# BOOK OF ABSTRACTS

# THE INTERNATIONAL CONFERENCE NEW APPROACHES TO BIOMATERIAL DEVELOPMENT

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**MEGAGRANT LABORATORY OF POLYMER BIOMATERIALS AND SYSTEMS**

**PROGRAM AND SCIENTIFIC COMMITTEE:**
MIKKO KARTTUNEN (chairman)
DMITRY TOLMACHEV
SERGEY LARIN
ANNA IVANOVA

**INVITED SPEAKERS:**
SERGEY SHEIKO, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-3290, USA.

HECTOR MARTINEZ-SEARA, Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Flemingovo nám. 542/2, 160 00 Prague 6, Czech Republic.

MARIA SAMMALKORPI, School of Chemical Engineering, Aalto University, Vuorimiehentie 1, 02150 Espoo, Finland.

RAFAEL MAGLIA DE SOUZA, Instituto de Química, Universidade de São Paulo, Avenida Professor Lineu Prestes 748, São Paulo, SP, Brasil

TATIANA BUDTOVA, MINES ParisTech, PSL Research University, Center for Materials Forming-CEMEF, UMR CNRS 7635, CS 10207, 06904, Sophia Antipolis, France

ANDREY GURTOVENKO, Institute of Macromolecular Compounds, Russian Academy of Sciences, Bolshoi Prospect V.O. 31, St. Petersburg 199004, Russia

MICHAEL SMIRNOV, Institute of Macromolecular Compounds, Russian Academy of Sciences, Bolshoi Prospect V.O. 31, St. Petersburg 199004, Russia

ALEXEY POLOTSKY, Institute of Macromolecular Compounds, Russian Academy of Sciences, Bolshoi Prospect V.O. 31, St. Petersburg 199004, Russia

Plenary program:

December 2

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| 16:20 | Greetings | |
| 16:30 | Hector Martinez-Seara | IMPROVING CHARMM36 SIMULATIONS BY REINTRODUCING THE MISSING ELECTRONIC POLARIZABILITY: PROSECCO |
| 17:00 | Sergei Sheiko | MOLECULAR ENGINEERING OF MATERIALS FOR RECONSTRUCTIVE SURGERY |
| 17:30 | coffee break | |
| 18:00 | Andrey Gurtovenko | CLOSE TO YOUR SKIN: ACIDITY CONTROLS BINDING OF CELLULOSE-BASED MATERIALS TO STRATUM CORNEUM |
| 18:30 | Michael Smirnov | APPLICATION OF DEEP EUTECTIC SOLVENTS FOR THE PRODUCTION OF CELLULOSE NANOMATERIALS |

December 3

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|---|---|---|
| 16:30 | Alexey Polotsky | STRETCHING OF LINEAR AND COMB-LIKE POLYMERS IN POOR SOLVENT: CONFORMATIONAL TRANSITIONS AND FORCE-EXTENSION RELATIONS |
| 17:00 | Maria Sammalkorpi | TOWARD UNDERSTANDING BIOMACROMOLECULAR MATERIALS VIA COMPUTATIONAL MODELLING: SILK-LIKE MODULAR PROTEIN CONSTRUCTS |
| 17:30 | coffee break | |
| 18:00 | Dmitry Tolmachev | ATOMISTIC SIMULATION OF POLYELECTROLYTES IN SALT SOLUTION |
| 18:30 | Tatiana Budtova | BIO-AEROGELS: NEW MATERIALS BORN IN THE 21 CENTURY |
| 19:00 | Ilya Averyanov | IMPROVEMENT OF OSTEOCONDUCTIVE PROPERTIES OF POLYESTER MATERIALS WITH CHEMICALLY MODIFIED NANOCRYSTALLINE CELLULOSE |
| 19:30 | Rafael Maglia de Souza | POLARIZABLE FORCE FIELDS FOR DEEP EUTETIC SOLVENTS |

# PLENARY LECTURES

# CLOSE TO YOUR SKIN: ACIDITY CONTROLS BINDING OF CELLULOSE-BASED MATERIALS TO STRATUM CORNEUM

Gurtovenko A.A.[1], Karttunen M.[1,2,3,4]

[1]*Institute of Macromolecular Compounds RAS,*
*199004, Saint-Petersburg, Bolshoy pr. 31, Russia*
[2]*Department of Chemistry, the University of Western Ontario, 1151 Richmond Street,*
*London, Ontario N6A 5B7, Canada*
[3]*The Centre of Advanced Materials and Biomaterials Research, the University of Western*
*Ontario, 1151 Richmond Street, London, Ontario, N6A 5B7, Canada*
[4]*Department of Physics and Astronomy, the University of Western Ontario, 1151 Richmond*
*Street, London, Ontario, N6A 3K7, Canada*
*a.gurtovenko@biosimu.org*

For many biomedical applications it is highly desirable to be able to control the interactions of biomaterials with living tissues and skin. Here we focus on cellulose-based materials which represent one of the most versatile platforms for wound dressing and tissue engineering due to their biocompatibility, abundance, and strength. To this end, we employed both biased and unbiased atomic-scale molecular dynamics simulations to explore how crystalline cellulose interacts with model stratum corneum bilayers, ternary mixtures of ceramides, cholesterol, and free fatty acids. Our computational findings show that acidity in the contact area directly affects binding between cellulose and the stratum corneum bilayer as protonation of free fatty acids in the bilayer promotes attractive cellulose–bilayer interactions. When less than half of the fatty acids in the bilayer are protonated, the electrostatic repulsion between a cellulose crystal and the surface of a stratum corneum bilayer dominates and there is no binding to skin. Larger degrees of fatty acid protonation make the cellulose–stratum corneum hydrogen bonding a major factor, leading to a tight binding. Overall, our findings highlight the critical role of acidity (or, in other words, fatty acid protonation) in biomaterial–stratum corneum interactions and can be used for optimizing the surface properties of cellulose-based materials aimed at their biomedical applications such as wound dressings [1].

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## Acknowledgements

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# APPLICATION OD DEEP EUTECTIC SOLVENTS FOR THE PRODUCTION OF CELLULOSE NANOMATERIALS

Smirnov M.A., Vorobiov V.K., Fedotova V.S., Sokolova M.P.

*Institute of macromolecular compounds RAS, 199004,*
*Saint Petersburg, Bolshoy pr. 31, Russia*
*Smirnov_Michael@mail.ru*

Cellulose is the most abundant renewable polymer, and its application in different fields meets the requirements of sustainable and green technology. Due to unique combination of properties, such as large specific surface area, high tensile strength and stiffness, the cellulose nanomaterials are widely studied as reinforcing fillers for polymer composites, templates for preparation of functional and stimuli-responsive materials, sensors or electrochemically active materials.

Deep eutectic solvents (DES) present a new and prospective alternative for ILs demonstrating the same beneficial physico-chemical properties while being cheaper and safer than ILs. Abilities of DES to act as media for processing various biomasses, including cellulose, have recently been under intensive investigation [1-3]. Typically, DES consist of a hydrogen bond donor and an acceptor which interact strongly with each other. As a result, an eutectic mixture with a melting point below that of both initial components is formed. DES can serve not only as a media for preparation or purification of cellulose nanomaterial, but also as a stimuli-responsible component in the cellulose based smart materials. Particularly, it was demonstrated that DES based on choline chloride and urea can serve as environment-friendly method for obtaining cellulose nanocrystals (CNC) [2]. It was shown that the type of cellulose crystal structure and the high degree of crystallinity are preserved under treatment conditions. Furthermore, the application of acrylic monomers as a hydrogen bond donors of DES can introduce the possibility of UV-curing for cellulose/DES based material. After elimination of DES components, prepared 3D-printed cellulose reinforced hydrogels have a potential interest in the field of medical implants.

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# STRETCHING OF LINEAR AND COMB-LIKE POLYMERS IN POOR SOLVENT: CONFORMATIONAL TRANSITIONS AND FORCE-EXTENSION RELATIONS

Polotsky A.A.[1], Ivanova A.S.[1], Borisov O.V.[1, 2], Birshtein T.M.[1]

*[1]Institute of Macromolecular Compounds RAS,*
*199004, Saint-Petersburg, Bolshoy pr. 31, Russia*
*[2]Institut des Sciences Analytiques et de Physico-Chimie pour l'Environnement et les Matériaux, UMR 5254 CNRS UPPA, 64053 Pau, France*
*alexey.polotsky@gmail.com*

In the last two decades, a significant progress in the development of experimental methods for manipulating single macromolecules has been achieved. The use of such instruments as an atomic force microscope, optical tweezers, and magnetic tweezers (magnetic traps) made it possible to study the mechanical properties of individual (bio)macromolecules and their complexes, as well as the mechanisms the work of molecular motors. Single molecule force spectroscopy has become a standard tool for modern biophysics, polymer physics and molecular biology. It allows to obtain information about the mechanical properties and also to get an insight into the conformational structure of the polymers under study.

In the present talk, we discuss the results of theoretical studies of mechanical unfolding of macromolecules collapsed in poor solvent in the isometric ensemble, i.e. when the macromolecule deformation is kept fixed or controlled. We consider three systems: linear homopolymer chain collapsed in a poor solvent, - comb-like homopolymer collapsed in a poor solvent, and amphiphilic comb-like copolymer with a solvophilic backbone and solvophobic side chains. Using self-consistent field modeling and analytical arguments we demonstrate that force-extension behaviour of these systems is highly non-trivial and, in the case of comb-like macromolecules, can demonstrate rather complex oscillatory, or "sawtooth", patterns due to the topological complexity.

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# TOWARD UNDERSTANDING BIOMACROMOLECULAR MATERIALS VIA COMPUTATIONAL MODELLING: SILK-LIKE MODULAR PROTEIN CONSTRUCTS

Sammalkorpi M.[1,2,3]

*[1]Department of Chemistry and Materials Science*
*[2]Department of Bioproducts and Biotechnology*
*[3]Centre of Excellence in Life-Inspired Hybrid Materials (LIBER), Aalto University, FI-00076 Aalto, Finland*
*maria.sammalkorpi@aalto.fi*
*https://www.aalto.fi/en/department-of-chemistry-and-materials-science/soft-materials-modelling*

Biologically in yeast and bacterial cultures synthesized proteins offer a scalable, environmentally sustainable means to self-assembling biomacromolecular materials. Such materials are both renewable and biodegradable but also enable advanced materials functionalities, for example, in terms of adaptive mechanical properties, adhesive characteristics, and biointeractions. However, to fully exploit the materials prospects, advanced approaches to design the protein systems are needed. We have combined molecular modelling with experimental physical characterization of tuneable biosynthetic block protein constructs toward this purpose.

I focus in this talk on our findings on spider-silk resembling recombinant proteins that have a modular tri-block structure. We have used both atomistic and coarse-grained computational modelling to study the assembly, solution structure formation, and interactions of these protein constructs at molecular level. We find that the formation of biosynthetic silk-like fibers requires the component proteins to have adhesive contact sites or domains, i.e. “stickers”, that vary in interaction strength. We combine the molecular modelling findings regarding the “sticker” interactions with analytical ultracentrifuge characterization of the associative interactions between the different protein blocks, diffusion characterization, and microscopy techniques. Based on the findings, we propose a mechanism for the molecular assembly structure – materials property relation for the examined silk-like protein system and discuss how this may be generalized to design of other block protein systems with tuneable materials properties.

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# ATOMISTIC SIMULATION OF POLYELECTROLYTES IN SALT SOLUTIONS

Tolmachev D.A.[1], Lukasheva N.V.[1], Karttunen M.[1,2]

[1]*Institute of Macromolecular Compounds RAS,*
*199004, St. Petersburg, Bolshoy pr. 31, Russia*
[2]*University of Western Ontario, 1151 Richmond Street, London, ON N6A 5B7, Canada*
*dm.tolmachev@yandex.ru*

In our study, we investigate the influence of mineral salts on the conformational and dynamic properties of polyelectrolytes. The information about the molecular structure of the organomineral complexes is useful in many fields of material development such as the development of corrosion inhibitors, cleaning drainage systems, filters for water purification, or synthesis of organomineral composites for bone implants. One of the irreplaceable ways to obtain this information is atomistic molecular dynamics simulation.

We have performed the simulation of anionic polyamino acids (polyaspartic and polyglutamic acids) in water with monovalent (sodium and potassium) and divalent (calcium) cations. The atomistic simulation of the polyelectrolytes in salt solutions related to the number of the challenges. The absence of polarization effect in charge-fixed force fields, which could lead to the overestimation of ion-ion interactions. In our work, we have checked the number of force fields and their corrections to obtain the most appropriate parameters for the simulation. It was shown that overestimation of electrostatic interaction leads to a full collapse of the polyelectrolyte chain due to the artificial formation of sodium bridges between carboxyl groups of amino acids. Moreover, the corrections to the force field should be chosen wisely due to the fact they can lead to unexpected artificial results.

The strong ion-ion interaction of carboxyl groups with divalent salt restricts conformational transitions of the chain and obstructs the sampling of the simulation. To increase the sampling one should use state-of-the-art methods of the simulation such as Hamiltonian replica exchange or methadynamics. The results of the simulation revealed the difference in the structure of organomineral complexes based on the different anionic aminoacids. These results allowed us to explain the number of experiments, which showed the different effects on the mineral formation of glutamic and aspartic acids.

## Acknowledgments

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# BIO-AEROGELS: NEW MATERIALS BORN IN THE 21st CENTURY

Budtova T.

*MINES ParisTech, PSL Research University, Center for Materials Forming (CEMEF), UMR CNRS 7635, CS 10207, 06904 Sophia Antipolis, France*
*Tatiana.Budtova@mines-paristech.fr*

Aerogels are open-pores low density (around 0.1 g/cm$^3$) nanostructured materials with very high internal pores' surface area (several hundreds of m$^2$/g). In the past century aerogels based on inorganic matter, mainly silica, and on synthetic polymers, were developed.

21st century was marked by an increased interest to bio-based materials, and the first bio-aerogels based on cellulose were born. In our days, bio-aerogels are mainly based on different polysaccharides.

In our work we use polysaccharides (cellulose [1, 2], starch [3.4], pectin [5, 6, 7], chitosan, hyaluronic acid) without any chemical modification. Bio-aerogels are made by polymer dissolution, gelation (in some cases this step can be omitted), solvent exchange and drying with supercritical $CO_2$. An overview of the properties and potential applications of bio-aerogels will be presented, and open questions discussed.

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# IMPROVEMENT OF OSTEOCONDUCTIVE PROPERTIES OF POLYESTER MATERIALS WITH CHEMICALLY MODIFIED NANOCRYSTALLINE CELLULOSE

Averianov I.V.[1], Stepanova M.A.[1], Solomakha O.A.[1], Gofman I.V.[1], Korzhikov-Vlakh V.A.[1,2], Korzhikova-Vlakh E.G.[1,2], Lavrentieva A.[3], Karttunen M.[1]

*[1]Institute of Macromolecular Compounds RAS,*
*199004, Saint-Petersburg, Bolshoy pr. 31, Russia*
*[2]Institute of Chemistry, Saint-Petersburg State University, Saint-Petersburg, Russia*
*[3]Institute of Technical Chemistry, Leibniz University, Hannover, Germany*
*averianovilia@gmail.com*

Numerous investigators have been currently addressing the means by which biological recognition might be imported in materials for tissue engineering [1]. Among these strategies might be the incorporation of biofunctional particles in the material. Such particles could create the time–spatial distribution of biological ligands while scaffold would be degraded *in vivo*. One of the candidates for creating such particles is the nanocrystalline cellulose (NCC). It shows biocompatibility and the possibilities for additional modification with a wide variety of ligands. In order to improve the interaction with polyesters (poly(lactide), poly(ε-caprolactone)) NCC could be modified with polymer or peptide molecules [2, 3].

In our recent work we developed an approach for chemical modification of nanocrystalline cellulose with poly(glutamic acid) (PGlu) [4]. We used NCC-PGlu to create composite materials on the basis of biodegradable polyesters. Here we studied the effect of NCC-PGlu addition in polyesters (poly(lactic acid) (PLA), poly(ε-caprolactone) (PCL)) on biological properties of resulting materials. We used these composites to 3D print scaffolds for cell culture and implantation. We carried out cell culture tests of scaffolds and films to study the difference in adhesion, proliferation and osteodifferentiation of human mesenchymal stem cells. Composite materials with NCC-PGlu showed improved calcification *in vitro* and *in vivo* [5, 6]. The X-ray tomography data allowed us to draw conclusions on improved regeneration of bone defects *in vivo* when using PCL composite with NCC-PGlu. Our studies show that NCC-PGlu increases the properties of tested materials aimed at successful regeneration of bone tissue.

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# POLARIZABLE FORCE FIELDS FOR DEEP EUTETIC SOLVENTS

Rafael Maglia de Souza[1], Mauro Carlos Costa Ribeiro[1]

[1]*Departamento de Química Fundamental, Instituto de Química, Universidade de São Paulo,*
*Avenida Professor Lineu Prestes 748, São Paulo (SP), Brasil*
*rafael.maglia.souza@usp.br*

Deep eutectic solvents1(DESs) are an interesting class of materials resembling ionic liquids (ILs) systems with great potential applications in synthesis, electrochemistry, extraction and separation processes, and biomass transformation. DESs are mixtures of two or more substances, with at least one being a hydrogen bond donor (HBD) molecule and one being a hydrogen bond acceptor (HBA) molecule.

Traditionally, molecular dynamics (MD) simulations of DESs have been performed with non-polarizable molecular mechanics force fields. However, polarizable force fields are emerging to provide physically sound simulations. Recently, the CLPol force field2became available for MD simulations of DESs, which is the first general, transferable and polarizable force field (based on Drude oscillators) for DESs.

In this work, we show and discuss the strengths and problems (and the necessary corrections) found when using the polarizable CLPol force field for MD simulations of DESs. In addition, we present some challenging aspects and routes concerning the development and calibration of polarizable force fields for other compositions of eutectic mixtures.

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# POSTER PRESENTATIONS

# ISOLATION OF BACTERIAL CELLULOSE NANOFIBERS USING MIXTURES OF CHOLINE CHLORIDE WITH GLYCEROL OR ETHYLENE GLYCOL

Batishcheva E.V.[1,2], Sokolova D.N.[1,2], Fedotova V.S.[1], Sokolova M.P.[1],
Vakulyuk A.Yu.[1], Shakhbazova Ch.Ya.[1,2], Karttunen M.[1,3,4,5], Smirnov M.A.[1]

*[1]Institute of Macromolecular Compounds RAS,*
*199004, V.O. Bolshoi pr. 31, 199004, State Petersburg, Russia*
*[2]Institute of Chemistry, Saint Petersburg State University, Universitetsky pr. 26,*
*Peterhof, 198504, Saint Petersburg, Russia*
*[3]Department of Chemistry, The University of Western Ontario, 1151 Richmond Street,*
*London, ON N6A 5B7, Canada; mkarttu@uwo.ca (M.K.)*
*[4]Department of Physics and Astronomy, The University of Western Ontario, 1151*
*Richmond Street, London, ON N6A 5B7, Canada*
*[5]The Centre of Advanced Materials and Biomaterials Research, The University of*
*Western Ontario, 1151 Richmond Street, London, ON N6A 5B7, Canada*
*batischevaelisaveta@gmail.com*

The outstanding mechanical properties of crystalline cellulose promote growing interest toward cellulose nanomaterials with high degree of crystallinity: cellulose nanocrystals and cellulose nanofibers (CNF). Bacterial cellulose is a unique non-wood source of high purity cellulose, which represents the network of interconnected CNF produced by bacteria (for example *Acetobacter xylinum*). However, the strong network of interfibrillar hydrogen bonds complicates the processing of bacterial cellulose and preparation of mixtures and composites on its base with other polymers. Thus, the effective process for isolation of bacterial cellulose nanofibers worth investigation.

In the recent years, deep eutectic solvents (DES) as «green» analogues of ionic liquids, are intensively studied for processing of carbohydrate polymers. Due to developed internal network DES, demonstrate possibility to interact with surface -OH groups of cellulose thus facilitating the isolation of CNF. In this work, the route for preparation of CNF dispersions from bacterial cellulose using DES based on choline chloride and ethylene glycol or glycerol was successfully demonstrated. Additionally, the effect of the combined treatment with DES and ultrasound on the morphology and structure of CNF was studied. Isolated CNF was obtained in the form of hydrogels and were characterised with FTIR, atomic-force microscopy (AFM) and measurements of degree of polymerisation of cellulose. It was demonstrated that treatment with DES leads to the decreasing of degree of polymerisation and application of ultrasound enhances this effect. AFM results demonstrate that application of ultrasound leads to the more pronounced swelling of CNF. This effect is more pronounced in the case of ethylene glycol based DES that can be connected with smaller sizes of its molecules in comparison with glycerol. At the same time, Wide-angle X-ray scattering data evidences the preservation of degree of crystallinity of CNF in all cases. This allows to suggest that all structural changing occur on the surface of CNF.

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# SYNTHESIS AND CHARACTERIZATION OF NOVEL SUCCINYL CHITOSAN-DEXAMETHASONE CONJUGATES FOR INTRAVITREAL DEXAMETHASONE DELIVERY

Bokatyi A.N.[1,2], Dubashynskaya N.V.[1], Skorik Y.A.[1]

*[1]Institute of Macromolecular Compounds RAS, 199004, St. Petersburg, Bolshoy 31, Russia*
*[2]St. Petersburg State University, 198504, St. Petersburg, Petergof, Universitetskii 26, Russia*
*antoniobokatyi@gmail.com*

Intravitreal injection is one of the most effective methods of drug delivery to the posterior segment of the eye for the treatment of ophthalmic diseases. However, with prolonged use, injections can lead to retinal detachment and reduced effectiveness of therapy. Therefore, intravitreal delivery systems are required, as they have a prolonged action and can maintain therapeutic concentrations for a long time [1]. The use of polymeric conjugates, such as the corticosteroid dexamethasone (Dex), for intravitreal delivery has excellent potential but is rarely used [2].

The aim of the study is to develop a method of conjugating Dex with chitosan (CS) for possible use as an intravitreal Dex delivery system. To achieve this goal, we pursued the following objectives: (i) preparation and characterization of succinyl dexamethasone (SucDex), (ii) development of a synthesis method and characterization of Dex-CS conjugates, (iii) succinylation of Dex-CS to form negatively charged particles (Dex-SucCS), and (iv) study of the physicochemical characteristics of conjugates (hydrodynamic diameter and ζ-potential) and the kinetics of the release of Dex.

We first used carbodiimide chemistry to conjugate Dex to CS via a succinyl linker and then modified the obtained conjugate with succinic anhydride to impart a negative ζ-potential to the polymer particle surface. The resulting polysaccharide carriers had a degree of substitution with Dex moieties of 2–4%, a Dex content of 50–85 μg/mg, and a degree of succinylation of 64–68%. The size of the obtained particles was 400–1100 nm, and the ζ-potential was −30 to −33 mV. In vitro release studies at pH 7.4 showed slow hydrolysis of the amide and ester bonds in the synthesized conjugate, with a total release of 8–10% for both Dex and SucDex after 1 month. The developed conjugates showed a significant anti-inflammatory effect in TNFα-induced and LPS-induced inflammation models, suppressing CD54 expression in THP-1 cells by 2- and 4-fold, respectively [3]. Thus, these novel succinyl chitosan-dexamethasone (Dex-SucCS) conjugates are promising ophthalmic carriers for intravitreal delivery.

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# INFLUENCE OF STRUCTURAL ORDERING OF POLYMER CHAINS ON GAS TRANSPORT PROPERTIES OF BPDA-P3 POLYETHERIMIDE

Dobrovskiy A.Yu.[1], Nazarychev V.M.[1], Volgin I.V.[1], Larin S.V. [1], Lyulin S.V.[1]

*[1]Institute of Macromolecular Compounds RAS,*
*199004, Saint-Petersburg, Bolshoy pr. 31, Russia*
*aleksey_dobrovsky@mail.ru*

The structural ordering of polymer chains in bulk samples can lead to the change in their physical, in particular, transport properties. Investigation of the processes taking place during the ordering is necessary for development of materials with controlled properties. The use of experimental research methods or analytical theories currently does not allow to establish exactly how the diffusion of gases through highly ordered polymer chains occurs. Molecular dynamics (MD) simulations based on all-atom models make it possible to study the molecular mechanisms underlying the process of gas diffusion through a polymer membrane at the nanoscale, which turns out to be difficult or completely impossible in experiments. Moreover, simulations are very helpful for investigation of the effect of structural ordering degree on transport properties of the polymer membrane.

Polyetherimides (PEI) are one of the most promising materials for using them in industry, in particular, in development of gas separation membranes due to their outstanding thermomechanical properties and resistance to aggressive media. In this work we researched the transport properties of semi-crystalline PEI BPDA-P3, based on 3,3',4,4'-biphenyltetracarboxylic dianhydride (BPDA) and diamine 1,4-bis[4-(4-aminophenoxy)phenoxy]benzene (P3). The investigation of the diffusion coefficient, solubility and permeability was carried out at different stages of structural ordering: in amorphous and highly ordered states. For this, long-term (~ 30 μs) MD simulations of BPDA-P3 were performed at $T$=600 K, close to the experimental value of melting temperature ($T_m$ ~ 580 K). It was found that mean square displacement of polymer chains in the amorphous state at this temperature turned out to be smaller than that in ordered one. This could be explained by the presence of polymer chains entanglements in the amorphous state and the "slipping" of the chains relative to each other in the highly ordered state. The study of free volume distribution in the simulation box in the amorphous and ordered states showed that in the process of structural ordering a redistribution of free volume took place: number of pores increased as their average size decreased.

The solubility of two gases ($CH_4$ and $CO_2$) was calculated in a wide temperature range: from 300 up to 480 K. It was found that in the process of structural ordering, the solubility decreased for both gases. In addition, temperature dependence for their diffusion coefficients at temperatures below the glass transition temperature (in the range from 430 to 480 K) was calculated. It was obtained that the diffusion coefficient of $CO_2$ were higher than for $CH_4$, both in the amorphous and in the highly ordered states, which may be related to the difference in the effective diameter of the gas molecules. It was also shown that in the process of structural ordering of polymer chains the value of the diffusion coefficients practically did not change, which indicated that the permeability in the system under consideration was largely determined by the solubility of gases, and not by the diffusion coefficient of them.

Thus, the results obtained have shown that the structural ordering of polymer chains could have a significant effect on the polymer transport properties. Better understanding of supramolecular structure-properties relationship could later be used in the development of new PEI-based membrane materials with controlled properties.

# COLISTIN DELIVERY SYSTEMS BASED ON POLYELECTROLYTE COMPLEXES OF HYALURONIC ACID AND CHITOSAN

Dubashynskaya N.V.[1], Shcherbakova E.S.[2], Dubrovskii Y.A.[3], Demyanova E.V.[2], Skorik Y.A.[1]

*[1]Institute of Macromolecular Compounds RAS, 199004, Saint-Petersburg, Bolshoy 31, Russia*
*[2]State Research Institute of Highly Pure Biopreparations, 197110, Saint-Petersburg, Pudozhsakya 7, Russia*
*[3]Almazov National Medical Research Centre, 197341, Saint-Petersburg, Akkuratova 2, Russia*
*dubashinskaya@gmail.com*

Improving the biopharmaceutical properties of antimicrobial drugs is an effective strategy for controlling the global growth of multidrug-resistant Gram-negative microorganisms, including ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) [1].

Nanoparticles (NPs) based on natural polysaccharides are well established as potential platforms for the treatment of severe infectious diseases. These drug delivery systems protect active pharmaceutical ingredients in the body from destruction, while also providing modified release and targeted delivery of active agents to infection sites, thereby reducing drug doses, toxicity, and side effects [2].

Colistin (CT) is an antimicrobial drug that could potentially benefit from complexation with polymer NPs. As a cationic peptide antibiotic, CT has the ability to interact with anionic polymers and form negatively charged NPs [3]. CT can also be loaded into a polymeric drug delivery system composed of a polycation and a polyanion [4].

The purpose of this study was to develop a CT delivery system based on hyaluronic acid (HA) and the water-soluble cationic chitosan derivative diethylaminoethyl chitosan (DEAECS). We used DEAECS with a degree of substitution of 84% synthesized by a method [2] from crab shell chitosan with an average molecular weight of 37,000 and a degree of acetylation of 26%. The CT delivery system was a polyelectrolyte complex (PEC) formed by interpolymeric interactions between the HA polyanion and the DEAECS polycation, with the inclusion of positively charged CT molecules in the resulting complex. The PEC had a hydrodynamic diameter of 250 nm and a negative ζ-potential of −19 mV. The encapsulation and loading efficiencies were 100 and 16.7%, respectively. The obtained CT delivery system had a modified release profile (40% and 90% of CT released in 15 and 60 min, respectively) compared to pure CT (100% CT released in 15 min). In vitro tests showed that the minimum inhibitory concentrations against *P. aeruginosa* of both encapsulated CT and pure CT were 1 μg/mL. Thus, the encapsulation of CT in polysaccharide PEC did not reduce its antimicrobial activity.

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# COMPUTER SIMULATIONS OF THE STRUCTURE OF GRAFTED LAYERS OF LACTIDE AND 3-HYDROXYBUTYRATE OLIGOMERS

Glova A.D.[1], Larin S.V.[1], Lyulin S.V.[1]

*[1]Institute of Macromolecular Compounds RAS, Saint-Petersburg, Bolshoy pr. 31, Russia*
*glova@imc.macro.ru*

Nowadays biodegradable polymer materials based on biopolymers are the subject of numerous studies, since the transition to their use reduces the consumption of traditional large-scale polymers posing a serious environmental hazard. To obtain biopolymer materials with the required physical characteristics, nanocomposites have been actively developed. Among biopolymers polylactide (PLA) and poly(3-hydroxybutyrate) (PHB) are the most promising for the development of nanocomposites for a wide range of applications. The physical characteristics of these nanocomposites largely depend on the interaction between nanofillers and polymer binders at the interface. Compared to widespread carbon nanoparticles, cellulose nanoparticles (CNPs) are promising biodegradable natural fillers due to their good mechanical characteristics and low cost. However, CNPs are hydrophilic and, therefore, they tend to aggregate in the nanocomposites based on hydrophobic PLA and PHB owing to poor compatibility between the fillers and polymer binders. To prevent aggregation, cellulose nanoparticles surface-modified by grafting oligolactide (OLA) and oligo(3-hydroxybutyrate) (OHB) chains can be used as PLA and PHB fillers, respectively. In this case, the compatibility between the corresponding hydrophobic polymer binders and modified nanoparticles and, hence, physical characteristics of nanocomposites can be determined by the structure of grafted layers of OLA and OHB chains. However, the investigation of their structural characteristics has not been carried out yet. Therefore, the reported results of molecular dynamic simulations were devoted to the study of the structure of OLA and OHB chains grafted onto CNPs surface immersed in PLA and PHB, respectively.

We found that the grafted OLA chains tend to fold back toward the filler surface, adopting a hairpin-like conformation. It was demonstrated that dipole–dipole interactions within the grafted layer, rather than hydrogen bonding with the cellulose surface, are the key factor determining the backfolding observed for the grafted chains. It was the attraction between the longitudinal components of dipole moments of OLA repeating units that caused the backfolding in order to form a favorable antiparallel orientation of the dipole moments of adjacent repeating units. Furthermore, we obtained that an increase in the length of the grafted OLA chains had practically no effect on the fraction of the hairpin-like conformations, but was able to promote the initial stage of crystallization of grafts at high grafting densities. The comparison of linear and branched OLA chains allowed us to conclude that the grafted OLA with a linear architecture, rather than their branched counterpart, may be preferable for the covalent modification of CNPs. Moreover, we showed that the structure of grafted OHB chains is qualitatively similar to that for the OLA chains. However, the OHB chains turned out to be more stretched from the CNPs surface due to their higher flexibility compared to the OLA chains.

The obtained results provide new insights on the structure of the considered nanocomposites. Thus, they may be relevant for future development and applications of the biopolymer-based systems.

**Acknowledgements**

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# LUMINESCENT POLYFLUORENE BRUSHES WITH POLYMETHACRYLIC ACID SIDE CHAINS

Kaskevich K.I.[1], Ilgach D.M.[1], Simonova M.A.[1], Nepomnyashaya M.I.[2], Litvinova L.S.[1], Yakimansky A.V.[1]

*[1]Institute of macromolecular compounds RAS,*
*199004, Saint-Petersburg, Bolshoy pr. 31, Russia*
*[2]Higher School of Technology and Energy,*
*198095, Saint Petersburg, Ivana Chernykh 4, Russia*
*kaskevich-ksenia@yandex.ru*

Amphiphilic polymer brushes with a conjugated backbone are of particular interest, because of their high luminescent quantum yields which allows them to be applied not only in drug delivery systems, but also in bioimaging [1]. Therefore, the aim of this work is to synthesize amphiphilic polymer brushes (ABP) with a polyfluorene backbone and polymethacrylic acid side chains (Figure 1), to study their luminescent properties, and to determine the size of micelles emerging in water.

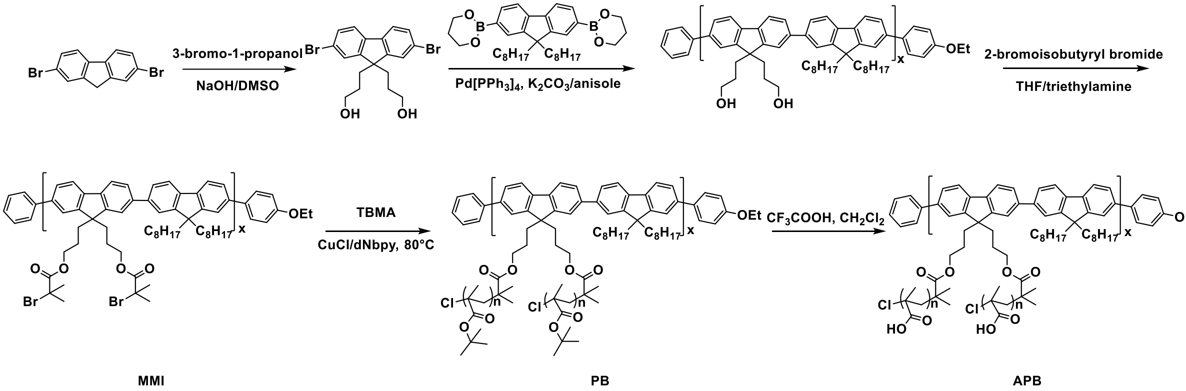

Figure 1 – Scheme for obtaining polyfluorene-*graft*-polymetgacrylic acid (**APB**)

It was demonstrated that the luminescence intensity and quantum yields of polymer brushes (64-71%) are higher than that of the native polyfluorene macroinitiator (61%). The luminescence quantum yields of amphiphilic polymer brushes were determined in solutions using quinine sulfate as a standard [2].

APB is not soluble water. However, it was shown by dynamic light scattering that the injection of an alcohol solution of APB into water under sonication leads to the formation of rod-shaped unimolecular micelles. Moreover, these micelles are stable under dilution. Curcumin was used as a model hydrophobic compound for encapsulation by APB. It was found that the micelles sizes have increased from 20 nm (brush without curcumin) to 50-92 nm by encapsulating different amounts of curcumin into APB. A complete Förster energy transfer from polyfluorene to curcumin is observed in the luminescence spectra of encapsulated curcumin.

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# SYNTHESYS AND SELF-ORGANIZATION OF THERMOSENSITIVE STAR-SHAPED POLYALKYLOXAZOLINE AND POLYALKYLOXAZINE IN WATER SOLUTIONS.

Kirila T.U., Blokhin A.N., Filippov A.P.

*Institute of macromolecular compounds RAS,*
*199004, Saint-Petersburg, Bolshoy pr. 31, Russia*
*tatyana_pyx@mail.ru*

Novel four-armed star poly(2-alkyl-2-oxazoline)s and poly(2-alkyl-2-oxazine)s with calix[4]arene branching center were synthesized by cationic ring-opening polymerization using sulfochlorinated calix[4]arene derivative as a multifunctional initiator. There are star-shaped poly-2-ethyl-2-oxazoline (PEtOx), poly-2-isopropyl-2-oxazoline (PiPrOx), poly-2-ethyl-2-oxazine (PEtOz) and poly-2-isopropyl-2-oxazine (PiPrOz).

Molar masses of samples and dispersity index *Đ* were determined by GPC, static light scattering and sedimentation-diffusion analysis in chloroform (Table). The hydrodynamic radii $R_h$, intrinsic viscosity [η] and arm length $L_a$ were obtained.

| **Sample** | $M_w$, **g·mol$^{-1}$** | ***Đ*** | $R_h$, **nm** | $L_a$, **nm** | **[η], cm$^3$g** |
|---|---|---|---|---|---|
| **PEtOx** | 11500 ± 300 | 1.17 | 3.1 ± 0.3 | 10.2 ± 0.4 | 6.6 ± 0.5 |
| **PiPrOx** | 15500 ± 400 | 1.25 | 2.9 ± 0.3 | 12.2 ± 0.4 | 9.9 ± 0.4 |
| **PEtOz** | 11650 ± 600 | 1.18 | 3.0 ± 0.3 | 9.1 ± 0.5 | 5.4 ± 0.4 |
| **PiPrOz** | 11600 ± 300 | 1.21 | 3.2 ± 0.3 | 8.0 ± 0.4 | 7.0 ± 0.3 |

Aqueous solutions of samples were investigated by methods of static and dynamic light scattering and turbidimetry.The temperature dependens of optical transmission $I^*$, intensity of scattering light $I$ and hydrodynamic radii $R_h$ of species and their fractions in solution were observed. The phase separation temperature of solution was determined.

It was shown that at a fixed concentration the phase separation temperature decreases in the following order: PEtOx – PEtOz – PiPrOx – PiPrOz. This is due to an increase in the hydrophobicity of polymers both with an increase in the side radical in the arms and with an extension of the monomer unit by the $–CH_2–$ group.

It was found that the phase separation temperatures decrease after the changeover from lower rim grafting to upper rim one due to varying configurations of calix[4]arene [1].

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# BACTERIAL CELLULOSE-BASED NANOCOMPOSITES WITH $CeO_2$ NANOPARTICLES: THEIR PHYSICO-CHEMICAL AND BIOLOGICAL PROPERTIES

Nikolaeva A.L.[1], Gofman I.V.[1], Khripunov A.K.[1], Ivan’kova E.M.[1], Yakimansky A.V.[1,2],
Popov A.L.[3,4], Ermakov A.M.[3], Baranchikov A.E.[4], Ivanov V.K.[4]

*[1]Institute of macromolecular compounds RAS, 199004, Saint-Petersburg, Bolshoy pr. 31, Russia*
*[2]St Petersburg State University, 199034, Saint-Petersburg, University Embankment 7/9, Russia*
*[3]Institute of Theoretical and Experimental Biophysics, 142290 Pushchino, Institutskaja str. 3, Russia*
*[4]Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 119991 Moscow, Leninsky pr. 31, Russia*
*a.l.nikolaeva@imc.macro.ru*

We have developed a new method of fabrication of composite bacterial cellulose (BC) films filled with $CeO_2$ nanoparticles (ceria). The structure and morphology of the films have been investigated as well as their thermal and mechanical characteristics in a dry and swollen state. The preparation technique used allows one to form composites with nanoparticles distributed uniformly in the films. The catalytic activity of ceria with regard to the thermo-oxidative destruction of BC has been corroborated by simultaneous thermogravimetric (TGA) and differential thermal (DTA) analyses. An increase in CeO2 concentration resulted in a certain rise in the stiffness and strength of the nanocomposite material, the effect being attributed to the formation of additional links between the polymer macromolecules via the surface of the nanoparticles. The materials fabricated were characterized by a limited ability to swell in water. Despite the fact that swelling caused a 20- to 30-fold reduction in the elastic modulus of the films, they remain suitable for practical use.

The possibility of applying the nanocomposite films in cell engineering as substrates for stem cells’ proliferation has been investigated. The increase in $CeO_2$ content in the films was found to enhance the proliferative activity of embryonic mouse stem cells, *e.g.*, the cells cultured on the scaffold with 5 wt.% of ceria demonstrated increased cell survival and migration activity. The gene expression analysis confirmed improved cultivation conditions on $CeO_2$-containing scaffolds in comparison with the pristine BC films.

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# POLYMER ADSORPTION ONTO A HETEROGENEOUS STRIPE-PATTERNED SURFACE: EFFECT OF BENDING STIFFNESS

Polotsky A.A.[1], Ivanova A.S.[1]

*[1]Institute of Macromolecular Compounds RAS,*
*199004, Saint-Petersburg, Bolshoy pr. 31, Russia*
*alexey.polotsky@gmail.com*

Polymer adsorption onto surfaces and interfaces plays an important role in various fields of polymer science such as surface modification, nanocomposites formation, adsorption chromatography, etc. When the surface is a chemically heterogeneous and the surface pattern is anisotropic, this anisotropy manifests itself in adsorption.

We consider a single polymer chain interacting with a flat heterogeneous surface containing adsorbing and non-adsorbing sites. The sites are organized into regular parallel stripes of fixed width. Chain conformations are modelled as nonreversal random walks (NRRWs) on the cubic lattice. In a NRRW, immediate reversal steps are forbidden. The chain stiffness is introduced by assigning different energies to a straight segment and a kink. Moreover, the stiffness is temperature-dependent: a change in temperature $T$ affects not only the statistical weight of the adsorbed unit but the chain stiffness too. We considered both positive and negative bending energy $\varepsilon_{bend}$ (the difference between the energies of a kink and of a straight segment): in the former case the chain is stiff and acquires a rod-like conformation as the temperature decreases, in the latter case kinks are preferable and the chain acquires a quasi-zigzag conformation at low temperature.

The problem was solved in the framework of the generating functions (GFs) approach. An equation for finding the GF smallest singularity, which gives the asymptotics of the chain partition function, was derived.

The dependence of the critical adsorption temperature on the bending energy is non-monotonous and has a minimum. This minimum is in the vicinity of $\varepsilon_{bend} = 0$ but its exact location depends on the details of the heterogeneous surface pattern.

It was shown that adsorption of stiff chains is accompanied by the chain extension and localization on a single adsorbing stripe: as the temperature decreases, the fraction of contacts with adsorbing stripes and fraction of bonds parallel to the stripes increase to unity while the fraction of contacts with non-adsorbing stripes and the fraction of bonds perpendicular to the stripes behave non-monotonically and decay to zero as $T \to 0$. In the case of the surface with adsorbing stripes of unit width this behavior persists for flexible chains ($\varepsilon_{bend} = 0$) and even for chains with weakly negative bending energy. For chains with strongly negative bending energy, chain localization on a single adsorbing stripe takes place too, delocalization is observed only in the single particular case of the surface made of adsorbing and nonadsorbing stripes of unit width.

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# SURFACE MODIFICATION OF THE BACTERIAL CELLULOSE NANOFIBERS WITH 3-(TRIMETHOXYSILYL) PROPYL METHACRYLATE

Prosvirnina A.P.[1], Bugrov A.N.[1,2], Vlasova E.N.[1], Fedotova V.S.[1], Nikolaeva A.L.[1], Sokolova M.P[1], Smirnov M.A.[1]

*[1]Institute of macromolecular compounds RAS, 199004, St. Petersburg, Bolshoy pr. 31, Russia*
*[2]Saint Petersburg Electrotechnical University (ETU “LETI”), 197376, St. Petersburg, ul. Professora Popova 5, Russia*

The main factors limiting the use of bacterial cellulose (BC) as a filament include low solubility both in water and in most organic solvents, small stiffness and elastic modulus in a wet state, and loss of dimensional stability at high humidity [1, 2]. Modification of BC nanofibers with 3-(trimethoxysilyl) propyl methacrylate (TMSPM) reduces their hydrophilicity and simultaneously allows the surface be functionalized with vinyl groups, which in turn makes it possible to form additional crosslinks between them. Depending on the conditions of hydrolysis and subsequent condensation of TMSPM in the presence of BC nanofibers, from one to three covalent Si-O-C bonds can form between them.

Surface modification of BC nanofibers previously dispersed in ethanol was carried out in two stages. First, the alkaline hydrolysis of the methoxy groups of TMSPM was carried out for 1 hour at room temperature, and then the condensation reaction was provided at 70 °C for 4 hours. The kinetics of the process was monitored using the gas chromatography method, the conversion of the modifier was about 58-93%, depending on the BC:TMSPM ratio. The $^{29}$Si-NMR spectra show chemical shifts at -48, -57 and -70 ppm corresponding to the formation of bonds $(BC\text{-}O)_2Si^*(OSi)R$, $(BC\text{-}O)Si^*(OSi)_2R$ and $Si^*(OSi)_3R$, respectively [3].

FTIR spectra were measured in two modes. In ATR spectra for modified BC nanofibers, absorption bands of carbonyl groups in the region of 1720 cm$^{-1}$ were observed. The appearance of this band indirectly indicates the presence of modifier molecules on the surface of BC. The DRIFT spectra also show the presence of carbonyl groups on the surface of nanofibers, along with a band at 1640 cm$^{-1}$ related to stretching vibrations of C=C bonds. It was noticed that with an increase in the degree of surface functionalization, the integral intensity of the above absorption bands increases.

As a result, a series of nanofiber samples with different amounts of vinyl groups on the surface was obtained. EDX analysis showed that, depending on the ratio of the modifier and nanofibers, the content of TMSPM on the surface of BC nanofibers can vary from 9 to 67 mmol per 1 g of BC. It has been shown that the polymerization products of modified cellulose nanofibers dispersed in a mixture of acrylic acid and choline chloride demonstrate the mechanical properties of a covalently crosslinked three-dimensional polymer material.

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# MECHANICAL UNFOLDING OF AN AMPHIPHILIC COMBLIKE COPOLYMER IN SELECTIVE SOLVENT

Ivanova A.S., Polotsky A.A.

*Institute of Macromolecular Compounds RAS,*
*199004, Saint-Petersburg, Bolshoy pr. 31, Russia*
*sasinaas@yandex.ru*

Amphiphilic comblike copolymers containing groups of different chemical nature in the main and side chains are capable of self-assembling into nanoscale superstructures in solutions. Amphiphilic comblike copolymers offer wide opportunities for design of smart materials, tissue-mimiking hydrogels, and nanocarriers for drug and gene delivery applications. The macromolecules of comblike copolymers are often exposed to external stress or deformation, hence the study of mechanical properties and conformational transitions in amphiphilic comblike copolymers induced by external action is an important fundamental and practical task.

In the present work, we have performed a self-consistent field (SCF) modeling of mechanical unfolding of an amphiphilic comblike macromolecule in a selective solvent by using the Scheutjens-Fleer numerical SCF approach. This method allows obtaining conformational and thermodynamic properties of the considered system (e.g., the force-extension curves) in a wide range of length and grafting density of the side chains, and the quality of the solvent for the side chains.

It was shown that for fixed side chain lengths, the character of the force-deformation curves depends significantly on the grafting density and the quality of the solvent. When an amphiphilic comblike macromolecule does not form an unimolecular micelle (in the case of loose grafting of side chains and dense grafting under moderately poor solvent conditions) the stretching of the comblike macromolecule is determined by deformation of its backbone. Amphiphilic comblike macromolecule with densely grafted side chains in the poor solvent can form a unimolecular micelle of spherical shape with the solvophobic core made of side chains and the soluble corona made of the loops of the backbone. Under these conditions, there are three regimes on the force-extension curve: (1) At small deformations the micelle shape changes from the sphere to the prolate spheroid, the restoring force grows. (2) At moderate deformations, microphase segregation within the macromolecule occurs, the macromolecule acquires the tadpole conformation with a large globular (micellar) head and stretched tail consisting of stretched segments of the main chain (spacers) with beads-globules formed by individual collapsed side chains attached to it at regular intervals. Formation of each new cluster is accompanied by a drop in the reaction force, and the force-extension curve in this regime has a saw-tooth shape. (3) At strong deformations, the clusters have approximately the same size, the restoring force grows, the deformation behavior is determined solely by the backbone stretching. In this regime, the stretching is accompanied by the increase in. the number of clusters and, correspondingly, the decrease in the aggregation number – the number of side chains in each cluster.

# POLYMER BRUSHES WITH ADSORPTION-ACTIVE CHAINS

Ivanova A.S.[1], Polotsky A.A.[1], Skvortsov A.M.[2], Klushin L.I.[1,3]

[1]*Institute of Macromolecular Compounds RAS,*
*199004, St. Petersburg, Bolshoy pr. 31, Russia*
[2]*Chemical-Pharmaceutical University, 197022, St. Petersburg, Professora Popova 14, Russia*
[3]*Department of Physics, American University of Beirut, P.O. Box 11-0236, Beirut 1107 2020, Lebanon*
*sasinaas@yandex.ru*

Polymer chains end-grafted onto a substrate, or the so-called polymer brushes, belong to the most studied and most promising systems in modern polymer science. Applications of polymer brushes range from colloidal stabilization to materials engineering and nanomedicine.

Recently we investigated a novel class of responsive uncharged polymer brushes formed by adsorption-active chains [1]. In this case the brush properties are affected by the short-range adsorption interactions between the substrate and the chain units. It was demonstrated that a monodisperse brush with a strong enough monomer attraction to the substrate forms a microphase separated system with a fraction of chains being almost completely laid out on the surface while the rest of the chains form a residual brush with a reduced effective grafting density.

In the present work, we consider bidisperse polymer brushes consisting of two types of linear flexible macromolecules differing only in the degree of polymerization grafted at one end onto a solid planar substrate. The surface is assumed to be attractive to all polymer chains.

To calculate the system's partition function and its various properties, we use the Scheutjens-Fleer self-consistent field method.

Polymer density profiles and the free ends distributions demonstrate that with increasing adsorption energy, short chains adsorb onto the grafting surface prior to the long ones, which only start adsorbing at stronger monomer-surface attraction. With increasing adsorption energy, the fractions of adsorbed units in short and long chains monotonically increase and reach saturation values. The fraction of adsorbed units in short chains is always larger than that in long chains which also indicates preference for the short chain adsorption in the brush. An increase in the grafting density leads to a decrease in average fraction of adsorbed monomers for both short and long chains because the adsorbing capacity of the surface is limited and more chains belong to the residual brush.

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# CONFORMATION, SELF-ORGANIZATION AND THERMORESPONSIBILITY OF POLYMETHACRYLATE MOLECULAR BRUSHES WITH OLIGO(ETHYLENE GLYCOL)-BLOCK-OLIGO(PROPYLENE GLYCOL) SIDE CHAINS

Simonova M.A.[1], Nepomnyashaya M.I.[2], Filippov A.P.[1]

*[1]Institute of macromolecular compounds RAS,*
*199004, Saint-Petersburg, Bolshoy pr. 31, Russia*
*[2]Higher School of Technology and Energy, 198095, Saint-Petersburg, Ivana Chernykh, 4, Russia,*
*mariasimonova1983@mail.ru*

Amphiphilic copolymers containing methoxy oligo(ethylene glycol) methacrylates (MOEGM) have been intensively studied over the last 20 years. Biocompatible MOEGM polymers are considered to be drug delivery polymers. The influence of the structure of such copolymers on solution behavior, self-organization, and association have been investigated. Recently, it has been shown that copolymers of MOEGM with higher alkyl methacrylates formed unimolecular micelles in aqueous solutions. The thermoresponsive behavior of this type of polymers has also been demonstrated.

The aim of this work is to investigate the effect of oligo(ethylene glycol) and oligo(propylene glycol) block lengths in polymers on the molecular and hydrodynamic characteristics of molecular dispersity solutions and the behavior of aqueous solutions (self-organization and thermoresponsibility) of polymethacrylic molecular brushes with oligo(ethylene glycol)-block-oligo(propylene glycol) side chains.

We used OEGeOPGpMA with the following average lengths of oligo(ethylene glycol) (e) and oligo(propylene glycol) (p) fragments: e = 7.0 and p = 2.8 in copolymer E7P3, e = 7.0 and p = 5.4 in brush E7P5, and e = 7.0 and p = 10.3 in sample E7P10 (Dzerzhinsk Polytechnic Institut, Dzerzhinsk, Russia). Polymers were synthesized by the conventional free-radical polymerization in organic solvents at 60–85 °C. The synthesis procedure of OEGeOPGpMAs was described in detail previously.

The structure of the polyOEGeOPGpMA samples was confirmed by nuclear magnetic resonance (NMR) spectroscopy in DMSO-D6.

Molecular brushes polyOEGeOPGpMA were investigated by the methods of molecular hydrodynamics and optics in dilute solutions in acetonitrile, THF, chloroform, and water. The polymerization degree of the studied samples was about 20. The copolymers are molecularly dispersedly dissolved in THF and acetonitrile. In these solvents, OEGe-OPGpMA are characterized by a high intramolecular density, and the shape of their molecules resembles a star-shaped macromolecule. The core of this “star” is the extended backbone of the grafted copolymer, and the arms are the side chains. In chloroform and water, the formation of small micelle-like aggregates was observed. CMC in water decreased with the lengthening of the hydrophobic OPG block.

In aqueous solutions, the studied copolymers demonstrated thermoresponsibility. The phase separation temperatures decreased with an increase in the content of the OPG block in the side chains. For all studied copolymers, phase separation occurred with the formation of large micron-sized aggregates.

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# MODIFICATION OF NANOCRYSTALLYNE CELLULOSE FOR PREPARATION OF COMPOSITE BIOMATERIALS

Stepanova M.A.[1], Averianov I.V.[1], Solomakha O.A.[1], Gofman I.V.[1], Korzhikov-Vlakh V.A.[1,2], Korzhikova-Vlakh E.G.[1,2], Karttunen M.[1]

*[1]Institute of Macromolecular Compounds RAS,*
*199004, Saint-Petersburg, Bolshoy pr. 31, Russia*
*[2]Institute of Chemistry, Saint-Petersburg State University, Saint-Petersburg, Russia*
*averianovilia@gmail.com*

The biodegradable polyester-based materials are widely used in biomedicine for many applications such as surgery, drug delivery and tissue engineering [1]. The major drawback of polyesters is hydrophobicity and lack of functional groups. The creation of composite materials on the basis of such polymers could be the way to improve biocompatibility and adjust their mechanical properties. Currently, the micro- and nanocrystalline cellulose are widely considered as fillers in polymer matrices to develop fully renewable and biocompatible materials [2]. However, the application of pure cellulose micro/nanocrystals as fillers to polyesters is accompanied with the interfacial incompatibility between the hydrophobic polymer matrix and the hydrophilic cellulose [3]. This could be overcome via surface chemical modification of cellulose nanocrystals (NCC). To equalize its distribution in polyester materials (e.g. PLA, PCL) NCC could be modified with polymer or peptide molecules [4]. NCC shows biocompatibility and the possibilities for additional modification with a wide variety of ligands. Thus, the aim of this work was the development of biocompatible composite materials based on PLA and PCL with modified NCC as filler. In our work we modified NCC with PLA chains [5] and developed an approach for chemical modification of NCC with poly(glutamic acid) (PGlu) [6]. Here we show the pathways of NCC modifications and the testing results of composite materials based on modified NCC. NMR, IR, TGA data of modified NCC are shown. Mechanical tests data and microphotography pictures show evidence of improved distribution of modified NCC in polyesters in comparison with neat NCC.

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# DIFFERENT CELLULOSE NANOCRYSTALS AS RHEOLOGY MODIFIER OF DEEP EUTECTIC SOLVENT FOR 3D PRINTING

Vorobiov V.K., Sokolova M.P., Elokhovsky V.Yu., Smirnov M.A.

*Institute of macromolecular compounds RAS,*
*199004, Saint Petersburg, Bolshoy pr. 31, Russia*
*vrbvrbvrb@mail.ru*

3D-printing of composite material with polysaccharides, such as cellulose, is modern method for production of medical scaffolds and next generation electronic devices. For example, the performance of a pressure sensor can be improved by using of sensitive layer with complex shape [1]. At the same time, deep eutectic solvents (DESs) are used for dissolution and treatment of polysaccharides during last years. Moreover, DESs have demonstrated potential application in electronics owing to their high ionic conductivity, high thermal and electrical stability and low toxicity [2].

In this work we used different cellulose nanocrystals (CNC) obtained by two methods: 1. Sulfuric acid hydrolysis of microcrystalline cellulose (MCC) for obtaining of sulfated CNC (s-CNC); 2. Treatment of MCC in DES based on urea/choline chloride (ChCl) that produces two isolated fractions with different sizes. Atomic force microscopy (AFM) measurements revealed that diameter distribution of s-CNC was 23–50 nm, while for CNC prepared by second method were 29–66 nm and 47–105 nm for top (t-CNC) and bottom (b-CNC) fractions, respectively. As-obtained s-CNC were dispersed in DES based on acrylic acid and ChCl in a concentration of 6, 9 and 15 wt%, while content of other type CNC was 9 wt%. Rheological measurements revealed that all the dispersions demonstrate non-Newtonian shear-thinning behavior. The aggregation of s-CNC occurred at the concentration of 15 wt%, resulting in a drop of viscosity due to diminished number of collisions and interaction points between aggregated particles. At the same time, cellulose flocculation in inks containing t-CNC and b-CNC was observed at 9 wt%. This has led to significant decrease in viscosity for corresponded inks in comparison with the ink containing the same amount of s-CNC. AFM and optical microscopy data measurements proved the presence of large aggregated particles in UV-cured gels with t-CNC and b-CNC, while isolate nanoparticles were observed in all gels with s-CNC. Apparently, a charged surface of the s-CNC was responsible for stability of dispersions. Dynamic frequency sweep tests showed that all inks with s-CNC have higher storage modulus ($G'$) than loss modulus ($G''$) in whole measured range of frequencies. The ink with 9 wt% of s-CNC has a higher viscosity, storage modulus and yield stress, and hence, gel strength that will lead to higher shape retention of filament in theory. Although the contact angle (CA) measurements have demonstrated, that the ink with 15 wt% of s-CNC has the highest CA-value, resulting in higher shape stability. We propose this was connected with higher resting viscosity for 15 wt% s-CNC. Therefore, the maximal printing accuracy values obtained for 9 and 15 wt% of s-CNC were 32 and 89 %, respectively.

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# ACRYLIC ACID/ACRYLAMIDE/CHOLINE CHLORIDE TERNARY DEEP EUTECTIC SOLVENT FOR PRODUCTION OF BACTERIAL CELLULOSE BASED GELS VIA 3D-PRINTING

Vorobiov V.K., Kurindin I.S., Sokolova M.P., Fedotova V.S., Smirnov M.A.

*Institute of macromolecular compounds RAS,*
*199004, Saint Petersburg, Bolshoy pr. 31, Russia*
*vrbvrbvrb@mail.ru*

Polymer hydrogels attract increasing attention as a prospective material for constructing of naturally inspired materials for producing artificial cartilage implants and scaffolds for tissue regeneration. The poor mechanical properties of hydrogels lead to the intensive elaboration of methods for improving of their mechanical characteristics. In this regard, cellulose nanofibers (CNFs) as a substitute for natural collagen fibers, are proved to be effective filler for enhancing the mechanical strength of the material [1]. At the same time, personified implants with complicated forms attracts special interest and can be realized via additive technics (3D-printing). The proper selection of solvents and monomers is also important in order to obtain optimal rheology for 3D-printing, as well as good compatibility of the formed polymer matrix with CNFs.

Deep eutectic solvents (DES) as a greener and cheaper alternative for ionic liquids are proved to be effective media for processing of polysaccharides, such as cellulose. DES consist of hydrogen bond donor and acceptor species, mixed in eutectic ratio. In result the melting point of DES is below than an ideal liquid mixture [2]. Moreover, DES may contain acrylic constituents (acrylic acid (AA), acrylamide (AAm)), that is beneficing to use this media for simultaneous stabilization of CNF/DES dispersion and polymerization. In this work the polymerizable binary and ternary mixtures AA:Choline chloride (ChCl) and AA:AAm:ChCl with different AA:AAm ratio and bacterial cellulose content were prepared. The cylindric-shape composites were prepared by UV-photocured polymerization in a mold and by 3D-printing, and after that ChCl was completely replaced by water. The introduction of a non-ionogenic component (AAm) into the polymer matrix improved the mechanical strength of the composites, that was connected with a change in the matrix-filler interaction. Maximum mechanical compressive strength of about 3.4 MPa was attained for 3D-printed sample with higher content of AAm in DES and BC content of 6 wt%. Moreover, 3D-printed samples demonstrated a higher strength, while samples prepared in mold had a higher elasticity modulus. Apparently, some defects in 3D-printed samples may be appeared, despite the continuity and close packing of the filaments. At the same time, the sample with parallel filament stacking had the highest strength than that with perpendicular stacking. This was probably due to the better filament overlap in the layers with a lower probability of occurrence of defects. We assume that the higher strength of the 3D-printed samples was due to the difference in the polymerization method: UV-curing during 3D-printing was performed for each thin layer, while transmission of UV light in molded samples can be hampered in thick layers.

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