# *In vitro* release testing system development for buprenorphine *in situ* forming implant

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CRS Leading Delivery Science and Technology

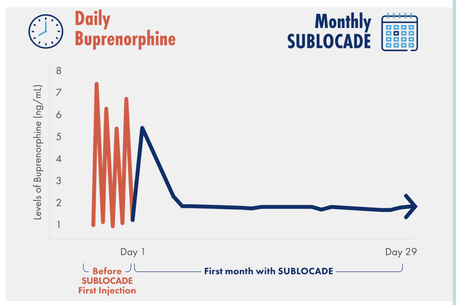
## BACKGROUND

**PLGA-based *in situ* forming implants (ISFM):**

- ❑ Complex parenteral delivery system
- ❑ Mixture of drug, poly lactic-co-glycolic acid (PLGA) and organic solvent
- ❑ Drug products : suspension or solution
- ❑ PLGA controls drug release rate

**Sublocade® buprenorphine (BUP) subcutaneous extended –release injection**

- ❑ Ready to use buprenorphine solution (300 mg BUP/1.5 mL) in prefilled syringe
- ❑ Monthly dosing




*In vitro release testing (IVRT) systems that are sensitive and can detect formulation differences are one of the major challenges in generic product development*

## OBJECTIVE

- ❑ Develop *in vitro* release testing system for the *in situ* forming implants.
- ❑ Evaluate similarity of Sublocade® and compositionally equivalent buprenorphine long acting injectable using established dissolution method

- Dissolution media
- Depot formation
- Apparatus USP II
- Reproducibility and discriminatory ability

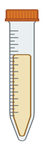
## METHODS

### Dissolution media selection

- ❑ Saturated solubility study: sink condition maintenance


Rotary shaker maintained at 37℃ for 72 h

Excess BUP in phosphate buffered saline (PBS) pH 7.4

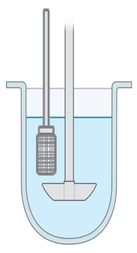


Excess BUP in PBS with surfactants (0.2% w/v)

### Depot formation and dissolution apparatus

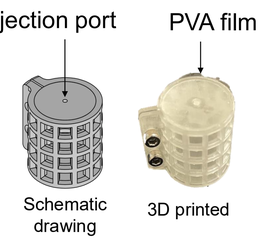
- ❑ Reproducible shape with high surface area
- ❑ USP apparatus II
- ❑ Media temperature: 37℃ ±0.5 ℃, 100 RPM

*Paddle over basket USP II*

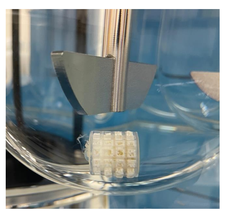


PVA film supports ISFM in basket kept at height while paddle maintains media agitation

*Adapter in USP II*



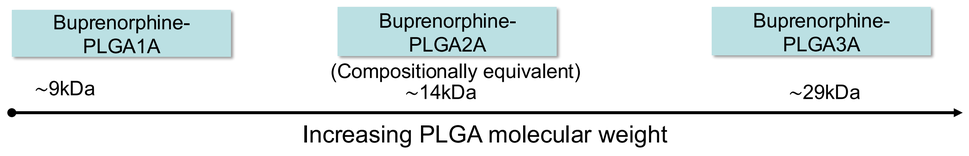

Cylindrical adapter with openings throughout circumference



Depot formation in USP II apparatus

### Reproducibility and discriminatory ability

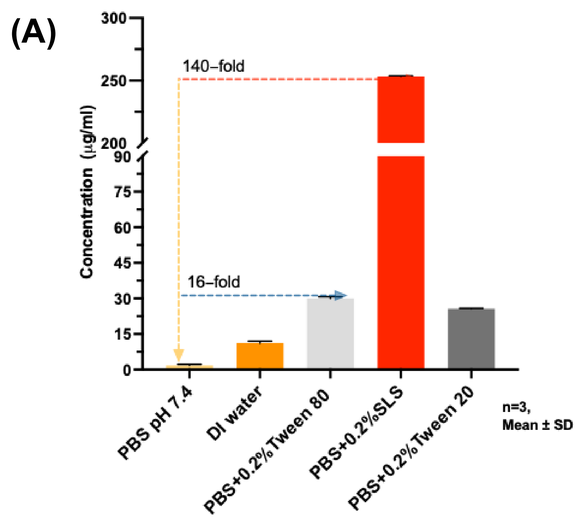
- ❑ ISFM formulations

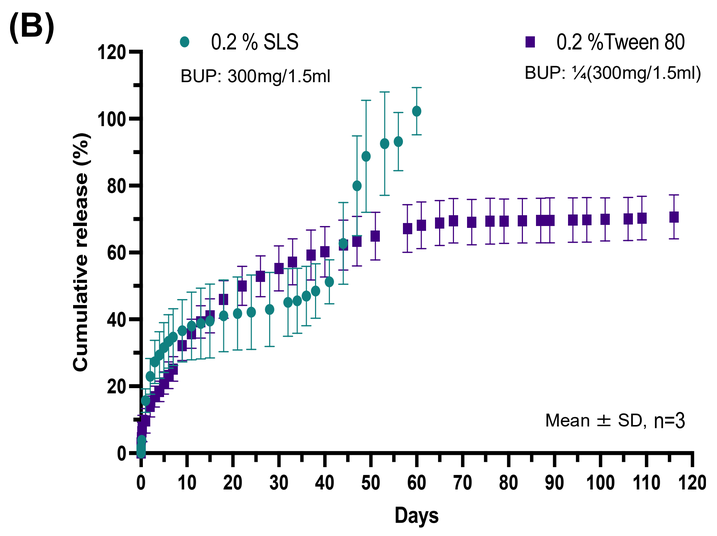



- ❑ Evaluating method reproducibility, discriminatory ability and drug release kinetics

## RESULTS

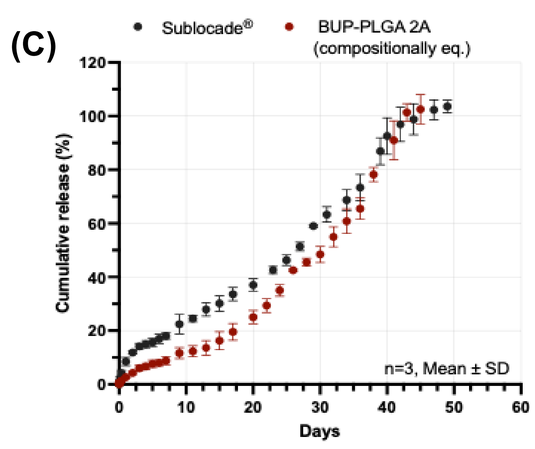
### Dissolution media selection




- ❑ In paddle over basket (**Fig B**), 0.2% SLS achieved over 85% BUP release in 1.5 months but showed higher variability than that in 0.2% Tween 80.

### Cylindrical adapter in USP II



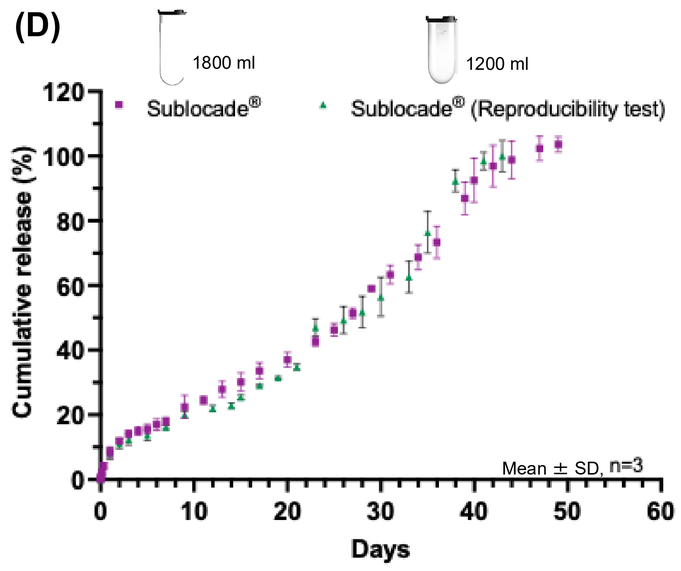

***Drug release kinetics***

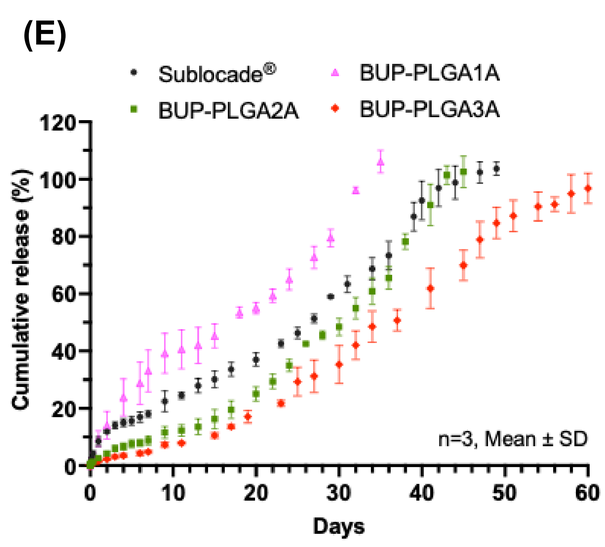
| | Initial release (First order) | | Diffusion facilitated (Zero order) | | Degradation facilitated (First order) | |
|---|---|---|---|---|---|---|
| | Sublocade | BUP-PLGA2A | Sublocade | BUP-PLGA2A | Sublocade | BUP-PLGA2A |
| Day | 0–2 | 0–3 | 3–34 | 4 – 34 | 36–44 | 36 – 41 |
| % | 11.9 | 5.9 | 68.7 | 60.8 | 98.8 | 91 |
| $R^2$ | 0.955 | 0.992 | 0.982 | 0.957 | 0.974 | 0.996 |
| Equation | Ln C = -0.03t + 1.99 | Ln C = -0.008t + 1.99 | Q= 1.73t +6.06 | Q = 1.78t + 5.47 | Ln C = -0.18t + 7.75 | Ln C = -0.12t + 5.78 |

where, C = unreleased fraction of drug (100-cumulative %drug release)
Q = cumulative % drug release; t = time

- ❑ Both Sublocade® and BUP-PLGA 2A (**Fig C**) showed a consistent triphasic release (%CV <10%): initial phase separation, diffusion-dominated, and final degradation-driven phases.

### Reproducibility and discriminatory ability assessment




| Formulation | Similarity factor ($f_2$) |
|---|---|
| BUP-PLGA1A vs BUP-PLGA2A | 31.4 |
| BUP-PLGA1A vs BUP-PLGA3A | 28.1 |
| BUP-PLGA1A vs Sublocade® | 41.5 |
| Sublocade® vs BUP-PLGA2A | 54.4 |
| Sublocade® vs BUP-PLGA3A | 40.3 |
| BUP-PLGA2A vs BUP-PLGA3A | 48.5 |

- ❑ In **Fig D**, reproducibility remained high across tests conducted at different times and with varying media volumes
- ❑ This IVRT method has ability to discriminate formulation change based on PLGA molecular weight (**Fig E**).

## CONCLUSIONS

- ❑ The developed cylindrical adapter in USP II ensures a reproducible depot shape. It has the potential to be used for various dissolution setups, such as USP IV 4, especially for a method that requires more than 1mL in situ forming formulation.
- ❑ The IVRT system has excellent reproducibility and discriminatory ability.
- ❑ This IVRT platform will be used to support the development of accelerated release testing and future *in vivo-in vitro* correlation studies.

## REFERENCES


- ❑ Kempe, S. & Mäder, K. In situ forming implants — an attractive formulation principle for parenteral depot formulations. J. Controlled Release 161,668–679 (2012).
- ❑ Wang, X., Wang, R., Roy, M., Kwok, O. & Burgess, D. J. Long-acting injectable in situ forming implants: Impact of polymer attributes and API. Int J Pharm 125080 (2024)
- ❑ Diaz, D. A. et al. Dissolution Similarity Requirements: How Similar or Dissimilar Are the Global Regulatory Expectations? AAPS J 18, 15–22 (2016)


## Acknowledgement

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