

Polymeric capsules and micelles as promising carriers of anticancer drugs

Kapsułki i micelle polimerowe jako nośniki leków przeciwnowotworowych

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Abstract

Polymeric micelles and capsules are promising candidates for carriers of antineoplastic medications. Biodegradability and broadly defined biocompatibility are the key features that should always characterize polymers intended for medical applications. A well-designed delivery system ought to ensure the safe transport of chemotherapeutic agents to the target area and thus minimize systemic exposure to these drugs, limiting their toxic effect, preferably to the cancer cells. Polymeric micelles are often tailored for encapsulation of water-insoluble drugs. Micellar structures are usually fabricated as a result of self-assembly of various amphiphilic block copolymers in aqueous environment. More advanced methods are used to form capsules with a liquid core and a shell made of fused polymer nano- or microparticles. Such a coating can have homogeneous or heterogeneous composition. Janus and patchy capsules are usually characterized by more useful and advanced properties. Although some polymeric carriers are designed for a sustained release of the cargo, more sophisticated approaches involve payload liberation on demand under the influence of selected chemical or physical stimuli. The variety of available polymers and a wide range of possibilities of forming copolymers from different kind of monomers make polymeric materials ideal for the production of drug delivery systems with the desired properties. The aim of the present review is to sum up selected aspects of the use of polymeric micelles as carriers of cytostatic drugs, taking into account clinical applications. The additional objective is to show the studies on creating alternative systems based on stimuli-responsive capsules with shells made of polymeric particles.

Key words: controlled release, block copolymers, drug carriers, microcapsules, polymeric micelles

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Streszczenie

Micelle i kapsułki polimerowe to dobrze zapowiadający się kandydaci na nośniki leków przeciwnowotworowych. Biodegradowalność i szeroko pojęta biokompatybilność zawsze stanowią kluczowe cechy, jakimi muszą charakteryzować się polimery przeznaczone do zastosowań medycznych. Poprawnie zaprojektowany system dostarczania powinien zapewniać bezpieczny transport chemioterapeutyków do obszaru docelowego, a tym samym minimalizować ogólnoustrojową ekspozycję na te leki, ograniczając ich toksyczne działanie (najlepiej tylko do komórek nowotworowych). Micelle polimerowe są często przystosowane do enkapsulacji leków słabo rozpuszczalnych w wodzie. Struktury micelarne powstają zwykle w wyniku samoorganizacji różnego typu amfifilowych kopolimerów blokowych w środowisku wodnym. Bardziej zaawansowane metody wykorzystuje się do formowania kapsułek z ciekłym rdzeniem i powłoką złożoną z połączonych nano- bądź mikrocząstek polimerowych. Taka powłoka może być jedno- bądź niejednorodna. Kapsułki Janusa i niejednorodne charakteryzują się zazwyczaj bardziej użytecznymi i złożonymi właściwościami. Chociaż niektóre nośniki polimerowe są zaprojektowane do przedłużonego uwalniania leku, bardziej zaawansowane podejścia obejmują uwalnianie ładunku na żądanie pod wpływem wybranego bodźca chemicznego lub fizycznego. Bogaty wybór dostępnych polimerów oraz szeroki wachlarz możliwości formowania kopolimerów z różnego rodzaju monomerów sprawiają, że materiały polimerowe idealnie nadają się do wytwarzania systemów dostarczania leków o odpowiednich właściwościach. Celem niniejszego przeglądu jest podsumowanie wybranych aspektów wykorzystania miceli polimerowych jako nośników leków cytostatycznych, z uwzględnieniem zastosowań klinicznych. Dodatkowym celem jest pokazanie badań nad alternatywnymi systemami opartymi na kapsułkach z powłokami utworzonymi z cząstek polimerowych.

Słowa kluczowe: kontrolowane uwalnianie, mikrokapsułki, micelle polimerowe, nośniki leków, kopolimery blokowe

Introduction

Although microencapsulation is useful in many branches of economy, the greatest hope lies in its application in pharmacy and medicine. On the one hand, capsules can protect various payloads from contamination, deactivation or oxidation caused by the reaction with the surrounding medium, but on the other hand, they may preserve the environment from toxic or harmful effect of the transported substance.^{1,2} Delivery of drugs, proteins, enzymes, nucleic acids, microorganisms (e.g., probiotics), or implantation of living cells (e.g., stem or hepatic cells) are just some of the tasks that scientists assign to polymer capsules.³ Most of the research is focused on their use in cancer therapy. The primary goal of the employment of polymeric carriers in this field is to deliver chemotherapy medications directly to the target area and thus, to minimize systemic exposure to these drugs, confining their action only to malignant tissues and cells. In general, the drug can be physically entrapped inside the shell, conjugated or complexed with the polymer, alternatively dissolved or dispersed in the liquid core.^{4,5} Capsules are often vesicular systems with liquid core (consisting of water or oil) acting as a drug reservoir, surrounded by a protecting shell.⁶ Polymeric micelles are self-assembled structures built out of amphiphilic copolymers. In aqueous media, hydrophilic groups form an outer shell and hydrophobic fragments face the core in which the lipophilic drug can be encapsulated.^{6,7} Polymeric micelles are typically more stable compared to traditional surfactant-based micelles.^{6,8} They also have an advantage over liposomes, because hydrophobic medications incorporated into the lipid bilayer tend to be released quite rapidly after systemic administration.⁹ Polymer structures do not only retain the drug longer, but also have better loading capacity than micelles and liposomes.⁴

The most commonly encapsulated anticancer drugs are: paclitaxel (chemotherapy medication originally isolated from the bark of the Pacific yew tree *Taxus brevifolia*),¹⁰ docetaxel (semisynthetic taxane obtained by chemical modification of 10-deacetylbaccatin III, isolated from needles of European yew tree *Taxus baccata*)¹¹ and doxorubicin (anthracycline antibiotic obtained from the *Streptomyces peucetius* bacterium species).^{9,12–14} Serious side effects caused by the standard formulations of the aforementioned drugs motivate scientists to search for efficient and safe intravenous delivery systems. Another significant problem is very poor water solubility of taxanes.¹⁵ However, the efficient delivery of small hydrophilic drugs is also complicated due to their rapid clearance from the bloodstream and the tendency to spread in the aqueous environment of the human body.¹⁶ Unplanned local aggregation of anticancer agents after intravenous injection may increase their toxic effect on healthy tissues and even be the cause of embolism.¹⁷ Therefore, targeted delivery of cytotoxic medications is needed to considerably increase their efficacy and significantly reduce their total concentration in the body.¹⁸ Thanks to the protective shell, the drug can be safely transported, because its release is delayed or completely prevented until the coverage is ruptured.¹⁹

The distribution and behavior of polymeric carriers in biological environment primarily depend on their size and surface properties.²⁰ Polymeric capsules with a size that does not exceed 200 nm may enter the tumor region through leaky vessels, which is related to the enhanced permeability and retention (EPR) effect.^{21,22} Proper composition of nanocarriers or chemical modification of their surface may contribute to the extension of their circulation time and thus the tumor site exposure to the drug formulation. Capsules should preferentially amass within neoplasm and should not accumulate in healthy tissues. However, many studies indicate that the role of passive

accumulation of nanomedications is overestimated, and the delivery strategy based merely on EPR effect can only be sufficient for a narrow subset of clinical tumors.²³ Therefore, more advanced solutions are needed. For example, active targeting utilizes surface-modified capsules with bioactive ligands (peptides, antibodies, etc.) that are recognized by receptors overexpressed in the tumor region.²⁴ There is still an issue of insufficient penetration of cytostatic drugs into the inner cell layers of solid tumors.²⁵ Nanocarriers after extravasation from tumor vessels still have to break through a series of obstacles including interstitial extracellular matrix, cellular membranes and nuclear envelope.²⁶ The strategies for promoting drug release from polymeric capsules and micelles are discussed in a separate section of this paper.

In the context of the functionality of polymeric carriers, it should be emphasized that the most important matter is their broadly defined biocompatibility. It means that structures administered to the body not only cannot be toxic and cause immune response, but they should also fulfill planned role in the biological environment.^{27,28} In case of core-shell type nanostructures, biocompatibility can be obtained by using appropriate polymer coating made of chitosan and poly(ethylene glycol) (PEG).²⁷ For example, one can mention chitosan or PEG-coated magnetite nanoparticles investigated by means of electron paramagnetic resonance technique,²⁹ also in human whole blood,³⁰ and polymer-coated gadolinium, platinum and gold nanoparticles designed as radiosensitizers in cancer treatment.³¹ In the case of nanoparticles, “stealth” polymers typically modify the surface of the solid core. For capsules which are hollow or liquid-filled structures, PEG chains are the integral part of the shell or are grafted on it. One can cite the examples of PEG-coated hollow polyelectrolyte microcapsules injected into the bloodstream of zebrafish,³² PEGylated poly(D,L-lactide) nanocapsules with aqueous-core containing hydrophilic anticancer drug – gemcitabine hydrochloride,³³ or even nanocapsules with the whole shell made of chitosan, chemically modified with PEG.³⁴ Nevertheless, the research on PEG-terminated multilayer polyelectrolyte nanocapsules indicated the necessity of checking the long-term immune response stimulated by PEGylated structures.³⁵ Poly(2-ethyl-2-oxazoline) (PEtOz) is considered as an alternative to PEG because of biocompatibility, biodegradability and ability to prolong the circulation time of nanocarriers.³⁶ Both PEG and PEtOz can constitute hydrophilic segments of copolymers forming polymeric micelles.

Copolymer micelles

Block copolymer micelles (Fig. 1A) are often tailored for encapsulation of water-insoluble drugs. Such artificial vesicles can mimic the structure and function of natural biological transport systems.⁵ In aquatic environment, amphiphilic properties of block copolymers favor

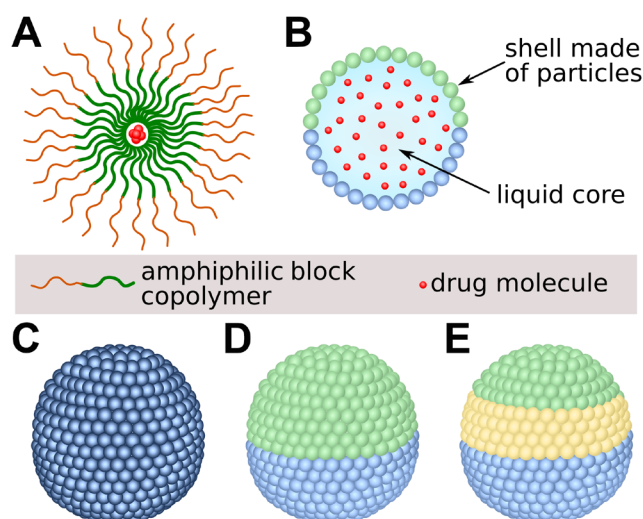


Fig. 1. Examples of polymer drug carriers. A. Amphiphilic copolymer micelle; B. Capsule with the shell composed of polymer particles; C. Capsule with homogeneous shell; D. Capsule with Janus shell; E. Capsule with patchy shell

self-organization into micelles, in which hydrophilic regions face outwards and hydrophobic inwards.³⁷ The decrease in free energy of the system due to the removal of hydrophobic regions from water neighborhood is the main driving force responsible for this process.¹⁷ In general, hydrophilic block is usually PEG or PEtOz, while hydrophobic block can be a polyester, e.g., poly(caprolactone) (PCL) or poly(DL-lactide) (PDLLA); a polyamino acid, e.g., poly(β -benzyl-L-aspartate) (PBLA), poly(lactic-co-glycolic acid) (PLGA); or a polyether, e.g., poly(propylene oxide) (PPO).^{9,13} As previously mentioned, the hydrophobic segments form a compartment in which the lipophilic payload is enclosed, while the hydrophilic parts are in contact with the biological environment. The great advantage of encapsulating drugs in polymer micelles is the ability to eliminate toxic solubilizers, including Cremophor EL or dimethyl sulfoxide (DMSO).³⁸ Drug preparations free of harmful surfactants and organic cosolvents are safer for patients and do not cause so many adverse side effects as traditional formulations.³⁹ It is worth presenting selected examples of utilizing various types of block copolymers for the formation of micelles designed as carriers of cytostatic drugs.

Self-assembled poly(ethylene oxide)-block-poly(L-amino acid) (PEO-b-PLAA) micelles, thanks to free functional groups of the PLAA block, easily form drug-polymer conjugates.⁵ In aqueous environment, amphiphilic PEO-PPO block copolymers also aggregate into stable micelles capable of transporting water-insoluble medications inside their hydrophobic cores.⁸ Pluronic P123 (PEO-PPO-PEO synthetic triblock copolymer) micelles loaded with paclitaxel were administered to rats and mice in order to check the pharmacokinetics and tissue distribution of this formulation.¹⁰ Study proved the prolonged circulation time of vehicles due to the presence of hydrophilic

PEO shell additionally protecting against the recognition by reticuloendothelial system.¹⁰ In vivo studies were also performed with spherical Pluronic P123 micelles containing docetaxel.^{40–42} It is worth mentioning that the thermodynamics of spontaneous Pluronic P123 micellization in water can be influenced by temperature changes and the addition of different solvents, e.g., ethanol, 1-propanol, glycerol, or protic ionic liquid ethylammonium nitrate.⁴³ Therefore, the self-assembly process of Pluronic drug carriers is adjustable.

Grafted polyphosphazenes are also promising candidates for microsphere and micelle forming materials due to biodegradability, tunable properties and flexibility in structural design.⁴⁴ The thermosensitive polyphosphazene micelles containing hydrophilic segments of oligo-poly(*N*-isopropylacrylamide) and hydrophobic groups of ethyl 4-aminobenzoate may be useful as carriers of hydrophobic medications.⁴⁵ Polymeric micelles built of amphiphilic graft polyphosphazenes with hydrophilic poly(*N*-isopropylacrylamide-co-*N*, *N*-dimethylacrylamide) (Poly(NIPAm-co-DMAA)) and hydrophobic ethyl glycinate as side groups have already been tested as doxorubicin carriers.⁴⁶ It is believed that desirable features of polyphosphazene-based polymers, in particular the self-neutralizing properties of their degradation products and the possibility of smooth integration of the polyphosphazene skeleton with the substituent groups, open up new prospects for the design of next-generation drug delivery systems.⁴⁷

The stability of vehicles composed of methoxy poly(ethylene oxide)-poly(*L*-lactide) (MePEO-PLLA) block copolymer depends on the polymerization method. Research showed that structures prepared with solution polymerization were kinetically more stable than those obtained using bulk polymerization.⁴⁸ The capability of (m)PEG-PDLLA micelles to be efficiently loaded with hydrophobic drugs can be qualitatively predicted based on calculated solubility parameters.⁴⁹ The PEG-PDLLA nanocarriers have already been tested with paclitaxel,⁵⁰ doxorubicin⁵¹ and tanespimycin.³⁹

One of the most studied drugs – doxorubicin – was also encapsulated in vehicles prepared using biocompatible copolymer composed of PEO and poly(γ -benzyl l-glutamate) (PBLG), which is synthetic polypeptide with the ability to form secondary structures such as α -helices or β -strands.³⁷ These PEO-PBLG diblock and PBLG-PEO-PBLG triblock copolymer micelles were effectively internalized by human head and neck squamous carcinoma cells in vitro.³⁷

Biodegradable diblock mPEG-PCL micelles were used for encapsulation of doxorubicin⁵² and paclitaxel.⁵³ The PEG-PCL copolymer and its modified version containing benzylcarboxylate side chain were also used for producing nanomicelles loaded with silibinin – a poorly water-soluble antioxidant and antineoplastic agent.²² A study showed that micelles provided high encapsulation efficiency and sustained release of this active substance, and also

contributed to its increased cytotoxicity against melanoma cells.²² Improved targeting ability was reported for rituximab-conjugated PEO-poly(ester) micelles of different structures prepared for treatment of lymphoma cells.⁷

Self-assembled nanocarriers composed of D- α -tocopheryl poly(ethylene glycol) succinate-block-poly(ϵ -caprolactone) (TPGS-b-PCL) and loaded with paclitaxel owe their properties to PEG, which extends their circulation time, and vitamin E, that enhances the cellular uptake of the medication.⁵⁴ The TPGS, which is a derivative of the natural vitamin E (α -tocopherol) conjugated with PEG, was also used as a component for the production of micelles containing docetaxel.⁵⁵ Among the advanced delivery systems, tested both in vitro and in vivo, one can mention pH-sensitive, multidrug (α -tocopherol and doxorubicin) grafted O-carboxymethyl chitosan polymeric micelles with chemically conjugated targeting ligand (anti-HER2/neu peptide-PEG).⁵⁶

In contemporary oncology, synergistic drug combinations are often used in order to increase the effectiveness of the therapy. The PEG-b-PDLLA micelles are capable of encapsulating up to 3 poorly water-soluble chemotherapeutic agents at the same time, which was proven in experiments with paclitaxel, etoposide, docetaxel, and tanespimycin.⁵⁷ The formulation of paclitaxel and tanespimycin, which utilized 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-methoxy(polyethylene glycol) ((m)PEG-DSPE) and TPGS copolymers, significantly extended the circulation time and increased the intratumoral accumulation of these synergistic drugs.³⁸ The co-encapsulation of sorafenib and all-trans retinoic acid in PEG-PLGA copolymer micelles allowed for obtaining prolonged release and effective cell uptake of both agents in thyroid cancer-bearing mice.⁵⁸ The co-encapsulation does not have to be limited to pharmaceuticals. Doxorubicin and microRNA-34a (tumor suppressor RNA) were trapped in hybrid nanomicelles containing 2 amphiphilic diblock copolymers PEG-PCL and polyethylenimine-PCL in order to combine the effects of chemotherapy and gene therapy.⁵⁹ The summary of different types of polymeric micelles used as drug carriers and their basic properties is presented in Table 1.

Micellar drug formulations designed by scientists are increasingly used in clinical trials and cancer treatment. One can mention commercially available delivery systems such as Genexol PM[®] (paclitaxel loaded mPEG-PDLLA diblock copolymer micelles),⁶⁰ Nanoxel – PM[®] (docetaxel loaded mPEG-PDLLA micelles),^{61,62} Apealea[®]/Paclical[®] (micellar paclitaxel),^{6,63} and Paxceed[®] (mPEG-PDLLA micellar formulation of paclitaxel, originally tested for the treatment of rheumatoid arthritis).⁶² Although more and more micellar drug formulations are approved for clinical trials, some of the products do not live up to expectations. Phase I clinical trial and pharmacokinetics evaluation of NK911 PEG-poly(aspartic acid) block copolymer micelles containing doxorubicin showed that these structures were less stable in plasma and less efficient at drug delivery to solid tumors

Table 1. Summary of different types of polymeric micelles and their basic properties

| Polymer/ copolymer type | Cargo | Size | Basic properties | Reference |
|--------------------------------|---------------------------|---|---|-----------|
| PEO-PCL | rituximab, paclitaxel | 95 ±20.6 nm | CMC = 18.2 ±2.5 µg/m PDI = 0.284 ±0.068 kinetically stable <6 h in SDS drug release = 40.7 ±4.5% within 48 h improved tumor targeting efficiency | 7 |
| | silibinin | 54.73 ±1.82 nm | PDI = 0.31 ±0.06 zeta potential of −2.23 ±0.14 mV drug release = 91.7 ±0.81% within 24 h | 22 |
| PEG-PCL/PEI-PCL | doxorubicin, miRNA-34a | ≈64.34 nm ≈105.4 nm ≈160.7 nm | hybrid micelles CMC ≈ 8.57 µg/mL PDI of 0.24–0.28 zeta potential of 5.43; 19.3; 32.6 mV (for different molar ratios of copolymers) pH dependent drug release: ≈78.2% (pH 7.4) and 88.6% (pH 5.5) within 24 h in PBS | 59 |
| mPEG-PCL | doxorubicin | 25.4 ±0.2 nm 22.9 ±0.2 nm 37.3 ±0.2 nm 84.0 ±0.3 nm 104.9 ±0.2 nm | CMC ≈ 20 µg/mL or ≈12 µg/mL size of micelles determined by PCL block length hemocompatibility pH dependent drug release influence on cellular distribution of drug | 52 |
| | paclitaxel | <124 nm (before core cross-linking) <202 nm (core- cross-linked) | size of micelles determined by PCL block length drug encapsulation dependent on the PCL length and cross-linking enhanced loading efficiency after cross-linking of micelle core stability against dilution in water weak stability in the presence of serum protein (BSA, 2.5%) | 53 |
| PEO-PBCL | rituximab, paclitaxel | 110 ±11.6 nm | CMC = 12.3 ±3.1 µg/mL PDI = 0.216 ±0.010 kinetically stable >24 h in SDS drug release = 60.75 ±3.70% within 48 h improved tumor targeting efficiency | 7 |
| | silibinin | 46.9 ±0.33 nm | PDI = 0.33 ±0.01 zeta potential of −3.23 ±0.32 mV sustained release of cargo 30.5 ±1.5% within 24 h | 22 |
| TPGS-PCL | paclitaxel | 60.6–209.4 nm (depending on MW of PEG and TPGS) | self-assembly only for copolymers with PEG molecular weights ≥2 kDa PDI of 0.16–0.53 (depending on MW of PEG and TPGS) CMC of 5.44–41.00 µM (depending on MW of hydrophobic block) extended circulation time sustained release of drug, e.g., 10% within 12 h and 36% within 72 h in PBS (pH 7.4) | 54 |
| TPGS | docetaxel | 12.4–14.4 nm | CMC < 2.2 mM PDI of 0.166–0.290 drug release ≈50% (pH 7.4) within 16 h, 24 h or 90 h in PBS depending on TPGS content influence on drug biodistribution | 55 |
| PEtOz-PU-PEtOz | doxorubicin | 175.9 ±6.6 nm | CMC ≈ 0.43 mg/L PDI ≈ 0.11 zeta potential of −20.6 mV high stability; “stealth” property pH dependent drug release ≈29% (pH 7.4); 92% (pH 5.0) within 24 h in acetate buffer | 36 |
| Pluronic P123 (PEO-PPO-PEO) | paclitaxel | 25.2 ±2.9 nm (freshly prepared) 28.5 ±2.1 nm (freeze-dried) | CMC ≈ 4.4 × 10 ^{−6} mol/L drug release ≈ 41.2% within 4 h and 87.8% within 24 h in sodium salicylate solution “stealth” property – prolonged circulation time in plasma influence on drug pharmacokinetics and biodistribution | 10 |
| | docetaxel | 9–55 nm (freshly prepared) 22–84 nm (freeze-dried) | physically entrapped drug zeta potential of −10.56 ±2.34 mV (fresh) and −12.45 ±3.24 mV (freeze-dried) remarkable antitumor activity high encapsulation efficacy drug release ≈84.05% within 24 h (in PBS, pH 7.4, 37 ±0.5°C) | 40 |
| | | 85.30 ±1.59 nm | covalently conjugated drug CMC = 1.34 ±0.05 × 10 ^{−5} mol/L PDI ≈ 0.267 zeta potential of −19.34 ±3.25 mV pH dependent drug release ≈1.83% (pH 7.4); 4.23% (pH 5.0); 8.67% (pH 1.2) within 24 h in PBS significant antitumor activity | 41 |
| | | ≈138 nm (average) | covalently conjugated drug (hydrazone bonds) CMC ≈ 7.232 × 10 ^{−5} mol/L pH dependent drug release ≈13.4% (pH 7.4); 84.9% (pH 5.0) within 48 h in PBS at 37 ±0.5°C | 42 |

Table 1. Summary of different types of polymeric micelles and their basic properties – cont

| Polymer/ copolymer type | Cargo | Size | Basic properties | Reference |
|----------------------------|---|-----------------------------------|--|-----------|
| PNIPAm/EAB- PPP | – | ≈80 nm (average) | CMC ≈ 0.1 mg/mL LCST ≈ 32.6°C | 45 |
| P (NIPAm-DMAA) | doxorubicin | <150 nm | CMC ≈ 0.281; 0.178; 0.0324 g/L (depending on the content of hydrophobic ethyl glycinate) LCST ≈ 39.2°C physically loaded drug pH dependent drug release: ≈8.5% (pH 7.4), ≈21% (pH 6.5), ≈28% (pH 5.5) within 24 h in PBS good biocompatibility | 46 |
| mPEG-PDLLA | doxorubicin, SPIO | 45 ±4 nm | multifunctional micelles (can incorporate lung cancer targeting peptide, drug and contrast agent) significantly increased cell targeting | 51 |
| PEO-PDLLA | tanespimycin | 257 ±2 nm | CMC ≈ 350 nM release half-life ≈4 h (37°C, in water) lack of substantial sustained release prolonged circulation time in blood low toxicity (micelles well tolerated by rats) | 39 |
| | paclitaxel, etoposide, docetaxel, tanespimycin | 30–40 nm | encapsulating up to 3 drugs high loading capacity PDI < 0.2 drug release profile dependent on drug combination | 57 |
| PEG-PLGA | sorafenib, all-trans retinoic acid | <200 nm | sustained release ≈56–62% within 72 h (pH 7.4) in PBS at 37°C effective cell uptake minimal systemic toxicity (mouse model) | 58 |
| OCMCh | α-tocopherol, doxorubicin | 124.7–244.9 nm, 151.9–311.2 nm | functionalized with targeting ligand (anti-HER2/neu peptide-PEG) stable in blood plasma pH dependent drug release ≈0% (pH 7.4) and 90% (pH 5.2) within 6 h in PBS | 56 |

CMC – critical micelle concentration; PDI – polydispersity index; LCST – lower critical solution temperature; MW – molecular weight; PBS – phosphate-buffered saline; PEO – poly(ethylene oxide); PCL – poly(ε-caprolactone); PBCL – poly(ε-benzylcarboxylate-ε-caprolactone); PEI – polyethylenimine; PEtOz – poly(2-ethyl-2-oxazoline); PU – polyurethane; PPO – poly(propylene oxide); PNIPAm – poly(N-isopropylacrylamide); EAB – ethyl 4-aminobenzoate; PPP – polyphosphazene; DMAA – dimethylacrylamide; PDLLA – poly(D, L-lactide); PLGA – poly(lactic-co-glycolic acid); SPIO – superparamagnetic iron oxide; TPGS – D-α-tocopheryl poly(ethylene glycol) succinate; OCMCh – O-carboxymethyl chitosan.

than PEGylated liposomal doxorubicin known as Doxil®.⁶⁴ Table 2 summarizes clinical applications of polymeric micelles as carriers of anticancer drugs. Clinical trials with published results have been already performed for formulations with names: Genexol-PM®,^{65–76} Nanoxel M®,⁷⁷ NK 911,⁶⁴ NK 105,^{78–82} NK 012,^{83–87} NC-6004,^{88–91} NC-6300,^{92–94} BIND-014,^{95–97} and Sp1049C.^{98–100}

The behavior of polymeric micelles after administration is related to several stress factors acting on these carriers. The major problems are: immediate dilution of the formulation following injection, biophysical interactions with corpuscular blood components, serum proteins, enzymes, etc., and immunological response of the body.¹⁰¹ If the shell of micelles fails to provide them “stealth” properties, they will be covered with opsonins and quickly removed by the mononuclear phagocyte system.^{24,101} Another issue associated with in vivo applications of some polymeric micelles is the premature release of the encapsulated drug due to the loss of integrity of these carriers in circulating blood.⁴⁸ As an example, it is worth mentioning the rapid separation of hydrophobic drug from the PEG-PDLLA micelles injected into the bloodstream of the tumor bearing mice.¹⁰² One approach to limiting the uncontrolled leakage of active content is the formation of multilayer

micelles. Each layer can be made of a different material and perform distinct function. This is the case for ABC triblock copolymer micelles, where A block (PEO) provides an outer covering, B block (PLA) forms a barrier against drug release, and C block (PCL) builds an inner core and a reservoir for the medication.¹⁰³ However, the properties of such structures in terms of kinetic stability and cargo release profile are still not optimal. Drug delivery systems based on polymeric micelles are constantly developed and improved to better protect the payload and meet the high safety standards set by modern medicine.

Capsules with the shell composed of polymer particles

Another group of capsules encompasses the structures with the shell built of many polymer particles (Fig. 1B). Such nano- or microparticles are usually fused, which ensures the integrity of the entire coating. One of the methods of fabricating particle capsules utilizes so called Pickering droplets. These liquid drops are covered with densely packed particles adsorbed on their surface.¹⁰⁴ The electric field-assisted mechanisms of assembling colloidal particles

Table 2. Clinical applications of polymeric micelles as carriers of anticancer drugs. Data based on the results of clinical trials published in journal articles

| Name/trade name | Copolymer type | Cargo | Applications (clinical trials with published results) | | | |
|-----------------|----------------|---|---|--------------------|-------------------------|-----------|
| | | | cancer type | combination | phase of clinical trial | reference |
| Genexol-PM® | mPEG-PDLLA | paclitaxel | advanced malignancies (lung, colorectal, renal, ovarian and breast cancers) | – | phase I | 65 |
| | | | lung, nasopharyngeal and breast cancers | – | phase I | 66 |
| | | | epithelial ovarian cancer | + carboplatin | phase I | 67 |
| | | | epithelial ovarian cancer | + carboplatin | phase II | 68 |
| | | | non-small cell lung cancer | + cisplatin | phase II | 69 |
| | | | head and neck squamous cell carcinoma | + cisplatin | phase II | 70 |
| | | | non-small cell lung cancer | + gemcitabine | phase II | 71 |
| | | | biliary tract cancer | + gemcitabine | phase II | 72 |
| | | | thymic epithelial tumors | + cisplatin | phase II | 73 |
| | | | metastatic breast cancer | – | phase II | 74 |
| | | | urothelial carcinoma | – | phase II | 75 |
| | | | HER2-negative breast cancer | – | phase III | 76 |
| Nanoxel M® | PVP-b-PDLLA | docetaxel | breast cancer | + cyclophosphamide | phase IV | 77 |
| NK 911 | PEG-PASP | doxorubicin | pancreatic cancer | – | phase I | 64 |
| NK 105 | PEG-PPBA | paclitaxel | breast, gastric, esophageal, renal pelvis, prostate and bladder tumors | – | phase I | 78 |
| | | | pancreatic, bile duct, gastric and colon cancers | – | phase I | 79 |
| | | | advanced gastric cancer | – | phase II | 80 |
| | | | breast cancer | – | phase III | 81 |
| | | | breast cancer | – | phase III | 82 |
| NK 012 | PEG-b-P(Glu) | SN-38 (active metabolite of irinotecan) | advanced solid tumors (lung, breast, ovarian, esophageal, gastric, colon, and endometrial cancers) | – | phase I | 83 |
| | | | solid tumors (colorectal, pancreatic, esophageal, and small and non-small cell lung cancers) | – | phase I | 84 |
| | | | gastrointestinal malignancies | + 5-fluorouracil | phase I | 85 |
| | | | multiple myeloma | – | phase I/II | 86 |
| | | | colorectal cancer | – | phase II | 87 |
| NC-6004 | PEG-P(Glu) | cisplatin | advanced solid tumors (lung, colon, pancreatic, esophageal, and renal cancers) | – | phase I | 88 |
| | | | advanced solid tumors (carcinoma, neuroendocrine tumors) | + gemcitabine | phase I | 89 |
| | | | advanced solid tumors (lung, colorectal, endocrine, squamous cell head and neck, breast, and gastro/esophageal cancers) | + gemcitabine | phase I b/II | 90 |
| | | | squamous non-small cell lung carcinoma, biliary tract and bladder cancers | + gemcitabine | phase II | 91 |
| NC-6300 | PEG-b-PASP | epirubicin | advanced solid tumors (urothelial, breast and other cancers) | – | phase I | 92 |
| | | | cutaneous and non-cutaneous angiosarcoma | – | phase I b | 93 |
| | | | sarcoma, osteosarcoma and other tumors | – | phase I b | 94 |
| BIND-014 | PEG-PLA | docetaxel | advanced solid tumors (lung, head and neck, ovarian, prostate, rectal, and other cancers) | – | phase I | 95 |
| | | | metastatic castration-resistant prostate cancer | + prednisone | phase II | 96 |
| | | | metastatic castration-resistant prostate cancer | + prednisone | phase II | 97 |

Table 2. Clinical applications of polymeric micelles as carriers of anticancer drugs. Data based on the results of clinical trials published in a journal article – cont.

| Name/trade name | Copolymer type | Cargo | Applications (clinical trials with published results) | | | |
|-----------------|---------------------------------|-------------|---|-------------|-------------------------|-----------|
| | | | cancer type | combination | phase of clinical trial | reference |
| Sp1049C | Pluronic F127 and Pluronic L61® | doxorubicin | colorectal, esophageal and lung cancer, soft-tissue sarcoma, mesothelioma and other cancers | – | phase I | 98 |
| | | | esophageal adenocarcinoma | – | phase II | 99 |
| | | | adenocarcinoma of the esophagus and gastroesophageal junction | – | phase II | 100 |

mPEG – methoxy poly(ethylene glycol); PDLLA – poly(D, L-lactide); PVP – poly(N-vinylpyrrolidone); PASP – poly(aspartic acid); PPBA – poly(4-phenyl-1-butanoate-L-aspartamide); P(Glu) – poly(glutamic acid); PLA – poly(lactic acid).

at the fluid interfaces are described in details in a study dedicated specifically to this subject.¹⁰⁵ Microwave heating of highly ordered jammed Pickering droplets allows for fusing (to a certain extent) and interlocking the shell particles, and thus creating capsules with the cohesive shells.¹⁰⁶ However, the electroformation method is used not only for the production of homogeneous capsules (Fig. 1C), but also for the fabrication of heterogeneous structures. Janus and patchy particle shells can be formed using the joint action of electrohydrodynamic flows and electrocoalescence of 2 or several leaky dielectric droplets partially covered with different kind of particles and embedded in another leaky dielectric medium.¹⁰⁷ It is worth recalling that the shell of the Janus capsule is composed of 2 similarly sized hemispheres, each made of separate material (Fig. 1D). The covering of patchy capsule (Fig. 1E) can comprise more regions with various shares in the total area of the sphere. When the patches are characterized by distinct chemical or physical properties, the functionality of the whole structure might be considerably extended.¹⁰⁸ The use of electroformation method followed by the thermal strengthening allowed to produce liquid-containing, ultrasound-sensitive capsules with a shell made of a monolayer of polyethylene and polystyrene microparticles.¹⁰⁶ An analogous preparation technique was used to fabricate Janus structures combining polystyrene particles with turmeric granules.¹⁰⁹

Elastic shells with adjustable permeability (dependent on the size of pores) are also produced through self-assembly of colloidal particles at the interface of emulsified droplets.¹¹⁰ The process of locking of the adsorbed particles can be performed in several ways, e.g., by sintering, the addition of polyelectrolyte molecules that bridge neighboring particles, or by inducing the van der Waals interaction between particles.¹¹⁰ For colloidal capsules with incorporated magnetite particles, the polymer shell strengthening was successfully performed with heating in the alternating magnetic field.¹¹¹ In case of submicron capsules prepared on the basis of the emulsion droplets stabilized by surface-modified gold nanoparticles, the shell reinforcement was carried out by chemical cross-linking (polymerization of olefinic bonds) induced by ultraviolet radiation.¹¹² Poly(methyl methacrylate) (PMMA) colloidal

particles adsorbed onto the surface of water droplets were held together by van der Waals forces.¹¹⁰

In the literature, the term “colloidosomes” often appears in reference to the structures having a shell comprising colloidal particles. This kind of capsules may be fabricated through Pickering emulsion interface-initiated atom transfer radical polymerization,¹¹³ using a double emulsification technique in a microfluidic device,¹¹⁴ and by extraction or dissolving of the template core of coated particles.^{115–117} Details about the techniques for preparing various sorts of colloidosomes can be found in a dedicated review.¹¹⁸ However, methods for producing colloidosomes are still being developed. Recently, emulsion droplets have been used as templates for interfacial polymerization of the monomers and thus, contributed to hierarchical assembly of two-dimensional polymers into colloidosomes and microcapsules.¹¹⁹

The majority of colloidosomes designed and manufactured so far had homogeneous shells, including those composed of charge-stabilized fluorescent polystyrene beads,¹²⁰ poly(vinyl difluoride) nanoparticles,¹¹⁴ polymeric microrods,¹²¹ or chitosan-modified silica nanoparticles.¹²² Due to the fact that capsules with particle shells are mainly intended for biomedical use, they are often tested in the role of anticancer drugs carriers. As an example, one can mention doxorubicin hydrochloride-loaded, poly(methyl methacrylate-co-butyl acrylate) colloidosomes protected with an additional silver shell¹²³ and their gold-coated counterparts with attached immunoglobulin G.¹²⁴ The second outer coating, comprising metal particles, was introduced in order to make the capsules impermeable, because pure polymer coverage was inherently porous and thus leaky to low-molecular-weight substances.^{123,125,126} Treatments such as cross-linking or increasing the thickness of the polymer coating may reduce the diffusion of small molecules through the shell, but cannot stop this process completely over a longer period of time.¹²⁶ Therefore, the additional protective layer made of interlocked solid particles seems to be an effective solution. Such a double casing was used in case of polyacrylamide/silica composite capsules¹²⁷ and gold-coated PMMA microcapsules.¹²⁸ In the latter, the growth of a secondary metallic film was catalyzed by metallic nanoparticles adsorbed onto polymeric shells.¹²⁸ Well-designed capsules

should prevent the leakage of active substances, and thus provide the long-term protection of the cargo during its storage and transport to the predefined destination.

Payload liberation strategies

The liberation of encapsulated anticancer drug can be sustained owing to the certain permeability of the shell or may result from the rupture of capsules. This disintegration must be triggered and take place near the predefined destination, i.e., tumor region. In general, factors provoking payload release can be divided into 3 groups: biological (mainly enzymes present at the target site), chemical (change in pH of a medium or salt effect on the coating) and physical (ultraviolet or infrared light, electric and magnetic field, temperature, mechanical force, and ultrasonic waves).¹²⁹

It is expected that faster release of the drug will take place within the solid tumor, where pH is lower in comparison with normal tissue and the bloodstream.^{52,130} Hence, the fabrication of pH responsive capsules is a very common practice – for example regarding doxorubicin-loaded polyelectrolyte microcapsules built of sodium poly(styrene sulfonate) and poly(allylamine hydrochloride),¹³¹ micelles made of mPEG-*b*-PCL,⁵² PEG-PBLA,^{20,130} and PEO-*b*-polyurethane-SS-*b*-PEtOz.^{36,132} In the abovementioned cases, the release of cytostatic drug was intensified as the pH decreased, because a slightly acidic conditions contributed to the rapid disassembling of polymer micelles.

Local heating of the target region to the temperature slightly higher than the normal human body temperature in order to induce breakage of polymer carriers is also considered as one of the controlled release strategies. The proper adjustment of the properties of comonomers, which allows to optimally tune a lower critical solution temperature (LCST), is crucial for thermosensitive polymers.¹³³ When the temperature of aqueous environment is below the LCST, hydrogen bonds between water molecules and polar groups of the polymer facilitate its solubility. When the temperature is above LCST, the network of hydrogen bonds breaks up and phase separation is observed.¹³⁴ The collapse of polymer chains followed by their aggregation cause the degradation of the entire vehicle. For polymeric drug carriers designed for medical applications, the LCST in which the material exhibits reversible thermo-responsive phase transition should be in a range of 37–42°C.^{133,135} Copolymers based on poly(*N*-isopropylacrylamide) are frequently used for preparation of thermo-triggered vehicles.²¹ Thermally sensitive micelles containing doxorubicin were produced using poly(*N*-isopropylacrylamide-co-*N*, *N*-dimethylacrylamide)-*b*-PLGA (P(NIPAAm-co-DMAAm)-*b*-PLGA) copolymer with various lengths of PLGA block.¹³⁶ The anticancer activity of methotrexate-loaded poly(*N*-isopropylacrylamide-co-acrylamide)-*b*-poly(*n*-butyl methacrylate) (P(NIPAAm-co-AAm)-*b*-PBMA) micelles was significantly improved

by local hyperthermia.¹³³ A similar situation was observed for docetaxel loaded poly(*N*-isopropylacrylamide-co-acrylamide)-*b*-PDLLA (Poly(IPAAm-co-AAm)-*b*-PDLLA) micelles.¹³⁵ Overall, well-designed thermoresponsive carriers should protect the whole organism against the toxic effect of the drug at physiological temperature and be able to release the payload on demand in the heated region.

It is well known that an alternating magnetic field acting on magnetic nanoparticles can induce hyperthermia.¹³⁷ Therefore, such nanoparticles are sometimes incorporated into capsules or micelles made of thermosensitive polymers. Thus, due to the magnetic hyperthermia, drug release can be remotely triggered. The enhanced hyperthermic release of doxorubicin was observed for poly(ethylene glycol)-poly(lactide) (PEG-PLA) micelles conjugated with iron oxide nanoparticles coated with citric acid.¹³⁸

In case of capsules with a liquid core, the radio-frequency magnetic heating of suspended nanoparticles can cause the local rise in liquid temperature. The temperature gradient between the inside and the outside of the shell promotes the increased diffusion of the drug.²⁵ Electromagnetic field easily penetrates human body, so it can be successfully used for deep tissue targeting. The latest trend is the fabrication of nanotransporters, which exhibit multiple magnetic-responsive behaviors under the influence of various electromagnetic frequencies, e.g., magnetophoresis in the range of 30–500 Hz and magneto-thermal effect in the range of 100–500 kHz.²⁶ The former of the mentioned physicochemical effects facilitates the mobility of the carrier through cellular barriers and the latter aids in burst release of a drug in the target. Such frequency-programmed operations were successfully performed for doxorubicin-loaded nanovehicles comprising ferrimagnetic iron oxide ring coated with a thermoresponsive polyethylenimine terminated with isobutyramide groups.²⁶

The inclusion of nanoparticles into polymeric carriers may also facilitate the ultrasound-triggered release of the drug. The study of microcapsules with polyelectrolyte: cationic poly(allylamine hydrochloride) and anionic poly(sodium styrene sulfonate) multilayer shells showed that the incorporation of iron oxide nanoparticles into these shells considerably enhanced their sensitivity to ultrasound.¹⁸ The addition of gold nanoparticles into the shells of polypyrrole capsules increased their sensitivity to ultrasound.¹³⁹ Capsules with the coating made of polymer particles can be inherently sensitive to ultrasound. The cargo from submillimeter- and millimeter-sized capsules with homogeneous, Janus and patchy shells was released in specific direction in fully controllable manner, under the influence of MHz-frequency acoustic waves.^{106,109} Other physical mechanisms were responsible for the ultrasound-induced doxorubicin liberation from polyelectrolyte microcapsules made of poly(allylamine hydrochloride)/polystyrene sulfonate,¹⁴⁰ microspheres composed of multilayers of tannic acid and poly(*N*-vinylpyrrolidone),¹⁴¹ or PLGA-based nanodroplets.¹⁴² In general,

ultrasonic waves show great potential as triggering factor, because they are harmless, easy to focus, and widely used thanks to the availability of commercial medical devices.¹⁴³

When discussing the physical factors that are capable of releasing active substances from polymer capsules, it is also worth mentioning ultraviolet (UV) radiation. Among the advantages of using UV light as a trigger, one can highlight the possibility of precise temporal and spatial control of this stimulus.¹⁴⁴ Micelles can be molded from amphiphilic block copolymers with photodegradable linker, acting as a junction between hydrophilic and hydrophobic chains.^{144,145} Polyurea microcapsules with liquid cores,¹⁴⁶ unimolecular micelles containing PMMA and poly(poly(ethylene glycol) methyl ether methacrylate)¹⁴⁷ and nanomicelles composed of PEG connected with doxorubicin via UV-sensitive amide linkage¹⁴⁸ are just a few examples of photocleavable polymeric structures.

Some drug delivery systems are sensitive to a variety of factors that allow to trigger the payload liberation at different timescales. For example, polyurethane nanocapsules released their payload under the action of UV light, temperature and pH change within minutes, hours and days, respectively.¹⁴⁹ Dual-responsive doxorubicin loaded poly(methacrylic acid)–poly(ϵ -caprolactone) micelles owe their properties to the linker containing adjacent photo- and redox-sensitive sites.¹⁴⁵

There is no doubt that stimuli-responsive polymer micelles and capsules will gain more and more applications, in particular in medicine. The fabrication of biocompatible and biodegradable drug carriers is especially important for contemporary oncology. The safe delivery of cytostatic medications to the tumor region and their controlled release on demand will allow to minimize the adverse effects of chemotherapy treatment.

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References

- Chen H, Li J, Wan J, Weitz DA, Stone HA. Gas-core triple emulsions for ultrasound triggered release. *Soft Matter*. 2013;9(1):38–42. doi:10.1039/C2SM26992A
- Urbas R, Milošević R, Kašiković N, Pavlović Ž, Elesini US. Microcapsules application in graphic arts industry: A review on the state-of-the-art. *Iranian Polym J (Eng Ed)*. 2017;26(7):541–561. doi:10.1007/s13726-017-0541-1
- Tomaro-Duchesneau C, Saha S, Malhotra M, Kahouli I, Prakash S. Microencapsulation for the therapeutic delivery of drugs, live mammalian and bacterial cells, and other biopharmaceuticals: Current status and future directions. *J Pharm (Cairo)*. 2013;2013:103527. doi:10.1155/2013/103527
- Szafraniec-Szczęśny J, Janik-Hazuka M, Odrobińska J, Zapotoczny S. Polymer capsules with hydrophobic liquid cores as functional nanocarriers. *Polymers (Basel)*. 2020;12(9):1999. doi:10.3390/polym12091999
- Lavasanifar A, Samuel J, Kwon GS. Poly(ethylene oxide)-block-poly(L-amino acid) micelles for drug delivery. *Adv Drug Deliv Rev*. 2002;54(2):169–190. doi:10.1016/s0169-409x(02)00015-7
- García MC, Aloisio C, Onnainty R, Ullio-Gamboa G. Part 3. Self-assembled nanomaterials. In: Narayan R, ed. *Nanobiomaterials*. Sawston, UK: Woodhead Publishing; 2018:41–94.
- Saqr A, Vakili MR, Huang YH, Lai R, Lavasanifar A. Development of traceable rituximab-modified PEO-polyester micelles by postinsertion of PEG-phospholipids for targeting of B-cell lymphoma. *ACS Omega*. 2019;4(20):18867–18879. doi:10.1021/acsomega.9b02910
- Chiappetta DA, Sosnik A. Poly(ethylene oxide)–poly(propylene oxide) block copolymer micelles as drug delivery agents: Improved hydro-solubility, stability and bioavailability of drugs. *Eur J Pharm Biopharm*. 2007;66(3):303–317. doi:10.1016/j.ejpb.2007.03.022
- Liu J, Lee H, Allen C. Formulation of drugs in block copolymer micelles: Drug loading and release. *Curr Pharm Des*. 2006;12:4685–4701. doi:10.2174/138161206779026263
- Han LM, Guo J, Zhang LJ, Wang QS, Fang XL. Pharmacokinetics and biodistribution of polymeric micelles of paclitaxel with Pluronic P123. *Acta Pharmacol Sin*. 2006;27(6):747–753. doi:10.1111/j.1745-7254.2006.00340.x
- Engels F, Mathot R, Verweij J. Alternative drug formulations of docetaxel: A review. *Anticancer Drugs*. 2007;18(2):95–103. doi:10.1097/CAD.0b013e3280113338
- Meredith AM, Dass CR. Increasing role of the cancer chemotherapeutic doxorubicin in cellular metabolism. *J Pharm Pharmacol*. 2016;68(6):729–741. doi:10.1111/jphp.12539
- Yang F, Xu J, Fu M, Ji J, Chi L, Zhai G. Development of stimuli-responsive intelligent polymer micelles for the delivery of doxorubicin. *J Drug Targeting*. 2020;28(10):993–1011. doi:10.1080/1061186X.2020.1766474
- Situ JQ, Wang XJ, Zhu XL, et al. Multifunctional SPIO/DOX-loaded A54 homing peptide functionalized dextran-g-PLGA micelles for tumor therapy and MR imaging. *Sci Rep*. 2016;6(1):35910. doi:10.1038/srep35910
- Nakamura J, Nakajima N, Matsumura K, Hyon SH. Water-soluble taxol conjugates with dextran and targets tumor cells by folic acid immobilization. *Anticancer Res*. 2010;30(3):903. PMID:20393013
- Li Q, Li X, Zhao C. Strategies to obtain encapsulation and controlled release of small hydrophilic molecules. *Front Bioeng Biotechnol*. 2020;8:437. doi:10.3389/fbioe.2020.00437
- Torchilin VP. Micellar nanocarriers: Pharmaceutical perspectives. *Pharm Res*. 2006;24(1):1–16. doi:10.1007/s11095-006-9132-0
- Kolesnikova TA, Khlebtsov BN, Shchukin DG, Gorin DA. Atomic force microscopy characterization of ultrasound-sensitive nanocomposite microcapsules. *Nanotechnologies in Russia*. 2008;3(9):560–569. doi:10.1134/S1995078008090048
- Sun Q, Chen JF, Routh AF. Coated colloidosomes as novel drug delivery carriers. *Exp Opin Drug Deliv*. 2019;16(9):903–906. doi:10.1080/17425247.2019.1652594
- Kataoka K, Matsumoto T, Yokoyama M, et al. Doxorubicin-loaded poly(ethylene glycol)–poly(β -benzyl-L-aspartate) copolymer micelles: Their pharmaceutical characteristics and biological significance. *J Controlled Release*. 2000;64(1–3):143–153. doi:10.1016/S0168-3659(99)00133-9
- Wei H, Cheng SX, Zhang XZ, Zhuo RX. Thermo-sensitive polymeric micelles based on poly(N-isopropylacrylamide) as drug carriers. *Prog Polym Sci*. 2009;34(9):893–910. doi:10.1016/j.progpolymsci.2009.05.002
- Rad A, Asiaee F, Jafari S, Shayanfar A, Lavasanifar A, Molavi O. Poly(ethylene glycol)–poly(ϵ -caprolactone)-based micelles for solubilization and tumor-targeted delivery of silibinin. *Bioimpacts*. 2019;10(2):87–95. doi:10.34172/bi.2020.11
- Dhaliwal A, Zheng G. Improving accessibility of EPR-insensitive tumor phenotypes using EPR-adaptive strategies: Designing a new perspective in nanomedicine delivery. *Theranostics*. 2019;9(26):8091–8108. doi:10.7150/thno.37204
- Conniot J, Silva J, Fernandes J, et al. Cancer immunotherapy: Nanodelivery approaches for immune cell targeting and tracking. *Front Chem*. 2014;2:1. doi:10.3389/fchem.2014.00105
- Kong SD, Zhang W, Lee JH, et al. Magnetically vectored nanocapsules for tumor penetration and remotely switchable on-demand drug release. *Nano Lett*. 2010;10(12):5088–5092. doi:10.1021/nl1033733
- Liu X, Zhang Y, Guo Y, et al. Electromagnetic field-programmed magnetic vortex nanodelivery system for efficacious cancer therapy. *Adv Sci (Weinh)*. 2021;8(18):2100950. doi:10.1002/advs.202100950
- Kubiak T. The use of shells made of poly(ethylene glycol) and chitosan to ensure the biocompatibility of nanoparticles in biomedical applications [in Polish]. *Polim Med*. 2014;44(2):119–127. PMID:24967783.

28. Rodrigues S, Dionisio M, Remuñán-López C, Grenha A. Biocompatibility of chitosan carriers with application in drug delivery. *J Funct Biomater*. 2012;3(3):615–641. doi:10.3390/jfb3030615
29. Krzymiński R, Kubiak T, Dobosz B, Schroeder G, Kurczewska J. EPR spectroscopy and imaging of TEMPO-labeled magnetite nanoparticles. *Curr Appl Phys*. 2014;14(5):798–804. doi:10.1016/j.cap.2014.03.021
30. Kubiak T, Krzymiński R, Dobosz B, Schroeder G, Kurczewska J, Hałupka-Bryl M. A study of magnetite nanoparticles in whole human blood by means of electron paramagnetic resonance [in Polish]. *Inżynieria Biomedyczna Acta Bio-Optica et Informatica Medica*. 2015;21:9–15. <http://yadda.icm.edu.pl/baztech/element/bwmeta1.element.baztech-46fd6649-cfe9-4ed2-aec5-7382ef9e429d>
31. Kubiak T. Nanoparticles as radiosensitizers in photon and hadron radiotherapy. *Acta Bio-Optica et Informatica Medica Inżynieria Biomedyczna*. 2017;23:29–36. <http://yadda.icm.edu.pl/baztech/element/bwmeta1.element.baztech-0799f4ea-89b2-4c4b-908a-726e9c0c5618>
32. Borvinskaya E, Gurkov A, Shchapova E, Baduev B, Meglinski I, Timofeyev M. Distribution of PEG-coated hollow polyelectrolyte microcapsules after introduction into the circulatory system and muscles of zebrafish. *Biol Open*. 2018;7(1):bio030015. doi:10.1242/bio.030015
33. Cosco D, Paolino D, De Angelis F, et al. Aqueous-core PEG-coated PLA nanocapsules for an efficient entrapment of water soluble anticancer drugs and a smart therapeutic response. *Eur J Pharm Biopharm*. 2014;89:30–39. doi:10.1016/j.ejpb.2014.11.012
34. Prego C, Torres D, Fernandez-Megia E, Novoa-Carballal R, Quiñoá E, Alonso MJ. Chitosan-PEG nanocapsules as new carriers for oral peptide delivery: Effect of chitosan pegylation degree. *J Control Release*. 2006;111(3):299–308. doi:10.1016/j.jconrel.2005.12.015
35. Hinz A, Szczepanowicz K, Cierniak A, et al. In vivo studies on pharmacokinetics, toxicity and immunogenicity of polyelectrolyte nanocapsules functionalized with two different polymers: Poly-L-glutamic acid or PEG. *Int J Nanomedicine*. 2019;14:9587–9602. doi:10.2147/IJN.S230865
36. Xu K, Liu X, Bu L, Zhang H, Zhu C, Li Y. Stimuli-responsive micelles with detachable poly(2-ethyl-2-oxazoline) shell based on amphiphilic polyurethane for improved intracellular delivery of doxorubicin. *Polymers (Basel)*. 2020;12(11):2642. doi:10.3390/polym12112642
37. Kakkar D, Mazzaferro S, Thevenot J, et al. Amphiphilic PEO-b-PBLG diblock and PBLG-b-PEO-b-PBLG triblock copolymer based nanoparticles: Doxorubicin loading and in vitro evaluation. *Macromol Biosci*. 2015;215(1):124–137. doi:10.1002/mabi.201400451
38. Katragadda U, Fan W, Wang Y, Teng Q, Tan C. Combined delivery of paclitaxel and tanespimycin via micellar nanocarriers: Pharmacokinetics, efficacy and metabolomic analysis. *PLoS One*. 2013;8(3):e58619. doi:10.1371/journal.pone.0058619
39. Xiong MP, Yáñez JA, Kwon GS, Davies NM, Laird Forrest M. A Cremophor-free formulation for tanespimycin (17-AAG) using PEO-b-PDLLA micelles: Characterization and pharmacokinetics in rats. *J Pharm Sci*. 2009;98(4):1577–1586. doi:10.1002/jps.21509
40. Liu Z, Liu D, Wang L, Zhang J, Zhang N. Docetaxel-loaded Pluronic p123 polymeric micelles: In vitro and in vivo evaluation. *Int J Mol Sci*. 2011;12(3):1684–1696. doi:10.3390/ijms12031684
41. Liu Z, Wang Y, Zhang J, Li M, Liu Y, Zhang N. Pluronic P123-docetaxel conjugate micelles: Synthesis, characterization, and antitumor activity. *J Biomed Nanotechnol*. 2013;9(12):2007–2016. doi:10.1166/jbn.2013.1706
42. Liang Y, Su Z, Yao Y, Zhang N. Preparation of pH sensitive Pluronic-docetaxel conjugate micelles to balance the stability and controlled release issues. *Materials (Basel)*. 2015;8(2):379–391. doi:10.3390/ma8020379
43. He Z, Alexandridis P. Micellization thermodynamics of Pluronic P123 (EO20PO70EO20) amphiphilic block copolymer in aqueous ethylammonium nitrate (EAN) solutions. *Polymers (Basel)*. 2017;10(1):32. doi:10.3390/polym10010032
44. Ullah RS, Wang L, Yu H, et al. Synthesis of polyphosphazenes with different side groups and various tactics for drug delivery. *RSC Advances*. 2017;7(38):23363–23391. doi:10.1039/C6RA27103K
45. Zhang JX, Qiu LY, Jin Y, Zhu KJ. Physicochemical characterization of polymeric micelles constructed from novel amphiphilic polyphosphazene with poly(N-isopropylacrylamide) and ethyl 4-aminobenzoate as side groups. *Colloids Surf B Biointerfaces*. 2005;43(3):123–130. doi:10.1016/j.colsurfb.2005.03.012
46. Qiu LY, Wu XL, Jin Y. Doxorubicin-loaded polymeric micelles based on amphiphilic polyphosphazenes with poly(N-isopropylacrylamide-co-N,N-dimethylacrylamide) and ethyl glycinate as side groups: Synthesis, preparation and in vitro evaluation. *Pharm Res*. 2009;26(4):946–957. doi:10.1007/s11095-008-9797-7
47. Ogueri KS, Ogueri KS, Ude CC, Allcock HR, Laurencin CT. Biomedical applications of polyphosphazenes. *Med Devices Sens*. 2020;3(6):e10113. doi:10.1002/mds3.10113
48. Soleymani Abyaneh H, Vakili MR, Lavasanifar A. The effect of polymerization method in stereo-active block copolymers on the stability of polymeric micelles and their drug release profile. *Pharm Res*. 2014;31(6):1485–1500. doi:10.1007/s11095-013-1255-5
49. Sun J, Wei Q, Shen N, Tang Z, Chen X. Predicting the loading capability of mPEG-PDLLA to hydrophobic drugs using solubility parameters. *Chin J Chem*. 2020;38(7):690–696. doi:10.1002/cjoc.202000078
50. Kim SC, Kim DW, Shim YH, et al. In vivo evaluation of polymeric micellar paclitaxel formulation: Toxicity and efficacy. *J Control Release*. 2001;72(1):191–202. doi:10.1016/S0168-3659(01)00275-9
51. Guthi JS, Yang SG, Huang G, et al. MRI-visible micellar nanomedicine for targeted drug delivery to lung cancer cells. *Mol Pharm*. 2010;7(1):32–40. doi:10.1021/mp9001393
52. Shuai X, Ai H, Nasongkla N, Kim S, Gao J. Micellar carriers based on block copolymers of poly(caprolactone) and poly(ethylene glycol) for doxorubicin delivery. *J Control Release*. 2004;98(3):415–426. doi:10.1016/j.jconrel.2004.06.003
53. Shuai X, Merdan T, Schaper AK, Xi F, Kissel T. Core-cross-linked polymeric micelles as paclitaxel carriers. *Bioconjugate Chem*. 2004;15(3):441–448. doi:10.1021/bc034113u
54. Yusuf O, Ali R, Alomrani AH, et al. Design and development of D- α -tocopheryl polyethylene glycol succinate-block-poly(ϵ -caprolactone) (TPGS-b-PCL) nanocarriers for solubilization and controlled release of paclitaxel. *Molecules*. 2021;26(9):2690. doi:10.3390/molecules26092690
55. Muthu MS, Kulkarni S, Liu Y, Feng SS. Development of docetaxel-loaded vitamin E TPGS micelles: Formulation optimization, effects on brain cancer cells and biodistribution in rats. *Nanomedicine (Lond)*. 2012;7(3):353–364. doi:10.2217/nnm.11.111
56. Nam JP, Lee KJ, Choi JW, Yun CO, Nah JW. Targeting delivery of tocopherol and doxorubicin grafted-chitosan polymeric micelles for cancer therapy: In vitro and in vivo evaluation. *Colloids Surf B Biointerfaces*. 2015;133:254–262. doi:10.1016/j.colsurfb.2015.06.018
57. Shin HC, Alani AWG, Rao DA, Rockich NC, Kwon GS. Multi-drug loaded polymeric micelles for simultaneous delivery of poorly soluble anticancer drugs. *J Control Release*. 2009;140(3):294–300. doi:10.1016/j.jconrel.2009.04.024
58. Li S, Dong S, Xu W, Jiang Y, Li Z. Polymer nanoformulation of sorafenib and all-trans retinoic acid for synergistic inhibition of thyroid cancer. *Front Pharmacol*. 2020;10:1676. doi:10.3389/fphar.2019.01676
59. Xie X, Chen Y, Chen Z, et al. Polymeric hybrid nanomicelles for cancer theranostics: An efficient and precise anticancer strategy for the co-delivery of doxorubicin/miR-34a and magnetic resonance imaging. *ACS Appl Mater Interfaces*. 2019;11(47):43865–43878. doi:10.1021/acsami.9b14908
60. Voci S, Gagliardi A, Molinaro R, Fresta M, Cosco D. Recent advances of taxol-loaded biocompatible nanocarriers embedded in natural polymer-based hydrogels. *Gels*. 2021;7(2):33. doi:10.3390/gels7020033
61. Do VQ, Park KH, Park JM, Lee MY. Comparative in vitro toxicity study of docetaxel and nanoxel, a docetaxel-loaded micellar formulation using cultured and blood cells. *Toxicol Res*. 2019;35(2):201–207. doi:10.5487/TR.2019.35.2.201
62. Zheng X, Xie J, Zhang X, et al. An overview of polymeric nanomicelles in clinical trials and on the market. *Chin Chem Lett*. 2021;32(1):243–257. doi:10.1016/j.ccllet.2020.11.029
63. Khanna C, Rosenberg M, Vail DY. A review of paclitaxel and novel formulations, including those suitable for use in dogs. *J Vet Intern Med*. 2015;29(4):1006–1012. doi:10.1111/jvim.12596
64. Matsumura Y, Hamaguchi T, Ura T, et al. Phase I clinical trial and pharmacokinetic evaluation of NK911, a micelle-encapsulated doxorubicin. *Br J Cancer*. 2004;91(10):1775–1781. doi:10.1038/sj.bjc.6602204

65. Kim TY, Kim DW, Chung JY, et al. Phase I and pharmacokinetic study of Genexol-PM, a Cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies. *Clin Cancer Res.* 2004;10(11):3708–3716. doi:10.1158/1078-0432.CCR-03-0655
66. Lim WT, Tan EH, Toh CK, et al. Phase I pharmacokinetic study of a weekly liposomal paclitaxel formulation (Genexol-PM) in patients with solid tumors. *Ann Oncol.* 2010;21(2):382–388. doi:10.1093/annonc/mdp315
67. Lee SW, Kim YM, Kim YT, Kang SB. An open-label, multicenter, phase I trial of a Cremophor-free, polymeric micelle formulation of paclitaxel combined with carboplatin as a first-line treatment for advanced ovarian cancer: A Korean Gynecologic Oncology Group study (KGOG-3016). *J Gynecol Oncol.* 2017;28(3):e26. doi:10.3802/jgo.2017.28.e26
68. Lee SW, Kim YM, Cho CH, et al. An open-label, randomized, parallel, phase II trial to evaluate the efficacy and safety of a Cremophor-free polymeric micelle formulation of paclitaxel as first-line treatment for ovarian cancer: A Korean Gynecologic Oncology Group study (KGOG-3021). *Cancer Res Treat.* 2018;50(1):195–203. doi:10.4143/crt.2016.376
69. Kim DW, Kim SY, Kim HK, et al. Multicenter phase II trial of Genexol-PM, a novel Cremophor-free, polymeric micelle formulation of paclitaxel, with cisplatin in patients with advanced non-small-cell lung cancer. *Ann Oncol.* 2007;18(12):2009–2014. doi:10.1093/annonc/mdm374
70. Keam B, Lee KW, Lee SH, et al. A phase II study of Genexol-PM and cisplatin as induction chemotherapy in locally advanced head and neck squamous cell carcinoma. *Oncologist.* 2019;24(6):751–e231. doi:10.1634/theoncologist.2019-0070
71. Ahn HK, Jung M, Sym SJ, et al. A phase II trial of Cremophor EL-free paclitaxel (Genexol-PM) and gemcitabine in patients with advanced non-small cell lung cancer. *Cancer Chemother Pharmacol.* 2014;74(2):277–282. doi:10.1007/s00280-014-2498-5
72. Kim JY, Do YR, Song HS, et al. Multicenter phase II clinical trial of Genexol-PM® with gemcitabine in advanced biliary tract cancer. *Anticancer Res.* 2017;37(3):1467–1473. doi:10.21873/anticancer.11471
73. Kim HS, Lee JY, Lim SH, et al. A prospective phase II study of cisplatin and Cremophor EL-free paclitaxel (Genexol-PM) in patients with unresectable thymic epithelial tumors. *J Thoracic Oncol.* 2015;10(12):1800–1806. doi:10.1097/JTO.0000000000000692
74. Lee KS, Chung HC, Im SA, et al. Multicenter phase II trial of Genexol-PM, a Cremophor-free, polymeric micelle formulation of paclitaxel, in patients with metastatic breast cancer. *Breast Cancer Res Treatment.* 2008;108(2):241–250. doi:10.1007/s10549-007-9591-y
75. Lee JL, Ahn JH, Park SH, et al. Phase II study of a Cremophor-free, polymeric micelle formulation of paclitaxel for patients with advanced urothelial cancer previously treated with gemcitabine and platinum. *Invest New Drugs.* 2012;30(5):1984–1990. doi:10.1007/s10637-011-9757-7
76. Park IH, Sohn JH, Kim SB, et al. An open-label, randomized, parallel, phase III trial evaluating the efficacy and safety of polymeric micelle-formulated paclitaxel compared to conventional Cremophor EL-based paclitaxel for recurrent or metastatic HER2-negative breast cancer. *Cancer Res Treat.* 2017;49(3):569–577. doi:10.4143/crt.2016.289
77. Kim TH, Gwak G, Chung MS, et al. Multicenter trial for safety and toxicity of a nanoparticle docetaxel formulation in breast cancer. *Ann Oncol.* 2018;29(Suppl 9):ix3. doi:10.1093/annonc/mdy426.010
78. Mukai H, Kato K, Esaki T, et al. Phase I study of NK105, a nanomicellar paclitaxel formulation, administered on a weekly schedule in patients with solid tumors. *Invest New Drugs.* 2016;34(6):750–759. doi:10.1007/s10637-016-0381-4
79. Hamaguchi T, Kato K, Yasui H, et al. A phase I and pharmacokinetic study of NK105, a paclitaxel-incorporating micellar nanoparticle formulation. *Br J Cancer.* 2007;97(2):170–176. doi:10.1038/sj.bjc.6603855
80. Kato K, Chin K, Yoshikawa T, et al. Phase II study of NK105, a paclitaxel-incorporating micellar nanoparticle, for previously treated advanced or recurrent gastric cancer. *Invest New Drugs.* 2012;30(4):1621–1627. doi:10.1007/s10637-011-9709-2
81. Saeki T, Mukai H, Ro J, et al. A global phase III clinical study comparing NK105 and paclitaxel in metastatic or recurrent breast cancer patients. *Ann Oncol.* 2017;28(Suppl 5):v80–v81. doi:10.1093/annonc/mdx365.013
82. Fujiwara Y, Mukai H, Saeki T, et al. A multi-national, randomised, open-label, parallel, phase III non-inferiority study comparing NK105 and paclitaxel in metastatic or recurrent breast cancer patients. *Br J Cancer.* 2019;120(5):475–480. doi:10.1038/s41416-019-0391-z
83. Burris HA, Infante JR, Anthony Greco F, et al. A phase I dose escalation study of NK012, an SN-38 incorporating macromolecular polymeric micelle. *Cancer Chemother Pharmacol.* 2016;77(5):1079–1086. doi:10.1007/s00280-016-2986-x
84. Hamaguchi T, Doi T, Eguchi-Nakajima T, et al. Phase I study of NK012, a novel SN-38-incorporating micellar nanoparticle, in adult patients with solid tumors. *Clin Cancer Res.* 2010;16(20):5058. doi:10.1158/1078-0432.CCR-10-0387
85. Jones SF, Burris HA, Infante JR, et al. A phase I study of NK012 in combination with 5-fluorouracil with or without leucovorin in patients (pts) with advanced solid tumors. *J Clin Oncol.* 2012;30(15 Suppl):e13076–e13076. doi:10.1200/jco.2012.30.15_suppl.e13076
86. Ri M, Suzuki K, Iida S, et al. A phase I/II study for dose-finding, and to investigate the safety, pharmacokinetics and preliminary efficacy of NK012, an SN-38-incorporating macromolecular polymeric micelle, in patients with multiple myeloma. *Intern Med.* 2018;57(7):939–946. doi:10.2169/internalmedicine.9567-17
87. Hamaguchi T, Tsuji A, Yamaguchi K, et al. A phase II study of NK012, a polymeric micelle formulation of SN-38, in unresectable, metastatic or recurrent colorectal cancer patients. *Cancer Chemother Pharmacol.* 2018;82(6):1021–1029. doi:10.1007/s00280-018-3693-6
88. Plummer R, Wilson RH, Calvert H, et al. A phase I clinical study of cisplatin-incorporated polymeric micelles (NC-6004) in patients with solid tumours. *Br J Cancer.* 2011;104(4):593–598. doi:10.1038/bjc.2011.6
89. Doi T, Hamaguchi T, Shitara K, et al. NC-6004 phase I study in combination with gemcitabine for advanced solid tumors and population PK/PD analysis. *Cancer Chemother Pharmacol.* 2017;79(3):569–578. doi:10.1007/s00280-017-3254-4
90. Subbiah V, Grilley-Olson JE, Combest AJ, et al. Phase Ib/II trial of NC-6004 (nanoparticle cisplatin) plus gemcitabine in patients with advanced solid tumors. *Clin Cancer Res.* 2018;24(1):43–51. doi:10.1158/1078-0432.CCR-17-1114
91. Volovat SR, Ciuleanu TE, Koralewski P, et al. A multicenter, single-arm, basket design, phase II study of NC-6004 plus gemcitabine in patients with advanced unresectable lung, biliary tract, or bladder cancer. *Oncotarget.* 2020;11(33):3105–3117. doi:10.18632/oncotarget.27684
92. Mukai H, Kogawa T, Matsubara N, Naito Y, Sasaki M, Hosono A. A first-in-human phase 1 study of epirubicin-conjugated polymer micelles (K-912/NC-6300) in patients with advanced or recurrent solid tumors. *Invest New Drugs.* 2017;35(3):307–314. doi:10.1007/s10637-016-0422-z
93. Riedel RF, Chua VS, Kim T, et al. Results of NC-6300 (nanoparticle epirubicin) in an expansion cohort of patients with angiosarcoma. *J Clin Oncol.* 2021;39(15 Suppl):11543–11543. doi:10.1200/JCO.2021.39.15_suppl.11543
94. Chawla SP, Goel S, Chow W, et al. A phase 1b dose escalation trial of NC-6300 (nanoparticle epirubicin) in patients with advanced solid tumors or advanced, metastatic, or unresectable soft-tissue sarcoma. *Clin Cancer Res.* 2020;26(16):4225–4232. doi:10.1158/1078-0432.CCR-20-0591
95. Von Hoff DD, Mita MM, Ramanathan RK, et al. Phase I study of PSMA-targeted docetaxel-containing nanoparticle BIND-014 in patients with advanced solid tumors. *Clin Cancer Res.* 2016;22(13):3157–3163. doi:10.1158/1078-0432.CCR-15-2548
96. Autio KA, Garcia JA, Alva AS, et al. A phase 2 study of BIND-014 (PSMA-targeted docetaxel nanoparticle) administered to patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol.* 2016;34(2 Suppl):233–233. doi:10.1200/jco.2016.34.2_suppl.233
97. Autio KA, Dreicer R, Anderson J, et al. Safety and efficacy of BIND-014, a docetaxel nanoparticle targeting prostate-specific membrane antigen for patients with metastatic castration-resistant prostate cancer: A phase 2 clinical trial. *JAMA Oncol.* 2018;4(10):1344–1351. doi:10.1001/jamaoncol.2018.2168
98. Danson S, Ferry D, Alakhov V, et al. Phase I dose escalation and pharmacokinetic study of Pluronic polymer-bound doxorubicin (SP1049C) in patients with advanced cancer. *Br J Cancer.* 2004;90(11):2085–2091. doi:10.1038/sj.bjc.6601856
99. Armstrong A, Brewer J, Newman C, et al. SP1049C as first-line therapy in advanced (inoperable or metastatic) adenocarcinoma of the oesophagus: A phase II window study. *J Clin Oncol.* 2006;24(18 Suppl):4080. doi:10.1200/jco.2006.24.18_suppl.4080

100. Valle JW, Armstrong A, Newman C, et al. A phase 2 study of SP1049C, doxorubicin in P-glycoprotein-targeting Pluronic, in patients with advanced adenocarcinoma of the esophagus and gastroesophageal junction. *Invest New Drugs*. 2011;29(5):1029–1037. doi:10.1007/s10637-010-9399-1
101. Miller T, Hill A, Uezguen S, Weigandt M, Goepferich A. Analysis of immediate stress mechanisms upon injection of polymeric micelles and related colloidal drug carriers: Implications on drug targeting. *Biomacromolecules*. 2012;13(6):1707–1718. doi:10.1021/bm3002045
102. Miller T, Breyer S, van Colen G, et al. Premature drug release of polymeric micelles and its effects on tumor targeting. *Int J Pharm*. 2013;445(1):117–124. doi:10.1016/j.ijpharm.2013.01.059
103. Soleymani Abyaneh H, Vakili M, Zhan F, Choi P, Lavasanifar A. Rationale design of block copolymer micelles to control burst drug release at a nanoscale dimension. *Acta Biomater*. 2015;24:127–139. doi:10.1016/j.actbio.2015.06.017
104. Rozynek Z, Bielas R, Józefczak A. Efficient formation of oil-in-oil Pickering emulsions with narrow size distributions by using electric fields. *Soft Matter*. 2018;14(24):5140–5149. doi:10.1039/C8SM00671G
105. Dommersnes P, Rozynek Z, Mikkelsen A, et al. Active structuring of colloidal armour on liquid drops. *Nat Commun*. 2013;4:2066. doi:10.1038/ncomms3066
106. Kubiak T, Banaszak J, Józefczak A, Rozynek Z. Direction-specific release from capsules with homogeneous or Janus shells using an ultrasound approach. *ACS Appl Mater Interfaces*. 2020;12(13):15810–15822. doi:10.1021/acsami.9b21484
107. Rozynek Z, Mikkelsen A, Dommersnes P, Fossum JO. Electroformation of Janus and patchy capsules. *Nat Commun*. 2014;5:3945. doi:10.1038/ncomms4945
108. Rozynek Z, Józefczak A. Patchy colloidosomes: An emerging class of structures. *Eur Phys J Special Topics*. 2016;225(4):741–756. doi:10.1140/epjst/e2015-50267-7
109. Kubiak T, Zubko M, Józefczak A. Ultrasound-triggered directional release from turmeric capsules. *Particuology*. 2021;57:19–27. doi:10.1016/j.partic.2020.12.010
110. Dinsmore AD, Hsu MF, Nikolaidis MG, Marquez M, Bausch AR, Weitz DA. Colloidosomes: Selectively permeable capsules composed of colloidal particles. *Science*. 2002;298(5595):1006–1009. doi:10.1126/science.1074868
111. Bielas R, Surdeko D, Kaczmarek K, Józefczak A. The potential of magnetic heating for fabricating Pickering-emulsion-based capsules. *Colloids Surf B Biointerfaces*. 2020;192:111070. doi:10.1016/j.colsurfb.2020.111070
112. Sobczak G, Wojciechowski T, Sashuk V. Submicron colloidosomes of tunable size and wall thickness. *Langmuir*. 2017;33(7):1725–1731. doi:10.1021/acs.langmuir.6b04159
113. Chen Y, Wang C, Chen J, Liu X, Tong Z. Growth of lightly crosslinked PHEMA brushes and capsule formation using Pickering emulsion interface-initiated ATRP. *J Polym Sci A Polym Chem*. 2009;47(5):1354–1367. doi:10.1002/pola.23244
114. Sander JS, Studart AR. Monodisperse functional colloidosomes with tailored nanoparticle shells. *Langmuir*. 2011;27(7):3301–3307. doi:10.1021/la1035344
115. Li Z, Lee D, Rubner MF, Cohen RE. Layer-by-layer assembled Janus microcapsules. *Macromolecules*. 2005;38(19):7876–7879. doi:10.1021/ma0513012
116. Shchukin DG, Shchukina E. Capsules with external navigation and triggered release. *Curr Opin Pharmacol*. 2014;18:42–46. doi:10.1016/j.coph.2014.09.002
117. Guan BY, Yu L, Lou XW. Chemically assisted formation of monolayer colloidosomes on functional particles. *Adv Mater*. 2016;28(43):9596–9601. doi:10.1002/adma.201603622
118. Thompson KL, Williams M, Armes SP. Colloidosomes: Synthesis, properties and applications. *J Colloid Interface Sci*. 2014;447:217–228. doi:10.1016/j.jcis.2014.11.058
119. Zhang Z, Wang S, Yang Y, Li W, Liu P, Wang WJ. Hierarchical assembly of two-dimensional polymers into colloidosomes and microcapsules. *ACS Macro Letters*. 2021;10(7):933–939. doi:10.1021/acsmacrolett.1c00380
120. Subramaniam AB, Abkarian M, Stone HA. Controlled assembly of jammed colloidal shells on fluid droplets. *Nat Mater*. 2005;4(7):553–556. doi:10.1038/nmat1412
121. Noble PF, Cayre OJ, Alargova RG, Velev OD, Paunov VN. Fabrication of “hairy” colloidosomes with shells of polymeric microrods. *J Am Chem Soc*. 2004;126(26):8092–8093. doi:10.1021/ja047808u
122. Su Y, Zhao H, Wu J, Xu J. One-step fabrication of silica colloidosomes with in situ drug encapsulation. *RSC Advances*. 2016;6(113):112292–112299. doi:10.1039/C6RA19048K
123. Sun Q, Gao H, Sukhorukov GB, Routh AF. Silver-coated colloidosomes as carriers for an anticancer drug. *ACS Appl Mater Interfaces*. 2017;9(38):32599–32606. doi:10.1021/acsami.7b11128
124. Sun Q, Du Y, Hall EAH, Luo D, Sukhorukov GB, Routh AF. A fabrication method of gold coated colloidosomes and their application as targeted drug carriers. *Soft Matter*. 2018;14(14):2594–2603. doi:10.1039/c7sm02485a
125. Sun Q, Du Y, Zhao Z, et al. Functional silver-coated colloidosomes as targeted carriers for small molecules. *Langmuir*. 2017;33(15):3755–3764. doi:10.1021/acs.langmuir.6b04594
126. White AL, Langton C, Wille ML, et al. Ultrasound-triggered release from metal shell microcapsules. *J Colloid Interface Sci*. 2019;554:444–452. doi:10.1016/j.jcis.2019.07.020
127. Zhang K, Wang Q, Meng H, Wang M, Wu W, Chen J. Preparation of polyacrylamide/silica composite capsules by inverse Pickering emulsion polymerization. *Particuology*. 2014;14:12–18. doi:10.1016/j.partic.2013.02.010
128. Hitchcock JP, Tasker AL, Baxter EA, Biggs S, Cayre OJ. Long-term retention of small, volatile molecular species within metallic microcapsules. *ACS Appl Mater Interfaces*. 2015;7(27):14808–14815. doi:10.1021/acsami.5b03116
129. Stavarache CE, Paniwnyk L. Controlled rupture of magnetic LbL polyelectrolyte capsules and subsequent release of contents employing high intensity focused ultrasound. *J Drug Deliv Sci Technol*. 2018;45:60–69. doi:10.1016/j.jddst.2018.02.011
130. Li B, Cai M, Lin L, et al. MRI-visible and pH-sensitive micelles loaded with doxorubicin for hepatoma treatment. *Biomater Sci*. 2019;7(4):1529–1542. doi:10.1039/C8BM01501E
131. Yang X, Han X, Zhu Y. (PAH/PSS)5 microcapsules templated on silica core: Encapsulation of anticancer drug DOX and controlled release study. *Colloids Surf A Physicochem Engineering Aspects*. 2005;264(1–3):49–54. doi:10.1016/j.colsurfa.2005.05.017
132. Bu L, Zhang H, Xu K, Du B, Zhu C, Li Y. pH and reduction dual-responsive micelles based on novel polyurethanes with detachable poly(2-ethyl-2-oxazoline) shell for controlled release of doxorubicin. *Drug Deliv*. 2019;26(1):300–308. doi:10.1080/10717544.2019.1580323
133. Sun F, Wang Y, Wei Y, Cheng G, Ma G. Thermo-triggered drug delivery from polymeric micelles of poly(N-isopropylacrylamide-co-acrylamide)-b-poly(n-butyl methacrylate) for tumor targeting. *J Bioactive Compatible Polym*. 2014;29(4):301–317. doi:10.1177/0883911514535288
134. Schild HG. Poly(N-isopropylacrylamide): Experiment, theory and application. *Prog Polym Sci*. 1992;17(2):163–249. doi:10.1016/0079-6700(92)90023-R
135. Yang M, Ding Y, Zhang L, Qian X, Jiang X, Liu B. Novel thermosensitive polymeric micelles for docetaxel delivery. *J Biomed Mater Res A*. 2007;81A(4):847–857. doi:10.1002/jbm.a.31129
136. Liu SQ, Tong YW, Yang YY. Incorporation and in vitro release of doxorubicin in thermally sensitive micelles made from poly(N-isopropylacrylamide-co-N,N-dimethylacrylamide)-b-poly(d,l-lactide-co-glycolide) with varying compositions. *Biomaterials*. 2005;26(24):5064–5074. doi:10.1016/j.biomaterials.2005.01.030
137. Kaczmarek K, Mrówczyński R, Hornowski T, Bielas R, Józefczak A. The effect of tissue-mimicking phantom compressibility on magnetic hyperthermia. *Nanomaterials (Basel)*. 2019;9(5):803. doi:10.3390/nano9050803
138. Kim HC, Kim E, Jeong SW, et al. Magnetic nanoparticle-conjugated polymeric micelles for combined hyperthermia and chemotherapy. *Nanoscale*. 2015;7(39):16470–16480. doi:10.1039/C5NR04130A
139. Kijewska K, Głowala P, Wiktorska K, et al. Bromide-doped polypyrrole microcapsules modified with gold nanoparticles. *Polymer*. 2012;53(23):5320–5329. doi:10.1016/j.polymer.2012.09.029
140. Timin AS, Muslimov AR, Lepik KV, et al. Intracellular breakable and ultrasound-responsive hybrid micro-sized containers for selective drug release into cancerous cells. *Part Part Syst Char*. 2017;34(5):1600417. doi:10.1002/ppsc.201600417

141. Chen J, Ratnayaka S, Alford A, et al. Theranostic multilayer capsules for ultrasound imaging and guided drug delivery. *ACS Nano*. 2017;11(3):3135–3146. doi:10.1021/acsnano.7b00151
142. Cao Y, Chen Y, Yu T, et al. Drug release from phase-changeable nanodroplets triggered by low-intensity focused ultrasound. *Theranostics*. 2018;8(5):1327–1339. doi:10.7150/thno.21492
143. Liu TY, Huang TC. A novel drug vehicle capable of ultrasound-triggered release with MRI functions. *Acta Biomater*. 2011;7(11):3927–3934. doi:10.1016/j.actbio.2011.06.038
144. Cabane E, Malinova V, Meier W. Synthesis of photocleavable amphiphilic block copolymers: Toward the design of photosensitive nanocarriers. *Macromol Chem Phys*. 2010;211(17):1847–1856. doi:10.1002/macp.201000151
145. Lo YL, Tsai MF, Soorni Y, Hsu C, Liao ZX, Wang LF. Dual stimuli-responsive block copolymers with adjacent redox- and photo-cleavable linkages for smart drug delivery. *Biomacromolecules*. 2020;21(8):3342–3352. doi:10.1021/acs.biomac.0c00773
146. Dispinar T, Colard CAL, Du Prez FE. Polyurea microcapsules with a photocleavable shell: UV-triggered release. *Polym Chem*. 2013;4(3):763–772. doi:10.1039/C2PY20735D
147. Liu X, Tian Z, Chen C, Allcock HR. UV-cleavable unimolecular micelles: Synthesis and characterization toward photocontrolled drug release carriers. *Polym Chem*. 2013;4(4):1115–1125. doi:10.1039/C2PY20825C
148. Chen J, Qian C, Ren P, et al. Light-responsive micelles loaded with doxorubicin for osteosarcoma suppression. *Front Pharmacol*. 2021;12:679610. doi:10.3389/fphar.2021.679610
149. Rosenbauer EM, Wagner M, Musyanovych A, Landfester K. Controlled release from polyurethane nanocapsules via pH-, UV-light- or temperature-induced stimuli. *Macromolecules*. 2010;43(11):5083–5093. doi:10.1021/ma100481s