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Recent Advances in Star Polymer Design: Degradability and the Potential for Drug Delivery

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The use of polymers as drug delivery devices represents an exciting area of development in the biomedical industry. This paper briefly highlights some of the different types of macromolecules that have attracted attention as potential drug delivery devices, with a particular focus on the class of star polymers known as core cross-linked star (CCS) polymers. The ability to control the rate at which encapsulated molecules can be released is an important factor in the design of efficient drug delivery devices. In this regard, several different techniques to incorporate degradable functionality into CCS polymers are examined as a potential means of controlling release kinetics.

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Introduction

In the past decade considerable attention has been focused on the merging fields of polymer chemistry and the biological sciences. One particular area that has attracted a great deal of interest concerns the use of polymers as potential drug delivery vehicles. Properties such as the capacity to solubilize hydrophobic drugs, target specific physiological sites such as cancerous cells, and control the rate of drug release have proven quite attractive for many potential applications.[1] The use of such macromolecules can also lead to reduced dosage requirements and consequently minimize any potentially undesirable side effects associated with the drug.

This paper examines several different macromolecular architectures with regard to their suitability for use as drug delivery vehicles, and highlights several recent developments in the design of degradable star polymers and their potential application in the pharmaceutical industry.

Macromolecular Architectures for Drug Delivery

Recent advances in controlled polymerization techniques have provided the capacity to synthesize macromolecules with precisely controlled architectures that contain a high degree of functionality. This has led to the synthesis of a variety of macromolecules that have shown potential in their ability to act as drug delivery vehicles. So far the main polymeric classes of interest have been block copolymer micelles, dendrimers, and star polymers with each type displaying certain advantages and disadvantages.

Of these three classes the most widely studied in terms of its drug delivery capabilities has been the micelle.[2–4] The self-assembly of amphiphilic block copolymers in aqueous media to form micelle structures with hydrophobic core domains surrounded by a hydrophilic corona provides a vessel that is particularly suited to pharmaceutical applications. The core domain of the micelle provides a region capable of solubilizing

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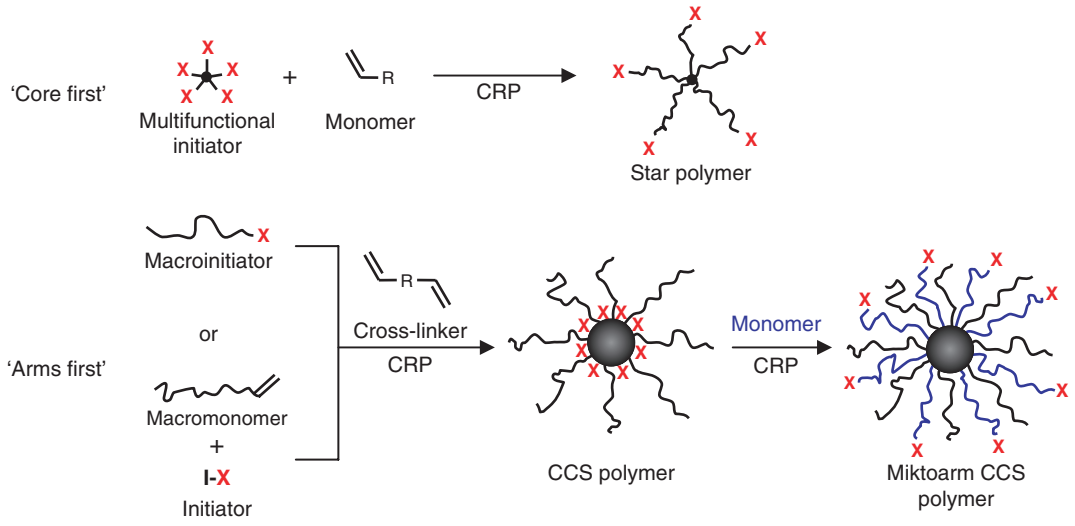

Fig. 1. Schematic representation of star polymer synthesis by the 'core first' and 'arms first' approach.

hydrophobic drug molecules while the hydrophilic corona acts to stabilize the particle in aqueous media.

The potential of micelles to be used as drug delivery devices is vast but unfortunately there are several issues that affect their usefulness. One such problem is related to the stability of these particles, a property that is intrinsically related to the polymer's critical micelle concentration (CMC). The CMC represents a specific concentration above which the formation of micelles is thermodynamically favourable. Consequently, when the concentration of the copolymer solution drops below the CMC the micelles will disassemble. This is a major concern for their application as drug carriers in vivo since severe dilution, which occurs upon injection into the bloodstream, can alter the micelle structure and size, and potentially result in total dissociation. This makes it difficult to control the rate of drug release and can even lead to serious toxicity issues if the micelles spontaneously dissociate and release high concentrations of the drug. Several attempts to overcome these stability issues have involved the covalent bonding of either the core[5] or the shell[6] domains of the micelle. This prevents any potential dissociation while still maintaining the capacity for drug delivery; however, this also introduces added complexity into the system.

Another drug delivery system that has attracted significant attention involves the use of dendrimers.[7,8] By growing or attaching hydrophilic polymers such as poly(ethylene glycol) (PEG) to the outer surface of hydrophobic dendrimers it is possible to synthesize amphiphilic dendrimers with a hydrophobic core and hydrophilic corona. Similar to the micelle system previously described, amphiphilic dendrimers have the capacity to accommodate hydrophobic drug molecules within the core and stabilize them within aqueous media. However, unlike micelles, the structural stability of amphiphilic dendrimers is not concentration dependant because of the covalent bonding of the dendrimer core. This results in drug delivery devices that are better suited for injection into the blood stream since they do not experience dissociation problems.

It has been demonstrated that amphiphilic dendrimers with larger cores have a higher encapsulation capability than those with smaller cores.[7,8] However, the synthesis of higher generation dendrimers becomes increasingly difficult because of the structural limitations imposed by the relatively compact architecture of dendrimers. This results in a size limitation of the hydrophobic dendrimer core which in turn limits drug loading capacities. In addition to this the two basic synthetic strategies generally employed in dendrimer synthesis, namely the divergent[9,10] and convergent[11] approaches, are tedious and time consuming. Both require a series of stepwise reactions with growth of each dendrimer generation that involves activation, coupling, protection, and purification steps. In an effort to make this a more commercially attractive process several methods have been developed to reduce the number of steps involved in the synthesis of dendrimers.[12–14]

A third class of polymer architecture that has found application in the field of drug delivery is the star polymer.[15] The structure of star polymers is unique, and consists of a three-dimensional architecture where linear arms are linked by a central core. They represent an interesting class of macromolecule because they can have very high molecular weights but still possess a solubility and viscosity similar to that of linear or branched polymers of relatively low molecular weight.[16] The combination of unique rheological properties and the ability to employ controlled polymerization techniques to obtain well-defined structures makes this class of macromolecule very attractive for use in a variety of applications including that of drug delivery.

Several methods for synthesizing star polymers have been developed that can generally be categorized as either following the 'core first' or the 'arms first' approach (Fig. 1). The 'core first' approach involves the use of a multifunctional initiator from which the arms of the star polymer are grown.[17–19] Using this method limits the number of arms on the star polymer to the initial functionality of the initiator and typically results in a relatively low-molecular-weight core with limited drug loading capacity. To overcome this problem, dendritic and hyperbranched polymers have been utilized as multifunctional macroinitiators to synthesize high-molecular-weight star polymers with many arms.[20–23] The use of dendrimers and hyperbranched polymers allows for the generation of star polymers with larger core domains, which have consequentially been shown to have significantly increased loading capacities.

The problem of limited core size can also be overcome by synthesizing star polymers by the 'arms first' approach. Here, living linear arms (macroinitiator) capable of further chain extension are initially synthesized. These terminally reactive linear polymer chains are subsequently used to initiate the polymerization of a cross-linkable monomer such that the active arm ends are coupled together. A variation of this technique involves the copolymerization of linear macromonomer with cross-linker using low-molar-mass initiators.[24] Both these techniques result in star polymers with high-molecular-weight cross-linked cores surrounded by many polymeric arms, the number of which follows a statistical distribution. This type of star, which will hereafter be referred to as core cross-linked star (CCS) polymer to avoid ambiguity, is ideally suited for use as a potential drug delivery device because of the large loading capacity of the hydrophobic core, the size of which can be easily altered through the use of a 'spacer monomer' during the core formation step.[25] The ability to independently control the length and type of arm relative to the core is also a very attractive property for pharmaceutical applications.

Traditionally, CCS polymers were synthesized using anionic polymerizations[26] because of the high degree of control afforded, which allowed for the synthesis of stars with narrow polydispersities and uniform arm lengths. However, anionic polymerizations required very stringent reaction conditions and as such have been superseded by recent developments in controlled radical polymerization (CRP) techniques. The advancement of CRP has made it possible to synthesize highly functionalized macromolecules with precisely controlled architectures under much less rigorous conditions than required for anionic polymerizations.[27–29] CRP techniques such as nitroxide-mediated radical polymerization (NMP),[30] atom transfer radical polymerization (ATRP),[31] and reverse addition–fragmentation chain transfer (RAFT)[32] polymerization have all been successfully employed in the synthesis of CCS polymers. With RAFT having only limited success[33] the most efficient and popular technique for synthesizing CCS polymers has been ATRP. Combining this with the recent development of the ATRP ARGET system by Matyjaszewski and coworkers,[34] a process that makes it possible to perform ATRP in the presence of a limited amount of air, the synthesis of CCS polymers could become much more commercially attractive in the future.

Recently another form of controlled polymerization known as ring-opening polymerization (ROP) has also been successfully employed in the synthesis of CCS polymers.[35] The ability to utilize a variety of controlled polymerization techniques means that we can now synthesize CCS polymers with low polydispersities and high functionality. Combining this with the capacity to easily tune the core/shell size, high loading capacities, and no inherent stability issues makes the CCS polymer ideally suited for drug delivery applications.

Degradable CCS Polymers

One important aspect of potential drug delivery systems lies in the ability to control the release kinetics of the drug from the delivery vehicle. The structural properties of CCS polymers play a significant role in influencing the diffusion rate of encapsulated molecules out from the core of the polymeric carrier. By tailoring the core/shell size ratio, overall hydrodynamic volume, arm density, and the degree of amphiphilicity, we can control the release kinetics. However, a more attractive method involves the incorporation of degradable functionality such that a higher degree of control can be exerted over the dynamics of drug release. The design of degradable stars that are pH-sensitive also opens the door for targeted drug release since various tissues and organs within the body exist within localized pH environments. Degradable drug delivery devices can also prevent unwanted bioaccumulation of the polymeric carriers by breaking them down into smaller molecules that can be excreted from the body.

The structural architecture of CCS polymers is such that it can be divided into two separate domains, that of the arms and the core. This allows for selective incorporation of degradable functionality into either of these domains, which makes it possible to tailor the degradability and, therefore, control the kinetics of drug release.

Arm Degradability

The method of CCS polymer synthesis allows for a large variety of choice in the type of arms we can attach to the core. In essence, if a linear polymer can be functionalized to act as macroinitiator or macromonomer it can then be used to form the arms in a CCS polymer. In some cases protective chemistry may need to be employed, such as in the synthesis of poly(acrylic acid) stars formed using ATRP,[23,36] but in the majority of cases this is not required. Therefore, by appropriately functionalizing degradable linear polymers we can effectively synthesize CCS polymers where the degradation rate of the arms can be controlled to modify the rate of drug release.

Polyester-based structures have attracted significant attention as degradable polymers because of the ease of degradation by hydrolysis of the ester linkages. Poly(ε-caprolactone) (PCL) in particular has proven to be quite useful in the biomedical field.[37,38] One particular advantage of PCL is that it is considered a biodegradable and biocompatible polymer with degradation products that are capable of being absorbed by the body with minimal tissue reaction.[39]

The incorporation of PCL arms into CCS polymers can easily be achieved through end functionalization of linear PCL with an alkyl halide group. This generates a PCL-based macroinitiator that can subsequently be cross-linked under ATRP conditions to form CCS polymer with degradable PCL arms.[40,41] Functionalization of PCL can be achieved either through the attachment of an alkyl halide group to preformed PCL or by using an alkyl halide functionalized alcohol to initiate the ROP of the ε-caprolactone monomer. Cross-linking of this PCL macroinitiator with divinyl monomers, such as ethylene glycol dimethacrylate (EGDMA) or divinyl benzene (DVB) yields CCS polymers that can easily be hydrolyzed to remove the arms without destroying the cross-linked core.

Perhaps of more relevance for drug delivery systems is the ability to generate a CCS polymer where only a fraction of the arms are degradable. This can be achieved by introducing a second type of arm to synthesize what is known as a miktoarm CCS polymer (Fig. 1). Since the initiating functionality of the macroinitiators is preserved within the cross-linked core, it is possible to utilize these to grow a second type of arm out from the core in what is typically referred to as the 'in–out' method.[16,40,42,43] However, low initiation efficiency of the second arm because of the reduced accessibility of the initiating sites within the core can be a problem. Alternatively, miktoarm CCS can be synthesized by simply introducing a second type of polymeric macroinitiator during the cross-linking step.[41] However, this requires that the two macroinitiators have similar reactivity such that the resultant miktoarm CCS contains both types of arm.

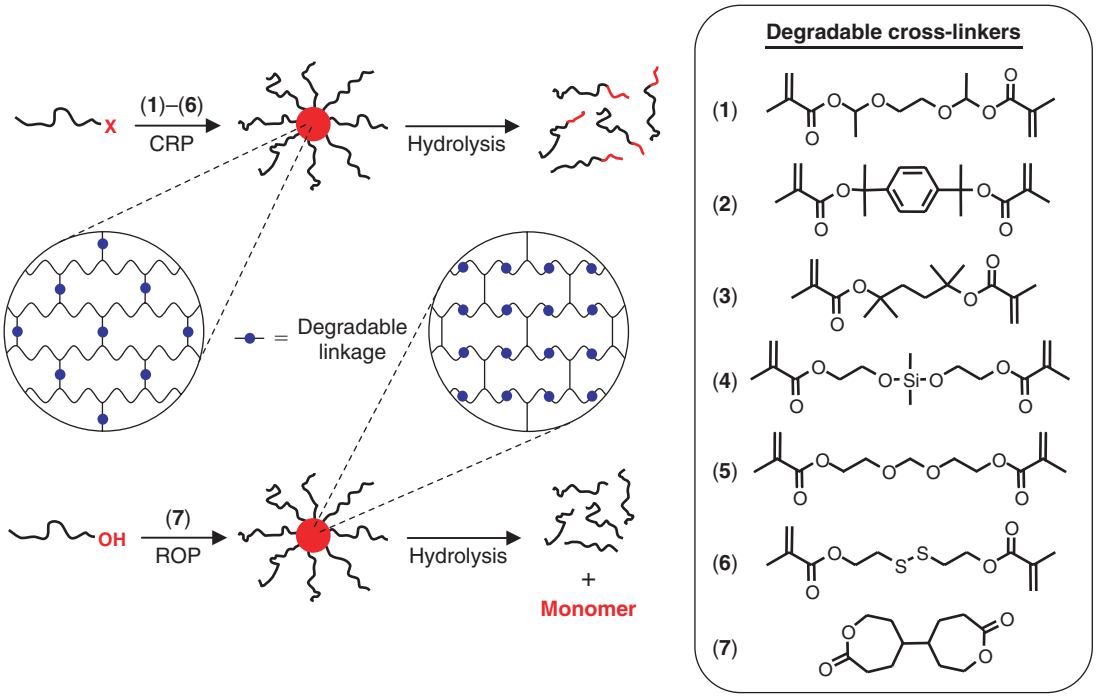

Fig. 2. Synthesis of CCS polymers with degradable cores.

Utilizing these techniques we can synthesize CCS polymers with a mixture of degradable and non-degradable arms.[40,41] This allows for a higher degree of control over the rate of drug release since the density of arms in the corona of the CCS affects the rate at which drug can diffuse out from the core. For example, hydrolysis of CCS polymers with a higher ratio of degradable arms should exhibit faster drug release kinetics compared to those with fewer degradable arms. The use of miktoarm CCS polymers also allows for the manipulation of arm degradation rates by the incorporation of polymers such as poly(lactic acid), which has been shown to increase the degradation rate of PCL.[44]

Core Degradability

Control over the degradability of the core domain is another important aspect in the use of CCS polymers as potential drug delivery devices. The ability to use CCS polymers as transport vehicles is related to the preferential encapsulation of drug molecules within the hydrophobic core domain. Therefore, the incorporation of degradable functionality into the core of CCS polymers has the potential to directly affect the kinetics of drug release. For example, complete degradation of the core domain removes the localized hydrophobic region that causes any encapsulated drugs to be immediately dispersed. This is vastly different to the case of degradable arm CCS polymers where the hydrolysis of arms only has the potential to affect the rate of diffusion of drug out from the core.

Several different techniques have been utilized to incorporate degradable functionality into the core of CCS polymers with the majority focusing on the use of modified dimethacrylate monomers as a degradable cross-linking component (Fig. 2). Ruckenstein and Zhang[45] synthesized core-degradable CCS polymers using a ethylene glycol di(1-methacryloyloxy)ethyl ether (**1**) cross-linker. This allowed for the incorporation of acid-labile ester linkages that could easily be hydrolyzed to break apart the core structure of the CCS polymer. Long and coworkers[46] also used a similar approach to show that both dicumyl alcohol dimethacrylate (**2**) and 2,5-dimethylhexane-2,5-diol dimethacrylate (**3**) cross-linkers could be used to incorporate acid-labile ester linkages into the core of CCS polymers. Each of these ester-based cross-linkers was polymerized under living anionic conditions but the resultant polydispersities of the stars turned out to be quite broad. Issues of low conversion and low molecular weight were also experienced, which indicated that the bulky structure of these monomers reduced their efficiency as cross-linkers for CCS formation.

Other degradable functionalities apart from ester linkages have also been incorporated into dimethacrylate-based cross-linkers. An example of this is shown by the work of Patrickios and coworkers[47–49] who, in addition to synthesizing degradable ester-based cross-linkers, also utilized acid-labile siloxane and acetal groups to synthesize a dimethyldi(methacryloyloxy-1-ethoxy)silane (**4**) and di(methacryloyloxy-1-ethoxy)methane (**5**) cross-linker, respectively. These degradable cross-linkers were subsequently polymerized under group transfer polymerization conditions to yield CCS polymers with degradable cores. However, this technique also suffered from the bulky nature of the cross-linkers to yield CCS polymers with broad polydispersities and, in the case of the siloxane cross-linker, low conversions. Another type of degradable cross-linker based on the incorporation of cleavable disulfide linkages, bis(2-methacryloyloxyethyl) disulfide (**6**), was synthesized by Matyjaszewski and coworkers.[43] This degradable cross-linker was subsequently used to generate a CCS polymer under ATRP conditions where the disulfide linkages within the core could easily be cleaved by use of a reducing agent. This technique allowed for high conversions but still suffered from broad polydispersities.

A more promising route for the synthesis of core degradable CCS polymers suitable for use in biomedical applications

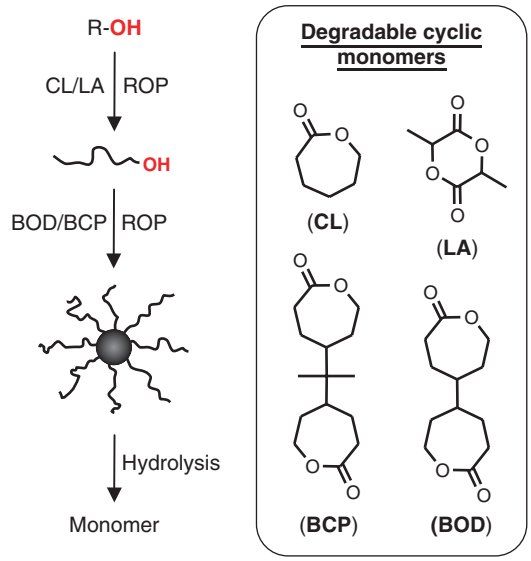

Fig. 3. Synthesis of fully degradable CCS polymers using ROP.

involves the use of bislactone cross-linkers. One such example has been in the use of 4,4′-bioxepanyl-7,7′-dione (BOD) (**7**), a bislactone that consists of two caprolactone rings bridged at the 4-position (Fig. 2), to cross-link end-functionalized linear polystyrene.[41] This allows for the production of CCS polymers with polyester-based cores that can easily be hydrolyzed. The structure of these cores is essentially that of cross-linked polycaprolactone and as such is expected to exhibit biocompatible and biodegradable properties similar to that of PCL. In addition to this, the use of lactone-based cross-linkers generates a core domain that can be completely degraded into small monomeric units and, therefore, release the original polymeric arms. This is different to methacrylate-based cross-linked cores, which when degraded will break apart to yield linear arms that have been chain extended. The reason for this lies in the location of the degradable linkage, which for lactone-based cores is situated in the backbone of the cross-linked chains, whereas for methacrylate-based cores it is located in the bridging unit between the cross-linked chains (Fig. 2).

The method of synthesis in this case is slightly different from that of the previous systems described since we are no longer making use of divinyl-based cross-linkers; instead we are using cyclic-based cross-linkers. This requires that the cross-linking step be performed under ROP conditions with the macroinitiator arms being hydroxy end-functionalized so they can initiate polymerization of the BOD cross-linker. Since ROP is a controlled polymerization technique the polydispersity of stars produced by this method are quite low ($M_w/M_n < 1.2$). Reasonably high conversions are also achieved, which shows that this technique has significant potential for use in synthesizing drug delivery devices suitable for use in the biomedical industry.

Fully Degradable CCS Polymers

The next obvious step in the evolution of degradable CCS polymers is the incorporation of degradable functionality into both the arm and core domains concurrently. This can be achieved by combining the use of any of the degradable arm and cross-linker systems previously described, but perhaps of greatest interest is the class of CCS polymers entirely derived from lactones (Fig. 3).[35,41,50] One of the advantages of this type of system lies in the ability to synthesize CCS polymers using only ROP. Unlike other forms of controlled polymerizations, such as ATRP, ROP is not a radical-based technique and is consequently not sensitive to the presence of radical scavengers such as oxygen. This makes it a much easier reaction to handle especially in terms of one-pot syntheses where cross-linker can be directly added to the system after arm formation without any need for isolation or purification of the intermediate products. One drawback of the ROP-based synthesis of CCS polymers is that the presence of hydroxy impurities such as water can potentially initiate undesirable side reactions such as star–star coupling.

Examples of CCS polymers with PCL arms and BOD cross-linked cores have been shown to be fully degradable under acidic conditions[35] and are broken down into small-chain acids. Since the core and the arms in this case are essentially the same polymer the degradation rates are expected to be similar. By employing a range of different cyclic esters, such as lactide (LA) or 2,2-bis(ε-caprolactone-4-yl)propane (BCP) (Fig. 3), it is possible to generate fully degradable CCS polymers with heterogeneous core/shell structures. The advantage of this kind of star polymer is that the arms should have a degradation rate different from that of the core, which allows for a higher degree of control over the drug release kinetics of the CCS polymer.

Functionalization of CCS Polymers

Apart from degradability there are several other factors that are just as important in the design of CCS polymers for drug delivery applications. One of these is the ability to introduce various functional groups, which allow for the incorporation of targeting, imaging, or biocompatible functionalities. The attachment of targeting ligands to create drug delivery devices capable of recognizing disease-affected sites (cancerous cells, tumours) has significant potential. Not only does this allow for more effective drug delivery but in combination with imaging functionalities could be used as a diagnostic tool to identify diseased tissue.

The surface modification of drug delivery devices with biocompatible polymers, such as PEG, is another desired property that can be achieved though the use of appropriate surface functionalities. The incorporation of PEG has widely been shown to prolong circulation times in vivo,[51–53] a property that can actually lead to significant passive targeting of tumours through the ‘enhanced permeability and retention’ (EPR) effect.[54]

The controlled polymerization techniques used to synthesize CCS polymers allow for incorporation of a wide variety of different functional groups, which range from hydrophilic groups such as hydroxy, carboxylic acid, and amine groups to click chemistry functionalities such as alkyne and azide groups. The unique three-dimensional architecture of CCS polymers also allows for the incorporation of these functionalities within different regions of the CCS polymer such as the core, the arms, or the surface of the star. For example, the use of functionalized monomer during the arm formation step can lead to CCS polymers where each arm contains a vast number of functional groups, either incorporated into the backbone of the polymeric arms or attached as pendant functionalities.[55] Alternatively, end-functionalized arms can be synthesized through the use of functional initiator to yield CCS polymers where only the periphery of the star is functionalized.[56,57] The core domain can be functionalized in a similar fashion through use of functional cross-linkers or functional monovinyl comonomers during the core formation step.[58,59] The macromonomer method of CCS synthesis provides an alternate route for core functionalization that has proven

to be slightly more efficient and involves the use of functional initiators.[60]

Through appropriate functionalization it is possible to overcome solvent compatibility issues associated with the synthesis of amphiphilic CCS polymers with a hydrophobic core and hydrophilic coronal domains. Hydrophobic CCS polymers that contain arms with appropriately protected functional groups can easily be synthesized such that deprotection of the arms can be used to generate a hydrophilic corona. For example, the deprotection of hydrophobic CCS polymer with poly(*tert*-butyl acrylate) arms can be used to generate a hydrophilic corona that consists of poly(acrylic acid) arms.[23,36] Alternatively, functional groups capable of initiating coupling reactions such as 'click chemistry' can be incorporated into the CCS polymer. This allows for the attachment of appropriately functionalized hydrophilic polymers such that the hydrophilicity of the CCS corona can easily be modified.

Conclusions

As highlighted in this article, CCS polymers represent an interesting class of macromolecule having many desirable attributes. High loading capacities, well-defined structures, and the ability to incorporate a wide variety of different functionalities have made CCS polymers particularly attractive in terms of their potential application as drug delivery devices. Although there is still a long way to go before this can be realized, there have been several recent developments in the field of degradable CCS polymers which provide some interesting possibilities. In particular the synthesis of lactone-based CCS polymers, both arm and core domains, provides an easy route for the synthesis of a biodegradable drug delivery system. However, several issues still need to be addressed such as the ability to effectively stop unwanted star–star coupling interactions that can lead to high-molecular-weight products and broad polydispersities.

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