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Analysis of Macromolecular Systems as Enabler for Energy and Life Science Applications

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Ideas concerning the conceptual existence of macromolecular and colloidal systems found their inception at the beginning of the last century. The experimental technology developed to discover and characterize those systems can be associated with seminal pioneers laying the foundations for microscopic, hydrodynamic, and light scattering approaches. In this perspective, we focus our attention on the origins of the discovery and characterization of macromolecular and colloidal systems with selected examples from the beginnings to the present. This perspective attempts to directly interconnect the design of new macromolecular as well as colloidal systems and the simultaneous development of using advanced characterization techniques for design verification. While not claiming a complete coverage of the entire field of modern polymer science, our selected examples concern the field of life science and the recently and rapidly developing area of energy materials.

1. Brief Historical Background

Discoveries in the natural sciences required inventions of analytical tools. Those tools were developed at the verge from the 19th to the 20th century. A perhaps arbitrary time point to start is the discovery of X-rays by Wilhelm Conrad Röntgen in 1895 (Nobel Prize in physics in 1901),[1] that, undoubtedly, laid the foundations of modern radiology and crystallography.[2] In 1903, a breakthrough in technology was the invention of the ultramicroscope by Henry Siedentopf (Carl Zeiss AG, Jena) and Richard Zsygmondy (University of Göttingen, formerly among others, Schott, Jena) (Nobel Prize in chemistry in 1925).[3] Here, light scattering was used to visualize matter that was smaller than the wavelength of visible light, enabling the observation of (colloidal) particles, which could not previously be observed using any other experimental technique.[4,5]

In 1920, Hermann Staudinger (Nobel Prize in chemistry in 1953)[6] published his seminal article "Über Polymerisation", which can be considered as the origin of modern polymer science and the beginning of the "polymer age".[7] In search for experimental methods to prove the existence and structure of macromolecules, the concept of the intrinsic viscosity was born, also known as the Staudinger-index.[8] In Staudinger's view, the intrinsic viscosity, $[\eta]$, determined from a polymer solution, can be related to the molar mass of the macromolecule, M, which was originally assumed being a linear relationship, $[\eta] \sim M$.[8,9] This linear relationship was later established being exponential in nature and described by a relation $[\eta] \sim M^{b_{[\eta]}}$, also known as Mark-Houwink equation.[10,11] In modern times, $[\eta]$ is a prime hydrodynamic characteristic for the characterization of polymers, is representative of the hydrodynamic volume of macromolecular or colloidal objects, and is used in the classical double-logarithmic Kuhn-Mark-Houwink-Sakurada relationships.[12] In his original publication, Staudinger hypothesizes on polymerization products being, e.g., "monomolecular objects colloidally dissolved" or defining "high molecular compounds behaving as one molecule". He also argues that there is no sense in determining the "molecular mass" of such systems because of variations in mass values depending on concentration, i.e., a nonideality problem.[7] These entities inevitably lead to a particular value of $[\eta]$, i.e., the viscosity of a polymer solution at infinite dilution.[7,13] From the very beginning of the "polymer age" a persistent bottleneck was the determination of molar masses of macromolecular substances in solution. Historically, the most common (absolute) method to determine the molar mass of "large" molecules or "aggregates" was osmotic pressure measurements, which were thought to be not suitable for the

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determination of the molar mass of polymers.[14] For example, Caspari reported osmotic pressure measurements on dilute rubber solutions in 1914. He observed the concentration dependence of the apparent molar mass, leading to the conclusion that it was impossible to use this method to determine the molar masses of components present in such systems.[15] However, nowadays osmotic methods are known as one of the few absolute methods in determining the molar mass of synthetic polymers. By the osmotic pressure being dependent on the number of molecules, the respective number average molar mass is obtained.

It needs to be emphasized that the precise structure of polymers and their molar masses were figures of merit of debate and only accessible by a limited selection of (absolute) techniques. Therefore, their discovery and description were closely connected to new analytical experimental methods. All those methods aim at the very same characteristics.

While $[\eta]$ represents one of the very first fundamental hydrodynamic characteristics (vide supra), other hydrodynamic measurement principles aiming at characteristics of sedimentation and diffusion were developed. In 1923, The Svedberg (Nobel Prize in chemistry in 1926)[16] invented the first concept of an analytical ultracentrifuge, and the modern field of analytical ultracentrifugation (AUC), with the aim of absolute molar mass determinations, was born. Early demonstrations of this new technology concerned the determination of size and distribution of sizes of so-called "amicroscopic" particles.[17] Svedberg's original motivation was the study of disperse systems for which he was awarded the Noble Prize. Conceptional access to those systems was possible by the observation of the movement of matter under action of a centrifugal force.[18] **Figure 1a** shows the overall lab setup including the centrifuge, while Figure 1b shows a photograph of the early ultracentrifuge. A pictorial representation of the centrifuge rotor with a cell containing a sector-shaped sample volume and housed in the centrifuge rotor is shown in Figure 1c. Such early system was used by Svedberg in his experiments.[19,20] First examples of study concerned "high-molecular substances" such as proteins as well as carbohydrates and disperse cellulose derivatives.[21,22]AUC became an integral part of biophysics for studying both biological (large) molecules and colloids.[23,24] Nowadays, though being very expensive and an experimental art, AUC is one of the most powerful analytical methods in the field of nanomedicine and the overarching area of the life sciences.[25–27]

The sedimentation coefficient, s, as formulated by Svedberg thereby represents another macromolecular hydrodynamic characteristic related to the molar mass and/or size of macromolecules and colloids. As for the intrinsic viscosity, $[\eta]$, the sedimentation coefficients relate to the molar mass within a series of macromolecules in an exponential fashion, $s \sim M^{b_s}$. So called sedimentation velocity experiments, e.g., performed with an apparatus such as in Figure 1 also allow the determination of the third hydrodynamic characteristic, i.e., the diffusion coefficient, D. Classically, D values can be determined by synthetic boundary experiments, in the AUC or with apparatuses developed in 1936.[28–30] D-values can be estimated by a multiplicity of (more modern) techniques for macromolecules and colloidal systems, e.g., dynamic light scattering (DLS),[31] nuclear magnetic resonance spectroscopy (NMR),[32] nanoparticle tracking analysis (NTA),[33] or fluorescence correlation spectroscopy (FCS).[34]

A seminal pioneer and Nobel Laureate famous for the concepts of diffusion was Albert Einstein (Nobel Prize in Physics in 1921).[35] In the Stokes–Einstein equation, the introduction of the hydrodynamic equivalent sphere was established. This was by considering both hydrodynamics (friction coefficient of a spherical particle) and thermodynamics (energy) formulated as a simple fraction.[36] Here, an inverse relation of the diffusion coefficient, D, to the hydrodynamic diameter, d_h, i.e., $D \sim 1/d_h$, is found. Thereby, the D-value determines the hydrodynamic equivalent size, d_h, of a spherical particle that diffuses at the same speed as the object under experimental investigation. In view of the above-mentioned relations, the diffusion coefficient, D, for a series of macromolecules or colloids is also related to the molar mass in an exponential fashion $D \sim M^{|b_D|}$. D is also representative of the size of macromolecules and colloids.

Interestingly, all the prime hydrodynamic characteristics, $[\eta]$, s, and D can be united by the concept of the hydrodynamic invariant, A_0, i.e., the relation of all hydrodynamic characteristics among each other (**Figure 2a**), respectively correlated to the molar mass (Figure 2b).[37–39] Fundamentally, the establishment of A_0 is possible with a singular molar mass and knowledge of all three hydrodynamic characteristics. The interplay for the exponents in the double logarithmic Kuhn–Mark–Houwink–Sakurada scaling relationships requires investigation of a series molar masses.[40] The meaning of both (hydrodynamic invariant A_0 and relation of scaling exponents among each other) is based on the same physical principles of $[\eta]$, s, and D.

The development of small angle X-ray scattering (SAXS) in the 1930s matured to a very useful tool for studying polymers until now.[41–43] The cutting-edge technique currently pursued involves using radiation from Synchrotrons, providing high-quality X-rays. The first ideas of Synchrotrons were developed in 1944, while the Synchrotron built in 1947 allowed observation of visible Synchrotron radiation.[44] Later, modern approaches for DLS were developed, which is one of the most used techniques in the areas of polymer and bioscience.[31] Though being not a hydrodynamic technique, scattering techniques provide important information on macromolecules and colloids, that, among structural insight allow the determination of molar masses, M, and / or radii of gyration as well as information on shape anisotropy.[45]

After groundbreaking work on microscopic techniques by Zsigmondy and Siedentopf (vide supra), the year 1932 marked another milestone in microscopy when Ernst Ruska (Nobel Prize in Physics 1986)[46] and Max Knoll presented the first electron microscope, initiating a shift from light-based to electron-based imaging of nano-objects.[47] The opportunities based thereon are obvious since smaller dimensions of matter are accessible. Beside the basics of the transmission electron microscope (TEM), Max Knoll also developed the scanning electron microscopy (SEM) technology which was first published in 1935.[48] Using the knowledge of the former project for the development of TEM, he was able to build the first SEM, which could scan as much as 50 frames per second. Further details about discoveries in electron microscopy were reviewed in detail elsewhere.[49] Microscopy facilitated by TEM and SEM enabled scientists to explore the realm of submicroscopic particles with nanometer-scale resolution, providing invaluable insights into the study of colloidal matter.[50] The boundaries of resolution are pushed downward with the newer generations of electron microscopes.

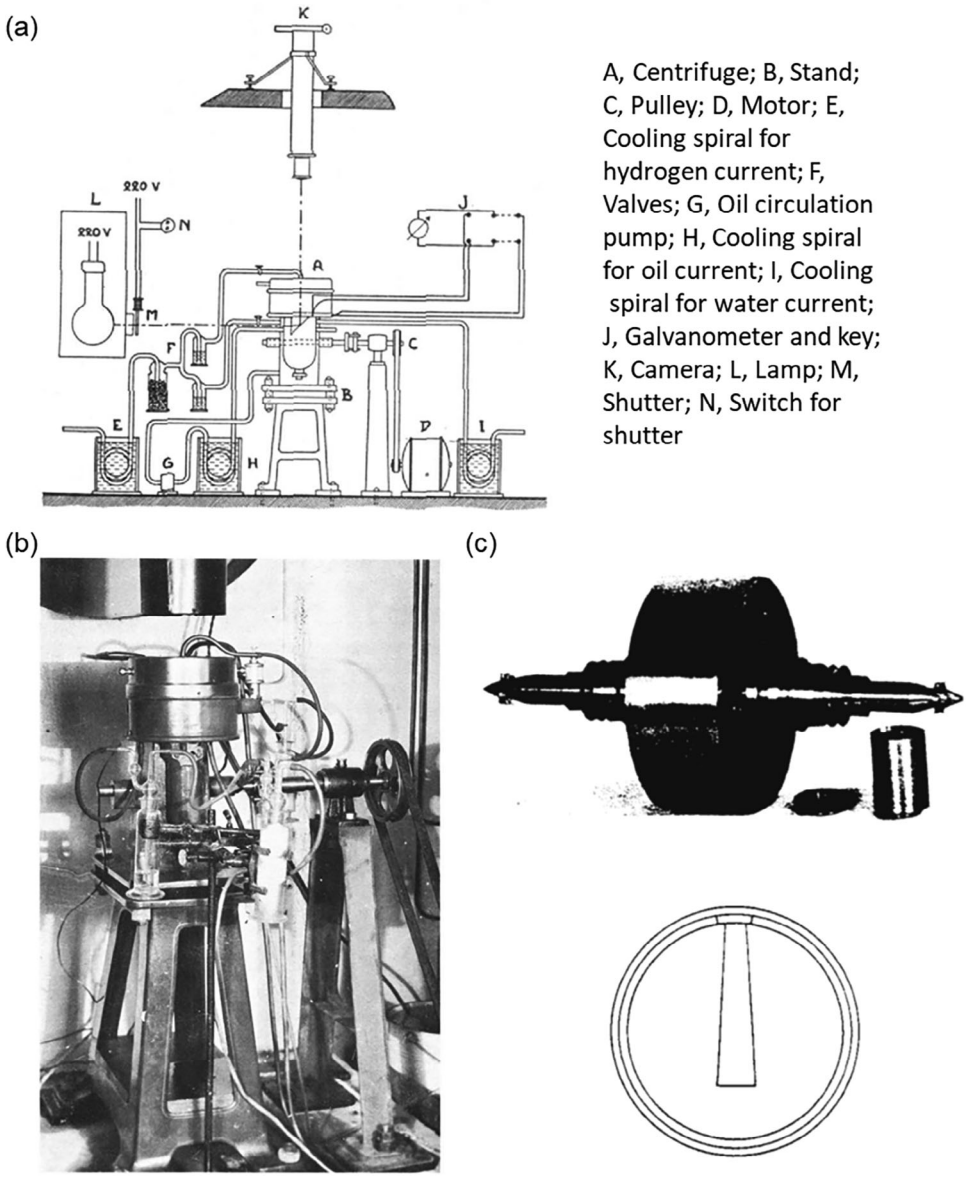

Figure 1. a) Overall lab setup including the ultracentrifuge, b) photograph from the first ultracentrifuge (Uppsala, 1924), and c) rotor and cell design. a) Adapted with permission.[17] Copyright 1924, American Chemical Society. b) Adapted with permission.[19] Copyright 1976, Elsevier B.V. c) Adapted with permission.[20] Copyright 1927, The Nobel Foundation.

It was the experimental understanding that was required to describe the physicochemical structure of such "molecular" systems represented by polymers and colloids.[51,52] Such work addressing the concept of "polymers" and "colloids", both, experimentally and theoretically, laid the foundations of modern polymer and colloid science. This included the concepts of statistical physics of macromolecules and the refined understanding of the connection between polymer properties as well as their dependence on the molar mass, *M* (Figure 2).[37,53–56] The perhaps most comprehensive book on early polymer concepts was written by Paul J. Flory published in 1953.[57] Flory received the Nobel Prize in chemistry in 1974 for his "epoch making research" on the physical chemistry of macromolecules.[58] At that time, the actual experimental opportunities developed to study matter, were closely connected to the chemistry of polymers, i.e., not treated as different disciplines. New analytical tools enabled discoveries while the discoveries helped further developing analytical tools. The subdivision of disciplines emerged later (vide infra). The combination of the discovery of experimental techniques and hypothesis together with theoretical opportunities and relations that were born at the early days, laid the foundation of modern polymer and colloidal science. In 1966, J. Calvin Giddings invented Field-Flow Fractionation (FFF)[59] as an addition to polymer and colloid analysis techniques with a variety of modii of the FFF family, such as sedimentation FFF, thermal FFF, gravitational FFF, and electrical FFF.[60] Interestingly, separation in FFF occurs based on the diffusion coefficients, which, according to Giddings considerations, can also be derived from the elution time in FFF.[61–63]

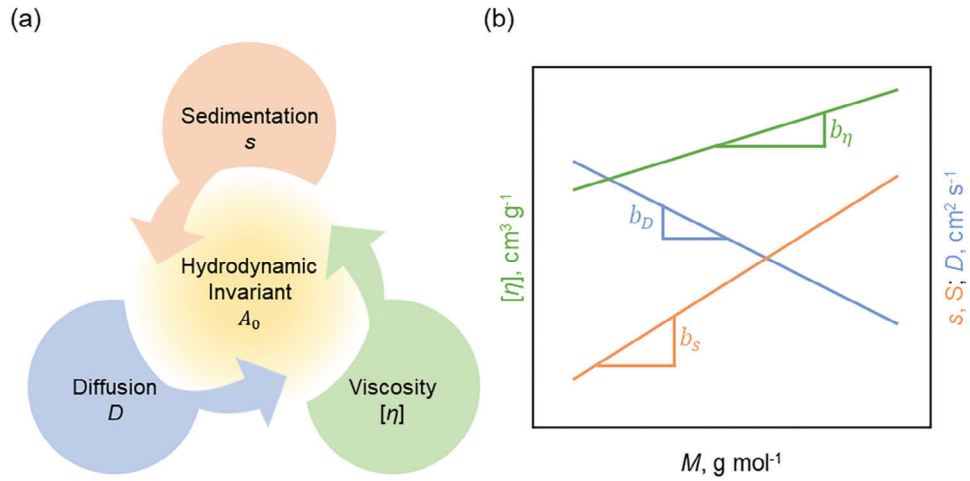

Figure 2. Simplified scheme of the major hydrodynamic characteristics [η], s, D. a) Their interplay can be expressed by the hydrodynamic invariant, A_0, that is a characteristic of macromolecules and colloids. b) [η], s, D are also proportional to the molar mass with particular exponential dependencies, determinable by double logarithmic plots.

Thereby, it also relates to the concept of primary hydrodynamic characteristics in Figure 2.

2. Early Examples of the Detailed Characterization of Macromolecules of Natural Origin

An early example of a macromolecular system that was studied is that of the most abundant natural macromolecule cellulose. It was hypothesized being a linear chain macromolecule based on X-ray diffraction measurements in 1926.[64] It was characterized in terms of its physicochemical characteristics and its molar mass, particularly with AUC, by Gralen and Svedberg in 1943.[22] Svedberg as reported in his Nobel Lecture in 1927,[65] their crystal structures were decrypted by X-ray scattering in the late 1950s by Max Ferdinand Perutz and John Cowdery Kendrew (Nobel Prize in Chemistry 1962).[66]

Another milestone in discovery that was supported by analytical methods was X-Ray crystallography aiming at the resolution of the structure of DNA. Experimental results by Raymond G. Gosling and Rosalind E. Franklin (also known as Photograph 51, **Figure 3a**) in 1952 suggested a helical structure,[67] inspiring James D. Watson and Francis H. C. Crick. J. D. Watson and F. H. C. Crick suggested such structure in their paper with a scheme (Figure 3b).[68] Both papers, the one from R. E. Franklin and R. G. Gosling (King's College London) containing experimental results and the one suggesting the DNA structure from J. D. Watson and F. H. C. Crick (Cavendish Laboratory, Cambridge) appeared in the same issue in Nature in 1953.[67,68] J. D. Watson and F. H. C. Crick eventually wrote in their acknowledgement "We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins and Dr. R. E. Franklin and their coworkers at Kings's college London." Unfortunately, R. E. Franklin being a key figure in the discovery of the structure of DNA passed away at the age of 37 in 1958. In 1962, J. D. Watson, F. H. C. Crick, and Maurice H. F. Wilkins received the Nobel Prize in Physiology or Medicine for their contribution in the discovery of DNA.[69] However, the seminal contribution of R. E. Franklin and R. G. Gosling in the line of discovery of DNA should not be forgotten. By density gradient centrifugation techniques utilizing cesium chloride, the replication mechanism of DNA was directly accessible and published in 1958. Here, labeled DNA strands with nitrogen isotopes were utilized that persisted during replication. The DNA strands were obtained from *Escherichia coli* lysates (Figure 3c).[23] In this experiment, mixtures of virgin DNA strands and those with the heavy isotope of nitrogen could be identified being present in certain quantities through the generations of replications. Though being chemically very similar, the different isotopes of nitrogen equip the DNA with physically different properties. Thus, it was established that during the replication process the daughter molecule receives one parent unit and the replicative act results in a molecular doubling, experimentally supporting the proposed mechanism of DNA replication by Watson and Crick (Figure 3c). Also, using density gradient centrifugation, the monodispersity and the precise molar mass of hemoglobin was found in 1926 by Svedberg already.[20,21]

3. From Past to Present

All analytical methods developed in the last century are under constant technological improvement and refinement. The timeline of those (selected) powerful methods described above and comprehended in **Figure 4**, middle, enabled understanding and development of the up-and-coming area of life sciences. Starting from the discovery of the structure of DNA as well as that of proteins (vide supra), synthetic polymers found their way into pharmaceutical applications, e.g., poly(lactic-*co*-glycolic acid) (PLGA)[70] and poly(ethylene glycol) (PEG).[71] After the discovery of liposomes,[72] liposome-coated mRNA transporters were reported in 1978.[73,74] The concerted use of biomacromolecules (e.g., DNA and mRNA) and synthetic polymers (e.g., PEG) in vaccinations to address the SARS-CoV-II pandemics, highlighted the dawn of modern mRNA vaccines, utilized large-scale in the form of lipid nanoparticles (LNPs) in 2020 (Figure 4, top).[75,76] The coming field of energy polymers dates back to the 19th century with polyaniline,[77] through to redox-active polymers,[78]

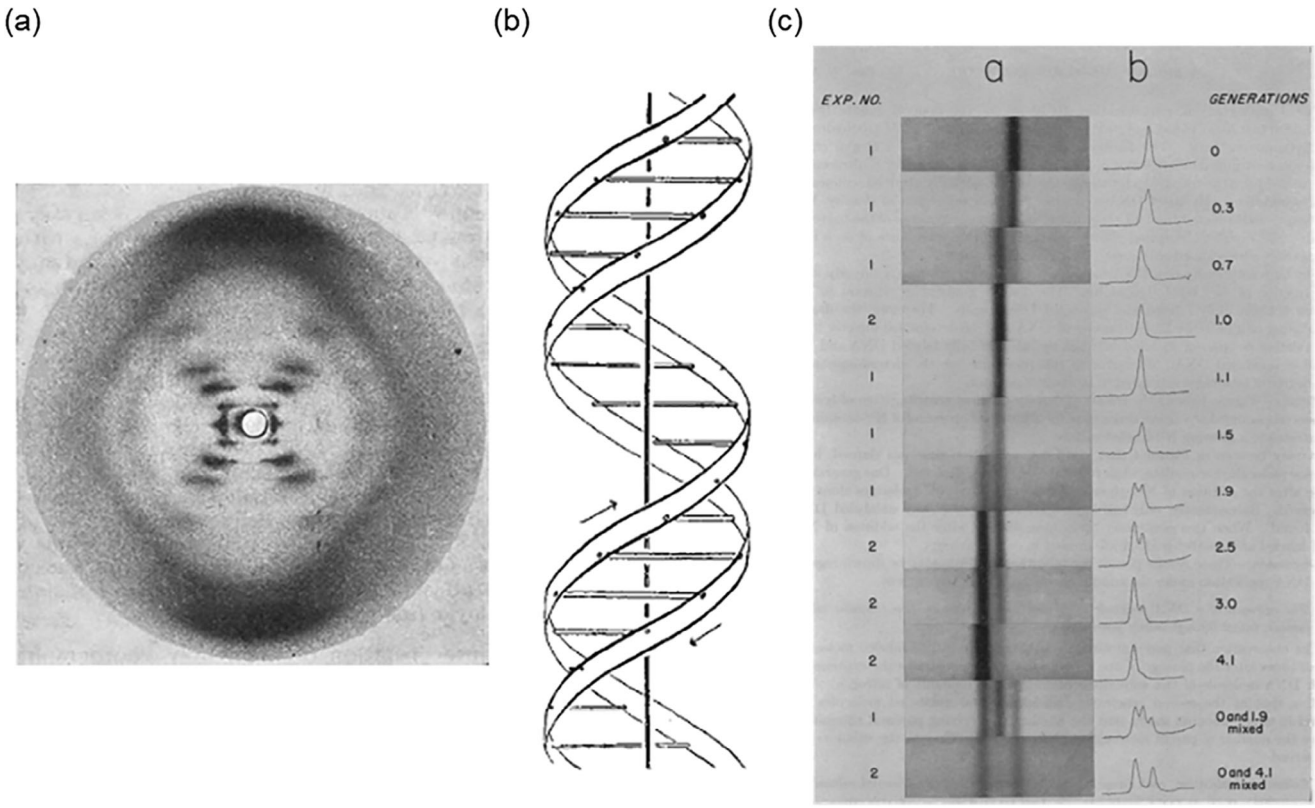

Figure 3. a) Photograph 51 from the work of R. G. Gosling and R. E. Franklin, suggesting b) the double helical structure of DNA proposed by J. D. Watson and F. H. C. Crick, and c) density gradient AUC experiments indicating the replication mechanism of DNA where photographs were taken after 24 h of centrifugation at 44 770 rpm and the microdensitometer tracings show the DNA distribution in the region of the bands. a) Adapted with permission.[67] Copyright 1953, Springer Nature. b) Adapted with permission.[68] Copyright 1953, Springer Nature. c) Adapted with permission.[23] Copyright 1958, National Academy of Sciences.

polymeric radicals,[79] and conductive polymers.[80] Technologically, this concerns the first polymer batteries in 1958,[81] a redox polymer battery in 1965,[82] and present prototypes of, e.g., polymer redox flow batteries (PRFB) in 2015.[83] Polymers for battery applications as well demand the precise structure-property relationships of those charge storage materials in, e.g., PRFBs or in photovoltaics (Figure 4, bottom).[84,85] Though having a long history, the area gained momentum, particularly in the modern times and the need for new, reliable, and green sources of energy.

Based on the above considerations, we describe selected examples and our perception of the area of pharmapolymers and those in the relatively new area of polymers for energy applications. These both areas are interlinked by the discovery and development of analytical methods that transformed from a tool of

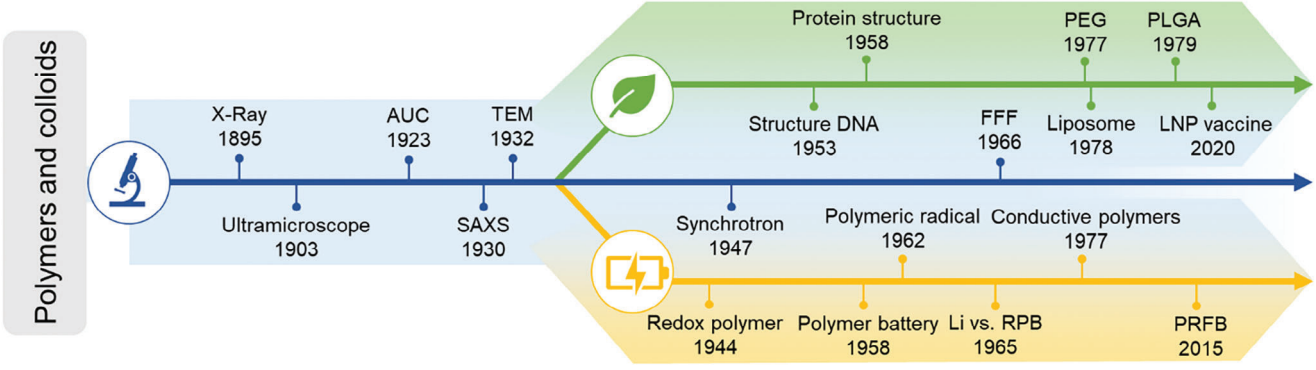

Figure 4. Selected events in the timeline of developed analytical tools (middle) enabling discovery and research in the modern field of life science (top) and energy materials (bottom).

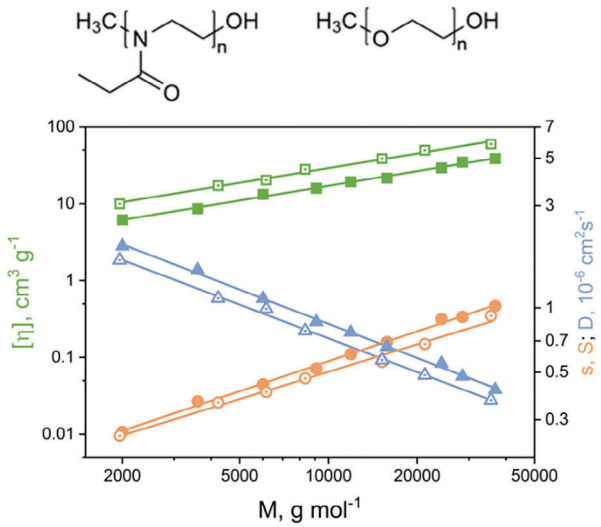

Figure 5. Example of scaling relationships of poly(2-ethyl-2-oxazoline)s (PEtOx), closed symbols, in reference to poly(ethylene glycol)s (PEG), open symbols. The hydrodynamic characteristics, represented by the intrinsic viscosity, [η], the sedimentation coefficient, s, and the diffusion coefficient, D, are plotted against the molar mass, M, in a double logarithmic fashion with the same color code as in Figure 2. Adapted with permission.[91] Copyright 2018, American Chemical Society.

discovery to an enabler in identification and verification of materials utilized in modern areas of research (Figure 4).

4. Pharmapolymers

In terms of historical development, the area of pharmapolymers can be considered huge and practically concerns all polymers that have desirable properties to be used in medical applications. It is outside the scope of the present perspective to provide an accurate account on the status quo of pharmapolymers, which have been reviewed.[86] Thereby, we focus on a few entries that have industrial relevance already or having potential to acquire this. A recent and very contemporary example of a very important hydrophilic polymer is PEG. It is approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). While having widespread use in pharmacy such as salves, cremes, etc.,[87] it is used in molecular engineering of medically relevant materials and used as a stealth polymer for protein conjugation.[88] It can even be found in LNPs as an excipient for formulations, contemporarily pursued to support vaccination strategies. LNP technology gained momentum during the SARS-COV-II pandemic starting at the end of 2019, where the mRNA vaccines were utilized in large scale to fight the pandemic.

Macromolecular hydrodynamic characteristics and values of [η], s, and D, their interrelation and use in scaling relationships are very practical to describe and understand pharmapolymers (vide supra, Figure 2). In other words, their properties are assigned to numerical values of quantitative nature. **Figure 5** exemplifies double-logarithmic scaling relationships of all the hydrodynamic characteristics of methoxy-PEGs as introduced above (Figure 2b), including values of [η], s, and D.[89] The three key hydrodynamic characteristics describe macromolecular and colloidal materials most comprehensively, i.e., their numerical value, are parameters needed to understand them. All double-logarithmic relationships are linear with typical slopes as expected for random coil polymers. A perhaps other more fundamental interrelation of those characteristics is the hydrodynamic invariant, A_0 (Figure 2a) that assumed typical values for random coil polymers, irrespective of absolute values of [η], s, and D, and / or the corresponding molar mass, M.[40,89] Knowing about the well-known potential difficulties of PEG, i.e., an increased amount of antibodies found in the human population,[90] due to its wide use, alternatives to its replacement are also being actively studied. Quantitatively, PEGs can be replaced by another stealth polymer, e.g., poly(2-alkyl-2-oxazolines) (POx) based on very first key principle hydrodynamic characteristics, a situation that allows their informed use as alternatives.[91] This informed use can address individual characteristics or combinations thereof (Figure 5). Of particular interest is the molecular conformation and the hydrodynamic volume required in certain applications. Other hydrophilic polymers are on the radar screen of research and development. Those are, e.g., linear poly(glycerols),[92] polysarcosines[93] to name a few. Alternate polymer architectures are receiving interest as well, e.g., hyperbranched PEG copolymers[94] or hyperbranched poly(glycerols).[95] It needs to be emphasized that the characteristics of those macromolecules are determined by values of [η], s, and D. The molar mass, M, is a direct consequence of those characteristics, in other words, all of those characteristics can also be related to M (Figures 2b and 5).

One very widespread method for characterizing soluble polymers is size exclusion chromatography (SEC), which provides quick values of (relative) molar masses and dispersity of the polymer.[96] Unless performing a calibration with precisely known polymer standards of the same chemical identity, including end groups, all measurements establish relative molar masses.[91] The meaning of such molar masses and interpretational efforts regarding molecular properties are very limited. One option is an absolute calibration based on the hydrodynamic volume of the polymers (a situation where the intrinsic viscosity, [η], is needed again, Figure 2). Such absolute calibration was established as early as 1967.[97] In any case, an absolute method is needed for establishing such calibration by a precisely known molar mass, M, associated to the intrinsic viscosity, [η]. The calibration relates the product [η]M (in cm^3 mol^{-1}) to the elution volume.

Analytical knowledge is of crucial importance in pharmaceutical applications. There are various polymers that can be used for pharmaceutical applications such as for the formulation of nanoparticles. The advantage of polymer systems is their adaptability to the specific requirements.[98] This includes, e.g., the design of micelles having better performance in polyplexes.[99] Precise knowledge of the polymer properties is a prerequisite of their performance in nanoparticles.

Polymers that could be used in such nanoparticle formulations are, for example, those that could encapsulate genetic material in polyplexes.[100] There exist many different synthetic polymer and inorganic systems for applications in nanoparticles with a wide range of uses in the life sciences.[101] A well-known system for the transport of genetic material is polyethyleneimine (PEI). Conceptionally it can be derived from POx (vide supra).[102,103] It has a high number of cationic charges since the backbone contains nitrogen in the form of a secondary amine. As a

result of the high charge density, it can bind genetic material in large quantities. On the other hand, PEI has a pronounced cytotoxic effect imposed by the cationic charges, which has been intensively investigated already.[104,105] To date, several different polymers have been described for gene delivery that show promising properties, e.g., poly(2-dimethylamino)ethyl methacrylate (PDMAEMA).[106] Recent experimental approaches focusing on copolymers with increased hydrophobicity, e.g., pH-responsive polymers made of poly((n-butylmethacrylate)-*co*-(methylmethacrylate)-*co*-(2-(dimethylamino) ethylmethacrylate)). AUC enabled unprecedented insight in studying those polyplexes, identifying concerted sedimentation of polymer and DNA in the form of a polyplex by colocalization experiments at low speed.[107] However, experiments at higher speed indicated the presence of free polymer used for formulation but apparently not being part of the polyplex. Such direct quantitative insight is difficult to obtain by other experimental techniques. When utilizing dynamic light scattering, it is typically performed on mixtures. Larger materials scatter more, making it difficult to identify free polymers in the presence of large polyplex material.

Besides the delivery of nucleic acids, polymers are also applied to encapsulate a wide range of active pharmaceutical ingredients (API). One of these gold-standard hydrophobic pharmapolymers is PLGA, also known as RESOMER RG/LG. It has some key properties as it degrades into nontoxic lactic acid and glycolic acid. It is also approved by the FDA and EMA. There are, therefore, various possibilities for PLGA to be used in applications on the nanoscale, which have already been discussed in detail elsewhere.[108–110] Besides those gold standard pharmapolymers, other polymers of interest for use as an excipient in nanoparticle formulation are, e.g., the surfactant polyvinyl alcohol (PVA) and poly(vinylpyrrolidone) (PVP),[111] also known as Mowiol or the poloxamer polymers, also known under the trademark Pluronic. Pluronic-based polymers can also be used to stabilize particles in formulations.[112]

An important requirement for polymers used in pharmaceutical applications is the high analytical standards needed to obtain safe products with low risks for patients. A technique that has gained relatively little attention in the scientific literature of polymer analysis is high-performance liquid chromatography (HPLC) that has high resolving power for impurities such as different end-groups and separating individual oligomers stemming from the polymers' dispersity.[113–115] This is important, particularly when, e.g., considering the well-known PEG-diol impurities in methoxy-PEG that impose difficulties in conjugation reactions with, e.g., therapeutic proteins.[113,116] Alternate stealth polymers require similar approaches in order to ensure quantification of their end groups, their high quality, repeatability, and reproducibility.

A relevant natural biomacromolecule example is the high-quality standards required for mRNA, which came especially to focus during the development of LNPs during the COVID-19 pandemic. It took several decades of dedicated research to make labile mRNA usable for practical applications, especially in the field of vaccines. Following the discovery of mRNA in 1961,[117,118] it was not until 1978[73] that the first liposome-coated mRNA transporter was developed. Forty-two years later, in 2020, the first mRNA LNPs were approved as a vaccine,[119,120] highlighting the challenges in developing a safe delivery system. There is also a need to analytically determine which system is best suited for transporting genetic material and how the genetic material works in the human body. Modified mRNA has been shown to be not only more stable, but also to have a higher translation efficiency, meaning more protein will be produced in cells in comparison to natural mRNA.[121–123] Some key findings made it possible to use the biomacromolecule mRNA in pharmaceutical applications. It was found that altering certain nucleosides suppresses the cells' response, while the natural form stimulates dendritic cells.[124] In 2023, Katalin Karikó and Drew Weissman earned the Nobel Prize in Physiology or Medicine for these groundbreaking findings.[125]

Furthermore, it has been shown, that a high purity in mRNA is advantageous as immune responses to mRNA could be attributed to impurities, e.g., double-stranded RNA. Highly purified mRNA has higher translation rates than the non-purified product.[126] Therefore, a method for purification and quantification is important. One way to achieve highly purified mRNA is the use of preparative chromatography techniques, which are an important tool for quantification and in lab scale for purification of mRNA to ensure high quality and pure product. Usually, a combination of analytical methods is required to analyze the properties of all components and those of the product.

5. Nanoscale Assemblies in Pharmaceutical Applications

There are several different approaches to obtain nanoscale assemblies via polymers or lipids to encapsulate APIs. In the following, we will focus on LNPs.

In the case of LNPs, the self-assembly is based on the use of different, partially charged lipids. The exact process of self-assembly is not understood to date.[100] Certainly, this also requires studies on the polymorphism of lipids and their behavior in solution.[127,128] Assessment of the formulated NPs can be performed by different methods. To obtain high-quality analytical knowledge, different analytical methods need to be combined. Those can be based on light scattering, such as DLS or zeta potential measurements as very standard techniques. More sophisticated methods utilize AUC or FFF coupled to suitable scattering techniques such as multi-angle light scattering (MALLS) or DLS.[129,130] The advantage of the use of separation techniques before the implementation of light scattering detection seems readily advisable, in particular for very dispersed and heterogeneous populations of species. Microscopic methods such as cryogenic-transmission electron microscopy (cryo-TEM), environmental scanning electron microscopy (ESEM), or atomic force microscopy (AFM) can be added to obtain a comprehensive overview of particle size, shape, and nanomechanical properties.[130] Fluorescent dyes can be used to assess the encapsulation efficiency. Those can only bind to unbound genetic material. Another approach to determine encapsulation efficiency is AUC, which allows the particles to be characterized by the amount of encapsulated mRNA. Besides, it can be also observed that there are LNPs present that do not contain any genetic material.[131] Although LNPs have been intensively studied, their exact structure is still under debate.[132]

Figure 6 shows SAXS experiments of LNPs using a Synchrotron light source, revealing differences in the structural

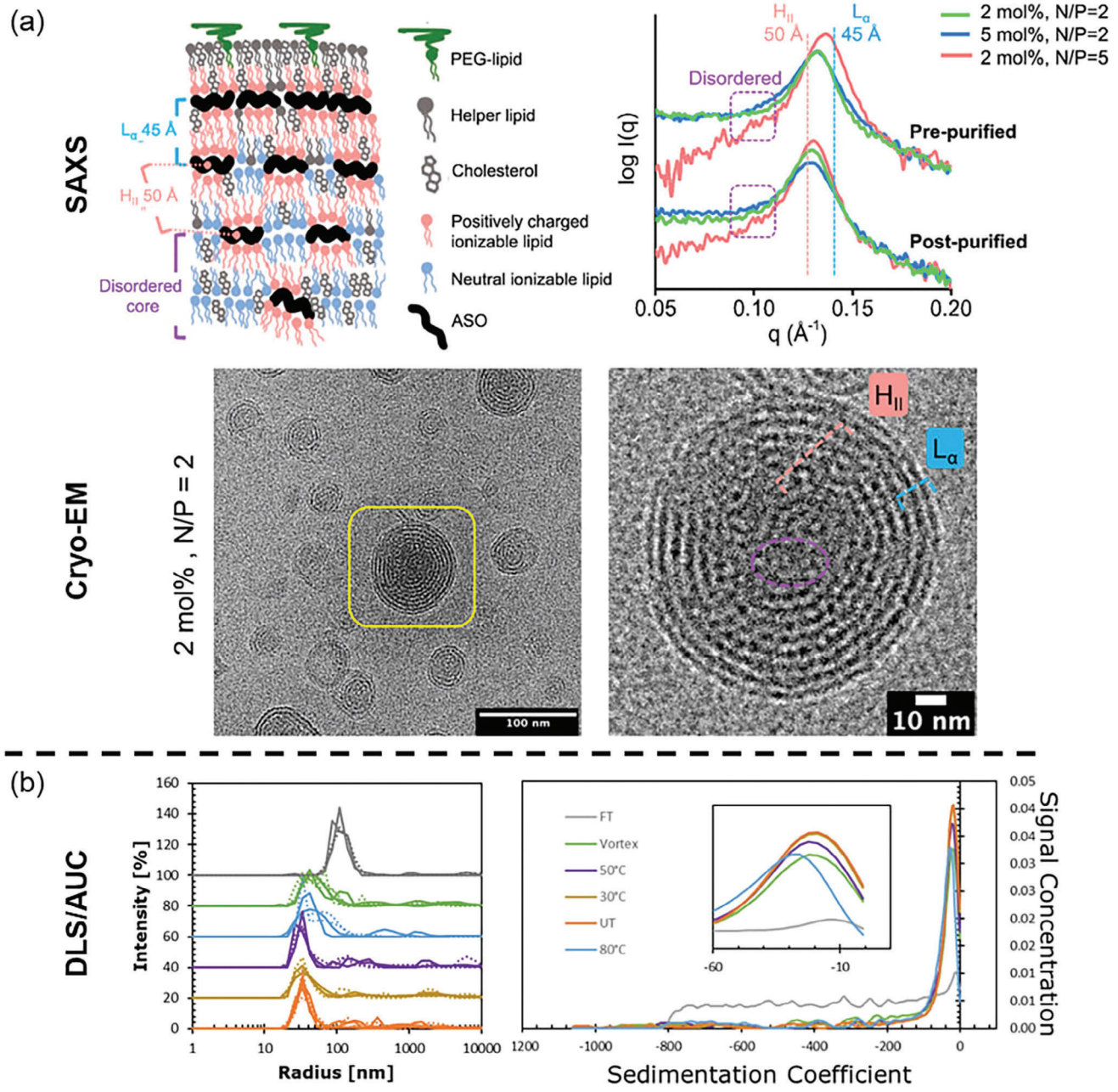

Figure 6. Possible (example) characterization methods of LNPs. a) SAXS with a Synchrotron source and cryo-EM enable analysis of the structure (ordered versus disordered). b) DLS provides properties of LNPs under different conditions of stress in the form of approximate size estimations by the hydrodynamic equivalent sphere concept. AUC can be used to investigate the integrity of LNPs under different conditions of stress. a) Reproduced under terms of the CC-BY license.[133] Copyright 2023, The Authors, published by American Chemical Society. b) Adapted with permission.[134] Copyright 2023, Elsevier.

properties associated with the presence of the genetic material. This could allow for possible conclusions regarding its structural arrangement in the LNPs (Figure 6a). Cryo-EM investigations allowed the identification of areas related to ordering as indicated by SAXS (Figure 6a).[133] In another study, standard DLS investigations of LNPs allowed the determination of intensity-based sizes under different conditions of stress. Sedimentation-velocity experiments with AUC and differential distributions of sedimentation coefficients could as well conclude on the impact of stress. Due to their actual low density imposed by their lipid content, flotation of LNPs instead of sedimentation in aqueous solution utilized here is observed (Figure 6b).[134] Alternatives of stealth polymers to formulate LNPs for immunotherapy have been reported. For example, LNPs using poly(sarcosines) were studied concerning their properties by SAXS with a Synchrotron radiation source.[135]

Besides LNPs, adeno-associated virus (AAV) vectors are known and were used earlier as carrier for genetic material and for therapeutic purposes. AAV vectors have been, e.g., also used in the Corona vaccine from AstraZeneca.[136,137] However, also empty capsids lacking the therapeutic transgene are present in the formulations, something that can be identified by AUC techniques.[138–140] Although the impact of these empty capsids on clinical outcomes is not well understood, analytical techniques for quantifying capsid content are needed. AUC, electron microscopy, or SEC-MALLS can be applied. SEC-MALLS was found to be suitable for the separation of empty, intermediate, and full capsids, which can also be achieved by density-based separation using AUC, visual identification by cryo-electron microscopy (cryo-EM), or charge detection mass spectrometry (CDMS).[141] AAVs were investigated in detail by X-ray crystallography diffraction data collected at the Cornell High Energy Synchrotron Source beam line.[142] AAVs have as also been investigated by FFF and AFM.[143]

While the described characterization methods allow analysis of materials in detail, the use of computational approaches is increasingly becoming the focus of scientific work. The use of algorithms can give predictions about, for example, NPs in cellular uptake, entrapment in endosomes as well as degradation of the same, immune responses, and various other aspects.[144] Computational models mimicking the conditions of the above-mentioned scenarios have the potential to reduce cost and time by generating probabilities for outcomes without the need for experiments.[145] Computational models could also be used to determine the risks of a potential nanomaterial in advance. They also offer the possibility of gaining initial insights into the toxicological properties and behavior of macromolecules and nanomaterials, which could be used for future applications.[146] Notwithstanding, one should keep in mind that also those computational methods need to be fed with high-quality experimental data in order to perform best.

From this and the previous section it is undoubted that analytical techniques are required in the approval of polymers and formulations. While the low molar mass drugs are straightforward to analyze by liquid chromatography and mass spectrometry, polymers represent challenges since those have inherent dispersity.[113,114] Quality control could be enabled by specifically developed liquid chromatography protocols. Potentially those could include both the analysis of small molecules and disperse polymers used for nanoparticle formulation in a single chromatographic run.[147] Alternate techniques such as AUC are as well representing a viable option to analyze complex nanoscale drug delivery systems.[148] Similar insight can be provided by techniques such as FFF coupled to a variety of detectors.[143] Quality control in the chemical and pharma industry could greatly benefit from further improvements of analytical technology. Particularly here, the demands for ensuring a minimum of batch-to-batch variations are high. While discussing all of those techniques and the high requirements, on a regulatory basis, the Organization for Economic Cooperation and Development (OECD)[149] and the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[150] play a role. On a more local basis, e.g., the FDA[137] and EMA[136] are relevant.

6. Energy Polymers

One of the contemporary most challenging needs in our society concerns concepts regarding green and sustainable energy.[151,152] A relatively new area of development is synthetic polymers that could play a key role in resolving modern challenges in the energy field by utilizing them in energy storage devices[153] or for energy conversion.[154] The development of polymeric materials used for organic batteries has been reviewed several times and such review is outside the scope of the present perspective.[152,153]

A typically used metal, e.g., vanadium that can have a variety of oxidation states, has already found widespread use, e.g., in vanadium redox flow batteries (RFBs). Those batteries already have advantages when compared to, e.g., lithium-ion batteries. Vanadium RFBs possess the potential to independently scale the power and capacity.[155] As stationary energy storage devices, they are particularly attractive for storing energy from resources such as wind and photovoltaics. They also allow for many charge-recharge cycles.[156] Though being the technologically most mature type of RFBs, the redox-active materials are the main cost driver. The cost of the cell stacks is also very high. In such batteries, the catholyte and anolyte are separated by ion-exchange membranes (separator), which are expensive (**Figure 7a**). Also, vanadium-based electrolytes are corrosive. The use of polymers makes the use of ion-exchange membranes as a separator obsolete and enables the use of cheap size-exclusion membranes, arguably reducing the stack costs. Before starting to look at battery research using polymers, it is useful to have a look at the long history of conducting polymers. The research on one of the "first" conducting polymers started in the 19th century of what was later called poly(aniline),[77] even before the area of energy polymers developed (Figure 4, bottom). Other historical examples that can be found in patents concern the redox polymer poly(resorcinol-trihydroxybenzene-formaldehyde) synthesized in 1944[78] and the first polymeric radical, poly(α-vinyldinitrophenyl-β,β-diphenyl hydrazine), reported in 1962.[79] The first polymer battery prototypes were proposed in 1958,[81] followed by the first lithium versus redox polymer battery (RPB) in 1965.[82]

One of the contemporary most prominent classes of polymers is so-called redox-active polymers. Those macromolecules possess moieties that can be oxidized and reduced reversibly, in other words can accept, store, and release electrons. Such property makes them suitable for substitution of inorganic materials, particularly in energy storage devices.[84] Currently, the most promising system for large-scale energy storage are RFBs.[157] The used polymers in those RFBs contain, e.g., 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), ferrocene, and viologen as moieties with a radical character (Figure 7b).[84] Typically, polymers of different properties form the catholyte and anolyte (n-type (reduction) and p-type (oxidation)).[158] For example, TEMPO derivatives have high electrochemical stability, however experience performance degradation due to the cleavage of the TEMPO ring.[159] They are also unstable at high temperatures.[160,161] Polymers containing ferrocene moieties offer advantages such as good stability, high redox potential, and environmental friendliness. At the same time, challenges related to the solubility, limit the potential of ferrocene as energy storage species

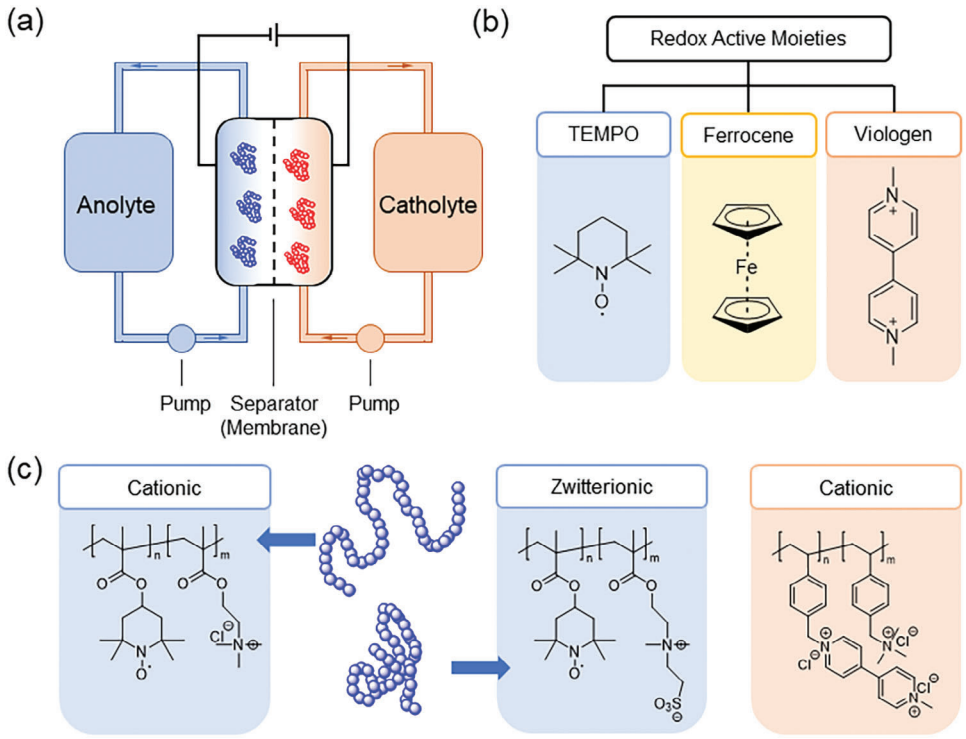

Figure 7. a) Simplified scheme of a redox flow battery (RFB). b) chemical structures of redox-active moieties used in modern polymer redox flow batteries (PRFBs). c) example anolyte TEMPO-copolymer containing cationic or zwitterionic moieties (leading to changes in molecular conformation) as well as an example anolyte with a cationic viologen copolymer.

in RFBs.[162] These solubility issues can be circumvented by comonomers enhancing the solubility of the copolymers, e.g., [2-(methacryloyloxy)-ethyl]-trimethylammonium chloride[163] or acrylic acid.[164] For utilization of aqueous electrolytes and the typically used organic moieties, copolymers form attractive solutions. Early generation battery polymers contained cationic moieties,[83] resulting in an electrolyte viscosity of 29 *mPas*@10 Ah L^{-1} by the polyelectrolyte effect (Figure 7c). Zwitterionic moieties in copolymers have also been reported to potentially reduce electrolyte viscosity, having its molecular origin in the reduction of polyelectrolyte effects, resulting in an electrolyte viscosity of 4.6 *mPas*@10 Ah L^{-1}, which is still arguably high.[165]

Ferrocenes are interesting moieties, however, some decomposition reactions of the polymers have also been reported recently.[166] Also, exchange of the cyclopentadienyl rings associated to the individual iron moieties could result in cross-linking of polymer chains and loss of solubility.[167] Viologen polymers offer advantages such as high redox potentials, high charge, and stability against degradation. A known disadvantage is an accelerated degradation in the presence of oxygen.[168,169]

Despite the charge properties, solubility, potentials, and capacities, polymers for aqueous PRFBs should have the following properties: be water soluble (ideally), have the desired molar mass, M (carry enough charge per molecule), and the viscosity of the solution should be low. The design criteria could be associated with the interplay of hydrodynamic characteristics (Figure 2). Any entity, may it be polymers, micelles, dendrimers, or NPs is located in the design space describing macromolecular and colloidal characteristics.

To comprehend, designing polymers for battery applications can be reduced to a few physical key characteristics (apart from the engineering technology of batteries). The polymers need to i) be large enough to avoid charge cross-over, i.e., being size excluded from the size exclusion membrane, ii) carry a maximum of charge that can be released or taken up in the form of electrons, iii) quickly diffuse, and associated to several characteristics, iv) enable fast electron transfer rates. As already seen in Figure 2, **Figure 8** shows that a polymer of a certain molar mass, M, is associated to a particular value of the intrinsic viscosity, $[\eta]$, sedimentation coefficient, s, and diffusion coefficient, D. The hydrodynamic volume is characterized by the product of $[\eta]M$. All those characteristics are related to the macromolecular dimensions/size (for a random coil expressed as the mean square end-to-end distance).[170] The degree of dilution (in percentage) of a polymer solution is simply the product of mass concentration, c, and $[\eta]$, i.e., $c[\eta] \times 100\%$. A value of 100% means the polymer chains occupy the entire solution volume, a value above this means spatial overlap of polymer chains.

Example scenario one is that of small ions, i.e., a small M, an infinitesimally small $[\eta]$, high D-values, an infinitesimally small hydrodynamic volume $[\eta]M$, appreciable electron transfer rates, and readily low overall electrolyte viscosities, i.e., low pumping costs. It can be the presently commercialized all vanadium RFBs that require ion-exchange membranes due to the readily small species.

In example scenario two, allowing for a maximum of charge carried by a common linear macromolecule would demand for a maximum of M that leads to large $[\eta]$ and low D-values (resulting

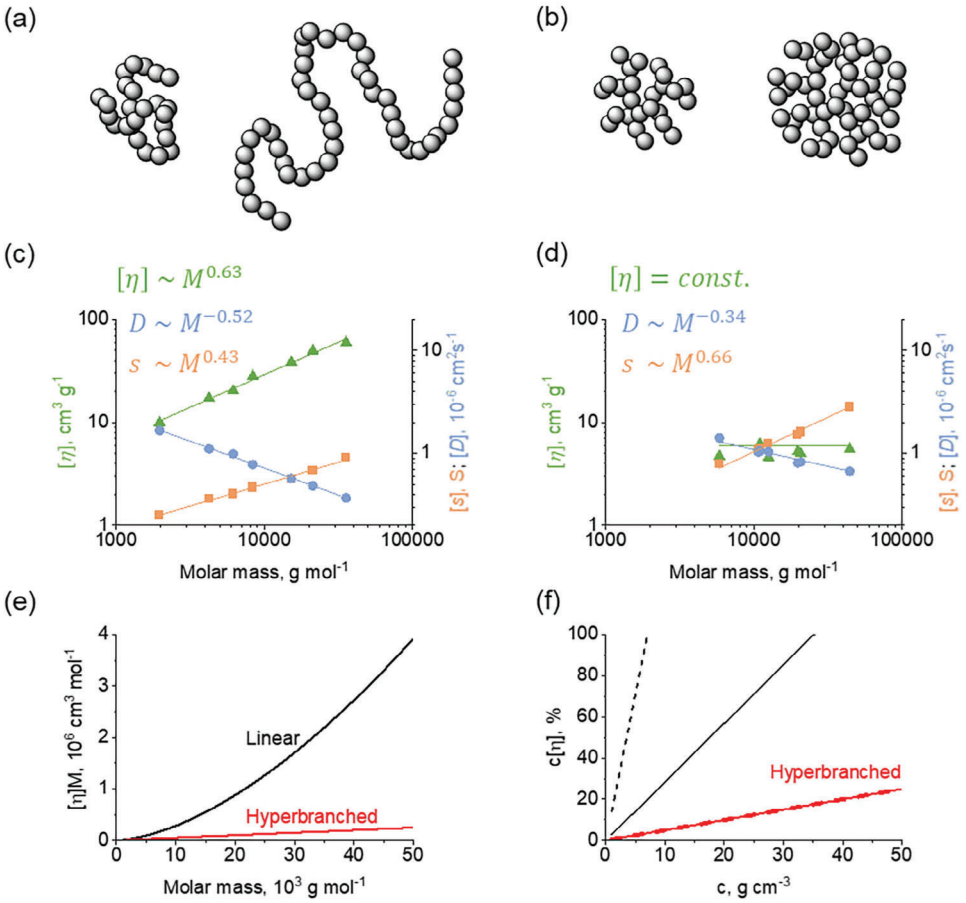

Figure 8. Example of molecular structure and scaling relationships with (a) and (c) of a linear PEG and (b) and (d) of a hyperbranched poly(glycerol) polymer system in water. The hydrodynamic characteristics, represented by the intrinsic viscosity, $[\eta]$, the sedimentation coefficient, s, and the diffusion coefficient, D, are plotted against the molar mass, M, in a double logarithmic fashion. c) Adapted with permission.[89] Copyright 2017. American Chemical Society. d) Adapted with permission.[95] Copyright 2020, American Chemical Society. Panel (e) shows a plot of the hydrodynamic volume, $[\eta]M$, against the molar mass and (f) the degree of dilution in values percent, $c[\eta] \times 100$ % for a 10 000 g mol^{-1} (solid lines) and 50 000 g mol^{-1} (dashed lines) polymer.

in a slow electron transfer rate) (Figure 8c). At the same time, the large hydrodynamic volume, $[\eta]M$ (Figure 8e), and highly concentrated electrolyte solution, $c[\eta]$ (Figure 8f), would lead to significant overlap of polymer chains in the occupied volume.[171] This is much earlier the case for the linear polymer example. In consequence, there are large contributions to the overall electrolyte viscosity that require a large amount of energy for the pumps to circulate the electrolyte. We are in a regime of highly nonideal properties of the respective electrolyte solutions and the entanglement of polymers is very high, further decreasing the diffusion coefficients beyond that of the dilute regime plotted, e.g., in Figure 8c,d). An aspect beyond that in Figure 8c is, that polyelectrolytes show dynamics depending on salt concentration. An increase in salt concentration reduces the polyelectrolyte effects. Also, scarce if no knowledge exists on changes in polymer structure upon charging and discharging, which would imply that the polymers carry varying amounts of charges, additionally complicating for a quantitative study of the polymer behavior.

One would, thereby, go for scenario three, i.e., choose a molar mass of a linear polymer that is just size excluded from the utilized membrane. Thereby, it allows the maximum possible reduction in electrolyte viscosity at still appreciable diffusion coefficients, in addition to that the solution ideality increases. However, the physics of the system impose the limitations.

In view of the above considerations, a promising polymer system that possesses potential benefits for battery applications are hyperbranched polymers (Figure 8b). It was demonstrated, that, hydrodynamically, they behave like a solid spherical particle in view of the double-logarithmic scaling relationships (Figure 8d). Particularly, the intrinsic viscosity, $[\eta]$, is independent on the molar mass.[95] At the same time, they are hydrated to a large extent and permeable to the solvent, i.e., the inner structure is accessible to the solvent and, if small enough, also to ions associated with the polyelectrolyte. Particularly important are the low values of $[\eta]$, even at high molar masses. A direct consequence of those low $[\eta]$-values is a small hydrodynamic volume, $[\eta]M$ (Figure 8e, red line), leading to much higher degrees of dilution, $c[\eta]$, at the same mass concentration when compared to linear systems (Figure 8f, red lines). In comparison to the linear polymer system, the hyperbranched polymer has, irrespective of the molar mass, the same degree of dilution at the particular mass concentrations (Figure 8f). In example, at a mass concentration

of 50 $mg\,cm^{-3}$, $c[\eta] \times 100\%$ has a value of ca. 25%. For a 10 000 g mol^{-1} linear polymer, this degree of dilution is exceeded at 9 mg cm^{-3} already, for a 50000 g mol^{-1} linear polymer below 2 mg cm^{-3} already, by playing the presented examples. The sweet spot for such hyperbranched system is the exact (minimum) molar mass (and associated hydrodynamic volume) that avoids charge cross-over. In this way, the electrolytes have optimized properties in terms of a maximum diffusion coefficient of charge carrying material and low electrolyte viscosity when utilizing size exclusion membranes. The system is predictably ideal in terms of all hydrodynamic characteristics, the degree of dilution is high. In terms of the polyelectrolyte effects, dynamic changes in the structure of the polymer are expected to a much lesser extent, which as for linear polymers need to be clarified experimentally. This rationale polymer described here was not yet reported in the literature. One should also not underestimate that the synthesis of such materials can become more demanding, and very cost intensive. Addressing electrolyte viscosity in battery application have already been reported by using a mere tetramer of, e.g., ferrocene moieties. Arguably this would even mean moving away from the "polymer" concept of batteries.[172] Considering, the at least theoretically favorable properties of hyperbranched polymers as solvated and hydrated spheres (vide supra), the use of spherical nanoparticles with TEMPO-, viologen-, and diazaanthraquinone-substituted polymer in an aqueous PRFB setting has been reported.[173] Due to electron propagation throughout the particle, overall charge transfer is enhanced.

At present, the challenges for polymers in energy storage devices are the precise control of their properties and the establishment of quantitative structure-property relationships that require first principle absolute methods, such as hydrodynamic analysis and light scattering. Another important aspect of polymers is their inherent dispersity. The dispersity plays some role since it influences the choice of the membranes cutoff limit to avoid charge crossover, deteriorating battery performance. The use of controlled polymerization techniques to reduce the polymers' dispersity appears not being an option when looking at the production costs of large amounts of redox-active materials. Increase in synthetic efforts to produce the desired polymer drastically rises the overall costs.

Research in the area of PRFBs must consider, next to chemistry where most of the studies are carried out, proper hydrodynamic studies of such systems via viscometric and densimetric methods on the electrolytes elucidating essential parametric characteristics of the macromolecules. Solution characterization techniques such as densimetry and viscometry on the global electrolyte properties are readily required, will, however be dictated by the molecular conformation of the macromolecules and the regimes of dilution (e.g., Figure 8). While it is the authors' perception that proper hydrodynamic studies are required, the power of light scattering techniques should not be forgotten. In the past, Synchrotron SAXS measurements were applied to study the morphology of the battery cathodes and polymer structures forming the solid materials.[174–177] Much less work has been performed in solution but may shed new light and insight into the materials, complementary to hydrodynamic studies. Particularly demanding aspects to further our understanding is the differences in conformational properties of the polymers when charging and discharging as well as their mechanism of degradation. The former can be accessed by methods such as AUC and light scattering, the latter certainly requires techniques such as liquid chromatography and mass spectrometry to look in detail at the polymers' functionality and chemistry and potential degradation products.[159] In addition, FFF coupled to MALLS enabled the molar mass determination for polymers in energy-related applications. FFF demonstrates opportunities when considering cases where SEC appeared not suitable.[165,178,179] Fundamentally looking at redox-active polymers makes us revisiting the polyelectrolyte effects that need to be understood particularly for linear polymers.[180] Branched polymers are studied to a lesser extent and changes in properties associated to salt concentration have been studied insufficiently.[181]

Polymers for PRFBs are in the dissolved state. Polymers that are used in the energy field in "bulk", as films, membranes, as well as electrode materials, may be less affected by the properties of the individual macromolecules they are created from or that they contain. However, one should consider that synthesis of polymers is often, though not exclusively, performed in solution aiming at a particular molar mass, structural, and compositional characteristics. Furthermore, the properties of polymers in solution or the colloidal precursor dispersion will, to a varying extend, determine properties in the solid state. For example, in thin film photovoltaics, the colloidal precursor for preparation of thin films determines device performance.[182–184] In case polymers are involved in inks, one could expect that the solution structure is as well highly relevant. When polymers are used for optoelectronic applications, aggregation in solution is also linked to thin film properties and properties of charge transport in those films.[185] Another example concerns colloids based on poly(ionic) liquid nanovesicles, utilized to construct nanomaterials for sustainable applications in carbon dioxide electroreduction[186] or as a template to create crafted composite nanostructures as cathode material in Li-S batteries.[187] While only being a few examples, the opportunities of solution characterization techniques to study disperse matter, playing a role in construction of energy-related materials, are, in our opinion, not yet fully exploited.

In a quest of finding the right polymer candidate for, e.g., PRFBs, contemporary approaches such as artificial intelligence (AI) and machine learning (ML) could be applied.[188,189] These tools could determine or predict chemical structures based on given desired properties of the polymer.[190,191] However, these models are based on an existing polymer database, and expanding this base can improve the predictive ability of these algorithms.[192,193] This will inevitably lead to a situation where it is necessary to synthesize and test large libraries of different polymers. To overcome this, modern methods for automation and robotization of the synthesis as well as for an automatized polymer analysis are needed to train the models.[194,195] In addition to selecting polymers, these algorithms can be applied to design and optimization of liquid flow fields in RFBs.[196] Models would have to be adapted particularly when polymers are involved. Though it may sound discouraging, the use of AI and ML is of limited importance when finding the hydrodynamically appreciable properties already well-known by the hydrodynamic considerations finding their inception in the last century (vide supra).

7. Future Developments

From the briefly drawn perspective, a century after its discovery, several aspects of modern macromolecular and colloidal science become clear in two very interesting branches of demand in our modern society. The development of analytical techniques was at the forefront to characterize macromolecular systems. Now, those function as an enabler for discoveries in the energy and life sciences. The further development of analytical tools will therefore be guided by a better understanding that is required for the up-and-coming materials in the energy and life sciences. To the majority, this will concern hydrodynamic methods, light scattering approaches, and further development of microscopic techniques.

While the area of the life sciences appears technologically much further ahead in its development than the energy field, translating laboratory-scale findings to large-scale production introduces challenges related to repeatability, reproducibility, scalability, and cost-effectiveness. Robust characterization methods that can be applied consistently at different production scales are needed to imply Good Manufacturing Practices. By using macromolecular delivery systems, e.g., nanoparticles, there is the possibility of safer and more efficient delivery of drugs with fewer side effects. In addition, polymeric nanoparticles have the potential to be used in individualized therapeutic approaches. In particular, the question of targeting structures, their 3D structure and availability for cellular interactions need to be addressed in the future to pave the way for targeted delivery besides, e.g., the liver as a prominent target. For gene therapy, the detailed investigation of the interactions between genetic material and polymers or lipids is essential for the further development and application of non-viral gene carrier systems.

Characterization plays a crucial role in elucidating the complex dynamics and optimizing the efficiency and tolerability of these carriers. While Synchrotron small-angle X-ray scattering provides a powerful means to resolve such interactions, its access and, thereby utility is limited. Hydrodynamic methods such as analytical ultracentrifugation are also not widespread though having high potential in the study of those systems. Undoubtedly, both methods are among the most powerful techniques. Therefore, there is an urgent need to develop and establish more available, robust, and effective methods to comprehensively characterize the intricate relationships between genetic material and transfer vectors. Thus, multi-modal characterization and standardization are critical for improving the precision and efficacy of nanoparticulate systems and pave the way for their broader application in various therapeutic contexts.

Beside the pharmaceutical macromolecules also used for nanoparticles, the field of energy polymers is still in its infancy. Critically, polymers have not yet demonstrated their full potential in replacing metals in, e.g., large-scale stationary storage devices such as redox flow batteries. Further key steps to address the energy transition with technology such as the redox flow battery are still to be made. This is because key issues regarding stability of the polymer components of the electrolyte are to be resolved to become industrial practice. Suitable materials also require cheap options for mass production and straightforward synthesis. The, at least theoretically, optimal polymer in redox flow batteries has not yet been synthesized. It should have a compact structure, high diffusion coefficients, and low contributions to the overall electrolyte viscosity by a small intrinsic viscosity. Macromolecular systems such as, e.g., micelles and polymer nanoparticles may possess interesting properties that are yet to be elucidated in detail. At the same time, standard conditions for the assessment of battery performance are required to be developed. In case of the construction of devices involving polymers, characterization of the disperse precursor state, the final device state and their correlation with the performance of materials in, e.g., thin film photovoltaics appears promising in the creation of better energy storage devices. Particularly, the climate change and the desire to reduce the carbon footprint has been gaining momentum in the polymer industry in recent years. This brings new challenges for researchers and will dictate the concepts for the future generation of materials from exclusively renewable ressources. Thus, sustainability has become one of the most important aspects of modern materials and should be considered in further developments, in almost any branch of chemistry.

An overarching great promise lies in the tools of machine learning and artificial intelligence, which cannot yet replace rational, experimental research and can just accompany breakthrough discoveries. However, those tools will save scientists' time and resources in the very near future. It should rely on high-quality data from a reasonable amount of performed or existent experimental research. Interrelated characterization data from combined methods can, thereby, help to understand the performance and application potential of existing and predicted macromolecular systems. A current lack of those "artificial intelligences" is that they are not really "intelligent" in adapting and continuously developing in as much as a living organism or human can do.

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Conflict of Interest

The authors declare no conflict of interest.

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analytical ultracentrifugation, characterization, colloids, disperse systems, energy storage, macromolecules, pharmapolymer

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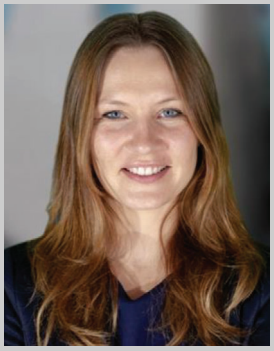

Anja Traeger was born in 1982 in Beeskow (Germany) and studied biochemistry at the University of Bayreuth (Germany; 2002–2007) with a stay at the University of York (UK). After her PhD studies (2007–2011) at the University of Bayreuth, she moved to the Friedrich Schiller University Jena to study at the Jena Center for Soft Matter (JCSM) supervised by Prof. Ulrich S. Schubert. In 2017 she started her independent research group (BMBF "NanoMatFutur") and became a Heisenberg fellow in 2024. Her research interests are the characterization and biological application of multi-functional nanomaterials for gene delivery.

Ivo Nischang graduated from the University of Magdeburg (Germany). After receiving his PhD, he carried out postdoctoral studies at the University of California at Berkeley (USA). Following his "Habilitation" degree in Austria, he was and is active at the Jena Center for Soft Matter (JCSM) and Center for Energy and Environmental Chemistry Jena (CECC Jena) at Friedrich Schiller University (FSU) Jena. In a joint appointment with the Helmholtz-Zentrum Berlin (HZB) and FSU Jena, he became a professor within the framework of the "Heisenberg Programme" and is active in the newly founded Helmholtz Institute for Polymers in Energy Applications Jena (HIPOLE Jena).