An Efficient Method to Alter the Drop Volume of Topical Ophthalmic Medications

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Introduction

An aqueous solution delivered topically to the corneal surface remains the preferred method of ophthalmic medication delivery (5,8). The current design of commercial eye drop bottles for multi-use ophthalmic solutions are fairly uniform in nature and involve plastic bottles of varying volumes that incorporate an applicator tip of a given bore size for solution release. However, this method of administration is fundamentally flawed as only a small portion of the applied dosage actually penetrates the eye while the majority is rapidly swept away where it is made available for absorption into the systemic circulation (2,3).

An upright patient, when not blinking, can maintain a maximum fluid volume of approximately 30 µl within the palpebral fissure (7). Normal human tear volume occupies approximately 7 µl of this volume, leaving an additional 23 µl before overflow occurs. The volume of commercially available ocular medications varies widely, but has been determined to range between 25.1 and 56.4 µl by Lederer et al (6). Cost-analysis studies have identified average drop volumes ranging from 26.4 to 69.4 µl (9). Following an increase in volume, the excess fluid volume is diminished rapidly by multiple mechanisms including reflex blinking, tearing, and drainage via the nasolacrimal system. Normal tear volume is restored within two to three minutes with a precipitous decrease in volume noted within the first thirty seconds (7,9). In animal models, drainage via the nasolacrimal ducts has been demonstrated to be have a linear relationship with the volume of drop administered (2). Within the nasopharynx, the drug may then be absorbed into the systemic circulation avoiding first-pass hepatic metabolism (9). Further, the ratio of absorbed to administered drug increases with decreasing volumes of instilled medications in rabbit models (1).

Reduction of eye drop volume has been demonstrated to provide equal or improved bioavailability with reduction of systemic drug loss, decreasing the potential for toxicities (3). Drop size is dependent on bore size of the applicator tip, surface tension of the medication, and the angle at which the drop is administered (4). The purpose of this study was to evaluate a novel method for reliably and predictably reducing the drop size of commercially available ophthalmic medications.

Methods

This study incorporated the utility of commercially available 15 mL low density polyethylene (LDPE) bottles with a curve from the bottle reservoir through the neck allowing smooth flow configured with a Luer lock cap. The bottle was configured with four 0.5 inch and one 1.5 inch long Luer lock flexible polypropylene dispensing tips of 0.250, 0.840 and 1.370 mm inside diameter bore size (Figure 1).

The mean drop volume for each tip size was determined by densitometric methodology using sterile water as the test article. An analytical balance with readability to 0.1mg was employed for determination of drop mass. An LDPE bottle was fitted with each dispensing tip, and then the bottle held at 90 degrees from the horizontal. Ten drops were administered into a plastic specimen dish and the mass calculated. This process was subsequently repeated so that 8-14 mass measurements were obtained, each for a set of ten drops.

The volume of each drop was determined by dividing each set of drops by ten (the number of drops dispensed) to determine the average mass which was then divided by the density of sterile water, 994.0 mg/ml. Coefficient of variation in drop volume for each dispenser tip was determined and ANOVA was used to determine if a significant difference in mean values existed.

Graphs and Figures

Graph 1: Drop Volume by Bore Diameter

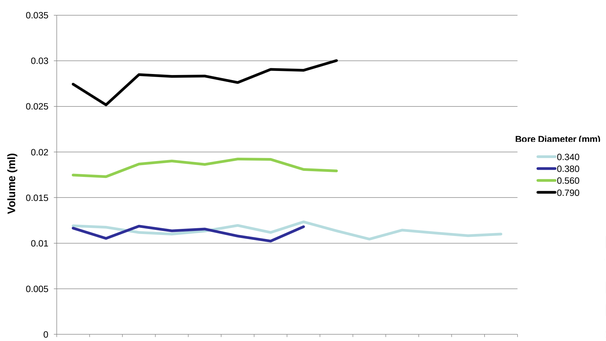
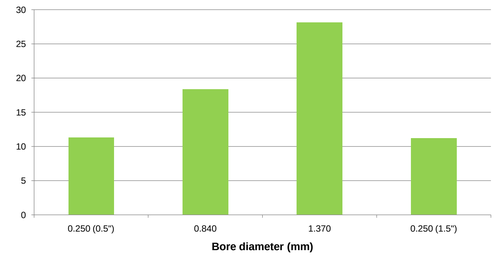


Figure 1:
Top: 1.5" 0.250 mm bore dispenser
Middle: 0.5" 0.840 mm bore dispenser.
Bottom: 0.5 " 0.840 mm bore dispenser with Luer lock cap affixed to a commercially available 0.5 oz artificial tear bottle.

All tips are composed of flexible polypropylene.

Graph 2: Average Volume Dispensed



Results

Drop volume measured for each experimental set is demonstrated on Graph 1. Mean drop volume for the 0.5" tips of 0.250, 0.840 and 1.370 mm bore size was 11.34, 18.39 and 28.15 µL respectively (Graph 2). Mean drop volume for the 1.5" 0.250 mm bore needle was 11.22 µL. Coefficient of variation in drop volume ranged from 3.96-5.57%. A one way analysis of variance (ANOVA) demonstrated a statistically significant difference between mean drop volumes ($p < 0.0001$). Tukey multiple comparisons post-test showed a statistically significant difference in all paired groupings with the exception of the 0.5 and 1.5" 0.250 mm bore size categories.

Conclusion

Topical ophthalmic drop volume can be modifiable in a reliable and precise manner through use of a novel Luer lock tip-bottle combination system. The system can provide desired flexibility in dosing topical ophthalmic medication simply through changes in the bore of the delivery tip. Further study will examine the safety and efficacy of such a system in-vivo through dose-response measurements.

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