Leopold-Franzens-Universität

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Development of a mucoadhesive nanoparticulate drug delivery system for a targeted drug release in the bladder

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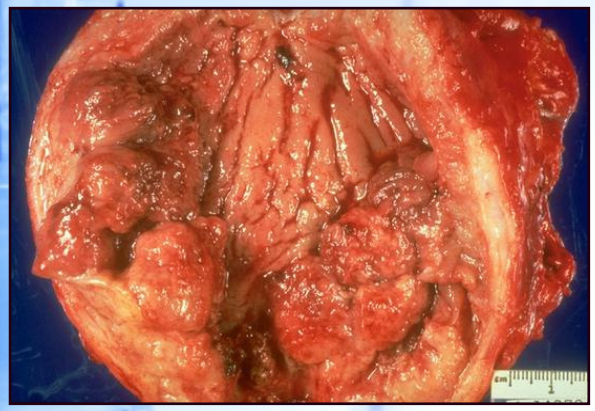
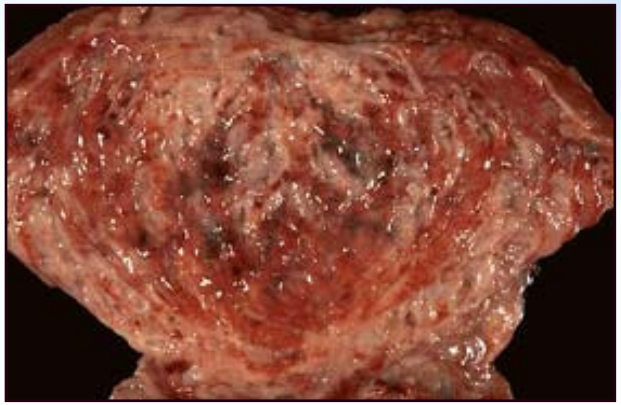
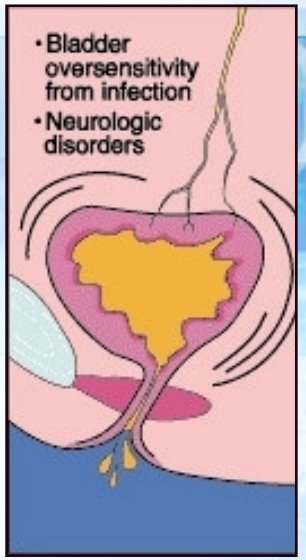
3. Conclusion

Introduction

Diseases of the urinary bladder



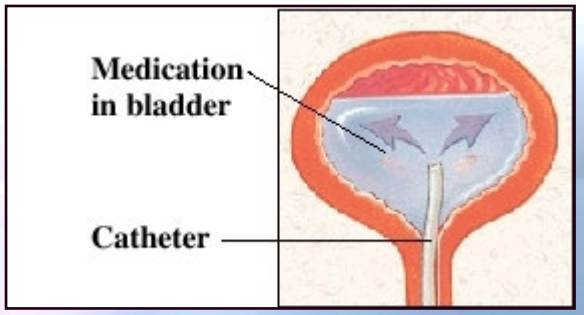




cancer inflammation, infection incontinence

- treated by oral administration of pharmaceutical compounds
  → systemic delivery

- Intravesical Drug Delivery (IDD)



Introduction

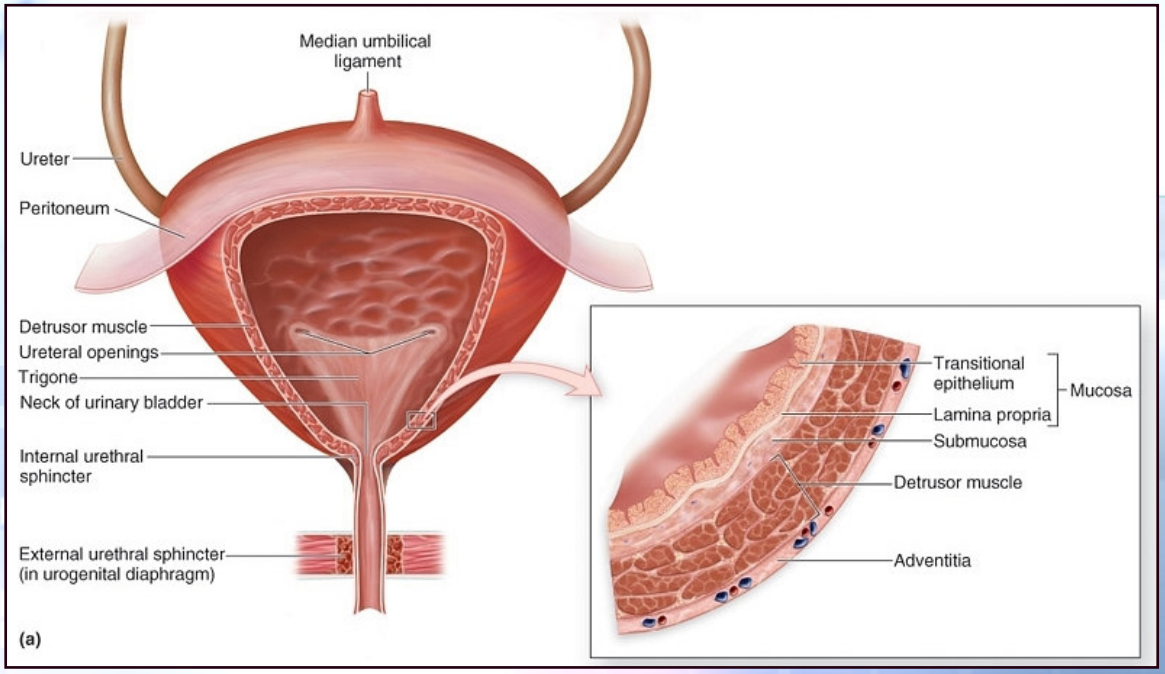
Intravesical drug delivery (IDD) limitations

- periodical voiding of urine dilutes and washes out the drug

→ reduces the residence time of drug and lead to a new administration

→ repeated catheterizations increase potential for infections

- very low permeability of the urothelium in the diseased state



Introduction

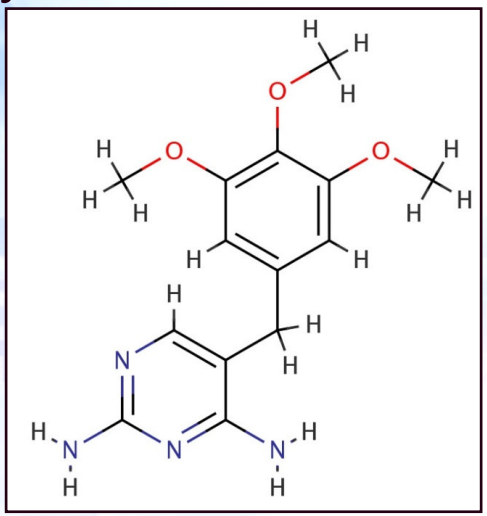
Purpose of the present study

- development of a mucoadhesive nanoparticulate drug delivery system for local use in intravesical therapy

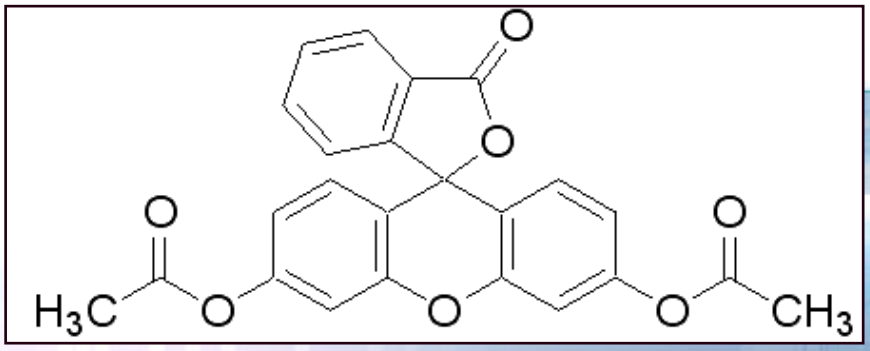
→ retarding release of the drug

→ prolong the residence time of the drug in the bladder

- trimethoprim (TMP) was used as an effective local therapy from cystitis in the bladder



- fluorescein diacetate (FDA) was used as fluorescent marker



Content

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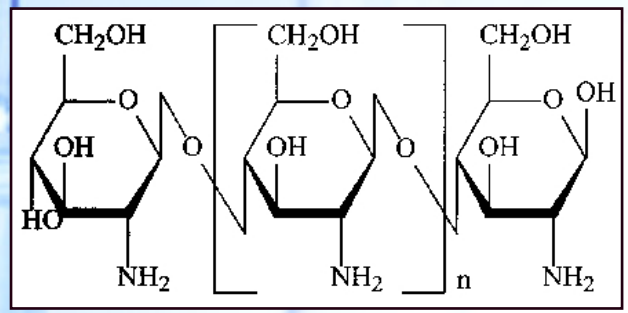
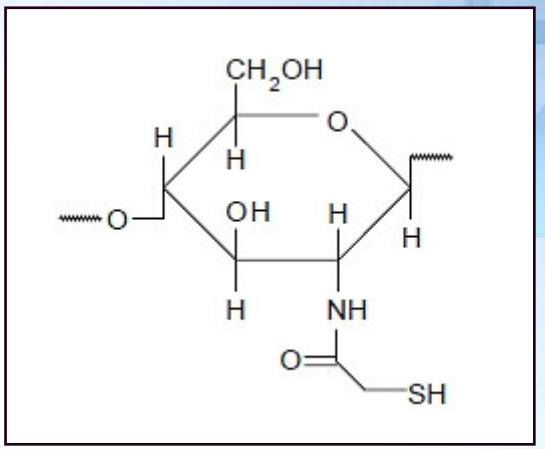
Methods & Results

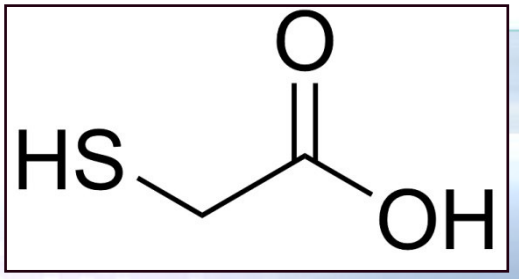
Preparation of the matrix of the drug delivery system



Chitosan



Chitosan - Thioglycolic acid (TGA)



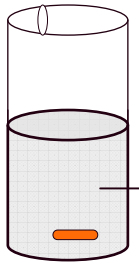
Thioglycolic acid

Methods & Results

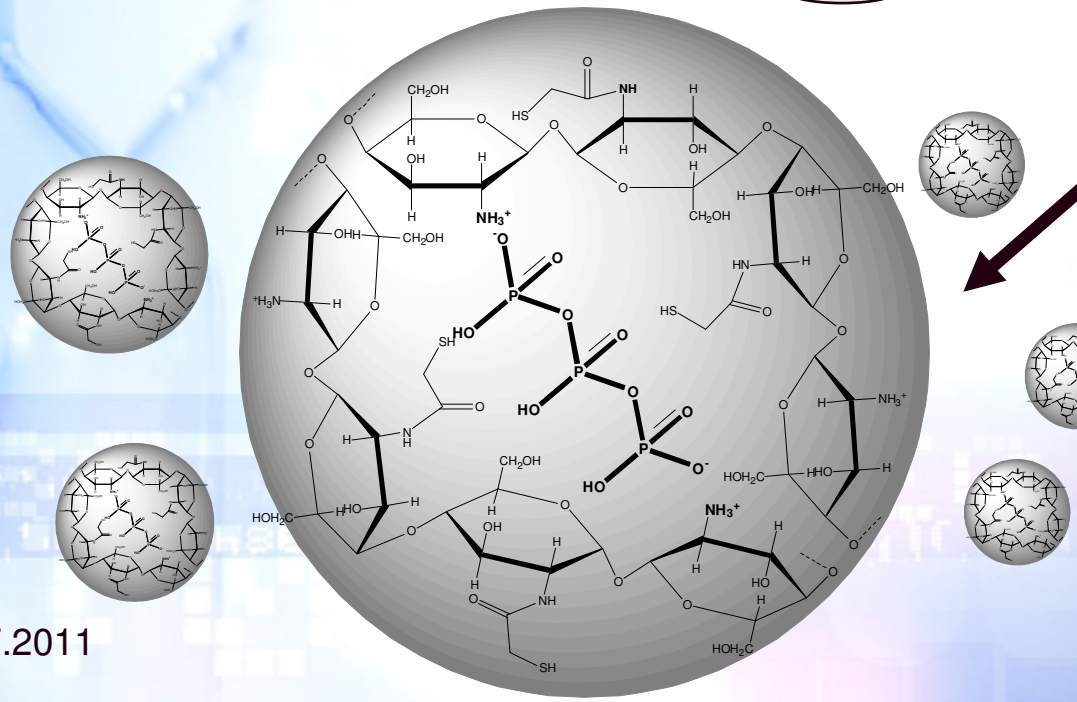
Preparation of the drug delivery system

TPP solution in demineralised water 0.2% (w/v)

Chitosan or chitosan-TGA in 0.01 M acetic acid /sodium acetat buffer 0.5% (w/v) pH 6.2

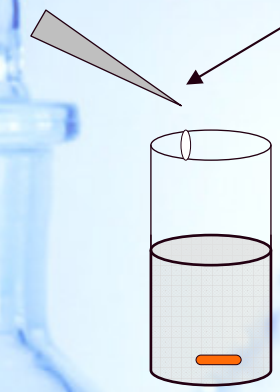


Nanoparticles (NP)



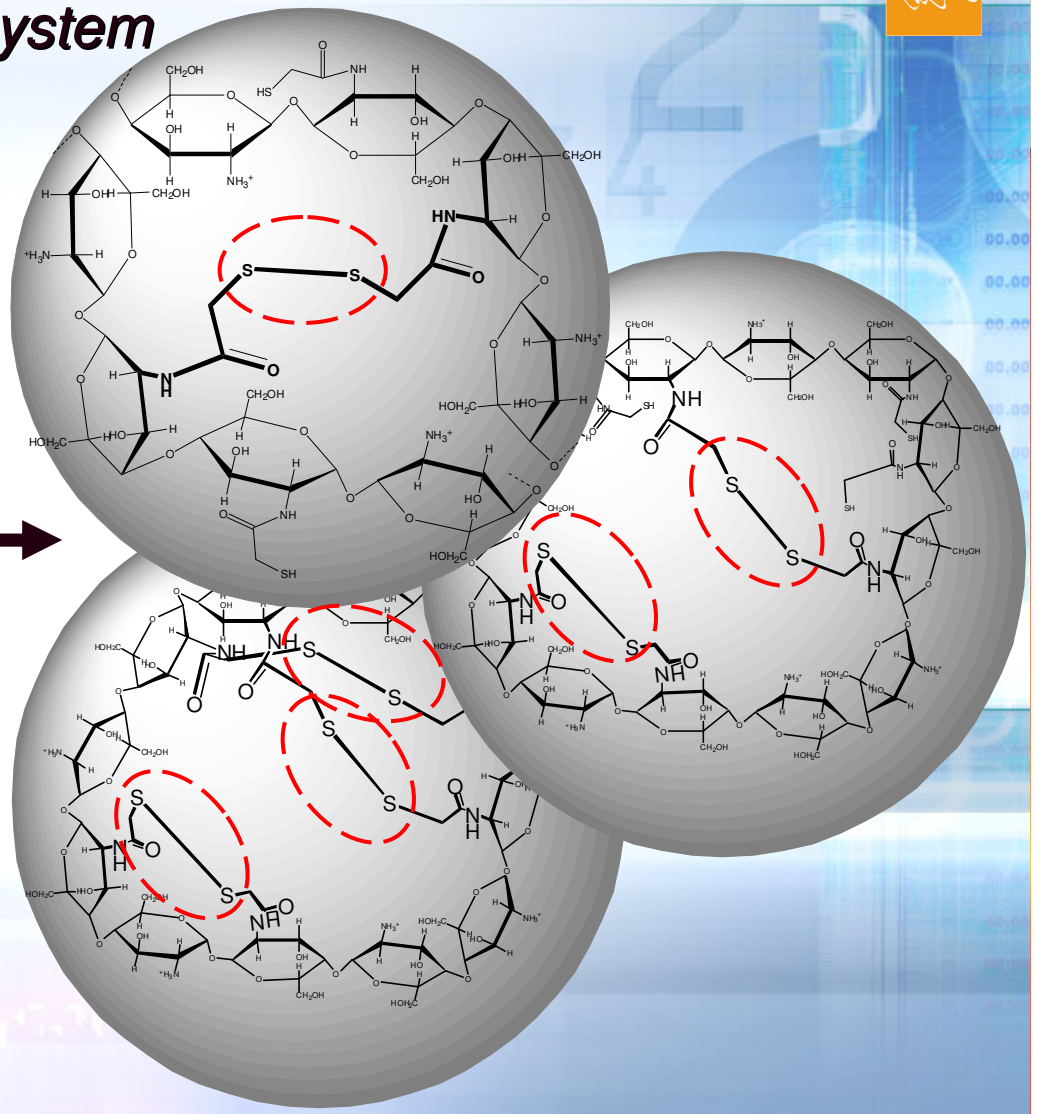
Methods & Results

Preparation of the drug delivery system



Different amounts of 0.5% (v/v) H_2O_2 solution

Nanoparticles (NP)



Methods & Results

Characterization of the drug delivery system

Table 1.
Mean particle diameter and zeta potential of chitosan-TGA nanoparticles obtained by ionic gelation with TPP and followed by different oxidation with H_2O_2, respectively. Indicated values are means ± SD (n ≥ 3).

Nanoparticles	Mean particle diameter [nm]	Polydispersity index	Zeta potential [mV]
Ionically crosslinked			
Chitosan	266 ± 64	0.44	7 ± 1
Chitosan-TGA	197 ± 24	0.38	7 ± 1
Covalently crosslinked			
Chitosan TGA (ox1)	183 ± 7	0.31	13 ± 3
Chitosan TGA (ox2)	186 ± 6	0.29	12 ± 1

Methods & Results

Characterization of the drug delivery system

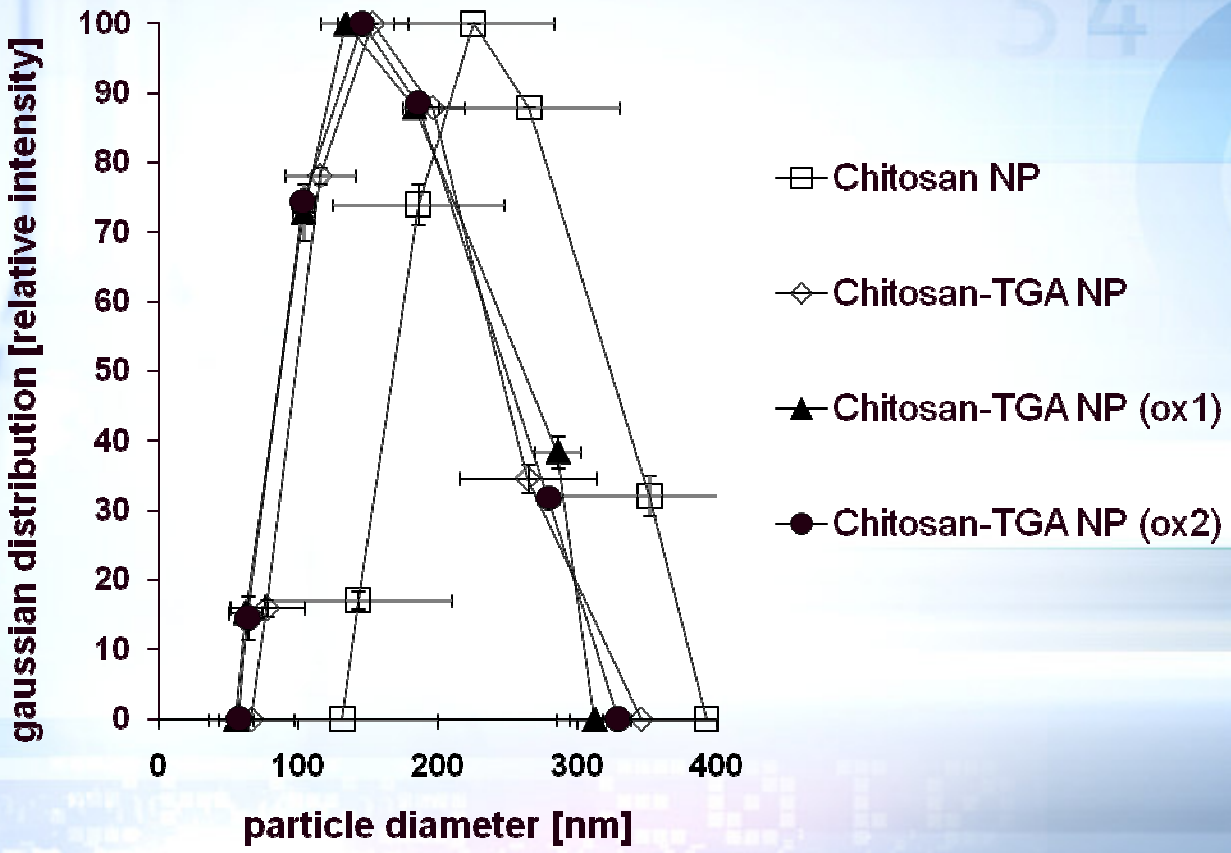


Fig. 2. Size distribution of ionically crosslinked nanoparticles as well as covalently crosslinked nanoparticles. Indicated values are means ± SD of last three experiments.

Methods & Results

Characterization of the drug delivery system

Table 2.
Amount of thiol groups and disulfide bonds immobilised on the basic thiomer Chitosan-TGA and nanoparticles after ionic gelation with TPP and different degrees of oxidation with H_2O_2, respectively. Indicated values are means ± SD (n ≥ 3).

	H_2O_2 [µmol]	-SH [µmol/g]	-S-S- [µmol/g]	Σ-SH [µmol/g]
Chitosan-TGA	-	1456	136	1728 ± 62
Chitosan-TGA NP	-	1391	178	1747 ± 36
Chitosan-TGA NP (ox1)	10.60	903	426	1753 ± 55
Chitosan-TGA NP (ox2)	21.21	641	559	1758 ± 27

Methods & Results

Characterization of the drug delivery system

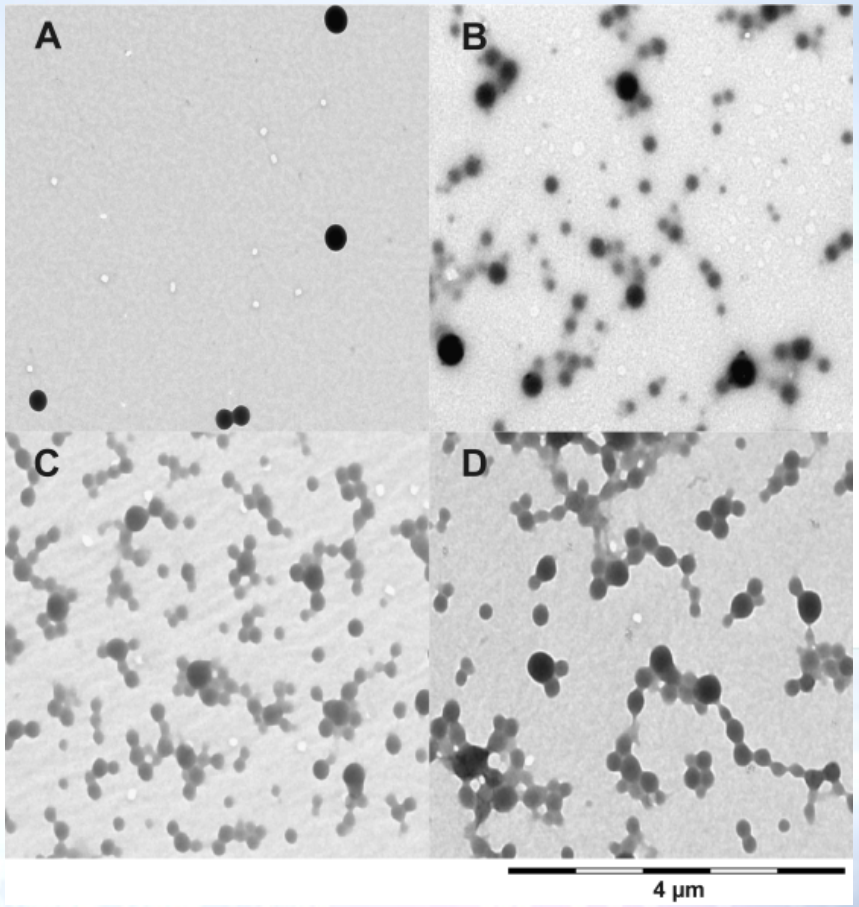


Fig. 3. Transmission electron microscopy images of the spherical shape of nanoparticles based on chitosan [A], chitosan-thioglycolic acid [B], chitosan-thioglycolic acid with 426 µmol/g disulfide bonds [C] and chitosan- thioglycolic acid with 559 µmol/g disulfide bonds [D]. Displayed bar represents 4.0 µm.

Methods & Results

Characterization of the drug delivery system

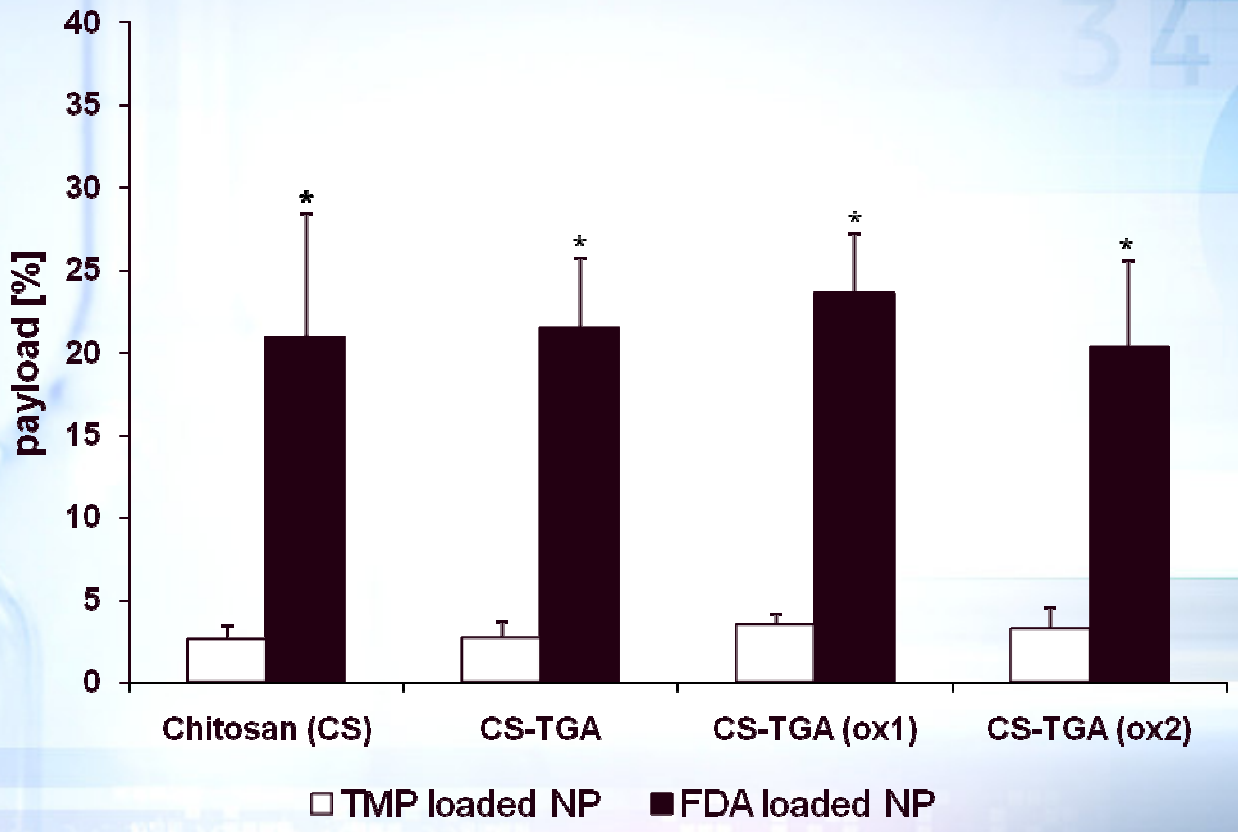
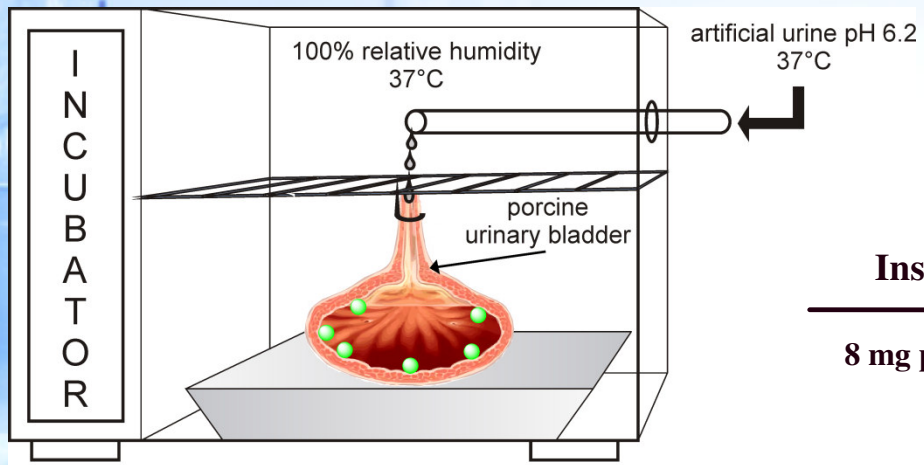


Fig. 4. Payload of trimethoprim [white bars] and fluorescein diacetate [black bars] loaded nanoparticles based on chitosan, chitosan-thioglycolic acid and thioglycolic acid with 426 µmol/g (ox1) and 559 µmol/g (ox2) disulfide bonds. Indicated values are means ± SD (n ≥ 3). * Differs from TMP, $p < 0.05$.

Methods & Results

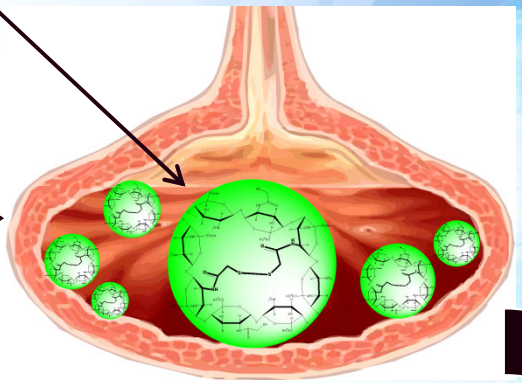
In vitro mucoadhesion studies on porcine urinary bladders

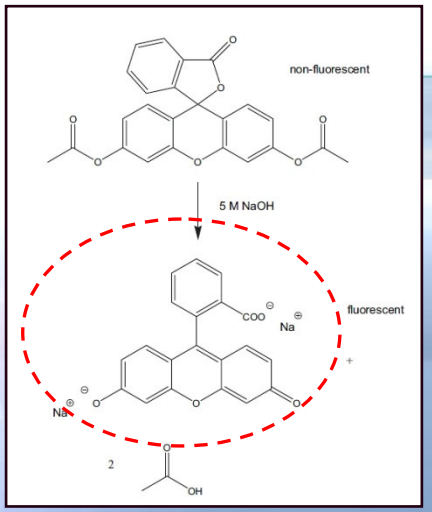


FDA loaded NP

Instillation of

8 mg prehydrated NP





Methods & Results

In vitro mucoadhesion studies on porcine urinary bladders

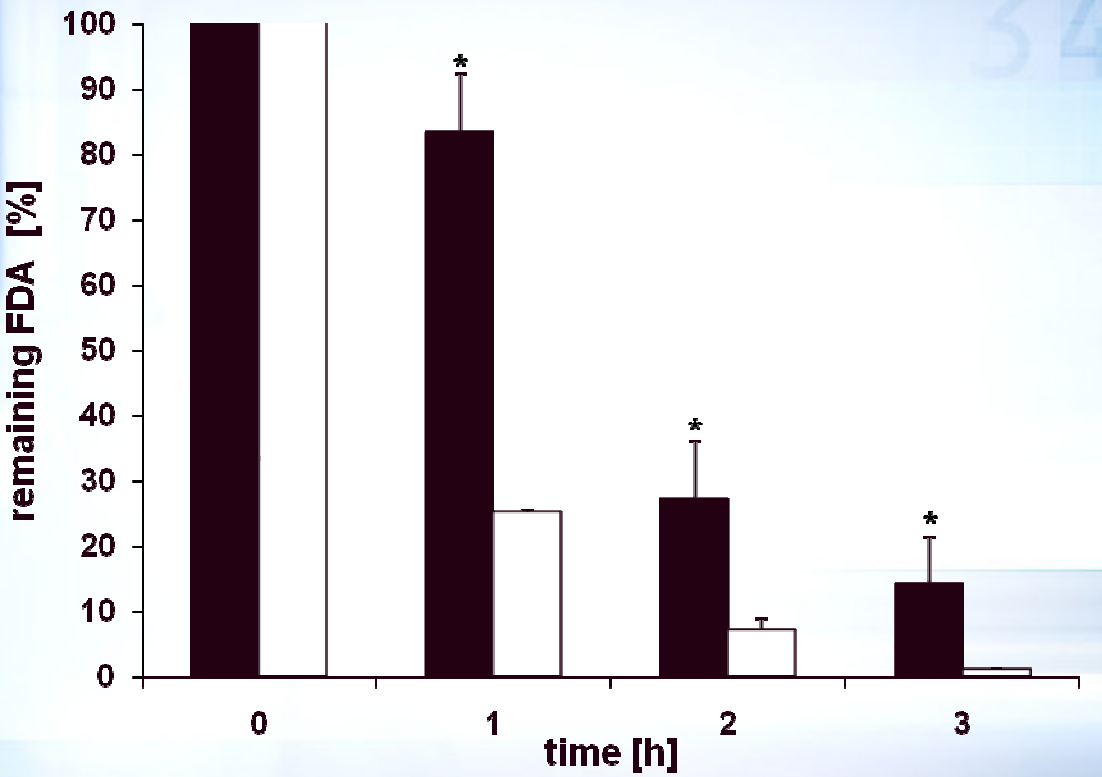
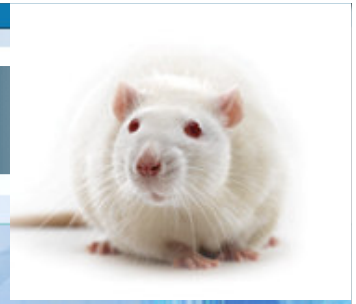


Fig. 5. Percentage of fluorescein diacetate remaining on porcine urinary bladders as a function of time. Studies were carried out with chitosan-thioglycolic acid nanoparticles [black bars] and unmodified chitosan nanoparticles [white bars] as control. Indicated values are means ± SD (n ≥ 3). * Differs from unmodified chitosan nanoparticles, $p < 0.05$.

Methods & Results



In vivo evaluation of particles with rats

- female Sprague-Dawley rats, average body weight 250 g
- rats were fasted but had free access to water
- anesthetized by an injection of ketamine (20 mg/kg)/xylazin-hydrochloride (4 mg/kg) mixture
- before urethral catheterization animals were positioned in supine position, and micturition was induced through mild caudal abdominal massage
- 500 µl of each formulation was administered

Animal grouping	Administrated formulations
Group 1	FDA suspension
Group 2	FDA loaded unmodified chitosan nanoparticles
Group 3	FDA loaded chitosan-TGA nanoparticles

Methods & Results

In vivo evaluation of particles with rats

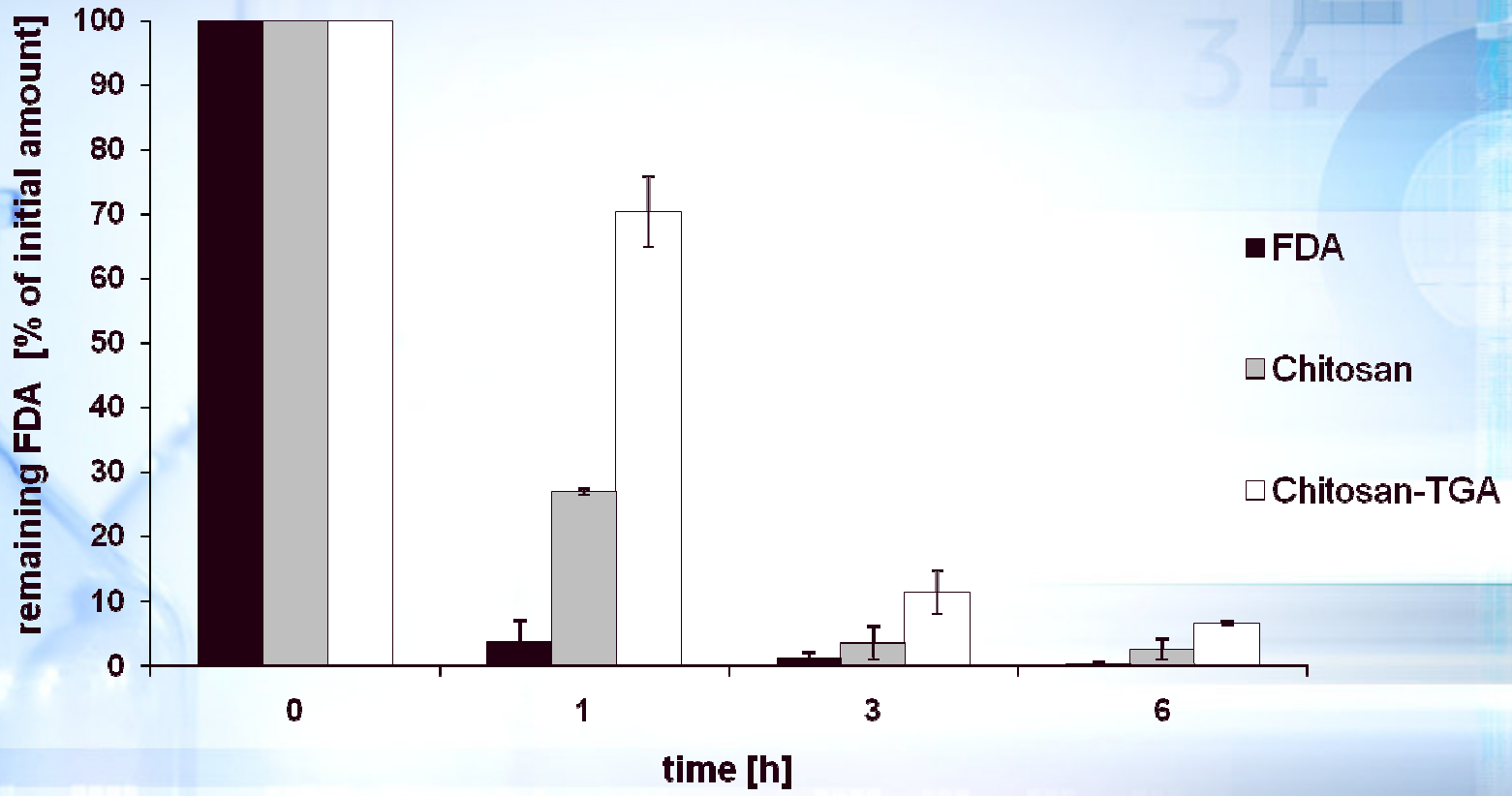
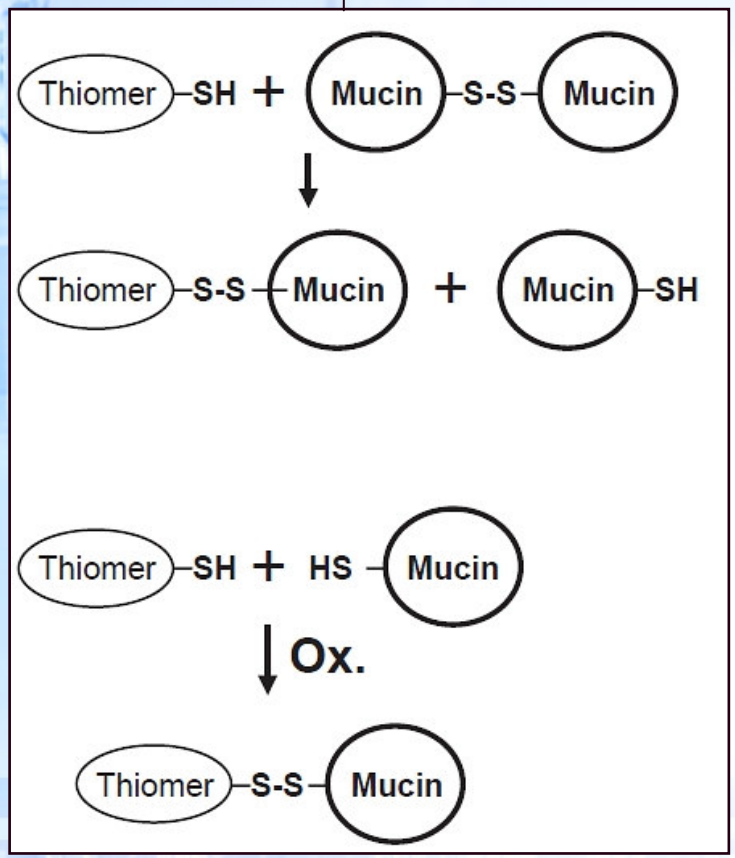


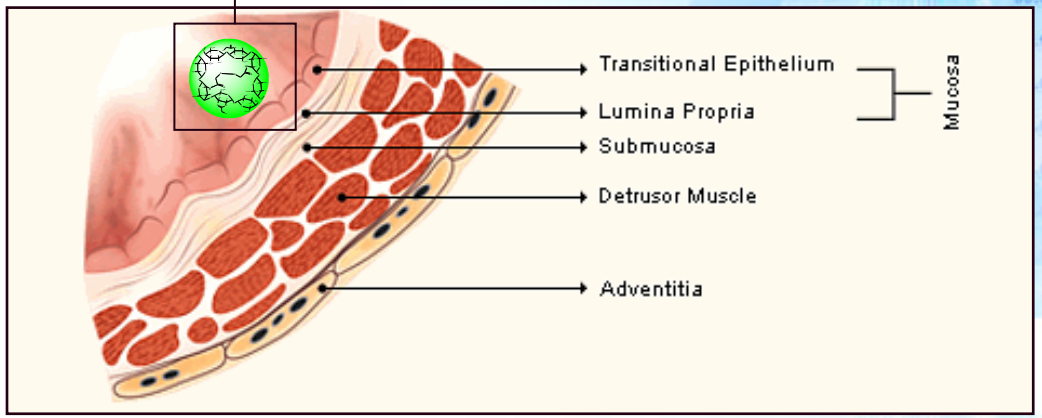
Fig. 6. Amount of fluorescein diacetate remaining on rats bladders. Fluorescein diacetate was applied without any excipients [black bars] or incorporated in unmodified chitosan nanoparticles [grey bars] or chitosan-thioglycolic acid nanoparticles [white bars]. Indicated values are means ± SD (n ≥ 3).

Methods & Results

Mucoadhesion on mucosa of urinary bladders



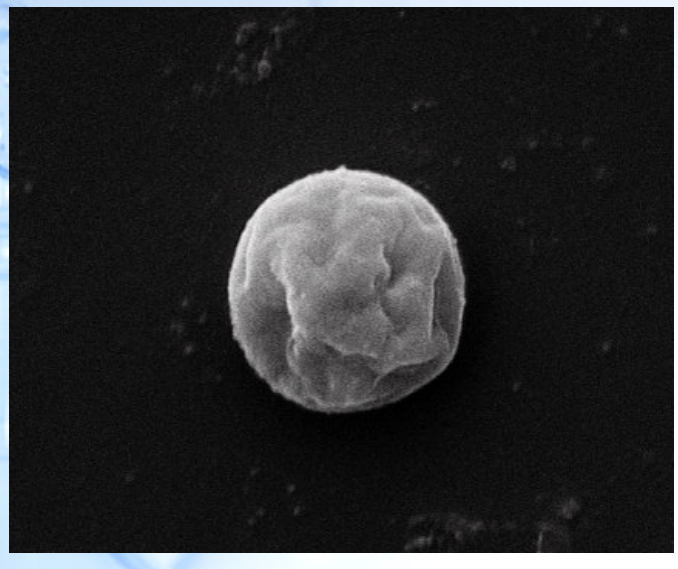
Mechanism of disulfide bond formation between thiomers and mucus glycoproteins

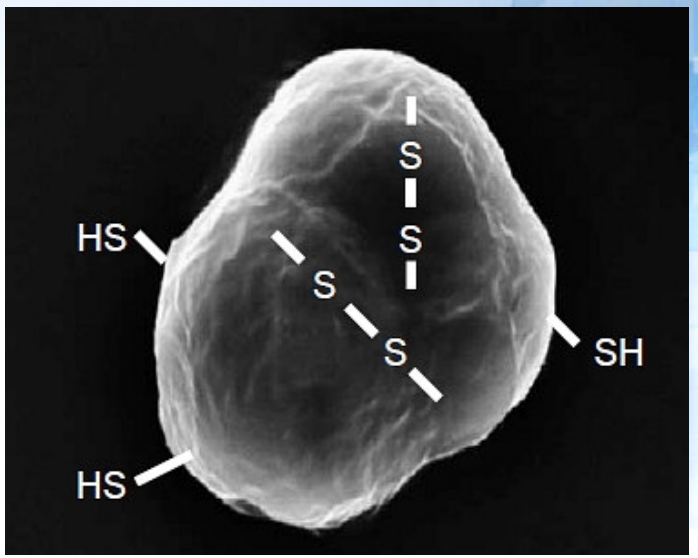


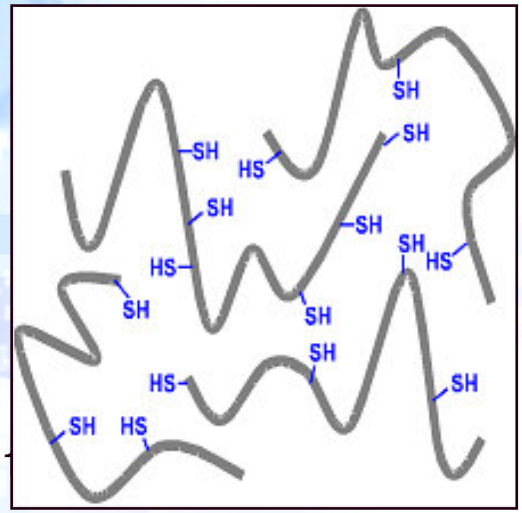
Layers in the bladder wall

Methods & Results

Release studies

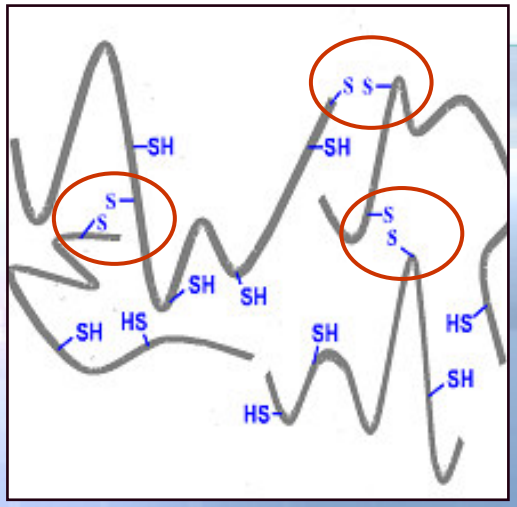






OXIDATION

H_2O_2



Methods & Results

TMP release studies

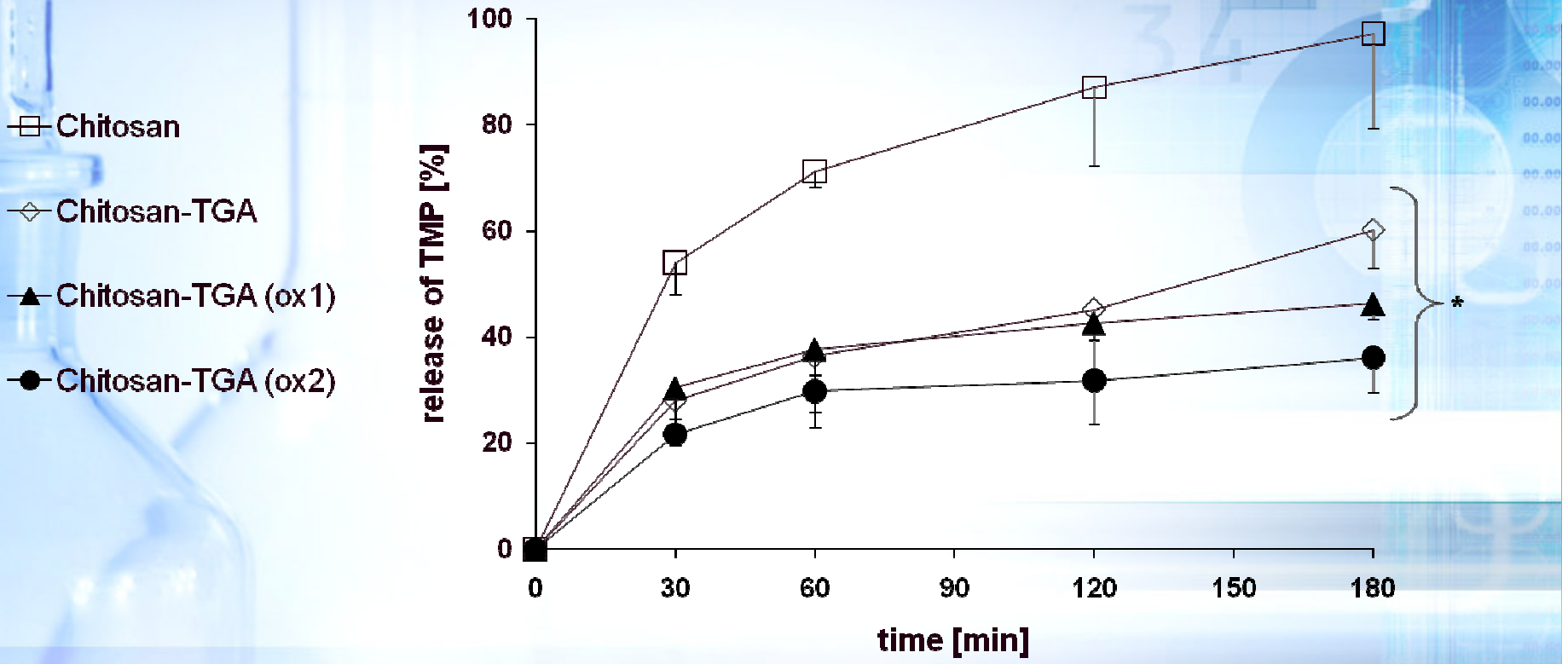


Fig. 7. Release properties of trimethoprim nanoparticles among simulated conditions with artificial urine as a function of crosslinking. Studies were carried out with nanoparticles based on chitosan [□], chitosan- thioglycolic acid [◊], chitosan-thioglycolic acid with 426 µmol/g disulfide bonds [▲] and 559 µmol/g [●] disulfide bonds. Indicated values are means ± SD ($n \geq 3$). Differs from chitosan nanoparticles, $p < 0.05$.

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Conclusion

- intravesical drug delivery system based on thiolated chitosan offers an adequate release profile besides its mucoadhesive properties
- chitosan-TGA NP showed: 1. greater stability
  2. superior mucoadhesion
  3. more sustained and controlled release

→ Finally, chitosan-TGA intravesical drug delivery system might be a useful tool for a local drug application in the urinary bladder, which allows:

1. prolonged residence time at the target site
2. enables sustained drug delivery of trimethoprim over a longer time span

THANK YOU FOR ATTENTION!