Bioequivalence Testing of Complex Periodontal Products: Drug Release, Matrix Degradation, and Pharmacodynamics in a Canine Periodontal Disease Model

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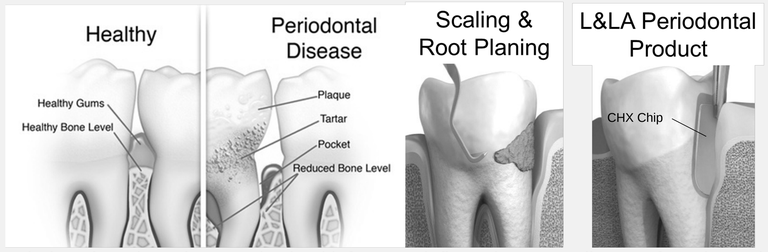
Complex Long-Acting Periodontal Products

Demonstrating BE of locally and long acting (L&LA) complex drug products is a regulatory challenge as traditional pharmacokinetic (PK) and in vitro release methods are often not suitable. Alternative PK or pharmacodynamic (PD) endpoints as well as in vitro release methods are needed. This study examined critical product attributes and potential PD BE endpoints of a L&LA chlorhexidine (CHX) gelatin chip indicated, as part of a periodontal maintenance program, to reduce periodontal pocket depth (PPD) in patients with periodontal disease.

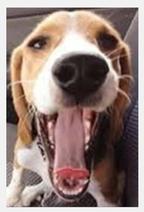


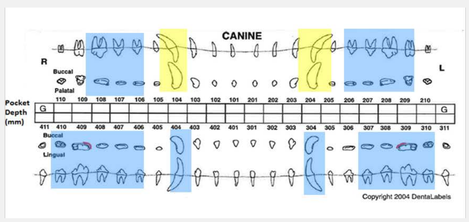
Periodontal pockets (>5 mm in depth) form as inflamed gums pull away from bacterial infected sites, leading to gum, tissue and bone deterioration. Treatment includes mechanical removal of etiologic agents via scaling and root planing. Implanted L&LA products slowly release bacteriostatic and/or antimicrobial agents to treat against remaining bacteria and facilitate reduction in inflammation and pocket size.

CHX gelatin chips are composed of 2.5 mg CHX di-D-gluconate, a broad spectrum anti-microbial agent, formulated in 4.4 mg of biodegradable hydrolyzed gelatin cross-linked with glutaraldehyde. Reported CHX drug release is local (not detectable in plasma or urine) over 7-10 days, but had high inter-subject variability and no information on matrix degradation kinetics.

Canine Study Design

To measure a relative PK profile, feasibility of a PD endpoint study, and the in vivo biodegradation rate, CHX chips were implanted in the periodontal pockets of 30 dogs with periodontal disease. The study consisted of 2 Arms; each Arm was composed of 6 time-groups that contained 5 dogs, each with 3 implanted chips. In general dogs and pockets from Arm 1 were used in Arm 2 if they still met all of the inclusion criteria: a minimum of 3 eligible naturally occurring periodontal pocket sites with a minimum depth of 5 mm with at least one eligible pocket in the upper canine (104 or 204) as an inter-subject control. PPD ranged from 5 – 12 mm.





"Control" pocket

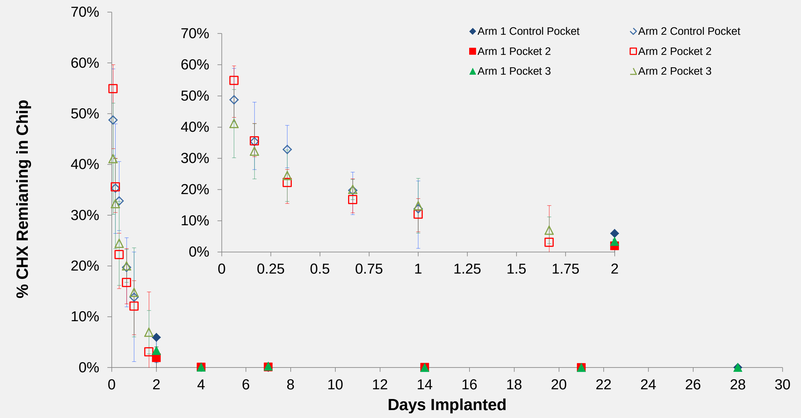
Eligible pockets

Each group of dogs was assigned an implantation time period between 1.5 hrs and 28 days. Dog, tooth location, and PPD were recorded prior to implantation and then implanted time, CHX remaining in chip, chip mass, chip degradation score (1-3), and PPD were recorded when chips were removed. All chips implanted within the group were implanted and removed at the same time.

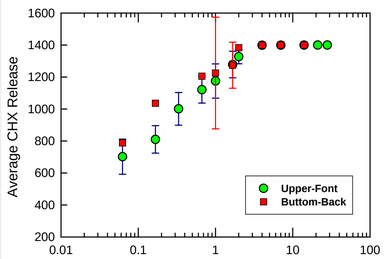
Dog Group	Arm 1	Arm 2
	Days	Hours
1	2	1.5
2	4	4
3	7	8
4	14	16
5	21	24
6	28	40

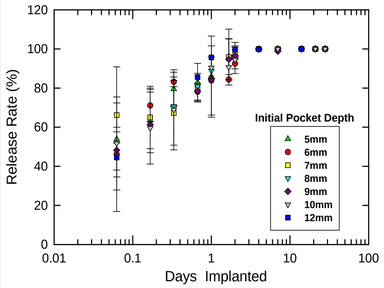
Canine Study Results: CHX Release, Chip Degradation and PPD change

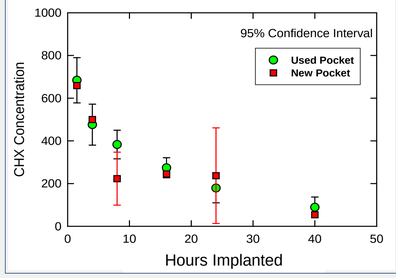
CHX Release: Effect of implantation time, initial PPD and pocket location
CHX rapidly released from implanted chips with ≤50% CHX remaining in chips implanted for 1.5 hrs and ≤10% CHX remaining after 40 hrs implantation. Higher inter-subject variability (>7.5%) was observed in groups implanted up to 24 hrs.



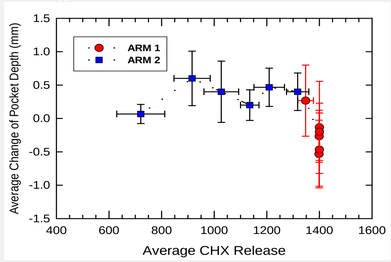
Pocket location, initial PPD, and pocket reuse on CHX released. Aside from implantation time only pocket location had an impact on CHX release. Bottom back teeth had faster release.



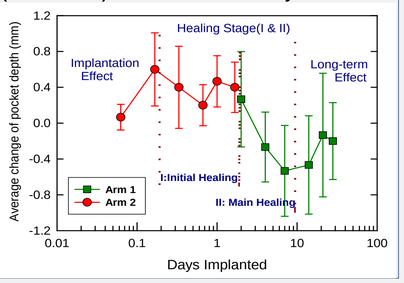




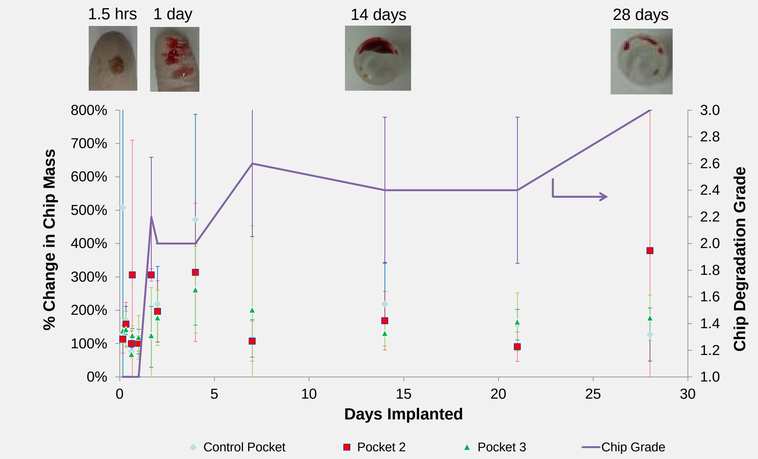
Change in PPD with amount CHX release, a potential PD endpoint. Significant relationship in PPD change and CHX released, after accounting for time effect ($p = 0.0246$). PPD was found to decrease, a sign of healing and potential PD endpoint, when > 1350 mcg CHX (96%) had released. Individual. PPD change varied from -3 mm to 2 mm.

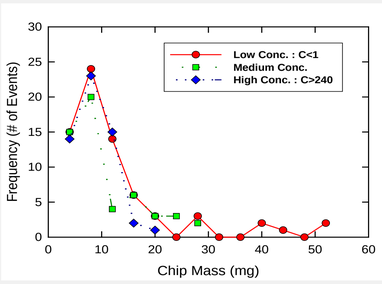


Change in PPD was time dependent PDD improved (< 0) after 2 days implantation. Earlier times showed worsening > 0 due to scaling and implant effects. Greatest improvement (-0.55 mm) was seen at 7 days.



Chip Degradation: Effect of implantation time, pocket location and reuse. CHX chips rapidly swell and become soft upon implantation (Grade 1). Only partial chips (Grade 2) were removable beyond 16 hrs implantation and only biomass/ tissue with no recognizable chip (Grade 3) was removed beyond 7 days implantation, much faster than predicted. Dried mass of removed material was always > 90%. Pocket location and reuse had no effect on chip mass.





No relationship was found between remaining chip mass and remaining CHX concentration. Data was classified into three groups of approximately equal sample size, corresponding to low ([CHX]<1), medium (1≤[CHX]<240), and high (240 ≤ [CHX]<1400) CHX concentration. All showed similar profiles however, longer incubation time which correspond to [CHX]<1 gives rise to a significant increase in chip mass

Conclusions

L&LA complex products present a unique BE regulatory challenge for generic approval. For periodontal CHX gelatin chips:

- Drug release and matrix degradation occurred quicker (<2 days) than expected 7-10 days.
- Chip degradation and mass is a poor indicator of in vivo product performance
- A PD approach measuring PPD change 4-14 days after implantation has potential.
- Additional studies on methods and accuracy of periodontal pocket PK measurements and in vitro release test are needed to assess if a PK BE approach is feasible and that a release method can discriminate formulation and manufacturing effects..

Disclaimer

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