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Tailoring Polymeric Nanoparticles as Nanocarriers via RAFT Polymerization

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ABSTRACT

Polymeric nanoparticles are really promising to be used as drug carriers, due to its ability to increase the aqueous solubility of drugs. Polymeric nanoparticles can regulate the drug activity by passive or active targeting to different tissues. RAFT polymerization has become the most approvable technique to synthesize polymeric nanocarriers for drug delivery. By using different RAFT agents, wide ranges of polymeric nanoparticles with various architecture and water solubility can be obtained under mild conditions.

Keywords: *polymeric, nanoparticles, nanocarriers, RAFT Polymerization*

1. INTRODUCTION

Polymeric nanoparticles are characterized as particulate dispersion or solid particles with size in the range of 10-1000 nm (Couvreur, 1988; Kreuter, 2014). In the past few deacdes, polymeric nanoparticles have attracted many attentions due to their unique properties that can meet wide range of applications, such as in biomedical (McNamara & Tofail, 2017), catalysis (Xia, Yang, & Campbell, 2013), food (Sozer & Kokini, 2009), and cosmetics industries (Raj, Jose, Sumod, & Sabitha, 2012). Many research have been performed to study the capability of polymeric nanoparticles to be used as drug or nanocarriers, including the applications for drugs with low molecular weight, peptides, and nucleotides via oral, topical and parental use (Koo, Rubinstein, & Onyuksel, 2005). Polymeric nanoparticles have the ability to increase the aqueous solubility of drugs. It also can modulate the drug's activity, either by passive or active targeting to different human tissues (Chan, Valencia, Zhang, Langer, & Farokhzad, 2010; Ragelle, Danhier, Préat, Langer, & Anderson, 2017).

The potential of block copolymers nanoparticles to be used as drug delivery vehicles has been recognized since the late 1960s. Some studies showed the properties of nanoparticles which can be easily to control. It also shown good pharmacological characteristic. The biocompatible nanotechnologies for drug delivery have been grown fast over the last half of a century. Nanoparticles as nanocarriers in drug delivery applications usually made by using a variety of materials including polymers, lipids (liposomes), and organometallic compounds. Recently, biodegradable nanoparticles also shown in many studies as a potential drug delivery devices. It has reported that the biodegradable nanoparticles can circulate for a prolonged period time for targetting a particular organ, including the ability as devices to deliver DNA in gene therapy, proteins, peptides, and genes (Duong, Marquis, Whittaker, Davis, & Boyer, 2011).

The use of polymeric nanoparticles as drug carriers also has been really attracted due to some specific advantages over another type of drug carriers, such as liposome. Another advantage from nanocarriers drug delivery system is the ability to deliver the drug directly to a target of human tissues, lowering the toxicity which contributes to minimize the side effects (Jagur-Grodzinski, 2009; Liechty, Kryscio, Slaughter, & Peppas, 2010).

In spite of these advantages, there are some limitations from polymeric nanocarriers as drug delivery system. Due to their small size and large surfaces, the intent to form particles aggregate will make polymeric nanocarriers difficult to handle physically in liquid and dry forms. In addition, the limitation amount of drug loading and burst release also become the practical problems that have to be solved before polymeric nanocarriers can be applied clinically.

There are three polymeric nanomaterial classes that the most widely used as drug delivery vehicles including the block copolymer micelles, dendrimers (hyperbranched polymer), and star polymer. Each these polymeric nanomaterials has been shown the advantages and disadvantages that can improve or will diminish the stability and capability to distribute the drug (Qiu & Bae, 2006).

1. Micelles

Micelles has been used as drug delivery devices since the late of 1960s. It easy to control the micelles properties which also has a good pharmacological characteristic (Kedar, Phutane, Shidhaye, & Kadam, 2010). Micelles can be formed when amphiphiles compounds are set in the water. It consist of an inner core which assemblied from hydrophobic segments and an outer hydrophilic corona. The hydrophobic segments has the ability of solubilizing lipophilic substances and the hydrophilic segments serving as the stabilizer interface between the hydrophobic core and the external aqueous environment (Figure 1). The size, charge, and surface properties of micelles can be select simply by adding new compounds to the mixture of amphiphilic substance. The modification can be done before the preparation of micelles and/ or by varying of the preparation method. It depends on the delivery purpose from the micelle application (Ebrahim Attia et al., 2011).

The preparation of polymeric micelles usually use amphiphilic diblock copolymers. This copolymers materials has unique advantages in drug delivery applications. Polymer with spesific properties usually used for particular purposes. The polymer can also be modified to achieve a long circulation time during the delivery time or to introduce targeting moieties. However, the linear structures of diblock copolymers have issued the micelle stability, as the influence of molecule architecture to polymer's physical properties (Riess, 2003).

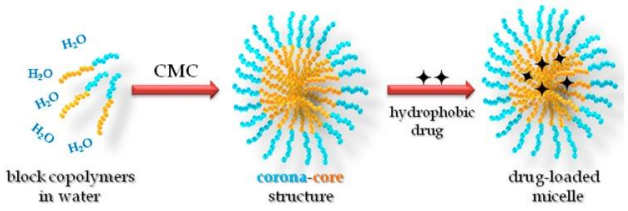

Fig 1. Schematic representation for the micellization of diblock copolymers and drug encapsulation in polymeric micelle (From (Hussein & Youssry, 2018), Copyright © 2018 by MDPI. Reprinted by permission of MDPI)

There are some advantages that can be provided by using micelles as drug delivery vehicles. The ability to deliver drug at specific target contributed by their higher intrinsic water solubility thus increase the bioavailability. Micelles has many desirable properties for drug delivery applications, including the small size,

biocompatibility with the drug, and unique morphology (Tyrrell, Shen, & Radosz, 2010).

The lack of of micelles is the particles stability which related to the polymer's critical micelle concentration (CMC). The CMC is the specific solution concentration above which the micelles start to form. If the concentration of the copolymer solution drops below the CMC, the micelles will not assembly. It really important to keep the CMC above the micelles concentration, because it can adjust the micelle structure and size. During the drug delivery, it will difficult to control the rate release of drug and release the drug at high concentration. At some points, the micelles can be dissosiate and cause the toxicity issues (Gaucher et al., 2005; Venkataraman et al., 2011).

The advantageous biocompability, biostability, and biodistribution of polymeric micelles have been attempted many researchers to use it for drug delivery applications, particularly to targeting solid tumors, cancer, and any other treatment. A poly(ethylene glycol)-*b*-poly(aspartic acid) (PEG-*b*-poly(aspartic acid)) micelles has been used to functionalize doxorubicin (DOX) in their cores, for treatment of pancreatic cancer (Sawdon & Peng, 2013). Many studies of micelles formulations for anticancer drug have been tested for preferential tumor accumulation such as methotrexate, paclitaxel, cisplatin (Nishiyama & Kataoka, 2006), and camptothecin (Ebrahim Attia et al., 2011). Overall, the use of micelles as drug carriers has been proved to be highly effective.

2. Dendrimers

Dendrimers are monodisperse macromolecules that have tridimensional structure (Figure 2). This globular macromolecule is highly branched with many arms originating from central core (Cheng, Xu, Ma, & Xu, 2008). The first reports of dendrimers study were about two decades ago, which only targeting on the synthesis process and their chemical and physical properties. The potential of dendrimers in biological application just start to explore in the past decade, and it is been really promising in so many applications including drug carrier, immunology and the development of antimicrobials (Patri, Majoros, & Baker Jr, 2002).

There are two general procedures to synthesis dendrimers that will have different branching resulting at the end of the reaction (Cheng et al., 2008), which are:

1. The divergent method.
2. The convergent method.

In divergent method, the monomers repeats and branched outward from a central core. On the other hand, the synthesis of dendrimers in the convergent method started at the periphery and growing inward. The convergent approach affords more advantages particularly in control of the ultimate dendritic structures. But compare to the convergent method, the divergent method can easily to scale-up the production of dendrimers. The dendrimers affords molecules with highly regular branching structures, a unique molecular weight and low polydispersity index, and a well-defined number of peripheral groups.

The application of dendrimers in biomedical application have been explored by numerous research group and becoming the most attractive research areas. Starting in 1993, the first report of the use of PAMAM (polyamidoamine) dendrimers for gene transfection had been published by Haensler and Szoka (Esfand & Tomalia, 2001). Followed by another research group, that reported the efficient transfer of genetic material by using the same type of dendrimers. Recently, dendrimers also have been used in Magnetic Resonance Imaging (MRI) as carriers of chelating groups for MRI agents (Patri et al., 2002).

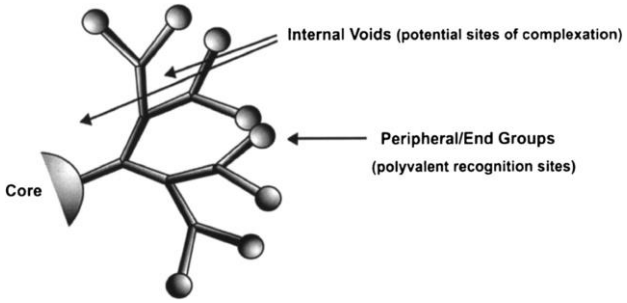

Fig 2. Three main parts of a dendrimer: the core, end-groups, and subunits linking the two molecules (From (Abbasi et al., 2014), Copyright © 2014 by Springer. Reprinted by permission of Springer)

Due to of the well-defined structure, compact globular shape, size monodispersity and controllable functionality, dendrimers are the excellent candidates for drug delivery vehicles (Cheng et al., 2008; Patri et al., 2002). It can be used as potential drug delivery carriers in two ways:

1. Drug molecules can be physically entrapped inside the dendritic structure, by using the internal 'cavity' of an appropriately designed dendritic structure or based on multiple noncovalent and hydrophobic interaction.
2. Drug molecules can be covalently attached onto surface or other functionalities to afford dendrimer-drug conjugate.

Dendrimers morphology, dendritic unimolecular micelles, have offer another advantages as drug delivery vehicles compare with conventional polymeric micelles. When the hydrophilic and hydrophobic segments are connected covalently, the unimolecular micelles can be form. It can be maintained at every stage of concentrations and in a variety of solvents, because it more static rather than dynamic.

The application of dendrimers as drug delivery vehicles has been started by exploits its excellent capability to attach drug molecules into the dendrimers periphery. The functionalization of PAMAM dendrimers with cisplatin as a potent anticancer drug, the antitumor drug, and any others drugs has

demonstrated the advantages of dendrimers for drug delivery (Esfand & Tomalia, 2001).

In every drug-dendrimers conjugation system showed that the water solubility and circulation time can be increased, as the opposite of the systemic toxicity has decreased. This report has shown that dendrimers can be use to overcome the drug delivery issues including the drug solubility, biodistribution and targeting. On the other hand, it is still a challenge to prepare dendritic that can be eliminated from the body at reasonable rate and to solve the tissue localization problems.

3. Star Polymer

Started in 1948, the first star polymer molecules had been synthesized by Schaefgen and Flory. Both researcher used ε-caprolactam in the presence of either cyclohexanonetetrapropionic or dicyclohexanoneoctacarboxylic and obtained tetra- and octachain star shaped polyamides. Followed by Morton and coworkers in 1962 that had successfully synthesized four-arm star polystyrene (PS) using anionic polymerization method. Furthermore, the study of star polymer synthesis has become more interesting using many different systems, such as: cationic, group transfer, or living ring-opening metathesis polymerization (Wiltshire & Qiao, 2007).

Star polymer has unique properties in terms of the relationship between arm number, arm molecular weight and solvent viscosity. It consists of a three-dimensional architecture where linear arms are linked by a central core (Figure 3). Hadjichristidis has been explained through his paper that star polymer represent an interesting class of macromolecule because it can have very high molecular weight but still provide a solubility and viscosity similar to that of linear or branched polymer of relatively low molecular weight (Hadjichristidis, Pispas, Pitsikalis, Iatrou, & Vlahos, 1999).

Star polymer can be classified into two categories: homo-arm (or regular) star polymer or miktoarm (or heteroarm) star copolymers (Hadjichristidis, Iatrou, Pitsikalis, & Mays, 2006). Homoarm star polymer consists of a symmetrical structure comprising radiating arm with identical chemical composition and similar molecular weight. In contrast, a miktoarm star molecule contains two or more arm species with different chemical compositions and/or molecular weight and/or different periphery functionality (Hadjichristidis, Pitsikalis, Pispas, & Iatrou, 2001).

Another way to classify the star polymer is based on the molecule architecture. Star polymer can be divided into dendristar and core cross-linked star (CCS) polymer, which the preparation also using two different ways. Compare to dendristar, the CCS polymer has become more interesting both in research and application area due to their unique three dimensional architecture and properties (Wiltshire & Qiao, 2007).

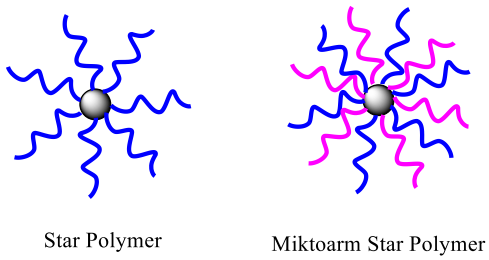

Fig. 3. Description of Star Polymer

The CCS polymer is made up of a strongly cross-linked core domain surrounded by a number of radiating linear arms, which can range from 10 to 100 per star depending on the reaction conditions. Since CCS polymers have a very high molecular weight, the architectural make-up of this form of polymer produces some very interesting rheological properties. However, the solubility and viscosity properties are close to those of low-molecular-weight linear or branched polymers. Because of these characteristics, CCS polymer has a broad range of potential applications, especially in the areas of drug delivery. (Blencowe, Tan, Goh, & Qiao, 2009).

In general, well-defined star polymer can be prepared via controlled polymerization techniques using three approaches: arm first approach, core first approach, and coupling onto (grafting to) approach (Hadjichristidis et al., 2001). Using a multifunctional low molecular weight molecule or a crosslinking agent, the arm-first technique connects multiple linear polymer chains at a single stage. The multifunctional initiator is used in the core-first procedure, and the number of arms is directly proportional to the number of initiating sites on the core. The last method can be described as the combination of controlled polymerization and coupling reaction. A well-defined polymer using as 'the arm', is prepared via controlled polymerization and coupled to a multifunctional linking agent that acts as 'the core'.

Because of their unique rheological and dilute solution properties, star polymers are gaining popularity. The ability to use regulated polymerization techniques to obtain well-defined structures, combined with specific rheological properties, makes this class of macromolecules very appealing for use in a variety of applications, including drug delivery. Because of the broad loading ability of the hydrophobic core, which can be easily altered by the use of a "spacer monomer" during the core forming process, the CCS polymer is ideally suited for use as a potential drug delivery system. For pharmaceutical applications, the ability to independently monitor the length and form of arm relative to the heart is also a very appealing feature. (Khanna, Varshney, & Kakkar, 2010; Wiltshire & Qiao, 2007).

4. Synthesis Polymeric Nanocarriers via RAFT Polymerization

The value of the polymer architecture-properties relationship has gradually been realized and emphasized as various nanosystems have been established. Polymer architecture refers to a single polymer molecule's shape, which influences its physicochemical properties. Due to its ability to synthesize various architecture of a wide variety of polymers with water solubility under mild conditions, RAFT polymerization has become the most approvable technique to new generation of polymeric nanocarriers.

The Australian CSIRO group was the first to announce RAFT polymerization in 1998. As originally suggested, the mechanism of RAFT polymerization is a degenerative chain transfer process. The RAFT method is similar to free radical polymerization but with the addition of a chain transfer agent (CTA). The CTA usually contains a thiocarbonylthio moiety that is reactive with radicals, allowing the intermediate radical species to be fragmented more easily. RAFT nanostructures, such as micelles, vesicles, and nanoparticles, are constructed from well-defined complex macromolecules. (Barner, Davis, Stenzel, & Barner-Kowollik, 2007; Boyer, Stenzel, & Davis, 2011). Synthetic polymers may also be combined with biomolecules or inorganic nanoparticles to solve medical and nanotechnology problems.

RAFT polymerization has been use as an effective process to design complex polymeric architectures, such as block copolymer, graft, star, dendrimers and micelle. Variety of copolymer is easily synthesized through this process under mild condition. The AB form of block copolymer is made by adding monomer "B" sequentially to a macro-RAFT agent, which is made by polymerization of monomer "A" mediated by the RAFT agent. (Gregory & Stenzel, 2012).

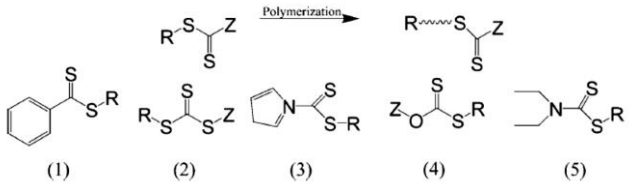

Fig. 4. Presentation of different RAFT agents: (1) dithioester; (2) trithiocarbonate; (3) and 5 dithiocarbonate; (4) xanthates (From (Boyer et al., 2011) Copyright © 2011 by John Wiley & Sons, Inc. Reprinted by permission of John Wiley and Sons, Inc.)

Graft copolymer can also be made with the RAFT method using the "grafting from" or "grafting through" techniques. The "grafting from" technique includes using an RAFT agent or radical initiation to functionalize a polymer backbone or substrate. The "grafting through" process, on the other hand, entails the polymerization of a polymer chain with reactive vinyl groups at the ends. (Boyer et al., 2011).

Extremely branched polymers and star polymers are another polymer structure that can be achieved using RAFT polymerization. Highly branched polymers can be made by polymerizing a monofunctional monomer in the presence of a difunctional monomer and RAFT agent, or by polymerizing a monofunctional monomer in the presence of a difunctional monomer and RAFT agent. The center first approach and the arm first approach are two major pathways for RAFT star polymer synthesis. The core first strategy necessitates the use of a multifunctional RAFT agent, with polymer chains (arms) growing from the core. The arm first approach entails the development of predetermined molecular weight polymeric arms that are then joined together after polymerization (Barner-Kowollik, Davis, & Stenzel, 2006; Boyer et al., 2011).

3. CONCLUSION

Polymeric nanoparticles can be used to improve the stability and bio distribution of drug delivery. There are some properties requirements of polymeric nanoparticles for drug delivery, includes: can release drug at slow rate, sufficiently small less than 100 nm, and high stability during the penetration or release process. These properties may only behave by polymeric nanoparticles with specific and complex structure, such as block copolymer, micelles, and multi arm (star) polymer. RAFT polymerization has the ability to prepare various architectures of wide variety polymers with defined end and pendant functionalities.

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