Stability of Voriconzaole 10mg/mL in Isopto Tears 0.5% stored in Glass Vials And Low Density Polyethylene Droppers at 4°C and 25°C for 28 Days

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INTRODUCTION

Fungal keratitis (keratomycosis) is a corneal infection which can lead to blindness[1]. There are over 70 different fungi which can cause fungal keratitis, but *Fusarium*, *Aspergillus*, and *Candida* species account for 95% of the cases. Management of fungal keratitis involves the local application of an antifungal agent with or without systemic administration.

Voriconazole is a triazole antifungal medication which disrupts ergosterol biosynthesis and is active against the pathogens which cause fungal keratitis[2]. While there are oral and intravenous formulations available for voriconazole, there are no commercially available voriconazole eye drops.

Compounded formulations of voriconazole eye drop using sterile water for injection and terminally filtered were found to be stable for 30 days[3]. However, the lack of any preservative raises the risk of microbial contamination. Isopto Tears 0.5% is a commercially available artificial tear preserved with benzalkonium, making it an attractive agent to reconstitute voriconazole.

OBJECTIVES

The objective of the study was to evaluate the stability of voriconazole 10mg/mL reconstituted with Isopto Tears 0.5% over 28 days at 4°C and 25°C stored in glass vials and low density polyethylene (LDPE) dropper bottles.

The concentration of voriconazole was evaluated during storage at each temperature and container using a validated, stability indicating, liquid chromatographic method using UV detection.

1: Wu J, et al. *Int J Ophthalmol*. 2016;9(11):1676-1683.
2: Scott LJ and Simpson D. *Drugs*. 2007;67(2):269-298.
3: Dupuis A, et al. *Antimicrob Agents Chemother*. 2009;53(2):798-799.

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METHODS

Liquid Chromatographic Method

The liquid chromatographic system consisted of a mixture of 40% acetonitrile and 60% distilled water which was pumped through 150mm x 4.6mm reverse-phase C18, 5µm column (Supelcosil ABZ Plus; Supelco, Toronto, ON) at 1.0 mL/min. The effluent was monitored with UV detection at 256nm.

Assay Validation

The method was evaluated to ensure reproducibility, accuracy and assay specificity. The system was shown to be capable of separating voriconazole from its degradation products (Figure 1). Accuracy and reproducibility of standard curves was tested over 5 days. Inter- and intra-day errors of reproducibility were assessed by the coefficients of variation and the standard deviation of regression.

Stability Study

On study day 0, 12 vials of 200mg voriconazole (Mfg: Sandoz, Lot: JY7776, Exp: Apr-2021) were reconstituted with 19 mL of Isopto Tears 0.5% (Mfg: Alcon, Lot: 19115BC, Exp: Aug-2020). Six were retained in the original glass vials and six were transferred into sterile low density polyethylene (LDPE) dropper bottles. Three containers of each type were stored at 4°C and there were stored at 25°C.

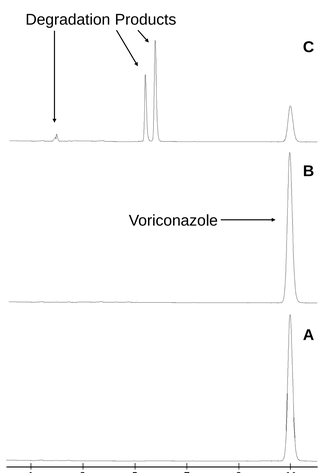
Concentration and physical inspection were completed on study days 0, 1, 3, 7, 10, 14, 21, and 28.

Data Reduction and Statistical Analysis

The concentration of a solution on a particular day was considered "acceptable" or "within acceptable limits" if it was greater than 90% of the initial concentration (as determined on day 0) and the amount found on that day, with 95% confidence, was also greater than 90% of the initial concentration.

Analysis of variance was used to test differences in degradation rate between the different storage temperatures and container combinations. The 5% level was used as the *a priori* cut-off for significance.

Figure 1. Representative Chromatograms



Chromatogram A represents a solution of voriconazole in Isopto Tears 0.5% on day 0. Chromatogram B shows the same sample after 28 days of storage in the refrigerator (4°C) with 99% remaining.

Chromatogram C represents a solution of voriconazole after storage at 80°C for 24 hours with 11.81% of the initial concentration remaining.

Voriconazole eluted at 10.9 minutes and degradation products eluted at 1.9, 2.0, 5.4, and 5.7 minutes.

RESULTS

Table 1. Percent Remaining of the Initial Voriconazole Concentration[1] when stored at 4°C and 25°C.

Container	Glass Vial	Glass Vial	LDPE Dropper	LDPE Dropper
Storage Temperature	4°C	25°C	4°C	25°C
Nominal Initial Concentration (mg/mL)	10	10	10	10
Initial Concentration ± SD (mg/mL)	10.08 ± 0.61	10.15 ± 0.39	10.02 ± 0.68	9.98 ± 0.86
Study day 1	99.53 ± 0.07	99.74 ± 0.12	100.78 ± 0.51	100.83 ± 0.45
Study day 3	100.06 ± 0.52	100.09 ± 0.40	101.00 ± 1.67	100.06 ± 0.31
Study day 7	99.65 ± 0.37	99.93 ± 0.46	100.57 ± 0.46	99.22 ± 1.11
Study day 10	99.54 ± 0.31	100.28 ± 0.55	99.38 ± 0.87	99.07 ± 0.22
Study day 14	99.21 ± 0.60	101.13 ± 1.28	99.85 ± 1.32	98.99 ± 0.13
Study day 21	98.98 ± 0.34	100.34 ± 0.48	99.59 ± 0.89	98.43 ± 0.25
Study day 28	97.54 ± 0.31	100.31 ± 0.52	99.90 ± 0.64	97.44 ± 0.62
Degradation Rate (%/day) [Slope]	-0.073	0.021	-0.033	-0.100
Standard Deviation of Regression (Sy.x)	0.358	0.390	0.515	0.354
Confidence interval for Degradation Rate	0.033	0.0361	0.0477	0.0328
Fastest Degradation Rate	-0.106	-0.0148	-0.0809	-0.1330
Shortest T-90 in days (95% CI)	94.20	676.65	123.62	75.15

[1]: Concentrations are shown as mean ± coefficient of variation, expressed as percentage.

Assay Validation

The analytical method separated the degradation products from voriconazole (Figure 1). Standards and quality control samples over the study period showed an average absolute deviation of 1.78% from expected concentration. Analytical error with replicate measurement (measured by coefficient of variation) averaged 0.45% within a day, 1.55% between days and the standard deviation of regression averaged 0.40%.

Concentration Results

Concentrations on each study day are reported in Table 1. All voriconazole solutions stored in the refrigerator (4°C) and at room temperature (25°C) retained more than 97% of their initial concentration at study day 28 when stored in the original glass vial and in LDPE dropper bottles. The shortest time to reach 90% of the initial concentration with 95% confidence was greater than the 28 day study period for all study conditions.

Analysis of variance did not identify significant differences in percent remaining due to temperature ($p=0.95$), study day ($p=0.26$), or container ($p=0.79$). The study was capable of detecting a <1.0% difference in concentration due to study day, temperature, concentration or container.

Physical Inspection

Glass vials and LDPE dropper bottles were visually inspected on each study day. All samples stored at 4°C remained colourless and free of particulate matter for the entire study duration. Samples stored at 25°C formed a milky layer after 1 day (Figure 2), which persisted for the 28 day study duration. The LDPE dropper bottle tip became occluded after day 3.

Figure 2. Physical inspection of voriconazole in Isopto Tears 0.5% stored in glass vials at 4°C (left) and 25°C (right) on day 1.

Voriconazole 10mg/mL stored in glass vials at 4°C (left) remained clear and colorless for the 28 day study duration. A milky layer formed after 1 day for voriconazole vials stored at 25°C (right) which persisted for the 28 day study duration.

CONCLUSIONS

Voriconazole 10mg/mL in commercially preserved Isopto Tears 0.5% is chemically stable for at least 28 days at 4°C and 25°C in the original glass vial and LDPE droppers. We recommend storage at 4°C to minimize the potential for microbial growth and due to the physical incompatibility when stored at 25°C.

When establishing a beyond use date (BUD), both the stability of the components and the sterility limits established by NAPRA/USP must be considered.