

# Reverse Engineering of the Sublocade® Buprenorphine *In Situ* Forming Implant

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## PURPOSE

Sublocade® (buprenorphine extended-release injection) is a biodegradable, *in situ* forming implant (ISFM) designed for the sustained delivery of buprenorphine with monthly dosing to treat moderate to severe opioid use disorder (OUD) patients.



- Clear-yellowish viscous liquid
- Buprenorphine free base (BUP) (18 %w/w)
- Poly lactide-co-glycolide (PLGA) (32% w/w)
- N-methyl pyrrolidone (NMP) (50% w/w)

### Challenges:

- Heterogeneous nature of PLGA
- Absence of standardized *in vitro* drug release testing

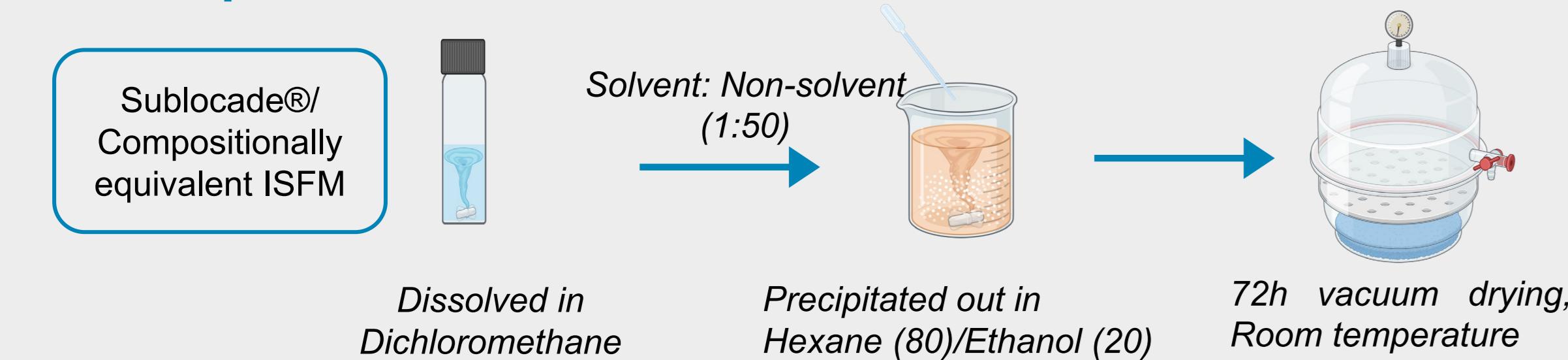
Limited generic buprenorphine ISFM for OUD treatment

## OBJECTIVES

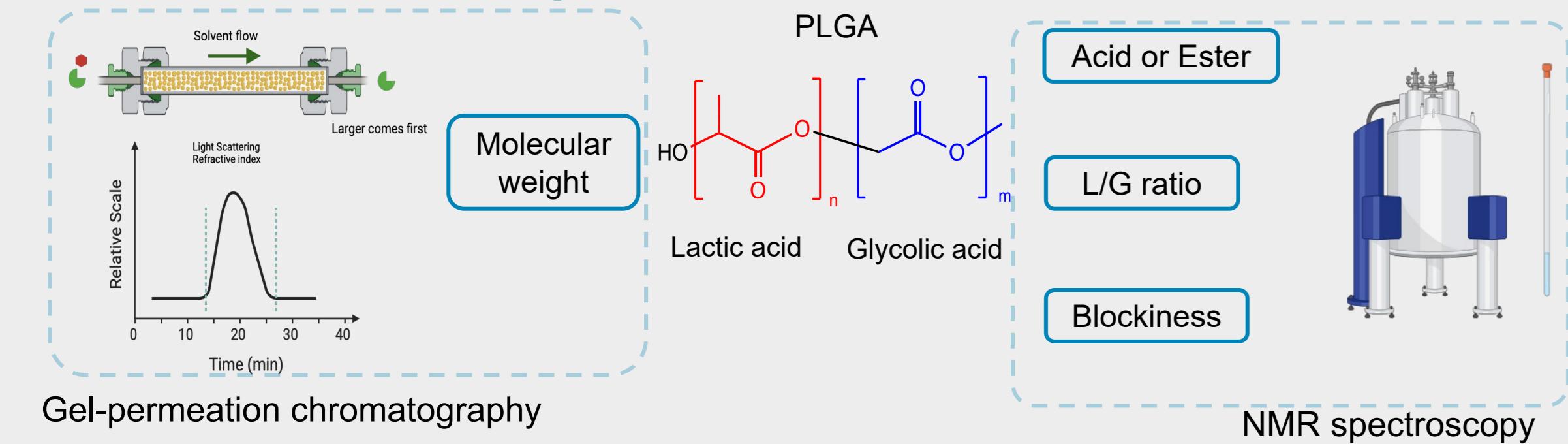
- To characterize Sublocade® (buprenorphine) ISFM in terms of PLGA's molecular weight (MW), lactide/glycolide (L/G) ratio, end groups and blockiness
- To understand the release of buprenorphine over time

## METHODS

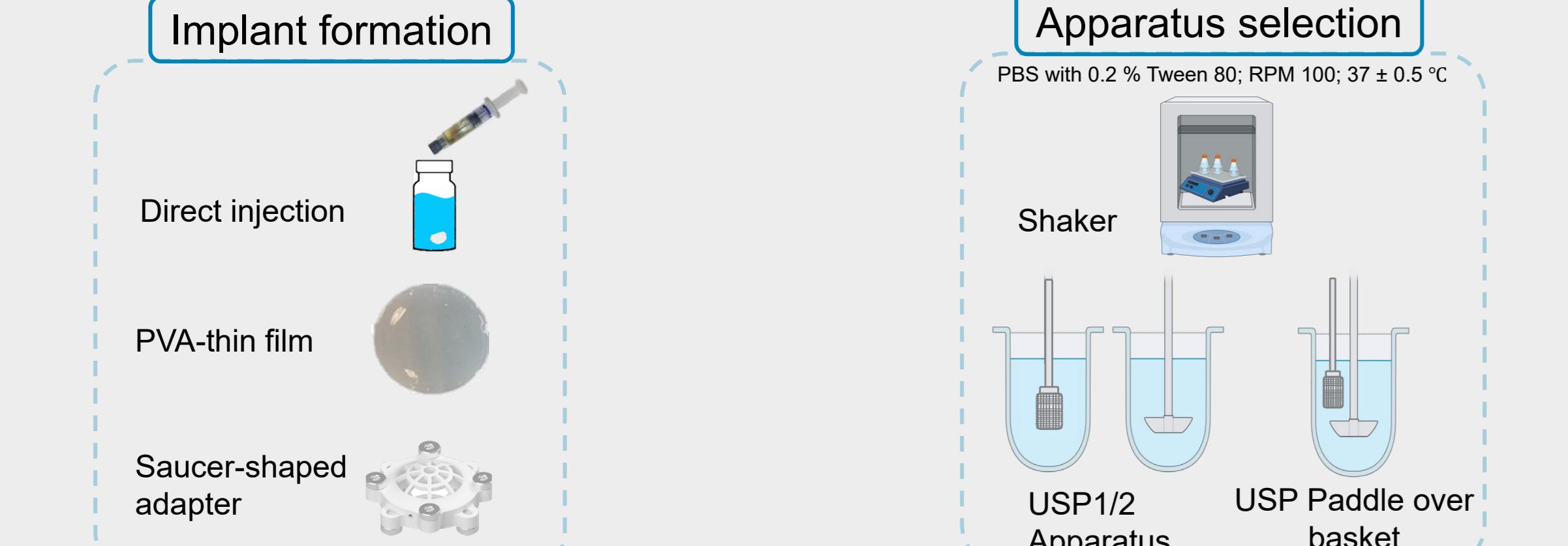
### PLGA purification from Sublocade®



### Characterization of purified PLGA



### In vitro release testing (IVRT) system



## RESULTS

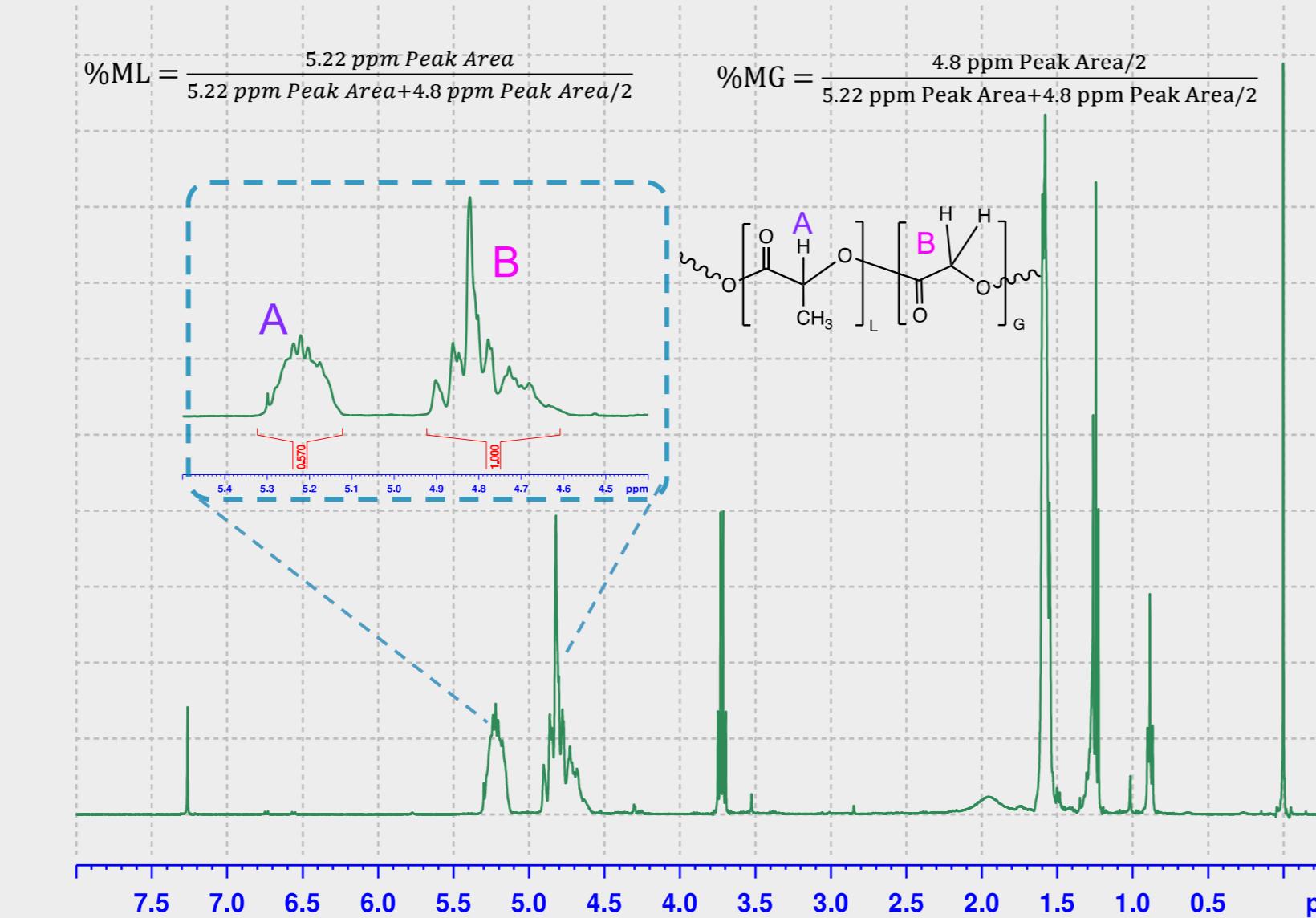


Figure 1. <sup>1</sup>H NMR spectra ( $CDCl_3$ , 400 MHz) of characteristic proton peaks of purified PLGA in Sublocade®. A and B corresponds to proton of methine in lactic mer units and methylene in glycolic mer units, respectively.

### Purified PLGA Characterization

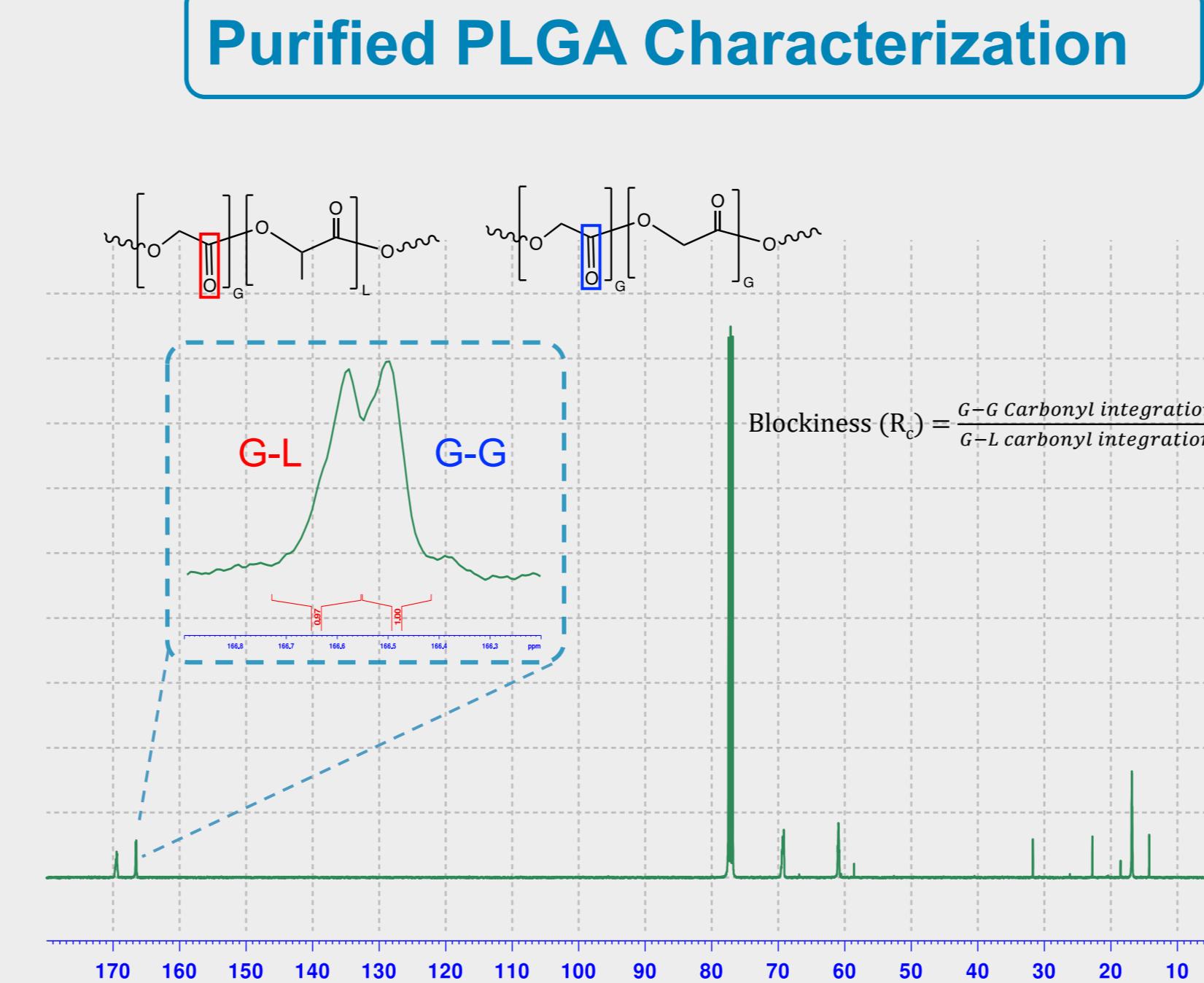


Figure 2. <sup>13</sup>C NMR spectra ( $CDCl_3$ , 400 MHz) of carbonyl regions of glycolic mer units of purified PLGA in Sublocade®. A and B corresponds to proton of methine in lactic mer units and methylene in glycolic mer units, respectively.

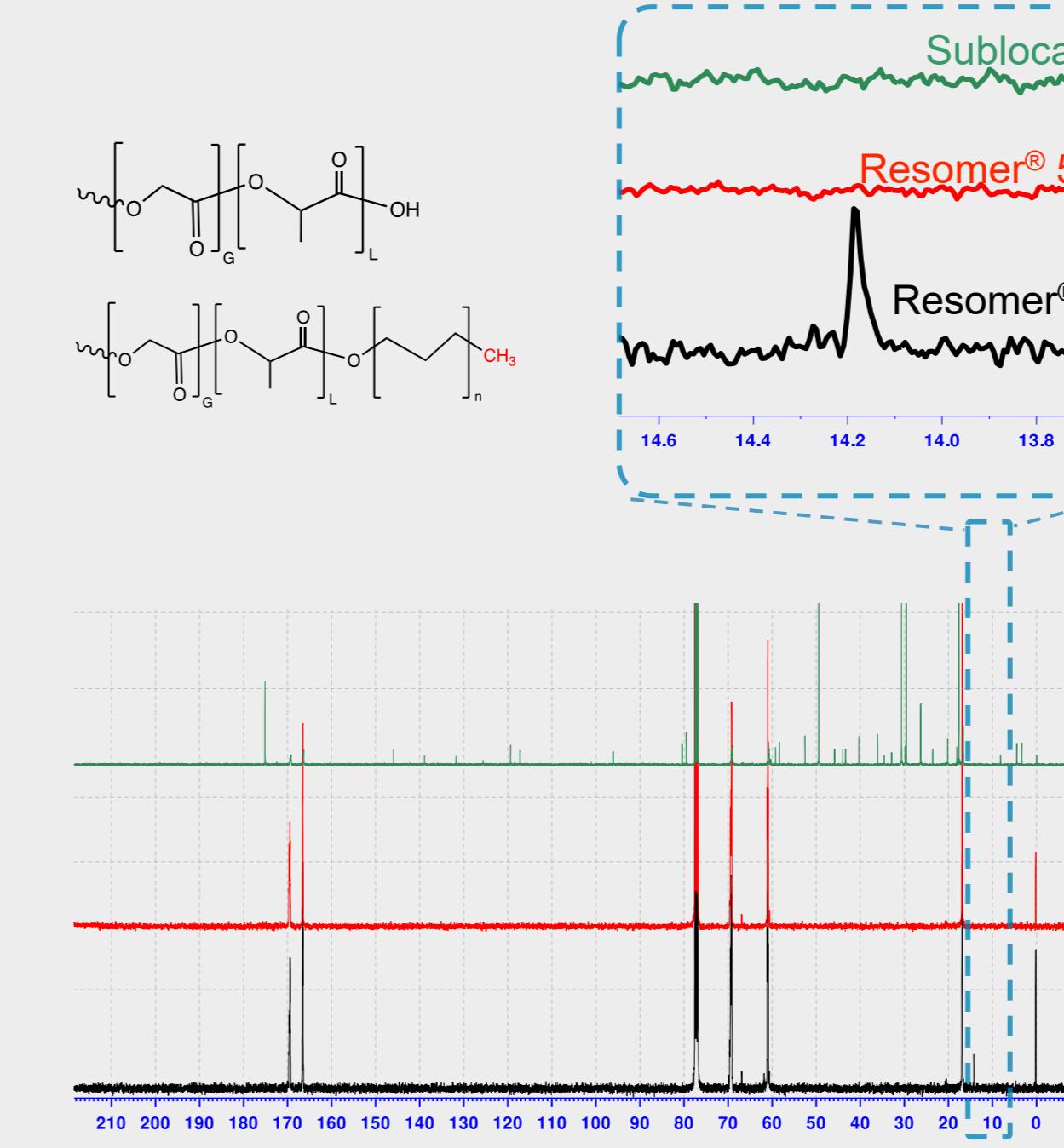


Figure 3. <sup>13</sup>C NMR spectra ( $CDCl_3$ , 400 MHz) of PLGA's with acid/ester end group. The carbon peak at  $\sim 14$  ppm represents the methyl group at the terminal ester bond.

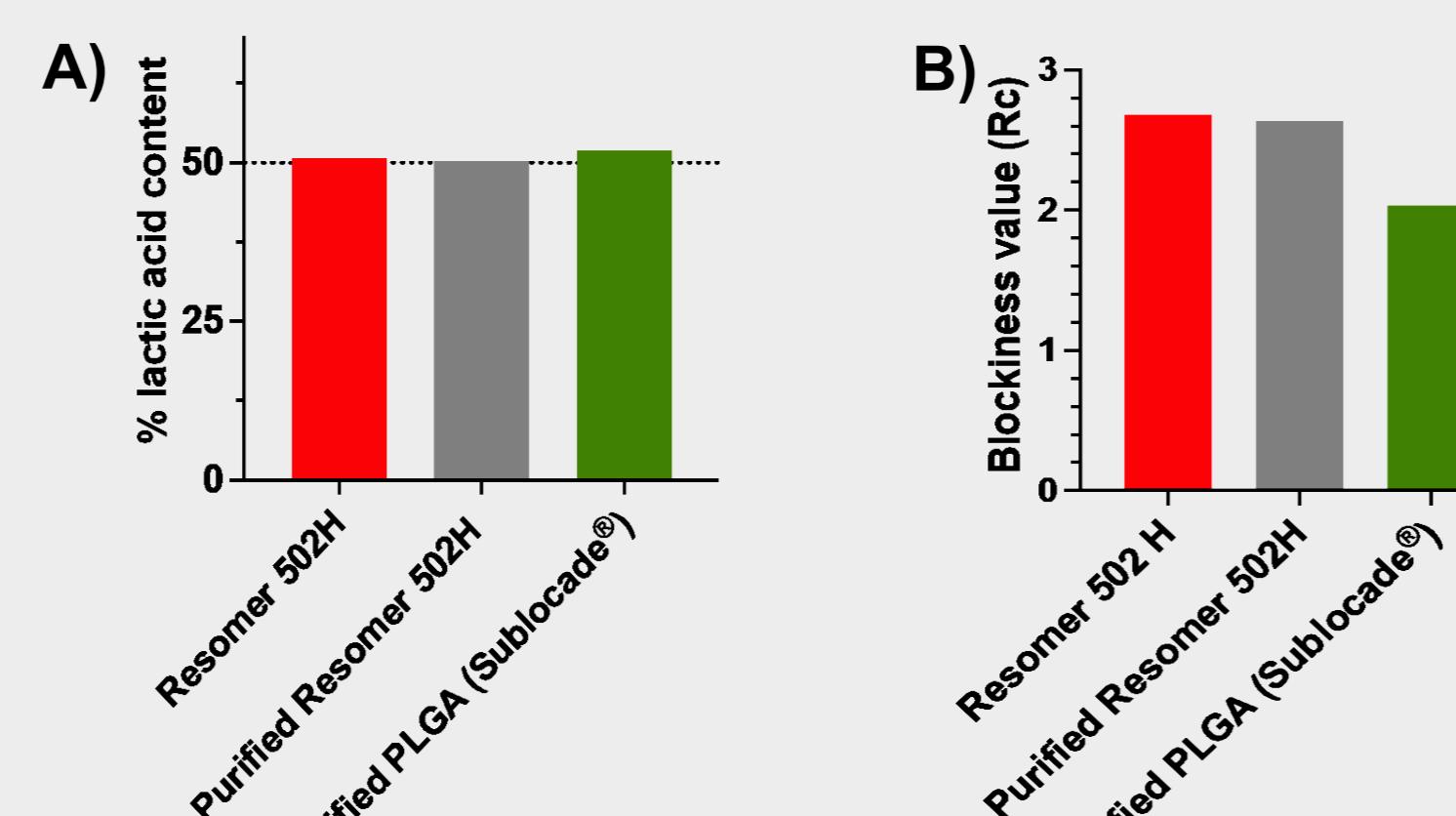


Figure 4. Characterization of PLGAs from different samples A) molar lactic acid content (%); B) Blockiness value

Table 1. Summary of purified PLGA characterization of Sublocade and compositionally equivalent ISFM

Product	Polymer	Mn (kDa)	Mw (kDa)	PDI	L:G ratio	Blockiness	End group
Sublocade®	PLGA	11.8	12.2	1.30	52:48	2.03	acid
Compositionally equivalent ISFM	PLGA 2A	11.8	14.1	1.2	50:50	2.6	acid

Figure 5. In vitro release of buprenorphine and NMP from Sublocade® with different combination of implant formation method and apparatus (mean  $\pm$  SD, n=3)

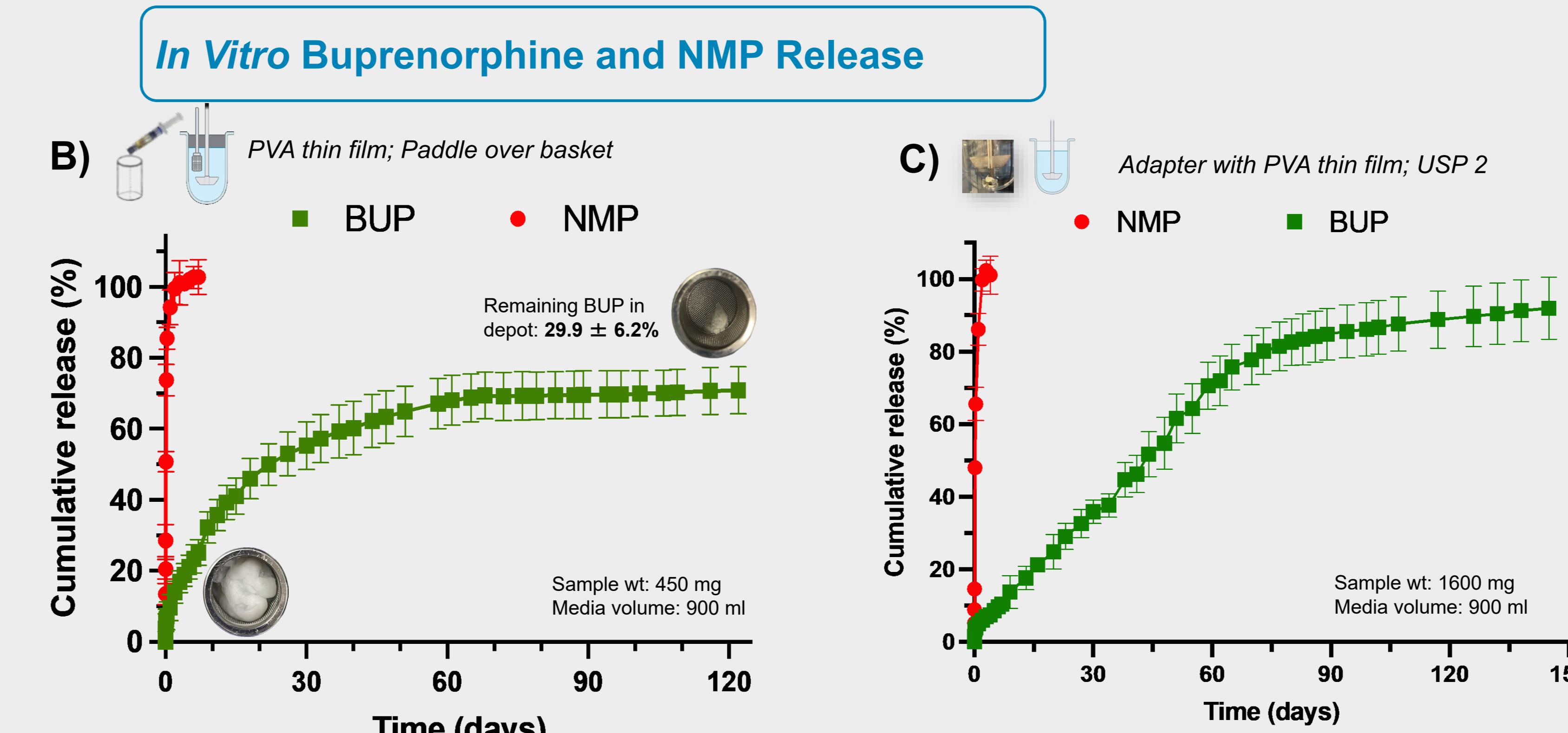
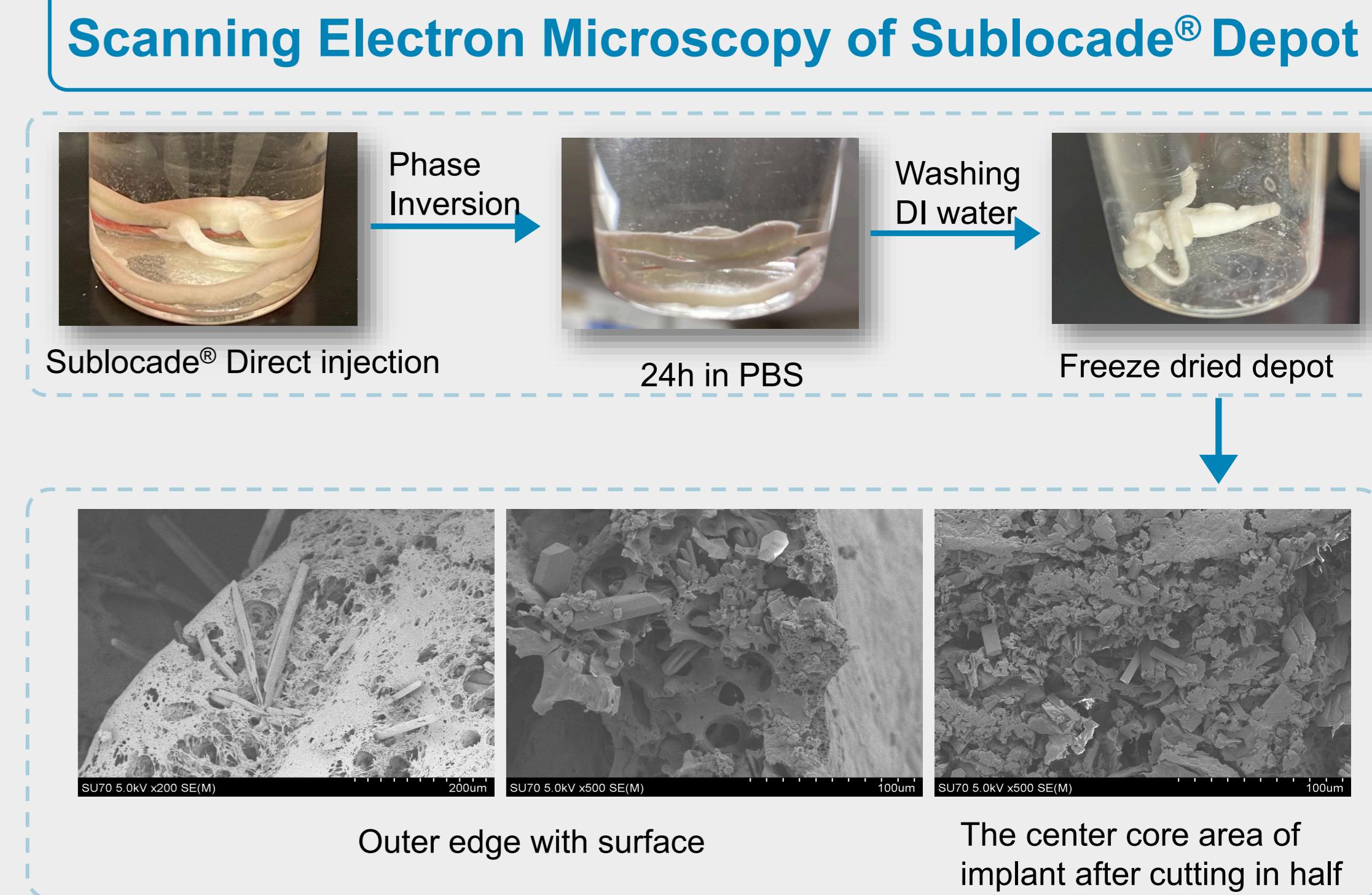


Figure 5. In vitro release of buprenorphine and NMP from Sublocade® with different combination of implant formation method and apparatus (mean  $\pm$  SD, n=3)

The saucer-shaped adapter in USP 2 had biphasic release, with 80% buprenorphine (BUP) within 2.5 months.



BUP crystal formed with heterogeneous distribution in PLGA matrix during phase inversion.

## CONCLUSIONS

- This is the first report of reverse engineering of Sublocade® in situ forming implant.
- PLGA in Sublocade® was characterized which will guide development of Q1/Q2 formulations.
- Our preliminary *in vitro* release study with a saucer-shaped adapter presents reproducible data and on further optimization will serve as a useful tool to understand the BUP release mechanism.

## REFERENCES

- Sublocade® (buprenorphine extended-release injection) Printed Labeling. Application number: NDA 209819, Food And Drug Administration, (2017).
- Garner J., et al., A protocol for assay of poly(lactide-co-glycolide) in clinical products. Int. J. Pharm. (495) 2015.

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