Polymeric capsules and micelles as promising carriers of anticancer drugs

Kapsułki i micele 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

Micele 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). Micele 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 własnościach. 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, micele 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

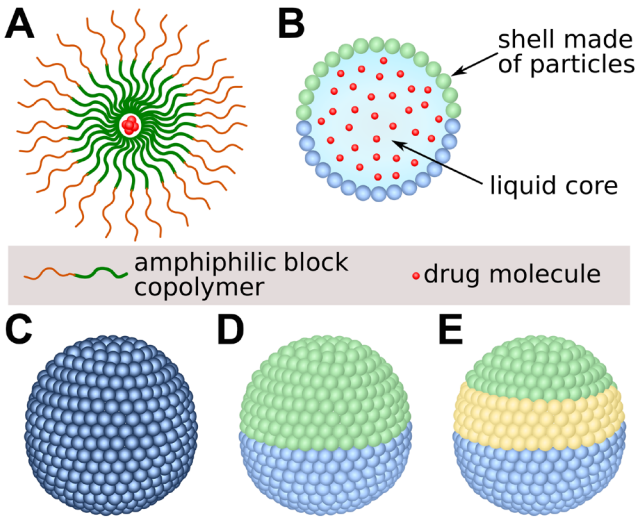

Fig. 1. Examples of polymer drug carriers. A. Amphiphilic copolymer micelle; B. Capsule with the shell composed of polymer particles; C. Capsule with homogeneous shell; D. Capsule with Janus shell; E. Capsule with patchy shell

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] doxorubicin[51] 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 doxorubicin[52] 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 = $1.34 \pm 0.05 \times 10^{-5}$ 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 shell[123] 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 capsules[127] 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 PEtOz-*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 linkage[148] 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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