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Low Volume Dissolution Devices for Long Acting Periodontal Drug Products

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PURPOSE

- Long acting periodontal drug products are complex dosage forms, and a compendial *in vitro* drug release assay for these products is currently not available.
- *In vitro* dissolution testing is an important tool to ensure product quality as well as to predict the *in vivo* performance of drug delivery systems.
- The large dissolution volume of conventional USP dissolution apparatuses (USP711, 2009), which provides sink conditions to simulate gastrointestinal absorption, may not accurately model the small periodontal pocket (~7 µL) where long-acting periodontal drug products are used.
- The objectives of this study were to (a) simulate long-acting periodontal product dissolution in the periodontal pocket using a computer model, (b) develop a flow-through dissolution apparatus of small dimensions for the testing of periodontal drug product, and (c) evaluate the dissolution system using PerioChip.

METHODS

- Periodontitis destroys the attachment apparatus of teeth resulting in a periodontal pocket (Fig. 1a).
- PerioChip (2.5 mg chlorhexidine gluconate, equivalent to approximately 1.4 mg chlorhexidine, CHX; Dexcel Pharma Technologies, Israel) was selected as the model long-acting periodontal product. The dimensions of PerioChip are approximately 3.5 mm x 4.5 mm x 0.2 mm.
- PerioChip is placed into a periodontal pocket (Fig. 1b), the swelling of the chip on contact with moisture retains it in place, and drug release is controlled by the biodegradable matrix.

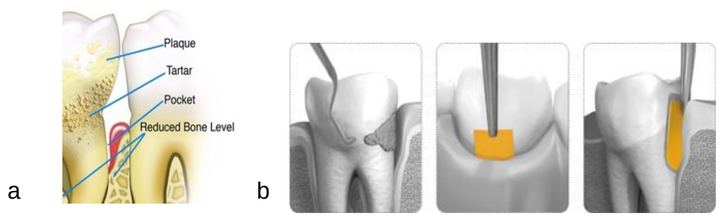

Fig. 1: (a) Schematic diagram of periodontal pocket and (b) administration of PerioChip (images obtained from Dexcel Pharma).

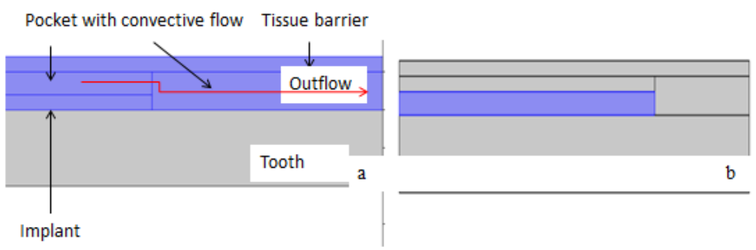

Fig. 2: Schematic diagram of 2D dissolution model of (a) original and (b) swollen implant.

METHODS

- Model simulation of diffusion/convection transport during drug dissolution in the dissolution chamber (Fig. 2) was carried out using COMSOL Multiphysics® Modeling Software to study drug release and drug concentration profiles in the dissolution chamber.
- Drug release and swelling of PerioChip were investigated under sink conditions with stirring in 10 mL dissolution medium in 20-mL vials, similar to the USP dissolution apparatus conditions (bulk solution condition). The experiments were performed in four different dissolution media: PBS at pH 7.4, 8.0, and 8.7, and 0.15 M NaCl at pH 8.0.
- Small flow-through dissolution chambers of different volumes (e.g., 4 mm x 5 mm x 3 mm = 0.06 mL and 8 mm x 10 mm x 3 mm = 0.24 mL chambers) were constructed stereolithographically using rapid prototyping for the PerioChip dissolution study.
- Drug release from PerioChip in the 3D printed prototyped flow-through dissolution chambers was compared to that under the bulk solution condition.
- Drug release from PerioChip in the flow-through dissolution chambers was determined at 37ºC (Fig. 3). Flow rates of 0.63, 1.5, 3, 10, and 20 µL/min were examined. Simulated saliva at pH 8.0 with or without 0.3% trypsin (porcine pancreas:1,000-2,000 BAEE units/mg) was the dissolution medium.

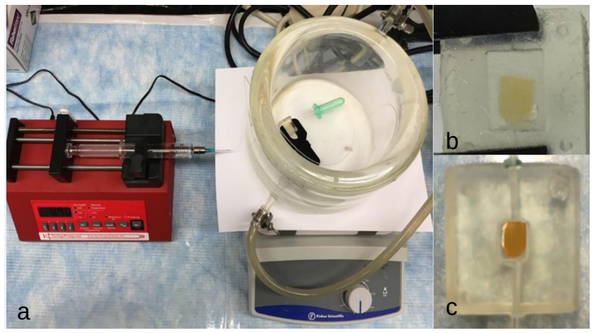

Fig. 3: (a) Experimental setup of CHX dissolution from PerioChip using the 3D printed dissolution apparatus; (b) PerioChip in the 0.24-mL dissolution chamber and (c) 0.06-mL dissolution chamber.

RESULTS

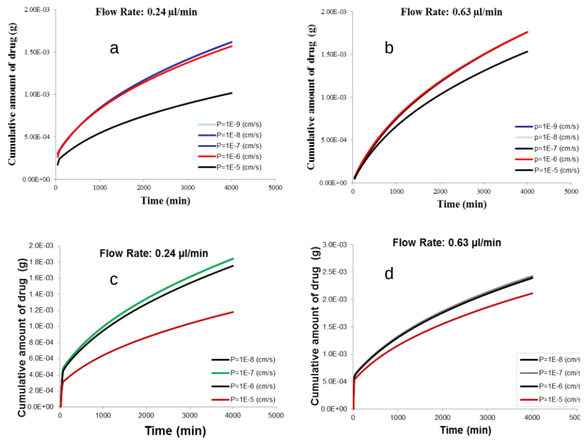

Fig. 4: Cumulative amount of drug released at the outflow under various tissue permeability coefficient conditions in the model simulation study. Original PerioChip at flow rate (a) 0.24 and (b) 0.63 µl/min; swollen PerioChip at flow rate (c) 0.24 and (d) 0.63 µl/min.

RESULTS

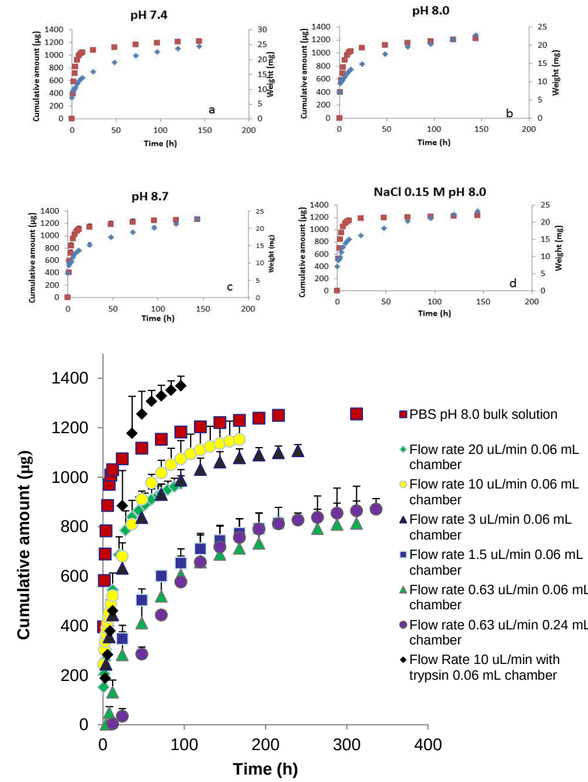

Fig. 5: Comparison of drug release and swelling profiles of PerioChip in dissolution experiments under the bulk solution conditions. Drug release (square) and swelling (diamond) profiles in (a) PBS, pH 7.4, (b) PBS, pH 8.0, (c) PBS, pH 8.7, and (d) 0.15 M NaCl, pH 8.0. (n=3)

Fig. 6: Comparison of drug release under bulk solution and flow-through chamber conditions: 10 mL PBS at pH 8.0 in a vial (red square); simulated saliva in 0.06 mL chamber at flow rate 20 (diamond), 10 (yellow circle), 3 (black triangle), 1.5 (blue square), and 0.63 µL/min (green triangle), and in 0.24 mL chamber at flow rate 0.63 µL/min (purple circle); and simulated saliva containing 0.3% trypsin in 0.06 mL chamber at flow rate 10 µL/min (black diamond). ($n \geq 3$)

CONCLUSIONS

1. In the model simulation study, the results show that drug permeation to the surrounding tissues should not affect drug release from the implant for most drugs (drug tissue permeabilities $<10^{-5}$ cm/s). This suggests that a flow-through dissolution apparatus with impermeable boundary conditions and an inflow/outflow can mimic drug dissolution in the periodontal pocket.
2. In the bulk solution release experiment, more than 60% CHX was released from PerioChip in the first 12 h and it reached a plateau at 24 h. No significant difference was observed between the drug release profiles of PerioChip under the pH conditions studied. No direct correlation was found between implant swelling and drug release from the implant.
3. CHX release from PerioChip in the flow-through chambers using simulated saliva as dissolution medium was significantly slower than those under the bulk solution conditions. The incorporation of an enzyme in the dissolution medium (0.3% trypsin) enhanced the rate of drug release.

ACKNOWLEDGEMENTS

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