction of blood glucose level
	P(MAA-EG) (poly(methacrylic acid-graft-ethylene glycol) (Schoener and Peppas 2013)	Insulin	Significant reduction of blood glucose level
Nasal mucosa	N-trimethyl-CS (Sayin et al. 2008)	Albumin	Significantly enhanced uptake of the model protein by the nasal mucosa
	PAA-cysteine/glutathione (Jespersen et al. 2014)	Human growth hormone (HGH)	Threefold improvement in the relative bioavailability of HGH
	Glycol CS (Lee et al. 2016)	DNA vaccine	Higher mucosal and cellular immune response

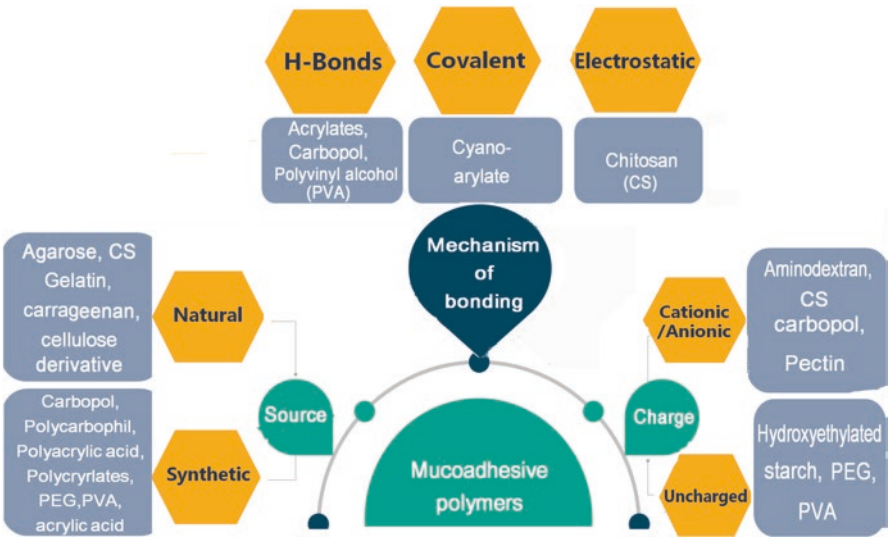

Fig. 13.2 An overview of polymeric materials used for mucoadhesive nanoparticles design and related mechanism of binding

groups and the sialic acid and sulfonic acid substructure of the mucus (Vanic and Skalko-Basnet 2014). Besides, enhancement of mucosal delivery may be obtained through the use of appropriate cytoadhesives nanobiomaterials that can bind to mucosal surfaces. Such widely used nanobiomaterials are lectins, which belong to a group of structurally diverse proteins and glycoproteins, and show the potential to bind reversibly to specific carbohydrate residues (Duennhaupt et al. 2012).

Despite of the advantages of mucoadhesive NPs, its limitation is also quite apparent. Mucoadhesive nanomaterials can efficiently adhere to the mucus layer before reaching the mucosa; however, this might prevent the particle from penetrating across the mucus layer and entering the underlying epithelia (Liu et al. 2018). Thus, for a more efficient transport of drugs to the tissue, the design of NPs with mucus penetration capability is crucially important, which can be achieved by using muco-inert NPs, virus-mimicking NPs, and enzyme-conjugate NPs as schemically described in (Fig. 13.3). Considering the lipophilic nature of mucus, muco-inert NPs, which were coated with "stealth" excipients, can be prepared aiming at decreasing mucous interaction and making the nanomaterials more slippery (Fig. 13.3a). Several polymers including poloxamers and PEG are widely used for surface modification of NPs for this objective (Netsomboon and Bernkop-Schnurch

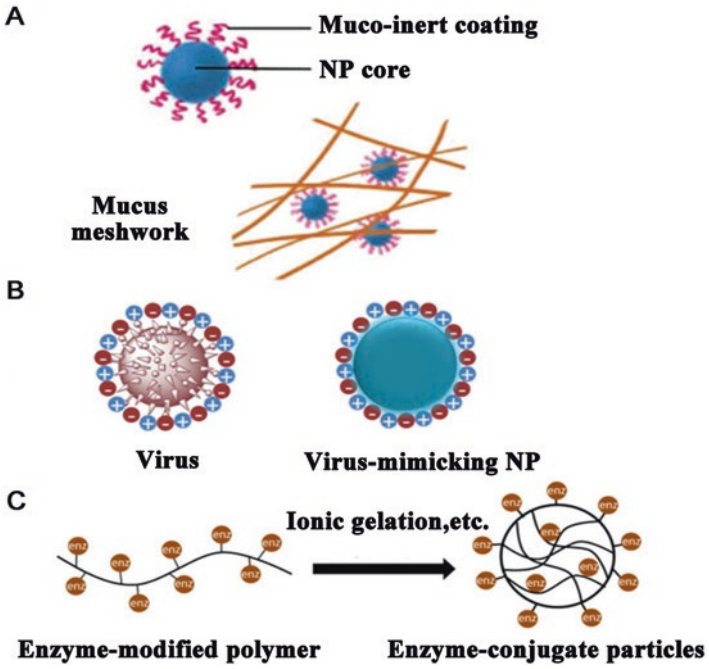

Fig. 13.3 Schematic representatives of the designed muco-permeation nanoparticles including muco-inert nanoparticles (**a**), virus-mimicking nanoparticles (**b**), and enzyme-conjugate nanoparticles (**c**). (Reproduced from (Netsomboon and Bernkop-Schnurch 2016) with copyright permission)

2016). Pluronic F-127, a type of poloxamer, is extensively used for mucopenetrating NPs preparation. Moreover, inspired by natural virus, NPs, which present a highly densely charged surface bearing both positive and negative charges, are formulated with the purpose to increase their mucus permeation ability (Fig. 13.3b). De Sousa et al. prepared NPs by combining chitosan with chondroitin sulfate with a slightly positive (4.02 mV) charge. Not surprising, positively charged NPs (high chitosan content) was found not permeating across the mucus due to the electrostatic interaction with the negatively charged components in the mucus, while negative (high chondroitin sulfate content) and near neutral particles revealed a higher permeation (de Sousa et al. 2015). Another strategy that can be used to create mucous-penetrating NPs is to coat particles with enzymes. Enzyme-conjugate NPs (Fig. 13.3c) are capable of cleaving certain substructures within the three-dimensional network of the mucus, without destroying the whole mucus gel layer. So far, mucolytic enzymes such as bromelain, papain, pronase, and trypsin are immobilized on the surface of nanomaterials (Shan et al. 2017). These enzymes are capable of cleaving amide bonds within mucin glycoproteins in a very efficient manner, which makes coated nanomaterials much easier to penetrate the mucus.

However, the variability of mucosa and their properties challenges the design of polymeric NP-based systems. Fortunately, the rapid development of natural, synthetic, and semisynthetic polymers commercially available and the fact that many of them have been approved by regulatory agencies enable the design of polymeric material-based NPs based on the intrinsic feature of a specific mucosa.

13.4 Challenges and Future Perspectives on Nanobiomaterials

So far, a series of natural or synthetic material-based nanodrugs are playing an important role in clinic for disease therapy or in clinical trials. A number of examples of both FDA-approved products and those under clinical trials are designed by utilization of nanomaterials as a modifying agent for drug delivery. The versatility and diversity of potential biomaterials allows for a flexible design of nanocarriers with tailor-made properties based on the requirement in clinical application. The fact that some nanosystem, such as liposomes, albumin NPs, and polymeric micelles, are on the market and several biomaterial-based nanodrug delivery systems are in clinical trials indicated that potentially more nanobiomaterials can be used as a drug carrier in the near future. However, the key to transform nanotechnology from basic research into clinical products involves further understanding of the surface chemistry of nanomaterials and the interaction of these nanomaterials with drug and in vivo environment. To design smarter, functional nanomaterials with maximized therapeutic efficacy and good safety in drug delivery, several impediments must be addressed right now, such as ambiguous structure-function relationship of these nanomaterials in drug delivery system design and varied material characteristics such as molecular weight, shape, charge, composition, and complex architectures of nanocarriers. Another challenge posing as a major hindrance for nanomedicine

design is the large-scale production of nanomaterials for commercialization purpose under Good Manufacturing Practices (GMP) conditions. And the safety of their administration must be carefully considered. With recent draft guidelines published by the FDA on the importance of nanomaterials characterization for different regulated environments, biomaterial-based nanocarriers will show superior capacity in drug delivery with tunable properties in the near future.

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References

Akbar MU, Zia KM, Nazir A, Iqbal J, Ejaz SA, Akash MSH (2018) Pluronic-based mixed polymeric micelles enhance the therapeutic potential of curcumin. AAPS PharmSciTech 19:2719–2739

An FF, Zhang XH (2017) Strategies for preparing albumin-based nanoparticles for multifunctional bioimaging and drug delivery. Theranostics 7:3667–3689

Andrews GP, Laverty TP, Jones DS (2009) Mucoadhesive polymeric platforms for controlled drug delivery. Eur J Pharm Biopharm 71:505–518

Autio KA, Garcia JA, Alva AS, Hart LL, Milowsky MI, Posadas EM, Ryan CJ, Summa JM, Youssoufian H, Scher HI, Dreicer R (2016) A phase 2 study of BIND-014 (PSMA-targeted docetaxel nanoparticle) administered to patients with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 34

Aziz ZABA, Ahmad A, Mohd-Setapar SH, Hassan H, Lokhat D, Kamal MA, Ashraf GM (2017) Recent advances in drug delivery of polymeric Nano-micelles. Curr Drug Metab 18:16–29

Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR (2016) Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. Pharm Res 33:2373–2387

Bose RJ, Lee S-H, Park H (2016) Lipid-based surface engineering of PLGA nanoparticles for drug and gene delivery applications. Biomater Res 20:34–34

Bosselmann S, Williams RO (2012) Has nanotechnology led to improved therapeutic outcomes? Drug Dev Ind Pharm 38:158–170

Cabral H, Kataoka K (2014) Progress of drug-loaded polymeric micelles into clinical studies. J Control Release 190:465–476

Chang HI, Yeh MK (2012) Clinical development of liposome-based drugs: formulation, characterization, and therapeutic efficacy. Int J Nanomedicine 7:49–60

Dandamudi S, Campbell RB (2007) Development and characterization of magnetic cationic liposomes for targeting tumor microvasculature. BBA-Biomembranes 1768:427–438

das Neves J, Sarmento B (2018) Technological strategies to overcome the mucus barrier in mucosal drug delivery preface. Adv Drug Deliver Rev 124:1–2

de Sousa IP, Steiner C, Schmutzler M, Wilcox MD, Veldhuis GJ, Pearson JP, Huck CW, Salvenmoser W, Bernkop-Schnuerch A (2015) Mucus permeating carriers: formulation and characterization of highly densely charged nanoparticles. Eur J Pharm Biopharm 97:273–279

Dodov MG, Calis S, Crcarevska MS, Geskovski N, Petrovska V, Goracinova K (2009) Wheat germ agglutinin-conjugated chitosan-ca-alginate microparticles for local colon delivery of 5-FU: development and in vitro characterization. Int J Pharm 381:166–175

Dong W, Wang X, Liu C, Zhang X, Chen X, Kou Y, Mao S (2018) Chitosan based polymer-lipid hybrid nanoparticles for oral delivery of enoxaparin. Int J Pharm 547:499–505

Duennhaupt S, Barthelmes J, Thurner CC, Waldner C, Sakloetsakun D, Bernkop-Schnuerch A (2012) S-protected thiolated chitosan: synthesis and in vitro characterization. Carbohyd Polym 90:765–772

Elgadir MA, Uddin MS, Ferdosh S, Adam A, Chowdhury AJK, Sarker MZI (2015) Impact of chitosan composites and chitosan nanoparticle composites on various drug delivery systems: a review. J Food Drug Anal 23:619–629

Elzoghby AO, Samy WM, Elgindy NA (2012) Albumin-based nanoparticles as potential controlled release drug delivery systems. J Control Release 157:168–182

Guan J, Liu Q, Zhang X, Zhang Y, Chokshi R, Wu H, Mao S (2018) Alginate as a potential diphase solid dispersion carrier with enhanced drug dissolution and improved storage stability. Eur J Pharm Sci 114:346–355

Guo B, Ma PX (2014) Synthetic biodegradable functional polymers for tissue engineering: a brief review. Sci China Chem 57:490–500

Hallan SS, Kaur P, Kaur V, Mishra N, Vaidya B (2016) Lipid polymer hybrid as emerging tool in nanocarriers for oral drug delivery. Artif Cells Nanomed Biotechnol 44:334–349

Han J, Zhao D, Li D, Wang X, Jin Z, Zhao K (2018) Polymer-based nanomaterials and applications for vaccines and drugs. Polymers 10

Immordino ML, Dosio F, Cattel L (2006) Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. Int J Nanomedicine 1:297–315

Inoo K, Bando H, Tabata Y (2018) Enhanced survival and insulin secretion of insulinoma cell aggregates by incorporating gelatin hydrogel microspheres. Regen Ther 8:29–37

Janas C, Mostaphaoui Z, Schmiederer L, Bauer J, Wacker MG (2016) Novel polymeric micelles for drug delivery: material characterization and formulation screening. Int J Pharm 509:197–207

Jeon YO, Lee JS, Lee HG (2016) Improving solubility, stability, and cellular uptake of resveratrol by nanoencapsulation with chitosan and gamma-poly (glutamic acid). Colloids Surf B Biointerfaces 147:224–233

Jespersen GR, Matthiesen F, Pedersen AK, Andersen HS, Kirsebom H, Nielsen AL (2014) A thiol functionalized cryogel as a solid phase for selective reduction of a cysteine residue in a recombinant human growth hormone variant. J Biotechnol 173:76–85

Jia H-J, Jia F-Y, Zhu B-J, Zhang W-P (2017) Preparation and characterization of glycyrrhetinic-acid loaded PEG-modified liposome based on PEG-7 glyceryl cocoate. Eur J Lipid Sci Tech 119

Jiao Y, Pang X, Zhai G (2016) Advances in hyaluronic acid-based drug delivery systems. Curr Drug Targets 17:720–730

Jones M-C (2015) Thinking outside the 'Block': alternative polymer compositions for micellar drug delivery. Curr Top Med Chem 15:2254–2266

Kapoor DN, Bhatia A, Kaur R, Sharma R, Kaur G, Dhawan S (2015) PLGA: a unique polymer for drug delivery. Ther Deliv 6:41–58

Kausar A (2017) Scientific potential of chitosan blending with different polymeric materials: a review. J Plast Film Sheet 33:384–412

Kocisova E, Antalik A, Prochazka M (2013) Drop coating deposition Raman spectroscopy of liposomes: role of cholesterol. Chem Phys Lipids 172:1–5

Larsen MT, Kuhlmann M, Hvam ML, Howard KA (2016) Albumin-based drug delivery: harnessing nature to cure disease. Mol Cell Ther 4:3

Lee YH, Park HI, Choi JS (2016) Novel glycol chitosan-based polymeric gene carrier synthesized by a Michael addition reaction with low molecular weight polyethylenimine. Carbohyd Polym 137:669–677

Li L, Zhang X, Gu X, Mao S (2015) Applications of natural polymeric materials in solid Oral modified-release dosage forms. Curr Pharm Des 21:5854–5867

Liu C, Kou Y, Zhang X, Cheng H, Chen X, Mao S (2018) Strategies and industrial perspectives to improve oral absorption of biological macromolecules. Expert Opin Drug Deliv 15:223–233

Liu C, Kou Y, Zhang X, Dong W, Cheng H, Mao S (2019) Enhanced oral insulin delivery via surface hydrophilic modification of chitosan copolymer based self-assembly polyelectrolyte nanocomplex. Int J Pharm 554:36–47

Makadia HK, Siegel SJ (2011) Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers 3:1377–1397

Makhlof A, Werle M, Takeuchi H (2008) Mucoadhesive drug carriers and polymers for effective drug delivery. J Drug Delivery Sci Technol 18:375–386
Mao S, Sun W, Kissel T (2010) Chitosan-based formulations for delivery of DNA and siRNA. Adv Drug Deliv Rev 62:12–27
Mariam J, Sivakami S, Dongre PM (2016) Albumin corona on nanoparticles - a strategic approach in drug delivery. Drug Deliv 23:2668–2676
Netsomboon K, Bernkop-Schnurch A (2016) Mucoadhesive vs. mucopenetrating particulate drug delivery. Eur J Pharm Biopharm 98:76–89
Ogunleye A, Bhat A, Irorere VU, Hill D, Williams C, Radecka I (2015) Poly-gamma-glutamic acid: production, properties and applications. Microbiology 161:1–17
Ohya Y, Takeda S, Shibata Y, Ouchi T, Kano A, Iwata T, Mochizuki S, Taniwaki Y, Maruyama A (2011) Evaluation of polyanion-coated biodegradable polymeric micelles as drug delivery vehicles. J Control Release 155:104–110
Ossipov DA (2010) Nanostructured hyaluronic acid-based materials for active delivery to cancer. Expert Opin Drug Deliv 7:681–703
Otto F, Brezesinski G, van Hoogevest P, Neubert RHH (2018) Physicochemical characterization of natural phospholipid excipients with varying PC content. Colloid Surface A 558:291–296
Pandita D, Kumar S, Lather V (2015) Hybrid poly(lactic-co-glycolic acid) nanoparticles: design and delivery prospectives. Drug Discov Today 20:95–104
Park C-K, Kang H-W, Kim T-O, Kim E-Y, Ban H-J, Oh I-J, Kwon Y-S, Lim S-C, Yoon B-K, Choi Y-D, Kim Y-I, Ki H-S, Kim Y-C, Kim K-S (2010) A case of ischemic colitis associated with paclitaxel loaded polymeric micelle (Genexol-PM®) chemotherapy. Tuberc Respir Dis 69:115–118
Pepic I, Lovric J, Filipovic-Grcic J (2013) How do polymeric micelles cross epithelial barriers? Eur J Pharm Sci 50:42–55
Qiu L, Zheng C, Jin Y, Zhu K (2007) Polymeric micelles as nanocarriers for drug delivery. Expert Opin Ther Pat 17:819–830
Rao NV, Yoon HY, Han HS, Ko H, Son S, Lee M, Lee H, Jo D-G, Kang YM, Park JH (2016) Recent developments in hyaluronic acid-based nanomedicine for targeted cancer treatment. Expert Opin Drug Deliv 13:239–252
Sakai-Kato K, Nanjo K, Kawanishi T, Okuda H, Goda Y (2015) Effects of lipid composition on the properties of doxorubicin-loaded liposomes. Ther Deliv 6:785–794
Samprasit W, Kaomongkolgit R, Sukma M, Rojanarata T, Ngawhirunpat T, Opanasopit P (2015) Mucoadhesive electrospun chitosan-based nanofibre mats for dental caries prevention. Carbohyd Polym 117:933–940
Sayin B, Somavarapu S, Li XW, Thanou M, Sesardic D, Alpar HO, Senel S (2008) Mono-N-carboxymethyl chitosan (MCC) and N-trimethyl chitosan (TMC) nanoparticles for non-invasive vaccine delivery. Int J Pharm 363:139–148
Schoener CA, Peppas NA (2013) pH-responsive hydrogels containing PMMA nanoparticles: an analysis of controlled release of a chemotherapeutic conjugate and transport properties. J Biomat Sci Polym E 24:1027–1040
Shan W, Cui Y, Liu M, Wu L, Xiang Y, Guo Q, Zhang Z, Huang Y (2017) Systematic evaluation of the toxicity and biodistribution of virus mimicking mucus-penetrating DLPC-NPs as oral drug delivery system. Int J Pharm 530:89–98
Shi C, Sun Y, Wu H, Zhu C, Wei G, Li J, Chan T, Ouyang D, Mao S (2016a) Exploring the effect of hydrophilic and hydrophobic structure of grafted polymeric micelles on drug loading. Int J Pharm 512:282–291
Shi D, Ran M, Zhang L, Huang H, Li X, Chen M, Akashi M (2016b) Fabrication of biobased polyelectrolyte capsules and their application for glucose-triggered insulin delivery. ACS Appl Mater Interfaces 8:13688–13697
Shiraishi K, Hamano M, Ma H, Kawano K, Maitani Y, Aoshi T, Ishii KJ, Yokoyama M (2013) Hydrophobic blocks of PEG-conjugates play a significant role in the accelerated blood clearance (ABC) phenomenon. J Control Release 165:183–190

Singh H, Sharma R, Joshi M, Garg T, Goyal AK, Rath G (2015) Transmucosal delivery of docetaxel by mucoadhesive polymeric nanofibers. Arti Cells Nanomed Biotechnol 43:263–269
Sleep D (2015) Albumin and its application in drug delivery. Expert Opin Drug Deliv 12:793–812
Socinski M (2006) Update on nanoparticle albumin-bound paclitaxel. Clin Adv Hematol Oncol 4:745–746
Song R, Murphy M, Li C, Ting K, Soo C, Zheng Z (2018) Current development of biodegradable polymeric materials for biomedical applications. Drug Des Devel Ther 12:3117–3145
Tagami T, Ozeki T (2017) Recent trends in clinical trials related to carrier-based drugs. J Pharm Sci 106:2219–2226
Tomkinson B, Bendele R, Giles FJ, Brown E, Gray A, Hart K, LeRay JD, Meyer D, Pelanne M, Emerson DL (2003) OSI-211, a novel liposomal topoisomerase I inhibitor, is active in SCID mouse models of human AML and ALL. Leukemia Res 27:1039–1050
Valle JW, Armstrong A, Newman C, Alakhov V, Pietrzynski G, Brewer J, Campbell S, Corrie P, Rowinsky EK, Ranson M (2011) A phase 2 study of SP1049C, doxorubicin in P-glycoprotein-targeting pluronics, in patients with advanced adenocarcinoma of the esophagus and gastro-esophageal junction. Invest New Drug 29:1029–1037
van Hoogevest P (2017) Review - An update on the use of oral phospholipid excipients. Eur J Pharm Sci 108:1–12
Vanic Z, Skalko-Basnet N (2014) Mucosal nanosystems for improved topical drug delivery: vaginal route of administration. J Drug Deliv Sci Technol 24:435–444
Wang X, Gu X, Wang H, Yang J, Mao S (2018) Enhanced delivery of doxorubicin to the liver through self-assembled nanoparticles formed via conjugation of glycyrrhetinic acid to the hydroxyl group of hyaluronic acid. Carbohydr Polym 195:170–179
Wu T, Li Y, Lee DS (2017) Chitosan-based composite hydrogels for biomedical applications. Macromol Res 25:480–488
Wu L, Shan W, Zhang Z, Huang Y (2018) Engineering nanomaterials to overcome the mucosal barrier by modulating surface properties. Adv Drug Deliver Rev 124:150–163
Xu Y, Kim C-S, Saylor DM, Koo D (2017) Polymer degradation and drug delivery in PLGA-based drug-polymer applications: a review of experiments and theories. J Biomed Mater Res Part B Appl Biomater 105:1692–1716
Yadav AK, Mishra P, Agrawal GP (2008) An insight on hyaluronic acid in drug targeting and drug delivery. J Drug Target 16:91–107
Yarmolenko PS, Zhao Y, Landon C, Spasojevic I, Yuan F, Needham D, Viglianti BL, Dewhirst MW (2010) Comparative effects of thermosensitive doxorubicin-containing liposomes and hyperthermia in human and murine tumours. Int J Hyperth 26:485–498
Yu M, Jambhrunkar S, Thorn P, Chen J, Gu W, Yu C (2013) Hyaluronic acid modified mesoporous silica nanoparticles for targeted drug delivery to CD44-overexpressing cancer cells. Nanoscale 5:178–183
Zahir-Jouzdani F, Wolf JD, Atyabi F, Bernkop-Schnuerch A (2018) In situ gelling and mucoadhesive polymers: why do they need each other? Expert Opin Drug Deliv 15:1007–1019
Zhang JA, Anyarambhatla G, Ma L, Ugwu S, Xuan T, Sardone T, Ahmad I (2005) Development and characterization of a novel Cremophor (R) EL free liposome-based paclitaxel (LEP-ETU) formulation. Eur J Pharm Biopharm 59:177–187
Zhang K, Tang X, Zhang J, Lu W, Lin X, Zhang Y, Tian B, Yang H, He H (2014) PEG-PLGA copolymers: their structure and structure-influenced drug delivery applications. J Control Release 183:77–86
Zhang Y, Mintzer E, Uhrich KE (2016) Synthesis and characterization of PEGylated bolaamphiphiles with enhanced retention in liposomes. J Colloid Interf Sci 482:19–26
Zhang X, Cheng H, Dong W, Zhang M, Liu Q, Wang X, Guan J, Wu H, Mao S (2018) Design and intestinal mucus penetration mechanism of core-shell nanocomplex. J Control Release 272:29–38
Zylberberg C, Matosevic S (2017) Bioengineered liposome-scaffold composites as therapeutic delivery systems. Ther Deliv 8:425–445