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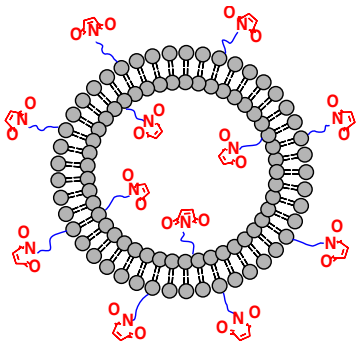
MALEIMIDE-FUNCTIONALISED LIPOSOMES AS MUCOADHESIVE VEHICLES FOR DRUG DELIVERY TO URINARY BLADDER



Daulet Kaldybekov, Vitaliy Khutoryanskiy

InEn2017, The Royal Society of Chemistry, London
8th December 2017

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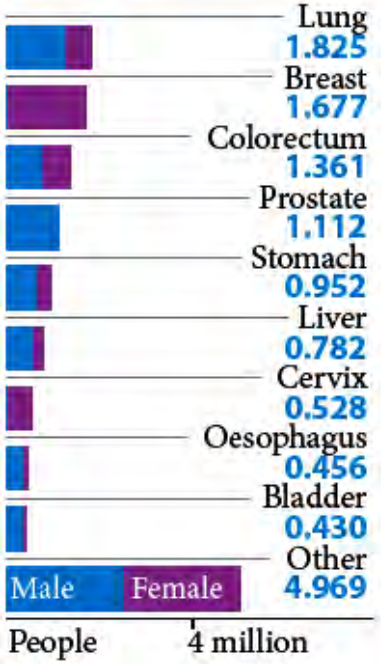
International Agency for Research on Cancer

World Health Organization

World cancer factsheet

January 2014

World cancer burden (2012)



Bladder cancer has the 9th highest incidence rate worldwide, with a greater prevalence among men than women.

In the UK:

- **10,100 new cases of bladder cancer in 2014, that's 28 cases diagnosed every day.**
- **BC is the 10th most common cancer (2014).**
- **In males, BC is the eight most common cancer and 14th in females**

https://www.iarc.fr

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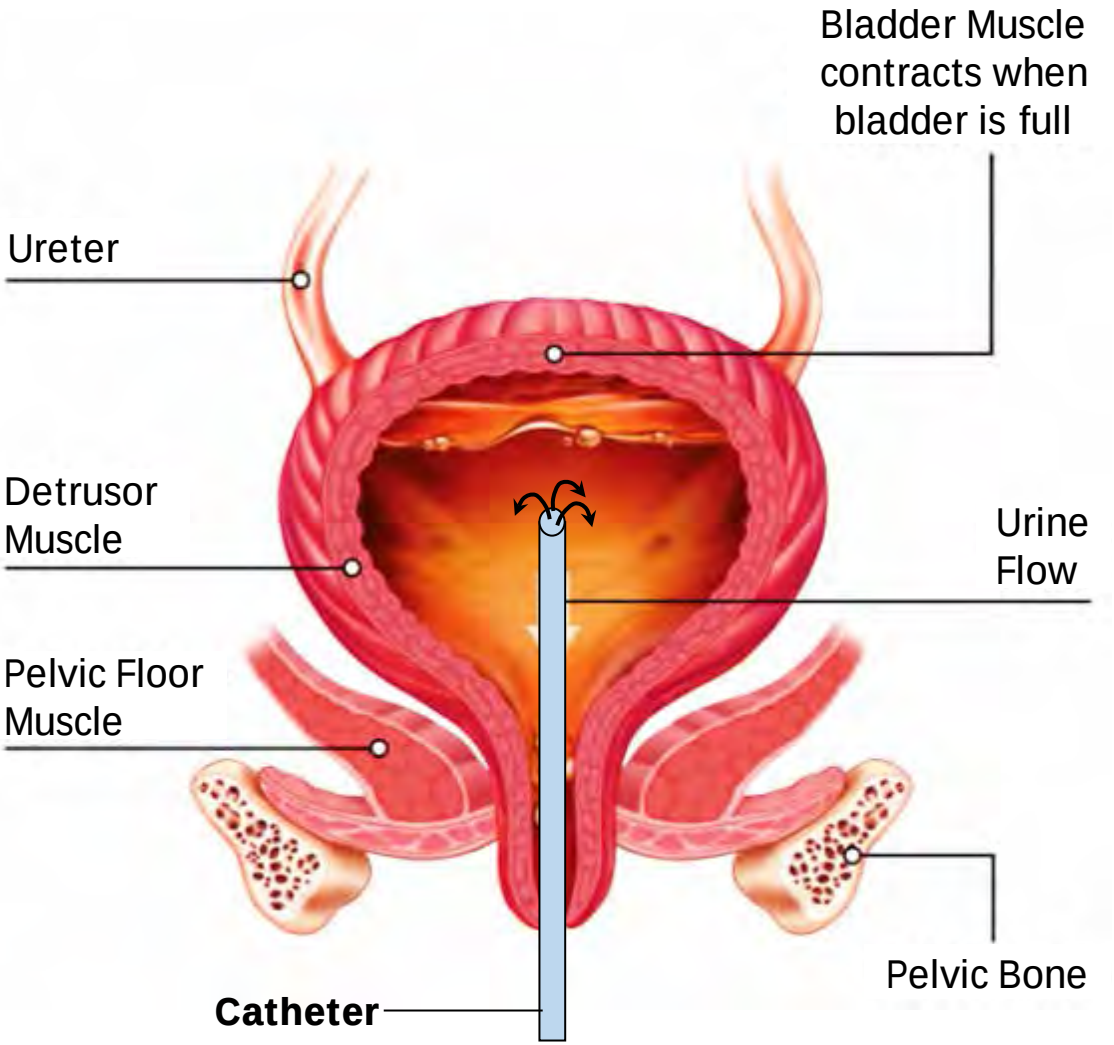
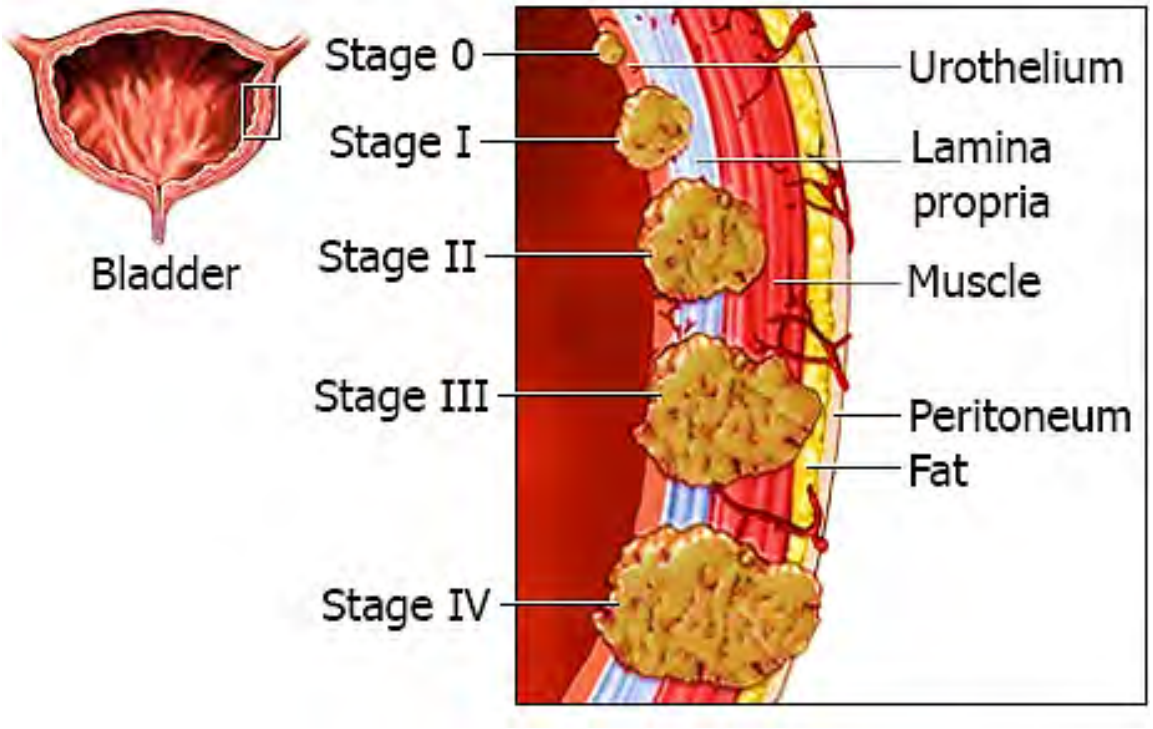
Urinary bladder: intravesical delivery



- Normal capacity: 400–600 mL;
- 150–300 mL triggers the urge to urinate;
- Urinary bladder wall is highly impermeable

http://peeingproblem.ca/en/what_is_oab/how_normal_bladder_works/

Bladder cancer

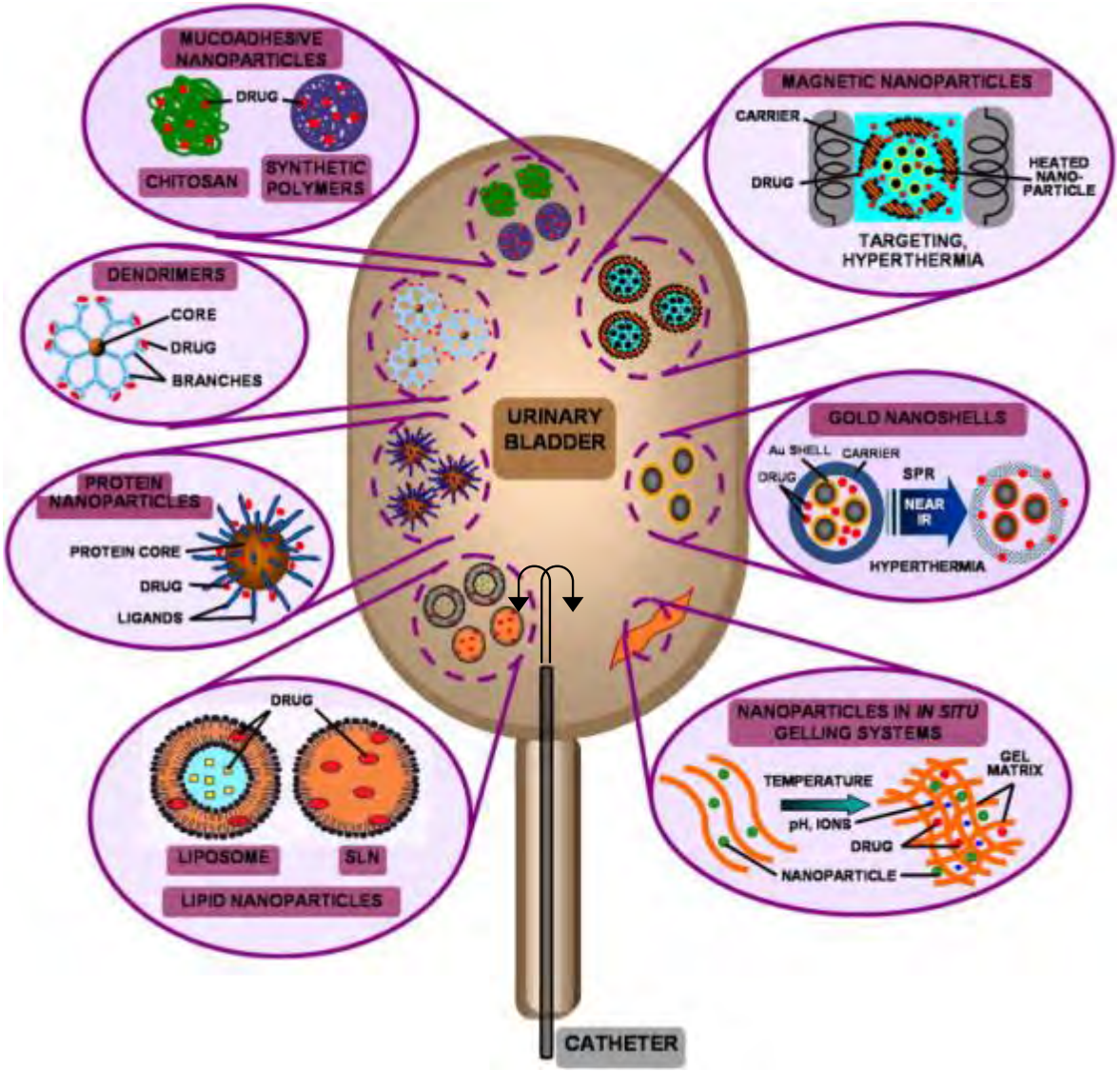


Intravesical therapy is used only for non-invasive (stage 0) or minimally invasive (stage I) bladder cancers.

Intravesical immunotherapy:
Bacillus Calmette-Guerin (BCG)

Intravesical chemotherapy:
Mitomycin, valrubicin, doxorubicin, and gemcitabine

http://www.urologycenter.com/conditions.cfm


MUCOADHESIVE NANOPARTICLES
DRUG
CHITOSAN
SYNTHETIC POLYMERS
MAGNETIC NANOPARTICLES
CARRIER
DRUG
HEATED NANO-PARTICLE
TARGETING, HYPERTHERMIA
DENDRIMERS
CORE
DRUG
BRANCHES
URINARY BLADDER
GOLD NANOSHELLS
Au SHELL
CARRIER
DRUG
SPR
NEAR IR
HYPERTHERMIA
PROTEIN NANOPARTICLES
PROTEIN CORE
DRUG
LIGANDS
DRUG
LIPOSOME
SLN
LIPID NANOPARTICLES
NANOPARTICLES IN IN SITU GELLING SYSTEMS
TEMPERATURE
pH, IONS
GEL MATRIX
DRUG
NANOPARTICLE
CATHETER

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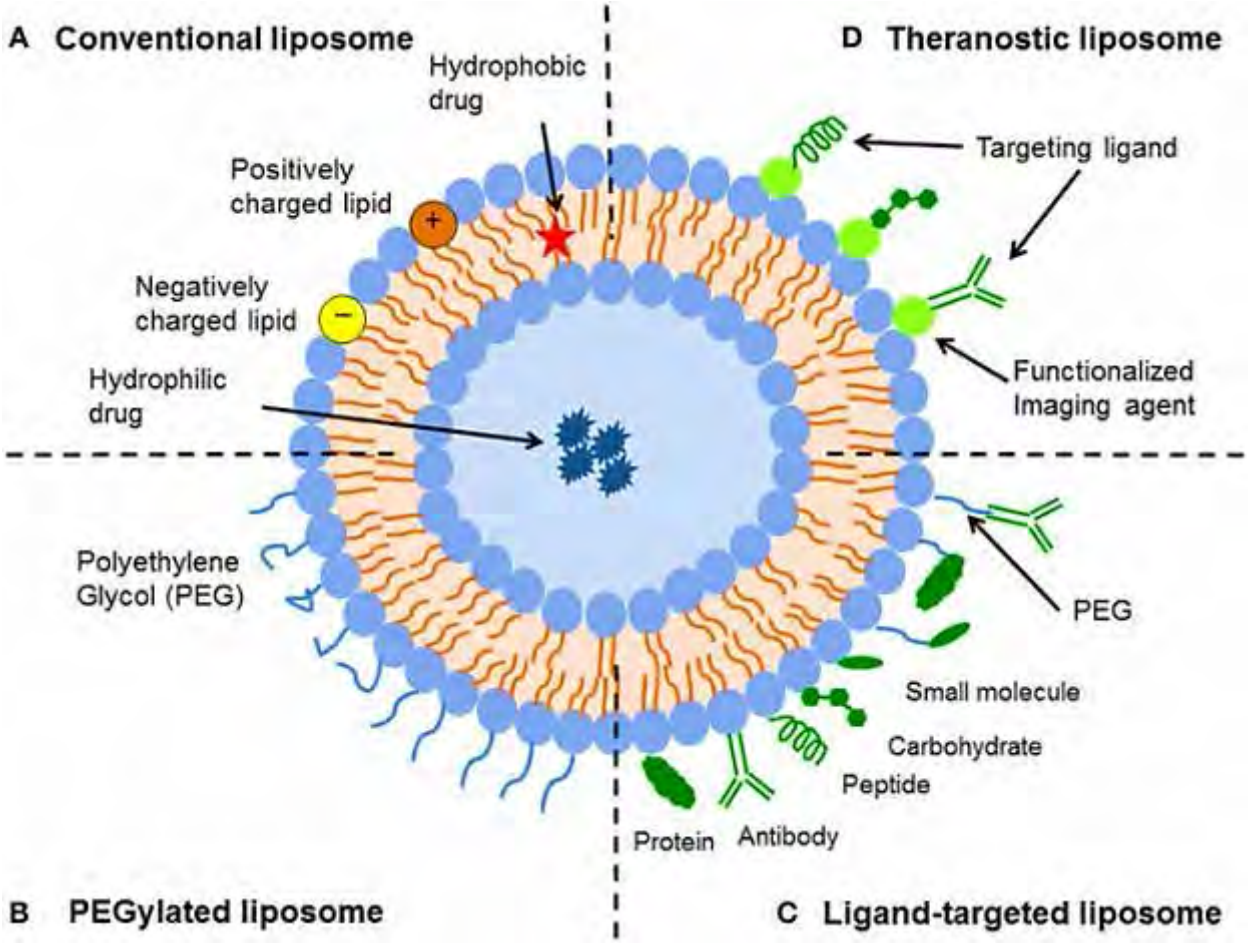
Types of liposomes



- **Non-toxicity, biocompatible, and completely biodegradable**
- **Increasing drug efficacy**
- **Site avoidance effect**
- **Increasing stability via encapsulation process**
- **Reducing the toxicity of encapsulated drugs**

Frontiers in Pharmacology, **2015,** *6,* 1–13

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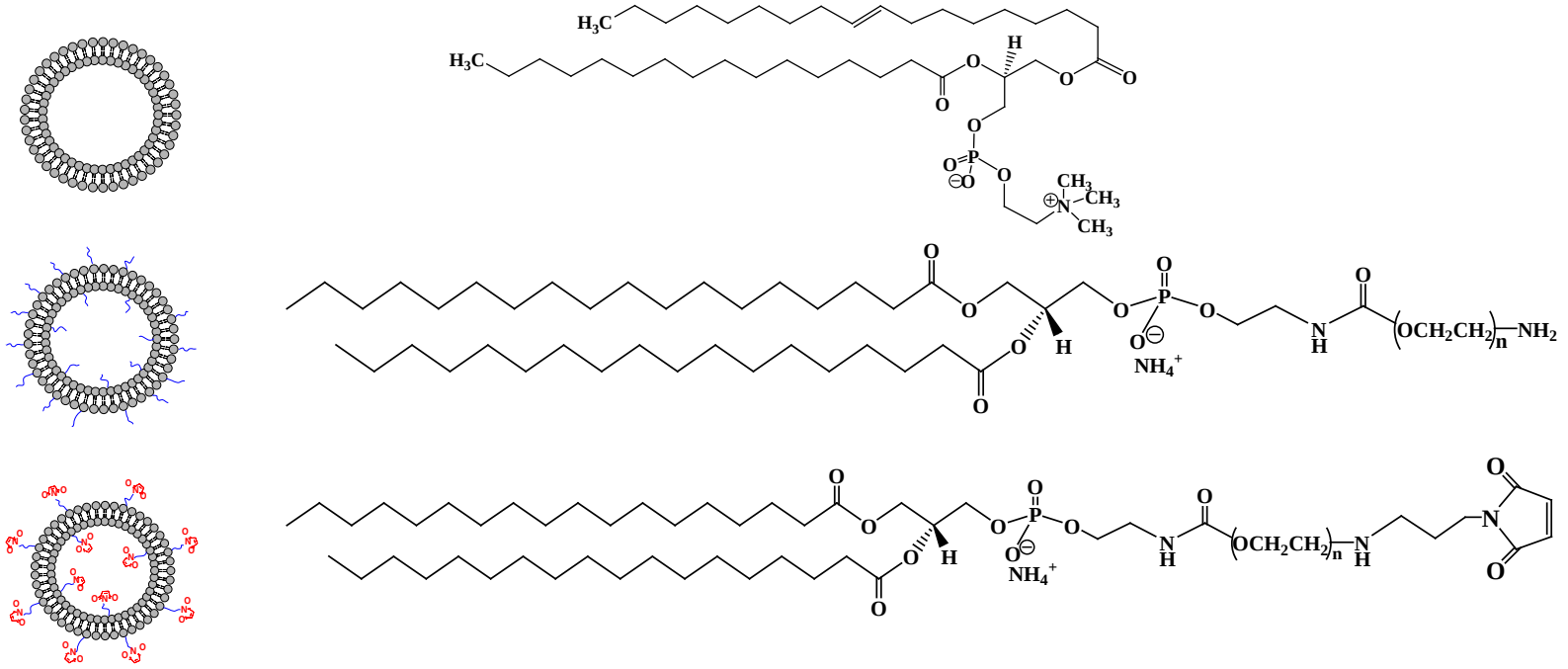
THE COMPOSITION OF LIPOSOMAL FORMULATIONS

Liposome formulations	PC (%)	Chol (%)	PEG_{2000}-DSPE (%)	PEG_{2000}-DSPE-Mal (%)	NaFlu (%)
Conventional	0.773	0.077	-	-	0.2
PEGylated	0.773	0.077	0.075	-	0.2
PEG-Mal	0.773	0.077	-	0.075	0.2



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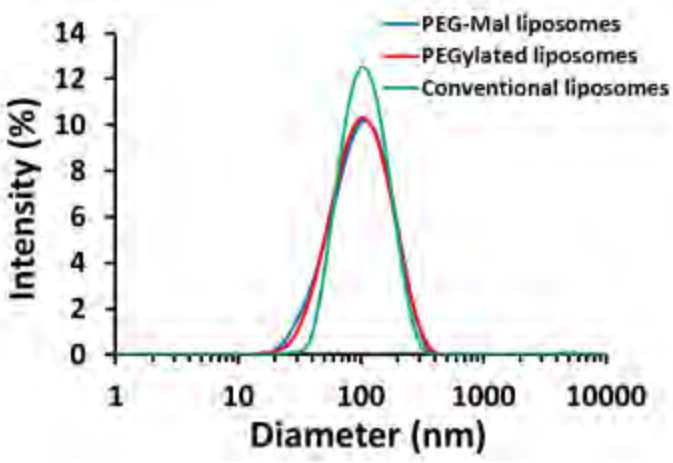
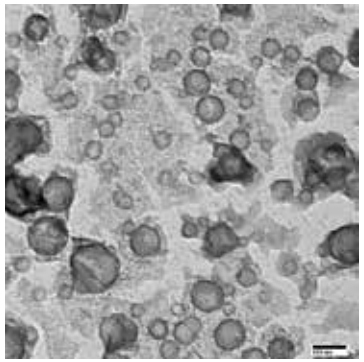
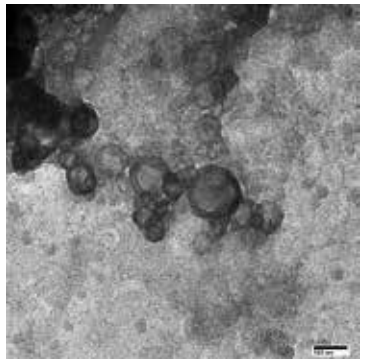
PHYSICOCHEMICAL CHARACTERISTICS

Liposome formulations	Mean diameter (nm)	PDI	Zeta potential (mV)	%EE	%LC
Conventional	97 ± 1	0.145	-53 ± 1	53 ± 6	12 ± 1
PEGylated	85 ± 1	0.217	-32 ± 2	27 ± 2	6 ± 1
PEG-Mal	86 ± 1	0.224	-37 ± 1	25 ± 2	5 ± 1

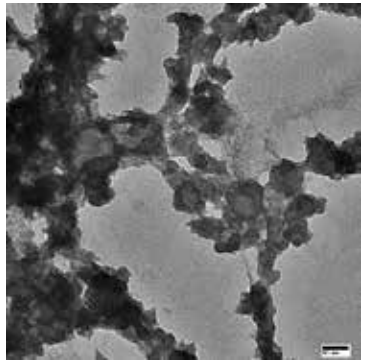




Conventional liposomes

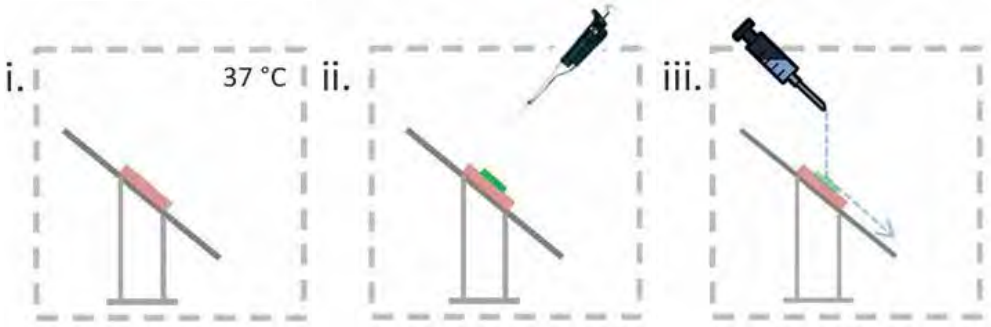


PEGylated liposomes



PEG-maleimide liposomes

Application of mucoadhesive onto a bladder mucosa



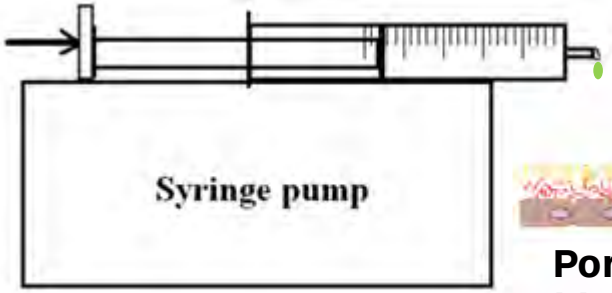
Chem. Commun., **2015**, *51*, 14447-14450

Fluorescence microscopy

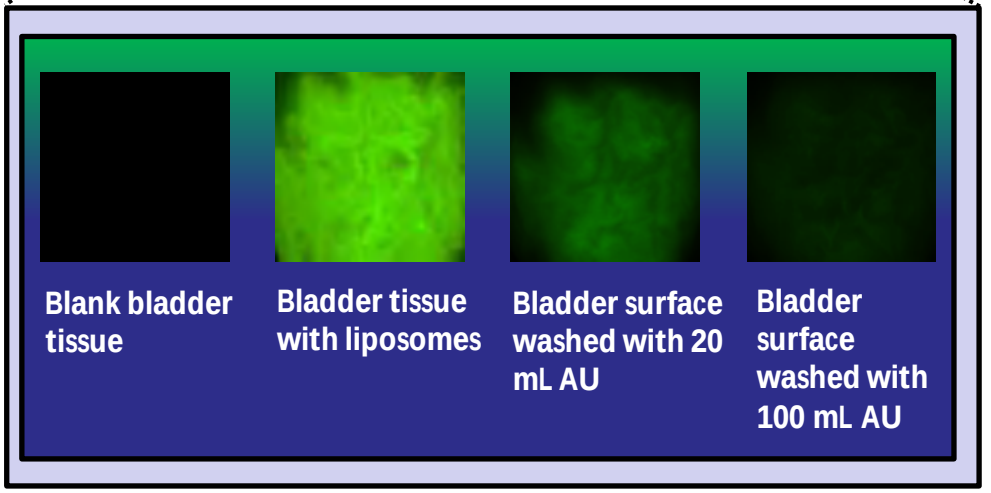
ImageJ

Image Processing & Analysis in Java

Artificial urine



Porcine bladder



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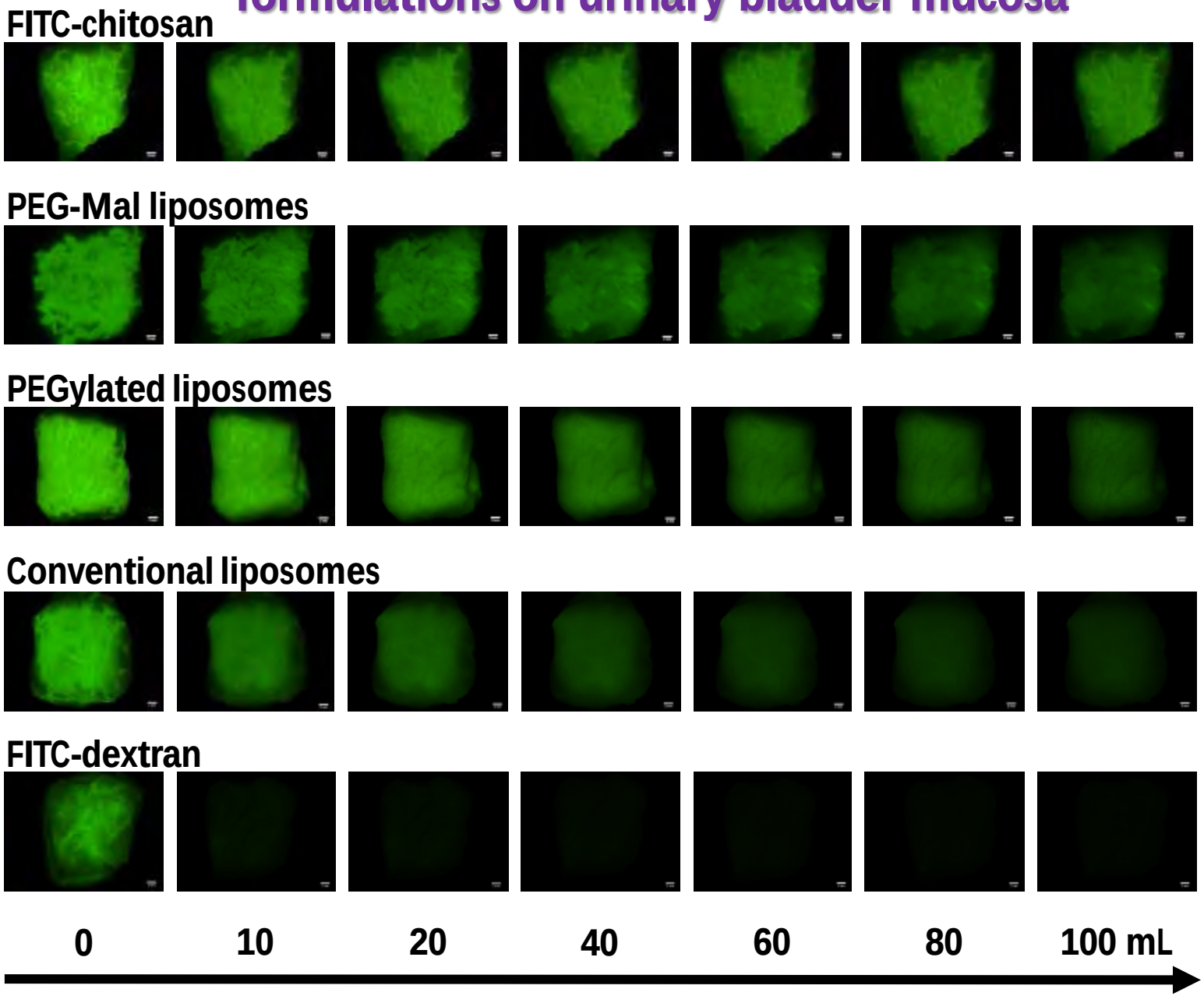
Exemplary fluorescent images of the retention of formulations on urinary bladder mucosa



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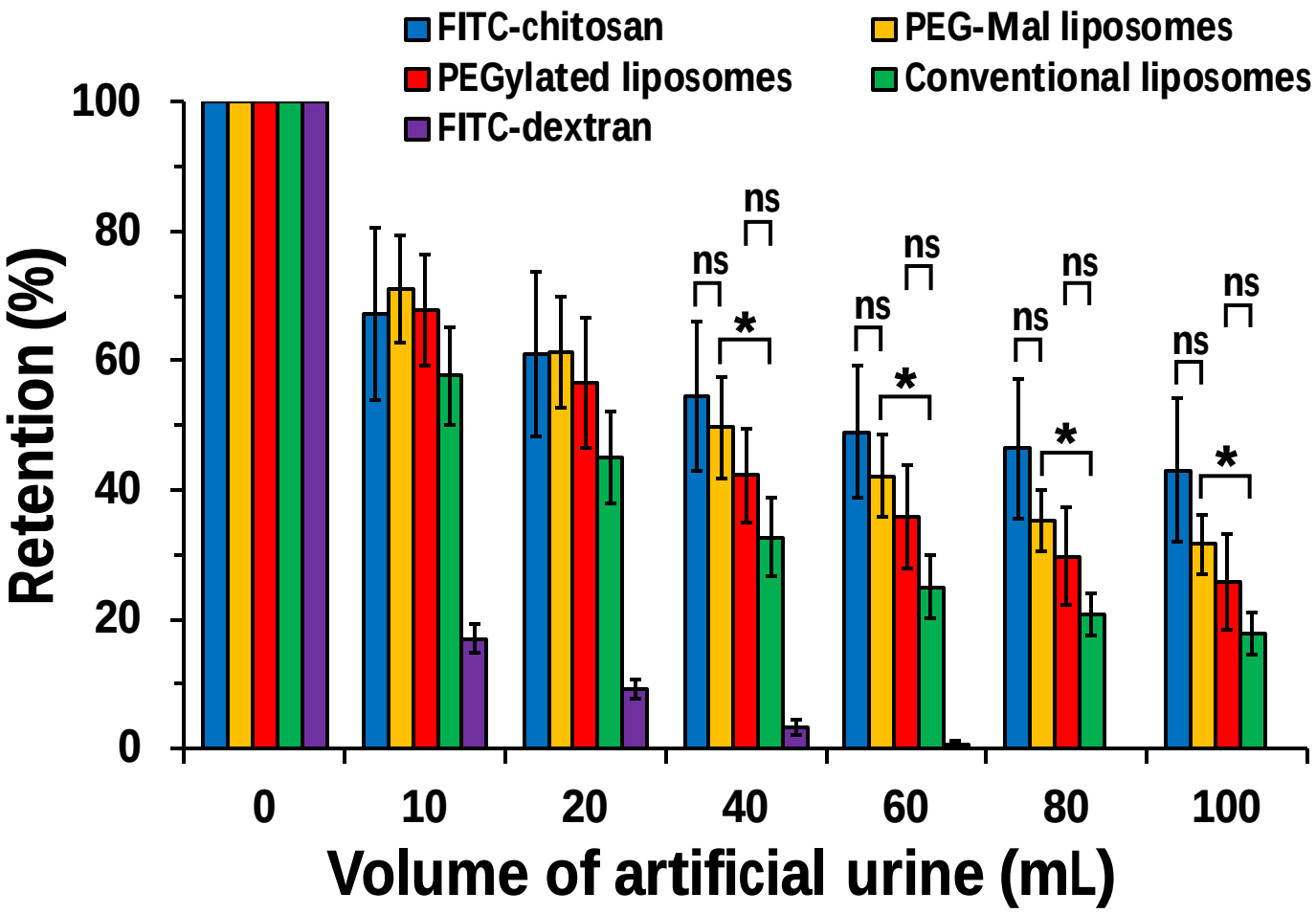

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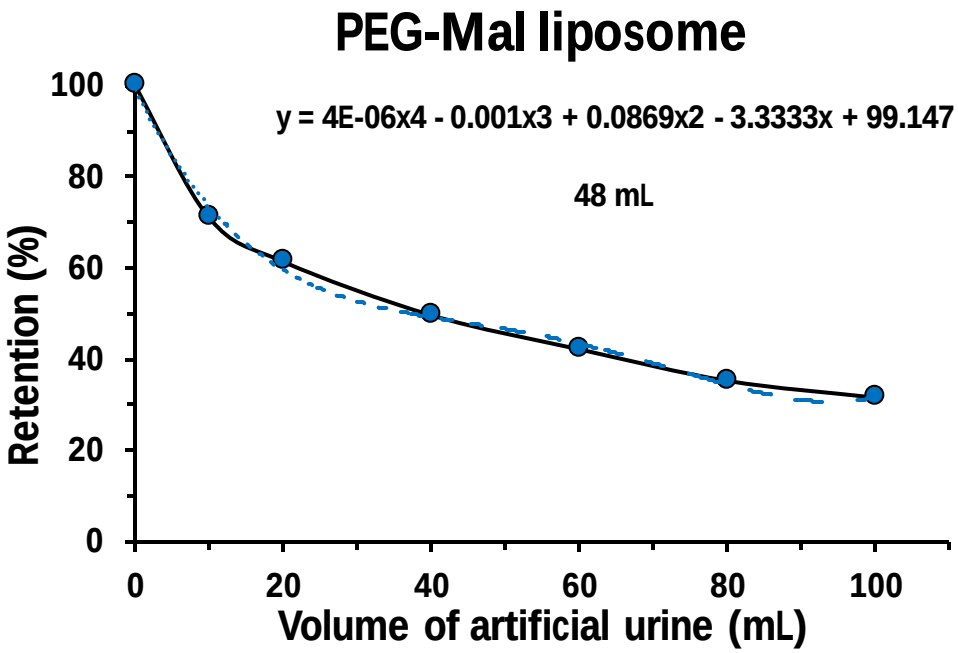
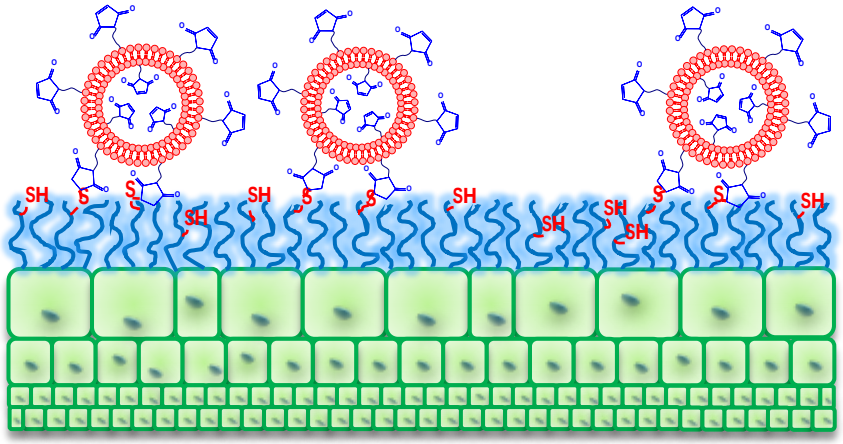
WASH OUT$_{50}$ PROFILES



Formulations	WO$_{50}$, mL
Conventional	15
PEGylated	24
PEG-Mal	48
FITC-chitosan	91
FITC-dextran	5



Proposed mechanism of bonding between maleimide-functionalised liposomes and mucosal surfaces

Wash Out$_{50}$ (WO$_{50}$) values are defined as the volume of liquid necessary to remove 50% of a mucoadhesive material from a substrate

Int. J Pharm., **2016**, *512*, 32-38

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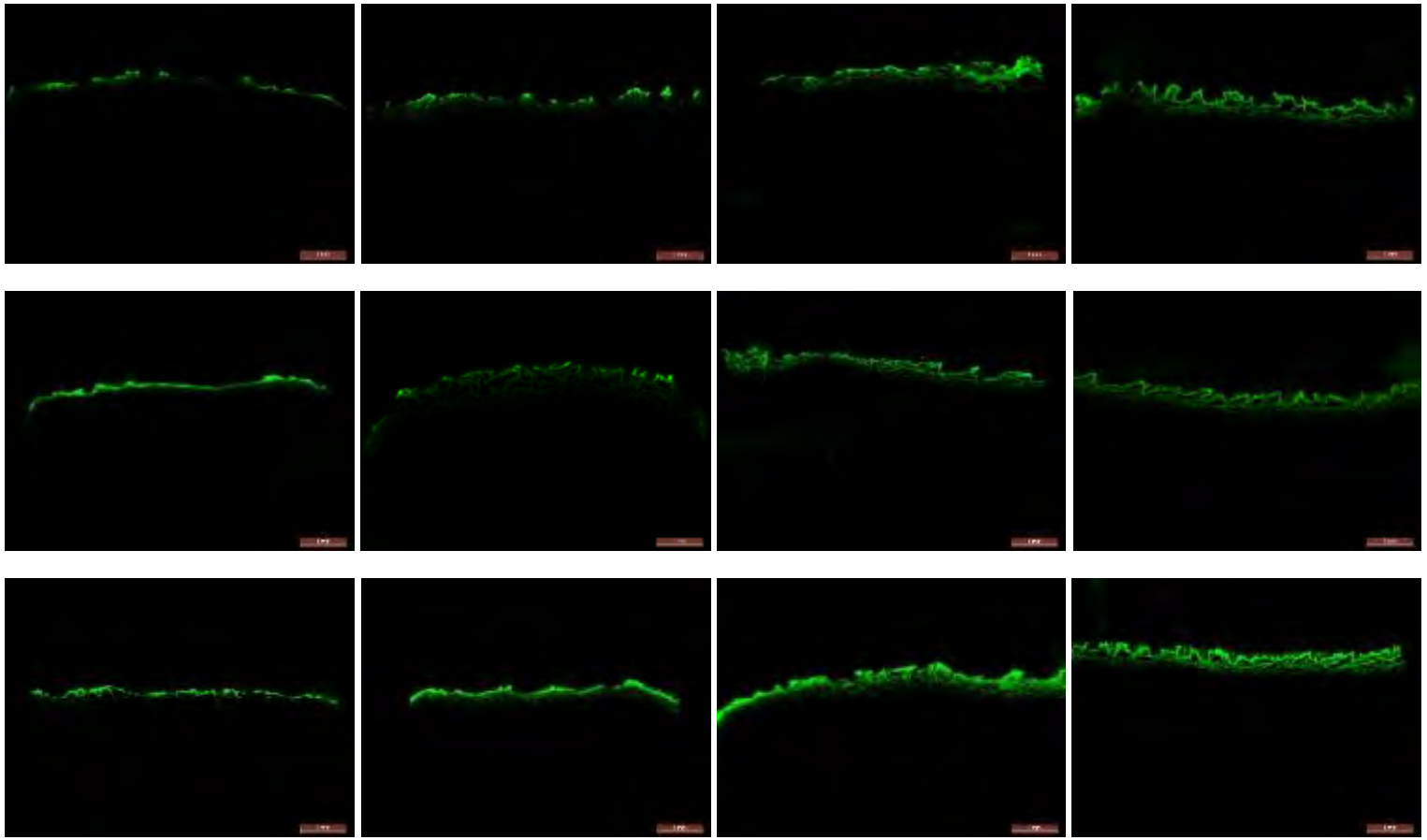
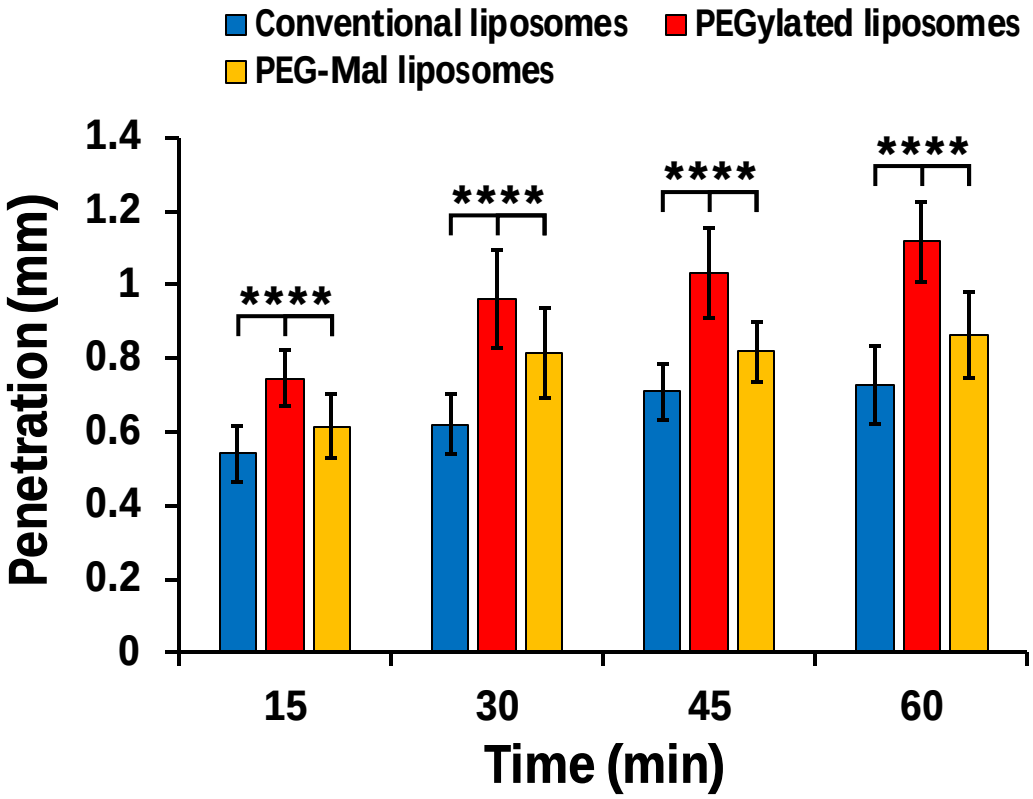
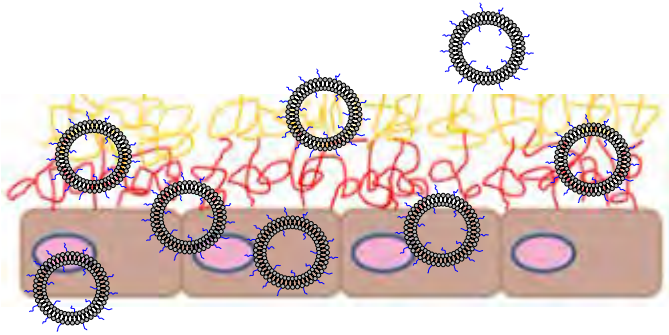
Penetration into bladder mucosa

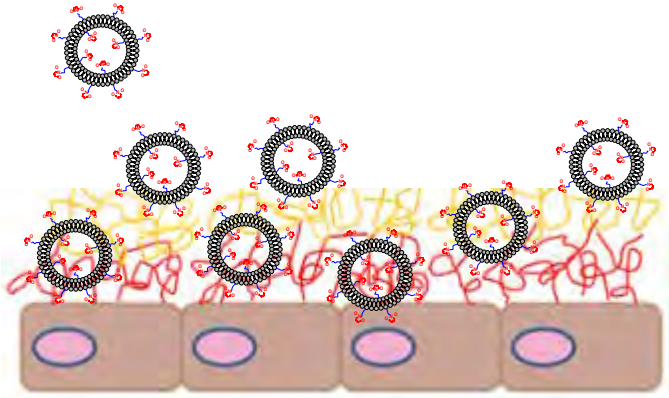
Exemplary fluorescence microscopy images:







PEGylated liposomes



Maleimide-terminated PEG liposomes

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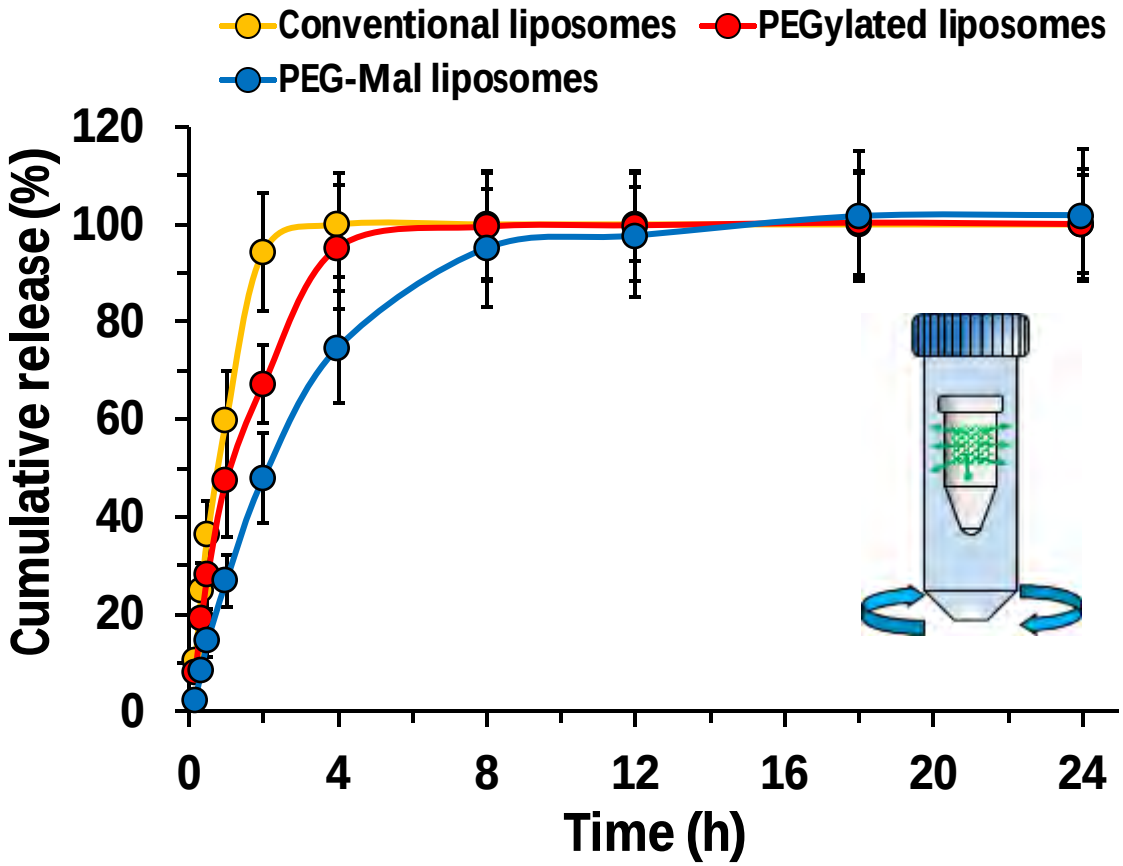
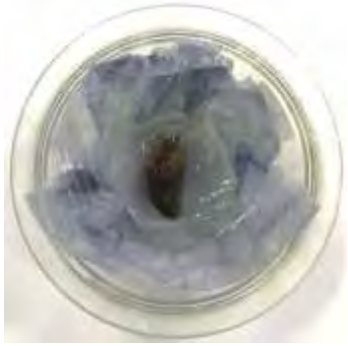


Toxicity – Slug mucosal irritation test

METHOD:

1

Slugs sourced from Harris Garden, UoR



Kept in desiccators lined with paper towels soaked with 20 mL of PBS at RT for 48 h

2

weighed before the experiment

filter paper moistened with test materials

Left to contact for 1 h

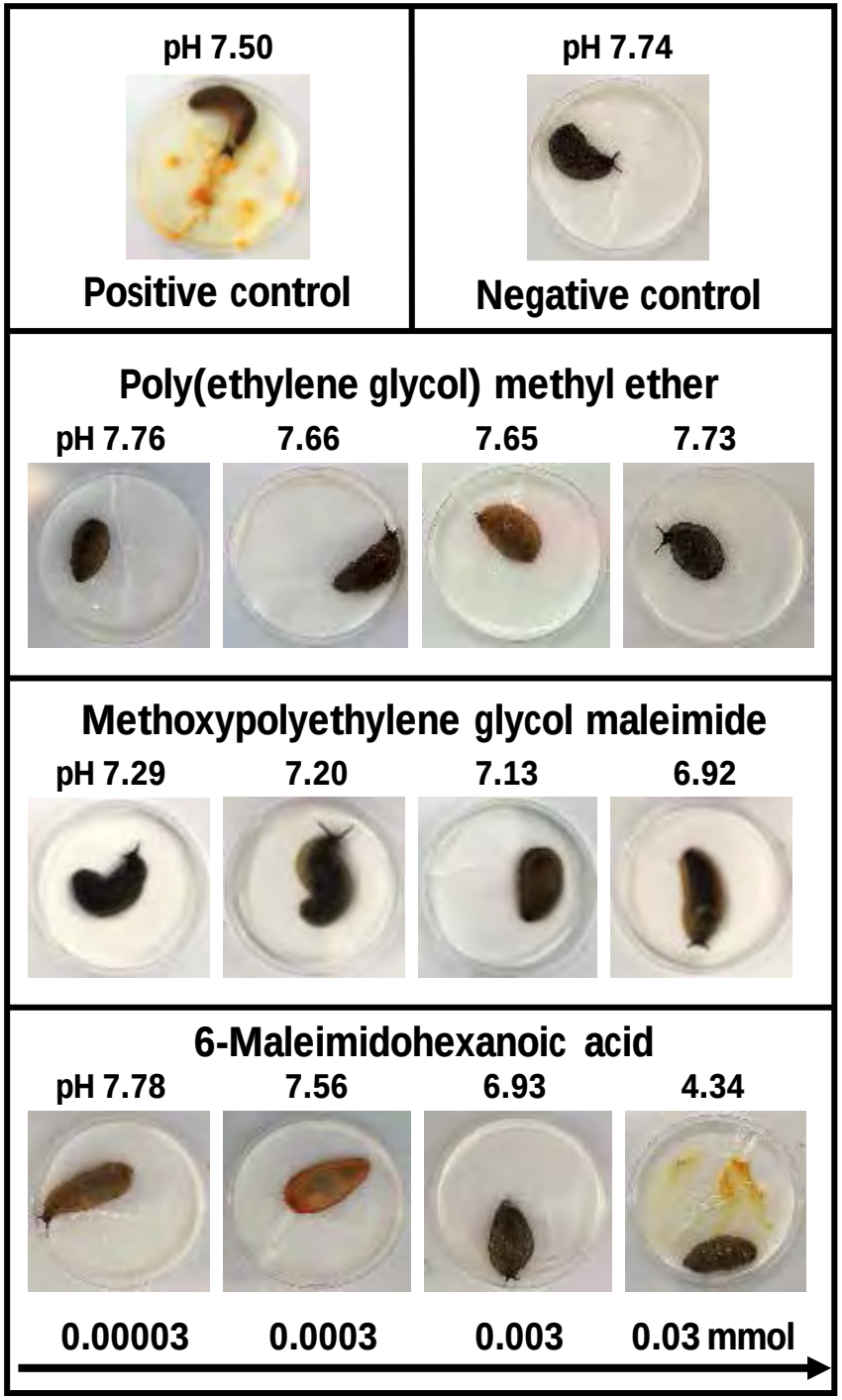
3

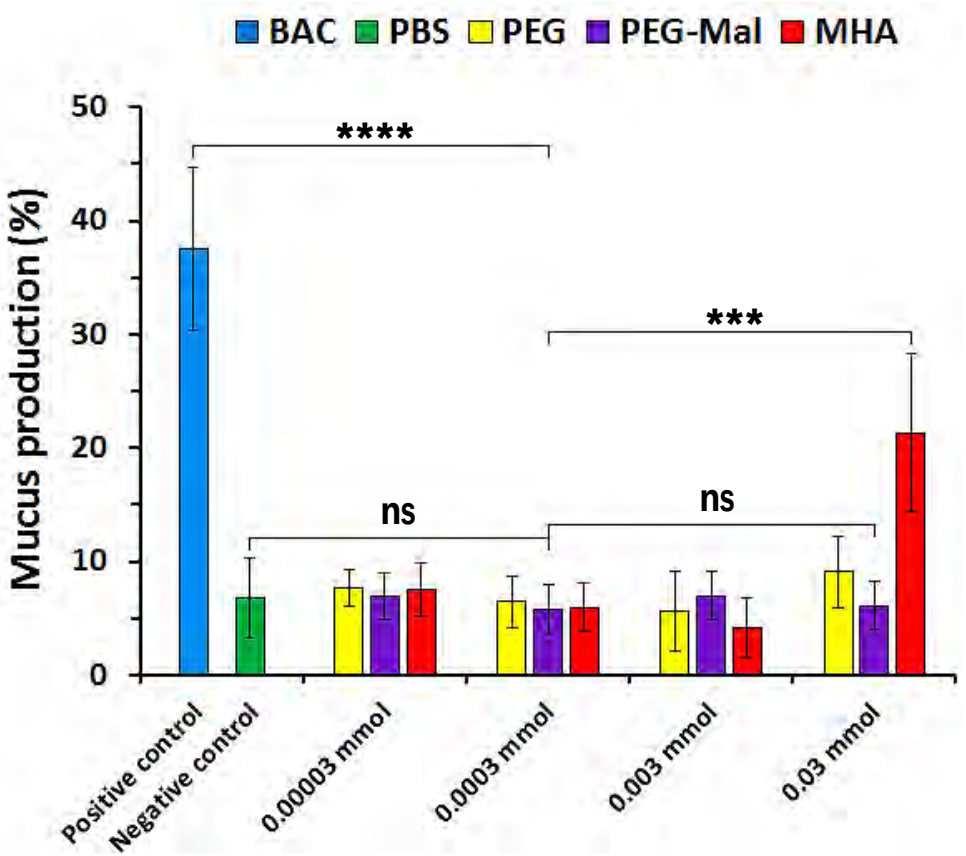
rinsed and wiped

re-weighed

Mucus production:

$$MP = \frac{(m_b - m_a)}{m_b} \times 100\%$$





BAC – Benzalkonium chloride
PBS – Phosphate buffered saline
PEG – Poly(ethylene glycol) methyl ether (average Mn 5,000)
PEG-Mal - Methoxypolyethylene glycol maleimide (average Mn 5,000)
MHA – 6-Maleimidohexanoic acid

Results published in

Eur. J Pharm. Sci. **2018**, *111*, 83-90

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THANK YOU!