T1330-09-49

In-Vivo and Biopredictive In-Vitro Dissolution Testing of Dexamethasone Intravitreal Implants in Rabbits

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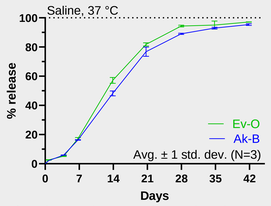
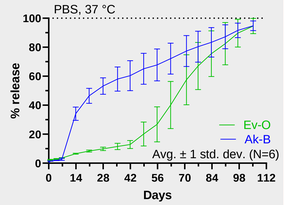
PURPOSE

- Previously, we reverse-engineered the OZURDEX® dexamethasone intravitreal implant and tested the effects of formulation changes on in-vitro release.[1]
- Two of these OZURDEX®-like formulations had different in-vitro release depending on the test medium (see right).
- This study evaluated the biorelevance and biopredictiveness of these two in-vitro methods.



In-vitro release of two implant formulations in unbuffered saline.



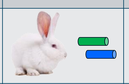
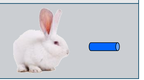
In-vitro release of two implant formulations in PBS.

EXPERIMENTS

OBJECTIVES

Implant formulation "Ev-O"

Implant formulation "Ak-B"

	Dissolution		Buffering capacity	Degradation of PLGA matrix (PLGA: poly(lactic-co-glycolic acid))	
	In vitro	*In vivo*	*Ex vivo*	*In vitro*	*In vivo*
1. *Evaluate biopredictiveness of 2 in-vitro release methods.*	PBS, Saline				
2. *Investigate physiological and physicochemical processes of in-vivo release.*				PBS, Saline	

METHODS

In-Vitro Release Testing

- In-vitro drug release of both formulations was measured in two media: unbuffered isotonic saline and phosphate-buffered saline (PBS), pH 7.4, 12 mM. Drug release was quantified by high pressure liquid chromatography (HPLC).
- In-vitro degradation of the PLGA matrix was measured with the Ev-O formulation in both media. PLGA degradation was quantified by gel permeation chromatography (GPC).

Ex-vivo Testing

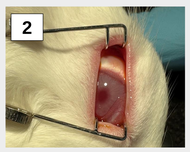
- Rabbit vitreous fluid was collected by dissecting eyes obtained from a supplier.
- Buffering capacity of both in-vitro media and rabbit vitreous were measured by acid titration at 37 °C.

In-Vivo Release Testing

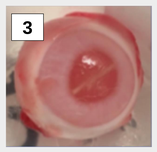
- New Zealand white rabbits were the chosen in-vivo model.

1. Implants were loaded into used OZURDEX® injectors obtained from an ophthalmologist's clinic and sterilized.
2. The two implant formulations were injected into contralateral eyes of 36 rabbits.
3. In-vivo drug release was determined by sacrificing rabbits at six timepoints after injection, recovering the remaining implant by dissection, and assaying drug content by HPLC.
4. Drug and degradant concentrations in the vitreous and aqueous were determined by LC/MS-MS.

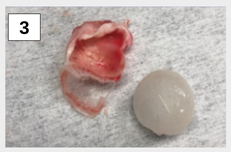
OZURDEX® injectors.



Anesthetized rabbit.

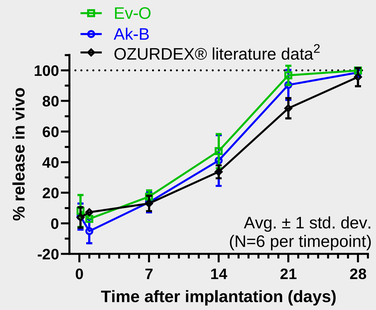


Recovered globe.



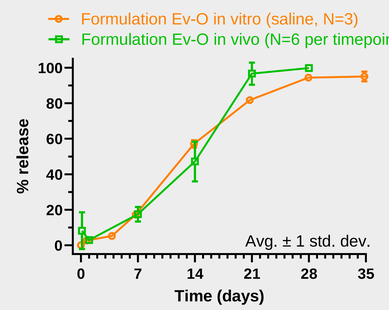
Implant in frozen vitreous.

RESULTS



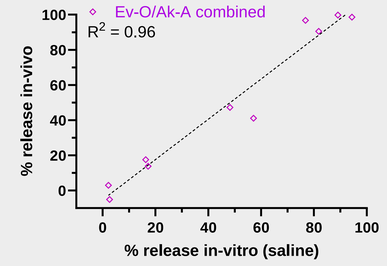
In-vivo drug release in rabbit vitreous of two "generic" formulations and OZURDEX®.

- Our formulations had similar drug release profiles with each other and published OZURDEX® rabbit data.[2]
- F2 similarity factors: Ev-O/Ak-B = 66; Ev-O/OZURDEX® = 48.



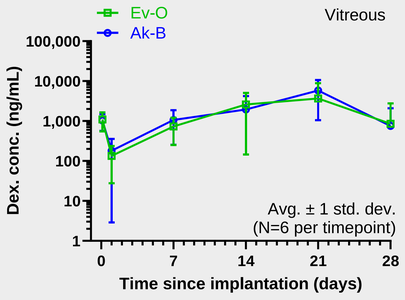
Comparison of rabbit in-vivo release and saline in-vitro release for the Ev-O formulation.

- In-vivo release was highly similar to saline in-vitro release.



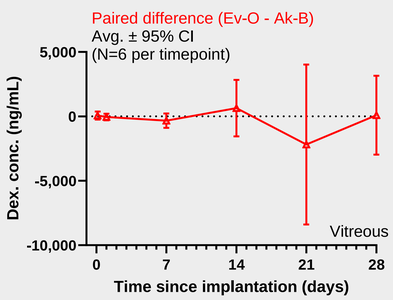
IVIVC chart using saline in-vitro release data of both formulations.

- The saline in-vitro method provided a good correlation with in-vivo data.



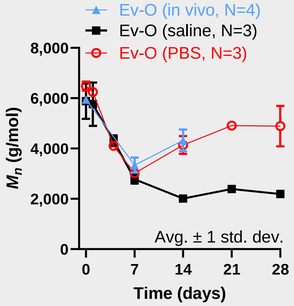
In-vivo drug concentrations in the rabbit vitreous.

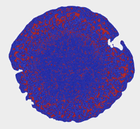
- Vitreous drug concentrations from the two formulations were indistinguishable.
- Aqueous drug concentrations and degradant concentrations in both compartments were also very similar (data not shown).



Paired analysis of vitreous drug concentrations.

- This analysis is necessarily more precise than the pooled analysis shown to the left.
- These 95% intervals quantify the performance difference of the two formulations.





MicroCT cross-section of Ev-O implant (saline, day 14) showing interconnected porous network.

PLGA matrix degradation in vitro and in vivo.

- A high-MW skin layer survives in PBS and in vivo due to buffering at the surface of the implant.
- The implant core nonetheless degrades rapidly in vivo. This may be due to limited diffusion of in-vivo buffering agents into the implant core.

CONCLUSIONS

1. The rabbit vitreous is buffered. The PBS in-vitro method is more biorelevant than the saline-based method in this respect.
2. However, the saline method was more biopredictive than the PBS method for the two OZURDEX®-like implant formulations we tested in the rabbit vitreous.
3. Neither in-vitro method perfectly simulated the in-vivo release mechanism.
4. The saline method could be helpful for evaluating the bioequivalence of OZURDEX®-like formulations in instances where this rabbit model is sufficiently representative of the human eye.

FUNDING AND REFERENCES

This work was supported by the Broad Agency Announcement (BAA) Contract # 75F40120C00198 from the U.S. Food and Drug Administration (FDA). The content reflects the views of the authors and should not be construed to present the FDA's views or policies.

(1) Costello, M. A., et. al. Role of PLGA Variability in Controlled Drug Release from Dexamethasone Intravitreal Implants. Mol. Pharmaceutics, 2023, 20(12), 6330-6344.

(2) Bhagat, R., et. al. Comparison of the release profile and pharmacokinetics of intact and fragmented dexamethasone intravitreal implants in rabbit eyes. J. Ocul. Pharmacol. Ther. 2014; 30(10):854-858.