Weak Polyelectrolytes for Nanoarchitectonic Design Tools

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The ionization degree, charge density, and conformation of weak polyelectrolytes can be adjusted through adjusting the pH and ionic strength stimuli. Such polymers thus offer a range of reversible interactions, including electrostatic complexation, H-bonding, and hydrophobic interactions, which position weak polyelectrolytes as key nano-units for the design of dynamic systems with precise structures, compositions, and responses to stimuli. From surface platforms to colloids and gels, weak polyelectrolytes have enabled the development of a wide range of functional materials owing to their intrinsic response to stimuli, including solvents, temperature, pH, and salt.

Keywords: polymer materials ; polyelectrolyte films ; electrodeposition

1. Weak Polyelectrolytes Layers for Stimuli-Responsive Surfaces

Coatings based on weak polyelectrolytes provide researchers with a convenient way to tune the properties of surfaces, ultimately adjusting their interactions through their environment and enabling the design of stimuli-responsive systems.

1.1. Brushes of Weak Polyelectrolytes

Polymer brushes are obtained through the chemical grafting of surfaces with a layer of polymers. The resulting coatings are considered more stable than those obtained from casting owing to their capability to withstand immersion in good solvent without dissolution. Polymer brushes are extensively used as colloidal stabilizers, lubricating layers, and drug delivery systems [1]. In that respect, elaborating brushes based on weak polyelectrolytes is generally aimed at developing stimuli-responsive systems, and was reviewed recently [2]. Grafting-from approaches, where polyelectrolyte chains grow in situ from their surface anchoring points, typically offering higher grafting densities than approaches where pre-synthesized polyelectrolyte chains are used [3][4], have therefore been developed by using several radical polymerization technics [1]. Accordingly, both polyanion [5] and polycation [6] brushes have been synthesized by using nitroxide-mediated polymerization (NMP). A larger variety of systems were made accessible using atom-transfer-radical-polymerization (ATRP) at the cost of using a metal catalyst, yielding routinely weak polycationic brushes such as PDMAEMA [7]. However, the growth of carboxylate-containing polyanions (PAA, PMAA) brushes is more complicated owing to interactions with the catalyst, leading researchers to polymerize their respective ester derivatives, followed by a deprotection step [8]. Finally, reversible addition-fragmentation chain transfer (RAFT), a catalyst-free polymerization method, was used for developing weak polycationic brushes [9][10] with the trade-off of using quite expensive chain transfer agents. However, this approach has so far been neglected with regard to the synthesis of weak polyanion brushes.

The pH response of weak polyelectrolyte brushes leads to conformational changes in polymer chains, resulting in thickness variations in the brush: when the ionization degree of the polyelectrolyte decreases (resp. increases), the brush tends to collapse (resp. swell). This effect is largely modulated by the concentration [11], type [12], and valency [13] of counter-ions and salt in the system. Changes in pH and ionic strength parameters can also be induced electrochemically, yielding a reversible swelling of brushes [14]. Among the most studied applications of polyelectrolyte brushes, both their lubricating and adhesion functions can be efficiently switched on and off by using weak polyelectrolytes [13][15]. Lubrication is ensured by the swollen hydrated state of polyelectrolyte brushes. Although polyzwitterionic brushes have been determined to perform better, brushes composed of weak polyelectrolytes offer an opportunity to modulate lubrication through pH and ionic (concentration, valency) stimuli [13]. Adhesion in water dependent on pH has also been demonstrated between a range of weak polyelectrolyte brushes, including PAA with poly(N,N-dimethylacrylamide) and PMAA with PDMAEMA. The adhesion mechanism is, however, different with H-bonding, ensuring the cohesion of the first polyelectrolyte couple (pH values smaller than 2) [16], while electrostatic interactions dominate for the PMAA/PDMAEMA couple [17]. The combination of electrostatic, H-bonding, and hydrophobic interactions in weak polyelectrolyte brushes

enable cargo (e.g., proteins) immobilization with a large binding capacity, reversible nature, and structure-preserving ability [18][19].

1.2. Electrodeposited Weak Polyelectrolytes Films

Electrochemically induced film deposition strategies have recently attracted a great deal of attention, as the localized nature of the electrochemical trigger enables spatially resolved film assembly in a conformal manner, including on substrates with complex topologies. Applications of such films are anticipated in many fields, as testified by pioneering work in biomaterials, energy storage and conversion, mass transport, and analytic tools [20]. Several electrochemical approaches to weak polyelectrolyte films have thus been developed by using electrochemically induced precipitation, electropolymerization, and electrochemically induced coupling reactions.

The electrochemically induced precipitation of weak polyelectrolyte films is typically achieved by locally changing the solubility of weak polyelectrolytes near the electrode, favoring their self-association and precipitation. This process can be triggered, among the most popular strategies, by changing the local pH through water electrolysis *(i)* or by enabling the complexation of the polyelectrolytes with multivalent ions *(ii)*. Electrodeposited weak polyelectrolytes films have mainly been developed from pure and composite assemblies of CHI, ALG, PAH, and gelatin on a large range of electrodes (including patterned electrodes) with spatial and temporal control [21].

(i) Water electrolysis allows increasing the local pH value at the cathode, favoring the deposition of films based on weak polycations, such as CHI, through decreasing their ionization degree [21]. Here, again, the ionic strength of the solution during the film deposition directly influences the thickness and mechanical properties of the polyelectrolyte assembly, with thicker and softer films obtained at higher salt concentrations [22]. At the anode, the proton gradient generated during water electrolysis promotes film assembly from weak polyanions such as HA, ALG, and silk fibroin through protonation and self-association. In contrast, a few examples have reported electrodeposition strategies where an increase in the charge density of weak polyelectrolytes was sought. In that case, proton and hydroxide ion gradients generated by electrolysis in aqueous solutions induce higher ionization degrees and/or acid deprotection of the weak polyelectrolytes, enabling their complexation and film precipitation with oppositely charged polymers [23][24][25] and multivalent MoO_4^{2-} ions [26].

(ii) The complexation of weak polyelectrolytes with multivalent ions leading to their film precipitation is another prominent electrodeposition strategy. The generation of the crosslinking ions is achieved either by the dissolution of oxide precursors [27] or by direct oxidation to the relevant cations [28]. Anodic electrolysis has been used to dissolve $CaCO_3$ (respectively, $Cu_2(OH)_2CO_3$), yielding Ca^{2+} and Cu^{2+} ions near the electrode and allowing the assembly of ALG films by complexation [27][29]. Allowing work to be carried out at milder oxidation potentials, the electrochemical generation of multivalent cations has been developed with Cu^{2+}, Fe^{3+}, and Ru^{2+} cations, allowing complexation and film deposition with ALG, Chitin, CHI, and PAA modified with terpyridine groups [29][30][31].

In situ polymerization on electrodes by electrochemical reaction (electropolymerization) is another popular strategy that can ensure the elaboration of functional films. Aniline, dopamine, carbazole, and vinylpyridine monomers and their derivatives have been extensively studied for use in the electropolymerization of weak polyelectrolyte films under oxidative potentials. The resulting films can combine electron conductivity with weak polybase characteristics, conferring them with doping, complexation, and molecular imprinting abilities. A large number of recent studies have used these appealing properties to design sensors, energy devices, light-emitting devices, and electrochromic and “smart” electrodes, as described in studies [30][31][32][33][34]. The presence of aromatic cycles in such polymers also confers them with a hydrophobic character and self-assembling properties that enable them not only to act as weak polyelectrolytes but also as structure directing nano-units.

Contrary to electropolymerization, electro-coupling relies on non-propagative covalent couplings induced electrochemically between functional nano-units bearing adequate moieties. To date, the alkyne-azide “click” cycloaddition *(i)* and the dimerization of 9-alkylcarbazoles *(ii)* are the most studied systems enabling the electrosynthesis of polymer and hybrid films [28][35].

(i) The alkyne-azide “click” cycloaddition, specifically leading to covalent triazole bonds under mild and aqueous conditions, is typically catalyzed by Cu(I) ions. The generation of these ions, which are unstable in water, by the electrochemical reduction of Cu(II) ions (using −0.3 V vs. Ag/AgCl), induces and confines the “click” coupling reaction in the vicinity of electrodes [28]. This film assembling strategy has been carried out with various weak polyelectrolytes (PAA, PAH) grafted with alkyne/azide groups, yielding covalently reticulated single-polyelectrolyte coatings that reversibly swell in response to post-assembly pH changes [28]. Accordingly, the covalent incorporation of fluorescent bis-pyrene moieties

in such coatings composed of PAA evidenced the buffer behavior of the film, which maintained its internal pH at a value close to 3.5, while the environmental pH was changed from pH 4 to 7 [36]. In most recent examples, this click electrosynthesis approach has been combined with the electropolymerization of PANI [37] and adapted to hybrid nano-units, leading to pH-responsive nanostructured coatings with cargo encapsulation/release abilities [38].

(ii) Various organic and inorganic nano-units have been substituted in the 9- position of 9-alkylcarbazoles, enabling their covalent coupling by the electrochemical dimerization of carbazole moieties in acetonitrile [20]. This unique behavior was attributed to the selective activation of 3- and 6- positions of carbazoles and exhibited sensitivity to the potential applied: +1.0 V (vs. Ag/AgCl) favored more dimerization while +1.2 V also led to oligomerization [39]. The obtained organic or hybrid films benefited from internal layered structures and unlocking optical limiting applications [40][41]. Following this concept, recent efforts to potentialize other electrochemical dimerization reactions for functional films have been reported, opening promising perspectives for multifunctional systems [42].

2. Layer-by-Layer Films and Vectors from Weak Polyelectrolytes

Over the past few decades, the Layer-by-Layer (LbL) strategy has enabled adsorbed polyelectrolyte films with unprecedented functional versatility. This approach, pioneered by Iler in 1966 and developed by Decher from 1991 [43], relies on the sequential adsorption of complementary chemical species (including polyelectrolytes), yielding coatings with controllable thickness whose growth can be driven by a range of interactions, including electrostatics, H-bonding, molecular recognition, and coordination[44]. LbL films have thus attracted attention relating to their use in Nanoarchitectonics, owing to their potential for assembling functional nano-units on a large variety of substrates and topologies [45].

2.1. Layer by Layer Films

Weak polyelectrolytes of both synthetic and natural origin have been incorporated in LbL films, influencing their structure and composition [46], as well as their response to stimuli. Such films have thus been readily employed as biointerfaces and platforms with tunable mass transport properties [44]. Accordingly, adjusting the charge density and conformation of weak polyelectrolytes via pH and ionic parameters during (*i*) and after (*ii*) assembling multilayer films has been exploited:

(i) Decreasing the charge density of weak polyelectrolytes, either by decreasing their ionization degree of by increasing charge screening by salts, typically favors coiled conformations. In the case of LbL film buildups relying on electrostatically driven interactions, assembly conditions with smaller polyelectrolyte charge densities result in less crosslinks and more loops between the layers, leading to larger thickness increments at each adsorption step of weak polyelectrolytes compared to conditions where an extended conformation of the polyelectrolyte is favored (corresponding to higher charge density). Accordingly, the growth mechanism of a polydiallyldimethylammonium chloride (PDADMAC)/ALG multilayer changed from linear to exponential behavior when the assembly pH value was changed from pH 10 (where both polyelectrolytes are ionized) to pH 3 (where ALG is protonated) [47]. It follows that the multilayer thickness, chemical composition, mechanical properties, permeability, and adhesion are largely determined by pH and ionic parameters during the LbL deposition process. Therefore, the swelling of PAH/PAA and PLL/HA multilayers in aqueous media increases when the charge density of their weak polyelectrolytes decreases, a behavior attributed to the reduced ionic crosslink density and to loopy chain conformations [48][49]. The same phenomenon controls the hardness and elastic modulus of PAH/PAA multilayers [50], leading to lower values being obtained for PAH(pH 7.5)/PAA(pH 3.5) when both polyelectrolytes have a smaller charge density than for PAH(pH 6.5)/PAA(pH 6.5). Consequently, the assembly pH has been demonstrated to influence the drug transport mechanism in PAH/PAA multilayer films [51].

(ii) Post-assembly changes in pH and ionic parameters have been extensively studied as external stimuli to weak polyelectrolyte multilayers with respect to their response in thickness, porous structure, and encapsulation/release changes [44][52]. For LbL films relying on electrostatic interactions, decreasing the charge density of weak polyelectrolytes, either by post-assembly pH changes or by increasing the solution ionic strength, resulted in the swelling of the films [53] and eventually their dissolution. Accordingly, swelling coefficients of, respectively, up to 5-fold and 8-fold were found for PLL/HA multilayers subjected to ionic strength [54] and pH [55] stimuli. The swelling process was accompanied by structural changes in multilayer films, such as the emergence of holes in PLL/HA films when the NaCl concentration was changed from 0.15 M to 0.48 M [55] and the growth of pores in (PEI/PAH)/PAA films after the post-assembly pH was decreased to pH 2 [56]. The potential of such porous coatings was tested for designing slippery liquid-infused porous surfaces [56][57]. Concurrently, the modulation of the mass transport properties of weak polyelectrolyte multilayer films by post-assembly treatment has attracted much attention [58], leading to systems with tailored functions, including ionic current rectification [59], enhanced Li^+ conductivity [60], and filtration [61]. Conversely, not only the ionic strength but also the nature and valence

of the salt used as the post-assembly stimulus were found to modulate the properties of weak polyelectrolyte multilayers: exposing a PAH/PAA multilayer film to various concentrations and type of metal ions enabled changing their pore sizes from 54 nm to 1.63 µm. This behavior was ascribed to phase separation in the film induced by metal-ion coordination with PAH [62], and was used to trap silver ions in the film to selectively detect methylmercaptan gas concentrations as low as 20 ppb [63].

2.2. Colloidal Systems Based on LbL Multilayers of Weak Polyelectrolytes

The LbL film deposition process has been adapted to colloidal substrates, providing an alternative to polymer self-assembly for designing nanocarriers, including hollow capsules[64]. This method requires a sacrificial template (such as melamine formaldehyde, polystyrene, poly(methacrylic acid), silica, calcium carbonates, hydrogel microspheres), which needs to be removed by calcination or etching, and can be used to develop biocompatible systems with encapsulated drugs. Nevertheless, such nanocarriers remain very efficient when applied to catalysis [65] and energy storage [66] or as antioxidants [67]. Recent development has gradually evolved from prominently using synthetic strong polyelectrolytes to weaker ones, including using PAH, PEI, PLL, and poly(N-isopropylacrylamide) (PNIPAM) as polycations, as well as PMAA and PAA as polyanions. The corresponding colloidal systems benefited from the better control and fine tuning of intermolecular forces by pH modulation [68], ionic strength [69], and temperature [70]. Biosourced charged species such as dextran [71], CHI [72], bovine serum albumin [73], and DNA have also been used as functional units to encapsulate and deliver genetic cargo [71] and even co-deliver a drug [74].

With their high degree of functionality as well as their versatility, weak polyelectrolytes have been widely used to develop new tools for precision medicine in order to simultaneously address precision diagnosis and precision therapy. The use of polymer nanocarriers offers three topological regions which can allow functionalization: the inner cavity, the surrounding shell, and the external surface exposed to the microenvironment. Polyelectrolytes have consequently led to the development of nanocarriers for applications in imaging and for therapeutic purposes. The on-demand release of cargo can be achieved by external or endogenous stimuli and provide a variety of ways to control the dosage, time, and location of release [75]. Temperature stands as a prominent stimulus, allowing changes in the hydration degree or layer organization which can be exploited for permeability changes and the release of the carrier [69]. Thermal responses can also be achieved by the use of inorganic nanoparticles such as gold [76], silver [77], and nanodiamond [78]. Under light irradiation, the local heating of nanoparticles can induce the rupture of the polymer shell or the modification of its permeability. This has been particularly demonstrated with polyelectrolytes such as PAH and poly(styrenesulfonate)(PSS) embedded with gold nanoparticles. Upon local heating by the gold nanoparticle, cargos retain their biological activities, although their diffusion within the cell is slightly decreased [79]. Ultrasounds can also be exploited as external stimuli to control the rupture of polyelectrolyte capsules. Ultrasounds are commonly used in imaging and ablative therapy. In the latter case, the mechanical deformation induced causes the bursting of the capsules, thus releasing their payload [80]. Magnetic fields have also been used to trigger the release of polymer capsules [75]. With the combination of magnetic nanoparticles such as iron oxide and electromagnetic fields of various frequency and power, different mechanisms can be induced. At low frequencies, a non-heating process can preferably be used to preserve tissues as well as a bioactive payload such as enzymes or DNA [81]. Meanwhile, with higher-frequency magnetic fields, a high increase in the local temperature induces the destruction of cellular and subcellular structures [82].

3. Gels and Vectors Based on Weak Polyelectrolytes Complexes

Processing weak polyelectrolyte into gels and vectors has been a very active research field for the past few decades. A range of approaches yielding prominently biosourced single-polyelectrolyte gels have been proposed based on precipitation/coagulation through H-bonding, hydrophobic interactions, and crosslinking through reactions with either ionic or covalent crosslinkers [83][84]. Recent works are highlighted for further reading on this topic [85][86][87]. In contrast, processing polyelectrolyte complexes formed from the spontaneous entropy-driven complexation of polyanions and polycations [88] into gels and membranes is a method that has only been developed recently [89][90].

3.1. Gels Based on Weak Polyelectrolyte Complexes

Polyelectrolyte complexation by the electrostatic association of oppositely charged polymers results in phase separation from the solution through the formation of either solid precipitates or liquid complex coacervates. Although fundamental studies to elucidate the exact nature and behavior of these different complexes are still ongoing [91][92][93], many recent studies have focused on using polyelectrolyte complexes for applied materials, including vectors and gels. Adjusting the density of electrostatic crosslinks in polyelectrolyte complexes is critical to ensure their material processability. In that context, processable gels made of PDADMAC/PMAA complexes have been developed by screening polyelectrolytes'

charge densities with high-ionic-strength solutions (e.g., 2.5 M NaCl) followed by compaction through ultracentrifugation [94]. The obtained gels are named “saloplastics” or “compacted complexes of polyelectrolytes (COPEC)” and correspond to the blending of polyelectrolyte chains at the molecular level, where charges are reversibly compensated either intrinsically between polyelectrolytes or extrinsically with counterions. This gel elaboration approach has been successfully applied to several other weak polyelectrolytes, including PAA, ALG, PAH, and CHI, yielding self-healing gels with applications as biomaterials and catalyst supports. The compaction process by ultracentrifugation initially represented a bottleneck for the larger-scale production of COPECs, triggering the development of alternative synthesis approaches based on simple centrifugation [95], injection [96], and sedimentation [97]. The properties of the resulting saloplastics vary greatly with the charge density and balance of their polyelectrolyte components both during and after synthesis, typically adjusted by pH and ionic force parameters. It follows that COPECs containing weak polyelectrolytes are dynamic stimuli-responsive materials that enable adjusting a large range of properties, including mechanical properties, composition, porosity, and sorption/release ability**.**

Polyelectrolyte complexes have also been processed into functional membranes by aqueous phase separation [89]. Briefly, polyelectrolytes are first blended at the molecular level in an aqueous solution where the pH or ionic strength values do not allow their complexation, and the subsequent change in that parameter enables the precipitation of polyelectrolyte complex membranes [89]. This approach provides control over membrane pore size and structure in ways analogous to traditional non-solvent-induced phase separation. The synthesis pathway based on pH stimulus was developed with mixtures of weak and strong polyelectrolytes, yielding membranes made from PEI/poly(styrenesulfonate)(PSS), PAH/PSS, and PDADMAC/PAA systems for use in nanofiltration and micropollutant removal [89][98][99].

3.2. Weak Polyelectrolyte Complexes for Pharmaceutical Vectorization

The emergence of new diseases and strains of micro-organisms requires constant evolution and research in the field of drug delivery and nanomedicine. The most straightforward strategy adopted by the pharmaceutical industry has been the synthesis of new drugs capable of combating these pathologies. This, in turn, triggers the demand for appropriate drug carriers that can be effectively loaded with these drugs and protect them until they are administered and delivered. Although great progress has been made in the development of new drug carriers, including weak polyelectrolyte complex systems, in recent years [100][101][102], there are still systems such as water-insoluble drugs that these strategies fail to encapsulate efficiently [103].

Polyelectrolytes used for pharmaceutical research must meet the requirements of biocompatible polymer systems and be suitable for use as carriers of active substances. In this sense, the use of weak biosourced polyelectrolytes such as chitosan or charged chitosan derivatives such as glycol-chitosan or N-dodecylated chitosan as polycations and natural polysaccharides such as alginate, pectin, or carrageenan as polyanions has received much attention in the design of polyelectrolyte complexes for drug delivery due to their excellent bioavailability and biodegradability [104][105][106]. In addition to the difficulty of efficiently encapsulating actives with poor water solubility, other challenges in drug delivery include (i) the development of drug delivery systems that provide the sustained release of the drug within a desired therapeutic window to ensure efficacy; (ii) non-specificity, toxicity, and lack of localized administration strategies for certain treatments such as chemotherapeutics; (iii) scalability; and (iv) the development of harmonized regulatory guidelines for the manufacture of nanotechnology products that require contact with the human body. All the challenges cited above make the design of drug delivery systems much more complex than that of non-biological material release. As a result, the construction of efficient drug delivery carriers is usually achieved by assembling several components, each with its own role in the unified delivery function. An interesting way to achieve this is to use nanoarchitectonics approaches to develop biocompatible weak polyelectrolyte complexes formed in water with stimuli-responsive properties. The charges on weak polyelectrolytes are dynamic, causing polymer chains to adopt different equilibrium conformations even with relatively small changes to the surrounding environment [107]. For instance, phosphonium polymer has been demonstrated to be able to control the physical and biological properties of sodium hyaluronate/phosphonium polyelectrolyte complexes [108]. The network swelling and therefore drug release rates of these systems can be controlled by varying the concentration of salt in the medium. Thus, while more hydrophilic molecules such as adenosine-5′-triphosphate can be released over 1–2 days, the sustained release of fluorescein and diclofenac over 60 days can be achieved, which is much longer than that previously reported for polyelectrolyte complexes [109][110][111]. On the other hand, only phosphonium polymers, including phenyl substituents, have shown a low cytotoxicity. Another example of improved control of drug release is in chitosan/alginate biocompatible pH-responsive polyelectrolyte complexes, which were developed as less invasive delivery systems for oral insulin administration [112].

Nanoarchitectonics approaches to develop drug reservoirs with collective nanosystem functionality have been used to address the clinical limitations of premature drug release and tumor non-specificity. For instance, a novel

superparamagnetic chitosan-based nanometer-sized colloidal polyelectrolyte complex integrating the water-soluble polymeric prodrug poly(L-glutamic acid)-SN-38 (PGA-SN-38) was designed using a one-shot manufacturing process to efficiently deliver SN-38 [113]. The combination of these systems enhanced drug solubility and tumor-targeting accumulation, thereby improving the therapeutic efficacy against colorectal cancer in vivo (tumor suppression rates of up to 81%). Interestingly, although the prepared material exhibited controlled release at pH 7.4, a burst release of the drug was observed during the first 12 h, which was attributed to the dissociation of the PGA-SN-38 prodrug from the nanopolyelectrolyte complexes due to the partial instability of the chitosan-based nanocomplexes in phosphate-buffered saline medium. The standardization and scale-up of polyelectrolyte complexes obtained through bottom-up methodologies is still a great challenge and necessitates carrying out arduous experimentation, since it depends on multiple intrinsic and extrinsic variables [114]. A means to improve the main problems generated during polyelectrolytic complexation, such as obtaining large particle sizes and highly polydisperse systems, is to employ top-down methods instead [115]. However, top-down methods such as high- or ultra-high-pressure homogenization also have some disadvantages, such as the chemical degradation of the material by excessive energy applied during the disaggregation process [116]. Nevertheless, the great benefit of these techniques is that the conditions implemented can be easily reproduced and scaled-up to industrial level. Thus, the polyelectrolyte complexes developed under these methodologies are suitable for easy technology transfer. Finally, the opportunities offered by nanotechnology in the health sector are also accompanied by challenges in the regulation of these products. One example of these concerns is the modification of the physicochemical properties of nanomaterials, which can lead to altered toxicity, solubility, and bioavailability profiles [117][118][119]. In addition, evidence regarding the potential safety issues of synthetic polymers appears to be the main driver of research on the use of natural polysaccharides in the application of more recent responsive polyelectrolyte complexes as drug delivery systems. Furthermore, the existence of strong regional differences in the regulation of nanomedicines confirms the need for the harmonization of information requirements for nanospecific properties.

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