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

SOFT MATTERS GROUP

Poly(amino acid) derivatives and hydrogels for biomedical application

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NanoMed

Budapest, 04/12/2018

Responsive polymers and hydrogels

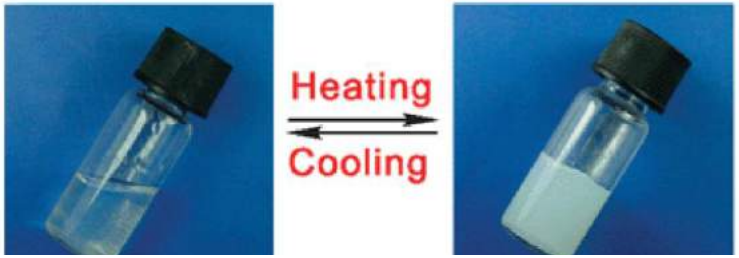
Responsive materials: abrupt change in physical properties in response to environmental stimuli

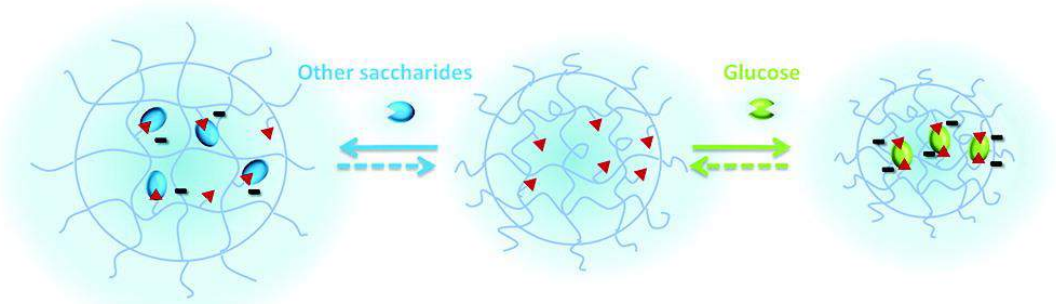
Stimuli:

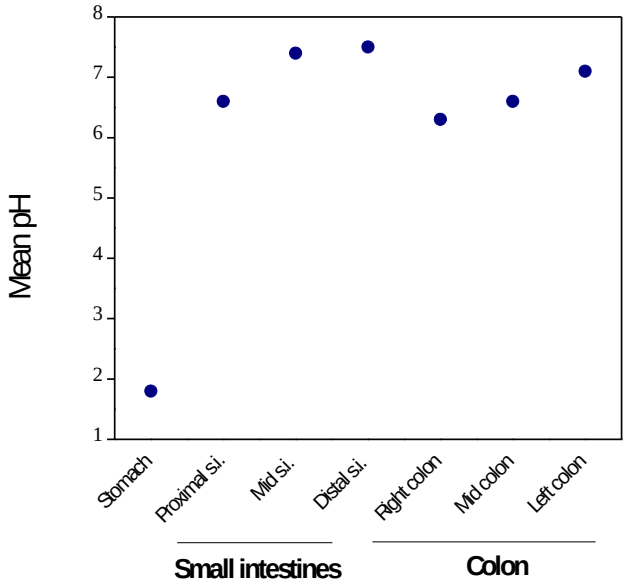
- Temperature, pH (gastrointestinal targeting)
- **Redox effects**
- Enzymes, biomolecules, saccharides

Response:

- Change in solubility, sol-gel transition
- Swelling, shrinking





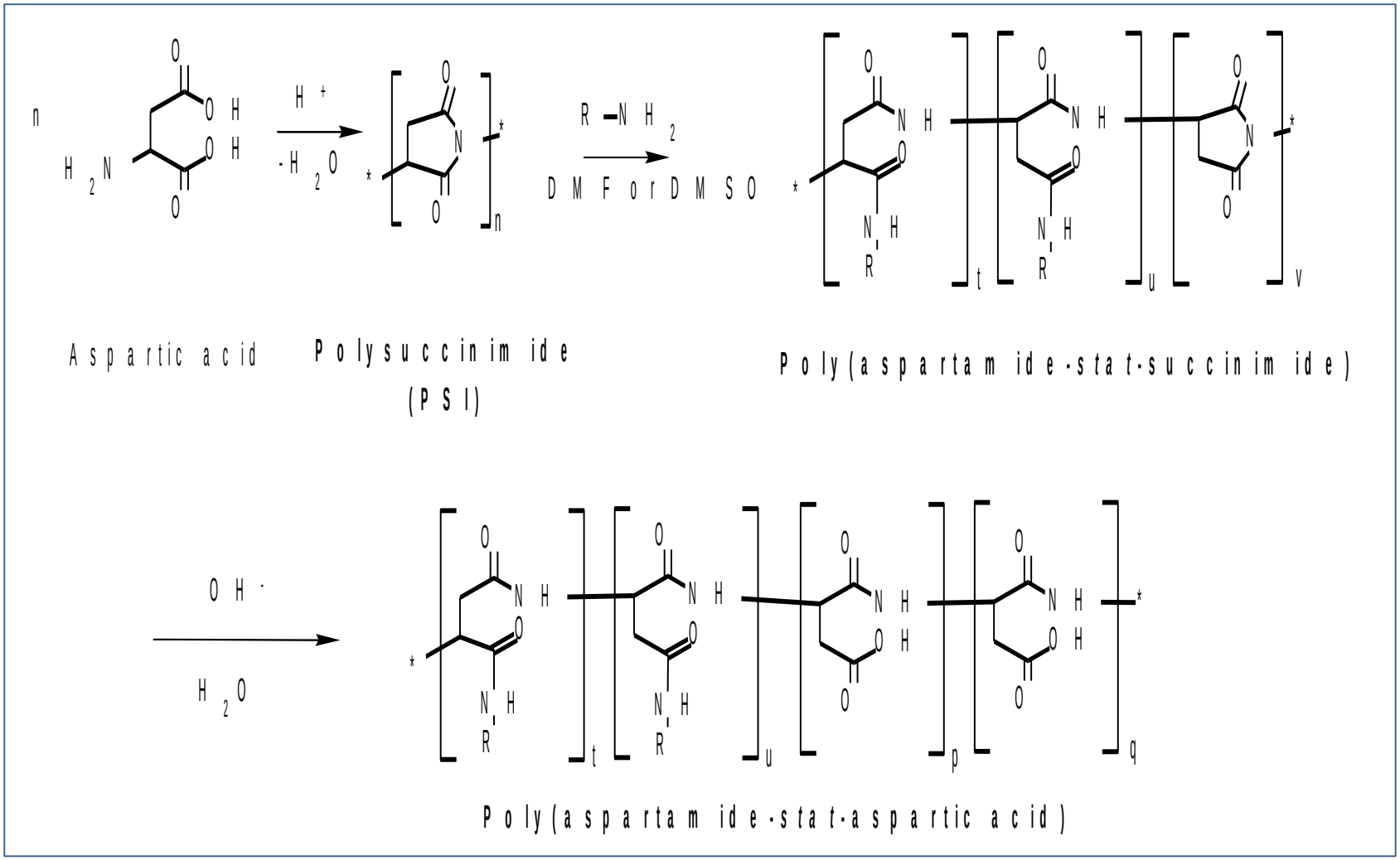




MIT

Hennink et al. Chem. Rev. 2012; 112: 2853.; Bernkop-Schnürch. Adv. Drug Deliver. Rev. 2005; 57: 1569.
Ancla et al. Langmuir. 2011; 27: 12693.

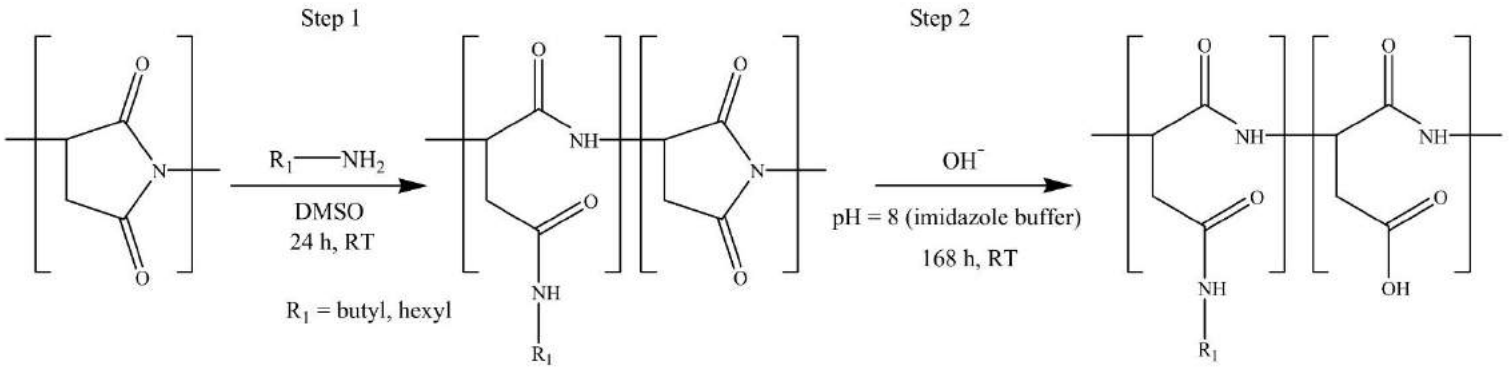
Chemistry of poly(aspartic acid)



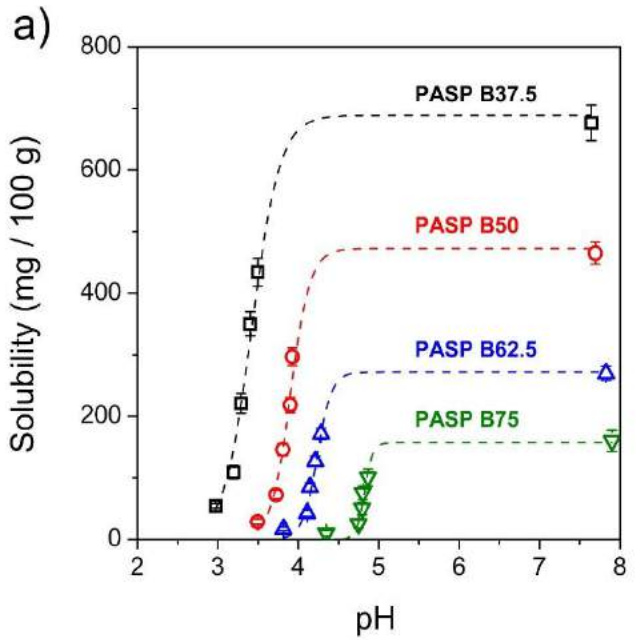
Natural amino acid (aspartic acid) as monomer

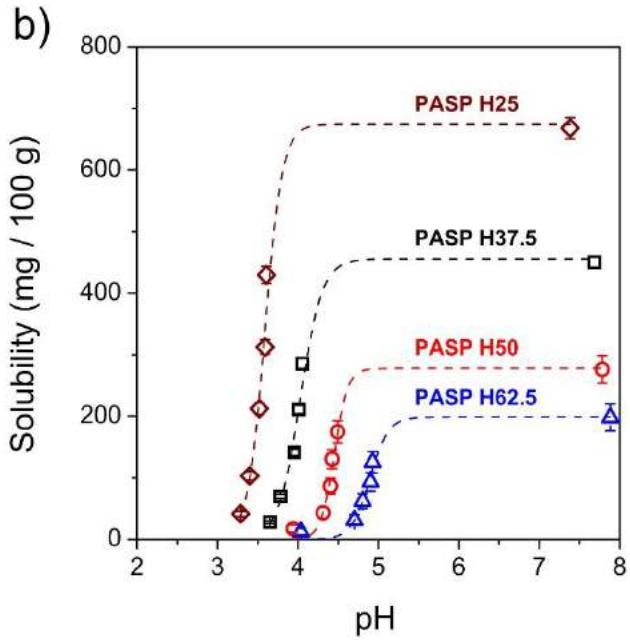
Polyanionic character (negative charge at neutral pH)

Poly(aspartic acid) (PASP) derivatives



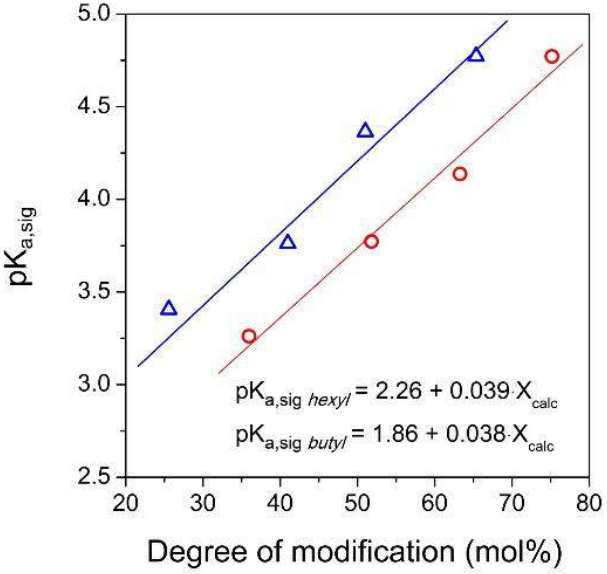


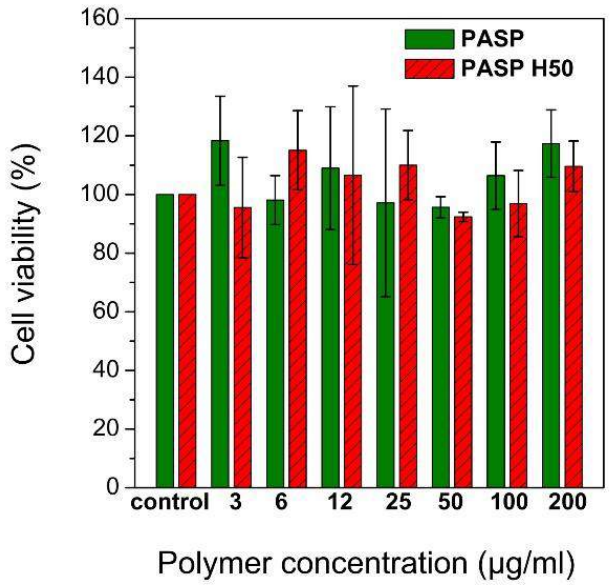


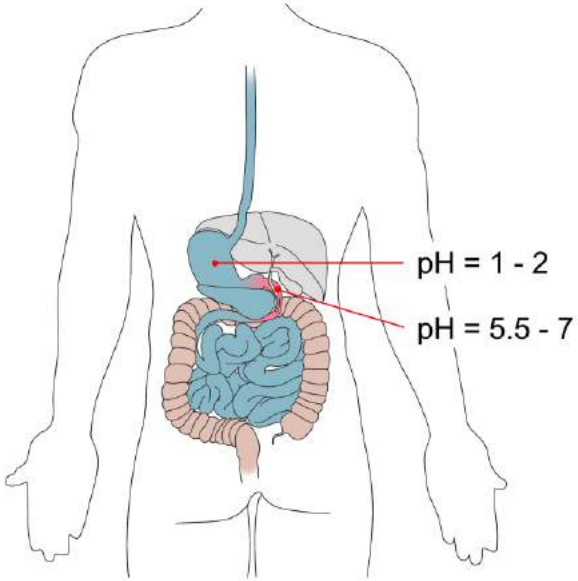


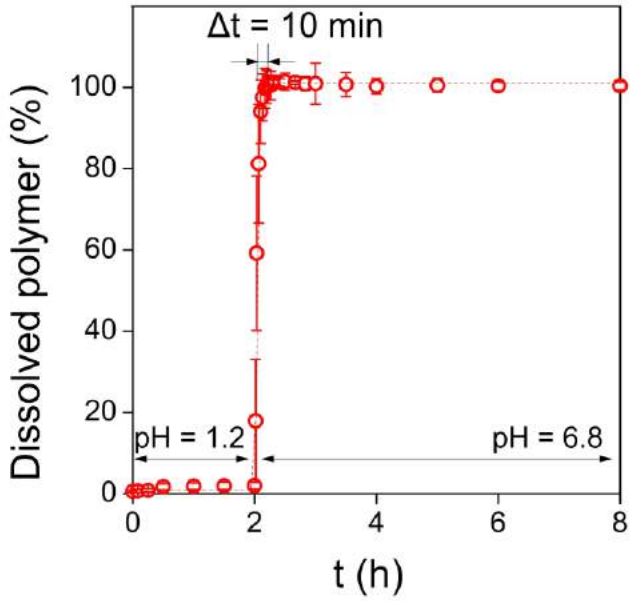
Németh et al. Acta Biomater., 49: 486-494 (2017)

pH-dependent dissolution of PASP



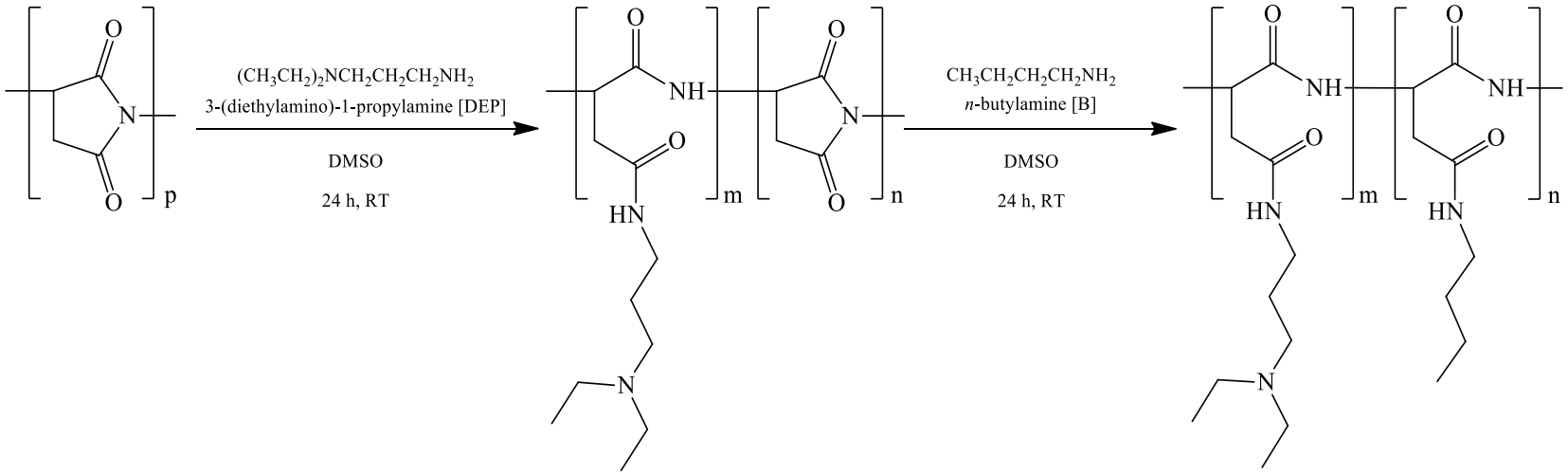


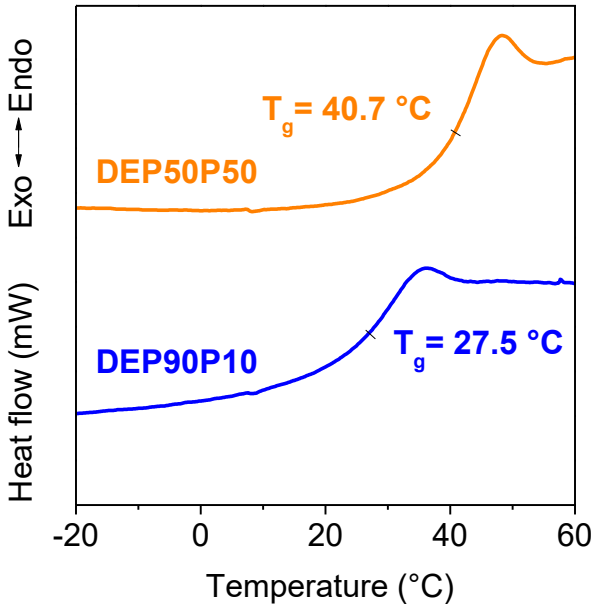


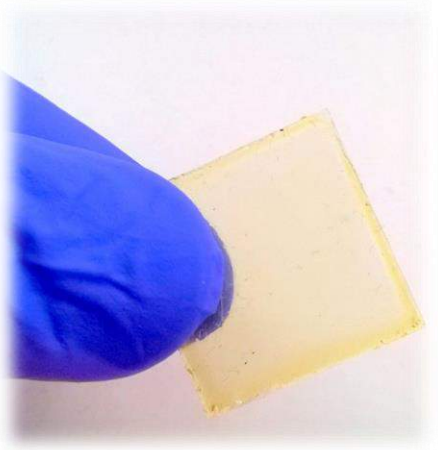


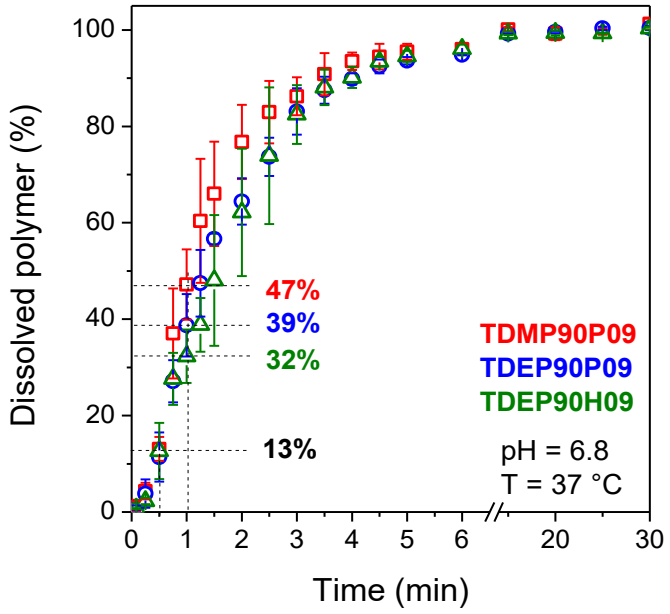
Németh et al. Eur. Polym. J. 93: 805-814 (2017)

Polyaspartamides with cationic side groups



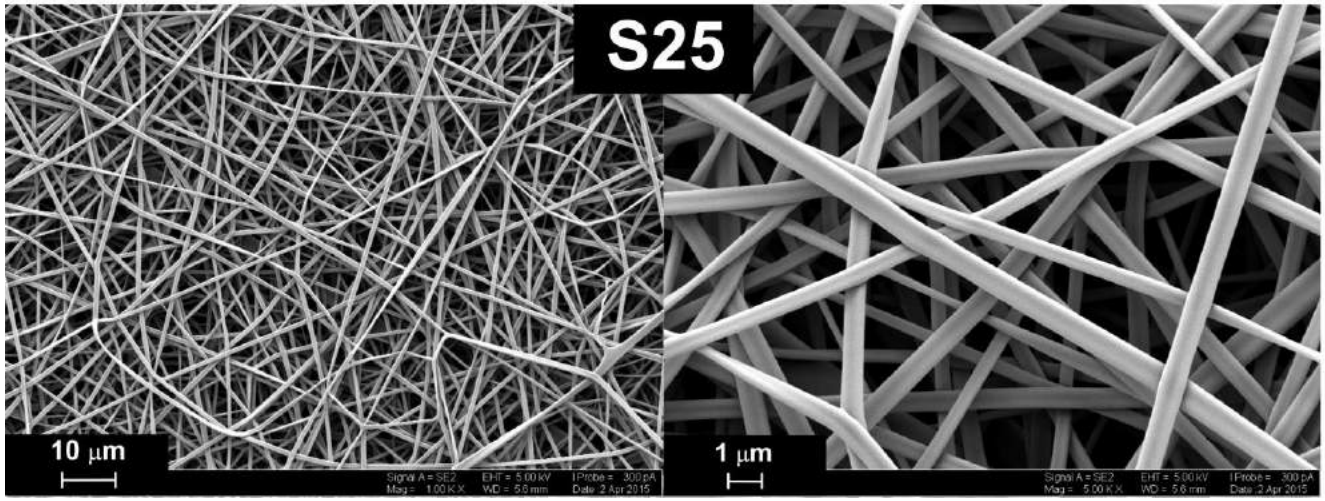


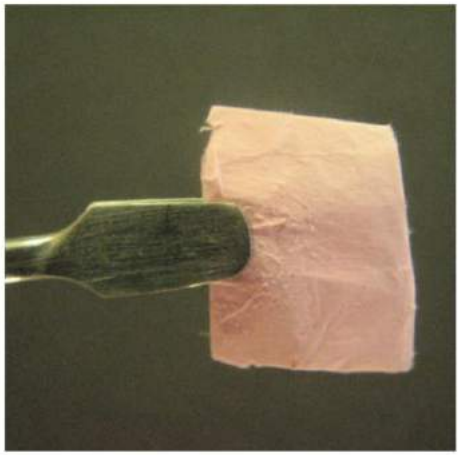


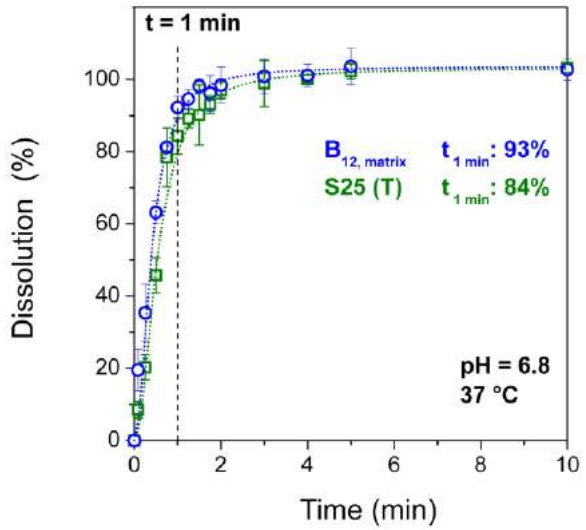


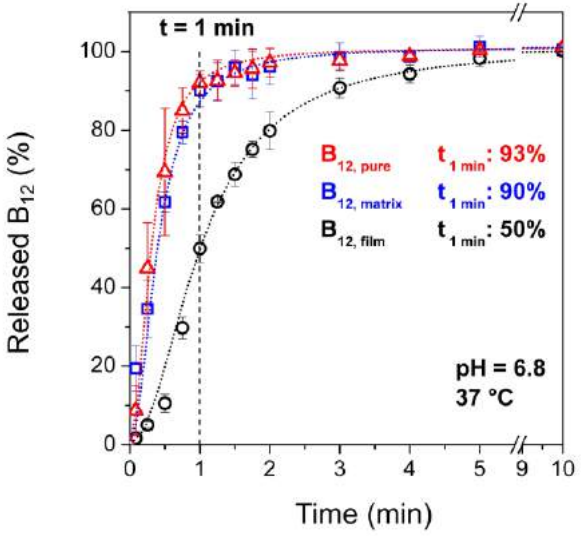
Németh et al. Acta Biomater., 49: 486-494 (2017)

Electrospun matrices

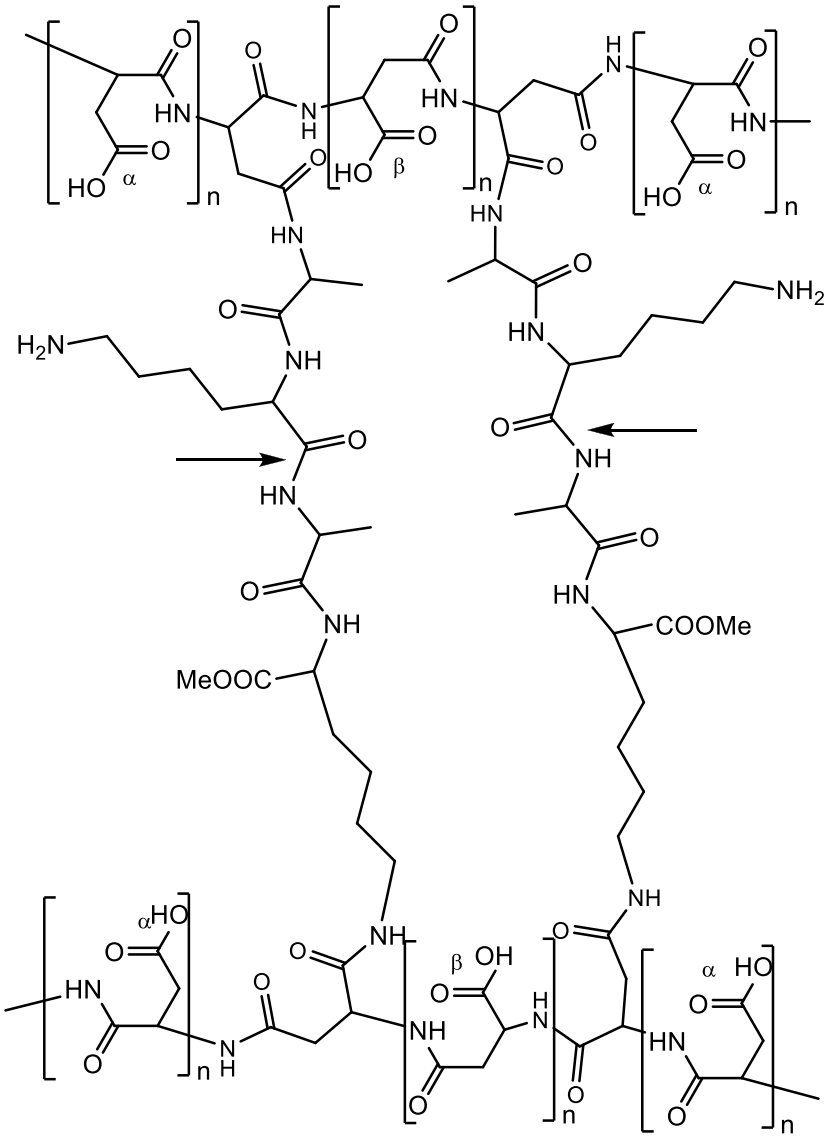


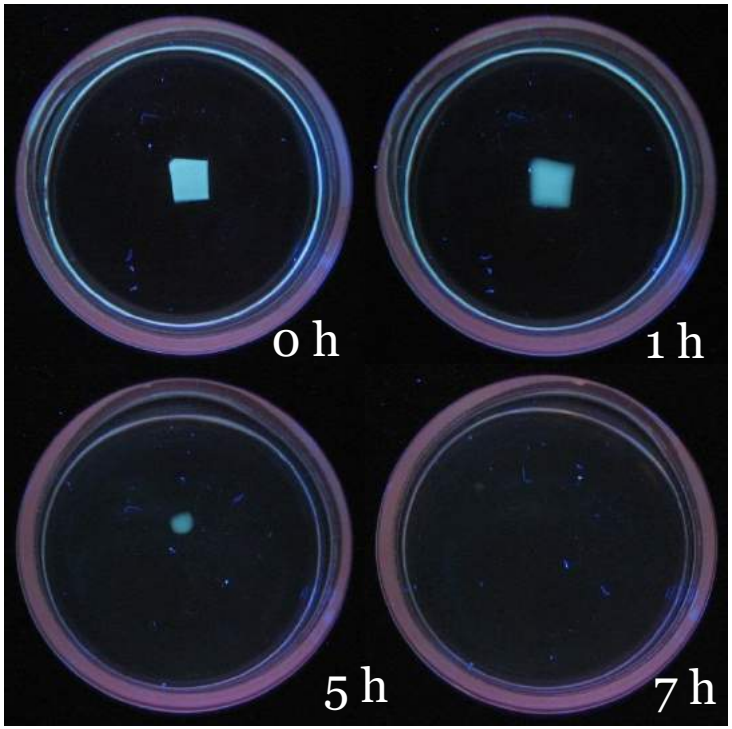


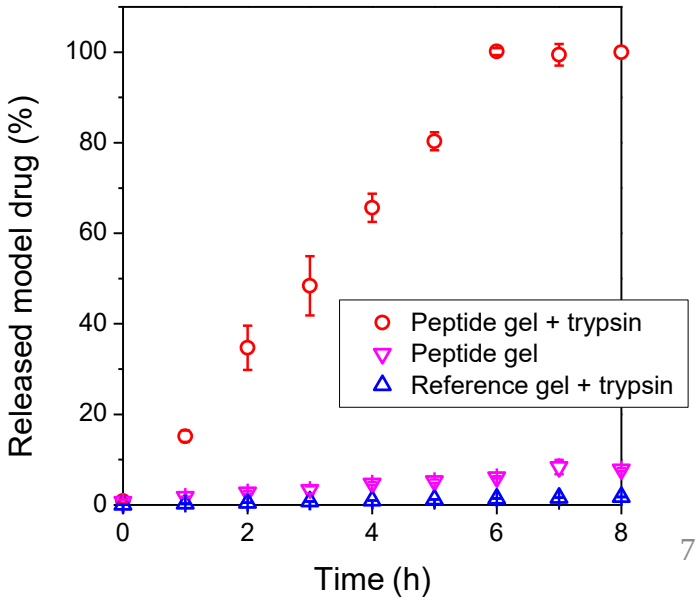




Enzymatically degradable cross-links





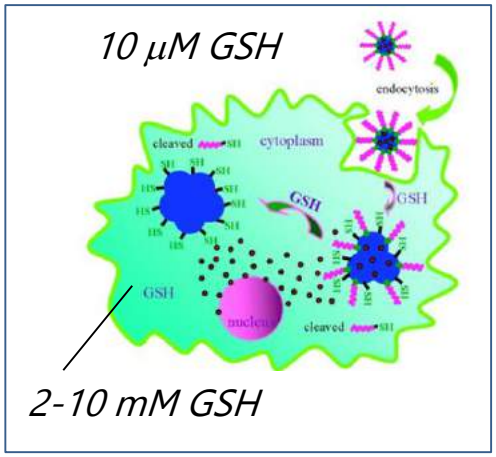


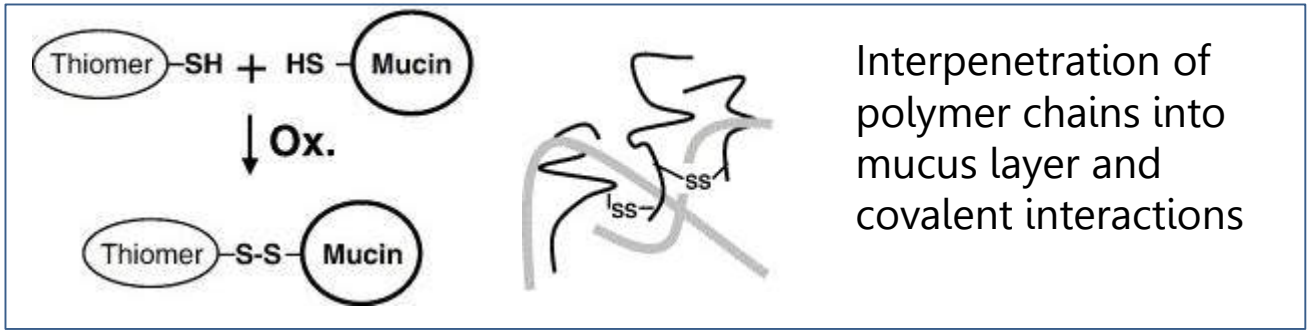
Szilágyi et al. React. & Funct, Pol. 133:21-28 (2018)

Redox response: thiol-disulphide transformation

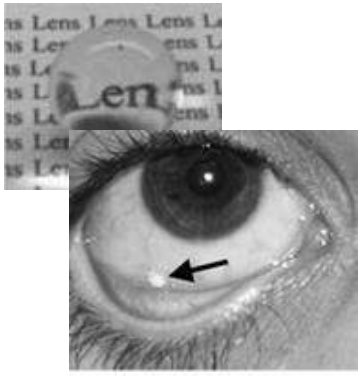
The role of thiol-disulphide transformation

- Glutathione-mediated redox processes to maintain **redox potential** in intracellular and extracellular milliue, intracellular targeting (e.g. chemotherapeutics)
- Bioadhesion, sustained release of encapsulated material





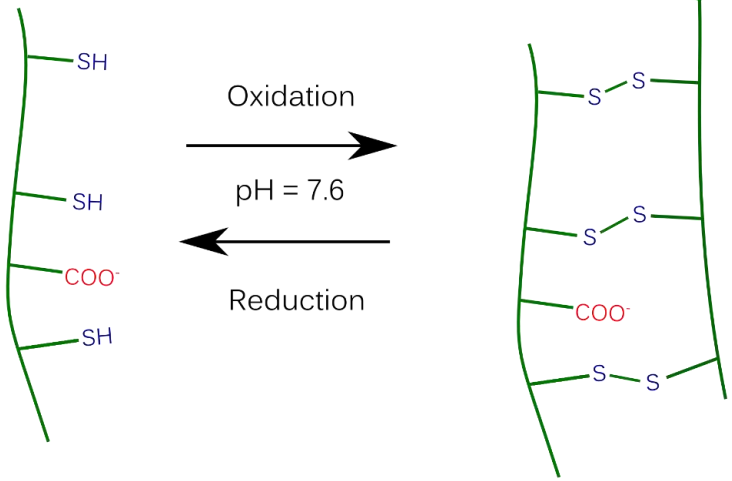
Interpenetration of polymer chains into mucus layer and covalent interactions

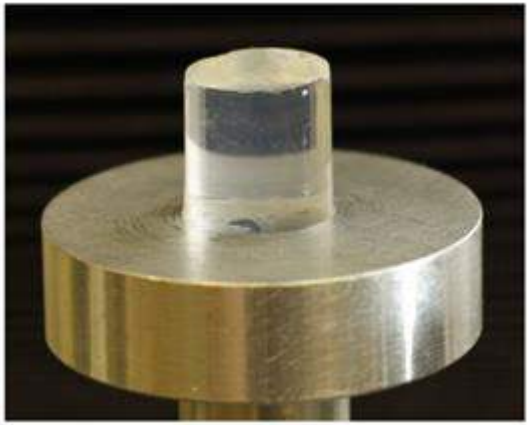


Bernkop-Schnürch. Adv. Drug Deliver. Rev. 2005; 57: 1569.
Zhong et al. Biomacromolecules, 2010; 11: 848.
Hisano et al. J. Biomed. Mater. Res. 1998; 40:115.

Redox-induced sol-gel transition





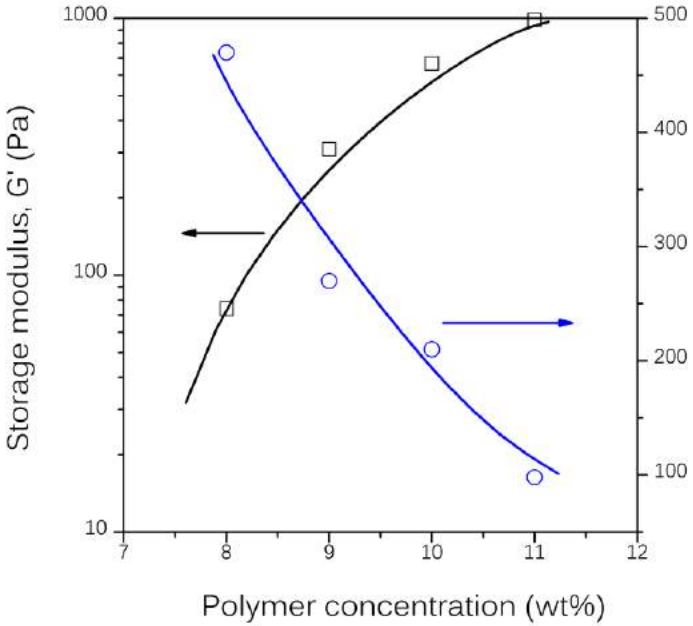


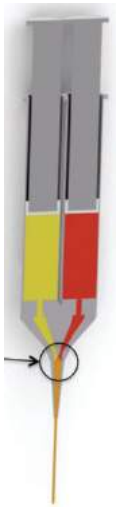
Thiolated PASP

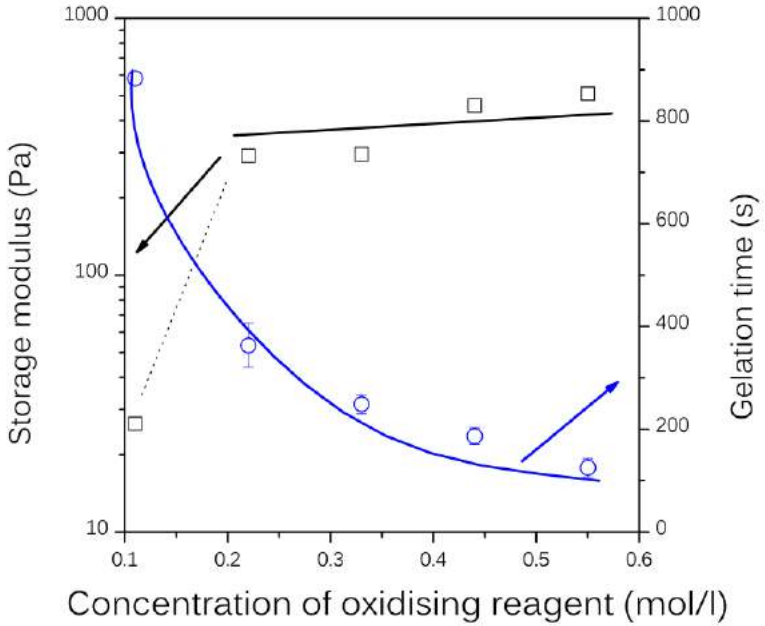
Disulphide cross-linked PASP gel

Gyarmati et al. Macromol. Biosci. 13:633-640 (2013)

Controllable gelation time and strength





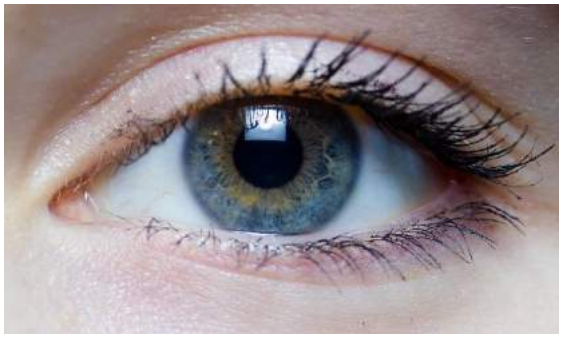


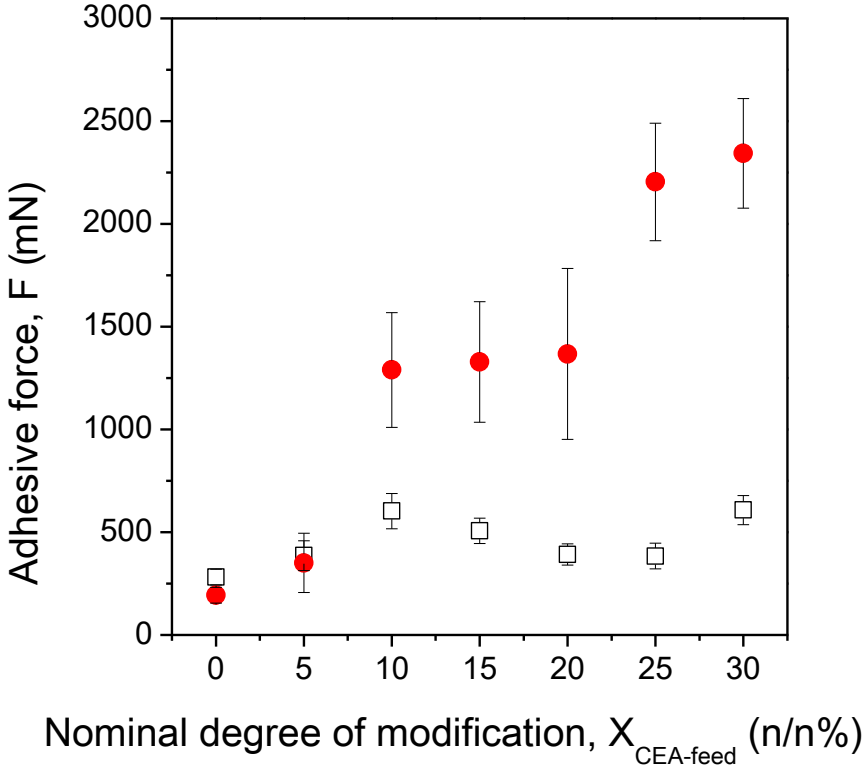
Gyarmati et al. React. & Funct. Pol. 84:29-36 (2014)

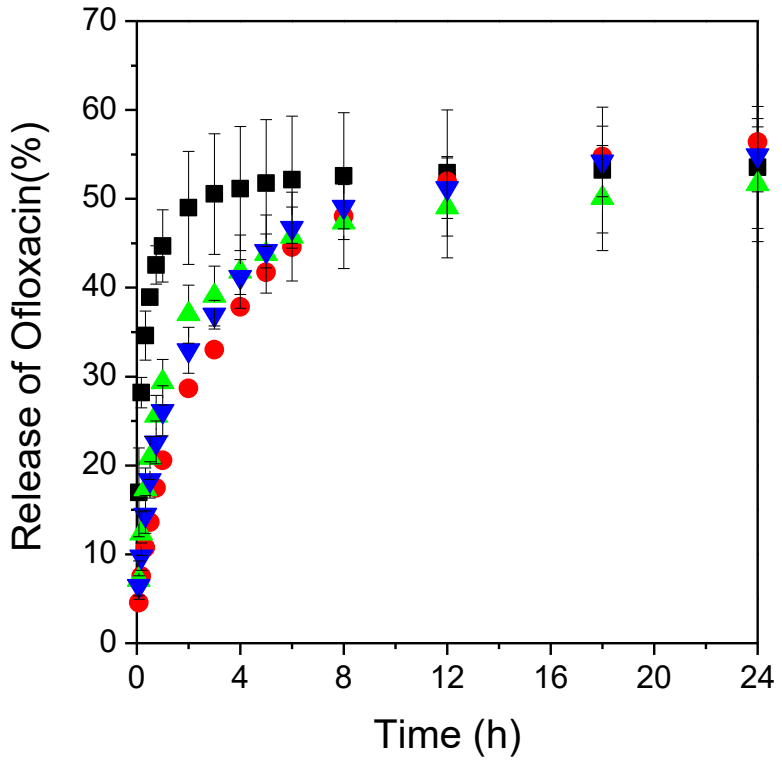
Mucoadhesion, sustained release

Biological barriers:

- Blinking (mechanical effect)
- Lachrimation
- Low corneal permeability

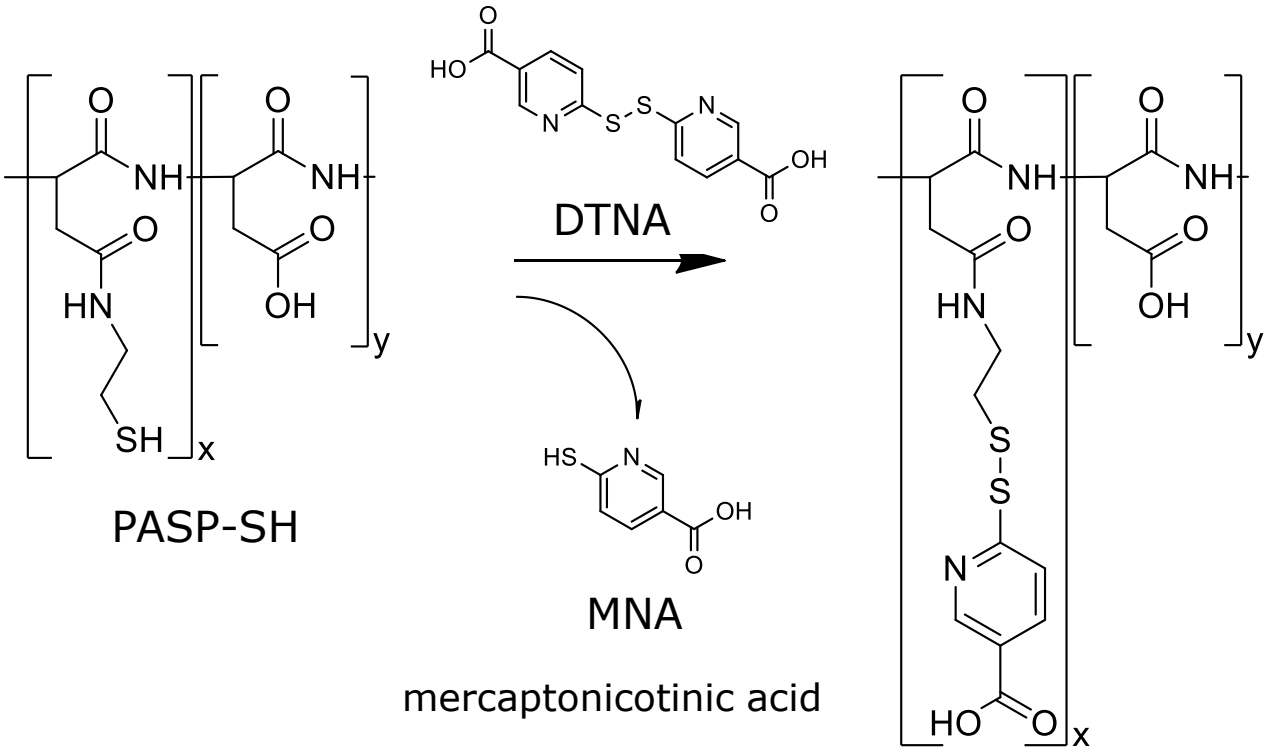






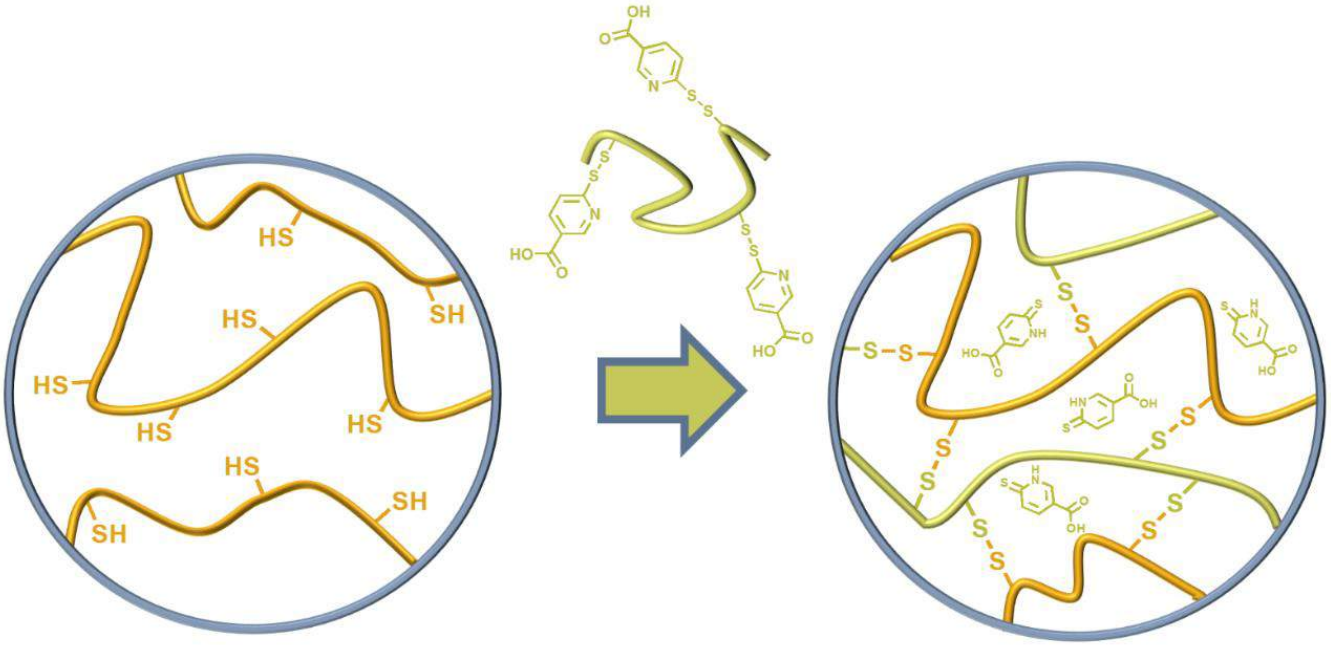
Szilágyi et al. Polym. Int. 66: 1538-1545 (2017); Morrison et al. Ther. Deliv. 5:1297 (2014)

Thiol-protected PASP



Low stability of thiols against atmospheric oxidation can be improved, mucoadhesion might increase
No need for external oxidizing agent

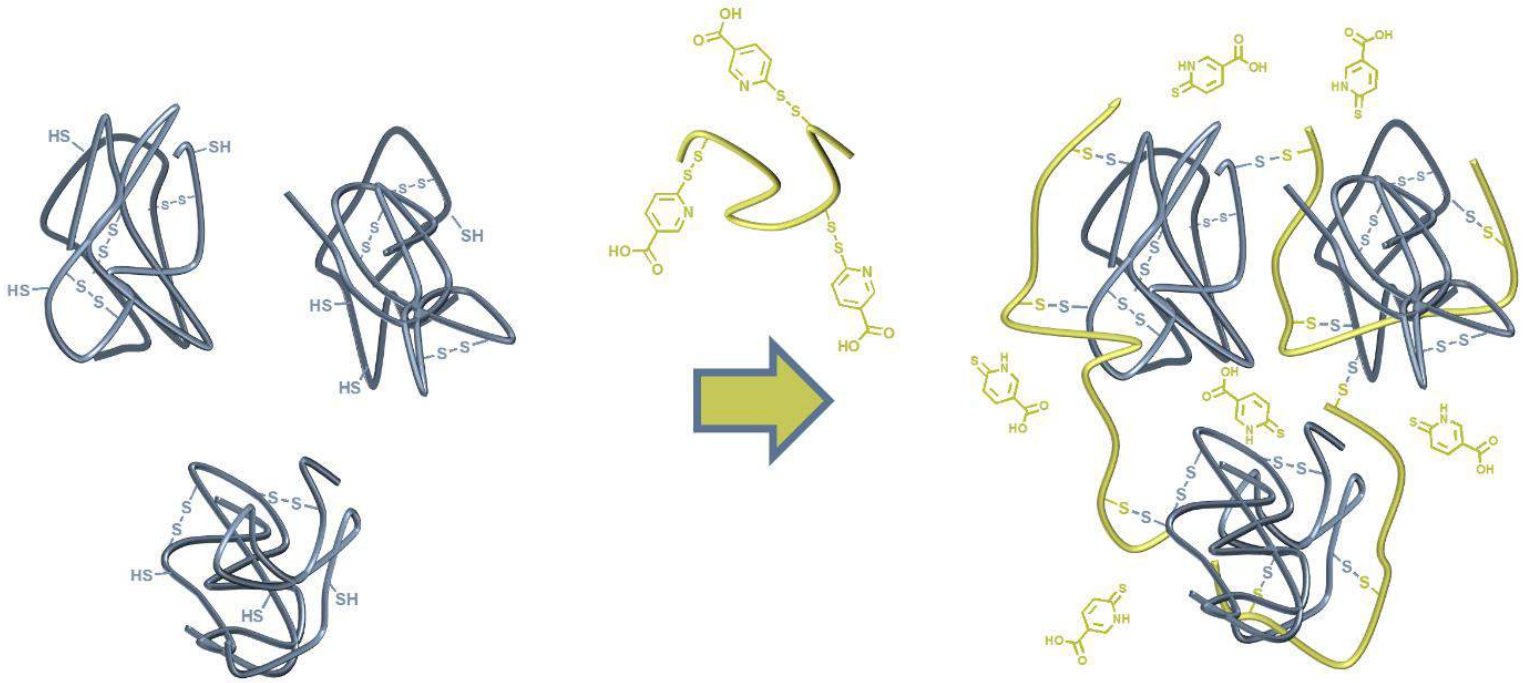
In situ gelation

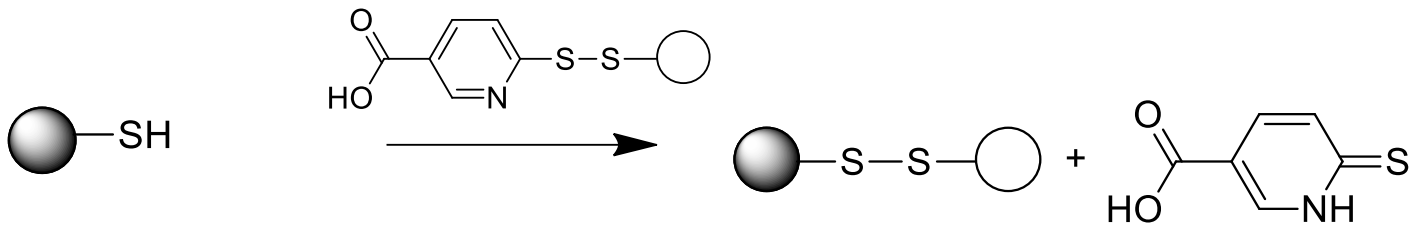

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Interaction of disulphides with mucin

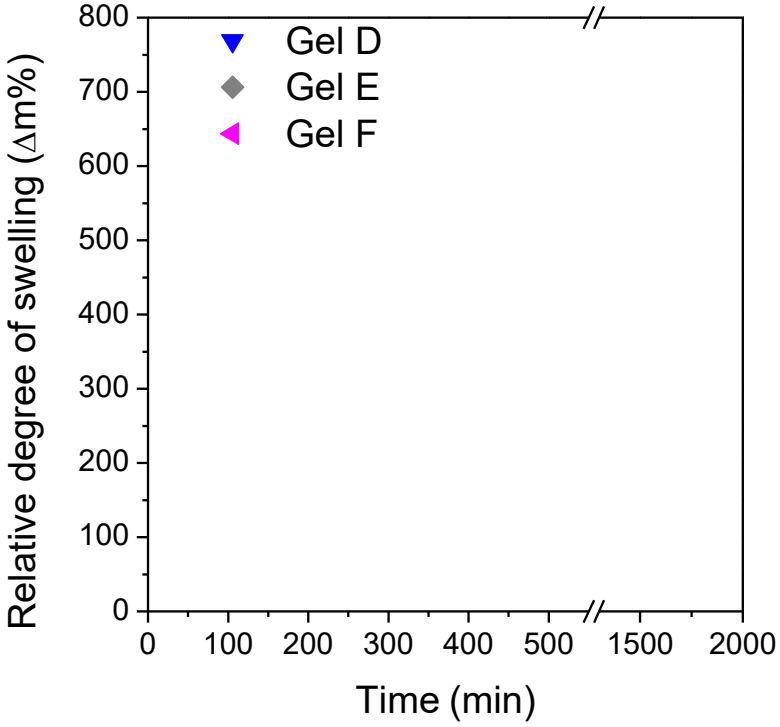
Mucin dispersion

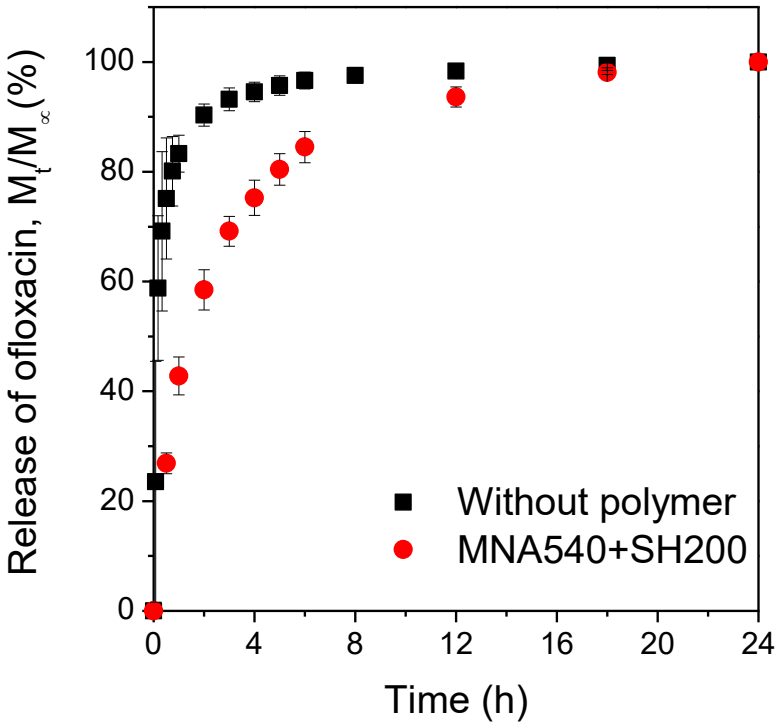
Mucin-polymer mixture





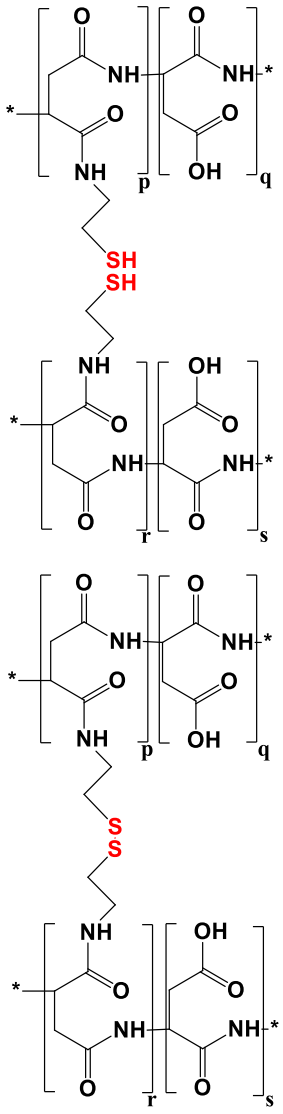
Composition-dependent stability, drug release

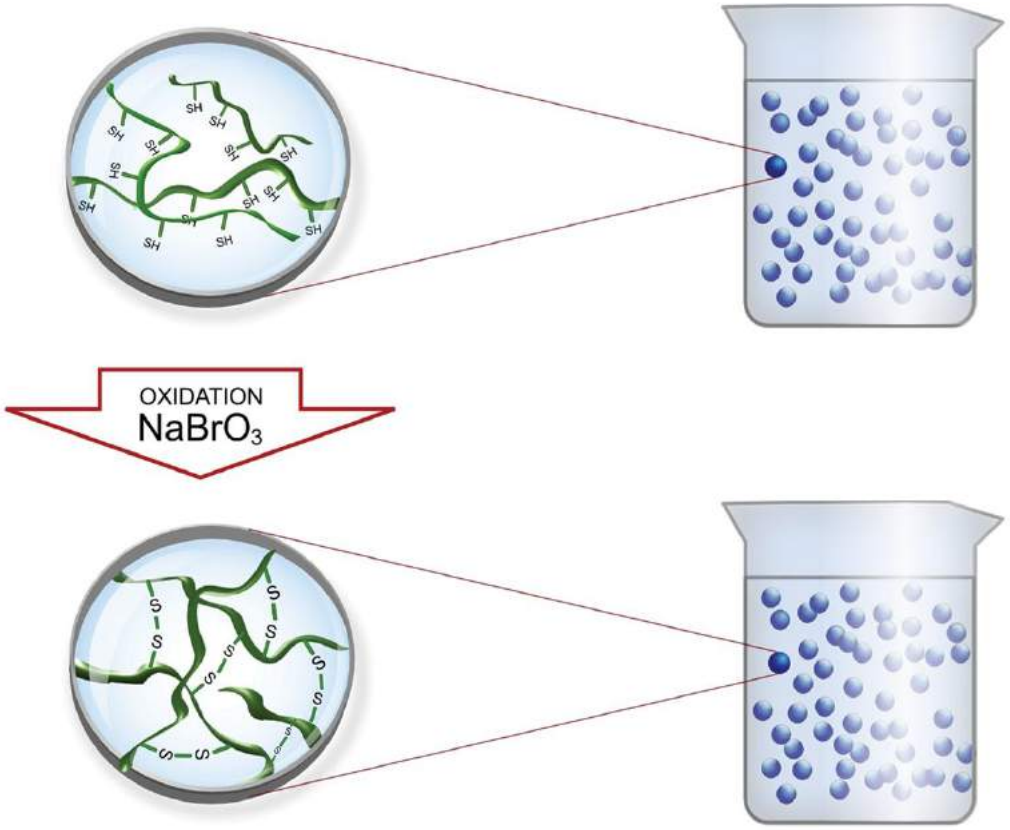




The presence of free thiols determines the hydrolytic stability of formulations

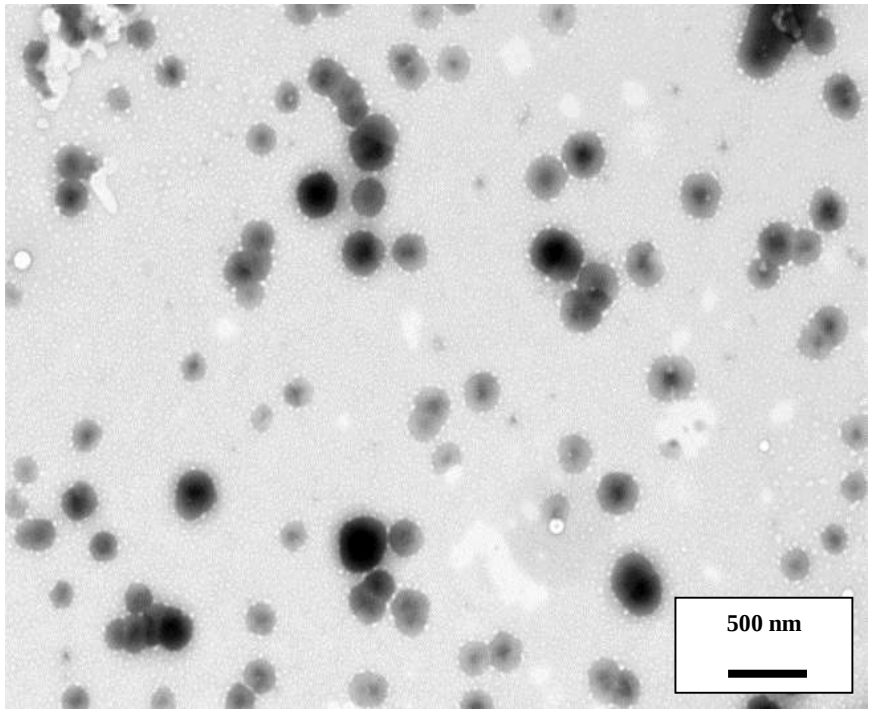
PASP nanogels with redox-triggered drug release

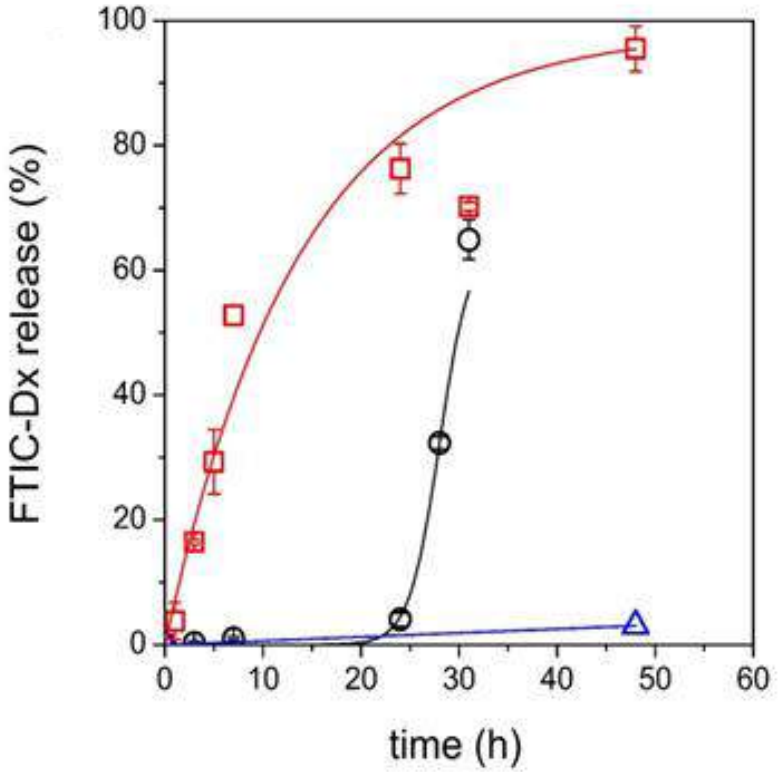




Krisch et al. Macromol. Mat. Eng. 301:260-266 (2016)

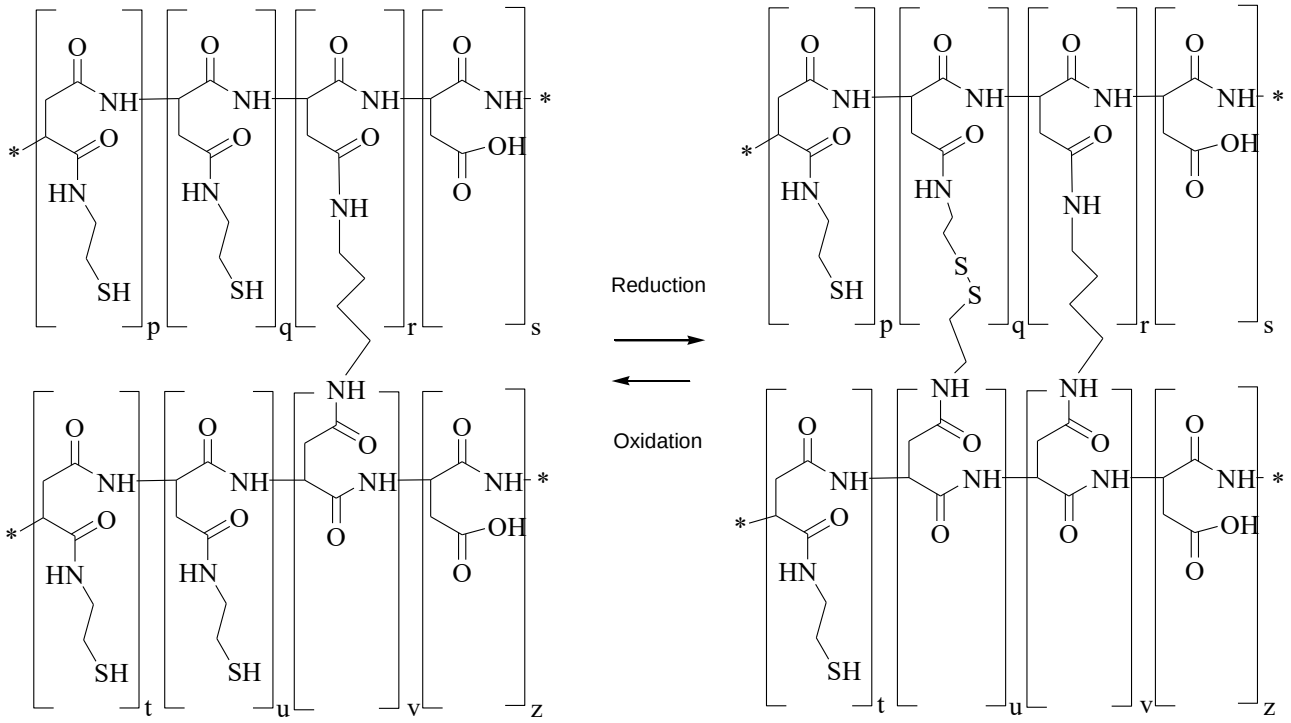
PASP nanogels with redox-triggered drug release

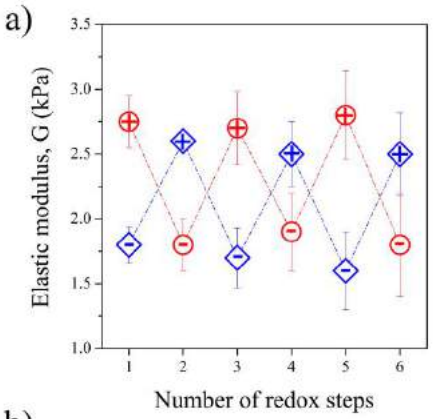


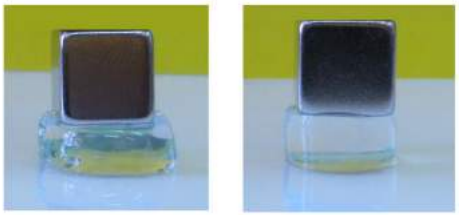


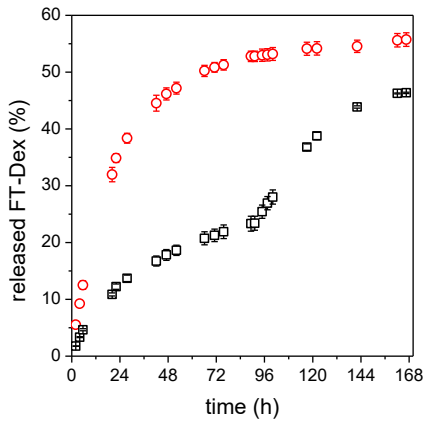
Krisch et al. Macromol. Mat. Eng. 301:260-266 (2016)

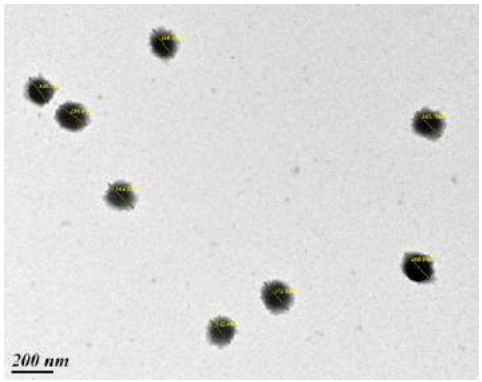
Redox-controlled swelling of PASP gels

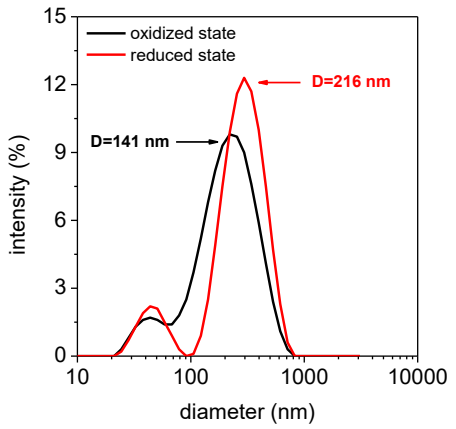






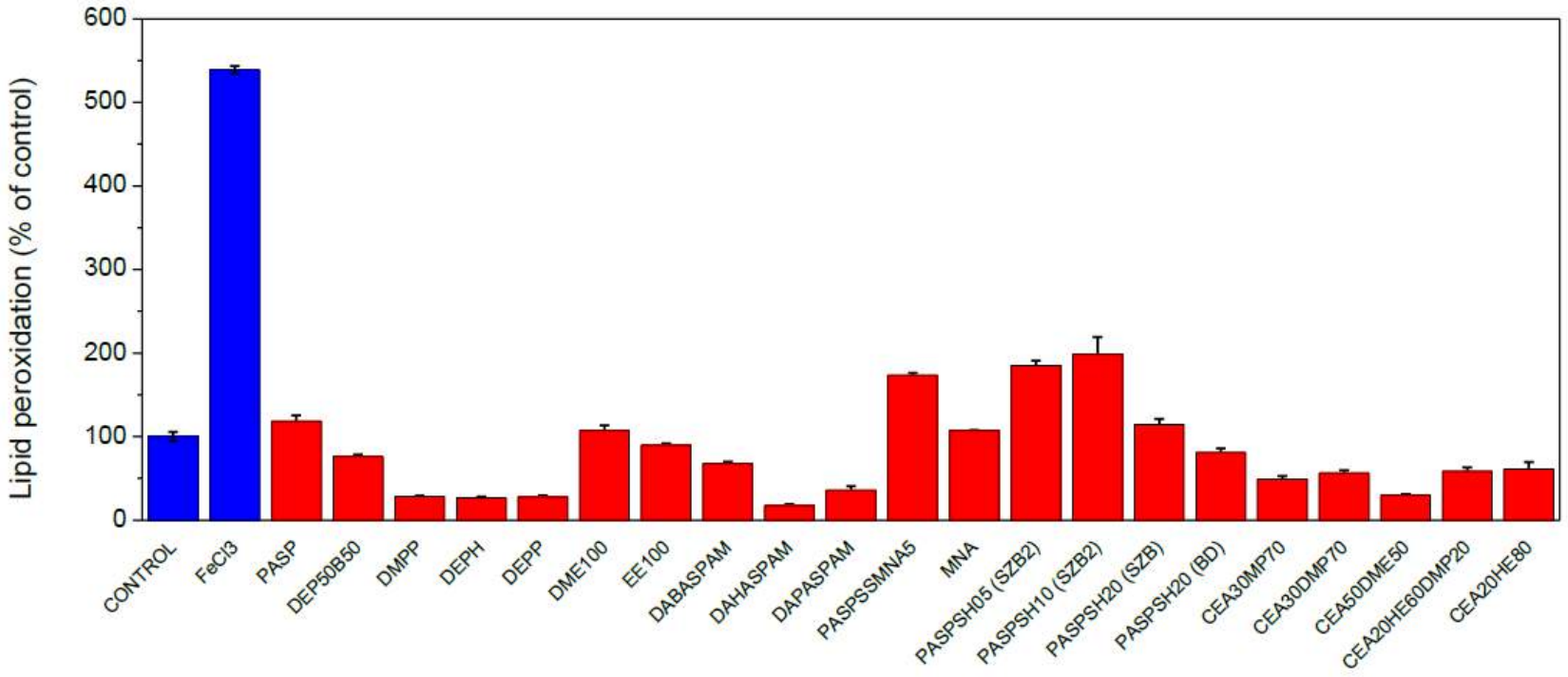






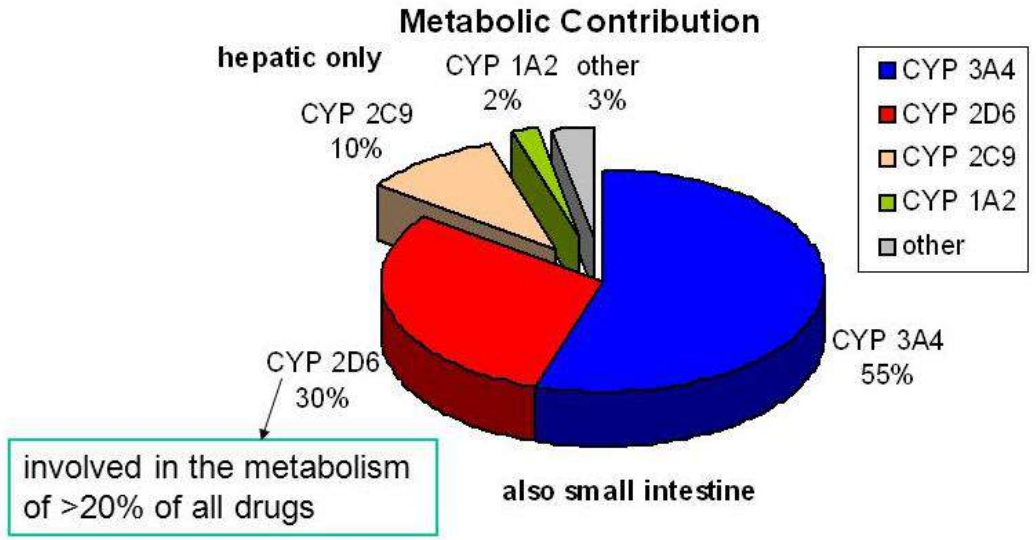
Gyarmati et al. RSC Advances 4, 8764-8771 (2014); Krisch et al. Eur. Polym. J. 105: 459-468 (2018)

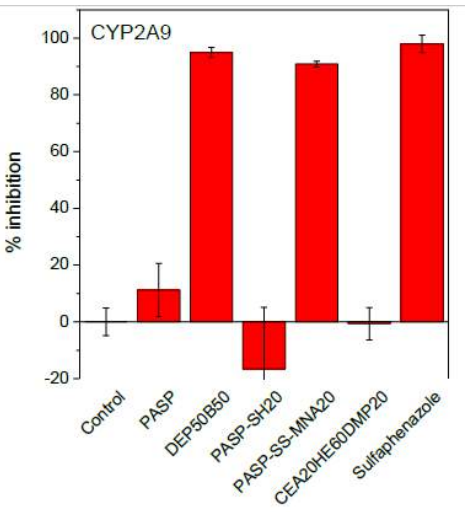
Lipid peroxidation assay

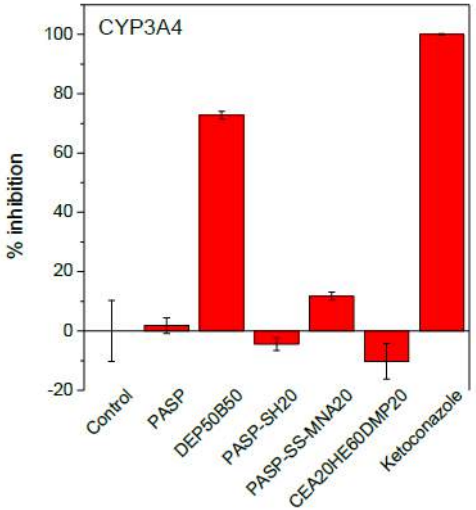


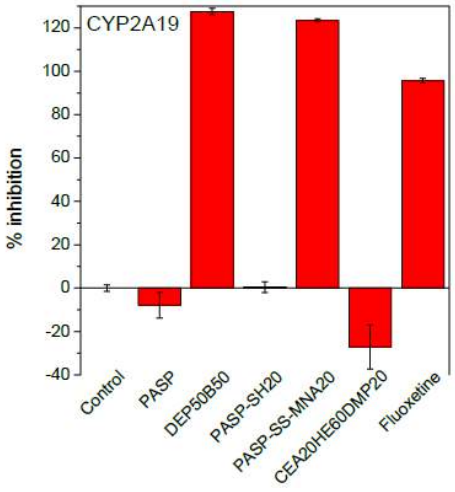
PASP (unmodified) gave similar result to control
Disulphide containing polymers caused some radicle damage
Most of thiolated polymers and cationic polymers had a protective effect

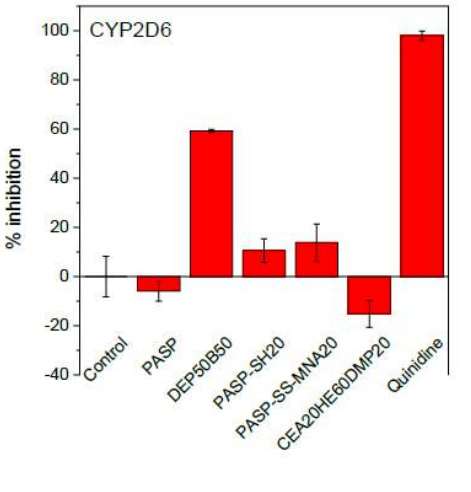
Enzyme inhibiton (human CYP enzymes)



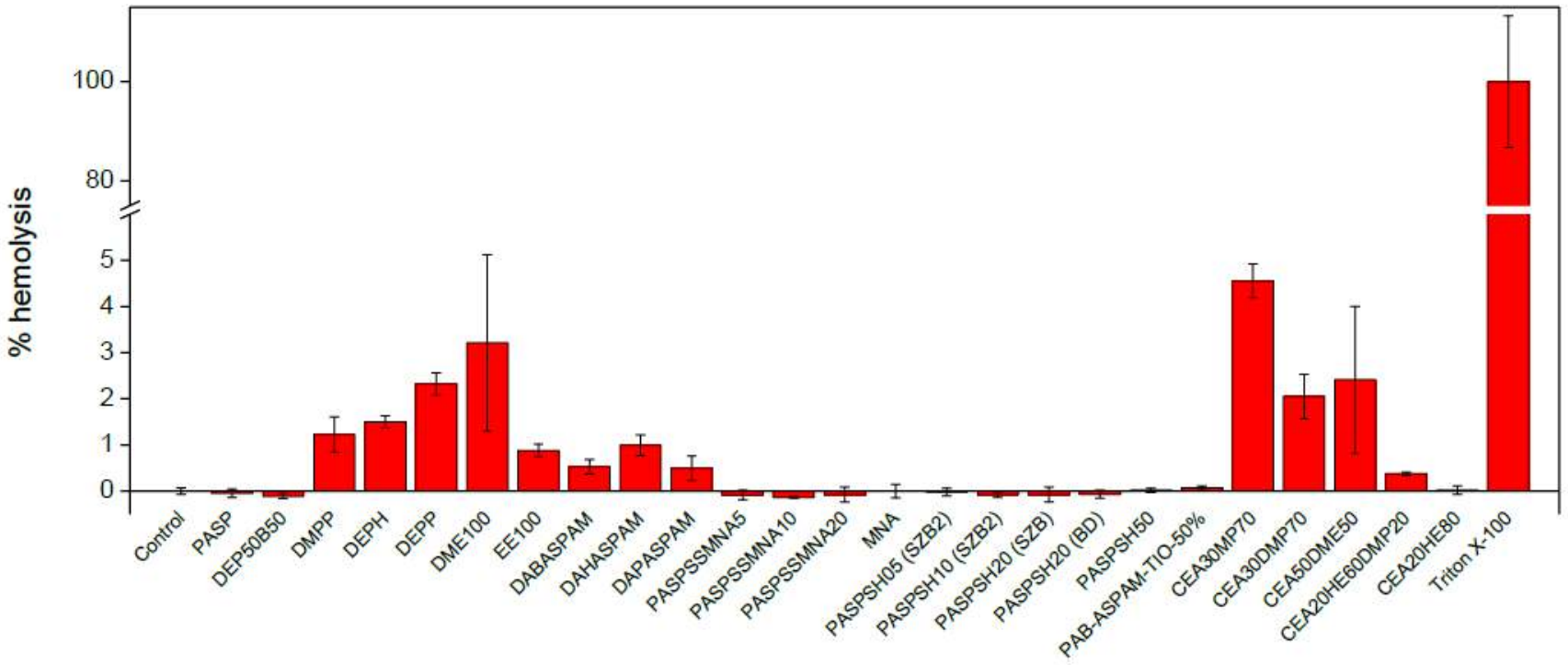






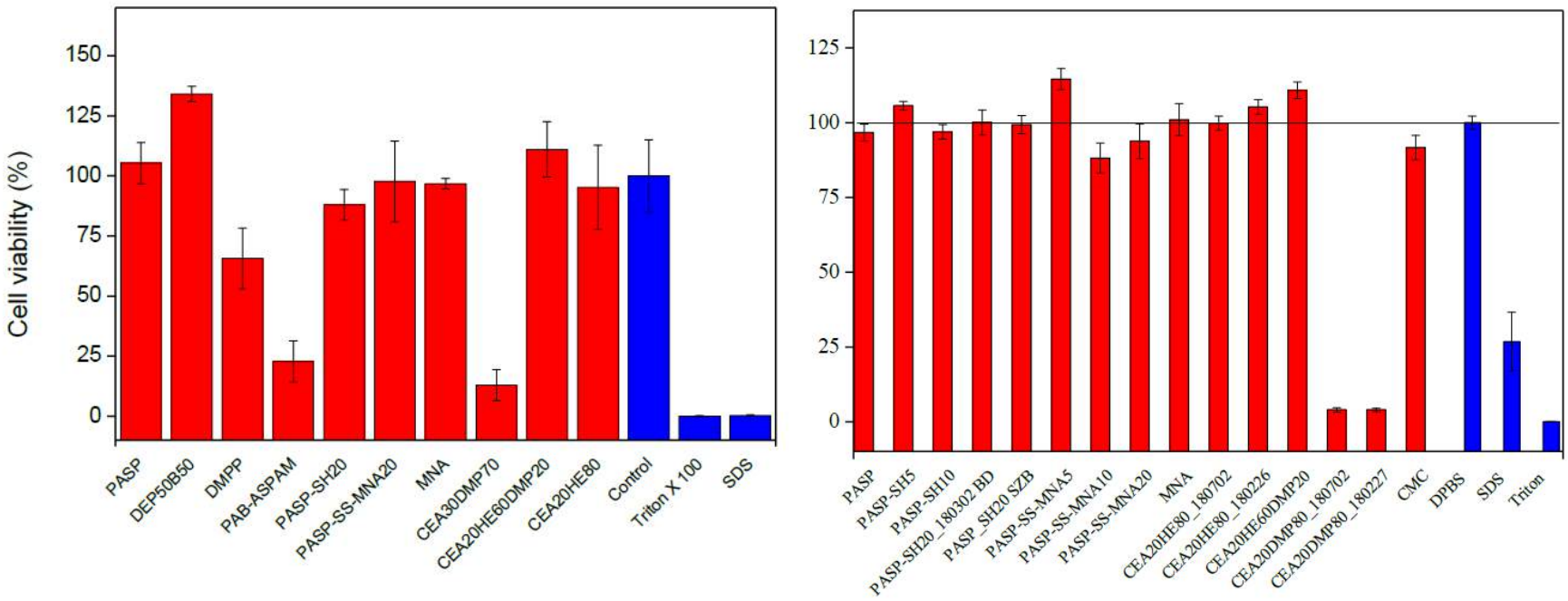


Hemolysis assay



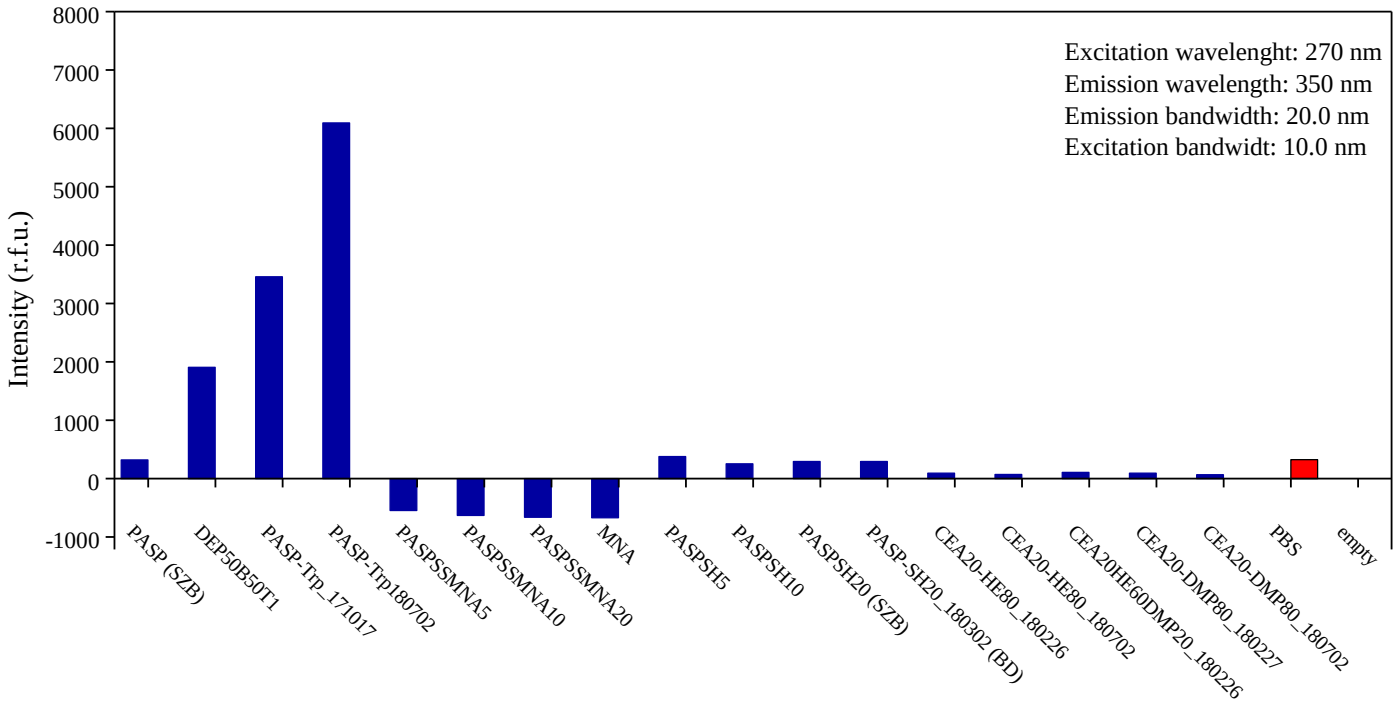
All polymers showed a hemolysis below 5% of positive control
Cationic polymers destabilized the membrane of RBC-s independently of composition (nanoparticle permeability!)

Citotoxicity assay



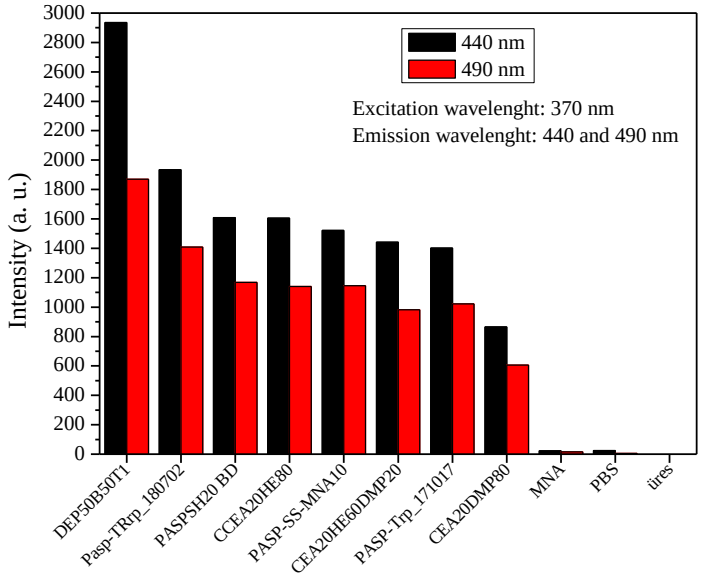
DEP50B50 polymer gave anomalous results due to its surfactant effect
Polymers with high positive charge density caused cell death (adjusting toxicity)

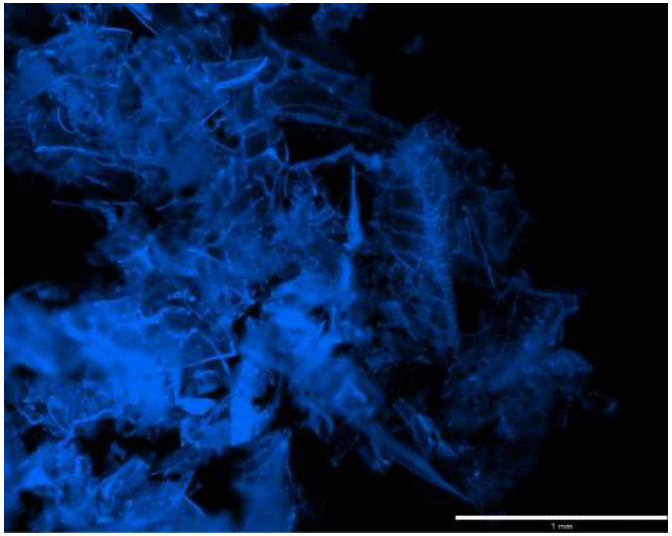
Fluorescent marking of PASP derivatives

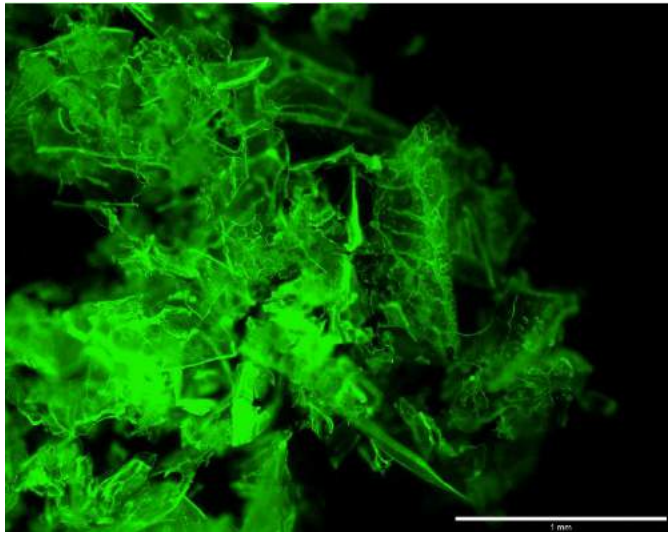


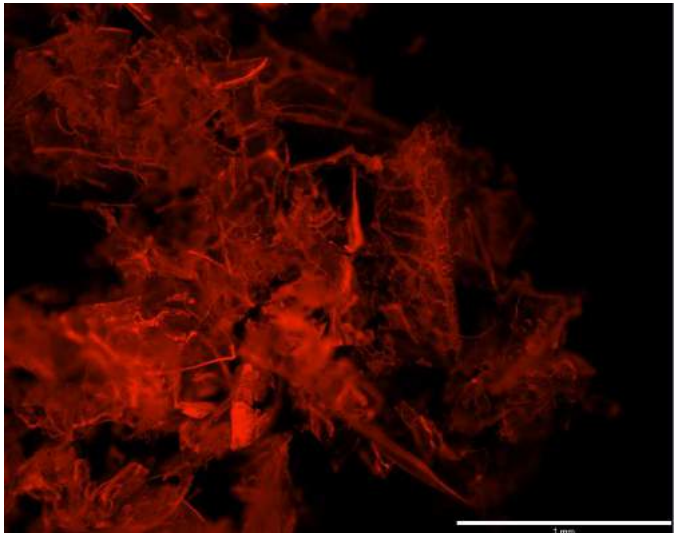
Labelling with tryptophan enables us to detect the polymers using UV excitation (relatively low intenstity)

Autofluorescence

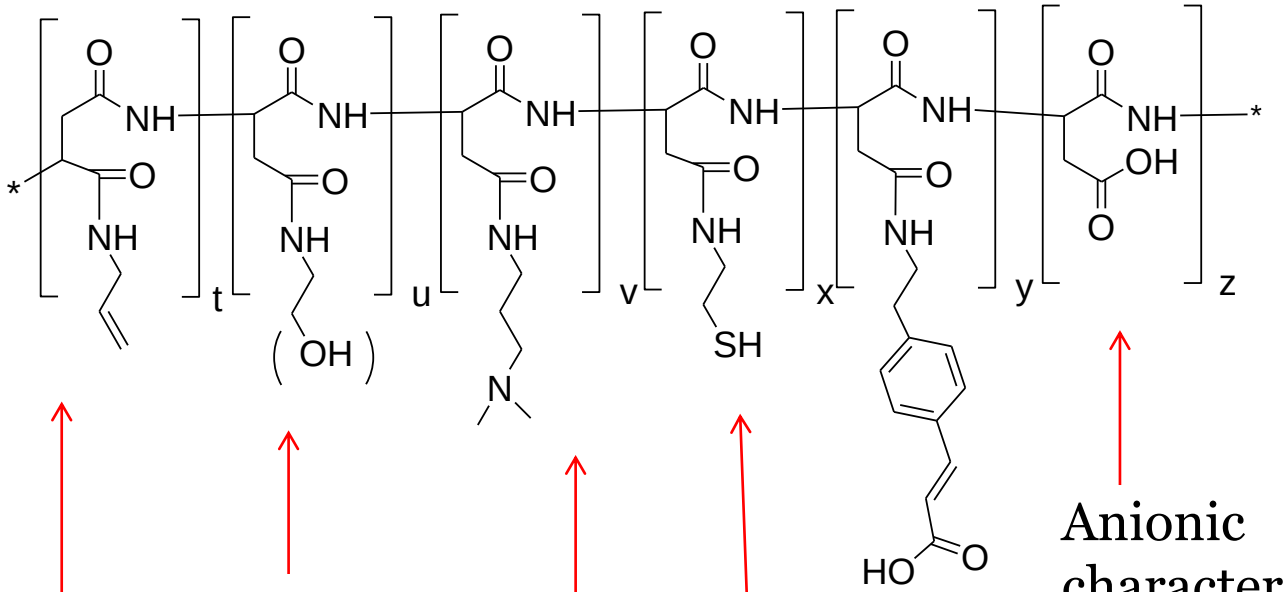








As a conclusion….



Anionic character

Adjustment of water-solubility

Redox response

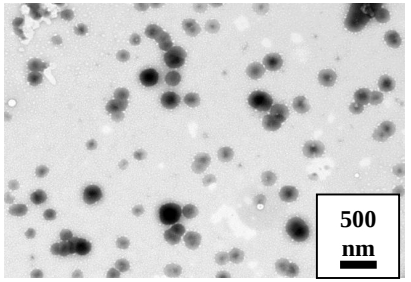
Cationic character

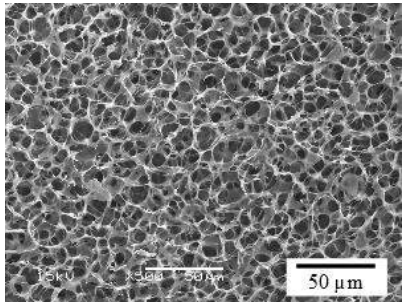
Photo-crosslinking

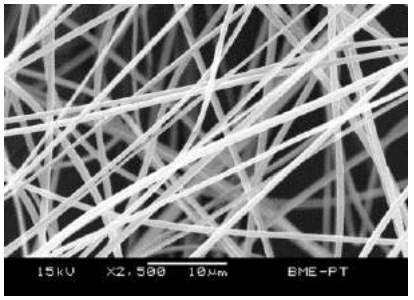
Additional functionalization via radical reaction

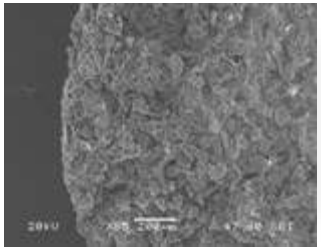














Versatile chemistry and formulations

Acknowledgement

Anil Misra, Ross Shevchenko, Mo Alavijeh (Pharmidex)

Krisztina László

MTA-ELTE Research Group of Peptide Chemistry

All the colleagues and students of Soft Matters Group, as well as of Department of Physical Chemistry and Materials Science

„Nanomed” Grant (Project Number: 734641)

National Research, Development and Innovation Office – NKFIH (FK 125074)

János Bolyai Research Scholarship (B. Gyarmati)

Thank you for your kind attention!



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