Nanostructured polymers

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13.1 Introduction

Nanotechnology provides the ability to work at the molecular level, atom by atom, to produce nanostructures with essentially new molecular organization. In recent years, the potential use of nanotechnology in order to reach medical and pharmaceutical goals has recently been defined as nanomedicine, and it is driving great attention in the clinical and research fields [1].

There are certain polymeric systems that exhibit unique properties which can be directly attributed to the presence of structural entities with nanometer-range dimensions. Due to the special contribution of these nanosized entities, this class of polymeric systems can be collectively designated as nanostructured polymeric materials [2].

In this sense, nanostructured polymers (NSPs) have great potential for developing new carriers for drug and gene delivery, and they represent a suitable class of materials to be employed in the biomedical field [3].

In the last few years, NSPs provoked great interest and received considerable attention to their exciting bulk and surface properties [4]. They may be appropriately tailored for a wide variety of biological and technological applications. Mainly due to the small size of the building blocks, which is in the nanometer scale, and the high surface-to-volume ratio, these nanomaterials are expected to demonstrate unique physicochemical properties and are promising for several uses including drug and gene delivery, tissue engineering, and biosensors, just to name a few [3].

The rapid and growing interest related to NSPs is because of their sized-coupled properties [5]. The size, shape, composition, molecular engineering, assembly, and nanostructures are key parameters which characterize NSPs, drive their functions, and allow achieving applications in different fields [3].

The control of the nanostructure of polymers has led to structural and functional property improvements in a number of polymeric systems as a new class of material that meets continuous requirements from advanced industrial sectors [4]. However, their potential is still strongly dependent on the development and scaling-up of reliable processing routes [3,4].

Bottom-up and top-down approaches have been typically reported for material nanotechnologies (Fig. 13.1) [4]. The synthesis approaches are mainly based on a bottom-up procedure: starting from the monomers to arrive at the whole nanostructure by rationally tailoring experimental parameters that readily and selectively lead to

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production of different types of micro/nano-materials with novel morphologies and high performance, to be applied for drug and gene delivery [3]. The application of typical processing technologies like extrusion are clear top-down processes in which ingredients (polymer and active agent) are introduced, and equipment processes them to obtain the nanostructure [4].

Considering the research priorities described earlier, this chapter will cover features of the main processing approaches for NSPs, first addressing bottom-up methods, and then discussing different technologies required by top-down processing for different types of polymeric matrices. Special interest will be focused on the use of amphiphilic block copolymers (ABCP), due to their versatility in allowing us to obtain different types of nanostructured polymeric materials. The recent advances in their main biomedical applications will be highlighted. Hybrid inorganic-organic nanocomposites are not covered in this chapter.

13.2 Amphiphilic block copolymers

Advances in drug delivery systems based on NSPs were significantly improved in the last two decades [6]. One of the supporting determinants is developments in the area of ABCP. These polymers are obtained by well-known techniques of co-polymerization typically using two or three kinds of co-monomers that usually form linear macromolecules in a block distribution of each monomer [7]. The hydrophilic and hydrophobic functional groups available in the respectively selected co-monomers confer amphiphilic characteristics to the copolymer formed [6,8].

In general, ABCP can be considered as a kind of polymer alloy, and linear di-block (AB), tri-block (ABA, BAB or ABC), multiblock, or star-block copolymers can be prepared [4] where A, B, and C represent distinct blocks based on different monomers [9]. In these sense, Fig. 13.2 shows typical schematic arrangements that could be obtained by the possibilities of sequencing and distribution of the blocks [8].

Hydrophobic biocompatible polymers, employed for assembly copolymer nano-

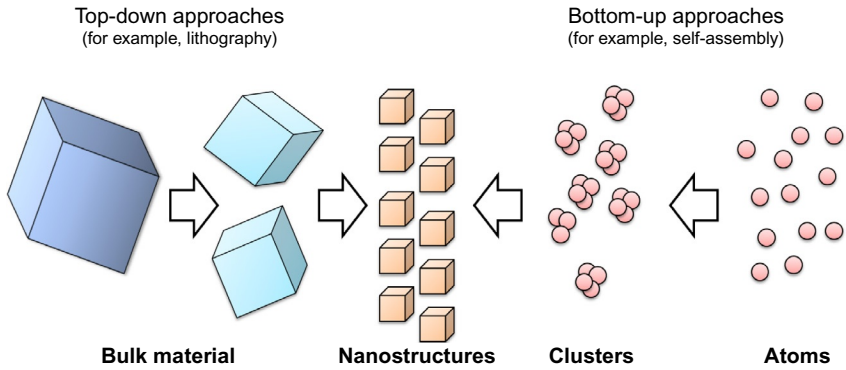

Fig. 13.1 Schematic representation of bottom-up and top-down approaches for obtaining nanostructures.

structures with pharmaceuticals and biomedicine applications, mostly consist of polyester and poly (amino acids) covalently bonded to a biocompatible hydrophilic block, such as poly(etilen glycol) (PEG) [6]. In the ABCP, PEG is the most commonly used hydrophilic block because of its minimal immunogenicity (PEG being listed as "Generally Recognized as Safe" (GRAS) by the Food and Drug Administration, FDA [10]), high water-solubility, high hydration, and flexibility, where biocompatible and biodegradable aliphatic polyesters and their copolymers, such as poly(L-lactide), poly(lactide-*co*-glycolide), and poly(ε-caprolactone) (Fig. 13.3), are often selected as the hydrophobic blocks. The system with hydrophobic linear aliphatic polyesters as the core-forming blocks has been approved by the FDA for therapeutic applications [11].

A particular class, the ABCP, are Poloxamers, which are poly((ethylene oxide)-*b*-(propylene oxide)-*b*-(ethylene oxide)) (PEO-*b*-PPO-*b*-PEO) tri-block copolymers (Fig. 13.4) widely used for drug delivery purposes [12]. They are based on ethylene oxide (hydrophilic) and propylene oxide (lipophilic), commercialized like Pluronic (Basf) or Synperonic (ICI). Their behavior in water is determined mainly by the PEG/PPO ratio, but other factors, such as temperature, also affect aggregates' formation, solubility, and hydrophilic-hydrophobic balance [8].

Pluronics are designated by L, P, or F for liquid, pastes, or flakes forms, respectively, followed by two or three digits; the first multiplied by 300 is used to describe the relative (hydrophilic-hydrophobic) average molecular mass (in the three digits case the two first numbers are used), and the last digit multiplied by 10 represents the approximate mass percentage of the hydrophilic part. For example, Pluronic P85 means a copolymer with a relative molecular mass of about 2400 (8×300) and the mass percentage of the PEO block about 50% (5×10) [8]. Pluronics are biocompatible and available at a relatively low cost. Typical applications include cancer treatments, controlled release of drugs for parenteral administration, and burn treatments [10].

In particular, ABCPs have the ability to assemble into multiple morphologies in aqueous solution in order to minimize energetically unfavorable hydrophobe-water

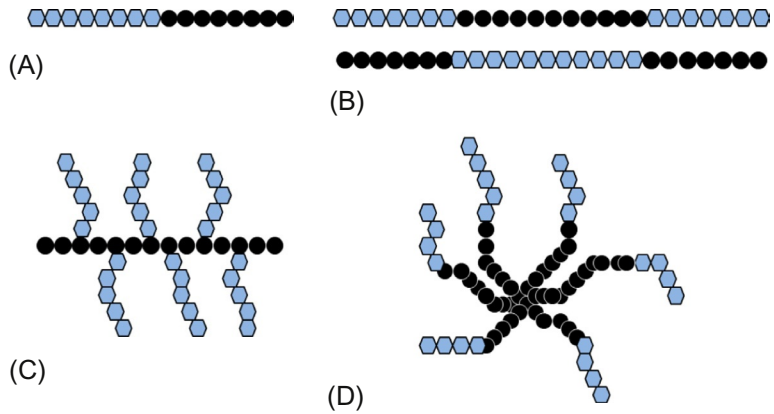

Fig. 13.2 Typical schematic arrangements of (A) diblock copolymer, (B) tri-block copolymer, (C) graft-polymer, and (D) star-block copolymer.

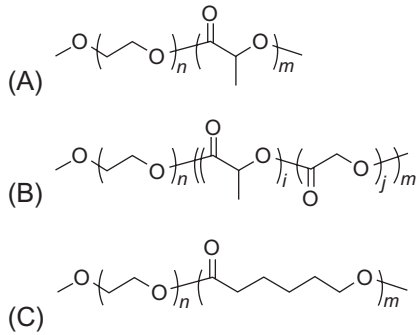

Fig. 13.3 Chemical structures of the most employed amphiphilic di-block copolymers. (A) Poly(etilen glycol)-*b*-poly(L-lactide), (B) poly(etilen glycol)-*b*-poly(lactide-*co*-glycolide), and (C) poly(etilen glycol)-*b*-poly(ε-caprolactone).

interactions [13]. Molecular self-assembly is a powerful approach for producing novel supramolecular architectures in which molecules assemble themselves without the presence of outside interactions [14,15]. Self-assembly is the spontaneous formation of well-ordered structures, and it occurs under kinetic and thermodynamic conditions which allow molecular interactions (electrostatic or hydrophobic interactions, π-π interactions hydrogen bonding, and van der Waals forces) to keep molecules at a stable state, achieving the minimal energy in the system [16,17]. Self-assembly processes are commonly low-cost and large-scale techniques, and they can be suitable for diverse purposes including the development of nanomaterials with potential biomedical application [18].

Several reported morphologies related to ABCP are primarily a result of the inherent molecular curvature and how this influences the packing of the copolymer chains: specific self-assembled nanostructures can be targeted according to a dimensionless "packing parameter," p, which is defined in Eq. (13.1):

$$p = \frac{v}{a_o \cdot l_c} \tag{13.1}$$

where v is the volume of the hydrophobic chains, a_o is the optimal area of the head

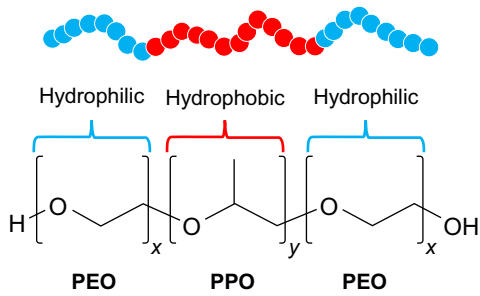

Fig. 13.4 Chemical structure of poloxamers, which are poly((ethylene oxide)-*b*-(propylene oxide)-*b*-(ethylene oxide)) (PEO-*b*-PPO-*b*-PEO) tri-block copolymers.

group, and l_c is the length of the hydrophobic tail. Thus, the p of a given molecule usually dictates its most likely self-assembled morphology. In general, spherical micelles are favored when $p \leq \frac{1}{3}$, cylindrical micelles when $\frac{1}{3} \leq p \leq \frac{1}{2}$, and enclosed membrane structures (vesicles, also known as polymersomes) when $\frac{1}{2} \leq p \leq 1$ [19].

When discussing self-assembly of ABCP, not only is the p a very important parameter to take into consideration. Also, a parameter known as hydrophilic volume fraction (f) is usually employed for this kind of polymer. The f is defined as the relation between the hydrophilic portion of the polymeric chain and the total molecular mass. For copolymers with poly(ethylene glycol) (PEG) as hydrophilic branch and considering the density of homopolymers, it is possible to predict the type of nanostructure aggregation analyzing the f value. Thus, spherical polymeric micelles are favored at values of $f > 50\%$, cylindrical micelles are favored at $40\% < f < 50\%$, and vesicular structures or polymersomes are preferentially formed at $25 < f < 40\%$ [20–22] (Fig. 13.5).

It is important to highlight that ABCP can be defined as one of the most important self-assembling nanostructured materials because of their ability to allow controlling both scalar behaviors over self-assembled process and advanced vectorial aspects regarding the application of the resulting nanostructured morphologies [4,23]. In particular, by using ABCP it is possible to obtain a precise control over the length scale of the dimensions of the nanostructured domains, and over morphology by taking into account the phase diagram as well as a quantitative prediction of the equilibrium structures [4]. Furthermore, it is possible to obtain control over domain functionality and properties, thus tailoring the materials for ultimate applications. In fact, they

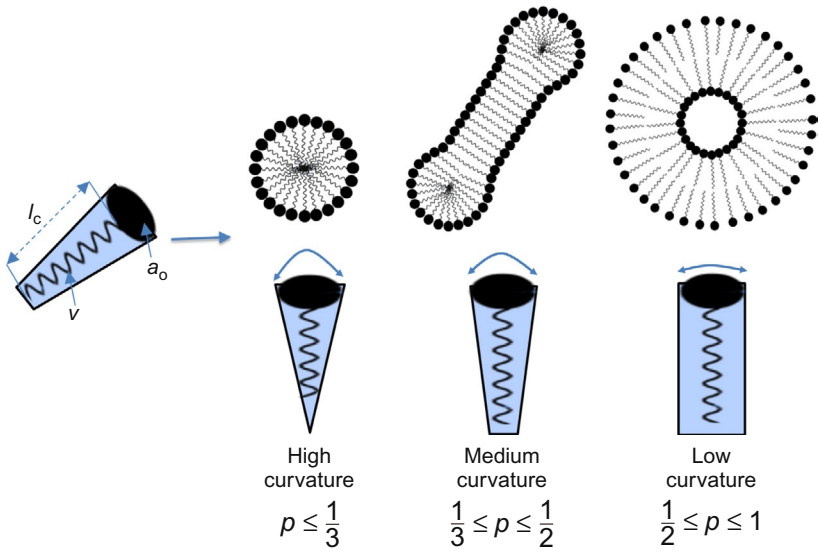

Fig. 13.5 Schematic illustration of association structures formed in block copolymer systems, packing parameter and hydrophilic volume fraction in the different nanostructures.

maintain the traditional advantages of polymeric materials including cost effectiveness and flexibility [4], providing extra advantages due to their ability to self-assemble.

In this context, the most interesting feature when working with ABCP is probably to understand their ability to self-assemble into nanodomains and to study their nanostructured ordered morphologies. Therefore, their phase behavior has been the matter of several theoretical and experimental studies over decades [22,24,25].

13.3 Nanostructuration methods

Nanofabrication involves methods building engineered nanostructures and devices having minimum dimensions, in most cases lower than 100 nm. This technology is the basis for nearly every aspect of nanomaterials research and development with emphasis on their use for complex multifunctional devices, with applications spanning over a wide technological field, including medicine and human health care [14,15]. In this sense, the last ten years have witnessed the development of a wide diversity of nanofabrication techniques fulfilling high expectations surrounding nanotechnology and nanofabrication [15].

As it was mentioned, nanofabrication methods can be divided roughly into two groups: bottom-up and top-down, and methods according to the processes involved in creating nanoscale structures. In the following sections, each one of them will be presented, but briefly, bottom-up methods begin with atoms or molecules to build up nanostructures, in some cases through smart use of self-organization [14,26], while top-down methods start with patterns made on a large scale and reduce their dimensions before forming nanostructures [26].

It is important to stress that novel nanofabrication tools or a combination of standard nanofabrication approaches may be needed in the future research and development of new nanomaterials including multicomponent nanomaterials [15].

13.3.1 Bottom-up approaches

Bottom-up nanofabrication approaches seek to have molecular or atomic components built up into more sophisticated nanoscale assemblies or directed self-assemblies based on complex mechanisms and technologies [13,27]. This area of nanofabrication uses atoms or small molecules as the building blocks of nanostructures that perform several operations, and is extremely promising for producing novel supramolecular architectures, without waste or the need for making or eliminating parts of the final system [14,15]. Methods of bottom-up fabrication rely on molecular self-assembly in supramolecular processes [27]. Self-organizing functional systems and devices are the ultimate goal of bottom-up fabrication [15]. In this sense, it is important to highlight that supramolecular chemistry was originally a branch of fundamental science, and currently it has become an important concept in nanotechnology [27].

Regarding NSPs, few bottom-up approaches have been reported, and typically these concern the use of ABCP nanostructuration. In this sense, they are a particular class of polymers that belong to a wider family known as soft materials [28–30] that,

independent of the synthesis procedure, can be considered to have been formed by two or more chemically homogeneous polymer fragments or blocks, joined together by covalent bonds. As was mentioned above, ABCP are able to self-assemble into well-defined and well-ordered nanostructures potentially used as the basis for a wide number of technological and biomedical applications [31–33]. The ABCPs are able to produce, under appropriate conditions, the spontaneous formation of periodic nanostructures, and consequently they are considered an example of bottom-up processing strategy. The constituent blocks can segregate at the local level, and their separation usually corresponds to the radius of gyration of the molecule, thus forming self-assembled ordered nanostructures in the range of 5–100 nm [4].

The strategies used for obtaining ABCP are not new and innovative, but these synthesis methods are not trivial, because high-purity starting monomers and high-vacuum procedures are required in order to prevent premature termination by impurities. In terms of synthesis methods, both anionic [34,35] and living radical polymerization [36–40] procedures are used now to obtain ABCP. It is important to note that the older anionic polymerization is still industrially used for producing ABCP, even when the first anionic polymerization techniques were conducted several years ago in 1956 [33,41].

New approaches in the synthesis of ABCP involve the use of atomic transfer radical polymerization [42–45], independently discovered in the same year by Kato et al. [46], and by Wang and Matyjaszewski [47]. This technique is currently one of the most often used synthetic polymerization methods for preparing well-defined polymers with complex architecture [45], including nanostructured ABCP [4]. This method allows defining the architecture of the synthesized polymer by choosing the adequate initiator [45], for obtaining AB di-block, and ABA, BAB, and ABC tri-block copolymers, both of them based on polystyrene and several polyacrylates [9].

On the other hand, ring-opening polymerization has also been used to build blocks of the ABCP [48]. Yasugi et al. developed galactose and glucose functionalized poly(L-lactide)-PEG block copolymers through this method of successively producing ethylene oxide and D,L-lactide, using protected sugars as the initiator [49]. Toyotama et al. prepared sugar-substituted poly(γ-methylglutamate)-*b*-poly(ethylene oxide) block copolymers of L-glutamic acid γ-methylester *N*-carboxy anhydride [50]. Lee et al. investigated the thermo-responsive phase transitions of poly(D,L-lactide)-*b*-PEG-*b*-poly(D,L-lactide) tri-block stereo-copolymers in aqueous solution, showing that there are a critical gel concentration and critical gel temperatures at which the thermo-responsive phase transition take place [51]. Regarding the poly(ester)s, Dove reviewed their application, obtained by living/controlled ring-opening polymerization of cyclic esters, as components of self-assembling ABCP [52]. Also, Chen et al. reported the design of novel functional nanomaterials obtained by the synthesis of hydrophobic polymer brushes based on a hard core of silica nanoparticles with a relatively soft shell of polystyrene-*b*-poly(ε-caprolactone) obtained by prepared via surface-initiated atom transfer radical polymerization of styrene, ring-opening polymerization of ε-caprolactone and click reaction [53]. More recently, Peponi et al. have been able to correlate the chemical structure with the crystallization behavior of each block in poly(ε-caprolactone)-*b*-poly(L-lactide) di-block copolymers starting from

cyclic molecules [54]. Lately, Pan et al. reported the synthesis of pseudopeptidic-type di-block copolymer of poly(2-oxazoline)-*b*-poly(peptoid), where poly[2-(3-butenyl)-2-oxazoline]-*b*-poly(sarcosine) comprising hydrophobic poly(2-oxazoline) segment bearing alkenyl side chain and hydrophilic poly(peptoid) segment of *N*-methyl glycine, namely, sarcosine, were prepared by ring-opening polymerization through a one-pot and three-step route [55].

In addition, Skandalis and Pispas reported the synthesis and self-assembly properties in aqueous solutions of novel ABCP composed of one hydrophobic poly(lauryl methacrylate) block and one hydrophilic poly(oligo ethylene glycol methacrylate) block using reversible addition fragmentation chain transfer polymerization [56]. These examples of synthesis are presented, just to name a few.

Furthermore, another important aspect to be considered when referring to bottom-up methods and ABCP structures is the block polydispersity effects. Particularly, these aspects are important when comparing phase diagrams obtained with ABCP synthetized by anionic or control free-radical polymerizations, or when comparing di-blocks and segmented ABCP. Related to that, it has been suggested that polydispersity effects are dramatically enhanced when polydisperse blocks are constrained by both ends to the internal interfaces of an ordered morphology [57]. Comparing a BAB tri-block copolymer with an AB di-block, the polydispersity induces shifts in the order-disorder transition of the tri-block copolymer system, attributed to a reduction of entropy in the A-rich domains due to the absence of chain ends [4,57].

In accordance with the discussion above, it is clear that the applications of self-assembling nanostructured ABCP are very broad, but the common factor is to understand their phase separation behavior. Due to the complexity of the self-assembling theories, computer simulations have been used in order to study the ABCP behavior during the self-assembly process. In fact, different simulation calculation methods, including Monte Carlo and dissipative particle dynamics simulations, have been employed in order to predict the phase diagram of ABCP [4].

It is important to note that the self-assembling of block copolymers has also been studied in thin film [58]. Thin block copolymers on surfaces are interesting materials for biomedical applications. Their chemical versatility allows for the adjustment of desired properties, namely as protein repellence or adhesion, and biocompatibility. Mostly, biodegradable poly(ε-caprolactone)- or poly(L-lactide)-based block copolymers are used as biomaterials [59].

On the other hand, ABCPs in solution are able to self-assemble in ordered nanostructures, in which the solvent is selective for one block of the ABCP leading to the formation of nanostructures (Fig. 13.5) [19]. In particular, when an ABCP is dissolved in a liquid that is a thermodynamically good solvent for one block and at the same time a precipitant for the other, the copolymer chains associate reversibly, thus forming micellar aggregates of nanoscopic dimensions and of various shapes. In fact, in selective solvents, some ABCPs form micelle-like aggregates that consist of an insoluble polymeric core surrounded by a solvent swollen corona [60]. The thermodynamically favored morphology and aggregate dimensions are determined by a force balance between the average degree of stretching of the core-forming block, by the steric crowding of chains in the corona and at the core-corona interface, and by the

quality of the core-solvent interaction [4]. This behavior related to the free energy contributions of the core, the corona, and the interface has been deeply studied to explain thermodynamic and kinetic aspects of the formation and morphological transitions by self-assembling block copolymers in solution [61,62].

13.3.2 Top-down approaches

A top-down approach corresponds to using nanofabrication tools that are controlled by external experimental parameters to produce nanoscaled structures/functional devices with the desired shapes and characteristics starting from larger dimensions and reducing them to the required values [15]. Several methods of lithography are used in the top-down approach, including serial and parallel techniques for patterning two-dimensional nanoscale features [5]. Also, photolithography and electron-beam lithography have been used to produce nanostructures [27].

In conventional lithography, required material is usually protected by a mask, and the exposed material is etched away. Chemical etching using acids or mechanical etching using ultraviolet light, X-rays, or electron beams is performed to determine the feature resolutions of the final product. Other top-down approaches include canning probe lithography, nanoimprint lithography, and block copolymer lithography, among others [5].

Segalman et al. reported one strategy to integrate block copolymers with conventional lithography, known as graphoepitaxy [63]. The purpose of graphoepitaxy is to enhance the resolution of the conventional lithographic process by subdividing the patterned features, and to improve the perfection of ordering of the dense periodic arrays of nanostructures that are naturally formed by block copolymers. In this method, small grooves (with micron/submicron dimensions) are patterned onto the substrate using photolithography and etching, and the domain structure of block copolymer films deposited in the grooves nucleates on the walls of the topographic features and propagates inward, so as to be well ordered across the width of the grooves and along their axes [64,65].

The patternability of ABCPs results from their ability to self-assemble into microdomains and the manipulation of these patterns by a variety of chemical and physical means [66].

Block copolymer lithography involves a combination of bottom-up self-assembly and top-down lithographic processes. The self-assembly of block copolymers is represented by two polymeric chains linked together, and it can result in domains with high periodicity (10 nm within a template or highly sophisticated patterns) [15]. Confinement of nanopatterns within addressable micro- or submicron-sized patterns is important to derive substantial benefits from the nanostructure properties [67]. Topographically or chemically patterned templates are used to control the orientation and placement of block-copolymer domains [15]. It has been reported that by accurately controlling properties such as the functionality or the molecular weight of ABCP, pattern generation can be achieved via molecular engineering. In this sense, using a combination of molecular interactions and topology, advanced surface chemistry processes, and structural control, it may be possible to produce and to design defect-free nanostructures with several dimensions and geometries [15,67].

Using block copolymers and self-assembling materials for the direct fabrication of complex three-dimensional structures in thin films promises to be an emerging area for directed assembly and nanolithography [64,65]. In top-down lithography, the structures formed are two-dimensional in nature. Control over the structure geometries, long-range ordering, and positioning has been achieved within the plane of the film. However, there has been no variation in the structures in the direction normal to the substrate. Top-down methods of modifying copolymer patterns can be achieved using localized modification of copolymer micellar thin films using deposition of selective solvents by printing or nanodispensing [67]. Also, it may be possible to encode additional information into the system through the choice of self-assembling material, so that three-dimensional structures are formed in a single processing step [64]. Thus, combining top-down lithographic approaches to guide this self-assembly process reduces the time to generate a pattern significantly. The direct self-assembly of block copolymers holds great promise for future applications over a wide range of size scales [68].

While significant advances have been made in understanding and developing top-down processes, there are still numerous challenges ahead [68]. To date, general methods for efficient top-down patterning of nanopatterns into periodic and aperiodic areas on a surface are still lacking [67].

On the other hand, extrusion is a typical processing technology widely used for obtaining nanostructures [4]. In this method, all components of the desired final system are introduced into equipment to achieve reduction of particle sizes. The quality of the dispersion is determined by macroscopic processing factors like equipment design, mixing velocity, residence time, etc., with very limited possibilities for processing optimization [4].

Fig. 13.6 summarizes the nanostructuration methods detailed above. Finally, regarding emerging methods, two methods in particular share an interesting point of commonality in that directed assembly occurs concurrently with sample deposition.

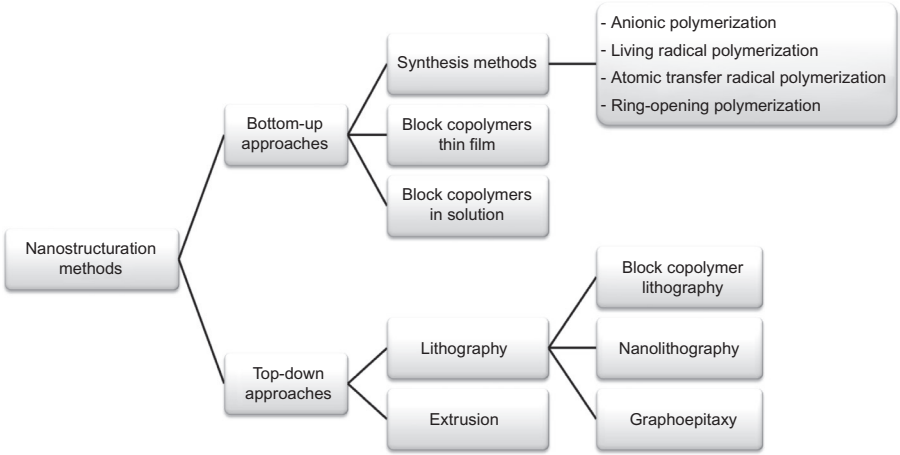

Fig. 13.6 Summary of the nanostructuration methods used for processing nanostructured polymers.

These two in situ techniques are zone casting and electrospray deposition. Zone casting involves slow deposition of an ABCP solution onto a moving substrate from a narrow line-shaped nozzle held perpendicular to the direction of motion at a small distance from the substrate. The potential for large-area processing and the versatility afforded by control of temperature and solvent composition make zone casting a very attractive method for depositing ABCP thin films. Electrospray deposition has been developed as a way to deposit equilibrium morphologies in a continuous fashion by producing submicron droplets of dilute ABCP solutions. This technique presents a versatile platform for depositing ordered thin films of a diversity of materials by controlling a range of process parameters [69].

13.4 Biomedical applications of NSPs

Polymeric nanostructured materials have been playing an increasingly important role in revolutionizing the diagnosis and treatment of several diseases. These nanomaterials provide significant improvement in the quality of health care, due to their better accuracy and reliability in diagnostics, more effective targeting of therapeutic agents, and improved usability of scaffolds for tissue engineering and regenerative medicine, just to mention a few applications [11,70].

In general, polymeric nanostructured materials for biomedical applications should have adequate properties, namely significant water solubility or dispersibility, well-controlled nanoparticle dimension to avoid fast clearance (10–200 nm) and to achieve preferred biodistribution, biodegradability to minimize side effects (residue with hydrodynamic size <10 nm for complete clearance from bloodstream), functionality to link with pro-drug, targeting component, or imaging agents, etc., and responsivity to release therapeutic loading under triggered conditions [11].

Several types of nanostructures belong to polymeric nanostructured materials, including micelles, polymersomes, nanoparticles, nanocapsules, nanogels, nanofibers, dendrimers, brush polymers, and nanocomposites. Their properties, such as stability, size, shape, surface charge, surface chemistry, mechanical strength, porosity, and so on, can be tailored toward the specific functionalities that are required to meet the needs of the targeted biomedical application [11]. Focusing on ABCP-based nanomaterials, we will detail the main biomedical applications of polymeric micelles and polymersomes [19]. It is important to note that these nanomaterials can be prepared via a variety of pathways. Briefly, polymeric micelles can be obtained by direct dissolution, film casting, dialysis, and oil-in-water emulsion methods. On the other hand, polymersomes can be prepared by organic solvent-based and solvent-free methods. A detailed description of these methodologies can be found in the chapter, *Self-Assembled Nanomaterials*, of this book and in a recent review about this topic [11].

It is important to stress that the major interest in ABCP block copolymers as drug delivery nanosystems stems from the ability to adjust the chemical nature of the blocks along with the molecular characteristics of the copolymer (molecular weight, composition, presence of functional groups for active targeting), thus optimizing the performance of the delivery system [60].

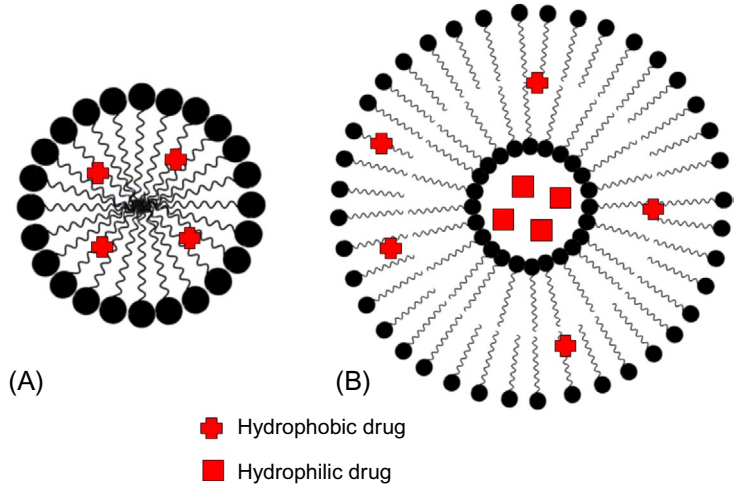

Fig. 13.7 Schematic structures of (A) polymeric micelles and (B) polymersomes as carriers of hydrophilic and hydrophobic drugs.

Regarding their application as drug delivery systems (Fig. 13.7), polymeric micelles for intravenous drug delivery administration use hydrophilic blocks of the ABCP often composed of zwitterionic materials or PEG, which can resist nonspecific protein adsorption and prolong the circulation time for nanostructures in the complex in vivo environment. The hydrophobic core can serve as a sustained release reservoir of bioactive low molecular weight drugs, including antitumor agents, whereas the hydrophilic shell can stabilize the hydrophobic core and make the micelle a stable vehicle for this administration. The small size of polymeric micelles (typically average diameter between 10 and 200 nm but with narrow size distribution) is similar to those of natural mesoscale vehicles, namely viruses and lipoproteins. This property is especially useful for cancer therapy, due to their small size, which allows them to participate in extravasation through the fenestrations in tumor vessels and limiting their uptake by the reticuloendothelial system (also known as the mononuclear phagocytic system) thus possessing enhanced permeation retention capability [71]. Some examples of the use of polymeric micelles for cancer treatment include PEG—phosphatidylethanolamine/vitamin E as carrier of paclitaxel and tariquidar for ovarian carcinoma treatment [72], PEG—phosphatidylethanolamine as carrier of paclitaxel and curcumin for the treatment of ovarian adenocarcinoma [73], PEG-*b*-poly(ε-caprolactone) as carrier of paclitaxel, cyclopamine, and gossypol for ovarian cancer [74], and glycine-tethered poly(lactide-*co*-glycolide) as carrier of methotrexate for the treatment of mammary gland/breast tumor [75], just to name a few. Currently there are ongoing clinical trials of polymeric micelles for cancer therapy [11].

On the other hand, in the case of polymersomes, hydrophilic drugs can be encapsulated in their aqueous cavities, whereas the hydrophobic component of the membrane can also incorporate hydrophobic drugs. Thus, the structure of polymersomes has the ability to deliver hydrophilic and hydrophobic drugs simultaneously to generate

synergistic effects for cancer therapies [76]. Some examples include poly2-(methacryloyloxy)ethyl phosphorylcholine-*b*-poly 2-(diisopropylamino)ethyl methacrylate loaded with doxorubicin and paclitaxel for the treatment of head and neck squamous cell carcinoma [77], and Poly(benzyl carbamate)-*b*-poly(*N*,*N*-dimethylacrylamide) as carrier of eosin or camptothecin and doxorubicin (co-encapsulated) for photodynamic and combinational cancer therapy [78], just to mention two examples.

Regarding gene therapy, polymer micelles are usually more stable than polyplexes (complex of polymer-nucleic acid) and their size is much smaller, which makes them a perfect nominee for nucleic acid delivery. Micelles based on PEG-poly(ε-caprolactone)-poly(2-aminoethyl ethylene phosphate) were used to concurrently deliver polo-like kinase 1 (Plk1) siRNA and paclitaxel for cancer gene therapy, Also, micelles consisting of PEG and arginine-grafted poly(cystaminebisacrylamidediaminohexane) loaded have been used for effectively co-delivering functional genes and chemotherapeutic agents, just to mention some examples [79]. Related to the use of polymersomes as gene carriers, plasmid DNA-loaded poly 2 (methacryloyloxy)ethyl phosphorylcholine-*b*-poly-2-(diisopropylamino)ethylmethacrylate, and siRNA loaded PEG-poly(lactic acid) and antisense poligonucleotides loaded PEG-poly(ε-caprolactone) are examples of polymersomes for gene therapy and anticancer therapy with improved delivery efficiency and fluorescently labeled for nuclear localization [80].

Regarding the use of polymersomes as imaging platforms, they provide higher resolution than conventional techniques and allow in vivo monitoring of biological pathways and cellular functions, besides being noninvasive [80,81]. On the other hand, polymersomes simultaneously encapsulating both therapeutic and diagnostic payloads, known as theranostics, have also been studied [81]. For instance, in theranostics, poly(trimethylene carbonate)-polyglycolic acid encapsulating doxorubicin and ultra-small superparamagnetic iron oxide (contrast agent) for the diagnosis and treatment of localized tumors, to provide contrast for magnetic resonance imaging, and to respond to the magnetic field, controlling the rate of doxorubicin release at the target site [82].

Considering the examples presented above, it can be seen that NSPs can provide great value for accurate diagnosis and effective treatment of diseases. For example, in controlled drug and gene delivery, these nanomaterials can be used to enhance the in vivo stability, increase the target specific delivery of drugs and genes, optimize the pharmacokinetics and biodistribution of the payload, reduce side effects, and improve the efficacy of the system. Polymer-based nanotechnology can also provide opportunities for personalized diagnosis and treatment by combining therapeutic and imaging contrast agents together.

13.5 Conclusions and future challenge

Several efforts to develop NSPs-based materials have attracted a great deal of attention because they represent a class of materials suitable to employment in the biomedical field. Recent and extensive reports on nanostructuration methods based on bottom-up and top-down approaches has been described for obtaining NSPs. Considering the

potential of ABCPs, several efforts has been conducted to deeply understand their ability to self-assemble into nanodomains and to study their nanostructured ordered morphologies. As detailed above, ABCP-based nanostructures include polymeric micelles and polymersomes which have been widely studied by several researchers aiming toward biomedical and pharmaceutical applications for various purposes, including cancer therapy.

However, though polymeric nanostructured materials have shown great potential to revolutionize the diagnosis and treatment of different diseases, there are also great challenges for the successful translation of basic research to clinical applications, even when some clinical trials are currently under study.

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