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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 investigation of molecular interactions of these materials with mucins.

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

Recent publications on mucoadhesion and mucoadhesive polymers:

- Dubolazov A.V., Nurkeeva Z.S., Mun G.A., Khutoryanskiy V.V. Design of mucoadhesive films based on poly(acrylic acid) and hydroxypropyl cellulose, *Biomacromolecules*, **7,** 1637-1643 (2006).
- Fefelova N.A., Nurkeeva Z.S., Mun G.A., Khutoryanskiy V.V. Mucoadhesive interactions of amphiphilic cationic copolymers based on [2-(methacryloyloxy)ethyl]trimethylammonium chloride, *Int. J. Pharm.*, **339**, 25-32 (2007).
- Luo K., Yin J., Khutoryanskaya O.V., Khutoryanskiy V.V. Mucoadhesive and elastic films based on blends of chitosan and hydroxyethylcellulose, *Macromol. Biosci.*, ***8,*** 184 – 192 (2008)
- Sogias I.A., Williams A.C., Khutoryanskiy V.V. Why is chitosan mucoadhesive? *Biomacromolecules*, **9**, 1837-1842 (2008)
- Khutoryanskaya O.V., Potgieter M., Khutoryanskiy V.V. Multilayered hydrogel coatings covalently-linked to glass surfaces showing a potential to mimic mucosal tissues, *Soft Matter*, **6,** 551-557 (2010)
- Khutoryanskiy V.V. Advanced in mucoadhesion and mucoadhesive polymers (feature article), *Macromol. Biosci.* 11, 748-764 (2011)
- 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)
- Hall D.J., Khutoryanskaya O.V., Khutoryanskiy V.V. Developing synthetic mucosa-mimetic hydrogels to replace animal experimentation in characterisation of mucoadhesive drug delivery systems, *Soft Matter,* **7,** 9620-9623 (2011)
- Cave R.A., Cook J.P., Connon C.J., Khutoryanskiy V.V. A flow system for the on-line quantitative measurement of the retention of dosage forms on biological surfaces using spectroscopy and image analysis, *Int. J. Pharm.*, **428**, 96-102 (2012)
- Sogias I.A., Williams A.C., Khutoryanskiy V.V. Chitosan-based mucoadhesive tablets for oral delivery of ibuprofen, *Int. J. Pharm.*, accepted (2012)

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:

- 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).
- 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).
- Khutoryanskiy V.V., Khutoryanskaya O.V. A basic guide to hydrogels, *United Kingdom and Ireland Controlled Release Society (UKICRS) Newsletter*, **14**, 26-30 (2009)
- Khutoryanskaya O.V., Potgieter M., Khutoryanskiy V.V. Multilayered hydrogel coatings covalently-linked to glass surfaces showing a potential to mimic mucosal tissues, *Soft Matter,* **6,** 551-557 (2010)
- Hall D.J., Khutoryanskaya O.V., Khutoryanskiy V.V. Developing synthetic mucosa-mimetic hydrogels to replace animal experimentation in characterisation of mucoadhesive drug delivery systems, *Soft Matter,* **7,** 9620-9623 (2011)
- Mi S., Khutoryanskiy V.V., Jones R.R., Zhu X., Hamley I.W., Connon C.J. Photochemical cross-linking of plastically compressed collagen gel produces an optimal scaffold for corneal tissue engineering, *Journal of Biomedical Materials Research: Part A*, 99A, 1–8 (2011)
- Wright B., Cave R.A., Cook J.P., Khutoryanskiy V.V., Mi S., Chen B., Leyland M., Connon C.J. Enhanced viability of corneal epithelial cells for efficient transport/storage using a structurally modified calcium alginate hydrogel, *Regen. Med*, **7**, 295-307 (2012)
- 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 ^{o}C 25 ^{o}C 35 ^{o}C 45 ^{o}C 55 ^{o}C

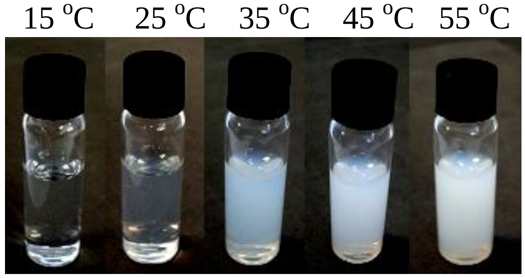


Fig.3. Phase-separation in an aqueous solution of a temperature-responsive polymer

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.

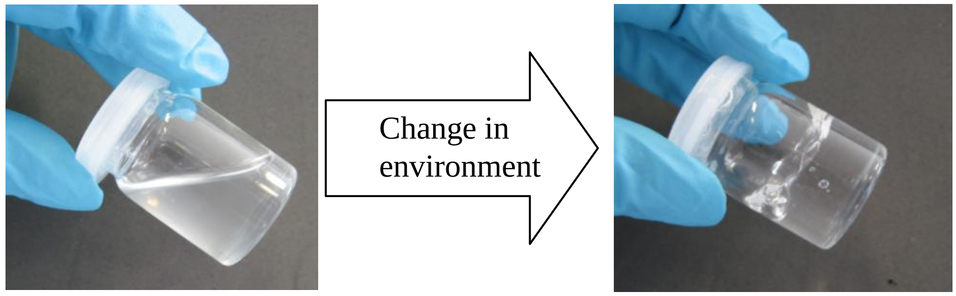


Fig.4. Gelation of aqueous dispersion of a polymer caused by changes of environment

Recent publications on stimuli-responsive polymers:

- Mun G.A, Nurkeeva Z.S., Beissegul A.B., Dubolazov A.V., Urkimbaeva P.I., Park K., Khutoryanskiy V.V. Temperature-responsive water-soluble copolymers based on 2-hydroxyethyl acrylate and butyl acrylate, *Macromol. Chem. Phys.*, **208**, 979-987 (2007)
- 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).
- Sogias I.A., Khutoryanskiy V.V., Williams A.C. Exploring the factors affecting the solubility of chitosan in water, *Macromol. Chem. Phys.*, macp.200900385 (2010)
- 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)

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.

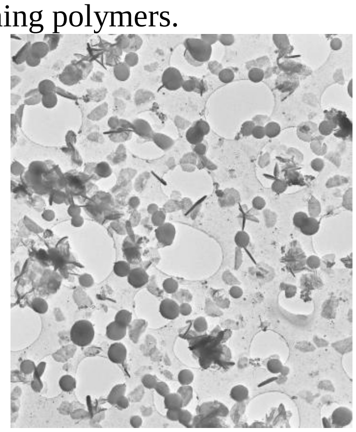


Fig.5. Polymeric nanoparticles formed by complexation between poly(acrylic acid) and methylcellulose in aqueous solutions

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.

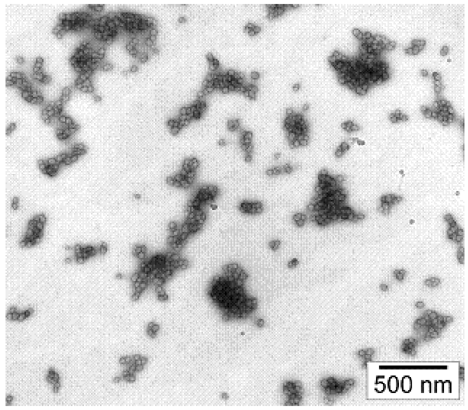


Fig.6. Novel organosilica nanoparticles

Recent publications on nanomaterials:

- Qu X., Khutoryanskiy V.V., Stewart A., Rahman S., Sternberg B., Dufes C., McCarthy D., Wilson C.G., Lyons R., Carter C., Schatzlein A., Uchegbu I.F**.** Carbohydrate-based micelle clusters which enhance hydrophobic drug bioavailability by up to 1 order of magnitude, *Biomacromolecules,* **7**, 3452-3459 (2006)
- 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).
- Khutoryanskiy V.V., Tirelli N. Oxidation-responsiveness of nanomaterials for targeting inflammatory reactions, *Pure & Applied Chemistry*, **80**, 1703-1718 (2008)
- 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).
- Al-Saadi A., Yu C.H., Khutoryanskiy V.V., Shih S.-J., Crossley A., Tsang S.C. Layer-by-layer electrostatic entrapment of protein molecules on superparamagnetic nanoparticle: new strategy to enhance adsorption capacity and maintain biological activity, *J. Phys. Chem. C.*, **113**, 15260-15265 (2009)
- 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)
- 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.

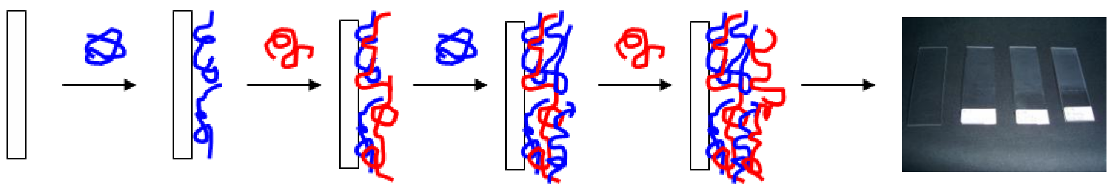


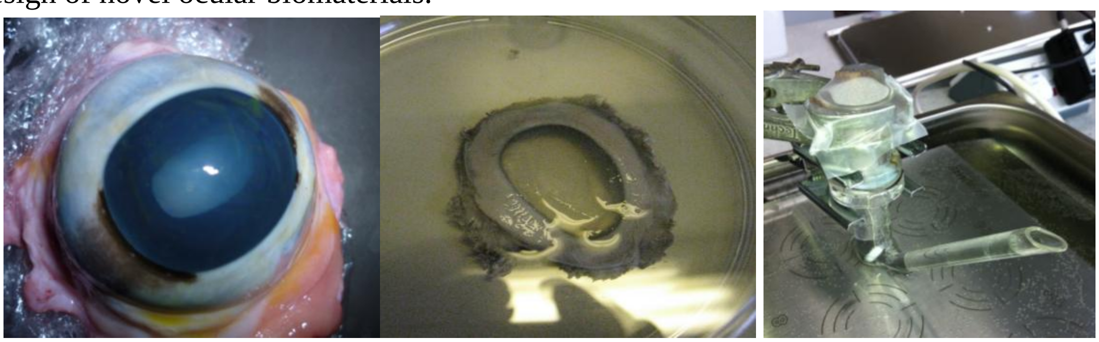
Fig.7. Multilayered self-assembly on the surface of glass-slides

Recent publications on multilayered assembly and coatings:

- 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).
- Al-Saadi A., Yu C.H., Khutoryanskiy V.V., Shih S.-J., Crossley A., Tsang S.C. Layer-by-layer electrostatic entrapment of protein molecules on superparamagnetic nanoparticle: new strategy to enhance adsorption capacity and maintain biological activity, *J. Phys. Chem. C.*, **113**, 15260-15265 (2009)
- Khutoryanskaya O.V., Potgieter M., Khutoryanskiy V.V. Multilayered hydrogel coatings covalently-linked to glass surfaces showing a potential to mimic mucosal tissues, *Soft Matter*, **6,** 551-557 (2010)
- 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)
- 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)

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

- Qu X., Khutoryanskiy V.V., Stewart A., Rahman S., Sternberg B., Dufes C., McCarthy D., Wilson C.G., Lyons R., Carter C., Schatzlein A., Uchegbu I.F**.** Carbohydrate-based micelle clusters which enhance hydrophobic drug bioavailability by up to 1 order of magnitude, *Biomacromolecules*, **7**, 3452-3459 (2006)
- 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)
- Mi S., Khutoryanskiy V.V., Jones R.R., Zhu X., Hamley I.W., Connon C.J. Photochemical cross-linking of plastically compressed collagen gel produces an optimal scaffold for corneal tissue engineering, *Journal of Biomedical Materials Research: Part A*, 99A, 1–8 (2011)
- Wright B., Cave R.A., Cook J.P., Khutoryanskiy V.V., Mi S., Chen B., Leyland M., Connon C.J. Enhanced viability of corneal epithelial cells for efficient transport/storage using a structurally modified calcium alginate hydrogel, *Regen. Med,* **7**, 295-307 (2012)
- Cave R.A., Cook J.P., Connon C.J., Khutoryanskiy V.V. A flow system for the on-line quantitative measurement of the retention of dosage forms on biological surfaces using spectroscopy and image analysis, *Int. J. Pharm.,* **428**, 96-102 (2012)

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.

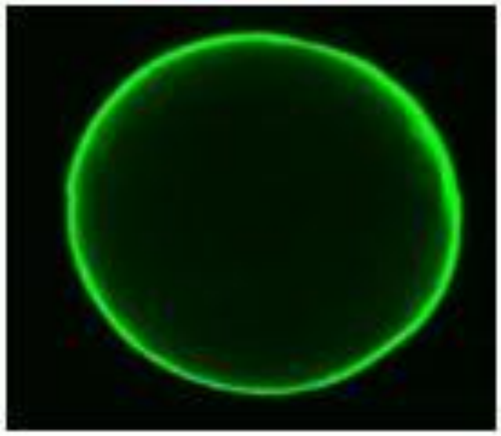


Fig.9. Alginate microcapsule coated with fluorescently-labelled chitosan

Recent publications on encapsulation of living cells

1. 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)
2. Wright B., Cave R.A., Cook J.P., Khutoryanskiy V.V., Mi S., Chen B., Leyland M., Connon C.J. Enhanced viability of corneal epithelial cells for efficient transport/storage using a structurally modified calcium alginate hydrogel, *Regen. Med*, **7**, 295-307 (2012)
3. Cook M.T., Tzortzis G., Charalampopoulos D., Khutoryanskiy V.V. Microencapsulation of probiotics for gastrointestinal delivery, *Journal of Controlled Release*, **162**, *56-67* (2012)
4. Nualkaekul S., Lenton D., Cook M.T., Khutoryanskiy V.V., Charalampopoulos D. Chitosan coated alginate beads for the survival of microencapsulated Lactobacillus plantarum in pomegranate juice, *Carbohydrate Polymers*, CARBPOL-D-12-00907R2, *accepted* (2012)

Cationic polymers for gene delivery

Many human diseases have a genetic origin and replacing defective genes with healthy substitutes offers an excellent approach for treatment. However the possibility of using DNA as a drug is still quite challenging because gene expression occurs only when DNA is transported inside the cell nucleus of the target cells. Cationic polymers can bind negatively charged DNA electrostatically and form compact particles known as *polyplexes*. Within the polyplex particles, DNA is protected from enzymatic degradation and can migrate into the cell nucleus. Our research efforts in this direction are concentrated on chemical modification of commercially-available and synthesis of novel cationic polymers and evaluation of their potential as vectors for gene delivery.

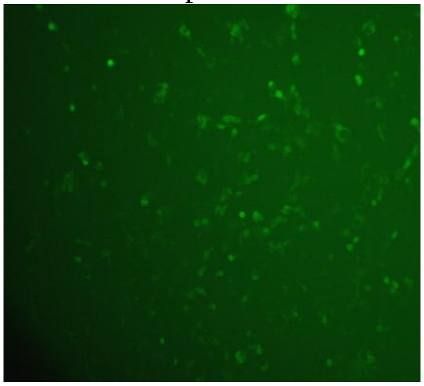


Fig.10. Fluorescence of cells transfected with polyplexes formed by polyethyleneimine and GFP-expressing DNA plasmid.

Recent publications on cationic polymers for gene delivery:

- Aravindan L., Bicknell K.A., Brooks G., Khutoryanskiy V.V., Williams A.C.* Effect of acyl chain length on transfection efficiency and toxicity of polyethylenimine, *Int. J. Pharm.,* **378**, 201-210 (2009)

Alternatives to animal experimentation

Currently approximately 2.7 million animals are used in scientific procedures in the UK each year (Home Office data), under the regulation of The Animals (Scientific Procedures) Act 1986. According to this Act, the development of alternatives which *Replace* animal use, *Reduce* the number of animals used, or *Refine* the procedures involved to minimise suffering (3Rs principle) is an urgent need.

We are interested in development and evaluation of animal alternative approaches to test drug delivery systems. In particular, we are developing novel materials to mimic the properties of mucosal membranes which can be used as substrates for examining mucoadhesive properties of new polymeric dosage forms in place of animal tissues. Additionally, we apply the methodology reported by Adriaens et al (*Pharm. Res.,* 1999, 16, 1240-1244; *Pharm. Res.,* 2001, 18, 937-942) on the use of terrestrial slugs as "lower" organisms in assessment of biocompatibility of chemicals.

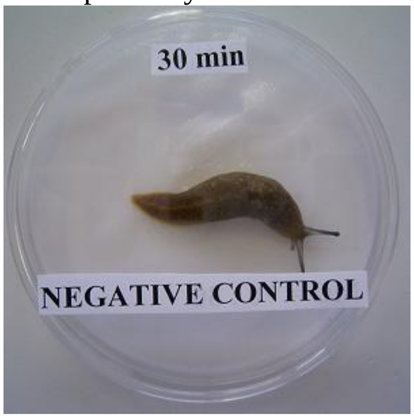


Fig.11. Slug *Limax flavus* in experiment

Recent publications on applications of 3Rs principles

- 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).
- Khutoryanskaya O.V., Potgieter M., Khutoryanskiy V.V. Multilayered hydrogel coatings covalently-linked to glass surfaces showing a potential to mimic mucosal tissues, *Soft Matter*, **6,** 551-557 (2010)
- Hall D.J., Khutoryanskaya O.V., Khutoryanskiy V.V.* Developing synthetic mucosa-mimetic hydrogels to replace animal experimentation in characterisation of mucoadhesive drug delivery systems, *Soft Matter,* **7,** 9620-9623 (2011)