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Natural polymers and bio-inspired macromolecular materials

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1 Introduction

Growing societal awareness of environmental issues has become a driver to promote the design and production of polymeric products based on renewable or biological materials, as we outlined in the preface of the special issues of European Polymer Journal related to previous BiPoCo (Bio-based Polymers and Composites) conferences [1, 2]. The BiPoCo 2016 Conference focused on the synthesis, characterization and degradation of biopolymers, the development of biocomposites and included topics on smart, nano-structured systems for controlled molecular release. We placed particular emphasis on issues about biocompatibility, biofunctionality and biodegradability of polymeric materials. Similarly to the previous two conferences, European

Polymer Journal is publishing a selection of papers related to the meeting and this special section contains three feature articles and several original research papers with topics on nanoparticle drug delivery, cell-material interaction, as well as synthesis and modification of biopolymers and hydrogels.

2 Biopolymers, natural building blocks

Increasingly stringent environmental regulations and the dwindling of fossil feedstocks have led to a growing interest in natural based and/or biodegradable polymers. The components of biomass have a huge potential to make building blocks and intermediates of various useful products [3, 4]. Biomass can be converted into valuable chemicals *via* platform molecules from which we outline lactic acid, the starting material of biodegradable polylactides which are now used in a quantity of few hundred tons, mainly in packaging applications [5]. Polyhydroxyalkanoates (PHAs) as an important class of biodegradable polymers can also be synthesized from renewable sources and PHAs with various chain length and degradation rate can be produced by fermentation processes [6]. The other approach is the modification of biopolymers already available in the biomass to produce functional and other value-added materials [3]. The main targets of such modifications are starch, cellulose, hemicellulose, inulin and chitosan from which several products have already been developed for the packaging and the food industry as well as for biomedical applications. Besides the huge promise of biopolymers and biomass conversion, we have to emphasize the enormous future challenges faced in this area. The purification, extraction, and fermentation processes must be improved to make the processes economic, green and energy-efficient. The quality and composition of biomass varies widely which makes purification difficult thus it is very important to develop products which do not need pure chemicals. An example of the

latter is the work of Kun and Pukánszky [7] in which the authors give a deep insight into the properties of blends prepared with lignin, a major component of all plants. This raw material is available in an enormous quantity as a side product in the paper industry, but the majority is burnt to provide heat and power for cellulose production. Although the global market of lignin is growing, valorization is in its infancy because of several challenges. As the feature paper outlines, lignin has a complex structure (a model structure is shown in **Fig. 1a**) which strongly depends on the source and the extraction technology, and also determines the properties of blends made from lignin. The authors discuss the terms blends and composites, the wrong usage of which causes a considerable confusion in the literature on lignin. Competitive interactions in polymer/lignin blends determine the structure and properties of blends prepared from thermoplastics, but complete miscibility could not be reached in the range of polymers studied up to now. Accordingly, chemical modification, plasticization or the use of coupling agents is needed to produce blends with relatively good properties. Further possible applications of lignin are also discussed in the paper, it can be used as reactive component in various resins (phenolic, epoxy) or in polyurethanes.

Similarly to lignin, several natural building blocks contain reactive phenolic groups which enables the preparation of functional monomers. Ladmiral et al. [8] used cardanol extracted from cashew nut shell liquid as biobased phenol source (**Fig. 1b**) to replace styrene in synthetic latex materials, e.g. paints, varnishes, coatings. The benefit of cardanol over lignin is its well-known chemical structure which was utilized in the present work to prepare a methacrylated derivative for radical polymerization. According to the authors, photo-crosslinked films and coatings can be made of the polymers but further studies must be carried out to exploit the full potential of cardanol-based chemistry. Hammami et al. [9] prepared linear and cyclic polyacetals with low glass transition temperature. They used renewable, isosorbide type raw materials with aliphatic hydroxyl

groups to replace bisphenol-A or similar compounds to address environmental issues and to increase yield.

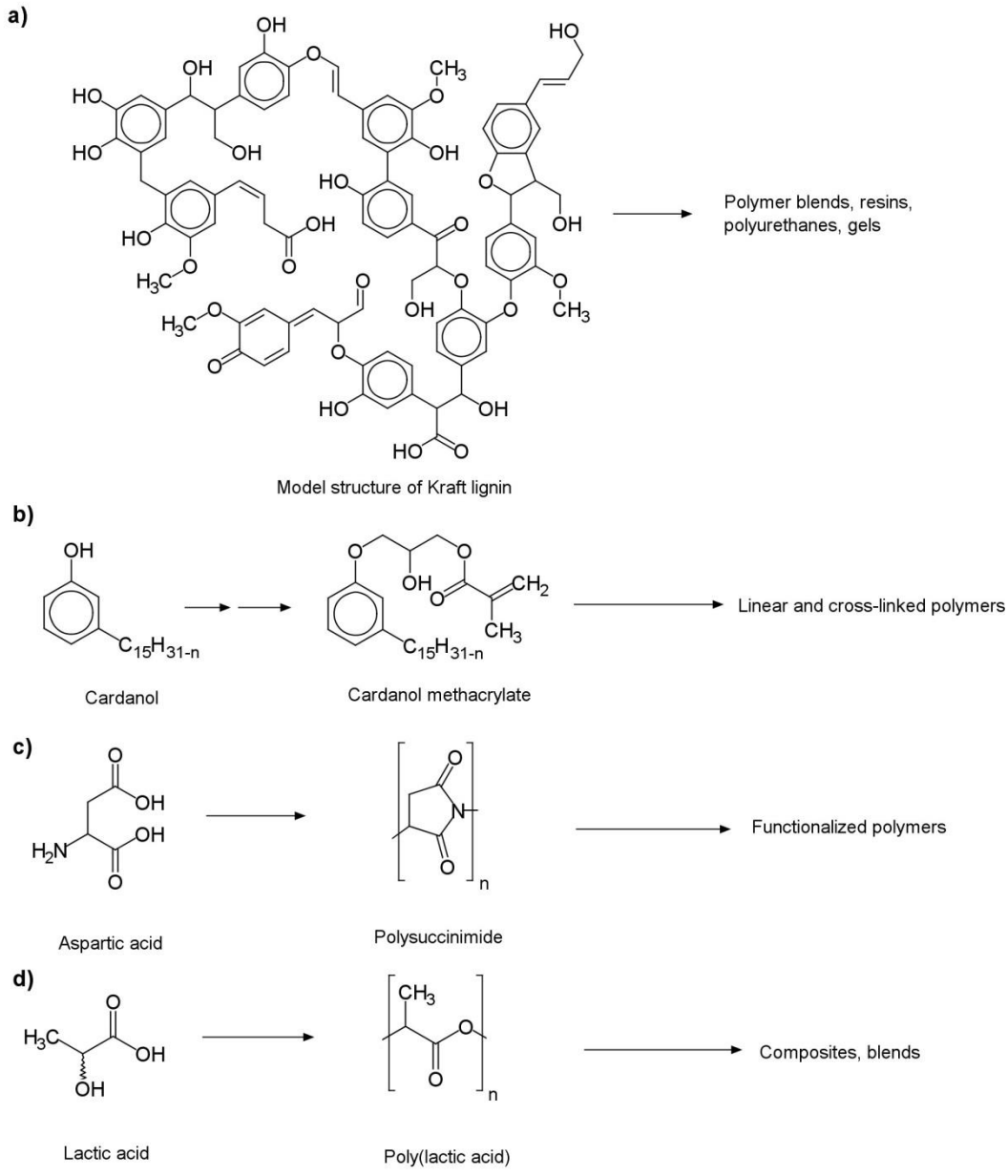

Fig. 1 Building blocks used in the synthesis of polymers, blends and composites [7, 8, 10, 11]; a) a model structure of lignin; b) synthesis of polymers from cardanol; c) synthesis of functionalized polymers from aspartic acid; d) polymerization of lactic acid.

Reactive monomers having carboxyl groups can be polymerized easily through the formation of ester, amide or imide groups. Németh et al. [10] prepared functional polymers from a natural amino acid, aspartic acid (see **Fig. 1c**). First they synthesized a reactive polyimide and then used various small molecular weight amines to modify the properties of the polyaspartamides obtained. The glass transition temperature of the polymers could be adjusted in a wide range including room temperature, and homogeneous films could be formed by solvent casting. Such films can be used as taste-masking pharmaceutical coatings proven by the controlled dissolution of the films in aqueous solution. As the final example for polymer synthesis, lactic acid can be polymerized to yield a biodegradable and biocompatible polymer with good processability (**Fig. 1d**). Although examples exist for the synthesis of poly(lactic acid) (PLA) by twin-screw extrusion, the technique has serious problems because of leakage. To overcome these difficulties, Liu et al. [11] recommend the use of static mixers to produce PLA at large scale. A polymer with relatively high molecular weight, narrow polydispersity and practically complete optical purity could be produced with a fast rate leading to the cost-effective production of fiber-grade PLA at industrial scale.

The synthesis of tailor made polymers can be the first step in the development of plastic products for everyday use. Usually, the properties of biopolymers need to be modified to achieve good material performance. To this end, Aliotta et al. [12] determined the effect of nucleating agents on the crystallinity and mechanical properties of PLA. Further papers are focusing on the improvement of the properties of the most abundant natural polymers, polysaccharides. Ivanic et al. [13] used glycerol and urea in various ratios to plasticize starch, and their approach may result in thermoplastic starch with outstanding processability and appropriate mechanical properties even without the use of other polymers and blending. Simanavicite et al. [14] prepared cross-linked starch for the immobilization of chlorogenic acid, an efficient antioxidant, and achieved the controlled release of the payload by the use of the proper amount of cross-linker. Finally, the group

of Borysiak [15] used nanocellulose to prepare chitosan biocomposite films with improved mechanical properties. The enzymatic production of crystalline nanocellulose is analyzed in the paper in detail in order to help the selection of the best material for reinforcement.

3 Interactions in biomaterial design

The application of biopolymers in life sciences is growing remarkably fast and a pronounced demand exists for materials interacting with their environment in a controllable manner [16]. The first step towards the development of such materials, mostly soft hydrogels, is the analysis of the interactions within the material, between the polymer and the active compound encapsulated in it and finally, between the gel and its biological environment [17-19]. In addition, the interest in biomimetic materials also increases rapidly; researchers try to exploit mechanisms that nature developed by evolution, like autonomous healing, for example. Accordingly, the feature paper of Gyarmati et al. [20] focuses on the utilization of reversible interactions in self-healing gels (see **Fig. 2**), which are able to mimic the healing of living tissues by the fast reformation of physical and/or chemical bonds broken by mechanical forces. Such behavior can extend the lifetime of biomaterials that is particularly important in long term applications like for implants. As pointed out by the authors, standardized testing methods are still missing in the literature for the characterization of self-healing performance, and they recommend basic criteria which should be considered in the study of self-healing hydrogels. Fixing the final shape of an implants is a strong challenge, but the shape memory of hydrogels offers an elegant solution for the problem. The paper emphasizes that self-healing and shape memory are rooted in the same mechanisms, thus both characteristics can be incorporated in the same hydrogel. However, examples for such dual behavior are rare, because self-healing is an autonomous characteristics, while shape memory is an

externally triggered process, which are apparently contradictory behaviors. However, the contradiction can be re-solved by using interpenetrating polymer networks. Currently, only a few examples exists for such hydrogels, but we expect much more to appear in the next few years.

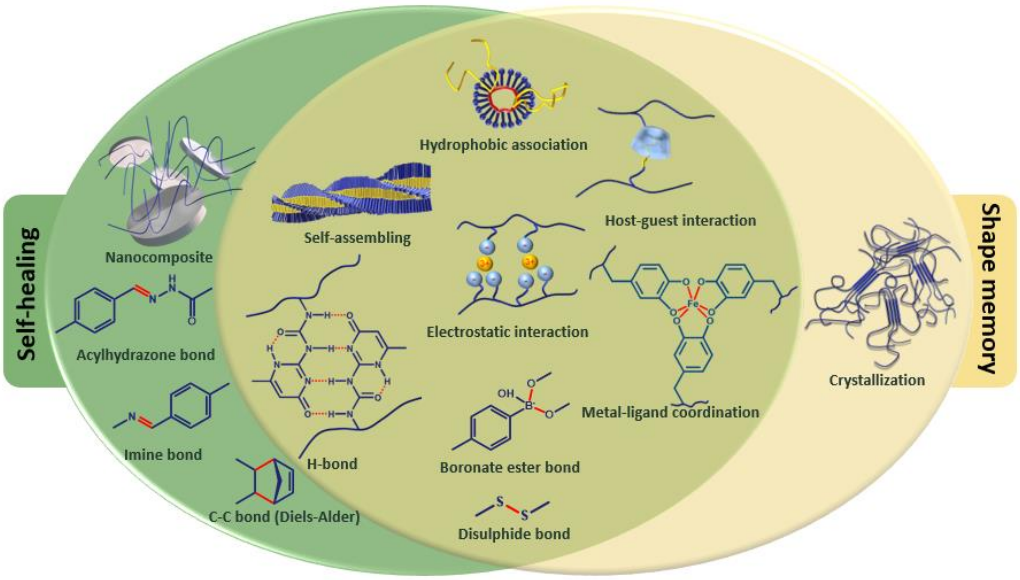

Fig. 2 Reversible interactions employed in self-healing and shape memory hydrogels [20].

Hydrogels responsive to the external temperature are widely investigated to prepare drug carriers for the targeted release of an encapsulated material. The group of László [21] synthesized composite hydrogels from poly(N-isopropylacrylamide) and graphene derivatives. The pioneering use of graphenes as reinforcements in hydrogels enabled the authors to improve significantly the usually poor mechanical strength of the gels. The paper also demonstrates that the response of the hydrogels, in this case the rate and extent of volume change due to changing temperature, can be adjusted by the use of graphenes. The understanding of the interactions of the polymer and the active compound is of crucial importance for reaching the final goal, i.e. the development of drug carriers from hydrogels. Domján et al. [22] used various NMR methods to analyze interactions

between the polymer and phenolic compounds with pharmaceutical relevance (dopamine, indole derivatives). The results can be exploited in the design of efficient carriers by predicting the release kinetics of drug molecules from the hydrogels.

Natural polymers with expected biocompatibility are important raw materials for the preparation of hydrogels. Jang et al. [23] made the first steps towards the synthesis of hydrogels from sericin extracted from silk fibers. Sahiner et al. [24] used hyaluronic acid to prepare porous hydrogels for applications in regenerative medicine. The papers mentioned focus on the synthesis of hydrogels, but the consideration of cell-material interactions is also very important during the development of biomaterials for life science applications. Raczkowska et al. [25] reports a method to prepare cellular patterns at large length scales on poly(dimethylsiloxane) substrates. Their results allow the controlled fabrication of cell groups in various sizes and shapes for use in biological experiments. Sumaru et al. [26] created cell monolayers by the micro-projection of a grid pattern onto a photosensitive substrate and this cell processing tool can replace time-consuming manual work in cellular tests. Zubareva et al. [27] investigated the cytotoxicity and cellular penetration of positively and negatively charged as well as neutral chitosan derivatives and showed that the hydrophobic derivative of quaternerized chitosan can be used as safe drug delivery carrier.

4 Nanotechnology in drug delivery

Nanotechnology is a rapidly growing field in materials science and it is used in diverse applications in electronics, manufacturing, agricultural science, chemistry, bioscience, pharmaceutics, etc. The most widely used nanostructures in medicine are nanoparticles which are often defined as particles with dimensions ranging from 1 to 100 nm, but in a wider sense sometimes the range up to 1000 nm is also considered as nano [28]. Cellular uptake and thus the

distribution of the particles across the body are strongly determined by particle size, e.g. nanoparticles with a size of 100 nm provide several folds larger uptake in Caco-2 cells than those with a size of about 1000 nm, but, of course, besides particles size several other factors must be considered in cellular uptake [29]. As the particles have large surface area, various components of their biological environment can adsorb onto them and they can strongly interact even with each other [19]. The tendency to aggregation limits their application in systemic circulation, but PLGA nanoparticles do not aggregate in serum, for example, thus they can be safely injected in blood capillaries [29]. Usually larger nanoparticles are needed for drug delivery (> 100 nm) in order to load sufficient amount of the active compound into or onto the particle. In addition to size, surface functionalization and charge also affect the fate of the particles and the efficiency of intracellular uptake in, e.g., cancer treatment [28, 30]. The same applies for a very challenging target, the brain, which cannot be reached by most of the pharmaceuticals because of the blood brain barrier (BBB). Considerable effort is aimed at the synthesis of nanoparticles for the transport of drugs across BBB; using anionic nanoparticles or coating the particles with polysorbates are examples of possible solutions [28].

Nanoparticles are especially useful in vaccine design as Toth et al. describe in their feature article [31]. Nanostructures often have immunostimulating characteristics and the surface of nanostructures can be modified with specific targeting. The authors prepared self-assembling structures of carrier-antigen conjugates by using polymers or lipids (Fig. 3). The advantage of such materials is their generally small toxicity, but the authors also call the attention to the drawbacks of the approach, which cannot be neglected, e.g. to the slow biodegradability and limited stability of certain polymer based nanostructures, or to the small efficiency of peptide based carriers. A deeper understanding of interactions between nanostructured vaccine and

immune cell receptors is needed for further development and for reaching the market with such formulations.

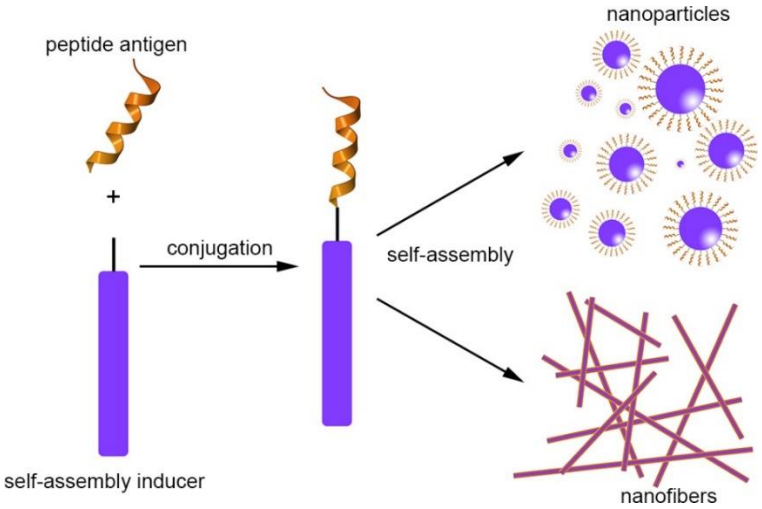

Fig. 3 The formation of nanoparticles and nanofibers by the self-assembly of antigen conjugates [31].

As the length scale of cells is in the nanometer range, the development of nanoparticle drug delivery systems are in the focus of an enormous number of research papers. In this issue, Raveendran et al. [32] report the synthesis of poly(2-oxazoline) block copolymer nanoparticles for the cellular delivery of curcumin, a natural antioxidant. The use of poly(2-oxazoline) makes possible the tailoring of chemical structure contrary to polyethylene glycol often used in this field. The authors synthesized amphiphilic polymer derivatives which self-assemble in aqueous solution. The paper nicely demonstrates the complexity of the development of a new nanoparticulate drug carrier systems covering synthetic work, colloid chemistry and cellular tests. Csaba et al. [33] prepared protamine nanocapsules by low-energy emulsification, and they did not use any organic solvent or heat in their unique approach. The as-prepared capsules had large

drug encapsulation efficiency and drug loading capacity, and according to cellular experiments they treated inflammatory bowel diseases very efficiently. Finally, an interesting aspect of nanoparticles is that although the majority of research focuses on drug delivery to human cells, these carriers may find their application also in agriculture as proven by the paper of Pérez Quinones et al. [34] The authors prepared steroid-modified cellulose nanoparticles by self-assembly for sustained release of a covalently linked active compound in acidic conditions.

5 Conclusions

The articles published in this special issue of European Polymer Journal offer a representative overview of synthesis, characterization and application of biopolymers and natural polymers, composites and blends, hydrogels and nanostructured systems in various fields from commercial plastic products to medicines. The papers represent and emphasize the strongly multi-disciplinary character of the conference simultaneously including chemistry, polymer physics, processing, nanotechnology, pharmaceutics and related biomedical fields. Remarkable progress has been seen in the past decades in these areas, but serious challenges must be faced also in the future. Several important questions have been identified during the BiPoCo 2016 Conference and the results reported in this issue indicate the need for a better valorization of naturally occurring, abundant raw materials in a sustainable manner, the deeper understanding of interactions between biomaterials and the cellular environment and the mimicking of the biofunctionality of living matter like in self-healing and responsive materials.

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