

# **XVIII INTERNATIONAL CONFERENCE ON SCIENCE AND TECHNOLOGY RUSSIA-KOREA-CIS**

**Polymer hydrogels: radiation synthesis,  
properties, the prospects of application in  
medicine»**

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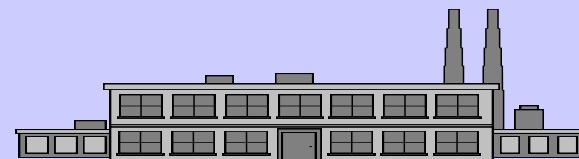
***August 26-28, 2018***

**This report presents the data obtained in recent years by our research group at Kazakh National University in the field of synthesis and characterization of water-swelling polymers (hydrogel) for biomedical application.**

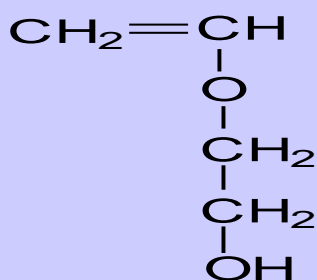
**In the research we use various monomers, including hydroxyl- and amino-containing vinyl ethers - vinyl ether of ethyleneglycol (VEEG), vinyl ether of diethyleneglycol (VEDEG), vinyl ether of monoethanolamine (VEMEA). All these monomers are produced in Kazakhstan in industrial scale.**

# Production of vinyl ethers

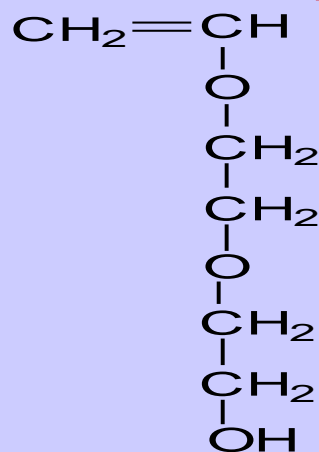
Vinyl ethers are commercially produced in Kazakhstan by the following procedure:



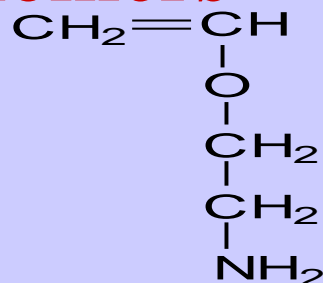
## Monomers



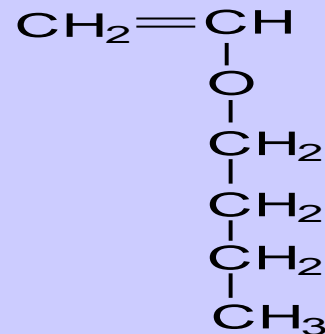
VEEG



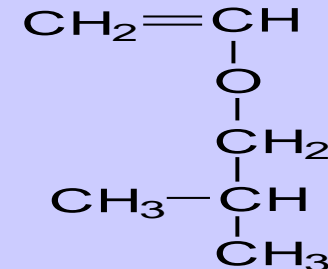
VEDEG



VEMEA



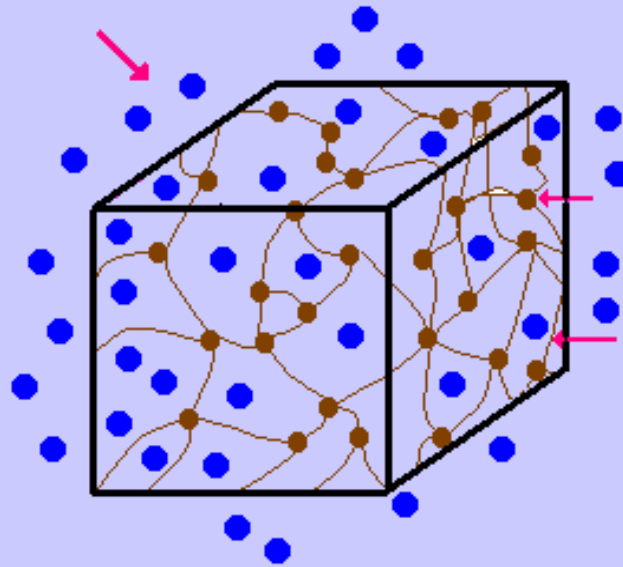
VBE



VIBE

# Schematic representation of polymer hydrogel

water  
molecules



cross-link

polymer  
chain

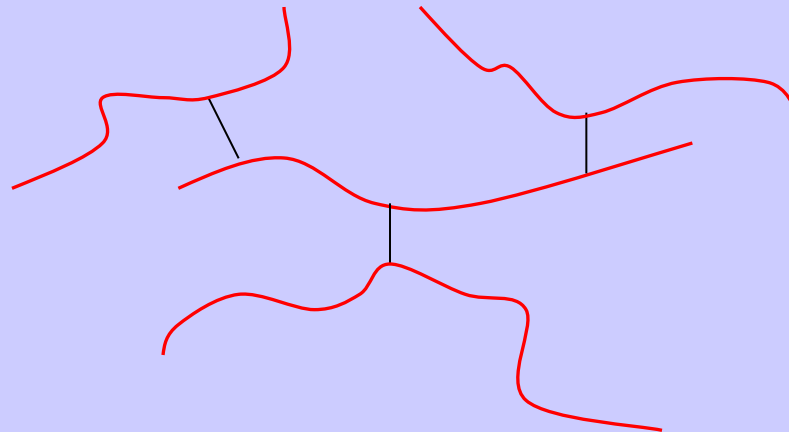
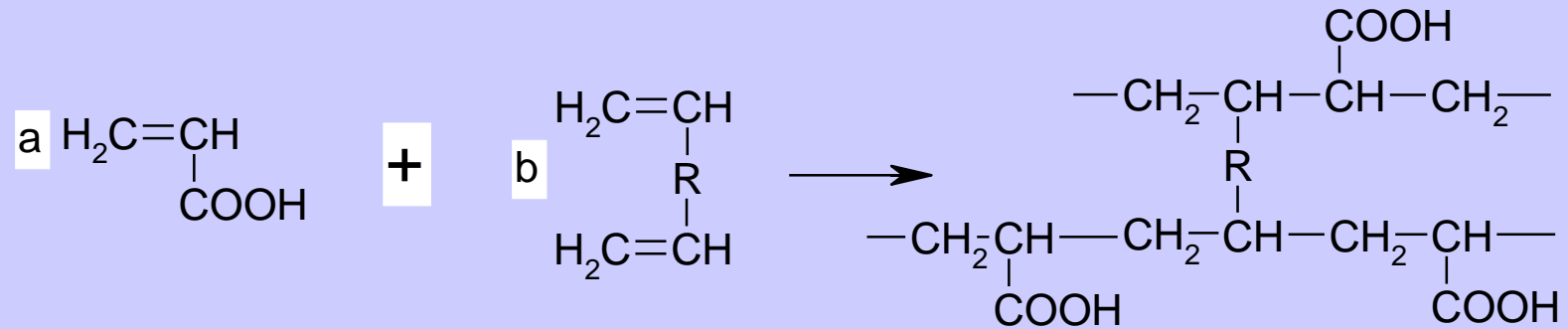
Hydrogels are two- or multicomponent systems consisting of three-dimensional network of polymer chains and water that fills the space between macro chains.

# Chemical and physical hydrogels

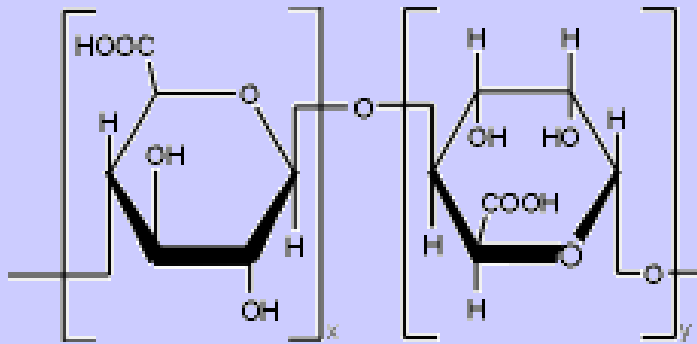
- **Chemical gels (type I gels)** are covalently cross-linked macromolecules. Their cross-linking is irreversible.
- **Physical gels (type II gels)** are macromolecules, cross-linked through physical interactions such as electrostatic attraction forces, hydrogen bonding or hydrophobic interactions. These gels are reversible, i.e. can be dissolved upon heating or cooling.

# Example of chemical gels

Acrylic acid copolymerised with some bifunctional monomer forms chemically cross-linked gel:



# Example of physical gels



Alginic acid

Sodium alginate + Calcium ions  
(water-soluble)



Calcium alginate  
(water-insoluble)



Calcium alginate beads

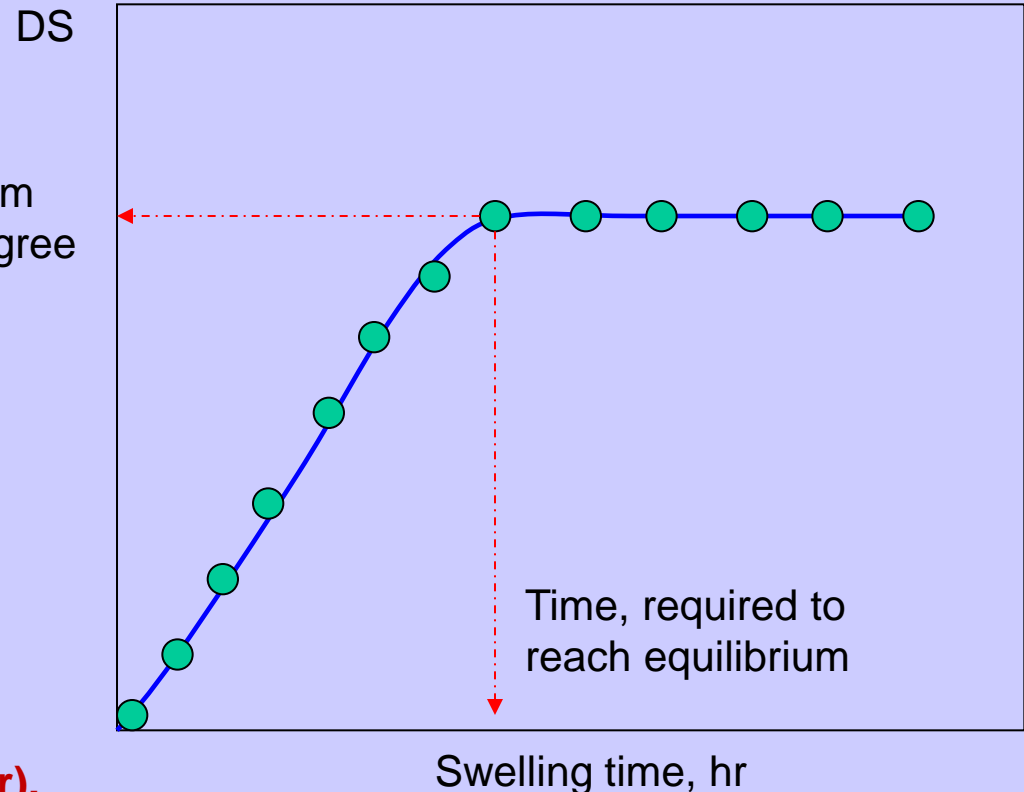


**Algisite\* M** Calcium Alginate Dressing

# Swelling of hydrogels

$$\text{Degree of swelling (DS)} = (m_{\text{swollen sample}} - m_{\text{dry sample}}) / m_{\text{dry sample}}$$

## Kinetics of swelling

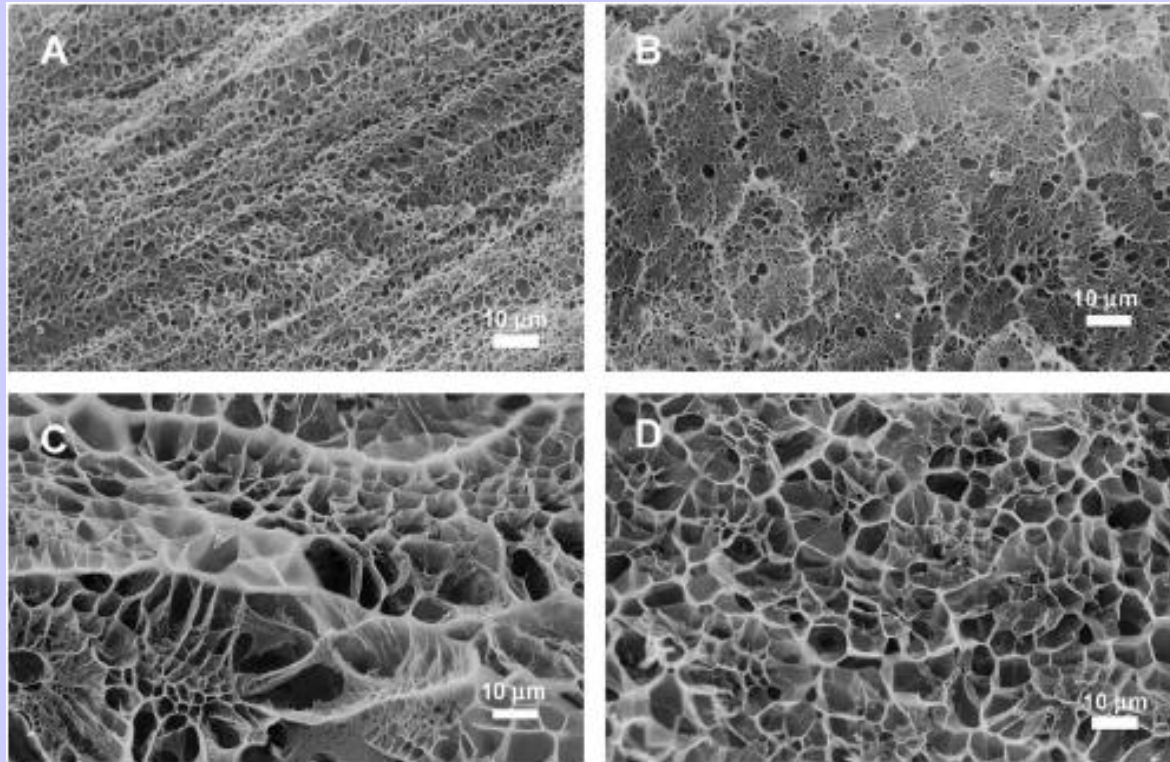


Some hydrogels can have equilibrium swelling degree up to 2000, which means that 2000 g of water (2 L) is absorbed by 1 g of dry polymer....

**Hydrogels are retaining possibly huge volumes of water in the swollen state (up to 10000 g water per 1 g of polymer).**



# Porous structure of hydrogels



J. Maia et al., Polymer 46, 9604–9614 (2005)

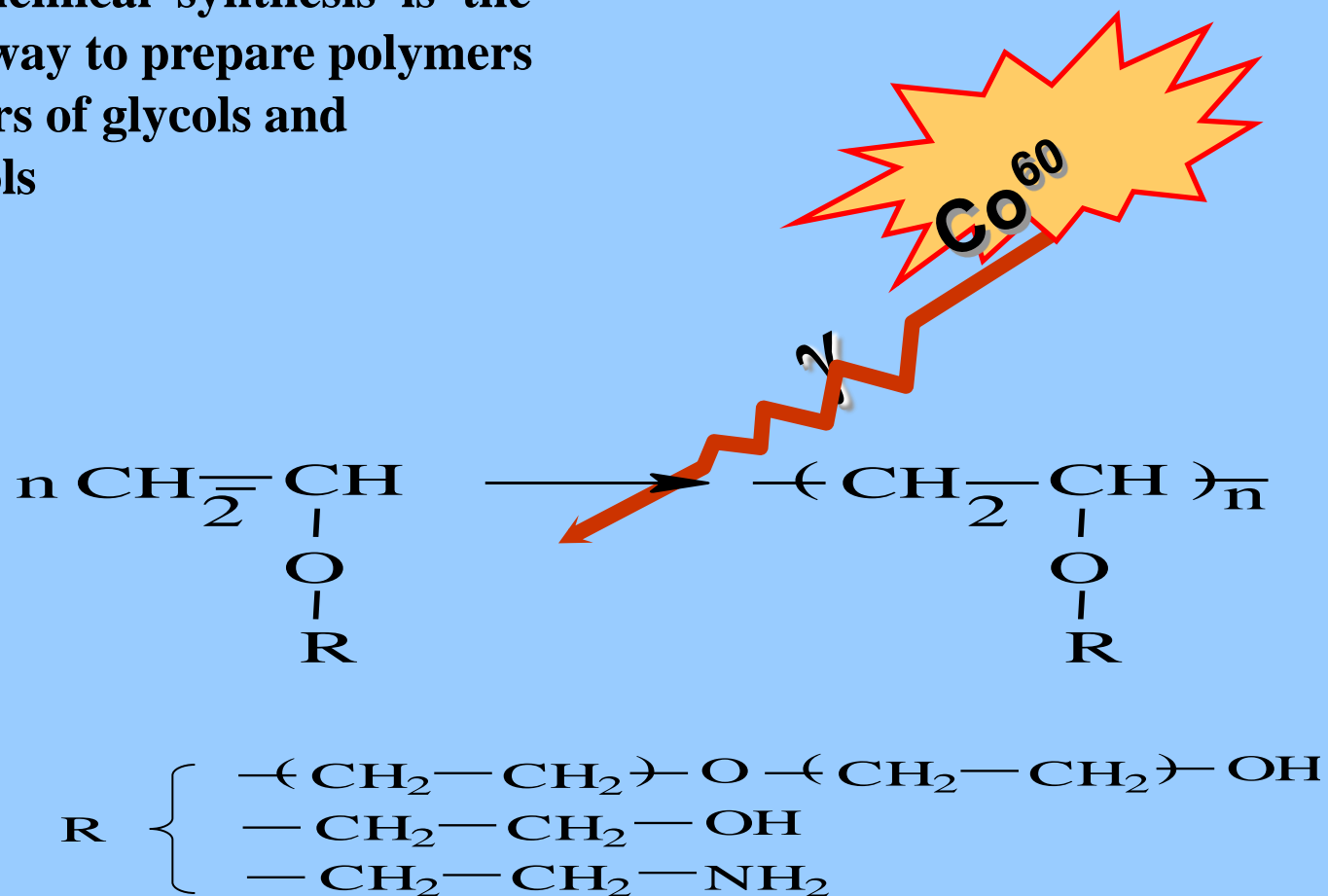
**It is known that vinyl alkyl ethers are readily polymerized by cationic mechanism. Unlike vinyl alkyl ethers the functional vinyl ethers of glycols and aminoalcohols do not polymerized by cationic mechanism. This is connected with the formation of acetals or stable complexes of ammonium type in the presence of cationic polymerization catalysts. The use of radical polymerization initiators results in the obtaining of oligomers only. Thus, in reactions of radical copolymerization the vinyl ethers show very low activity.**

**In order to study the reasons of this low activity we have used the ESR method with a spin-trap. This method allows obtaining the direct quantitative information about mechanism and kinetics of different radical processes, including radical polymerization. The obtained results allows suppose the main reason of vinyl ethers low activity in radical polymerization is their electron-donating properties or very high electron-density of their vinyl binding.**

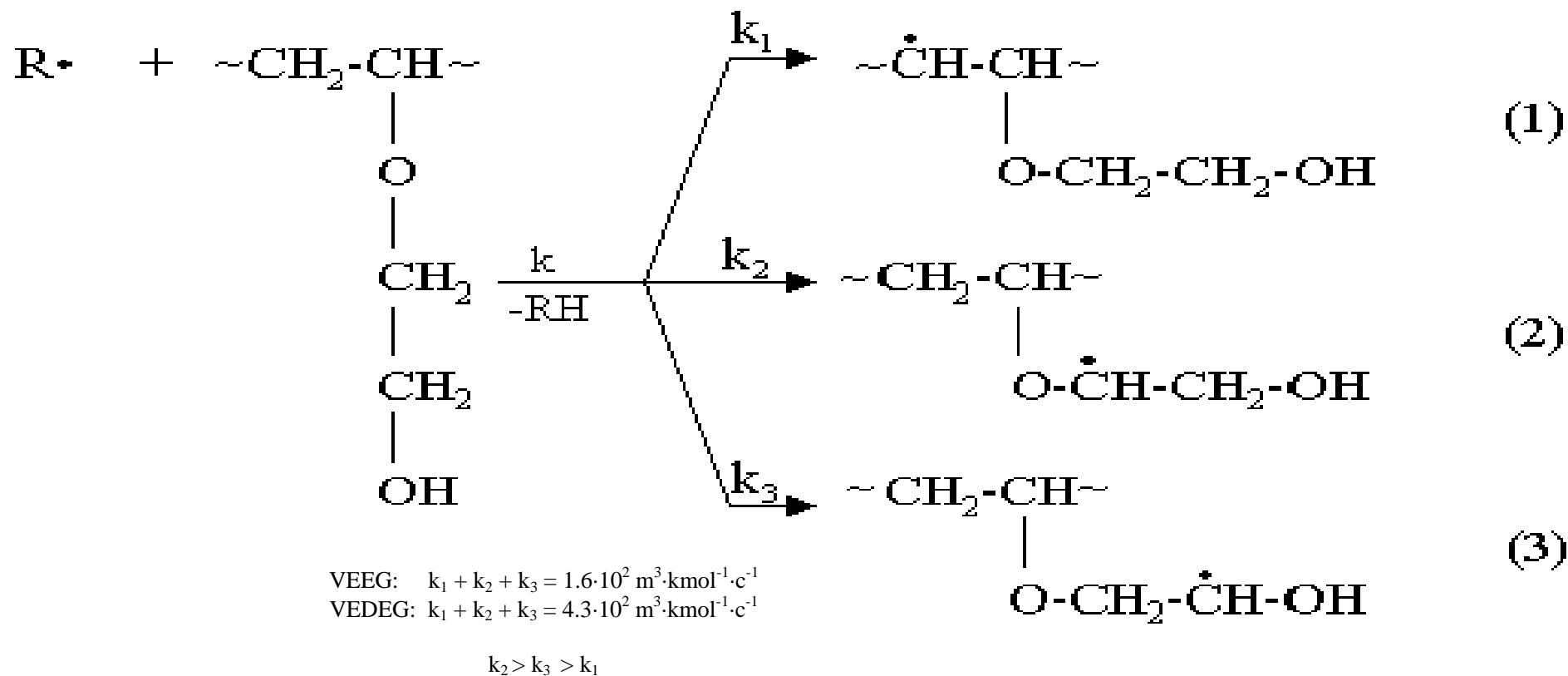
**The further research indicated that the method of radiation polymerization could be successfully used for preparation of polymers based on these low active monomers.**

## Radiation-chemical synthesis of polymers of vinyl ethers

Radiation-chemical synthesis is the perspective way to prepare polymers of vinyl ethers of glycols and aminoalcohols

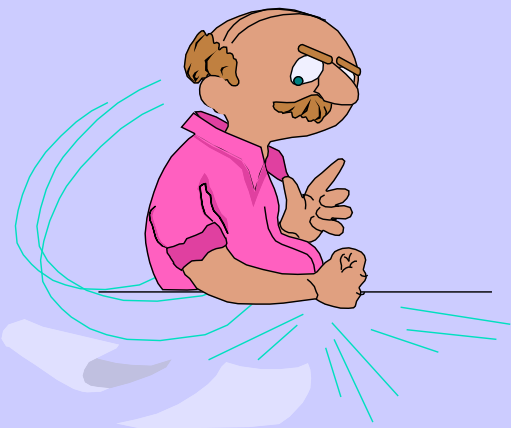


# Mechanism of branched and network structure formation of poly(vinyl ethers of glycols) under $\gamma$ -irradiation



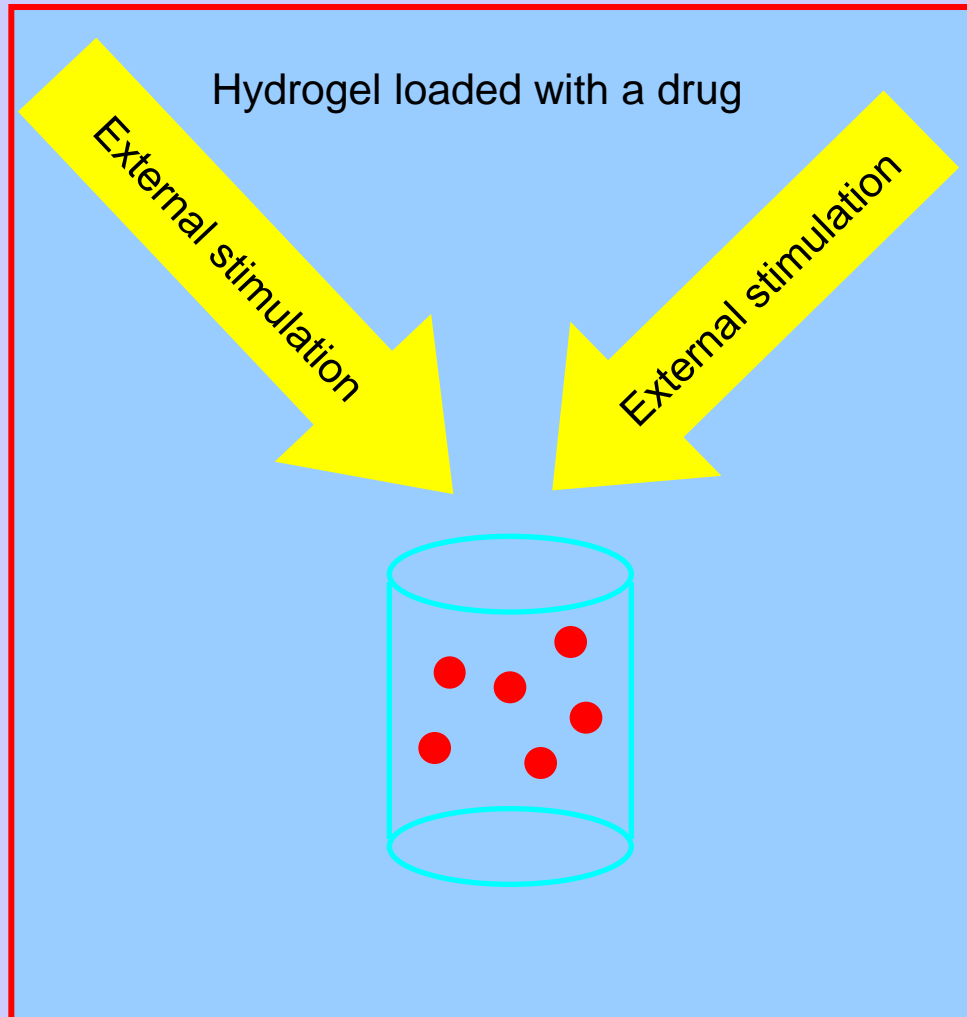
The growth of molecular weight in radiation polymerization of VEEG with increase of absorbed dose and formation of three-dimensional polymeric structure are caused by the branching processes due to elimination of H-atom from  $\text{CH}_2$  and OH groups in side chains of macromolecules as a result of the chain transfer to a polymer.

**The ability of polymer gels to undergo substantial swelling and collapse, as a function of their environment is one of the most remarkable properties of these materials. By this reason such polymer hydrogels belong to so-called “intelligent”, “smart” or stimuli-responsive materials. The phenomenon of gel volume transitions, which can be induced by temperature, pH, ionic environment and electric fields, has prompted researchers to investigate gels as potential sensors, force actuators, controllable membranes for separations, and modulators for delivery of drugs and other molecules.**



**One of the most perspective applications of stimuli-responsive hydrogels is the designing of controlled drug delivery devices for medicine. In particular, so-called thermo-responsive hydrogels, which undergo a phase transition in an aqueous environment induced by a change in temperature, are the most interesting class of stimuli-responsive polymers.**

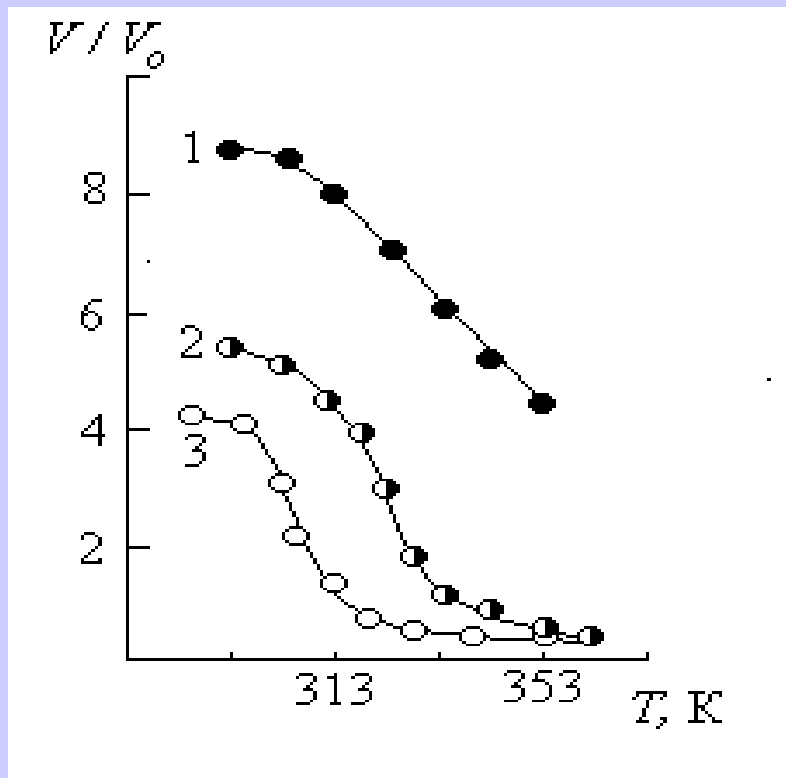
# Stimuli-responsive hydrogels



- Stimuli
- Temperature
- pH and ionic strength
- Electric field
- Light
- Presence of different substances

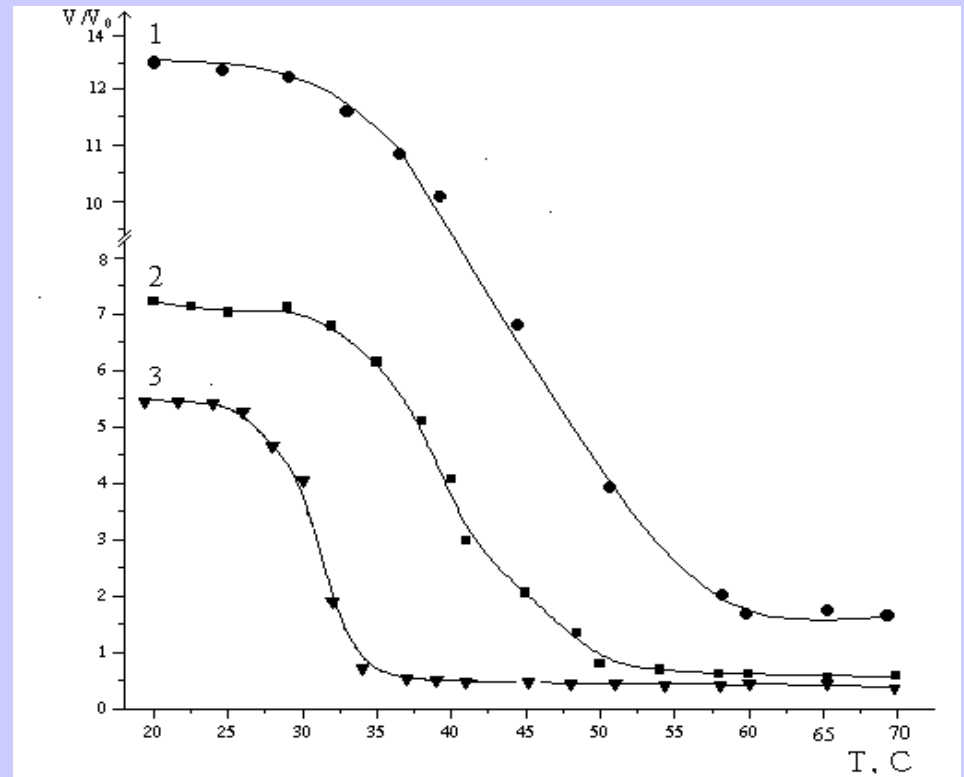


The hydrogels were obtained by gamma-radiation polymerization of VEEG with VBE, NIPAAM and HEMA in the presence of divinyl ether of diethyleneglycol as a crosslinking agent. These hydrogels undergo volume phase transition upon increase in temperature. The transition point can be easily regulated by changing the copolymers composition (fig.3, 4).



**Fig.3. Swelling behavior of VEEG-VBE depending on temperature.**

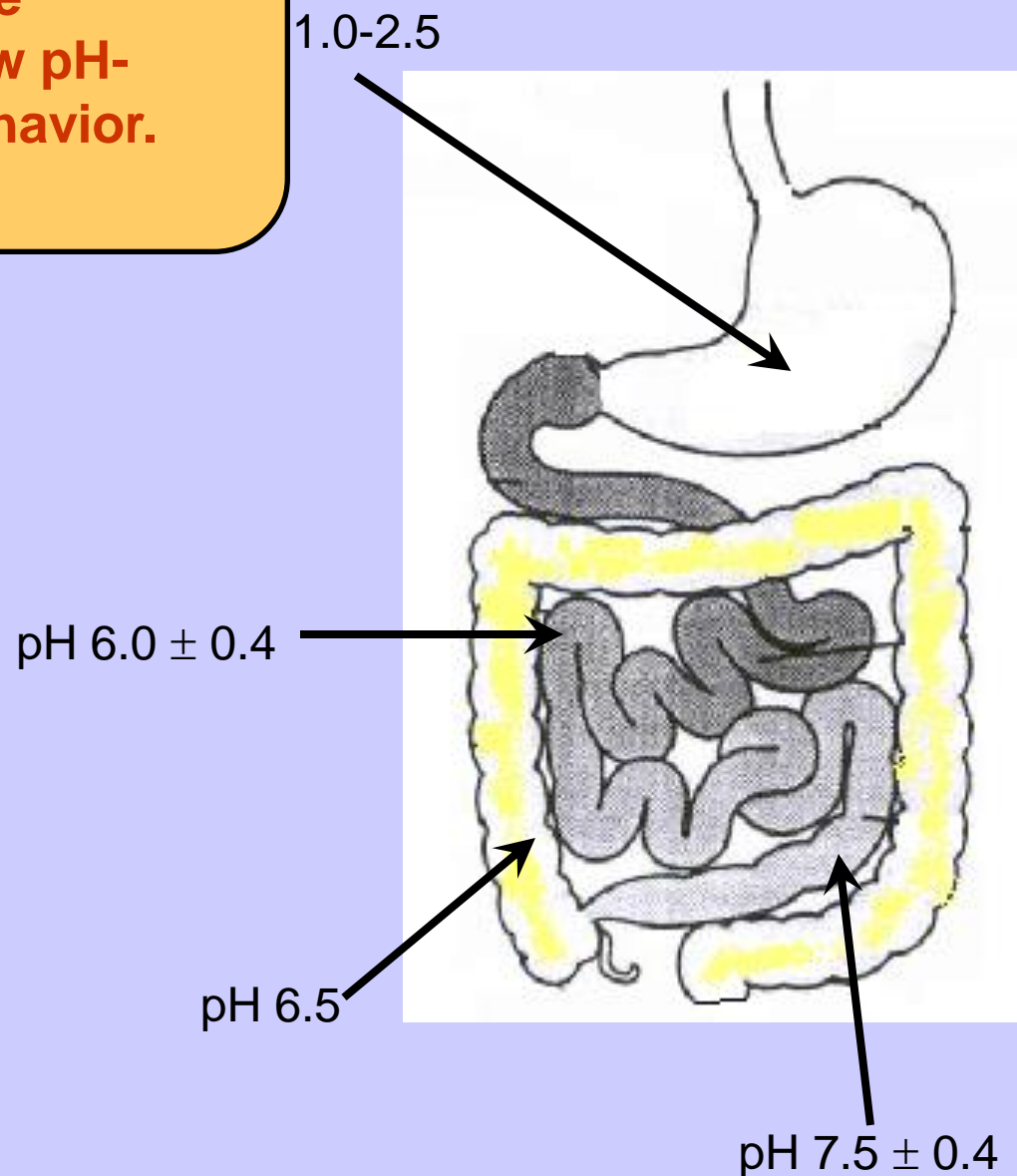
[VEEG]:[VBE]: 93:7 (1), 84:16 (2); 78:22 mol. % (3)



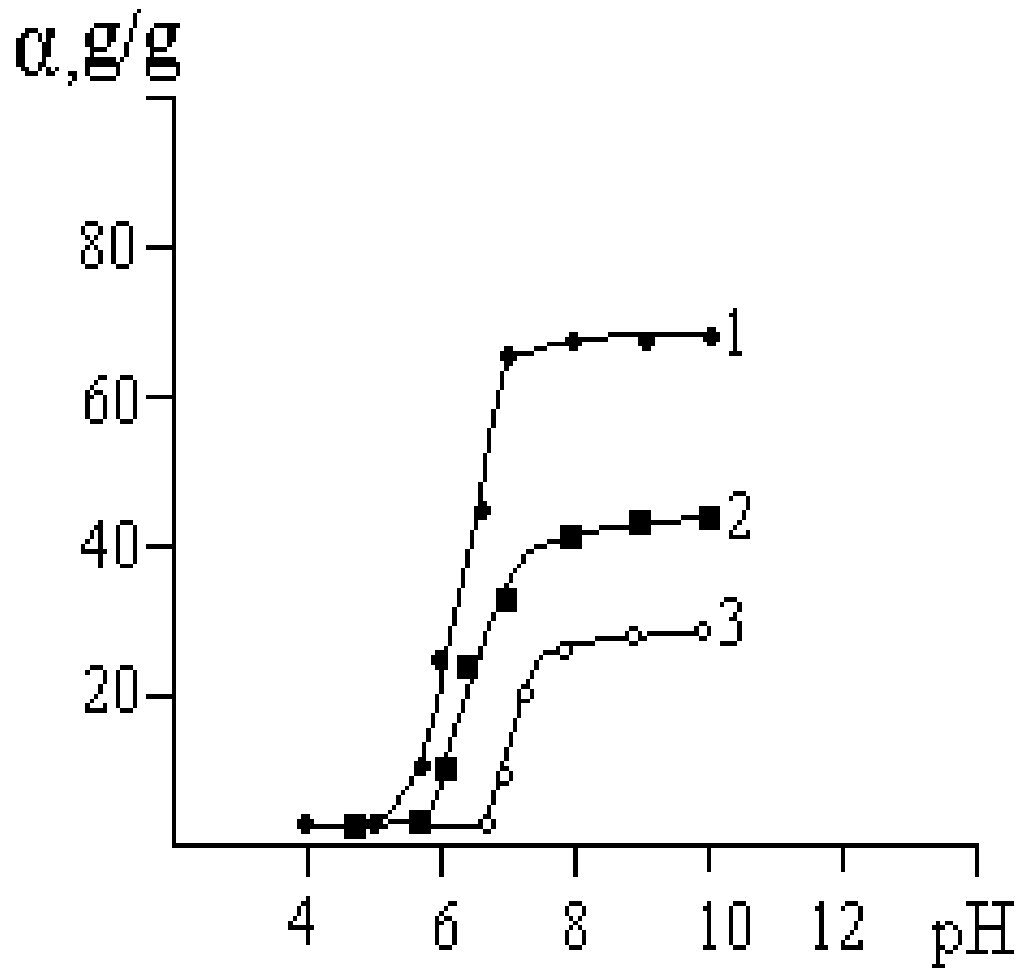
**Fig.4. Swelling behavior of VEEG-NIPAAM**  
VEEG-NIPAAM: 40:60 (2), 36:64 (2), 21:79 mol. (3)

**Different pH values in different parts of gastrointestinal tract can be used for targeted delivery of drugs. For these purposes the polymers should show pH-dependent solubility or swelling behavior.**

**Novel pH-sensitive anionic polymer network were synthesized by three-dimensional  $\gamma$ -initiated copolymerization of acrylic acid (AA) as ionogenic component and ethers vinyl alkyl ethers – vinyl butyl (VBE) and vinylisobutyl (VIBE) ethers of hydrophobic nature.**



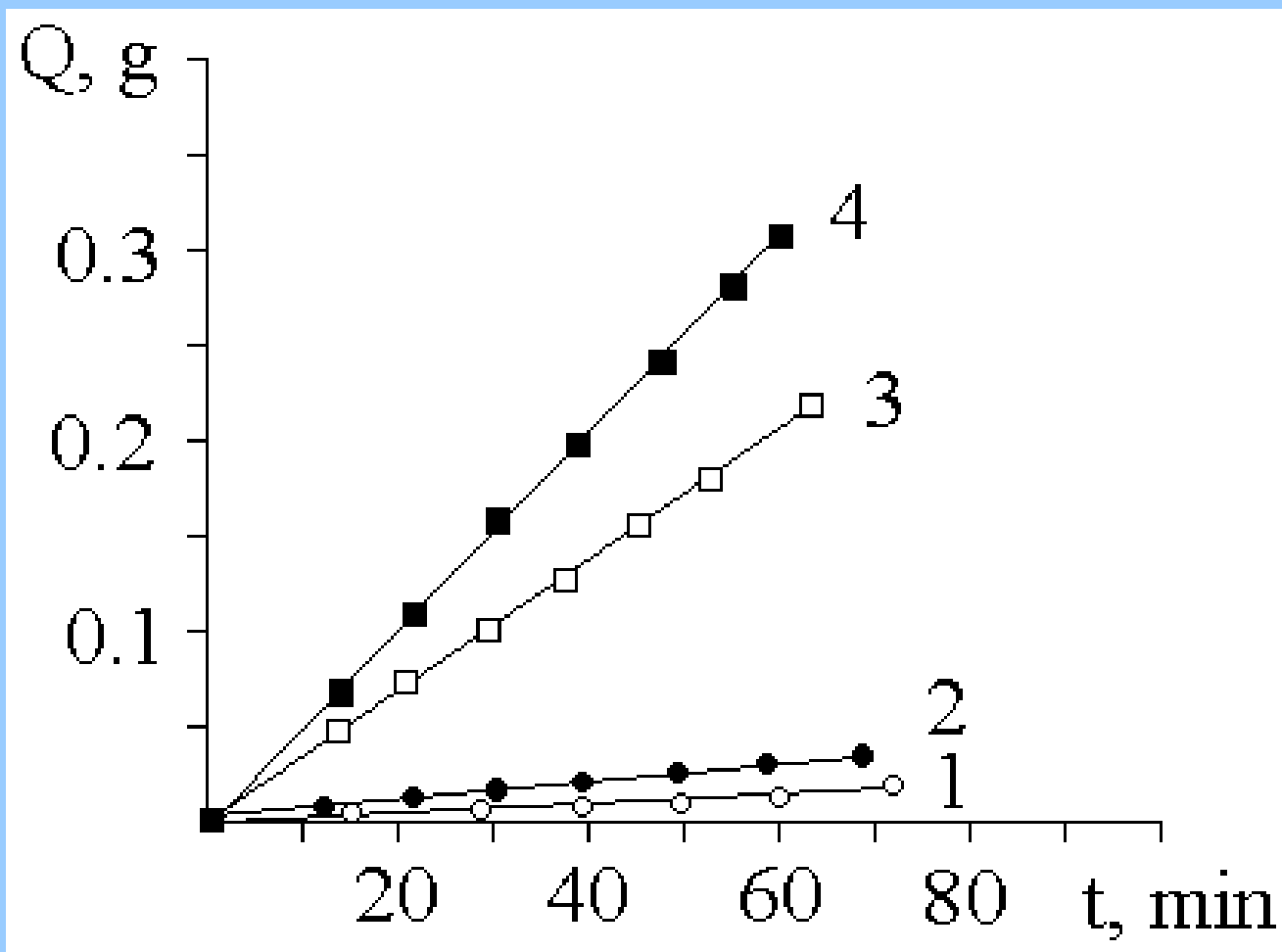
# Effect of composition of copolymers VBE-AA on pH-induced collapse



$\mu=0,05$ ; [VBE]:[AA]: 10:90 (1); 15:85 (2);  
28:72 mol.% (3)

The obtained hydrogels are characterized by pH-induced collapse. The pH – interval phase transition of this hydrogels from swelling state to collapsed one can be governed by varying of content of hydrophobic component in the structure of polymer network. Namely, an increase of VIBE content in copolymers shifts the transition pH to the higher values.

## Effect of pH on release of Brilliant Green from ViBE-AA hydrogels



[ViBE]:[AA]=9.8:90.2 mol.%  
pH: 5.0 (1), 6.0 (2), 7.0 (3), 8.0 (4)

The practical application of stimuli-responsive systems frequently requires the possibility to control the parameters of hydrogels by simultaneous varying of both pH and temperature. Especially it is important for biomedical application of polymers because many pathologies in organism are accompanied by simultaneous changes of pH and temperature.

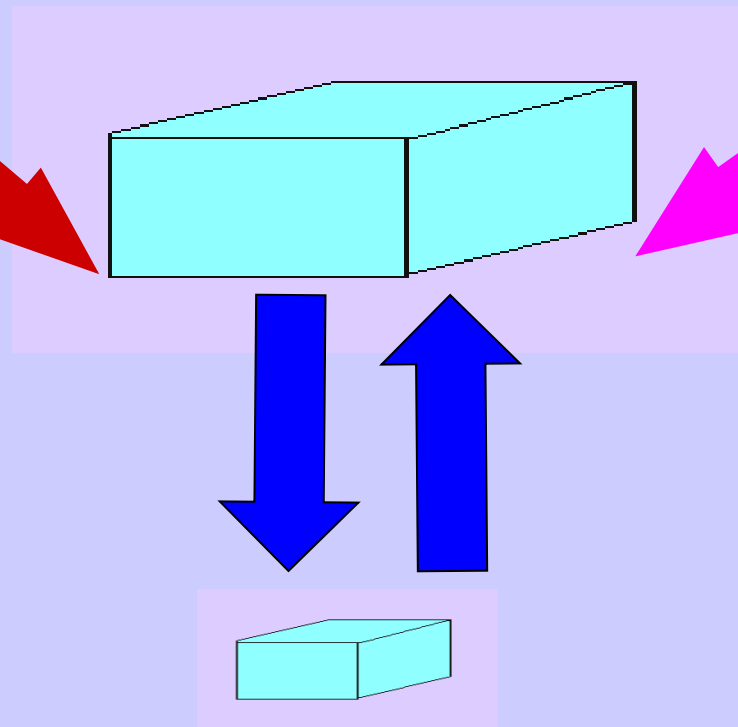
Novel pH-dependent thermo-sensitive hydrogels, i.e. the polymeric networks with simultaneous sensitivity in respect to pH and temperature, were synthesized by copolymerization of VEEG, VBE and AA with DVEDEG as a cross agent.

# Hybrid hydrogels

Hybrid polymers, which simultaneously sensitive to both temperature and pH are of great interest for development of novel drug delivery systems and materials for biotechnology

**Temperature**

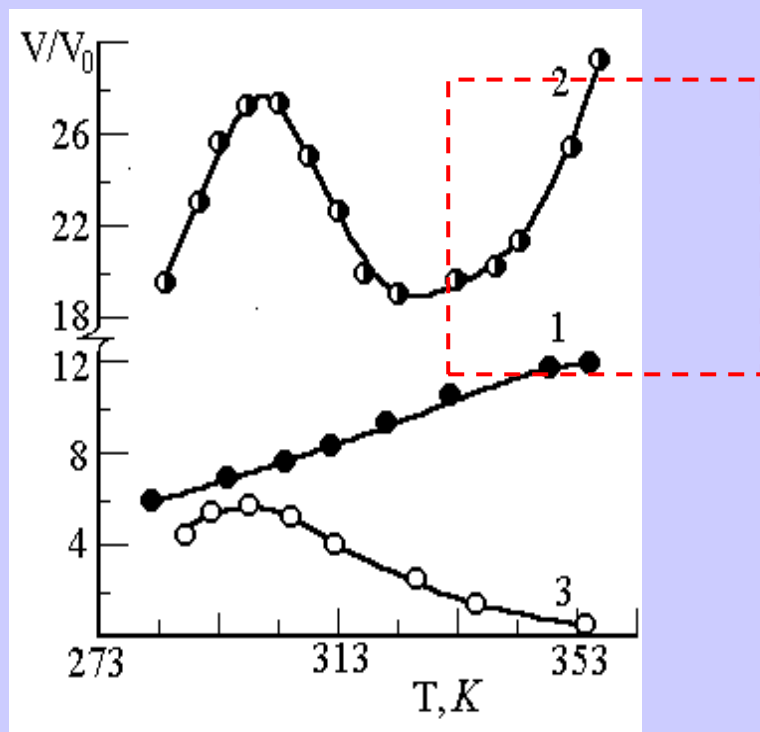
**pH**



Novel pH-dependent thermo-sensitive hydrogels, i.e. the polymeric networks with simultaneous sensitivity in respect to pH and temperature, were synthesized by copolymerization of VEEG, VBE and AA with DVEDEG as a cross agent.

Such terpolymer hydrogels represent a hybrid sensitivity both to pH and temperature. The phenomenon of secondary reswelling and oscillation volume change upon increase in temperature has been for the first time discovered for hybrid pH-dependent thermo-sensitive network.

# Temperature dependence of swelling ratio of VEEG-VBE-AA hydrogel



Dependence of swelling ratio  $V/V_0$  of polymer hydrogels based on copolymer VEEG – VBE – AAc on temperature

Composition of initial monomer mixture:

[VEEG]:[VBE]:[AAc], mole. %:

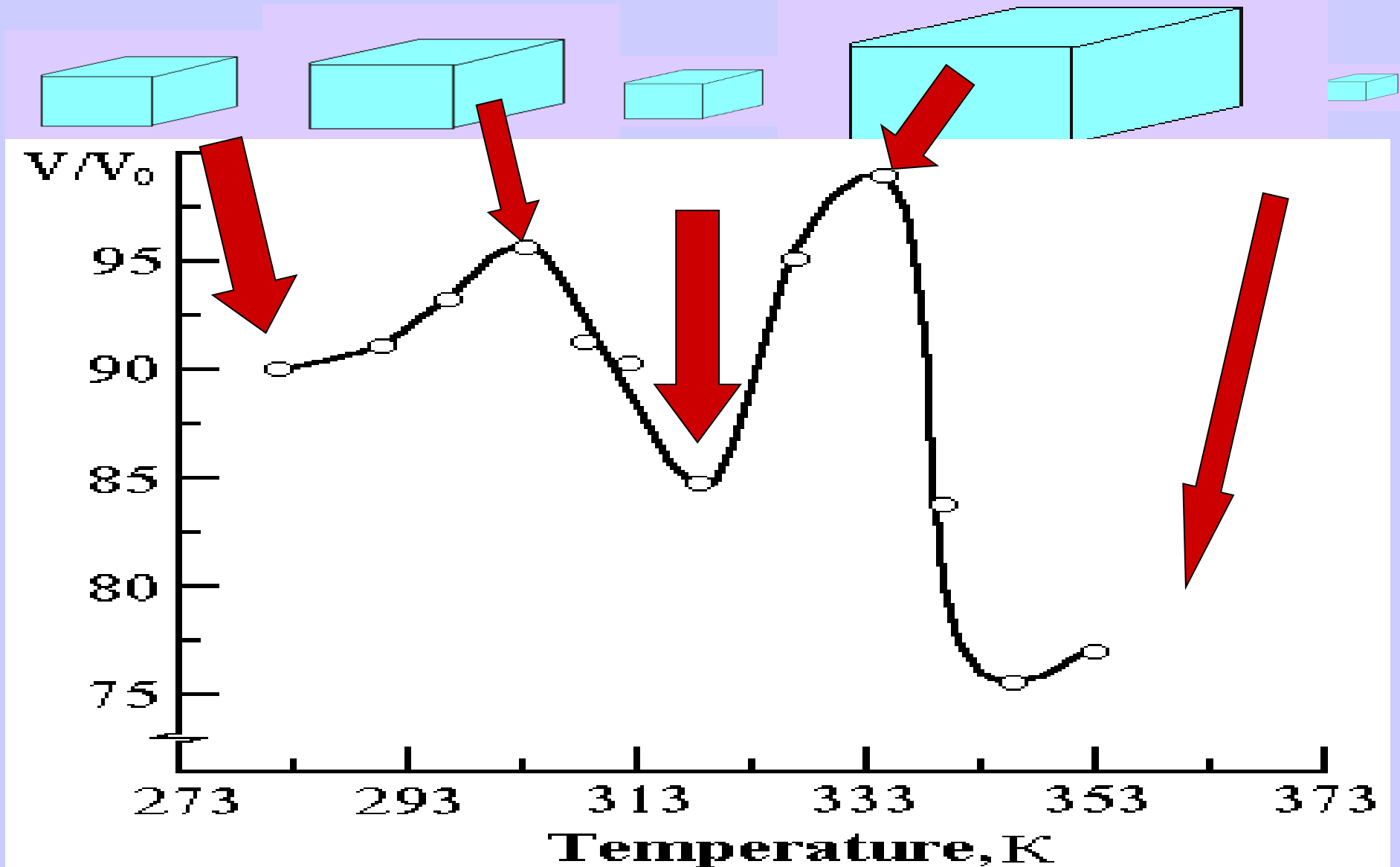
63,2:14,5:17,3 (1);

57,2:20,5:17,3 (2);

52,7:25,0:17,3 (3)



# Temperature Dependence of Swelling Ratio of VEEG-VBE-AA Hydrogel



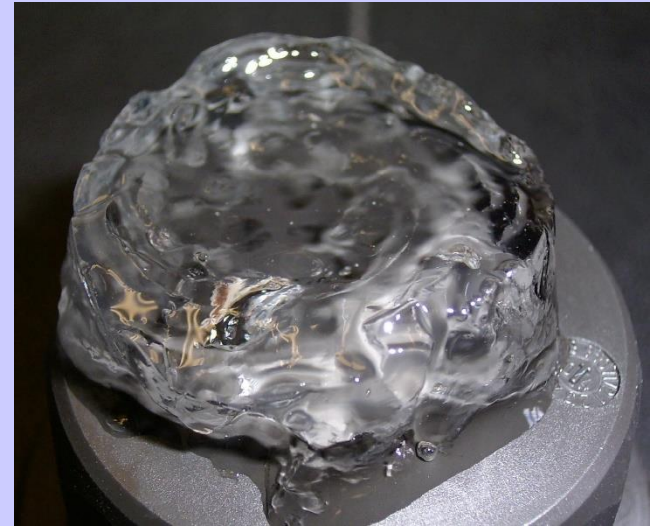
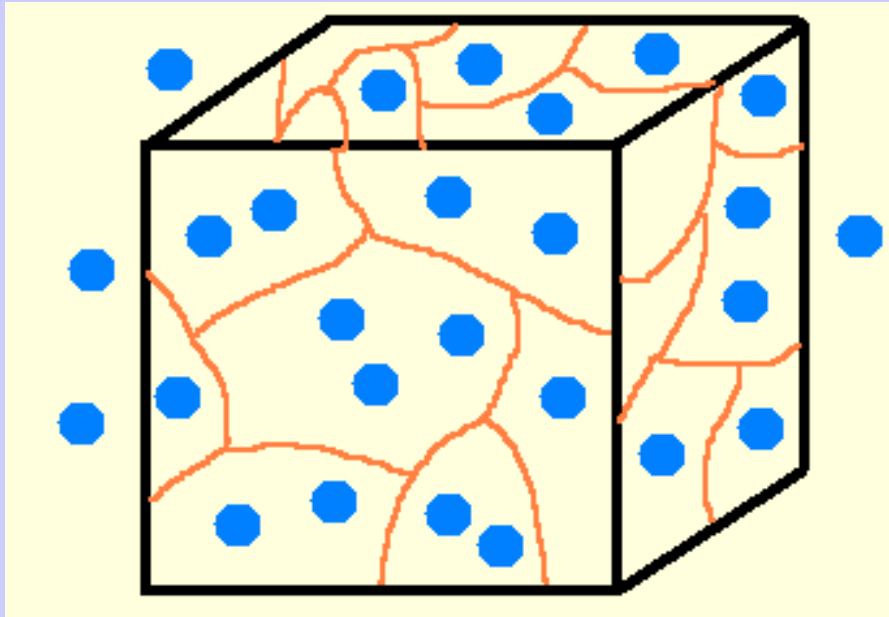
**As the result of many years collaboration with a number of leading medical centers of Kazakhstan and Russia the possibility of wide and effective application of these hydrogel materials in different areas of medicine has been found.**

**At present new composite hydrogel material “Polygel” have been developed. “Polygel” was approved by Ministry of Healthcare (Kazakhstan) for production and application as a contact medium for ultrasonic diagnostics of cardiovascular and internal organs (liver, kidneys, pancreas, spleen, etc.) disabilities.**

## Hydrogel as a contact medium for ultrasonic and encephalographic diagnostic investigations



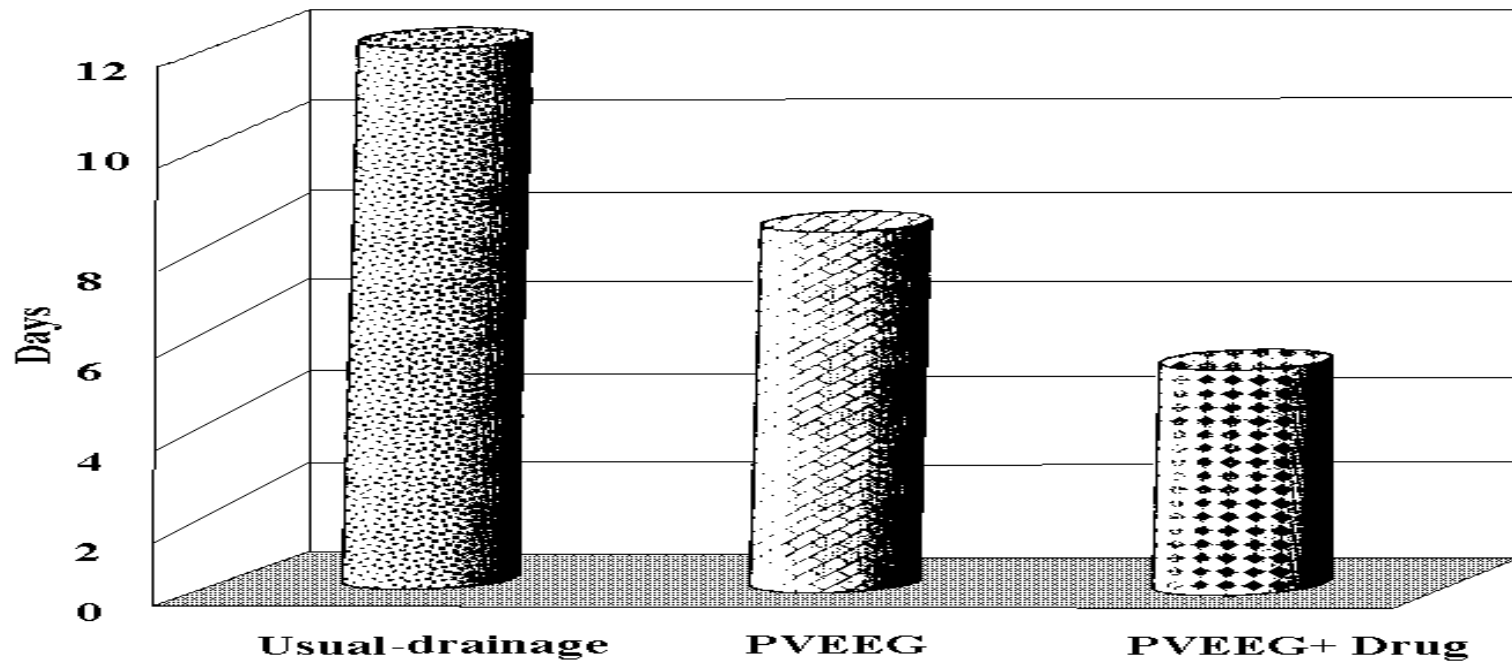
# Hydrogels as biomaterials



- Soft, wet and porous materials
- Tissue-like consistency
- Biocompatible

New water-swelling absorbing polymer of vinyl ether of ethyleneglycol (PVEEG) in both pure and saturated with silver nanoparticles forms has been investigated as drainages in ophthalmology. Surgical treatment was performed on 155 patients with the extraorbital suppurative inflammations. The PVEEG drainages and the PVEEG drainages saturated with silver nanoparticles was carried out. The offered method of the treatment of extraorbital suppurative inflammations provides active, long draining and fast lowering of the inflammation. The period of treatment reduce to 1.5-2 times in comparison with the control traditional method.

## Duration of patient treatment with extra-orbital pus-inflammatory processes



**•The new injection implant material (IIM) for application in plastic surgery as well as in endoscopic correction of bladder ureter reflux (BUR) in has been developed by our team. BUR is the most frequent form of urodynamic disorders, and this disease affects mostly children, in which case it progresses much faster and leads to serious irreversible morphofunctional changes in the kidneys and the superior urinary tracts.**

**•Unlike the hydrogel implant materials used today in soft tissue, the rheological properties of the IIM allow to transport it into the corrected areas of the body with an endoscope or with a regular syringe (injector) and a needle in quantities sufficient for the achievement of a stable functional and cosmetic effects.**

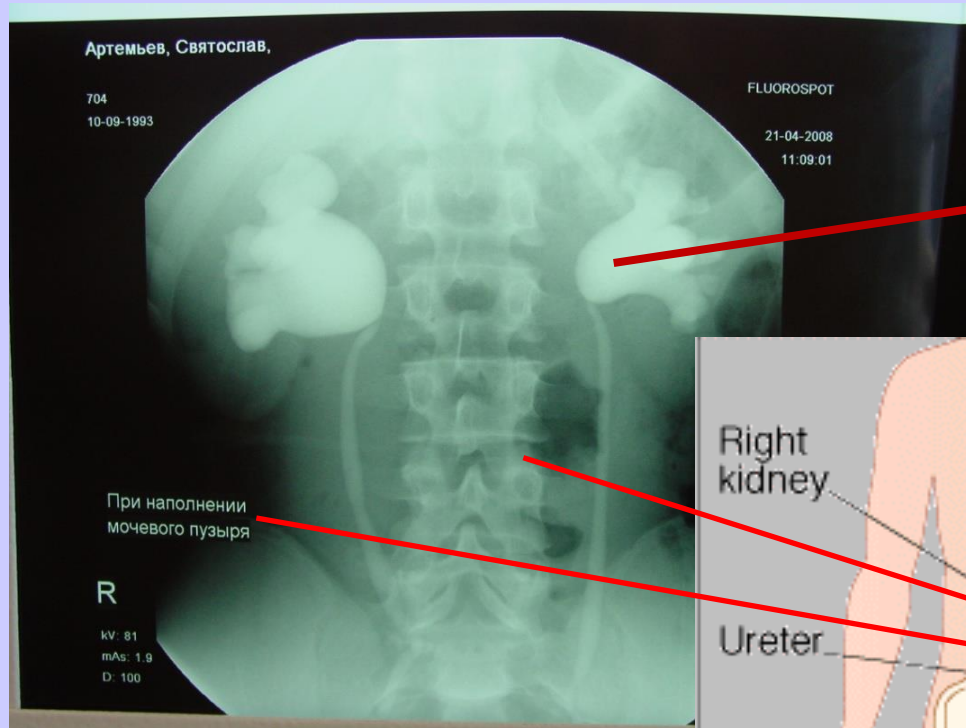
**• At the use of such material the necessity of extensive traumatic incisions disappears, which frequently allows the soft tissue plastic surgery on an outpatient basis. The traditional treatment of BUR is connected to surgical intervention accompanied by traumatic operation and possibility of complications in sick children.**

**•The IPIM has undergone a full complex of preclinical testing. It is established that IPIM is completely conforms to the medical and biologic requirements for the implantation materials: it does not render any of the following: toxic, sensibilizing, pyrogenetic, allergizing, cancerogenic or mutagenic effects; it is completely compatible with mammal tissue at long-term implantation.**

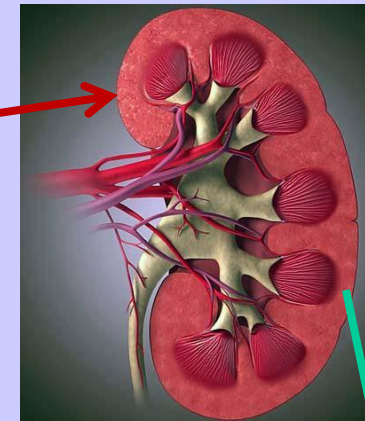
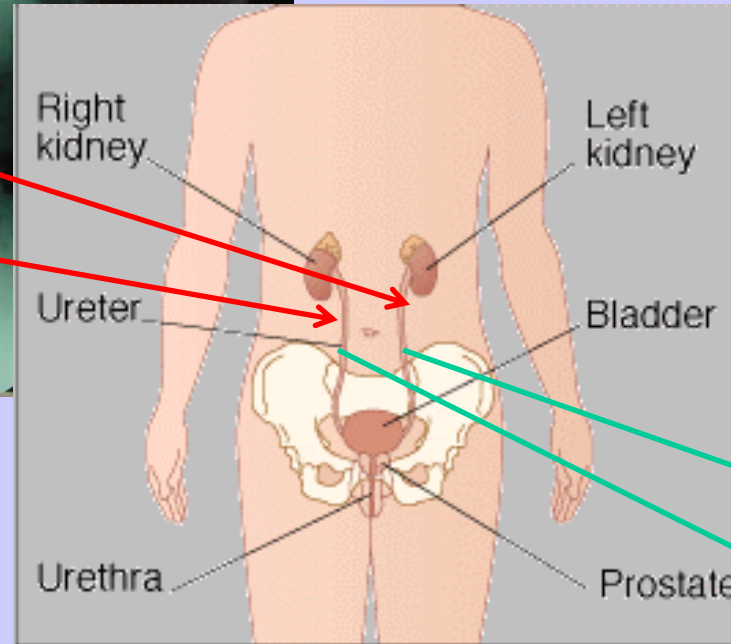
**• Clinical tests estimating safety, tolerability and efficiency of IPIM for the treatment of VUR have begun and are in the process. Now we obtained very good result in klinical testing. The results of the clinical research for a period up to 24 months for more than 100 children testify high efficiency of IIM application in urology at endoscopic correction of bladder ureter reflux (BUR).**



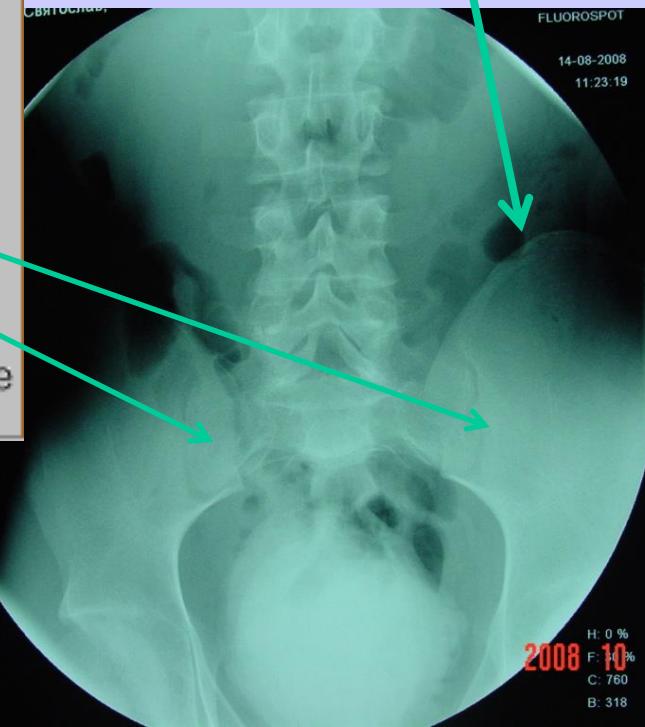
# Endoscopic correction of bladder ureter reflux by using of new injection implant material



Before the surgery



After the surgery



kV: 75  
mAs: 3.2  
D: 100

**Thank you for your  
kind attention!**