

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

Surendra Poudel¹, Rudra Pangeni¹, Ziyu Huo², Dale Farkas³, Qiangnan Zhang⁴, Yan Wang⁴, Bin Qin⁴, Worth Longest³, Rong Tong², Matthew S Halquist¹, Qingguo Xu¹

W1130-11-64 ¹Department of Pharmaceutics, Virginia Commonwealth University, Richmond, VA, USA

²Department of Chemical Engineering, Virginia Polytechnic Institute and State University, Blacksburg, VA, USA

³Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, VA, USA

⁴ Office of Research and Standards, Office of Generic Drugs, CDER, U.S. Food and Drug Administration, Silver Springs, MD, USA

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CONTACT INFORMATION: qxu@vcu.edu, poudels6@vcu.edu

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

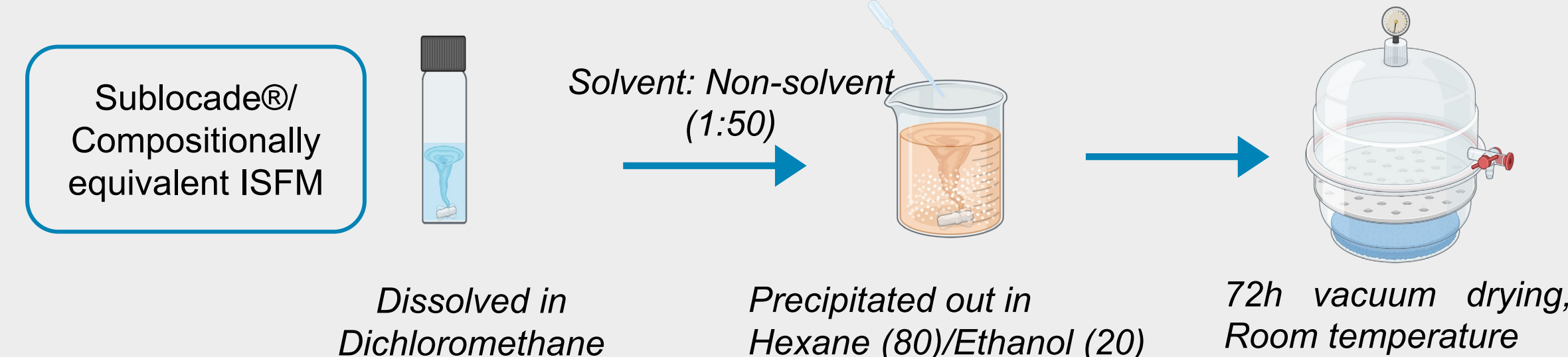
Limited generic buprenorphine ISFM for OUD treatment

OBJECTIVES

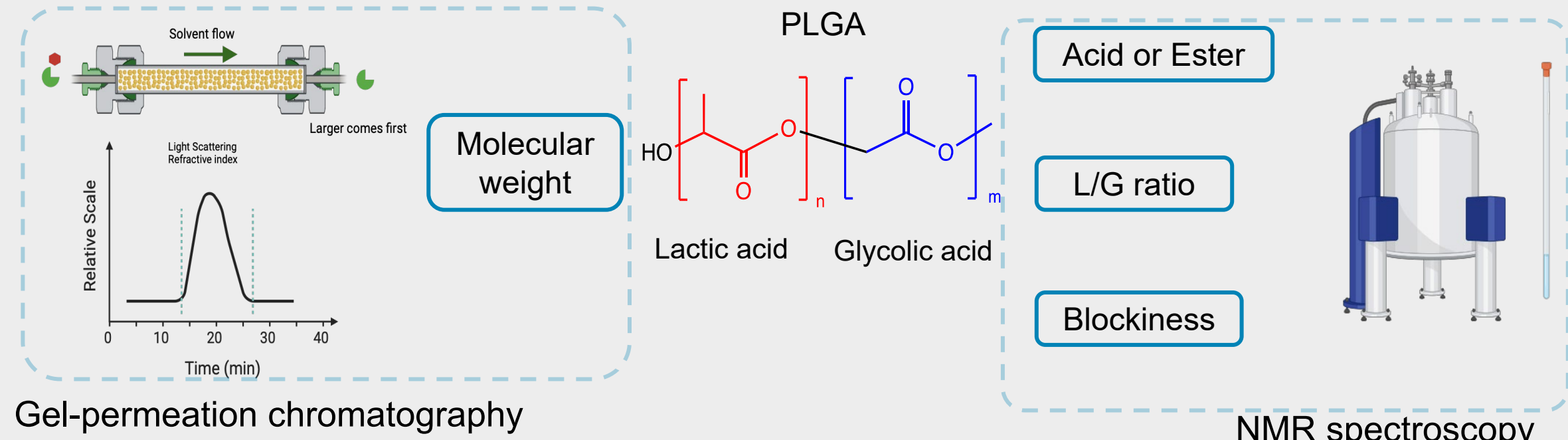
- ❑ To characterize Sublocade® (buprenorphine) ISFM in terms of PLGA's molecular weight (MW), lactide/glycolide (L/G) ratio, end groups and blockiness
- ❑ To understand the release of buprenorphine over time

METHODS

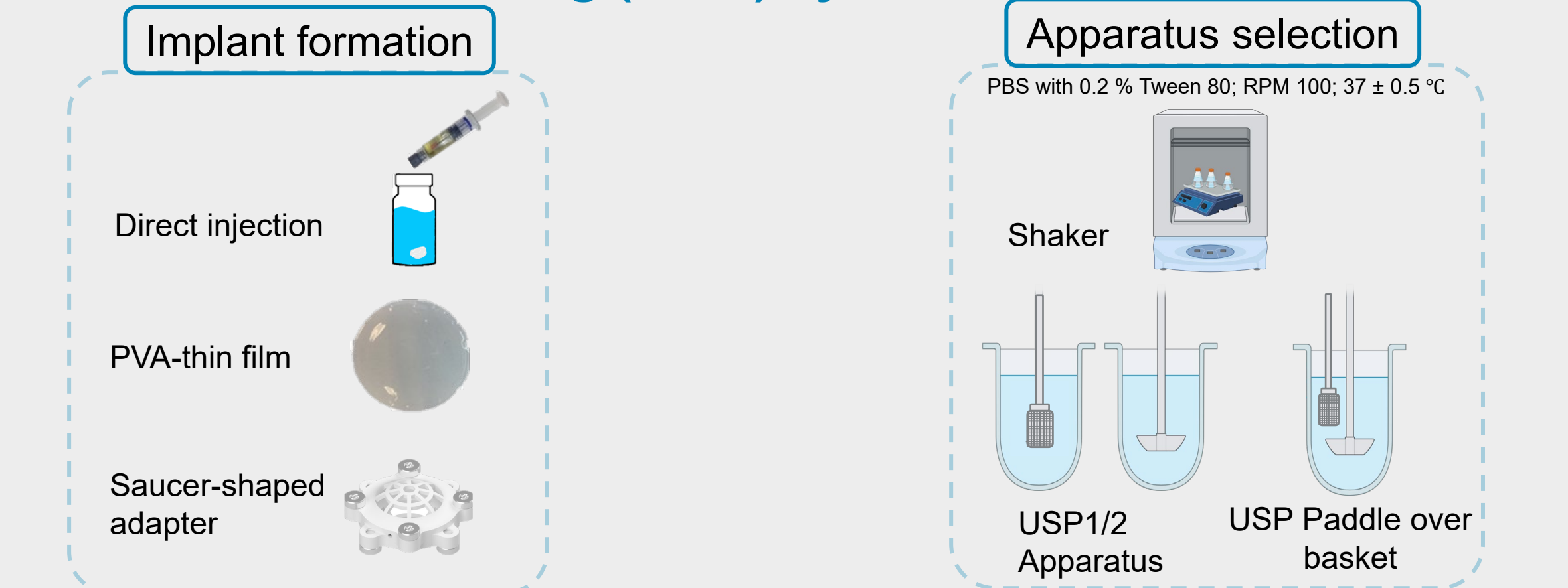
PLGA purification from Sublocade®



Characterization of purified PLGA



In vitro release testing (IVRT) system



RESULTS

Purified PLGA Characterization

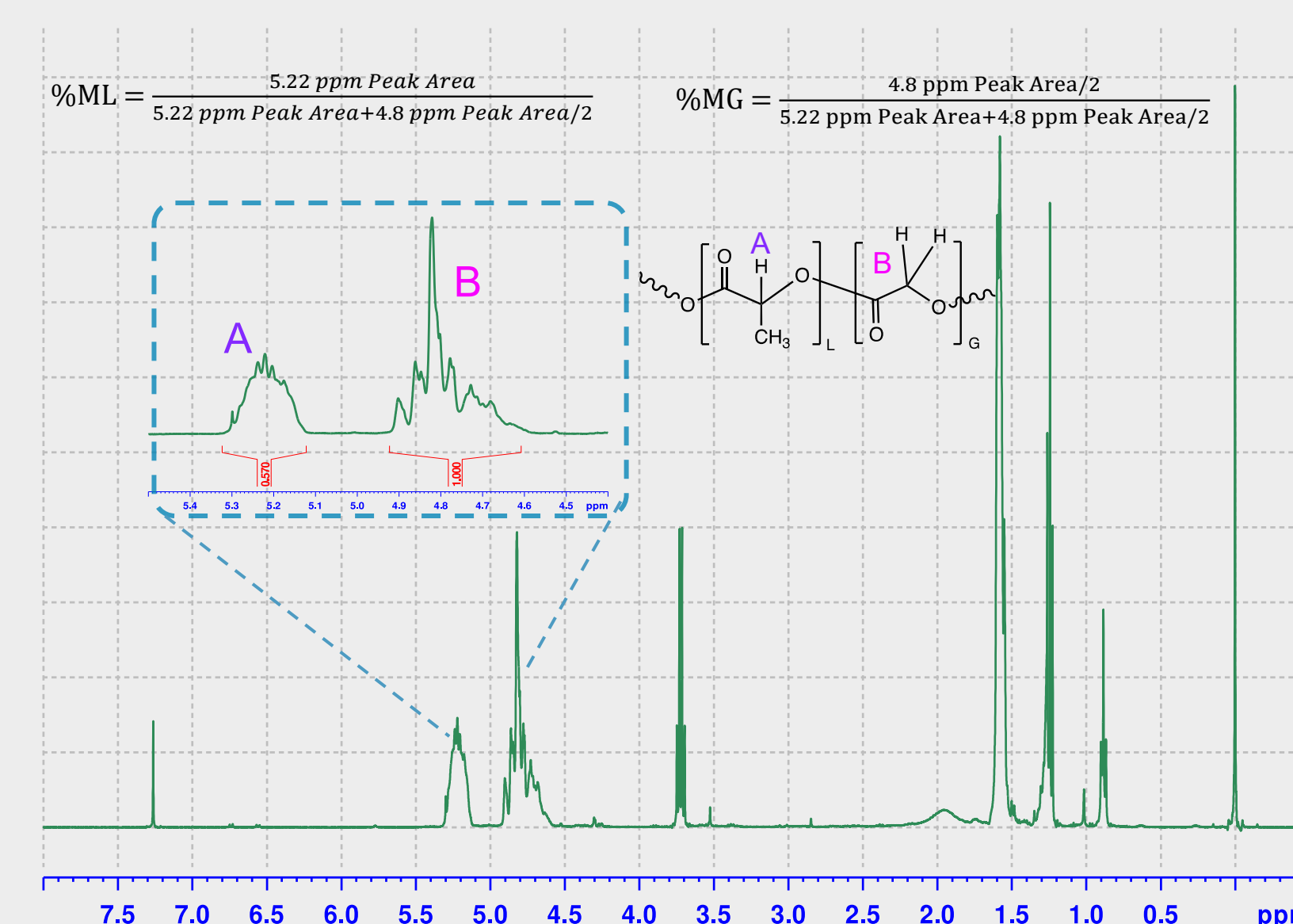


Figure 1. ¹H NMR spectra (CDCl₃, 400 MHz) of characteristic proton peaks of purified PLGA in Sublocade®. A and B corresponds to proton of methine in lactic mer units and methylene in glycolic mer units, respectively.

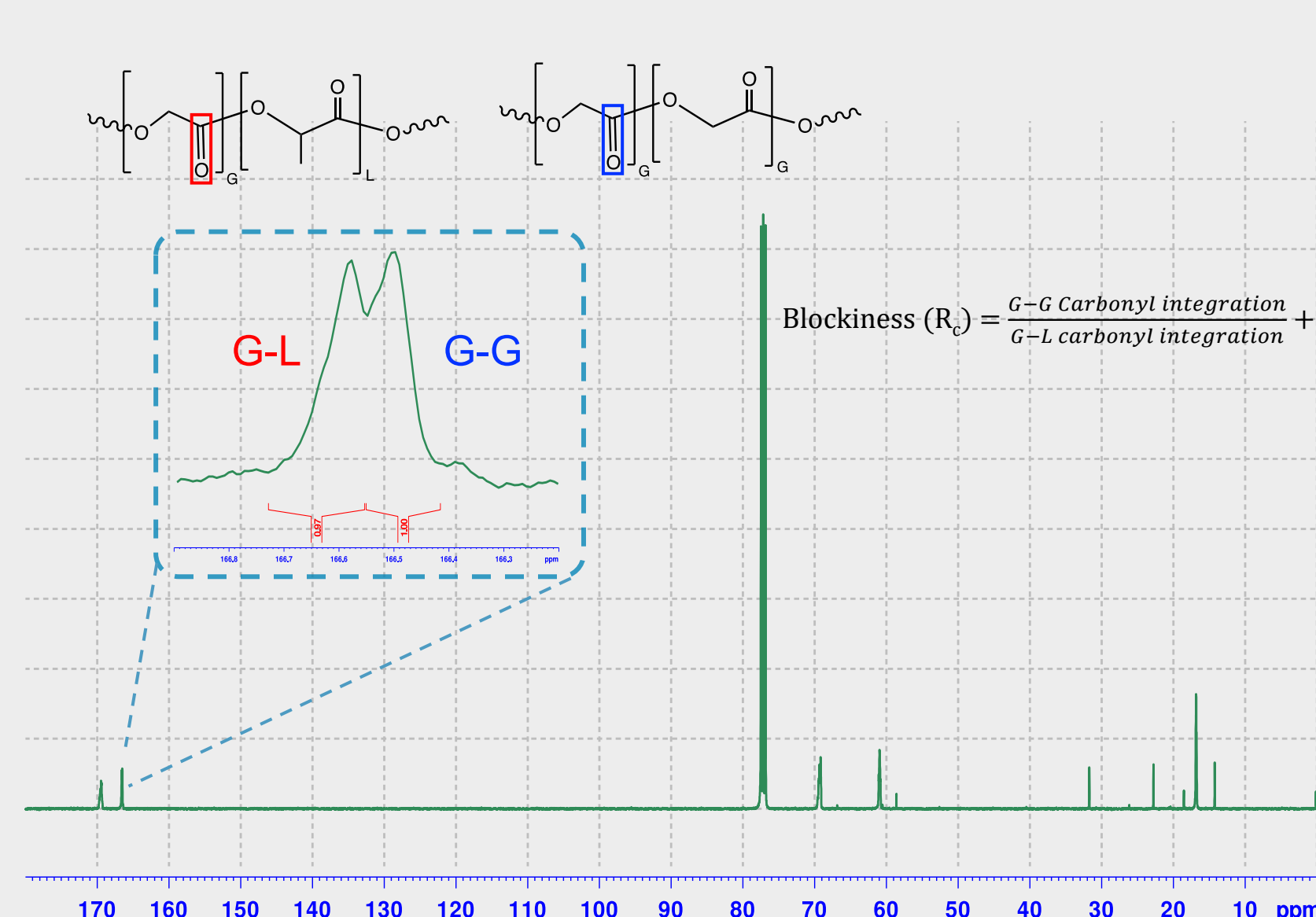


Figure 2. ¹³C NMR spectra (CDCl₃, 400 MHz) of carbonyl regions of glycolic mer units of purified PLGA in Sublocade®. A and B corresponds to proton of methine in lactic mer units and methylene in glycolic mer units, respectively.

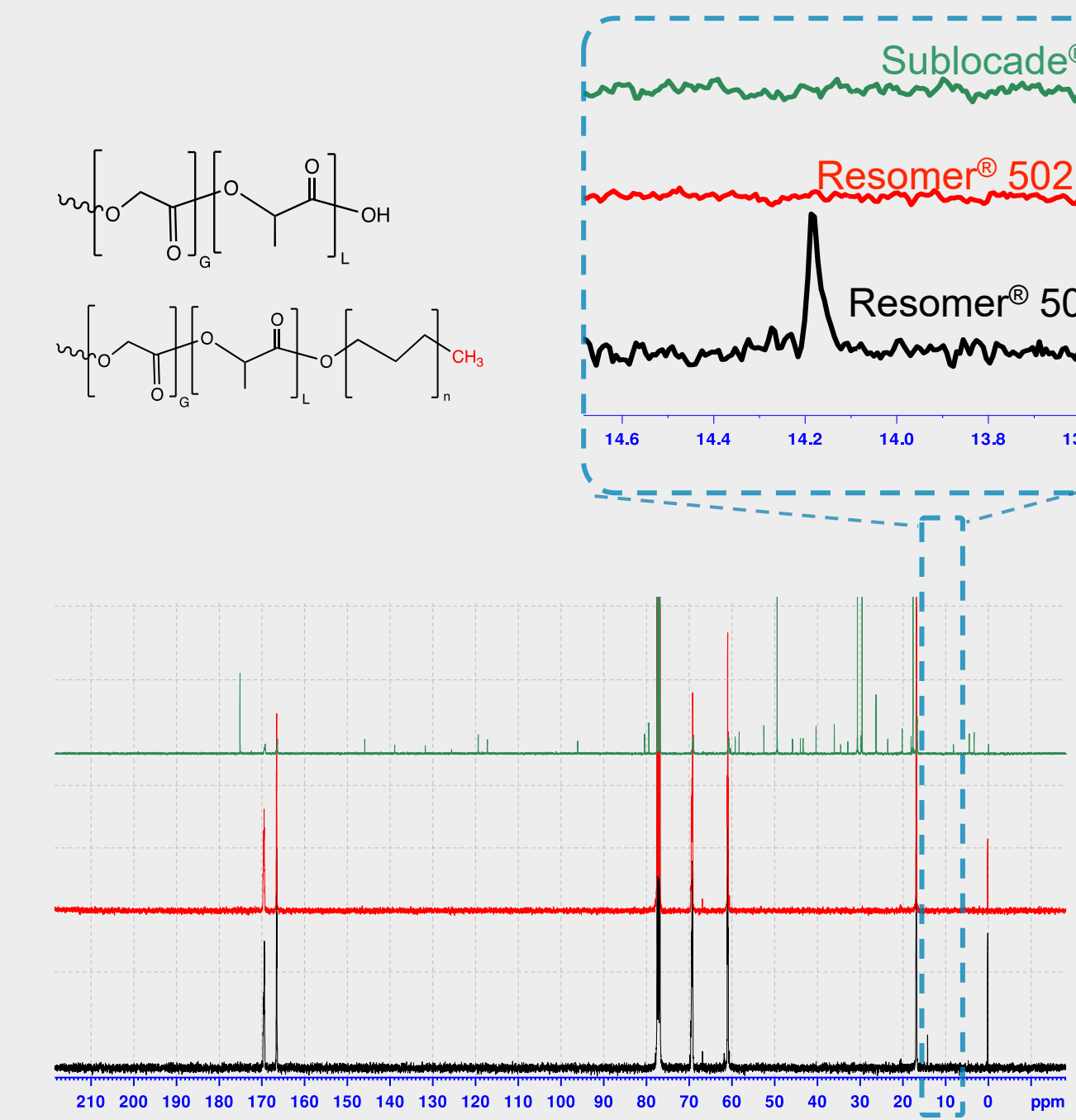


Figure 3. ¹³C NMR spectra (CDCl₃, 400 MHz) of PLGA's with acid/ester end group. The carbon peak at ~14 ppm represents the methyl group at the terminal ester bond.

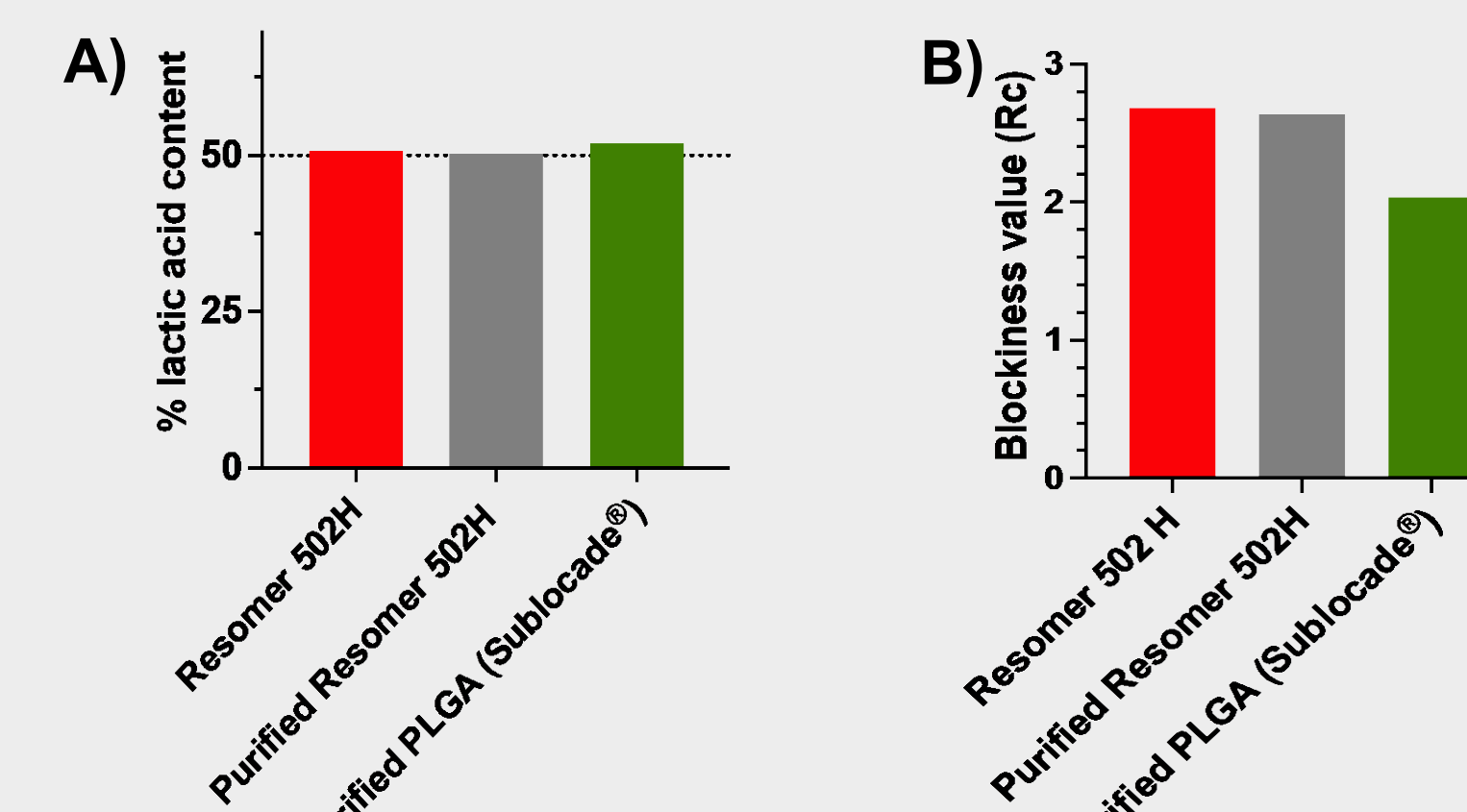


Figure 4. Characterization of PLGAs from different samples A) molar lactic acid content (%); B) Blockiness value

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

In Vitro Buprenorphine and NMP Release

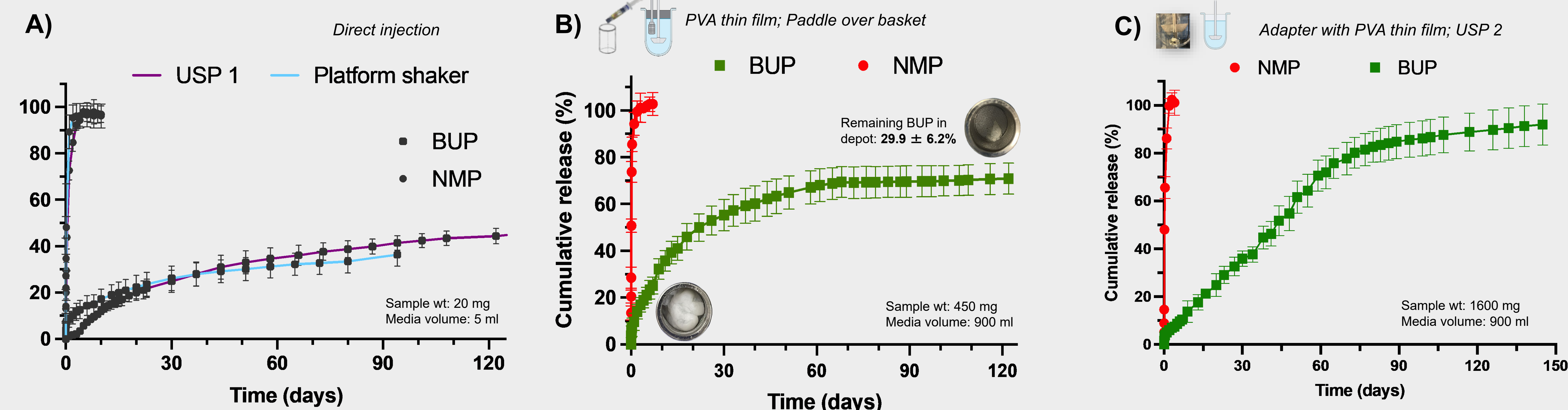
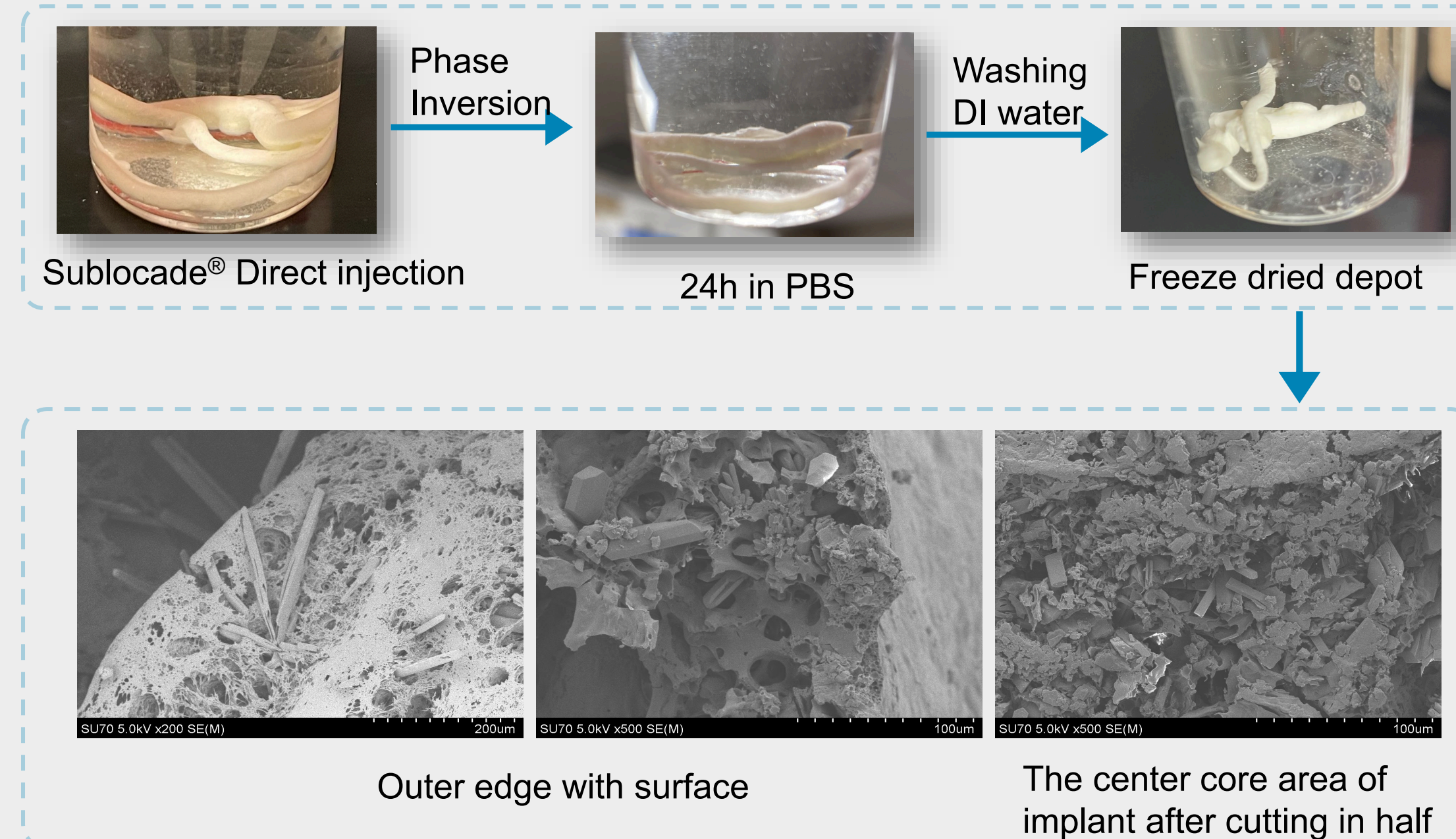


Figure 5. *In vitro* release of buprenorphine and NMP from Sublocade® with different combination of implant formation method and apparatus (mean ± SD, n=3)

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

Scanning Electron Microscopy of Sublocade® Depot



- ❑ BUP crystal formed with heterogenous 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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