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Research activities

Mucoadhesive materials and drug delivery systems

Mucoadhesion is defined as interfacial force interactions between synthetic or natural polymeric materials serving as a dosage form and a mucus layer that covers a mucosal tissue. In the last two decades mucoadhesive polymers have received considerable attention as platforms for controlled delivery due to their ability to prolong the residence time of dosage forms as well as to enhance drug bioavailability. Our current research efforts are focused on evaluation of mucoadhesive properties of various materials and development of systems for transmucosal drug delivery.

Fig.1. Testing mucoadhesive properties of tablets using texture analyser

Recent publications on mucoadhesion and transmucosal drug delivery:

- Kolawole O.M., Lau W.-M., Khutoryanskiy V.V.* Methacrylated chitosan as a polymer with enhanced mucoadhesive properties for transmucosal drug delivery, Int. J. Pharm., 550, 123–129 (2018)
- Ways T.M.M., Lau W.M., Ng K.W., Khutoryanskiy V.V.* Synthesis of thiolated, PEGylated and POZylated silica nanoparticles and evaluation of their retention on rat intestinal mucosa in vitro, Eur. J. Pharm. Sci., 122, 230-238 (2018)
- Ruiz-Rubio L.*, Alonso M.L., Pérez-Álvarez L., Alonso R.M., Vilas J.L., Khutoryanskiy V.V.* Formulation of Carbopol®/poly(2-ethyl-2-oxazoline)s mucoadhesive tablets for buccal delivery of hydrocortisone, Polymers, 10, 175, 1-13 (2018)
- Kaldybekov D.B., Tonglairoum P., Opanasopit P., Khutoryanskiy V.V.* Mucoadhesive maleimide-functionalised liposomes for drug delivery to urinary bladder, Eur. J. Pharm. Sci., 111, 83-90 (2018)
- Cook S.L., Woods S., Methven L.*, Parker J.K., Khutoryanskiy V.V.* Mucoadhesive polysaccharides modulate sodium retention, release and taste perception, Food Chemistry, 240, 482-489 (2018)
- Brannigan R.P., Khutoryanskiy V.V.* Synthesis and evaluation of mucoadhesive acryloyl-quaternized PDMAEMA nanogels for ocular drug delivery, Colloids and Surfaces B: Biointerfaces, 155, 538-543 (2017)
- Tonglairoum P., Brannigan R.P., Opanasopit P., Khutoryanskiy V.V.* Maleimide-bearing nanogels as novel mucoadhesive materials for drug delivery, J. Mater. Chem. B., 4, 6581-6587 (2016)
- Mansfield E.D.H., Sillence K., Hole P., Williams A.C., Khutoryanskiy V.V.* POZylation; a new approach to enhance nanoparticle diffusion through mucosal barriers, *Nanoscale*, 7, 13671-13679 (2015)
- Cook M.T., Schmidt S., Lee E., Samprasit W., Opanasopit P., Khutoryanskiy V.V.* Synthesis of mucoadhesive thiol-bearing microgels from 2-(acetylthio)ethylacrylate and 2-hydroxyethylmethacrylate: novel drug delivery systems for chemotherapeutic agents to the bladder, *J. Mater. Chem. B,* 3, 6599-6604 (2015)

Polymeric hydrogels

Hydrogels are three-dimensionally cross-linked networks of hydrophilic polymers. The unique ability of hydrogels to swell in water and living tissue-like consistency make them significant candidates for developing various biomaterials and dosage forms. The applications of hydrogels in biomedical and pharmaceutical sciences include soft contact lenses, drug delivery systems, and wound dressings. Our research is focused on design of novel hydrogels, characterisation of their structure and properties and application in drug delivery and tissue engineering.

Fig.2. Different hydrogel samples based on copolymers of 2-hydroxyethylmethacrylate – 2-hydroxyethylacrylate

Recent publications on hydrogels:

- Hackl E.V., Khutoryanskiy V.V., Ermolina I.* Hydrogels based on copolymers of 2-hydroxyethylmethacrylate and 2-hydroxyethylacrylate as a delivery system for proteins: Interactions with lysozyme, J. Appl. Polym. Sci., 134, 44768 (2017)
- Caló E., de Barros J.M.S., Ballamy L., Khutoryanskiy V.V.* Poly (vinyl alcohol)-Gantrez® AN cryogels for wound care applications, RSC Advances, 6, 105487 - 105494 (2016)
- Caló E., de Barros J.M.S., Fernández-Gutiérrez M., San Román J., Ballamy L., Khutoryanskiy V.V.* Antimicrobial hydrogels based on autoclaved poly(vinyl alcohol) and poly(methyl vinyl ether-alt-maleic anhydride) mixtures for wound care applications, RSC Advances, 6, 55211-55219 (2016)
- Hackl E.V., Khutoryanskiy V.V., Tiguman G.M.B., Ermolina I.* Evaluation of water properties in HEA-HEMA hydrogels swollen in aqueous-PEG solutions using thermoanalytical techniques, Journal of Thermal Analysis and Calorimetry, 121, 335-345 (2015)
- Cook J.P., Goodall G.W., Khutoryanskaya O.V., Khutoryanskiy V.V. Microwave-Assisted Hydrogel Synthesis: A New Method for Cross-linking Polymers in Aqueous Solutions, *Macromol. Rapid Commun.,* **33**, 332-336 (2012)

Stimuli-responsive polymers and *in situ* gelling systems

Stimuli-responsive polymers are materials that undergo phase transitions in response to small changes in their environment. The environmental stimulation can be achieved by changes in temperature, solution pH, ion concentration, electric field, solvent composition and light.

15 ºC 25 ºC 35 ºC 45 ºC 55 ºC

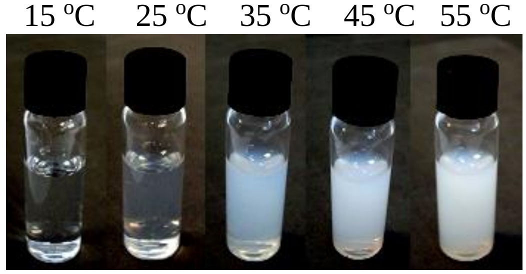


Fig.3. Phase-separation in an aqueous solution of a temperature-responsive polymer

Polymers, which aqueous solutions exhibit sol-gel transitions, triggered by insignificant changes in environment, can be used for development of *in situ* gelling drug delivery systems. These systems exist as free-flowing liquid formulations and undergo phase transition (gelation) upon administration into the human body. Our current research is focused on the development of polymers, which gelation can be triggered by changes in temperature and solution pH.

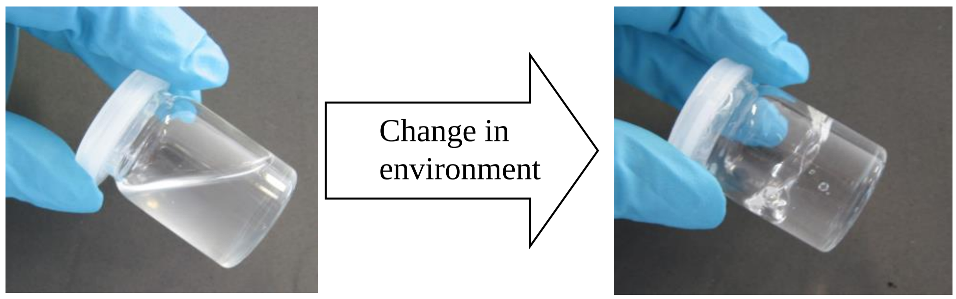


Fig.4. Gelation of aqueous dispersion of a polymer caused by changes of environment

Recent publications on stimuli-responsive polymers:

- Filippov S.K.*, Bogomolova A., Kaberov L., Velychkivska N., Starovoytova L., Cernochova Z., Rogers S.E., Lau W.M., Khutoryanskiy V.V., Cook M.T.* Internal Nanoparticle Structure of Temperature-Responsive Self-Assembled PNIPAM-b-PEG-b-PNIPAM Triblock Copolymers in Aqueous Solutions: NMR, SANS, and Light Scattering Studies, Langmuir, 32 (21), 5314–5323 (2016)
- Al Khateb K., Ozhmukhametova E.K., Mussin M.N., Seilkhanov S.K., Rakhypbekov T.K., Lau W.M.*, Khutoryanskiy V.V.* In situ gelling systems based on Pluronic F127 / Pluronic F68 formulations for ocular drug delivery, Int. J. Pharm., 502, 70–79 (2016)
- Zhunuspayev D.E., Mun G.A., Khutoryanskiy V.V. Temperature-responsive properties and drug solubilization capacity of amphiphilic copolymers based on N-vinylpyrrolidone and vinyl propyl ether, *Langmuir*, **26**, 7590-7597 (2010)
- Khutoryanskaya O.V., Mayeva Z.A., Mun G.A., Khutoryanskiy V.V. Designing temperature-responsive biocompatible copolymers and hydrogels based on 2-hydroxyethyl(meth)acrylates, *Biomacromolecules*, **9**, 3353-3361 (2008).

Nanomaterials for drug delivery

Polymeric micelles and nanoparticles have been extensively used for formulation of poorly-soluble drugs and biopharmaceutical products. We are interested in the development and characterisation of novel polymer colloids by self-assembling of amphiphilic and complex-forming polymers.

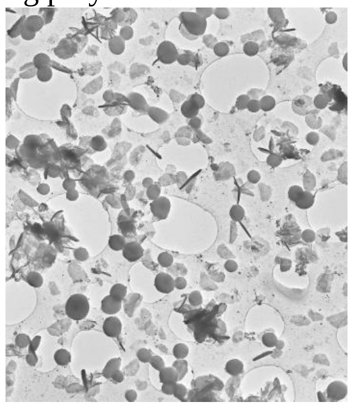


Fig.5. Polymeric nanoparticles formed by complexation between poly(acrylic acid) and methylcellulose in aqueous solutions

We are also interested in the synthesis of novel well-defined nanoparticles for their application in encapsulation technologies and drug delivery. We are looking into the surface-functionalised nanoparticles (thiolated and PEGylated nanoparticles) and how surface functionality affects their interaction with biological tissues and diffusion through various physiological barriers.

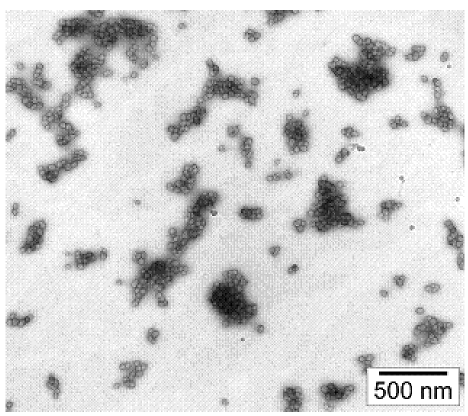


Fig.6. Novel organosilica nanoparticles

Recent publications on nanomaterials:

- Al Mahrooqi J., Mun E.A., Williams A.C., Khutoryanskiy V.V.* Controlling the size of thiolated organosilica nanoparticles, Langmuir, 34 (28), 8347–8354 (2018)
- Serres-Gomez M., González-Gaitano G., Kaldybekov D.B., Mansfield E.D.H., Khutoryanskiy V.V., Isasi J.R., Dreiss C.A.* Supramolecular hybrid structures and gels from host-guest interactions between α-cyclodextrin and PEGylated organosilica nanoparticles, Langmuir, 34 (36), 10591-10602 (2018)
- Mun E.A., Hannell C., Rogers S.E., Hole P., Williams A.C., Khutoryanskiy V.V.* On the role of specific interactions in the diffusion of nanoparticles in aqueous polymer solutions, Langmuir, 30, 308-317 (2014)

- Irmukhametova G.S., Mun G.A., Khutoryanskiy V.V. Thiolated mucoadhesive and PEGylated non-mucoadhesive organosilica nanoparticles from 3-mercaptopropyl-trimethoxysilane, *Langmuir*, **27**, 9551-9556 (2011)
- Irmukhametova G.S., Fraser B., Keddie J.L., Mun G.A., Khutoryanskiy V.V. Hydrogen-Bonding-Driven Self-Assembly of PEGylated Organosilica Nanoparticles with Poly(acrylic acid) in Aqueous Solutions and in Layer-by-Layer Deposition at Solid Surfaces, *Langmuir*, **28**, 299-306 (2012)

Multilayered self-assembly and coatings

Layer-by-layer (LBL) sequential adsorption of polymers on solid surfaces is a simple and versatile technique for producing ultrathin polymeric films and coatings. The LBL approach involves an alternating immersion of solid substrates (planar or spherical surfaces) in solutions of interacting polymers resulting in formation of insoluble multilayered polycomplex film, which thickness may be precisely controlled by a number of deposition cycles. The LBL methodology was demonstrated to be useful for encapsulation of drugs, biomacromolecules and living cells, development of solid state electrolytes, ultrathin hydrogel membranes, and coating of surfaces. We are focusing our current research on developing novel multilayered materials by utilising LBL assembly driven by interpolymer hydrogen bonding.

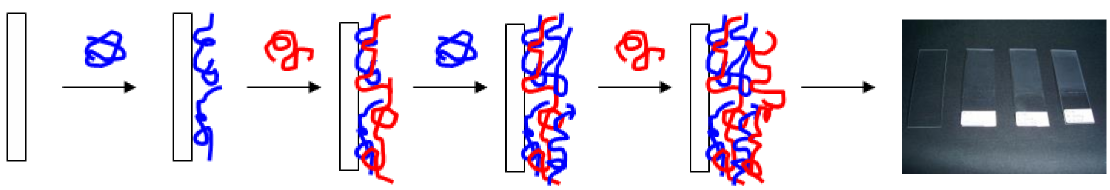


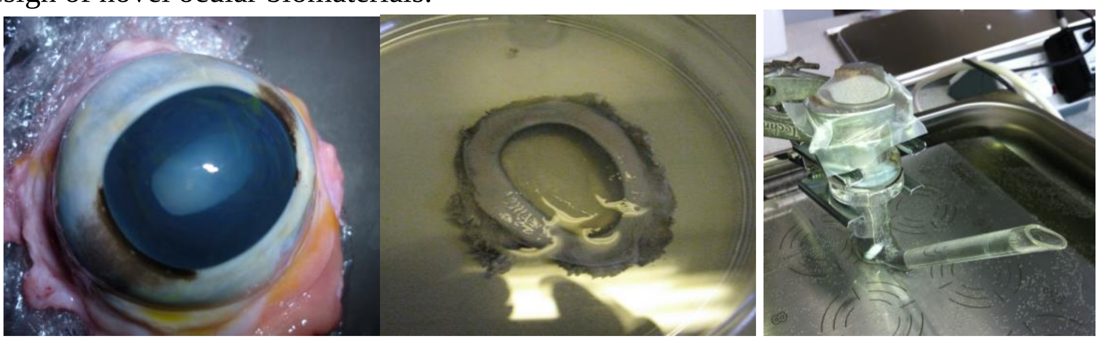
Fig.7. Multilayered self-assembly on the surface of glass-slides

Recent publications on multilayered assembly and coatings:

- Mirgorodskayaa A.B.*, Kushnazarova R.A., Nikitina A.V., Semina I.I., Nizameev I.R., Kadirov M.K., Khutoryanskiy V.V., Zakharova L.Ya., Sinyashin O.G. Polyelectrolyte nanocontainers: controlled binding and release of indomethacin, Journal of Molecular Liquids, 272, 982-989 (2018)
- Bizley S., Williams A.C., Khutoryanskiy V.V. Optimizing Layer-by-Layer Deposition of Interpolymer Complexes on Solid Substrates Using Biacore, *Soft Matter*, **8**, 6782-6787 (2012)
- Khutoryanskaya O.V., Williams A.C., Khutoryanskiy V.V. pH-mediated interactions between poly(acrylic acid) and methylcellulose in the formation of ultrathin multilayered hydrogels and spherical nanoparticles, *Macromolecules,* **40**, 7707-7713 (2007).
- Zhunuspayev D.E., Mun G.A., Hole P., Khutoryanskiy V.V. Solvent effects on the formation of nanoparticles and multilayered coatings based on hydrogen-bonded interpolymer complexes of poly(acrylic acid) with homo- and copolymers of N-vinyl pyrrolidone, *Langmuir*, **24**, 13742–13747 (2008).

Ocular drug delivery and biomaterials

Ocular diseases affect the quality of life of millions of people worldwide. Currently there are about 314 million of visually impaired people with 45 million of them being completely blind. A further growth in the incidence of ophthalmic conditions is expected with the aging population. The leading causes of chronic blindness include cataract, glaucoma, age-related macular degeneration, corneal opacities, diabetic retinopathy, trachoma, and eye conditions in children. The eye is becoming increasingly important target for drug delivery with an urgent need in further advances in ocular therapy. Our research efforts are focused on novel drug delivery systems for ocular drug delivery, development of strategies to enhance drug permeability through the cornea and design of novel ocular biomaterials.



(a) (b) (c)

Fig.8. Bovine eye (a), bovine cornea (b) and diffusion Franz cell experiments with bovine cornea to assess drug permeability (c)

Recent publications on ocular drug delivery and biomaterials

- Morrison P.W.J., Porfiryeva N.N., Chahal S., Salakhov I.A., Lacourt C., Semina I.I., Moustafine R.I., Khutoryanskiy V.V.* Crown Ethers: novel permeability enhancers for ocular drug delivery? Mol. Pharm., 14, 3528–3538 (2017)
- Kandzija N., Khutoryanskiy V.V.* Delivery of riboflavin-5'-monophosphate into the cornea: can liposomes provide any enhancement effects? J. Pharm. Sci., 106, 3041–3049 (2017)
- Rodriguez, Vázquez J.A., Pastrana L., Khutoryanskiy V.V.* Enhancement and inhibition effects on the corneal permeability of timolol maleate: Polymers, cyclodextrins and chelating agents, Int. J. Pharm., 529, 168–177 (2017)
- Brannigan R.P., Khutoryanskiy V.V.* Synthesis and evaluation of mucoadhesive acryloyl-quaternized PDMAEMA nanogels for ocular drug delivery, Colloids and Surfaces B: Biointerfaces, 155, 538-543 (2017)
- Al Khateb K., Ozhmukhametova E.K., Mussin M.N., Seilkhanov S.K., Rakhypbekov T.K., Lau W.M.*, Khutoryanskiy V.V.* In situ gelling systems based on Pluronic F127 / Pluronic F68 formulations for ocular drug delivery, Int. J. Pharm., 502, 70–79 (2016)
- Mun E.A., Morrison P.W.J., Williams A.C., Khutoryanskiy V.V.* On the barrier properties of the cornea: A microscopy study of the penetration of fluorescently labelled nanoparticles, polymers, and sodium fluorescein, Mol. Pharm., 11, 3556-3564 (2014)
- Morrison P.W. and Khutoryanskiy V.V.* Enhancement in Corneal Permeability of Riboflavin Using Calcium Sequestering Compounds, Int. J. Pharm., 472, 56-64 (2014)

Encapsulation of living cells into polymer matrices

Incorporation of living cells into the polymeric matrices is of significant interest of researchers because of the number of potential applications. Encapsulation of probiotic bacteria can improve their storage stability and survival during the passage through the gastrointestinal tract. Polymers can also serve as scaffolds for promoting stem cell storage, growth and differentiation towards the formation of tissues that could be used in regenerative medicine. In collaboration with food researchers and cell biologists we are developing novel approaches for microencapsulation of probitic bacteria and materials used as substrates for stem cells transportation, storage and delivery.

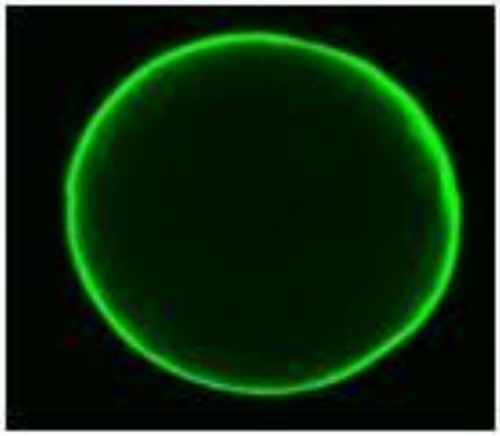


Fig.9. Alginate microcapsule coated with fluorescently-labelled chitosan

Recent publications on encapsulation of living cells

- Albadran H.A., Chatzifragkou A., Khutoryanskiy V.V.*, Charalampopoulos D.* Development of surfactant-coated alginate capsules containing Lactobacillus plantarum, Food Hydrocolloids, 82, 490-499 (2018)
- Bepeyeva A., de Barros J.M.S., Albadran H., Kakimov A.K., Kakimova Zh.Kh., Charalampopoulos D., Khutoryanskiy V.V.* Encapsulation of Lactobacillus casei into calcium pectinate-chitosan beads for enteric delivery, J. Food Sci., 82, 2954–2959 (2017)
- Albadran H., Chatzifragkou A., Khutoryanskiy V.V.*, Charalampopoulos D.* Stability of probiotic Lactobacillus plantarum in dry microcapsules under accelerated storage conditions, Food Research International, 74, 208-216 (2015)
- de Barros J.M.S., Scherer T., Charalampopoulos D., Khutoryanskiy V.V. Edwards A.D.* A Laminated Polymer Film Formulation for Enteric Delivery of Live Vaccine and Probiotic Bacteria, J. Pharm. Sci., 103, 2022–2032 (2014)
- Cook M.T., Tzortsis G., Charalampopoulos D.*, Khutoryanskiy V.V.* Microencapsulation of a synbiotic into PLGA/alginate multiparticulate gels, Int. J. Pharm., 466 (1), 400-408 (2014)
- Cook M.T., Tzortzis G., Charalampopoulos D., Khutoryanskiy V.V. Microencapsulation of probiotics for gastrointestinal delivery, *Journal of Controlled Release*, **162**, *56-67* (2012)
- Cook M., Tzortzis G., Charalampopoulos D., Khutoryanskiy V.V. Production and Evaluation of Dry Alginate - Chitosan Microcapsules as an Enteric Delivery Vehicle for Probiotic Bacteria, *Biomacromolecules*, **12**, 2834–2840 (2011)