How to Cite: Bekturov, E.A., Moustafine, R.I., Kudaibergenov, S.E., & Khutoryanskiy, V.V. (2022). Interpolymer Complexes of Synthetic, Natural and Semi-Natural Polyampholytes: A Review. *Bulletin of the University of Karaganda – Chemistry, 107(3), 14-34.* https://doi.org/10.31489/2022Ch3/3-22-9

SPECIALTY POLYMERS IN OIL INDUSTRY, BIO-, NANOTECHNOLOGY AND MEDICINE

Review Received: 24 May 2022 | Revised: 15 June 2022 | Accepted: 1 July 2022 | Published online: 18 July 2022

UDC 541.64+678.744 https://doi.org/10.31489/2022Ch3/3-22-9

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Interpolymer Complexes of Synthetic, Natural and Semi-Natural Polyampholytes: A Review

This review is focused on synthetic, natural and semi-natural polyampholytes and their ability to form interpolymer complexes with other polyelectrolytes and non-ionic polymers. It provides definition, classification and overview of physicochemical properties of polyampholytes. The conformation and phase behaviour of intrinsically disordered proteins and semi-natural polyampholytes derived from aminoacids is discussed. The ability of synthetic, natural and semi-natural polyampholytes to form interpolymer complexes with water-soluble polymers is considered. Most of the research in this area is focused on interpolyelectrolyte complexes of polyampholytes with oppositely charged polyelectrolytes; however, there are also studies demonstrating the formation of hydrogen-bonded complexes. The nature of the complexation is often affected by solution pH and also isoelectric point of polyampholytes. The complexation between polyampholytes and other polymers may lead to formation of colloidal dispersions (nano- and microparticles), liquid-liquid phase separation (called complex coacervation), fully soluble polycomplexes or physically cross-linked gels. A substantial body of studies in this area was focused on the complexes formed by proteins. Application of interpolymer complexes formed by polyampholytes in biotechnology, medicine, encapsulation technologies, separation science, biocatalysis, food science and pharmaceutics is discussed.

Keywords: polyampholytes, polypeptides, proteins, intrinsically disordered proteins (IDPs), intra-macromolecular complexes (intra-MMC), inter-macromolecular complexes (inter-MMC), interpolyelectrolyte complexes, drug delivery, complex coacervation, gelatin.

Content

Esen Bekturov is an outstanding Kazakh polymer scientist, Doctor of chemical sciences, Professor, Academician of the Kazakh National Academy of Sciences, Laureate of Kazakh State Prize, and Honored science worker of the Republic of Kazakhstan. His achievements in polymer science have been recognized by numerous awards and honors, including the Al-Khorezmi International science and technique festival, the N. Bohr UNESCO gold medal, National Independent Prize "Tarlan" in the nomination of science, K.I. Satpayev Prize for the development of specialty polymers for application in petrochemistry and nanotechnology. Prof. Esen Bekturov has about 950 papers and reviews, including more than 100 papers published in English in peer reviewed journals. He is author and coauthor of 35 books published in Kazakhstan, Russia, Poland, Germany, and Japan. For the contribution to development of science in Kazakhstan he was awarded by the Medals "For Labor's Heroism", "Labor's Veteran", and "10 Years of the Constitution of the Republic of Kazakhstan".

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Vitaliy Khutoryanskiy is a Professor of Formulation Science at Reading School of Pharmacy, University of Reading (UK). Prof Khutoryanskiy has researched broadly in the area of new polymers, nanomaterials and biomaterials for pharmaceutical, biomedical, agrochemical and food applications, with a particular emphasis on transmucosal drug delivery, mucoadhesive and mucus-penetrating nanocarriers and hydrogels. He was the recipient of the 2012 McBain Medal from the Society of Chemical Industry and Royal Society of Chemistry (UK), was elected as a Fellow of the Royal Society of Chemistry in 2015, received Sentinel of Science Award from Publons in 2016, was selected as a PhD supervisor of the Year by FindAPhD in 2020, and was chosen to deliver Innovative Science Award Lecture by the Academy of Pharmaceutical Sciences (UK) in 2022. He has published >200 original research articles and reviews, indexed by Scopus, edited 5 books and filed 3 patent applications.

List of abbreviations

BPA: blockpolyampholyte
BSA: bovine serum albumin
CS: chitosan sulfate
DAA: diallylamine
DNA: deoxyribonucleic acid
IA: itaconic acid
LPEI: linear poly(ethyleneimine)
MA: maleic acid
2M5VPy-AA: 2-methyl-5-vinylpyridine-acrylic acid
MDAA-MA: N-methyldiallylamine-maleic acid

MIP: Molecularly-imprinted polyampholyte
NaPSS: poly(styrene sulfonate sodium salt)
NIPAM: N-isopropylacrylamide
PAA: poly(acrylic acid)
PDMDAAC: poly(N, N-dimethyl-N, N-diallylammonium chloride)
PDMAPS: poly[3-dimethyl(methacryloyloxyethyl ammonium propane sulfonate)]
PMPC: poly(2-(methcaryloyloxy)ethylphosphorylcholine
PAMPS: poly(2-acrylamido-2-methyl propane sulfonic acid)
PDMAPAA-Q: poly(3-acrylamidopropyltrimethyl ammonium chloride)
PEG: poly(ethylene glycol)
PVBTMAC: poly(vinylbenzyltrimethylammonium chloride)
VI: N-vinylimidazole
VCL: N-vinylcaprolactame

Review Plan

Inclusion and Exclusion Criteria: The present review is devoted to interpolymer complexes of synthetic, natural and semi-natural polyampholytes with polyelectrolytes, proteins, DNA, and non-ionic polymers.

The review data mostly cover the publications from 1949 to 2022. However, some old literature sources dated on 1896, 1929, 1934 are also cited. In addition to a survey of the prevalent literature, most attention is paid to the authors' own research into the field of polyampholytes and interpolymer complexes since 1981. Articles in the relevant area were searched and analysed from the databases like Scopus, Web of Science, PubMed etc. along with other online scientific search engines (Google Scholar). The keywords used for the search were: "polyampholytes", "polypeptides", "proteins", "intrinsically disordered proteins", "DNA", "polyelectrolyte complexes", "intra- and inter-macromolecular complexes". No statistical methods were used in this review.

Introduction

The analysis of literature published over the past half century shows that the number of publications on polyampholytes generally continues to increase each year, starting from 1970. Figure 1 presents the data on the number of publications and citations in this area.

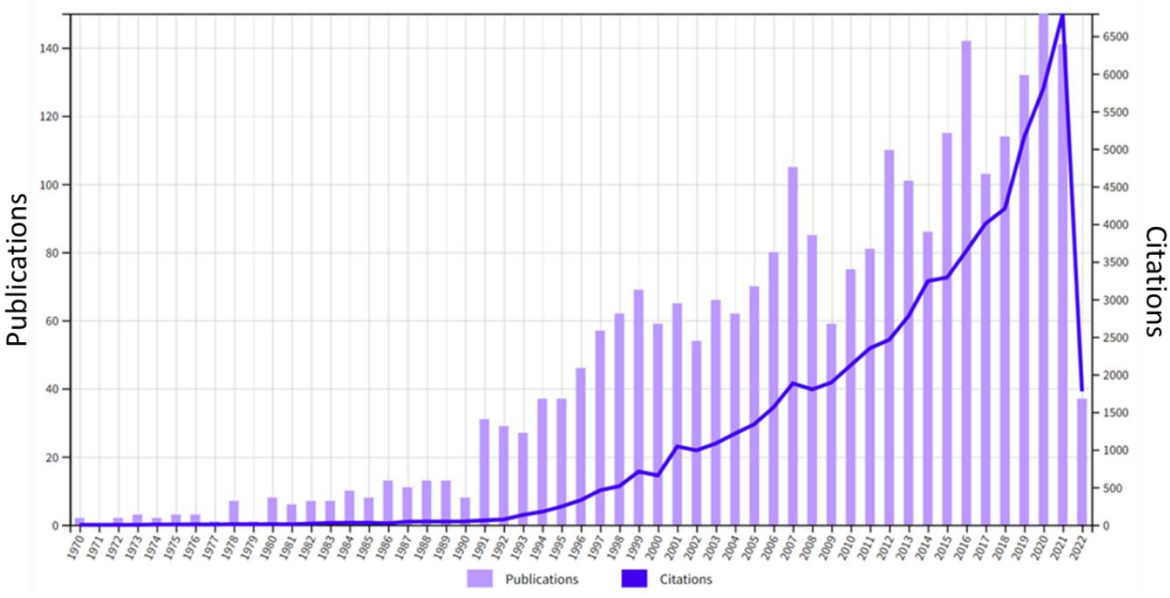


Figure 1. Progress of publications and citations on polyampholytes according to the data of Web of Knowledge, generated using the keywords "polyampholyte*" or "amphoteric polymer*".

This review aims to present the analysis of literature on synthetic, natural and semi-natural polyampholytes, focusing on their ability to form complexes with various water-soluble polymers of ionic

and non-ionic nature. Examples of applications of these complexes in different areas are also presented and briefly discussed.

1 Synthetic, natural and semi-natural polyampholytes

According to IUPAC terminology [1], ampholytic polymer is defined as a polyelectrolyte consisting of macromolecules that contain both cationic and anionic groups, or corresponding ionizable groups. An ampholytic polymer (synonym is polyampholyte) in which ionic groups of opposite signs are incorporated into the same pendant groups is called, depending on the structure of the pendant groups, a zwitterionic polymer, polymeric inner salt, or polybetaine.

The intensive development of research on polyampholytes since 1950s included the pioneering studies of Alfrey, Morawetz, Fuoss [2–4], Katchalsky [5–7], Ehrlich, Doty [8]. The interest to this type of polymeric materials was due to several reasons. One of the reasons is the similarity of the hierarchical structure of amphoteric macromolecules to structural organization of proteins [9, 10]. Second is the possibility of modeling protein folding using synthetic polyampholytes [11]. Third is the advances in the synthesis of amphoteric polypeptides [12–17] based on amino acids. Fouth is the possibility of preparing semi-natural polyampholytes by modification of natural building blocks [18, 19].

Proteins are amphoteric biopolymers, which from polymer science point of view, represent copolymers consisting of aminoacid (peptide) sequences (–NH–CHR–CO–), where their side groups (pendant groups) have acidic, basic, hydrophilic or hydrophobic moieties while the terminal groups are capped with carboxylic and amine groups. However, proteins have unique structure, properties and functions that can only be achieved in a living organism [20]. The number of possible conformations of globular proteins is exponentially dependent on the number of aminoacid residues in their chain. Some specific functions of these biopolymers can be successfully modeled using synthetic polyampholytes.

In the last years, mimicking the behavior of biopolymers through amphoteric macromolecules became the subject of numerous discussions [21–24]. Among the natural polyampholytes the intrinsically disordered proteins (IDPs) (also known as intrinsically unstructured proteins) attracted a great interest [25–29]. The IDPs can adopt random coil, pre-molten globule, molten globule, and folded conformations in aqueous solutions that can also exhibit transitions between each other [22]. The stimuli-responsive phase behavior of IDPs is governed by relationships between the information encoded in their aminoacid sequences and ensembles of conformations [30]. Synthetic polypeptides derived from aminoacids belong to semi-natural polyampholytes. Insertion of amino acids into the structure of synthetic polymers is an effective tool for the design of different non-biological bio-mimetic polyampholytes with unique physicochemical properties [12–19].

Synthetic amphoteric macromolecules comprise combinations of weak acid-weak base, strong acid-strong base, strong acid-weak base or weak acid-strong base monomers. Conditionally they can be classified as annealed, quenched, and betainic (or zwitterionic) types [31–40]. Annealed polyampholytes have acid-base monomers that are ionized depending on pH, while quenched polyampholytes with strongly charged cationic and anionic monomers retain their charges independently on pH. The “semi-annealed” or “semi-quenched” polyampholytes are amphoteric macromolecules formed with weak acid/cationic or weak base/anionic monomeric units. Betainic (or zwitterionic) polyampholytes are macromolecules with identical number of acid-base (or fully charged anionic-cationic) species in the same monomer units. Polybetaines may be grouped into polycarboxyl-, polysulfo-, and polyphosphobetaines [35, 36]. The macromolecules formed with the compensation of the cationic-anionic monomer pairs without counterions also belong to zwitterionic polymers [37] or polyampholytic ionic liquids [41, 42]. In the current literature the terms “zwitterionic polyampholytes”, “polybetaines”, “zwitterionic polyelectrolytes”, “polyzwitterions” are also widely used. Figure 2 illustrates the examples of synthetic polyampholytes with different chemical structures.

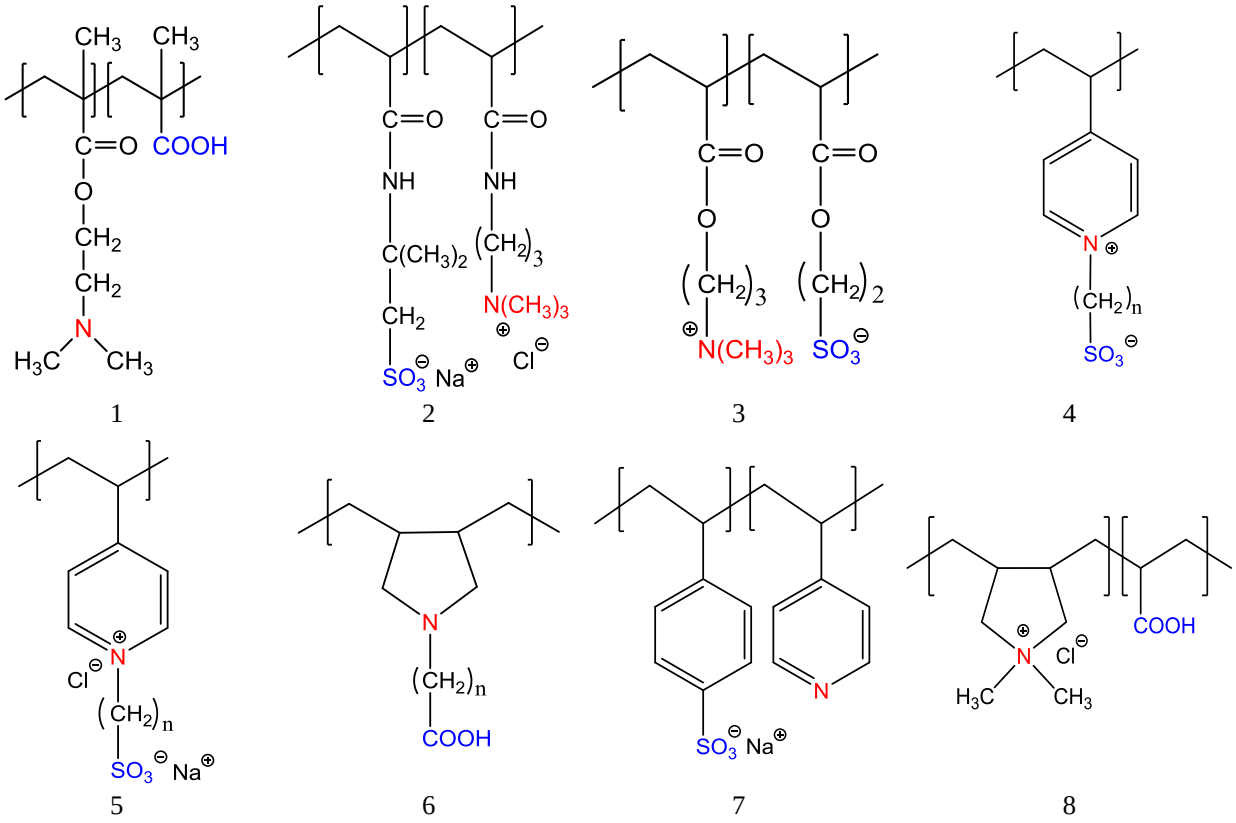
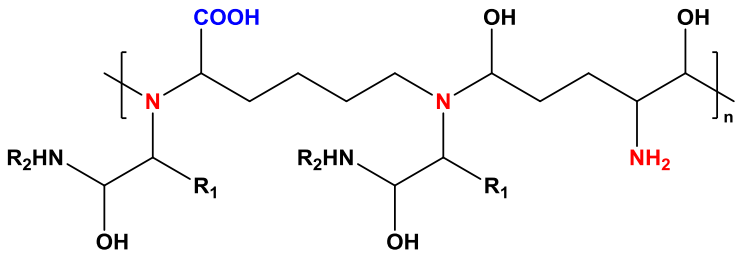
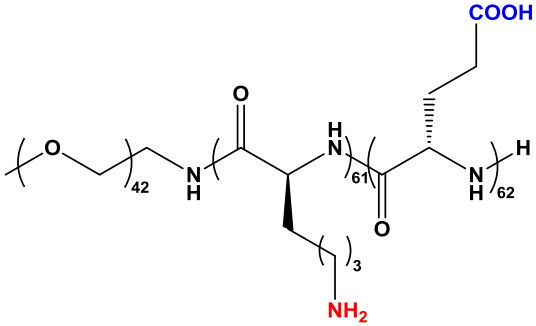


Figure 2. Repeating units of annealed (1), quenched (2), zwitterionic (3, 4), quenched betainic (5), annealed betainic (6) and self-annealed (or self-quenched) (7, 8) polyampholytes

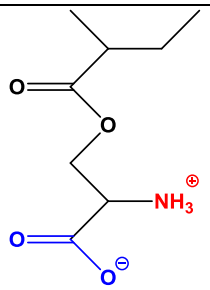
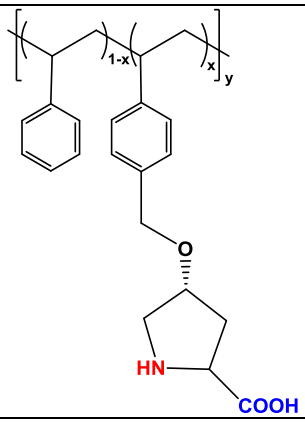
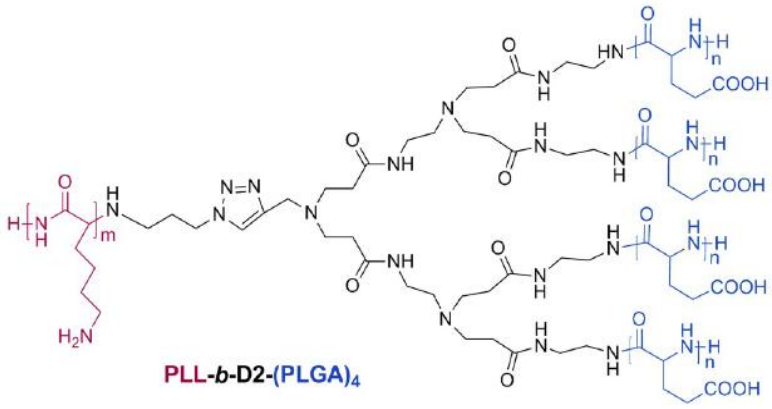
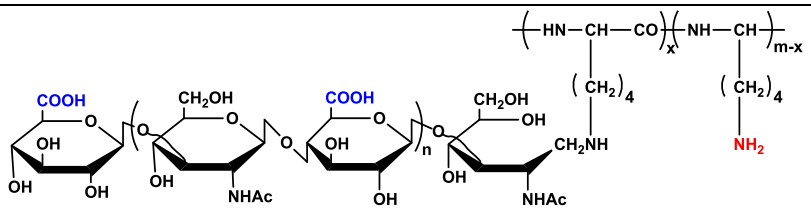
Table 1 provides some examples of amphoteric polypeptides based on L-lysine, L-serine, L-proline, and L-glutamic acid.

Table 1

Examples of amphoteric polypeptides

No.	Structural units of polypeptide-based polyampholytes	Name	Refs
1	2	3	4
1		Alternating amphoteric polypeptide obtained *via* the Ugi reaction	[43]
2		Triblock amphoteric co-polymer derived from PEO_{42}–$PLLys_{61}$–$PLGlu_{62}$	[44]

Continuation of Table 1

1	2	3	4
3		Poly(L-serinyl acrylate)	[45]
4		Styrene copolymers containing L-proline functionality	[15]
5		Linear-dendron-like polyampholyte, poly-(L-lysine)-*b*-D2-poly(L-glutamic acid) [PLL-*b*-D2-(PLGA)$_4$], where D2 is the second generation of poly(amido amine)	[46]
6		Comb-type amphoteric copolymers composed of a poly(L-lysine) backbone and hyaluronic acid side chains	[47]

Semi-natural polyampholytes can be prepared by modification of natural polysaccharides, such as chitosan, cellulose, starch, gellan, alginic acid, by introducing either carboxylic (sulfo) or amine (ammonium) groups or both into their macromolecules [48–58]. For instance, to introduce sulfonate or carboxylic groups into chitosan chain it was modified by 1,3-propane sultone, 5-formyl-2-furansulfonic acid sodium salt, 2-formyl benzene sulfonic acid sodium salt, 4-formyl-1,3-benzene disulfonic acid disodium salts [58] or sodium alginate [18]. An amine derivative of gellan gum, exhibiting polyampholyte character, was obtained by functionalizing the polysaccharide backbone with pendant ethylenediamine moieties [59]. The physicochemical properties of amphoteric macromolecules were characterized by spectroscopy, colorimetry, chromatography, and rheological methods. Quaternized gellan derivatives were prepared by grafting N-(3-chloro-2-hydroxypropyl)-trimethyl ammonium chloride onto gellan's hydroxyl groups under alkali conditions at different gellan/N-(3-chloro-2-hydroxypropyl)-trimethyl ammonium chloride molar ratios [57].

2 Interpolymer complexes of synthetic and natural polyampholytes

In early 1970th, V.A. Kabanov et al. [59], E. Tsuchida et al. [60] and E.A. Bekturov et al. [61] started a new scientific direction, so-called interpolymer complexes (IPCs). IPCs are the products of interactions of two complementary macromolecules stabilized by cooperative ionic and/or hydrogen bonds. The specific interactions between macromolecules are important in biological systems and these assemblies are controlled by intra- and inter-macromolecular (intra-MMC and inter-MMC) complexation [60]. The latest developments in the area of interpolymer complexation via hydrogen bonding are presented in the book entitled "Hydrogen-bonded interpolymer complexes. Formation, structure and applications", representing a collection of original and review articles written by recognized experts from Germany, Greece, Kazakhstan, Poland, Romania, Russia, UK, Ukraine, and the USA [62]. This book highlights many important applications of interpolymer complexes in stabilization of colloidal systems, ecology, biotechnology, nanotechnology, medicine, and pharmaceutics.

Formation of intra-MMC and inter-MMC complexes with participation of synthetic polyampholytes was reviewed in [63]. The complexation between statistical polyampholyte derived from copolymer of 2-methyl-5-vinylpyridine-acrylic acid (2M5VPy-AA) and poly(acrylic acid) (PAA), was first studied by V.A. Kabanov et al. [64]. It was found that the common cooperative system with ionic and hydrogen bonds between the 2M5VPy-AA and PAA is responsible for inter-MMC formation (Fig. 3).

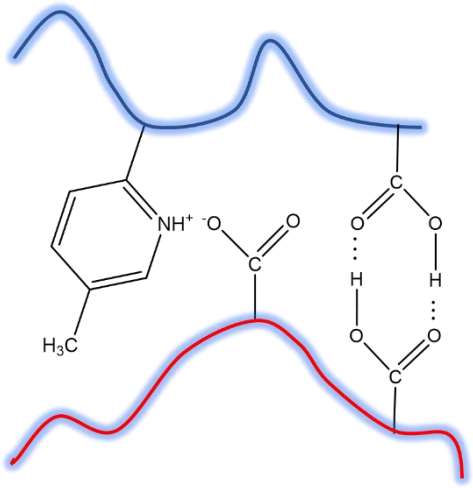


Figure 3. Schematic representation of formation of inter-MMC between copolymer of 2M5VPy-AA and PAA

The competition between the intra-MMC and inter-MMC was established in the mixture of N-methyl-diallylamine-maleic acid (MDAA-MA) and poly(N,N-dimethyl-N,N-diallylammonium chloride) (PDMDAAC) at pH = 3.9 corresponding to the isoelectric point (pH_{IEP}) of alternative polyampholyte [65]. As revealed from ^{13}C NMR and Raman spectra, some parts of carboxylate anions of MDAA-MA are involved in the formation of intra-MMC while some other parts form inter-MMC between carboxylate anions of MDAA-MA and quaternary nitrogen atoms of PDMDAAC.

Alternating copolymers of N, N-dimethyldiallylammonium and alkyl (or aryl) derivatives of maleamic acids were used to form complexes with PAA and poly(styrene sodium sulfonate) (NaPSS) [66]. It was found that the polyelectrolyte-polyampholyte complexes form compact core-shell particles and preserved in aqueous solution as a result of liberated edges from the carboxylic groups of polyampholyte.

The complexation of amphoteric dendrimers with linear and crosslinked anionic and cationic polyelectrolytes was studied by Zansokhova et al. [67, 68]. The efficiency of binding of polyampholyte dendrimers by oppositely charged linear or crosslinked polyelectrolytes was determined by the competition between intra-dendrimeric zwitterions and interionic salt bonds of functional groups of dendrimers and polyelectrolytes.

Formation of both intra-MMC and inter-MMC stabilized by cooperative ionic bonds is mostly specific for block polyampholytes [69–72]. It was found that the phase diagram of BPA-cationic polyelectrolyte system is dependent on the inter-MMC concentration and pH and may result in the formation of solution, gel or precipitate (Fig. 4).

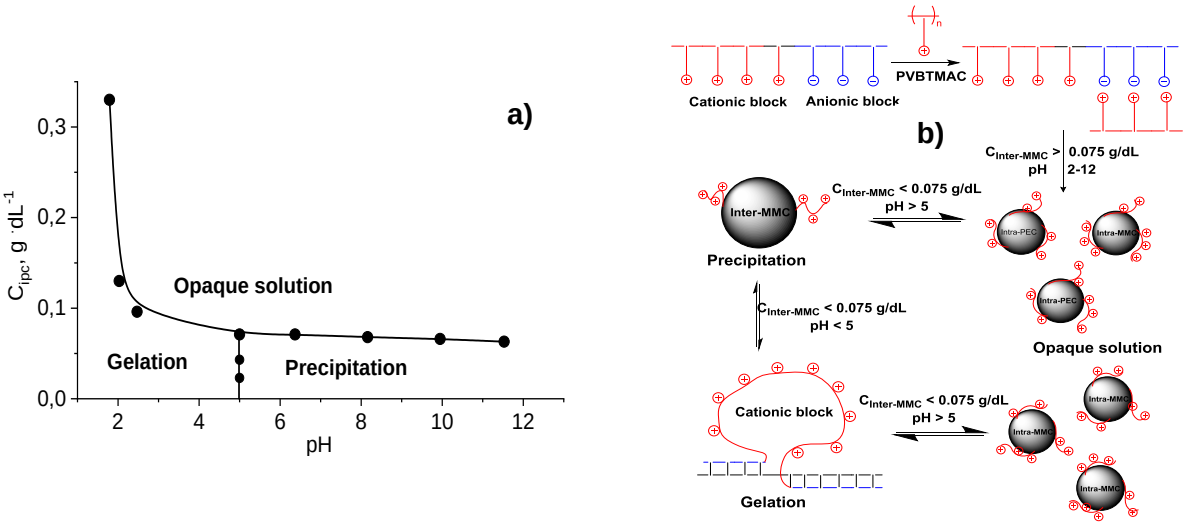


Figure 4. Phase diagram of inter-MMC composed of BPA and cationic polyelectrolyte — poly(vinylbenzyltrimethylammonium chloride) (PVBTMAC) (*a*) and schematic representation of phase transitions in dependence of inter-MMC concentration and solution pH (*b*). Reprinted from [64]

The complexation of polyampholyte gels with linear polyelectrolytes and/or between polyelectrolyte gels and linear polyampholytes is a less studied subject [74]. It is expected that the mechanism of sorption of polyelectrolytes by amphoteric gel is similar to the diffusion of linear polyelectrolytes within the oppositely charged polymer networks. Penetration of macromolecules into the hydrogel proceeds via "race-relay ion transport" (or "ion-hopping transportation") mechanism leading to a gel deswelling. The swelling-deswelling behavior of amphoteric gel made of maleic acid (MA), N,N'-dimehyldiallylammonium chloride (DMDAAC) and diallylamine (DAA) was studied in the absence and presence of NaPSS [67]. The pristine amphoteric gel MA-DMDAAC-DAA shrinks at $pH_{IEP} \approx 4.6$ while the swelling degree of the inter-MMC composed of amphoteric gel MA-DMDAAC-DAA and linear NaPSS is minimal in a wide pH range between 3.5 and 8.5 (Fig. 5). It increases significantly in the strongly acidic and alkaline regions. The complex of MA-DMDAAC-DAA with NaPSS contracts over a wide range of pH because NaPSS present in the network acts as an additional physical crosslinker.

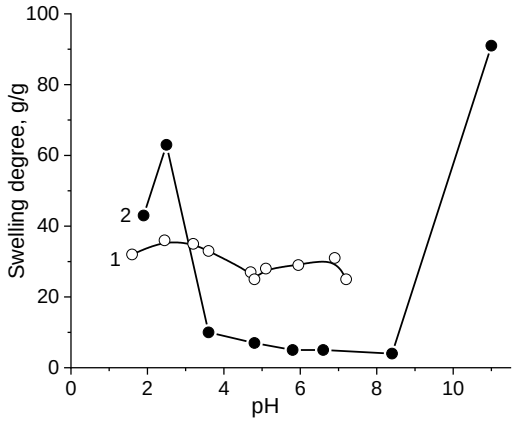


Figure 5. pH dependent swelling of amphoteric gel MA-DMDAAC-DAA (*1*) and inter-MMC formed between MA-DMDAAC-DAA and NaPSS (*2*) in pure water. Reprinted from [64]

Chen et al. [75] studied the complexes formed by poly(zwitterion) — poly[3-dimethyl(methacryloyloxyethyl ammonium propane sulfonate)] (PDMAPS) with polymeric anion: poly(2-acrylamido-2-methyl propane sulfonic acid) (PAMPS) or polymeric cations: poly(3-acrylamidopropyltrimethyl ammonium chloride) (PDMAPAA-Q) and *x*,*y*-ionene bromides ($x = 3,6$; $y = 3,4$). They found that the complexation of PDMAPS with PAMPS substantially increases the viscosity to form a network and decreases the upper criti-

cal solution temperature (UCST) while PDMAPS-PDMAPAA-Q complexes first decrease the UCST and then increase without formation of the network.

The formation of inter-MMC between anionic diblock $(AMPSNa\text{-}APTAC)_{91}\text{-}(AMPS)_{67}$ (denoted as $P(SA)_{91}S_{67}$) and cationic diblock $(AMPSNa\text{-}APTAC)_{91}\text{-}(APTAC)_{88}$ (denoted as $P(SA)_{91}A_{88}$) polyampholytes was studied by Yusa et al. [76]. They form stoichiometric inter-MMC micelles in aqueous solution (Fig. 6).

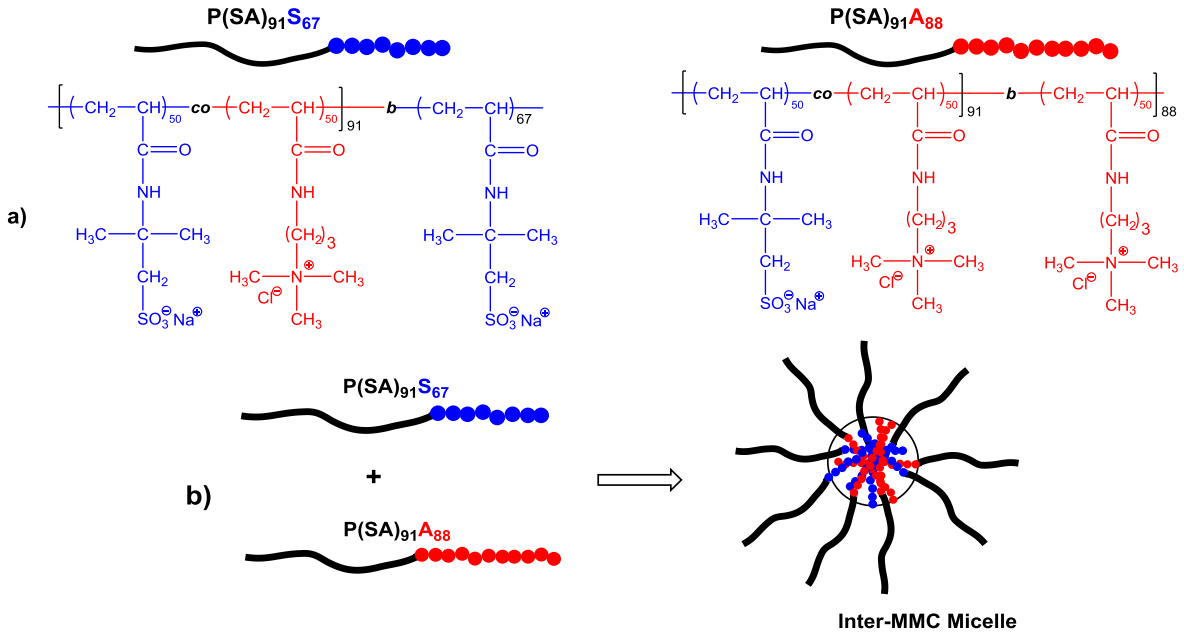


Figure 6. Structure of random copolymers of 2-acrylamido-2-methyl-1-propanesulfonic acid sodium salt-*co*-(3-acrylamidopropyl)trimethylammonium chloride-*block*-2-acrylamido-2-methyl-1-propanesulfonic acid sodium salt (AMPSNa-*co*-APTAC-*b*-AMPSNa) and 2-acrylamido-2-methyl-1-propanesulfonic acid sodium salt-*co*-(3-acrylamidopropyl)trimethylammonium chloride-*block*-(3-acrylamidopropyl)trimethylammonium chloride (AMPSNa-*co*-APTAC-*b*-APTAC) (*a*) and formation of inter-MMC micelle (*b*). Adapted and redrawn from Ref. [76]

The inter-MMC vesicles were also prepared from mixtures of aqueous solutions of diblock copolymers with a hydrophilic poly(2-(methacryloyloxy)ethylphosphorylcholine (PMPC) block and either a cationic (APTAC) or anionic (AMPSNa) blocks [77]. Both inter-MMC micelles and vesicles may be considered as suitable carriers for pharmacologically-active compounds and used as drug delivery systems.

The presence of charged groups in natural and semi-natural polyampholytes, including proteins, results in a possibility of their involvement in specific interactions with oppositely charged polyelectrolytes of either synthetic or natural origin in solutions. If a solution of polyampholyte is mixed with solution containing oppositely charged polyelectrolyte this will often lead to the formation of interpolyelecrolyte complexes (IPEC). These IPECs depending on the nature of interacting species, their concentration in solutions, component ratio and environmental factors (pH and ionic strength of solution, solvent nature and temperature) will be formed as fully soluble associates, colloidal dispersions (nano- or micro-particles) or physically-cross-linked gels. In some cases, these interactions may also cause liquid-liquid phase separation called complex coacervation. The studies of these interactions date back to 1896, when Kossel reported the first observations of precipitation of egg albumin with addition of oppositely charged protamine [78]. In 1920–1930, Bungenberg de Jong et al. [79, 80] published several studies on the interactions between gelatin and gum arabic and observed liquid-liquid phase separation and formation of complex coacervates. The research of IPECs formed by natural and semi-natural polyampholytes has substantially progressed since these early studies with numerous reviews and monographs published [81–84].

The main driving force for the formation of these IPECs is electrostatic attraction; therefore, polyelectrolytes would not interact with proteins of the same net charge unless they have non-uniform charge distribution [83]. The electrostatic attraction between proteins and polyelectrolytes could potentially be completely suppressed in solutions with high ionic strength. For example, titration of 0.5 g/L solution of bovine serum albumin (BSA) with 0.5 g/L solution of strong cationic polyelectrolyte poly[2-methacryloyloxy)ethyl]trimethyl ammonium chloride (PMADQUAT) result in formation of cloudy mixtures in the ab-

sence of inorganic salt (Fig. 7); however, the maximum turbidity in this mixture is lower when the ionic strength of solution is increased to 0.05 [85]. When the ionic strength of solutions increased to 0.2 and 1, mixing BSA and PMADQUAT does not result in appearance of turbidity. This could be either because the complexation is completely suppressed in this system or the polycomplex formed is fully soluble.

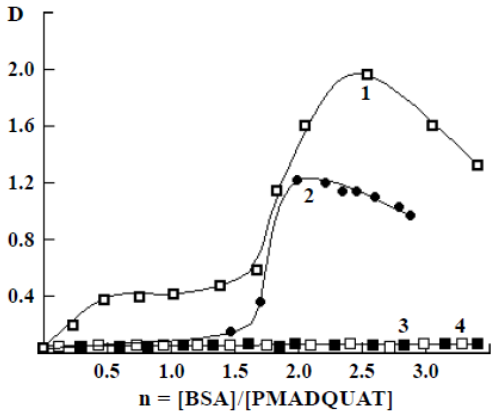


Figure 7. Turbidimetric titration curves of 0.5 g/L PMADQUAT solutions by 0.5 g/L BSA with different ionic strength: 0 (1), 0.05 (2), 0.2 (3), and 1 (4). Reprinted from [85]

The appearance of turbidity in protein-polyelectrolyte solution mixtures indicates the presence of the complexation but it does not show whether this interaction leads to formation of solid colloidal particles (precipitation) or liquid droplets (complex coacervation). Complex coacervation is a special case of this interaction, resulting in formation of two phases; one of those is dense and rich in protein and polyelectrolyte, whereas another one is dilute and contains an equilibrium mixture of protein and polyelectrolyte [82]. A centrifugation of the mixture and visual observation can be used to distinguish between precipitation and coacervation.

Polyampholyte-protein interaction of random- and block polyampholytes based on N,N-dimethylaminoethylmethacrylate-*co*-methacrylic acid-*co*-methylmethacrylate (DMAEM-MAA-MMA) with soybean tripsin inhibitor (STI), ovalbumin, ribonuclease and lysozyme was comprehensively studied [86]. The most favorable region of interaction of polyampholyte and protein is between their isoelectric points. An increase in the salt concentration suppresses polyampholyte-protein interactions confirming that the main driving force of self-aggregation is electrostatic [87]. The study of the supernatant and precipitate has shown that only about 10 % of the protein precipitates with the random polyampholyte DMAEM-MAA-MMA, while 90 % of the protein remains in the equilibrium liquid. While block polyampholyte DMAEM-MAA-MMA gives the opposite trend with 90 % of precipitation of protein [88]. Separation of protein mixture using random triblock polyampholyte $DMAEM_8MMA_{12}MAA_{16}$ was reported in [89–91]. In this method proposed for protein separation by precipitation, a polyampholyte should be added to a mixture of two proteins to be separated, one of which should have a net negative charge and the other one should be with a net positive charge. A prerequisite in the process is that the two oppositely charged proteins do not interact strongly with each other. Depending on the net charge of the polyampholyte used, one of the proteins will form a complex with the polyampholyte, resulting in precipitation, while the other one will remain in a supernatant phase. The protein-polyampholyte precipitate formed can be isolated and redissolved at a different pH. Then, protein and polyampholyte can be separated from each other by precipitating the polyampholyte at the pH_{IEP}. The separation of protein mixture can be also performed at the pH_{IEP} of block polyampholytes. Through this method, one of the blocks of the polyampholyte will interact with the oppositely charged groups of the protein, while the main chain (or other block) — with another protein charge as shown in Figure 8 [64]. In both cases protein release will occur at the pH_{IEP} of BPA due to the formation intra-MMC between anionic and cationic blocks within one macromolecular chain.

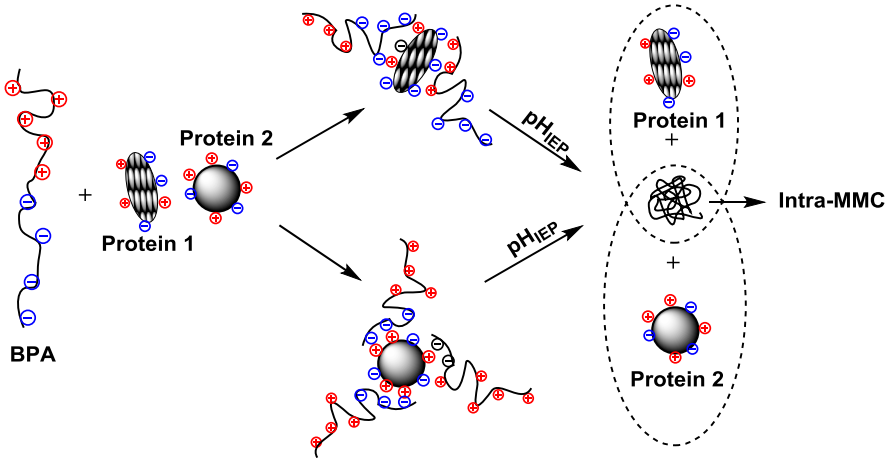


Figure 8. Separation of protein mixture at the pH_{IEP} of BPA. Reprinted from [64]

Uptake/release of cytochrome C by random and "core-shell" polyampholyte microgels consisting of N-vinylcaprolactame (VCL), itaconic acid (IA) (VCL-IA "core" part) and N-isopropylacrylamide (NIPAM), N-vinylimidazole (VI) (NIPAM-VI "shell" part) [91] and sorption/desorption of NaPSS by "core-shell" polyampholyte microgels composed of anionic — an itaconic acid monomethyl ether (NIPAM-*co*-MIA) "shell" and cationic — N-(3-aminopropyl)methacrylamide hydrochloride (NIPAM-*co*-APMH) "core" was carried out in [92]. The isoelectric points pH_{IEP} of random and "core-shell" polyampholyte microgels (VCL-IA/NIPAM-VI) were replaced near of pH ~ 6.0. Random and "core-shell" polyampholyte microgels were loaded with cytochrome C at pH 8.0. The pH triggered protein release results show that cytochrome C releases at the pH_{IEP} (pH ~ 6.0) much faster for both polyampholyte system due to formation of intra-MMC between oppositely charged groups of amphoteric macromolecules. The uptake and release of NaPSS by "core-shell" amphoteric microgels was observed at pH 2.0 and 11.0, respectively. Strong binding of NaPSS with cationic fragment of APMH in "core" of NIPAM-*co*-APMH requires high pH 10 for full deprotonation of APMH groups to dissociate the amphoteric microgel-NaPSS complexes.

The complexation of zwitterionic monolithic column derived from crosslinked N,N-dimethyl-N-methacryloxyethyl-N-(3-sulfopropyl)ammonium betaine with proteins (lysozyme, ovalbumin, conalbumine, cytochrome C, and myoglobin) leads to efficient separation of lysozyme by changing the pH of mobile phase [94].

Molecularly-imprinted polyampholyte (MIP) hydrogels based on nonionic acrylamide, anionic AMPS and cationic APTAC were used for selective separation of bovine serum albumin (BSA) and lysozyme [95]. It was established that the best sample for sorption of BSA is amphoteric hydrogel with excess of APTAC while for sorption of lysozyme the polyampholyte gel with excess of AMPS is more suitable. The sorption capacity of amphoteric hydrogels with respect to BSA and lysozyme is 305.7 and 64.1-74.8 mg per 1 g of hydrogel, respectively. Desorption of BSA and lysozyme from MIP template conducted in 1M aqueous NaCl was found to be 82–88 %. The separation of BSA and lysozyme from their mixture was performed using MIP templates. The study of adsorption-desorption of polyampholyte hydrogels adjusted to either BSA or lysozyme shows that the mixture of BSA and lysozyme can be efficiently separated using MIP hydrogels.

Polyampholytes are able to bind polynucleotides and oligonucleotides, such as siRNA, or DNA, and deliver to mammalian cells for the treatment of genetic-based diseases [96]. The literature analysis indicates that synthetic polyampholytes are less studied with respect to gene delivery compared to cationic polyelectrolytes (Fig. 9) [48]. Several types of BPA, especially highly charged BPA composed of linear poly(ethyleneimine) (LPEI) and poly(methacrylic acid) and low charge BPA composed of LPEI and poly(glutamic acid) [97], multi-stimuli-responsive chiral-achiral amino acid-based block copolymers composed of poly(N-acryloyl amino acid) and poly(vinyl amine) [98] and comb-type polyampholyte consisting of a poly(L-lysine) backbone and hyaluronic acid side chains [99] were tested with respect to DNA delivery. It was found that the efficiency of DNA delivery is increased and toxicity is reduced relative to complexes formed between polycations and DNA (or siRNA). The delivered DNA (or siRNA) is effective in inhibiting specific gene expression in cells. In the context of DNA delivery, the release mechanism of DNA from inter-MMC is shown in Figure 10 [100]. The resulting BPA-DNA may aggregate with the formation of "core-shell" structure where the "core" part is the inter-MMC formed between cationic block of BPA and

anionic DNA, while the "shell" part consisting of the anionic block preserves the solubility of BPA-DNA complexes in water and simultaneously prevents interaction with proteins. The cooperative intra-ionic contacts between anionic and cationic blocks prevail over the inter-ionic contacts between cationic block and DNA at or near the isoelectric point (pH_{IEP}). As a result, anionic and cationic blocks of BPA form intra-MMC themselves and DNA releases. Ff intra-chain interaction between anionic and cationic blocks of BPA (intra-MMC) dominates over inter-chain interaction between BPA and DNA (inter-MMC) the latter can be detached from BPA-DNA complex and released at the pH_{IEP} of BPA.

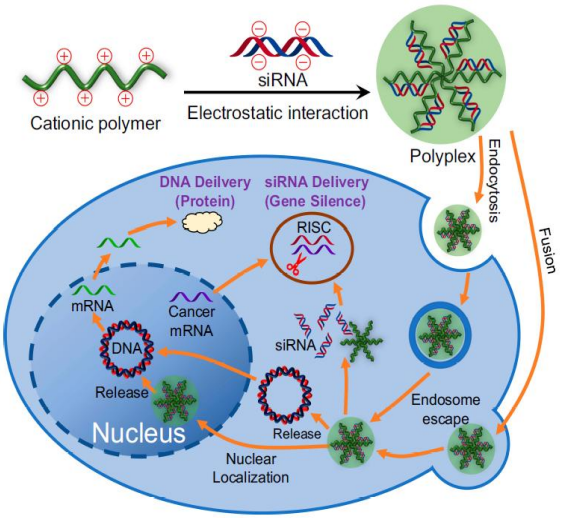


Figure 9. Gene delivery mechanism into the cell by polycomplex formed between cationic polymer and siRNA. Reproduced from [48] with permission from Dove Medical Press Ltd

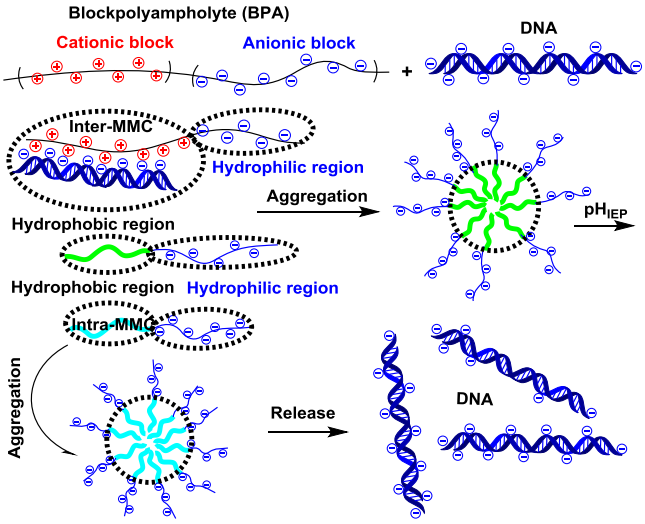


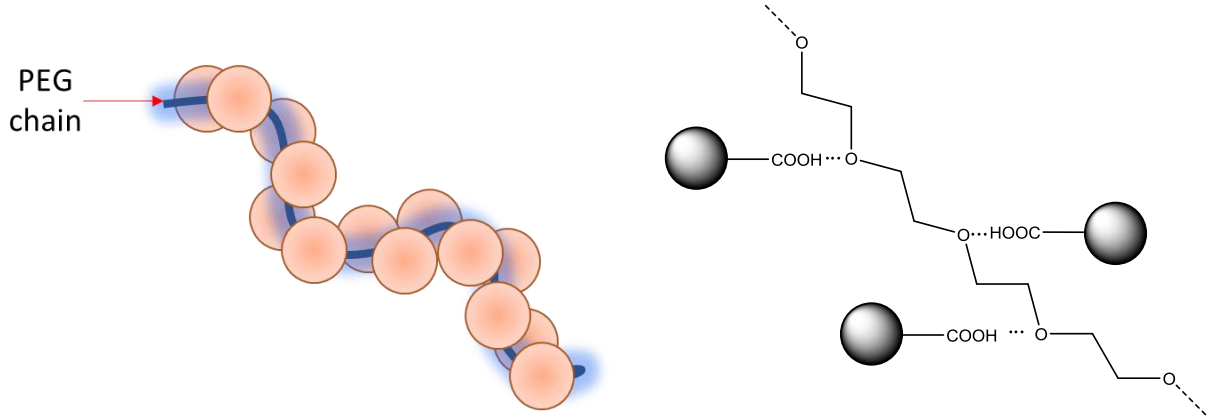
Figure 10. Schematic routes of BPA-DNA complex formation and proposed release mechanism of DNA at the pH_{IEP} of BPA. Adapted and modified from [100]

Skorikova et al. [101] studied the formation of inter-MMC between sulfated chitosan, a polyampholyte with amine and sulfo groups, and 2,5-ionene bromide. The turbidimetric titration of 2,5-ionene bromide with chitosan sulfate (CS) at pH = 2.5 and 11.5 indicates that the composition of MMC is different in acidic and alkaline regions. At acidic pH only a half of sulfate groups participate in the formation of nonstoichiometric complex because the rest exists in the form of intra-MMC. At alkali pH the composition of polyelectrolyte complexes is stoichiometric because all sulfate groups are involved in formation of inter-MMC. Formation of inter-MMC between cellulose-based polyampholyte and PDMDAAC was studied by Elschner et al. [102]. The inter-MMC exhibited pH-responsive character, was switchable in a physiologically relevant pH range and is a promising nanocarrier in the field of drug delivery.

Protein-polyelectrolyte complexes with participation of proteins (insulin and glucose oxidase), antimicrobial peptide (LL-37), polysaccharides (heparin and alginate), and synthetic polyelectrolytes (NaPSS and poly(allylamine hydrochloride)) were assembled by layer-by-layer (LbL) technique [103]. It was shown that the adsorption behavior and the multilayer growth are strongly dependent on the nature of the protein and polyelectrolyte used. Integrating proteins in LbL thin films is sometimes challenging due to their amphoteric nature and is beneficial for surface modification with hard-to-immobilize proteins and peptides.

In addition to interpolyelectrolyte complexes formed by natural and semi-natural polyampholytes with oppositely charged polyelectrolytes, there are also reports on the complexes stabilised by hydrogen bonding. One of the early reports of the complexation via hydrogen bonding is the study on the interactions between pepsin and poly(ethylene glycol) (PEG) by Kokufuta and Nishimura [104]. They established that addition of PEG to pepsin leads to the increase of reduced viscosity of enzyme solution, when the solutions had a pH of 3; however, this increase in viscosity was not observed at pH 4.5. The authors interpreted these observations as a formation of water-soluble complexes, in which ether groups of PEG bind to carboxylic groups of the enzyme via hydrogen bonding. Later, Xia, Dubin and Kokufuta [105] reported the use of quasi-elastic light scattering measurements to confirm the complexation between pepsin and non-ionic polyethylene glycol via hydrogen bonding. Subsequently, Azegami et al. [106] reported the formation of complexes between human serum albumin (HSA) and PEG, in which several HSA macromolecules are bound to PEG chain at pH 2.

Based on these studies of complexation between proteins and PEG the following structural organisation for these complexes was proposed (Fig. 11).



(*a*) (*b*)

Figure 11. Structural organisation of protein — PEG complexes (*a*) and mechanism of hydrogen bonding between proteins and PEG under acidic conditions (*b*). Protein molecules are shown as spheres in these images

Later, Matsunami et al. [107] also reported the complex formation between various proteins (HSA, ovalbumin and lysozyme) and non-ionic poly(N-isopropylacrylamide). They established that hydrophobic interactions play an important role in the formation of these complexes.

3 Application of interpolymer complexes derived from synthetic, natural and semi-natural polyampholytes

Multifunctional nature of polyampholytes and their diverse physicochemical properties open numerous opportunities for applications, including the use of materials resulting from their complexes with other polymers. One of the most widely industrially used polyampholytes is gelatin, which is a product of partial hydrolysis of collagen, present in bones, cartilage and skin of slaughter animals. It is industrially one of the most important semi-natural polyampholyte with unique set of physicochemical properties. The properties of gelatin depend on the method of its production either through acid or alkaline-based processes. The gelatin prepared using the alkaline process exhibits the isoelectric point in the region of 4.8–5.2 (gelatin B), whereas gelatin A, manufactured via the acid process, will have the isoelectric point at 7–9 [108, 109]. The unique ability of gelatin to form concentrated (up to 40 w/v %) and relatively non-viscous aqueous solutions at 50 °C and their quick gelation upon cooling is one of the main reasons for its wide application in pharmaceutical and food industry (Fig. 12).

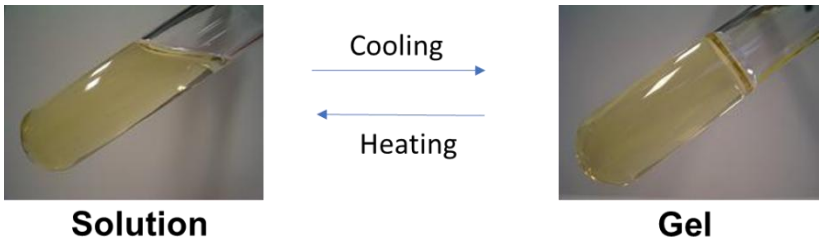


Figure 12. Reversible gelation in 40 w/v % solutions of gelatin upon changes in temperature

The complexation of gelatin with oppositely charged synthetic and natural polyelectrolytes received a lot of attention since the pioneering studies by Bungenberg de Jong et al. [79, 80]. The classical gelatin – Arabic gum system forming complex coacervates received a lot of interest for the preparation of microcapsules delivery of drugs and other active ingredients. For example, Chang et al. [110] reported encapsulation of camphor oil together with polystyrene into gelattin-gum Arabic microcapsules. Shaddel et al. [111] reported microencapsulation of black raspberry water extracts by double emulsion technique prior to complex coacervation to stabilise anthocyanins under harsh processing and storage conditions. Complexes of gelatin

with gum arabic are also promising for applications as food additives, stabilisation of dairy products, for increasing water retention capacity in meat products, and as emulsifiers in ice creams [112].

Interpolyelectrolyte complexes formed by gelatin and oppositely charged polyelectrolytes can also be used in the design of solid dosage forms for drug delivery. For example, Moustafine [113] studied the complexation between gelatin and weakly cross-linked poly(acrylic acid) in aqueous solutions. These complexes were then isolated in solid state and compressed into tablets with and without a model drug (diclofenac sodium). The studies of swelling of these tablets in phosphate buffer (pH 7.5) demonstrated that the swelling degree of the matrices decreases with increase in the polyampholyte content in the dosage form. When the behaviour of these tablets was studied in acidic media (pH 1.2), imitating the environment in the stomach, these dosage forms undergo erosion. The release of the drug from these tablets was also found to correlate with gelatin/poly(acrylic acid) ratio in the dosage form.

Complexes of polyampholytes with other polymers are also found interest as nano-vehicles for drug delivery. For example, an interesting application of protein — polyelectrolyte complexation was reported by Al-Saadi et al. [114]. They studied an alternate deposition of bovine serum albumin (BSA) and glycol chitosan on the surface of magnetic iron oxide nanoparticles, forming a multi-layered coating. Using circular dichroism technique, it was demonstrated that the secondary structure of BSA present in the formed multilayer coating remains unaltered and the protein was capable of binding small drug molecules such as diazepam, ibuprofen and warfarin. The drug binding constants (K) measured for BSA deposited on the magnetic nanoparticle surface are almost identical to the K values typical for native protein. The authors considered the application of layer-by-layer deposition of protein — polyelectrolyte complexes as a method promising for developing magnetically-driven drug delivery systems, which may be used for protein delivery. Lomova et al. [115] utilised the complexation between bovine serum albumin and tannic acid to prepare biodegradable capsules using a layer-by-layer deposition approach. Hydrogen bonding was proposed to be the main driving force for the complexation between BSA and tannic acid. These capsules were prepared using $CaCO_3$ microparticles as a sacrificial template. Calcium carbonate microparticles were prepared by the reaction between $CaCl_2$ and Na_2CO_3 in the presence of fluorescently labelled BSA as a model drug. Then a multilayered coating with 6 bilayers was formed on the surface of these microparticles using the layer-by-layer complexation between BSA and tannic acid. Subsequently, these particles were treated with ethylenediamine tetraacetate to extract $CaCO_3$. These microcapsules were discussed as a promising vehicle for applications in drug delivery and cosmetics.

The complexation of proteins with polyelectrolytes and selective phase separation in these systems can be successfully used to isolate specific proteins from their mixture. For example, Wang et al. [116] studied the efficiency of separation in the mixtures containing proteins bovine serum albumin, β-lactoglobulin, γ-globulin, and ribonuclease A using their complexation with poly(diallyldimethylammonium chloride). They established that the selectivity of separation depends on pH and increases with molecular weight of cationic polyelectrolyte and reduction in solution ionic strength.

Other applications of polyampholyte-polymer complexes include systems with immobilised enzymes, where complexation with polyelectrolytes can boost their catalytic performance. This could potentially be of importance for enzymes used in complex multicomponent formulations, such as laundry, food, pharmaceutical or cosmetic applications. For example, Thiele et al. [117] reported the observation of the enhancement effects in catalytic activity of a nonspecific subtilisin protease upon its complexation with poly(acrylic acid) and poly(L-γ-glutamic acid).

Conclusions

It is expected that understanding of the fundamental relationships between the microstructure and property of synthetic, natural and semi-natural polyampholytes can expand our knowledge and cause the renewed interest of both theorists and experimentalists in advanced experimental and theoretical investigations. Future possibilities regarding polyampholytes may be related to semi-natural polyampholytes that can be prepared through modification of such natural polysaccharides as chitosan, cellulose, starch, gellan, and alginic acid, among others, through introduction of either carboxylic (sulfo) or amine (ammonium) groups, or both, into the macromolecular chains. A further potential development in polyampholytes in our mind will include intrinsically disordered proteins (IDPs), which belong to strong polyampholytes, polypeptide-based polyampholytes and polyampholytic ionic liquids. Inter-macromolecular complexes of polyampholytes are the products of complexation between linear and crosslinked synthetic polyampholytes, of random, regular, graft, block and dendritic microstructures, with polyelectrolytes, proteins and polynucleotides. The applica-

tions of interpolymer complexes formed by various polyampholytes are currently growing, with particular interest in microencapsulation technologies, food and pharmaceutical industries, protein separation and formulation of enzymes.

Acknowledgements

R.I. Moustafine and V.V. Khutoryanskiy gratefully acknowledge Russian Science Foundation–RSF (project no. 20-65-46007) for partial financial support of work on this review.

References

1 Hess, M., Jones, R.G., Kahovec, J., Kitayama, T., Kratochvíl, P., Kubisa, P., Mormann, W., Stepto, R.F.T., Tabak, D., Vohlídal, J., & Wilks, E.S. (2006). Terminology of polymers containing ionizable or ionic groups and of polymers containing ions (IUPAC Recommendations 2006). *Pure and Applied Chemistry, 78(11),* 2067–2074. https://doi.org/10.1351/pac200678112067

2 Alfrey, T., Morawetz, H., Fitzgerald, E.B., & Fuoss, R.M. (1950). Synthetic electrical analog of proteins. *Journal of the American Chemical Society, 72(4),* 1864. https://doi.org/10.1021/ja01160a532

3 Alfrey, T., & Morawetz, H. (1952). Amphoteric polyelectrolytes. I. 2-vinylpyridine—methacrylic acid copolymers1, 2. *Journal of the American Chemical Society, 74(2),* 436–438. https://doi.org/10.1021/ja01122a046

4 Alfrey, T., Fuoss, R.M., Morawetz, H., & Pinner, H. (1952). Amphoteric polyelectrolytes. II. Copolymers of methacrylic acid and diethylaminoethyl methacrylate1. *Journal of the American Chemical Society, 74(2),* 438–441. https://doi.org/10.1021/ja01122a047

5 Katchalsky, A., & Gillis, J. (1949). Potentiometric behavior of polyampholytes. Copolymers of 2-vinylpyridine-acrylic acid. *Recl Trav Chim-Pays Bas, 68,* 871–877.

6 Katchalsky, A., & Miller, I.R. (1954). Polyampholytes. *J Polym Sci, 13,* 57-68. https://doi.org/10.1002/pol.1954.120136805

7 Mazur, J., Silberberg, A., & Katchalsky, A. (1959). Potentiometric behavior of polyampholytes. *J Polym Sci, 35,* 43–70. https://doi.org/10.1002/pol.1959.1203512805

8 Ehrlich, G., & Doty, P. (1954). Macro-ions. III. The solution behavior of a polymeric ampholyte1. *Journal of the American Chemical Society, 76(14),* 3764–3777. https://doi.org/10.1021/ja01643a053

9 Ciferri, A., & Kudaibergenov, S. (2007). Natural and synthetic polyampholytes, 1. *Macromolecular Rapid Communications, 28(20),* 1953–1968. https://doi.org/10.1002/marc.200700162

10 Kudaibergenov, S.E., & Ciferri, A. (2007). Natural and synthetic polyampholytes, 2. Functions and applications. *Macromolecular Rapid Communications, 28(20),* 1969–1986. https://doi.org/10.1002/marc.200700197

11 Edwards, S.F., King, P.R., & Pincus, P. (1980). Phase changes in polyampholytes. *Ferroelectrics, 30(1),* 3–6. https://doi.org/10.1080/00150198008209479

12 Roy, S.G., & De, P. (2014). pH responsive polymers with amino acids in the side chains and their potential applications. *Journal of Applied Polymer Science, 131(20).* https://doi.org/10.1002/app.41084

13 Mori, H., & Endo, T. (2012). Amino-acid-bosed block copolymers by RAFT polymerization. *Macromolecular Rapid Communications, 33(13),* 1090–1107. https://doi.org/10.1002/marc.201100887

14 Kruse, J.-H., Biehl, P., & Schacher, F.H. (2019). Different routes to ampholytic polydehydroalanine: orthogonal versus simultaneous deprotection. *Macromolecular Rapid Communications, 1800857.* https://doi.org/10.1002/marc.201800857

15 Evans A.C., Skey, J., Wright, M., Qu, W., Ondeck, C., Longbottom, D.A., & O'Reilly R.K. (2009). Functional and tunable amino acid polymers prepared by RAFT polymerization. *J Polym Sci Part A: Polym Chem, 47,* 6814–6826. https://doi.org/10.1002/pola.23721

16 Shirbin, S.J., Lam, S.J., Chan, N.J.-A., Ozmen, M.M., Fu, Q., O'Brien-Simpson, N., Reynolds, E.C., & Qiao, G.G. (2016). Polypeptide-based macroporous cryogels with inherent antimicrobial properties: the importance of a macroporous structure. *ACS Macro Letters, 5(5),* 552–557. https://doi.org/10.1021/acsmacrolett.6b00174

17 Tao, Y., Wang, S., Zhang, X., Wang, Z., Tao, Y., & Wang, X. (2018). Synthesis and properties of alternating polypeptoids and polyampholytes as protein-resistant polymers. *Biomacromolecules, 19(3), 936–942.* https://doi.org/10.1021/acs.biomac.7b01719

18 Janciauskaite, U., Visnevskij, C., Radzevicius, K., & Makuska, R. (2009). Polyampholytes from natural building blocks: synthesis and properties of chitosan-O-alginate copolymers. *Chemija, 20,* 128–135.

19 Lin, M., Liu, H., Deng, J., An, R., Shen, M., Li, Y., & Zhang, X. (2019). Carboxymethyl chitosan as a polyampholyte mediating intrafibrillar mineralization of collagen via collagen/ACP self-assembly. *Journal of Materials Science & Technology, 35,* 1894–1905. https://doi.org/10.1016/j.jmst.2019.05.010

20 Cohn, E.J., & Edsall, J.T. (1943). Proteins, amino acids and peptides as ions and dipolar ions. New York: Reinhold Publishing Corporation.

21 Laschewsky, A., Marsat, J.N., Skrabania, K., Berlepsch, H., & Böttcher, C. (2009). Bioinspired block copolymers: translating structural features from proteins to synthetic polymers. *Macromol Chem Phys, 211,* 215–221.

22 Sackmann, E. (1994). Intra- and extracellular macromolecular networks: physics and biological function. *Macromol Chem Phys, 195,* 7–28.

23 Gunliffe, D., Pennadam, S., & Alexander, C. (2004). Synthetic polymers—merging the interface. *Eur Polym J*, *40*, 5–25.

24 Grinberg, V.Y., Burova, T.V., Grinberg, N.V., Alvarez-Lorenzo, C., & Khokhlov, A.R. (2019). Protein-like energetics of conformational transitions in a polyampholyte hydrogel. *Polymer*, *179*, 121617. https://doi.org/10.1016/j.polymer.2019.121617

25 Bright, J.N., Woolf, T.B., & Hoh, J.H. (2001). Predicting properties of intrinsically unstructured proteins. *Progress in Biophysics and Molecular Biology*, *76(3)*, 131–173. https://doi.org/10.1016/s0079-6107(01)00012-8

26 Uversky, V.N. (2019). Intrinsically disordered proteins and their "mysterious" (meta)physics. *Frontiers in Physics*, *7*. https://doi.org/10.3389/fphy.2019.00010

27 Van der Lee, R., Buljan, M., Lang, B., Weatheritt, R.J., Daughdrill, G.W., Dunker, A.K., Fuxreiter, M., Gough, J., Gsponer, J., Jones, D.T., Kim, P.M., Kriwacki, R.W., Oldfield, C.J., Pappu, R.V., Tompa, P., Uversky, V.N., Wright, P.E., & Babu, M.M. (2014). Classification of intrinsically disordered regions and proteins. *Chemical Reviews*, *114(13)*, 6589–6631. https://doi.org/10.1021/cr400525m

28 Wright, P.E., & Dyson, H.J. (2015). Intrinsically disordered proteins in cellular signalling and regulation. *Nature Reviews Molecular Cell Biology*, *16(1)*, 18–29. https://doi.org/10.1038/nrm3920

29 Oldfield, C.J., & Dunker, A.K. (2014). Intrinsically disordered proteins and intrinsically disordered protein regions. *Annual Review of Biochemistry*, *83(1)*, 553–584. https://doi.org/10.1146/annurev-biochem-072711-164947

30 Das, R.K., & Pappu, R.V. (2013). Conformations of intrinsically disordered proteins are influenced by linear sequence distributions of oppositely charged residues. *Proceedings of the National Academy of Sciences*, *110(33)*, 13392–13397. https://doi.org/10.1073/pnas.1304749110

31 Kudaibergenov, S.E. (2002). Polyampholytes: Synthesis, Characterization and Application. New York: Kluwer Academic/Plenum Publishers, 220. https://doi.org/10.1007/978-1-4615-0627-0

32 Lowe, A.B., & McCormick, C.L. (2002). Synthesis and solution properties of zwitterionic polymers. *Chemical Reviews*, *102(11)*, 4177–4190. https://doi.org/10.1021/cr020371t

33 Kudaibergenov, S.E. (1999). Recent advances in studying of synthetic polyampholytes in solutions. *Adv Polym Sci*, *144*, 115–197.

34 Kudaibergenov, S.E. (2008). Polyampholytes. *In Encyc Polym Sci Technol. John Wiley Interscience: Hoboken, NJ, USA*, 1–30.

35 Kudaibergenov, S., Jaeger, W., & Laschewsky, A. (2006). Polymeric Betaines: Synthesis, Characterization, and Application. *Advances in Polymer Science*, *157–224*. https://doi.org/10.1007/12_078

36 Laschewsky, A. (2014). Structures and synthesis of zwitterionic polymers. *Polymers*, *6(5)*, 1544–1601. https://doi.org/10.3390/polym6051544

37 Singh, P.K., Singh, V.K., & Singh, M. (2007). Zwitterionic Polyelectrolytes: A Review. *e-Polymers*, *7(1)*. https://doi.org/10.1515/epoly.2007.7.1.335

38 He, X.Y., Zhou, W.R., Xu, X.J., & Yang, W. (2013). Preparation and application of zwitterionic polymers. *Prog in Chem*, *25(6)*, 1023–1030. https://doi.org/10.7536/PC121106

39 Bernards, M., & He, Y. (2014). Polyampholyte polymers as a versatile zwitterionic biomaterial platform. *Journal of Biomaterials Science, Polymer Edition*, *25(14-15)*, 1479–1488. https://doi.org/10.1080/09205063.2014.938976

40 Liu, H., & Zhou, J. (2012). Biological applications of zwitterionic polymers. *Prog in Chem*, *24(11)*, 2187–2197.

41 Ohno, H., Yoshizawa-Fujita, M., & Ogihara, W. (2011). Electrochemical Aspects of Ionic Liquids. New Jersey: John Wiley & Sons, Inc., Hoboken, 433–439.

42 Fouillet, C.C.J., Greaves, T.L., Quinn, J.F., Davis, T.P., Adamcik, T., Sani, M.A., Separovic, F., Drummond, C.J., & Mezzenga, R. (2017). Copolyampholytes produced from RAFT polymerization of protic ionic liquids. *Macromolecules*, *50*, 8965. https://doi.org/10.1021/acs.macromol.7b01768

43 Tao, Y., Wang, S., Zhang, X., Wang, Z., Tao, Y., & Wang, X. (2018). Synthesis and properties of alternating polypeptoids and polyampholytes as protein-resistant polymers. *Biomacromolecules*, *19(3)*, 936–942. https://doi.org/10.1021/acs.biomac.7b01719

44 Sun, J., Černoch, P., Völkel, A., Wei, Y., Ruokolainen, J., & Schlaad, H. (2016). Aqueous self-assembly of a protein-mimetic ampholytic block copolypeptide. *Macromolecules*, *49(15)*, 5494–5501. https://doi.org/10.1021/acs.macromol.6b00817

45 Maji, T., Banerjee, S., Biswas, Y., & Mandal, T.K. (2015). Dual-stimuli-responsive L-serine-based UCST-type polymer with tunable thermosensitivity. *Macromolecules*, *48(14)*, 4957–4966. https://doi.org/10.1021/acs.macromol.5b01099

46 Chen, L., Chen, T., Fang, W., Wen, Y., Lin, S., Lin, J., & Cai, C. (2013). Synthesis and pH-responsive "Schizophrenic" aggregation of a linear-dendron-like polyampholyte based on oppositely charged polypeptides. *Biomacromolecules*, *14(12)*, 4320–4330. https://doi.org/10.1021/bm401215w

47 Asayama, S., Nogawa, M., Takei, Y., Akaike, T., & Maruyama, A. (1998). Synthesis of novel polyampholyte comb-type copolymers consisting of a poly(L-lysine) backbone and hyaluronic acid side chains for a DNA carrier. *Bioconjugate Chemistry*, *9(4)*, 476–481. https://doi.org/10.1021/bc970213m

48 Chen, L., Tian, Z., & Du, Y. (2004). Synthesis and pH sensitivity of carboxymethyl chitosan-based polyampholyte hydrogels for protein carrier matrices. *Biomaterials*, *25(17)*, 3725–3732. https://doi.org/10.1016/j.biomaterials.2003.09.100

49 Ouerghemmi, S., Dimassi, S., Tabary, N., Leclercq, L., Degoutin, S., Chai, F., Pierlota, C., Cazauxa, F., Ungd, A., Staelensa, J.-N., Blanchemain, N., & Martel, B. (2018). Synthesis and characterization of polyampholytic aryl-sulfonated chitosans and their in vitro anticoagulant activity. *Carbohydrate Polymers*, *196*, 8–17. https://doi.org/10.1016/j.carbpol.2018.05.025

50 Meng, P.R., & Li, L.B. (2014). Study on the preparation of starch-based polyampholyte and slow release performance. *Materials Science Forum, 809–810,* 302–307. https://doi.org/10.4028/www.scientific.net/msf.809-810.302

51 Yin, Q., Zhou, G., Liu, Y.-Y., Yin, Q.-J., Luo, J.-H., & Jiang, B. (2010). Molecular dynamic simulation of carboxyethyl chitosan: effect of temperature, salt concentration and pH. *Journal of Theoretical and Computational Chemistry, 09(supp01),* 167–176. https://doi.org/10.1142/s0219633610005487

52 Yu, C., Liu, Y.-F., Tang, H.-L., & Tan, H.-M. (2010). Study of carboxymethyl chitosan-based polyampholyte superabsorbent polymer (Part II): Investigating the state of water in CMCTS-g-(PAA-co-PTMAAC) hydrogel. *Iranian Polym J., 19,* 417–425.

53 Yu, C., Liu, Y.-F., Tang, H.-L., & Tan, H.-M. (2010). Study of carboxymethyl chitosan based polyampholyte superabsorbent polymer. Optimization of synthesis conditions and pH sensitive property study of carboxymethyl chitosan-g-poly(acrylic acid-co-dimethyldiallylammonium chloride) superabsorbent polymer. *Carbohydrate Polymers, 81,* 365–371. https://doi.org/10.1016/j.carbpol.2010.02.007

54 Dhar, N., Akhlaghi, S.P., & Tam, K.C. (2012). Biodegradable and biocompatible polyampholyte microgels derived from chitosan, carboxymethyl cellulose and modified methyl cellulose. *Carbohydrate Polymers, 87(1),* 101–109. https://doi.org/10.1016/j.carbpol.2011.07.022

55 Cheng, B., Pei, B., Wang, Z., & Hu, Q. (2017). *Advances in chitosan-based superabsorbent hydrogels. RSC Advances, 7(67),* 42036–42046. https://doi.org/10.1039/c7ra07104c

56 Kono, H., Oeda, I., & Nakamura, T. (2013). The preparation, swelling characteristics, and albumin adsorption and release behaviors of a novel chitosan-based polyampholyte hydrogel. *Reactive and Functional Polymers, 73(1),* 97–107. https://doi.org/10.1016/j.reactfunctpolym.2012.08.016

57 Novac, O., Lisa, G., Profire, L., Tuchilus, C., & Popa, M.I. (2014). Antibacterial quaternized gellan gum based particles for controlled release of ciprofloxacin with potential dermal applications. *Materials Science and Engineering: C, 35,* 291–299. https://doi.org/10.1016/j.msec.2013.11.016

58 Dimassi, S., Tabary, N., Chai, F., Blanchemain, N., & Martel, B. (2018). Sulfonated and sulfated chitosan derivatives for biomedical applications: a review. *Carbohydrate Polymers, 202,* 382–396. https://doi.org/10.1016/j.carbpol.2018.09.011

59 Fiorica, C., Pitarresi, G., Palumbo, F.S., Mauro, N., Federico, S., Giammona, G. (2020). Production and physicochemical characterization of a new amine derivative of gellan gum and rheological study of derived hydrogels. *Carbohydrate Polymers,* 236, 116033. https://doi.org/10.1016/j.carbpol.2020.116033

60 Kabanov, V.A., & Zezin, A.B. (1984). Soluble interpolymeric complexes as a new class of synthetic polyelectrolytes. *Pure and Applied Chemistry, 56(3),* 343–354. https://doi.org/10.1351/pac198456030343

61 Tsuchida, E., & Abe, K. (1982). Interactions between macromolecules in solution and intermacromolecular complexes. *Advances in Polymer Science*, 1–119. https://doi.org/10.1007/bfb0017549

62 Bekturov, E.A., & Bimendina, L.A. (1981). Interpolymer complexes. *Advances in Polymer Science,* 99–147. https://doi.org/10.1007/3-540-10554-9_11

63 Khutoryanskiy, V.V., & Staikos, G. (2009). Hydrogen-bonded interpolymer complexes: formation, structure and applications. Singapore: World Scientific Pub. Co., 366. ISBN 978-981-270-977-6

64 Kudaibergenov, S., & Nuraje, N. (2018). Intra- and interpolyelectrolyte complexes of polyampholytes. *Polymers, 10(10),* 1146. https://doi.org/10.3390/polym10101146

65 Savinova, I.V., Fedoseeva, N.A., Evdakov, V.P., & Kabanov, V.A. (1976). Polymer-polymer complexes with participation of synthetic polyampholytes. *Vysokomol.Soedin. Ser. A, 18,* 2050–2057.

66 Kudaibergenov, S.E., Sigitov, V.B., Bekturov, E.A., Koetz, J., & Philipp, B. (1989). Studing of novel polyampholytes based on allylamines and maleic acid by ^{13}C NMR and Raman spectroscopy. *Vysokomol.Soedin. Ser.B, 31,* 132–136.

67 Ibraeva, Z. E., Hahn, M., Jaeger, W., Bimendina, L.A., & Kudaibergenov, S.E. (2004). Solution properties and complexation of polyampholytes based on N, N-dimethyldiallylammonium chloride and maleic acid or alkyl (aryl) derivatives of maleamic acids. *Macromolecular Chemistry and Physics, 205(18),* 2464–2472. https://doi.org/10.1002/macp.200400242

68 Zansokhova, M.F., Rogacheva, V.B., Gulyaeva, Z.G., Zezin, A.B., Joosten, J., & Brackman, J. (2008). Interaction of ampholyte dendrimers with linear polyelectrolytes. *Polymer Science Series A, 50(6),* 656–664. https://doi.org/10.1134/s0965545x08060096

69 Rogacheva, V.B., Panova, T.V., Bykova, E.V., Zezin, A.B., Joosten, J., & Brackman, J. (2009). Interaction of ampholyte dendrimers with network polycations and polyanions. *Polymer Science Series A, 51(3),* 242–249. https://doi.org/10.1134/s0965545x0903002x

70 Bekturov, E.A., Kudaibergenov, S.E., Frolova, V.A., Schultz, R.S., & Zoller, J. (1990). Conformational and complex formation ability of poly(methacrylic acid)-block-poly(1-methyl-4-vinylpyridinium chloride). *Makromol.Chem., 191, 1329–1333.* https://doi.org/10.1002/macp.1990.021910220

71 Bekturov, E.A., Kudaibergenov, S.E., Khamzamulina, R.E., Frolova, V.A., Nurgalieva, D.E., Schulz, R.C., & Zöller, J. (1992). Phase behavior of block-polyampholytes based on poly(methacrylic acid)-block-poly(1-methyl-4-vinylpyridinium chloride) in aqueous salt solutions. *Makromol. Chem., Rapid Commun., 13,* 225–229. https://doi.org/10.1002/marc.1992.030130407

72 Kudaibergenov, S.E., Frolova, V.A., Bekturov, E.A., & Rafikov, S.R. (1990). Interpolymer reactions with participation of blockpolyampholyte poly(1-methyl-4-vinylpyridinium chloride)–poly(methacrylic acid). *Proceedings of Academy of Sciences of USSR, 311,* 396–398.

73 Bekturov, E.A., Kudaibergenov, S.E., Frolova, V.A., Khamzamulina, R.E., Schulz, R.C., & Zoller, J. (1990). Conformational and complex formation ability of poly(methacrylic acid)-block-poly(1-methyl-4-vinylpyridinium chloride) in aqueous solution, *Makromol. Chem*., *191*, 457–463.

74 Kabanov, V.A. (2005) Polyelectrolyte complexes in solution and in the condensed phase. *Uspekhi Khimii*, 74, 5–23. [in Russian].

75 Chen, L., Honma, Y., Mizutani, T., Liaw, D.-J., Gong, J.P., & Osada, Y. (2000). Effect of polyelectrolyte complexation on the UCST of zwitterionic polymer. *Polymer*, *41*, 141–147. https://doi.org/10.1016/S0032-3861(99)00161-5

76 Nakahata, R., & Yusa, S. (2018). Preparation of water-soluble polyion complex (PIC) micelles covered with amphoteric random copolymer shells with pendant sulfonate and quaternary amino groups. *Polymers, 10(2),* 205. https://doi.org/10.3390/polym10020205

77 Nakai, K., Ishihara, K., Kappl, M., Fujii, S., Nakamura, Y., & Yusa, S. (2017). Polyion complex vesicles with solvated phosphobetaine shells formed from oppositely charged diblock copolymers. *Polymers*, 9, 49. https://doi.org/10.3390/polym9020049

78 Kossel, A. (1896). Uber die basischen Stoffen des Zellkerns (The basic substances of the cell nucleus). *Z. Physiol. Chem.*, *22*, 178.

79 Bungenberg de Jong, H.G. (1934). Complex relationships in lyophilic colloidal systems. I. General introduction. *Recl. Trav. Chim. Pays-Bas*, *53*, 163-170. https://doi.org/10.1002/recl.19340530207

80 Bungenberg de Jong, H.G. & Kruyt, H.R. (1929). Coacervation (Partial miscibility in colloid systems). *Proc. KNAW*, *32*, 849–856.

81 Xia, J. Protein-polyelectrolyte complexes / J. Xia, P. Dubin, J. Bock, R. Davis, D.N. Schulz, C. Thies. — Berlin, Heidelberg: Macromolecular Complexes in Chemistry and Biology. Springer, 1994.

82 Cooper, C. L., Dubin, P. L., Kayitmazer, A. B., & Turksen, S. (2005). Polyelectrolyte–protein complexes. *Current Opinion in Colloid & Interface Science*, *10(1-2)*, 52–78. https://doi.org/10.1016/j.cocis.2005.05.007

83 Kayitmazer, A.B., Seeman, D., Minsky, B.B., Dubin, P.L., & Xu, Y. (2013). Protein–polyelectrolyte interactions. *Soft Matter*, *9(9)*, 2553. https://doi.org/10.1039/c2sm27002a

84 Gao, S., Holkar, A., & Srivastava, S. (2019). Protein–polyelectrolyte complexes and micellar assemblies. *Polymers*, *11(7)*, 1097. https://doi.org/10.3390/polym11071097

85 Khutoryanskiy, V.V., Nurkeeva, Z.S., Mun, G.A., Rebenchuk, N.L., Ivaschenko, A.T., & Rosiak, J.M. (2002). Polycomplexes of bovine serum albumin with poly[2-methacryloyloxy) ethyl]trimethyl ammonium chloride. *Euras. Chem. Tech. J.*, *4*, 195-198. https://doi.org/10.18321/ectj534

86 Patrickios, C.S., Jang, C.J., Hertler, W.R. & Hatton, T.A. (1993). Protein interactions with acrylic polyampholytes, *Polym.Prepr*., *34(1)*, 954-955. https://doi.org/ 10.1002/bit.260440903

87 Viklund, C. & Irgum, K. (2000). Synthesis of porous zwitterionic sulfobetaine monoliths and characterization of their interaction with proteins, *Macromolecules*, 33, 2539-2544. https://doi.org/10.1021/ma991965

88 Patrickios, C. S., Sharma, L. R., Armes, S. P., & Billingham, N. C. (1999). Precipitation of a water-soluble ABC triblock methacrylic polyampholyte: effects of time, pH, polymer concentration, salt type and concentration, and presence of a protein. *Langmuir, 15(5)*, 1613–1620. https://doi.org/10.1021/la970662a

89 Nath, S., Patrickios, C.S., & Hatton, T. A. (1995). Turbidimetric Titration Study of the Interaction of Proteins with Acrylic Polyampholytes. *Biotechnol.Prog*. *11(1)*, 99–103. https://doi.org/10.1021/bp00031a014

90 Nath, S. (1995). Complexation behavior of proteins with polyelectrolytes and random acrylic polyampholytes using turbidimetric titration. *J.Chem.Tech.Biotech., 62(3),* 295-300. https://doi.org/10.1002/jctb.280620313

91 Patrickios, C.S., Hertler, W.R. & Hatton, T.A. (1994). Protein complexation with acrylic polyampholytes. *Biotechnol.Bioeng*., *44*, 1031–1039. https://doi.org/10.1002/bit.260440903

92 Xu, W., Rudov, A. A., Schröder, R., Portnov, I. V., Richtering, W., Potemkin, I. I., & Pich, A. (2019). Distribution of ionizable groups in polyampholyte microgels controls interactions with captured proteins: from blockade and "levitation" to accelerated release. *Biomacromolecules. 20 (4)*, 1578-1591. https://doi.org/10.1021/acs.biomac.8b01775

93 Gelissen, A.P.H., Scotti, A., Turnhoff S.K., Janssen C., Radulescu, A., Pich, A., Rudov, A.A., Potemkin, I.I., Richtering, W. An anionic shell shields a cationic core allowing for uptake and release of polyelectrolytes within core-shell responsive microgels. *Soft Matter*, 2018, vol. 14, p.4287. https://doi.org/10.1039/C8SM00397A

94 Gao, W., Liu, X.-L., Li, J.-Y., Lian, H., & Mao, L. (2019). One-pot preparation of zwitterionic sulfoalkylbetaine monolith for rapid and efficient separation of lysozyme from egg white. *Journal of Pharmaceutical and Biomedical Analysis*, *175*, 112761. https://doi.org/10.1016/j.jpba.2019.07.009

95 Shakhvorostov, A.V., & Kudaibergenov, S.E. (2021). Molecular imprinting of bovine serum albumin and lysozyme within the matrix of polyampholyte hydrogels based on acrylamide, sodium salt of 2-acrylamido-2-methyl-1-propanesulfonic acid and (3-acrylamidopropyl)trimethyl ammonium chloride. Chemical Bulletin of Kazakh National University**,** *100(1),* 4-11. https://doi.org/https://doi.org/10.15328/cb1182

96 US Patent 6383811. Polyampholytes for delivering polyions to a cell / Wolff J.A., Hagstrom J.E., Budker V.G., Trubetskoy V.S.

97 US Patent 2004/0162235 A1. Delivery of siRNA to cells using polyampholytes / Trubetskoy V.S., Rozema D.B., Monahan S.D., Budker V.G., Hagstrom J.E., Wolf J.A.

98 Koseki, T., Kanto, R., Yonenuma, R., Nakabayashi, K., Furusawa, H., Yano, S., & Mori, H. (2020). Multi-stimuli-responsive chiral-achiral ampholytic block copolymers composed of poly(N-acryloyl amino acid) and poly(vinyl amine). *Reactive and Functional Polymers, 104540*. https://doi.org/10.1016/j.reactfunctpolym.2020.104540

99 Asayama, S., Nogawa, M., Takei, Y., Akaike, T., & Maruyama, A. (1998). Synthesis of novel polyampholyte comb-type copolymers consisting of a poly(L-lysine) backbone and hyaluronic acid side chains for a DNA carrier. *Bioconjugate Chemistry, 9(4),* 476–481. https://doi.org/10.1021/bc970213m

100 Kudaibergenov, S.E. (2020). Advances in synthetic polyampholytes for biotechnology and medicine. *Rev. J. Chem., 10(1–2),* 12–39. https://doi.org/10.1134/S2079978020010021

101 Skorikova, Y.Y., Vikhoreva, G.A., Kalyuzhnaya, R.I., Zezin, A.B., Gal'braikh, L.S., & Kabanov, V. A. (1988). Polyelectrolyte complexes based on chitosan. *Polymer Science U.S.S.R., 30(1),* 49–55. https://doi.org/10.1016/0032-3950(88)90253-5

102 Elschner, T., & Heinze, T. (2014). A promising cellulose-based polyzwitterion with pH-sensitive charges. *Beilstein Journal of Organic Chemistry, 10,* 1549–1556. https://doi.org/10.3762/bjoc.10.159

103 Vranckx, C., Lambricht, L., Préat, V., Cornu, O., Dupont-Gillain, C., & vander Straeten. A. (2022). Layer-by-layer nanoarchitectonics using protein–polyelectrolyte complexes toward a generalizable tool for protein surface immobilization. *Langmuir, 38(18),* 5579-5589. https://doi.org/10.1021/acs.langmuir.2c00191

104 Kokufuta, E., & Nishimura, H. (1991). Complexation of pepsin poly(ethylene glycol). *Polymer Bulletin, 26,* 277–282. https://doi.org/10.1007/BF00587970

105 Xia, J., Dubin, P.L., & Kokufuta E. (1993). Dynamic and electrophoretic light scattering of a water-soluble complex formed between pepsin and polyethylene glycol. *Macromolecules, 26,* 6688–6690. https://doi.org/10.1021/ma00076a066

106 Azegami, S., Tsuboi, A., Izumi, T., Hirata, M., Dubin, P.L., Wang, B., & Kokufuta E. (1999). Formation of an Intrapolymer Complex from Human Serum Albumin and Poly(ethylene glycol). *Langmuir, 15,* 940-947. https://doi.org/10.1021/la9809269

107 Matsunami, H., Fujita, C., Ogawa, K., & Kokufuta, E. (2007). Static light scattering study of complex formation between protein and neutral water-soluble polymer. *Colloids and Surfaces B: Biointerfaces, 56(1-2),* 149–154. https://doi.org/10.1016/j.colsurfb.2006.10.01

108 Gullapalli, R. P. (2010). Soft gelatin capsules (softgels). *Journal of Pharmaceutical Sciences, 99(10),* 4107–4148. https://doi.org/10.1002/jps.22151

109 Alipal, J., Mohd Pu'ad, N. A. S., Lee, T. C., Nayan, N.H., Sahari, N., Basri, H., Abdullah, H. Z. (2021). A review of gelatin: properties, sources, process, applications, and commercialisation. *Materials Today: Proceedings, 42,* 240–250. https://doi.org/10.1016/j.matpr.2020.12.922

110 Chang, C.-P., Leung, T.-K., Lin, S.-M., & Hsu, C.-C. (2006). Release properties on gelatin-gum arabic microcapsules containing camphor oil with added polystyrene. *Colloids and Surfaces B: Biointerfaces, 50(2),* 136–140. https://doi.org/10.1016/j.colsurfb.2006.04.008

111 Shaddel, R., Hesari, J., Azadmard-Damirchi, S., Hamishehkar, H., Fathi-Achachlouei, B., & Huang, Q. (2018). Use of gelatin and gum Arabic for encapsulation of black raspberry anthocyanins by complex coacervation. *International Journal of Biological Macromolecules, 107,* 1800–1810. https://doi.org/10.1016/j.ijbiomac.2017.10.044

112 de Oliveira, L.C., Barbosa, J.R., da Conceição Amaral Ribeiro, C., Marçal de Vasconcelos, M.A., de Aguiar, B.A., da Silva Pereira, J.V., Albuquerque, G.A., da Silva, F.N.L., Crizel, R.L., Campelo, P.H., & de Fátima Henriques Lourenço, L. (2019). Improvement of the characteristics of fish gelatin — gum arabic through the formation of the polyelectrolyte complex. *Carbohydrate Polymers, 223,* 115068. https://doi.org/10.1016/j.carbpol.2019.115068

113 Moustafine R.I. (1991). Development and studies of prolonged release dosage forms based on interpolymer complexes. PhD thesis, I.I. Sechenov Moscow Medical Academy, Moscow.

114 Al-Saadi, A., Yu, C.H., Khutoryanskiy, V.V., Shih, S.-J., Crossley, A., & Tsang, S.C. (2009). Layer-by-layer electrostatic entrapment of protein molecules on superparamagnetic nanoparticle: a new strategy to enhance adsorption capacity and maintain biological activity. *The Journal of Physical Chemistry C, 113(34),* 15260–15265. https://doi.org/10.1021/jp903100j

115 Lomova, M.V., Brichkina, A.I., Kiryukhin, M.V., Vasina, E.N., Pavlov, A.M., Gorin, D.A., Sukhorukov, G.B., Antipina, M.N. (2015). Multilayer Capsules of Bovine Serum Albumin and Tannic Acid for Controlled Release by Enzymatic Degradation. *ACS Appl. Mater. Interfaces*, 7, 11732−11740. https://doi.org/10.1021/acsami.5b03263

116 Wang, Y.-F., Gao, J.Y., & Dubin, P.L. (1996). Protein separation via polyelectrolyte coacervation: selectivity and efficiency. *Biotechnol. Prog.,12,* 356– 362. https://doi.org/10.1021/bp960013+

117 Thiele, M.J., Davari, M.D., König, M., Hofmann, I., Junker, N.O., Garakani, T.M., Vojcic, L., Fitter, J., Schwaneberg, U. (2018). Enzyme–polyelectrolyte complexes boost the catalytic performance of enzymes. *ACS Catal., 8,* 10876–10887. https://doi.org/10.1021/acscatal.8b02935

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Жасанды, табиғи және жартылай табиғи полиамфолиттердің интерполимерлі кешендері: Шолу

Бұл шолу жасанды, табиғи және жартылай табиғи полиамфолиттерге, олардың басқа полиэлектролиттермен және иондық емес полимерлермен кешен түзу қабілетіне арналған. Полиамфолиттердің анықтамасы мен классификациясы беріліп, олардың физика-химиялық қасиеттеріне қысқаша шолу жасалған. Амин қышқылдарынан алынған ішкі ретсіз ақуыздар мен жартылай табиғи полиамфолиттердің конформациялық және фазалық сипаттамалары берілген. Шолудың негізгі бөлімі полиамфолиттері бар полимерлі кешендердің түзілуіне арналған. Осы саладағы зерттеулердің көпшілігі қарама-қарсы зарядталған полиэлектролиттері бар полиамфолиттердің полиэлектролиттік кешендерімен ұсынылған; алайда, әдебиеттерде сутегі байланыстарымен тұрақтанған комплекстердің түзілуі туралы мәліметтер де бар. Бұл жағдайда кешендер түзілу табиғаты көбінесе ерітіндінің pH-мен полиамфолиттердің изоэлектрлік нүктесімен анықталады. Полиамфолиттер мен басқа полимерлер арасындағы кешендердің түзілуі коллоидтық дисперсиялардың (нано- және микробөлшектердің) түзілуіне, сұйық-сұйық типі бойынша фазаның бөлінуіне (кешенді коацервация деп аталады), толық еритін кешендердің, сондай-ақ физикалық тігілген гельдердің пайда болуына әкелуі мүмкін. Бұл саладағы зерттеулердің едәуір бөлігі ақуыздар түзетін кешендерге арналған. Полиамфолиттердің интерполимерлік кешендерін биотехнологияда, медицинада, инкапсуляция технологиясында, әртүрлі қоспаларды бөлу ғылымында, биокатализде, тамақ ғылымында және фармацевтикада қолданылуы талқыланған.

Кілт сөздер: полиамфолиттер, полипептидтер, ішкі ретсіз белоктар (ІРБ), ішкі-макромолекулалар аралық кешендер (ішкі-МАК), макромолекулалық аралық кешендер (МАК), интерполиэлектролиттік кешендер, дәрілік заттарды жеткізу, кешенді коацервация, желатин.

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Интерполимерные комплексы синтетических, природных и полуприродных полиамфолитов Обзор

Данный обзор посвящен синтетическим, природным и полуприродным полиамфолитам и их способности к образованию комплексов с другими полиэлектролитами и неионными полимерами. Даны определение и классификация полиамфолитов, приведен краткий обзор их физико-химических свойств. Описано конформационное и фазовое поведение внутренне разупорядоченных белков и полуприродных полиамфолитов, полученных из аминокислот. Основная часть этого обзора посвящена образованию полимерных комплексов с полиамфолитами. Большинство исследований в этой области представлено полиэлектролитными комплексами полиамфолитов с противоположно заряженными полиэлектролитами; однако в литературе имеются и сведения об образовании комплексов, стабилизированных водородными связями. Природа комплексообразования в данном случае часто определяется pH раствора, а также изоэлектрической точкой полиамфолитов. Комплексообразование между полиамфолитами и другими полимерами может приводить к формированию коллоидных дисперсий (нано- и микрочастицы), фазовому разделению по типу жидкость–жидкость (называемому комплексной коацервацией), образованию полностью растворимых комплексов, а также физически сшитых гелей. Значительная часть исследований в этой области посвящена комплексам, образованным белками. Обсуждено применение интерполимерных комплексов полиамфолитов в биотехнологии, медицине, технологиях инкапсулирования, науке о разделении различных смесей, биокатализе, пищевой науке и фармацевтике.

Ключевые слова: полиамфолиты, полипептиды, внутренне разупорядоченные белки, внутримакромолекулярные комплексы, межмакромолекулярные комплексы, интерполиэлектролитные комплексы, доставка лекарств, комплексная коацервация, желатин.

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