Polymersomes as Novel Drug Delivery Alternative to Conventional Liposomes

Marwa malik Kamil*, Mohammed J. Neamah, Yasir Qasim almajidi*****
Pharmaceutical Development, College of Pharmacy, Mustansiriyah University
****Department of Pharmacy, Baghdad College of Medical Sciences, Baghdad, Iraq***
*****Baghdad College of Medical Sciences-department of pharmacy (pharmaceutics), Baghdad-Iraq***

Article Info:

Received Jan 2023
Revised Oct 2023
Accepted Nov 2023
Corresponding Author email:
almajidiyasir@gmail.com
Orcid: https://orcid.org/0000-0001-9632-0444

DOI:https://doi.org/ 10.32947/ajps.v24i4.955

Abstract:

The goal of medical research across the world is to improve the health of patients. Nanotechnology is an emerging field that is now heavily concentrated in the realm of medicine continuous research in the sector has resulted in the emergence of a new discipline known as "nanomedicine," which attempts to provide new treatment options while also improving the therapeutic efficacy of existing medications. polymersomes have gotten a lot of attention in recent research all around the world, and it's led to the creation of novel medical therapies. Solubilization, cancer therapy targeting, and usage as diagnostic tool are some of these techniques. Polymersomes, which are artificial amphiphilic vesicles made up of a variety of chemical polymers, are presently being investigated for delivering different probes for imaging target tissues/ organs, as well as cytotoxic medicines to tumor cells for gene therapy. Thorough analysis has been confirmed that polymersomes will surely compete in the future in the rapidly developing field of nanotechnology. Polymersomes have great stability, ease of flexibility, and capacity to encapsulate a variety of different drugs will ensure that they play a significant role in the development of sophisticated drug delivery systems.

Keywords: Nanomedicine, Preparation Methods, Characterization of polymersomes

مقالة عن البوليمروسومات كبديل جديد لتوصيل الأدوية للجسيمات الشحمية التقليدية

مروة مالك الفتلاوي*,محمد جاسم نعمة,ياسر قاسم الماجدي*****
التطوير الصيدلي كلية الصيدلة الجامعة المستنصرية
**** قسم الصيدلة، كلية بغداد للعلوم الطبية، بغداد، العراق***
*****كلية بغداد للعلوم الطبية-قسم الصيدلة (الصيدلانيات)بغداد-العراق***

الخلاصة:
الهدف من البحث الطبي في جميع أنحاء العالم هو تحسين صحة ورفاهية المرضى. تعد تقنية النانو مجالًا ناشئاً يركز الآن بشكل كبير على مجال الطب أدى البحث المستمر ف ي هذا القطاع إلى ظهور نظام جديد يعُرف باسم "طب النانو"، والذي يحاول توفير خيارات علاج جديدة مع تحسين الفعالية العلاجية الحالية الأدوية. لقد حظي الطب النانوي باهتمام كبير في الأبحاث الحديثة في جميع أنحاء العالم، وأدى إلى ابتكار علاجات طبية جديدة. تتضمن بعض هذه الطرق الإذابة أو استهداف علاج السرطان أو استخدامها كأداة تشخيصية. تدُرس الآن البوليمرات، وهي حويصلات برمائية صناعية مكونة من بوليمرات كيميائية مختلفة، لتقديم تحقيقات مختلفة لتصوير الأنسجة / الأعضاء المستهدفة بالإضافة إلى الأدوية السامة للخلايا للخلايا السرطانية من أجل العلاج الجيني. أكد تحليلنا الشامل أن البوليمررسوم ستتنافس بالتأكيد في المستقبل في مجال تكنولوجيا النانو سريع التطور. يضمن ثباتها الكبير وسهولة مرونتها وقدرتها على تغليف مجموعة متنوعة من الأدوية المختلفة أنها تلعب دورًا مهمًا في تطوير أنظمة توصيل الأدوية المتطورة.

الكلمات المفتاحية: الطب النانوي، طرق التحضير، توصيف البوليمرات البوليمرية.

Introduction

Nanotechnology has taken on a high attraction in recent years, and this has appeared in several areas, for example, drug delivery, photonics, supramolecular assemblies, and finally in nanomedicine, where it was identified by the National Institute of Health in 2006 as the medical use of nanotechnologies, and thus it has led to the emergence of numbers an increasing number of new pharmaceutical therapies [(1)]. Examples of existing nanomedicines on the market that are characterized by their great ability to encapsulate and transport therapeutic chemicals include liposomes, DNA-drug complexes, drug-polymer conjugates, polymer-protein conjugates, and micelles [(2)]. It has been suggested that liposomes, which are self-assembling lipid vesicles constructed of synthetic phospholipid derivatives owing to an aqueous core, are the best class of organic nanoparticles for treating cancer [(3)]. Liposomes are able to entrap hydrophilic molecules in their aqueous core and hydrophobic molecules in their lipid bilayer due to the particular self-assembled architectures of these molecules. Although liposome structures have some benefits, including the ability to combine hydrophilic and lipophilic molecules, biocompatibility, biodegradability, and targeted drug delivery, they also have some drawbacks, including low stability, lower solubility, hydrolysis, and oxidation of phospholipids, and significant pharmacokinetic deficiencies [(4)].

Polymersomes, which have distinct qualities like long-term physical and chemical stability, customizable membrane features, and surface changes, are one of flexible carriers for encapsulating medicines. The shear viscosity of polymersome membranes was calculated to be 500 times that of lipid membranes [(5)].

The words "polymer" and "liposome" have been combined to form the moniker "polymersome." Despite sharing some similarities with liposomes, polymersomes have some advantages because of their thicker membranes facilitated by the higher molecular weight of the hydrophobic polymer segments compared to thinner lipid bilayers enclosing a liposome (Figure 1) [(6)].

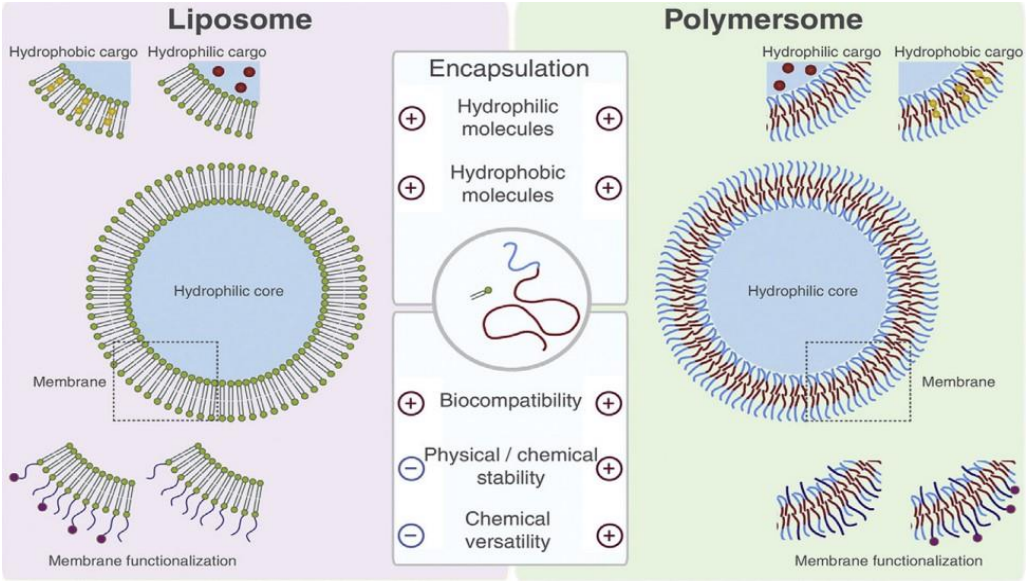

Figure 1: Segments compared between liposomes (left) and polymersomes (right) adapted from Messager L et al. [(7)]

Polymersome Design: Amphiphilic Block Copolymer Self-Assembly

As previously stated, amphiphilic block copolymers may self-assemble into various forms in an aqueous solution. Several variables impact the resultant architecture, including concentration, molecular weight, amphiphilic polymer form, and block ratio [8]. Because polymersomes are the desired structure, the triblock copolymers must be adjusted to form vesicular structures with an aqueous core. Similar behavior may be observed when lipids, which are naturally amphiphilic molecules, are dissolved in an aqueous solution. Liposomes (from the Greek words lipids and soma (body)) are generally generated in analogue: block copolymers [9]. The aqueous phase favours the hydrophilic blocks, which initiates the self-assembly process to avoid water contact with the block copolymer's hydrophobic component [10]. Polymersomes range in size from 10nm to a few µm so-called massive polymersomes [11]. The amphiphilicity of the polymers, as well as the preparatory procedures employed to self-assemble the polymersomes, impact the size of the polymersomes.

Extrusion, sonication, and freeze/thaw cycles are all examples of external forces that can alter the structure of polymersomes after they have been created [12].

Table 1 shows the various polymers utilized in the production of polymersomes adapted from Zhang XY, Zhang PY et al. [13]

Polymers	Formation method	Drug/stimulus for release	Degradability
PEG-PEE	Film rehydration	None reported	No
PEG-PBD	Film rehydration	Paclitaxel, doxorubicin	No
PMOXA-PDMS-PMOXA	Phase inversion, UV crosslinking	Calcein	No
PEG-PLA	Phase inversion	Carboxyl fluorescein	Yes
PEG-PCL	Phase inversion	Carboxyl fluorescein	Yes
PEG-PTMC	Phase inversion	none reported	Yes
PEG-PTMBPEC	Phase inversion	Paclitaxel, doxorubicin/ pH-triggered hydrolysis	Yes

PEG-PEE: poly(ethylene glycol)-b-poly(ethyl ethylene); PEG-PBD: poly(ethylene glycol)-b-poly(butadiene); PMOXA-PDMS-PMOXA: poly(2-methyl-2-oxazoline)-b-poly(dimethylsiloxane)-b-poly(2-methyl-2-oxazoline); PEG-PLA: poly(ethylene glycol)-b-poly(lactide); PEG-PCL: poly(ethylene glycol)-b-poly(ε-caprolactone), PEG-PTMC: poly(ethylene glycol)-b-poly(trimethylene carbonate); PEG-PTMBPEC: poly(ethylene glycol)-b-poly(2,4,6-trimethoxybenzylidenepentaerythritol carbonate).

Polymersomes Preparation Methods.

1. Hydration of Polymer films.

A common method is to evaporate amphiphilic block copolymer solutions in organic solvents, and this results in the formation of thin films, followed by rehydration or direct dissolution of the polymeric components. Only by using these methods can they be used to regulate the size of the polymers, thus obtaining a wide range of sizes of vesicles that require later processing such as extrusion through a polycarbonate membrane, sonication, or freeze/thaw cycle (14).

2. Co-solvent Addition (phase inversion).

The copolymer solution is added dropwise to amphiphilic masses (in an aqueous miscible solvent) in water or vice versa starting with solvent formulation procedures including solvent displacement or nanoprecipitation [15]. Despite producing polymers with well-controlled sizes and polydispersions, these techniques require the removal of the organic solvent by evaporation, dialysis, or drying before they

can be used downstream, which in turn exposes fragile proteins and macromolecules. DNA at risk of denaturation [16].

3. Electroporation

This method is considered one of the ideal and easy methods, as it is used to encapsulate macromolecules in polymers by exploiting their supramolecular nature. Where anionic biomacromolecules such as proteins (Bovine serum albumine, BSA), myoglobin, enzymes (Lysozyme), antibodies (IgG), and nucleic acids (pDNA, siRNA) are all loaded into Poly (2-(methacryloyloxy) ethyl phosphorylcholine)-b- poly (2-(diisopropylamino) ethyl methacrylate)-based polymersomes by temporary destabilization of vesicle membranes. Due to the pH-sensitive nature of PMPC-b-PDPA (owing to pH-responsive nature of PDPA block), encapsulation of macromolecules was mediated by simply changing the pH to control self-assembly of the copolymer) [17].

4. Bioinspired Approaches.

Polymeric vesicles can be encapsulated using membrane proteins as an alternative to the traditional methods for polymeric vesicles. Using phage transfection, DNA was loaded into vesicles of the ABA - triblock copolymer. The membrane protein LamB, known to bind lambda phages, was inserted into the polymer membrane, allowing the transfer of DNA into the hydrophilic core. The above study determined how enveloped DNA is maintained, as well as the role of proteins in polymeric membranes [18].

5. Microfluidics.

Microfluidic devices, like cellular microenvironments, provide greater control over self-assembly in a controlled setting. Complex multicompartment polymersome structures were also created using a basic coflow microfluidic device [19]. A flow-focusing microfluidic device was created to create a more reliable manufacturing method that provided more favorable encapsulation conditions and therefore enhanced encapsulation efficiency [20]. Self-assembly of the PMPC-b-PDPA (poly(2-(methacryloyloxy) ethyl phosphorylcholine)–poly(2-(diisopropylamino)ethyl methacrylate) block copolymer was induced by altering the pH of the flows within the microchannels. This method had a protein encapsulation effectiveness of 29%, which was comparable to the conventional aqueous polymersome manufacturing methods (27%), but it did away with the need for organic solvents and batch-to-batch variability in polymersome creation [21].

6. Polymerization-Induced Self-Assembly (PISA).

Organic solvents are frequently used in traditional self-assembly processes, rendering them incompatible with specific proteins. Their potential scalability is further limited due to low concentrations and complex formulation and purification procedures. To circumvent this constraint, several solutions have lately been created [22]. An effective method discovered by PISA that encapsulates functionalized macromolecules (eg, Bovine serum albumin, BSA) with potential for large-scale production is through the use of a live polymerization method of an anti-dissolving polymer, which in turn induces situ self-assembly ([23].

7. Flash Nanoprecipitation.

There is a difficulty in high-throughput techniques for assembling copolymers into soft nanostructures and solving this problem will open up broad prospects on different levels as the production process will be easier, and there will be scalability, repeatability, and loading efficiency will be high, all of which are important for clinical translation [24]. The solution to this problem is a newly developed flash nanodeposition (FNP) method. A rapid and scalable method for creating vesicular nanoarchitecture, Filomicelles, nanospheres, tubular and multilayer vesicles, and other

nanostructures were created using PEG-b-PPS block copolymers [25].

The result of many collisions reduced the size and dispersion of the polymers formed, which enables the rapid synthesis of monodisperse polymers on the gram scale. This technique considers its success in loading both hydrophobic and hydrophilic compounds into the aqueous core/cavity and polymeric membranes. After liberation from the hydrolyzed polymers, the encapsulating enzyme (alkaline phosphatase, AP) retained its activity [26].

Encapsulation of payload within polymersomes:

One of two main polymer formation strategies can be used to encapsulate the payload (attached drug): either from bulk polymers (using a top-down approach i.e., chopping up huge materials to create the needed nanostructures from them) or from monomers (using bottom-up approach i.e., requires putting together individual molecules and atoms to form bigger nanostructures) using monoblock chains of copolymer [27]. The first method (a top-down approach) involves suspending a polymer block or film in an aqueous solution (Figure 2); Water or a buffer solution is commonly introduced into a polymer film in the presence of an energy source such as a shear rate (eg, stirring), ultrasound, or alternating current. When the film is wet, the polymeric fragments separate from it. Several stages have been described, ranging from lamellar phases at high polymer concentrations to vesicles at low polymer concentrations. Water-soluble drugs can be loaded with this method by dipping the polymeric film into an aqueous solution that contains the medication [28].

The second method (bottom-up approach), which involves starting self-assembly from a unimer solution, is the second most used method (Figure 2). In general, the polymer is dissolved in a suitable solvent before being used in both blocks and then this solvent is replaced by another that is used exclusively in the hydrophilic block [29]. This switch may be a physical change in the conditions of the solvent (eg , change of solvent) or a change in the solvent conditions (eg, pH, temperature) [17]. As an illustration of solvent exchange-mediated encapsulation, hydrophobic (lipophilic anti-cancer drugs) and hydrophilic drugs may both be encapsulated within the polymersomes. If the pH or temperature switch approach is employed (for instance, if a pH-sensitive polymer is present), the formulation remains in an aqueous solution throughout, making it possible to entrap water-soluble substances like DNA and proteins during polymersome synthesis [30].

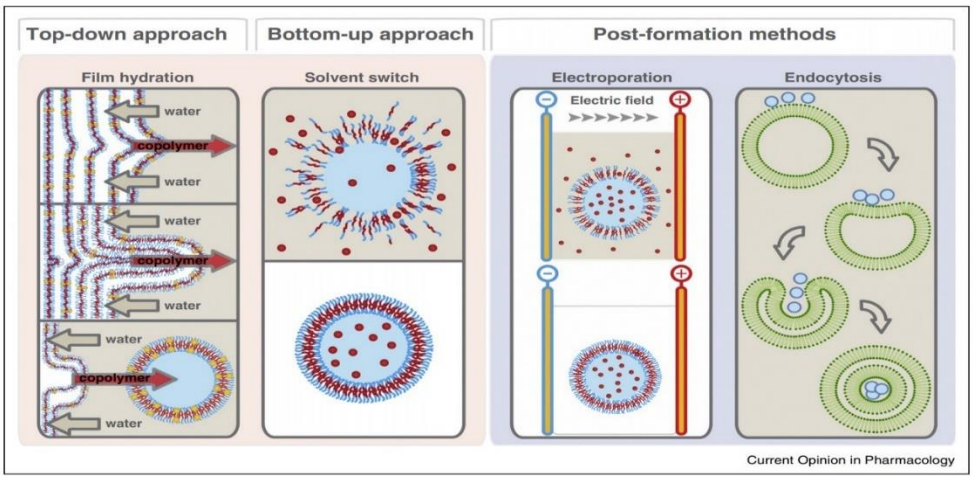

Figure 2: Payload can be introduced into polymersomes, during (left) or after (right) production (right) adapted from éa Messager et al [31]

Polymersome for drug loading and release

In general, all Polymers (Ps) are mostly more stable in circulation than liposomes [32]. We may find it loaded with hydrophilic, hydrophobic, or amphibious compounds and this is done by using the water core or the bilayer membrane [33]. Similar to cell membranes composed of cholesterol and transmembrane proteins, the Ps membrane may be seen as a reservoir system for both hydrophobic and amphipathic substances. In addition to amphiphilic dyes like octadecyl rhodamine B and membrane proteins like outer membrane proteins F (OmpF), substrate-specific porins (LamB), and TonB-dependent iron siderophore transporters (FhuA), it has been observed that extremely lipophilic anticancer drugs and quantum dots can also be integrated within the membrane of Ps while still functioning [34]. These above molecules can be incorporated into Ps by either dissolving or dispersing them in an organic solvent, and this solvent contains film-forming polymer building blocks. The organic solution/dispersion is then added to water or an aqueous solution [35].

Like liposomes, the Ps' aqueous core can be used to encapsulate hydrophilic therapeutic molecules. The membranes of such vesicles, like the membranes of natural vesicles in the body, act as physical barriers to protect the encapsulated molecules from the external environment. It resembles the body's natural vesicles [36]. There are several techniques used to load hydrophilic compounds. Of these, the most widely used methods are the direct encapsulation method during Ps synthesis or the diffuse loading methods that use a pH or salt gradient over a previously prepared Ps membrane. On the other hand, it is possible to use drugs with hydrophilic properties. Where the drug is introduced into the organic phase with the polymer and then the mixture is used to synthesize Ps in the core [37].

The release of drugs from the Ps is controlled by drug diffusion across the membrane [38]. A drug concentration gradient between Ps and the surrounding medium is the driving force. The rate at which a medication diffuses from the Ps core to the surrounding media is determined by the square root of time [39]. The overall release rate will be affected by the size distribution of the Ps. Using the theoretical method, appropriate Ps for the administration of certain medications may be constructed, and release kinetics can be predicted [40]. Nevertheless, because the features of the Ps membranes cannot be greatly modified due to restrictions on the composition of block copolymers, which can be utilized to construct Ps membranes, the rate and spatial control for drug release are frequently not able to be adjusted to the necessary level [41].

There have been significant efforts to create controlled pharmaceutical delivery. Smart Ps have required a significant amount of time and effort to develop in order to enable controlled medication delivery. Some Ps membranes can modify their physical and chemical characteristics in response to external stimuli. pH, temperature, redox conditions, and light are all elements to consider, as with magnetic field and ionic strength [42]. Ps for planned drug administration has been developed utilizing glucose concentration and glucose concentration [21]. The pH response to Ps is very good given that the pH of various tissues and cell compartments in the body ranges from 2 to 8 [43]. For a long period, oral medications relied on a pH shift along the gastrointestinal tract (pH 2 in the Stomach, intestinal pH ranges from 5-8) [22]. The cancerous tissues have an acidic environment ranging between 6.5-7.2. Both endosomes (pH 5.0–6.5) and lysosomes (pH 4.5–5.0) are preferred for intracellular and anticancer drug delivery [44].

Transporters are one of the most common types of technology used for targeted drug delivery. At physiological pH (7.4) in the blood, pharmaceuticals are contained

during circulation and once they reach the acidic target site they are rapidly released. Previously in the past the use of heat sensitivity as a trigger [45].

PNIPAAm-based copolymers have been widely used in the development of thermosensitive Ps [46]. By dissolving PEG-PNIPAAm in the water below the lower critical solution temperature (LCST) in the polymer and generating Ps above the LCST [47]. Upon cooling Ps, the PNIPAAm polymer chains in the Ps films become soluble. When simple ice packs or highly penetrating dry needles are used a local drug release is achieved with Ps [48]. The effect of magnetism, light, and other external stimuli has been studied to modulate local drug delivery. Generation of Ps based on a diblock copolymer with a side-chain azobenzene comprising poly(methacrylate) and PAA (PAA-PAzoMa), which is photolyzable by UV light (Figure 3) [49]

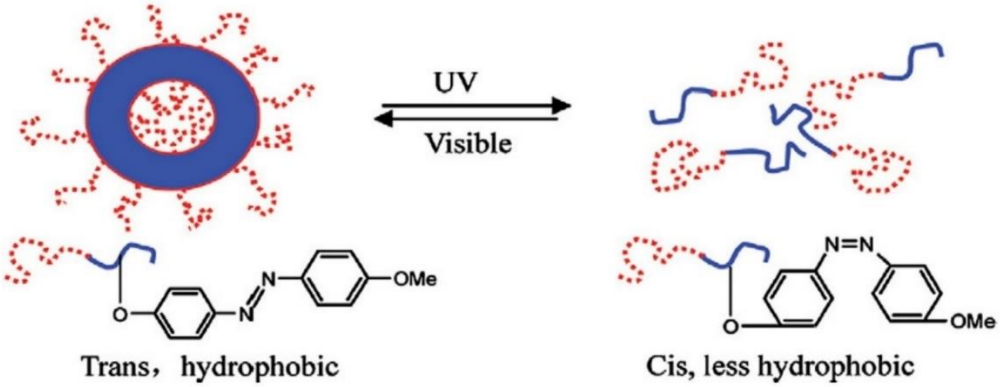

Figure 3: Reversible polymer some formation by UV/visible illumination with permission, adapted from Lee, Jung Seok et al. [50].

Characterization of polymersomes

Dynamic/static light scattering is the most frequent method for studying Ps in an aqueous dispersion. This approach has been utilized to evaluate vesicle size and dispersion (polydispersity index), as well as the critical aggregation concentration, vesicle disruption, and size change with pH or temperature fluctuation [51]. Using dynamic light scattering in this way the zeta potential of Ps can be calculated as the electrophoretic mobility of Ps in a lattice cell is tracked [52].The most frequent means for viewing Ps directly are light or electron microscopy. Microscopy scanning may be used to examine several important aspects of Ps, including size, shape, and homogeneity [52]. Nanovesicles can be examined with high resolution (>1 nm) using scanning electron microscopy (SEM) or transmission electron microscopy (TEM) (Figure 4a) [53], but the specimens must be dried and may need to be dyed to improve contrast. In contrast, Ps in the hydrated condition have been investigated using cryogenic TEM (Cryo-TEM) after specimens have been rapidly frozen (Figure 4b). By breaking and etching the frozen samples, freeze-fracture TEM can be utilized to analyze the interior structure of Ps. However, electrons cannot pass through the Ps membrane deeply, and the optical qualities of the used polymers determine the quality of the photographs [54]. Compared to electron microscopy, fluorescence microscopy has some advantages. Fluorescence labeling of certain Ps components provides information about their location within the Ps, and repeated staining using several probes enables the detection of the presence of specific molecules in Ps compartments. One of the most used methods for seeing Ps Is Confocal Laser

Scanning Microscopy (CLSM) (Figure 4c) [55]

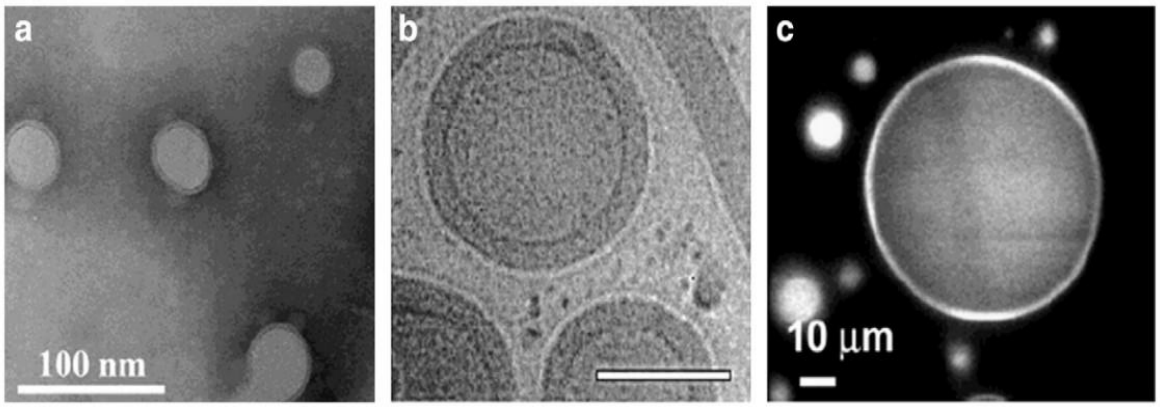

Figure 4: Microscopic images of Ps (a) TEM micrograph of Ps made from PEG-PLA by injecting an acetone solution of the polymer into DI water, (b) Cryo-TEM image of Ps based on PEG-PBD. The hydrophobic cores of PBD are the darker areas, and (c) CLSM image of giant Ps prepared by adding a solution of PEG-PLA in chloroform to PBS in the presence of Nile red as a fluorescent probe with permission, adapted from Lee, Jung Seok et al ([50])

POLYMERSOMES FOR THERAPEUTIC PROTEIN DELIVERY

1. Applications in Cancer Delivery: Several studies have shown the in vitro anticancer potential of polymersomes, which has expanded the range of applications for therapeutic protein delivery. In order to optimize the delivery of protein-loaded polymersomes to their target site, nonspecific distribution has been worked to prevent [(4)]. Recently, it was revealed that redox-responsive virus-mimicking polymersomes, surface-decorated with angiopep-2 (ANG-PS), could deliver saporin (SAP), a strong natural protein toxin, to human glioblastoma xenografts in mice in a selective and effective manner (Figure 5). In vitro, SAP-loaded polymersomes significantly inhibited the growth of human glioma cell lines U-87 MG (IC50 = 30.2 nM). In mice carrying U-87 MG orthotopic glioblastoma tumors, they showed stronger transcytosis across the blood brain barrier (BBB) (for 20% angiopep density) and boosted tumor accumulation (1.71% ID/g), which effectively inhibited tumor growth and increased survival rate with little negative effects [(57)].

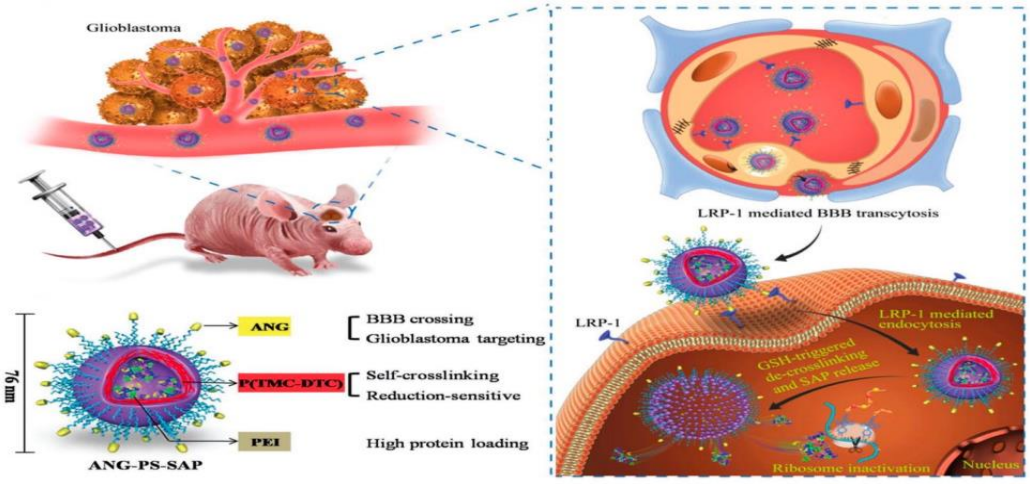

Figure 5: Selective SAP administration to orthotopic mouse glioma xenografts using ANG-directed redox-responsive polymersomes (ANG-PS), adapted from Yu Jiang et al. (58)

2. Applications in Vaccine Delivery:
Antigens and adjuvants can be transported safely inside polymersomes' aqueous interior without the need for chemical modification. The development of novel adjuvant formulations and antigen delivery technologies may help to better match the specific requirements of target recipients. Due to their better stability and adjustable characteristics, polymersomes may be advantageous for encapsulating small chemical adjuvants and unmodified protein antigens. The association of antigen with polymersomes as hybrid assemblies was the focus of early research. The influenza hemagglutinin (HA)-loaded polypeptide-b-peptide copolymer-based vesicles demonstrated improved immunogenicity of the antigen in vivo, with polymersomes functioning as an adjuvant [(59)].

3. Nucleic Acid Delivery:
An innovative approach to treating diseases has been thought to involve the delivery of nucleic acid-based compounds into the target cells. Because to their vacuum, hydrophilic inner core for effective encapsulation, and hydrophobic membrane for greater protection and controlled release, depending on the nature of the constituent polymers, polymersomes have attracted increasing interest in this respect. They also offer a way for these delicate payloads to enter cells and be released there. pDNA, AON, and siRNA are a few examples of nucleic acids macromolecules that have been produced with polymersomes recently for both in vitro and in vivo administration [(60)]. Discher and colleagues showed that biodegradable block copolymers, including PEG-b-PCL, PEG-b-PLA, and PEG-b-PBD-based nonionic polymersomes, may deliver siRNA and antisense oligonucleotides. It was discovered that siRNA encapsulation efficiencies in PEG-b-PLA polymersomes were 30%, and AON encapsulation efficiencies in PEG-b-PCL polymersomes were 20% (Figure 6) [(61)].

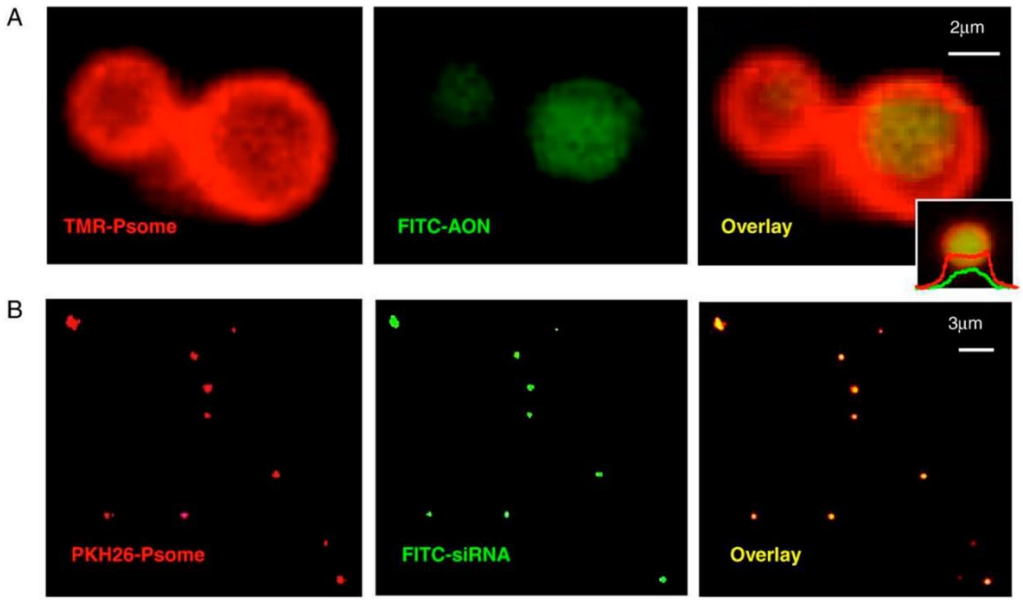

Figure 6: Encapsulation of AONs and siRNAs in polymersomes. (a) Fluorescence images of FITC-AON (green)-loaded fluorescently labeled polymersomes (red). (b) Fluorescence images of FITC-siRNA (green)-loaded into polymersomes (red), adapted from Shoaib Iqbal et al. [(62)]

Conclusions

The creation of nano-sized polymersomes as carriers for many medical applications, including protein delivery, gene therapy, and the transport of imaging and other therapeutic probes to specific sites in the body, is a result of achievements in nanomedicine. Polymersome use seems to be a potential approach. More clinical research, though, is necessary to establish these as the gold standard of care.

Reference:

1- Porges E et al. Antibiotic-loaded polymersomes for clearance of intracellular Burkholderia thailandensis. ACS nano. 2021; 15.12: 19284-19297.
2- Kauscher U et al. Physical stimuli-responsive vesicles in drug delivery: Beyond liposomes and polymersomes. Advanced drug delivery reviews. 2019; 138: 259-275.
3- Moulahoum H et al. Surface biomodification of liposomes and polymersomes for efficient targeted drug delivery. Bioconjugate Chemistry. 2021; 32.8: 1491-1502.
4- Aibani N, Khan TN. Callan B. Liposome mimicking polymersomes; A comparative study of the merits of polymersomes in terms of formulation and stability. International Journal of Pharmaceutics: 2020; 2: 100040.
5- Safa Mohammed Nser‹Athmar Dhahir Habeeb Al-Shohani‹Alaa Abuawad.Effect of using high molecular weight crosslinker on the physical properties of super porous hydrogel composite. https://ajps.uomustansiriyah.edu.iq/index.php/AJPS/issue/view/76
6- Gouveia MG et al. Polymersome-based protein drug delivery–quo vadis. Chemical Society Reviews. 2023.
7- Messager L, Gaitzsch J, Chierico L, Battaglia G. Novel aspects of encapsulation and delivery using polymersomes. Current Opinion in Pharmacology. 2014; 18:104-111.
8- Kuperkar K et al. Amphiphilic Block Copolymers: Their Structures, and Self-Assembly to Polymeric Micelles and Polymersomes as Drug Delivery Vehicles. Polymers. 2022; 14.21: 4702.
9- Da silva YP et al. Polymersomes for Targeted Drug and Gene Delivery Systems. In: Pharmaceutical Nanobiotechnology for Targeted Therapy. Cham: Springer International Publishing. 2022: 399-427.
10- Baghbanbashi M, Kakkar A. Polymersomes: Soft Nanoparticles from Miktoarm Stars for Applications in Drug Delivery. Molecular Pharmaceutics. 2022; 19.6: 1687-1703.
11- Katterman C, Pierce C, Larsen J. Combining nanoparticle shape modulation and polymersome technology in drug delivery. ACS Applied Bio Materials. 2021; 4.4: 2853-2862.
12- Wang X; Hu J, Liu S. Overcoming the Dilemma of Permeability and Stability of Polymersomes through Traceless Cross-Linking. Accounts of Chemical Research. 2022; 55.23: 3404-3416.
13- Ahmed A. Albadri‹Mustafa R. Abdulbaqi‹Yasir Q. Almajidi.Recent Trends in Chronopharmaceutics, Pulsatile Drug Delivery System.https://ajps.uomustansiriyah.edu.iq/index.php/AJPS/issue/view/55
14- Meerovich I, Dash AK. Polymersomes for drug delivery and other biomedical applications. In: Materials for biomedical engineering. Elsevier. 2019:269-309.
15- Mora H, Claudia E, Fessi H; Elaissari A. Polymer-based nanocapsules for drug delivery. International journal of pharmaceutics. 2010; 385.1-2: 113-142
16- Hasannia M et al. Synthesis of block copolymers used in polymersome

fabrication: Application in drug delivery. Journal of Controlled Release. 2022; 341: 95-117.
17- Setia A et al. Advances in Hybrid Vesicular-based Drug Delivery Systems: Improved Biocompatibility, Targeting, Therapeutic Efficacy and Pharmacokinetics of Anticancer Drugs. Current Drug Metabolism. 2022.
18- Pippa Net al. Targeting cellular and molecular mechanisms of nanovesicular systems for the treatment of different diseases. In: Applications of Nanovesicular Drug Delivery. Academic Press. 2022: 1-20.
19- Wei P et al. Ultrasound-responsive polymersomes capable of endosomal escape for efficient cancer therapy. Journal of Controlled Release. 2020; 322: 81-94.
20- Canaparo Ret al. Recent developments in antibacterial therapy: Focus on stimuli-responsive drug-delivery systems and therapeutic nanoparticles. Molecules. 2019; 24.10: 1991.
21- Shoaib Iqbal, Mark Blenner, Angela Alexander-Bryant, and Jessica Larsen. Polymersomes for Therapeutic Delivery of Protein and Nucleic Acid Macromolecules: From Design to Therapeutic Applications. Biomacromolecules. 2020, 21; (4), 1327-1350
22- Gu W et al. Actively targeted nanomedicines for precision cancer therapy: Concept, construction, challenges and clinical translation. Journal of controlled release. 2021; 329: 676-695.
23- Guo C et al. Asymmetric polymersomes, from the formation of asymmetric membranes to the application on drug delivery. Journal of Controlled Release. 2021; 338: 422-445.
24- Wong CK, Stenzel MH, Thordarson P. Non-spherical polymersomes: formation and characterization. Chemical Society Reviews. 2019; 48.15: 4019-4035.
25- Singhvi G et al. Nanocarriers as potential targeted drug delivery for cancer therapy. Nanoscience in Medicine. 2020: 51-88.
26- Bej R et al. Polymersome formation by amphiphilic polyglycerol-b-polydisulfide-b-polyglycerol and glutathione-triggered intracellular drug delivery. Biomacromolecules. 2020; 21.8: 3353-3363.
27- Singh V et al. Taxanes loaded polymersomes as an emerging polymeric nanocarrier for cancer therapy. European Polymer Journal. 2022; 162: 110883.
28- Travanut A et al. Passerini chemistries for synthesis of polymer pro-drug and polymersome drug delivery nanoparticles. Journal of Materials Chemistry B. 2022; 10.20: 3895-3905.
29- Iqbal S et al. Polymersomes for therapeutic delivery of protein and nucleic acid macromolecules: from design to therapeutic applications. Biomacromolecules. 2020; 21.4: 1327-1350.
30- Gu W et al. A6 peptide-tagged, ultra-small and reduction-sensitive polymersomal vincristine sulfate as a smart and specific treatment for CD44+ acute myeloid leukemia. Journal of controlled release. 2021; 329: 706-716.
31- éa M, Jens G, Luca C, Giuseppe B. Novel aspects of encapsulation and delivery using polymersomes, Current Opinion in Pharmacology. 2014; 18:104-111
32- Alibolandi M, SHahriari M, RamezanI M. Smart polymersomes as intelligent nanomedicines in cancer treatment. Polymeric Nanoparticles as a Promising Tool for Anti-Cancer Therapeutics. 2019: 343-371.
33- Damera DP, Nag A. Exploring the membrane fluidity of phenyl boronic acid functionalized polymersomes

using the FRAP technique and their application in the pH-sensitive release of curcumin. New Journal of Chemistry. 2022; 46.23: 11329-11340.
34- Xiao Q et al. Co-assembly of liposomes, Dendrimersomes, and Polymersomes with amphiphilic Janus dendrimers conjugated to Mono-and Tris-Nitrilotriacetic Acid (NTA, TrisNTA) enhances protein recruitment. Giant. 2022; 9: 100089.
35- Ghorbanizamani F et al. pH-bioresponsive poly (ε-caprolactone)-based polymersome for effective drug delivery in cancer and protein glycoxidation prevention. Archives of Biochemistry and Biophysics. 2020; 695: 108643.
36- Pallavi P et al. Fabrication of Polymersomes: A Macromolecular Architecture in Nanotherapeutics. Chemistry. 2022; 4.3: 1028-1043.
37- Trombino S, Curcio F, Cassano R. Polymersomes as a promising vehicle for controlled drug delivery. In: Stimuli-Responsive Nanocarriers. Academic Press. 2022: 351-366.
38- Kim M et al. Development of a Polymersome-Based Nanomedicine for Chemotherapeutic and Sonodynamic Combination Therapy. International Journal of Molecular Sciences. 2023: 24.2: 1194.
39- Seo H, Lee H. Recent developments in microfluidic synthesis of artificial cell-like polymersomes and liposomes for functional bioreactors. Biomicrofluidics. 2021: 15.2: 021301.
40- Wang Tet al. Intelligent design of polymersomes for antibacterial and anticancer applications. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2022: 14.5: 1822.
41- Bobde SS. Polymersomes for targeting to brain tumors. In: Nanocarriers for Drug-Targeting Brain Tumors. Elsevier. 2022: 451-481.
42- Ferrero C, Casas M, Caraballo I. Redox-Responsive Polymersomes as Smart Doxorubicin Delivery Systems. Pharmaceutics. 2022; 14.8: 1724.
43- Abdul R et al. DENV-Mimetic polymersome nanoparticles bearing multi-epitope lipopeptides antigen as the next-generation dengue vaccine. Pharmaceutics. 2022; 14.1: 156.
44- Bhushan V et al. Ionic Liquid-Controlled Shape Transformation of Spherical to Nonspherical Polymersomes via Hierarchical Self-Assembly of a Diblock Copolymer. Langmuir. 2021; 37.16: 5081-5088.
45- García MC. Stimuli-responsive polymersomes for drug delivery applications. In: Stimuli responsive polymeric nanocarriers for drug delivery applications. Woodhead Publishing. 2019: 345-392.
46- Liu J et al. Polymersome-stabilized doxorubicin-lipiodol emulsions for high-efficacy chemoembolization therapy. Journal of Controlled Release. 2022; 350: 122-131.
47- Li X et al. Emulsion-Induced Polymersomes Taming Tetrodotoxin for Prolonged Duration Local Anesthesia. Advanced Therapeutics. 2023; 6.1: 2200199.
48- Luo R et al. DNA-based assembly of multi-compartment polymersome networks. Advanced Functional Materials. 2020; 30.46: 2003480.
49- Virmani M, et al. Self-reporting polysaccharide polymersome for doxorubicin and cisplatin delivery to live cancer cells. ACS Polymers. 2021; 2.3: 181-193.
50- Lee JS. Biodegradable polymersomes for drug delivery: circulation kinetics and biodistribution, modulated drug delivery and cellular uptake. 2011.
51- Wei Y et al. Low-toxicity transferrin-guided polymersomal doxorubicin for potent chemotherapy of orthotopic hepatocellular carcinoma in vivo. Acta biomaterialia. 2019; 92: 196-204.

52- Gurnani P, Perrier S. Controlled radical polymerization in dispersed systems for biological applications. Progress in Polymer Science. 2020; 102: 101209.
53- Yue S et al. Cetuximab–Polymersome–Mertansine Nanodrug for Potent and Targeted Therapy of EGFR-Positive Cancers. Biomacromolecules. 2021; 23.1: 100-111.
54- Gomes CP et al. Polymersomes as versatile drug delivery vesicular carriers. In: Systems of Nanovesicular Drug Delivery. Academic Press. 2022; p. 155-190.
55- Haghshenas V et al. Encapsulation of docetaxel into Diblock polymeric polymersome as a nanodrug. ChemistrySelect. 2020; 5.29: 8924-8928.
56- Ramezani P et al. Targeted MMP-2 responsive chimeric polymersomes for therapy against colorectal cancer. Colloids and Surfaces B: Biointerfaces. 2020; 193: 111135.
57- Hernández B et al. Light-triggered polymersome-based anticancer therapeutics delivery. Nanomaterials. 2022; 12.5: 836.
58- Yu J, Weijing Y, Jian Z, Fenghua M, Zhiyuan Zg. Protein Toxin Chaperoned by LRP-1-Targeted Virus-Mimicking Vesicles Induces High-Efficiency Glioblastoma Therapy In Vivo. Adv. Mater. 2018: 30(30).
59- Rijpkema SJ et al. Designing molecular building blocks for functional polymersomes. Israel Journal of Chemistry. 2019; 59.10: 928-944.
60- Benito E et al. Structurally simple redox polymersomes for doxorubicin delivery. European Polymer Journal. 2020; 137: 109952.
61- Wang X et al. Regulating vesicle bilayer permeability and selectivity via stimuli-triggered polymersome-to-PICsome transition. Nature Communications. 2020; 11.1: 1524.
62- Shoaib I, Mark B, Angela AB, Jessica L, Polymersomes for Therapeutic Delivery of Protein and Nucleic Acid Macromolecules: From Design to Therapeutic Applications. Biomacromolecules. 2020; 21 (4), 1327-1350