

Introduction & Objectives

Goal: Development of a local long-acting release of an Active Pharmaceutical Ingredient (API)

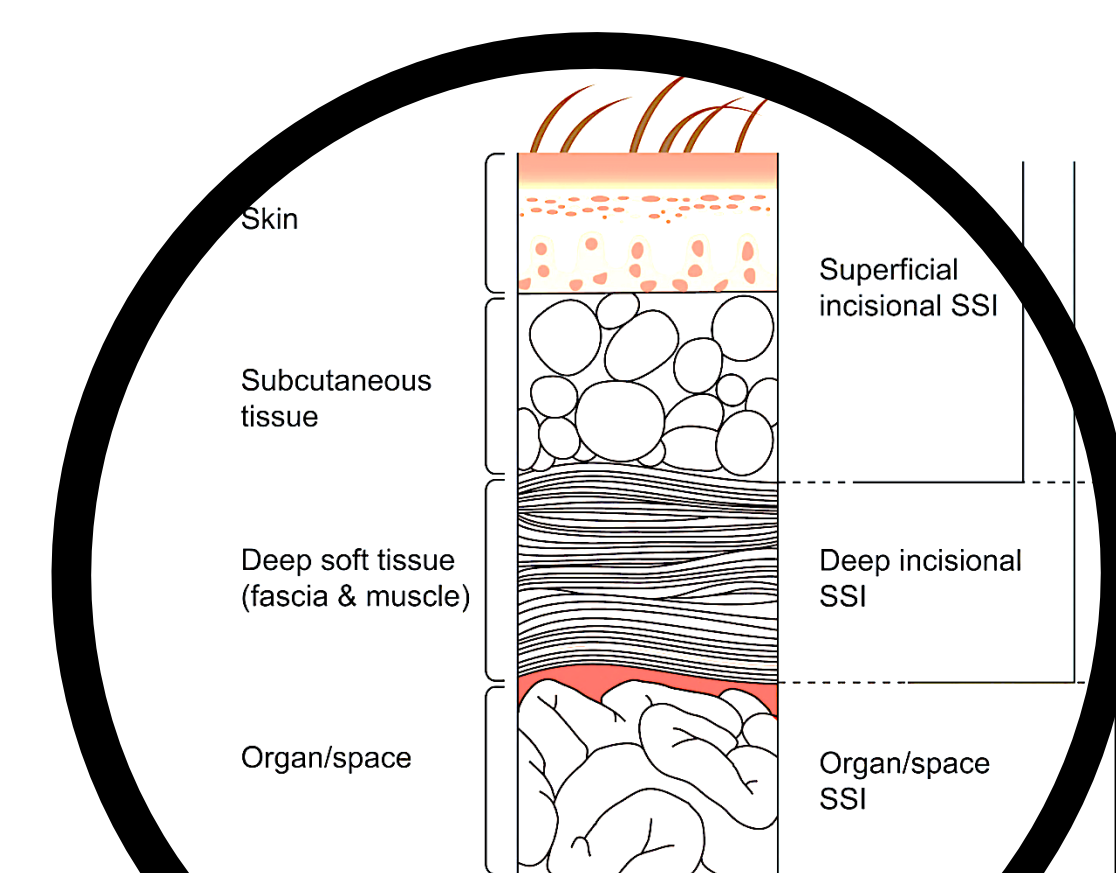
In order to:

- Use as antibiotic prophylaxis to prevent post-surgical site infections and limit the development of antibiotic resistance
- Decrease surgical site infection (SSI) (average : 3,4% in US/EU up to 12% in LMIC)
- Reduce side effects
- Sustain the release of antibiotics with an initial burst

- Avoid residual antibiotics remaining

- Biodegradation of the polymers

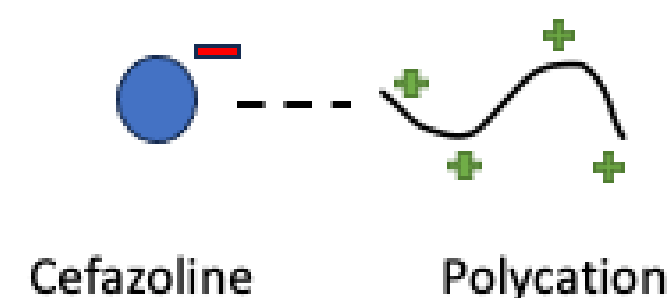
- Tissue adherence



Open wound

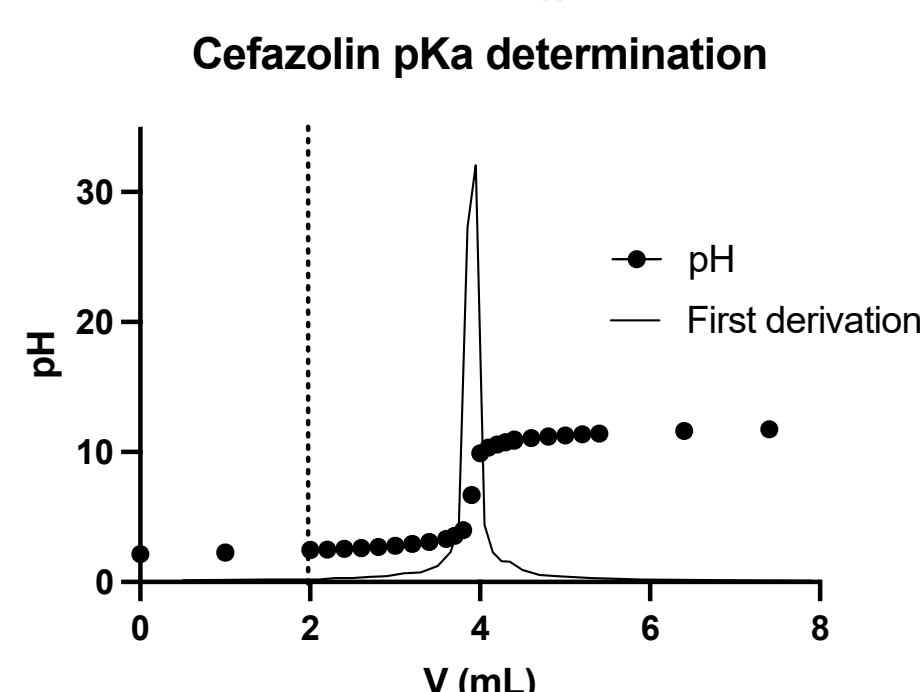
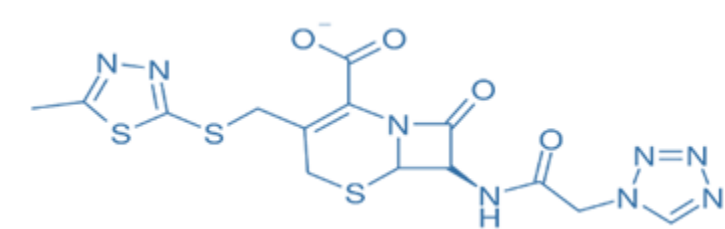
The simplest system...

A negatively charged antibiotic : Cefazoline



A Polycation: PDADMAC ((poly(diallyldimethylammonium chloride)))

- First generation cephalosporin antibiotic
- Broad spectrum
- Active on gram positive aerobic
- Used to treat many infections
- Interfering with the bacteria's cell wall
- **High water solubility**

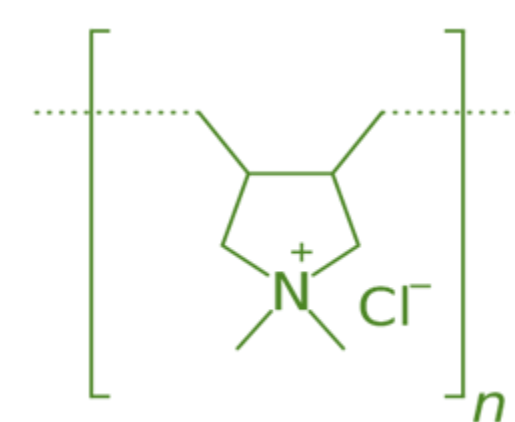


- Water soluble cationic polymer
- pH- independent charge density (strong PE)
- High molecular weight and charge density
- Utilized for wastewater purification

- Toxic at high concentration (inflammation and tissue damage)

- Immunogenicity

- **Not Biodegradable**



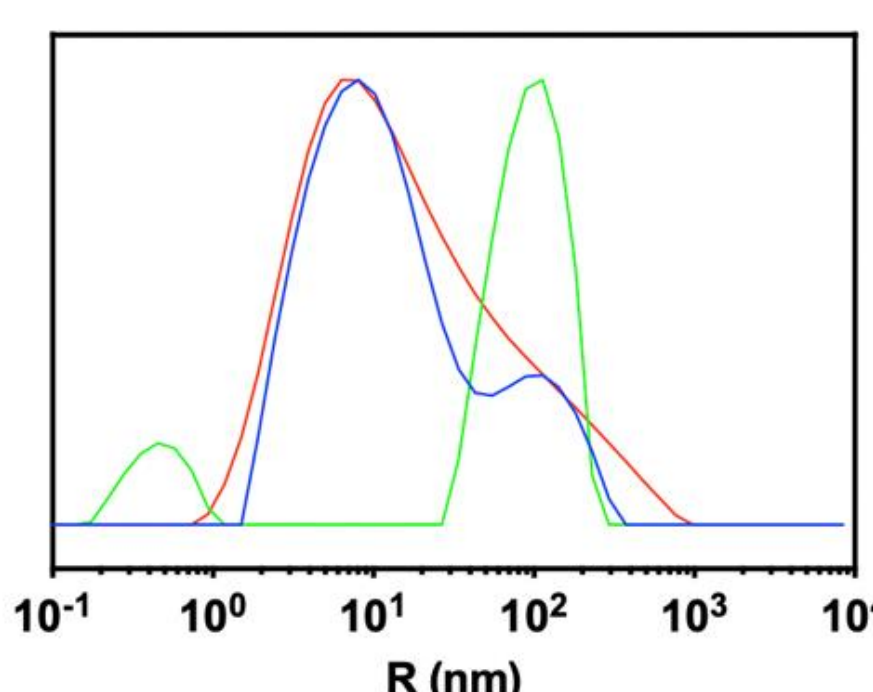
Widely known and cost-effective synthetic PE used as a roof of concept (POC)

Complex formulation

- Solution of PDADMAC and Cefazolin at pH= 10 and at 20 mM (in molar charge)
- Addition of Cefazolin solution at different Z

$$\text{Molar charge ratio : } Z = \frac{[-]}{[+]}$$

Polyelectrolyte relaxation (DLS)



Salt-free polyelectrolytes have two modes of relaxation:

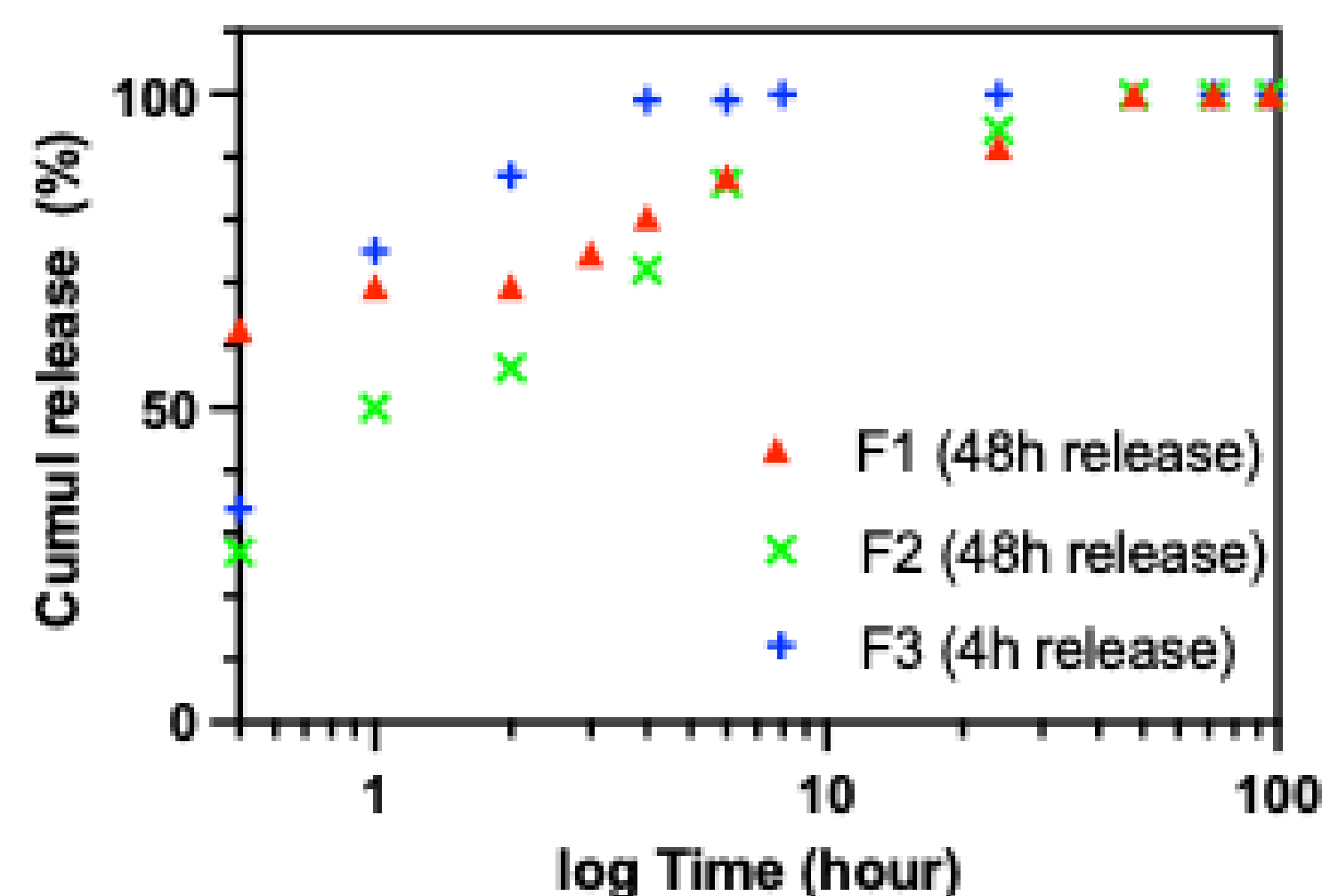
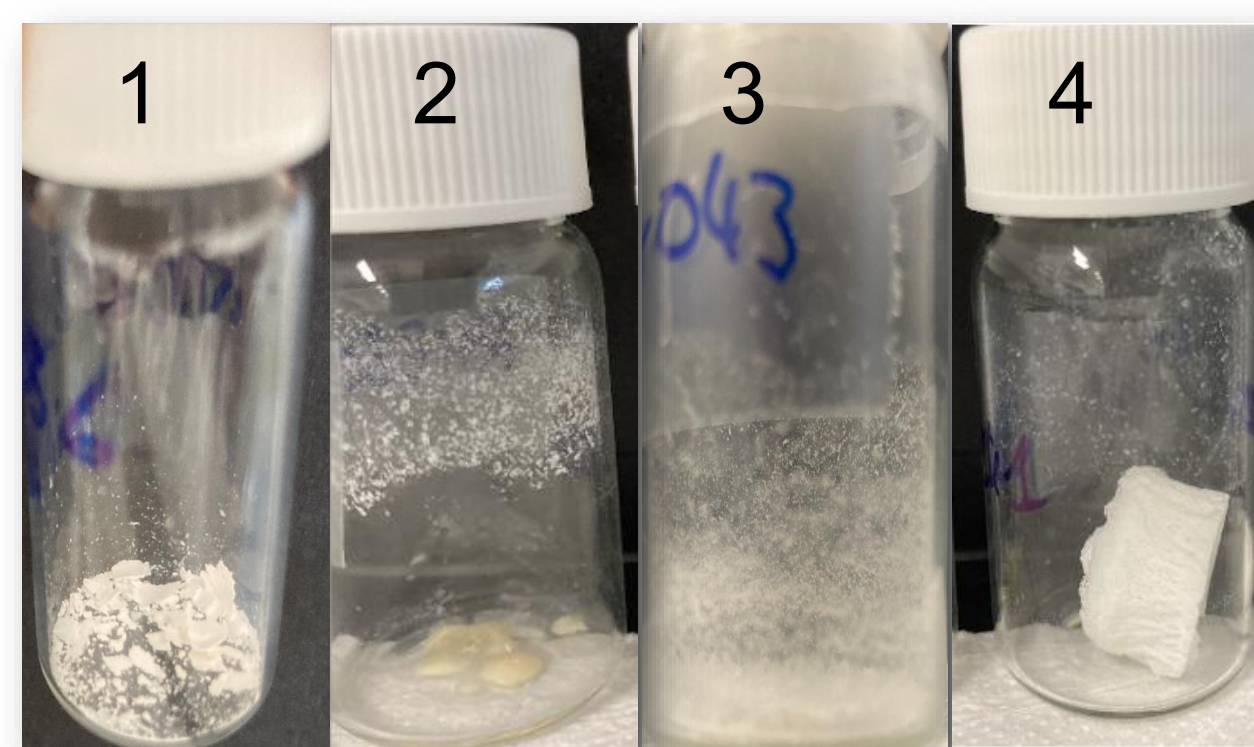
- Fast – chain / counter-ion coupling
- Slow - transient aggregates/dipole-dipole interactions

As the ionic strength increases, the two modes merge - neutral PE dimension

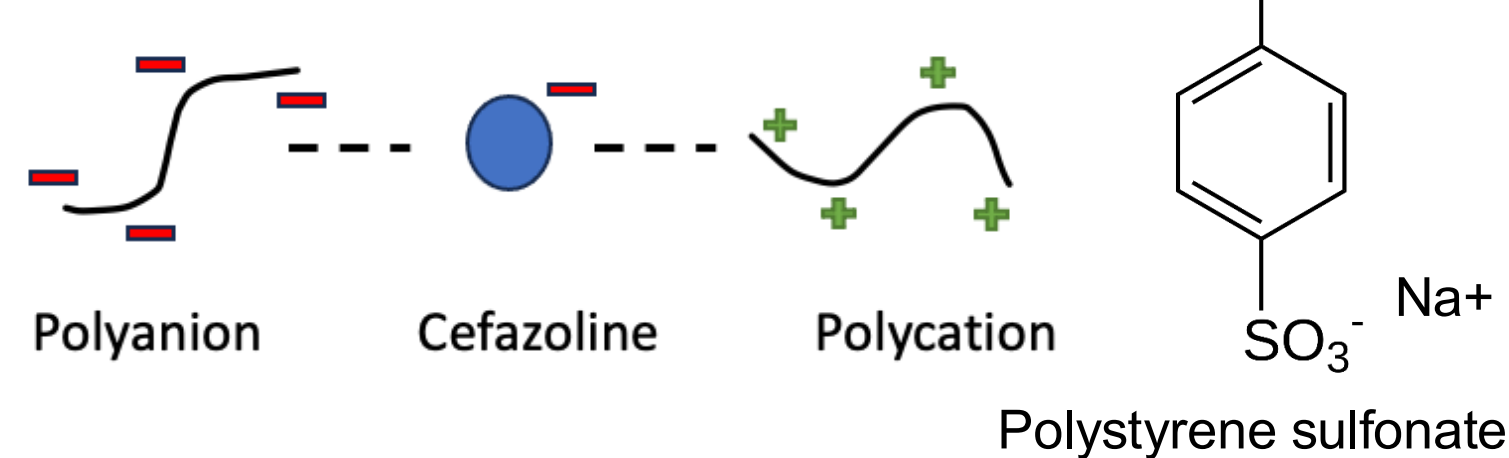
Stronger PDADMAC/Cfz+PSS complexes

Tuning the out-of-equilibrium formulation pathways

- 1) PDAD + PSS + CFZ centrifuged + precipitate freeze dried (FD)
- 2) CFZ/PDADMAC Z=0.2 FD + PSS Z=1 FD
- 3) PSS/PDADMAC Z=0.8 FD + CFZ Z=1 FD
- 4) PSS/PDADMAC Z=1 FD



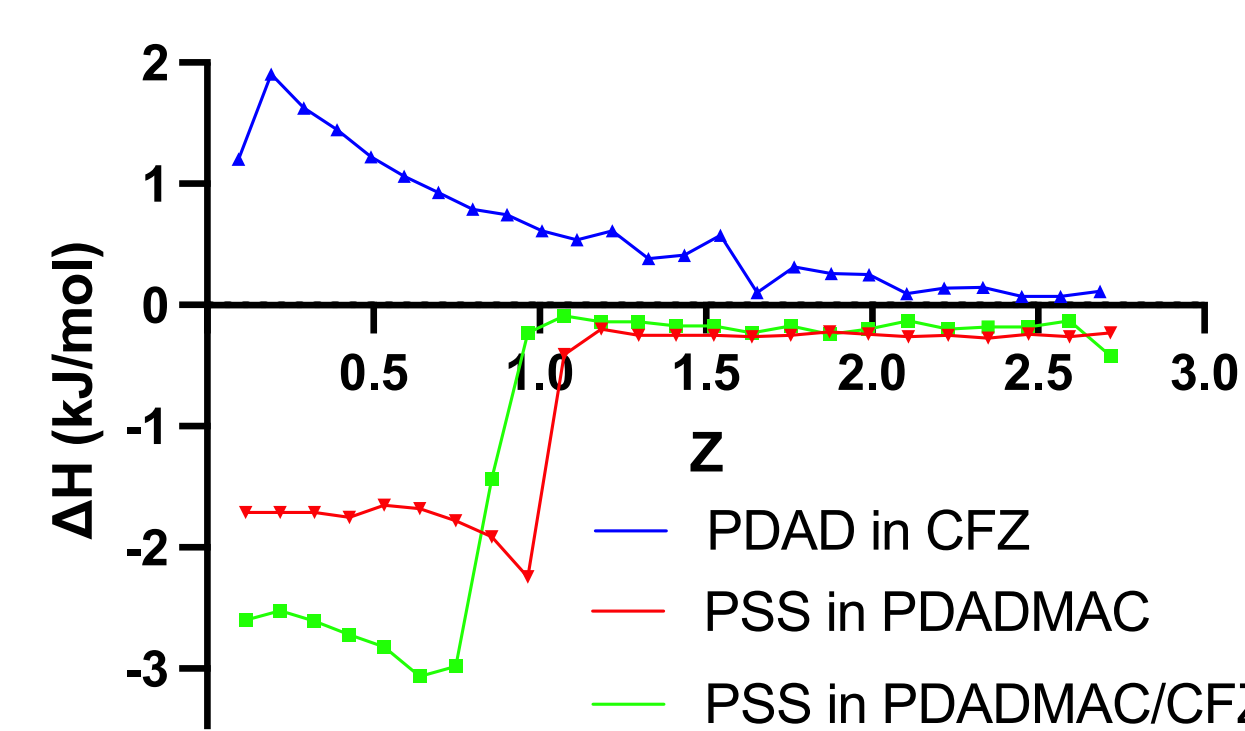
Strengthen the complexation:



DSC

Batch	Dissolution in KBr (2M) (min)	Tg (°C)
1	ND	ND
2	15	64
3	0	95
4	0	95
4+cfz	0	97

ITC



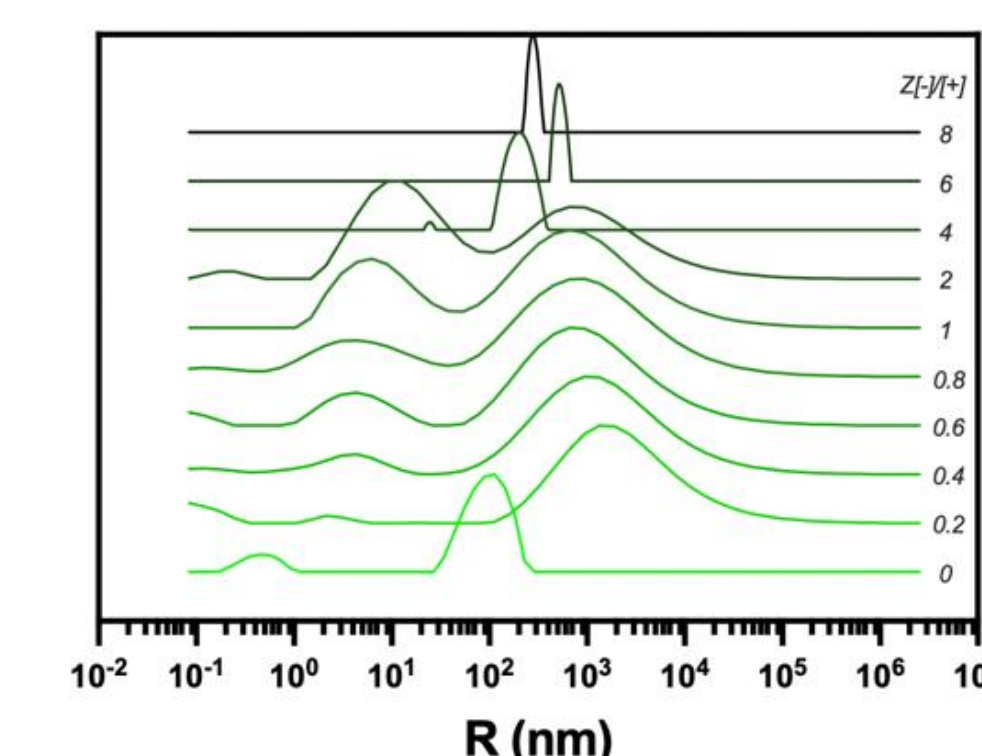
- PSS helps to strengthen complexes
- Increase duration release and burst reduction

Conclusions

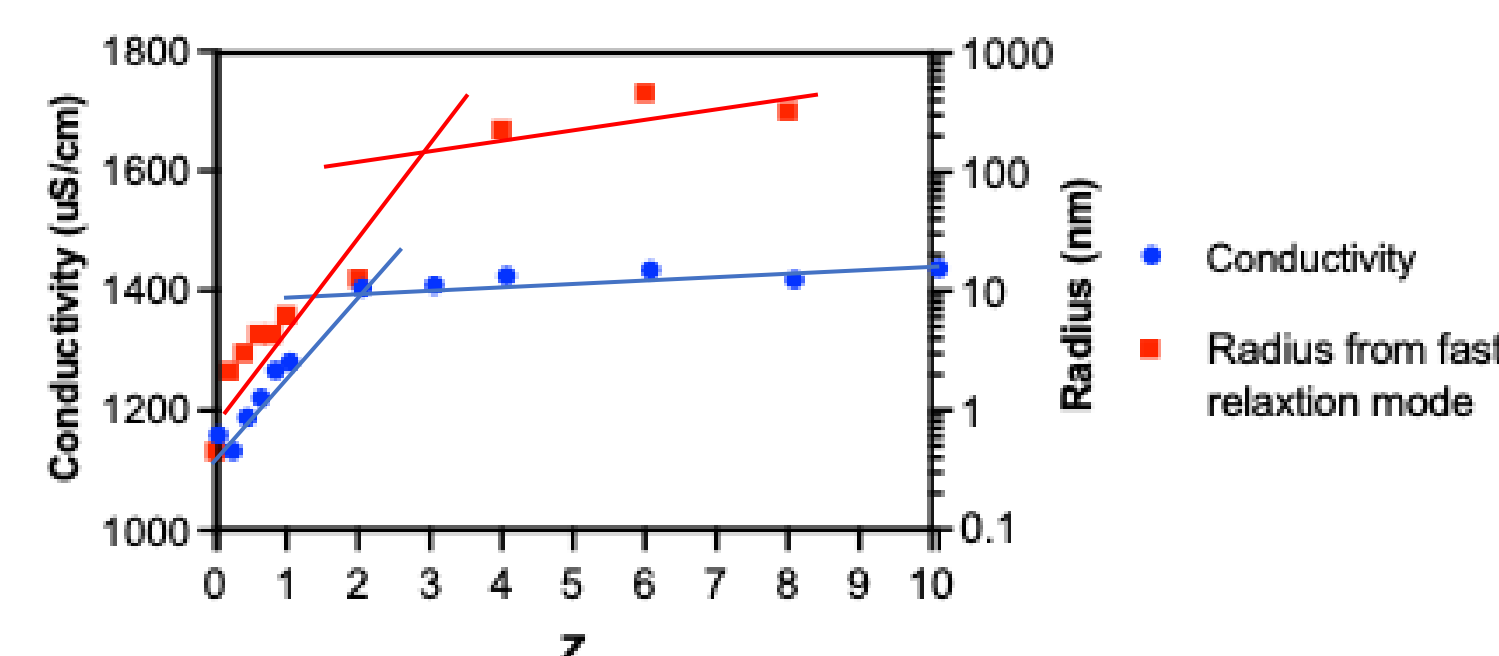
- ❑ Complexation can be strengthened by introducing an oppositely charged PE
- ❑ Formulation pathway influences the final complex structure, properties & release kinetics
- ❑ Ongoing work focuses on biodegradable & biocompatible PEs via careful optimization of the complexation pathway.

PDADMAC-Cfz complexes

DLS



Conductivity

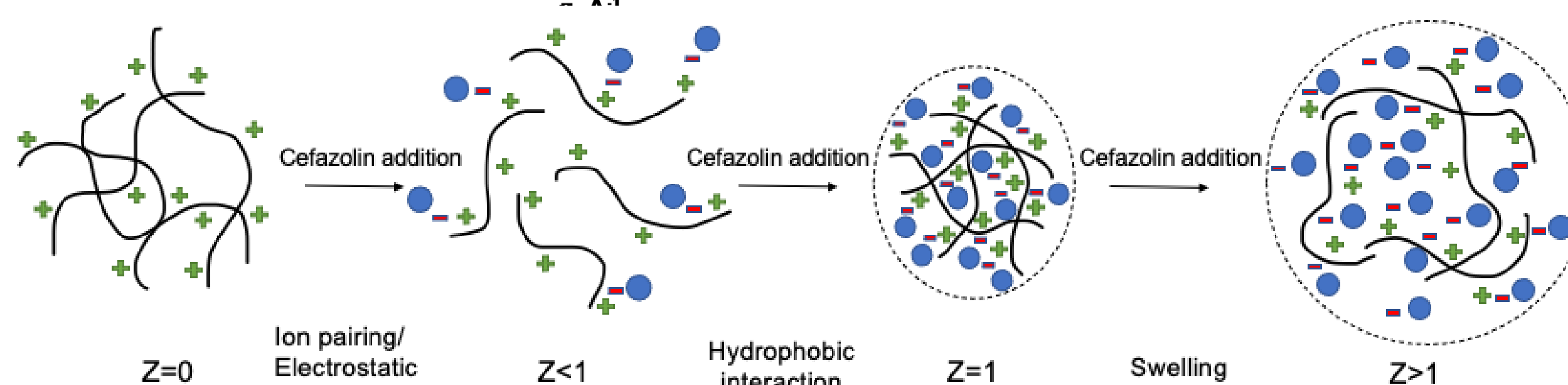
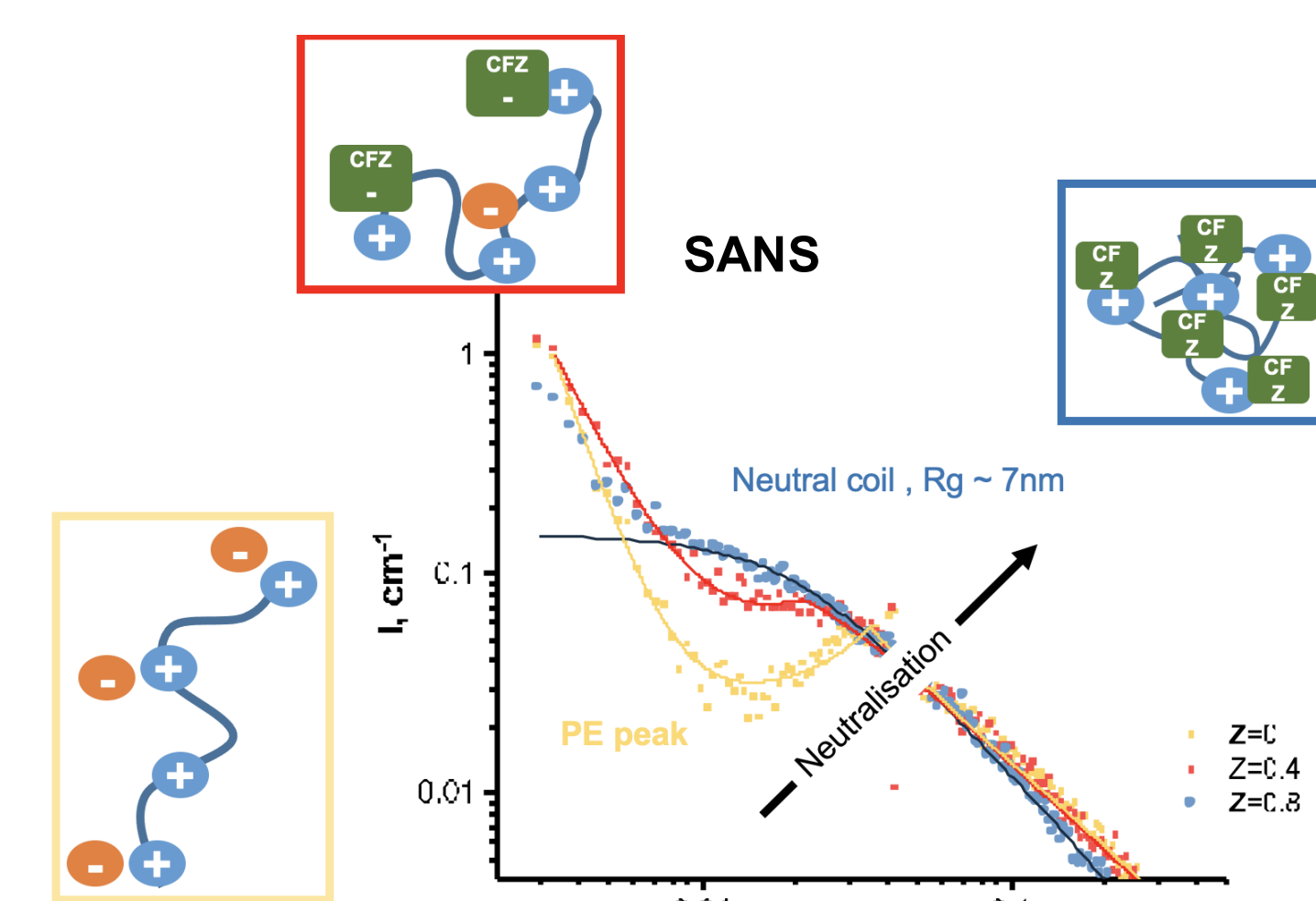
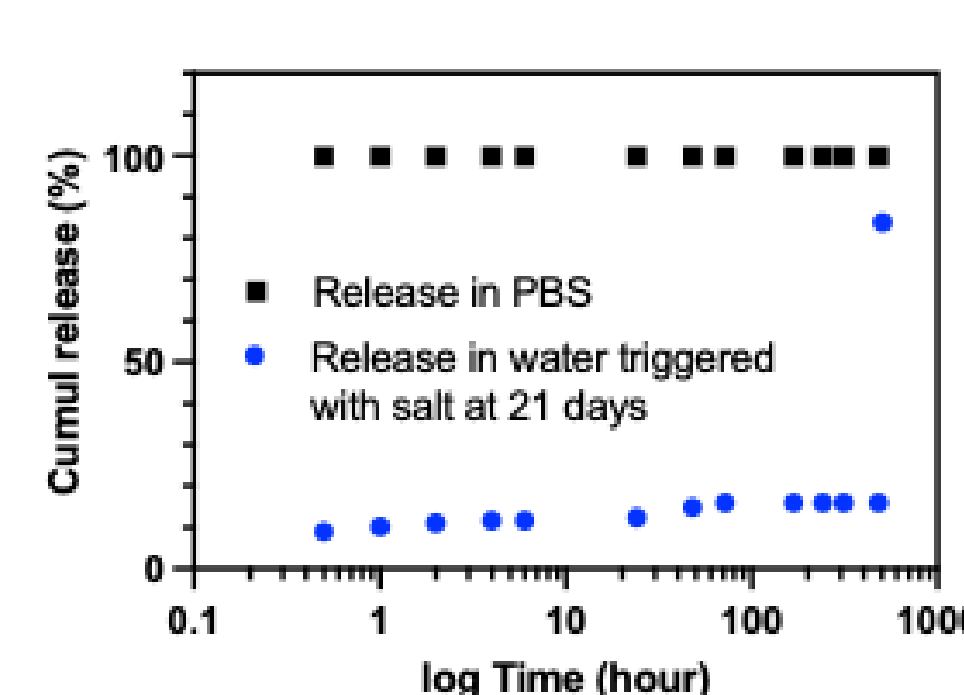


DSC

Compound	Tg (°C)
PDADMAC	106
Cefazolin	N.A
Complex	70



Release Test



- Neutralization : merging of the fast and slow relaxation modes -
- At Z = 1, a kink or slope change occurs in both the 'fast' radius and conductivity
- Charge neutralization observed by SANS (PE to neutral coil)
- Decrease of the PDADMAC's Tg by DSC
- Slow release triggered by addition of salt

Need to strengthen the system