Design, Fabrication, And Evaluation Of A Small Volume Biorelevant Dissolution Apparatus For Extended-release Periodontal Microparticles

S. Patel[1], A. Greene[1], J. MacPherson[1], I. Basha[1], S. Desai[1], Y. Zou[2], C. Sfeir[1], S. Rothstein[3], S. Little[1], L. Rohan[1];
[1]University of Pittsburgh, Pittsburgh, PA, [2]FDA/CDER/ Office of Generic Drugs, Office of Res. and Standards, Silver Spring, MD, [3]Qrono Inc., Pittsburgh, PA

PURPOSE

- Dissolution testing can provide a sensitive measure to evaluate differences in product formulation and/or manufacturing as well as a quality control measure of batch-to-batch reproducibility.
- Currently, there are no biorelevant dissolution method available for microparticles used in periodontitis.
- Microparticles (Arestin®) containing minocycline hydrochloride are deposited as dry powder directly into the periodontal pocket.
- This pocket displays extremely low volume (0.5 µL) and fluid flow rates (0.3-0.5 µL/min), which give rise to dissolution environment and release conditions that are challenging to simulate in vitro.
- We developed a novel, more biorelevant, dissolution apparatus for long acting periodontal products which can discriminate between formulations.

METHODS

Microparticle Preparation: Polylactic acid-co-glycolic acid (PLGA) microparticles were prepared by emulsion evaporation method. Microparticles were assessed for drug content, surface morphology, and particle size. Initial screening of microparticle performance was conducted using a modified USP IV method.[1]

Biorelevant Dissolution Device

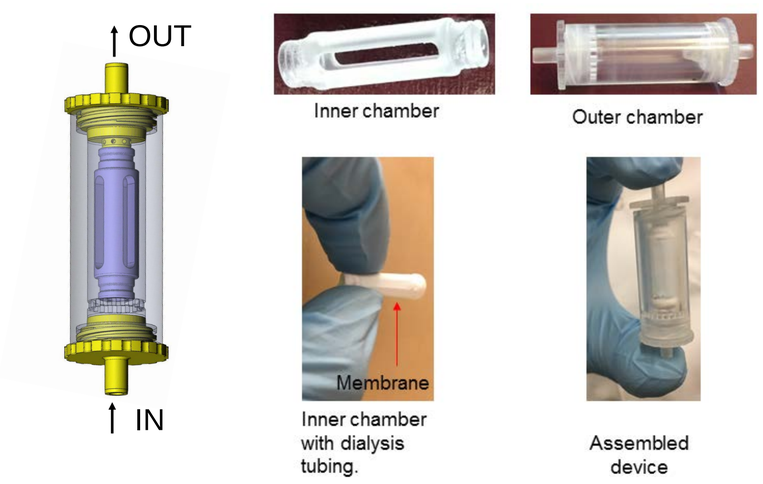


Figure 1. Design and assembly of the dissolution device. (Will be replaced with a comprehensive flow diagram)

Media: A simulated gingival crevicular fluid (GCF) was prepared which mimics pH, ionic content (sodium, potassium, calcium, and chloride)[2], and total protein content (0.054% w/v).

Device: The device (Figure 1) was fabricated using polycarbonate material.

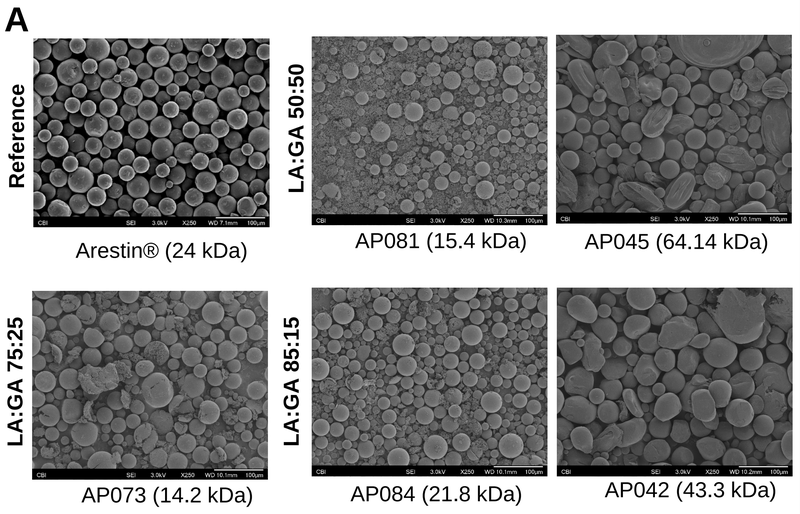
- Microparticles are dispersed in the inner dialysis chamber using 0.25 mL media.
- GCF simulant, continuously delivered through the device at 0.5 µL/min, was collected and analyzed for drug content using UPLC methods.

RESULTS

Table1. Characterization of microparticles with Q1/Q2 changes (L/G, molecular weight, drug loading)

Microparticle	LA:GA Ratio	Mwt of polymer (KDa)	Drug loading– mg/mg particles	Size (µm) - volume
AP042	85:15	43.3	0.155 ± 0.002	33.9 ± 11.9
AP084	85:15	21.8	0.099 ± 0.010	39.2 ± 11.3
AP073	75:25	14.2	0.1142 ± 0.0011	36.9 ± 12.8
AP045	50:50	64.14	0.0910 ± 0.0001	32.9 ± 10.1
AP081	50:50	15.4	0.2105 ± 0.0009	28.7 ± 9.6
Arestin®	50:50	24	0.25 (theoretical)	28.6±12.3

A



B

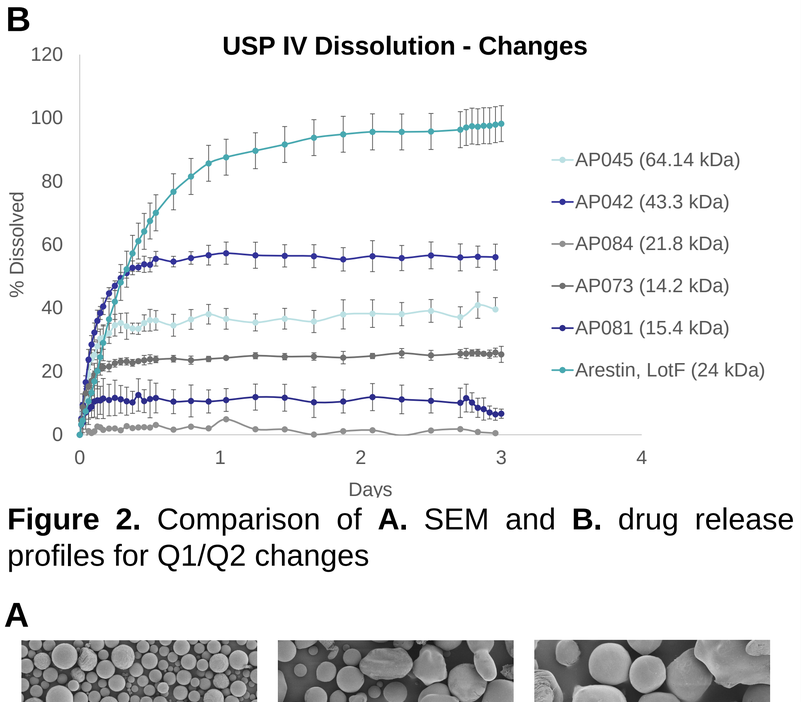
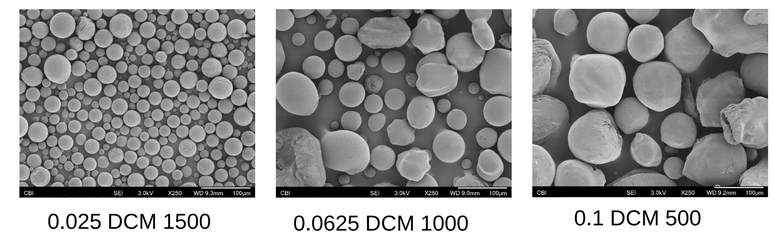


Figure 2. Comparison of **A.** SEM and **B.** drug release profiles for Q1/Q2 changes

A



B

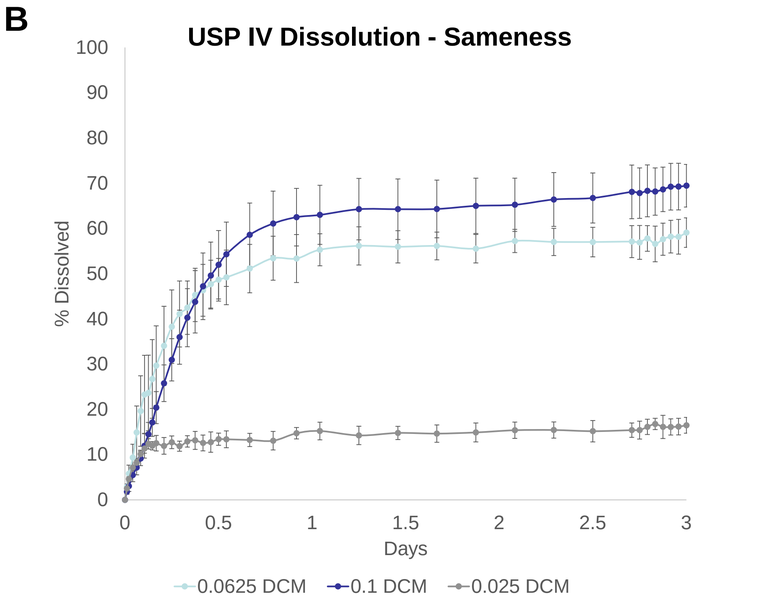


Figure 3. Comparison of **A.** SEM and **B.** drug release profiles for microparticles prepared with 24 kDa PLGA (50:50) at varying amounts of DCM and stir rate.

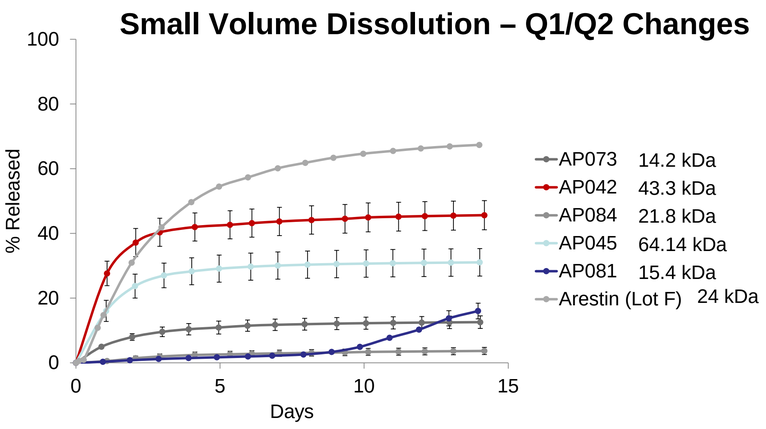


Figure 4. Comparator dissolution using small volume device.

RESULTS

$$\frac{\partial C_A}{\partial r}(R_P, t) = \frac{q}{A}$$ Rate of Drug Clearance *(q)* ∝ Flow rate (VF); Area to be Cleared *(A)* ∝ 1/(polymer Mw)

$$\frac{\partial C_A}{\partial r}(R_P - R_{occ}, t) \propto VF \cdot \exp(-kCw \cdot t)$$

Point where polymer impedes drug access to flowing media

System:	USP4	Small Vol.
VF =	10mL/min	0.5µL/min

Figure 5. Drug release kinetics from USP IV and small volume apparatus modeled taking into account flow rate, polymer molecular weight, particle physicochemical properties and pore formation.

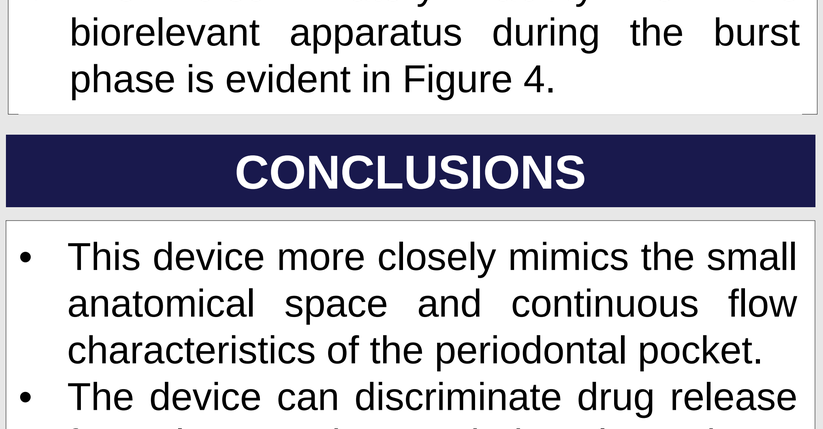


Figure 6. Simulated (Model-based) vs. actual release profile for Arestin® and AP045 using USP IV and small volume apparatus. Line represents simulated data and symbols represent actual data points.

- The release differences between comparators could be due to the differences in available number of end-groups for association with minocycline, size, and L/G ratio.
- The discriminatory ability of the biorelevant apparatus during the burst phase is evident in Figure 4.

CONCLUSIONS

- This device more closely mimics the small anatomical space and continuous flow characteristics of the periodontal pocket.
- The device can discriminate drug release from long acting periodontal products, especially during initial release phase.
- The continuous flow feature allows for assessment of hydrophobic and rapidly degrading drugs.
- Modeled release agrees well with actual release profiles.
- Future studies will compare dissolution results with pharmacokinetic data to develop in vitro-in vivo correlations.

REFERENCES / FUNDING/Disclaimer

1. Bharadwaj, U., Burgess, D.J. A novel USP apparatus 4 based release testing method for dispersed systems. *Int J Pharm.* 388: 287-294, 2010.
2. Bang, J., Cimasoni, G., Rosenbusch, C., and Duckert, A.: Sodium, potassium and calcium contents of crevicular exudate: their relations to gingivitis and periodontitis. *J Periodontol.* 49: 770-774, 1973.

- This work is funded by U.S. Food and Drug Administration (Grant Award 1U01FD005447-01).
- Disclaimer: This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.