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Nanomicellar formulations for sustained drug delivery: strategies and underlying principles

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Abstract

Micellar delivery systems smaller than 100 nm can be readily prepared. While micelles allow a great depth of tissue penetration for targeted drug delivery, they usually disintegrate rapidly in the body. Thus, sustained drug delivery from micellar nanocarriers is a challenge. This article summarizes various key strategies and underlying principles for sustained drug delivery using micellar nanocarriers. Comparisons are made with other competing delivery systems such as polymeric microparticles and nanoparticles. Amphiphilic molecules self-assemble in appropriate liquid media to form nanoscale micelles. Strategies for sustained release nanomicellar carriers include use of prodrugs, drug polymer conjugates, novel polymers with low critical micellar concentration or of a reverse thermoresponsive nature, reverse micelles, multi-layer micelles with layer by layer assembly, polymeric films capable of forming micelles *in vivo* and micelle coats on a solid support. These new micellar systems are promising for sustained drug delivery.

Keywords

drug delivery; micelles; nanotechnology; sustained delivery

A molecule that has polar or hydrophilic groups as well as nonpolar or hydrophobic portions is known as an amphiphilic molecule. Amphiphilic molecules exhibit a unique behavior of self-assembly when exposed to a solvent. In a hydrophilic solvent, the polar part orients itself towards the solvent, while the hydrophobic part of the molecule orients away from the solvent. In doing so, the molecules form clusters where the hydrophobic portions are clustered in a core away from the solvent and the hydrophilic portions are aligned towards the solvent. When formed in this orientation, such aggregates of an amphiphilic molecule are known as normal or regular micelles. Amphiphilic molecules, when exposed to a hydrophobic solvent, can form micelles with an opposite orientation, that is, with the hydrophobic part on the outside and hydrophilic part on the inside. These micelles are known as reverse micelles.

By definition, micelles can be formed by any amphiphilic molecule. Early on, pharmaceutically acceptable surfactants were investigated for regular micelle formation in aqueous media. However, conventional surfactants have a very high critical micelle concentration (CMC), a concentration beyond which the surfactant forms micelles. High CMCs implies that the micelles can dissociate upon dilution in the bloodstream or other biological fluids following dosing [1]. Due to this limitation, alternative amphiphilic materials including amphiphilic

copolymers have been developed. Similar to surfactants, these new polymers can form micellar structures in aqueous media, but at lower concentrations [2].

Although various drug types can be encapsulated in micelles to different extents, the above described normal or regular micelles are primarily suited for poorly soluble drugs, which can be encapsulated in the micellar core. Since several new drugs under development are poorly soluble, regular micelles are expected to be of value in enhancing solubility and hence bioavailability of these drugs. However, reverse micelles are good candidates for the encapsulation and delivery of hydrophilic drugs. Reverse micelles were investigated for the delivery of proteins such as lysozyme [3] and other solutes including trypan blue [4] and fluorescein [5]. Furthermore, these reverse self-assemblies can also be used to encapsulate polymeric microparticles [4]. Qiu *et al.* showed that reverse micelles made of amphiphilic phosphazene polymers can enhance the encapsulation efficiency and the *in vitro* release profile of poly(lactide-co-glycolide) (PLGA) microparticles [4]. While plain PLGA micro particles released more than 50% of the drug in 1 day, optimal micelle formulations encapsulating PLGA particles released less than 30% of the drug at the end of 60 days.

Figure 1 shows several types of micelles including regular micelles, reverse micelles and unimolecular micelles used for drug delivery. Regular micelles are self-assemblies of amphiphilic copolymers in an aqueous medium while reverse micelles are self assemblies of amphiphilic copolymers in a nonaqueous medium. Unimolecular micelles are made from the block copolymers such as core(laur)-polyethylene glycol (core[laur]PEG). These polymers have several hydrophilic and hydrophobic regions in one molecule, which enables the self-assembly of one molecule into a micelle. Reported advantages of micelles as delivery systems include simple preparation, increased drug solubility, reduced toxicity, increased circulation time, enhanced tissue penetration and targetability [2]. However, the conventional micelles also have several disadvantages such as system instability over long periods of time, sustained release only for short periods of time, inadequate suitability for hydrophilic drugs and the need for system optimization with each drug [6]. These properties of the micelles depend on the material used for the preparation of micelles. Table 1 summarizes some of the materials used for the formulation of micelles. In addition to conventional pharmaceutical surfactants and amphiphilic block copolymers, oligopeptides, lipids and polysaccharides can be used in conjugation with polymers for preparing micelles.

Nonionic surfactants such as tween 80 can form micelles. However, the CMC of these surfactants is 2.2 mM [7]. A higher CMC of the nonionic surfactants means that a higher concentration of the surfactant is required to keep them in the micelle form. At high concentrations, the surfactants might be toxic. Cationic surfactants such as cetyl trimethyl ammonium bromide have a CMC of 0.92 mM [8]. However, quaternary ammonium compounds can potentially be toxic due to their ability to interact with the negatively charged cell membranes, thereby causing cell damage [1].

Amphiphilic block copolymers are more promising as micellar carriers, especially to minimize micelle disintegration after dilution and to potentially prolong drug delivery [2]. Amphiphilic copolymers like PLGA-PEG H40 (dendritic boltron H40 [40 hydroxyl groups])-PLA-mPEG (dendritic boltron H40 core-poly(lactide acid-methoxy polyethylene glycol)) have a CMC of less than 100 µg/ml. When used at high concentrations, a significant dilution is feasible for these polymers before the micellar structure falls apart. Despite such innovative polymers, there is still an unmet need for the development of sustained release micelles that are capable of releasing the drug for more than 2–3 months. Sustained drug release is required for treating chronic diseases. Sustained drug delivery is also expected to be beneficial in treating some infectious diseases and cancers. Current approaches to achieve sustained drug release from the micelles include prodrug synthesis, use of novel polymers, layer by layer assembly of micelles

on a solid support, formation of reverse micelles, preparation of drug polymer conjugate micelles and development of polymer films that form micelles *in vivo*. Some other applications of the micelles also include improving solubility of poorly soluble drugs and targeting using pH responsive micelles. But these applications do not necessarily offer sustained release and hence, their discussion is beyond the scope of this review. The small size of the micelles does provide some advantages over larger particulate systems in terms of drug targeting. However, significant progress needs to be made in the field before we can achieve sustained release from the micelles that is comparable to larger particulate delivery systems and implants.

This article discusses some of the investigational approaches for the development of sustained release micelles in order to facilitate further development in the future.

Approaches to sustain drug delivery from micelles

Table 2 summarizes some of the investigational approaches for sustaining drug release from micelles. Broadly, these approaches can be classified as those using prodrugs, drug polymer conjugates, novel polymers with low critical micellar concentrations, reverse micelles, multilayer micelles, reverse thermoresponsive micelles, polymer films capable of forming micelles *in vivo* and micelles coated on solid support. All these approaches are further discussed below.

■ Prodrugs

Synthesizing a prodrug of the drug of interest and encapsulating in a micelle is useful for sustaining drug release. In this approach a prodrug that is most compatible with the micelle-forming amphiphilic molecule is desirable. Prodrug release from the micelles and prodrug conversion to drug are the two limiting processes controlling drug release in this approach. One such example is paclitaxel palmitate, a paclitaxel prodrug, which was synthesized by Forrest *et al.* [9] and encapsulated in PEG-b-polycaprolactone (PEG-b-PCL) (M_w of PEG: 5000, M_w of PCL: 10,500) micelles. The mean diameter of these micelles was about 27–44 nm. The prodrug micelles released the prodrug over 14 days compared with 1 day release with the plain drug. However, this study did not assess the release of the drug from the prodrug by itself. The prodrug micelles also showed better antiproliferative effects in breast cancer cells when compared with the unencapsulated prodrug or paclitaxel itself [9], although the improvements were marginal (~10–20% greater inhibition of cell growth). Further, the micelles sustained serum drug as well as prodrug levels for prolonged periods in Sprague Dawley rats. Encapsulation of paclitaxel in micelles increased the time for which the drug was detected in the serum from less than 10 to 25 h. For prodrug, micelles retained drug levels up to 50 h when compared with approximately 11 h for plain prodrug. Thus, the prodrug approach in conjunction with micelles prolongs drug release and hence, potentially its effects as well. Apart from increasing the release time and effect, this approach may lead to an increase in tolerability of the drugs among drug recipients. Another study by Xiong *et al.* showed an increase in tolerability towards geldanamycin prodrug in rats when formulated in methoxy PEG-b-PCL (5000:9200) micelles [10]. Free prodrug was administered to Sprague Dawley rats at 10, 20 and 40 mg/kg doses and prodrug encapsulated in micelles was administered at 10, 20, 40, and 200 mg/kg doses. Blinded observers made observations of nose bleeding, diarrhea and visible behavioral changes associated with geldanamycin prodrug toxicity. The encapsulated prodrug did not show any signs of toxicity for 24 h at 40 mg/kg dose while the free prodrug showed signs of toxicity within 12 h of administration of 10 mg/kg and higher doses. Thus, micellar formulation improves the tolerability of geldanamycin prodrug. However, a disadvantage for this approach is that the drug has to be modified to suit the delivery system and the chemistry of the drug may not always be amenable for suitable manipulations.

■ Drug polymer conjugates

This is one of the most effective ways to sustain drug release from a micellar delivery system. This approach typically involves forming a conjugate of the drug with the hydrophobic part of an amphiphilic polymer and then forming micelles out of this conjugate. Such a formulation will add two steps for the release of the drug. First, the drug is released from the polymer through enzyme hydrolysis or other means of breakdown and second, the drug is released via diffusion of the drug out of the micelles, with the former typically being the rate-limiting step. A major advantage of this method is that the drug remains in the micelle for a long period of time due to conjugation. However, this method needs some complex chemistry in forming a drug-polymer conjugate. Yoo and Park conjugated doxorubicin (DOX) with PLGA portion of PLGA-PEG ($M_n = 13000$, $M_w = 23000$), wherein the molecular weight of the PEG used to prepare the copolymer was 2000 [11].

In this preparation, PLGA-DOX formed the core and PEG formed the shell of the micelle. The reported size of the micelles was approximately 61.4 nm. The CMC of the micelles with or without DOX was found to be 0.1 $\mu\text{g/ml}$, indicating that the conjugated DOX did not affect the micelle-forming properties of the polymer. The drug-loading efficiency of the conjugate in micelles was approximately 99% while that of the physically entrapped drug was about 23%. *In vitro* drug release studies indicated approximately 60% drug release over 16 days for conjugate micelles as opposed to physical entrapment micelles, which released the entire dose in about 4 days [11]. Comparison of drug-conjugated micelles with the plain drug indicated that the micelles were 10-fold more cytotoxic than the free drug in HepG2 cells. Jeong and Park synthesized a conjugate of an oligodeoxynucleotide (ODN) and PLGA polymer using carbodiimide chemistry. The ODN acted as the hydrophilic portion and the PLGA acted as the hydrophobic portion of the conjugate. Micelles formulated using this conjugate had a mean diameter of approximately 65.2 nm and sustained *in vitro* release of the ODN up to 50 days. The CMC of the ODN conjugated micelles was found to be 7.5 $\mu\text{g/ml}$, which was higher than that of the PEG-PLA (<2 $\mu\text{g/ml}$) [12]. Higher CMC was attributed to the negative charge of the ODN and the associated charge repulsion. However, the CMC was lower than that of oligomethyl methacrylateacrylic acid polymers (> 100 $\mu\text{g/ml}$) [12]. The ODN uptake in mouse fibroblasts was higher for the conjugated micellar formulation compared with the plain ODN [11,12]. Figure 2 shows a comparison of *in vitro* drug release from some drug-polymer conjugates. A PLGA-DOX conjugate shows an *in vitro* release for at least 16 days compared to 4 days when the drug is physically entrapped in the micelles. On the other hand, an oligodinucleotide-PLGA conjugate sustained *in vitro* drug release up to 50 days. ODN-PLGA and PEG-PLGA-DOX represent the micelles prepared by the same strategy – polymer-drug conjugates. Hence, it is informative to compare the *in vitro* release from both these types of micelles.

■ NK012 micelles

NK012 polymeric micelles with a 20 nm diameter were developed by Kuroda *et al.* to encapsulate 7-ethyl 10-hydroxy camptothecin (SN38) and was compared with its prodrug irinotecan hydrochloride (CPT11). The formulation and the prodrug were tested using five human glioblastoma cell lines. The IC_{50} of plain drug SN38 was found to be 0.052 $\mu\text{mol/l}$, while that of the micellar formulation was found to be 0.069 $\mu\text{mol/l}$. The IC_{50} of the prodrug CPT11 was found to be 13 $\mu\text{mol/l}$, which is significantly higher than both the plain drug and the micellar formulation. The micelle formulation and the plain drug were also tested in orthotopic glioblastoma xenografts in nude mice. The micellar formulation of SN-38 demonstrated a significant (almost six times) decrease in the relative tumor volume until day 25 compared with the prodrug CPT11. The relative tumor volume was maintained near zero until 80 days with the micellar formulation. The relative body weight change in the mice during

treatment was also about 10% less for the micellar formulation than the prodrug, which indicates that the micellar formulation was relatively better tolerated than the prodrug [13].

Thus, conjugating the drug with the polymer and then forming micelles out of the conjugate leads to a sustained release of the drug.

■ Novel polymers

This is the most common approach used to prepare sustained release micelles. Polymers with very low CMC ($< 0.1 \mu\text{g/ml}$) can be used for prolonging the circulation time before the micelle degrades. Upon intravenous injection, the micelles undergo dilution in the body. If the CMC of the micelles is high, the concentration of the polymer or surfactant falls below the CMC upon dilution and hence, the micelles dissociate. Therefore, a higher concentration of the polymer or surfactant has to be used to prepare the micelles so that they withstand the dilution up to 5 l in the blood. However, the use of high concentrations might not be feasible due to toxicity related dose limitations. If the polymer or surfactant has a CMC lower than $0.1 \mu\text{g/ml}$, concentrations as low as 5 mg/ml may be used to prepare a micelle formulation in order to counter the dilution effects in the blood. A variety of polymers including diblock copolymers, triblock copolymers and graft copolymers have been synthesized for this purpose. Figure 3A–C show the shapes and arrangement of the micelles based on such polymers. The structures shown in Figure 3A–C do not always have a low CMC. The CMC depends on the polymer that is used to prepare the micelles. Diblock copolymers have two different blocks of different polymers while triblock copolymers have three different blocks of polymers. A graft polymer is comprised of one polymer that is attached to the backbone of another polymer.

Block copolymers with lipids—Block copolymers between a polymer and a lipid is one useful approach in preparing micelles. It has been shown that increasing the length of the hydrophobic portion of a micelle will lead to a decrease in its CMC [14]. Lipids are more hydrophobic than most polymers and hence, a micelle made with a lipid as its hydrophobic part might lower the CMC. Hence, using fatty acyl chains as hydrophobic segments in an amphiphilic copolymer might be a useful approach. Distearoyl phosphatidyl ethanolamine (DSPE) has been used as the hydrophobic block in a diblock copolymer with hydrophilic polyethylene oxide (PEO) to form 22 nm micelles [15]. These micelles sustained release of lipophilic beclomethasone dipropionate (partition coefficient $[\log D] = 3.49$) for up to 6 days [15]. Lavasanifar *et al.* prepared micelles of polyethylene oxide-poly[*N*-(6-hexyl stearate-*L*-aspartamide)] (PEO-PHSA) to encapsulate amphotericin B (an antifungal) [15]. The plain drug was released within 10 mins while the encapsulated drug was only 20% released in 1 h. The release depended inversely on the degree of fatty acid substitution in the core. A higher substitution leads to a slower release of the drug from the micelles. The slow release was attributed to the favorable interactions between the drug and the micellar core consisting of fatty acids. Slower release also protected the red blood cells from hemolysis, a side effect of the drug. However, the sustained release was only maintained up to a few hours [16].

Block copolymers with cyclodextrins—Another approach for drug delivery is supramolecular polymeric micelles. This involves non-covalent interactions between a macromolecular polymer, which works as a host, and a small polymer molecule, which works as a guest. One such attempt was made using α -cyclodextrins (α -CDs) as the hydrophilic macromolecular host and PCL ($M_n = 37,000$) as the hydrophobic guest molecule [17]. Using this approach, supramolecular polymeric micelles with a mean diameter of 30 nm were made. These micelles resulted in sustained release of an anti-inflammatory drug up to 700 h. One pot chemistry was used to synthesize the micelles. Figure 3E shows the formation of a supramolecular micelle. Urea was used in the formation of the supramolecular micelles to facilitate formation of the copolymer. Urea is protonated before addition to the mixture. When

it is added to the mixture, at a pH below its acid dissociation constant (pK_a), deprotonation of urea occurs leading to the release of a proton from urea. The deprotonation leads to a weakening of the strong intermolecular H-bonds between the CDs, thereby, allowing it to interact with PCL leading to the formation of PCL- α -CD copolymer.

Diblock copolymer micelles—Using a polymer that physically interacts with the drug can result in drug retention and sustained release of the drug from such polymer micelles. If the drug can form hydrogen bonds with the core of the micelle, then the release obtained from the micelle will be much more sustained. For example, Yang *et al.* prepared micelles from PEG-b-poly-L-lactic acid (PEG-b-PLLA; M_w : 8500 Da) and PEG-b-PCL (M_w : 10,050 Da) block copolymers and studied the *in vitro* release of the hydrophobic drug quercetin from these micelles. The release of quercetin was sustained from PEG-PLLA and PEG-PCL micelles for approximately 160 h. The *in vitro* release studies also showed that the total amount of drug released in 160 h was less for the PEG-PCL micelles than the PEG-PLLA micelles [18]. The sustained release was attributed to the H-bonds formed between the drug and the hydrophobic core of the micelle. The lower amount of drug released by the PEG-b-PCL micelle was attributed to a higher degree of H-bonding between quercetin and PCL than quercetin and PLLA.

Using a polymer that participates in hydrophobic interactions with the drug can also sustain the release of the drug from the micelle. If the polymer hydrophobically interacts with the drug, then the hydrophobic core of the micelle resists the migration of the drug from the core to the media, thus resulting in sustained drug release. This means that the release is affected not only by micelle properties but also by polymer and drug properties. An attempt to form such micelles was made by Xiangyang *et al.*, who synthesized micelles of *N*-succinyl, *N'*-octyl chitosan (chitosan M_w : 100,000 Da) and loaded DOX [19]. The mean diameter of the micelles was 100–200 nm and the CMC ranged from 2.4 to 5.9 $\mu\text{g/ml}$, depending on the percentage octyl content. The release inversely depended on the number of octyl chains, indicating that the octyl chain participates in the hydrophobic interactions with the drug [19]. The cytotoxicity of the micelles was tested on HepG2, A549, BGC and K562 cancer cell lines and was compared with free DOX. The IC_{50} for the drug and the micelles was compared and the IC_{50} for the micelles was found to be lower than the free drug by two- to six-fold.

Polymeric micelles made from PEG-poly(benzyl aspartate) were used to encapsulate synthetic retinoids Am80 and LE540. *In vitro* release studies at 37°C in phosphate buffered saline (PBS) showed that only 10% of the highly hydrophobic retinoid LE540 was released in 4 days while the less hydrophobic retinoid Am80 was approximately 100% released in 4 days. This again shows that hydrophobic interactions between the drug and the polymer may play a role in sustaining the release of the encapsulated drug [20].

A highly hydrophobic drug, griseofulvin, was entrapped in PLA-PEG ($M_n = 11,800$; $M_w = 14,000$) micelles [21]. The mean diameter of the micelles was 26.9 nm and the CMC of the polymer was 0.07–0.09 mg/ml. These micelles exhibited biphasic drug release, with 66% released within 20 days, and the rest by 30 days. On the other hand, the untrapped drug was released completely within 24 h. The slow release may be due to hydrophobic interactions between the drug and the core polymer.

Zhang *et al.* prepared micelles from amphiphilic graft polyphosphazenes with poly(*N*-isopropylacrylamide) (PNIPAAm) as the hydrophilic segment and ethyl 4-aminobenzoate (EAB) as the hydrophobic group [21]. PNIPAAm oligomer with a number average molecular weight of 1800 Da were synthesized by radical polymerization, which was used to synthesize amphiphilic polyphosphazene. A copolymer with a PNIPAAm/EtGly (Ethyl Glycinate) ratio of 1:5 was synthesized. The M_w and M_n of this copolymer was 26,000 Da and 14,000 Da,

respectively [22]. The CMCs obtained for the polymers were 0.089, 0.087, 0.083, 0.072 and 0.047 g/l at 15, 20, 25, 30 and 35°C, respectively. The average particle size of plain micelles was 85.2–389.7 nm. Loading 10.4% indomethacin resulted in micelles of 65.0–359.7 nm. Increasing the drug loading to 25.3% resulted in micelles of 201–412.4 nm. Further increase in indomethacin content led to a decrease in particle size to 96.6 nm [21]. These changes in size might occur because of the strong hydrogen bonding between the amide group of the PNIPAAm group of the polymer and the carboxylic group of the drug. This interaction might lead to the formation of a pseudo-hydrophobic amphiphilic copolymer compared with the copolymer itself. *In vitro* release profiles showed drug release for at least 40 h and indicated an increase in the release times with a decrease in pH. The micelles and the drug were injected subcutaneously in male Sprague Dawley rats and the pharmacokinetic profiles were compared. The T_{max} increased from 0.5 h for the free drug to 2 h for the micelles. The area under the curve (AUC) increased from 279.4 to 551.3 $\mu\text{g h/ml}$. The efficacy of the formulation was tested in a carrageenan-induced rat paw edema model. The micellar formulation showed a consistently higher decrease in the degree of rat paw edema over a period of 6 h [22]. At 6 h, the edema volume of the control group was 0.61 ml, edema in plain indomethacin oral administration group was 0.52 ml while that in the micelle formulation was 0.36 ml. The same group of investigators reported that polyphosphazene micelles were also more effective in Complete Freund's Adjuvant (CFA)-induced ankle arthritis model of Sprague Dawley rats. The swelling degree after 7 h for indomethacin micelle formulation decreased to 0.5 compared with 0.62 for the control. Indomethacin by oral administration also showed a swelling decrease from 0.62 to 0.52 after 7 h. However, the dose of indomethacin was 5 mg/kg compared with 1.5 mg/kg for micelles. This means that the micelle formulation was helpful in achieving a similar therapeutic effect at lower doses. The micelle formulation also showed no ulceration in the rats compared with higher dose free indomethacin oral administration, which showed considerable gastric ulceration (degree of ulceration: 2.75) [23].

Pegylated poly(L-lactide) (PLL), polyvalerolactone (PVL) and PCL ($M_w = 15,000\text{--}31,000$ g/mol) were used to prepare polymeric micelles. The CMC of the micelles ranged from 10^{-7} to 10^{-8} M. The particle size ranged from 159 to 206 nm and the release of the encapsulated indomethacin lasted at least until 14 days. Drug was not released fully by this time. *In vivo* pharmacokinetics after subcutaneous injections in rats showed a statistically significant increase in the AUC of the drug from 518.9 $\mu\text{g h/ml}$ for plain drug to 721.32 $\mu\text{g h/ml}$ for the micellar formulation. Reduced clearance of the micelles (and thus the drug) by the liver and the kidneys is the proposed mechanism for sustained drug release by these pegylated lactone micelles. This was shown by a statistically significant decrease in the levels of drug found in kidney and liver in the micelle formulation compared with the free drug. The plasma clearance values were not statistically significant for micelles and free drug [24]. The advantage of this strategy is the low CMC of the polymers, which makes the micelles very stable to dilution. However, the large size of the micelles might hinder their delivery.

Triblock copolymer micelles—Flower-like micelles can be formed with a triblock copolymer with small hydrophobic ends and a long hydrophilic midsection. When dissolved in water, such polymer molecules assemble to form flower-like micellar structure. These flower-like micelles can dissolve the drug in the hydrophobic core and sustain drug release for long periods of time. Sustained, zero-order release has been reported using PLA–PEO–PLA (M_w of PEO = 8900 Da; M_w of PLA = 4100–6500 Da) triblock flower-like micelles (mean diameter of approximately 7–13 nm) for sulindac (20 days) and tetracaine (10 days) [24]. Figure 3D shows the formation of flower-like micelles. The hydrophobic interactions between the micellar core and the drugs was proposed to be responsible for the sustained release of the drugs. Drug release was faster with crystalline PLA blocks than amorphous PLA blocks, possibly because crystalline PLA stacks together, leaving the drug largely at the periphery while amorphous PLA might better integrate/disperse the drug within the polymer matrix.

Most micelle-forming polymers are first dissolved in organic solvent followed by addition to an aqueous medium to form micelles. The use of organic solvents can be avoided for some triblock copolymer micelles. Furthermore, through suitable selection of polymers, greater drug loading as well as sustained drug release can be achieved. For example, PCL-PEG-PCL (M_w of PEG = 4000 Da; M_w of copolymer = 6000 Da) micelles were formed by Wei *et al.* [26]. This polymer can be thermally induced to self-assemble when the polymer is added to water at 50°C. The mean diameter of these micelles was 61 nm. Furthermore, the freeze-dried micelles were easily redispersable [26]. These micelles sustained the release of honokiol, an anticancer herbal drug from magnolia leaves, for at least 144 h. During this period, about 50% of the loaded drug was released from the micelles. On the other hand, the plain drug was released completely by 24 h. The cytotoxicity of the free drug and the drug encapsulated in micelles was also compared in lung cancer cells and both were found equally effective, which implies that the encapsulation in micelles did not improve the cytotoxic potency of the drug. However, the micelles might be advantageous *in vivo* due to prolonged circulation and/or drug targeting to the tumor sites.

■ Pluronics

Paclitaxel-loaded pluronic micelles of 150 nm in diameter were prepared from pluronic P105 polymer [27]. The pharmacokinetics and biodistribution of paclitaxel was studied in rats following intravenous administration. The half-life and AUC of the drug in micelle formulation were 4.0- and 2.2-fold higher, respectively, when compared with plain taxol.

■ Unimolecular micelles

Formation of a unimolecular micelle also helps sustain release of very fast-acting drugs. The unimolecular micelle is made out of a polymer that has several hydrophilic and hydrophobic portions in itself and forms a single molecular micelle. Hence, by definition, unimolecular micelles do not have a clear CMC. Figure 1C shows a unimolecular micelle. Lipids and PEG-like hydrophilic polymers can be conjugated to form such unimolecular micelles. One such polymer is core(laur) PEG, which, when formed into unimolecular micelles, prolongs the release of lidocaine to about 20 h from less than 10 h observed for the plain drug. The core (laur)PEG polymer consists of a core of lauroyl ester of mucic acid (19,000 Da) and a shell of mPEG-5000. The unimolecular micelles formed had a mean diameter of 50 nm [28]. Kainthan *et al.* prepared unimolecular micelles with a mean diameter of less than 10 nm from hyperbranched polyglycerols conjugated to PEG [29]. These micelles released paclitaxel up to 15 days in a sustained manner. However, the CMC of the surfactant (polyglycerol-PEG) was found to be > 1mM, which is very high when compared with the CMC of the block copolymers.

Unimolecular micelles were also prepared from hyperbranched glycerol-block-PEG [30]. The micelles had a hydrodynamic diameter of less than 10 nm and loading of paclitaxel did not affect the particle size of the micelles. The micelles were compared for their efficacy in four human bladder cancer cell lines and *in vivo* in athymic nude mice. These micelles had mucoadhesive properties and showed significantly greater reduction in orthotropic tumor growth and they were better tolerated when compared with taxol [30].

■ Multi-arm block copolymers

Synthesizing multiarm block copolymers can also be useful to overcome the stability problem of regular micelles. For instance star-shaped or multiarmed micelles can be formed with an amphiphilic block copolymer with multiple hydrophilic blocks and a single hydrophobic block. These polymers can form micelles if the number of arms is high enough. One such polymer is H40-PLA-mPEG (M_n = 108,516 Da; M_w = 148,678 Da). H40 is a polyol that contains 64 hydroxyl groups and is hydrophilic. This means that the multi-arm copolymer has two

hydrophilic portions and one hydrophobic region. This polymer was used to form micelles containing 5-FU (5-fluorouracil). The micelles sustained 5-FU release for up to 80 h, unlike plain drug, which was released completely in 4 h [31]. The CMC of this polymer was found to be 4.5 µg/ml and the mean diameter of the micelles was 74 nm. Neither the polymer (400 µg/ml) nor the micelle (up to 400 µg/ml) exposure up to 24 h showed any cytotoxicity in cultured human endothelial cells. Such a polymer with some stabilizing strategies (discussed later) might result in more prolonged release of the drug.

■ Graft polymers

Graft polymers have recently attracted significant attention in preparing micelles. Figure 3C shows a graft polymer. Cellulose graft polymers can be used to form micelles for sustained drug release. The cellulose portion of the polymer can be the hydrophilic part, with any hydrophobic segment conjugated to it to form an amphiphilic graft polymer. Such polymers are claimed to be biodegradable. Cellulose-g-PLLA (M_n of cellulose = 1.2×10^5 g/mol; M_n of PLLA = 11,000 g/mol) polymer has been used for the sustained delivery of prednisone acetate [33]. Delivery of prednisone acetate was sustained up to more than a week with the use of these micelles. However, drug release for plain drug was not reported. The polymer had a CMC of 47.1–58.1 µg/ml and the mean diameter of the micelles was 30–80 nm [32]. Similarly, graft polymer micelles of phthaloyl chitosan ($M_w = 5.78 \times 10^5$ Da) and mPEG-2000 sustained the release of camptothecin for 96 h. Moreover, this polymer was synthesized in such a way that the release rate and the percentage yield depended on the degree of deacetylation of chitosan. The CMC of the polymer was 28 µg/ml and the mean diameters ranged from 100–250 nm. The diameter increased with an increase in the degree of deacetylation. Further, higher amounts of drug were incorporated with an increase in the degree of deacetylation of chitosan. The cytotoxicity in HeLa cells also increased with the degree of deacetylation, most likely due to a greater amount of drug incorporated in the micelles [33].

■ Oligopeptides

Polymers have some degree of toxicity even if they are biocompatible. Therefore, there is a need to synthesize materials that are more biocompatible for the preparation of micelles and incorporation of drugs. Oligopeptides can be very useful amphiphilic molecules for the preparation of micelles. Hydrophobic residues, such as alanine, can be used to synthesize the hydrophobic block and hydrophilic residues like histidine or lysine can be used to synthesize the hydrophilic block. Such molecules can be used as amphiphilic molecules to formulate micelles. Histidine residues can facilitate endosomal escape and lysine residues can facilitate DNA binding. Using other similar amino acids, the peptide sequences can be tailored to meet the requirements for the drug to be incorporated and therefore, such micelles may have the potential to deliver genes or drugs. For instance, Ac-(AF)6-H5-K15-NH₂ peptide ($M_w = 3977.92$ Da) was synthesized and used for the delivery of DOX. The peptide is made of three blocks: one hydrophobic block of 6 alanine residues, one hydrophilic block of 5 histidine residues and one hydrophilic block of 15 lysine residues. The CMC of the oligopeptide was 42 µg/ml and the reported mean diameter was 102 nm. The uptake of DOX was studied in HepG2 cells by confocal microscopy, which showed a higher uptake of DOX from micelles. This system released approximately 35% of DOX in 40 h [34]. Interestingly, in this study, the plain drug was more cytotoxic than the micellar drug.

Okuda *et al.* prepared 173 nm polymeric micelles using a PEG–polyaspartic acid co polymer. They encapsulated the anti-tumor drug fenretidine in the polymeric micelles and demonstrated a significant increase in the AUC and half-life in mice, when compared with O/W and pegylated O/W emulsion formulations. Reduced drug clearance was considered to be the reason for the observed increase in AUC. The AUC values were 197, 225, and 4717 µg/h/ml, for O/W

emulsion, pegylated O/W emulsion and polymeric micelle, respectively. The corresponding clearance values were 382, 333 and 15.9 ml/h/kg, respectively [35].

Combination of polymer & polyamino acid—A combination of polymer and polyamino acid can form an amphiphilic polymer. PEG–polyglutamic acid copolymer was used to prepare micelles for the delivery of cisplatin. The mean diameter of the micelles was 28 nm. The micelles showed a consistent and sustained release of the drug during a 150 h release study. Only 60% of the drug was released during 150 h. The micelles were injected *in vivo* in mice and compared with the free drug. After 25 h, approximately 10% of the injected dose was found in plasma with micelles compared with 0.1% with the plain drug. This increase was attributed to the decrease in clearance of the micelles compared with the plain drug. This corresponded to less accumulation of the drug in liver, kidney and spleen compared with the tumor with the micelles [36].

Wei *et al.* reported the synthesis of a polyglutamic acid–poly(propylene oxide) (PPO)–poly glutamic acid polymer (PPO-4000) that is pH sensitive [37]. At high pH, the polyglutamic acid residues form a coil conformation. But at low pH, it transforms to an α -helix conformation. Therefore, at low pH, the polyglutamic acid chain shrinks and creates a stress on the core and hence, results in the distortion of the core of the micelles, which causes the entrapped drug to leak out. DOX showed release up to 168 h with this system. Further, this system can be dispersed in a temperature-sensitive gel and hence, a very sustained release dual drug delivery system might be feasible [37]. However, using peptides to encapsulate drugs is relatively a new field and *in vivo* work needs to be done further on this delivery system to ensure that this system indeed works as it promises. Figure 4 summarizes release from sustained release micelles.

■ Reverse micelles

All the above mentioned approaches have been designed for the delivery of largely hydrophobic drugs. However, these approaches are not as useful for the delivery of hydrophilic drugs. Reverse micelles can be used for the delivery of hydrophilic drugs. Figure 1B shows the alignment of the hydrophobic and hydrophilic regions in a reverse micelle.

Reverse micelles are especially useful for administration in oily vehicles. Usually the nutrients required for comatose patients are given as oily injections. Moreover, USP injections of steroids can also be made as oily injections. Reverse micelles can prove to be useful for the coadministration of hydrophilic drugs in such injections. Some biocompatible oils are also used as vehicles in oral delivery. Thus, reverse micelles may be useful in oral delivery of some drugs by dispersion of micelles in oily vehicles. Reverse micelles may be particularly useful for protein delivery. For instance, ovalbumin was encapsulated in poly caprolactone-poly(2-vinyl pyrrolidone) (PCL-b-P2VP; M_n PCL = 35,400 g/mol, M_n P2VP = 20,900 g/mol) reverse micelles and dispersed in an oily medium (oleic acid) [38]. The mean hydrodynamic diameter of the ovalbumin-loaded micelles was 157 nm. The protein was entrapped in the aqueous core and the micelles sustained protein release up to 200 h upon contact of the micelle containing oily medium with an aqueous medium. The release of hydrophilic dyes such as fluorescein sodium and trypan blue have been reported from this system up to 60 days. The dyes were dispersed in PLGA polymeric nanoparticles and the nanoparticles were encapsulated in micelles to provide a greater sustained release [6].

■ Multi-layer micelles with layer by layer assembly

Multi-layer micelle assembly can be used to achieve greater sustained release of drug from micelles than any other techniques. Micelles can be formed from an H-bond acceptor and an H-bond donor can be added to the micellar shell. Then, the micelles can be arranged layer by

layer on a support to form a micro-sized film containing several layers of drug-loaded micelles. The H-bonding can be tailored to be broken under desired conditions to release the micelles. Figure 5 shows a schematic of this strategy. Kim *et al.* showed sustained release of triclosan (an antibacterial) up to 15 days from these 3 μm thick films of PEO-b-PCL (PEO-5000, PCL-6500). The mean diameter of the micelles was 71 nm and the CMC of the polymer was 1.2 $\mu\text{g}/\text{ml}$. Upon release, the drug maintained its antibacterial activity [39]. A H-bond donor, polyacrylic acid (PAA; $M_w = 90,000$ Da), was added to the polymer to introduce H-bonding capability. The carboxylic groups on PAA were crosslinked to retard the release of the drug. The uncrosslinked film released all the drug in 120 min, while the release from the crosslinked films was maintained up to 15 days. This way, more drug can be loaded and a better release profile can be achieved. The release of the drug and the total amount of the drug in these cases depends on the number of layers and the thickness of the film synthesized.

■ Reverse thermo-responsive polymers

These polymers have special properties. They exist as a solid at room temperature but at higher temperatures such as the body temperature, these polymers form gel-like structures. This property can be used to form micelles, which will form a gel-like structure at body temperature. These structures can lock the drug in the core, resulting in a sustained release of the drug. These polymers, however, are complicated to synthesize and very long release times have not been reported. For instance, polyether carbonate copolymers PEG–polypropylene glycol (PPG) have been developed by Yang *et al.* to prepare such micelles [40]. The polymer had a CMC of 38.5 $\mu\text{g}/\text{ml}$ and the mean particle size of the micelles obtained was 65.5 nm. A varying ratio of PEG–PPG was used in the synthesis of these polymers to obtain polymers with molecular weights ranging from 10,416 to 15,238 Da. Aqueous solutions of these polymers have low viscosity at room temperature but show an increase in viscosity at body temperature. This system showed sustained release of hydroxycamptothecin (HCPT) for 80 h compared with less than 20 h for plain drug [40]. The *in vivo* pharmacokinetics of HCPT-loaded micelles were studied in rabbits. Plain HCPT, HCPT in pluronic micelles and HCPT in polyether carbonate micelles were compared for *in vivo* half-life. The HCPT in polyether carbonate micelles increased the *in vivo* half-life from 1.3 h for plain HCPT and 10.4 h for HCPT in pluronic micelles to 12.4 h in HCPT in polyether carbonate micelles. Similarly, pentablock polymers such as poly(2-diethylaminoethyl-methyl methacrylate) (PDEAEM25)–PEO100–PPO65–PEO100–PDEAEM25 ($M_n = 21,900$ Da) form a gel-like structure at body temperature [3]. Micelles made out of such pentablock amphiphilic polymer sustained release of lysozyme for up to 80 h. The release was pH dependent and a 49% increase in the lysozyme release was seen at pH 7 when compared with pH 8. PDEAEM has a pK_a of 7.8 and the tertiary amines in this polymer are protonated below 7.8, resulting in an elevated polymer hydrophilicity and drug release.

■ Polymer films converted to micelles at body temperature

This is a unique strategy that involves formation of a drug-containing copolymer film at room temperature. At body temperature, this film collapses into micelle-like particles, which entrap the drug. A higher amount of drug can be entrapped in the micelles with such a technique, and sustained drug release can be achieved. However, the synthesis of polymer films requires great technical expertise and can easily go wrong, resulting in burst release of the drug. Moreover, this approach tends to form micelles of a higher diameter than several of the above approaches. Such a technique using the polymer monomethoxy PEG-block-poly(trimethylene carbonate) (M_n of mPEG = 3100 Da; M_n of polytrimethylene carbonate = 10,800 Da) was investigated for dexamethasone by Zhang *et al.* [41]. This study reported sustained release of dexamethasone up to 20 days. The CMC of the polymer was 1.35 $\mu\text{g}/\text{ml}$. However, the mean diameter of the micelles was 210 nm, which was higher compared with some of the methods discussed above.

■ Micelles coated on metal stents

Metallic stents are in use for patients suffering from cardiovascular problems. If such patients need to be given medication, the stents can be a good source for drug release. Drug-eluting stents have been long investigated for treatment of lesions and other cardiovascular problems [42]. Drug-loaded micelles can potentially be coated on stents to achieve sustained drug release in patients. In this approach, the stent will perform the function it is supposed to perform, that is, widening the coronary arteries. Second, such a coated stent will release the drug of choice into circulation or arterial walls in a sustained manner. The stents can be appropriately heparinized and chemically treated so that they last for prolonged periods. However, it is a complicated system to manufacture and coating the micelles on the stents can be difficult. One such system was reported by Kim *et al.* They heparinized the metallic stents to create a nonthrombogenic environment and then PLL (poly-L-lactide) ($M_w = 70$ kDa) was adsorbed. On this preparation, hyaluronic acid- ($M_w = 17$ kDa) g-PLGA micelles were coated. The micelles (mean diameter 202.8 nm) were loaded with paclitaxel and the release of the drug was confirmed by release studies as well as the ability of the stent to arrest the growth of human coronary artery muscle cells. The drug release was sustained for at least 25 days [43]. Such a strategy can potentially be used with some of the micelle stabilizing strategies (discussed later) to further sustain drug release up to 6–12 months.

Figure 6 compares *in vitro* drug release for formulations prepared using various micelle-forming strategies including prodrugs, layer by layer assembly of micelles as a film, use of reverse thermoresponsive polymers to form micelles and layer by layer assembly of micelles on a stent. Figure 7 compares plasma clearance profiles of paclitaxel from PEG–PCL micelles, indomethacin from polyphosphazene micelles, indomethacin from PCL–PEG micelles, cisplatin from PGLA micelles and SN38 from NK012 micelles.

Micelle-stabilizing strategies

Up to now, some of the approaches used for creating sustained-release micellar delivery systems have been discussed. Below, some strategies useful for stabilizing the micelles are described. Stabilizing the micelles leads to reduced degradation or dissociation of the micelles. Stabilized micelles might circulate for a longer period, leading to a more sustained release of the drug from the system. Also, if stabilizing strategies are used in conjunction with some of the strategies mentioned above, a more prolonged release of the drugs can be achieved compared with what was reported above. Figure 8 summarizes some micelle stabilization strategies.

■ Cross-linking the shell

This strategy involves introduction of cross-linkable groups within the hydrophilic portion of the copolymer and then using polymer chemistry to cross-link the hydrophilic shell portion after the micellization of the polymer. Such cross-linking leads to a stabilization of the micelle system and delays the degradation of the micelle. This chemistry can be used in a biodegradable system and a shell cross-linked micelle can be prepared for drug delivery. The use of shell cross-linking with some other approaches, such as conjugation of the core with the drug, can be useful in preparing sustained-release micellar systems. For instance, multifunctional, multi-armed PEG can be used with some commonly used degradable hydro-phobic polymers to form an amphiphilic block copolymer. PEG branching in this polymer can be used to create cross-linkable groups in the system to prepare a shell cross-linked micelle system. Thurmond *et al.* [44] and Li *et al.* [45] reported interesting approaches for cross-linking of the micellar shell in order to stabilize the micelles. Thurmond *et al.* [44] prepared micelles from polyvinyl pyridine-*b*-poly styrene ($M_n = 52,500$ Da) block copolymer, which on self-assembly, forms shell cross-linked knedel-like micelles, which appear to be a hybrid between dendrimers, hollow spheres,

latex particles and block copolymer micelles. Li *et al.* reported similar stabilization of the micelles by cross-linking the shell of the micelles made from a poly(styrene-*b*-butadiene-*b*-styrene) polymer [45]. Their approach involved formation of the micelles in aqueous medium and then cross-linking the hydrophobic portion of the micelles using chloromethylation and amination. However, the usefulness of the above polystyrene systems for pharmaceutical purposes is unclear at this stage. In these approaches, since these cross-linking groups are on the shell, the individual micelles have to be kept sufficiently away from each other so that these cross-linking groups do not interact with the groups of other micelles but only interact with the cross-linking groups of the same micelle to cross-link the shell. This is required to prevent aggregation of the micelles. Hence, they have to be prepared under highly dilute conditions. Surface functionalities attached to the shell can add a new dimension of targetability to the sustained release already obtained. However, the chemistry used here is not simple to perform. Moreover, the chemical groups added to the polymer may contribute to its toxicity, change its properties and may render the micelle useless for drug delivery. Hence, such an approach should only be followed with some amount of caution.

■ Cross-linking the core

Crosslinking the shell has been tried by many groups with only moderate success. However, such a shell cross-linking needs preparation at a high dilution. This decreases the efficiency of the process [22]. Hence, the stabilization of micelles needs something other than shell cross-linking. The strategy of core cross-linking involves cross-linking the core to form a matrix that traps the drug inside it, thereby controlling the diffusion of the drug from the core. Such an approach is easy to use and different polymeric core portions can be used to suit the drug that is to be encapsulated. Many approaches have been tried to stabilize the core by cross-linking it with different functional groups. Addition of thiol group to the core of the micelle can be used to cross-link the core with a disulfide group. This has been done with polyion complex micelles by Kakizawa *et al.* [46]. In a polyion complex, the electrostatic interaction between two polymer segments drives association. Kakizawa *et al.* synthesized micelles using PEG-5000-*b*-poly(lysine) diblock copolymer. The polymerization degree of poly(lysine) was 22. The cross-linking of the poly(lysine) core was achieved using thiolation chemistry. The lysines in the core were thiolated and hence, they cross-linked with a disulfide bond. This stabilizes the core of the micelle and increases the micellar stability. A completely biodegradable system was prepared by Hu *et al.* using the polymer PEG-*b*-PLA with a 5-methyl-5-allyloxycarbonyl-1,3-dioxane-2-1 ($M_n = 4500$ Da) group as the polymerizable group for crosslinking the core [47]. The cross-linking was achieved postmicellization by reaction with 2,2-azoisobutyronitrile. The mean diameter of the resultant micelles was reported to be 130 nm. The micelles were shown to survive water dilution and temperature better than non-crosslinked micelles. This property of the core crosslinked micelles can be utilized to prepare drug-loaded micelles that offer a longer sustained release than non-modified regular micelles. Moreover, this modification can be used along with other techniques to further enhance sustained release by the system.

The chemistry involved in such crosslinking is comparatively simpler than the one used to crosslink the shell. Moreover, the core is the part that encapsulates the drug. A stabilized core will hold the drug for a longer period of time. In addition, drug-loaded nanoparticles can also be crosslinked to the core to achieve a higher control over the release of the drug. Strategies like this may make the system highly complicated while allowing formulation of a drug in a controlled delivery system.

■ Use of a low critical solution temperature hydrogel to stabilize the micelles

We have already discussed the use of polymers that change their viscosity with temperature to form micelles. Similarly, a low critical solution temperature (LCST) hydrogel can be used to

stabilize the micelles. An LCST gel can be polymerized along with the core of the micelle to stabilize the core. LCST gels remain in a swollen state at room temperature, allowing drug loading. But at physiological temperatures, these gels collapse and lock the hydrophobic portion of the micelle forming a locked core that contains the drug. Such a locked interpenetrating network in the core prevents the breakdown of the core upon dilution. This means that a drug loaded in the core would remain in the micelles for prolonged release. Such a system with pluronic micelles and an LCST gel was reported by Rapoport [48]. Rapoport suggested three ways to stabilize pluronic micelles, namely, core crosslinking, introducing vegetable oil in the hydrophobic portion to stabilize the micelles and polymerizing an LCST gel with the hydrophobic portion of the micelle to stabilize the core. The core crosslinking strategy decreased the drug loading capacity of the micelle. Addition of vegetable oil to the core increases the hydrophobicity of the core. However, the release is not as sustained as seen with an LCST gel core LCST gel in the core allows incorporation of hydrophilic as well as lipophilic drugs. One major disadvantage of using an LCST gel in the core of the micelle is that it increases the micellar size by several fold. Rapoport reported a size increase from 12–15 nm to 30–400 nm [48].

■ Ongoing clinical trials

A few clinical trials are being conducted for polymeric micelles. These clinical trials employ polymeric micelle delivery systems for improving the solubility of poorly soluble drugs such as anti-cancer drugs. None of the ongoing clinical trials are for sustained release micellar formulations. Some important clinical trials for micelle delivery systems going on are as follows:

- A Phase IV clinical trial for paclitaxel-loaded polymeric micelles in patients with taxanepretreated recurrent breast cancer is ongoing. Genexol-PM (a cremophor free polymeric micelle formulation of paclitaxel) protocol calls for drug administration at a dose of 300 mg/m² on day 1, with treatment being repeated every 3 weeks until either disease progression or intolerance. Disease progression would mean that the formulation is not working and hence, the patients should be withdrawn from the trial so that they can be treated with drugs that are effective. All doses are presented in 500 ml of 5% dextrose solution or normal saline as intravenous infusions administered over 3 h. A minimum of six cycles is being recommended [103].
- A Phase III clinical trial for paclitaxel-loaded polymeric micelles to treat recurrent or meta-static breast cancer is underway and currently recruiting participants [104].
- A Phase II clinical trial of paclitaxel-loaded polymeric micelles for the treatment of advanced pancreatic cancer was completed in 2008 [49]. Treatment was performed with polymeric micelles at a dose of 300 mg/m² q 3 weeks and this dose was well tolerated as indicated by the time for manifestation of common toxicities such as neutropenia, fatigue, infection, dehydration, neuropathy and abdominal pain. Further, common toxicities were qualitatively similar to cremophor-based paclitaxel. Micellar monotherapy resulted in overall survival and other efficacy parameters preferable to that seen historically with gemcitabine;
- A Phase II trial for treating advanced ovarian cancer with paclitaxel-loaded polymeric micelles is currently recruiting participants. The goal of this study is to determine the tolerated doses and efficacy of paclitaxel-loaded polymeric micelles in the treatment of advanced ovarian cancer [105];
- A Phase III clinical trial is currently ongoing to compare the efficacy of paclitaxel (Genexol®) and paclitaxel-loaded polymeric micelles (Genexol-PM®) when given in combination with cisplatin for the therapy of non-small cell lung cancer [106].

Comparison with other delivery systems

Thus far, several strategies that are useful in achieving sustained release micelles have been discussed. Below, some competing alternative delivery systems for sustained drug delivery are briefly discussed. The discussion has been restricted to particulate delivery systems since these are more similar to micelles. However, it should be noted that implantable drug delivery systems are also clinically relevant for prolonged drug delivery.

■ Polymeric microparticles

Polymeric microparticles have been most successfully employed in the sustained delivery of drugs. Release profiles of drugs up to 6 months have been reported with polymeric microparticles (e.g., Lupron Depot®). Furthermore, sustained release up to 287 days has been shown in dogs with ivermectin in PLGA microparticles [50]. Such formulations are polymeric matrix formulations that are injected as suspensions [51]. These particles are micron size in diameter and hence, they exhibit low burst effects/release. However, such particles are large in size and hence, they are not suitable for applications where the particles need to pass through leaky blood vessels. Also, they are not as effective as micelles in solubilizing a poorly soluble drug. Hence, there is a need for better formulations that have both the solubilizing capacity of micelles and sustained release capacity of microparticles.

■ Polymeric nanoparticles

Polymeric nanoparticles have also been used for targeted and sustained release of drugs. For instance, Singh *et al.* reported targeted gene delivery to the retina following intravenous administration of functionalized PLGA nanoparticles [52]. Furthermore, PLGA polymeric nanoparticles have been shown to sustain the release of tetanus toxoid *in vivo* for 4 months [53]. Nanoparticles increase the surface area of the formulation and hence, result in significant burst effects/release [54]. Moreover, drug loading can be limited in these nano particles. Further, they tend to aggregate more readily, resulting in larger particles compared with micelles less than 100 nm. Hence, polymeric nanoparticles do not completely alleviate the need for a better delivery system at the nanoscale.

■ Liposomes

Liposomes have also been used for sustained release of drugs. Liposomes are comprised of lipids that are largely endogenous in the human body. Hence, they avoid the toxicity issues. Although, release profiles up to a month have been reported with liposomes for anti-tubercular drugs [55], they are not the first choice delivery systems for prolonged drug delivery. Doxil, a pegylated liposomal formulation of DOX, demonstrates an *in vitro* release of 100% over 24 h [101]. Atyabi *et al.* showed that 100% release of SN-38 occurs from pegylated liposomes in 25 days as compared with 60% from non-pegylated liposomes [55].

Conclusion

Micelles have the distinct advantages of having a small size, less toxicity, solubilizing the drug and targetability. However, owing to their fragile structure and tendency to breakdown beyond CMC, preparation of long-circulating micelles and sustained-release micelles is a challenge. In the past few years, significant advances were made in overcoming these challenges. Currently, investigational micelle technologies are available for sustaining drug release from a few hours to a few months. However, the ease of preparation, shelf-stability and safety have to be factored prior to choosing a delivery system that is most appropriate in treating a particular disorder.

Future perspective

Micellar delivery systems are well recognized for their ability to enhance solubility and delivery of poorly soluble drugs. Recent advances, as described in this article, are enabling the use of micelles as sustained release delivery systems. Novel technologies described in this paper allow sustained drug delivery up to a maximum duration of approximately 2 months. It is anticipated that some of these sustained release micelles might be approved for human use in future. In order to sustain drug delivery beyond 2 months, for instance up to 6 months or a few years, microparticles and implant delivery systems are currently suitable options. Further advances are required with micellar delivery systems to sustain effective drug delivery beyond a few months.

Executive summary

- Current approaches to achieve sustained drug release from the micelles include use of prodrug synthesis, novel polymers, layer by layer assembly of micelles on a solid support, reverse micelles, drug–polymer conjugate micelles, and polymer films that form micelles *in vivo*. However, the sustained release achieved by these strategies lasts only up to a maximum of few weeks. Larger particles such as microparticles are more appropriate for sustained drug release for up to six months (e.g., Lupron Depot®). The small size of the micelles does provide some advantages such as more efficient drug targeting when compared with larger particulate systems. However, significant progress needs to be made in the field before we can achieve sustained release from the micelles that is comparable to larger particulate systems.
- Micelle stabilizing strategies can be used to stabilize the core or shell of the micelles to decrease the CMC of the micelles and make them resistant to dilution. Such strategies when combined with approaches for sustained release would allow the development of stable micelle formulations for treating chronic disorders.

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Figure 1. Different types of micelles

(A) Normal micelles: micelles that are prepared in aqueous medium and have a hydrophilic portion on the outside and a hydrophobic portion on the inside (e.g., PEG–PLGA, PEG–poly(lactic acid), poly(ethylene oxide)–poly(propylene oxide) micelles in aqueous medium).

(B) Reverse micelles: micelles that are prepared in organic medium and have a hydrophobic portion on the outside and a hydrophilic portion on the inside (e.g., phosphazene micelles in chloroform, PCL–P2VP micelles in oleic acid). **(C)** Unimolecular micelles: micelles formed from amphipathic molecules (e.g., Core(Laur)PEG micelles in aqueous medium).

P2VP: Poly caprolactone–poly(2-vinyl pyrrolidone); PEG: Poly(ethylene glycol); PCL: Polycaprolactone; PLGA: Poly(lactide-co-glycolide).

Figure 2. *In vitro* drug release from micelles prepared by the polymer-drug conjugate strategy Drug release was assessed in phosphate buffer saline (PBS) at 37°C. **(A)** Triangles show the *in vitro* release in PBS of DOX from PEG-PLGA-DOX micelles. The micelles showed 60% *in vitro* release of the drug on day 15. **(B)** Squares show the *in vitro* release of oligodeoxynucleotide (ODN) from ODN-PLGA micelles in phosphate buffered saline. ODN was conjugated to PLGA forming an amphiphilic polymer. The micelles showed a full release in approximately 50 days.

DOX: Doxorubicin; ODN: Oligodeoxynucleotide; PEG: Polyethylene glycol; PLGA: Poly(lactide-co-glycolide).

(A) Release data based on [11].

(B) Release data based on [12].

Figure 3. Represents different types of polymers used to prepare micelles

(A) Diblock copolymer micelles prepared from polymers with two different blocks (e.g., PEG-PLGA, PEG-PLA, PEO-PPO micelles). (B) Triblock copolymer micelles prepared from polymers with three different blocks, for example PLA-PEO-PLA micelles in aqueous medium (flower-like micelles). (C) Graft copolymer micelles prepared from polymers where a side chain is grafted onto a main polymer (e.g., cellulose-PLLA micelles in aqueous medium, phthaloyl chitosan-mPEG micelles in aqueous medium). (D) Flower-like micelle prepared from triblock copolymers (e.g., PLA-PEO-PLA micelles). (E) Formation of supramolecular micelles: α -CD and urea in water and PCL in THF were gently mixed at 60°C. Urea facilitates the initialization of polymerization of α -CD and PCL and on dialysis against water, the supramolecular micelles are obtained. This concept is called one pot chemistry. PEO: Polyethylene oxide; PCL: Polycaprolactone; PEG: Polyethylene glycol; PLGA: Poly (lactide-co-glycolide); PLLA: Poly-L-lactic acid.

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Figure 4. *In vitro* drug release from polymeric micelles

Drug was entrapped and not conjugated to the polymer. *In vitro* drug release was performed in phosphate buffer saline at 37°C. Green circles show the *in vitro* release profile of quercetin from PEG-PCL micelles. Release data based on [18]. Brown circles show the *in vitro* release profile of quercetin from PEG-PLLA micelles. Release data based on [18]. Purple circles show the *in vitro* release profile of doxorubicin (DOX) from *N*-succinyl,*N'*-octyl chitosan graft polymer micelles. Release data based on [19]. Red circles demonstrate the *in vitro* release profile of griseofulvin from PLA-PEG micelles. Release data based on [21]. Orange circles show the *in vitro* release profile of indomethacin from PLA-PEG micelles. Release data based on [24]. Pink circles show the *in vitro* release profile of sulindac from PLA-PEO-PLA triblock copolymer micelles. Release data based on [25]. Dark blue circles show the *in vitro* release profile of tetracaine from PLA-PEO-PLA triblock copolymer micelles. Release data based on [25]. Gray circles show the *in vitro* release profile of Honokiol from PCL-PEG-PCL triblock copolymer micelles. Release data based on [26]. Yellow circles show the *in vitro* release profile of paclitaxel from hyperbranched polyglycerol-PEG micelles. Release data based on [29]. Light blue circles show the *in vitro* release profile of prednisone acetate from PLLA-cellulose graft polymer micelles. Release data based on [32]. Light green circles show the *in vitro* release profile of cisplatin from PEG-polyglutamic acid micelles. Release data based on [36]. The hydrophobic interactions between the PLA polymer and the hydrophobic drug griseofulvin resulted in the most prolonged sustained release.

PEG: Polyethylene glycol PEO: Polyethylene oxide; PCL: Polycaprolactone; PLLA: Poly-L-lactic acid.

Figure 5. Formation of a film through H-bonding of multiple layers of polymeric micelles
PEO–PCL diblock copolymer is used along with PAA as an H-bond donor. The micelles form H-bonds with each other when assembled layer by layer and form a film like structure. These films disintegrate in phosphate buffer saline to release micelles.
PEO: Polyethylene oxide; PCL: Polycaprolactone.
Illustration based on [39].

Figure 6. In vitro drug release from micelles formed using various polymers

Diamonds show the multi-layer assembly of polyethylene oxide–polycaprolactone micelles as a film using PAA as a hydrogen bond donor. The drug employed was triclosan. Release data based on [39]. Squares show micelles from reverse thermoresponsive polymer poly(ether carbonates). The polymer increases in viscosity at body temperature and hence, sustains the release of hydroxycamptothecin. Release data based on [40]. Triangles show the release from layer by layer assembly of hyaluronic acid-g-Poly(lactide-co-glycolide) micelles on a heparinized stent. The micelles separate from the stents at body temperature in a sustained manner, thus giving a sustained release of paclitaxel. Release data based on [41]. Circles show the release of polyethylene –polycaprolactone polymer and encapsulating prodrug of paclitaxel from micelles, which breaks down into paclitaxel to give a sustained release. Release data based on [19]. Drug release was assessed in phosphate buffered saline at 37°C.

Figure 7. Comparison of *in vivo* plasma clearance profiles from micelles

The graph shows the comparison of plasma concentration profiles with the use of different polymeric micelles. PEG-PCL micelles (purple circles) for the administration of prodrug of paclitaxel. *In vivo* data is based on [9]. Polyphosphazene micelles (green circles) for the administration of indomethacin. *In vivo* data is based on [22]. PCL-PEG micelles (yellow circles) for the administration of indomethacin. *In vivo* data is based on [24]. PEG-polyglutamic acid micelles (blue circles) for the administration of cisplatin. *In vivo* data is based on [36]. NK105 micelles (red circles) for the administration of SN38. *In vivo* data based on [13].

PCL: Polycaprolactone; PEG: Polyethylene glycol.

Figure 8. Some stabilization strategies involving crosslinking

(A) Shell crosslinking (e.g., using chloromethylation and amination in a styrene-*b*-butadiene-styrene copolymer). **(B)** Core cross-linking (e.g., PEG-*b*-PLA with a 5-methyl-5-allyloxycarbonyl-1,3-dioxane-2-1 group as the polymerizable group for cross-linking the core).

PEG: Polyethylene glycol; PLA: Polylactic acid.

Table 1

Some materials used to prepare micelles and the release obtained from these micelles.

Material	Size	Duration of <i>in vitro</i> release	Ref.
Lipids (DSPE)	22 nm	6 days	[12]
Polymers (PLGA)	65 nm	50 days	[15]
Oligopeptide	102 nm	40 h	[19]
Polysaccharides (chitosan)	100–200 nm	15 days	[34]

DSPE: Distearoyl phosphatidyl ethanolamine; PLGA: Poly(lactide-co-glycolide).

Table 2

Some existing approaches to achieve sustained release from micelles.

Approach	Polymer used	Drug	Duration of <i>in vitro</i> release	Comments	Size (nm)	CMC	Ref.
Prodrug synthesis	PEG–PCL	Paclitaxel	Up to 14 days	Release varied with the prodrug chemistry.	27–44		[9]
Drug–polymer conjugate	PEG–PLGA	Doxorubicin	>15 days	Loading efficiency was almost 100% with drug conjugated micelles compared with encapsulated micelles.	61.4	0.1 µg/ml	[10]
	ODN–PLGA	Oligodinucleotide	>50 days	ODN was directly conjugated to PLGA to form amphiphilic molecule.	65.2	7.5 µg/ml	[11]
Novel polymer	PEO–DSPE	Beclomethasone Dipropionate	>6 days	No chemical or physical interaction between drug and polymer.	22		[12]
	α-CD–PCL	Anti-inflammatory drug	>700 h	One pot chemistry used.	30		[13]
	PLA–PEO–PLA flower-like micelles	Sulindac	20 days	Crystalline PLA blocks showed faster release than amorphous PLA blocks.	7–16		[15]
	PLA–PEO–PLA flower-like micelles	Tetracaine	10 days	Crystalline PLA blocks showed faster release than amorphous PLA blocks.	7–16		[17]
	Core(laur)PEG	Lidocaine	Up to 50 h	Unimolecular micelles.	50		[18]
	H–40–PLA–mPEG	5-FU	Up to 80 h	Multi-arm block copolymer.	74		[19]
	PCL-PEG-PCL triblock	Honokiol	Up to 144 h	Self-assembly without using organic solvent.	61	4.5 µg/ml	[21]
	Cellulose–PLLA	Prednisone acetate	40% first day, 20% next 2 days, 30–40% next 7 days	Graft polymer synthesized instead of block copolymer.	30–80	47.1–58.1 µg/ml	[24]
	Oligopeptide	Doxorubicin	~35% in 40 h	Peptide micelles loaded with doxorubicin.	102	42 µg/ml	[25]
	mPEG–PLLA	Quercetin	75% in 160 h	Only 8% burst release. Strong H-bonding interactions result in delayed release.			[25]
	mPEG–PCL	Quercetin		Stronger interactions between polymer and drug. Hence, lesser release.			[26]
	Phthaloyl/chitosan–mPEG	Camptothecin	~96 h	Release depends on degree of deacetylation of the polymer.	50–100	28 µg/ml	[28]
	N-succinyl,N'-octyl chitosan	Doxorubicin	>15 days	Release rate inversely depends on amount of octyl chain. CMC depended on the % octyl content.	100–200	2.4–5.9 µg/ml	[31]
	PLA–PEG	Griseofulvin	30 days	Micelles equally stable in SGF and SIF. Oral administration desired.	26.9	70–90 µg/ml	[32]

Approach	Polymer used	Drug	Duration of <i>in vitro</i> release	Comments	Size (nm)	CMC	Ref.
Reverse micelles	<u>Polyphosphazenes</u>	<u>Fluorescein sodium, Trypan Blue</u>	<u>60 days</u>	Dye loaded on PLGA microparticles encapsulated in phosphazenes reverse micelles.	<u>Up to 5000</u>		[4]
	PCL–P2VP	Ovalbumin	200 h	Ovalbumin slowly released from reverse micelles from a biocompatible oily medium.	104		[38]
H-bonding layer by layer assembled micelles	PEO–PCL with PAA as H-bond donor	Triclosan	15 days	Release profile depends on degree of crosslinking and the number of layers.	71		[39]
Reverse thermo-responsive polymers	<u>Polyether carbonates</u>	<u>HCPT</u>	<u>72 h</u>	Viscosity increase at body temperature led to swelling of polymer and hence, delayed release of drug.	<u>65.5</u>	<u>38.5 µg/ml</u>	[3]
	Pentablock PDEAEM25–PEO100–PPO65–PEO100–PDEAEM25	Lysozyme	80 h	Polymer forms a gel-like material at body temperature; release is pH dependent.			[40]
Polymer films converted to micelles	Monomethoxy poly(ethylene glycol)-block-poly(trimethylene carbonate)	Dexamethasone	20 days	Stable film at room temperature; forms nanosized micelles at body temperature.	210		[41]
Reverse micellar suppository	Solid reversed micellar solution from 70% isopropyl myristate and 30% lecithin	Metaclopramide	15% in 6 h	Useful for delivery of antiemetic drug where constant levels of drug need to be maintained.			[43]
Layer by layer assembly of micelles on a stent	HA–g–PLGA	Paclitaxel	25 days	Release depends on the number of layers of micelles coated on the stents	202.8		[43]

5-FU: 5-Fluorouracil; CD: Cyclodextrin; CMC: Critical micelle concentration; DSPE: Distearoyl phosphatidyl ethanolamine; H-40: dendritic boltron with 40 hydroxyl groups; HA: Hyaluronic acid; HCPT: Hydroxycamptothecin; mPEG: Methoxy polyethylene glycol; ODN: Oligodeoxynucleotide; P2VP: Poly(2-vinyl pyridine); PAA: Polyacrylic acid; PCL: Polycaprolactone; PDEAEM: Poly(2-diethylaminoethyl-methyl methacrylate); PEG: Polyethylene glycol; PEO: Polyethylene oxide; PLA: Polylactic acid; PLGA: Poly(lactide-co-glycolide); PLLA: Poly-L-l-lactic acid; PPO: Poly(propylene oxide); SGF: Simulated gastric fluid; SIF: Simulated intestinal fluid.

Table 3

A comparison of the release obtained from various particulate delivery systems.

Delivery system	Maximum release reported	Advantages	Limitations	Ref.
Polymeric micelles	60 days	Smaller size, solubility increased	Longer release times not possible	[12]
Polymeric microparticles	287 days	Longer release times and higher drug loading	Micron size, which is unsuitable for some applications, problems in syringeability	[49]
Polymeric matrix (Atrigel delivery system)	6 months	Longer release times and higher drug loading	Matrix not always suitable for drug delivery, large size	[102]
Polymeric nanoparticles	4 months	Very large surface area, longer release times	Large surface area can also be a disadvantage leading to faster degradation, nanotoxicity	[52]
Liposomes	1 month	Made of materials already present in the human body and hence, less toxicity, especially if negatively charged	Large sizes, not long circulating enough	[54]