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Controlled Drug Release from Pharmaceutical Nanocarriers

Jinhyun Hannah Lee¹ and Yoon Yeo^{1,2,*}

¹College of Pharmacy and Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN 47907, USA

²Biomedical Research Institute, Korea Institute of Science and Technology, Hwarangno 14-gil 5, Seongbuk-gu, Seoul 136-791, Republic of Korea

Abstract

Nanocarriers providing spatiotemporal control of drug release contribute to reducing toxicity and improving therapeutic efficacy of a drug. On the other hand, nanocarriers face unique challenges in controlling drug release kinetics, due to the large surface area per volume ratio and the short diffusion distance. To develop nanocarriers with desirable release kinetics for target applications, it is important to understand the mechanisms by which a carrier retains and releases a drug, the effects of composition and morphology of the carrier on the drug release kinetics, and current techniques for preparation and modification of nanocarriers. This review provides an overview of drug release mechanisms and various nanocarriers with a specific emphasis on approaches to control the drug release kinetics.

Keywords

Nanocarriers; controlled release; drug delivery; drug release kinetics; drug release mechanisms

1. Introduction

Pharmaceutical nanotechnology has gained increasing interest in the past few decades as promising therapeutic and imaging tools. Based on the global market growth by 2011, a market research organization predicted that the global sales of nanomedicine would increase from \$50.1 billion in 2011 to \$96.9 billion in 2016 with a compound annual growth rate of 14.1%, where products for central nerve system disorders and cancer treatment account for 43.8% of the total sales (Evers, 2012).

Advantages of nanotechnology-based drug carriers (nanocarriers) include the small sizes compatible with intravenous injection and the large surface area per unit volume amenable to modification for targeted delivery (Langer, 1998; Petros and DeSimone, 2010; Shi et al.,

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*Corresponding author: Yoon Yeo, Ph.D., Phone: 765.496.9608, Fax: 765.494.6545, yyeo@purdue.edu.

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2010; Torchilin, 2012). Nanocarriers that can deliver drugs in a spatiotemporally controlled manner can potentially enhance therapeutic efficacy of the drugs, reduce their systemic side effects, and improve patient's adherence to regimen by reducing the dose and administration frequency. To achieve this goal, various nanocarriers have been developed with unique compositions, morphologies, and surface properties (Chan et al., 2010; Gao et al., 2008; Huschka et al., 2011; Ohya, 2013; Siegel, 2012; Slowing et al., 2008).

For spatial control of drug delivery, nanocarriers are designed to selectively localize and accumulate in tumors by taking advantage of abnormal vasculature structure of solid tumors, known as the enhanced permeability and retention (EPR) effect (Matsumura and Maeda, 1986). Many solid tumors are known to develop leaky capillary walls, through which drug-loaded nanocarriers can extravasate and access tumors. Since nanocarriers do not readily traverse normal endothelium, the EPR effect enables the nanocarriers to reach tumors more selectively than free drugs, which translate to relatively low toxicity in normal tissues and high therapeutic efficacy in tumors (Acharya and Sahoo, 2011; Maeda et al., 2000). To take advantage of the EPR effect, nanocarriers should remain stable in blood stream resisting aggregation and premature drug leakage and avoid removal by renal filtration and the organs of the reticuloendothelial system (RES) (Ohya, 2013). For this reason, particles smaller than 10 nm are barely considered systemic drug carriers as they are subject to clearance by the kidney excretion (Petros and DeSimone, 2010). Particles larger than 10 nm are more appropriate for drug delivery; however, particles of this size can be eliminated by the RES. Therefore, nanocarrier surface is typically modified with polyethylene glycol (PEG), or "PEGylated", which forms a hydrated layer and prevents opsonization. It is shown that PEGylated nanocarriers can have a longer circulation time than nanocarriers without PEGylation, attaining a greater chance to accumulate in tumors (Gref et al., 1994; Moghimi et al., 2001; Owens and Peppas, 2006; Torchilin, 2005). Moreover, PEGylation of nanocarriers reduces their accumulation in the RES (Kojima et al., 2010). To further enhance delivery of nanocarriers to tumors beyond the level achieved by the EPR effect, the surface of nanocarriers is additionally functionalized with ligands that can bind to specific receptors overexpressed in pathological tissues (Byrne et al., 2008; Ghosh et al., 2008; Sutton et al., 2007; Webster et al., 2013; Yoo and Park, 2004).

Temporal control of drug release from carriers aims to maintain drug concentration in blood or target tissues at the efficacious level. Since the first report of sustained drug release from a polymeric device in 1964 (Folkman and Long, 1964), temporal control of drug release from polymeric particles has been extensively studied. Several mathematical models account for drug releases kinetics from drug delivery systems, such as zero order model, first order model, Higuchi model, Hixson-Crowell model, Korsmeyer-Peppas model, and Regression model (Dash, 2010; Hayashi et al., 2005). Various mechanisms drive drug release from the carriers. For example, drug release kinetics can be controlled by diffusion of a drug molecule through a carrier matrix or a barrier surrounding the matrix. Alternatively, degradation or swelling of the carrier matrix and the cleavage of drug-polymer linkage can control the drug release rate from the carrier (Bajpai et al., 2008; Freiberg and Zhu, 2004).

Several nanocarriers have been developed to maximize therapeutic efficacy of a drug (Fig. 1). Although the spatial control of nanocarrier-based drug delivery is widely reviewed in

recent articles (Acharya and Sahoo, 2011; Brannon-Peppas and Blanchette, 2012; Lu and Low, 2012; Maeda et al., 2013; Xu et al., 2013), the significance of drug release control from nanocarriers is often overlooked partly due to the well-established literature of drug delivery systems with larger dimensions. However, nanocarriers face a unique challenge in temporal control of drug release because of the large surface area per volume ratio and the short diffusion distance. This review focuses on various efforts to control the drug release kinetics from different types of nanocarriers.

2. Drug Release Mechanisms

One of the main goals of release kinetics control is to maintain the drug level in blood within the therapeutic window, between the minimum effective concentration (MEC) and the minimum toxic concentration (MTC) (Siegel, 2012). When a drug is administered as a single large dose, the drug level is elevated above MTC, causing toxic side effects, and then rapidly drops below the MEC (Fig. 2). Multiple dosing with a certain interval may reduce the fluctuation of drug levels in plasma but can face patient non-compliance issues. Therefore, it is desirable to develop drug carriers that provide sustained or controlled release of a drug with a low dosing frequency. For this purpose, a constant drug release rate (zero-order drug release profile) is frequently pursued (Bajpai et al., 2008; Siegel, 2012). On the other hand, an excessive attenuation in drug release can compromise therapeutic effectiveness of a system; therefore, pulsatile or stimuli-responsive drug release is also explored to achieve timely drug release (Abouelmagd et al.; Ehrbar, 2008; Mura, 2013).

Drug release from carriers is influenced by several factors including the composition (drug, polymer, and additives), their ratio, physical and/or chemical interactions among the components, and the preparation methods. According to the mechanism by which a drug escapes a carrier, drug release can be classified into four categories (diffusion, solvent, chemical reaction, and stimuli controlled release) (Langer and Peppas, 1983; Siegel, 2012), as briefly summarized below (Fig. 3).

2.1 Diffusion-controlled release

Diffusion-controlled drug release is shown in a capsule-type reservoir system, in which a drug is dissolved or dispersed in a core surrounded by polymeric membrane (Cauchetier et al., 2003) (Fig. 1a). Drug diffusion is driven by the difference in its concentration across the membrane (Crank, 1975). Here, the drug first dissolves in the core then diffuses through the membrane. Matrix-type nanospheres (Fig. 1b), where drug molecules are dispersed throughout the polymer matrix, also show a diffusion-controlled release profile. In the matrix-type systems, there is no membrane that serves as a diffusion barrier; therefore, this system usually shows high initial release, followed by a decreasing release rate with the increasing diffusion distance for drug molecules located interior of the carrier.

2.2 Solvent-controlled release

Solvent transport into a drug carrier can influence the drug release behavior from the carrier. The solvent-controlled release includes osmosis-controlled release and swelling-controlled release (Langer and Peppas, 1983). Osmosis-controlled release occurs in a carrier covered

with a semi-permeable polymeric membrane, through which water can flow from outside of the carrier (with a low drug concentration) to the drug-loaded core (with a high drug concentration). This mechanism results in a zero-order release profile as long as a constant concentration gradient is maintained across the membrane (Herrlich et al., 2012).

When glassy hydrophilic polymeric systems are placed in an aqueous solution including body fluids, water diffuses into the system. The water uptake results in the swelling of the polymeric particles followed by drug release (swelling-controlled release). The drug release rate is determined by the diffusion rate of water and the chain relaxation rate of polymers (Peppas et al., 2000). The swelling-controlled systems consist of polymeric materials with three dimensionally crosslinked network such as hydrogels, where the mesh size plays a central role in controlling the drug release behavior (Lin and Metters, 2006; Peppas et al., 2000). Drug release from hydrogels can be analyzed by the semi-empirical Peppas model ($M_t/M_\infty = kt^n$), where M_t and M_∞ are the absolute cumulative amount of drug released at time t and infinite time, respectively, k is a constant, and n is the release exponent. This equation allows for the determination of the release mechanism (e.g., Fickian or non-Fickian diffusion) (Hayashi et al., 2005; Korsmeyer et al., 1983; Peppas et al., 2000; Ritger and Peppas, 1987; Siepmann and Peppas, 2001). The swelling-controlled systems may achieve a zero-order drug release, depending on the initial drug distribution in the system (Lee, 1984) or polymer composition (Kaity et al., 2013).

2.3 Degradation-controlled release

Drug carriers comprising biodegradable polymers such as polyesters, polyamides, poly(amino acids), and polysaccharides release drugs via hydrolytic and/or enzymatic degradation of ester, amide, and hydrazone bonds in their backbones (Lee et al., 2011; Prabakaran et al., 2009; Yoo and Park, 2001). Matrices made of polymers like poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), and polycaprolactone (PCL) undergo bulk degradation, resulting in simultaneous degradation of entire matrices. On the other hand, those made of polyanhydrides and poly(orthoesters) typically erode from the surface into the core (surface degradation) as the polymer degradation occurs faster than water diffusion into the matrix (Burkersroda et al., 2002; Middleton and Tipton, 2000). However, in a small-dimension matrix like NPs, where the distance of water diffusion is short and the domain size of crystallization is restricted, the polymer degradation is substantially accelerated, and these polymers do not necessarily follow the typical surface erosion behavior but show a sign of bulk degradation (constant particle size during polymer degradation) (Lee and Chu, 2008).

Drug release kinetics is determined by the degradation rate of polymers, which depends on their molecular weight, end groups, monomer composition, and crystallinity (Fredenberg et al., 2011). Biodegradable polymeric systems are preferable, because they are disintegrated into compounds that are readily removed from the body without causing long-term side effects. From drug-polymer conjugates, a drug is released from the carrier via hydrolytic or enzymatic cleavage of the linkage between the drug and the polymer. The rate of cleavage controls the drug release kinetics (Kopeček, 1984). Enzymatically cleavable drug-polymer

conjugates may be used for target-specific drug delivery, if the enzyme is concentrated in target tissues (Medina et al., 2013).

2.4 Stimuli-controlled release

Drug release from stimuli-responsive nanocarriers is controlled by internal or external stimuli such as temperature, pH, ionic strength, sound, and electric or magnetic fields (Abouelmagd et al.). As it is possible to localize the stimuli, these carriers have been explored for target-specific drug delivery. For example, capitalizing on weakly acidic pH of many solid tumors (Chang W. Song, 2006), nanocarriers with pH-sensitive linkers have been developed for tumor-specific drug delivery (Min et al., 2010; Talelli et al., 2010). pH-sensitive carriers are also developed to increase the contrast between intracellular and extracellular drug release (Lai et al., 2007; Talelli et al., 2010; Yuba et al., 2013). In thermosensitive drug carriers, drug release is caused by temperature-induced phase transition of the polymer (Chang et al., 2008; Li et al., 2011).

3. Drug Release Control in Nanocarriers

In general, more than one mechanism contributes to the drug release from nanocarriers, although one may be more influential than the other. For instance, in drug-loaded nanogels coated with a polymer membrane, drug release is controlled by swelling as well as diffusion through the membrane (Tan et al., 2008; Torres et al., 2011). Nanocarriers are modified in various ways to achieve further control over the drug release kinetics, as described in the following section.

3.1 Liposomes

Liposomes were first discovered by Bangham and coworkers in 1960s (Bangham, 1962; Bangham et al., 1965) and have widely been used as a drug carrier since then. Liposomes are vesicles made of lipid bilayers in aqueous solution (Fig. 1c), where water-soluble drugs are encapsulated in the hydrophilic compartment surrounded by lipid bilayers and hydrophobic drugs in the lipid layer. Since Doxil, a PEGylated liposome with doxorubicin (DOX), was approved by the US Food and Drug Administration (FDA) in 1995, more than ten liposomal drugs including Myocet (non-PEGylated liposome carrying DOX) and DaunoXome (daunorubicin-loaded liposome) have been approved for clinical uses (Torchilin, 2005). Liposome surface is typically modified with PEG to prolong its circulation half-life, thereby taking advantage of the EPR effect (Torchilin, 2005). For the same purpose as PEG, hydrophilic polymers such as poly(N-vinyl pyrrolidone) (PVP), poly(vinyl alcohol) (PVA), polyoxazoline (Pox), hyperbranched polyglycerol, or zwitterionic polymers are also used (Cao et al., 2012; Nag and Awasthi, 2013).

A liposome system containing a poly(acrylic acid) (PAA) hydrogel core ("lipogel") was developed for sustained release of a geldanamycin-tertiary amine derivative (17-DMAPG) (Wang et al., 2013). Sustained drug release was achieved via electrostatic interactions between a cationic drug (17-DMAPG) and anionic gel and a barrier function of the lipid bilayer (Wang et al., 2013). For drug delivery to infected and inflamed tissues or tumor sites with acidic pHs, pH-sensitive liposomes are explored as drug carriers. A pH-sensitive

liposome system was prepared by modifying the surface of liposomes with 3-methylglutaryl-terminated poly(glycidol) (MGLu-PG) (Yuba et al., 2013). The pH sensitivity came from carboxylates on the MGLu-termini, which destabilized liposomes as they were protonated in acidic pH (Yuba et al., 2013). Compared to the unmodified liposome, MGLu-PG modified liposomes showed pH-dependent release profiles with a relatively high release of a model compound at pH 5.5 (Yuba et al., 2013). In another pH-sensitive liposomes, Gadoteridol (paramagnetic compound) was encapsulated to visualize pH-triggered release of payloads using magnetic resonance imaging (Torres et al., 2011). The liposomes made of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine (POPE) and D- α -tocopherol-hemisuccinate (THS) were destabilized at pH 5.5, due to the protonation of THS followed by vesicle aggregation, and released Gadoteridol, as evidenced by the increased relaxivity (Torres et al., 2011). Interestingly, the pH-sensitivity disappeared with the addition of PEG on the surface, as the vesicle aggregation was prevented (Torres et al., 2011). Difference in redox potential between tumors and normal tissues is also used as a stimulus to trigger the drug release from liposomes (Ong et al., 2008). Here, liposomes are made with quinone-dioleoyl phosphatidylethanolamine (Q-DOPE) lipids, which are reduced by quinone reductases, enzymes abundant in tumor tissues, and undergo cleavage into DOPE that does not maintain a stable liposomal structure (Ong et al., 2008).

3.2 Polymeric micelles

Polymeric micelles (PMs) are formed by self-assembly of amphiphilic block copolymers, making up a core-shell structure. PMs are used as drug carriers due to the simple preparation methods, narrow size distribution with a diameter up to 100 nm, and the ability to solubilize hydrophobic drugs (Kwon and Okano, 1996). PMs are typically composed of hydrophobic segments forming an inner core loading hydrophobic drugs and hydrophilic segments forming an outer shell in an aqueous solvent (Fig. 1d). In contrast, PMs formed in organic solvents have a hydrophobic shell and a hydrophilic core, referred to as reverse polymeric micelles (RPMs), suitable for the encapsulation of hydrophilic drugs (Jones et al., 2008).

Poly(ethylene glycol) (PEG), PVP, and poly (N-isopropyl acrylamide) (PNIPAAm) are representative hydrophilic segments, whereas biodegradable polymers such as PLGA, PCL, poly(L-aspartic acid) and their derivatives are widely used as hydrophobic segments of PMs. Genexol-PM, approved in South Korea, is a paclitaxel (PTX) encapsulated in a PEG-poly(L-lactic acid) PM system (Kim et al., 2001). PEG-poly(aspartic acid) PMs loaded with DOX or PTX (Nishiyama et al., 1998) and PEG-poly(glutamic acid) PMs with cisplatin or 7-ethyl 10-hydroxy camptothecin (SN-38) (Nishiyama et al., 2003) are under investigation for clinical uses.

Drug release from PMs is dependent on the interactions between drugs and micellar cores, such as hydrophobic and electrostatic interactions or hydrogen bonding; therefore, molecular weight and hydrophobicity of the hydrophobic segments of amphiphilic block copolymers play an important role (Pierri and Avgoustakis, 2005; Xiangyang et al., 2007). Drug release can be extended by conjugating a drug to the hydrophobic segment of PM via a covalent linker that is cleaved over time. For example, in vitro DOX release from DOX-conjugated PLGA-PEG PMs was 4 times longer than that of DOX physically entrapped in PLGA-PEG

PMs (Yoo and Park, 2001). In another example, DOX was conjugated via hydrazone linkage to amphiphilic hyperbranched block copolymer, consisting of hyperbranched aliphatic polyester Boltorn[®] H40 core, poly(L-aspartate) as a hydrophobic inner shell, and PEG as an outer arm (Prabaharan et al., 2009). DOX release from the hyperbranched PMs occurred as the hydrazone linkage between DOX and poly(L-aspartate) was hydrolyzed in an acidic condition (Prabaharan et al., 2009). In a PEG–poly(glutamic acid) block copolymer PM containing cisplatin (*cis*-dichlorodiammineplatinum(II)), metal coordination bond between platinum and carboxylic group of poly(glutamic acid) controls the release of platinum (Nishiyama et al., 2003). More than one type of molecular interaction may be employed in controlling the release of active ingredients. In one example, siRNA was conjugated to PLGA via disulfide bond forming a micellar structure, where PLGA was a core and siRNA a shell (Prabaharan et al., 2009). The anionic micelles were covered with a cationic polyethyleneimine (PEI) via ionic complexation. Here, siRNA release from the micelles depended on the intracellular cleavage of disulfide bond as well as the dissociation the complex of PEI and siRNA (Lee et al., 2011).

In addition to intracellular conditions like pH or reductive potential, external stimuli such as heat, light, sound, electric or magnetic fields are used for controlling drug release (Prabaharan et al., 2009; Talelli et al., 2010). PMs made of triblock PCL-PNIPAAm-PCL copolymers show thermal responses due to PNIPAAm, hydrophilic at a temperature below the lower critical solution temperature (LCST) and hydrophobic above the LCST. When heat is locally applied to increase the temperature above the LCST, the triblock copolymer loses amphiphilicity, and the encapsulated drug is released as the micelle structure is destroyed (Chang et al., 2008). The triggering temperature can be controlled by the composition and ratio of building blocks (Rapoport, 2007). Ultrasound is also used as a way of triggering drug release from PMs (Husseini et al., 2000). The ultrasound-responsive PM is made of Pluronic P-105, a block copolymer of PEG-*b*-poly(propylene glycol)-*b*-PEG, and the degree of drug release from the PMs depends on the frequency, power density, pulse density, and inter-pulse intervals of the ultrasound (Husseini et al., 2000).

One of the main challenges in PM development is their instability in physiological fluid. Chen et al reported that PMs made of PEG-PDLLA block copolymer destabilized quickly upon the contact with hydrophobic components in cell membrane or blood stream and released the encapsulated dyes immaturely (Chen et al., 2008a; Chen et al., 2008b). To overcome this problem, the core or the shell of PMs is stabilized via covalent or electrostatic interactions. For covalent crosslinking of DOX to the core of PMs, DOX was conjugate to methacrylamide via a hydrazone linker (Talelli et al., 2010). This DOX-methacrylamide derivative was loaded in PMs based on PEG and poly(N-(2-hydroxypropyl) methacrylamide (HPMA)-lactate block copolymers and copolymerized with the methacrylate groups of the PM cores, resulting in core-crosslinked micelles with covalently linked DOX (Talelli et al., 2010). Due to the pH-sensitivity of the hydrazone linker, DOX was released from the PMs in acidic environment (Talelli et al., 2010). Similarly, a thermosensitive PM system based on poly(methyl methacrylate)-*b*-PNIPAAm-co-N-acryloxysuccinimide (PMMA-*b*-P(NIPAAm-co-NAS)) block copolymer was stabilized by crosslinking the shell part with ethylenediamine as a di-functional crosslinker (Chang et al., 2011). The shell-stabilized PMs

showed greater stability than uncrosslinked ones even at 40°C and delayed the drug release (Chang et al., 2011). Alternatively, PMs were stabilized via the formation of mineralized midlayer in the PMs. Lee et al. reported a PM system based on PEG-*b*-poly(L-aspartic acid)-*b*-poly(L-phenylalanine). Poly(L-aspartic acid) (pAsp) was introduced to form an anionic middle layer, which attracted Ca²⁺ ions that formed water-insoluble calcium phosphate in the presence of phosphate ions (Lee et al., 2010). The mineralization suppressed the drug release in the extracellular environment with neutral pH and relatively high CaCl₂ concentration, but intracellular drug release was comparable to that of destabilized PMs (Lee et al., 2010).

3.3 Polymeric nanoparticles

Polymeric nanoparticles (PNPs) refer to polymeric particles in the form of either capsules or solid spheres (Figs. 1a and 1b). A drug is typically incorporated in the polymer matrix, and its release is driven by polymer degradation and/or drug diffusion. Polymers used for this application include natural polymers such as albumin, dextran, hyaluronate, and chitosan and synthetic polymers such as PLGA, PLA, PCL, PEG, PVA, poly(cyanoacrylate) (PCA), poly(N-(2-hydroxypropyl) methacrylamide) (PHPMA), and PEI. PNPs may be prepared by various methods such as precipitation, emulsification, coacervation, and layer-by-layer methods (Mora-Huertas et al., 2010).

Drug release kinetics is affected by carrier structures. PLGA nanospheres loaded with PTX were prepared by adding an organic solution of PLGA and PTX in acetone to an aqueous poloxamer 188 solution (Fonseca et al., 2002). PTX release showed a typical biphasic pattern characterized by a fast initial release during the first 24h followed by a slower and continuous release over the next 9 days (Fonseca et al., 2002). On the other hand, nanocapsules with polymeric membrane showed low initial burst release. Nanocapsules were formed by interfacial deposition of hydrophobic polymers such as PCL, PLA and PLGA, around droplets of Atovaquone (ATV) solution in benzyl benzoate, which resulted in approximately 20 nm thick polymeric shell (Cauchetier et al., 2003). ATV release varied with the type of the polymer: there was no release from PCL NPs for 4 months, 25.9 % of ATV from PLA NPs in 4 months, and 18.9% from PLGA NPs in 3 months, indicating that ATV release rate depended on polymer degradation kinetics (Cauchetier et al., 2003). A combination of nanospheres and nanocapsules is also used for drug release control. Docetaxel (DTX) was loaded in a PLGA NP, surrounded by PEGylated lipids (Chan et al., 2009). DTX release was extended as the lipid/polymer mass ratio increased. Here, the lipid monolayer acted as a barrier for drug diffusion. Molecular weight of PLGA had no effect on drug release kinetics, indicating that the drug release is mainly driven by diffusion (Chan et al., 2009). In another example, polymeric multilayers were combined with liposomes to achieve simultaneous delivery of siRNA and DOX. Layer-by-layer films consisting of anionic siRNA and cationic poly-L-arginine were formed atop a DOX-loaded liposome (Deng et al., 2013). The coated liposome delivered DOX and siRNA targeting multidrug resistance protein-1 to tumor, enhancing in vivo DOX efficacy by 8 folds compared to the saline-treated group (Deng et al., 2013).

Drug release from PNPs may be extended by placing the NPs in hydrogel matrix. For example, PLGA NPs loaded with dexamethasone (DEX), showing 60% DEX release in the first 2 days, showed 20% release during the first day followed by sustained release over 9 days when entrapped in the hydrogels (Kim and Martin, 2006). The sustained release is attributable to the formation of molecular aggregates of the released DEX, which has a limited mobility in the hydrogel (Kim and Martin, 2006). Drugs are covalently conjugated to polymers to further delay drug release from PNPs (Khandare and Minko, 2006; Pasut and Veronese, 2007). The release behavior of drugs conjugated to carrier polymers is determined by the rates of polymer degradation and drug-polymer dissociation. For example, PTX, camptothecin (CPT), or DTX were conjugated to PLA via drug-initiated polymerization in the presence of a metal catalyst (Tong and Cheng, 2008). NPs were formed as a self-assembly ('nanoprecipitation') of the drug-polymer conjugates. Drug release from the nanoprecipitates occurred as the ester bonds between the drug and PLA hydrolyzed. Accordingly, the drug release rate was better controlled (60% release of PTX for 4 days) without distinct initial burst release, as compared to PLA NPs physically entrapping a drug (82% release for 1 day) (Tong and Cheng, 2008).

3.4 Nanogels

Nanogels (hydrogel NPs) are three dimensionally crosslinked structures of hydrophilic polymers in a nanometer scale (Fig. 1e). Drug release from a nanogel is controlled by swelling, degradation, and diffusion, which depend on the network size, density and composition of the gel. Drug release from a covalently crosslinked nanogel is controlled by the gel degradation, whereas physically crosslinked structures depend on dissociation of the components. When a drug is covalently bound to polymer chains, enzymatic or hydrolytic cleavage of drug molecules from the chain plays an additional role in determining the release kinetics. For the physically bound drugs, there is the dissociation step of the physical bonds between drugs and carrier molecules. Nanogels offer a chemical flexibility to accommodate physical stimuli such as temperature, light, and electric (or magnetic) fields and chemical stimuli such as pH, ionic strength, and enzyme for stimuli-controlled drug release (Hamidi et al., 2008; Zha et al., 2011).

Chitin nanogels loaded with DOX show an example of pH-sensitive drug release. At acidic pH, where chitin was partially protonated and thus swelled, DOX was released to a greater extent than at neutral pH (Jayakumar et al., 2012). A hybrid nanogel comprising a bimetallic nanoparticle (Ag-Au) core and PEG-based (2-(2-methoxyethoxy) ethyl methacrylate) hydrogel shell showed a thermo-responsive drug release (Wu et al., 2010). Temozolomide (TMZ) was loaded in the shell via hydrogen bonding, and its release was induced by endogenous local hyperthermia or heat generated by near-infrared irradiation of Ag-Au core. Here, the increasing temperature induced drug release by causing a gradual transition of PEG network from hydrophilic to hydrophobic and thereby disrupting the hydrogen bond between the gel and TMZ. Moreover, gel collapse and increased drug mobility at high temperature further enhanced drug release (Wu et al., 2010). Thermo-responsive release of TMZ from the hybrid nanogels followed the empirical Peppas model (Siepmann and Peppas, 2012).

The surface of nanogels is modified to further control the drug release. DOX-loaded polysulfide nanogels were modified with glucose oxidase (GOx)-Pluronic F-127 conjugates on the surface to provide glucose-sensitive drug release (Rehor et al., 2005). In the presence of glucose, GOx on polysulfide nanogels triggered the oxidation of sulfide by producing hydrogen peroxide as a byproduct, which would cause nanogel swelling followed by drug release (Rehor et al., 2005). In another example, drug release from methylacrylic acid-ethyl acrylate (MMA-EA) nanogels was controlled by layer-by-layer surface coating with cationic poly(allylamine hydrochloride) (PAH) and anionic poly(sodium 4-styrenesulfonate) (PSS) (Tan et al., 2008). Each layer of polyelectrolyte added 2 nm thick layer, which limited swelling of nanogels and drug permeability, hence reducing the initial burst release (Tan et al., 2008).

Nanogels can be designed to respond to multiple stimuli for a greater control of the drug release (Morimoto et al., 2008; Qiao et al., 2011). PNIPAM-*g*-polysaccharides with thiol end groups produced nanogels responsive to both temperature and redox conditions (Morimoto et al., 2008). The resulting nanogels shrunk upon heating above LCST and swelled back when treated with a reducing agent, providing an opportunity to control drug release via local hyperthermia and intracellular particle uptake (Morimoto et al., 2008). A nanogel system made by the miniemulsion copolymerization of monomethyl oligo(ethylene glycol) acrylate (OEGA) and an ortho ester-containing acrylic monomer, 2-(5,5-dimethyl-1,3-dioxan-2-yloxy) ethyl acrylate (DMDEA), with bis(2-acryloyloxyethyl) disulfide (BADs) as a crosslinker, showed swelling and deswelling behaviors according to changes in temperature, pH, and redox potential (Qiao et al., 2011). Here, temperature increase caused shrinkage of the gel (i.e., formation of hydrophobic microdomains) and encapsulation of hydrophobic compounds, whereas the drug release was accelerated by acid-triggered hydrolysis and degradation induced by a reducing agent (Qiao et al., 2011).

3.5 Dendrimers

Dendrimers are natural and synthetic polymers with a central structure labeled as “the core”, from which branches of other groups called “dendrons” grow through various reactions (Fig. 1f). The continuous reaction produces multiple layers of branches called “generations”, resulting in dendrimers with different sizes, shapes, and functionalities. Drug molecules may be covalently conjugated to the end groups of a dendrimer or entrapped inside the core via hydrogen bonding, hydrophobic linkage, or electrostatic interactions (Hughes, 2005). The number of generations influences the drug loading capacity: A relatively high generation number provides more space for guest drugs and has a larger number of functional groups on the surface for drug conjugation. Dendrimers used as a drug carrier are created with polymers such as poly(amidoamine) (PAMAMs), polyamine, polypeptide, polyesters, PEI, PEG, or carbohydrates (Menjoge et al., 2010; Turnbull and Stoddart, 2002). PAMAM is frequently used for making dendrimer carriers, due to the high density of function groups (amine groups) on the surface. In addition, its cationic charges enable the delivery of nucleic acids.

Drug release from dendrimers depends on the type of interactions between a drug and a dendrimer. A generation 4.5 (G4.5) PAMAM dendrimer with carboxylate terminal groups

was used for the delivery of platinum compounds (Howell and Fan, 2010). Diaquo intermediates of (1,2-diaminocyclohexane)platinum(II) [(DACH)Pt] were conjugated to the surface of G4.5 PAMAM dendrimers via coordination with carboxylate groups. Sustained release of (DACH)Pt was achieved over 24 hours with the dissociation of Pt from the carboxylate groups of dendrimers (Howell and Fan, 2010). In another example, PAMAM dendrimers were loaded with DOX via hydrazone linkage. The PAMAM-DOX conjugates showed acid-sensitive DOX release kinetics and higher release at acidic pH than at neutral pH (Lai et al., 2007). On the other hand, physically entrapped drugs show much faster release than covalently conjugated drugs. Methotrexate (MTX) entrapped in hydroxyl-terminated G5 PAMAM dendrimers was released by 60% in 2h, whereas MTX conjugated to dendrimers via ester bond showed less than 5% release in 2h (Patri et al., 2005). Surface modification of a dendrimer influences the drug release profile. 5-fluorouracil (5-Fu) was entrapped in a G4 PAMAM dendrimer, whose end groups were modified with mPEG (5000 Da) (Bhadra et al., 2003). The PEGylated dendrimer showed 6 time slower 5-Fu release than non-PEGylated one, due to dense chains of PEG covering the periphery of dendrimers (Bhadra et al., 2003). Similarly, release of lamivudine entrapped in G5 poly(propyleneimine) (PPI) dendrimers was extended by the modification of terminal groups with mannose (Dutta and Jain, 2007). The mannose-modified dendrimers showed a prolonged drug release over 6 days, whereas the unmodified PPI dendrimers released most drugs in 1 day. The prolonged drug release was attributed to the terminal mannose groups, which provided an increased number of functional groups for complexation with drug molecules as well as steric hindrance preventing the drug release from the open structure (Dutta and Jain, 2007).

3.6 Silica-based nanocarriers

Porous silica NPs have gained increasing interest as a nanocarrier due to their structural, thermal, and chemical stability (Tan et al., 2004), tunable pores that can accommodate drugs and diagnostic agents, and the functionalizable surfaces (Lai et al., 2003; Zhao et al., 2009). Porous silica NPs provide gradual and sustained release of drugs by confining them in the cage structure (Li et al., 2004). Brilliant Blue F (BB) was loaded in the hollow interior of porous silica NPs using a high pressure. The hollow porous silica particles delayed the dye release over 1140 min, as compared to normal silica NPs, which released all BB in 10 min (Li et al., 2004). However, the sustained release effect diminished at relatively high pH where BB showed the same anionic charge as silica particles (Li et al., 2004). Drug release from silica particles could be extended by modifying the surface. For the delivery of ibuprofen, silica NPs were modified with 3-(aminopropyl) triethoxysilane, which established ionic interactions with carboxyl group of ibuprofen. Compared to the unmodified NPs with silanol groups, the amine-modified particles showed a greater ibuprofen loading per surface area and a substantial delay in the drug release (Kim et al., 2005).

Another approach to prevent inadvertent burst release from the porous silica NPs is to cap (block) their surfaces with “gate keepers,” organic or inorganic NPs or supramolecular assemblies, which may be removed by specific stimuli, such as pH, light, redox potential (Slowing et al., 2008). For example, mesoporous silica NPs were capped with calcium phosphate (CaP) precipitates (Rim et al., 2011). To localize CaP deposition on the surface,

the surface of silica particles was functionalized with urease, which catalyzed the hydrolysis of urea creating hydroxide ions. The urease-modified silica NPs suspended in an acidic solution of CaP obtained water-insoluble CaP layer on the surface as the local pH increased upon the addition of urea. DOX encapsulated in the CaP-coated mesoporous silica particles showed negligible release at pH 7.4, whereas DOX release at pH 4.5 was comparable to that of uncapped silica particles (Rim et al., 2011). A light-activated silica particle system was created by functionalizing the NPs with azobenzene derivatives, which had one end attached to the interior of the NPs and the other end free to undergo photoisomerization, serving as a gate keeper (Lu et al., 2008). Light illumination of 0.1 W/cm² at 413 nm induced a constant trans-cis photoisomerization about the N=N bond causing dynamic wagging motion of the molecules, resulting in the release of the encapsulated drugs such as CPT (Lu et al., 2008).

3.7 Hollow metal or carbon-based nanocarriers

Hollow metal nanocarriers based on gold (Au), platinum (Pt), or palladium (Pd) have been investigated for drug delivery. Hollow metal nanocarriers are generated by reacting solutions of metal salts (e.g., H₂AuCl₄) with solid template of relatively more reactive metals (e.g., Ag) (Sun et al., 2002). Hollow Au nanosphere system is frequently chosen as a drug carrier because its photothermal activity provides additional therapeutic utility. PEGylated Au particles were loaded with DOX via electrostatic interactions (You et al., 2012). Drug release was triggered by near-infrared (NIR) laser irradiation, which induced photothermal conducting effect (You et al., 2010). Due to the dual function of photothermal activity of Au NPs (thermal ablation and local drug release), the NP treatment combined with NIR irradiation had greater antitumor activity than those with NP alone, free DOX, and liposomal DOX (You et al., 2012). Titanium oxide (TiO₂) nanotubes with amphiphilic interior have also been pursued for drug delivery (Song et al., 2009). Here, amphiphilic TiO₂ nanotubes were fabricated by a first anodization step that formed tube structure, followed by a hydrophobic surface modification. A second anodization formed hydrophilic tube structure underneath the hydrophobic tubes. A hydrophilic biomolecule (e.g., enzyme) was linked to the hydrophilic part of the tube via covalent bonding. The enzyme release was controlled by two mechanisms: limiting the wetting of the entrance of the tube by the hydrophobic cap and destroying the hydrophobic molecules and the linkers between TiO₂ surface and enzyme by UV illumination (Song et al., 2009). Additional coating with polyelectrolyte complexes provides further control of drug release from hollow metal NPs. Fluorescein isothiocyanate (FITC) was loaded in porous iron oxide nanorods, modified with anionic polyacrylic acid (PAA) and cationic PEI (Wu et al., 2007). FITC release depended on the packing degree of electrolyte layers (Wu et al., 2007).

Carbon-based nanocarriers such as carbon nanotubes and fullerenes, which have cylindrical and spherical shape of hexagonal networks of carbon atoms, respectively, have received an increasing attention due to their controllable size, reactive and large surface area, and unique geometry (Shenderova et al., 2002; Yang et al., 2006). Their hydrophobic surface is modified to prevent aggregation and opsonization, via oxidation, carboxylation or amidation of the oxidized surfaces, or conjugation with functional molecules (Prajapati et al., 2011; Prato et al., 2007). Such surface modifications also contribute to drug loading by increasing the interaction between a drug and the carbon structures. For example, amphotericin B

(AmB) was attached to carbon nanotubes that had been modified in two-step processes involving carboxylation and amidation (Prajapati et al., 2011). AmB bound to carbon nanotubes showed greater anti-leishmanial efficacy than free AmB due to the enhanced intracellular delivery mediated by nanotubes (Prajapati et al., 2011). For the same reason, amine-functionalized carbon nanotubes served as an efficient carrier of siRNA (Zhang et al., 2006).

Recently, functionalized fullerenes (C60) have also been pursued as a drug carrier (Partha et al., 2008; Ranga Partha, 2009; Shi et al., 2013). C60 modified with PEI and folic acid (C60-PEI-FA) was used as a carrier of DTX (Shi et al., 2013). DTX adsorbed to C6-PEI-FA showed slower release than free DTX and enhanced cellular uptake by PC3 human prostate cancer cell (Shi et al., 2013). Similarly, PTX delivered by amphiphilic C60 modified with carboxylate-terminated dendritic moieties showed comparable cytotoxicity to that of Abraxane (albumin-bound formulation of PTX) (Partha et al., 2008).

3.8 Nanocarriers for delivery of multiple drugs

Nanocarriers with more than one type of drugs have been pursued for synergetic effects or multiple functions. PMs based on PEG-PLA block copolymers were used for combined delivery of PTX, DTX, etoposide (ETO), and/or 17-allylamino-17-demethoxygeldanamycin (17-AAG) (Shin et al., 2009). Due to the hydrophobicity of the drugs, they were encapsulated in the core of PEG-PLA NPs. Physical stability of PMs and drug retention were superior to those of single drug-loaded PMs, attributable to hydrophobic interactions among the drugs (Shin et al., 2009). Drug release followed the first-order kinetics, which indicated that drugs were released by diffusion irrespective of the type (Shin et al., 2009).

In developing nanocarriers for the delivery of multiple drugs with different chemical properties and functions, it is necessary to consider their physicochemical compatibility and the desired release kinetics of each drug. For example, hydrophilic compounds like nucleic acids and hydrophobic drugs such as PTX are difficult to deliver simultaneously in one type of carrier but rather require amphiphilic carriers. For instance, co-encapsulation of hydrophilic DOX and hydrophobic PTX was achieved in nanocapsules composed of a hydrophilic drug reservoir and a hydrophobic shell made of PVA and iron oxide (Hu et al., 2012). In the absence of external stimuli, DOX loaded in the hydrophilic core showed zero-order release kinetics with minimal initial burst release, whereas PTX in the shell showed initial burst release, both releasing <10% of the total drug in 4h. The drug release was substantially enhanced (to 45–75% depending on the MW of PVA in 10h) with the application of magnetic field, which created local heating and polymer chain relaxation in the shell (Hu et al., 2012). Amphiphilic cationic micelles, made of PEI-grafted PCL, were developed for the co-delivery of DNA (luciferase reporter gene, pCMV-Luc) and anti-cancer drug DOX (Qiu and Bae, 2007). DOX free base was loaded in the hydrophobic PCL core, and DNA on the cationic PEI shell via electrostatic interactions. Each active ingredient did not interfere with the loading of the other, allowing the micelles to release DOX in a sustained manner and to condense DNA for efficient gene transfection (Qiu and Bae, 2007).

Recently, three different drugs, salvianolic acid B (Sal B), tanshinone IIA (TS IIA), and panax notoginsenoside (PNS) were simultaneously loaded in PLGA NPs for the treatment of

brain diseases (Zhang et al., 2013). The NPs were formed by the double emulsion ($W_1/O/W_2$) method, where water-soluble PNS was added as primary aqueous phase (W_1) and TS IIA and Sal B were dissolved in an organic solvent (O) along with the polymer. The three drugs were released from the PLGA NPs showing distinct patterns according to their aqueous solubility ($PNS > Sal\ B > TS\ IIA$) (Zhang et al., 2013). In another example, DOX and PTX or another hydrophobic immunosuppressant rapamycin (RAPA) were loaded in mesoporous silica NPs with an iron oxide core (Qian Liu, 2012). Co-encapsulation of two drugs with different water solubility was achieved by a sequential adsorption procedure, namely, loading DOX in aqueous solution first, followed by adsorbing RAPA (or PTX) in non-aqueous medium, where the former was attracted to the silica matrix via electrostatic interactions and the latter through hydrogen bonding and polar interactions with silica (Qian Liu, 2012). The drug release followed the Korsmeyer-Peppas model with a release exponent n value of 0.45, indicative of simple diffusion-controlled Fickian process. The presence of hydrophobic RAPA or PTX restricted the kinetics of water diffusion, the first step of diffusion-controlled release process, resulting in slower DOX release than from the system with DOX alone (Qian Liu, 2012).

A “nanocell” system reported by Sengupta et al shows an example of temporal control of multiple drug release (Sengupta et al., 2005). The nanocell consisted of PLGA core and PEGylated lipid envelope, which carried a chemotherapy agent DOX and an anti-angiogenic agent combrestatin, respectively (Sengupta et al., 2005). The system was designed to release combrestatin entrapped in the lipid envelope first to induce a rapid deployment of anti-angiogenic effect, followed by slow release of DOX that would kill tumor cells (Sengupta et al., 2005). The timed delivery of DOX and combrestatin with nanocells achieved superior anti-tumor effects to those of each drug, a simple mixture of the two, or liposomes containing both drugs (Sengupta et al., 2005). Similarly, for sequential delivery of two drugs, Janus PEG-based dendrimers were prepared by reacting a dendron conjugated with a model compound benzyl alcohol (BA) via a carbonate linker and another dendron with the other compound 3-phenylpropionic acid (PPA) via an ester linker (Acton et al., 2013). This system released BA first and then PPA, according to the chemical susceptibility of the linkers (Acton et al., 2013).

4. Future perspectives

Ideally, systemically administered nanocarriers should retain drugs during circulation but release them with no substantial delay once they arrive at target tissues or intracellular organelles. The state of art drug delivery technology has fulfilled this requirement by employing various types of nanocarriers and biomaterials. The inclusion of stimuli-responsive materials has enabled additional control of the kinetics and locations of drug release. However, a lot remains to be done for translating new technologies to clinically effective products. One of the issues that warrant immediate attention of the formulation scientists is the *in vitro* conditions in which drug release kinetics are tested in the development stage. A buffered saline, the most widely used release medium, barely reflects the complexity of blood with serum proteins and lipids, which can greatly challenge the stability of nanocarriers. Consequently, it is often observed that drug release in serum-complemented cell culture medium or in blood occurs much faster than that predicted in a

buffered saline (Liu and Yeo, 2013). Moreover, the assumption for a sink condition is not necessarily valid when the target tissues contain a limited amount of fluid (e.g., lungs) and/or the delivered drug has limited water solubility and low transepithelial permeability. While the efforts to develop functional biomaterials and new carrier assemblies will continue to be well justified, equally important in the future endeavor is to develop a methodology to examine drug release profiles in conditions highly relevant to the physiological environment.

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Highlights

- Drug release mechanisms utilized in nanocarriers
- Approaches to control drug release kinetics in various nanocarriers
- Main achievements and limitations of each approach

Fig. 1.

Various types of pharmaceutical nanocarriers for drug delivery. (a) nanocapsule, (b) nanosphere, (c) liposome, (d) polymeric micelle, (e) nanogel, and (f) dendrimer.

Fig. 2.

Plasma drug concentration profiles obtained by single dosing (short dashed line), multiple dosing (dotted line), and zero order controlled release (solid line). The range formed by two levels of the minimum toxic concentration (MTC) and the maximum effective concentration (MEC) displays the therapeutic window, where drug is effective without displaying toxicity.

Fig. 3.
Drug release mechanisms utilized in nanocarriers.