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Targeted Drug Nanoparticles: An Emphasis on Self-assembled Polymeric System

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Encouraged by rapid and promising progress in cancer nanotechnology, researchers continue to develop novel and efficacious nanoparticles for drug delivery. The interest in self-assembling polymeric nanoparticles as drug delivery vehicles is growing now a day, in which polymers can lead to supramolecular systems and is related to their functions as carrier for targeting the various cytotoxic drugs. This review article gives the idea of selection, preparation, morphology, stability and drug release characteristics of self-assembled polymeric systems. The release characteristic of drugs from these polymeric systems is dependent on the drug loading contents and chain length of the hydrophobic/hydrophilic part of the copolymers. The review also focuses the recent advances in self-assembled polymeric system.

Key words: Self-assembly, polymeric system, targeted drug delivery, nanoparticles, amphiphilic polymer

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INTRODUCTION

Self assembly is the spontaneous organization of molecular systems that enable them to form well defined nano and microscopic structures under equilibrium conditions into stable, structurally well defined aggregates by non covalent bonds, eventually leading to the formation of supramolecular systems and taking responsibility over their functions (Chong *et al*., 2003). Among the nanoscale drug carriers, self-assembled nanoparticles from amphiphilic copolymers are of particular interesting due to their unique physico-chemical properties. Given the great opportunity in terms of diversity and functionality in the design of the polymeric building blocks, various amphiphilic copolymers have been developed for defined drug delivery purposes (Meng, 2008). Polymeric amphiphiles such as amphiphilic diblock or triblock copolymers, hydrophobically modified water-soluble polymers and graft copolymers are able to spontaneously form micellar aggregates through inter- or intramolecular association during which drug molecules are incorporated (Sutton *et al*., 2007; Nasongkla *et al*., 2004; Allen *et al*., 1999; Wang *et al*., 2006; Torchilin *et al*., 2003; Kumar *et al*., 2004). Self-assembled polymeric nanoparticles have many advantages as highly efficient drug delivery vehicles including nanoscale size, controlled composition and capacity to encapsulate a wide range of drug molecules. In particular, by using advanced polymer chemistry and precision engineering at a molecular level, these synthetic polymers provide a wide opportunity for functionalization and versatility which impact the physico-chemical properties of self-assembled systems. Self assembly finds application in generating materials regular structures (e.g., honeycomb structured film) and highly ordered nano structures (e.g., vesicles, tubes). Since, cancer is a rapid growing disease in the world and the peoples in all ages are suffering from cancer by various ways including breast cancer (Madan *et al*., 2001). Therefore, the interest in self-assembling polymeric nanoparticles as drug delivery vehicles is growing in which extended research has been conducted or is ongoing (including phase I and II clinical evaluation) which show the great promise of self-assembled polymeric nanoparticles in cancer chemotherapy (Matsumura, 2007).

Suitable polymeric system for self-assembly: Various types of polymeric systems are available as drug carrier i.e., hydrophilic, hydrophobic and Amphiphilic polymeric system. Apart from hydrophilic and hydrophobic polymeric system, amphiphilic polymers gain popularity in recent days because it contains both hydrophobic and hydrophilic segments in one macromolecule. It has been demonstrated that amphiphilic copolymers with various architectures are capable of self-assembly in a way to minimize unfavorable segment/solvent interactions while maximizing favorable segment/solvent interactions (Sutton *et al*., 2007). In most of the cases, the self-assembly occurs in aqueous environments where the hydrophobic segments of amphiphilic copolymers form the inner core via intra/intermolecular association and the hydrophilic segments orient to contact with outer aqueous environments forming the outer shell (Allen *et al*., 1999). As a low toxicity and water-soluble polymer, poly(ethylene glycol) (PEG) or poly(ethylene oxide) (PEO) has been widely used as hydrophilic segments in amphiphilic block or graft copolymers (Sutton *et al*., 2007; Allen *et al*., 1999, 2002). Owing to its high degree of hydration and large excluded volume, the PEG corona creates repulsive forces which sterically stabilize self-assembled systems during the circulation. While PEG remains the most popular choice of hydrophilic segments, other water-soluble polymers have been explored in micellar systems featuring additional functionalization, such as, poly(acrylic acid) (PAAc) is able to form a negative-charged hydrophilic corona, while the presence of negative charges at the surface has been believed to enhance the extent of *in vitro* cellar uptake (Tian *et al*., 2007; Zhang and Eisenberg, 1995). Poly(*N*-isopropylacrylamides) (PIPAAm), which is water-soluble below its lower critical solution temperature (LCST) but hydrophobic above, can introduce temperature-sensitivity to the self-assembled systems (Liu *et al*., 2005; Chung *et al*., 1998; Akiyoshi *et al*., 2000). By contrast to the universal use of PEG as hydrophilic segments, a wide range of hydrophobic polymers has been explored as hydrophobic segments (Sutton *et al*., 2007; Allen *et al*., 1999) including synthetic polymer poly(*D,L*-lactide) (PLA) (Lee *et al*., 2005; Cheng *et al*., 2007; Govender *et al*., 2000), poly(styene) (PS) (Zhang and Eisenberg, 1995; Bhargava *et al*., 2007), poly(caprolactone) (PCL) (Nasongkla *et al*., 2004; Wang *et al*., 2005a), poly(aspartic acid) (PAA) (Yamamoto *et al*., 2007), poly(propylene oxide) (PPO) (Cau and Lacelle, 1996), phosphatidylethanolamine (PE) (Torchilin *et al*., 2003), poly(trimethylene carbonate) (PTMC) (Zhang *et al*., 2006), poly(L-lysine) (Kim *et al*., 2005), poly(L-histidiene) (Lee *et al*., 2005), poly(aspartic acid) (PASP) (Bae *et al*., 2005) or natural polymer chitosan (Kwon *et al*., 2003). These various hydrophilic-hydrophobic segment combinations have given rise to micellar self-assembled systems with distinct physico chemical properties and *in vitro/vivo* biological significance as drug carriers. For example, the composition of copolymers (length, charge, relative hydrophobicity, or pH/temperature sensitivity of the hydrophobic/hydrophilic segments) impacts the morphologies of the self-assembled nanoparticles formed (Zhang and Eisenberg, 1995; Zhang *et al*., 2006; Wang *et al*., 2005b). The hydrophobicity and

mobility/rigidity of the hydrophobic core plays an import role in the drug-polymer compatibility which decides largely the drug loading in the inner core and drug release from the micelles (Govender *et al*., 2000; Yamamoto *et al*., 2007). The pharmaceutical characteristics and biological significance of the self-assembled polymeric nanoparticles are largely influenced by the size, structure (e.g., length of hydrophobic/hydrophilic segments) and surface properties (e.g., length of PEG corona and surface decoration of targeting ligands) (Nishiyama and Kataoka, 2006; Mahmud and Lavasanifar, 2005). Given the significant importance of polymer composition on the physico-chemical properties of self-assembled systems, it is critical to define the chemistry to create effective carriers for a particular type of drug delivery system. Some hydrophilic and hydrophobic polymers used in self-assembled system have been given in Table 1.

Preparation of polymeric self-assembly: Self-assembly of amphiphilic copolymers in aqueous environments is driven by the hydrophobic association along with the hydrophobic segments (Allen *et al*., 1999). There are two principle methods to prepare the self-assembled systems: the dissolution method and the dialysis method. The dissolution method involves directly dissolving the copolymer in an aqueous solution and allowing self-assembly occurring spontaneously (Fig. 1). The method is suitable for the amphiphilic copolymers that are easily soluble in water. However, for the copolymer that is not easily soluble in water, the dialysis method is a simple preparation method and easy to control. The amphiphilic copolymers are first dissolved in a common organic solvent that is miscible with water such as dimethylformamide (DMF). The copolymer solution is then dialyzed against distilled water in a dialysis bag made from dialysis membranes with a molecular weight cut-off (MWCO) larger than solvent molecules (e.g., 12-14 kg mol^{-1}). With solvent exchange, the self-association of amphiphilic copolymers is induced during which hydrophobic drug molecules can be incorporated in the hydrophobic polymeric system (Meng, 2008). The hydrophilic and hydrophobic drugs can incorporate in different segments of self-assembled system at same time. In addition, it is important to enhance the dissolution of drugs (Deepti *et al*., 2007) before using with polymeric self-assembled system for better results.

Stability of self-assembled polymeric systems as drug carriers is essential for *in vivo* applications of systems. High thermodynamic stability, evaluated by the Critical Aggregation Concentration (CAC) below which self-assembled systems found in disassemble and kinetic stability, demonstrated by the rate of disassembly are crucial for the self-assembled systems to deliver loaded drugs to the desired site of action. The CAC value is usually determined by monitoring the assembly under various polymer concentrations which is reflected by the changes in the fluorescent spectroscopy of pyrene (Kwon *et al*., 2003; Wilhelm *et al*., 1991). Pyrene is

Table 1: Polymers used in self-assembled system

Polymer	Examples	Attributes
Hydrophilic	Poly(ethylene glycol) (PEG)	Peg corona creates repulsive forces which sterically stabilize self-assembled systems (Sutton *et al*., 2007; Allen *et al*., 1999)
	Poly(ethylene oxide) (PEO)	Having high degree of hydration and large excluded volume (Allen *et al*., 2002)
	Poly(acrylic acid) (PAAC)	Form a negative-charged hydrophilic corona, which has been believed to enhance the extent of *in vitro* cellar uptake (Tian *et al*., 2007; Zhang and Eisenberg, 1995)
	Poly (*n*-isopropylacrylamides) (PIPAAM)	Introduce temperature-sensitivity to the self-assembled systems (Liu *et al*., 2005; Akiyoshi *et al*., 2000)
Hydrophobic	Poly(*d,l*-lactide) (PLA)	Give rise to micellar self-assembled systems with hydrophilic polymers and form the inner core via intra/intermolecular association (Lee *et al*., 2005; Cheng *et al*., 2007; Govender *et al*., 2000)
	Poly(styene) (PS)	Give rise to micellar self-assembled systems with hydrophilic polymers and form the inner core via intra/intermolecular association (Zhang and Eisenberg, 1995; Bhargava *et al*., 2007)
	Poly(caprolactone) (PCL)	Give rise to micellar self-assembled systems with hydrophilic polymers and form the inner core via intra/intermolecular association (Wang *et al*., 2005b; Yamamoto *et al*., 2007)
	Poly(aspartic acid) (PAA)	Give rise to micellar self-assembled systems with hydrophilic polymers and form the inner core via intra/intermolecular association (Cau and Lacelle, 1996)
	Poly(propylene oxide) (PPO)	Give rise to micellar self-assembled systems with hydrophilic polymers and form the inner core via intra/intermolecular association (Zhang *et al*., 2006)
	Phosphatidylethanolamine (PE)	Give rise to micellar self-assembled systems with hydrophilic polymers and form the inner core via intra/intermolecular association (Torchilin *et al*., 2003)
	Poly(trimethylene carbonate) (PTMC)	Give rise to micellar self-assembled systems with hydrophilic polymers and form the inner core via intra/intermolecular association (Kim *et al*., 2005)
	Poly(l-lysine)	Give rise to micellar self-assembled systems with hydrophilic polymers (Bae *et al*., 2005)
	Poly(l-histidiene)	Give rise to micellar self-assembled systems with hydrophilic polymers and form the inner core via intra/intermolecular association (Lee *et al*., 2005)
	Poly(aspartic acid) (PASP)	Give rise to micellar self-assembled systems with hydrophilic polymers and form the inner core via intra/intermolecular association (Kwon *et al*., 2003)
	Natural polymer chitosan	Give rise to micellar self-assembled systems with hydrophilic polymers and form the inner core via intra/intermolecular association, also produce rigidity (Wang *et al*., 2005b)

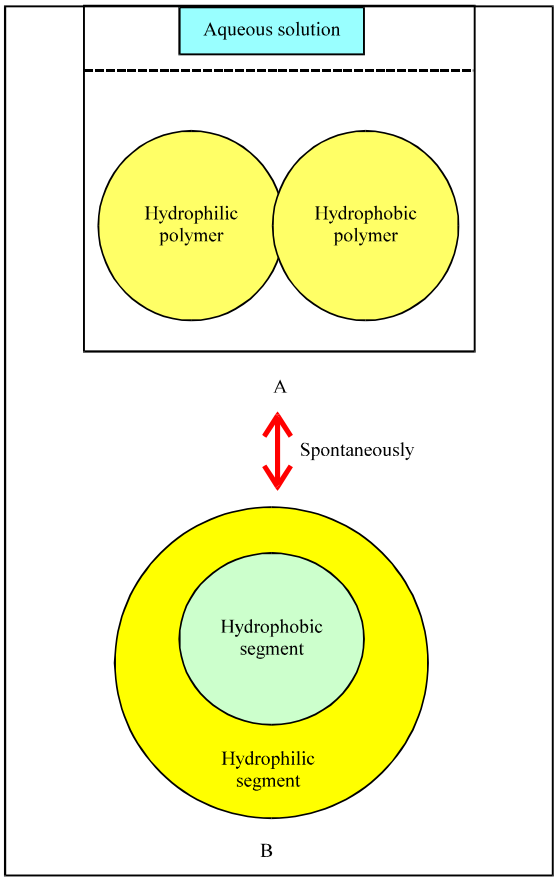

Fig. 1: Dissolution method to prepare the self-assembled systems. A: Involves directly dissolving the copolymer in an aqueous solution; B: Self-assembly of amphiphilic polymers in which hydrophobic segment make its inner core and the hydrophilic segments orient towards outer aqueous environments

co-incubated with polymers of various concentrations in aqueous solutions. When polymer aggregates, the hydrophobic pyrene molecules preferably partition inside the hydrophobic microdomains resulting in different photophysical characteristics compared to those of free pyrene molecules. The red-shift of the pyrene (0, 0) band from 334 to 336 nm reflects the partitioning of pyrene into the hydrophobic region of the micellar nanoparticles. The crossover points at the low concentration ranges indicate the apparent critical aggregation concentration (CACapp) which is the minimum copolymer concentration required for the formation of self-assembled structures. It has been demonstrated that the CAC values of amphiphilic copolymers (1-100 μg mL^{-1}) are significantly lower than those of low molecular weight surfactants (1-10 mg mL^{-1}), suggesting their high thermodynamic stability under extremely dilute conditions (Meng, 2008). The kinetic stability of self-assembled systems depends largely on the physical state of the inner core (Allen *et al*., 1999). It is believed that the self-assembled system disassembles more slowly if they have inner cores with high glass transition temperatures. In addition, incorporation of drug in the inner core may enhance the kinetic and thermodynamic stability due to existence of the association between drugs and polymers strengthens the overall association in the core of polymeric systems.

Morphology of self-assembled polymeric system: The molecular weight, the relative block length and the chemical nature of the repeat unit in amphiphilic copolymer constitute the morphology of self-assembled system (Allen *et al*., 1999). In most cases, amphiphilic copolymers self-assemble into a nano-sized spherical core-shell structure (Lee *et al*., 2005; Nasongkla *et al*., 2004; Bae *et al*., 2003) where the hydrophobic segments aggregate to form the inner core and the hydrophilic segments orient towards outer aqueous environments. Owing to the nanoscale size, they are suitable for intravenous administration where prolonged circulation time is promised by the hydrophilic shell and selective tissue accumulation (i.e., passive targeting) is facilitated via the EPR effect. Furthermore, these nanoscale polymeric systems have high surface-area-to-volume ratio and are able to achieve high ligand density on the surface for active targeting purposes. Interestingly, multiple morphologies have been obtained from a same functionalized copolymer where the self-assembly conditions control over the aggregate architecture (Wang *et al*., 2005a, b; Choucair and Eisenberg, 2003). For example, different stable aggregate morphologies of core-shell spheres, rods, vesicles and large compound micelles were prepared from a polystyrene-b poly(acrylic acid) block copolymers by adjusting the composition of the solution where the copolymer self-assembled (Yu and Eisenberg, 1997; Cheng *et al*., 2007). The multiple morphologies formed were attributed to various stretching and repulsion of the corona-form chains resulting from the various degrees of the ionization of poly (acrylic acid) chain. Most of the amphiphilic copolymers does not have the functional groups that play roles in the self-assembly, therefore these amphiphilic copolymers lack the ability to precisely control the morphologies of self-assembles such as limited control over the size of self-assembled nanoparticles from an amphiphilic copolymer system (Jette *et al*., 2004; Gillies and Frechet, 2005). The distribution of drug in core and coat portion of self–assembled nanoparticulate system is depending upon their nature and partition coefficient (Fig. 2).

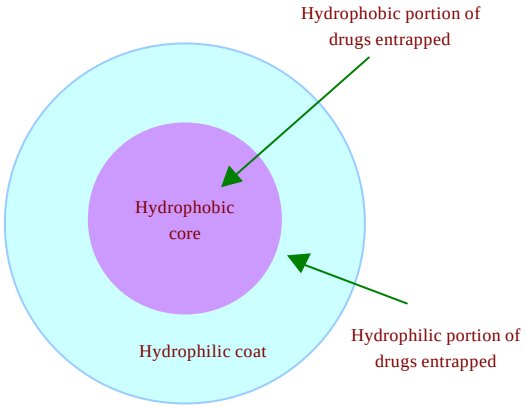

Fig. 2: Distribution of hydrophilic, hydrophobic and amphiphilic drugs in self-assembled nanoparticle system

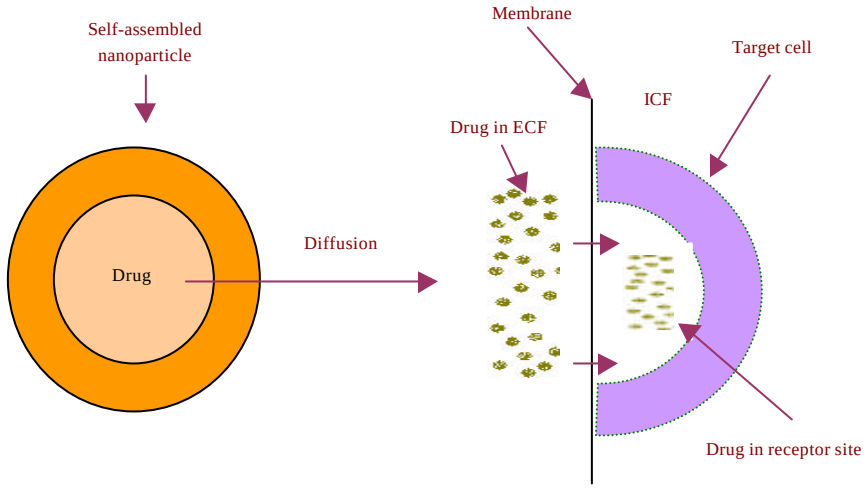

Fig. 3: Drug release from self-assembled nanoparticle

Drug release from self-assembled polymeric system: The release characteristics of drugs from these polymeric systems are dependent on the drug loading contents and chain length of the hydrophobic/hydrophilic part of the copolymers. Moreover, the release pattern in self-assembled polymeric system would be similar to that of ordinary polymeric systems (Monika *et al*., 2008; Phromsopha and Baimark, 2009; Baimark, 2009). Generally, anticancer drugs are incorporated in the inner core of polymeric nanoparticles by physical encapsulation, where the release of drugs depends largely on the rate of drug diffusion (Fig. 3), system disassembly, the interaction of system with target cells (e.g., nanoparticles being internalized into target cells) and the microenvironment (e.g., the structure of the nanoparticles being altered due to a stimuli-responsive targeting mechanism) (Gillies and Frechet, 2005; Nasongkla *et al*., 2004; Liu *et al*., 2005; Huang *et al*., 2007). For the drugs that take action extracellularly, it is preferable that drug carriers release the drugs near the target sites (e.g., tumour tissue). For DNA interacting anticancer drugs such as doxorubicin (DOX), however, the cell nucleus is the target organelle where intracellular delivery is preferable and the defined mechanism for nuclear targeting incorporated in the drug carrier design is important. In this case, nanoparticles with targeting ligands incorporated in the formulation design which can facilitate the cellular uptake of nanoparticles via receptor binding, have been demonstrated to be efficacious in intracellular drug delivery (Nasongkla *et al*., 2004; Kim *et al*., 2005).

Recent advances in self-assembled polymeric systems: Recently, as a new generation of polymer-drug therapeutics, core-shell polymeric nanoparticles have been designed to have DOX covalently bound to the hydrophobic segments and incorporated into the inner core of the polymeric micelles during self assembly. The new formulation combines the advantage of conventional

drug encapsulated micelles and water-soluble polymer-drug conjugates: prolonged circulation time, good storage stability and low systemic toxicity. To achieve localized drug release, defined biological rationales have been incorporated into the formulation design such as coupling targeting ligands on the surface (to promote carrier-cell interaction and cellular internalization) and enzyme/acid-sensitive linker between the drug and polymer (to cleave and release free drugs in response to the inner environment of the endo-lysosome) (Bae *et al*., 2003; Oh *et al*., 2007; Haag, 2004; Kataoka *et al*., 2001). These new formulations are under active study in anticancer therapy and have shown promise in terms of cell growth inhibition *in vitro*. Although environmental stimuli strategies have been incorporated into the self-assembled nanoparticles in promoting the nuclear localization of DNA-interacting drugs, those well-established techniques are limited by the complexity of the synthesis and the relatively low cleavage efficiency of the linkers (e.g., <50% over 72 h at stimuli conditions) (Bae *et al*., 2003).

Recently a Simulated graft copolymer of poly(acrylic acid-*co*-stearyl acylate) [P(AA-*co*-SA)] and poly(ethylene glycol) (PEG) was synthesized, where acrylic acid, stearyl acylate and PEG was employed as the pH-sensitive, hydrophobic and hydrophilic segment, respectively. Polymeric nanoparticles prepared by the dialysis of simulated graft copolymer solution in dimethylformamide against citrate buffer solution with different pH values (Shou-Chen *et al*., 2009). A new class of nanobiosensors of colloidal gold nanocrystals has been developed to recognize and detect specific DNA sequences and single base mutations in a homogeneous format. At the core of this biosensor, a 2.5 nm gold nanoparticle that functions as both a nano-scaffold and a nano-quencher, attached to the oligonucleotide molecules labeled with a thiol group at one end and a fluorophore at the other. This hybrid bio/inorganic construct is found to spontaneously assemble into a constrained arch-like conformation on the particle surface (Maxwell *et al*., 2002). Another very interesting self assembly of amphiphilic graft copolymer have been developed with poly(ε-caprolactone) and dextran, which was synthesized by ring opening polymerization of ε-caprolactone initiated through the hydroxyl end of dextran in the presence of stannous 2-ethylhexanoate {Sn (oct)$_2$} as a catalyst (Bajgai *et al*., 2008). Self-assembling nanospheres of hydrophobized pullulan have been recently developed with Pullulan acetate (PA), as hydrophobized pullulan, which was synthesized by acetylation. Carboxymethylated poly(ethylene-glycol) (CMPEG) was introduced into pullulan acetate (PA) through a coupling reaction using N,N'-dicyclohexyl carbodiimide (DCC) (Jung *et al*., 2004).

CONCLUSIONS

Apart from various other approaches of drug targeting, the self assembled polymeric nanoparticles type of drug delivery is gaining popularity in recent days due to its unique physico-chemical properties, better in vivo stability, structural integrity and high efficiency as drug delivery vehicles. The self assembly is useful for most of the cytotoxic agent as targeted nanoparticles there by reducing their toxicity. In future, the different type of self assemble systems may exist for most of the cytotoxic drugs for enhance the effectiveness and diminish the toxicity by targeting the drug in the direction of specific site with high affinity characteristics.

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