Overcoming Biological Barriers using Stimuli Responsive Silica Nanoparticles

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The University of Queensland

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Advanced Delivery Science

Acknowledgements

Australian Government
National Health and Medical Research Council
NHMRC

Mater Research

TRI
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Australian Microscopy & Microanalysis Research Facility

Evolving Role of Controlled Drug Delivery Systems

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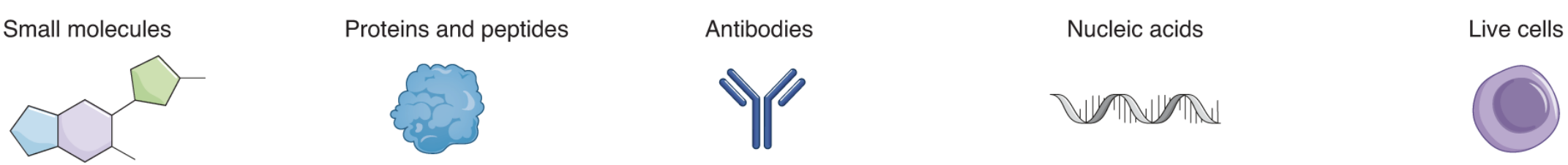
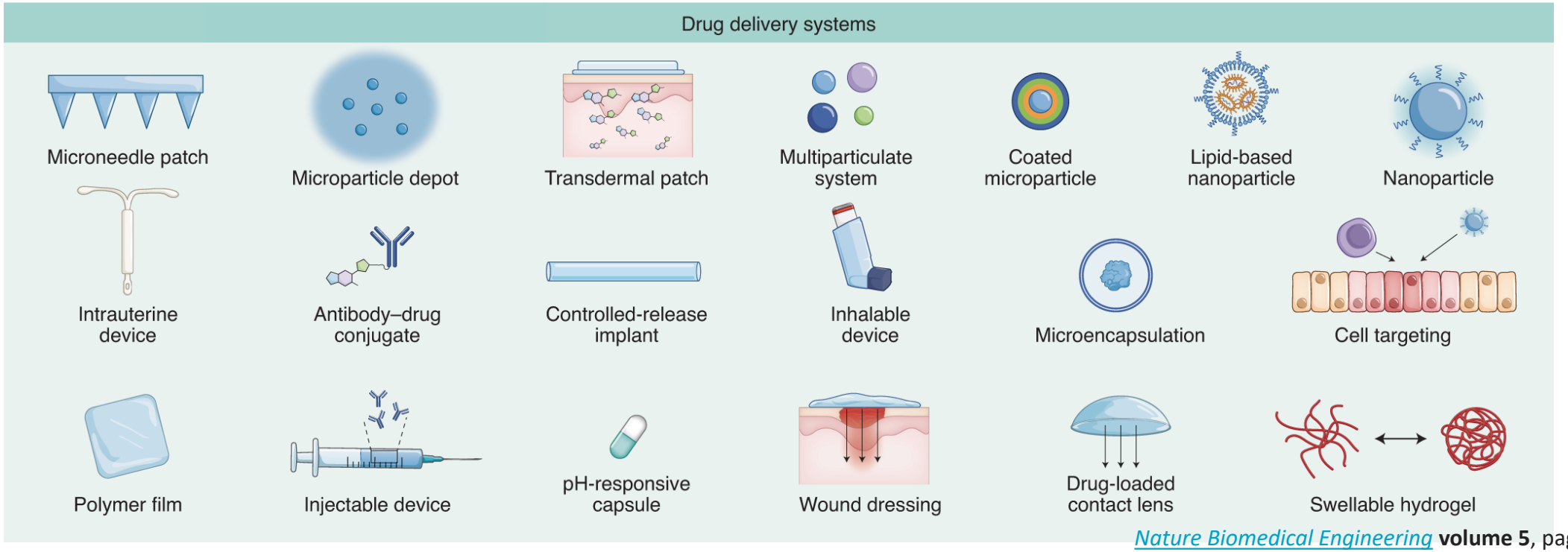


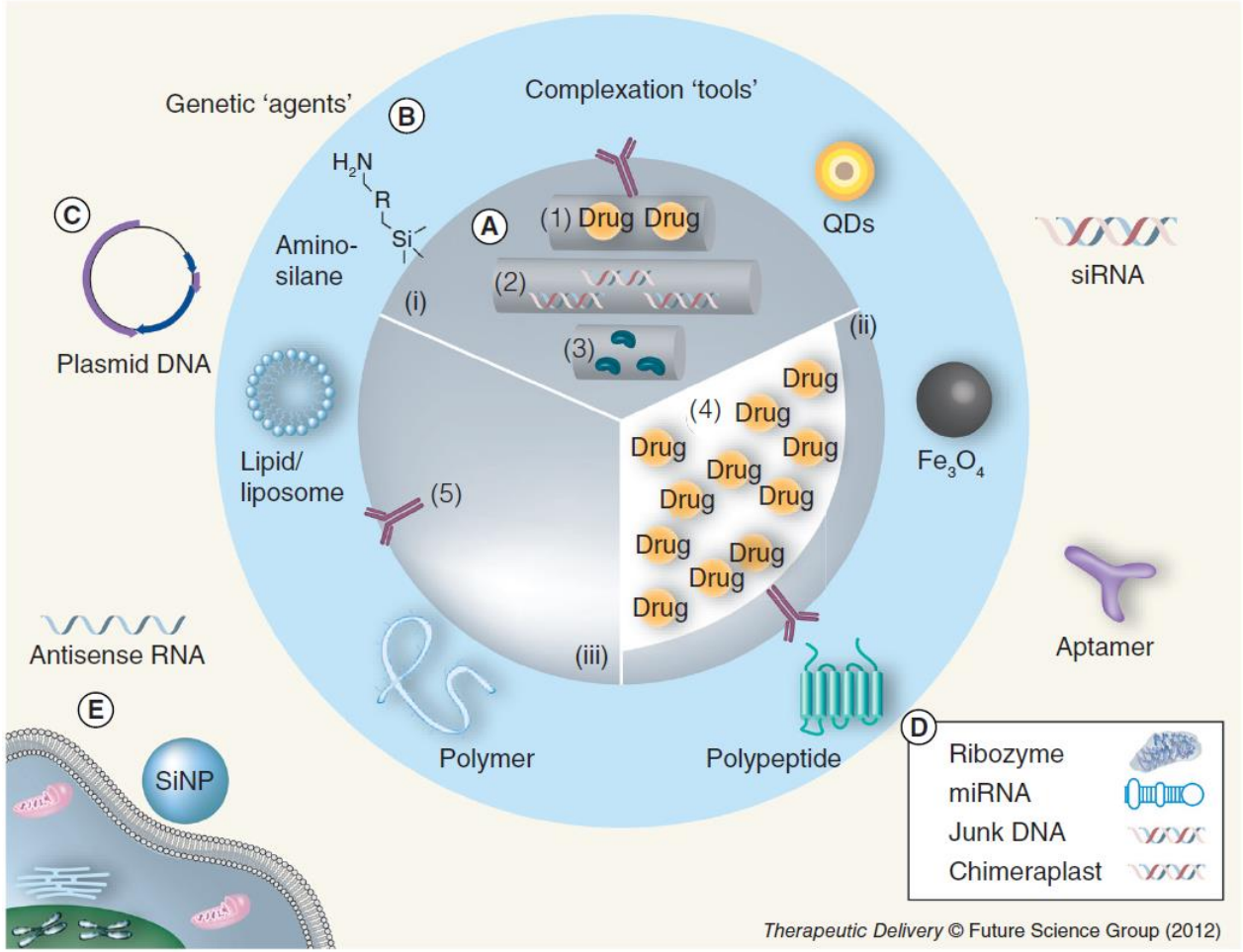
Challenges				
Controlling PKs Improving solubility Improving permeability Target development Reducing off-target toxicity	Controlling PKs Improving stability Non-invasive administration Bypassing biological barriers Reducing immunogenicity Improving target selectivity	Controlling PKs Improving stability Non-invasive administration Bypassing biological barriers Reducing immunogenicity Achieving high doses	Controlling PKs Improving stability Bypassing the target cell membrane Accessing the cytosol or nucleus Reducing immunogenicity Preventing off-target gene editing	Controlling unpredictable PKs In vivo persistence and viability Reducing immunogenicity Maintaining therapeutic cell phenotype Targeting to disease location Manufacturing and scale-up



Nature Biomedical Engineering **volume 5**, pages951–967 (2021)

Mesoporous silica nanoparticles (MSNs)

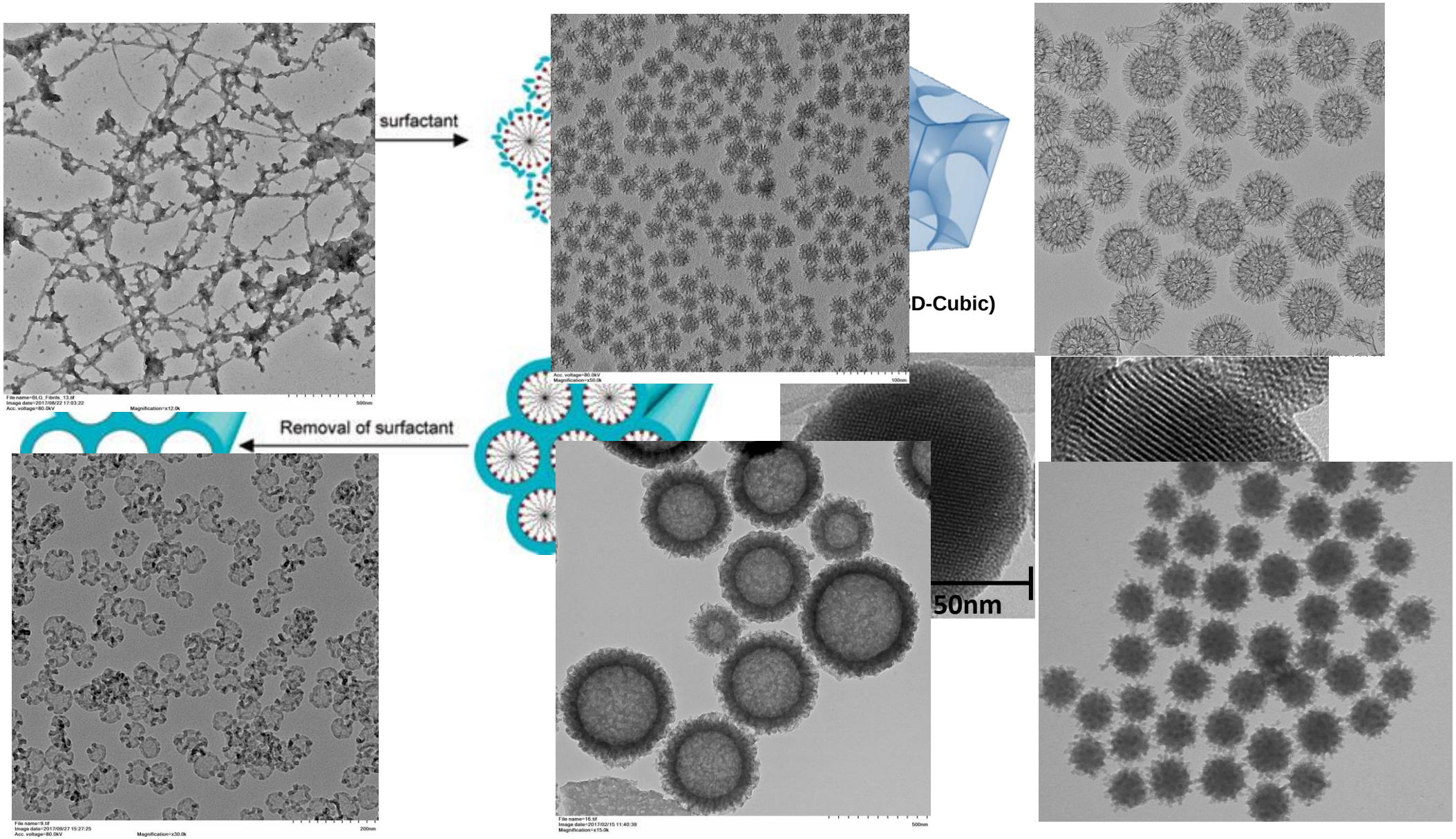
- MSNs are inorganic nanoparticles discovered by Mobil and co-workers in 1992
- They possess high surface area (>1000 m^2/g), small particle size (50-500nm), large pore volumes and ease of surface modifications
- They are biocompatible and their use in oral drug delivery is proven by the use of aerosil in tablet excipient since decades



Niu, Popat et al., *Therapeutic Delivery* (2012) 3(10), 1217–1237

A.Popat et al*. Nanoscale*, 2011, 3, 2801–2818

Synthesis



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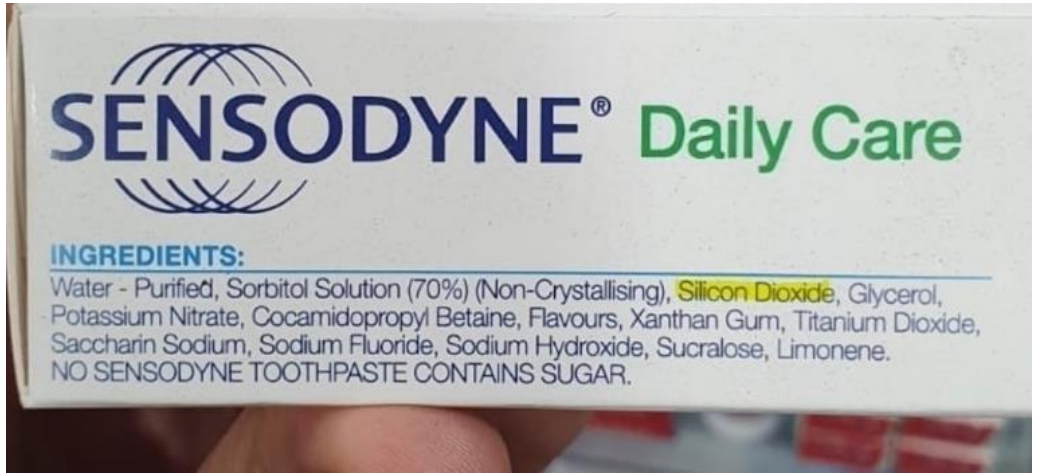
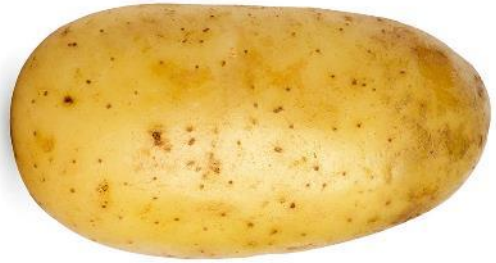
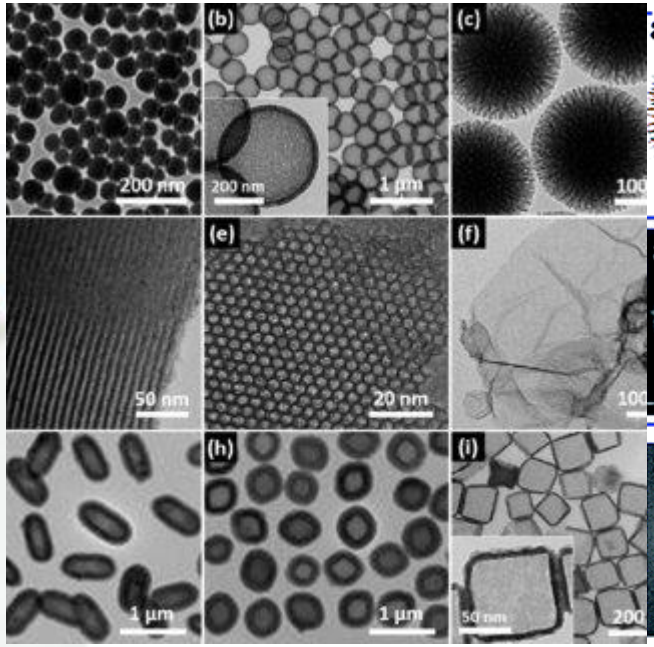
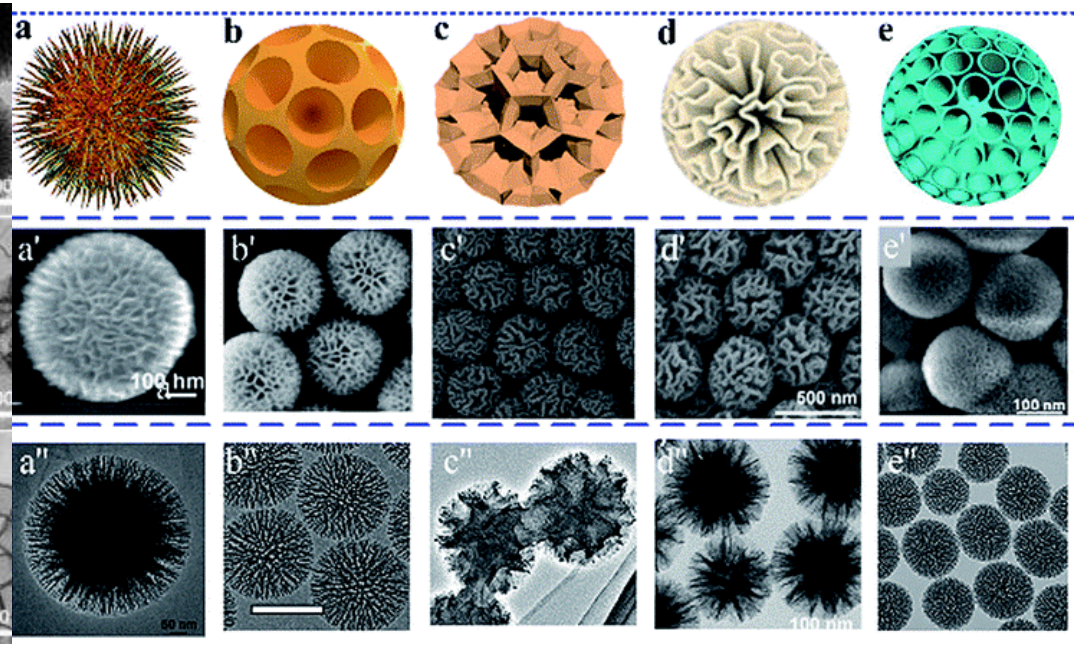
Silica – an emerging material





Silica nanoparticles





- Wang, Yabin, et al. "Dendritic fibrous nano-particles (DFNPs): rising stars of mesoporous materials." *Journal of Materials Chemistry A* 7.10 (2019): 5111-5152.
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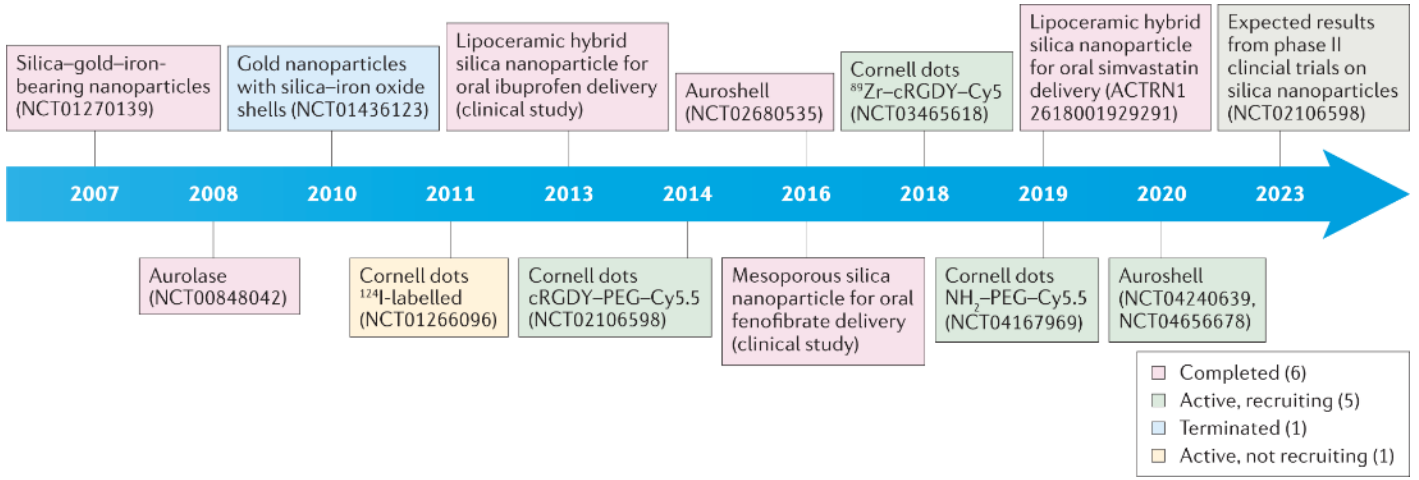
Can silica nanoparticle be used as delivery system?

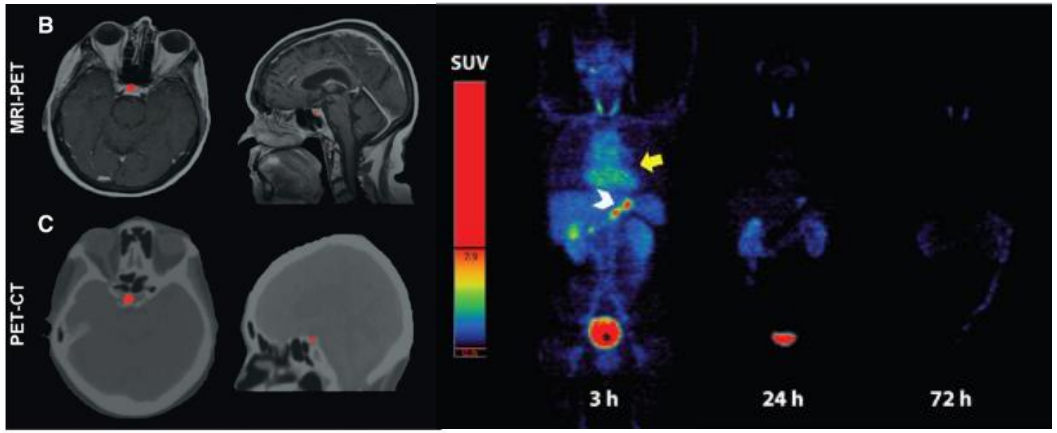
nature reviews materials

Clinical translation of silica nanoparticles

Taskeen Iqbal Janjua, Yuxue Cao, Chengzhong Yu & Amirali Popat

Nature Reviews Materials **6**, 1072–1074 (2021) | Cite this article

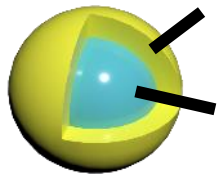




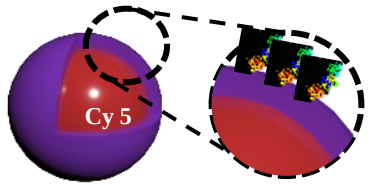
Silica nanoparticle have been tested in clinical trials for:

1. Drug delivery
2. Plasmonic/ photothermal therapy
3. Cancer diagnostic – including head and neck tumours

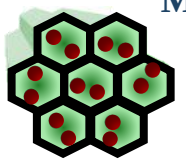
Silica nanoparticle with gold shell

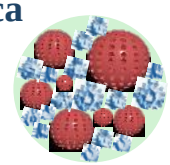


Cornell dots



Mesoporous silica





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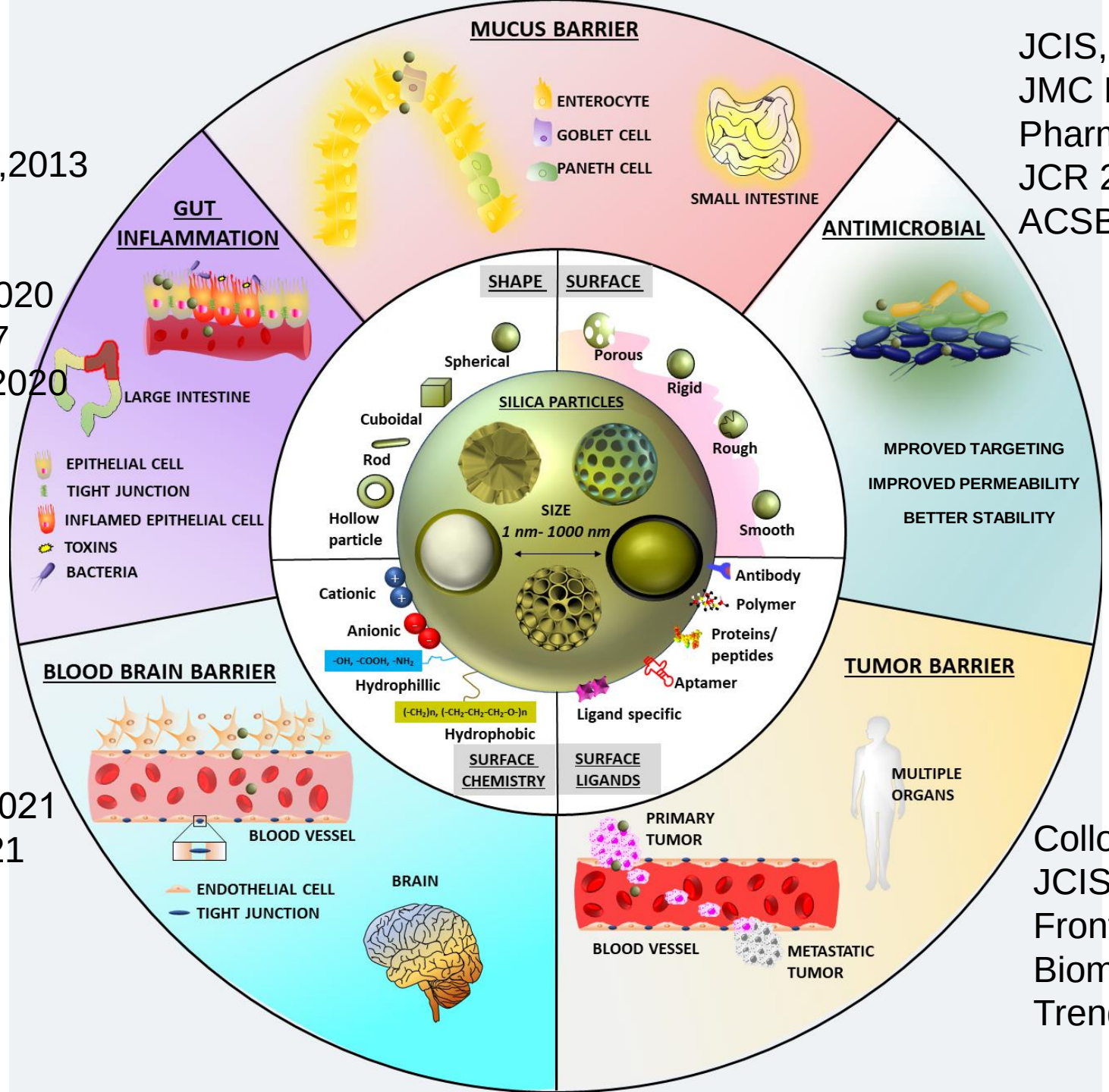
ACSBiomat Sci Eng 2021



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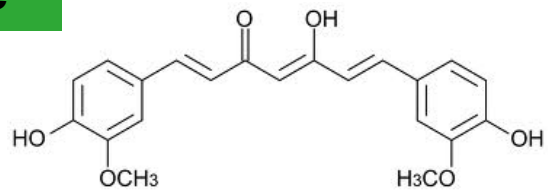
IJP 2020, IJP 2021
ACSBiomat Sci Eng 2021
ACS applied Nano, 2020

Editor's Choice ADDR 2021
ACSBiomat Sci Eng 2021
Nanoscale 2021

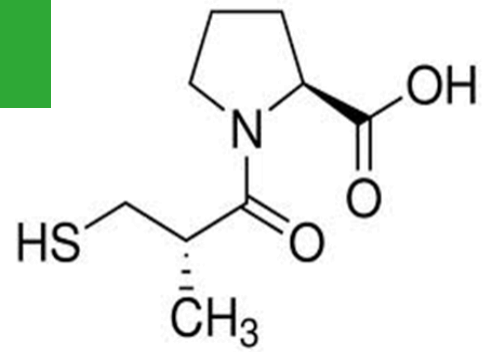
Colloids ad Surfaces B 2016
JCIS 2014
Front BioEng BioTech 2019
Biomaterials Science 2020
Trends in Biotech 2022

Floating Tablet using MSNs

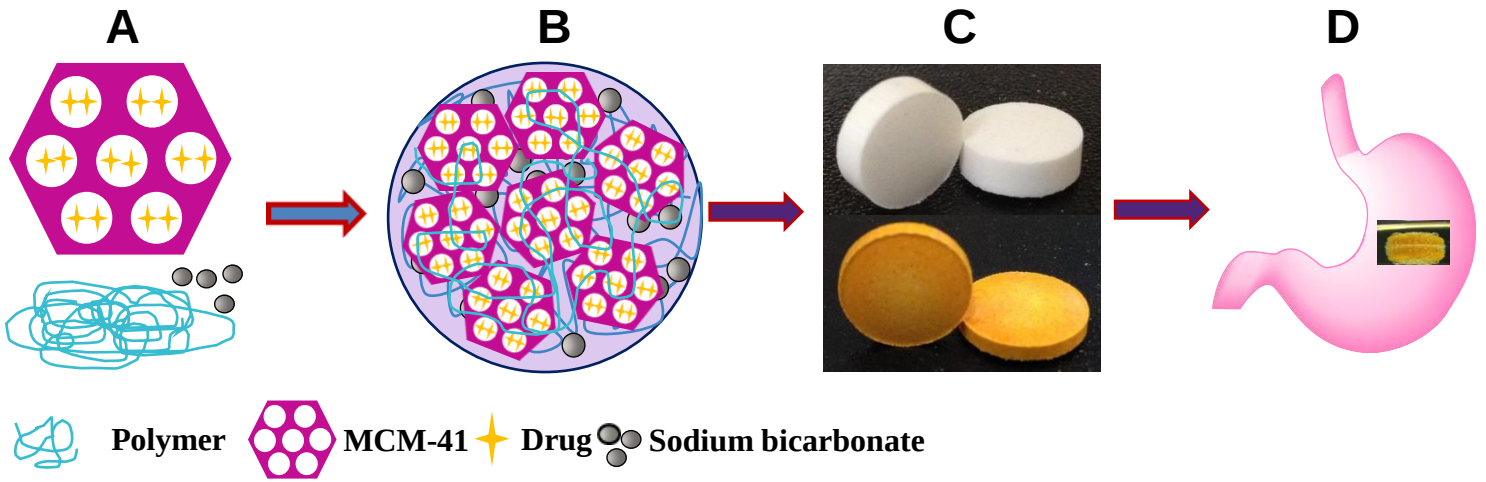
Curcumin
Hydrophobic



Captopril
Hydrophilic



- **unstable at high pH**



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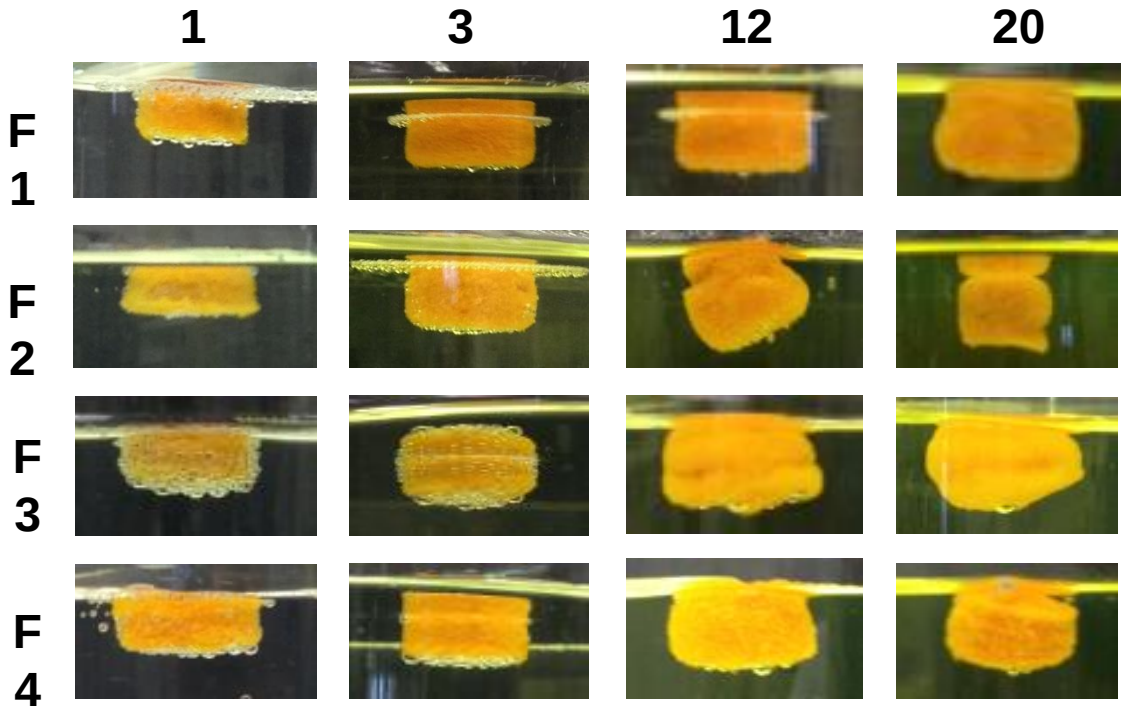


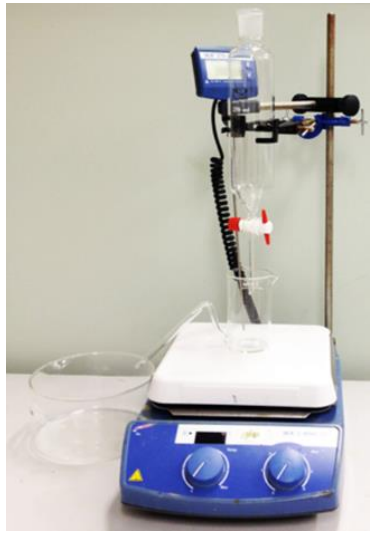
F1- 1.7nm + Polymer

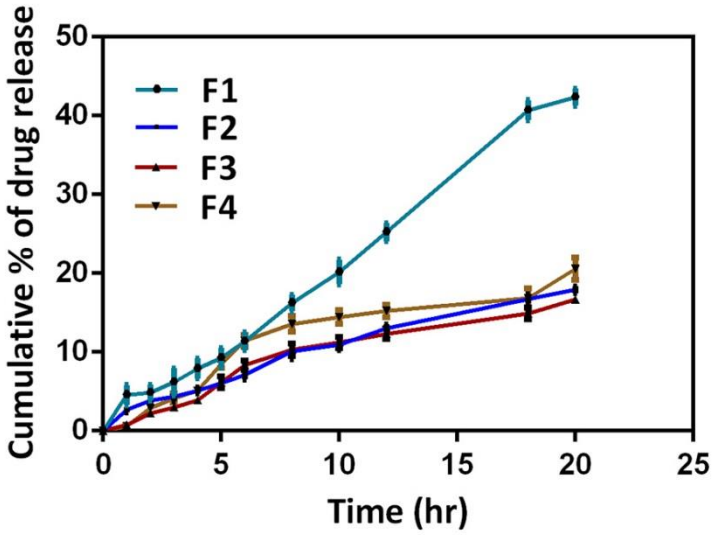
F2- Drug + Polymer

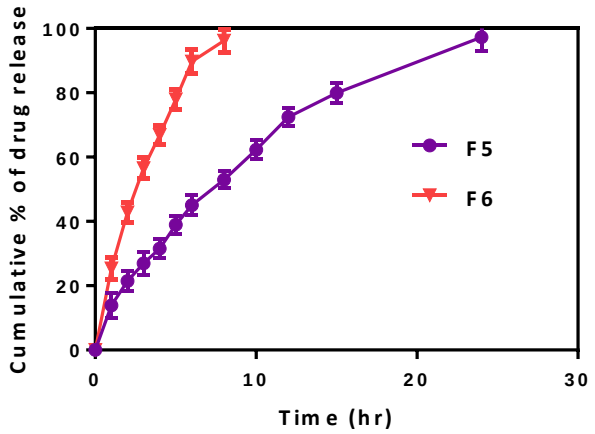
F3- Drug + Polymer

F4- 2.1nm + Polymer

All the tablets contain $NaHCO_3$

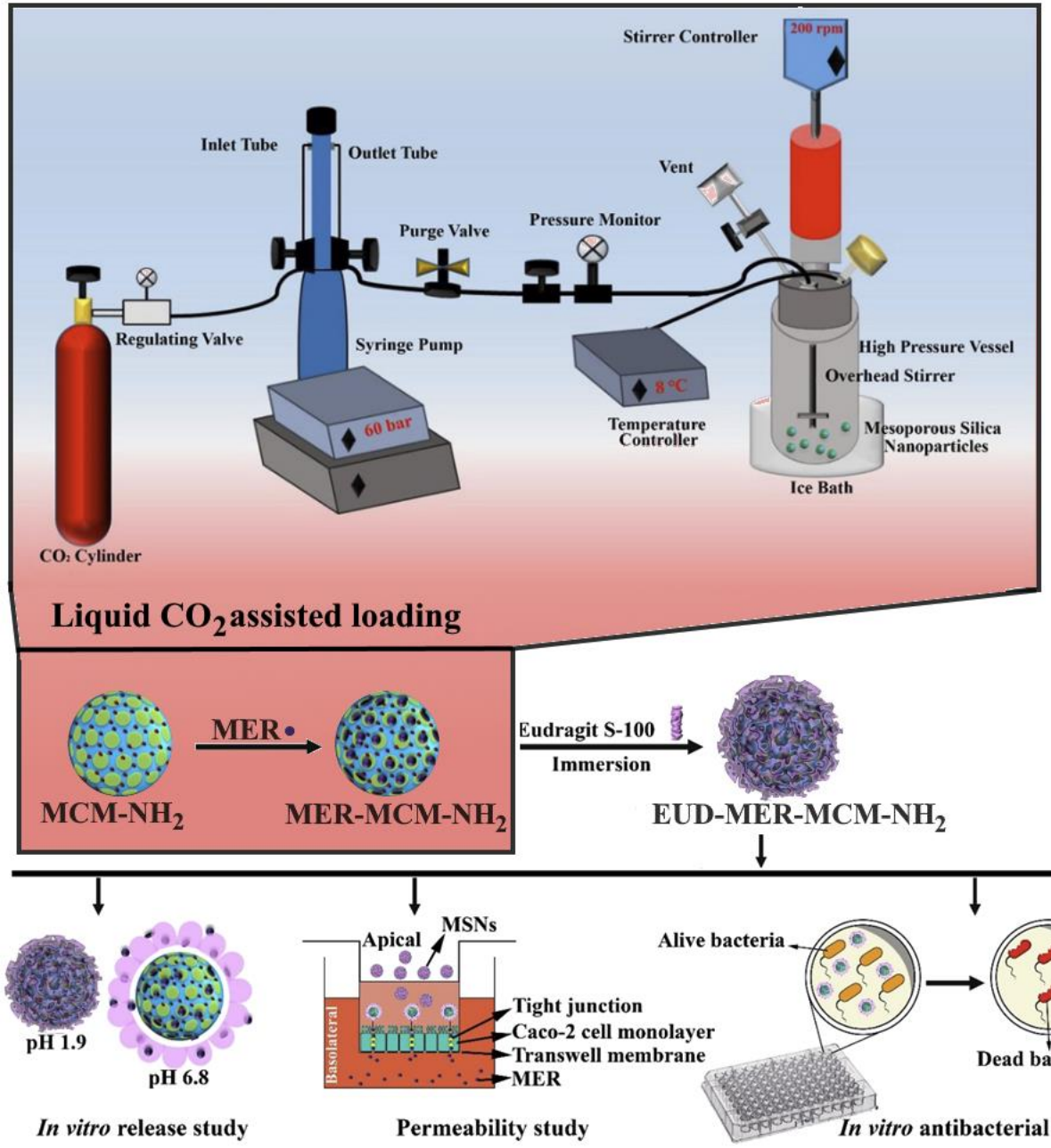


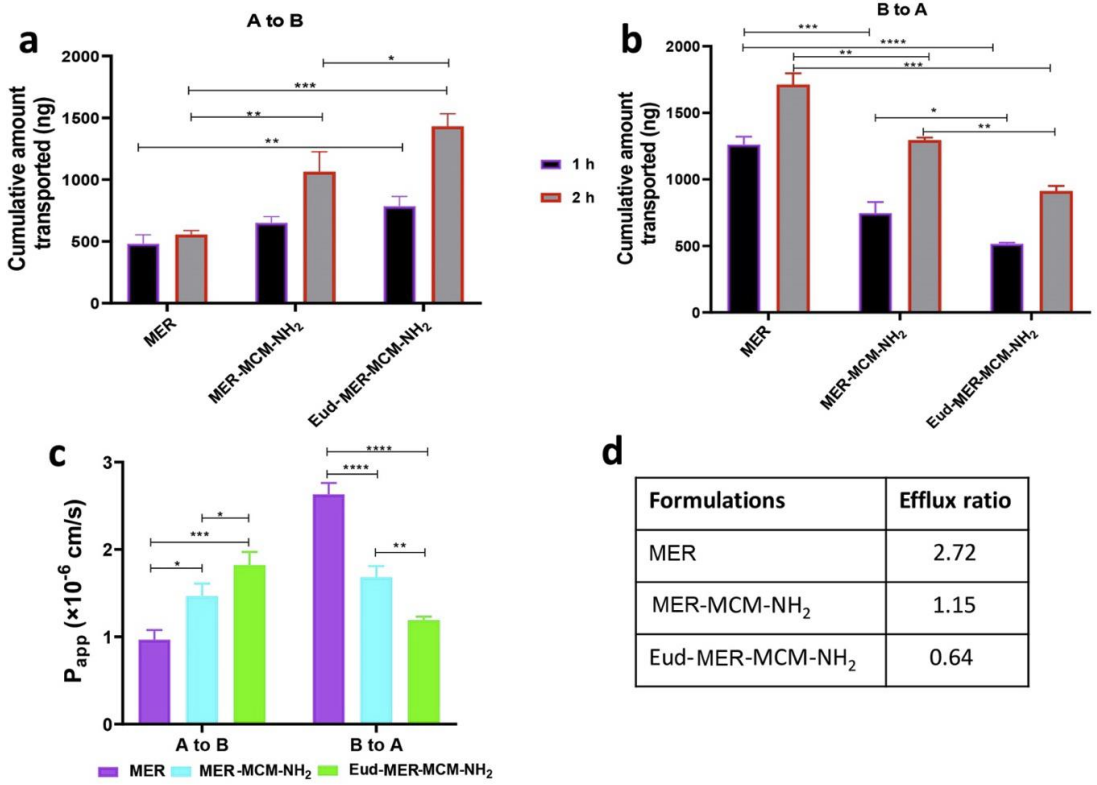




Release profile of curcumin from floating tablet

Oral Delivery of MEROPENEM





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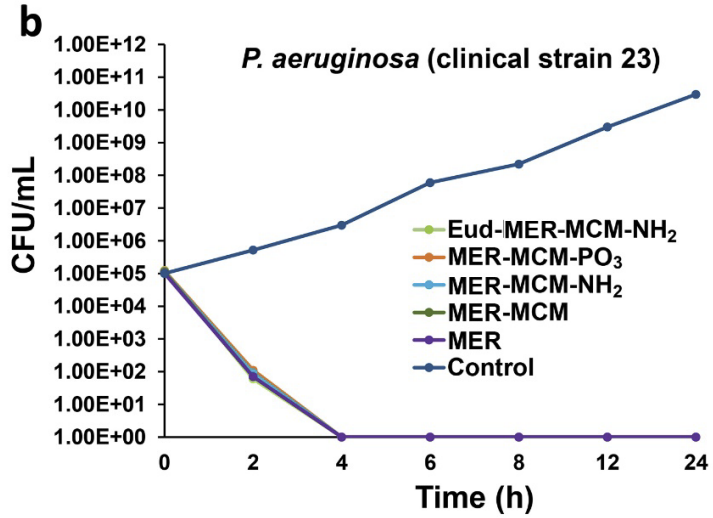
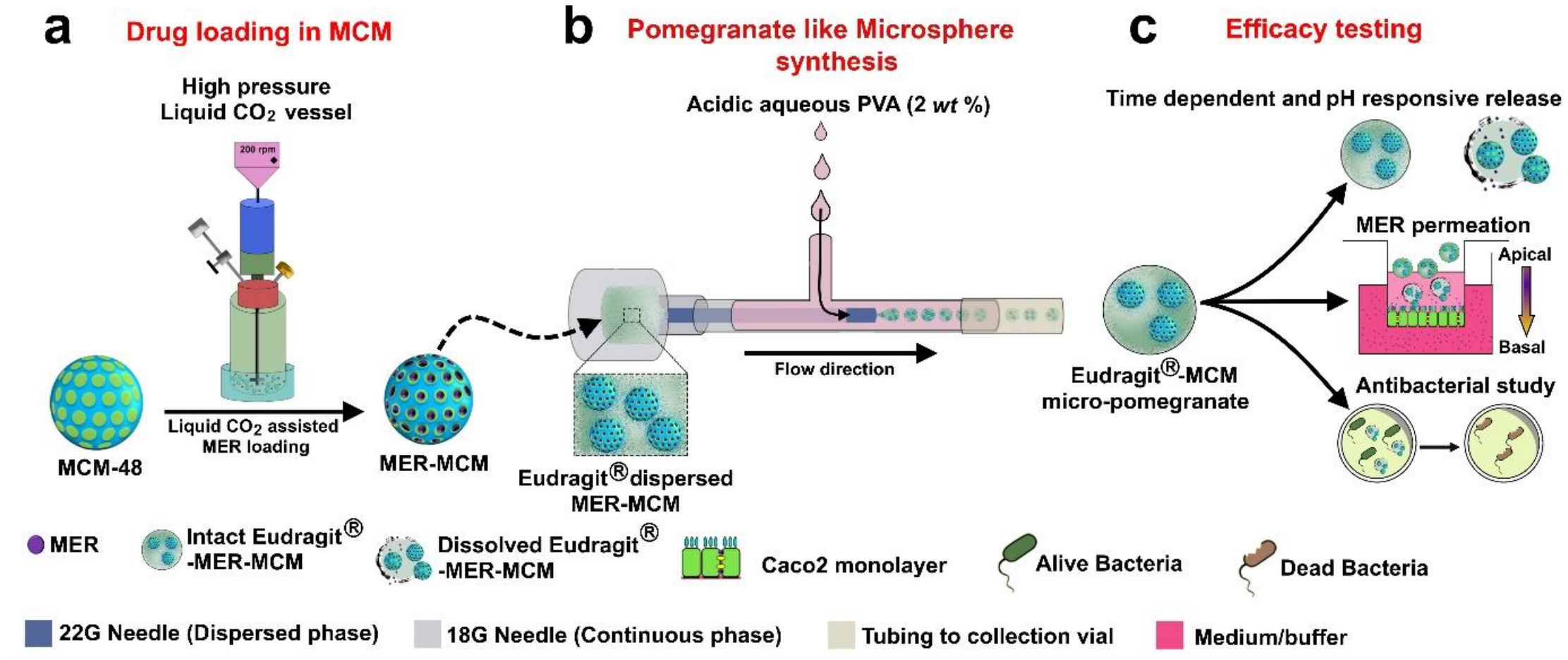
Formulations	Efflux ratio
MER	2.72
MER-MCM-NH_2	1.15
Eud-MER-MCM-NH_2	0.64

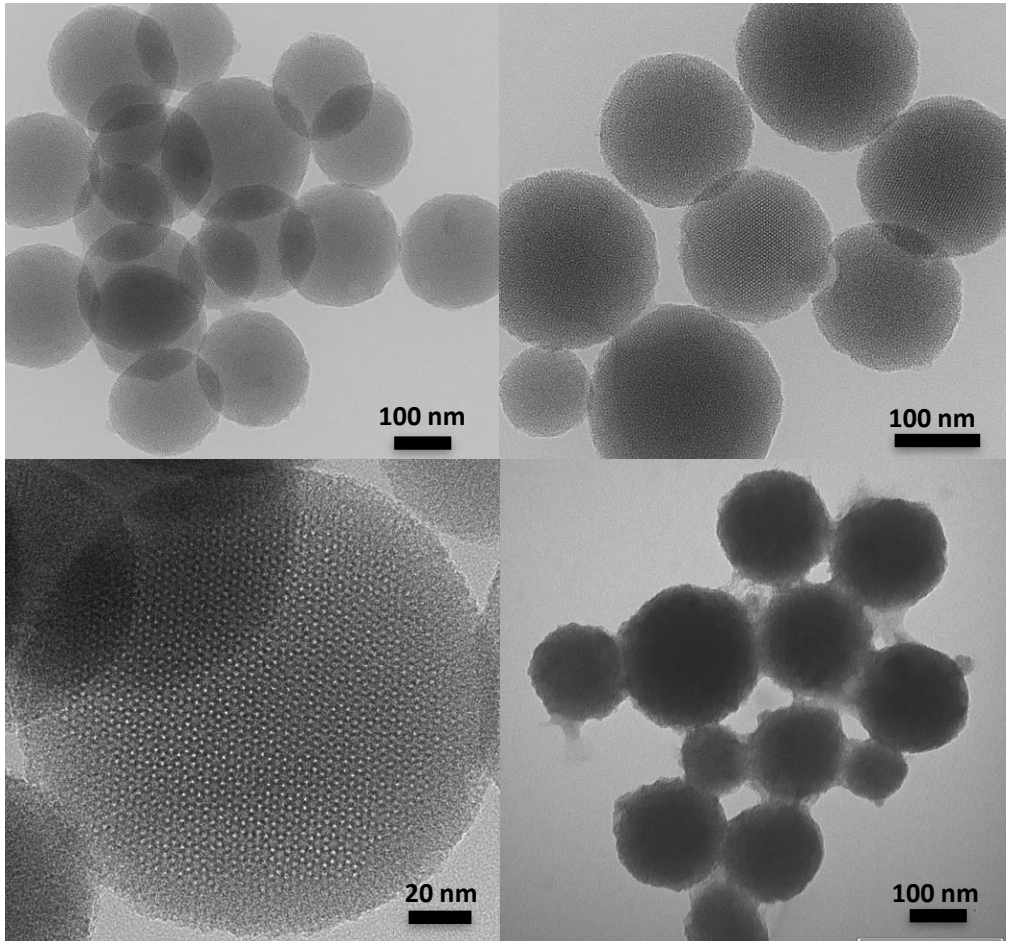


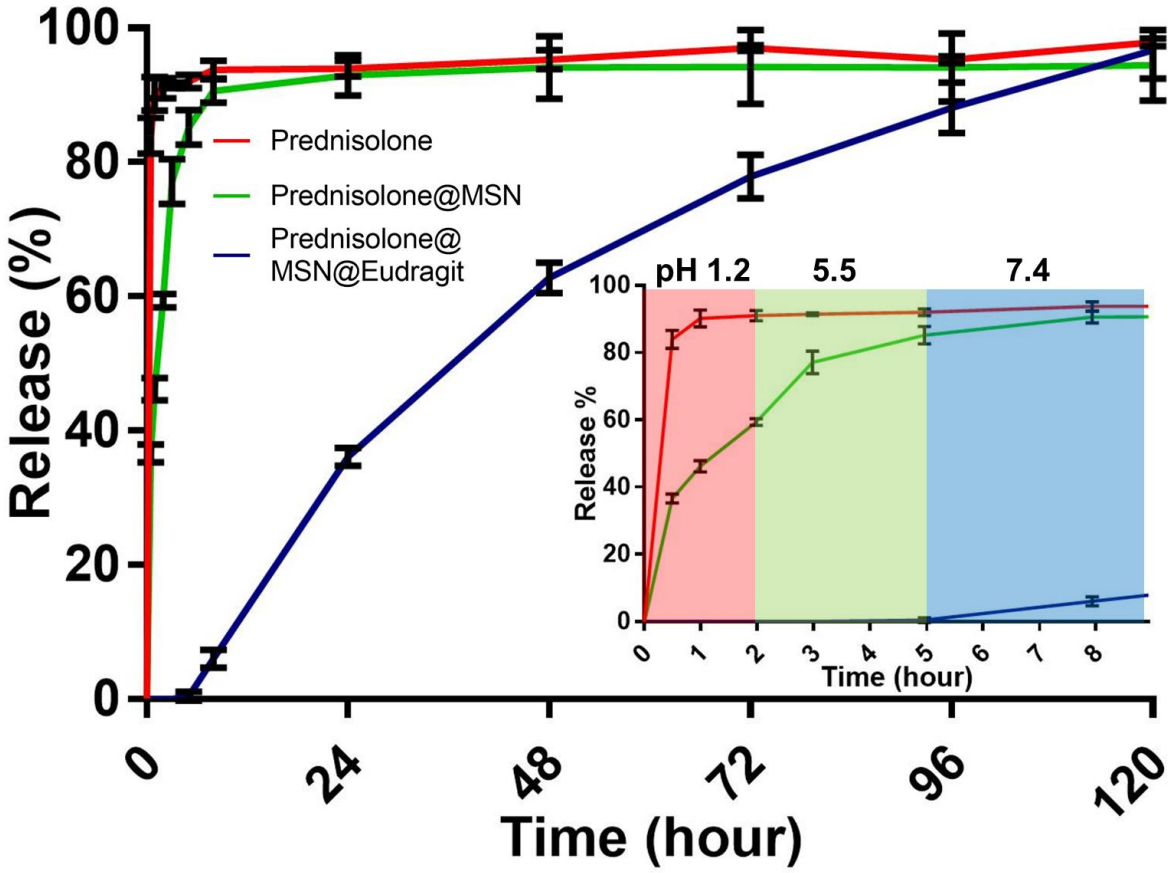
Microfluidic assembly of hierarchical microparticles



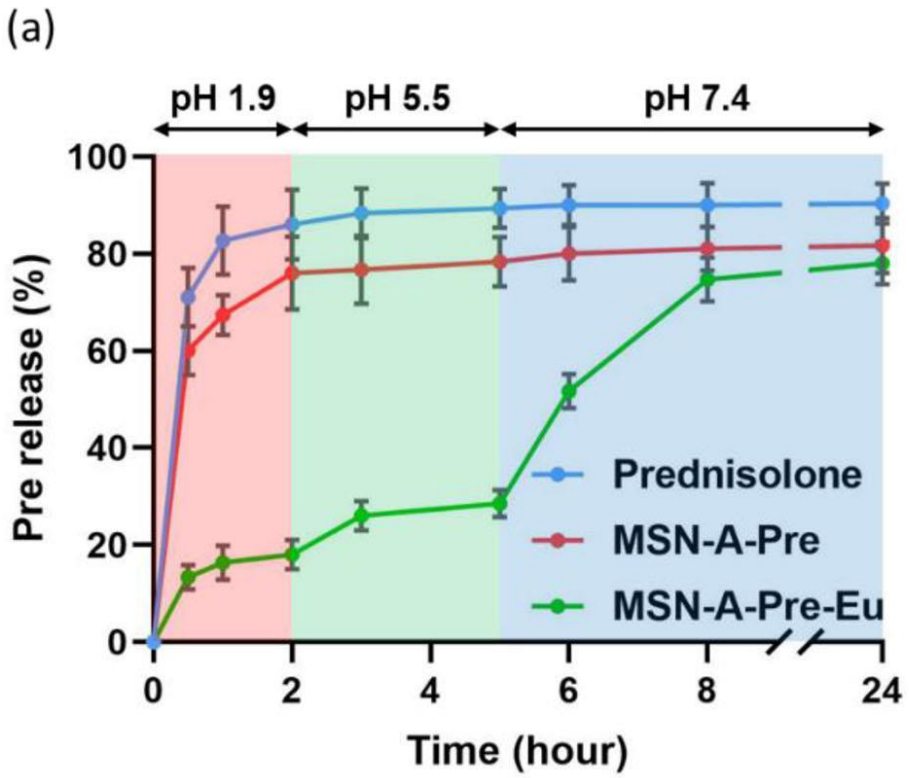
Raza et al., Acta Biomaterialia, 2021, 126, 277-290

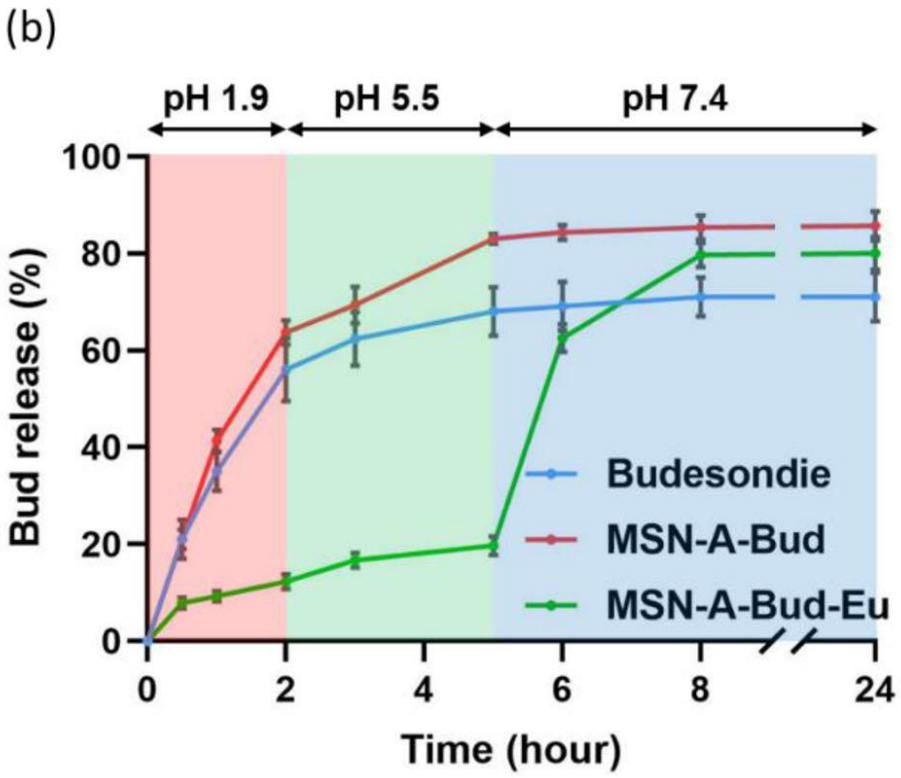
Programmable MSNs for Oral Delivery





In-vitro release

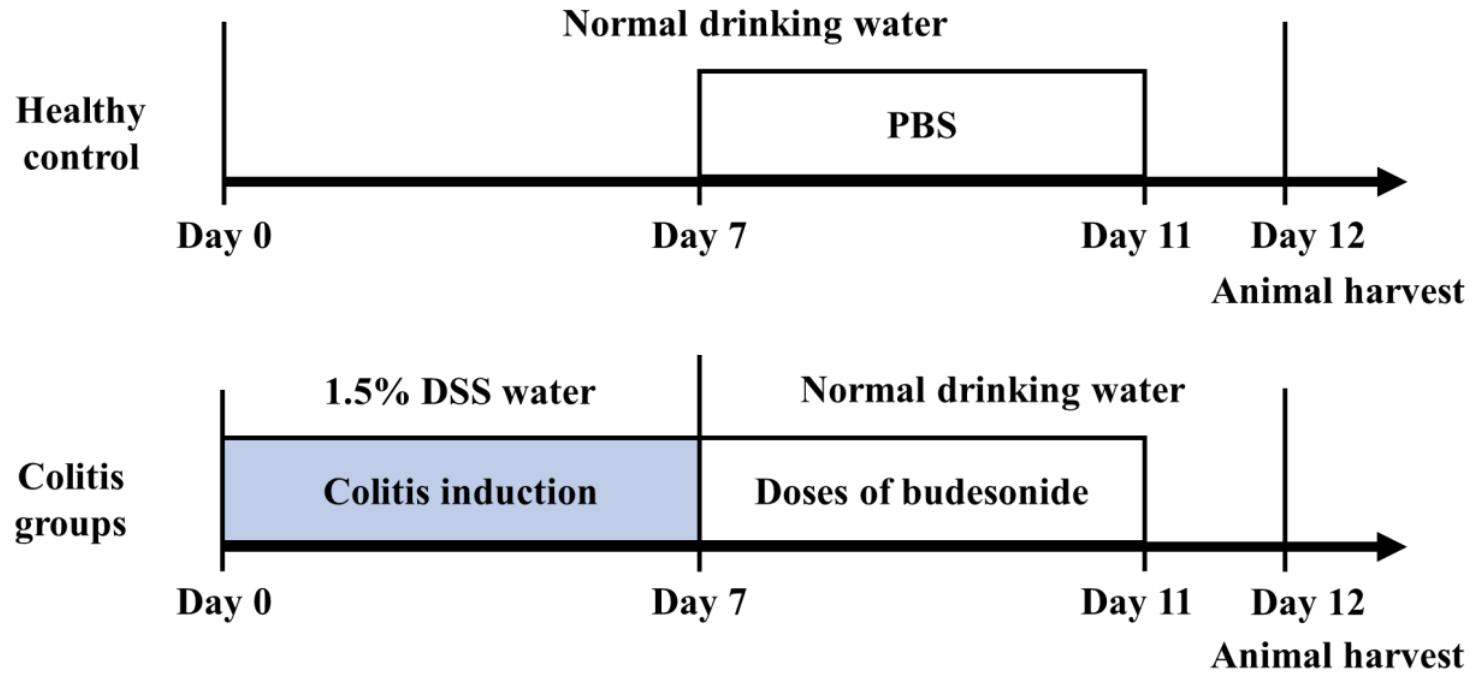


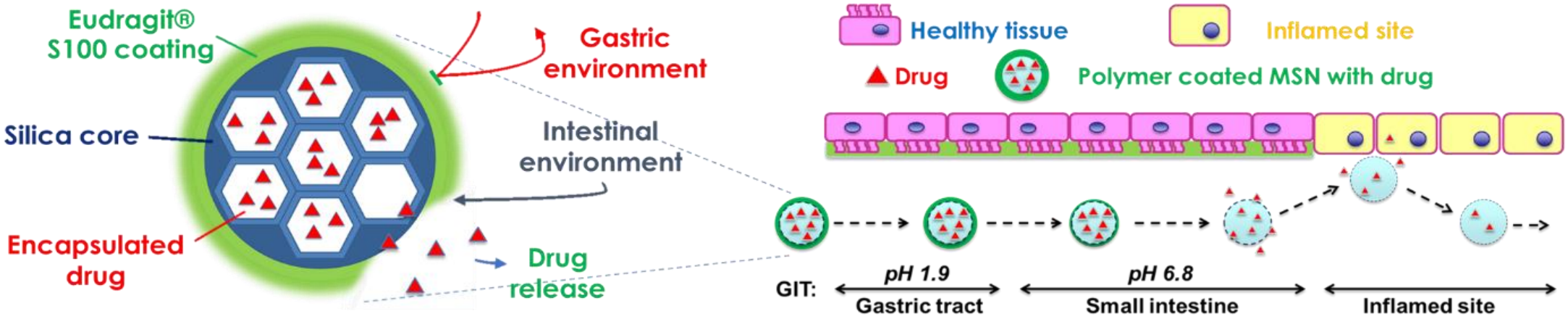


	Free drug	MSN-A-Bud	MSN-A-Bud-Eu
pH 1.9	56.25 ± 6.86%	63.57 ± 2.69%	12.08 ± 0.17%
pH 5.5	11.89 ± 2.96%	19.63 ± 1.09%	7.36 ± 0.78%
pH 7.4	5.56 ± 3.22%	2.69 ± 0.93%	65.45 ± 1.50%

(a). Cumulative release of budesonide from free budesonide, MSN-A-Bud and MSN-A-Bud-Eu in a series of pH universal buffers at 37 ºC. pH was changed at 3 h and 5 h. (b). Percentage of budesonide released in pH 1.9, 5.5 and 7.4 after 24 hours. Data represent mean ± SD. (n=3).

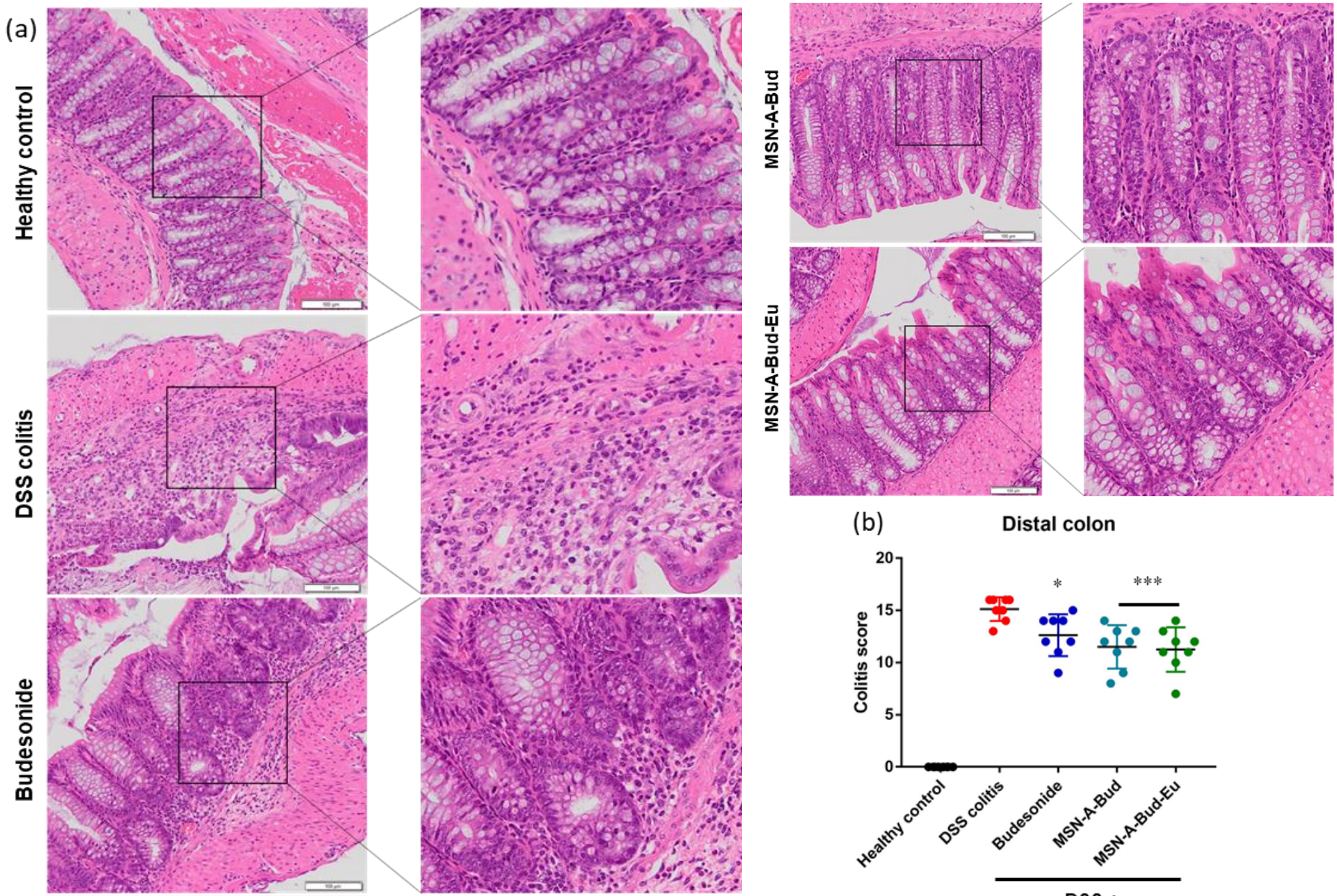
In-vivo



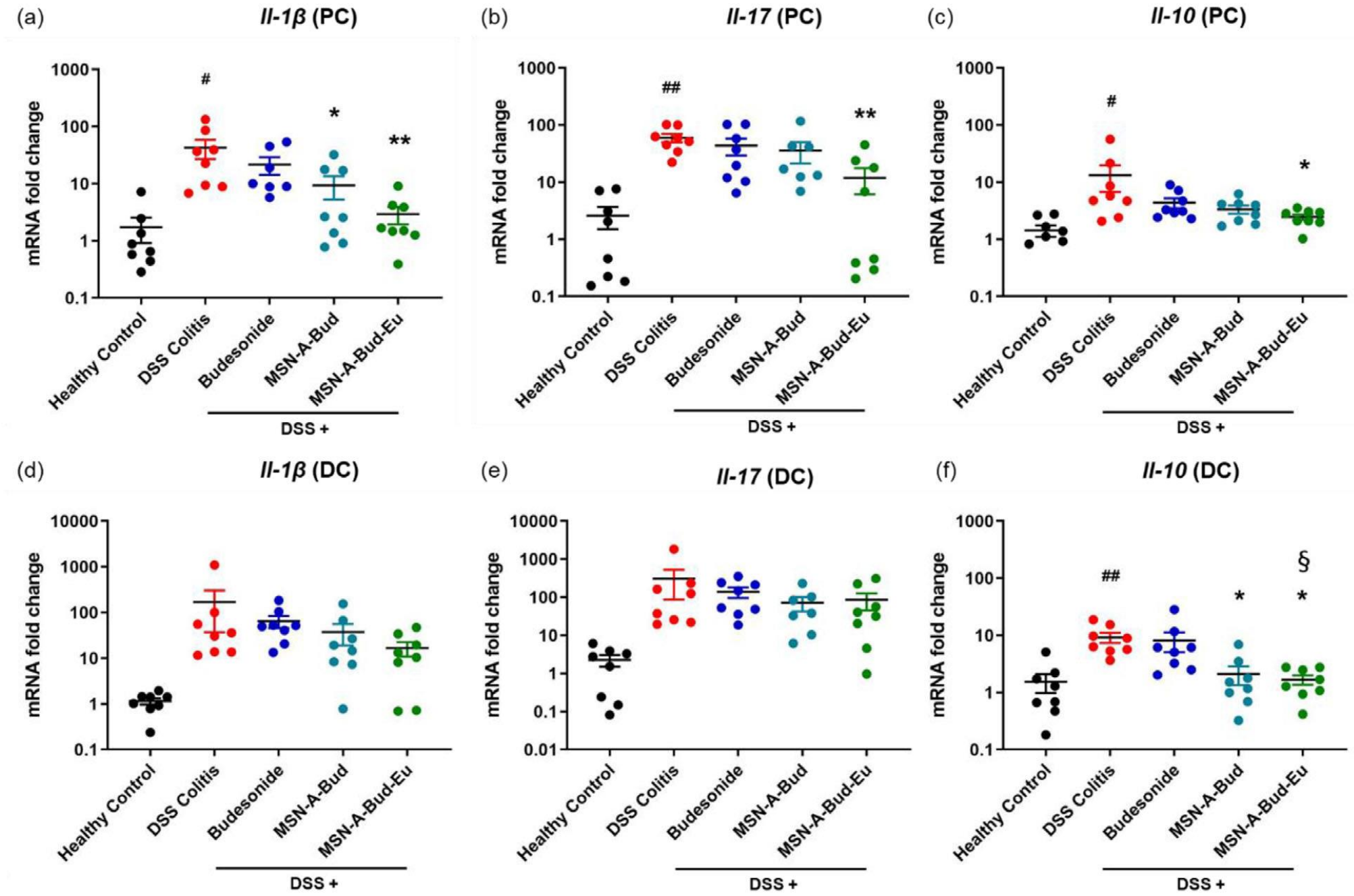


Zhi et al. Advanced Therapeutics, 2000165

Histology


(a)
Healthy control
DSS colitis
Budesonide
MSN-A-Bud
MSN-A-Bud-Eu
(b)
Distal colon
Colitis score
20
15
10
5
0
*
***
Healthy control
DSS colitis
Budesonide
MSN-A-Bud
MSN-A-Bud-Eu

qPCR


(a)
Il-1β (PC)
(b)
Il-17 (PC)
(c)
Il-10 (PC)
(d)
Il-1β (DC)
(e)
Il-17 (DC)
(f)
Il-10 (DC)
mRNA fold change
Healthy Control
DSS Colitis
Budesonide
MSN-A-Bud
MSN-A-Bud-Eu
DSS +
#
##
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§

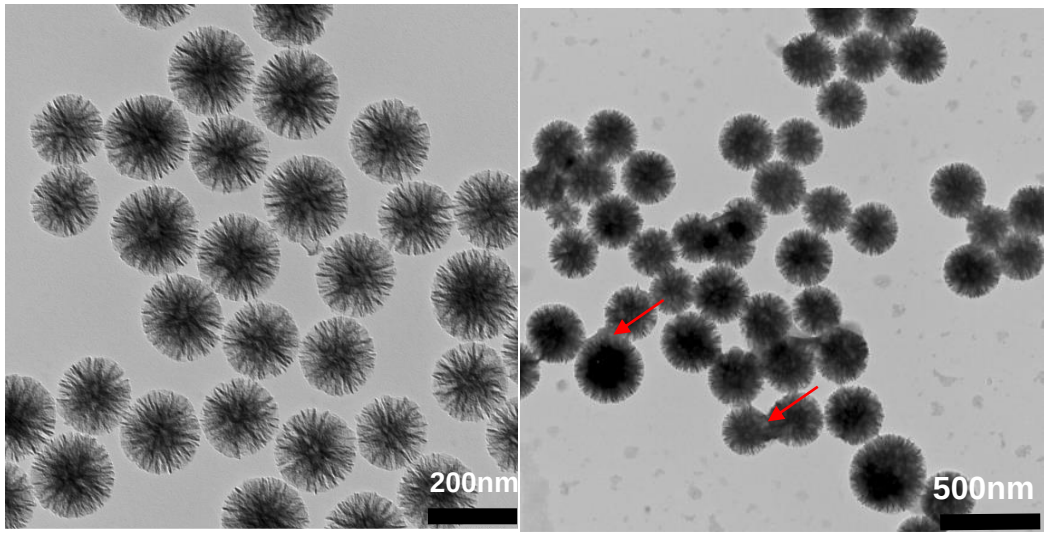
pharmaceutics

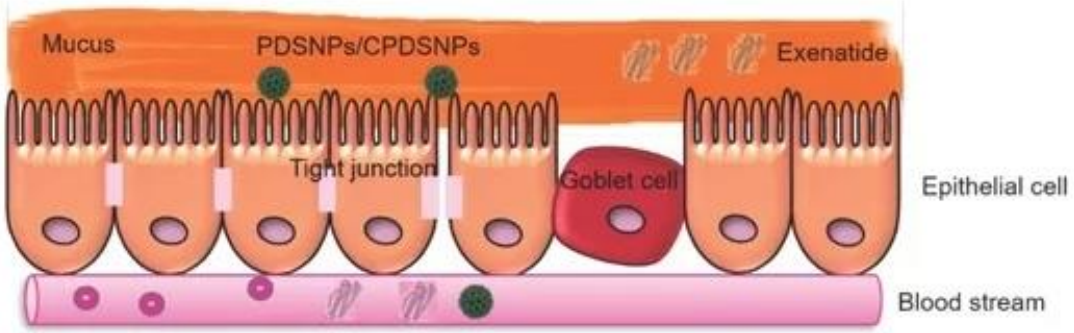
MDPI

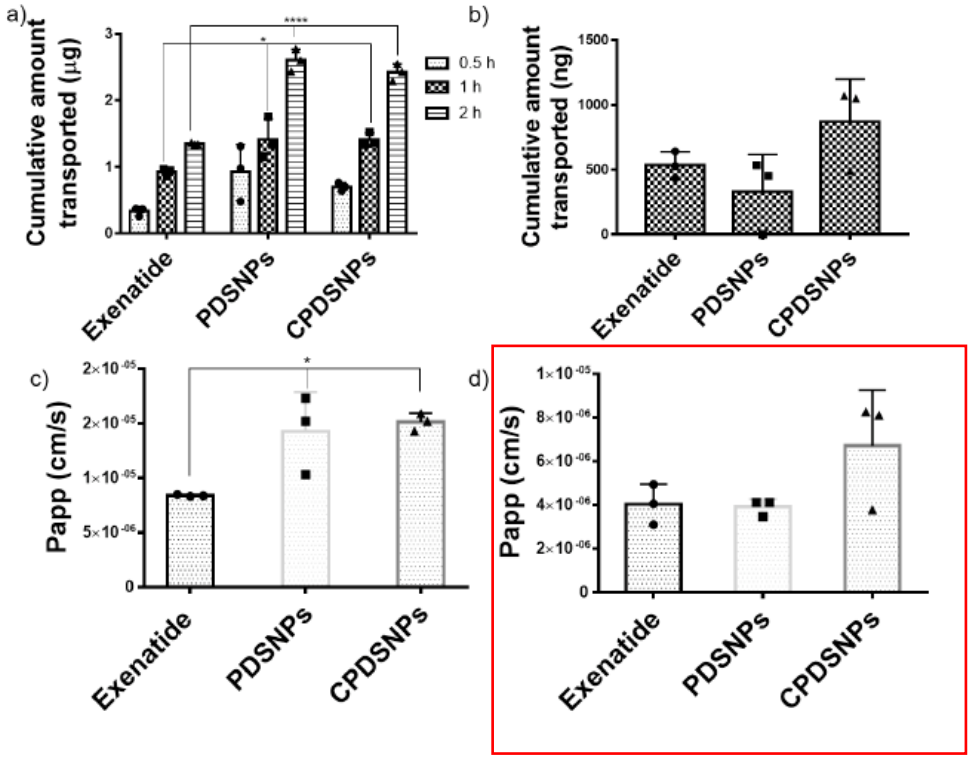
Article

Rationally Designed Dendritic Silica Nanoparticles for Oral Delivery of Exenatide

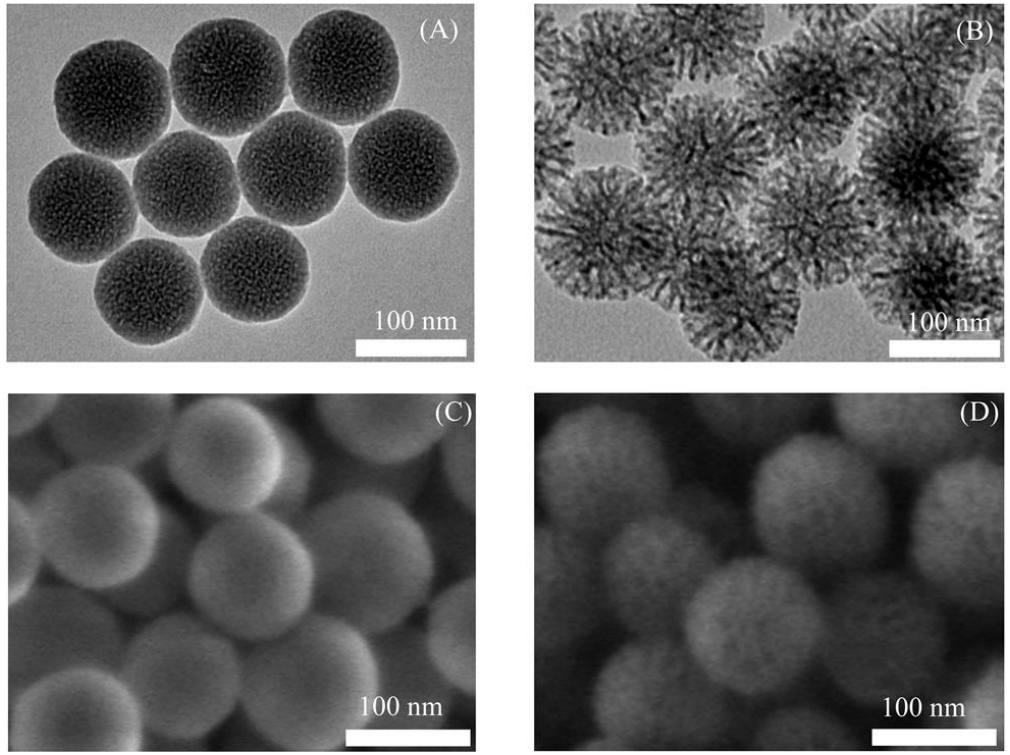
Muhammad Mustafa Abeer [1], Anand Kumar Meka [1], Naisarg Pujara [1], Tushar Kumeria [1,2], Ekaterina Strounina [3], Rute Nunes [4,5], Ana Costa [4,5], Bruno Sarmento [4,5,6], Sumaira Z. Hasnain [2,7], Benjamin P. Ross [1] and Amirali Popat [1,2,*]

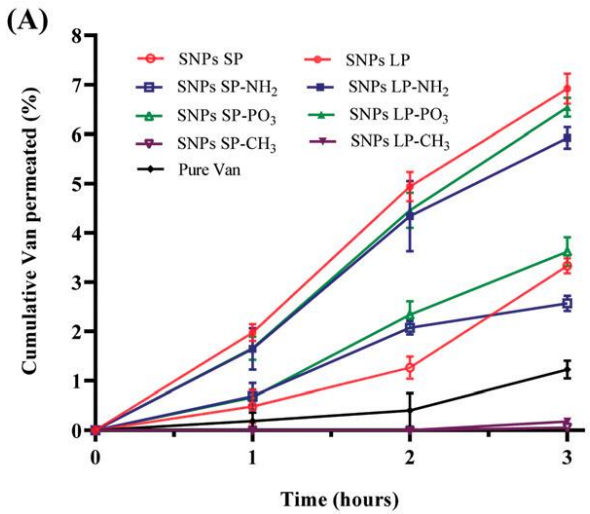


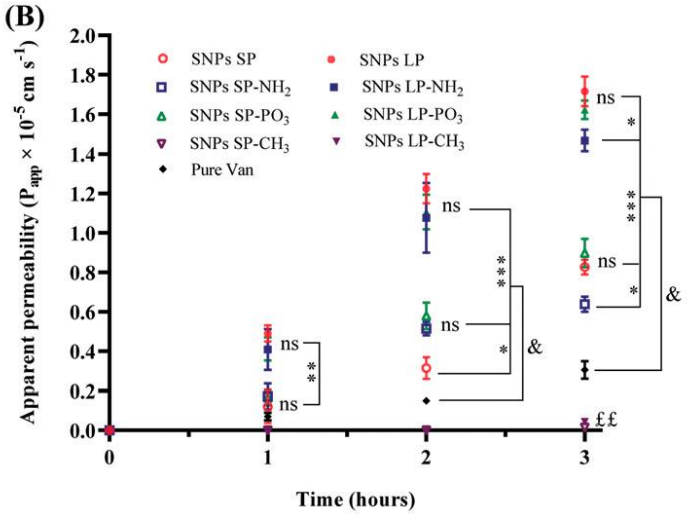


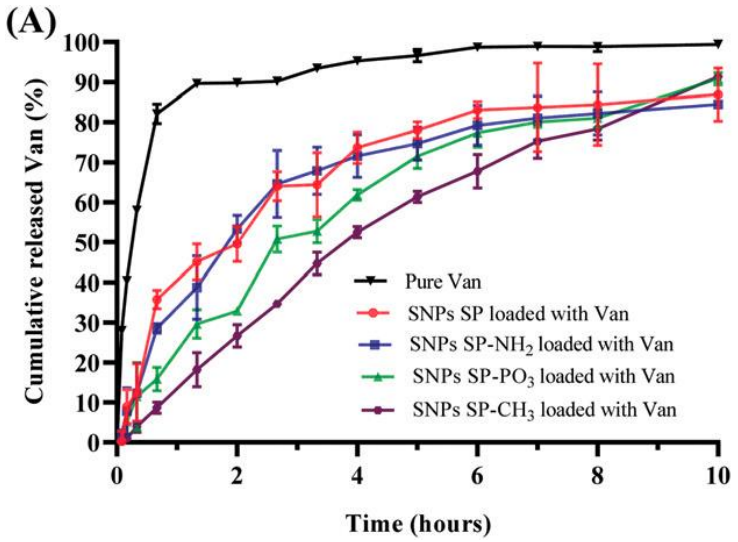


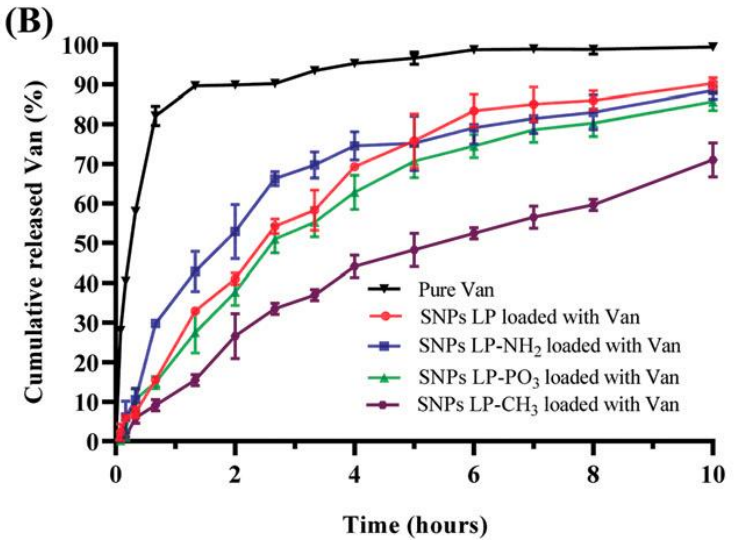
Improved permeability of Vancomycin

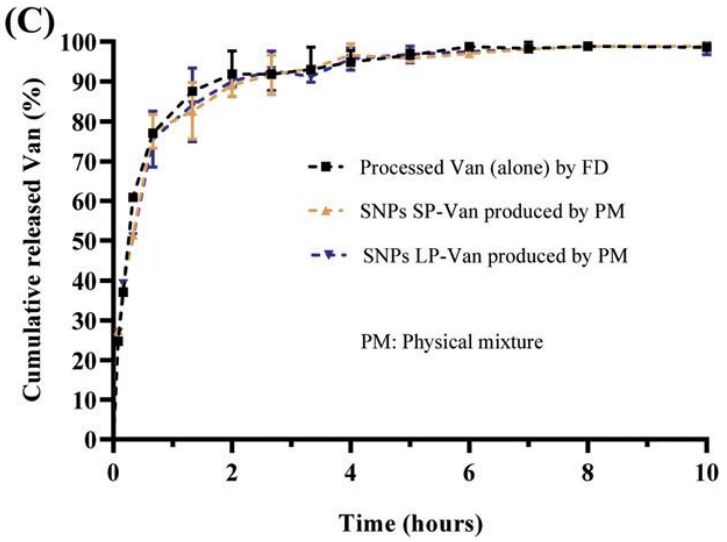




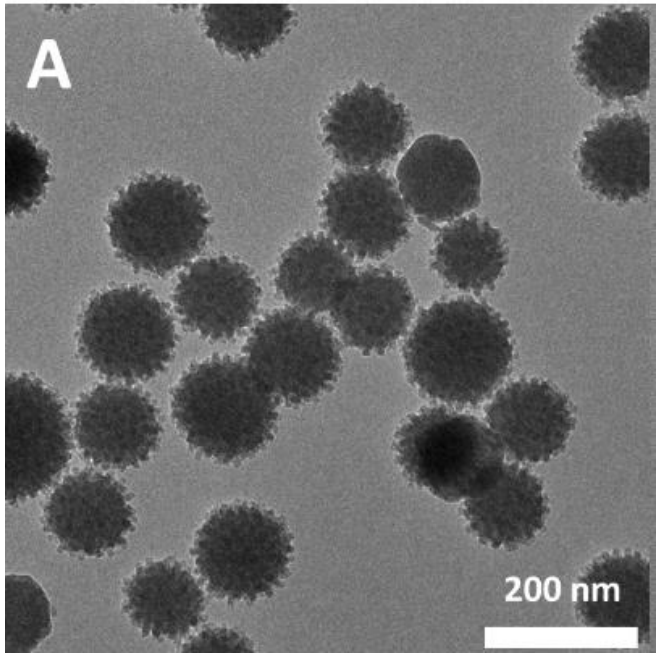


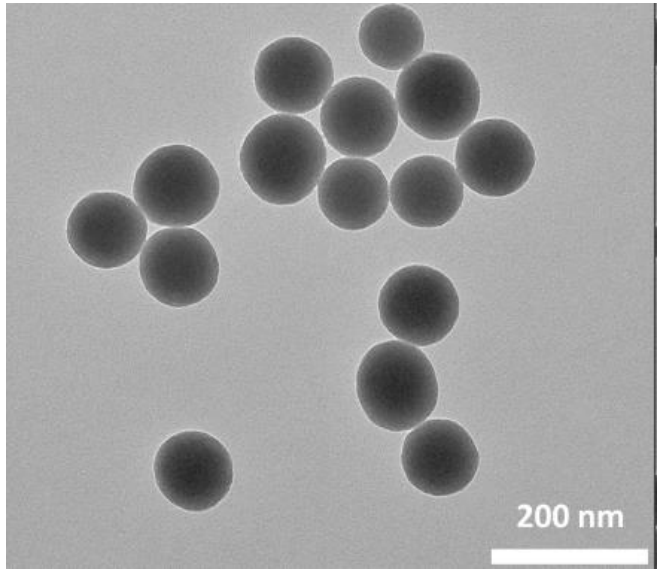


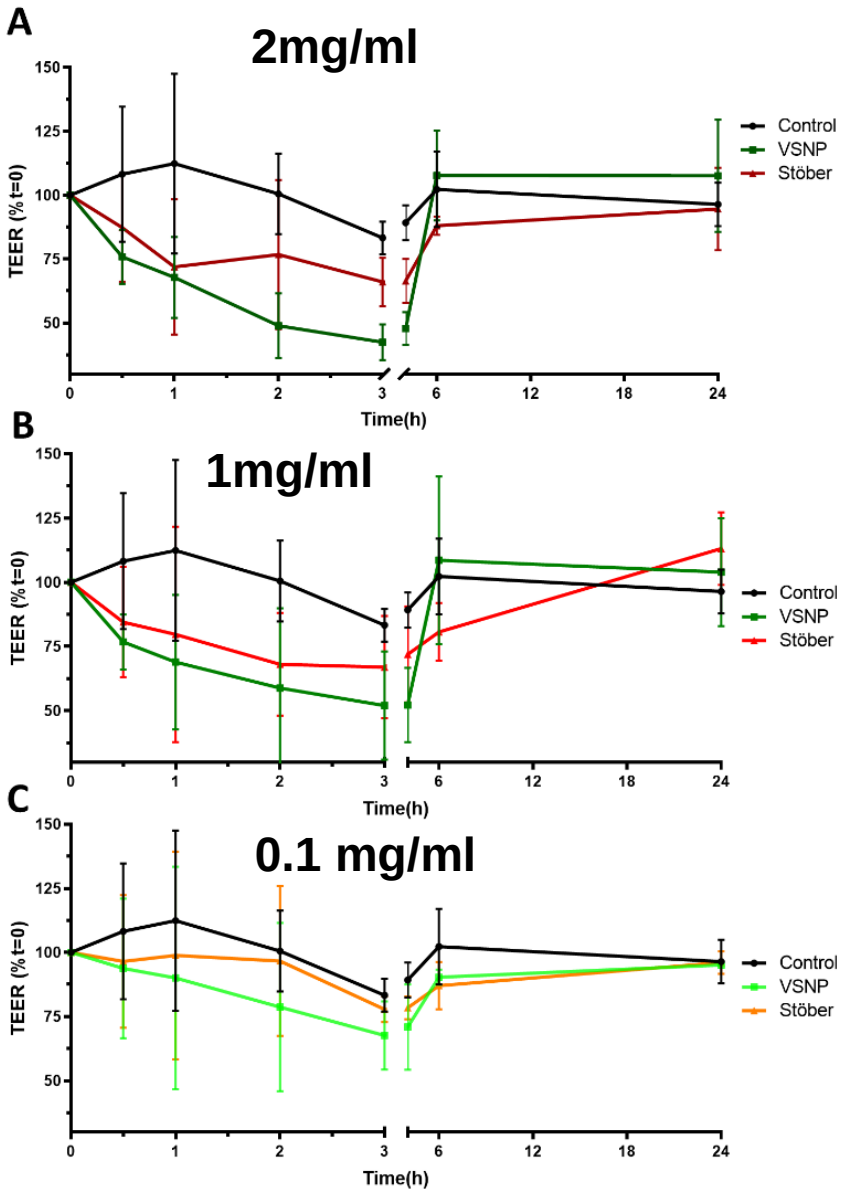


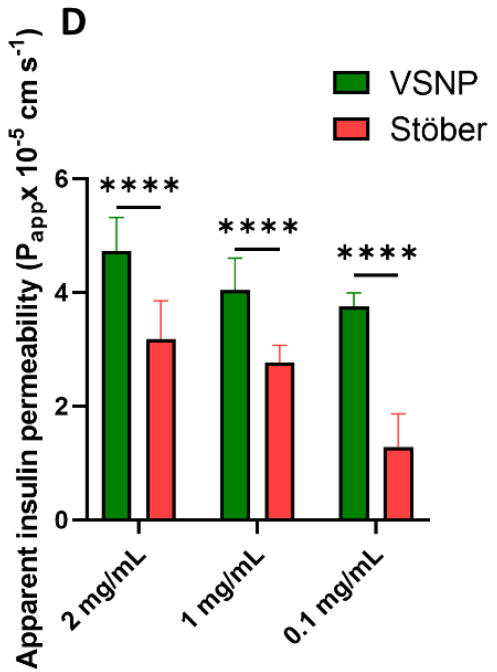


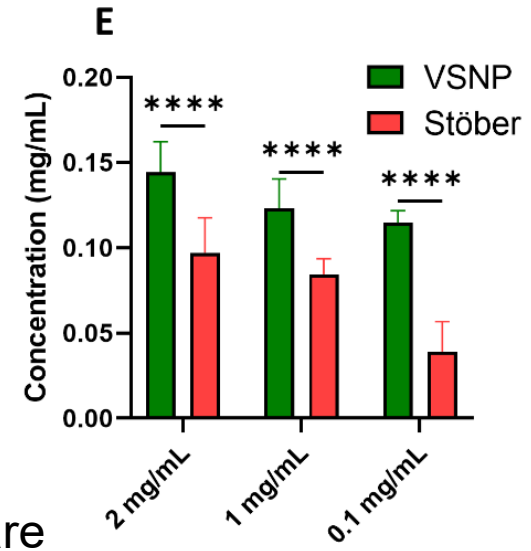
Ndayishimiye et al., J. Mater. Chem. B, 2021, 9, 7145–7166

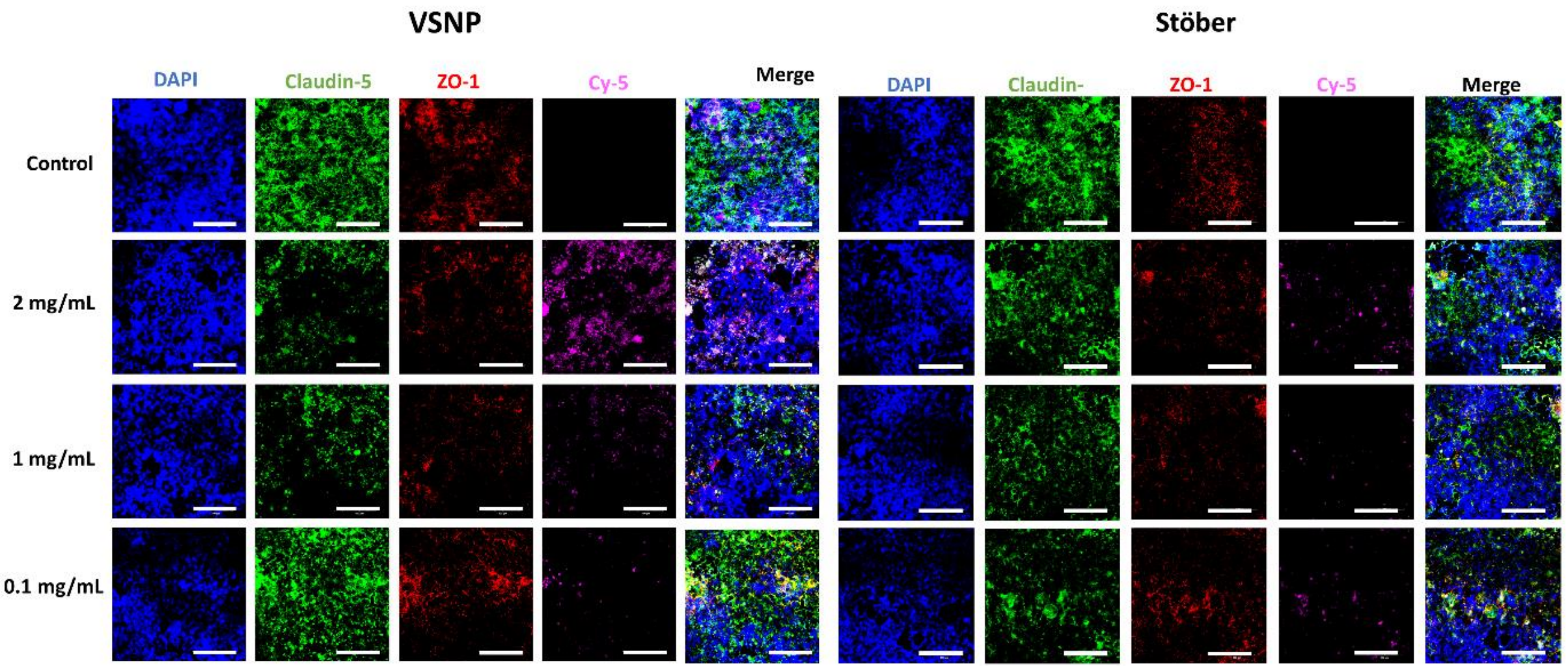






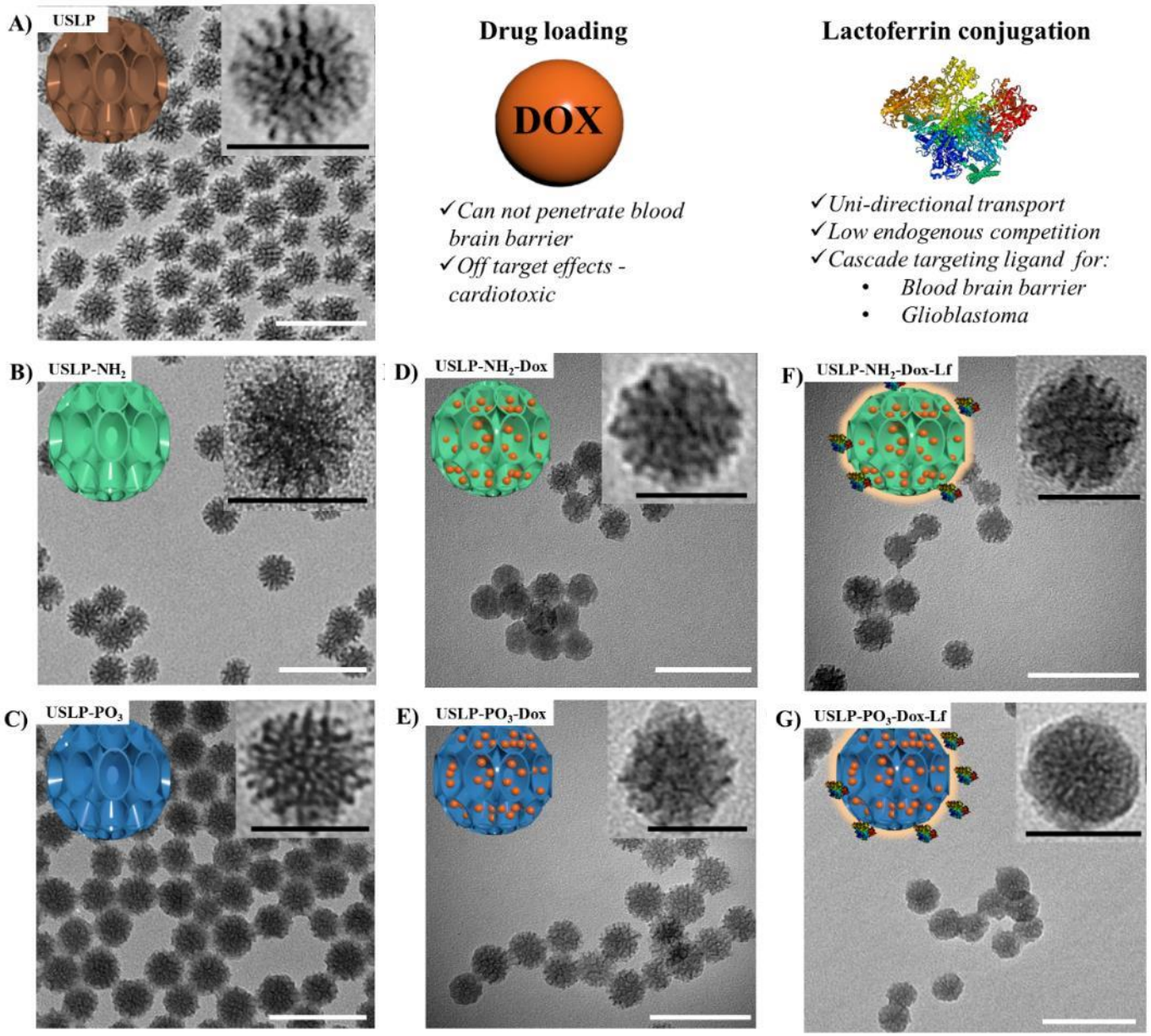


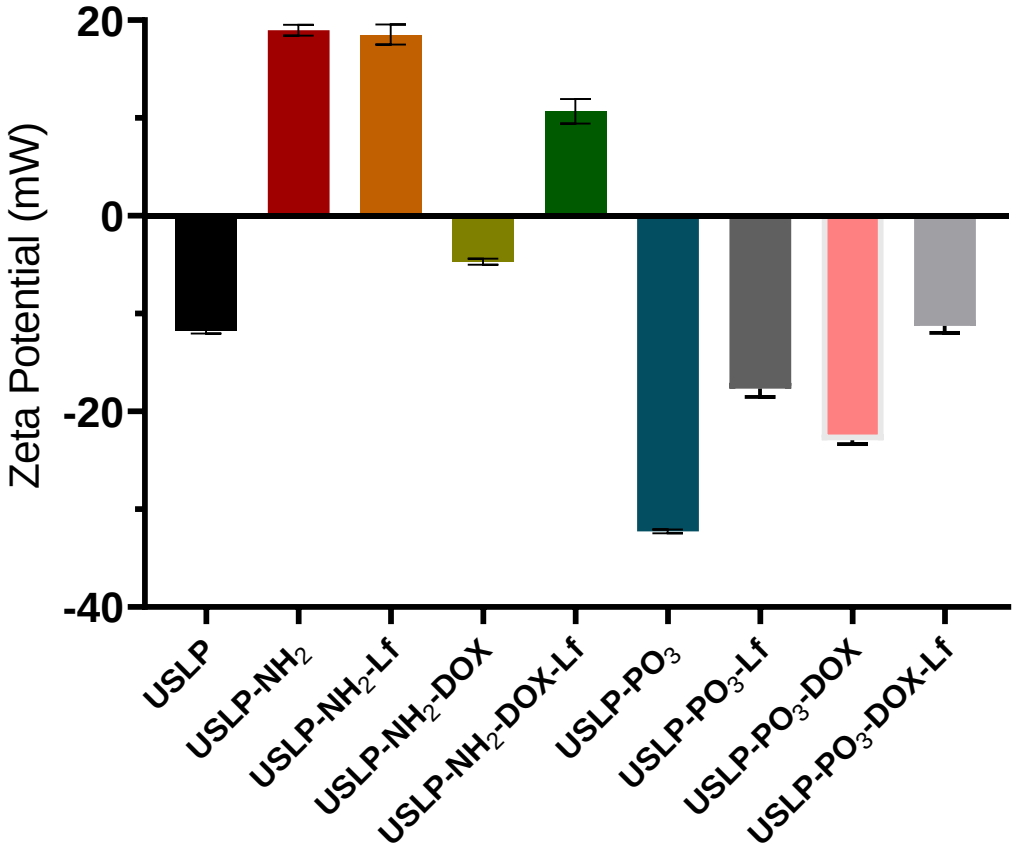




Unpublished – don't share

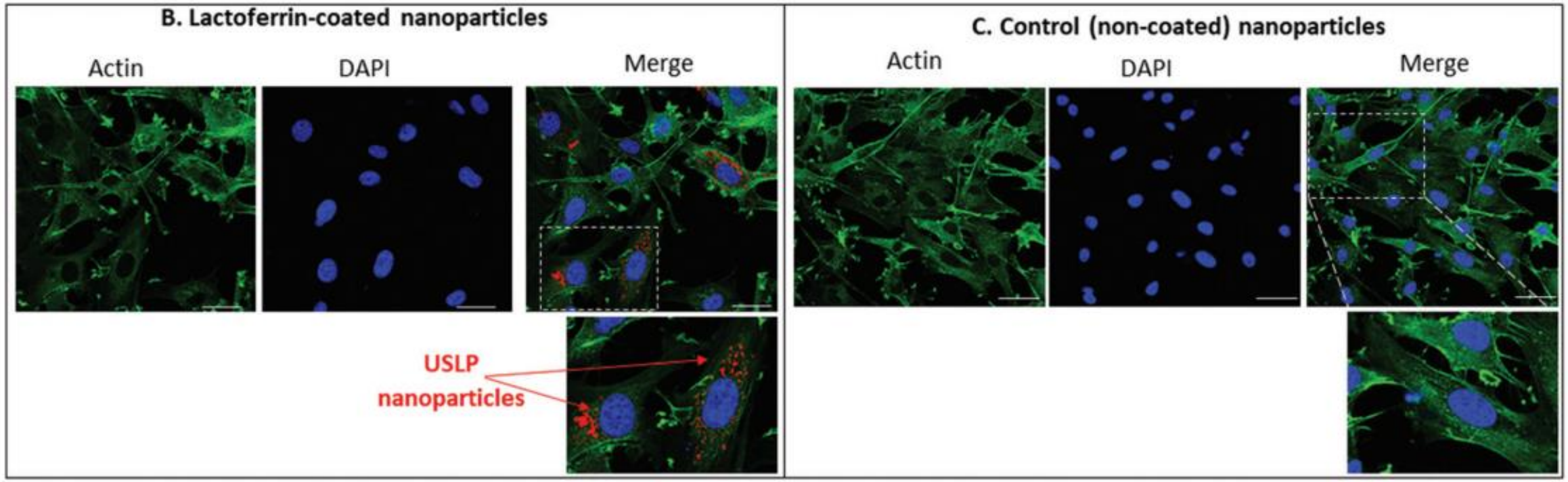
Results - Design and Synthesis of USLP delivery system





Results – USLP permeates *in vitro* blood brain barrier

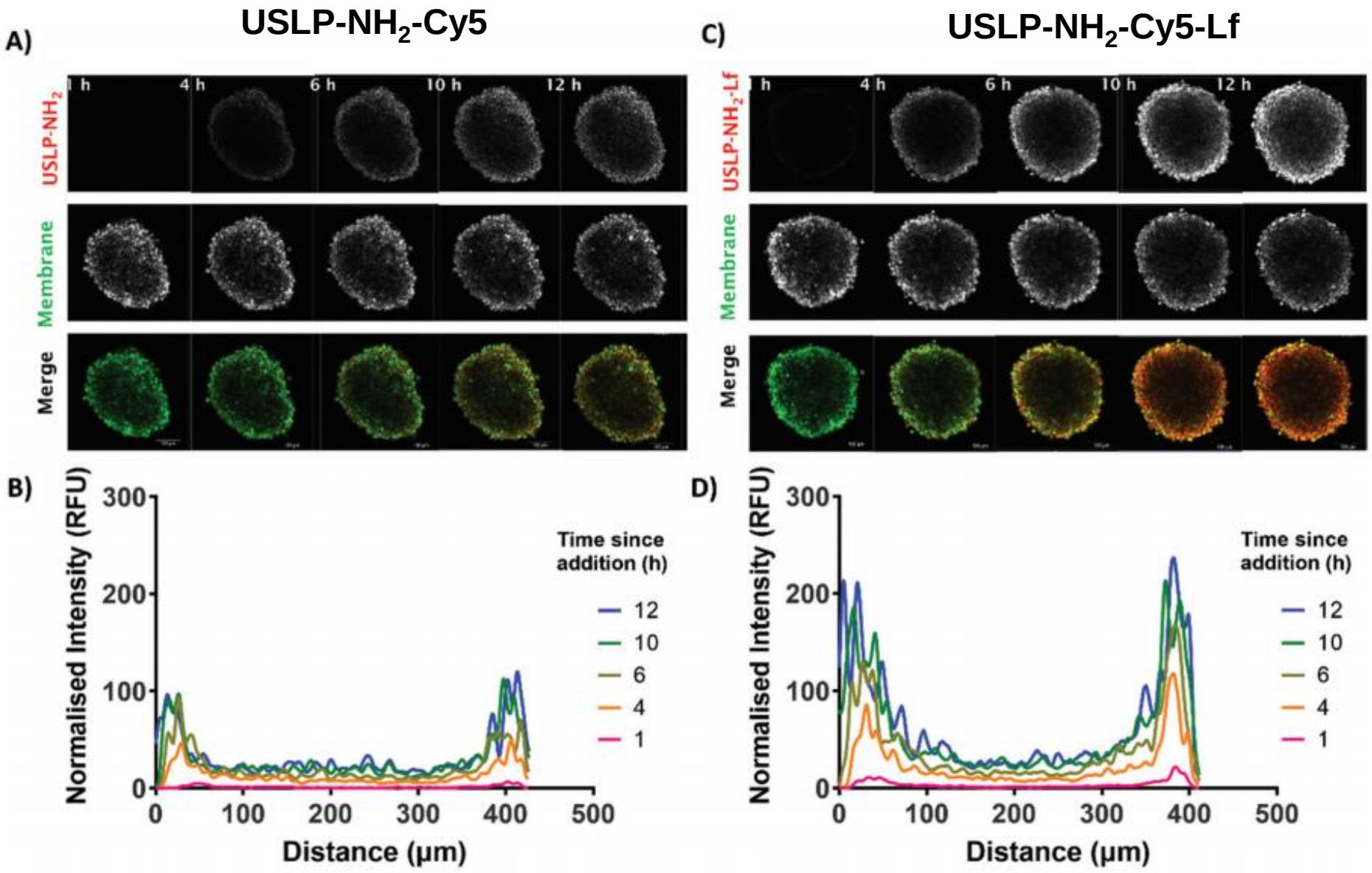
Joshua A. McCarroll



scale bars = 30 µm

Janjua TI…, Popat A.et al. Nanoscale. 2021.

Results – USLP permeates glioblastoma cell line



3D U87 tumour Spheroid – Aria

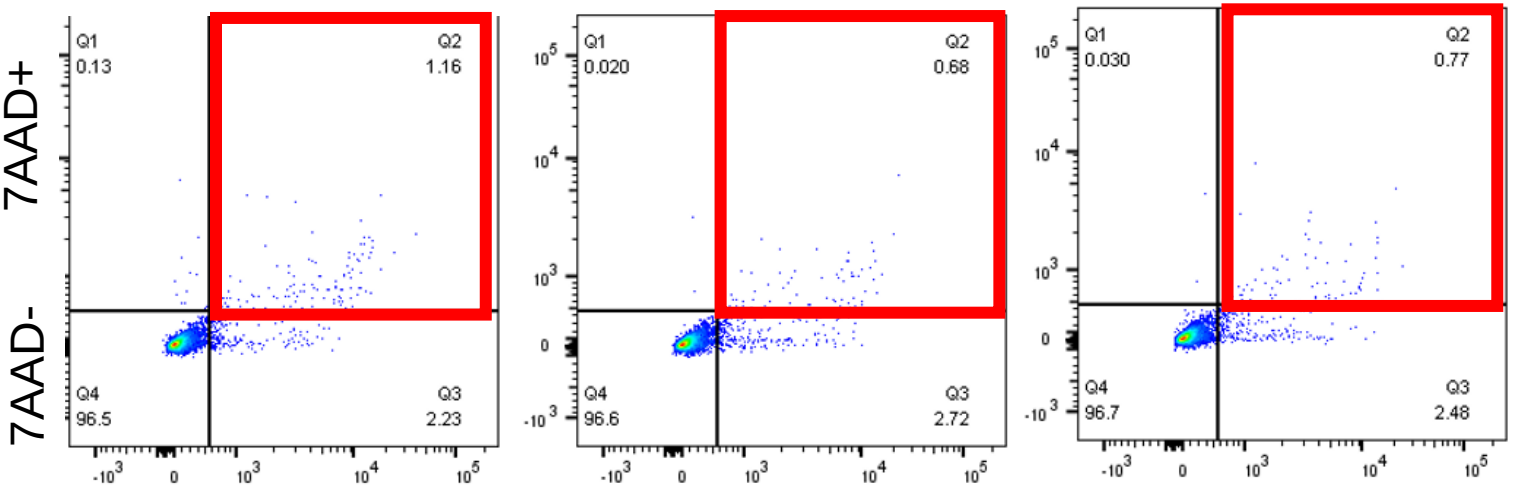
Janjua TI…, Popat A.et al. Nanoscale. 2021, 13, 16909

Cell apoptotic studies U87 GBM cells

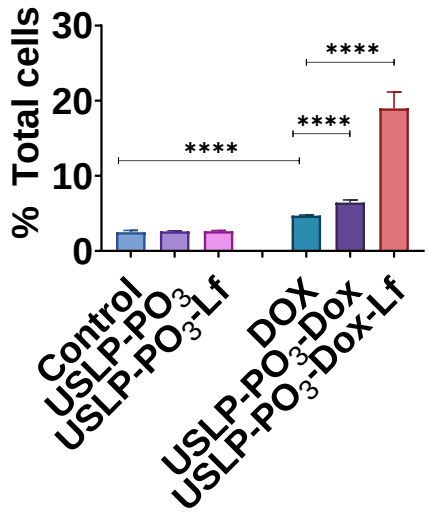
No treatment

USLP-PO_3

USLP-PO_3-Lf



B) Early apoptosis

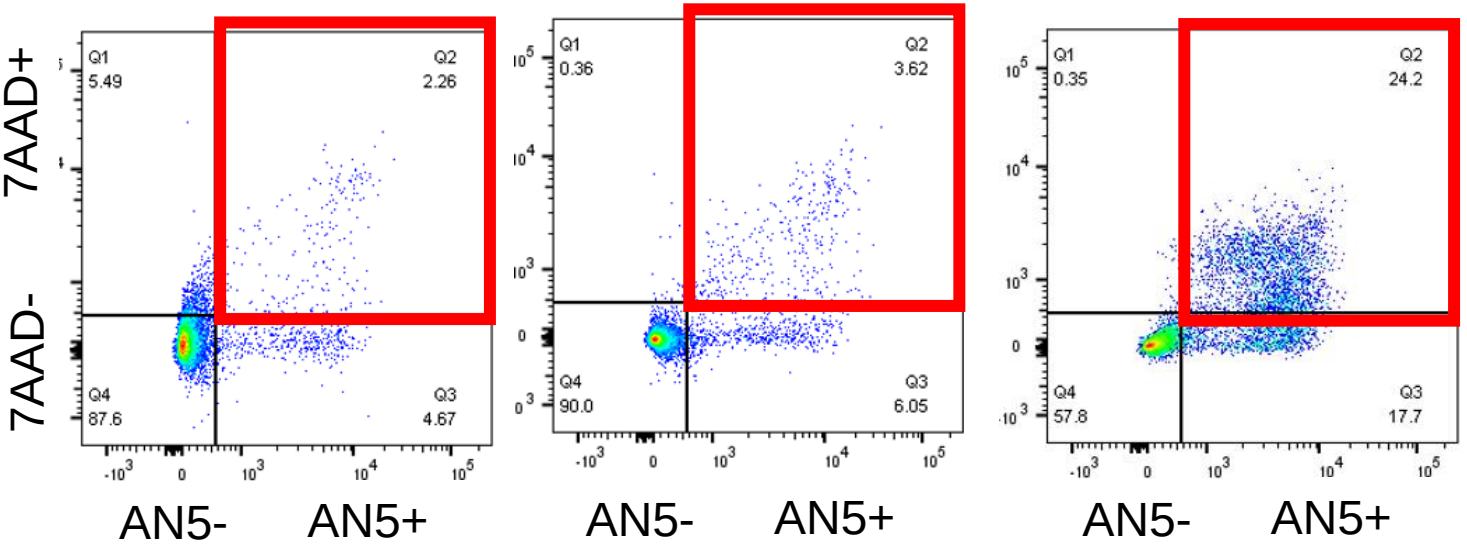


2D Cell culture

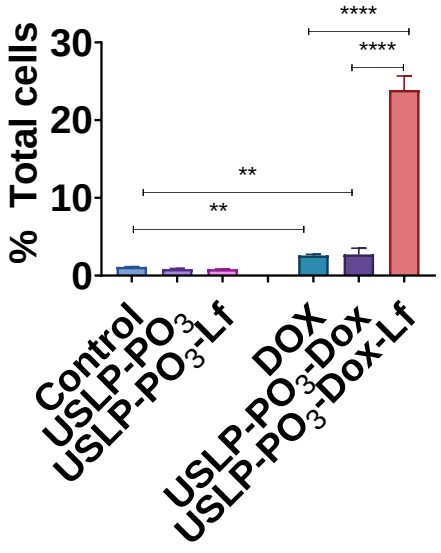
DOX

USLP-PO_3-DOX

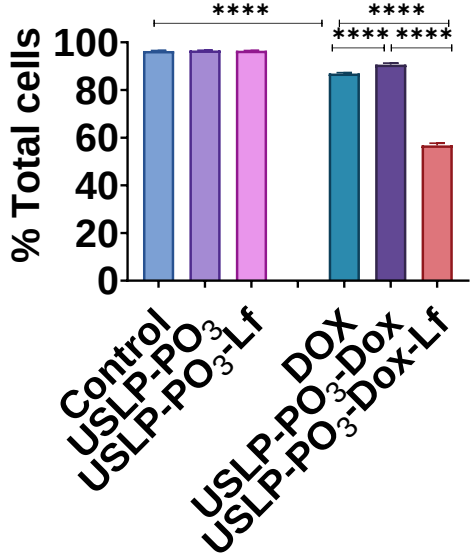
USLP-PO_3-DOX-Lf



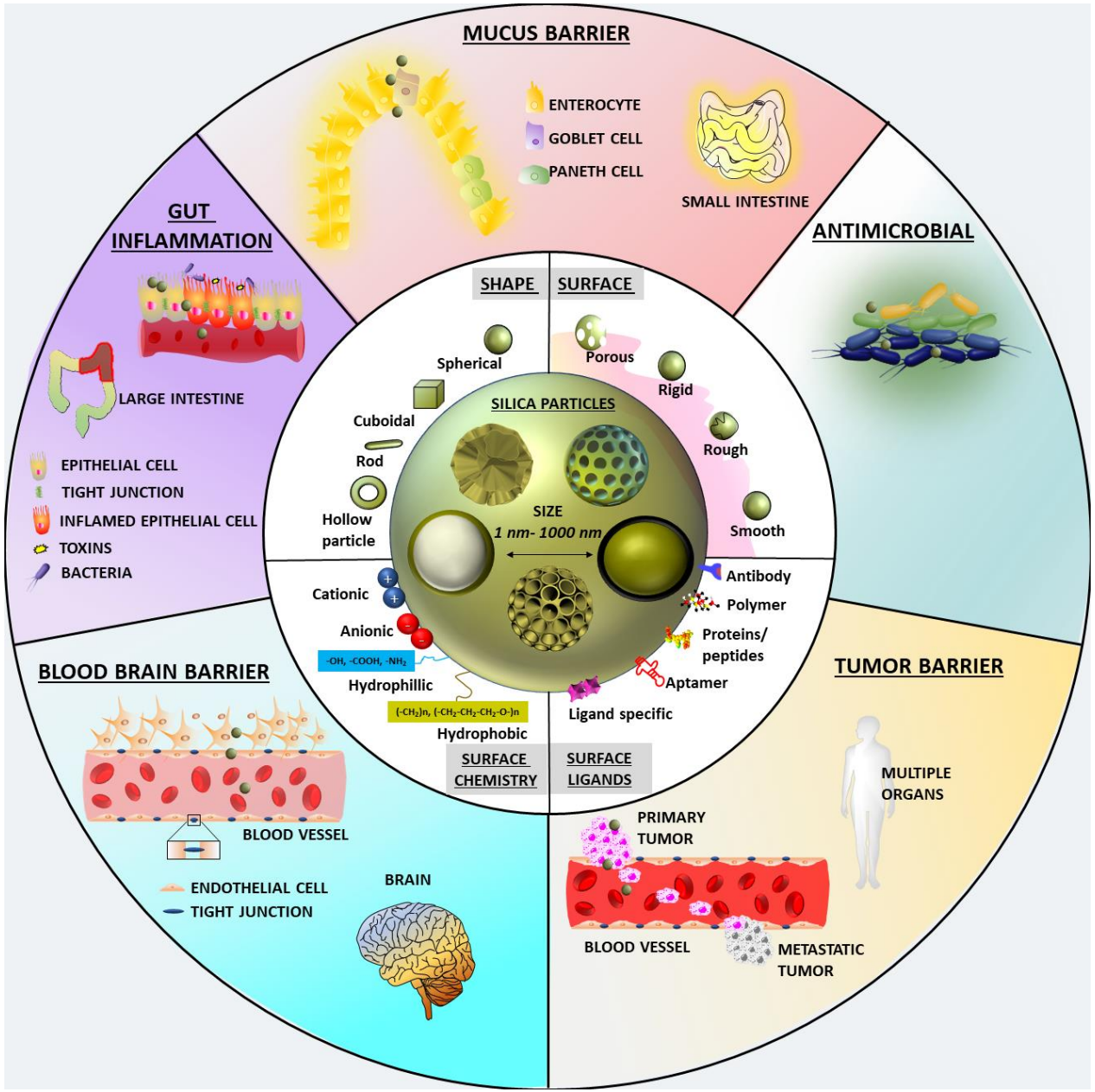
C) Late apoptosis

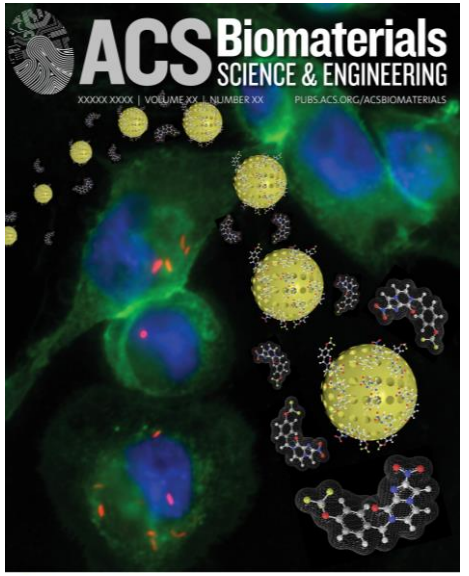


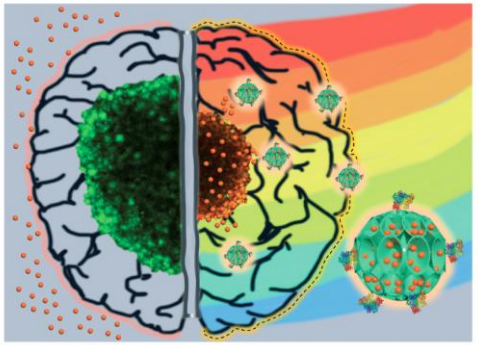
D) Alive cells



Janjua TI…, Popat A.et al. Nanoscale. 2021.



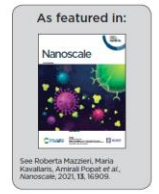




Showcasing the work of Taskeen Iqbal Janjua from A/Prof Amirali Popat's group at the School of Pharmacy, The University of Queensland, Australia in collaboration with Prof Maria Kavallaris at Children's Cancer Institute, University of New South Wales and Dr. Roberta Mazzieri, Peter MacCallum Cancer Centre, Victoria.

Facile synthesis of lactoferrin conjugated ultra small large pore silica nanoparticles for the treatment of glioblastoma

Treatment of brain cancer is challenging due to difficulty in delivering drugs across the blood brain barrier (BBB) into the tumour microenvironment. This work highlights the potential of Ultra Small Large Pore Silica (USLP) to significantly improve the utility of chemotherapeutic drugs such as doxorubicin, which cannot otherwise cross the BBB and thereby improve penetration of chemotherapy deep into the brain tumour.



See Roberta Mazzieri, Maria Kavallaris, Amirali Popat et al., Nanoscale, 2021, 13, 16909.

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