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"BIOMATERIALS AND BIONANOMATERIALS: RECENT ADNANCES AND SAFETY - TOXICOLOGY ISSUES"

1st Russian - Hellenic Symposium with International Participation and Young Scientist's School

3-9 MAY, 2010

Crete - Greece, Heraklion

UNIVERSITY OF CRETE

D. MENDELEEV UNIVERSITY OF CHEMICAL TECHNOLOGY OF RUSSIA

M. LOMONOSOV MOSCOW STATE UNIVERSITY

N.M. EMANUEL AND YU.A. ERMAKOV INSTITUTE OF BIOCHEMICAL PHYSICS

HELLENIC SOCIETY OF TOXICOLOGY

EUROTOX

Final Program/Abstract Book

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Invitation Letter

On behalf of the organizing committee of the 1st Russian – Hellenic Symposium on Polymeric Biomaterials and Bionanomaterials: Recent Advances Safety and Toxicology Issues, we are privileged to welcome you to grace with your presence and participation the works of the Symposium, which is to be held in Heraklion, in the beautiful island of Crete, in May 2010.

Crete is an island with numerous coves, bays, peninsulas, and sandy beaches along the beautifully blue Mediterranean Sea. After all, it's among the finest in the world and has established Crete as one of Europe's most popular holiday destinations. And, of course, the island's historic importance in today's world as Knossos, Phaistos and Gortys, is evidenced by the tens of thousands of visitors to these sites each year. Located almost in the centre of Crete, Heraklion has since the early years played a significant part in the history of the island.

The theme of the Symposium concerns one of the most progressing directions of science and technology. BioNanoToxicology Issues lie at the interface of many disciplines, ranging from biology to chemistry, toxicology, computational science chemistry, nanotechnology and biotechnology.
The Symposium is a continuation of a long term co-operation between Russian and Hellenic scientists in this field that has been ongoing for the last 20 years, in the frame of the bilateral scientific state programs.

The International Advisory Board of the Symposium is chaired by the president of the D. Mendeleyev University of Chemical Technology of Russia, Academician of the Russian Academy of Sciences, P. D. Sarkisov, and the Rector of the University of Crete, world-wide known Professor of Ophthalmology Ioannis Palikaris and the Vice Rector of M. Lomonosov Moscow State University, Academician of the Russian Academy of Sciences, A.R. Khokhlov.

It is anticipated that scientists from the Russian Academy of Science, the most prominent Universities as well as Technological Institutes and Companies and distinguished field specialists coming form many countries will attend the symposium. Reduced registration rates will be provided, in order to enable more young scientists to attend the Symposium.

At this symposium the attendee will have the chance to meet important representatives of research in the field, discuss with them and exchange ideas. This will accomplish the aim of the symposium, which is the generation of new and vigorous interactions between the different aforementioned disciplines, which will have enormous positive effects in our societies.

We would like to ask you to publicize the first Russian-Hellenic conference on Polymeric Biomaterials and Bio-nanomaterials: Recent Advances Safety and Toxicology Issues, in your Organizations and Institutes in Russia and Greece.

We are pleased to welcome you to our Symposium. Crete will offer you outmost hospitality with its smiling Cretan sun, the sounds of the Cretan lyre, the scents of orange blossom and jasmine, a slice of cool red watermelon and a glass of iced raki.

Co-Chairmen of the Organizing Committee

Aristidis Tsatsakis, PhD, DSc, ERT ***Mikhail Shtilman, PhD, DSc***

Committees

Co-President	Co-President	Co-President
Palikaris Ioannis	**Sarkisov Pavel**	**Khokhlov Alexey**

International Advisory Board

Co-President	Palikaris Ioannis	Professor, Rector of Crete University
Co-President	Sarkisov Pavel	Academician of RAS, President of D.Mendeleyev University of Chemical Technology of Russia
Co-President	Khokhlov Alexey	Academician of RAS, Vice-Rector of M. Lomonosov Moscow State University
	Berlin Alexander	Academician of RAS, Director of N.Semenov Institute of Chemical Physics of RAS
	Efremov Roman	Professor, Vice-Director of Shemyakin-Ovchinikov Institute of Bioorganic Chemistry of RAS
	Ozerin Alexander	Corresponding member of RAS, Director of Institute of Synthetic Polymeric Compounds of RAS
	Panarin Eugenii	Corresponding member of RAS, Director of Institute of Macromolecular Compounds of RAS
	Torchilin Vladimir	Professor, Center of Pharm. Biotech & Nanomedicine, Northeastern University, Boston, USA
	Varfolomeev Sergey	Corresponding member of RAS, Director of Institute of Biochemical Physics of RAS
	Zezin Alexander	Corresponding member of RAS, Head of Chair of Moscow State University
	Lappas Alexander	Principal Researcher, Foundation for Research and Technology, Crete
	Rizos Apostolos	Professor, Department of Chemistry, University of Crete
	Andreas Tsakalof	Ass. Professor in Medical Chemistry, University of Thessaly

Organizing Committee

Co-Chairman of Symposium	Tsatsakis Aristidis	Professor, Director of Forensic Sciences & Toxicology, University of Crete
Co-Chairman of Symposium	Shtilman Mikhail	Professor, Head of Research and Teaching Center "Biomaterials", D.I. Mendeleyev University of Chemical Technology of Russia
	Artyukhov Alexander	Ass. Prof., PhD, D.I.Mendeleyev University of Chemical Technology of Russia
	Klyachko Natalia	Professor, Moscow State University
	Markvicheva Elena	Professor, Shemyakin-Ovchinikov Institute of Bioorganic Chemistry of RAS
	Toutoudaki Maria	Lecturer, Technological Educational Institute of Crete
	Tzatzarakis Manolis	Lecturer, University of Crete

Scientific program

Sunday, May 2, 2010

Arrival – Registration

20.00 Welcome Cocktail

Monday, May 3, 2010

08.00-09.00 Breakfast

10.00 **Opening Ceremony**

Chairmen: Prof. I. Pallikaris, Prof. P.D. Sarkisov

WELCOME ADDRESS
Ioannis Pallikaris
Professor, Rector of University of Crete, Co-President of Symposium

OPENING LECTURE
TWENTY YEARS OF RUSSIAN-GREEK COLLABORATION IN THE AREA OF BIOMATERIALS
Pavel D. Sarkisov[1], Aristidis Tsatsakis[2]
[1]D. Mendeleyev University of Chemical Technology of Russia, Moscow, Russia
[2]University of Crete, Iraklion, Greece

10.30-10.45 **BIOMATERIALS AND NANOBIOMATERIALS – THE IMPORTANT AREA OF MEDICAL AND BIOTECHNOLOGICAL CHEMISTRY AND TECHNOLOGY**
Mikhail I. Shtilman
D. Mendeleyev University of Chemical Technology of Russia, Moscow, Russia

10.45-11.10 **MULTIFUNCTIONAL PHARMACEUTICAL NANOPREPARATIONS: SUCCESSES AND CHALLENGES**
Vladimir P. Torchilin
Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston, MA, USA

11.10-11.30 Coffee break, Poster session

BIONANOMATERIALS IN BIOLOGICALLY ACTIVE SYSTEMS DRUG DELIVERY SYSTEMS - Session 1

Chairmen: Prof. V.P. Torchilin, Prof. V. Tkachuk

11.30-11.55 **BIONANOMATERIALS FOR GENE AND CELL THERAPY OF ISCHEMIC DISEASES**
Vsevlod A. Tkachuk
Faculty of Fundamental Medicine of M. Lomonosov Moscow State University, Moscow, Russia

11.55-12.20 **BIOMATERIAL CHOICES IN DESIGN OF COMPLEX NANOPARTICULATE CARRIERS FOR ORAL DELIVERY OF INSULIN**
R.J. Neufeld[1], C. Pinto Reis[1,2], B. Sarmento[1,3], C. Woitiski[1,2], F. Veiga[2], A. Ribeiro[2], D. Ferreira[3], C. Damgé[4]
[1]Queen's University, Kingston, Ontario, Canada
[2]University of Coimbra, Portugal
[3]University of Porto, Portugal
[4]Université Louis Pasteur, France

12.20-12.45 **FUNCTIONALIZATION OF NANOPARTICLES. NANOZYMES – POLYMERIC MODELS OF ENZYMES**
Sergey D. Varfolomeev
N. Emanuel Institute of biochemical physics, RAS, Moscow, Russia

13.00-14.00 Lunch

14.00-16.30 Break

BIONANOMATERIALS IN BIOLOGICALLY ACTIVE SYSTEMS DRUG DELIVERY SYSTEMS - Session 2

Chairmen: Prof. I.M. Papisov, Prof. T. Bronich

16.30-16.55 **NANOGEL NETWORKS FOR DRUG DELIVERY IN CANCER**
T. Bronich
Center for Drug Delivery and Nanomedicine, College of Pharmacy, University of Nebraska Medical Center, Omaha, NE, USA

16.55-17.20 **FEATURES OF FUNCTIONING OF ENZYMES IN NANOSTRUCTURES**
N.L. Klyachko
M. Lomonosov Moscow State University, Moscow, Russia

17.20-17.45 **THE SELECTIVITY OF NON-COVALENT INTERACTIONS BETWEEN MACROMOLECULES AND NANOPARTICLES**
I.M. Papisov, O.E. Litmanovich, A.A. Litmanovich, G.Yu. Ostaeva
Moscow Automobile and Road Institute (State Technical University, Moscow, Russia

17.45-18.10 **DEVELOPMENT OF MICROPARTICLES AND FILMS FROM NATURAL POLYSACCHARIDES FOR CONTROLLED RELEASE OF LOCAL ANESTHETICS**
E.O. Batyrbekov, R.M. Iskakov, T.N. Akylbekova, B.A. Zhubanov
Institute of Chemical Sciences, Almaty, Kazakhstan

18.10-19.00 Break

19.00-20.00 Dinner

Tuesday, May 4, 2010

08.00-09.00 Breakfast

BIOANALYTICAL METHODS IN BIOMATERIALS AND BIONANOMATERIALS – Session 1

Chairmen: Prof. A.N. Murashov, Prof A.M. Tsatsakis

10.00-10.25 **ASSESSMENT OF EXPOSURE AND RISKS FROM BIONANOMATERIALS**
Jurki Liesivuori[1], A.M. Tsatsakis[2]
[1]*Institute of Biomedice, University of Turku, Finland*
[2] *Forensic Sciences & Toxicology Department, University of Crete, Iraklion, Greece*

10.25-10.50 **INVESTIGATION OF LARGE MOLECULE PHARMACOKINETICS BY QUANTITATIVE PET IMAGING**
Mikhail I. Papisov, Alan J. Fischman, Vasily Belov
Massachusetts General Hospital, Harvard Medical School and Shriners Burns Hospital, USA

10.50-11.15 **MODERN METHODS IN BIO MONITORING, TOXICOLOGICAL ANALYSIS AND EXPOSURE ASSESSMENT**
A.M. Tsatsakis
Forensic Sciences & Toxicology Department, University of Crete, Greece

11.15–11.35 Coffee break, Poster session

BIOANALYTICAL METHODS IN BIOMATERIALS AND BIONANOMATERIALS – Session 2

Chairmen: Prof. S.D. Varfolomeev, Prof N.V. Bovin

11.35-11.55 **GLYCAN MICROARRAY FOR CANCER DIAGNOSTICS**
N.V. Bovin
M. Shemyakin & Yu. Ovchinnikov Institute of Bioorganic Chemistry, RAS, Moscow, Russia

11.55-12.15 **APPLICATION OF MOLECULARLY IMPRINTED POLYMERS (MIP) IN DRUG DISCOVERY**
A. Lakka, I. Mylonis, G. Simos, A. Tsakalof
Department of Biochemistry, School of Medicine, Faculty of Life Sciences, University of Thessaly, Larissa, Greece

12.15-12.35 **IN VIVO PHARMACOLOGICAL AND TOXICOLOGICAL STUDIES OF PERFLUOROCARBON NANOEMULSION**
A.N. Murashev, D.A. Bondarenko, I.A. Ilushkina
Branch of M. Shemyakin & Yu. Ovchinnikov Institute of Bioorganic Chemistry, RAS, Pushino, Moscow region, Russia

12.35-12.55 **RECENT ADVANTAGES OF IMMUNOASSAYS FOR THE DETECTION OF TOXIC COMPOUNDS IN FOOD AND ENVIRONMENTAL SAMPLES**
S.A. Eremin
M. Lomonosov Moscow State University, Moscow, Russia

13.00-14.00 Lunch

14.00-16.30 Break

BIOANALYTICAL METHODS IN BIOMATERIALS AND BIONANOMATERIALS – Session 3

Chairmen: Prof. S.A. Eremin, Prof A. Tsakalof

16.30-16.50 **NOVEL ACCELERATED AGEING TEST FOR DEGRADABLE/ BIODEGRADABLE POLYPROPYLENE FILM**
A.A. Kuznetsov[1], N.M. Surin[1], E.A. Svidchenko[1], G.K. Semenova[1], I.A. Tchmutin[2]
[1]Enikolopov Institute of Synthetic Polymer Materials, Russian Academy of Sciences, 70, Profsoyuznaya ul., Moscow, Russian Federation
[2]Concern "Nanoindustry", Moscow, Russian Federation

16.50-17.10 **STUDYING INTERACTIONS OF DRUGS AND DRUG-ENRICHED LIPOSOMES WITH LIPID BILAYERS USING FLUORESCENT SPECTROSCOPY**
I. Boldyrev
M. Shemyakin & Yu. Ovchinnikov Institute of Bioorganic Chemistry, RAS, Moscow

17.10-17.30 **TOXICOLOGICAL ASPECTS OF CARBON BASED NANOPARTICALS USING IN MEDICINE: SIMULATIONS AND EXPRERIMENTS**
V.V. Barkaline[1], A.G. Soldatov[2], A.S. Chashynski[1], V.A. Goranov[3], N. Guskos[4], V.A. Kulchitsky[5]
[1] Belarusian National Technical University, Minsk, Belarus
[2]Scientific-practical Materials Research Center of the NAS of Belarus, Minsk, Belarus
[3]Central Scientific Research Laboratory of the Belarus State Medical University, Minsk, Belarus
[4]Solid State Physics, Department of Physics, University of Athens, Athens, Greece
[5]Institute of Physiology National Academy of Sciences of Belarus, Minsk, Belarus

17.30-17.45 **DEVELOPMENT OF FLUORESCENCE POLARIZATION BASED DIAGNOSTIC ASSAY FOR TREPONEMA PALLIDUM**
I.S. Nesterenko, D.V. Korogodin, S.A. Eremin
M. Lomonosov Moscow State University, Moscow, Russia

17.45-18.05 **MOLECULAR METHOD BASED EVALUATION OF ANTIOXIDANT/ CHEMOPREVENTIVE PLANT EXTRACT ACTIVITY**
D. Kouretas
University of Thessaly, Larissa, Greece Greece

18.05-19.00 Break

19.00-20.00 Dinner

Wednesday, May 5, 2010

08.00-09.00 Breakfast

NEW BIOMATERIALS - Session 1

Chairmen: Prof. A.A. Berlin, Prof. I.M. Papisov

10.00-10.25 **BIOPLASTOTAN™ - PHAs FOR BIOMEDICINE – SYNTHESIS, PROCESSING, RESEARCH**
E.I. Shishatskaya[1,2], T.G. Volova[1,2]
[1]Institute of biophysics RAS SB, Krasnoyarsk, Russia,
[2]Siberian Federal University, Krasnoyarsk, Russia

10.25-10.45 **BIODEGRADABLE BLENDS OF SYNTHETIC POLYMERS WITH CHITIN AND CHITOSAN: PRODUCTION, STRUCTURE, PROPERTIES**
S.Z. Rogovina, Ch. V. Alexanyan, E.V. Prut
N. Semenov Institute of Chemical Physics of Russian Academy of Sciences, Moscow, Russia

10.45-11.05 **CONDUCTING POLYMERS IN BIOMEDICAL APPLICATION**
Yu. V. Korshak
D. Mendeleyev University of Chemical Technology of Russia, Moscow, Russia

11.05-11.25 **POLYVINYL ALCOHOL MACROPOROUS HYDROGELS AS NEW MATERIALS FOR MEDICINE**
A.A. Artyukhov[1], A.P. Fomina[1], A.S. Golunova[1], A.N. Kuskov[1], D.E. Lisovyy[2], M.I. Shtilman[1]
[1] D. Mendeleyev University of Chemical Technology of Russia, Moscow, Russia
[2] M. Lomonosov Moscow State University, Moscow, Russia

11.25-11.45 Coffee break, Exhibition, Poster session

NEW BIOMATERIALS - Session 2

Chairmen: Prof. Yu.V. Korshak , Prof. R.D. Katsarava

11.45-12.05 **TITANIUM-FULLERENE COATING FOR BIO-MEDICAL APPLICATION**
E.M. Shpilevsky[1], M.E. Shpilevsky[1], A.G. Soldatov[2], L.A. Matveeva[3]
[1]Heat and Mass transfer Institute, NAS of Belarus, Minsk, Belarus
[2]Scientific-practical Materials Research Center of the NAS of Belarus, Minsk, Belarus
[3]Institute of Semiconductor Physics of the NAS of Ukraine, Kiev, Ukraine

12.05-12.20 **NEW CHITIN/CHITOSAN BASED AFFINITY SORBENTS FOR RECOMBINANT PROTEIN PURIFICATION**
D.V. Kurek, S.A. Lopatin, M.A. Eldarov, V.P. Varlamov
Centre "Bioengineering", Russian Academy of Sciences, Moscow, Russia

12.20-12.40 **BIODEGRADABLE ARGININE-BASED POLYMERS WITH PEG-LIKE BACKBONES AS POTENTIAL NON-VIRAL GENE DELIVERY SYSTEM**
T. Memanishvili[1], N. Kupatadze[1], D. Tugushi,[1] V.P. Torchilin[2], R. Katsarava[1]
[1]Institute of Medical Polymers & Materials, I.Javakhishvili Tbilisi State University, Tbilisi, Georgia
[2]Center for Pharmaceutical Biotechnology and Nanomedicine Northeastern University, Boston, MA, USA

12.40-12.55 **POROUS SCAFFOLDS FORMATION FROM POLY(D,L-LACTIDE) AND POLYETHYLENEOXIDE BLEND FOR CELL SKIN CULTIVATION**
Yu. A. Shved [1,2], M. I. Blinova [1], A. Yu. Bilibin [2], G. P. Pinaev [1]
[1] Insitute of Cytology, St.-Petersburg, Russian Federation
[2] Chemical Department of St.-Petersburg State University, Russian Federation

12.55-13.10 **CALCIUM-PHOSPHATE BIOGLASS-CERAMICS FOR BONE IMPLANTS - REGULATION OF STRUCTURE AND PROPERTIES**
N.Yu. Mikhailenko, E.E. Stroganova, P.D. Sarkisov
D. Mendeleyev University of Chemical Technology of Russia, Moscow, Russia

13.10-14.00 Lunch

14.00-16.40 Break

BIONANOMATERIALS IN BIOLOGICALLY ACTIVE SYSTEMS. DRUG DELIVERY SYSTEMS - Session 3

Chairmen: Prof. E.A. Markvicheva, Prof. N.L. Klyachko

16.30-16.50 **POSSIBILITIES OF METAL NANOPARTICLES STABILIZATION IN CARBOXYMETYLCHITIN MATRIX**
V.A. Alexanderova, L.N. Shirokova
A. Topchiev Institute of Petrochemical Synthesis RAS, Moscow, Russia

16.50-17.05 **POLYELECTROLYTE MICROCAPSULES WITH MULTICELLULAR TUMOR SPHEROIDS AS A NOVEL IN VITRO MODEL IN TUMOR BIOLOGY**
D. Zaytseva-Zotova[1], N. Jablokova[1], A. Tsoy[1], M. Drozdova[1], J-L. Goergen[2], E. Markvicheva[1]
[1] M. Shemyakin & Yu.Ovchinnikov institute of bioorganic chemistry RAS, Moscow, Russia
[2]ENSAIA – Institut National Polytechnique de Lorraine, Vandoeuvre-lès-Nancy, France

17.05-17.20 **THE CONDITIONS OF LACCASE AND CHITOSAN CONJUGATION PROCESS**
A.S. Aksjonov, K.G. Bogolytsin, I.A. Palamarchuk, T.A. Boitsova, O.S. Brovko
Institute of Ecological Problems of the North, Ural Branch RAS, Arkhangelsk, Russia

17.20-17.35 **THEORETICAL STUDY OF MICELLES WITH ION-CONTAINING CORES**
E.Yu. Kramarenko, I.I. Potemkin, E.S. Patyukova, A.R. Khokhlov
Physics Department, Moscow State University, Moscow, Russia

17.35-17.50 **POLYELECTROLYTE COMPLEX MICROPARTICLES FOR ORAL DRUG DELIVERY**
M.A. Pechenkin[1], N.G. Balabushevich[1], E.V. Mikhalchik[2], N.I. Larionova[1]
[1] M. Lomonosov Moscow State University, School of Chemistry, Moscow, Russia
[2]Scientific research Institute of Physico-Chemical Medicine, Moscow, Russia

Thursday, May 6, 2010

08.00-09.00 Breakfast

BIONANOMATERIALS IN BIOLOGICALLY ACTIVE SYSTEMS. DRUG DELIVERY SYSTEMS - Session 4

Chairmen: Prof. S. Burov, Prof. S.Z. Rogovina

10.00-10.20 **THE WAY OF CORRECTION OF ISCHEMIC AND PERFUSION DEFECTS IN MIOCARDIUM USING VESICULAR NANOSYSTEMS**
A.V. Veremeev, R.A. Mukhamadiarov, I.Yu. Zhouravleva
Siberian Branch of Russian Academy of Medical Science, Scientific research institute of Complex problems of cardiovascular diseases, Kemerovo, Russia

10.20-10.35 **A NOVEL APPROACH FOR THE FABRICATION OF BIOACTIVE FILM WITH EMBEDDED VITAMIN E LOADED MICROSPHERES**
T.N. Borodina[1], D.O. Grigoriev[2], D.G. Shchukin[2]
[1]A.V. Shubnikov Institute of Crystallography, RAS, Moscow, Russia
[2]Max Plank Institute of Colloids and Interfaces, Potsdam/Golm, Germany

10.35-10.50 **PREPARATION AND CHARACTERIZATION OF ACYL-β-CYCLODEXTRIN NANOCAPSULES LOADING 4 – THIOUREIDOIMINOMETHYLPYRIDINIUM PERCHLORATE**
D.V. Popov[1], L.D. Radnaeva[1, 2], V.N. Elokhina[3], S.V. Amosova[3], B.A. Trofimov[3]
[1] Baikal Institute of Nature Management SB RAS, Ulan-Ude, Russia
[2] Buryat State University, Ulan-Ude, Russia
[3] A.E. Favorsky Irkutsk Institute of Chemistry SB RAS, Irkutsk, Russia

10.50-11.05 **TRANSMEMBRANE DOMAINS OF PROTEINS AS DRUG TARGETS: KNOWLEDGE-ASSISTED COMPUTATIONAL STRUCTURE PREDICTION**
A.O. Chugunov[1], R.G. Efremov[1]
[1] M. Shemyakin & Yu.Ovchinnikov Institute of Bioorganic Chemistry RAS, Moscow, Russia

11.05-11.30 Coffee break, Poster session

BIONANOMATERIALS IN BIOLOGICALLY ACTIVE SYSTEMS. DRUG DELIVERY SYSTEMS - Session 5

Chairmen: Prof. M. Shtilman, Prof. Yu. Korshak

11.30-11.45 **BIODEGRADABLE MICROBEADS BASED ON POLY(L-LACTIDE) AND POLY(D,L-LACTIDE) AS MICROCARRIERS FOR TISSUE ENGINEERING**
A.M. Tsoy[1], C. Kottgen[2], Ch. Grandfils[2], E.A. Markvicheva[1]
[1]M. Shemyakin & Yu. Ovchinnikov Institute of Bioorganic Chem., RAS. Moscow, Russia
[2]Interfacultary Biomaterial Center (CEIB), University of Liege, Belgium

11.45-12.05 **MOSAIC NATURE OF THE LIPID MEMBRANE SURFACE GIVES UNIQUE OPPORTUNITIES TO DESIGN SELECTIVE AGENTS**
A.A. Polyansky, P.E. Volynsky, A.A. Vassilevski, R.G. Efremov
M. Shemyakin & Yu. Ovchinnikov Institute of Bioorganic Chemistry RAS, Moscow, Russia

12.05-12.25 **SELF-ASSOCIATION OF TRANSMEMBRANE HELICES: STRUCTURAL INSIGHT FROM COMPUTER SIMULATIONS**
P.E. Volynsky, A.A. Polyansky, D.E. Nolde, R.G. Efremov
M. Shemyakin & Yu. Ovchinnikov Institute of Bioorganic Chemistry, RAS

13.00-14.00 Lunch

14.00-16.30 Break

Workshop of ISTC: THE ISTC PROJECT IN AREA OF BIOMATERIALS AND BIONANOMATERIALS: SUCCESSES AND PERSPECTIVES

16.30-18.00 **Moderator: L.M. Mitina**
International Science and Technical Center

18.00-19.00 Break

19.00-20.00 Dinner

Friday, May 7, 2010

08.00-09.00 Breakfast

BIONANOMATERIALS IN BIOLOGICALLY ACTIVE SYSTEMS. DRUG DELIVERY SYSTEMS - Session 6

Chairmen: Prof. S. Rogovina, Prof. Yu. Korshak

10.00-10.20 **POLYMER BIODEGRADABLE MICROCONTAINERS FOR DELIVERY OF BIOACTIVE MOLECULES: PREPARATION AND APPLICATIONS IN BIOMEDICAL FIELDS**
E. Markvicheva[1] and T. Borodina[2]
[1] M. Shemyakin & Yu. Ovchinnikov Institute of Bioorganic Chemistry, Rus. Acad. Sci., Moscow, Russia; email :lemark@mx.ibch.ru;
[2]Shubnikov Institute of Crystallography, Rus. Acad. Sci., Moscow, Russia

10.20-10.45 **POLYPEPTIDE/DNA COMPLEXES FOR TARGETED NON-VIRAL GENE DELIVERY**
S.V. Burov[1], T.V. Yuablokova[1], M.V. Leko[1], M.Yu. Dorosh[1], A.A. Ivanov[2], S.V. Orlov[3]
[1]Institute of Macromolecular Compounds, St-Petersburg, Russia
[2]Pharma Gen Ltd., St-Petersburg, Russia
[3]Institute of Experimental Medicine, St-Petersburg, Russia

10.45-11.10 **AGREGATES OF AMPHIPHILIC POLYMERS – THE IMPORTANT GROUP OF NANOSIZED SYSTEMS**
A.M. Kuskov[1], A.V. Goryachaya[1], A.M. Tsatsakis[2], V.P. Torchilin[3], M.I. Shtilman[1]
[1]D. Mendeleyev University of Chemical Technology of Russia, Moscow, Russia
[2]University of Crete, Heraklion, Crete, Greece
[3]Northeastern University, Boston, USA

11.10-11.30 Coffee break

CLOSING CEREMONY

Moderators: Prof. M.I. Shtilman, Prof. A.M. Tsatsakis

11.30-12.30 **Farewell Address – Closing Remarks**
Prof. I. Pallikaris, Prof. P.D. Sarkisov

13.00-14.00 Lunch

19.00-22.00 Farewell Dinner

Saturday, May 8, 2010

Saturday, May 8, 2010

08.00-09.00	Breakfast
10.00-13.00	Excursion in Knosos Palace
13.00-14.00	Lunch
19.00-21.00	Dinner

Sunday, May 9, 2010

Sunday, May 9, 2010

08.00-09.00	Breakfast
	Departure of Participants

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Abstract Book

BIOMATERIAL CHOICES IN DESIGN OF COMPLEX NANOPARTICULATE CARRIERS FOR ORAL DELIVERY OF INSULIN

R.J. Neufeld[1], C. Pinto Reis[1,2], B. Sarmento[1,3], C. Woitiski[1,2], F. Veiga[2], A. Ribeiro[2], D. Ferreira[3], C. Damgé[4]
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Abstract
Nanoparticulate multilayer structures were developed for oral delivery of insulin and potentially other peptide/protein-based biopharmaceuticals. Formulation methods involved one or a combination of: nanoemulsion dispersion/triggered *in situ* polymer gelation; ionotropic colloidal pregel/polylectrolyte complex coating; and nanospray drying. The most effective polymeric formulation involves an insulin-loaded alginate-dextran nanoparticulate core, complexed with a chitosan-PEG shell and finally with an albumin coat.

In vitro bioactivity was assessed by stimulation of rat L6 myoblasts with insulin released from nanoparticulate complex, assayed through detection of phosphoylated AKT, a downstream product of the insulin signaling cascade. Insulin released from nanoparticulate complex was shown fully bioactive.

Oral dosage of nanoparticulate insulin to diabetic rats reduced glycemia over a 24h period, in a dose dependent manner with the maximum effect after 14h. Increased plasma insulin levels improved glycemic response to an oral glucose overload. Pharmacological activity was 42% and relative bioavailability was 30% for the orally dosed formulation, relative to subcutaneous insulin administration. FITC-insulin/RBITC-nanospheres adhered strongly to villus apical enterocytes and Peyer's patches, and were internalized via the intestinal mucosa. The antidiabetic effect of oral dosed insulin was thus preserved in nanoparticulate form, explained by the protective effect of albumin against gut proteases, by the pH-responsive impermeable structure of alginate polymer in gastric pH, by the mucoadhesive properties of chitosan and PEG, and by the role of chitosan in opening tight junctions between cells, improving insulin and nanoparticulate absorption.

Toxicological assessment after 15 days oral administration to diabetic rats included haematological, biochemical and urine-based assays, and organ and tissue histology. Absence of toxicological effects was shown over the short term, with some observed effects attributed to diabetes physiopathology, diabetes inducement or diabetes evolution status. Lack of toxicity associated with nanoparticulate administration was also demonstrated by absence of mortality over the short term.

Rationale behind the selection of the various polymers used in the nanoparticulate complex will be discussed, as it may apply to other therapeutic applications.

NANOGEL NETWORKS FOR DRUG DELIVERY IN CANCER

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Nanoscale polymeric particles are emerging as novel drug delivery systems in biomedical applications. In particular, nanosized hydrogels (nanogels) have been utilized in pharmaceutics for development of novel therapeutic and diagnostic modalities. They can be designed to facilitate the incorporation of a variety of compounds or even particles through a combination of electrostatic, hydrophobic, and hydrogen bonding interactions. Nanogel structure can be tuned to control the drug-release characteristics of the nanogel carriers. Recently, a novel type of nanogels with controlled spatial distribution of polymer chains was developed. The fabrication procedure involved a preparation of micellar templates by the self-assembly of ionic blocks of double hydrophilic block copolymers (e.g. poly(ethylene oxide)-b-polycarboxylic acid) with oppositely charged condensing agent were used as templates. The ionic chains in the cores of the micelles were cross-linked chemically followed by the removal of condensing agent. The resulting nanogels have swollen cores of crosslinked hydrophilic polyions surrounded by nonionic hydrophilic shell. The ionic character of the core provided for pH-dependent swelling behavior of the nanogels and allowed for the encapsulation of charged therapeutic molecules with very high efficiency. Chemical functionalization of nanogels with various ligands was also explored for targeted drug delivery, triggered drug release, or preparation of composite materials. The potential application of such hydrophilic nanogels as carriers for delivery of anticancer drugs will be discussed.

THE SELECTIVITY OF NON-COVALENT INTERACTIONS BETWEEN MACROMOLECULES AND NANOPARTICLES

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Weak cooperative non-covalent interactions with the participation of macromolecules and either other macromolecules or the surface of such species as nanoparticles result in formation of products the stability of which depends on the size of the smallest component of the complex formed. In particular, in the case of the interaction between long macromolecule and a nanoparticle, the stability of corresponding complex (MNC) representing the nanoparticle screened ("dressed") with polymer chain is exponentially increased with nanoparticle's surface area. The last turns out the reason of essential consequences such as:

- In dilute MNC dispersions (sols), very low energy of polymer – nanoparticle interaction ($-\Delta G$ of order 10^{-3} - 10^{-4} J/m^2) is enough to ensure the stability of MNC including nanoparticles with the diameter (D) from 1 to 10 nm.
- Small size and narrow size distribution of nanoparticles is typical of the soles obtained in processes of new phase formation proceeding in solutions of appropriate polymers (pseudo-template processes).
- The selectivity of polymer – nanoparticle interactions with regard to chemical structure of macromolecules manifesting itself in:

the recognition of optimal polymer "dress"

$P + M_1 + M_2 = complex(PM_1) + M_2$

the substitution of polymer screen ("changing clothes")

$M_1 + complex(PM_2) = complex(PM_1) + M_2$

(P – nanoparticle, M_1 and M_2 – macromolecules of different structure), is the fundamental feature on the interactions.

Theoretical dependence of the selectivity on D, temperature, and $\Delta\Delta G = \Delta G_1 - \Delta G_2$ (the difference in the energies of $P+M_1$ and $P+M_2$ interactions) was derived. It is in good agreement with experimental data. The selectivity was shown to be the necessary condition of high conversion in the case of polymer analogous reactions proceeding in polymer screens of nanosized catalyst. Various aspects of the use of the selectivity phenomenon in investigations dealing with the interactions of nanoparticles with macromolecules and other species are discussed.

DEVELOPMENT OF MICROPARTICLES AND FILMS FROM NATURAL POLYSACCHARIDES FOR CONTROLLED RELEASE OF LOCAL ANESTHETICS

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Drug delivery systems have wide biomedical applications owing to their distinct therapeutic advantages, such as controlled release of drugs over prolonged periods, protection against premature drug degradation, reduction in drug toxicity and drug-drug interactions. Among of the many polymers, natural polysaccharides widely used as carriers for drug delivery systems.

The goal of the present work is development a new drug delivery systems based on polymeric microparticles and films preparing from natural polysaccharides such as chitosan and alginic or pectic acid for treatment of parodontal diseases. Local anesthetics kazkain, rikhlokain and phytopreparation limonidin were used as model drugs. Influence of various factors on process of drugs release from polymeric films in conditions «*in vitro*» was investigated. It was shown that drugs practically completely diffused in Ringer-Lock solution within 4-6 hours, not undergoing any changes. With increase in thickness of film process of drug diffusion is slowed down. So, the 50 % of drugs from system by thickness 0,3 mm was released for 0,5-0,7 h, but the same quantity of drugs by thickness of film 0,6 mm was diffused for 1,3-1,5 h. Coefficients of diffusion of released drugs have been calculated and is shown that with increase in thickness of the films in 3 times this parameter decreases approximately in 2 times. The profile of kinetic curves testifies that process of release occurs according to the first order kinetic and controlled by diffusion of the therapeutic agent in polymeric matrix. Values of the diffusion coefficients has appeared within the limits of 2,5-3,0x10^{-7} sm^2/sec for four concentration that testified to absence of significant influence of drug loading for rate release from films.

Pharmaceutical forms of local anesthetics as microparticles on the base of calcium alginate gels have been obtained. The optimal conditions of alginate microparticles synthesis and drugs introduction in its were determined. The quantitative data of dependence of anesthetics release rate from polymeric composition and micropartical dehydration regime have been obtained. Release of drug from the alginate gel beads of various mannuronic/guluronic ratios in physiological solution was examined. It was found that discontinuous time of the Fickian diffusion of the drug was followed by a burst release of the remaining drugs. The lag time preceded the burst release depended on mannuronic/guluronic ratio. It was revealed that the burst release of anesthetics was initiated by a swift disintegration of calcium-alginate due to exchange on sodium ions.

The interaction of anesthetics with polysaccharides was studied from the viewpoint of thermodynamic behavior from Klotz equation. It was shown that the electrostatic binding plays the significant role in the interaction of the drugs with ionogenic polymers. In all cases the thermodynamic parameters and their temperature dependence show the existence of hydrophobic interaction between drugs and polysaccharides.

The anesthetic action of polymeric systems was studied in experiments on animals. Data of medical-biological tests show the advantages of polymeric drugs application in comparison with low-molecular anesthetics. Duration of kazkain anesthetic action in the case of water-soluble forms increases in 1.1-1.6 times as compared to the nearest analogue and in 3-4 times in comparison with low-molecular substance.

Polymeric films were successfully used in dental therapy for treatment of parodontal diseases. Data of clinical tests show the advantages of polymeric films application in comparison with traditional treatment. Polymeric forms with prolonged and controlled anesthetic action can be recommended to application in medicine for long-term elimination of pain syndrome.

INVESTIGATION OF LARGE MOLECULE PHARMACOKINETICS BY QUANTITATIVE PET IMAGING

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Positron Emission Tomography (PET) is a powerful, fully quantitative tool for in-vivo tracking of molecules labeled with positron-emitting radionuclides. With the growing number of macromolecular drugs that have non-trivial pharmacokinetics (PK), PET will play an increasingly significant role in the preclinical and, likely, human studies.
Imaging of the slow PK typical for macromolecular drugs requires radionuclides that have long physical half-lives. Among isotopes suitable for PET, ^{124}I has the longest physical half-life, 4.2 days. The objective of this study was to determine whether the properties of ^{124}I as a "non-pure" positron emitter translate into data quality suitable for PK studies.
Spatial resolution of the PET imager with ^{124}I was studied using a line ^{124}I source (Ø=0.19 mm) in water. A 51x127 mm cylindrical phantom was used to evaluate the count-rate performance and coincidence detection. Two reconstruction algorithms were examined for their impact on spatial resolution, the most commonly used Filtered Back Projection (FBP) and a more computation-demanding OSEM3D/MAP algorithm.
The transaxial and axial limiting spatial resolutions in the center of the camera were satisfactory and higher for OSEM3D/MAP than FBP (2.4 vs. 3.3 mm, and 3.2 vs. 3.6 mm, respectively). Some degradation of resolution in the periphery of the camera was observed in both the transaxial (34%) and axial (26%) directions. A good linearity of the "true" coincidence count-rate was observed with up to 1.2 mCi. Thus, ^{124}I was found to be an excellent label for quantitative investigation of molecules with slow PK by PET at doses between 0.1 and 1.2 mCi per 10 cm of body length.
Animal studies in rats and monkeys were carried out using ^{124}I-labeled human recombinant proteins and other macromolecules. We were able to measure the biokinetics of all macromolecules in rats and monkeys over 8 days after the injection, including the initial fast kinetics and the slow kinetics of label washout from tissues.
Thus, ^{124}I is an excellent label for quantitative investigation of complex pharmacokinetics by PET. At doses conventional for preclinical research (0.1-1 mCi/animal), PET imaging with ^{124}I provides quantitative coverage of all timeframes of interest, from seconds to several days.

GLYCAN MICROARRAY FOR CANCER DIAGNOSTICS

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Design of glyco-multiarray, immobilisation techniques. Microarray technology has rather evident potential advantages both as research tool and diagnostic module: unlimited number of ligands (in our case glycans) coated onto one small size chip, enormously low consumption of glycans, automation/standardization, etc. Basically, four approaches are used for glycoarray design. The first one is based on the physical adsorption of glycomolecules on a surface (as in a common ELISA), the second one – on covalent immobilization, the third approach – on a streptavidin-biotin system, and the fourth one – on 3D polyacrylamide gel technology. In all of the described methods carbohydrate ligands were placed on chips as a multiarray and high sensitivity was achieved due to fluorescent detection. Notably, a tendency of stepping from model chips toward real multi (hundreds) arrays, has been observed the last years, this already producing a number of interesting findings when studying carbohydrate-binding proteins. Here we overview numerous techniques, as done in our group and report most challenging findings in studying natural auto-antibodies of big cohort of healthy donors.
Glycan multiarray in cancer diagnostics. Glycans are critically important in remodeling of the microenvironment during tumorigenesis, dozens of glycans well known as tumor-associated antigens. Alterations to the normal glycosylation are "recorded" by immune system as specific pattern of anti-glycan antibodies and could be investigated with help of corresponding glycan arrays. Moreover, repertoire of anti-carbohydrate IgMs in normal humans seems to reflect probability of a malignancy because such antibodies play a surveillance role. Study of hundreds sera using array represented by 200 mammalian glycans (including number of tumor-associated antigens) supported by computational analysis demonstrated unlimited potential of printed glycan array as a tool in a development of clinical serum-based screening test for early detection and evaluation of malignancy status, and that the presence of autoantibodies in sera of breast cancer patients permits to differentiate healthy donors and breast cancer patients. Also, glycan array data dictate optimal regimens for cancer treatment, for instance, herceptin-based therapy.

APPLICATION OF MOLECULARLY IMPRINTED POLYMERS (MIP) IN DRUG DISCOVERY.

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Molecularly imprinted polymers (MIP) are highly cross-linked polymer materials with molecular recognition properties, that is, the ability to interact selectively with molecules of specific shape, size and functionality. MIPs are often referred as receptor mimics or synthetic receptors, since they share this common feature of molecular recognition with natural receptor. Molecular recognition properties are grafted to the polymer by the imprinting process schematically presented on fig.1.

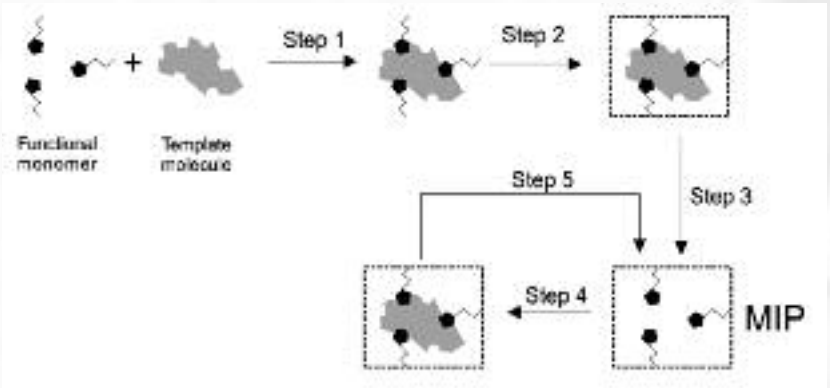

Figure 1. Schematic representation of quercetin imprinting and application of imprinted polymer for SPE: Step 1- pre-polymerisation complex formation of functional monomer (4-vinylpyridine) with template (quercetin) in acetone solution; Step 2 – radical polymerization in the presence of cross-linker to stabilize the imprinted geometry; Step 3 – washing out the template; Step 4 – selective extraction of the molecules that fit the formed cavities by size and functionality; Step 5 – washing out the extracted molecules.

The synthesis of polymer is template guided and, after template removal, the empty imprinted cavities are left in the polymer matrix. These cavities have a shape, size and functionalities that are complimentary to the template molecule and thus, the imprinted polymer, can selectively rebind the template or template analogues of similar shape, size and functionality.
In case that a polymer is imprinted with an inhibitor of a signalling pathway of interest, the synthesized MIP can be considered as a 3D imitation of this inhibitor's target (receptor, enzyme etc.) and can be used for screening of different sources for bioactive analogues of the initial inhibitor-template. It is important to realize that MIP application in drug discovery has the advantage of the simultaneous identification (as receptor mimic) and isolation (as separation phase) of bioactive compounds. The application of molecularly imprinted polymers (MIP) in drug discovery is a new approach in screening of both pure compounds libraries and natural products extracts with as yet mainly unrealised potential.
Tow biologically active and significant molecules, quercetin and tri-O-acetyladenosine, were successfully imprinted with the use of different monomers and porogens. The binding characteristics of the synthesized polymers were determined and demonstrated medium to high affinity and specificity to the initial templates ($(K_d)_{average}$ as low as 2μM and imprinting factor up to 35). The synthesized polymers were subsequently used for the selective isolation of new bioactive compounds from natural sources by SPE on MIP. The new bioactive compounds demonstrated their inhibitory effect on the Hypoxia Inducible Factor-1 signalling pathway, pathway highly involved in the pathology of cancer and inflammatory diseases.

IN VIVO PHARMACOLOGICAL AND TOXICOLOGICAL STUDIES OF PERFLUOROCARBON NANOEMULSION
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The trophic skin changes (ulceration and erosion) may be occurred following sensory denervation and blood supply disturbance (local ischaemia). Over skin areas with moderate to severe trophic changes, transcutaneous oxygen tension averaged 22.5+7.0 mm Hg, this value is significantly lower than that in healthy subjects (56.8+9.9 mm Hg). Artificial oxygen carriers are synthetic solutions with the ability to bind, transport, and unload oxygen in the body. Fluid resuscitation based on perfluorocarbon is intended to eliminate microcirculatory disorders and restore adequate tissue oxygenation. Perfluorocarbons are compounds characterized by high gas-dissolving capacity. Lipophilic drugs contained within molecularly targeted nanoemulsions can result in contact facilitated drug delivery to target cells. The dual use of perfluorocarbon nanoparticles for both site targeted drug delivery and molecular imaging may provide both imaging of disease states as well as conclusive evidence that drug delivery is localized to the area of interest. The purpose of the present study is to investigate the pharmacological and toxicological effects of perfluorocarbon nanoemulsion.
The pharmacological effects of perfluorocarbon nanoemulsion were obtained for male CD rats with trophic changes in the skin of foot of hind limbs promoted by excised tibial nerve and ligated popliteal artery. After 3-5 weeks of surgical operation, an erosion of foot developed. The erosion repair may be observed during 5-6 weeks. Subcutaneous injections of perfluorocarbon nanoemulsion reduced a repair period of the erosion until 2 weeks.
The toxicological studies were carried out in 6-8 weeks old CD-1 mice. Perfluorocarbon nanoemulsion was given a repeated IV dose. Animals received 12,5 ml/kg/day for 14 days. Nanoemulsion caused hyperplasia of white blood cells precursor and suppression of red blood cells precursor proliferation. There was a decrease of a number of erythrocytes and a hemoglobin concentration. Monocytes and macrophages had a different level of vacuolization (from single vacuole in cytoplasm to large cells with ample and foamy cytoplasm). In these cells, nucleus was pressed back to periphery and cytoplasm had cellulite structure. Morphological changes were detected by histopathological examination of brain, heart, lungs, liver, spleen, kidneys, adrenals, duodenum, lymph nodes, testis and ovarys. Single granuloma and an assemblage of granulomas were visualized in all organs.

RECENT ADVANTAGES OF IMMUNOASSAYS FOR DETECTION OF TOXIC COMPOUNDS IN FOOD AND ENVIRONMENTAL SAMPLES

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Sulfamilamides, chloramphenicol, streptomycin, tetracyclines, penicillins, aminoglycoside antibiotics (Gentamicin and etc.) and other veterinary drugs are the most often used veterinary drugs in the world. These drugs are toxic and could be found as contaminants in food and environmental samples. The level of these toxic chemicals could be up to 10-100 ng/ml in environmental and drinking water samples and must be monitored. It is clear, that the monitoring and screening for toxic compounds must be in global scale with high-throughput screening (HTS). The current methods of assays like chromatography techniques have several limitations for HTS. One of the optimal method for detection of small toxic compound is immunoassay, which based on specific and high affinity antibodies. New immunoassays like: enzyme-linked immunosorbent assay in flow system (ELISA), immunochromatography techniques (strip-test) and fluorescence polarisation immunoassay (FPIA) will be described. These immunoassays need very small sample volume (typically 10-50 µl) and immunoreagents (total cost for reagents are low than 1$). The time required for an immunoassay is short and varied from few seconds to 1-2 h in depends from required sensitivity. The recent results, advantages and perspectives for detection of toxic compounds in food and environmental samples will be discussed.

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NOVEL ACCELERATED AGEING TEST FOR DEGRADABLE/ BIODEGRADABLE POLYPROPYLENE FILM

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Synthetic biodegradable polymers used for packaging can be classified in two groups, the former being so called "compostable" polymers, and the other – so called the "degradable/ biodegradable" ones. The former group includes polycondensation- type polymers such as aliphatic polyesters obtained either by polycondensation or the ring opening polymerization (polylactic acid, polyglycolide, polycaprolactone, polybutylene succinate). These polymers are capable to degrade directly in the presence of water and bacteria.
The latter group (widely used in food packaging) includes non- polycondensation- type polymers (such as modified polypropylene (PP)) which are hydrophobic, stable to hydrolysis and bacteria attack, but are capable to slow biodegradation after preliminary oxidation (photo oxidation) step. It is of least importance to get comparable data on the capability of polymers belonged to the first and the second groups to degrade by different factors of the environment.
In this work, we have developed novel accelerated ageing test (express test) for the second group polymers comprising photo irradiation of the film samples by the wide band xenon lamp followed by ageing of the samples at elevated temperature. Also, a non- sample- destructive spectroscopic estimation method of the degradation degree has been developed. One in combination with the other, fast degradation and non-destructive control, represent convenient express-test method for estimation ability of polymer film to degrade in environment.
Application of the "accelerated ageing" method developed was demonstrated using commercially available "Supereco^{R}" 20 μm thickness degradable/biodegradable BOPP film (Superfilm, Turkey). It was shown that "Supereco^{R}" film sample had lost mechanical properties completely after one hour of heating whereas similar additive-free Suplain^{R} BOPP film (Superfilm^{R}) retains mechanical properties at least for 18 hours at the same conditions. The loss of mechanical properties by "Supereco^{R}"film sample means that tensile strength and elongation at break of the film become close to zero, and the sample mechanically decay into small pieces on touching the sample with the pincers. It is thought that in such an oxidized form, polymer is "prepared" for the bioderadation step by bacteria.

STUDYING INTERACTIONS OF DRUGS AND DRUG-ENRICHED LIPOSOMES WITH LIPID BILAYERS USING FLUORESCENT SPECTROSCOPY

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The heading problem is important because of (a) the need to understand traditional drugs' interactions with cell membrane on one hand and (b) the need to construct lipid-based drug delivery systems, on the other. In an ideal case one needs to know the behavior of a single molecule, kinetics of its absorption on bilayer surface, location and orientations inside the bilayer. Unfortunately, powerful methods like NMR and X-Ray can not operate on such diluted systems. On the other hand, fluorescent spectroscopy can give us an insight into the topic, but it is restricted
with the types of molecules it can sense. In brief, one can study molecules which absorb light above 350 nm. In this case drug molecules quench fluorescence of the bilayer probes, and thus their position inside the bilayer can be resolved. Using fluorescent spectroscopy we have shown that even a hydrophobic molecule attached to the end of acyl chain of a phospholipid is located near the bilayer surface. It is still in the hydrophobic region but as close to the bilayer surface as possible. This surprising result is a consequence of lateral pressure profile inside the bilayer. Any alien molecule inside the bilayer tends to be displaced by acyl chains and thus it is pushed to the surface. The above-mentioned phenomenon results in noticeable changes of the bilayer surface properties, e.g. it affects the ability of modified bilayer to fuse with other bilayers. The latter again can be easily observed by fluorescent spectroscopy.

TOXICOLOGICAL ASPECTS OF CARBON-BASED NANOPARTICALS USING IN MEDICINE: SIMULATIONS AND EXPERIMENTS

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The influence of carbon nanotubes (CNT) and fullerene based nano-particles on cells proliferation *in vitro* to estimate the cytotoxic effect as well as the possibility to use them for medical applications was studied. *In vivo* experiments on the development of Ehrlich's carcinoma and hepatoma on mice of Af line in the presence of different fulleride' types were undertaken.
Nanocrystals of $C_{60}(MeCp_2)_2$ and its derivatives were grown from the solution of stoichiometric mixture of C_{60} and metallocene in benzene by slow evaporation at 300 K. Dissolution of carbon nanotube ordered arrays in deionized water was made under spark and followed strimmer discharges using home-made impulse voltage generator. It was found that CNT solutions have magnetic properties due to an presence of cementite. Fulleride nanocrystals were examined by ESR. In order to study the influence of the fulleride presence on cell proliferation the nanoparticles were introduced directly into culture medium of the cells RINmF5.
The most intelligible effect of the cell proliferative activity was found in presence of the fullerides nanoparticles. This can be related to increasing in surface area of the crystals. The possible mechanisms of bioactivity of these compounds were discussed basing on ESR measurement results.
To study various types of CNT functionalization in water solution we undertook quantum mechanical and molecular dynamical simulations. Oxidation of CNT in solutions leads to covering of its external surface by carboxylic (–COOH), carbonyl (–CO) or hydroxyl (–OH) groups. Quantum mechanical calculations of interaction of $–O–C_nH_{2n+1}$ groups with (6,6) CNT surface were undertaken using PM3 approach. CNT functionalization with carboxylic group –COOH was examined.
According to *in vivo* experiments on mice no cytotoxic effect in presence of CNTs was detected. This allows to use magnetic CNTs functionalized by bioactive specimens as inert carries. The most intelligible effect of the proliferative activity was found in presence of the $C_{60}(FeCp_2)_2$ nanoparticles. We guess that metallocene fullerides as well as CNTs will have good prospects for bio-medical applications.

DEVELOPMENT OF FLUORESCENCE POLARIZATION-BASED DIAGNOSTIC ASSAY FOR *TREPONEMA PALLIDUM*

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Syphilis is one of the most prevalent sexually transmitted infections worldwide. Its control and surveillance require careful screening tests by reliable methods. We describe here the development of a rapid solution-phase assay for the presence of serum antibodies to *Treponema Pallidum* based on fluorescence polarization (FP). Peptides derived from antigenic regions of *Treponema Pallidum* envelope proteins were initially screened for their utility as probes in an FP assay to select the best peptide antigen candidates. The FP assay was optimized to detect the presence of *Treponema Pallidum* specific antibodies by a change in the FP of a fluorescein-labeled immunoreactive peptide diagnostic antigen.
This probe was tested for its reactivity in the optimized FP assay with 100 *Treponema Pallidum* specific antibodies-positive human sera and 1000 negative serum samples. The results of these studies demonstrated that the FP assay reactivity correlated with reported results, which carried out by serological methods. The developed *Treponema Pallidum* FP assay is rapid (5 to 20 min) and simple to perform and is equally suitable for use both in the field and in the diagnostic laboratory, thus providing the basis of an improved commercial diagnostic assay for *Treponema Pallidum*.

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BIOPLASTOTAN ™- PHAs FOR BIOMEDICINE – SYNTHESIS, PROCESSING, RESEARCH

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Investigations of PHA-devices for medical applications are conduct in vitro and in vivo in accordance with rules of estimation of biological safety of medical materials and devices, established now in Russian Federation, USA and EU. Two types of PHAs – polyhydroxybutyrate (PHB) and a hydroxybutyrate/hydroxyvalerate copolymer (PHB/PHV), synthesized by the bacterium Wautersia (Ralstonia) eutropha B5786 using the technology developed at the Institute of Biophysics of the Siberian Branch Russian Academy of Sciences and having trade mark BIOPLASTOTAN ™ – have been processed into various devises and proven to be biocompatible in vitro and in short- and long-duration experiments on animals.
Cytotoxicity of PHB and PHB/PHV films was investigated in NIH 3T3, hepatocytes and endothelicytes of the mouse liver. Cell metabolic activity was measured at 3 days using MTT.
Short- and long-term experiments were conducted with laboratory white mice, rats, rabbits, and dogs from 7 days to 6 months.
In short toxicological studies extracts from polymers were applied to the skin, instilled into anymals' eyes, injected intra-abdominally. The formation of the antigen-antibody complex was determined using a standard method. The estimated parameters were also general condition of the animals and the mass of the body and internal organs. At the end of the experiment the phagocytic activity of macrophages was measured to determine immunotoxicity of the polymers. The biological action of PHAs in the form of monofilament surgical sutures has been investigated in a 6-month chronic toxicological experiment on white Wistar rats. The rats' blood, internal organs, lymph nodes, and fragments of tissues surrounding the suture implants were isolated for analysis. We studied the physiological and biochemical characteristics that allowed us to most comprehensively assess the animals' condition. PHA fibers were also used as suture material for the inter-intestinal anastomoses in 100 days-experiment in dogs. Animal condition, all zones of anastomoses and other organs were analyzed. Osteogenic potential of the PHB and PHB/HA composites, seeded with cells was determined in ectopic bone formation assay in Wistar rats. Experiment with the model of segmental osteotomy was performed using scaffolds made of different materials: PHB, PHB/HA, PHB+rhBMP-2. Morphological examination was performed using an Axioskop 40 Pol., transmitted light polarizing microscope Karl Zeiss (Germany) with an AxioCam MRc-5 digital camera.
Results of the investigations performed in vitro and on laboratory animals allow the conclusion that PHAs are highly biocompatible and have good functional properties, thus suggesting their good potential for a wide range of biomedical applications.

BIODEGRADABLE BLENDS OF SYNTHETIC POLYMERS WITH CHITIN AND CHITOSAN: PRODUCTION, STRUCTURE, PROPERTIES

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An increasing scientific and practical interest in biodegradable polymers has led to the availability of a large variety of novel polymer composites. One of the promising ways of design of such systems is the production of blends of renewed nature polysaccharide chitin containing mainly in shells of crabs and shrimps and its deacetylated derivative chitosan with synthetic polymers. The addition of synthetic polymers leads to the enhancement of stability of the systems in water-acid media. The presence of chitin and chitosan, in turn, increase the biocompatibility and biodegradation of materials, endow them with ion exchange and complexing properties, enhance the hydrophilicity and colorability.
In this work, the binary blends from LDPE, chitin and chitosan as well as ternary blends of these polymers with polyethylene oxide (PEO) were studied. The content of polysaccharides in blends was 20-50 wt %. The mixing of polymers was performed at 130-150°C in a single-screw extruder where the principle of joint action of pressure and shear deformation on material is realized.. Although one of the components is an infusible polymer (polysaccharide), the fine homogenous powder was obtained at the output from the extruder. The fractional composition of the powder blends was estimated and it was shown that it is identical to the initial ratio of components. During the blending under the action of shear deformation the structure changes in the polymers occur. X-ray diffraction analysis of the obtained blend showed the decrease of the reflections, which are characteristic of crystal structure that is indicative of the polymer amorphization upon blending. Tests for fungus resistance showed that addition of PEO to binary blends PE-polysaccharide promotes an improvement in their biodegradability. The biodegradation investigations were carried out by placing the samples into a container with wet soil for 5 months. The obtained results showed a significant change in the film weight. Using the method of TGA the regularities of thermo- and photooxidative degradation were studied and it was established that the presence of PEO results in a drop of thermostability similar to that observed at the preliminary photooxidation. The comparative analysis of mechanical characteristics of the films obtained showed that the addition of PEO leads to increasing modulus E with some decrease in the ultimate tensile strength and elongation at break.

CONDUCTING POLYMERS IN BIOMEDICAL APPLICATION

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Inherently conducting polymers, now referred to as conducting polymers, is a group of polymers with backbones comprising a system of conjugated π-electrons. The latter provides some specific properties of such polymers, including deep coloring due to light absorption in a visible wave range and increased electron mobility. Being insulators, these polymers can be easily transformed to conducting materials comparable in conductivity with that of metals by simple treatment with some substances, so-called, dopants of n- or p-type. Therefore, these polymers have been defined as "synthetic metals". The first conducting polymer studied in detail – polyacetylene showed the highest conductivity of 10^5 S/cm approaching to that of copper. However, poor processability and stability in air did not allow this polymer to use for various applications. Meanwhile, the family of heterochain conductive polymers has been developed including polyaniline, polypyrrole, and polythiophene and their derivatives that could be easily prepared by chemical or electrochemical oxidation. These new conductive polymers (NCPs) showed high stability to oxygen, good processability, nontoxic behavior, and good bio-compatibility. Along with the idiotic simplicity of their preparation, NCPs became an object for curiosity and attempts of using in various fields including biomedical application.
Nowadays, the family of NCPs affords some new ways for biomedical applications such as participation in biochemical redox systems by electron transfer reactions likewise it takes place in the case of naturally occurring porphyrins, well-known, e.g. as the pigment in red blood cells. The macrocyclic structure of porpherins is formed by modified pyrrole subunits, the most similar structure being realized in polypyrrole samples. In addition, the ability of NCPs to absorb many types of organic and inorganic molecules resulting in the measurable changes in conductivity values became a background for using these polymers in biosensor devices. Some characteristics may be useful in other biomedical applications including tissue-engineering scaffolds, neural probes, drug-delivery devices, and bio-actuators.
NCPs have been tested in biochemical application for tissue engineering, neural probes, biosensors, drug delivery, and bio-actuators [1]. The special pretreatment should be applied to make NCPs applicable for the biomedical purposes due to specific morphology and chemical properties of those substances. The data concerning these and related topics will be presented.

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POLYVINYL ALCOHOL MACROPOROUS HYDROGELS AS NEW MATERIALS FOR MEDICINE

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The present-day development of medicine and other sciences and technologies connected with human health requires creation of new highly-effective and harmless materials which allow to broaden possibilities of surgical, therapeutic and bio-analytical methods and systems.
In this study novel method of creation of macromolecular materials for medical application on the basis polyvinyl alcohol macroporous hydrogels is proposed. Polyvinyl alcohol finds wide application for medicine, hydrogels on the basis of polyvinyl alcohol also attracts great attention. However, easily prepared physical gels of polyvinyl alcohol formed by freezing of its aqueous solutions are unstable and readily turn reversibly into solution.
Suggested novel method of preparation of polyvinyl alcohol hydrogels consists in formation of polymeric net by cross-linking of unsaturated derivatives of this polymer. Such method allows to form macroporous systems with broad set of pores of dozens and hundreds micrometers size, and stands out due to their high stability and good swelling capacity in water and salt solutions. It is also very important that obtained cross-linked products were made on the basis of beforehand synthesized and characterized polymers and that is why did not contain residua of monomers and other toxic agents.
Investigation of the influence of reaction conditions on the formation of porous gels allowed revealing of the conditions which provides reproducible preparation of the final product with high yield and adjusted overall porosity, pores size, polymer cross-linking degree.
Investigation of interaction of synthesized hydrogels with living organism tissues showed that introduction of developed preparation do not provoke inflammatory reaction on the initial stages of traumatic process and during the long-term contact novel hydrogels biodegrades fully with their substitution by conjunctive tissue.
High biocompatibility, biodegradation with adjusted speed, good mechanical properties, stability under the conditions of application of standard sterilization methods, ability to sorb considerable amounts of liquids including salt solutions without changing of volume characteristics, availability of parent substances and of preparation methods allowed to propose obtained materials for medical application, especially in thoracic surgery, for treating of trophic ulcers and burns, in cosmetic surgery, for creation of therapeutic systems with controlled release of active substance and in several other areas.

TITANIUM-FULLERENE COATING FOR BIO-MEDICAL APPLICATION

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The properties of films obtained by join condensation of titanium and fullerene C_{60} in vacuum were investigated. X-ray diffraction data reflects that Ti-C_{60} films consist of three phases: titanium, fullerite and $Ti_xO_yC_{60}$ alloys. The structural unit size of the $Ti_xO_yC_{60}$ layers depends on the fullerene content and varies from 10 to 100 nm. Lowering of the structural unit sizes followed with fullerene content increasing can be explained by a little mobility of C_{60} molecules and bordering by them of the titanium atoms mobility. Change of the structural unit sizes of metal-fullerene coating with density of atomic-molecular flow and substrate temperature confirms typical dependences of metallic films. The surface of the Ti_x-C_{60} layers was relatively smooth.
Titanium-fullerene coatings possess a relatively low friction coefficient, with has a nonlinear dependence on concentration and high adhesive strength. Coating friction coefficients (sliding speed 0,12 m/sec and pin load $5{,}0 \cdot 10^6$ N/m^2) are 0,16-0,17 on the glass substrate and 0,11–0,12 on the titanium substrate. Adhesive strengths of the titanium-fullerene coatings are 0,62 GPa on the glass substrate and 0,84 GPa on the titanium substrate.
The low friction coefficient values can be explained by possible change of the friction mechanism. Fullerene molecule has no free bonds and can display molecular bearing properties. So even pin – coating scheme is used during the tribological tests implying friction sliding mechanism the presence of fullerene molecules can lead to friction rolling mechanism.
To our opinion high strength of the coatings is caused by nanosize structure and formation of the chemical compound $Ti_xO_yC_{60}$. High quality strength and tribology characteristics of the coatings excel the pure Ti and C_{60} ones. Comparison of the coating strength characteristics and human bone ones (strength tension 120–175 MPa, Young's modulus 17–27 MPa) as well as the characteristics of some ceramic biomaterials displays superiority of the studied coatings.
The described coatings exhibit high chemical stability in diluted acids and bases (3% solutions of HCl, NaOH, KOH). Soaking in these reagents during 2400 hrs does not lead to any visible changes on the coating surface.
Titanium-fullerene coatings possess important for biomedicine properties: high adhesion, low friction coefficient, high strength and flexibility.

NEW CHITIN/CHITOSAN BASED AFFINITY SORBENTS FOR RECOMBINANT PROTEIN PURIFICATION

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Genomics and protemoics nowdays are one of the most significant fields in scientific research. Due to this such an aiding techniques as affinity chromatography, which could efficiently be used for purification of protein without proper knowledge about its structure or functions, became critically important. Application of affinity tags dramatically helps to overcome some disadvantages of affinity chromatography and to make purification process cheaper and more universal. There is a large number of commercially available affinity purification techniques but each has it's own disadvantages.
About fifteen years ago chitin-binding domain from bacterial chitinase was suggested for application as an affinity tag for recombinant proteins purification [1]. But the main disadvantage of such a type of affinity tags was their almost irreversible binding to a chitinous substrate. One of finished commercial affinity chromatography systems applying chitin-binding domain as an affinity tag now is Chitin Beads produced by New England Biolabs (USA), but still this system uses enzymatic cleavage from tag instead of straight elution. Previously in literature possibility of creation of elutable chitin-binding affinity tag applying one point mutation in domain amino acid sequence in order to lower binding strength was discussed.
Recently in Centre "Bioengineering" RAS a number of new chitin/chitoasn based sorbents were synthesized for application in affinity chromatography. Investigation of dependence of main parameters (molecular weight, deacetylation degree) of these biodegradable biopolymers on selectivity, purification efficiency and loading capacity allowed to find optimized parameters of affinity sorbents. Further cross-linking with epichlorohydrin enabled an increase of mechanical strength of obtained sorbents.
Affinity chromatography experiments showed that application of these new chitin/chitosan based sorbents made possible straight elution of native chitin-binding affinity tag without any point mutations in it. Several different recombinant proteins were tested and summarizing obtained results we can declare that constructed affinity chromatography system with the use of novel chitin based sorbents has a promising application as a purification system for recombinant proteins due to its satisfactory characteristics, inexpensiveness and ease conditions of routine work.

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BIODEGRADABLE ARGININE-BASED POLYMERS WITH PEG-LIKE BACKBONES AS POTENTIAL NON-VIRAL GENE DELIVERY SYSTEM

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Delivery of a therapeutic plasmid DNA (pDNA) into target cells represents the primary method of gene therapy. The success of gene therapy fully depends on safe and effective gene delivery systems. Non-viral delivery systems have been introduced in the art to overcome the safety issues and limitations associated with current viral vectors, including immune response, toxicity, chromosomal integration, short shelf-life, etc. Synthetic polymers (polycations) like poly-L-lysine (PLL), polyethylenimine (PEI), Polyarginine (Poly-Arg) or Superfect® are widely used as nucleic acid carriers. They are particularly attractive because of low immunogenicity, versatility of properties, unrestricted plasmid size, and better shelf-life. However, these gene carriers are also far from being perfect. Major limitations of known synthetic polymers as compared to viral carriers are their relatively low transfection efficiency and high cytotoxicity. It is also desirable that synthetic non-viral carriers are biodegradable, and can (in contrast to such carriers as PEI and Superfect®) be easily cleared from the body after their function is fulfilled. Biocompatibility and biodegradability become increasingly important for the long-term gene therapy. Hence, the development of new cationic polymer-based gene carriers/delivery systems free of the mentioned limitations represents an important task.
We have developed new arginine(R)-based biocompatible and biodegradable polycations of various classes: poly(ether ester amide)s, poly(ether ester urethane)s, and poly(ether ester urea)s. The backbones of these cationic polymers contain the ester bonds that impart biodegradability, and ether bonds that impart the PEG-like structure to these polymers and increase their water-solubility and transfection efficiency.
R-based polycations were synthesized by solution (in DMSO) polycondensation of active diesters of different class with tetra-p-toluenesulfonic acid salts of bis-(L-arginine)-a,w-alkylene diesters, where "alkylenes" contain ether bonds.
The cytotoxicity (using MTT assay) and DNA binding ability, as well as biosafety and transfection efficiency of newly synthesized R-based biodegradable polycations in cervical cancer HeLa cells and mouse breast cancer model 4T1 were studied. Newly synthesized polycations are less cytotoxic than commercially available PEI, PLL, and Poly-Arg (at similar concentrations w/w) and form stable and compact nano-complexes (200-250 nm) with DNA thus demonstrating a high potential for being used as non-viral carriers for gene therapy.

POROUS SCAFFOLDS FORMATION FROM POLY(D,L-LACTIDE) AND POLYETHYLENEOXIDE BLEND FOR CELL SKIN CULTIVATION

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At the last time synthetic polymer porous scaffolds are used at tissue engineer. The properties of polymer porous scaffolds are specific for different aims. In depend of these aims different methods of porous scaffolds formation are used: gas formation, faze separation at the system – polymer/solvent, formation porous system for 3-D pattern, faze separation of two polymer and next remove one of them by selective dissolution or resorption. Last method is most simple and accessible. Polylactide and polyethileneoxide blends are porous scaffolds formation method which is interest for scientist at the last time. Scaffolds from crystalline poly(l,l-lactide) and polyethileneoxide blend and them properties have studied very much (1). So that amorphous poly(d,l-lactide) is important for short time degradable system formation (1-2 mouths). The aim of this study was formation study and porous scaffolds by blend amorphous poly(d,l-lactide) and polyethileneoxide (PEO).
Poly(d,l-lactide) was synthesized by literature methods (2). Polymer films was made by dissolution 500 g polymer mixture poly(d,l-lactide) and 10 or 30 % polyethileneoxide at 15 ml methilyne chloride. The polymer films thickness was 50 μm.
Polymer films surface was analyzed by Atom-force microscopy and Scan electronic microscopy. The analyses of side microscopic section was demonstrated pores for all films sick. On the film surface which consist from 10 % PEO with molecular weight 6000, pores quantity of 1 μm diameter yield to film surface which consist from 30 % PEO. Forming pores distribution on the polymer surface have polymodal distribution. Pore sizes on polymer surface which consist 30 % PEO with molecular weight 15000 have polymodal distribution. Pore diameters are from 1 to 10 mkm.
Cell attachment and proliferation. Human fibroblasts were seeded into sterilized PLA /PEO (10 and 30 wt%) blend scaffolds with the cell density of 1.5_105 cells/scaffold. It was observed from investigation that the cells are adhered, spread, and grown more onto the surfaces with moderate hydrophilicity (water contact angles, around 40–60_, regardless of cell types used) than onto the more hydrophobic or even hydrophilic surfaces. This may be closely related to the serum protein adsorption on the surfaces; the preferential adsorption of some serum proteins like fibronectin and vitronectin from culture medium onto the moderately hydrophilic surfaces may be a reason for better cell adhesion, spreading, and growth. It was also observed that hydroxyl groups on polymer surfaces play a positive role for cell adhesion and growth.
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CALCIUM-PHOSPHATE BIOGLASS-CERAMICS FOR BONE IMPLANTS - REGULATION OF STRUCTURE AND PROPERTIES

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The possibility of a wide variation a chemical composition, in structural parameters and kinetics of biochemical processes into the human body is an important advantage of calciumphosphate bioglassceramics. It opens up opportunity for the design of implantation biomaterials with directed and adjusted physiological action for the specific application according to medical indications.
The behavior of calciumphosphate glassceramics is studied in water and physiological environment «in vitro» during temperature controlled and after implantation by animals «in vivo».
As variable parameters are considered: ratio of Ca/P in the in the material; presence of additives Al_2O_3, SiO_2, B_2O_3, TiO_2, ZrO_2; regulation microphase separation and crystallization at material synthesis; regulation of character and porosity of materials. Using this approach a large group of the materials is synthesized. Chemical behavior of the materials varied widely - from the relatively fast restorable (weight losses reached 2 % after treatment in water for 48 h, the degradation time - 44 days in simulated plasma at the dispersion 220 microns) to resistive, exhibiting improved stability in a physiological environment.
Kinetic curves of dissolution in most cases are sinusoidal, which indicates at least two processes – the dissolution of the material and sedimentation on its surface components of the solution after the supersaturation of calcium and phosphorus ions. The formation and growth of apatite crystals on the surface of the materials treated in physiological environments are established. The parameters of their crystal lattice change during the growth of crystals. The quantity of the formed crystals is correlated with parameters of solubility of the biomaterial.
Using of various technologies has allowed to obtain materials with different open porosity: molding technology ? 0 %; sintering of glass powders ? to 30 %; sintering of glass powders with thermal gas-forming agent ? to 55 %; sintering of glass powders with burning out additives ? channel porosity to 50 %; impregnation of the cellular polymeric matrix by a slurry ? cellular porosity more than 80 %.
Materials tests on rabbits showed intensive biointegration of bone cells inside pore structure in 2 months and all pore space is filled with bone tissue and blood vessels in 12 months.
The developed materials are tested as biocoating on titanic grids, filling compound in polymer-inorganic composites, composites «hydroxyapatite – bioglassceramics».

POSSIBILITIES OF METAL NANOPARTICLES STABILIZATION IN CARBOXYMETYLCHITIN MATRIX

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A number of studies are concentrated on the modification of polymers of chitin–chitosan series with metal nanoparticles. Chitin and chitosan are known to be bactericidal biopolymers, which makes reasonable the choice of these polymers as starting materials for the preparation of biodegradable film wound coatings and other materials with silver nanoparticles to enhance the effect.

The aim of this study was to obtain stable macromolecular systems based on a water-soluble chitin derivative - carboxymethylchitin (CMC) and silver nanoparticles (Ag-NP). Besides, we made an attempt to realize the mechanism of metal nanoparticles stabilization in CMC matrix in connection with shield composition of Ag-NP micelles. Nanosized silver particles used in the present work were obtained by biochemical synthesis or generated by radiation-chemical way in reversed micelles of an anionic surface-active agent - sodium bis(2-ethylhexyl) sulfosuccinate (AOT). Ag-NP were used in the form of reversed micellar solution (RMS) in isooctane or in the form of water dispersion of silver obtained from RMS. In the case of RMS (as a source of Ag-NP) we used ultrasonic treatment of heterophase system to transport Ag-NP from isooctane to water polymer solution.

Stabilizing ability of the polymer matrix in the composite was investigated using FTIR. As a result of interaction between protons of CMC acetamide groups and the oxygen atom of AOT ester groups hydrogen bonds formation took place. Therefore, the increase in amide bond intensity in CMC-WDS system at 1608 cm^{-1} as compared to the peak at 1601 cm^{-1} and 1650 cm^{-1} of the initial polymeric matrix – CMC was noted. In consequence of our preliminary studies CMC was chosen as polymer matrix as long as it lacked functional groups competing with the stabilizing shield around Ag-NP micelles. Furthermore metal nanoparticles in such polymer solutions are stabilized owing to steric protection of macromolecule fragments and hydrogen bonds AOT–CMC formation.

To elevate the aggregative stability of Ag-NP in CMC matrix the number of plant antioxidants (AO) was investigated. The quantitative determination of Ag-NP and the evaluation of aggregation stability of nanoparticles in solutions with CMC were performed by measuring Ag-NP optical absorbance at 420 nm. Analysis by FTIR spectroscopy supported the hydrogen bonds formation between CMC and AO functional groups. Such interaction of AO with macromolecule resulted in improved stabilization of Ag-NP in CMC matrix.

POLYELECTROLYTE MICROCAPSULES WITH MULTICELLULAR TUMOR SPHEROIDS AS A NOVEL IN VITRO MODEL IN TUMOR BIOLOGY

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Cell-based assays are now routinely used to screen anticancer drug safety and efficacy. Three dimensional (3D) models based on multicellular tumor spheroids (MTS) have a potential to improve the physiological relevance of *in vitro* cell culture test-systems and to advance quantitative modeling of biological systems from cells to living organisms. MTS were proposed by R. Sutherland as a 3D *in vitro* model to mimic small size solid tumors. However, generation of MTS by classical methods has many disadvantages, and therefore an effective technique for MTS formation is still required. Microencapsulation could be proposed as a simple method to form MTS.

Careful material selection and adopting microcapsules to cell properties are of great importance for the advancement of encapsulation strategy. A well known cell microencapsulation technique is based on coating calcium alginate beads with entrapped animal cells with poly-L-lysine (PLL) and subsequent dissolving a calcium alginate core with EDTA or sodium citrate. However, PLL is an expensive and rather toxic material.

The aim of the present study was to increase biocompatibility of microcapsules for MTS fabrication and to evaluate an anticancer effect of chemo- and photodynamic therapies on encapsulated MTS.

To form microcapsules a series of polycations, in particular dextrans modified by various chloramines and oligochitosan produced from a high molecular weight commercial chitosan were used. The biocompatibility of the polysaccharides was examined using mouse fibroblast L929 cell line. The microcapsules with polyelectrolyte semi-permeable membrane were obtained from the prepared biopolymers, and microcapsules mechanical stability, membrane thickness as well as microcapsule swelling behavior under various conditions were studied. Then we embedded human breast adenocarcinoma MCF-7 cells in microcapsules and carried out long-term cell cultivation to generate MTS. Cytostatic activity of methotrexate and photocytotoxicity of chlorine e6 were then assessed on the generated MTS. Our results confirmed that 3D organization of MTS leads to the remarkable decrease in anticancer therapy efficacy, compared to 2D monolayer cell cultures. Thus, biocompartible polyelectrolyte microcapsules with generated MTS could be proposed as a novel *in vitro* model in tumor biology. as a novel in vitro model of solid tumor to study anticancer therapy effects.

THE CONDITIONS OF LACCASE AND CHITOSAN CONJUGATION PROCESS

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Laccase catalyses reaction of oxidation a variety of aromatic compounds. In particular, laccase is one of lignolytic enzymes playing great role in lignin degradation in nature. Due to remarkable affinity to proteins, chitosan is able to interact with oxidative enzyme. This conjugation process between laccase and chitosan allows to obtain a new functional biomaterial with changed activity and stability by the side of native enzyme. The polymers, studied in this paper are laccase manufactured by Myceliophthora thermophila strain and chitosans produced of chitin from Far East crabs. The methods of UV and FT-IR spectroscopy and HPLC were used for surrey. Influence of such significant factors as pH, proportion of components and molecular weights of chitosan upon interaction between enzyme and polyaminosaccharide were studied. It's revealed that laccase-conjugate is formed within slightly acidic and neutralize area of pH. It's shown that under the increase of enzyme content the new formation opalesces and then precipitates. All chitosans (molecular weights 30, 87 and 240 kDa) interact with laccase forming soluble and insoluble conjugates. Being introduced into the system, a third components helps to construct more strong complexes with unique properties. These complexes are the basis for construction of biomembranes and biosensors with specific activity to aromatic compounds.

THEORETICAL STUDY OF MICELLES WITH ION-CONTAINING CORES

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Much attention has been paid recently to micellization of ionic amphiphilic block copolymers in aqueous solutions. These systems are of special interest because of potential in various applications, in particular, for design of nanocontainers for controlled delivery of water insoluble functional molecules, including drugs. Most of the studies were focused on water solutions of diblock copolymers with a hydrophobic block and a charged block which associate into micelles with a hydrophobic core and a polyelectrolyte shell.
We report on the theoretical study of quite different type of micelles, i.e. micelles with hydrophilic coronae but ionic cores. One of the main driving force for such micelle formation is ion association (electrostatic interactions). Two types of systems will be considered. The first one includes micelles formed in aqueous solutions of diblock copolymers with a hydrophilic non-ionic block and a polyelectrolyte block complexed with oppositely charged polyions. Polyelectrolyte complex comprises the core of the micelles which is surrounded by the shell of hydrophilic non-ionic blocks. These systems are prospective for various applications in biomedical fields, including the delivery of DNA. We study theoretically how the equilibrium aggregation number of the micelles depends on such important system parameters as the charge density of the polyions as well as the solvent properties (solvent quality and polarity).
The second type of micelles under consideration are micelles formed by block copolymers with a hydrophilic non-ionic block and a hydrophobic block containing a fraction of polar groups capable to be ionized. The hydrophobic cores of such micelles should demonstrate a kind of a mixed polyelectrolyte/ionomer behavior. Polyelectrolyte micelles appear when practically all the counterions released in the course of dissociation of the polar groups leave for the outer solution. Ionomer micelles can be formed when the counterions condense on the micelle core and become bound with the ions on the polymer chains. Our theoretical analysis indicates that the transition between polyelectrolyte and ionomer micelles takes place upon an increase of the ionization degree of the hydrophobic block and it is accompanied by a non-monotonous behavior of the micelle aggregation number. Theoretical predictions are confirmed by experimental data. Block copolymer micelles with a stimulus responsive core block are promising nano-carriers for controlled delivery applications.

POLYELECTROLYTE COMPLEX MICROPARTICLES FOR ORAL DRUG DELIVERY

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Oral delivery is the preferred route for drug administration because it is non-invasive, avoids infections, and improves patient compliance. However, this pathway is the most complex one and bioavailability of perorally administered proteins does not exceed 1-2%.

Mucoadhesive micron-sized or nanoparticulate systems were shown to be favourable for drug absorption because they can be efficiently immobilized at the intestinal surface through a bioadhesion phenomenon. That can guarantee an intimate contact of the delivery system with the absorption membrane providing the basis for interactions of multifunctional polymers with the epithelium such as permeation enhancement. Chitosan was used as polycation because of its mucoadhesive properties and ability to protect delivered protein from enzymatic degradation, prolong the retention time, as well as to bind Ca^{2+} and to open the inter-epithelial tight junctions to facilitate systemic protein transport.

The present study aimed to develop microparticles based on biopolyelectrolyte multilayer assembling, intended for oral protein administration. Microparticles were fabricated via layer-by-layer adsorption of chitosan and dextran sulfate on insoluble protein-dextran sulfate microaggregates at pH 3. Human recombinant insulin (M.M.Shemyakin & Yu.A.Ovchinnikov Institute of Bioorganic Chemistry, Russia) was used as a model protein. Aprotinin and soybean Bowman-Birk inhibitor were used as protease inhibitors which were shown to be highly effective in overcoming the enzymatic barrier. They were introduced during insoluble protein-dextran sulfate complex formation.

Microparticle characterization included particle size and content determination, ζ-potential & Ca^{2+} binding capacity measurements & study of particle protective effect against enzyme degradation. The hypoglycemic effect of perorally administrated insulin-containing microparticles was studied on streptozotocin-induced diabetic male Wistar rats.

These microparticles had high insulin encapsulation efficiency (60%) and loading (50%). They were also shown to be pH-sensitive: no protein release was observed at pH 1.1-6.0 and over 80% of insulin released at pH 7.4. Absence of the protein release at acid pH preserves insulin from its inactivation at extreme stomach medium. The sign of ζ-potential was dependent on the number of polyelectrolyte layers. Particles were also shown to posses Ca^{2+} binding capacity. Due to the presence of mucoadhesive polymer chitosan on microparticle surface they were expected to possess mucoadhesive properties. The protective effect of microparticles with & without inhibitors for insulin toward protease degradation was compared by FPLC studies.

Prolonged hypoglycemic effect of perorally administrated microparticles were shown by in vivo studies.

Conclusion. Multifunctional polyelectrolyte microparticles with mucoadhesive, pH-sensitive, Ca^{2+} binding, protease inhibiting properties represent a promising oral protein delivery system.

THE WAY OF CORRECTION OF ISCHEMIC AND REPERFUSION DEFECTS IN MYOCARDIUM USING VESICULAR NANOSYSTEMS

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Aim of Research: Study of the effect that vesicular nanosystems of different composition produce on ischemia- and reperfusion-related damages of rat heart.
Materials and methods: Liposomes were produced by extrusion through polycarbonate filters using a Lipex Biomembranes Inc. extruder. The liposome preparations were introduced in Wistar-line male rats via their caudal veins (15 perfusions every 48 hrs). The controls received 0.9% NaCl solution; test Group I got drug-free, "pure" liposomes; test Group II were perfused liposomes containing macroergic phosphates: ATF and creatine phosphate; test Group III were introduced liposomes carrying antioxodants: superoxide dismutase (SOD), reduced glutathione (RG) and tocopherol (a-T). 24 hours after the last infusion, hearts were removed from the rats under thiopental narcosis and then perfused for 20 min using the Langendorff technique. Upon perfusion, a 30-min total ischemia was produced, followed by a 15-minute reperfusion; 10^{-8} M of adrenaline were then added to the perfusate at minute 10; We evaluated contractile function by curve and reperfusion-related by the EG. Estimated was the activity of lactate dehydrogenase (LDG) contained in the outflow.
Results and discussion: 30-min normothermic ischemia and a subsequent reperfusion cause an irreversible damage to the myocardium: the controls showed 60% decrease in contractive strength, vast rhythm disturbance, while LDG activity value went up by 1.5-2 to dominate in the test. Introduction of the SOD, RG and a-T liposome preparations proved to curb the development of ischemia-, reperfusion-linked dysfunctions in an isolated heart: in Group III, contractile strength hightened by the value of 1.5 at reperfusion, arrhythmia lengths became noticeably shorter, the outflow LDG activity was reduced to one-second of the control's value. Antioxidant-liposome preparations acted similarly after adrenaline had been introduced at the tenth minute of reperfusion. Introduction of liposomes with macroergic phosphates (Group II) resulted in observably moderated arrhythmic manifestations, boosted the contractive strength by 20% as compared to the controls, and lowered the LDG activity by the value of 1.5. Introduction of "pure" liposomes produced but a low-grade effect: in Group I, the values of contractive strength, arrhythmia length and LDG activity only differed insignificantly ($p<0.05$) from the respective control values.
Conclusion: Thus, upon the intravenous introduction of liposome preparations containing antioxidants the reduction of contractile function was less than that of the controls after total ischemia and reperfusion, the contractive strength grew in response to the introduction of adrenaline, arrhythmia lengths and LDG activity were reduced.

A NOVEL APPROACH FOR THE FABRICATION OF BIOACTIVE FILM WITH EMBEDDED VITAMIN E LOADED MICROSPHERES

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Vitamin E (VE) plays an important role in healthy skin care. It possesses antioxidant activity, thereby protects skin cells from ultra violet light, pollutions, drugs etc. Moreover, VE provides a photoprotective effect, the prevention and treatment of sunburns as well as anti-aging and wound healing effects [1]. Therefore, VE is employed in therapy of various skin diseases, such as photodermatoses, psoriasis [2]. Unfortunately, free VE is unstable and easily decomposes under an influence of oxygen, light, heat, etc. The encapsulation of VE is one of the most promising approaches to retain VE during the storage.
Here we propose a new system for a biodegradable film fabrication with entrapped microspheres loaded with VE. To avoid hazardous conditions, the spheres were produced by ultrasonic emulsification of the VE in an aqueous solution of heteropolysaccharide extruded from *Acacia* trees (GA). The emulsification was performed at an ultrasonic intensity of 23 $W \cdot cm^{-2}$ and frequency of 20 kHz. It was investigated that ultrasound of this intensity does not influence significantly the VE chemical structure. Using the proposed approach we obtained stable microspheres for hydrophobic materials due to bonding between GA molecules induced by the ultrasonic treatment. Changes in IR spectrum of GA treated by ultrasound suggest the chemical interaction between two kinds of GA moieties (C=O stretching band of carboxylic group and N-H stretching band of amide group) via amide linkage formation. The fabricated MS were coated with a poly-L-lysine (PLL) layer and embedded into a polymer Ca-alginate film fabricated from sodium alginate (SA). The *in vitro* VE release kinetics demonstrated that the VE-loaded MS embedded into the polymer coating provide a more prolonged VE release compared to the release of VE free in the coating. The system is attractive due to its ability to encapsulate various unstable bioactive substances by a simple and reproducible procedure. The approach demonstrated here could be used for various biomedical applications, including tissue repair and controlled drug delivery.
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PREPARATION AND CHARACTERIZATION OF ACYL-β-CYCLODEXTRIN NANOCAPSULES LOADING 4 – THIOUREIDOIMINOMETHYLPYRIDINIUM PERCHLORATE

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Many drugs have unwanted side effects on the human organism. Reduction of these effects is possible with encapsulated drugs. In addition, the use of nanocapsules based on β-cyclodextrin not only significantly reduces the systemic toxicity of the drugs, but also makes it possible targeting and retard release in the organism. New antitubercular drug 4 – thioureidoiminomethylpyridinium perchlorate was used for encapsulation.
The ability to incorporate various molecules inside the cavity, as well as transport properties of amphiphilic compounds allow to use cyclodextrins to obtain new supramolecular structures, such as nanoparticles.
In order to facilitate the interaction of natural cyclodextrins with biological membranes, it is useful modification to enhance the amphiphilic properties of cyclodextrins. The ability of amphiphilic derivatives of β-and γ-cyclodextrin to the formation of nanoparticles has been shown in various studies.
The purpose of this work - synthesis, study of new amphiphilic β-cyclodextrins and evaluation of their ability for 4 – thioureidoiminomethylpyridinium perchlorate nanocapsulation.
Partially substituted amphiphilic β-cyclodextrins were synthesized, modified with acyl residues of fatty acids (myristic and stearic). Acylation reactions of β-cyclodextrin were carried out in various ways - in the presence of hydrogen chloride acceptor (pyridine), and without the acceptor (in DMF).
It was estimated the average degree of substitution of β-cyclodextrin (according to elemental analysis), in a medium of pyridine was for myristic and stearic acid 1,6 and 1,8 respectively, and in the DMF - 1,3 and 1,1 respectively. In the IR spectra obtained derivatives presents a signal of the carbonyl group at 1735 $cm^{-1,}$ characteristic for ester bond.
In the NMR spectrum of amphiphilic cyclodextrins appears intensive signal of $-CH_2-$ groups (1.28 ppm), signals at 2.32, 1.54, 1.19 ppm correspond to nonequivalent methylene fragments near the ester group, the signal 0.9 ppm refers to the methyl fragment at the end of the chain.
Nanocapsules were prepared by the method of spherical crystallization. SEM was used for determination of size of nanocapsules (50-150 nm).
The degree of nanocapsules loading with 4 – thioureidoiminomethylpyridinium perchlorate was evaluated using conductometry and reached for at least 42%.
Thus, it was shown the possibility of amphiphilic derivatives of β-cyclodextrin for 4 – thioureidoiminomethylpyridinium perchlorate nanocapsulation.

TRANSMEMBRANE DOMAINS OF PROTEINS AS DRUG TARGETS: KNOWLEDGE-ASSISTED COMPUTATIONAL STRUCTURE PREDICTION

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Integral membrane proteins (MPs) represent the core of the cell machinery that is responsible for transmembrane (TM) signaling, perception of various stimuli, transport and other vital functions — therefore making up a considerable part of pharmaceutical targets. TM domains of MPs propagate biological signals into the cell — via conformational switch in G–protein-coupled receptors (GPCRs) structure upon ligands binding, or phosphorylation of cytoplasmic domain of receptor tyrosine kinases (RTKs) that follows dimerization, or in some other way. Given the difficulties related to experimental structural characterization of the most novel MPs, computational structure prediction of TM domains of essential MPs may be of substantial help for pharmaceutical industry and structure-based design of new drugs — e.g., high-affine GPCR ligands or antitumor inhibitors of RTK dimerization.
In consideration of constantly (though rather slow) growing body of structural data on TM domains, it's becoming possible to take into account peculiarities of MPs organization for purposes of building and optimizing computer models of TM domains. (Notwithstanding already four structures of GPCR A family receptors have been elucidated to date, every next receptor or receptor model makes a challenge.) We propose a method for evaluation of "packing quality" of TM domains models — e.g., homology-built. The approach is based on determination of structural preferences of aminoacid residues types to predefined "classes of membrane–protein environment" over the representative set of available MPs structures, thus enabling construction of the "membrane score" function that estimates the reasonableness of the model under evaluation.
The "membrane score" method proved itself useful for identification of close-to-native structures among massive sets of native-like and erroneous models. This was demonstrated for 7-TM proteins like rhodopsin and bacteriorhodopsins as well as non-covalent TM-dimers like glycophorin A and BNIP3. Other capabilities — such as detection of alignment errors, optimal choice of template for modeling, coarse-grained optimization of models — are inherent in the method as well. Furthermore, the membrane score may assist in construction of sequence alignments between low-homology targets — such as GPCR A and B subfamilies, for latter of which there's no complete structures available so far.
Consideration of MPs distinctive features is prerequisite for successful modeling of TM domains structures which may be of help in the drug-design process. The "membrane score" method, especially if accompanied by efficient conformational sampling strategies, will supply industry with realistic models of TM domains of membrane proteins.

BIODEGRADABLE MICROBEADS BASED ON POLY(L-LACTIDE) AND POLY(D,L-LACTIDE) AS MICROCARRIERS FOR TISSUE ENGINEERING

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Synthetic polyesters, such as poly(L-lactide) (PLLA) and poly(D,L-lactide) (PDLLA) are attractive biomaterials for tissue engineering due to their mechanical properties, biocompatibility and biodegradability. These materials can be customized to be used for cell cultivation *in vitro* with a view to implant them for promoting tissue repair. Microcarriers can be designed to improve cell attachment, spreading, proliferation and differentiation. One of a key parameters promoting cell growth which should be taken into consideration is grafting adhesion moieties on the microcarrier surface. The aim of the study was to prepare and optimize novel PLLA and PDLLA microbeads for their further surface modification, in order to promote cell adhesion. Preliminary *in vitro* study on cultivation of animal cells on the obtained microbeads has been also carried out.
To prepare PLLA and PDLLA microbeads an oil-in-water emulsion/evaporation technique was adopted. After purification, sieving and drying microbeads were characterized using Coulter Counter Multisizer as well as by optical microscopy combined with image analysis software (Lucia, Nikon). The mean size of PLLA and PDLLA microbeads was adjusted to the appropriate size range for microcarrier i.e. 125-250 μm. The microbead surface morphology was observed by Scanning Electron Microscopy (SEM). In relation to the difference of crystallinity between two polymers, an important contrast in surface roughness between two microcarrier sets was observed. While amorphous PDLLA allows to produce smooth microbeads, irregular surface morphologies were observed in the case of microbeads prepared from semi-crystalline PLLA. In order to promote cell attachment to PLLA microbead surface, the microbeads were modified by a physical sorption of chitosan or poly(dimethylaminethylmethacrylate) (PDMAEMA). Mouse fibroblasts L929 as model animal cells were used to test the obtained modified microbeads as potential microcarriers. *In vitro* study showed rapid cell attachment on PLLA microbead surface but without promoting a strong spreading of the cells to the microcarrier surface. This observation could be related to the rugosity of the surface of the PLLA microcarriers.
Thus, it was shown that PLLA and PDLLA are appropriate polymers to manufacture biodegradable microcarriers which are adjustable in degradation rate and surface roughness. *In vitro* study showed rather good cell attachment and proliferation on PLLA microbead surface. Further *in vitro* study with smooth PDLLA microbeads are scheduled in order to optimize the microbead surface properties to promote efficient cell attachment, spreading and proliferation which will allow to use microbeads as microcarriers for tissue engineering.

MOSAIC NATURE OF THE LIPID MEMBRANE SURFACE GIVES UNIQUE OPPORTUNITIES TO DESIGN SELECTIVE AGENTS

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According to modern conceptions, the cell membrane possesses mosaic and multilevel organization with the nanosized heterogeneous in-plane distributions of lipids, along with their structural and dynamic properties. Here we scrutinize a phenomenon of a mosaic polarity nature of the membrane-water interfaces. This issue was successfully addressed using combination of several molecular modeling approaches, including molecular dynamic simulations of hydrated lipid bilayers and further analysis of their solvent accessible surfaces (SAS). To assess numerically the spatial hydrophobic/hydrophilic properties of SAS we applied conception of molecular hydrophobicity potential. From the hydrophobicity point of view, SAS of lipid bilayers possess a distinctly "mosaic" character. This correlates well with the occurrence of dynamic clusters of hydrophobic surface area formed by hydrocarbon tails of phospholipids exposed on the interface. Such "mosaic patterns" are specific for lipid bilayers of particular composition.
These findings give unique opportunities to design membrane-active agents selective to cells of different types. For instance, a-helical antimicrobial peptides (AMPs) display membrane disrupting activity underlying their biological function of protection the host organism from invading noxious microorganisms. Hence, to be efficient therapeutic agents, AMPs should discriminate between zwitterionic eukaryotic and anionic bacterial membranes possessing high selectivity to the latter ones. Taking into account differences in the mosaic nature of anionic and zwitterionic lipid bilayers we proposed a new algorithm for design AMPs with the predefined spectrum of biological activity.We showed that differences between hemolytic and non-hemolytic AMPs are revealed in organization of their N-terminal region. A parameter related to hydrophobicity of the N-terminal part is proposed as a measure of the peptide propensity to exhibit hemolytic and other unwanted cytotoxic activities. A proof of concept is gained through engineering specific mutations into highly active AMPs (latarcins) that resulted in elimination of their hemolytic activity while leaving the beneficial antimicrobial effect intact.

SELF-ASSOCIATION OF TRANSMEMBRANE HELICES: STRUCTURAL INSIGHT FROM COMPUTER SIMULATIONS

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Association of membrane proteins plays a very important role in cell life. Many of membrane proteins (MP) accomplish their function in a complex of several subunits. Often, protein-protein interactions have a regulatory function. Thus, understanding on the atomic level the driving forces of membrane protein association is crucial for deciphering of their mechanisms of action. One of the most common elements of membrane proteins fold is an alpha-helix intersecting the membrane (transmembrane helix, TMH). So, it is rational to start the solution of MP's association from the simplest case – namely from dimerization of isolated TMH. In spite of its simplicity, such a system includes all important characteristics encountered in more complex MPs. Moreover, interaction of individual TMH has a serious biological impact – for instance, receptor tyrosine kinases are activated in answer to dimerization, which in turn depends on association of their single TMH. Therefore, delineation of molecular mechanisms of such processes will facilitate prediction of membrane protein structure and make possible design of membrane proteins with predefined structure/activity.

As for the dimerization of TMH, the two main questions appear: (1) How does the dimeric structure look like and what are the determinants of the dimerization? Partial answer on these questions can be provided by experimental methods (although they are resource and labour- demanding). Alternative approach consists in using of molecular modeling techniques. In this work TMH dimerization is studied via computer simulations. In the first part of the work, different approaches to prediction of dimeric spatial structure are described. Strengths and weaknesses of the methods and choice of the optimal computational strategy are discussed. Applications of the methods are illustrated in studies of several biologically relevant dimers. The second part of work is devoted to ranging of the predicted structural models through the calculations of free energy of dimerization. In addition to selection of the 'native-like' structure, this approach permits qualitative assessment of the molecular determinants responsible for the dimerization. Combination of the presented methods provides novel information about interaction of TMH and opens up new opportunities to design of TMH with predefined dimerization ability.

POLYMER BIODEGRADABLE MICROCONTAINERS FOR DELIVERY OF BIOACTIVE MOLECULES : PREPARATION AND APPLICATIONS IN BIOMEDICAL FIELDS

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Biodegradable polymer systems, such as nano- and microparticles/microcapsules can be used due to their specific properties for various biomedical applications. For instance, they can offer many advantages being used as controlled and/or target drug delivery systems, microcontainers for protection of sensitive drugs (proteins and peptides, DNA and oligonucleotides etc), as promising gene delivery systems for somatic gene therapy, as carriers to transport antigens or plasmid DNAs (encoding protein antigen) into the cell for development of new DNA vaccines.
Biodegradable polyelectrolyte microcapsules can be fabricated by a simple universal technique based on layer-by-layer (LbL) adsorption of oppositely charged macromolecules onto a surface of inorganic colloid microbeads. Hollow nano- or microcapsules can be easily prepared by an inorganic core decomposition. The microcapsules can be loaded with bioactive molecules or their mixture, such as proteins, DNA, peptides, some other (for instance bioactive flavonoids etc). A sustained release of bioactive molecules from the microcapsules could be based on enzyme-mediated self-degrading microcapsules or digesting polymer shell using enzyme treatment from outside.
We developed biodegradable polyelectrolyte microcapsules based on natural (alginate, κ-carrageenan, chitosan etc) and synthetic (P-Arg, P-Asp, PLL) polycations and polyanions. Several examples for fabrication of polyelectrolyte microparticles based on natural polysaccharides and synthetic polypeptides loaded with various biomolecules differed in nature and properties will be discussed. The microcapsules were used for encapsulation of a wide spectrum of biomolecules like DNA, proteins, peptides, bioactive flavonoids from herbal extracts etc. The microcapsules membrane can be easily destroyed by using appropriate enzymes (trypsin, pepsin, pronase etc), in order to release encapsulated biomaterial. The release kinetics of the biomolecules can be controlled by varying the enzyme concentration. The enzyme could be co-encapsulated with biomolecule in one microcapsule or can occur out of microcapsule. The described microcapsules could be promising for development of novel formulations providing controlled drug release.
Microencapsulation of several DNA plasmids in biodegradable polyelectrolyte microcapsules will be also discussed. Several types of microcapsules were injected into mice and were shown to induced an immune response. The proposed method for entrapment of DNA encoding protein antigen in biodegradable microcapsules could be used for development of encapsulated "single dose" DNA vaccines.

POLYPEPTIDE/DNA COMPLEXES FOR TARGETED NON-VIRAL GENE DELIVERY

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The main objectives of gene therapy comprise development of efficient, non-toxic carriers for the delivery of genetic materials into the target cells. Although peptide vectors are less efficient than viral ones, their advantages comprise reduced toxicity and side effects, little health risk and possibility of repeated administration. In our study we focused on two examples of peptide carriers application: targeted gene delivery to the cancer cells and stimulation of wound repair.
Suicide gene therapy, using herpes simplex virus thymidine kinase (HSV-TK) represents the promising approach to the cancer treatment. Recently it was shown that GnRH is able to potentiate treatment efficiency both in vitro and in vivo. One can expect that further improvements can be achieved by the application of GnRH analogues for targeted gene delivery to cancer cells. Considering that "classical" GnRH analogues have no ability interact with DNA, we investigated two possibilities: conjugation of peptides with nuclear localization signal (NLS) from large antigen of SV40 virus and attachment of intercalating agent such as doxorubicin. While NLS/DNA complexes are unable to penetrate cellular membrane by the endocytic pathway, application of suggested carriers resulted in efficient HSV-TK gene delivery into human hepatocarcinoma cells, expressing GnRH receptors. The suicide effect was estimated after acyclovir treatment of transfected tumour cells, using luminescent microscopy. The structure of peptide carrier determines the mechanism and efficiency of peptide/DNA complexes penetration via membrane of tumour cells. It was shown that application of reference gene delivery system, based on cationic peptide, killed about 50% of cancer cells. Application of GnRH-based peptide carriers efficiently suppressed tumour growth in vitro. Preliminary data on laboratory animals evidenced possibility of tested peptides usage in vivo. Similar peptide carriers comprising NLS and different ligands of mammalian transferrin receptor have been applied for the acceleration of wounds healing. Tested peptides were capable efficiently deliver reporter genes into cells expressing transferrin receptors. Transfer of luciferase gene expression vector in the complex with carrier molecule to murine surface tissues led to about 100 fold increasing of luciferase activity as compared to free expression vector. Treatment of mice with cut wounds by peptide/DNA complexes containing synthetic human gene encoding insulin-like growth factor 1 led to significant acceleration of wound healing.
These results demonstrate practical utility of suggested peptide carriers in different formats of targeted gene delivery systems.

AGGREGATES OF AMPHIPHILIC POLYMERS – THE IMPORTANT GROUP OF NANOSIZED SYSTEMS

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Nanosized systems of various types like nanospheres, nanoparticles, dendrimeres, and liposomes have been used as carriers of medicinal and generally biologically active substances. Recently appreciable place among such systems was occupied by the so called aggregates of amphiphilic polymers.
In this report we present the methods of synthesis of amphiphilic derivatives of various water-soluble polymers – poly-N-vinylpyrrolidone, polyacrylamide, polyacrylic acids etc. It is shown that such amphiphilic polymers can form aggregates in water systems with size ranging from tens to hundreds nanometers. The influence of the polymers structure on their ability to aggregate was studied.
It was established that synthesized amphiphilic polymers can be used for modification of the membranes of the liposome's resulting in the increase of the membrane stability from the influences of various effects. Examples of the use of nano-aggregates as carriers for immobilization of different drugs and biologically active substances with anti-inflammatory, anti-fungal, anti-cancer activity has been shown. They can also be used for modification of protein and polypeptide drug products raising the stability.
It is shown that in synthesized amphiphilic polymers various functional groups can be introduced such as aldehyde, epoxide, carboxylic, amino acid, etc. So on the basis of the nano-aggregates it was allowed to receive systems with biological activity which can be used as anti-virus, immunoadjuvants, etc.
The promising toxicological characteristics of the systems based on amphiphilic polymers of N-vinylpyrrolidone permits us to consider the perspective of their application in the near future.

Posters

P01

AMPHIPHILIC BLOCK - POLYMERS AS PROTECTORS OF METAL NANOPARTICLES

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The influence of hydrophobic blocks of amphiphilic block polymers on the formation of metal nanoparticles in polymer solutions and the properties of the sols of resulting polymer – nanoparticle complexes was studied. The sols were obtained by the reducing of metal (copper, palladium) ions in solutions of the polymers Two classes of amphiphilic polymers were used as models: (a) diblock polymers composed of hydrophobic laurate or stearate blocks and short blocks of either poly(ethylene glycol) or poly(N-vinyl pyrrolidone), and (b nonstoichiometric interpolymer complexes formed with high molecular poly(acrylic acid) and poly(ethylene glycols) of various molecular weights (the complexes may be regarded as amphiphilic polymers including hydrophilic free fragments ("blocks") of poly(acrylic acid) chains and hydrophobic blocks each of which represents the complex formed with poly(ethylene glycol) chain and a fragment of long poly(acrylic acid) macromolecule.
The investigation of the sols formed in the solutions of "classical" diblock polymers showed that:
- the attachment of hydrophobic block to hydrophilic polymer chain essentially increases the capacity of the latter to shadow metal nanoparticles and to stabilize metal sol;
- the presence of hydrophobic block can result in the change of the character of temperature dependence of the stability of corresponding sol in comparison with that of the sol stabilized with subsequent linear polymer.
- the micelles in polymer screens of nanoparticles can be substituted with appropriate linear homopolymers; this points out that (1) metal nanoparticles are localized in hydrophilic edges of amphiphilic polymer micelles, and (2) the mobility of cooperative systems of noncovalent bonds between the nanoparticles and polymer chains in the edges of micelles.
What about nonstoichiometric interpolymer complexes ("non-clasical" block polymers), two aspects of their interaction with metal nanoparticles are worthy of note:
- the complexes, due to their amphiphilic nature, turn out much more effective protectors of metal nanoparticles than each of their components taken separately;
- mutual enhancement (the synergism) of complex forming capacities of the nanoparticles and both polymer components of the interpolymer complexes was shown to be observed in subsequent metal sols.
The revealed features of the interactions between metal nanoparticles and amphiphilic polymers were treated in frame of the theory of noncovalent cooperative interactions between nanoparticles and macromolecules and the concept of pseudo-template synthesis of nanoparticles in polymer solutions.
The methods allowing measuring the sizes and size distributions of nanoparticles both in insoluble polymer – particle complexes and in sols stabilized with aggregates of micelles were developed. The methods are based on the phenomenon of molecular recognition which is familiar of the interaction between nanoparticles and macromolecules.

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P02

DEVELOPMENT AND PRECLINICAL TRIALS OF MATRIX TRANSDERMAL ACETYLSALICYLIC ACID DELIVERY SYSTEM

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Goal: The main task of the study was the development of delivery system for acetylsalicylic acid (ASA), which allows to reduce the administered dose in comparison with oral form with the purpose of decrease in undesirable platelet aggregation. Antiaggregation efficiency TTS ASA and pharmacological properties of ASA after transdermal and conventional administration to animals were studied.
Methods: In conditions in vitro investigated TTS with different containing of ASA: from 5 up to 100 mg. Dynamics of output ASA from TTS through non-preserved rabbit skin in vitro was investigated in the Frantz diffusion cells. The concentration of ASA primary metabolite salicylic acid (SA) registered spectrophotometrically at 295 nm wavelength was used to quantify ASA which have penetrated through the skin. Antiaggregation efficiency ASA TTS containing 50 mg ASA after application was studed in vivo. Placebo TTS was used as the control sample. Time of application made of 24 hours on rabbits. The time of curtailing platelet rich plasma and platelet poor plasma was defined before and after transdermal application ASA TTS. The conclusion about platelets aggregation activity was

done on the basis of a degree of aggregation, a kind of curves and size of a maximum aggregation. ASA and SA pharmacokinetics after oral and transdermal administration were studed within 24 hours. Samples of blood selected from a regional ear vein. Concentration ASA and SA in plasma of experimental animals defined by a high-performance liquid chromatography using ultraviolet detector.
Results: The increasing of ASA content in TTS led to rising of diffusion rate from 13.6 ± 2.0mg/cm^{2}h to 88.8 ± 13,1 mg/cm^{2}h. After the TTS application ($T_{1/2}$ = (7.26±1.05) h; MRT= (10.48±1.13) h) the amount of the elimination half-life and mean residence time increased 4 times in comparison with oral administration ($T_{1/2}$ = (1.71±0.39) h; MRT= (2.46±0.23) h).The bioavailability for ASA rose 9 times after transdermal administration as compared to orally administered ASA. Changing of curtailing time of blood plasma and the decreasing of platelet aggregation activity after application ASA TTS proved the presence of specific activity ASA after transdermal administration.
Conclusion: The possibility of transdermal ASA delivery in low doses using matrix TTS was demonstrated in vitro. The optimal composition of the matrix form has been determined to maintain constant diffusion rate for 24 hours in the experiments in vitro. Antiaggregation efficiency ASA TTS during 24 hours after application was shown in vivo. The results of this pharmacokinetic research of ASA TTS allow recommend it for clinical trials.

P03

INFLUENCE OF $C_{60}(Fe(C_6H_5)_2)_2$ COMPLEX ON CELL PROLIFERATION IN VITRO

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Detection of the influence of various compounds (including fullerene based) on vital activity of cells in vitro is very actual to estimate the cytotoxic effect as well as the possibility to use them for medical applications.
Single crystalline specimens of $C_{60}(FeCp_2)_2$ were grown from the solution of a stoichiometric mixture of C_{60} and ferrocene in benzene by slow evaporation at 300 K. In order to study the influence of the fulleride presence on cell proliferation we chose the cell line RINmF5 (cell derivatives of the human insular tissue). Under the experimental conditions studied substances were introduced directly into culture medium of the cells RINmF5, grown in the RPMI 1640 medium. The results were examined in comparison with the cell amount grown in the same conditions without any additive.
The most intelligible effect of the proliferative activity of the cell line RINmF5 was found in presence of the $C_{60}(FeCp_2)_2$ nanoparticles. Large crystals can be used as a substrate for adhesion and growth of cells. At the same time the crystals with size of more the 10 μm do not have reliable influence on the proliferative activity of the cells in monolayer culture. After 24 hours of incubation the cell amount in the experimental samples (n = 6) was larger (but less than 40%) than that observed in control samples. We found an intelligible effect of the proliferative activity increase of the RINmF5 cells (53% vs. control) in presence of the $C_{60}(FeCp_2)_2$ nano-size particles (500 particles/cm^2). Moreover it was registered that at the places where the fulleride particles are accumulated the cell culture becomes multi-layered and secreted basophile matrix. To our opinion it can be related to increasing in surface area of the fulleride crystals.
No cytotoxic effect in presence of $C_{60}(FeCp_2)_2$ has been detected. It is proposed that the proliferation rate depends on the surface area of fulleride particles. The most intelligible effect of the proliferative activity was found in presence of the $C_{60}(FeCp_2)_2$ nanoparticles.

P04

NANOSTRUCTURED AMPHIPHILIC MATERIALS BASED ON CHITOSAN: SOLID-STATE SYNTHESIS AND CHARACTERIZATION

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Chitosan is a natural cationic linear polymer that is currently receiving a great deal of interest for medical and pharmaceutical applications. Chitosan is biodegradable, bioadhesive and has bacteriostatic effects. Use of chitosan as a biomaterial that can support chondrogenesis has drawn a considerable attention in the applications for the repair of articular cartilage. Copolymers of chitosan with biopolymers, like proteins and polysaccharides, or synthetic

polymers, have of great practical and theoretical importance. They are better biocompatible polymers with desired properties of degradation, hydrophilic-hydrophobic balance, and other physicochemical properties to meet the need of medicine and nanoparticle technology for stabilizing compounds of various natures.
The novel approach to new polysaccharide-based materials in simple one-step procedure under conditions of shear deformation (using Bridgman's anvils or a twin-screw extruder) - Solid-State Reactive Blending (SSRB) - was employed to obtain polysaccharides-based systems. The entire modification process proceeds in the solid state of the components, and does not require catalysts or any solvents as reaction medium. This is desirable for biomedical applications and provides numerous possibilities to circumvent many processing obstacles typical for preparation of natural-polymers-based materials.
Chitosan with low degree of acetylation (in range 0.03-0.10), low crystallinity and various (20-60 kDa) Mw prepared from crab chitin by SSRB was used. Biodegradable polyesters - semi-crystalline polylactide and amorphous poly(lactide-co-glycolide) were used to prepare chitosan-based copolymers. D,L-Lactide polymerization in presence of chitosan at SSRB conditions was studied as well. Self-assembling conjugates obtained by SSRB based on proteins (Na-caseinate, protein hydrolyzates) and polysaccharides (chitosan, maltodextrine) were investigated.
Conventional organic preparative techniques (like sequential precipitation, viscometry, potentiometric methods etc) in combination with IR analysis in transmission and ATR modes, X-ray diffraction measurements, GPC, DLS, DSC, DMTA and electron microscopy are the methods which were employed to chancterize the bulk and sulface properties of the materials obtained.
It was shown that the products of solid-state synthesis in major part are graft copolymers with respect to the entire blend composition. The obtained graft-copolymers of chitosan unlike non-modified polysaccharide possess amphiphilic properties and form micelle-like stable ultra fine dispersions in organic or water medium. The mean size of dispersed phases is in range 80-700 nm and depends on characteristics (in particular, crystallinity and average Mw) of parent materials. NMR data and IR-ATR analysis confirm that the polysaccharide chains are mainly internalized within a core of the chitosan-polyester nanoparticles generated within organic solvents, whereas the surface of protein-polysaccharide conjugates is enriched with chitosan in water medium.
The obtained materials can be transformed into films, microfibers and nanoparticles and were demonstrated to be very promising materials for numerous applications, in particular, as carriers of bioactive compounds and stabilizers of nano-scale dispersions of various origin.
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P05

IRON NANOPARTICLES COATED WITH CARBOXYMETHYLCHITIN

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The iron nanosized particles showing magnetic properties are known to be widely applied in medicine, electronics and environmental protection. In turn, polysaccharide 6-O-Carboxymethylchitin (CMC), derived from biopolymer chitin (poly β-1,4-linked 2-deoxy-2-acetamido-D-glucopyranose), is known to possess biocompatibility, low toxicity, biodegradability, that causes it's wide application in biochemistry and medicine. Due to such properties we find polymers of chitin-chitosan row promising for creation of composites with metal nanoparticles on their basis.
The purpose of the present study was to develop the new composite film materials based on water-soluble chitin derivative – CMC (MW $2.2x10^5$ and carboxymethylation degree 1.0) and iron nanoparticles (Fe-NP).
In this investigation we used Fe-NP, which was received by a radiation-chemical way in the reversed micelles of anionic surface-active agent - sodium bis(2-ethylhexyl) sulfosuccinate (AOT) in isooctane.
In our earlier studies for introduction of metal nanoparticles into water polymer solution we used water dispersion of metal nanoparticles (obtained from their miccelar solution). It should be noted, however, that formation of Fe-NP water dispersion is connected with oxidation and destabilization of particles. To overcome such loss of nanoparticles we tried to transfer Fe-NP from their miccelar solution to water polymer solution directly, using ultrasonic treatment of heterophase system. It was shown that intensity of Fe-NP absorption in a polymer solution remained invariable during two weeks (UV-Vis control).
WITH USING FTIR IT HAS BEEN FOUND, THAT METAL NANOPARTICLES STABILIZATION IN A POLYMER MATRIX WAS CAUSED BY HYDROGEN BOUNDS FORMATION BETWEEN FUNCTIONAL GROUPS OF POLYMER (AMIDE GROUPS) AND AOT (ESTER GROUPS), AND SHIFT OF ITÝS STRIPS OF ABSORPTION TOWARDS LONG WAVES.
The polymer composite films were prepared from CMC modified with Fe-NP. Note that absorption strips (∂_{max} 290 nm) in Fe-NP – CMC composite films were identical for that of Fe-NP in their miccelar solution in isooctane. Nanoparticles size (2-3 nm) was characterized by TEM. Besides, formation of zero-valent iron nanoparticles was revealed using XRD analysis.

The anionic polyelectrolyte CMC can be used successfully as an initial polymeric matrix for creation of Fe-NP – CMC composites. The polymer matrix in such composites is bearing the function of Fe-NP stabilizer.
We are grateful to B.T. Dubinchuk for TEM and XRD analysis investigations.

P06

COMPARISON ANALYSIS OF HYDRODYNAMIC CHARACTERISTICS OF THE NEW MODELS OF EPOXY-TREATED HEART VALVE BIOPROSTHESES "UNILINE" AND "PERICOR"

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Objectives: Comparison evaluation the hydrodynamics properties of the epoxy-treated xenopericardial "UniLine" and xenoaortic "PeriCor" heart valve bioprostheses models.
Material and methods:
The 35 epoxy-treated "UniLine" and 28 pieces "PeriCor" heart valve bioprostheses of different diameters (28, 30, 32 mm) were underwent the testing procedure in test system imitating the "mitral" and "tricuspid" positions. The testing procedure was realized using the pulse-duplicator Model SD 2001-1 (ViVitro Systems Inc., Canada), which constructed according to ISO 5840 «Cardiovascular implants - Cardiac valve prostheses». The pulse-duplicator consists of the peripheral resistance model combining with model of left heart. This construction makes possible the biomechanical characteristics researching of heart valves functioning by data acquisition from pressure (aortic, ventricle, atrium) and flow transducers. The integrated software allows a real-time data acquisition with the calculating the obtained measurement results. The value of leakages was obtained using additional device Leakage Tester LT 9891.
Results:
The results of research are the main hydrodynamic characteristics of "UniLine" and "PeriCor" heart valve bioprostheses in accordance with requirements ISO 5840.
The reliable differences in maximal orifice area are obtain in "mitral" and "tricuspid" position - for valve "UniLine" it exceed the same figures of the "PeriCor" valve at the average on 20% for all sizes.
There was no received reliable difference ($p>0.05$) between models on transprosthetic flow volume. Also there was no reliable difference on factor of leakage.
Average transprosthetic gradient was reliable above on "PeriCor" bioprostheses (1.6 ± 0.2 and 1.7 ± 0.3 mm Hg in "mitral" and "tricuspid" position, accordingly). The transprosthetic gradient on valve "UniLine" is not exceeding 0.5 mm Hg in "mitral" and 0.7 mm Hg in "tricuspid" position.
Conclusions: 1) This hydrodynamic heart valve prostheses testing system allows to carry out the research in accordance the rules of international standard ISO 5840. It is the possibility for comparison acquired the data by us with the hydrodynamic results of other models of bioprostheses presented in foreign publications.
2) Heart valve bioprostheses "UniLine" demonstrate the perfect hydrodynamic features in comparison with the "PeriCor" valve and, consequently, provides it functioning in recipient`s organism, which is close to physiological.

P07

EFFECT OF THE EPOXY PRESERVATIVES AND IMMOBILIZED HEPARIN ON ARTERIAL BIOPROSTHESES HEMOCOMPATIBILITY

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Objectives: Study of the effect of different preservatives and immobilized anticoagulants on the luminal surface structure and hemocompatibility of arterial bioprostheses.
Materials and methods: Segments of the bovine internal mammary artery were used in the experiment. Biomaterial was preserved using glutaraldehyde (GA), ethylene glycol diglycidyl ether (EGDE) and SM preparation - a mixture of epoxy compounds with different chain length and number of branches.
Additional modification was performed as covalent immobilization of non-fractionated heparin "Biochemie" (Aus-

tria) or low-molecular weight heparin Enoxaparin sodium "Clexane" (Aventis, France). Biomaterial surface was studied using scanning electron microscopy (SEM), thrombotic resistance of the biomaterial by the method of estimation of the platelet aggregative activity. The control figures were those of the aggregation of platelets out of contact with the biomaterial.
Results: SEM data showed that the luminal surface of all the samples have a distinctive corrugated structure. The GA-treated biomaterial proved to have the most manifested relief with the roughest microcorrugations. The EGDE-treated samples have a more uniform and ordered surface structure. Additional heparin immobilization resulted in relief smoothening. Preservation with SM with additional Enoxaparin modification produced a smoother surface.
Velocity of platelet activation after contact with non-modified EGDE-treated samples made up 39%/min, with SM preservation – 38%/min. This parameter was reduced to 34-35%/min after modification with non-fractionated heparin. After contact with the surface of SM-preserved arteries and additionally modified with Enoxaparin the velocity of platelet aggregation was minimal and reached the reference value of 30%/min. The same tendency was observed for the figures of maximum platelet aggregation.
Conclusion: Biomaterial preservation with epoxy mixture is a way in the perfection of arterial bioprostheses. The epoxy-treated surfaces additionally modified with low-molecular weight heparin (Enoxaparin sodium) have the optimal relief and the least contact-initiated activity.

P08

TECHNOLOGY OF ANTITHROMBOTIC MODIFICATION OF THE VENOUS VALVE BIOPROSTHESIS

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Research aim: Elaboration of antithrombotic modification of venous valve bioprosthesis.
Materials and methods: The present study used bovine v. saphena medialis of 4-5 mm in diameter. The biological material was treated with 0,625% solution of glutaraldehyde (GA) and 5% solution of ethylene glycol diglycidyl ether (EGDE). The modification of venous segments was performed in series with ungraded heparin solution and then with human albumin solution, then again with ungraded heparin solution. Amino-acid content of the biomaterial was studied after conservation. Stress/strain properties was carried out stretching the samples lengthwise in the Zwick/Roel tensile-testing machine. Changes in the luminal surface of the samples were estimated using scanning electron microscopy (SEM), hemocompatibility of the material by the method of estimation of the platelet aggregative activity with an aggregometer "ARACT-4004". Platelet aggregation was induced with ADF (5 mcg/ml) and collagen. Biomaterial thrombotic resistance was studied by estimation of the parietal platelet formation after contact with blood.
Results: It was found that GA-treated biomaterial contains 15% free lysine residuum, while that epoxy-preserved only 4% (100% made up by free amino acid remains in native samples). 14.9% hydroxylizine was left after EGDE, and 17% after GA-treatment. The EGDE reaction also involved tyrosine and histidine. Tyrosine content is reduced by 98%, histidine content by 100% as compared to the native samples. Evaluation of the physical and mechanical properties of the
xenoveins showed that the GA-treated ones are somewhat ($p>0,05$) stronger than those treated with epoxy – 2.5±0.63 MPa and 1.73±0.3 MPa respectively. In elasticity both GA-treated (71.0±6.6%) and EGDE-treated (76.9±5.8%) biomaterials are practically identical.
Study of the surface structure of the venous segments showed that modification with heparin smoothes the surface relief. Vein wall being initially rough, the optimal structure is formed by the phasic modification "heparin-albumin-heparin". Study of the platelet aggregative activity induced with collagen showed that GA-preserved biomaterial is the most aggressive against platelet – aggregation maximum increased by 21% as compared to the reference (74%) and made up 90%. After contact with xenoveins preserved with EGDE the maximum aggregation was 81.2%. The phasic modification allowed to decrease this figure to 71.5%. The same dependence was noticed for platelet aggregation induced by ADF. The in vitro study of thrombotic resistance of the biological tissue showed that parietal clot mass in the GA-treated samples within 60-min contact with blood made up 1.97 mg/cm^2. The surface of EGDE-preserved xenoveins proved to be less thrombogenic – 1.73 mg/cm^2, and the additional "heparin-albumin-heparin" treatment allowed to decrease the mass of the parietal clot by 59.5% (0.7 mg/cm^2).
Conclusion: EGDE followed by layer-based "heparin-albumin-heparin" modification, the latter increasing thrombotic resistance of xenoveins.

P09

CORE-SHELL NANOPARTICLES PREPARING BY THE METHOD OF MOLECULAR IMPRINTING FOR BIOLOGICAL APPLICATIONS

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Molecularly imprinted polymers (MIPs) are being increasingly used as selective adsorbents, sensor materials and antibodies in different bioanalytical and biomedical applications. To satisfy the different application purposes, MIPs with well controlled physical forms in different size ranges are highly desirable. For examples, MIP nanoparticles are very suitable to be used to develop binding assays for detecting different drugs, pathogens and proteins.
While various imprinted materials were made, these efforts have met with many limitations including incomplete template removal, small binding capacity and irregular material shape. One of the main reasons is that the extraction of original templates located in the interior area of bulk materials is quite difficult. Traditional imprinting techniques often produce materials exhibiting low rebinding capacity and poor site accessibility to target species. Therefore preparing MIP core-shell nanoparticles with the imprinting molecules situated at the surface or in the proximity of materials surface is quite desirable[1].
We have developed a method for the synthesis of high-quality SiO_2@MIP nanoparticles with a molecular recognition sites. As a core we used silica particles, prepared by Stober method[2], as a shell polymeric layer of hyperbranched polyethoxysiloxane[3], with high functionality, globular shape and other regulated parameters. These allow us to add template molecules by different methods and to realize the subsequent functionalization and shell modification under controlled conditions. The completeness of the reactions of modification and capping was checked basing on methods of transmission electron microscopy (TEM), dynamic light scattering (DLS), spectroscopic and chromatographic methods.

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P10

HYBRID NANOPARTICLES AND THE APPROACH TO THE SHELL DENSITY REGULATION

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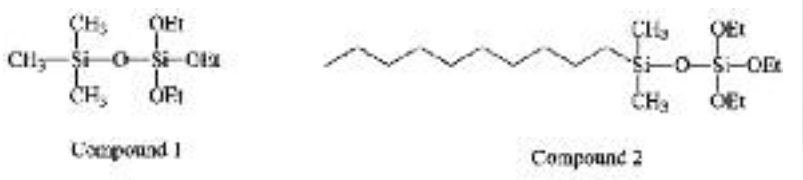
The data appeared recently in literature discribing methods of the synthesis of hybrid particles with the effect of recognition of certain chemical compounds involve the use of complex procedures of forming a shell on the surface of silica particles[1]. In this paper, functional shell on the surface of monodisperse silica particles is created by the introduction into the reaction mixture at the certain stage hybrid molecules containing trimethylsiloxy (compound 1) and decyldimethylsiloxy (compound 2) groups.



Such molecules contain in their structure a certain amount of organic groups as substituents at the first silicon atom and alkoxy groups, similar in its reactivity to tetraethoxysilane, at the second. By using them in different proportions with tetraethoxysilane one can regulate the structure of the surface layer of the hybrid particles, which in this particular application means the cross-linking functional layer. The report will examine the results of experiments forming the functional layer of varying density and selectivity of prepared particles against used model biomedical site.
Obtained particles were investigated by various methods, such as transmission electronic microscopy, dynamic light scattering, spectroscopic and chromatographic methods.

1. D Gao, Z Zhang, M Wu, C Xie G Guan, and D Wang // J. Am. Chem. Soc. 2007, 129, 7859-7866

P11

COMPOSITES BASED ON BIS-GMA AND CALCIUMSILICATE AND CALCIUMPHOSPHATE GLASSES

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Light curable composite materials based on Bis-GMA are widely used in dental treatment. The matrix filler in such light curable composites shall reduce shrinkage caused by polymerization and enhance fixing of a dental filling within tooth cavity. It is well known that calcium ions loss causes lots of dental deceases; therefore inclusion of Ca^{2+} donor into the matrix filler composition seems to be a perspective development in the researching of new dental materials.
The aim of study is the synthesis of composites based on Bis-GMA and calcium-silicate and calcium-phosphate glasses and behavior of the obtained materials in water media.
The initial matrix was obtained using Bis-GMA and powders of calciumsilicate and calciumphosphate glasses (average particle size 20 mm and 10 mm, respectively) characterized with molar ratio RO/(SiO_2 or P_2O_5) from 0,9 to 1,1. Matrix : filler weight ratio in composite was equal to 24:76, the thickness of samples was less than 1 mm and their diameter was equal to 30 mm. Cured composites was translucent and characterized with uniform distribution of calciumsilicate and calciumphosphate filler in matrix. This samples were further tested in distilled water, which was changed after 1, 3, 7, 11, 18 and 35 days. Calcium ions concentration and pH of the solutions were measured with ionometer and calcium ion detecting electrodes.
It was found that calcium ion concentration in water solution decreases to the range of from 0.008 to 0,002 mmol/g for the materials containing calciumsilicate filler. For the materials containing calciumphosphate filler the calcium ion concentration is in the range of from 0,04 to 0,06 mmol/g. The pH value of the water solutions remains 7,5 – 8,5 for the materials containing calciumsilicate filler, and reduces from 6,8 to 3,5 for the materials containing calciumphosphate filler. The pH of the obtained composite material based on calciumphosphate glass are worse than the corresponding characteristics of the initial calciumphosphate glass powder. The pH value low than 6,0 is unacceptable for dental materials, therefore it is not possible to use the calciumphosphate glasses as an effective matrix fillers.
The investigation illustrates that the light curable composite materials based on Bis-GMA and calciumsilicate glasses demonstrate a perspective combination of chemical and mechanical properties that makes them useful as base compositions for calcium-producing dental fillers.

P12

THE METHOD OF layer-by-layer FORMATION OF ACTIVE BIOANALYTICAL SURFACES BASED ON CHOLINE OXIDASE AND POLYELECTROLYTES

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Design of biosensors with different constructions is one of major subjects of modern biotechnology. Layer-by-layer technology (LBL technology), being a method of electrostatic polyelectrolytes self-organization, is a perspective approach to formation of surfaces with specific properties. This method is based on the consequent adsorption of positively and negatively multi-charged objects (polyelectrolytes, proteins, enzymes, nanoparticle etc.) onto solid supports. Thus, it results in multilayered nanostructured films of various composition deposited onto solid substrates of any size and shape, which can be perspective, for instance, for miniaturization of sensor elements.
A quantity of enzyme incorporated into polymer films and a strength of its bounding have the most important influence on characteristics of bioanalytical surfaces such as stability and activity. Actually, it extremely depends on the conditions at which the adsorption of components is carried out (components concentrations, type of polyelectrolyte, salt composition, solvent quality, etc.). Herein the activity of choline oxidase adsorbed on the preliminary formed layers of polycations was studied. Films were formed on the surface of screen-printed graphite planar sensors. The activities of films formed in different adsorptive conditions were studied amperometrically (as a response to choline concentration). The activity of sensor coatings was studied depending on the structure and the topology of polyelectrolytes, the charge of polymer chains, and the presence of substitutions of different hydrophobicity. Furthermore, the optimum polyelectrolyte and choline oxidase concentrations, adsorption times of the components and methods of surface drying were chosen.
Besides, the kinetic parameters and the stability of choline oxidase incorporated into the self-organized films were also investigated.
The received sensor coating is characterized by high sensitivity for choline (with detection limit below 10^{-7} M), reproducibility of manufacturing (CV < 15 %), reproducibility of response (CV < 5 %), and operation stability (no more than 3% activity decrease after 20 measurements).
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P13

DEVELOPMENT OF AMPHIPHYLIC IRON-OXIDE NANOCLUSTERS AND THEIR MAGNETIC RESPONSE

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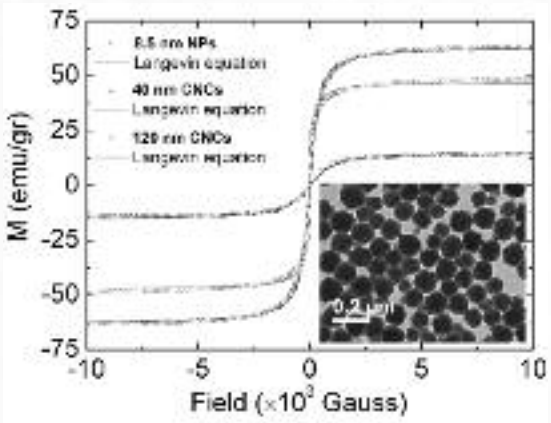

Figure 1. Hysteresis loops at room temperature of various iron oxide entities: 8.5 nm nanoparticles, 40 nm CNCs (grain size 12.2 nm) and 120 nm (grain size 7.7 nm). Inset: TEM

The synthesis of monodispersed magnetic nanoparticles is a particularly important area of research and attracts a growing interest because of the potential applications in ferrofluids, in biotechnology/biomedicine and in optoelectronics devices. Here we report on a high-temperature colloidal chemistry protocol for the growth of iron-oxide nanoclusters (CNCs) with tunable dimensions (ranging from 40 to 120 nm). The use of an amphiphylic polymer (i.e. polyacrylic acid) as a surfactant renders the nanoclusters highly dispersible in aqueous media. Such a capability is a critical parameter if functionality in bio-sciences is desirable. Our transmission electron microscopy (TEM) results suggest that primary iron-oxide nanocrystals (NCs; average diameter about 10 nm) out of which the CNCs are composed are the species that control the CNCs' macroscopic magnetic response. These studies point to a large ensemble of NCs self-assembled within CNCs (inset Fig. 1). It is worth noting that depending on the choice of the synthetic parameters, CNCs can be grown to incorporate different size primary particles. Ultrasensitive SQUID magnetometry methods help us to uncover the unusual magnetic properties of such nanomaterials (Fig. 1). We are of the opinion that the directed aggregation of individual NCs leads to raised saturation magnetization values in the CNCs, a property which makes them exploitable in diverse fields, not limited only to ferrofluids and magnetic memory devices but also to nanomedicine. Despite their increasing volume size, the CNCs are found to be superparamagnetic at room temperature, which further improves their prospects for biomedical applications (e.g. MRI agents, targeted drug delivery etc). We note that our CNCs are covered with a layer of polyacrylate, giving rise to a negatively charged surface. This can be used to offer a variety of functionalizations, amongst which we demonstrate that silica coating (based on the Stöber method) improves the stability of the CNCs in various media. Such treatment may also extend their selectivity in terms of their potential applications (e.g. drug delivery *versus* bioseparation), while the composite core-shell entity, CNC@SiO_2, retains the morphological characteristics of the nanocluster seeds and their magnetism.

P14

LIPOPEROXIDATION LEVEL IN LIPOSOMES AS SAFETY INDEX OF THEIR IMPLEMENTATION

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Aim of Research: Study of the change of concentration level products lipoperoxidation in liposomes depending on structure, a way of reception and temperature storage.
Materials and methods: To prepare "standard" liposomes egg phosphatidylcholin and cholesterol in the ratio of 7:5. For preparation of liposomes with α-tocopherol (α-TF liposomes) the ratio of phosphatidylcholin:cholesterol:α-tocopherol made up 6:3:1. Extrusion method («Lipex Biomembranes Inc.», Canada) was employed to make liposomes (EL) as well as the method of ultrasonic sonification (USL) («type UD-20»,TECHPAN, Poland). The studied materials were divided into four groups: "standard" EL (group I), "standard" USL (group II), «α–TF» EL (group III), «α–TF» USL (group IV). The liposomes were stored at 4^0C or 25^0C. For each group diene- (DC) and triene- (TC) conjugate and malondialdehyde (MDA) content was determined. Lipoperoxidation products were detected in 3, 24, 48 and 72 hours.
Results: The initial level and further dynamics of lipoperoxidation product accumulation in liposomes depend at least on three factors: membrane lipide composition, production method and storage temperature. The investigation revealed α-TF effects positively the level DC in liposomes produced by both methods. Thus the initial level of DC in

all the "standard" liposomes was 1.5 higher than that in α–TF liposomes. By the 24th hour the DC level in the "standard" liposomes was significantly ($p>0,05$) the same as the initial level, while. In the α-TF liposomes stored at 4^{0}C, independent of the production method, was significantly ($p<0,05$) 1.3 times lower. By the 48th hour the DC concentration in groups II, III, IV was significantly ($p<0,05$) increasing from the initial level. By the 72^d hour DC level in the groups mentioned was significantly ($p<0,05$) 1.4 times the initial level. However, in group I liposomes stored at 4^{0}C, the DC level by the 72^d hour went down to the initial figures. TC concentration in group IV was 1.4 times ($p<0,05$) than that of group III, and the dependence held out during the whole observation period. The highest figures were observed in group III stored at 25^{0}C.The initial concentration of MDA in group II was 3 times that of group I. Further on, during the whole observation period, the MDA concentration in group I was growing sharply. By the 72^d hour MDA concentration was 1.5 times the initial level. Liposomes of group demonstrated nonsignificant tendency to MDA level decrease at 4^{0}C during the first 24th hours, followed by the significant increase in its concentration. At 25^{0}C, the MDA level by the 72^d hour was 1.3 times that of the initial level. For α–TF liposomes the initial MDA concentration was significantly ($p<0,05$) 9 times lower in groups I - III, 2,5 times lower for groups II - IV. For EL stored at 4^{0}C till 48th hour no significant change in MDA concentration was observed.
Conclusion: For liposomes produces by both extrusion and ultrasonic sonification methods, the increase in storage temperature to 25^{0}C contributes to the activation of lipoperoxidation. The liposomes produced by the extrusion method are more resistant against peroxidation. Introduction of α-TF in the membrane composition results in decrease in concentration of DC, TC and MDA.

P15

BIOACTIVE POROUS GLASS-CERAMIC MATERIALS FOR BONE PROSTHESIS

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Materials for bone trauma and injury curing must possess high pore structure including open pores with diameter 100-1000 μm to allow blood vessels and bone cells growing inside material and pores with diameter 10-100 μm to permeate physiological solutions after implantation. The present study subject of inquiry is bioactive calcium-phosphate glass with CaO/P_2O_5 ratio 1,1 and B_2O_3, Al_2O_3, TiO_2, ZrO_2 as processing aids. The purpose of the study is to obtain glass-ceramic materials based on concerned glass with properties listed over.
Porous glass-ceramic materials were obtained by means of ceramic processing using combustible pore-formers – granules and bars. Paraffin, starch, gelatin, NH_4OH, NH_4NO_3 with dispersion from 50 to 2000 μm were used as materials for granules. Graphite, nylon, cotton with diameter from 100 to 500 μm were used as materials for bars. Glass powders dispersion in slurries was varied from 40 to 400 μm. Sintering was conducted at temperature 900 °C during 1 hour.
Following methods of forming raws for sintering were used: glass powders molding with starch acting as gas-forming agent, glass powders molding with bars acting as channel pore-forming agents, mixing slurries with granules acting as cell pore-forming agents. Using these three forming methods allowed to obtain correspondingly three series of materials with different pore structures:
1. Open porosity – 25-50 %, pore sizes – 10-200 μm.
2. Total open porosity – 25-50 %, channel porosity – 5-15 %, channel pore diameter – 480-530 μm. Interchannel pore diameters – 10-200 μm.
3. Total open porosity – 40-80 %, open cell porosity – 20-60 %, cell pore diameters – 100-2000 μm. Intercellular pore sizes – 10-40 μm.
Materials implantation in rabbits for a period from 2 to 12 months showed absence of encapsulation with connective tissue. Intensive biointegration of bone cells inside pore structure occured in 4 months on average. All pore space is filled with bone tissue and blood vessels in 12 months. Higher porosity level leads to higher rate of material coalescence with bone. Thus, neogenic bone tissue forms in 2 months of implantation inside materials with 55 % open porosity, and only in 4 months of implantation inside materials with 30 % porosity.

P16

HYBRID MOLECULAR SILICA PARTICLES WITH HYDROPHILIC EXTERNAL LAYER FOR BIOMEDICAL RESEARCHES

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One of the most perspective methods of hybrid molecular silica particles obtaining which can be successfully used as carriers for medicinal and pharmacological forms is the developed method of synthesis superbranched poly-

ethoxysiloxanes – the first representatives of inorganic polymers of dendritic structures – and molecular silica, soluble in waterless organic solvents.
In this paper schemes of synthesis of several silica particles organic derivative with hydrophilic external layer are presented.
As modifying hydrophilic components di - and triethylene oxide olygomers and alcogol derivatives with various organic chain length have been used.

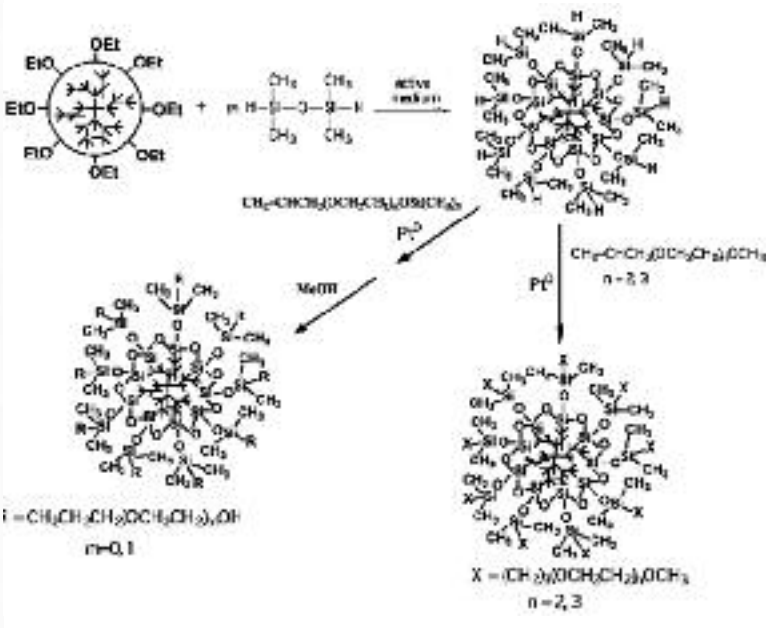

Fig. 1. The general scheme of synthesis of hybrid silica particles with hydrophilic external layer.

As a result of the presented sequence of chemical operations the soluble polymeric product which structure is possible to be presented as organo-inorganic hybrid core - cover system has been obtained. The core is an ordered nanogel silica structure.
The obtained stable products were divided into fractions and typical for polymeric objects physical and chemical parameters have been defined for every fraction.

P17

SYNTHESYS AND PROPERTIES OF NANOCOMPOSITES BASED ON CHITIN AND POLYACRILYC ACID

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Chitin as a perspective material, as it maintains a unique set of physical, chemical and biological properties. While bearing function of polysaccharide is ensured by high characteristic ratio, chitin possess useful characteristics for biological applications: antibacterial activity, animal tissue regeneration acceleration.
In the present work we used β-chitin from squid pen. The crosslinked protein was removed by refluxing in 5% aqueous KOH during 24 hours. After deproteinization the specimen was washed by water during 24 hours. In the first series of experiments the swollen in water β-chitin was placed in 30% aqueous acryl acid containing 0,4% hydrogen peroxide. The polymerization was carried out during 3–24 hours at different temperatures: from 20 to 70°C. Obtained nanocomposite was washed by water for removing the surface polymer and was dried at room temperature. The structural changes at deproteinization, swelling in water and aqueous acryl acid, polymerization were followed by x-ray method and IR-spectroscopy. The thermal and mechanical properties of nanocomposite films of different compositions were measured.
As result of deproteinization described above the squid pen sample loses about 50% of weight mainly due to the removing protein component. Such specimen can be swollen in water 8-10 times without the loosing of integrity.

The next step of the nanocomposite preparation is the exchange of water to acryl acid solution, which is accompanied by very similar swelling. The swelling degree changes from 10 in water to 7-8 in aqueous acryl acid.
It was shown by SAXS and WAXS methods that the fibril separation increases gradually during polymerization of water-soluble unsaturated monomer.
In the second experimental series nanocomposites based on polyacrilyc acid as a polymer matrix and β-chitin fibrils as a reinforcing elements were obtained by in situ polymerization on pre exfoliated chitin. Prepared films of PAA with 1 and 2% vol. of chitin reveals high modulus not only at room but even at 150°C as was shown by DMA .

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P18

LIPOSOME-LIKE LIPID-DNA COMPLEXES BASED ON CATIONIC DERIVATIVE OF CHOLESTEROL

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Lipid-DNA complexes can be used as the instrument of gene therapy. Evolution of this field is now restricted by existing techniques of targeted delivery of DNA to cells. Lipofection, which is a cationic lipid based transfection technology, has a number of advantages: DNA molecules, covered by lipid shield, are protected from decomposition in blood flow; lipid-DNA complexes are neither infectious nor immunogenic. Perspective structure of such complexes includes DNA surrounded with a cationic lipid layer and a second lipid layer which provides a steric barrier to interaction with biological fluid components and prevents uptake of complexes by cells of the RES. However, depending on lipid nature and preparation procedure the structure of resulting lipid-DNA complexes can vary significantly. Previously, we have synthesized cationic derivative of cholesterol, N-[4-(Cholest-5-en-3β-yloxycarbonil)butyl] peridinium bromide. This lipid in a mixture with dioleoylphosphatidylethanolamine (DOPE) in water gives inverted hexagonal phase. But in the presence of DNA these lipids yield lamellar phase which upon freeze-thawing and extrusion results in liposome like structures. It is supposed that the wall of this "liposome" consists of several lipid layers containing DNA chains in between.
This work was financially supported by Federal Education Agency grant #P-715.

P19

P19. PHYTOACTIVE POLYMERS: THE BIOACTIVE BIOMATERIALS FOR PLANT GROWING

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Polymeric derivatives of plant growth regulators (phytoactive polymers) are a new group of biomaterials for plant growing. They represent a system with controlled release of bioactive substance in which an active component (in this case, the fragment of plant growth regulator) is connected to a polymeric matrix by a hydrolytically labile chemical bond, which can be destroyed chemically or in the presence of enzymes.
Phytoactive polymers posses such essential advantages over the low-molecular weight analogues as expansion of the range of active concentration, absence of phytotoxicity, increase in time of influence and reduction of doses, lower toxicity to the human organism and warm-blooded animals.
In the report new polymeric derivatives of aryl- and aryloxyalkanecarboxylic acids, belonging to the plant growth regulators of auxin class – 3-indoleacetic, 3-indolebutyric, 1-naphthylacetic, 2,4-dichlorophenoxyacetic, etc. are described.
Various methods of synthesis of auxin-containing polymers are considered, allowing to receive water-soluble products with the high amount of immobilized active substance.
Correlation between the rate of release of regulator from the macromolecular system at the hydrolysis in experiences in vitro and its action on plants is revealed.

P20

SYNTHESIS OF POLYLACTIDE BY SIMULTANEOUS POLYMERIZATION AND EXTRUSION

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Biodegradable and biocompatible polylactide is one of the most perspective polymers for large-scale production of eco-friendly packaging, disposables and a great variety of biomedical products. PLA is one of the few polymers which stereochemical structure can be easily modified through controlling of L- and D-lactide relative ratio thus obtaining either amorphous or crystalline polymer. PLA can be degraded by hydrolysis of ester bond without presence of enzymes. Recent methods do not allow to synthesize PLA at low cost limiting large-scale production of biodegradable polymer products.
The goal of this work is to develop method of continuous synthesis of PLA by simultaneous polymerization and extrusion at various times and temperatures of reaction. Polymerization was carried out at temperatures 140-240°C and concentration of catalyst ($SnCl_2 \bullet 2H_2O$) ranging from 10^{-4} up to 10^{-1} M. To determine the time required to synthesize polymer of reasonable molecular weight, viscosity and molecular mass of PLA samples were investigated. It was found that polymerization temperatures above 200°C lead to decomposition of polymer, while temperatures below 200°C require long presence (up to several hours) in extruder, which is not appropriate for this technology.
In order to accelerate the polymerization process the another catalyst $Sn(Oct)_2$ was chosen due to higher activity, the concentration was in range of 10^{-4} to 10^{-2} M. Polymerization was carried out in rheoscope at temperatures 150-180°C and polymers synthesized at different times were used to study conversion kinetics. 95% conversion of PLA was achieved at 15 min, while molecular mass of amorphous samples was about 120 000 Da, glass transition temperature - about 40°C.
Mechanical properties were studied by uniaxial streching of PLA monofilaments synthesized in rheoscope. It was showed that the variety of polymers with different mechanical and structural characteristics can be prepared by developed method changing the time-temperature parameters of reaction at extrusion.

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P21

DEVELOPMENT OF IMMUNOCHROMATOGRAPHIC STRIP TEST FOR GENTAMICIN DETERMINATION IN MILK SAMPLES

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Use of illegal fodder additives, drugs for treatment of livestock diseases along with food supplements influence on man's health. There are many standard techniques for detection of different food pollutants, but the most of them require long time period, complicated equipment, skilled workers. Sometimes it is necessary to receive rapid results, screen many samples in short time; for this aim immunochemical methods are suitable. They are characterized by high specificity and sensitivity; they are very simple for use, quite quick. The lateral-flow format is by far the most common, because it is easier to manufacture and use.
There are many different kinds of label for result detection, but the most popular is colloidal gold (CG). It is characterized by quite stability, good visualization, essentially inertness, simplicity and cheapness.
Along with CG quantum dots (QD) are used as label for strip test. They are ideal label, because QD give very good analytical signal.
Lateral-flow test (LF) for gentamicin detection in milk was developed. The first step of this research was antibody checking with fluorescence polarization immunoassay (FPIA). Calibration curve was built, and it was shown that detection limit was 10 ng/ml and it was allow to detect of gentamicin in real milk samples. But FPIA is instrumental and it require to build calibration curve each day. So, rapid test was developed.
Selected antibodies were used to prepare conjugate with CG and QD. As test line gentamicin-OVA in definite concentration was exploited. Strip test allow to check the sample during 5-7 min. Antibody concentration for conjugate with GNP and for conjugate with QD preparation was chosen, optimal kinds of nitrocellulose membranes, glass membranes were found. Milk is characterized by very complicated matrix, but sample pretreatment is not suitable for test-method. Thereby, buffer solution, containing small quantity of detergent was selected as carrier for matrix effect leveling and analysis acceleration.
The LF test with GNP detection allows to detect of gentamicin presence in concentration equal or more, then 50 ng/ml. It was less, then MRL for gentamicin in milk (100 ng/ml).
Also, QD was checked as label for strip test. It was found limit of detection in this case was 50 ng/ml too, but analytical signal was high and non-specific interaction did not prevent to measure.
Metrological performances were calculated statistically.

P22

POLYMERIC HYDROGELS ON THE BASIS OF POLYVINYL ALCOHOL AND STARCH DERIVATIVES

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Polymeric hydrogels owing to their unique properties (high biocompatibility, swelling ability in water solutions, ability to biodegradation, elasticity, etc.) are widely applied in medicine and allied sciences in the capacity of implants, substrates in cellular engineering, materials for filling of postoperative cavities, etc. The problem of creation new hydrogel materials with the improved properties still faces to the scientists, working in the field of creation of polymeric biomaterials.
As objects of research for creation materials with the set speeds of biodegradation we have chosen derivatives of starch, polyvinyl alcohol and their mixtures. Under various conditions we had been synthesized some series of isotropic and anisotropic polymeric hydrogels. The process of gelation has been investigated in order to define the optimum conditions of reception of target products. Also it was studied modification kinetics of derivatives of starch and polyvinyl alcohol.
The carried out biological tests have shown absence of toxicity and high biocompatibility of developed hydrogel materials. It has been shown that at contact to organism living tissues the synthesized hydrogels practically did not cause inflammatory reaction, and completely degraded, being replaced with organism tissues. Speed of biodegradation was defined by character, degree of development of porous structure, quantitative composition of polymeric hydrogels and made from to 2 about 6 months.

P23

DRUG CONTROLLED RELEASE SYSTEMS ON THE BASIS OF MACROPOROUS POLYMERIC HYDROGELS CONTAINING NANO-AGGREGATES OF N-VINYLPYRROLIDONE AMPHIPHILIC POLYMERS

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For the last several years macroporous polymeric hydrogels attract growing attention as a basis for creation of systems with controlled release of drugs and biologically active substances. But in spite of their numerous advantages comparing to "simple" isotropic polymeric hydrogels such as greater osmotic stability, better mechanical durability and increased stability during long-term storage, such polymeric systems possess sufficiently high rates of release of substances introduced in hydrogel volume due to their well-developed specific surface.
For the purpose of elimination of this and some other disadvantages, in present study we propose novel combined material which represents cross-linked macroporous polymeric hydrogel of polyvinyl alcohol with introduced nanoscaled aggregates on the basis of amphiphilic poly-N-vinylpyrrolidone containing immobilized drugs or biologically active substances. Well-known antifungal antibiotics nystatin and amphotericin B were chosen as model drugs for our investigations.
Combined polymeric hydrogels were prepared by cross-linking of polyvinyl alcohol acrylic derivative solutions, mixed with preliminarily obtained solutions containing nano-aggregates with encapsulated drugs.
Several series of polymeric hydrogels containing different amounts of polymeric nano-scaled particles were prepared. Also several polymeric hydrogel samples containing "plain" dispersed nystatin and amphotericin B were obtained simultaneously for comparison.
The investigation of model drugs release from the prepared hydrogels volume showed that preliminary encapsulation of drug in polymeric nanoparticles allowed increase its release time from hydrogel volume (time was evaluated which corresponded with 90 % drug release) comparing to samples with "plain" antifungal drugs, approximately by 3-4 times (up to 72-96 hours), and dependence of released drug amount on time during practically all the process bore linear character.

P24

DEVELOPMENT OF NOVEL BIOAVAILABLE FORM OF BIOLOGICALLY ACTIVE SUBSTANCES ON THE BASIS OF POLYMERIC MICELLES

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Recently, the achievements in such areas of science like pharmaceutical chemistry, biochemistry and biotechnology have led to discovery, synthesis and research of numerous different biologically active substances. But in most cases the potential for application of such substances is used insufficiently. The plain low-molecular drugs and other active substances are quickly eliminated from organism by different defensive mechanisms or metabolizes as they frequently possess poor solubility in aqueous media and low capability to penetrate through cells membrane. The mentioned above disadvantages can be removed or their effect can be considerably decreased by loading of biologically active substances and drugs in specially designed delivery vesicles, for example micelle-like nanoparticles on the basis of amphiphilic polymers, which can provide targeted transport to the disease nidus with prolonged and controlled release of active substance.

The inclination of amphiphilic polymers with different structure, especially amphiphilic block copolymers, to form micelle-like aggregates in aqueous media is well-known. In present study we propose novel amphiphilic derivatives of poly-N-vinylpyrrolidone with molecular weight 2000-15000 containing one terminal hydrophobic octadecyl fragment, prepared by original single-stage method, as perspective basis for creation of highly-effective drug delivery systems. The sizes of polymeric micelle-like vesicles were determined by dynamic light-scattering method and depending on polymer molecular weight were 20-250 nm. The spherical shape of prepared polymeric nanoparticles was confirmed by means of electron microscopy.

The possibility poor soluble drugs solubilization by loading them into hydrophobic core of polymeric nanoparticles was demonstrated by preparation of water-compatible form of model hydrophobic drug – felodipine, which is a calcium channel blocker with high vessel selectivity used to control hypertension. After administration felodipine is quickly absorbed and consequently possess low bioavailability. Depending on technique and conditions of felodipine encapsulation and drug / amphiphilic polymer weight ratio, the drug loading efficiency determined spectrophotometrically was from 10 up to 60 %. Felodipine-loaded nanoparticles were isolated from obtained dispersions by freeze-drying, and there stability during short-term and long-term storage was studied and confirmed.

It becomes obvious, that preparation of novel biocompatible amphiphilic polymers with optimal properties combination and development of delivery systems for biologically active substances on their basis are urgent and promising direction in area of creation of novel highly-effective preparations for medicine, veterinary, biotechnology and agriculture.

P25

BIORESORBABILITY POROUS HYDROXYAPATITE-SILICATES GLASS MATERIALS FOR OSTEOPLASTY

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In the present work a porous biocomposition material (BCM) consisting of bioactive 50S25N5P glass and hydroxyapatite (HA) was synthesized, the influence of the composition and the sintering parameters on its porosity, water absorption and strength of materials was studied. The resorption of BCM in 0,6n. HCl, distilled water and behaviour this material in physiological medium "in vitro", was investigated after implantation by animals "in vivo".

Materials and methods. The 50S25N5P glass (composition: % mass: 50 SiO_2, 25 Na_2O, 20 CaO, 5 P_2O_5) crushed into 30-90 μm pieces. A 1:1 mixture of the crushed glass and the HA powder (dispersion: 3-7 μm) was granulated and a 400-620 μm fraction was selected. Porous composites were prepared from those granules of bioactive glass and HA (BioG/HA) and powder of the crushed glass (Gr:P) using water for binding. This composition was pressed for making a product possessing 1,2–1,7g/cm^3 volume weight, dried and sinteing at 700-740°C.

Results. Varying the composition and the sintering parameters, we obtained materials with open porosity 15-25 %, compressive strength up to 50 MPa, similar to the cortical bones, and materials with open porosity 20-45%, compressive strength up to 10 MPa, similar to cancellous bones.

Microporous structure of the sintered specimen is determined by Gr:P ratio and by the sintering temperature. It is characterized by a bimodal pore distribution and contains larger pores 200-300 μm in size, smaller pores 40-80 μm in size, and inhomogeneities of less than 1 μm size.

Investigation of resorbing, using 0,6n. HCl and water showed that the sintered specimen undergo partial dissolution. The wight losses of specimens is depend on porosity. Specimens with high porosity, have high level of weight losses. Buffering BCM in the physiological medium, promote precipitation of carbonate-apatite layers on the sur-

face of specimens.
Porous BCM tests by rabbits up to 12 months. All specimens showed intensive biointegration of bone cells inside pore structure in 2 months and pore space is filled with bone tissue and blood vessels in 8 months. The higher porosity materials possess, the higher rate of neogenic bone tissue growing into pore space.
Combining properties of BCM, such as bone bonding osteoproduction and bioresorbability with dissolution products that stimulate osteogenesis at the genetic level, high open porous these scaffolds have high potential as scaffolds for bone tissue engineering applications.

P26

JOINT IMPLANTS FROM UHMW POLYETHYLENE WITH OPEN POROSITY PRODUCED BY SINTERING/COMPACTION TECHNIQUE

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A novel family of joint plants based on solid (nonporous) Ultra High Molecular Weight (UHMW) polyethylene have serious disadvantages such as generation of fine polymer particles, because of the lack of synovial liquid (internal natural lubricant) inside the implant body. Extremely high viscosity of UHVW PE melt makes impossible to create the porous structure by regular foaming techniques. To make an open pore structure of implants which should be fully permeable for synovial liquid, it has been developed a family of composites based on UHMW PE fibers and fabrics. These porous composites have controllable pore size and flexibility and produced by compaction/sintering technique.
Key Words: porous Ultra High Molecular Weight (UHMW) polyethylene • biomedical implant • porous polymer composites • biomedical application

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P27

CAPABILITIES OF IN SITU SYNTHESES OF SILVER AND MAGNETITE NANOPARTICLES ON THE POLYELECTROLYTE CAPSULE SHELLS

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Due to monodispersity, simplicity of permittivity control, and possibility of choosing the shell material, polyelectrolyte microcapsules became a promising technological object. Embedding of metal nanoparticles into walls of polyelectrolyte capsules can ensure such additional properties as conductivity and optical and microwave absorption for temperature release of the capsule content. Magnetic nanoparticles provide extensive functionalities for the microcapsules, enabling manipulation and position control. To extend the capabilities of nanoparticles distribution control and simplify the nanoparticles deposition onto polyelectrolyte microcapsules, we have developed controlled syntheses of silver and magnetite nanoparticles directly on polyelectrolyte multilayer shells.
The polyelectrolyte capsules with controlled distribution of silver nanoparticles are obtained by the in situ reduction of Ag^{+} ions by the so-called "silver mirror", Tollens, reaction. Such capsules are promising for designing tools to deliver drugs with remote control of capsule content release by laser irradiation.
Magnetite nanoparticles were synthesized on the polyelectrolyte shell by chemical co-precipitation of Fe^{3+} and Fe^{2+} ions in aqueous suspension of the microcapsules under the heating. As a result, the obtained modified polyelectrolyte capsules became magnetic field responsive. This important properties give a perspective to apply them for the targeted drug delivery.

P28

ALGINATE MICROPARTICLES COATED WITH CHITOSAN AND LOADED WITH SYNTHETIC LIGANDS FOR SPECIFIC REMOVAL OF PROTEINS FROM WHOLE BLOOD

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Specific elimination of pathogenic proteins from bloodflow is a serious challenge, especially when the protein should be

removed from whole blood, without plasma separation procedure. Adsorbent or adsorbing material/device in this case should have additional properties, namely, it should be hemocompatible. Presently used techniques require plasma separation from blood cells before to remove specific ligands by the immunosorption column. Alginate-chitosan microspheres are potentially hemocompatible, and therefore could be proposed as immunoadsorbents for use with whole blood. We are developing a new type of immunosorbent based on alginate microparticles coated with semipermeable alginate-chitosan membrane which are loaded with synthetic A and B antigens (glycoconjugates) for the direct removal of ABO blood group antibodies from whole blood, without the need for plasma separation and plasma exchange. The coating is designed as a wide-pore polyelectrolyte membrane permeable for proteins to be sorbed within the microparticles, whereas the water soluble ligand-linked polymer can not be released due to its extra-high molecular weight (Mw 1500-2000 kDa) . Two types of proteins to be removed were used in this study: 1) human anti-A/B antibodies (IgM) to blood group B (or A) antigen; 2) low density lipoproteins. First task was dictated by a need in removal of blood group anti-A and anti-B antibodies which can prevent hyperacute organ rejection in ABO-incompatible transplantation, whereas second one could be an intelligent procedure for atherosclerosis treatment. The sorption capacity of the supports obtained was compared to this one of Sepharose modified by the same oligosaccharides.
Ca-alginate miocrobeads loaded with appropriate ligands can be prepared from sodium alginate by using Ca^{2+} ions providing a hydrogel network using a special sprayer (with air flow) or electrostatic bead generator. Microbead size could be varied within 200-900 mm by varying concentration of a sodium alginate solution, a needle diameter and some other parameters.. Ca-alginate beads with the entrapped ligands were coated with chitosan, in order to prevent their release from the microparticles. The stability of the microparticles depends upon the inner structure and the thickness of the polyelectrolyte membrane.
Experiments with purified antibodies and cell-free serum demonstrated good capacity of alginate-chitosan microparticles with blood group active polymer inside, comparable with this one of corresponding sepharose adsorbent. Complex study of hemocompatibility of the obtained alginate-chitosan microparticles showed that they did not lead to platelets and red blood cells damage and did not activate complement system. Further improvement of this material deals with elevation of its protein-binding specific capacity.

P29

POLYANILINE – MATERIAL FOR MEDICINE AND BIOLOGY

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Polyaniline finds application in medico-biological areas as a component of biosensor controls, matrices for tissue engineering, substrates possessing high biocompatibility, electroconducting material, capable to modify the cellular activity.
Its properties defining the possibility of an effective use in these areas depend upon the structure of a macromolecule, level of difference of chain rings type, and molecule-weight distribution.
These characteristics are appreciably defined by conditions of a polymer synthesis, the efficiency of which depends upon the scope of the study of mechanism of polymerization of this biologically important polymer.
In this research we proposed a new mechanism and kinetic model of polymerization of aniline and its structural analogs - anthranilic acid, 2,4,6-trimethylaniline, and N-ethylaniline.
It was shown that when the substances which can form complexes with components of reaction systems are introduced in the system the properties of prepared polymers cardinally change.

P30

NEW BIOLOGICALLY ACTIVE MACROMOLECULAR SYSTEMS ON THE BASIS OF HUMIT ACIDS

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The new macromolecular systems have been prepared by immobilizing of humic acids on polymer carriers – water-soluble and water swelling copolymers of maleic anhydride and vinyl monomers. These preparations showed prolonged stimulating growth and development activity for plants due to increased stability of plants to stressed circumstanced and higher water and nutritious content in soil.
Biologically active polymeric preparations were synthesized by grafting of humic acids on copolymers in the pres-

ence of the basic or/and acid catalysts at 90-100°C followed by neutralization of the reaction mixture by potassium hydroxide.
The grafting was studied by IR-spectroscopy and DSC. IR-spectra were recorded on IR-Fourier spectrometer Magna-750 Nicollet firm (USA) with the resolution of 2 sm^{-1} within of 4000-400 sm^{-1}, DSC by using instrument Metler Toledo FP99A (Switzerland) from 20 to 125°C at the heating rate of 2°C/minute. The kinetic and thermodynamic parameters of the reaction were found. There main features of crosslinking resulting in a wide spectrum of physical and chemical properties of products were revealed as well as the influence of conditions of reaction, time of hydrolysis and pH-values on environmental properties of hydrogels was found.
Two types of preparations – the water-soluble and the water swelling preparations containing humic acids were tested in laboratory for potato microcloning reproduction as phytohormones in nutrient medium of Murasige-Skuga for cultivating explants of apical meristem. The optimum ratios between preparations and cultivated environment were revealed promoting the increase in amount of plants-regeneration.
A complex of screening and field tests of humit acids polymeric forms was conducted. The results gave evidence that new macromolecular systems considerably promoted rooting of plants, earlier awakening of potato bourgeons (based on the quantity of the sprouted eyeholes), cause considerable formation of stem runaways and occurrence of shoots for 3-4 days earlier in comparison with raw tubers. Plants were found to enter earlier into the phases of budding and flowering, which positively influenced the increasing potato productivity.
The laboratory tests were made in sixfold repetition. The concentrations of solutions varied from 0.004 to 0,0015%. Control tubers were presoaked in water. To be compared as the standard, amber acid was used. Soaking of potato tubers was carried out within 2 hours.
The field experiment was conducted four times. Phonological observations and biometric recording of growth and development potato plants were conducted. Treatment of tubers with new polymeric forms of preparations showed prolonged effect on growth and development of plants. The increase of potato crops was equal to 9.8-12.0 % compared to appropriate monomeric form of the regulators. The maximum additional crop was raised up to 28-30.2 % by using hydrogel forms of preparations.

P31

AMINOACID DERIVATIVES OF POLY-N-VINYLPYRROLIDONE

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A method of synthesis of derivatives of α,ω – amino acids and epoxy containing poly-N-vinylpyrrolidone was developed. Among the used amino acids were glycine, β-alanine, γ-aminobutyric, and ε-aminocaproic acid. Epoxy containing poly-N-vinylpirrolidone has been synthesized based on the"Darzan "modified reaction.
The synthesized polymers with 7-10 mol% side amino acid groups' content did not show sharp toxicity in experiments on cellular cultures and animals and possessed different types of biological activity, such as immunoadjuvant, ability to stimulate I interferon induction, antiviral activity, strengthening action of antibiotics.
The polymers containing side amino acid groups possess ability form biologically active complexes with transition metals like Cu, Co, Pt, Ge. Such polymeric metal complexes were capable to stimulate the process of heamopoiesis and showed immunostimulatory activity.

P32

MODIFIED MAGNETIC NANOPARTICLES Fe_3O_4@Au: SINTHESIS AND PROPERTIES

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Particles in the nanometer size range are attracting increasing attention with the growth of interest in nanotechnological disciplines. Among different nanoparticles, magnetic nanoparticles deserve a special attention, for example Fe_3O_4. They are widely used in different fields, such as medical diagnosis, therapeutics, magnetic resonance imaging for detections, high-density magnetic recording, controlled drug delivery, biological targeting or separa-

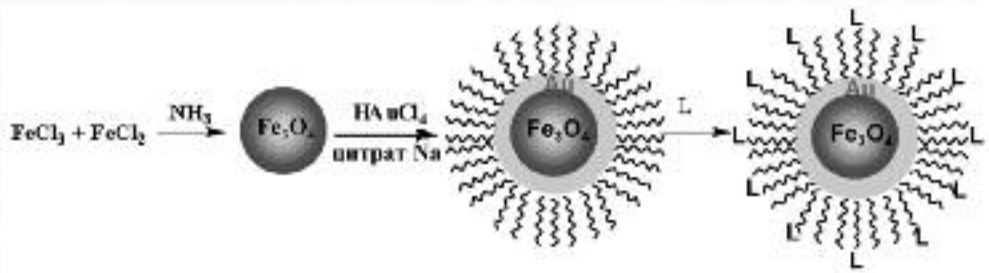
tion, and catalysis. Fe_3O_4 nanoparticles have attracted the great interest due to their strong magnetic properties. However, the applicability of Fe_3O_4 nanoparticles is often hindered by their own spontaneous oxidisable surfaces. Modification of surface can help to control size and structure of Fe_3O_4 nanoparticles. Here, we report modification of surface of Fe_3O_4 by gold nanoparticles. Gold represents by itself an excellent candidate by virtue of its easy reductive preparation and functionalization, high chemical stability and biocompatibility.

In this study, we report modification of surface of Fe_3O_4 by gold nanoparticles and functionalization of gold surface for application prepared core-shell Fe_3O_4@Au nanoparticles in the separation of enantiomers.

The two enantiomers of racemic chiral compounds, including chiral drugs, often show different pharmacological, toxicological and metabolic activities in living systems. Consequently, methods of separating enantiomers are essential. There are various methods that can be applied for the separation of enantiomers, such as various chromatographic methods, electromigration capillary methods, enzymatic or non-enzymatic dynamic kinetic resolutions. Here, we demonstrate that our Fe_3O_4@Au·L nanoparticles can be used in the direct separation of enantiomers.

Our new strategy for the separation of enantiomers with core-shell nanoparticles is the utilization of Fe_3O_4@Au nanoparticles and an appropriate chiral selector. Fe_3O_4@Au tagged with chiral selector (L) are expected to select a single enantiomer from a racemic mixture and the resulting Fe_3O_4@Au·L – enantiomer complexes can be easily removed by using a magnet.

A new type of bifunctional ligand-protected gold-coated iron oxide nanoparticles Fe_3O_4@Au·L are synthesized by a three-step reaction (Scheme 1). At first we synthesized magnetic core – Fe_3O_4 from iron (II, III) salts. Then Fe_3O_4 were coated with citrate-protected gold by the citrate reduction of Au^{3+}. Afterwards, Fe_3O_4@Au·L was synthesized by a ligand place-exchange reaction between the citrate and chiral ligand (L-cysteine) on the surface of Fe_3O_4@Au nanoparticles.



Scheme 1. Illustration of the chemistry and processes involved in the synthesis of the Fe_3O_4, Fe_3O_4@Au and Fe_3O_4@Au-L nanoparticles.

Nanoparticles with average size 30 nm were prepared, what was shown by TEM (transmission electron microscopy) (Fig.1). Fe_3O_4@Au·L nanoparticles have been characterized by physical and chemical methods.

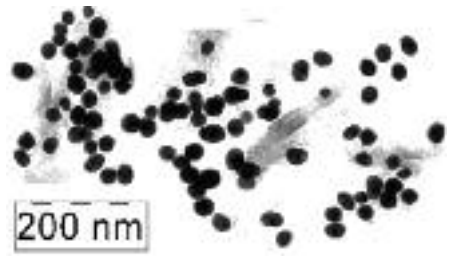


Fig.1 TEM images of Fe_3O_4@Au-L nanoparticles.

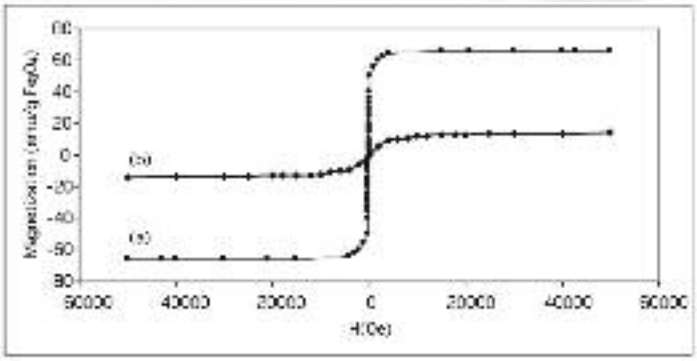


Fig.2 Magnetization hysteresis at 273 K for Fe_3O_4 (a) and Fe_3O_4@Au (b) nanoparticles.

P33

BIOMIMETIC SUPERHYDROPHOBIC POLYMER COMPOSITION FOR THE PROTECTION OF STONE MONUMENTS AND BUILDINGS

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In many plants, notably the Lotus flower, leaves demonstrate super-hydrophobicity characterized by very high water contact angle and a very low roll-off angle, defined as the inclination angle at which a water drop rolls off the surface. This superhydrophobicity assures the self-cleaning effect of the Lotus leave: water drops completely roll off the leaf, carrying undesirable particulates. A two-scaled surface roughness at nano- and micron-scale has been considered responsible for the development of these super-hydrophobic and self-cleaning properties. The natural superhydrophobicity gained much attention and inspired mimetic attempts.
In the current study, we demonstrate that so called "lotus effect" can be achieved by the modification of a commercial siloxane stone protective composition with silica nanoparticles. This modification leads to the development of a two scale surface structrures roughness, micro- and nano-roughness, on the surface of treated substrates and renders the surface super-hydrophobic and self-cleaning. The extent of surface hydrophobization depends on the nanoparticle concentration and reaches a maximum value of ~160° at 1% w/v of nanoparticles for the case of white Greek marbles (Naxos, Pentelic and Thassos) treated with the modified composition.
The investigation of the surface morphology by scanning electron microscopy (SEM) reveals the presence of micron-sized protrusions (10–100 μm in diameter) formed by nanoparticle aggregates and consolidated by the siloxane polymer. The diameter and surface density of the protrusions depend on nanoparticle concentration. The developed nanostructure of the protrusions was observed by atomic force microscopy (AFM). The nanodimensions of the silica particles are essential for the superhydrophobization of the treated marble surfaces. In the case of micron-sized silica particles that were mixed with siloxane and were applied accordingly on similar white Greek marbles, the superhydrophobic effect was not achieved and the observed water contact angles were substantially lower.
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P34

AGGREGATES OF AMPHIPHILIC POLYMERS – THE IMPORTANT GROUP OF NANOSIZED SYSTEMS

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Nanosized systems of various types like nanospheres, nanoparticles, dendrimeres, and liposomes have been used as carriers of medicinal and generally biologically active substances. Recently appreciable place among such systems was occupied by the so called aggregates of amphiphilic polymers.
In this report we present the methods of synthesis of amphiphilic derivatives of various water-soluble polymers – poly-N-vinylpyrrolidone, polyacrylamide, polyacrylic acids etc. It is shown that such amphiphilic polymers can form aggregates in water systems with size ranging from tens to hundreds nanometers. The influence of the polymers structure on their ability to aggregate was studied.
It was established that synthesized amphiphilic polymers can be used for modification of the membranes of the liposome's resulting in the increase of the membrane stability from the influences of various effects. Examples of the use of nano-aggregates as carriers for immobilization of different drugs and biologically active substances with anti-inflammatory, anti-fungal, anti-cancer activity has been shown. They can also be used for modification of protein and polypeptide drug products raising the stability.
It is shown that in synthesized amphiphilic polymers various functional groups can be introduced such as aldehyde, epoxide, carboxylic, amino acid, etc. So on the basis of the nano-aggregates it was allowed to receive systems with biological activity which can be used as anti-virus, immunoadjuvants, etc.
The promising toxicological characteristics of the systems based on amphiphilic polymers of N-vinylpyrrolidone permits us to consider the perspective of their application in the near future.

P35

ASSESSMENT OF THE INTRAVITREAL PHARMACOKINETICS AND POTENTIAL RETINAL TOXICITY OF THE NSAID LORNOXICAM

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Purpose: To evaluate the pharmacokinetic and toxicological profile of intravitreally injected lornoxicam in rabbit eyes.
Methods: For the determination of the pharmacokinetic characteristics of the drug, both eyes of 15 albino rabbits were intravitreally (IVT) injected with 250 μg of commercially available lornoxicam (*Xefo*® 8 IV/IM Injection, Nycomed Hellas S.A.). Both eyes of 3 rabbits were enucleated at time points 0(right after injection), 1, 2, 6 and 24 hours after injection. Lornoxicam was extracted (LLE) from the vitreous and sample concentrations were measured with HPLC (UV/VIS). For the investigation of retinal toxicity of intravitreal lornoxicam, two concentrations of the drug were tested in 10 albino rabbits that formed two groups of 5 animals. Group I (low dose-group) received intravitreally 250 μg/0.1 ml of lornoxicam and Group II (high dose-group) 1.500μg/0.1 ml of lornoxicam, always in the right eyes (study eyes), while the fellow eyes served as controls (received 0.1ml of Water For Injection intravitreally). All animals underwent indirect ophthalmoscopy, tonometry and electroretinography before the injection (day 0-baseline), at day 1, 15 and 30 after the injection. At the end of follow-up, all animals were sacrificed and the retinas were isolated and prepared for histological examination. For the statistical analysis, Repeated measures ANOVA was used.
Results: Lornoxicam was detected at 372nm. It was found to follow first order kinetics, with an elimination rate constant of $0.235h^{-1}$ and a half-life of 3.0 hrs. No difference was observed in indirect ophthalmoscopy findings before and in any time point after injection. For the ensemble of values, no significant difference in IOP was detected at any time point tested (p=0.419). Moreover, the amplitude of either photopic or scotopic flash b-waves in ERG didn't prove to differ significantly with time (p= 0.154 and p = 0.568 respectively). Eventually, in Group I the study eye retinas didn't differ histologically from the controls, whereas in Group II extended retinal damage was observed in the study eyes.
Conclusions: Intravitreal lornoxicam causes dose-related toxic effect to the retina. On the other hand, a dose smaller or equal to 250 μg is safe and could be considered as an alternative treatment to ocular inflammatory conditions.

P36

BIOACTIVE POROUS GLASS-CERAMIC MATERIALS FOR BONE PROSTHESIS

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Materials for bone trauma and injury curing must possess high pore structure including open pores with diameter 100-1000 μm to allow blood vessels and bone cells growing inside material and pores with diameter 10-100 μm to permeate physiological solutions after implantation. The present study subject of inquiry is bioactive calcium-phosphate glass with CaO/P_2O_5 ratio 1,1 and B_2O_3, Al_2O_3, TiO_2, ZrO_2 as processing aids. The purpose of the study is to obtain glass-ceramic materials based on concerned glass with properties listed over.
Porous glass-ceramic materials were obtained by means of ceramic processing using combustible pore-formers – granules and bars. Paraffin, starch, gelatin, NH_4OH, NH_4NO_3 with dispersion from 50 to 2000 μm were used as materials for granules. Graphite, nylon, cotton with diameter from 100 to 500 μm were used as materials for bars. Glass powders dispersion in slurries was varied from 40 to 400 μm. Sintering was conducted at temperature 900 °C during 1 hour.
Following methods of forming raws for sintering were used: glass powders molding with starch acting as gas-forming agent, glass powders molding with bars acting as channel pore-forming agents, mixing slurries with granules acting as cell pore-forming agents. Using these three forming methods allowed to obtain correspondingly three series of materials with different pore structures:
1. Open porosity – 25-50 %, pore sizes – 10-200 μm.
2. Total open porosity – 25-50 %, channel porosity – 5-15 %, channel pore diameter – 480-530 μm. Interchannel pore diameters – 10-200 μm.
3. Total open porosity – 40-80 %, open cell porosity – 20-60 %, cell pore diameters – 100-2000 μm. Intercellular pore sizes – 10-40 μm.
Materials implantation in rabbits for a period from 2 to 12 months showed absence of encapsulation with connective tissue. Intensive biointegration of bone cells inside pore structure occured in 4 months on average. All pore space is filled with bone tissue and blood vessels in 12 months. Higher porosity level leads to higher rate of material coalescence with bone. Thus, neogenic bone tissue forms in 2 months of implantation inside materials with 55 % open porosity, and only in 4 months of implantation inside materials with 30 % porosity.

P37

BIOMATERIALS AND THEIR MAJOR ROLE IN MEDICO-BIOLOGICAL AREAS

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Biomaterials are functioning in direct contact and interaction with living tissues and organisms and play a major role in modern medicine, biotechnology, bioengineering, agriculture, cosmetic, food- industries and also other life sciences and technologies. Some examples of their application are:

- Materials for the creation of various implants intended for cardiovascular and orthopedic surgery for ophthalmology and other applications.
- Materials for cellular, tissue and gene engineering,
- Various drug preparations for directed and programmed delivery
- Biologically active and biocide systems for various technological areas
- Bioanalytical systems, in particular, biotest systems and biochips
- Membrane and sorption materials, including products for the detoxication of the organism,
- Biodegraded materials several other applications

All the above areas of biomaterial preparations and products have now occupied a steady sphere of use, which undoubtedly defines quality of human life.
The important feature of biomaterials is that preparations and products should possess inherent properties such as biocompatibility and haemocompatibility, ability for biodegradation and biodestruction, absence of immunoactivity, high level of purity, etc.
Among various types of biomaterials an essential role is played by metals, inorganic and carbon materials, composites of various designs. Various polymers occupied a major place among assortment of biomaterials and increased their application possibilities. That is the area of biomaterials connected to many fundamental directions of chemical technology.
As so, we can with confidence ascertain that the science of biomaterials generated during the last years in various specific key basic branches of the industry possess universal and economic importance in chemical technology, biotechnology, nanotechnology, medical and bioengineering technologies.

P38

CORE-SHELL NANOPARTICLES PREPARING BY THE METHOD OF MOLECULAR IMPRINTING FOR BIOLOGICAL APPLICATIONS

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Molecularly imprinted polymers (MIPs) are being increasingly used as selective adsorbents, sensor materials and antibodies in different bioanalytical and biomedical applications. To satisfy the different application purposes, MIPs with well controlled physical forms in different size ranges are highly desirable. For examples, MIP nanoparticles are very suitable to be used to develop binding assays for detecting different drugs, pathogens and proteins.
While various imprinted materials were made, these efforts have met with many limitations including incomplete template removal, small binding capacity and irregular material shape. One of the main reasons is that the extraction of original templates located in the interior area of bulk materials is quite difficult. Traditional imprinting techniques often produce materials exhibiting low rebinding capacity and poor site accessibility to target species. Therefore preparing MIP core-shell nanoparticles with the imprinting molecules situated at the surface or in the proximity of materials surface is quite desirable[1].
We have developed a method for the synthesis of high-quality SiO_2@MIP nanoparticles with a molecular recognition sites. As a core we used silica particles, prepared by Stober method[2], as a shell polymeric layer of hyperbranched polyethoxysiloxane[3], with high functionality, globular shape and other regulated parameters. These allow us to add template molecules by different methods and to realize the subsequent functionalization and shell modification under controlled conditions. The completeness of the reactions of modification and capping was checked basing on methods of transmission electron microscopy (TEM), dynamic light scattering (DLS), spectroscopic and chromatographic methods.

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P39

DEVELOPMENT OF AN INDIRECT ELISA FOR TETRACYCLINES RESIDUES IN MILK

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Tetracyclines (TCs) are a broad-spectrum antibiotic used increasingly in animal husbandary to treat diseases or to promote growth as feed addivities. To avoid using labor-intensive instrumental methods to detect residues of TCs in food, a simple and convenient indirect enzyme-linked immunosorbent assay (ELISA) method for TCs was developed using polyclonal antibody prepared in this study.

Materials and Methods. To get antigens there have been synthesized conjugates of tetracycline-HCl (TC), chlortetracycline-HCl (CTC) and oxytetracycline-HCl (OTC) with bovine serum albumin (BSA) by means of modified Mannich reaction (1, 2). Structure and epitopic density of conjugates has been controlled by UV-spectrum. Polyclonal rabbit sera have been received by immunization of rabbits

Results and Discussion. All antibody raised in rabbits and synthesized antigen were screened and characterized using homologous and heterologous competitive ELISA (cELISA) formats to select the best combinations.

IC_{50} for different TCs are shown in Table 1.

Table 1. IC_{50} values of TCs in homologous format cELISA by using anti-tetracycline rabbit sera

Serum, N	Immunogen	IC_{50}, ng/ml		
		TC	CTC	OTC
1/4	BSA-OTC	45	115	2000
7/1	BSA-CTC	10	10	100
9/1	BSA-TC	15	20	70

Developed technique was optimized for screening TCs residues in milk. The sample preparation procedure was developed. The limit of TC and CTC detection was 2,6 μg l^{-1}. The 150 samples was analyzed and results was submitted by HPLC-MS.

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P40

FABRICATION AND CHARACTERIZATION OF TRI-O-ACETYLADENOSINE IMPRINTED POLYMERS FOR SCREENING AND ISOLATION OF PROTEIN KINASE INHIBITORS.

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Introduction: A number of diseases including cancer, diabetes and inflammation are linked to deregulation of cell signaling pathways controlled by protein kinases. Inhibition of the involved kinases can interrupt the aberrant signaling and have a specific therapeutic effect. Nowadays protein kinases are recognized as validated therapeutic targets for treatment of number of diseases. An occupation of ATP-binding cleft by ATP mimetic compounds is the main mechanism of kinase inhibition – ATP competitive mechanism.

Objectives: Fabrication of ATP binding cleft imitation by molecular imprinting of ATP analog tri-O-acetyladenosine and thus production of polymer suitable for screening and isolation of new protein kinases ATP-mimetic inhibitors from different sources.

Results: Polymers imprinted with tri-O-acetyladenosine were created by the use of methacrylic acid (MAA) or 3-vinyl benzoic acid (VBA) as functional monomer and ethylene glycol dimethacrylate (EGDMA) as cross-linking agent. Radical polymerization was thermally initiated by azobisisobutyronitrile (AIBN) and carried out for 12hrs. The binding characteristics of the imprinted polymers were evaluated by batch rebinding experiments and binding parameters (Table 1) were calculated by the application of Freundlich continuous affinity distribution model. The binding isotherms for MIP and control NIP polymer plotted in logarithmic format are in excellent agreement with Freundlich isotherm (R^2>0, 99).

Conclusions: Tri-O-acetyladenosine was successfully imprinted giving the polymers with high affinity to the initial template (K_d as low as 2μM), sufficient concentration of the binding sites N and pronounced specificity (k'_{impri-}

nted >> k' control). The vynilbezoic acid proved to be better monomer in comparison to methacrylic acid giving polymers with higher affinity and increased number of binding sites. This can be attributed to the additional hydrophobic and π-π interactions assured by benzol ring of the VBA monomer. It is also important that hydrophobic interactions are essential in ATP binding to protein kinase.

Table 1. Binding characteristics (N, K_d) and specificity ($k'_{imprinted}$ vs $k'_{control}$) of tri-O-acetyladenosine imprinted polymers.

Monomer	**MAA**	**VBA**	**VBA**	**VBA**
Ratio (Template/monomer/cross linker)	1/6/30	1/6/30	1/4/30	1/3/30
N, µmole/gr	6.2	32	35.5	22
K_d, µM	16	2	2.5	4.7
$k'_{imprinted}$	10.6	4.7	3.2	1.5
$k'_{control}$	0.3	0	0	0

P41

FEATURES OF BIOLOGICAL EXPOSURE TO NANOCOMPOSITES BASED ON NATURAL BIOPOLIMER IN EXPERIMENT

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Using the silver as the nanoparticles allows hundreds of times lower concentration of silver, with keeping all the bactericidal properties, while the use of the arabinogalactane hemicellulose as the stabilizing agent may increase the aggregate stability and water solubility of the nanocompositions as well as may give them the immunomodulating and transmembraneous properties. Increased interest in the development of products containing nanoscale silver, especially using as the nanostabilizing matrices of the natural substances indicates the need to study the toxicological properties of the nanocompositions at the different intake ways into organism including the peroral ones. The preparation based on the nanoparticles of metallic silver, placed into the membranetransport biopolymer matrix of the arabinogalactane produced by the institute of Chemistry named by A.E. Favorsky (Siberian Division of Russian Academy of Science, Irkutsk) was used in the experiment. The nanobiocomposition, argentoarabinogalactane, is known to be considered as the narrowdispersive one: the particle proportion with size 6-12 nm amounts 80 % and the silver content is 16.73 %. 32 albino mongrel rats males with body weight 250-300 g which are maintain on the standart ration of the vivarium with water and food access libitum were used in this study. All the studies were performed according to the rules adopted by the European Convention on the vertebral animal protection used for the experimental and other purposes (Strasburg, 1986). The animals of the first group were intragastrically administrated, using the probes, with aqueous solution of the argentoarabinogalactane (100 mkg silver per kg body weight) at the dose 0.5 ml for 9 days. The albino rats in the control group received the solution of the stabilizing arabinogalactane in the equivalent amounts or the aqueous dispersion of the colloid silver, stabilized with casein, with the silver content 8%, while the control animals received the distilled water. While performing the experiment the dynamics of the body weight increase was studied in the animals of all the groups. The animals were killed using the decapitation the next day after the last administration of the preparations tested and then we determined the absolute mass of the internal organs, the concentrations of the reduced glutathione in the blood and liver homogenate as well as the catalase and peroxidase activity in the blood. The study results have shown that the alterations in the states and behaviour were not observed to occur among the animals in all the groups tested, as the external examination indicated. The albino rats were not found to differ in the dynamics of the body mass increase during the experimental process. In addition, the intragastric injection of the preparation containing the nanoparticles of the metallic silver resulted in the significant increase in the catalase activity and the increase in the level of the reduced glutathione in the blood compared with the control group which may indirectly testify the activation of the natural antioxidant protection in the response to the organism intake of the foreign agents. Furthermore, argentoarabinogalactane and the pure arabinogalactane resulted in the increase in the blood peroxidase activity having the character of a trend. The increase in the absolute weight of the spleen was observed to occur in the albino rats exposed to the argentoarabinogalactane which may testify the immunomod-

ulating effect of the preparation while in the isolated injection of the arabinogallactane the spleen mass was not found to differ from the results obtained in the control animal group. Noteworthy result, showing an increase of absolute mass of the left and right kidney, observed under the influence argentoarabinogalactane. This fact needs performing the further studies.

P42

FLUORESCENCE POLARIZATION IMMUNOASSAY DEVELOPMENT FOR DETECTION OF FUNGICIDES KRESOXIM-METHYL, TRIFLOXYSTROBIN AND PICOXYSTROBIN

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Kresoxim-methyl, trifloxystrobin and picoxystrobin are among strobilurin fungicides which are widely used for fungus pest control since they were introduced in 1996. Their extensive use and postharvest application makes them easier to reach environmental objects and human consumers. These facts lead to the necessity of development of analytical techniques for the detection of residues of these pesticides in environmental and food samples.
In this study Fluorescence Polarization Immunoassay (FPIA) was used because it possess a number of advantages such as rather high sensitivity, selectivity, it demands few minutes for entire analysis and doesn't need complicated sample pretreatment.
Several derivatives of the target molecule with different chemical structure were synthesized. These derivatives were used for the generation of antibodies and for the synthesis of fluorescein-labeled tracers. Structures of tracers were confirmed via mass-specroscopy. The optimal combination of immunoreagents (antibodies and tracer), which is the key factor for any kind of immunoassay, was selected. Moreover values of affinity constants of antibodies for free analyte and for tracer (antigen with fluorescent label) were determined, because the ratio between them is important for the analytical performance of an immunoassay. For example we have found that the affinity constant of monoclonal antibodies KM6#22 for kresoxim-methyl was equal 1.16×10^9 M^{-1} and the affinity constant of same antibodies for fluorescein-labeled kresoxim-methyl was 1.36×10^{10} M^{-1}.
Using different tracers and antibodies highly specific FPIA for three strobilurins was developed with limits of detection 21 ng/ml for kresoxim-methyl, 10 ng/ml for trifloxystrobin, 3 ng/ml for picoxystrobin. Sensitivities for all of these three strobilurins are well below common maximum residue level for these pesticides (50 ng/ml).
Acknowledgements:
The research was supported by Grant of Russian Foundation for Basic Research "New strategy for robust and sensitive chemiluminescent immuno-bio-technology for detection of chlorinated herbicides in environment". (RFBR 08-03-90301).
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P43

INTERACTION OF VARIOUS BIOLOGICAL OBJECTS WITH DIFFERENT NANO-SIZED COMPLEXES OF POLYANILINE

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This report presents the results of study on the interaction of various biology objects with nano-sized polyaniline (PANI) derivatives synthesized using low-molecular and high-molecular polymeric acids. It was shown that A- and B-type influenza viruses isolated in the period of 1977-2008 can be adsorbed on PANI sorbents independently of the antigen structure of outer-sphere albumins. The immobilized viruses interacted with antibodies from homological antibodies from immune sera. The hemagglutination titer of the virus solutions decreased 8-256 times. It was shown that besides influenza viruses, bacteriophages and antibiotics PANI-based sorbents are capable of interact-

ing with enteroviruses, in particular, poliomyelitis virus, which size is 3-times smaller than that of influenza virus. Therefore, modern polymers-derivates of PANI due to its high ability to adsorb different biological materials and their physical and chemical properties are promising materials for production of filters for decontamination of solutions from viruses and drugs purification.

P44

NOVEL BIOMATERIALS AND TECHNIQUES FOR THE ENHANCHMENT OF THE OPTICAL AND MECHANICAL PROPERTIES OF THE CORNEA

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Introduction: The cornea is the most important optical element of the human eye. In certain conditions such as keratoconus or iatrogenic keratectasia the cornea has compromised mechanical stiffness and as a result irregular shape. The purpose of this study is to evaluate novel bio-compatible materials and techniques for their use for the in-vivo enhancement of the optical and mechanical properties of the cornea. We report on the preliminary results following implantation of hybrid hydrogel comprising a polysaccharide and a synthetic macromolecule (poly-ethylene-oxide).
Materials and methods: The material described above possesses the physical properties necessary to form a transparent, mechanically stable and biologically inert intracorneal implant. This implant can be molded in situ in lamellar cavites formed in the cornea either manually or by means of a femtosecond laser. This ensures that the implant may have the shape (thickness distribution) needed to restore corneal geometrical uniformity, resulting to better image quality.
Results: Preliminary implantation in rabbit corneas resulted to no adverse effect and stable implants for at least one week after implantation. The animals underwent confocal microscopy and macroscopic clinical (ophthalmological) evaluation.
Discussion: Although the development of this technique is at a very early stage the results seem very promising indicating that in-situ molded intracorneal implants may be employed for the customized restoration of corneal symmetry as well as for its mechanical reinforcement.

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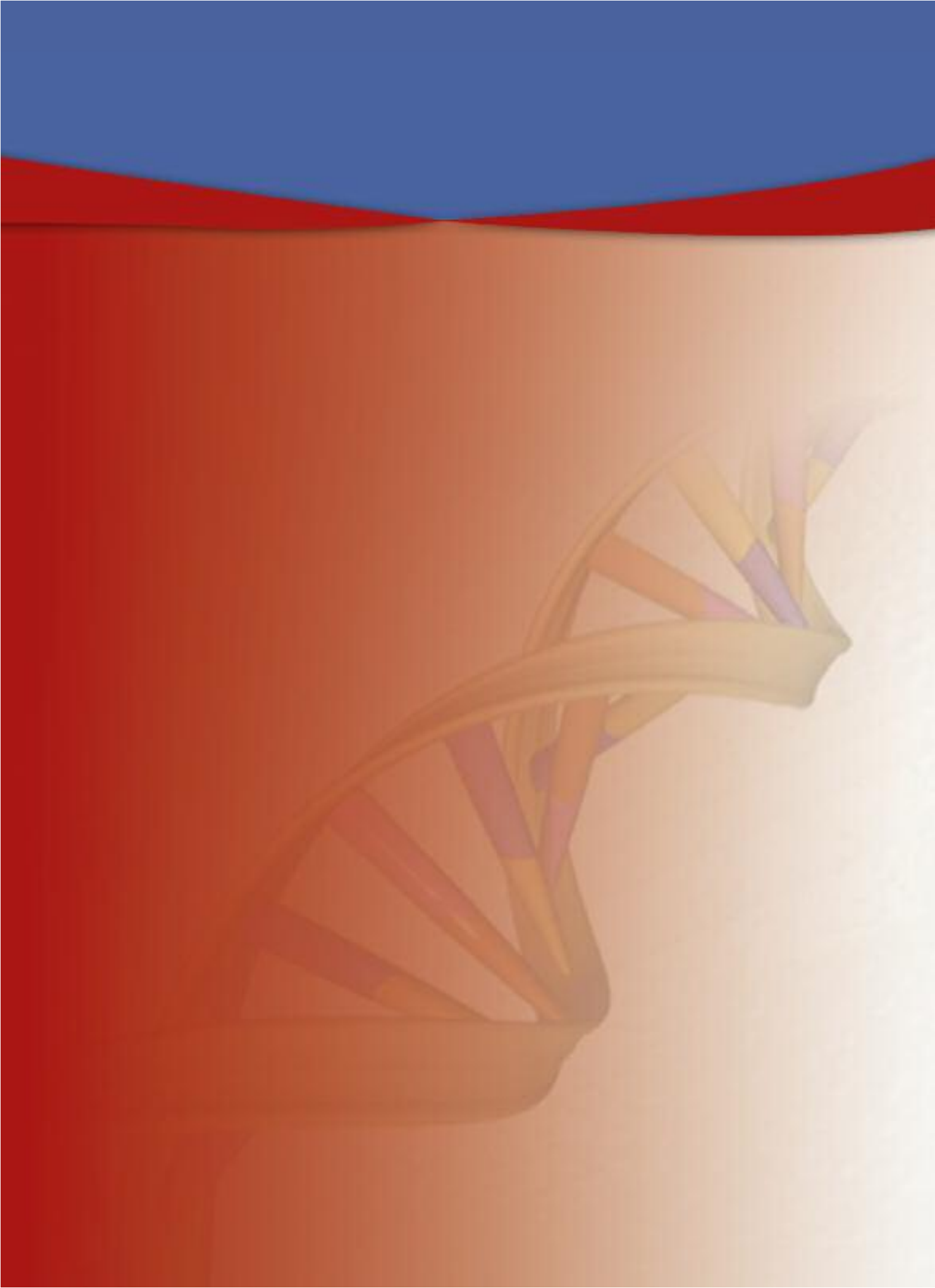
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