Sustained Release Dexamethasone Implants for In Vitro – In Vivo Correlations

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Abstract

Purpose: To prepare qualitatively (Q1) and quantitatively (Q2) identical dexamethasone-poly(lactic-co-glycolic acid) (PLGA) implants with variable diameters and mechanical properties in order to identify implants suitable for developing in vitro-in vivo correlations. **Methods:** Powders of dexamethasone and PLGA-503H were mixed at a ratio of 1:4 and implants with different diameters were manufactured with Teflon molds and warm compression. The blade cutting mode of the Texture Analyzer was used to measure the firmness and toughness of implants. Dexamethasone content in implants was quantified using a QTRAP 4500 LC-MS instrument. **Results:** Warm compression followed by cooling of the molds allowed easy removal of the implants from the mold using a stylus. Dexamethasone loaded implants of diameters about 1 and 0.8 mm with a drug content of about 20 and 17%, respectively, were made. Implants with the larger diameter exhibited higher hardness (1074.6 vs 344.1 g) and toughness (108.7 vs 31.4 g.sec). **Conclusions:** Using Teflon molds and warm compression, dexamethasone-PLGA implants of various diameters could be prepared. Future studies will involve preparation of implants with low, medium, and high in vitro release rates for in vivo studies and the development of in vitro-in vivo correlations.

Introduction

- Methods for bioequivalence are lacking for generic ophthalmic implant drug products.
- Our long term goal is to understand the relationship between in vitro and in vivo drug release from ophthalmic intravitreal implants and develop in vitro-in vivo correlations (IVIVC).
- The objective of this study was to develop implants of various properties and release rates. An additional objective was to assess the stability of dexamethasone during the release study.

Methods

Implant manufacturing: Poly(lactic-co-glycolic acid) Q1/Q2 implants loaded with 20% w/w dexamethasone were prepared using melt compression and custom made Teflon molds. Implant diameter (1 vs 0.8 mm) or polymer (using 0.5 mm implants) was varied to identify implants with varying release rates.

Implant characterization: Implants of 1 and 0.8 mm diameter were characterized for mechanical properties using Texture Analyzer. Implants of 0.5 mm diameter were analyzed for drug release.

Dexamethasone quantification and stability: Dexamethasone was quantified using LC-MS analysis and stability was assessed in PBS pH 7.4 at 37°C.

Results

Table 1. Implant Weight/Length, Drug Loading, Firmness, and Toughness for 1 and 0.8 mm Dexamethasone-PLGA Implants.

Diameter (mm)	1	0.8
Weight/length (mg/mm)	1.07 ± 0.05 (n = 5)	0.91 ± 0.08 (n = 5)
Dexamethasone (%w/w)	20.27 ± 0.55 (n =3)	17.00 ± 0.56 (n = 3)
Firmness (g)	1075 ± 225 (n = 3)	344 ± 78 (n = 2)
Toughness (g.sec)	109 ± 20 (n = 2)	31.4 ± 10.6 (n = 2)

Results

Figure 1. Dexamethasone Stability *In Vitro* (PBS, pH 7.4, 37°C)

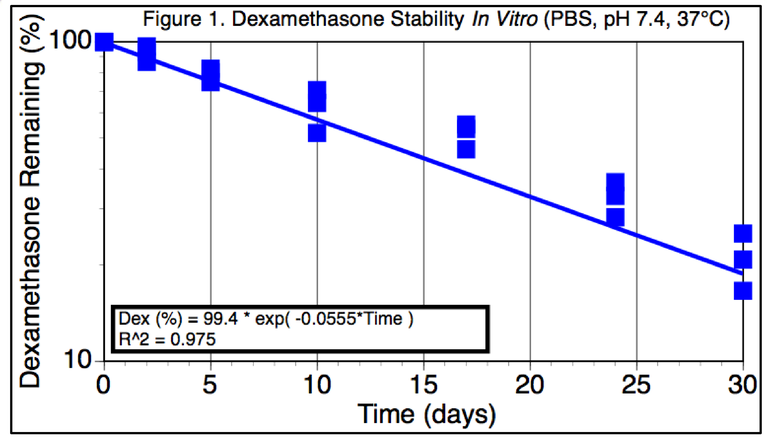
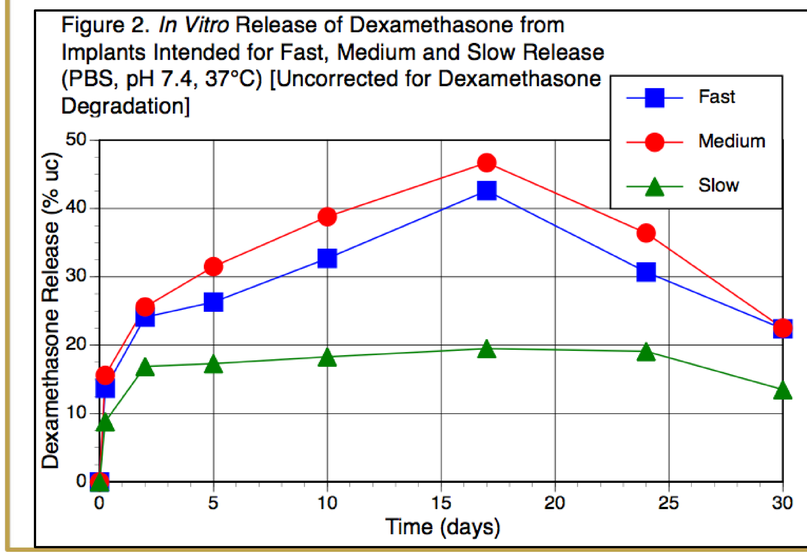


Figure 2. *In Vitro* Release of Dexamethasone from Implants Intended for Fast, Medium and Slow Release (PBS, pH 7.4, 37°C) [Uncorrected for Dexamethasone Degradation]



Conclusion

- Dexamethasone-PLGA implants with varying mechanical properties can be prepared using melt compression.
- Q1/Q2 dexamethasone-PLGA implants with varying release rates can be prepared using melt compression.
- Dexamethasone degrades during in vitro release in PBS at physiological temperature.

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