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Preclinical Evaluation of Brinzolamide Ophthalmic Suspensions with Variations in Critical Quality Attributes and Considerations for Pharmacokinetic/Pharmacodynamic Study Designs

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PURPOSE

Brinzolamide ophthalmic suspensions are designed for treating elevated intraocular pressure (IOP), a key factor contributing to optic nerve damage and glaucomatous visual field loss (Fig. 1). Elevated IOP primarily results from disruptions in aqueous humor outflow within the eye.

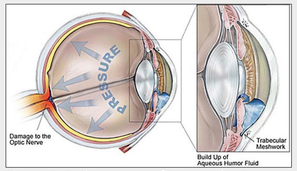


Figure 1. Pathogenesis of Intraocular Pressure.
Adapted from https://www.brightfocus.org/glaucoma/

Upon ocular absorption, brinzolamide exerts its effect at the iris-ciliary body (ICB) by reducing aqueous (AH) humor secretion, likely by inhibiting bicarbonate ion formation and fluid flow. This mechanism leads to a reduction in IOP.

To explore the impact of critical quality attributes (CQAs) that can potentially impact ocular drug absorption on the pharmacokinetic and pharmacodynamic (PK/PD) performance of topically-administered brinzolamide ophthalmic suspensions, a study using a rabbit model was conducted, investigating the influence of variations in viscosity and particle size distribution (PSD) on the PK/PD profile of the drug.

METHODS

Test Articles

Reference Listed Drug (RLD), AZOPT (brinzolamide ophthalmic suspension 1%, NDA 020816), and five test formulations (BRZ_001 to _005), prepared with variations in PSD and viscosity, achieved by shear using a planetary centrifugal miller, and by tailoring the concentration of thickening agent, respectively. pH and osmolality of all formulations were 7.5 – 7.9 and 258 – 289 mOsm/kg, respectively.

Physicochemical Characterization

PSD of brinzolamide was determined by laser diffraction on a Mastersizer 3000 (Malvern). Rheological properties were evaluated using a hybrid rheometer (TA Instrument) at 20°C.

In Vivo Study Design

Multi-dose, parallel study with once-daily topical ophthalmic instillations of brinzolamide ophthalmic suspensions (0.5 mg/eye) for up to 14 days in New Zealand White (NZW) rabbits.

Pharmacodynamic Measurements

IOP measurements via applanation tonometer (Reichter Model 30TM), at the same time of day, for 5 days prior to dosing (acclimation) and on Days 1, 7, and 14 pre-dose, and at select time-points post-dosing each day (n=3).

Pharmacokinetic Measurements

Animals were euthanized at select time-points post-dosing, and relevant ocular tissues were harvested for drug quantification via LC-MS/MS (n=2/group/time-point). Pharmacokinetic parameters were determined with Phoenix WinNonlin 8.0 (non-compartmental model).

RESULTS

Physicochemical Characterization of Brinzolamide Suspensions

Brinzolamide ophthalmic suspensions yielding variable physicochemical properties were prepared in-house and characterized, along with the reference comparator AZOPT, for PSD and shear rheology. Significant disparities in CQAs were observed, both exceeding and falling below the target values established for the comparator AZOPT (Table 1). It's noteworthy that there is a considerable overlap in particle size descriptors between the formulations (Fig. 2 left). Formulations display a non-Newtonian shear-thinning behavior, and their viscosity reduces substantially with shear rate (Fig. 2 right), likely becoming indistinguishable at rates representative of ocular shear (>100 s^{-1}).

Table 1. *CQAs of brinzolamide ophthalmic suspensions (mean ± standard deviation; n=3).*

Product	Particle Size (µm)				Viscosity (mPa·s)		
	D_{10}	D_{50}	D_{90}	$D_{[4,3]}$	1 s^{-1}	10 s^{-1}	100 s^{-1}
AZOPT	1.48 ± 0.01	2.60 ± 0.03	4.59 ± 0.10	2.84 ± 0.05	1179.5 ± 192.2	256.9 ± 30.9	71.7 ± 15.8
BRZ_001	0.02 ± 0.01	0.10 ± 0.01	7.78 ± 0.55	1.59 ± 0.10	2178.2 ± 11.1	446.6 ± 52.4	96.3 ± 15.8
BRZ_002	1.90 ± 0.01	3.86 ± 0.02	8.64 ± 0.08	4.76 ± 0.07	1363.6 ± 414.3	260.1 ± 51.4	73.8 ± 12.1
BRZ_003	2.83 ± 0.02	8.05 ± 0.08	21.0 ± 0.50	10.20 ± 0.2	1099.2 ± 261.9	221.0 ± 20.7	64.6 ± 5.3
BRZ_004	1.95 ± 0.01	3.98 ± 0.01	8.62 ± 0.13	4.72 ± 0.05	253.8 ± 50.3	57.2 ± 7.0	22.8 ± 2.4
BRZ_005	2.02 ± 0.02	4.13 ± 0.02	9.78 ± 0.08	5.13 ± 0.03	3425.0 ± 860.0	636.7 ± 27.8	140.9 ± 3.4

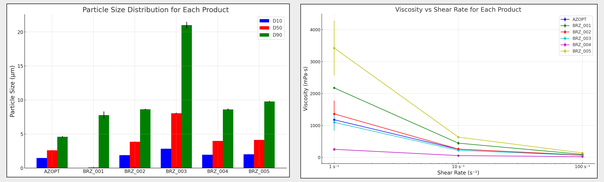


Figure 2. *Physicochemical characterization of brinzolamide ophthalmic suspensions.* ***(Left)*** *Particle size distribution (n=3).* ***(Right)*** *Viscosity over shear (1 – 100 s^{-1}; n=3)*

Pharmacokinetics Upon 14-Day Once-Daily Ocular Instillations

Following the instillation of the Day 1 dose, the ocular concentration *versus* time profiles for all formulations exhibited no substantial disparities in the AH and ICB compartments (Fig. 3). Furthermore, there were no discernible patterns or trends observed in other ocular tissues that could be linked to specific variations in PSD or viscosity. Intra- and inter-subject variability analyses of the first-day PK data for C_{max} in AH was 21%, whereas the total variability was 44%.

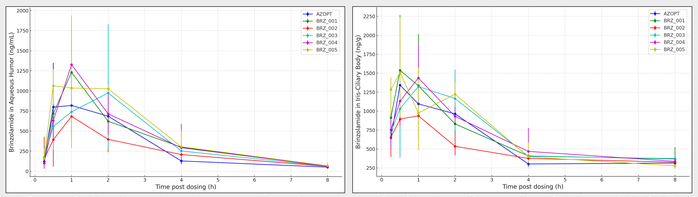


Figure 3. *Day 1 ocular pharmacokinetic profiles of brinzolamide post instillation of AZOPT and test ophthalmic suspensions (mean ± standard deviation; n=2/group/time-point).*

Administering brinzolamide ophthalmic suspensions once daily for a duration of up to 14 days did not result in distinguishable PK parameters across the evaluated tissues on both Day 7 and Day 14. Variability in PK parameters was observed from Day 1 to Day 14. However, this variability did not exhibit a clear trend, and there was no indication of concentration build-up in the ocular tissues.

Table 2. *NCA analyses of brinzolamide in select ocular compartments upon once-daily instillation of AZOPT and test formulations with variations in CQAs for up to 14 days.*

Compartment		Aqueous Humor						Iris-Ciliary Body					
	Formulation	AZOPT	BRZ_001	BRZ_002	BRZ_003	BRZ_004	BRZ_005	AZOPT	BRZ_001	BRZ_002	BRZ_003	BRZ_004	BRZ_005
Day 1	AUC_{last} (hour*ng/L)	3251.69	2997.84	1944.18	3261.71	3052.71	3251.69	4343.79	4943.84	3757.1	3761.56	3468.21	3174.87
	AUC_{inf} (hour*ng/L)	3324.73	3161.06	2135.73	3503.23	3209.83	3324.73	6022.44	7090.15	8040.03	9068.47	10077.3	11086.06
	C_{max} (ng/L)	1064.25	1231.5	683.75	1096.75	1215.75	1064.25	1343.25	1538.1	938.48	1325.25	1437.75	2283.75
	T_{max} (h)	0.5	1	1	1	1	0.5	0.5	0.5	1	1	1	0.25
	$T_{1/2}$ (h)	1.29	1.81	2.21	1.85	1.73	1.29	3.69	4.04	9.11	4.2	4.43	3.09
Day 7	AUC_{last} (hour*ng/L)	3542.85	2246.24	1896.27	1444.08	1198.17	3251.69	4621.35	4650.44	3713.25	3713.25	3260.43	4363.6
	AUC_{inf} (hour*ng/L)	3913.55	2375.49	2081.52	1539.93	1295.07	3339.85	5969.18	6475.66	5853.87	5853.87	5487.93	6699.27
	C_{max} (ng/L)	1830	1346.5	653.5	491.75	665.75	1064.25	2475	1878.75	1507.05	1507.05	1194.75	2470.5
	T_{max} (h)	0.5	0.5	2	1	0.5	0.5	0.5	0.5	0.25	0.25	0.5	0.25
	$T_{1/2}$ (h)	2.24	1.88	2.45	2.12	2.26	1.55	3.05	3.76	4.38	4.38	5.1	4.62
Day 14	AUC_{last} (hour*ng/L)	2862.89	3420.93	2406.6	2395.16	2375.29	3542.85	6452.47	5974.52	5707.75	5509.31	5072.36	5932.09
	AUC_{inf} (hour*ng/L)	3060.23	3693.54	2639.91	2768.89	2618.17	3913.55	10025.2	21457.7	8437.17	10396.6	9788.19	9380.14
	C_{max} (ng/L)	1449.5	1488.75	1417	773.25	666.5	1830	1660.5	1757.25	1590.75	1221.08	1253.25	2297.25
	T_{max} (h)	0.5	0.5	0.5	1	0.5	0.5	0.5	0.5	0.5	0.25	0.25	0.5
	$T_{1/2}$ (h)	2	2.84	2.29	2.63	2.39	2.24	4.65	13.3	4.57	6.56	6.51	4.59

Intraocular Pressure Upon 14-Day Once-Daily Ocular Instillations

Across all measured days, all formulations consistently exhibited the most significant percentage decrease in IOP within the first hour post dosing (Fig. 5). Despite the presence of noticeable differences, these variations could not be correlated with the formulation characteristics examined in this study. Furthermore, the substantial variability in IOP values prevented the effective differentiation of formulations at any given time-point, and there was no clear cumulative effect to PD (Fig. 4).

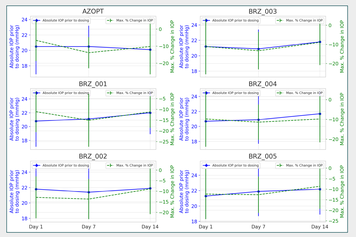


Figure 4. *Evaluation of potential cumulative effect to intraocular pressure reduction.*

Notably, on Day 14 at the 1-hour mark, BRZ_002 and BRZ_005, which had similar particle sizes but differed in viscosity (ranging from average to the highest, respectively), demonstrated the most substantial reduction in IOP relative to the baseline. In contrast, BRZ_001, with the smallest particle size but the second-highest viscosity, showed a comparable IOP reduction to BRZ_003, which had the largest particle size and an average viscosity. Thus, a clear cause-effect relationship between CQAs and PD could not be determined.

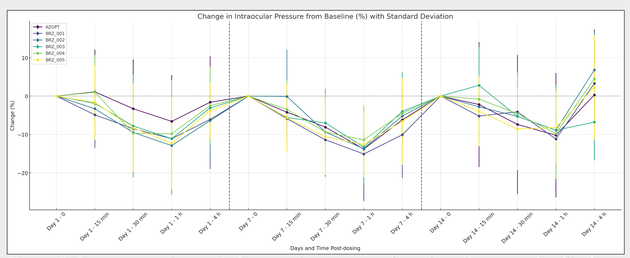


Figure 5. *Percentage change in intraocular pressure from baseline upon instillation of brinzolamide ophthalmic suspensions once-daily for 14 days.*
Dashed vertical lines represent time-lapse. Data expressed as mean ± standard deviation; n= 8 – 12.

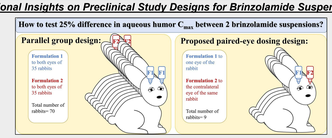
CONCLUSIONS

Brinzolamide ophthalmic suspensions with variations in PSD and viscosity, within the ranges studied, did not lead to a clear cause-effect relationship in terms of PK and PD upon daily dosing of brinzolamide for 14 days. Several potential factors likely contributed to this observation:

i. Reduced dosing frequency (once-daily *vs.* thrice-daily) limited brinzolamide accumulation in ocular tissues.
ii. Variations in PSD of brinzolamide (D_{50} 2.6 – 8.0 µm) and viscosity of formulations (22.8 – 140.9 mPa·s at 100 s^{-1}) did not appear to impact product performance.
iii. High variability observed in PK and PD measurements may have contributed to obscuring potential correlations to differences in CQAs.

This study contributes valuable insights into potential relationships between CQAs of the drug product and its performance in terms of ocular PK/PD of brinzolamide in rabbits.

Additional Insights on Preclinical Study Designs for Brinzolamide Suspensions



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