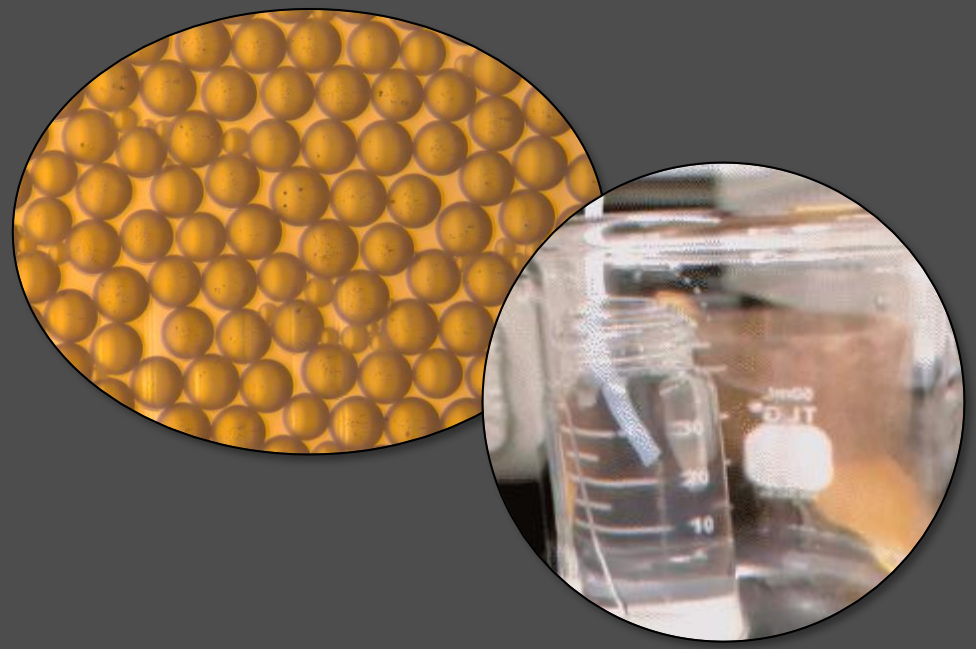
UNIVERSITY OF TORONTO
LESLIE DAN FACULTY OF PHARMACY

ALLEN LAB

Towards Microfluidics Manufacturing of Next-Generation Polyester Microparticles



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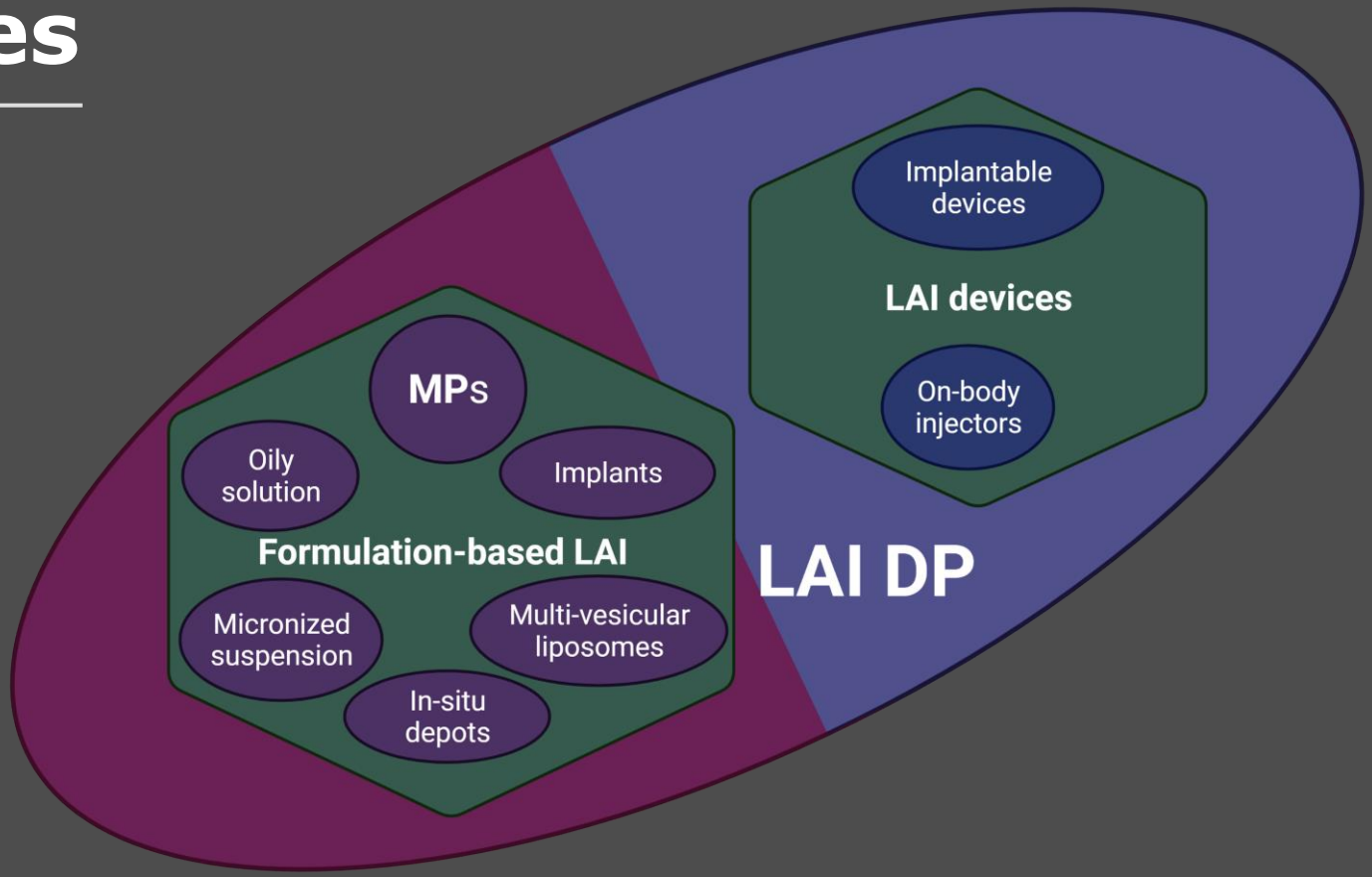
Dr. Christine Allen's Research Group

University of Toronto

July 14th 2022

Polymeric microparticles

- Polymeric microparticles (**MP**s) are long-acting injectable (**LAI**) drug products (**DP**s)
- LAI DPs are a broad class of **parental** dosage forms

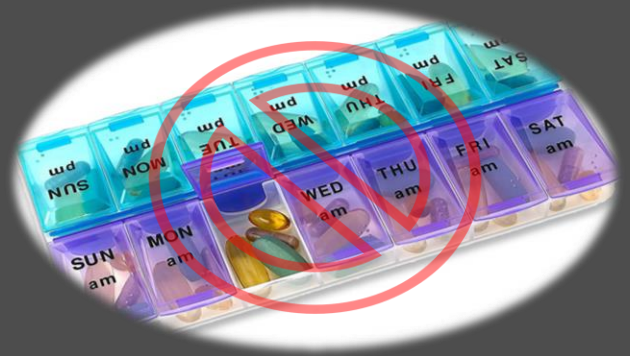


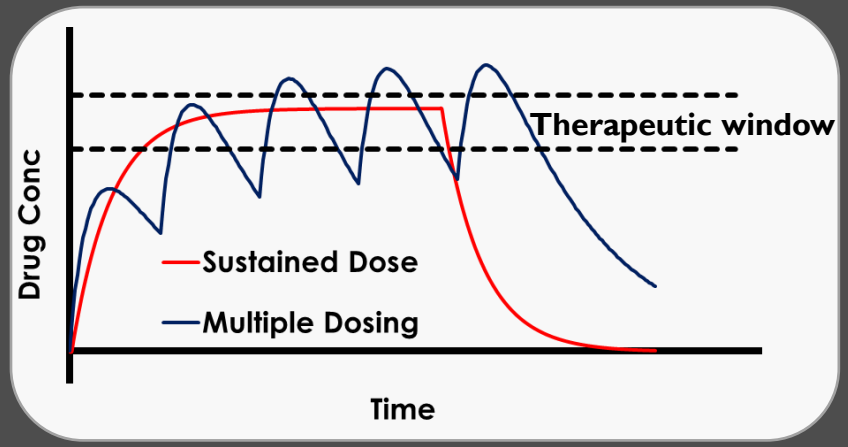
"**Drug product** means a **finished dosage form**...that contains an active drug ingredient ... in association with inactive ingredients"[1]

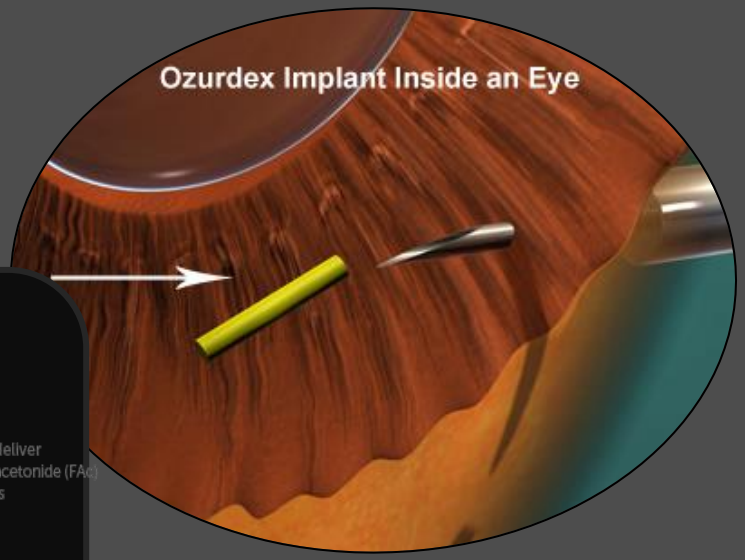
1) www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=210.3

Rationale for MPs vs. conventional dosage forms

1. **Sustained** release
2. Improved bioavailability
3. **Tailored** biodistribution





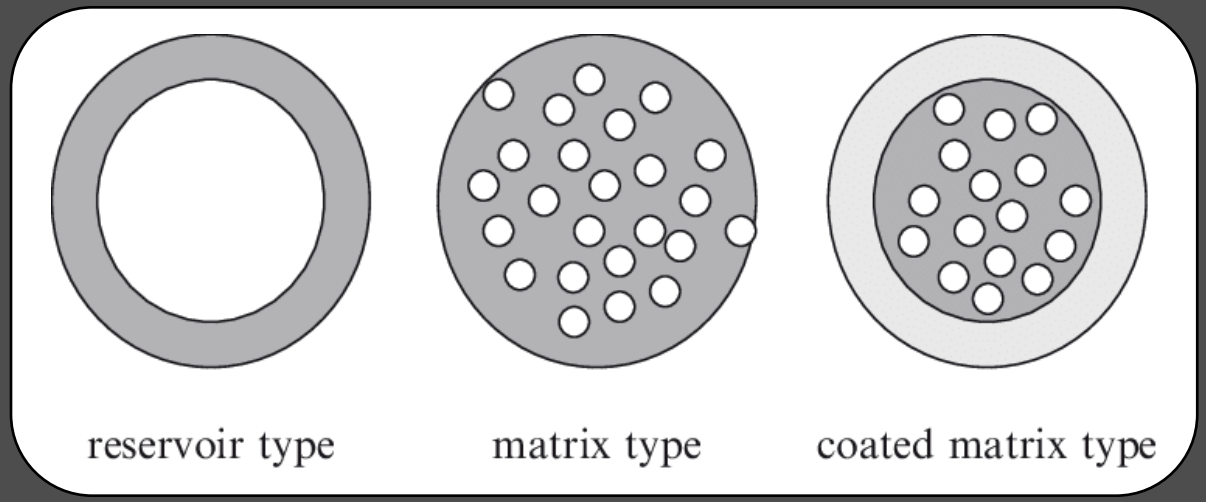


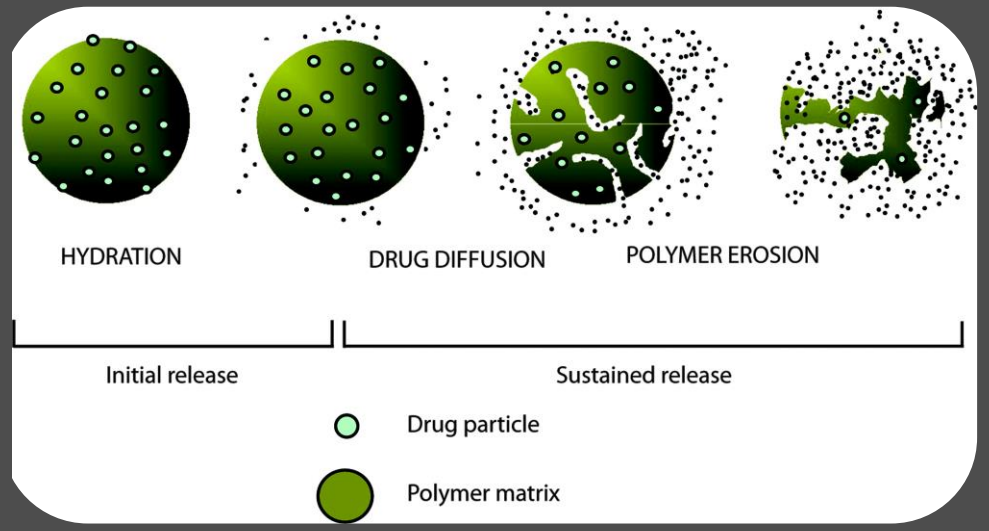
Overview of Ozurdex implant. Adapted from[1]

1) www. www.ozurdex.com

MPs - a closer look

- Particles **1 - 1000 µm** in diameter
- Can be further **subdivided** depending on **internal structure** and **drug disposition**

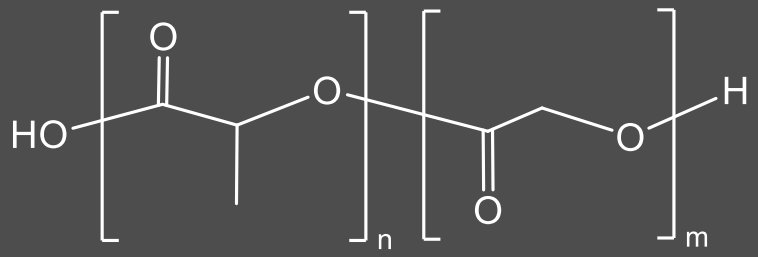




Drug release from MPs. Adapted from[1]

1) DeYoung M.. *et al.. Diabetes Technology & Therapeutics,* 3 (11), (2011)

Approved 1989-Prostate cancer



Poly(lactide-*co*-glycolide) (PLGA)

Approved 2001-Periodontitis

Systemic ⟷ Localized

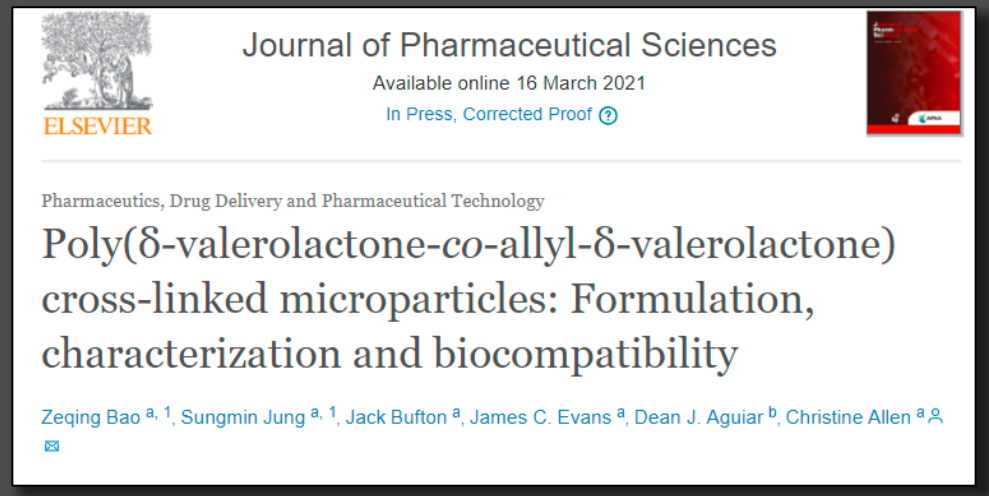
Approved 2019-Diabetes

19 drugs have been FDA-approved as **PLGA**-based LAIs

Approved 2017-Osteoarthritis

Drug-polymer compatibility

- Compatibility will affect MP drug **loading**, **stability**, and **release** kinetics
- A **single** polymer is **unlikely** to be **optimally** compatible with all drugs
- Our lab has investigated use of **allyl-functionalized** polyester MPs as an alternative material produced using **solvent-evaporation** techniques

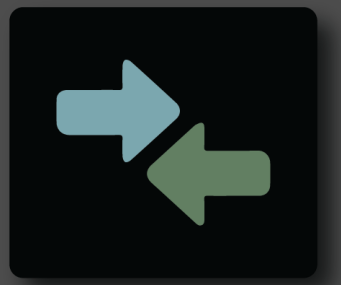


> "Compatibility "refers to **miscibility** and/or **interaction** with no alteration in the chemical structure of the **polymer** or the **drug**" 1)

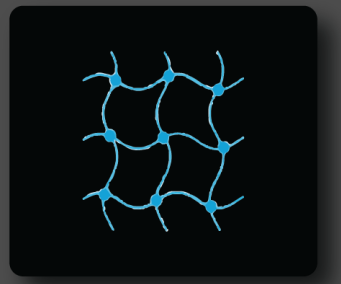
1) Liu, J., *et al.*. *Journal of Pharmaceutical Sciences* 93, 132–143 (2004)

Pivots to current studies

Use of **microfluidic** techniques to manufacture MPs.

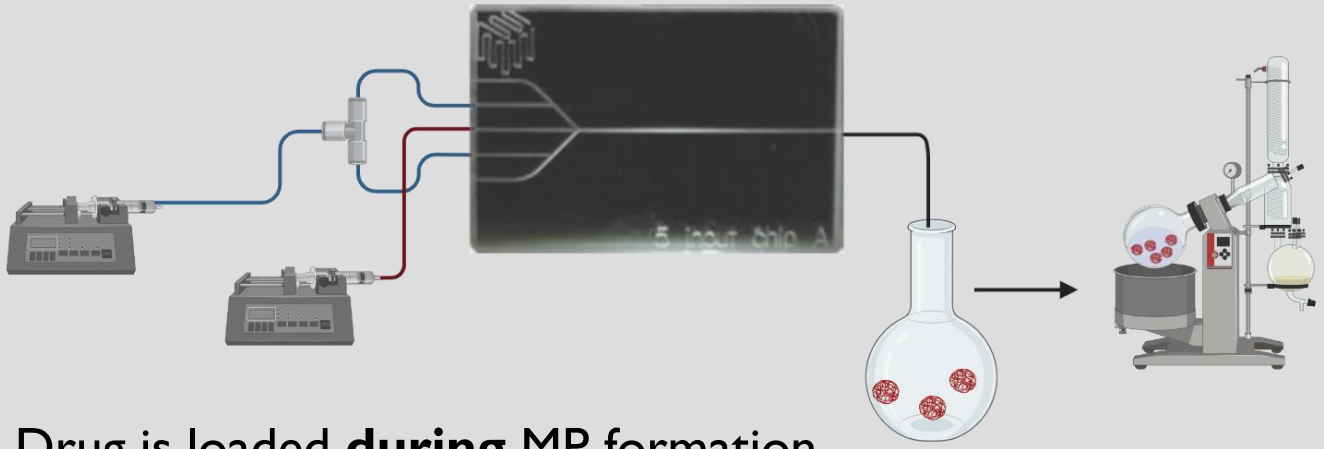


Parallel preparation of conventional PLGA MPs to **compare** *in vitro* performance with that of cross-linked MPs.

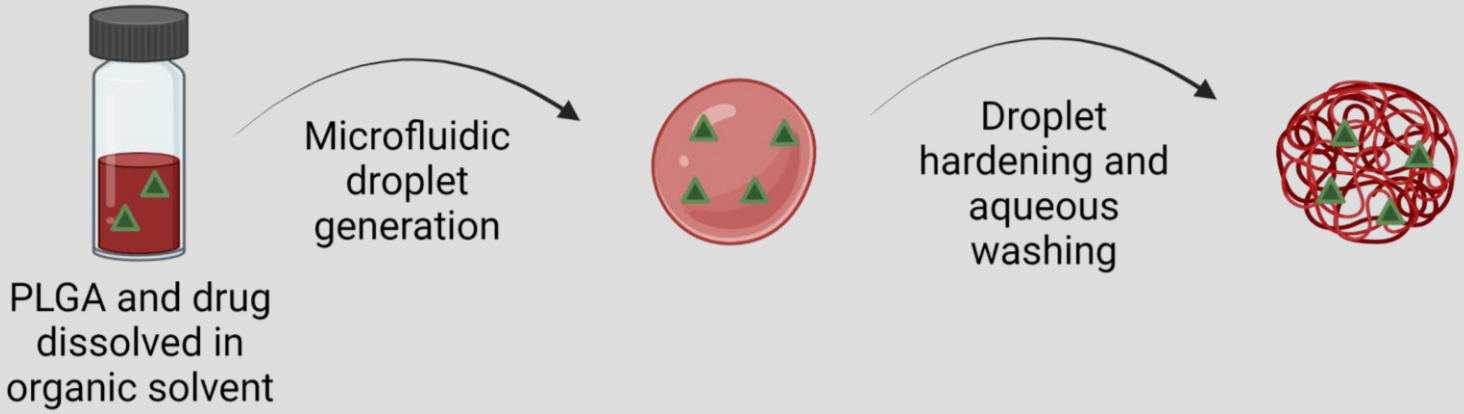


Use of a **lactide-based** cross-linkable polyester to evaluate the effect of **cross-linking** on MP performance.

Producing conventional PLGA MPs

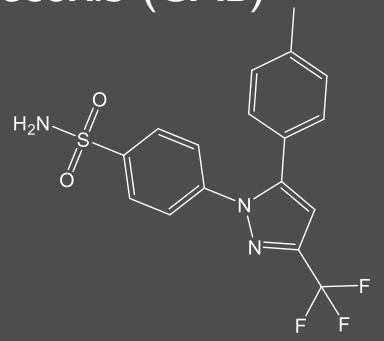


Drug is loaded **during** MP formation

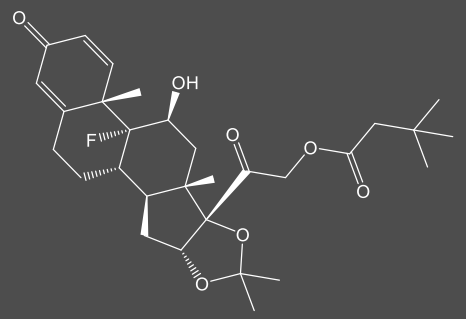


MPs were loaded with:

Celecoxib (CXB)

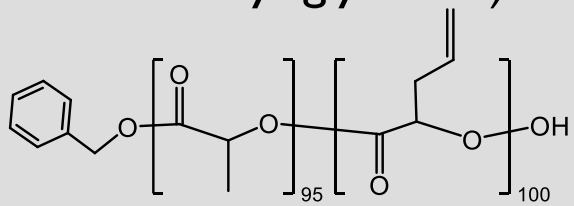


Triamcinolone hexacetonide (TAH)



Cross-linked MP (xMP) production steps

Poly(lactide-*co*-allyl-glycolide)



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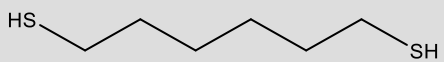
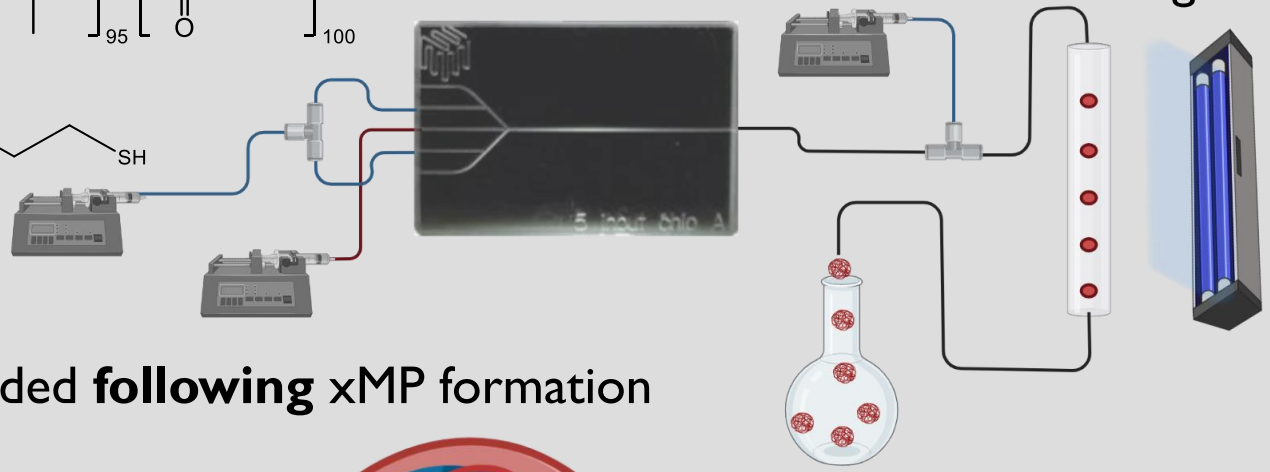
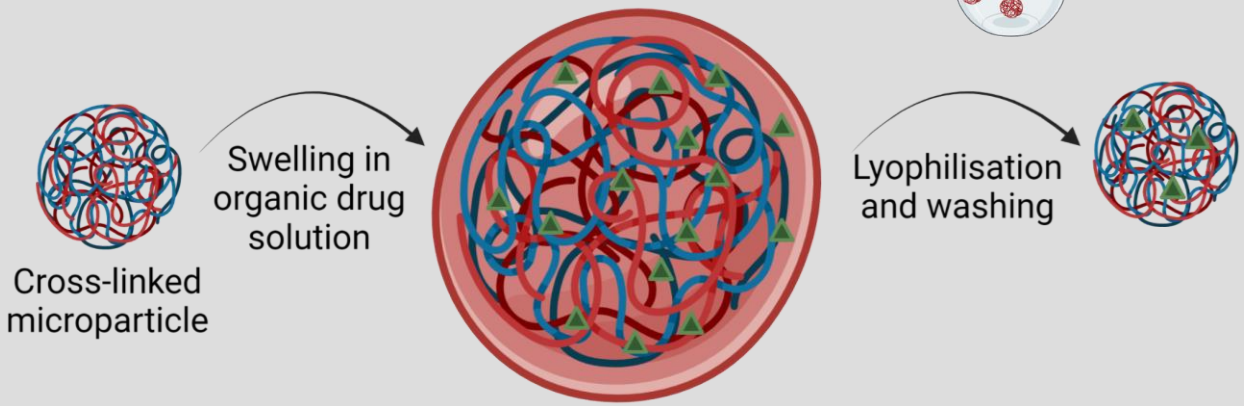


Hexanedithiol

Thiol-ene cross-linking

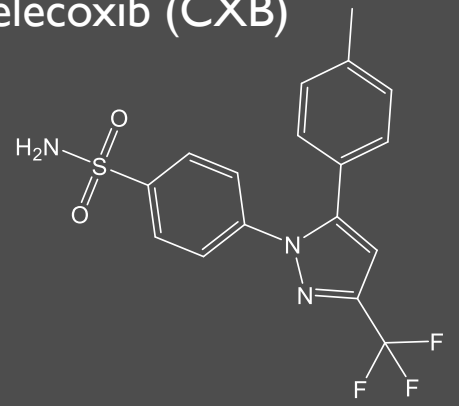


Drug is post-loaded **following** xMP formation

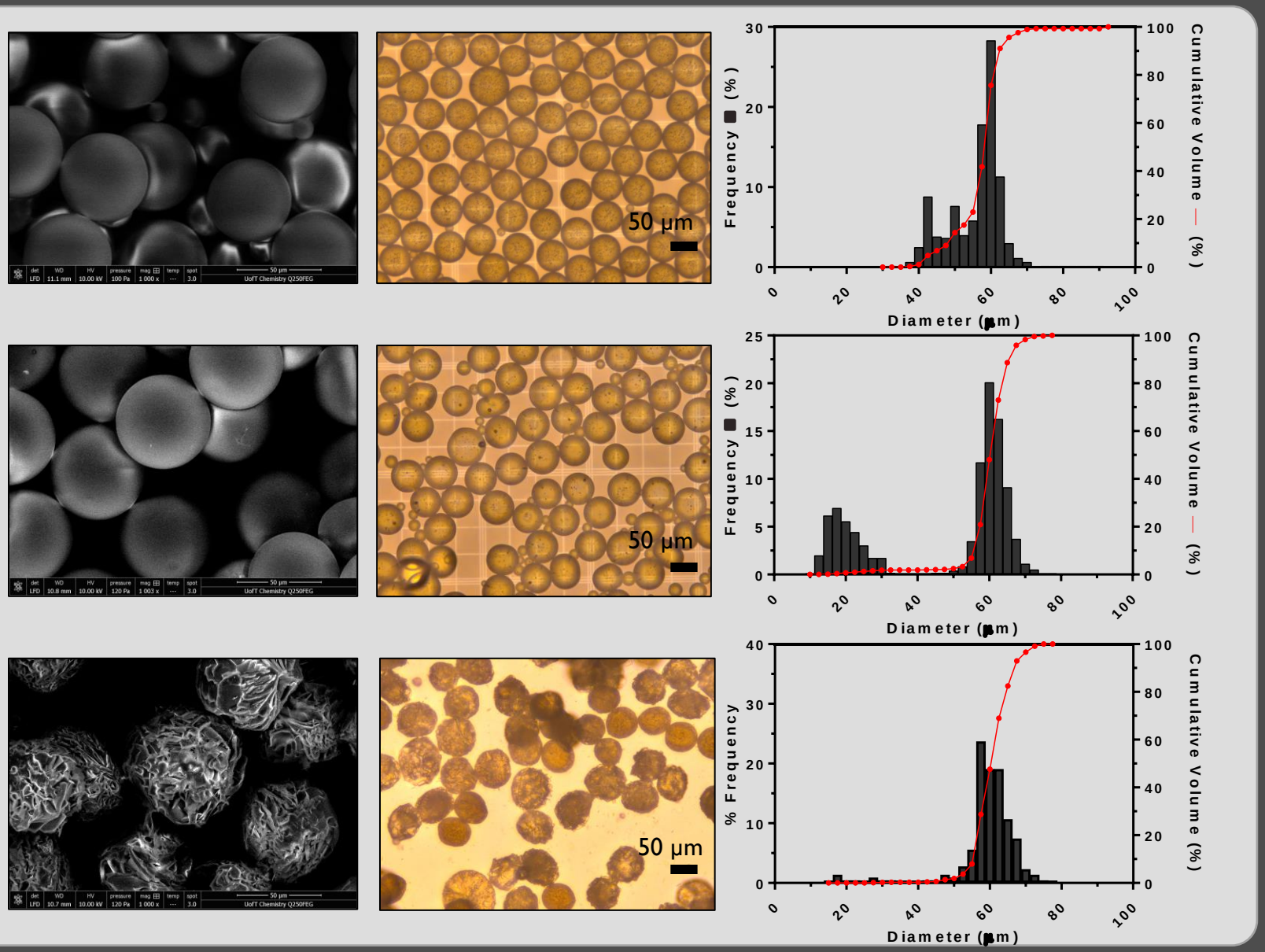


xMP was loaded with:

Celecoxib (CXB)



Conventional MP size and morphology

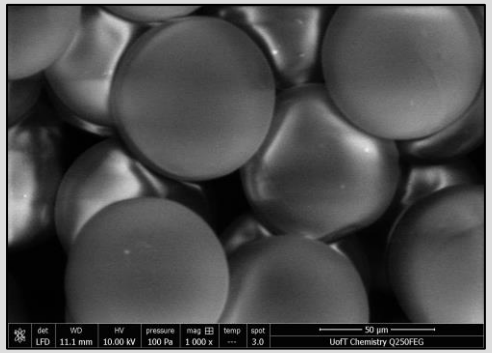


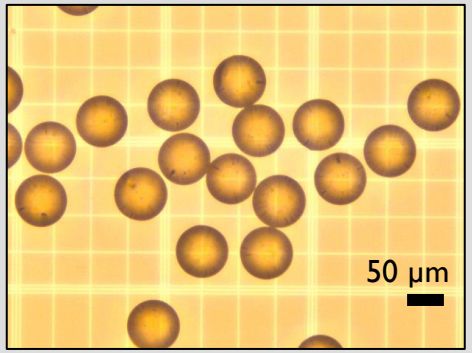
Non-drug loaded (MP)

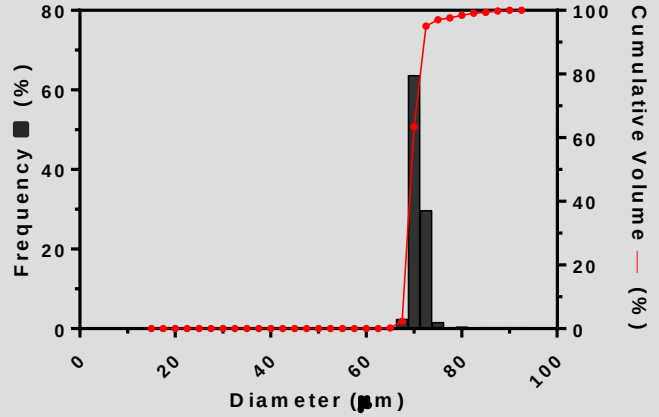
CXB-loaded at 20wt% (MPCXB20)

TAH-loaded at 20wt% (MPTAH20)

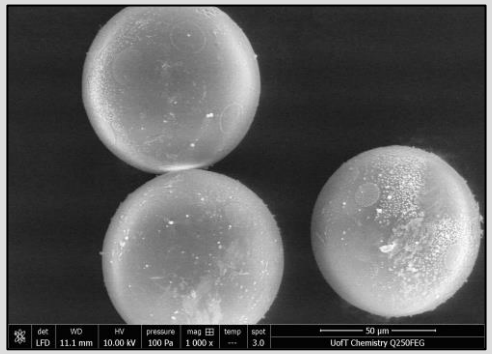
Cross-linked MP size and morphology

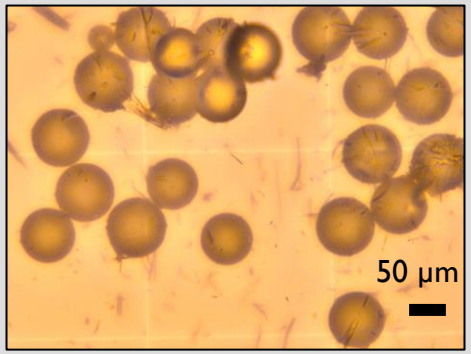


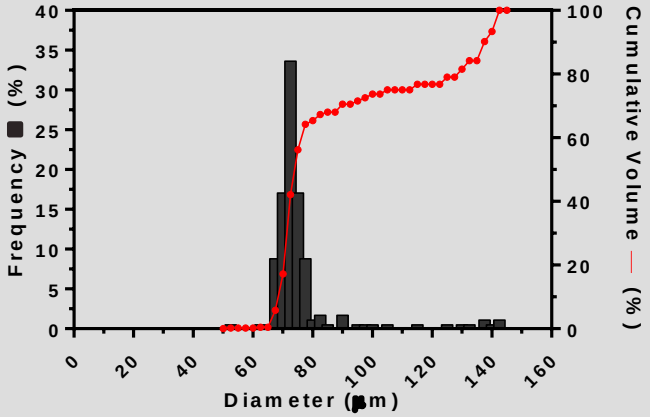




Non-drug loaded (xMP)

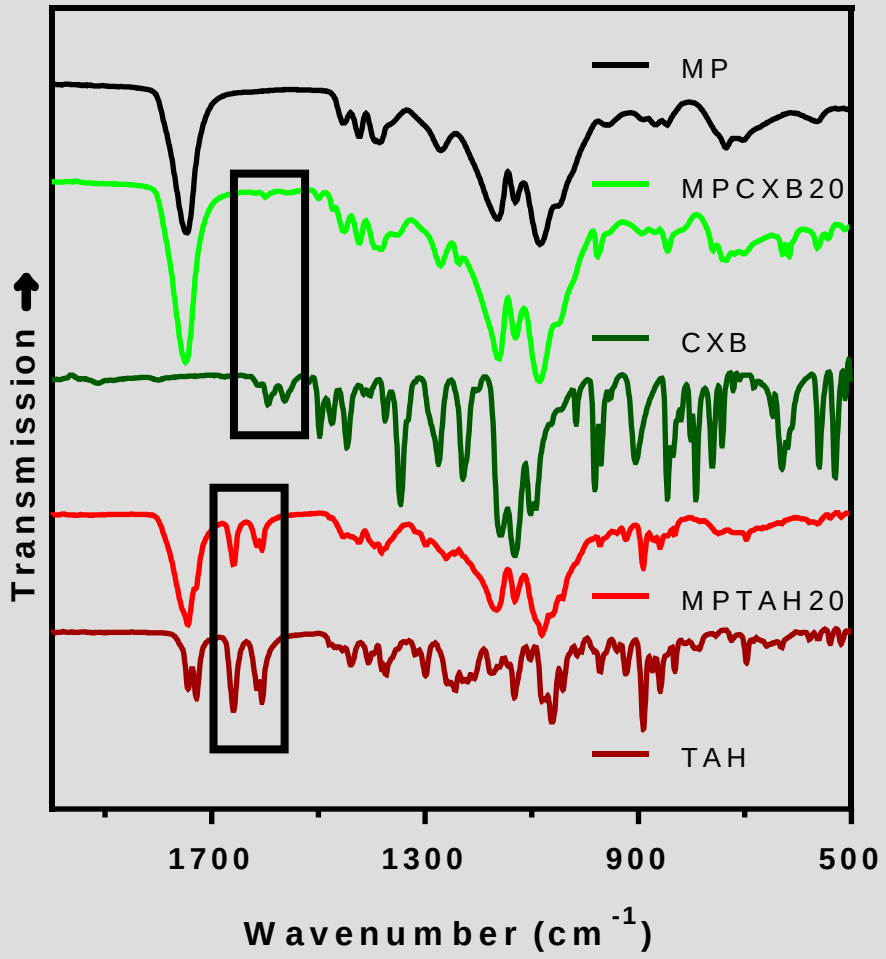


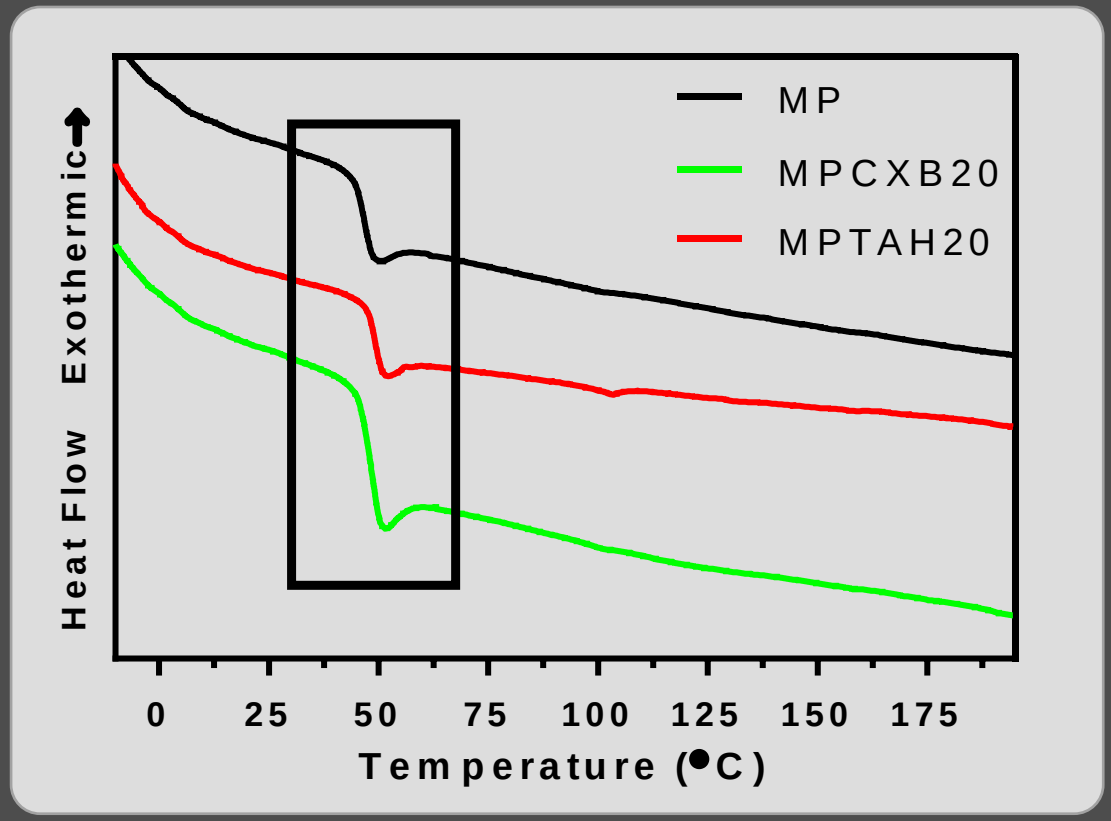




CXB-loaded at 60wt% (xMPCXB60)

Physico-chemical properties of conventional MPs

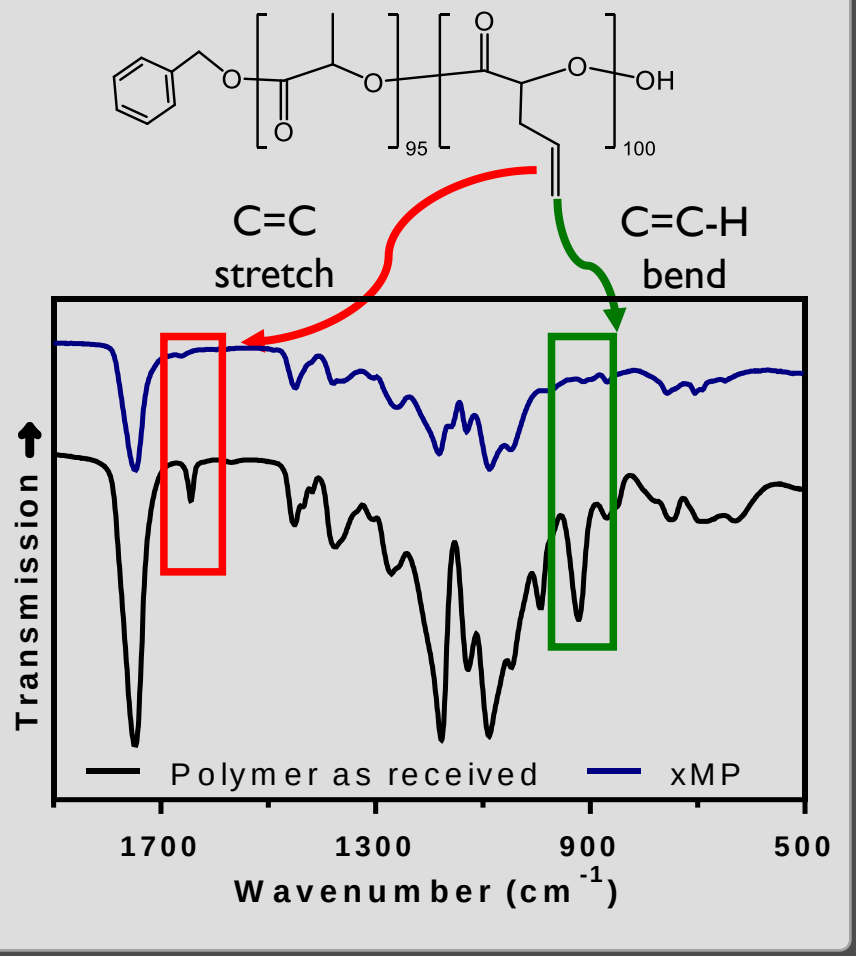




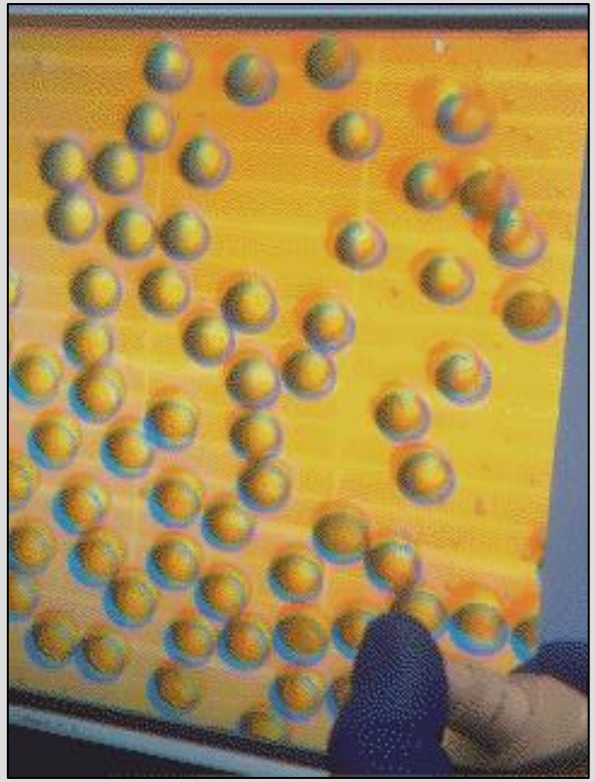
- T_g remained similar **irrespective** of drug loading
- **Stronger** IR peaks characteristic of **TAH** compared to **CXB** in drug-loaded MPs

Evidence of in-line cross-linking of xMP

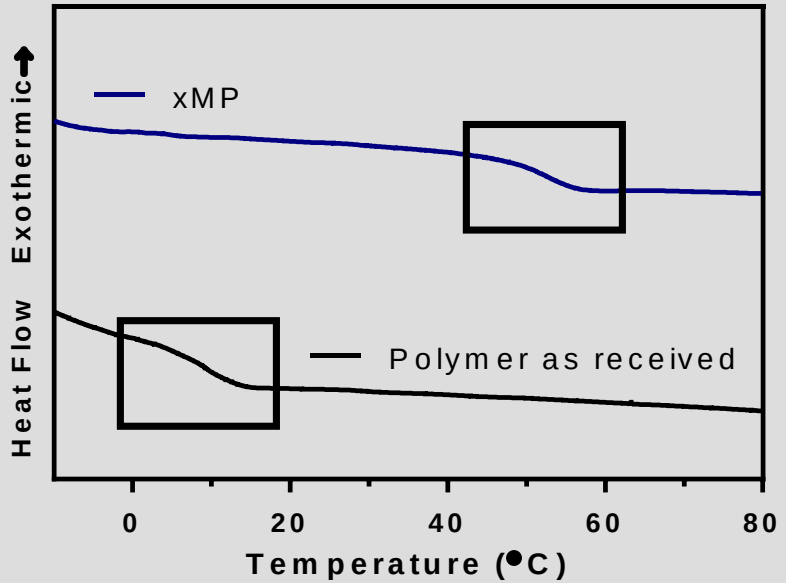
1) Disappearance of characteristic IR peaks



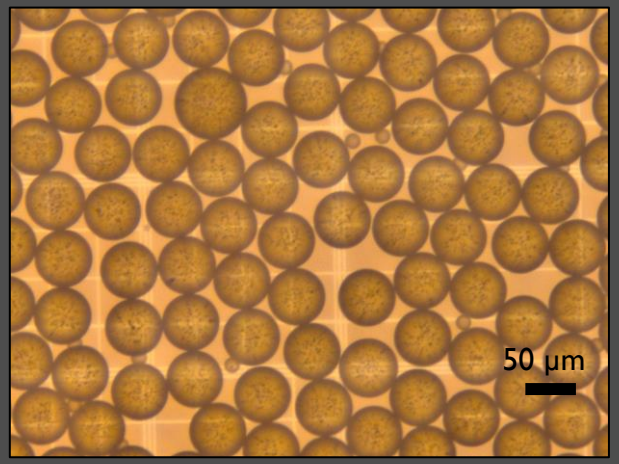
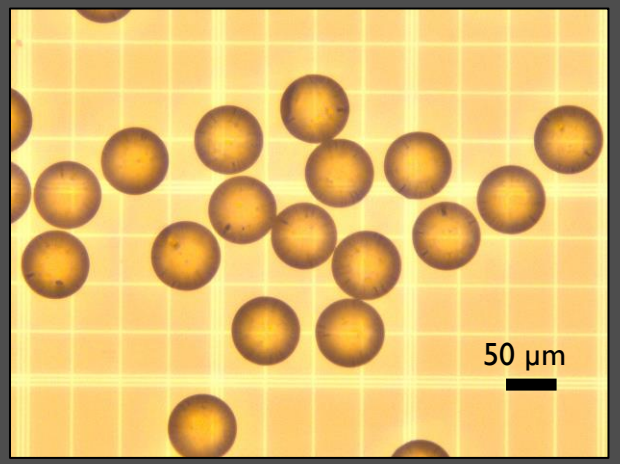
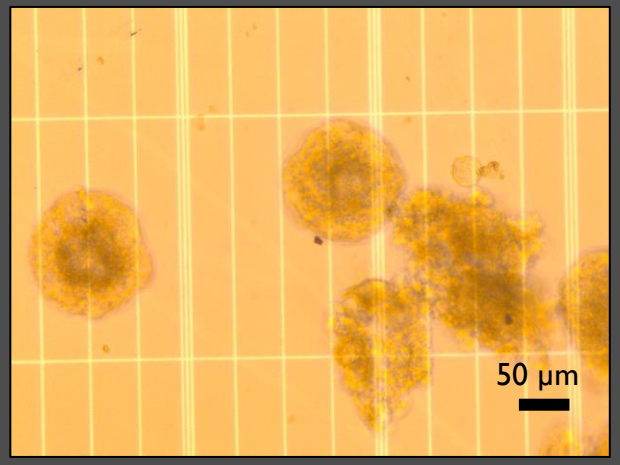
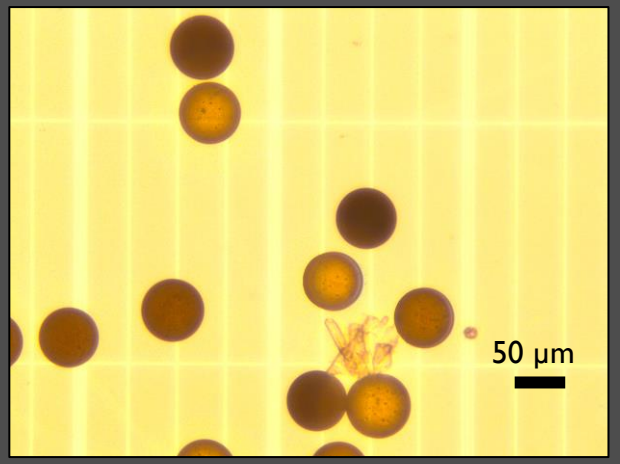
2) Reversible swelling in organic solvent



3) Increase in T_g by 40 °C



In vitro stability of non-drug loaded MPs

Mn [Mw] by GPC (kDa)	MP	xMP
33.0 [53.1]		
2.3 [18.7]		

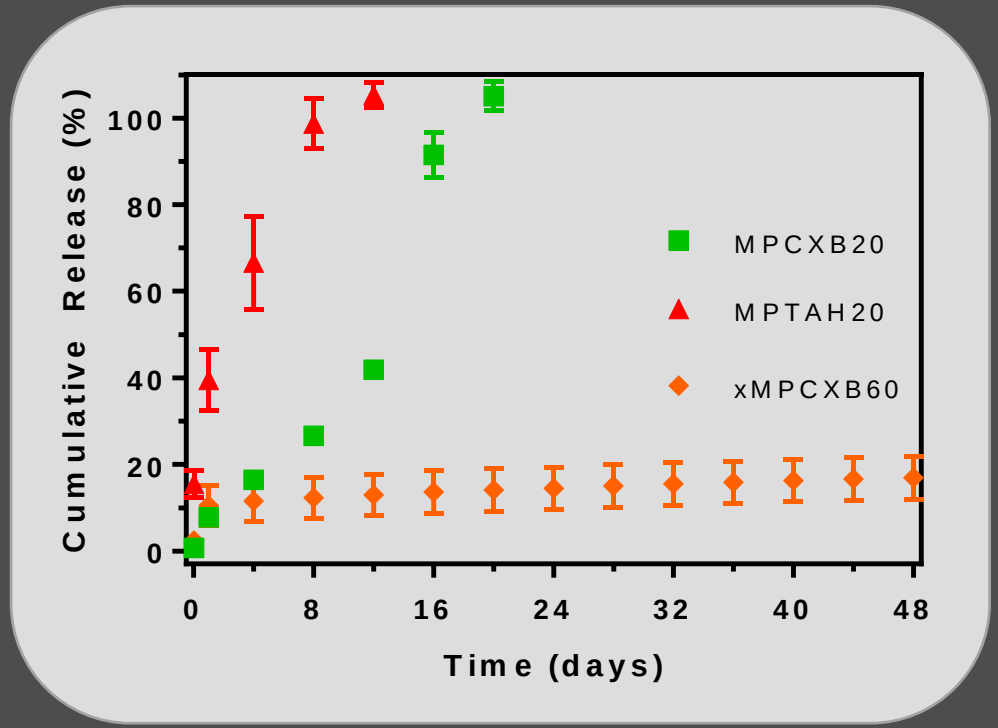
0 days

16 days

xMP is more **stable** under *in vitro* release conditions

Loading and in vitro release

Formulation	Encapsulation Efficiency (%)	Remaining drug after *in vitro* release (%)
MPCXB20	82 ± 2.5	0.72 ± 0.3
MPTAH20	73.8 ± 1.5	7.5 ± 2.8
xMPCXB60	49.8 ± 1.5	96.9 ± 11.8



Conclusions

- xMP show increased **stability**, can achieve a **high** drug-loading, and show **slower** *in vitro* release compared to conventional PLGA microparticles.
- The **morphology**, **loading** efficiency and *in vitro* **release** kinetics were **drug dependent** in conventional PLGA microparticles.

Future directions

- Post-load a range of drugs into xMP (e.g., TAH).
- **Optimize** the polymeric matrix of xMP (i.e., by adjusting the **extent** and **chemistry** of cross-linking) to **tailor** xMP stability.



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Lab Members: Dr. Pauric Bannigan

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Dr. Craig Simmons

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