



Budapest University of Technology and Economics  
Faculty of Chemical Technology and Biotechnology  
Department of Physical Chemistry and Materials Science

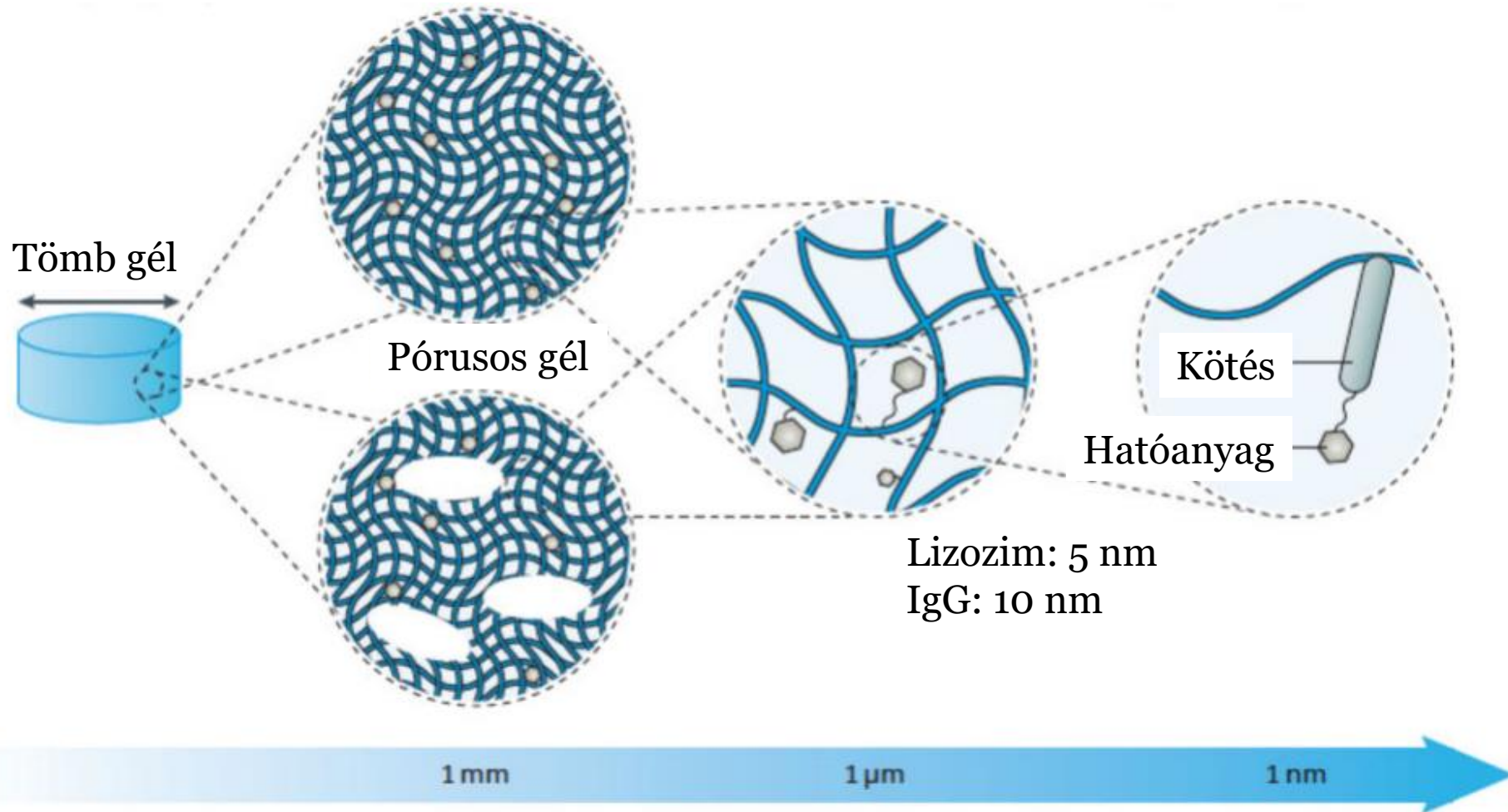


# **Hatóanyag-leadás hidrogélekből – a szerkezet, a rezponzív tulajdonságok és a kölcsönhatások szerepe**

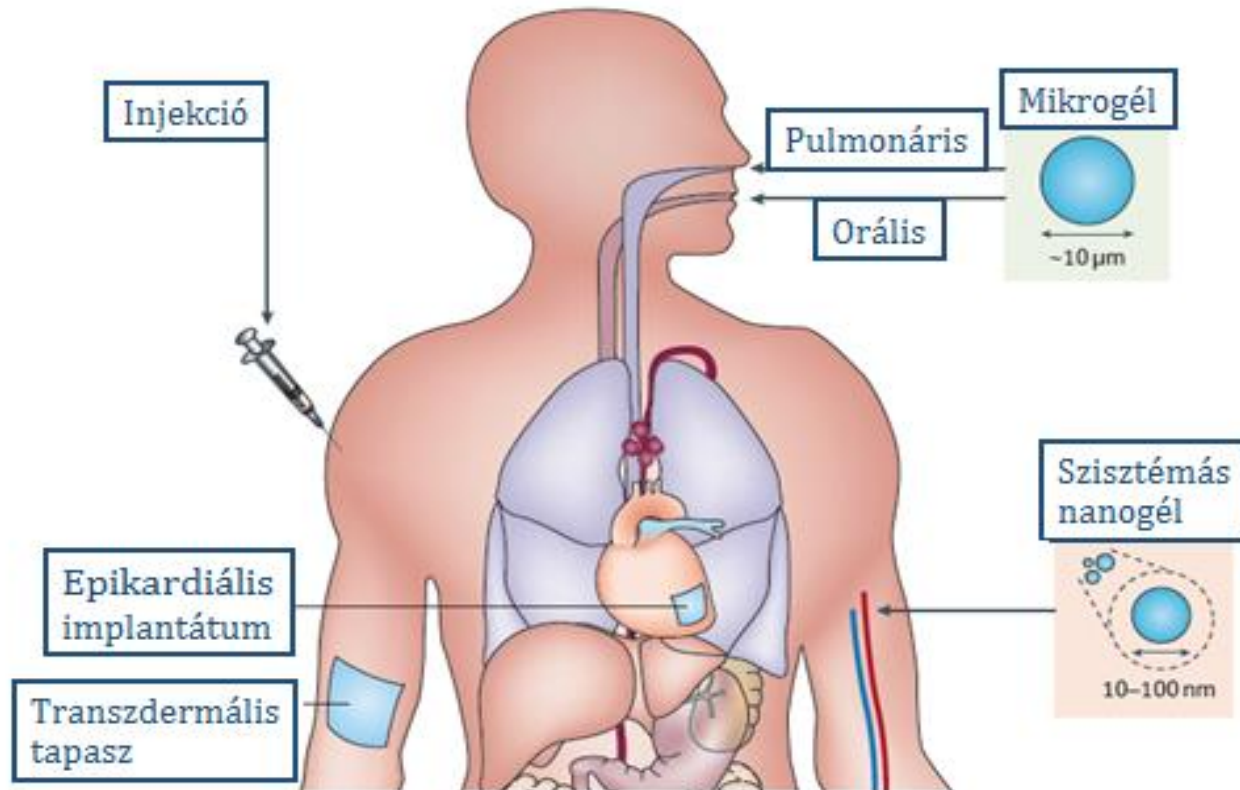
Gyarmati Benjámín

2020. május 6.

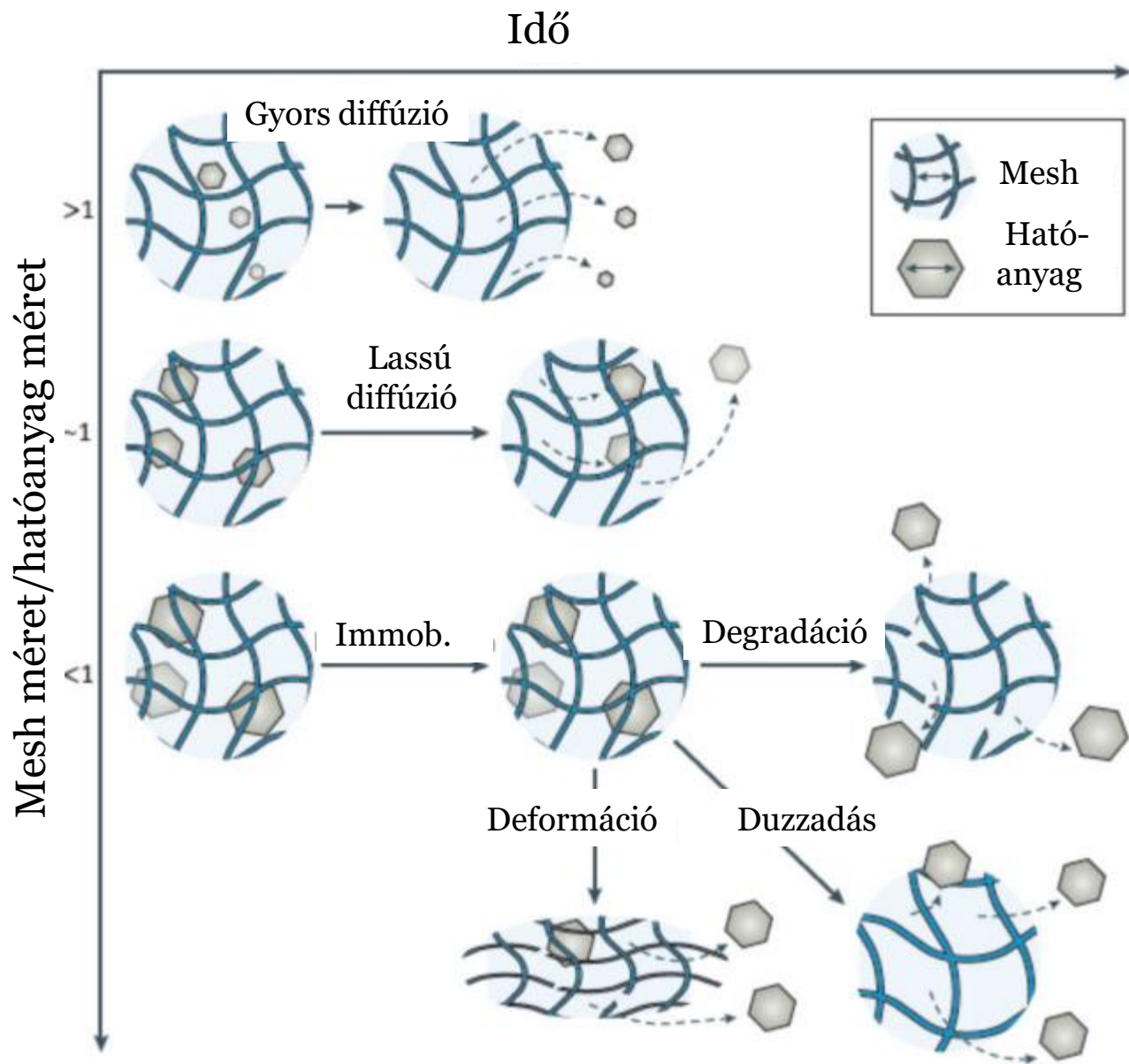
# Méretskálák hidrogélekben



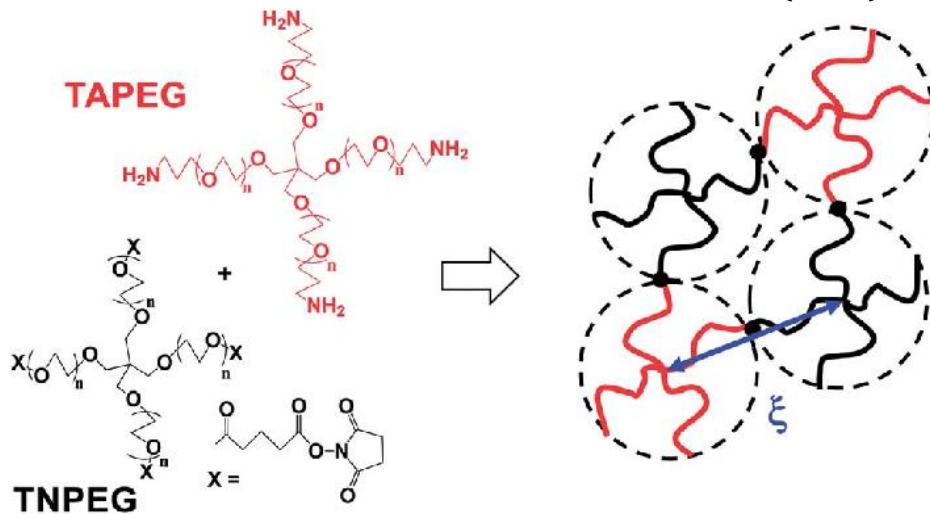
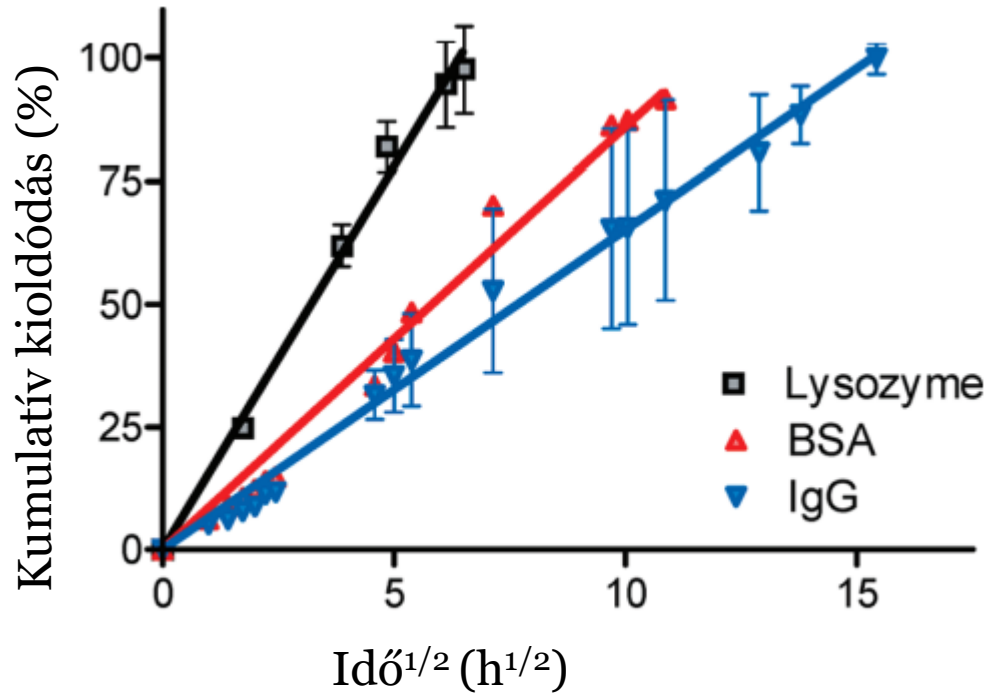
# Méretskálák – terápiás célpontok



# Kioldódási mechanizmusok



# Diffúziókontrollált kioldódás (TetraPEG gélek)

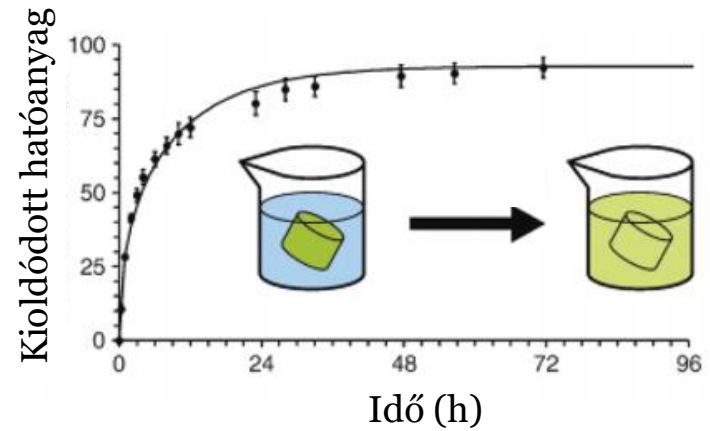
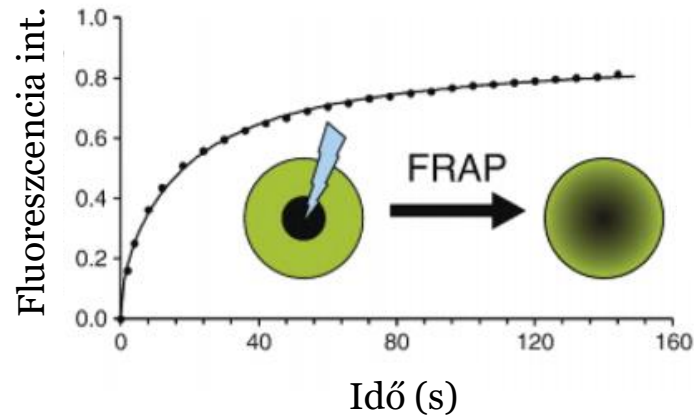


$$G = \frac{\rho RT}{M_c} \frac{r_0^2}{r_f^2} \left( 1 - \frac{2M_c}{M_n} \right)$$

$$G = \rho RT / M_c$$

$$\xi = \left( 6M_c / \pi \rho N_A \right)^{1/3}$$

# Diffúziós tényező meghatározása



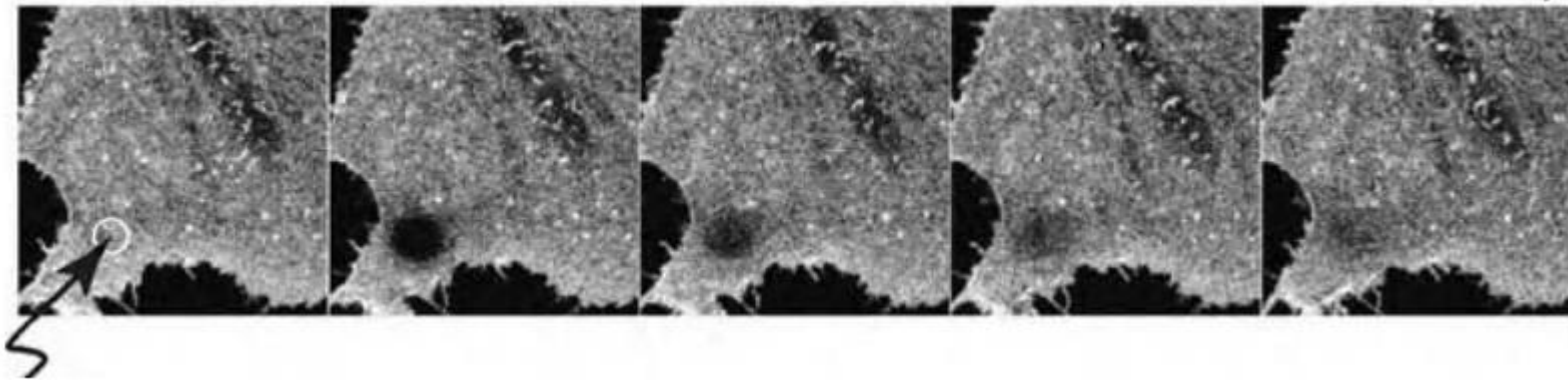
Fluorescence photobleaching recovery (FPR)

„Kisütés”

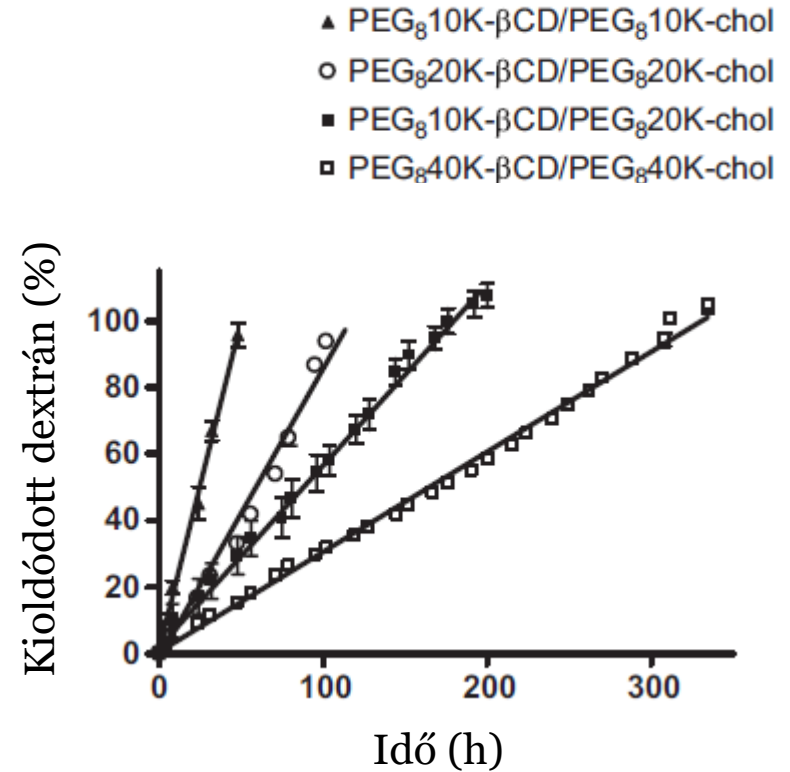
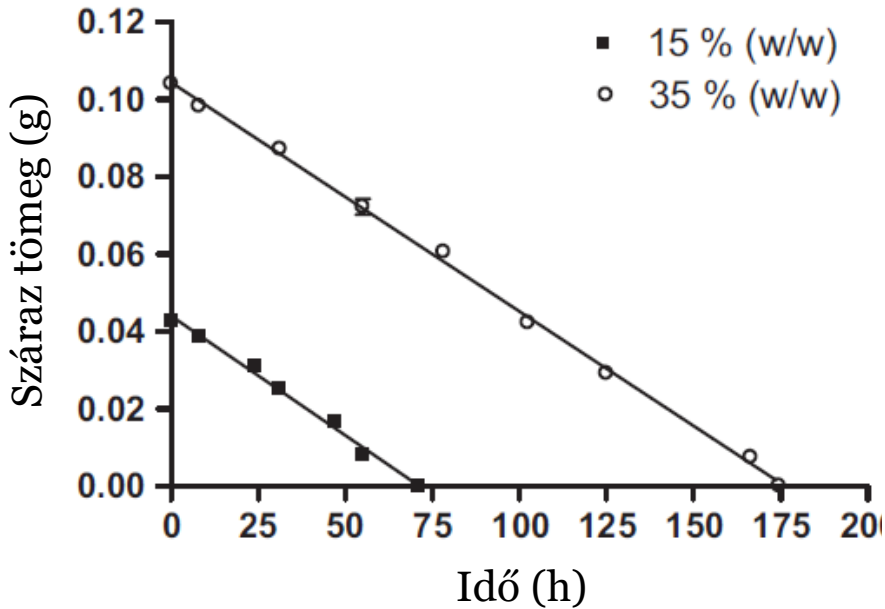
Bleach

Visszaalakulás

Recovery



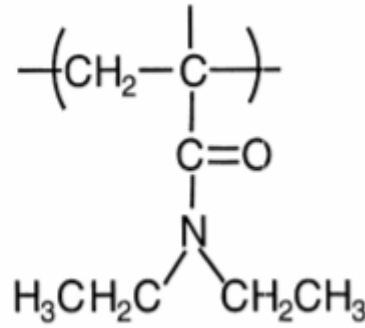
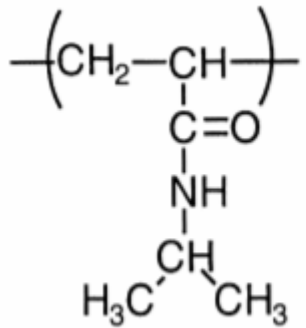
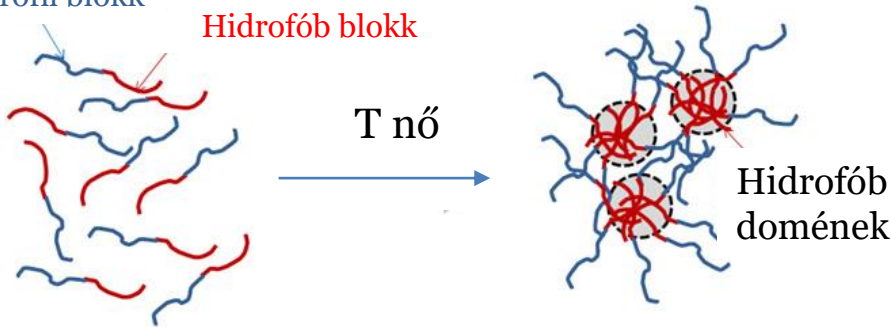
# (Gél)Degradáció-indukált kioldódás



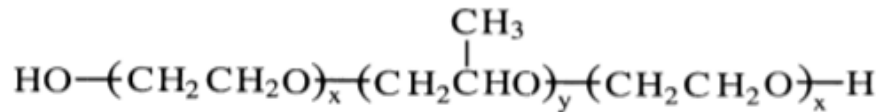
# Reszponzív hidrogélek (mesh szabályozása)

Hidrofil blokk

Hidrofób blokk

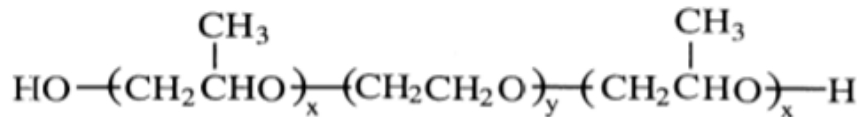


Pluronic®

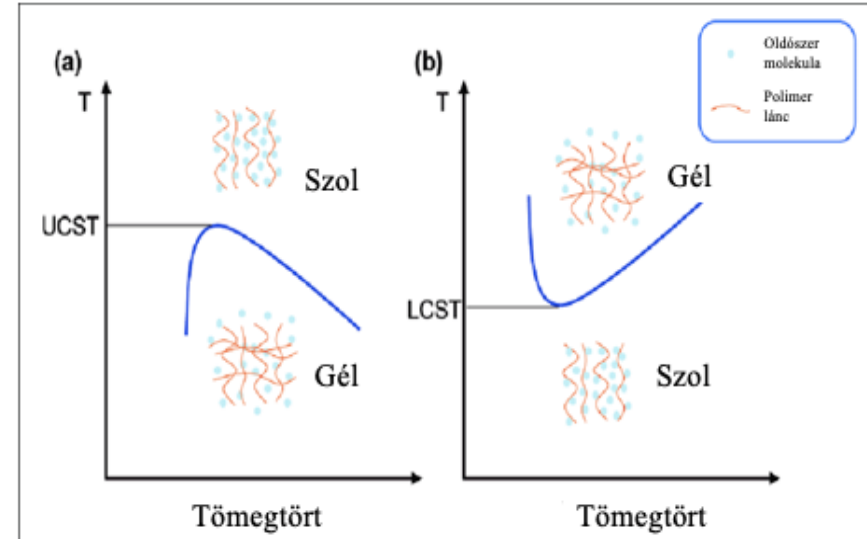


PEO-PPO-PEO

Pluronic® R

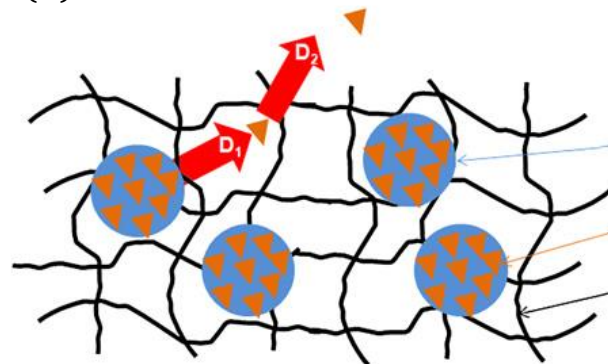
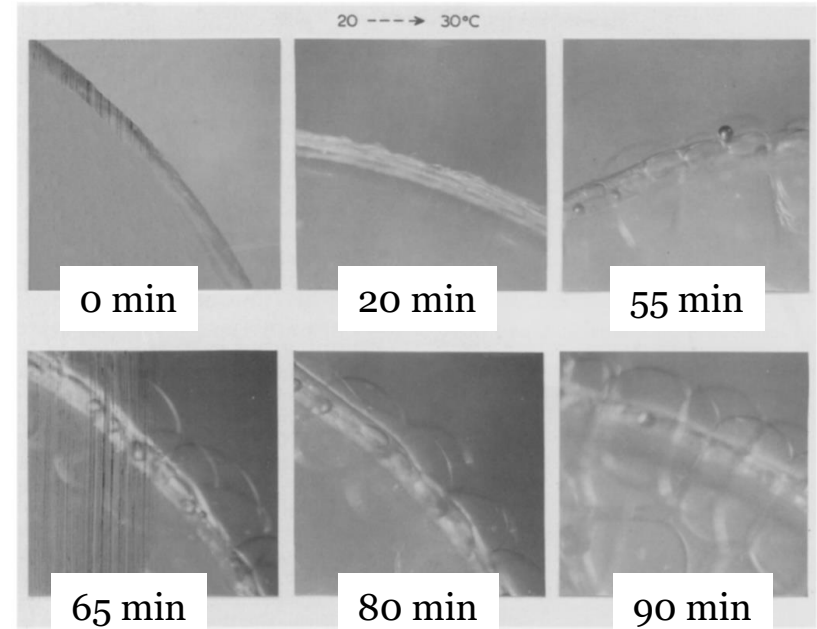
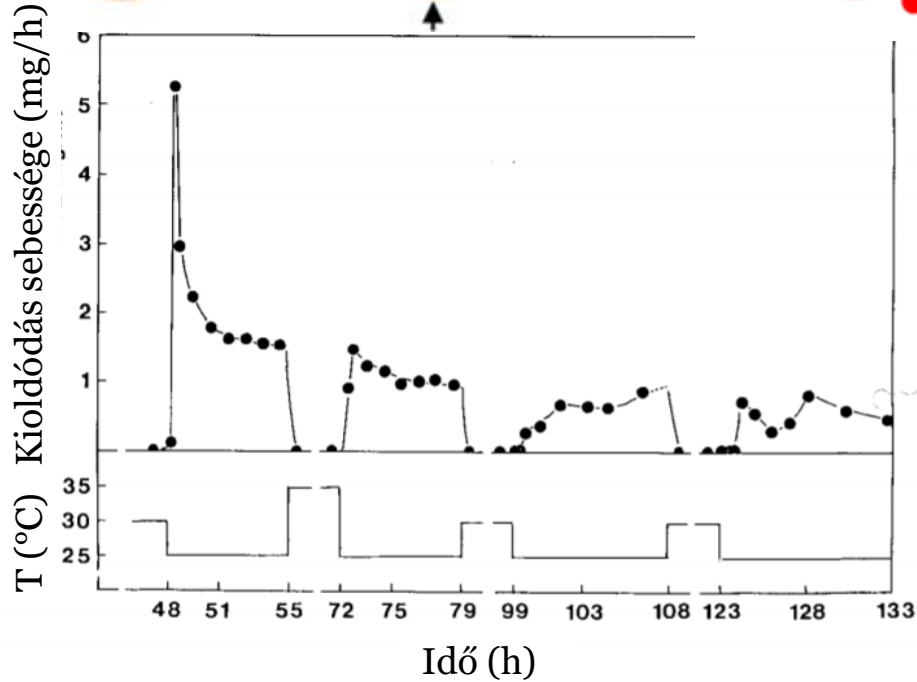
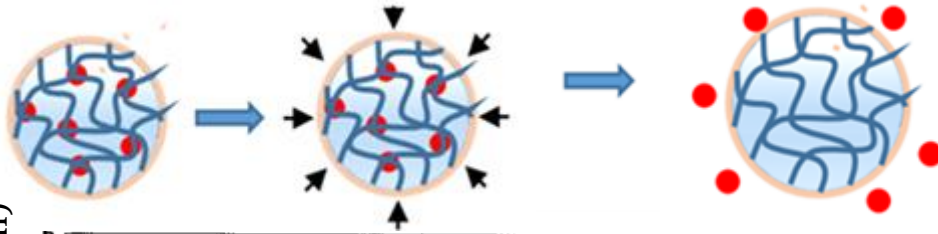


PPO-PEO-PPO





# Hőmérsékletérzékeny hatóanyag-leadás



Másodlagos  
hatóanyag-  
hordozó  
Hatóanyag  
Térháló

# Hőmérsékletérzékeny hatóanyag-leadás



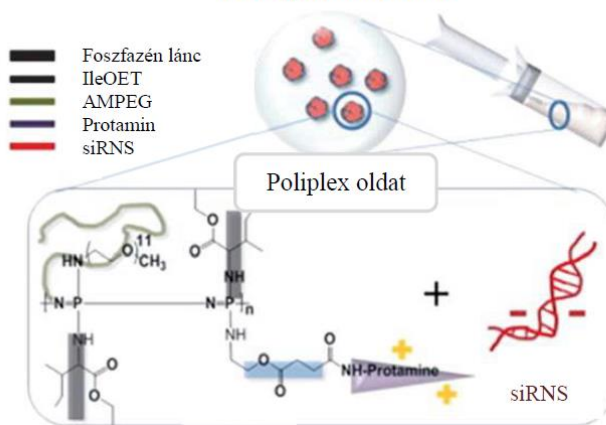
$T < T_{gel}$



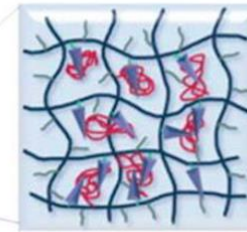
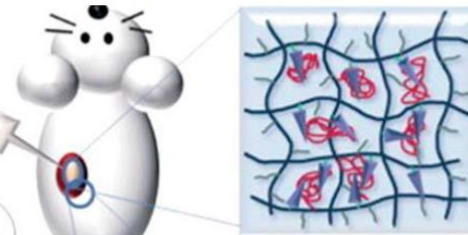
$T_{body} > T_{gel}$



## 1. Poliplex kialakulása



## 2. Injektálást követő szol-gél átmenet



Poliplex hidrogél

## 3. Poliplex felszabadulása



Célsejt

## 4. Poliplex sejtbe jutása

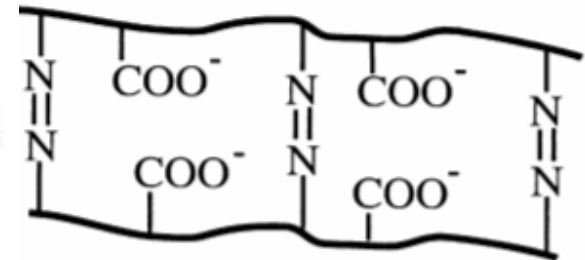
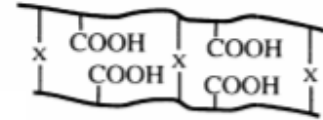
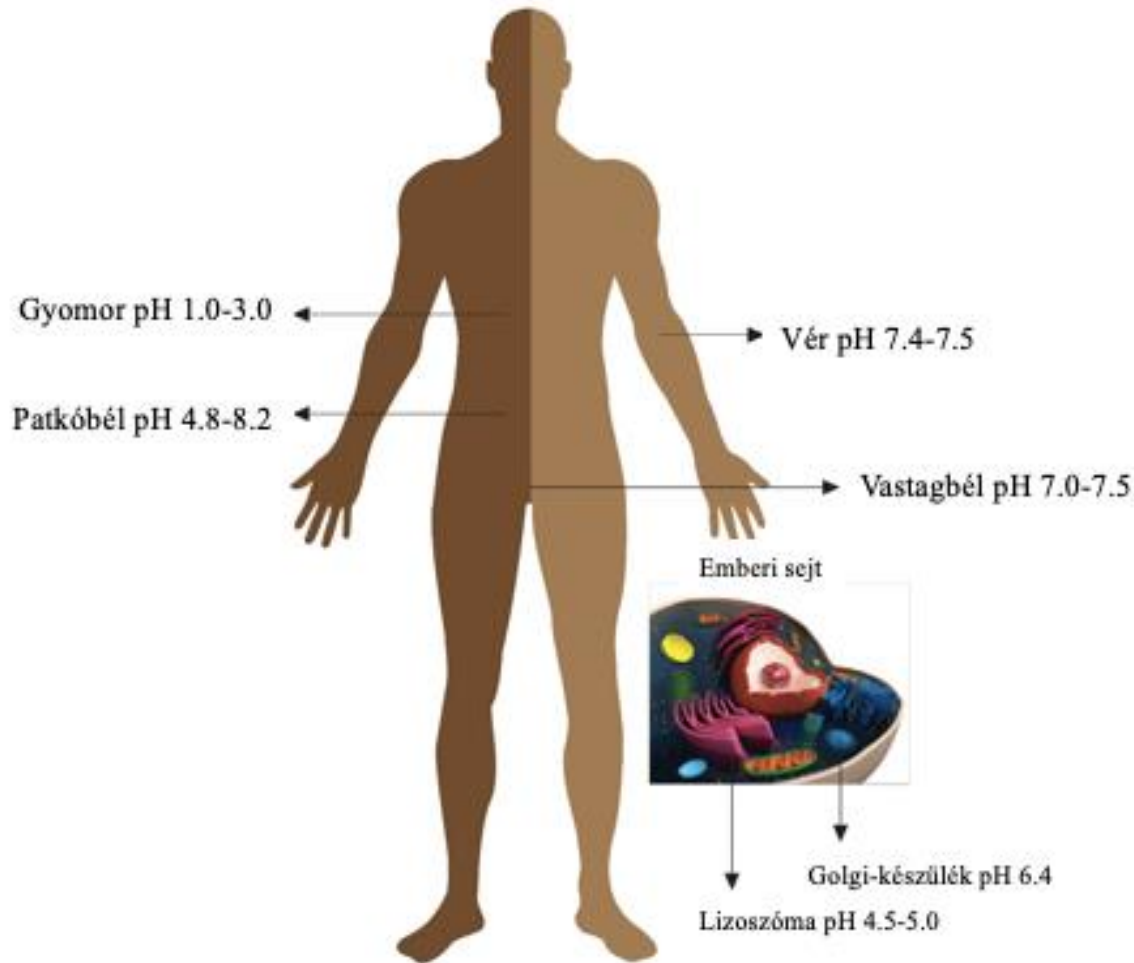


Singh NK, Lee DS. In situ gelling pH- and temperature-sensitive biodegradable block copolymer hydrogels for drug delivery. *Journal of Controlled Release* 2014;193:214-27.

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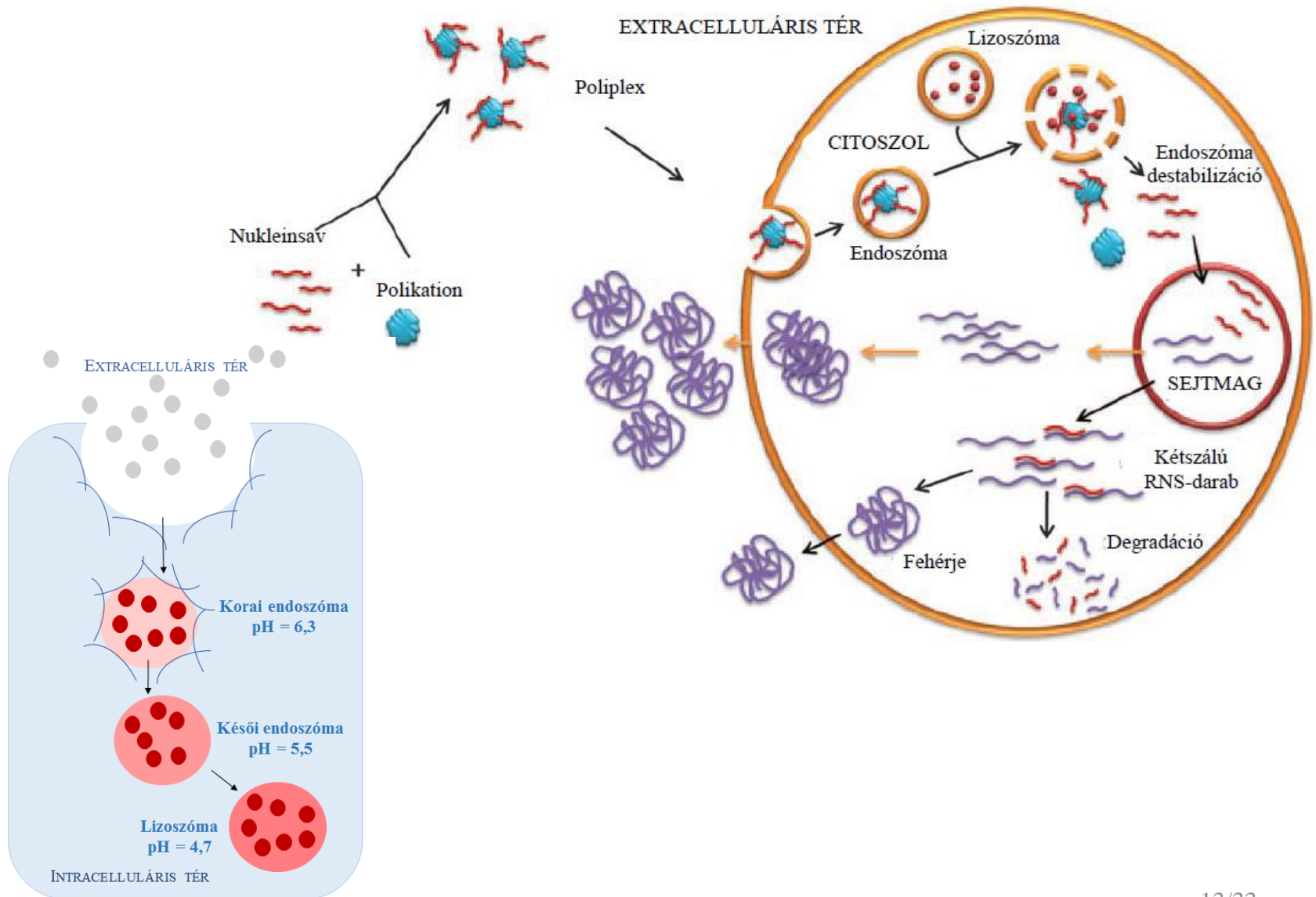
Bae KH, Wang L-S, Kurisawa M. Injectable biodegradable hydrogels: progress and challenges. *Journal of Materials Chemistry B* 2013;1:5371-88.

# pH-érzékeny hatóanyag-leadás

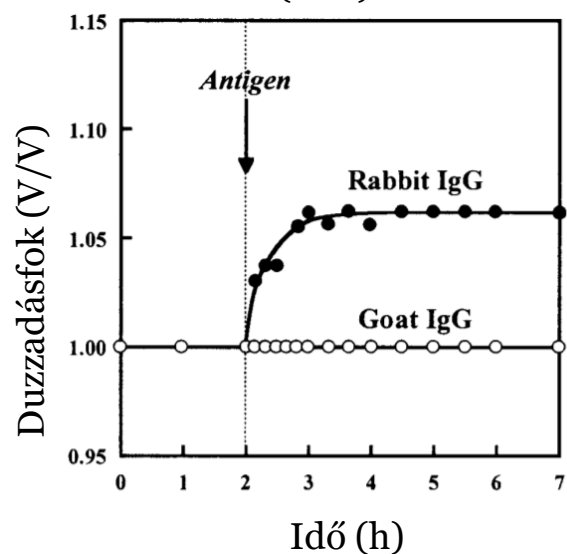
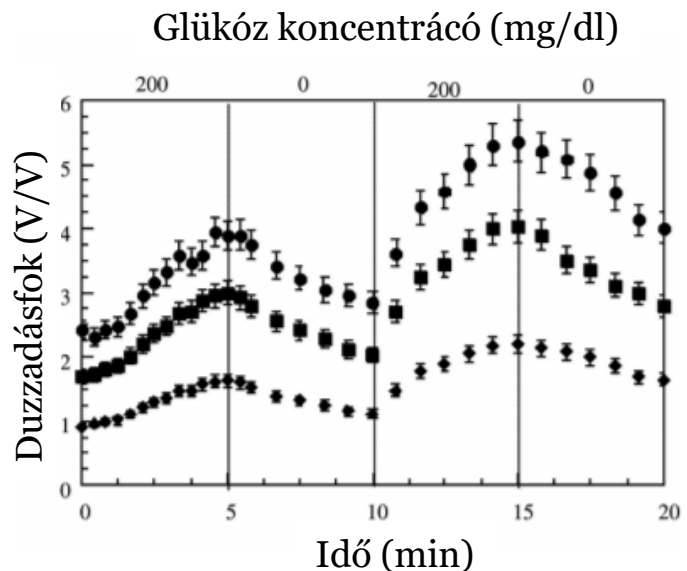
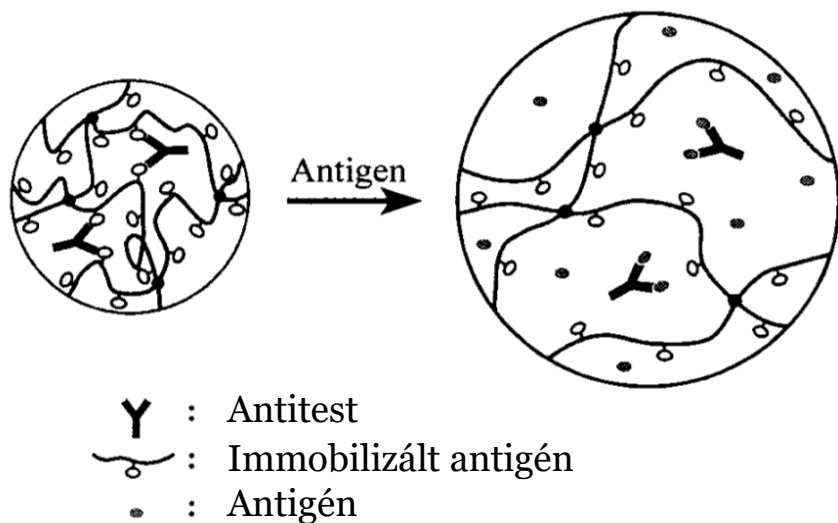
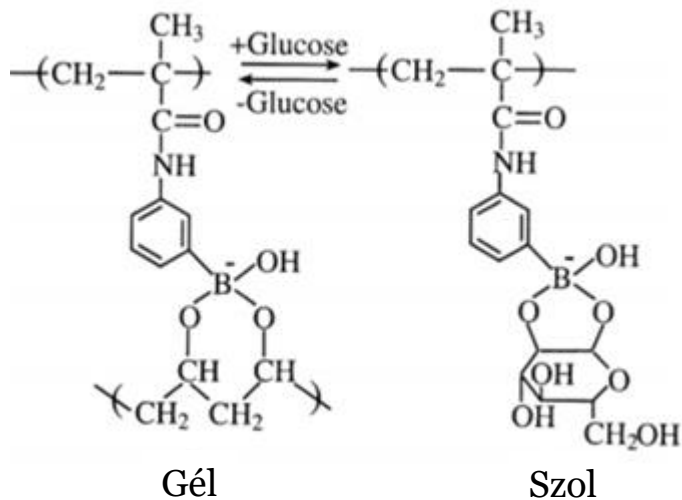




# Nem virális génvektorok



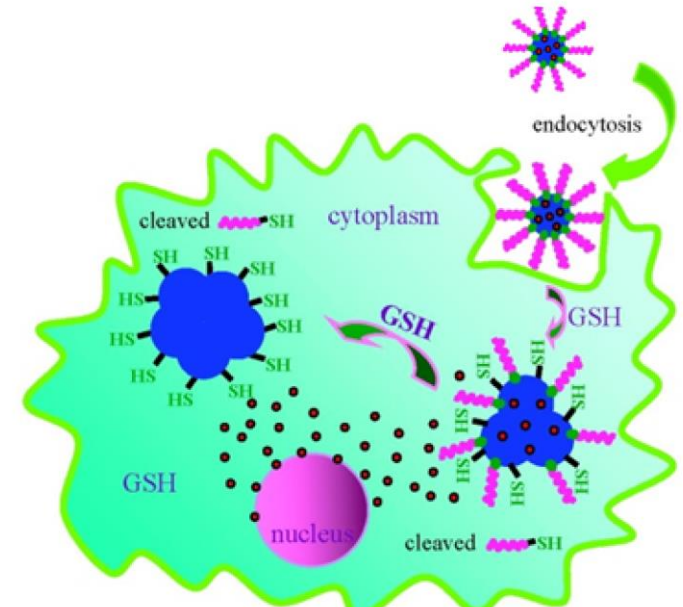
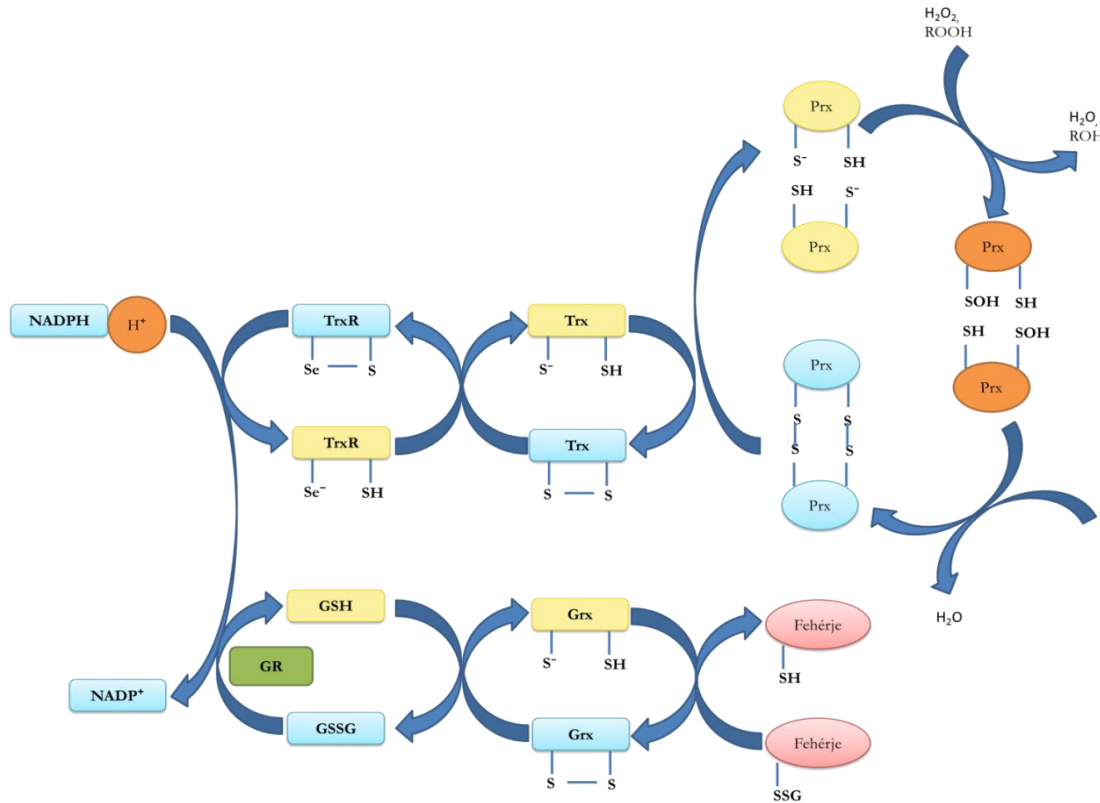
# Biomolekula-indukált hatóanyag-leadás



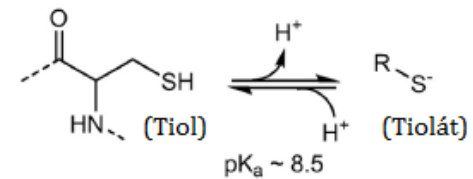
Podual K, Doyle FJ, Peppas NA. Glucose-sensitivity of glucose oxidase-containing cationic copolymer hydrogels having poly(ethylene glycol) grafts. *Journal of Controlled Release* 2000;67:9-17.

Miyata T, Asami N, Uragami T. Preparation of an Antigen-Sensitive Hydrogel Using Antigen–Antibody Bindings. *Macromolecules* 1999;32:2082-4.

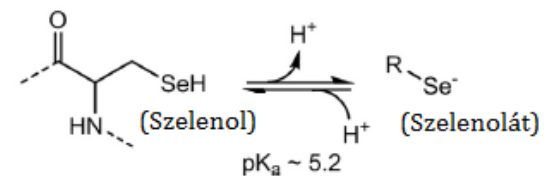
# Sejtszintű redox folyamatok



Cisztein



Selenocisztein

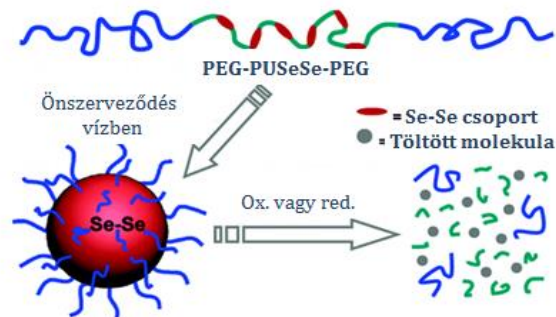
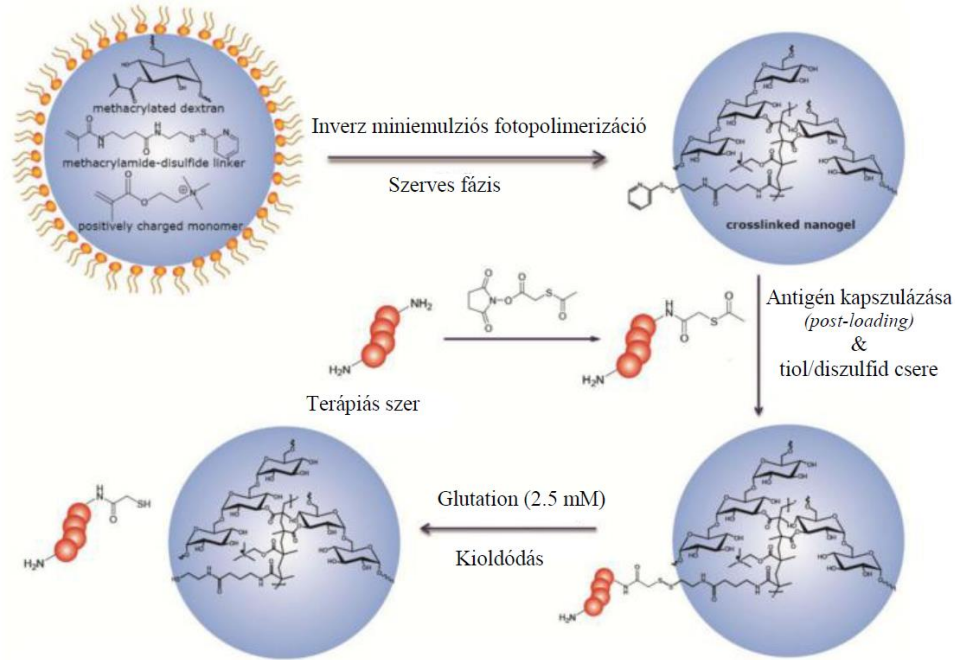


Lu J, Holmgren A. The thioredoxin antioxidant system. *Free Radical Biology and Medicine* 2014;66:75-87.

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Meng F, Hennink WE, Zhong Z. Reduction-sensitive polymers and bioconjugates for biomedical applications. *Biomaterials* 2009;30:2180-98.

# Redukció-indukált hatóanyag-leadás



Meng F, Hennink WE, Zhong Z. Reduction-sensitive polymers and bioconjugates for biomedical applications. *Biomaterials* 2009;30:2180-98.

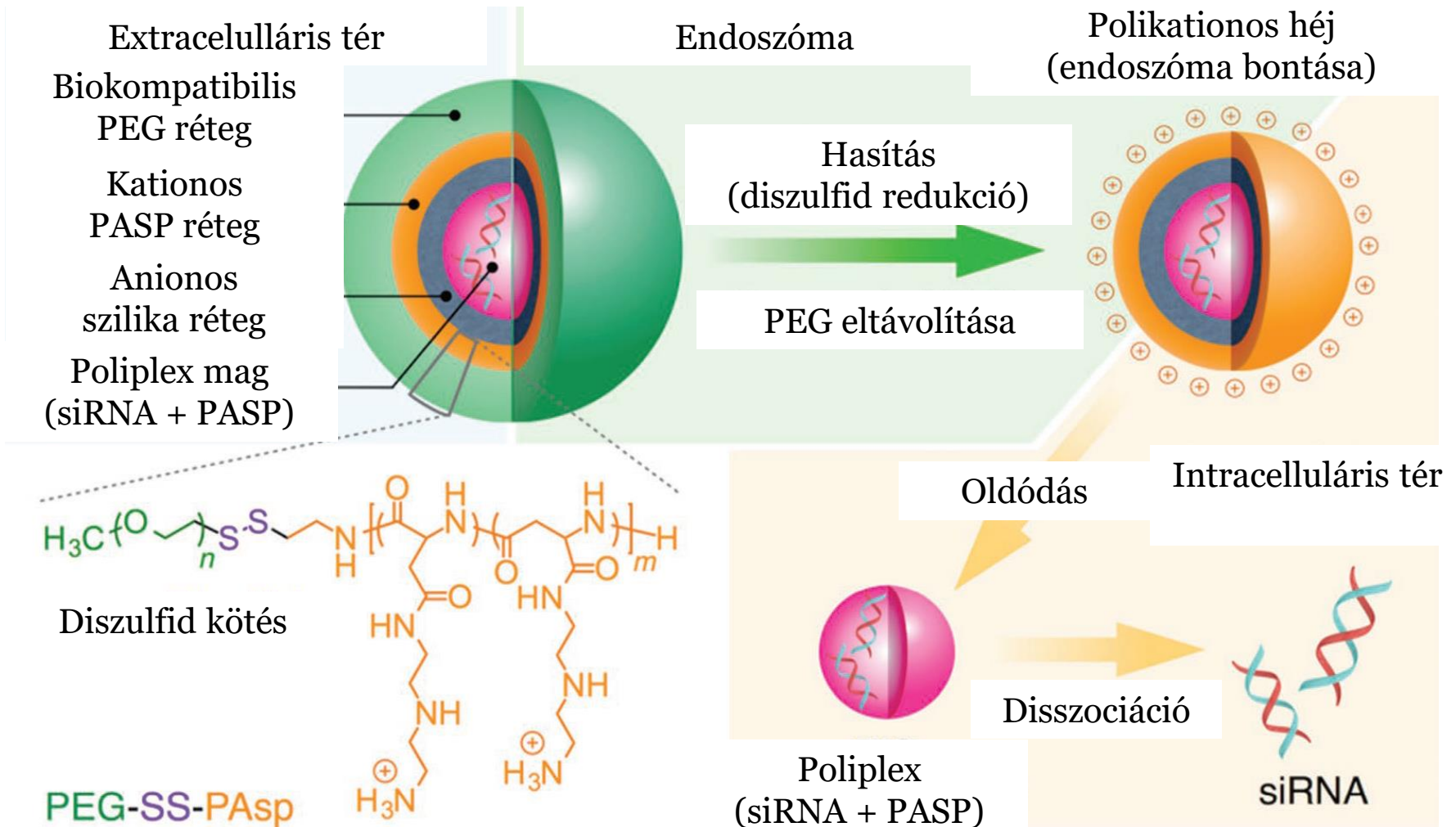
Li D, Kordalivand N, Fransen MF, Ossendorp F, Raemdonck K, Vermonden T, et al. Reduction-Sensitive Dextran Nanogels Aimed for Intracellular Delivery of Antigens. *Advanced Functional Materials* 2015;25:2993-3003.

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Ma N, Li Y, Xu H, Wang Z, Zhang X. Dual Redox Responsive Assemblies Formed from Diselenide Block Copolymers. *Journal of the American Chemical Society* 2010;132:442-3.



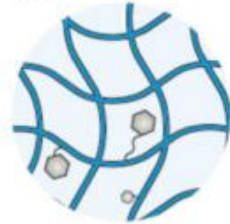
# Redukció-indukált hatóanyag-leadás



# Hatóanyag-polimer kölcsönhatástípusok

## a Covalent linkage

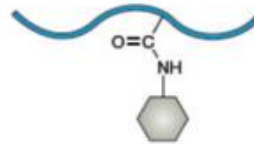
Highly stable



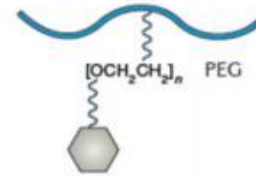
Cleavable



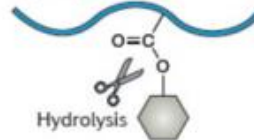
Amide bond



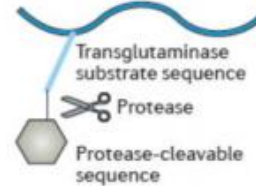
Bifunctional PEG linkage



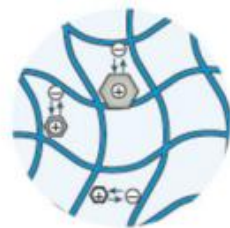
Hydrolytic linkage



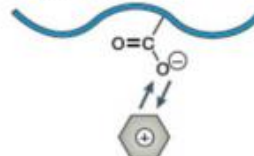
Protease linkage



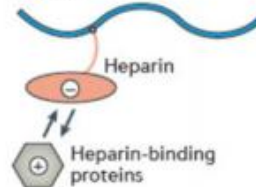
## b Electrostatic interaction



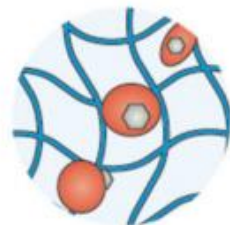
Carboxylate



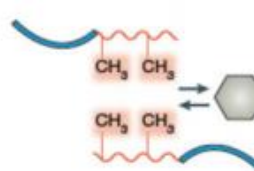
Heparin



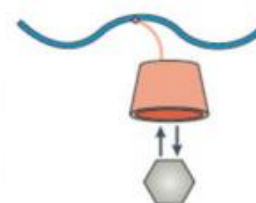
## c Hydrophobic association



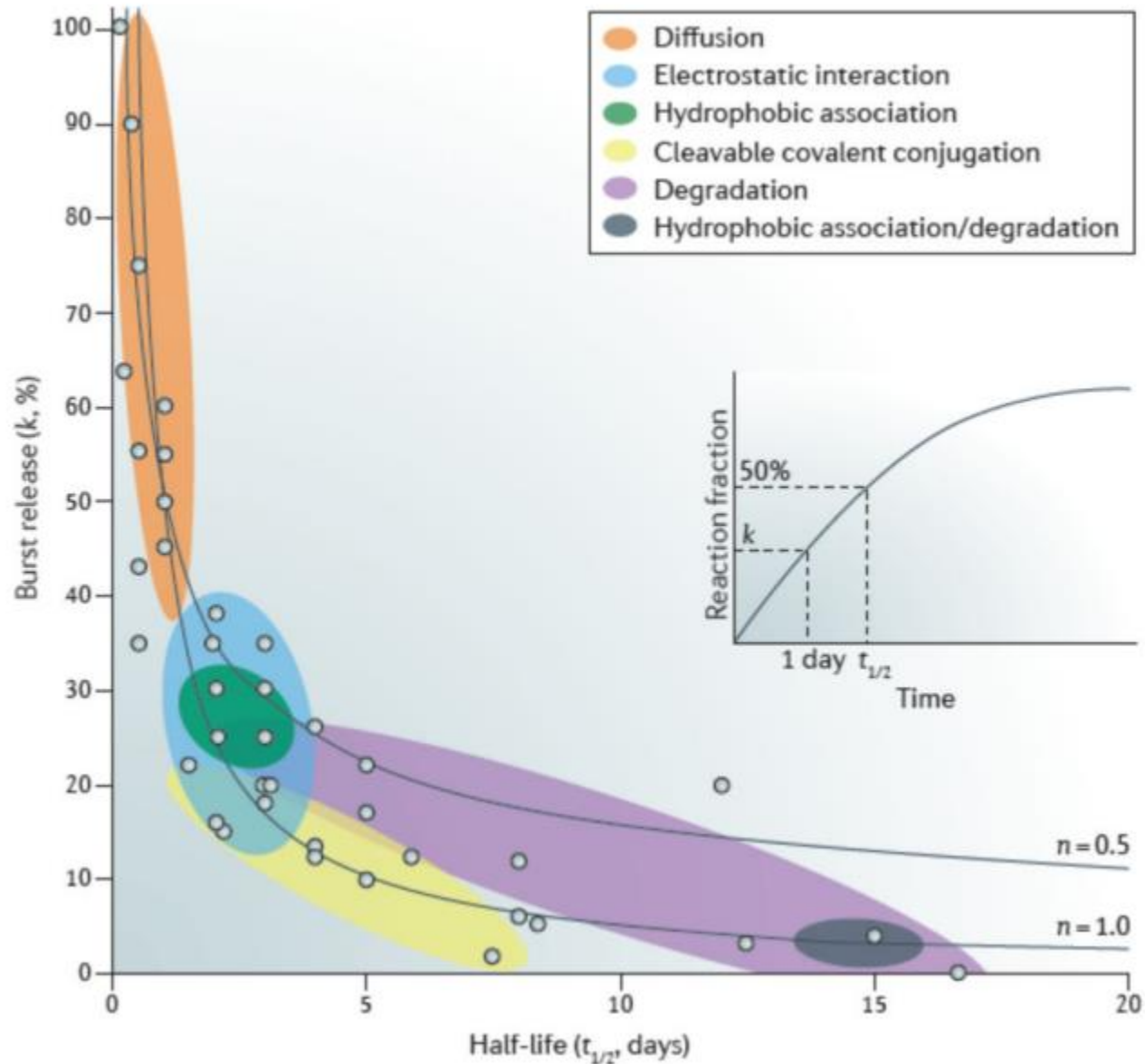
Aliphatic chains



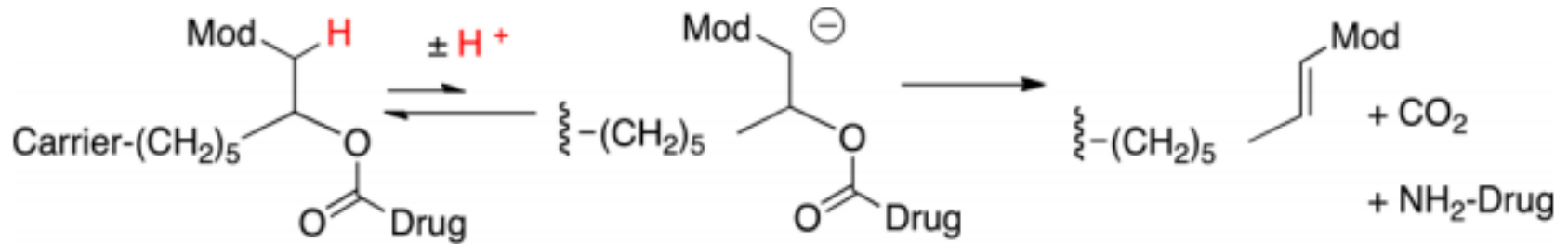
Cyclodextrin



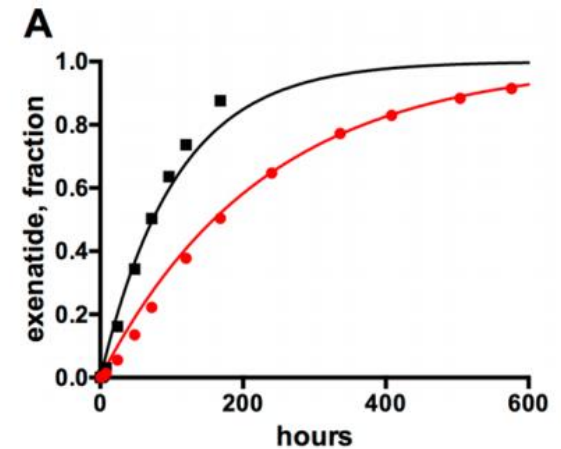
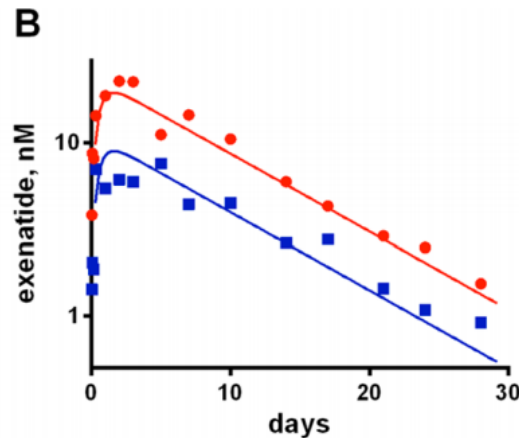
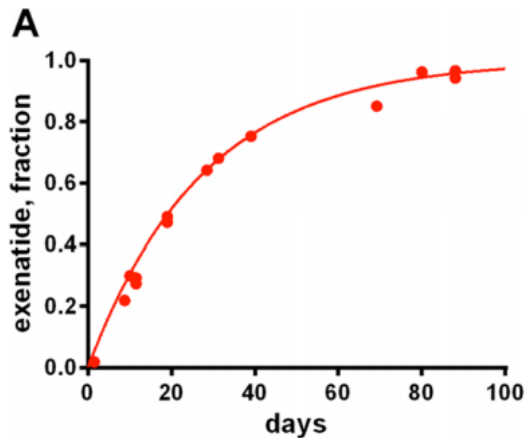
# A hatóanyag-leadás időfüggése



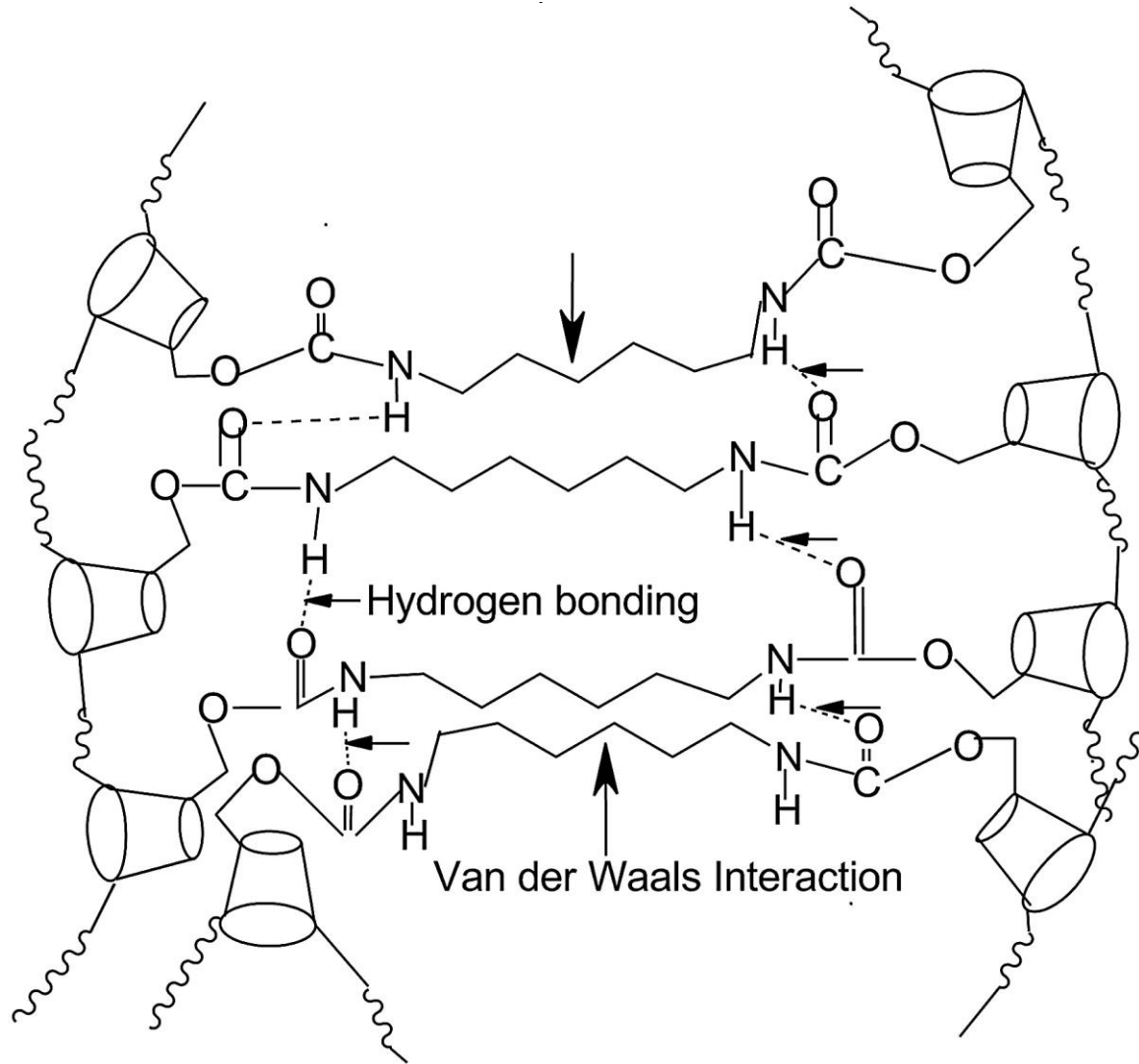
# Kovalensen kötött hatóanyag kioldódása



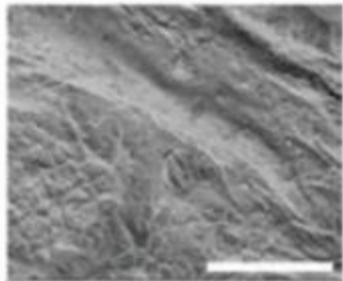
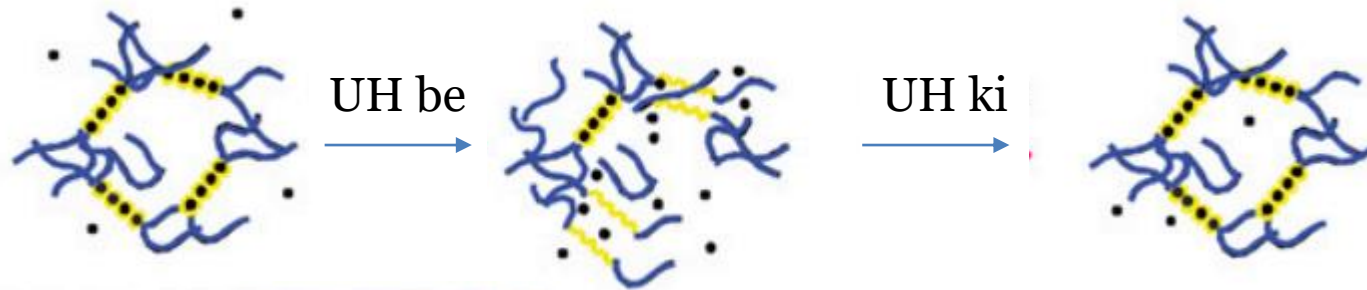
Hidrolízisre hajlamos kötés, pK<sub>a</sub> modulációval  
(erősebb elektronszívó csoport csökkenti a pK<sub>a</sub>-t)



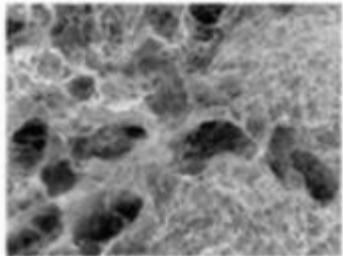
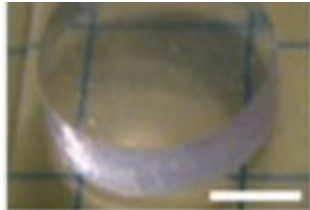
# Hidrofób hatóanyagok szállítása



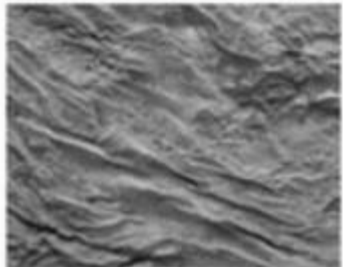
# Deformáció-indukált hatóanyag-leadás



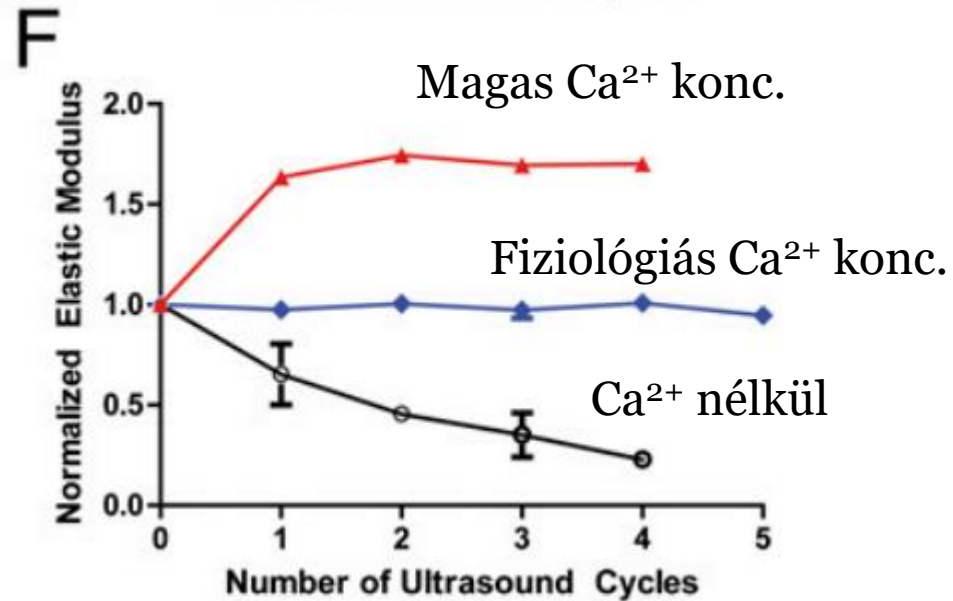
UH nélkül



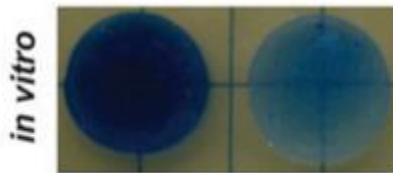
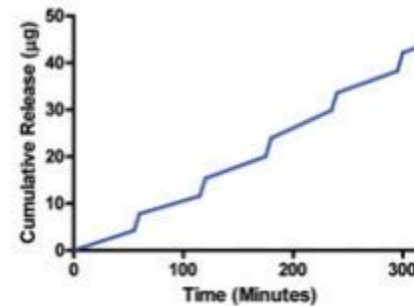
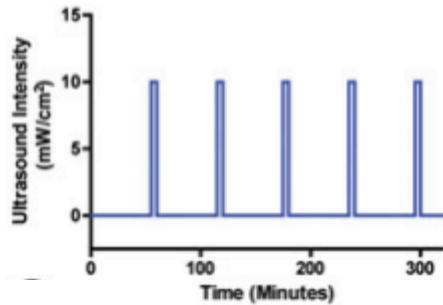
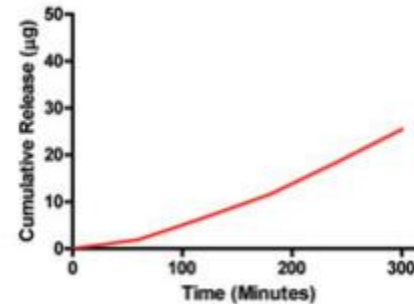
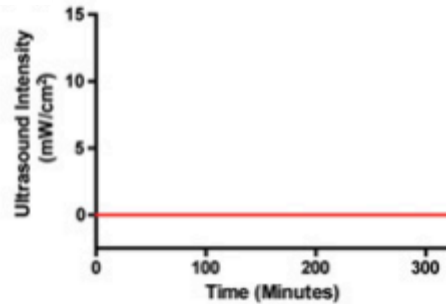
UH, Ca<sup>2+</sup> nélkül



UH, fiziológias Ca<sup>2+</sup> konc.

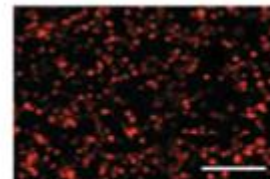


# Deformáció-indukált hatóanyag-leadás

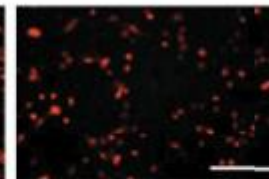


Diffúziós  
leadás

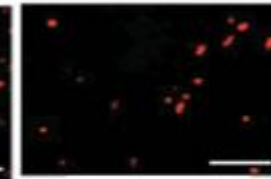
Leadás  
UH  
hatására



Kezelés nélkül



Elnyújtott  
leadás

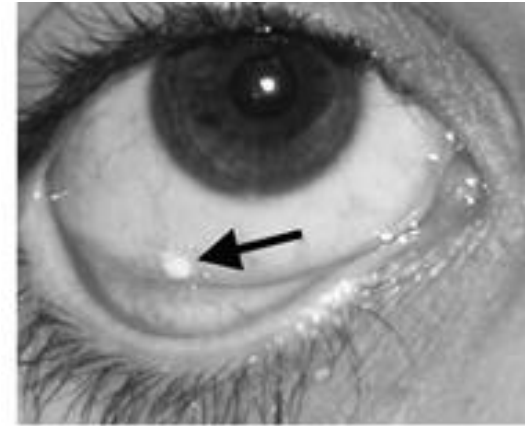


Pulzáló  
leadás

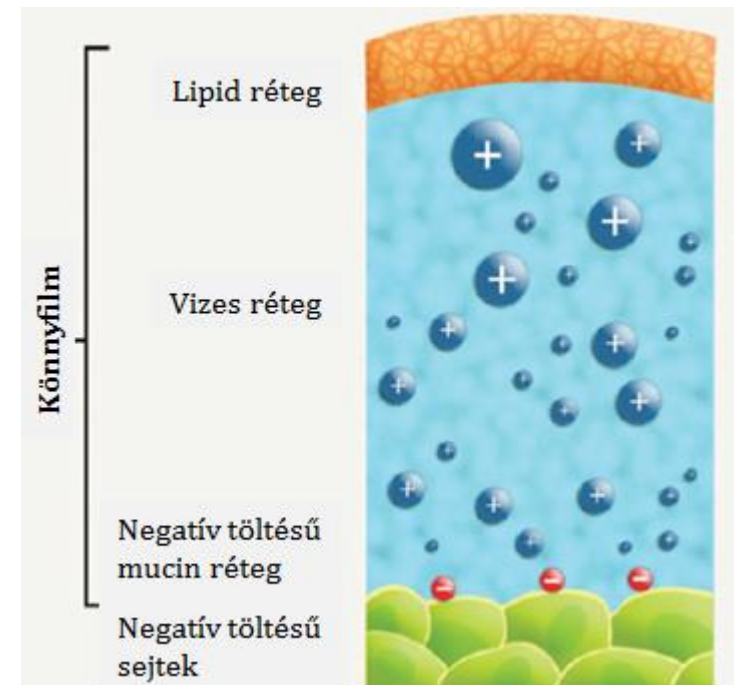
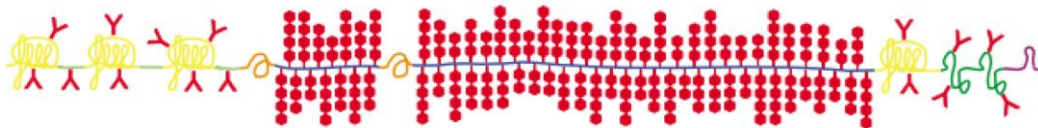
# Nyálkahártyák, mucin

Mucin előfordulása:

- Gastrointesztinális rendszer
- Szájüreg
- Orrnyálkahártya
- Szem
- Tüdő stb.

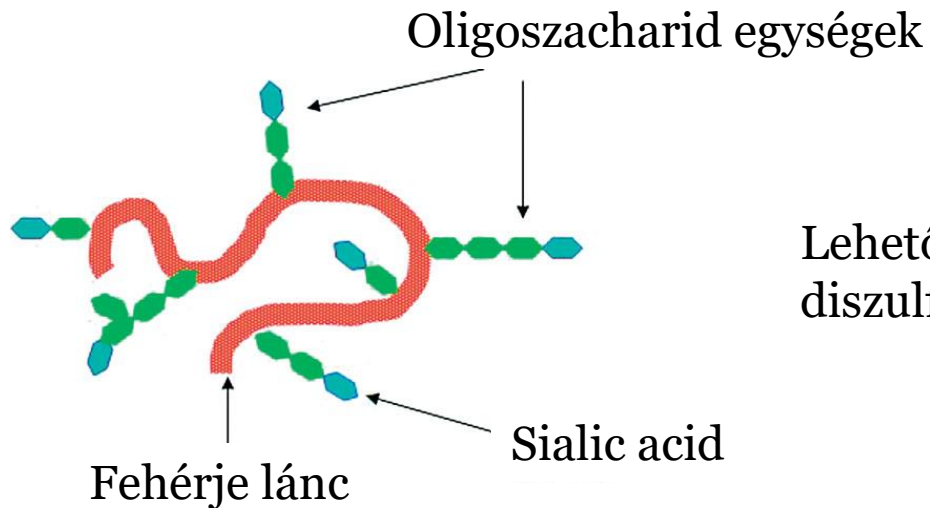
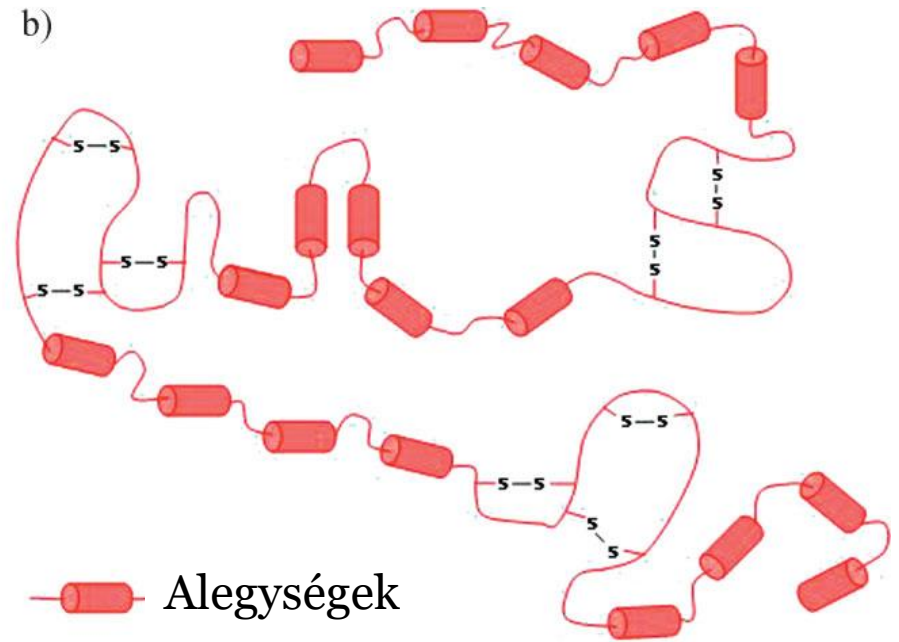
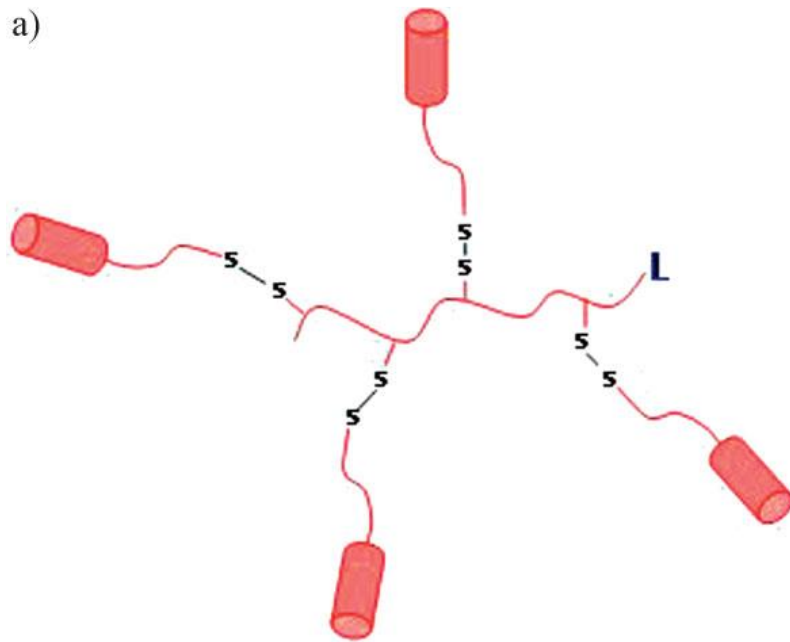


Nagy molekulatömegű fehérje  
(tipikusan 0.2-50 MDa)  
PTS régió (proline, threonine and  
serine) glikozilált



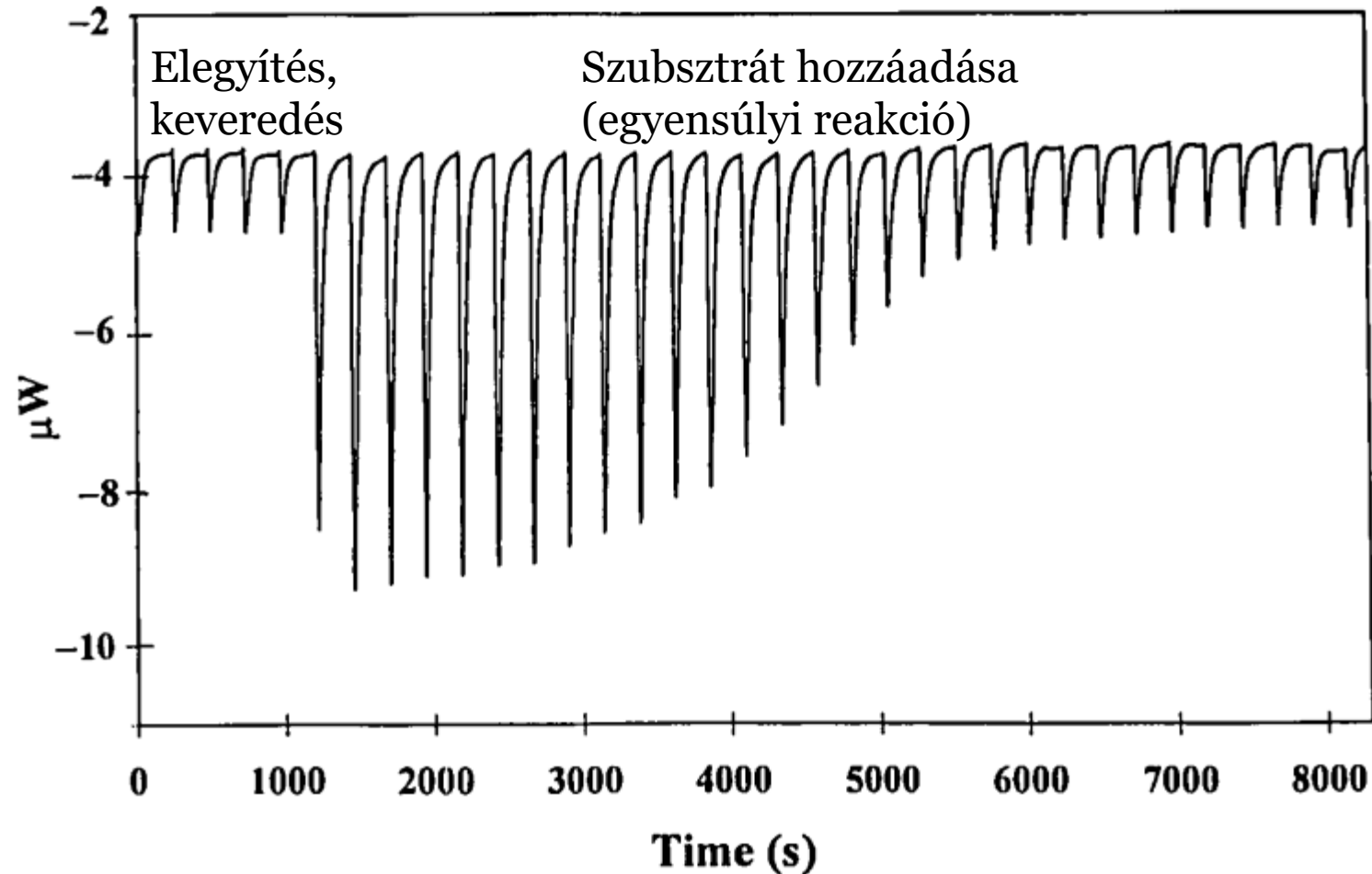


# A mucin szerkezete, kölcsönhatások



Lehetőség erős kölcsönhatásokra: H-híd, diszulfid híd, gélszerű állag

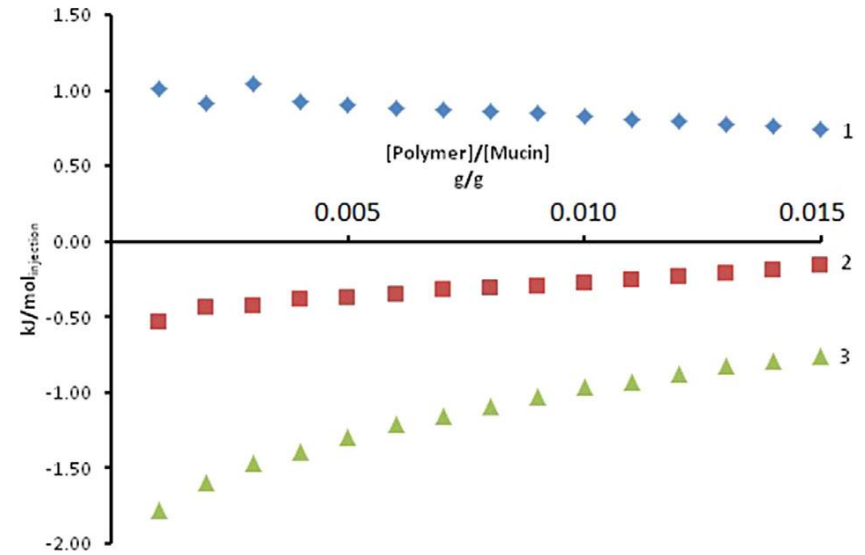
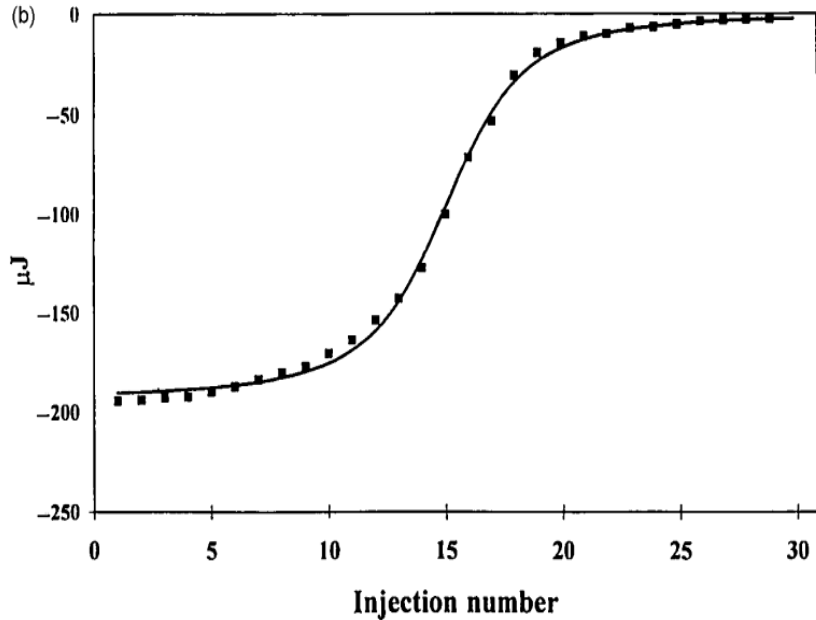
# Polimer – mucin köcsönhatás: Izoterm titrálós kalorimetria (ITC)



Nagy mintatérfogat (1 ml), a minták hozzáadagolását követően mérjük az izoterm állapothoz szükséges hőteljesítményt

# ITC titrálási görbe

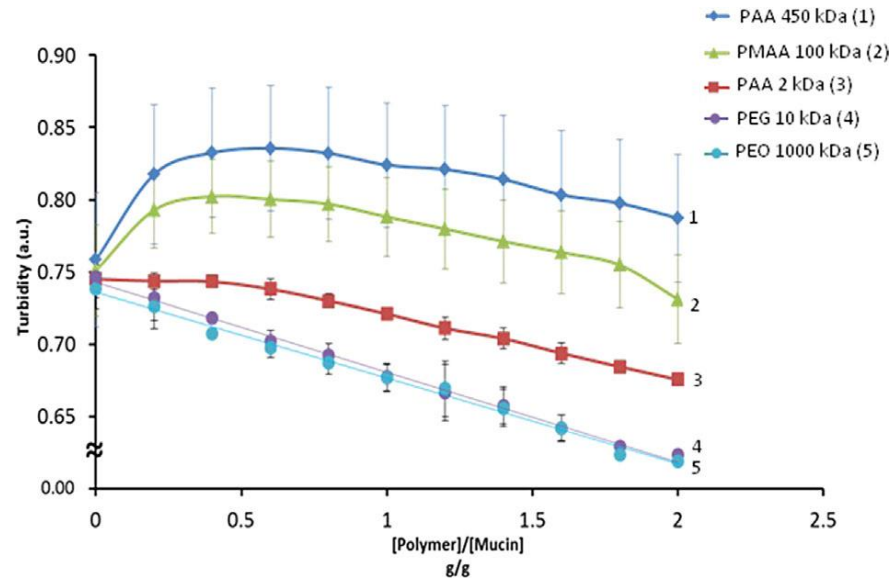
PAA 2 kDa (1), PMAA 100 kDa (2),  
PAA 450 kDa (3)



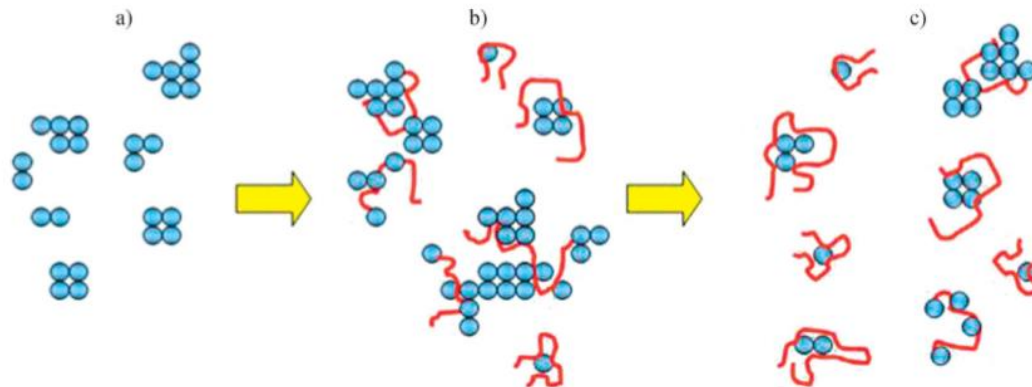
RNase A enzim titrálása ciklikus foszfáttal

Molekulatömeg- és  
szerkezetfüggő kölcsönhatás-  
erősség

# Polimer – mucin kölcsönhatás kolloid méretben

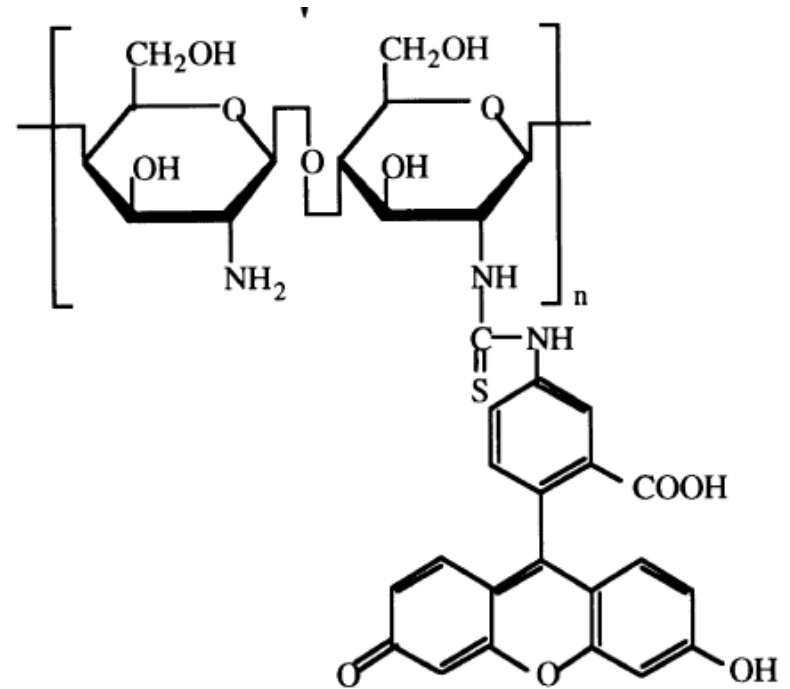
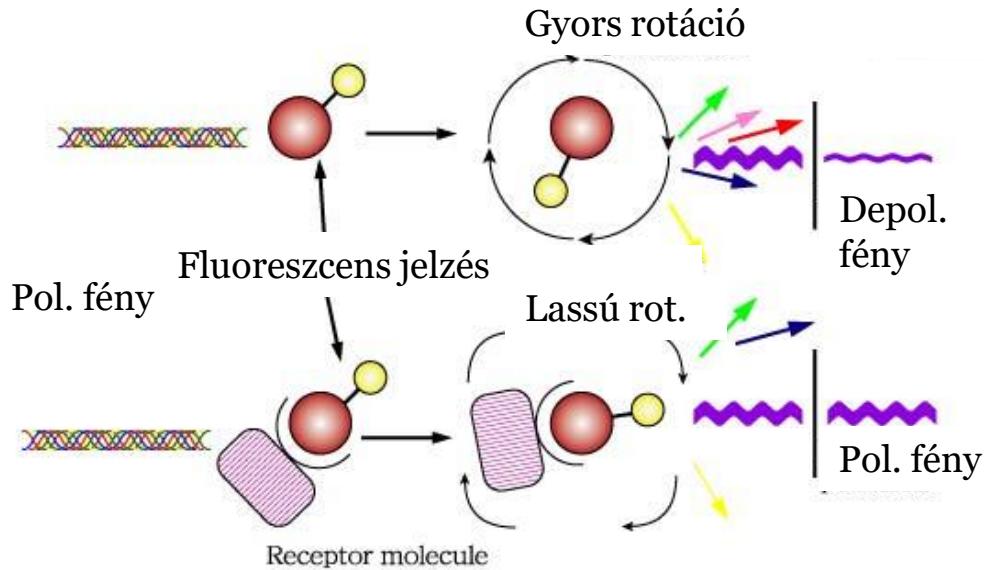


Turbiditás maximum: aggregátumok kialakulása, majd hígulás



Sogias IA, Williams AC, Khutoryanskiy VV. Why is Chitosan Mucoadhesive? *Biomacromolecules* 2008;9:1837-42.  
Khutoryanskiy VV. Advances in Mucoadhesion and Mucoadhesive Polymers. *Macromolecular Bioscience* 2011;11:748-64.  
Albarkah YA, Green RJ, Khutoryanskiy VV. Probing the Mucoadhesive Interactions Between Porcine Gastric Mucin and Some Water-Soluble Polymers. *Macromolecular Bioscience* 2015;15:1546-53.

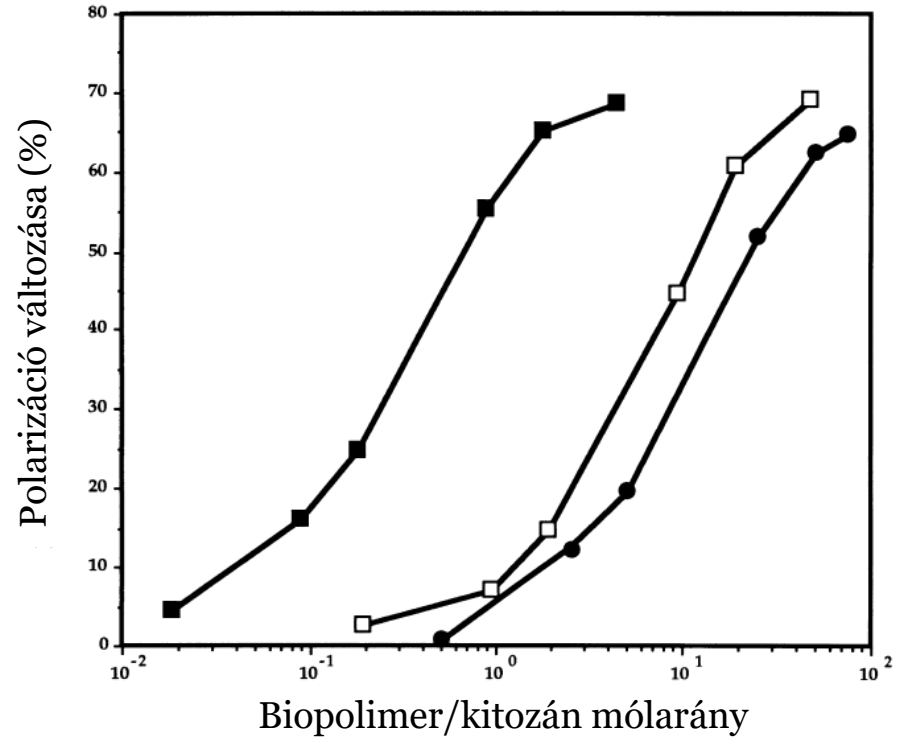
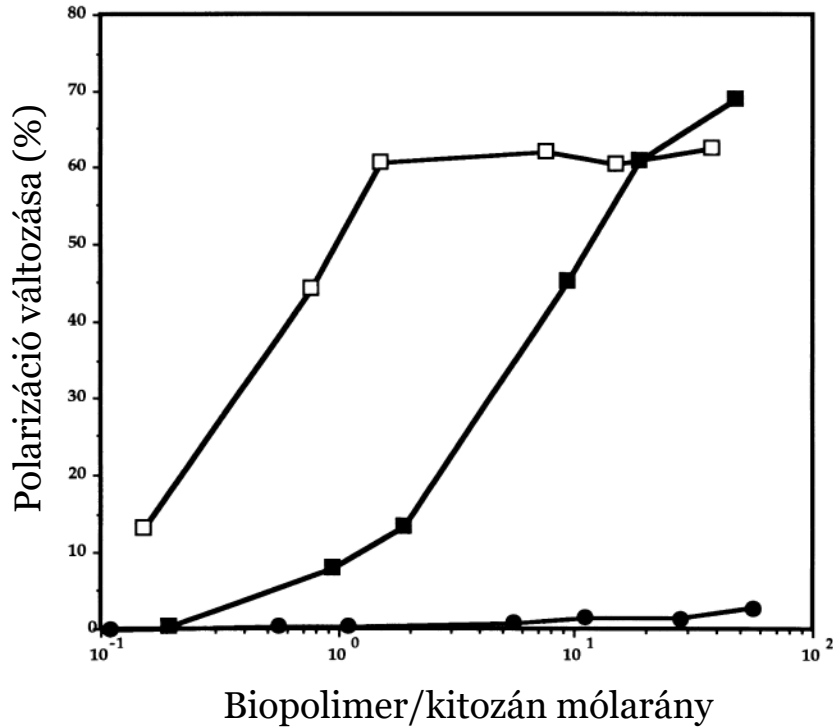
# Fluoreszcencia depolarizáció



Fluoreszcens kitozán

- Kismolekulák esetén gyors depolarizáció
- Makromolekulák esetén maradó polarizáció, steady-state mérhető

# Fluoreszcencia depolarizáció

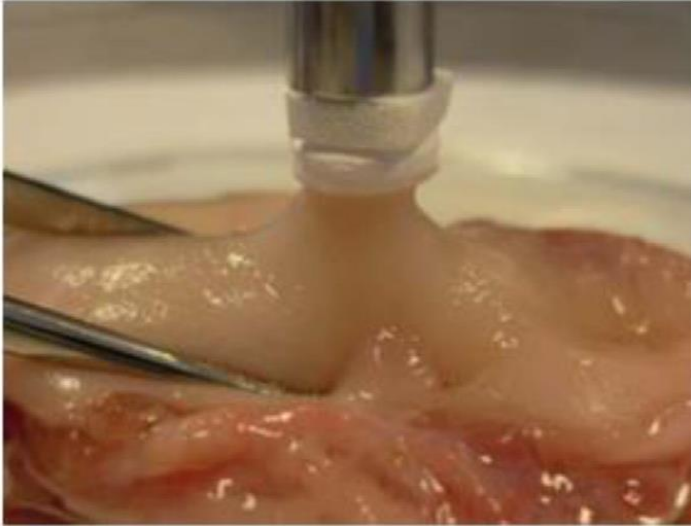


Kitozán: polikation

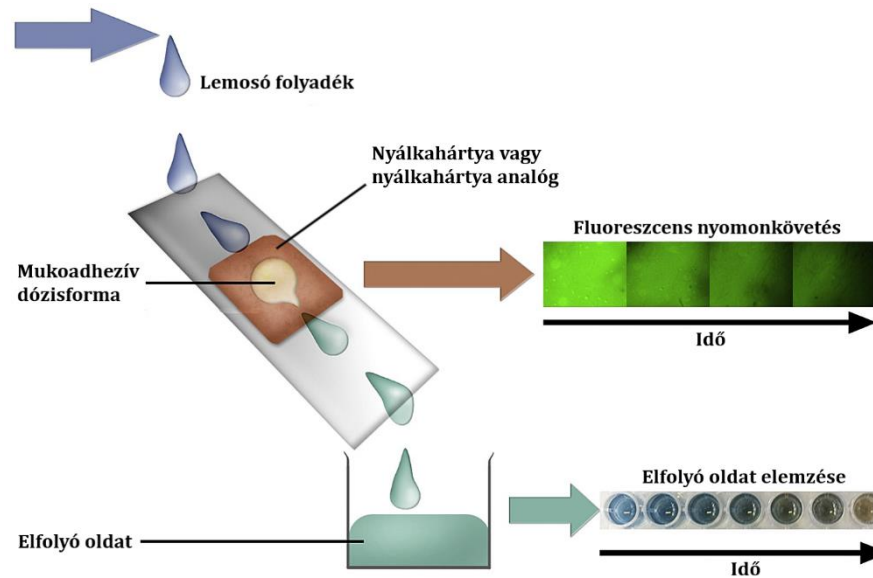
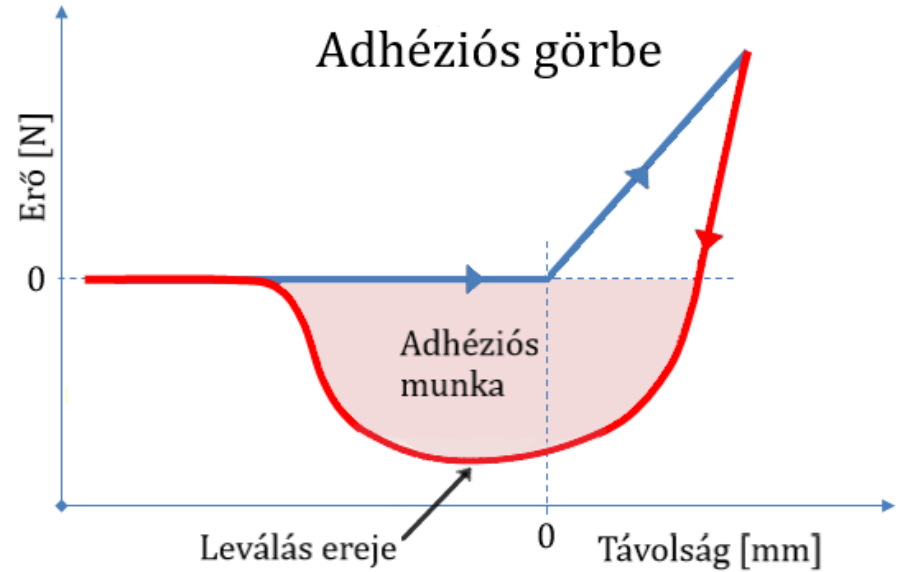
- Negatív kontroll: albumin
- Pozitív kontroll: dextrán szulfát (polianion)

Növekvő molekulatömeggel növelhető a mukoadhézió mértéke (több kölcsönhatási pont)

# Mechanikai mérések, ex vivo

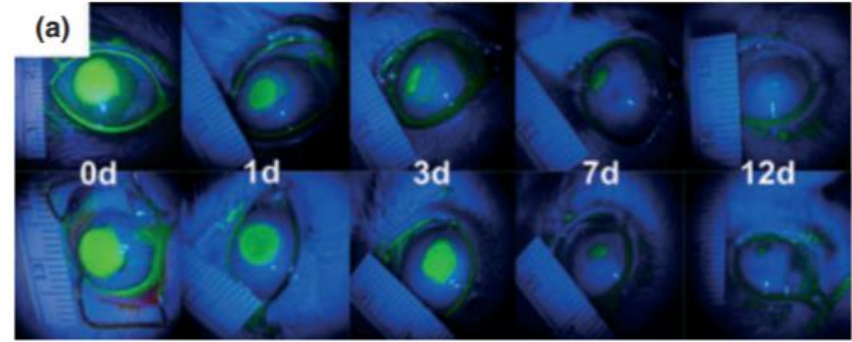


Szakító vizsgálat

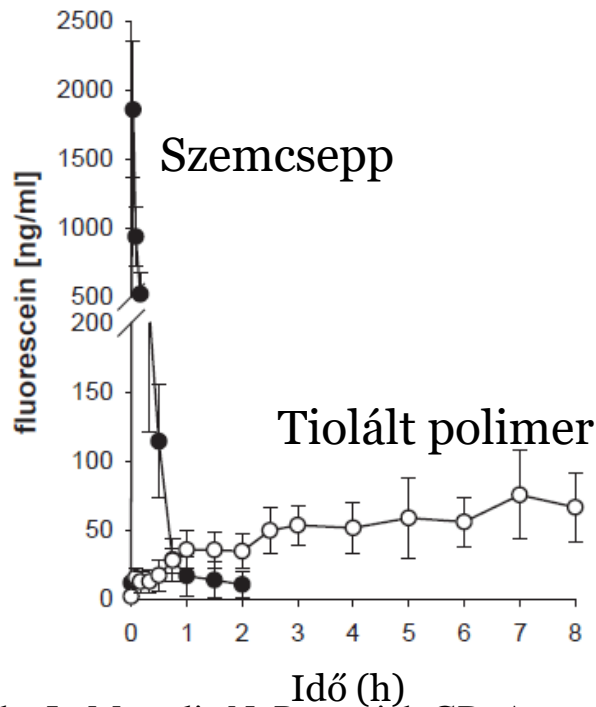
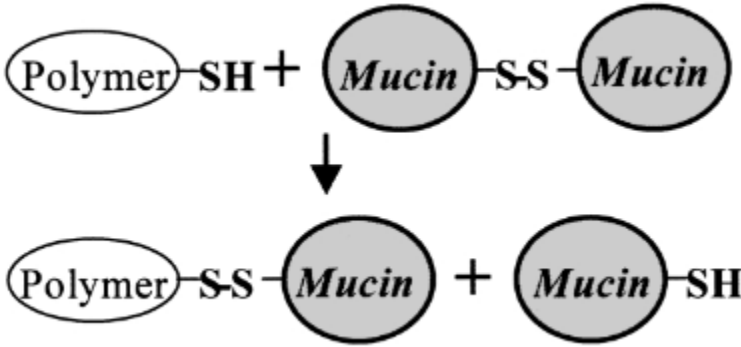
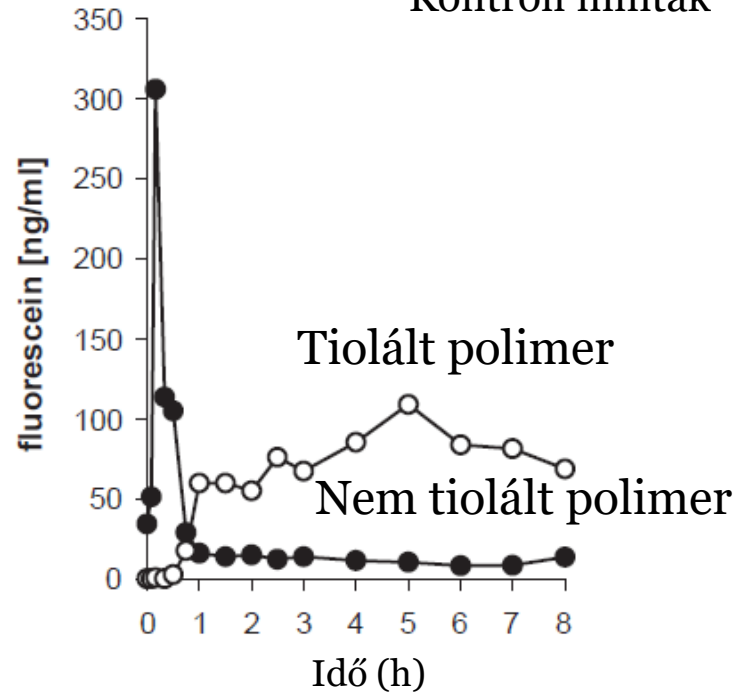


# Mukoadhézió – *in vivo*

Tiolált hialuronsav



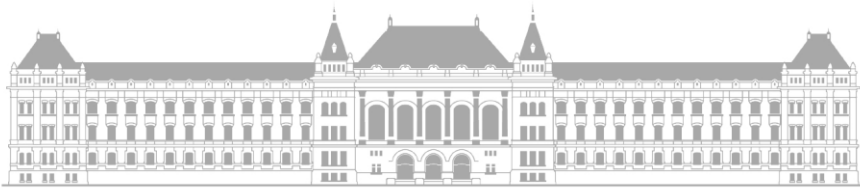
Kontroll minták



Yang G, Espandar L, Mamalis N, Prestwich GD. A cross-linked hyaluronan gel accelerates healing of corneal epithelial abrasion and alkali burn injuries in rabbits. *Veterinary Ophthalmology* 2010;13:144-50.

Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. *Advanced Drug Delivery Reviews* 2005;57:1595-639.





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Budapesti Műszaki és Gazdaságtudományi Egyetem  
Vegyészmérnöki és Biomérnöki Kar  
Fizikai Kémia és Anyagtudományi Tanszék

**Köszönöm a figyelmet!**

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