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Study of Eye Drops Dispensing and Dose Variability by Using Plastic Dropper Tips

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ABSTRACT The application of eye drops from flexible dropper bottles fitted with different types of dropper tips is associated with the high variability of eye drop weights. The aim of this report was to investigate the simultaneous effect of three factors influencing the mean weight of drops dispensing from two plastic dropper tips. Using a designed experiment (Box-Behnken), the effect of the concentration of benzalkonium chloride solutions (BAC) in the range of 0–0.02%, the dispensing angle from 90° to 30° from horizontal, and the residual volume of liquid in the dropper bottle from 4 to 10 mL on the mean drop weights were examined. The significant effect of the increase in BAC concentration resulted in a linear decrease in drop weights for both of the dropper tips investigated. The significant effect of the dispensing angle was influenced by the dropper tip design. For the dropper tip A, the effect of the dropper tip tilt was described by the quadratic equation with a minimum, which corresponded to the dispensing angle equal to that of 48° from horizontal. Below this angle, the increase in drop weights occurred due to the drop formation from the wetted external surface of the tip orifice. The linear decrease in drop weights in response to the decrease in dispensing angle was detected for the dropper tip B. The regression equations and the contour line plots obtained allowed the drop weights to be estimated for the actual combinations of both the BAC concentration and the dispensing angle. The effect of the residual volume was found to be non-significant. Based on the formula of Tate's law, the direct proportion between surface tension of a solution and the radius of the effective perimeter of a dropper tip can be used to estimate the theoretical maximal weight of drops at the dispensing angle of 90°. Using the stalagmometric values of surface tension of the BAC solutions, the maximal drop weights were estimated for both of the dropper tips investigated. A comparison between the theoretical and the experimentally measured drop weights enabled the dropper tips behavior to be discussed by using Harkins and Brown correction factor *F*. The *F*-value of 0.74 noted for the dropper tip A differed from that of stalagmometer *F*-value (0.61) indicating a deviation from the simple drop formation process in answer to more complicated design of the dropper tip A. On the other hand, the *F*-value of 0.6 observed for the dropper tip B demonstrated the better consistency with stalagmometry. As a

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result, the dropper tip B with the linear decrease of drop weights in response to the increased concentration of BAC and the decreased dispensing angle without the adverse external drop formation could be recommended in real drop dispensing.

Keywords Eye drops, Eye drops dispensing, Dose variability, Response surface

INTRODUCTION

Most ocular diseases are treated with a topical application of solutions administered as eye drops. After the application, the preparation spreads over the eye surface covered by a tear film. Normally, the human tear volume in the palpebral fissure averages 7 µl in the up-right position, with 1 µl in the precorneal tear film and about 3 µl in each marginal tear meniscus. The maximum volume of fluid held in the cul-de-sac without overflowing onto the check was estimated at about 20 to 30 µl of fluid (Mishima et al., 1966). The average drop size of commercially available topical eye medications has been found to be of about 39 µl, within a range of 25–56 µl (Lederer & Harold, 1986). Volume instilled in excess results in the patient's reflex blinking, which accelerates the elimination process through the nasolacrimal system into the nasal cavity. From a biopharmaceutical and toxicological point of view, it has been suggested that the decrease in drop size to between 5–15 µl would reduce the rate of drug loss through drainage, the incidence of systemic toxic effects, and, in addition, the cost of therapy (Patton et al., 1999).

The composition and physico-chemical properties of tears vary with the secretion level of basal tears and tear turnover rate. The surface tension of human tear fluid was found to be between 43.0–46.0 $mN \cdot m^{-1}$ (Pandit et al., 1999). During the formulation of ophthalmic solutions, a dynamic surface tension of the solution should be determined, since, in contact with surface-active solutes in eye drops, the surface tension of tears might be changed and film rupture might occur as it is known for penetration enhancers (Van Santvliet & Ludwig, 1998).

Flowing slowly from a vertical tube, a liquid breaks into drops and falls down as a result of gravity constant (g). At an instant of breaking away from the outer orifice of the tube with a radius (r), equilibrium forms between the gravitational force of the drop ($m \cdot g$) and the capillary force ($2\pi r \sigma$) holding the drop at the end of the tube:

$$m \bullet g = 2\pi r \bullet \sigma \quad (1)$$

The weight of the falling drop (m) is, therefore, primarily a function of the surface tension of the liquid (σ) and the capillary radius (r). Thus, theoretically, if we knew the capillary radius and the surface tension of a solution, the maximal weight of drop could be estimated from the equation:

$$m = 0.64 \bullet r \bullet \sigma \quad (2)$$

For example, for capillary radius r = 1.2 mm, the weight of a water drop (σ = 72.8 $mN \cdot m^{-1}$) could be estimated as equal to that of 56 mg. Formula of Tate's law (Eq. 1) assumes that the tube resembles a thin-walled pipette. The real weight of the detached drop is lower since a small portion of liquid remains at the capillary end. As known for stalagmometry decrease in drop weight is a function of Harkins and Brown correction factor F.

Many factors determine size of drops delivered from a flexible dropper bottle. The most important of them, the design and dimension of the dropper tip and the physico-chemical properties of solution to be dispensed (i.e., formulation factors) as well as the design of the dropper bottle and the volume of the solution are controlled by the manufacturer. Although viscous properties can also alter drop size, up to a value of 25 mPa s, viscosity and rheological behavior of the solution were usually found to produce a non-significant effect on the weight of drops dispensed from the flexible dropper bottle (Van Santvliet & Ludwig, 1999). Further factors, such as temperature, drop dispensing rate, and dispensing angle (i.e., dispensing factors) can be poorly controlled since they are determined by the patient's manipulation at the moment of use (Van Santvliet & Ludwig, 2004).

Ophthalmic solutions are available in a wide variety of dropper bottles fitted with different types of dropper tips. Several dropper tip designs can be distinguished: the simplest design is a nozzle with a small calibrated opening for the passage of the liquid; the earliest dropper tips with a straight elongated cylindrical channel of uniform cross-section and narrower inner aperture; tips with a conical outward channel below a cylindrical recess channel (the outer orifice sits on the hemispherical outer surface); and previous tip with the addition of a narrow cylindrical segment containing the inner aperture (Van Santvliet & Ludwig, 2004). Changes in dimension of eye dropper tip can alter drop volumes markedly. Brown et al. (1985) studied the influence of the dropper tip dimension on drop size. With a constant inner diameter of the dropper tip orifice, the eye drop size increased linearly with the outer diameter. An inner diameter also affected drop size but the relationship was not linear. The smallest eye drops were obtained with a tip having the inner diameter that was approximately one-half of the size of the outer diameter.

Van Santvliet and Ludwig (2001) studied drop formation rates and the air pressure differences created inside the plastic dropper bottle under standard conditions. When squeezing the bottle rapidly, the higher flow rates through the tip capillary resulted in an increase in drop size. At a higher drop formation rate, the tail of liquid created by the falling drop results in an extra pulse of liquid into the drop and, hence, an increase in drop size. As demonstrated in our previous study, if drop delivery followed in a regular manner slow squeezing of the plastic dropper bottle resulted in slow drop formation rates allowing the individual drop volume and, hence, drops volume variability to be controlled (Šklubalová & Zatloukal, 2005). Tilting of a dropper tip from a vertical position to 45° from the horizontal reduced the perimeter of the outer orifice of the dropper tip at which a drop was formed, and smaller drops were noted (Van Santvliet & Ludwig, 2001). Wetting of the external lateral surface of some tips can mitigate the drop reducing effect of tilting due to an overflow of liquid over the perimeter of the outer orifice (Van Santvliet & Ludwig, 1999).

The aim of the present study was systematic investigation of three factors influencing the weight of eye drops expelled from two different plastic dropper tips fitted to a flexible plastic dropper bottle: firstly, the surface-activity of the solution; secondly, the residual volume of liquid inside the dropper bottle; and thirdly, the drop dispensing angle.

EXPERIMENTAL

Materials

Two different dropper tips for the dispensing of eye drops, made of low-density polyethylene (LDPE), were examined, both described previously by authors Van Santvliet and Ludwig (2001). The dropper tips had the same total length of capillary (10.80 mm) but differed in outer orifice diameter and design. An annular recess surrounded the outer orifice of dropper tip A (outer orifice diameter was 2.40 mm). Dropper tip A comprises a special design of four branches in the lower part of the tip capillary, arranged in the shape of cross. The four small size rectangular (0.05×0.2 mm) inlets to the capillary are perpendicular to the axis of the capillary. Dropper tip B had a hemispherical surface of outer orifice with outer orifice diameter of 3.30 mm. The capillary of dropper tip B consists of two conical, vertical positioned parts, the upper one (part 1) and the lower one (part 2), both characterized by the upper and lower diameter (2.40 and 1.00 for part 1 or 0.38 and 0.30 mm for part 2). The dimensions of dropper tips A and B are listed in Table 1.

The dropper tips were fitted to commercially available 10 mL round white opaque flexible plastic dropper bottle also made of LDPE.

Methods

Preparation of Solutions

Solutions of antimicrobial preservative, benzalkonium chloride (BAC) (Acros Organics, New Jersey, USA), were prepared by the addition of the required volume of 50.0% v/v solution of BAC to water to achieve the concentration of 0.01% v/v or 0.02% v/v, respectively. Solutions were kept in dark at room temperature. Deionized freshly double-distilled water has been used throughout the study.

Measurement of Surface Tension

Surface tension measurements were performed using Traube's stalagmometer with the volume of

TABLE 1 Dimensions of Dropper Tips A and B

Dimensions (mm)	Dropper tip A	Dropper tip B
Outer orifice diameter	2.40	3.30
Upper diameter of part 1	—	2.40
Lower diameter of part 1	—	1.00
Upper diameter of part 2	—	0.38
Lower diameter of part 2	—	0.30
Inner orifice diameter	0.05×0.2	—
Length of capillary in the form of a cross	3.20	—
Total capillary length	10.80	10.80
Base diameter	9.80	8.40

2.83 mL at 20.5 ± 0.5°C. The stalagmometer was fixed at vertical position and calibrated with distilled water. Surface tensions of 0.01% v/v or 0.02% v/v solutions of BAC were calculated from mean drop weights assuming that the densities of the very low concentration aqueous solutions were equal to that of water. An average of five measurements is reported.

Drop Weights Determination

The 10 mL plastic dropper bottle was filled with 4.0, 7.0, or 10.0 mL (factor X_2) of water and an aqueous 0.01% v/v or 0.02% v/v solution of BAC (factor X_1), respectively. The bottle was fitted with the dropper tip under investigation (A or B, respectively) and then fixed to the holder that allowed to keep it correctly in the upright position (90° angle), at a dispensing angle of 60° from horizontal or 30° from horizontal (factor X_3). The bottle was squeezed by its side-walls in the middle of its body so slowly that a drop was formed at the top of a dropper tip until it fell into a glass beaker. At this moment, the squeezing of the bottle was stopped and the inner pressure was equalized with the atmospheric one. At those constant conditions, with a time interval of 5 seconds between expelling of drops, this procedure was repeated 10 times (n = 10) in each experimental trial. Each drop was weighed immediately on an analytical balance (model 2462, readability 0.1 mg, Sartorius, Göttingen, Germany) and recorded. All experiments were realized at 20.5 ± 0.5°C. The mean drop weights (mg) of ten drops (response variable Y) and the relative standard deviation (RSD in %) were calculated.

Box-Behnken Design

A three-factor, three-level Box-Behnken experimental design was employed consisting of three independent variables of concentration of BAC (factor X_1), residual volume of liquid inside the dropper bottle (factor X_2), and dispensing angle (factor X_3). The variables used in the design, shown in their low (−1), medium (0), and high (+1) levels, are summarized in the upper part of Table 2. Factors with constant level (fixed) are shown in the bottom part of Table 2.

The experimental Box-Behnken design matrix involved 15 experimental trials consisting of 12 factor combinations (trials 1 to 12) and three replicated central points (trials 13 to 15) summarized in Table 3. For both of the tested dropper tips (A or B, respectively), experiments were performed by using the same experimental design. The mean drop weights were obtained for dropper tip A (Y_1) and dropper tip B (Y_2).

RESULTS AND DISCUSSION

Box-Behnken Design

Good experimental design enables the precise study of many factors at some levels. For the purpose of the pharmaceutical technology research, the Box-Behnken experimental design could be suitable (Prvan & Street, 2002). This experimental design enabled concurrent investigation of three selected factors (the concentration of BAC, the residual volume inside the dropper bottle, and the dispensing angle) at three different levels. The experimental matrix (Table 3) comprises 15 experimental trials consisting of 12 factor combinations and three replicated central points. This aggregate design makes it possible to estimate studied variables in surface response to effect of significant factors and their interactions.

Mathematical relationships between three chosen factors and response mean drop weights in the form of a regression equation was generated for both of dropper tips investigated. For all the applied levels of factors, the equations would predict the theoretical

TABLE 2 **The Initial Experimental Domain for Drop Weights Determination**

Factor	Associate variable	Low factor level (-1)	Medium factor level (0)	High factor level (+1)
Concentration of BAC	X_1	0%	0.01%	0.02%
Residual volume	X_2	4 mL	7 mL	10 mL
Dispensing angle	X_3	30°	60°	90°
Time interval	fixed		5 sec	
Bottle volume	fixed		10 mL	

TABLE 3 Box-Behnken Design of Drop Weights Determination

Trial	X_1 (%)	X_2 (mL)	X_3 (°)
1	0.02	10	60
2	0.02	4	60
3	0	10	60
4	0	4	60
5	0.02	7	90
6	0.02	7	30
7	0	7	90
8	0	7	30
9	0.01	10	90
10	0.01	10	30
11	0.01	4	90
12	0.01	4	30
13	0.01	7	60
14	0.01	7	60
15	0.01	7	60

values of drop weights for dropper tip A (Y_1) or dropper tip B (Y_2), respectively:

$$\hat{Y}_1 = 40.98 - 212.5\,X_1 - 0.1381\,X_3 + 0.0014286\,X_3^2 \tag{3}$$

$$\hat{Y}_2 = 38.96 - 212.5\,X_1 + 0.0583\,X_3 \tag{4}$$

In the above equations, only coefficients of the significant factors ($P \leq 0.05$) are presented. The coefficient with the higher-order term indicates the quadratic (non-linear) nature of the relationship. The remaining factor (X_2) and all factors interactions were found to be non-significant and, therefore, confounded to residual.

Table 4 compares the values of the mean drop weights measured in each of the 15 experimental trials for dropper tip A (Y_1) with those estimated using Eq. 3 (Y_1). Data are shown with their RSD in per cent. Similarly, the values of the mean drop weights measured (Y_2) or estimated using Eq. 4 (Y_2), as well as RSD, are shown for dropper tip B in Table 5. The theoretical and observed values were found to be in good agreement.

Using analysis of variance (ANOVA), estimation of the significant regression coefficients for dropper tip A (Eq. 3) and dropper tip B (Eq. 4) permitted to discriminate total variance obtained in experiment between the square multiple correlation (R^2, SMC) and the residual square as summarized in Table 6. In the case of dropper tip A, from 81.6% of explained variance more than two third (exactly 58.6%) corresponded to the effect of surface activity (factor X_1), since the rest

TABLE 4 Measured (Y_1) and Estimated (Y_1, Eq. 3) Mean Drop Weights for Dropper Tip A

Trial	Y_1	RSD (%)	Y_1
1	33	2.4	33.6
2	34	1.3	33.6
3	36	1.7	37.8
4	39	1.2	37.8
5	36	1.6	35.9
6	34	1.8	33.9
7	40	2.1	40.1
8	39	2.0	38.1
9	37	1.8	38.0
10	36	1.3	36.0
11	39	2.1	38.0
12	35	1.6	36.0
13	36	1.3	35.7
14	37	1.6	35.7
15	35	1.2	35.7

TABLE 5 Measured (Y_2) and Estimated (Y_2, Eq. 4) Mean Drop Weights for Dropper Tip B

Trial	Y_2	RSD (%)	Y_2
1	37	3.6	38.2
2	38	6.5	38.2
3	42	2.0	42.5
4	43	2.0	42.5
5	41	2.5	40.0
6	36	3.4	36.5
7	44	2.8	44.2
8	40	2.6	40.7
9	42	2.5	42.1
10	39	3.1	38.6
11	41	3.0	42.1
12	39	1.4	38.6
13	41	1.8	40.3
14	42	1.9	40.3
15	40	1.6	40.3

TABLE 6 Relative Variance and Its Differentiation

Factor	Dropper tip A	Dropper tip B
X_1	0.586	0.521
X_3	0.130	0.353
X_3^2	0.100	—
R^2 (SMC)	0.816	0.874
Residual	0.184	0.126

part of explained variance was divided into effects of the dispensing angle (factor X_3) and its second power (X^2_3). In the case of dropper tip B, on the other hand, from 87.4% of explained variance, 52.1% corresponded to the effect of surface activity and 35.3% to the effect of dispensing angle. No quadratic relationship was observed for the dropper tip B. From this point of view, both tested dropper tips produced drops on which weight depended more on the surface activity of solution than on the dispensing angle used. Dropper tip B was more sensitive to changes in dispensing angle than dropper tip A. It should be noted that although more than 80% of variance could be explained there is quite a large residual variance for both tips indicating however that drop formation is a more complex process.

The relationship between the significant variables and the response mean drop weights could be further explained by the contour line plots. Figure 1 illustrates the effect of the BAC concentration (X_1) and the dispensing angle (X_3) on response drop weights for dropper tip A (Y_1). The increase in BAC concentration led to decrease in eye drop weights. For example, at the dispensing angle of 90°, drop weights of 40 mg, 38 mg, and 36 mg corresponded to 0%, 0.01%, and 0.02% solution of BAC, respectively. The effect of the dispensing angle on the resulting drop weights for dropper tip A is more complicated. The quadratic relationship obtained is symmetrical around a central line corresponding to the dispensing angle of 48° from horizontal. Decreasing the dispensing angle from 90° resulted in a decrease in drop weights until 48° from horizontal was reached when the smallest drops were noted. Below this axis, increase in drop weights arises.

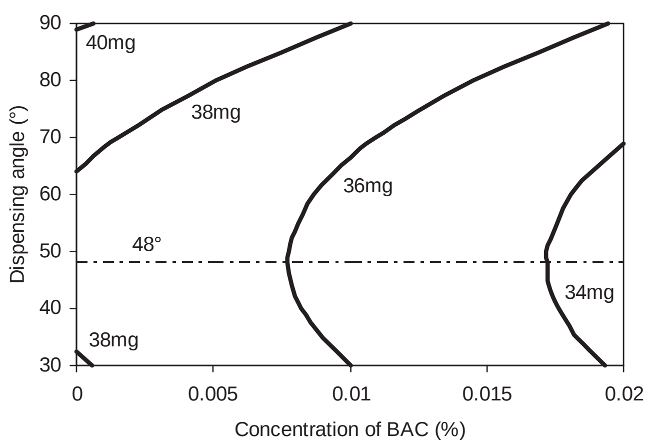

FIGURE 1 **Effect of Concentration of BAC (X_1) and Dispensing Angle (X_3) on the Mean Drop Weight (Y_1) for the Dropper Tip A; Calculated by Using Eq. (3).**

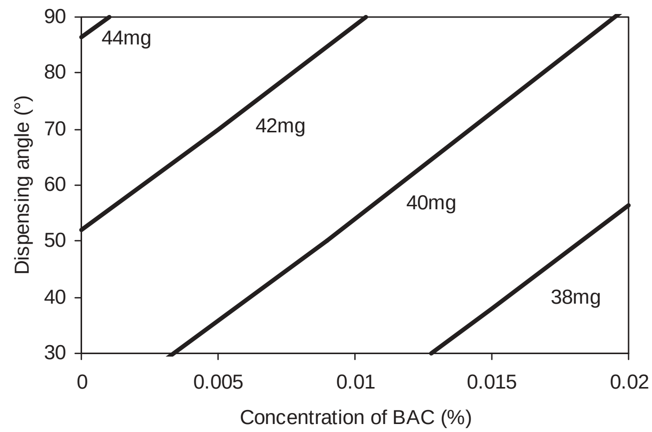

FIGURE 2 **Effect of Concentration of BAC (X_1) and Dispensing Angle (X_3) on the Mean Drop Weight (Y_2) for the Dropper Tip B; Calculated by Using Eq. (4).**

Similarly, Fig. 2 demonstrates the effect of the BAC concentration (X_1) and the dispensing angle (X_3) on response drop weights (Y_2) for dropper tip B. The increase in concentration of BAC led to a linear decrease in eye drop weights. For example, at the dispensing angle of 90°, drop weights of 44 mg, 42 mg, and 38 mg corresponded to 0%, 0.01%, and 0.02% solution of BAC, respectively. No quadratic relationship was observed for the dropper tip B indicating linear decrease in drop weights in response to decrease in dispensing angle (within investigated range from 90° to 30°).

Formulation Factors

Requirements concerning the volume, composition, and properties of a solution to be dispended, as well as the dropper bottle and dropper tip design (formulation factors) are determined by the manufacturer.

The residual volume of liquid in the dropper bottle is generally believed to produce a minimal effect on eye drop size and no change in drop weights as a consequence of the residual volume decrease could be expected during administration of eye drops. The effect of residual volume within the tested range from 4 to 10 mL was found to be non-significant for eye drop weights. In such circumstance, from results here, only two formulation factors directly influence eye drop weight: surface tension of a solution and dropper tip dimensions, in particular, outer orifice diameter.

Basic principles of eye drops delivery could be compared with formation of drops at the end of the glass tube. If a liquid flows slowly from a vertical capillary edged with a defined horizontal flat end, the surface tension of liquid causes the formation of drops. In stalagmometry, basic assumptions given mean the correct upright position of the tube and wetting of its end on which a drop will be formed. According to Tate's law (Eq. 1), the maximal weight of the pendent drop is primarily a function of surface tension of the liquid and the radius of capillary perimeter. In comparison to theoretical maximal weight of the drop, the real weight of the falling drop is lower due to the volume of liquid remaining at capillary end. The proportionality coefficient is called Harkins and Brown correction factor.

Although administration of eye drops might be compared with stalagmometry, many differences could be noted:

Traube's stalagmometer	Dropper tip
Perimeter of the tube end	Perimeter of the dropper tip orifice
Good wetting of glass	Low wetting of LDPE
Hydrostatic pressure	Squeezing of the dropper bottle
Strong upright position	Various drop dispensing angles
Several drops	One individual drop

In view of these facts, however, formula of Tate's law cannot be directly applied to eye drops in real drop dispensing. On the other hand, using Tate's law, the theoretical maximal weight of a drop can be calculated (Eq. 2) if the surface tension of the solution being dispensed and the radius of the dropper tip outer orifice are known. Comparison of the theoretical maximal weight of a drop with the drop weight measured at the dispensing angle of 90° might be very useful in evaluation of drop formation principles, and, consequently, in investigation of dropper tip behavior. This hypothesis will be discussed further below.

The lower the surface tension of a solution the smaller drop will be expected. To discuss the effect of surface tension on drop weight, measurements of surface tension of BAC solutions were performed using Traube's stalagmometer. The results are given in Table 7. When concentration of BAC in solution is increased, the surface tension linearly decreases. Results presented here and discussed in previously have shown that the increase in concentration of BAC (X_1) caused the decrease in mean drop weights for both of dropper tips investigated. The results are therefore in agreement with the theoretic principles of Tate's law.

The eye drop weight depends also on the dimensions of the dropper tip outer orifice (Brown et al., 1985). The greater the outer diameter, the greater the drop created since the eye drop size increases linearly with the outer orifice diameter. The effect of the outer orifice radius on the drop weight is declared in Table 7 where the mean drop weights measured experimentally (m') for stalagmometer and both of the dropper tips investigated, as well as those calculated using Eq. 2 (m), were summarized. The smaller radius, the smaller the drops registered.

It should be noted that another important factor might complicate the estimation of outer orifice radius (and consequently the drop weight) in the real drop dispensing: the wetting of outer orifice. Wetting of outer orifice could cause the increase in effective diameter of the dropper tip perimeter at which a drop is formed leading to significant increase in drop size. The shape of a dropper tip markedly influences the effective perimeter. When the flat end lacks or the annular recess surrounds the spout of the capillary, the

TABLE 7 **Comparison of Theoretical[a] (m) and Measured (m') Mean Drop Weights (mg)**

		Traube's stalagmometer[b]			Dropper tip A[c]			Dropper tip B[d]		
BAC (%)	σ (mN·m^{-1})	m	m'	F	m	m'	F	m	m'	F
0	72.8	119	73	0.61	56	40	0.71	77	44	0.57
0.01	66.8	109	67	0.61	51	38	0.75	71	42	0.59
0.02	60.8	100	61	0.61	47	36	0.77	64	41	0.64

[a]Calculated using Eq. 2.
[b]r = 2.56 mm.
[c]r = 1.20 mm.
[d]r = 1.65 mm.
F is Harkins and Brown correction factor (m'/m).

effective size of the outer orifice is clearly defined. This was observed with the annular recessed dropper tip A and the effective outer orifice corresponds to that quoted in Table 1. The dropper tip B, although hemispherical shaped, had a small flat end surrounding the spout of capillary which resulted in the difference between the effective outer orifice diameter (3.30 mm) and the diameter of capillary spout quoted in Table 1 as the upper diameter of conical capillary part 1 (2.40 mm). Larger drop weights were observed for the dropper tip B in comparison with the dropper tip A.

In all cases, the measured drop weights (m') were lower than the theoretical maximal drop weights (m), which is consistent with the theory of stalagmometry. The values given in Table 7, in particular Harkins and Brown correction factors (F), made it possible to discuss dropper tips behavior. Due to this fact, the F-values seem to be very illustrative.

The F-value of 0.74 noted for dropper tip A is greater than that of stalagmometer F-value (0.61) indicating marked deviation from the simple drop formation process. This could probably arise from the more complicated design of this dropper tip. Quadratic relationship between the weight of the drop and the significant factors observed in Box-Behnken experiment proved this hypothesis. On the other hand, the F-value of 0.6 observed for the dropper tip B is almost identical with that of the stalagmometer F-value pointing to the hypothesis that the drop formation process for both of them is very similar. It corresponds to the results of the Box-Behnken experiment when the simple linear relationship between the weight of drop and the significant factors was found.

The findings here verify the importance of quantitative definition of two formulation parameters: the surface activity of the solution to be administered as eye drops and the effective diameter from which a drop will fall in a real drop dispensing. The classification of dropper tips not only on base of geometric parameters but also with Harkins and Brown correction factor might be very useful in future.

Dispensing Factors

No guidelines concerning the drop dispensing system are available however. Generally, to form a drop, the bottle has to be inverted and squeezed carefully. This usually results in variability of dose influenced by a patient's manipulation technique, in particular by dispensing angle used and drop formation rate (dispensing factors).

In answer to higher inner pressure created inside the bottle during squeezing, the higher drop formation rates resulted in an increase in drop size, contrary to slow rates (Van Santvliet & Ludwig, 1999, 2001). In our opinion, frequency of the drop formation at the approximately same inner pressure seems to be simpler to imagine than changes in inner pressure, and thus more useful for a patient in real drop dispensing. A time interval of 5 sec was kept constantly and respected all the time at drop dispensing in our experiments since it allows to form a drop slowly and weigh it immediately.

Changing the dispensing angle from vertical to 45° from horizontal resulted in the decrease in drop weights (Van Santvliet & Ludwig, 2001). On the other hand, the resultant effect of tilting on drop size depends also on the surface tension of solution and wetting of the dropper tip orifice. As a result, formation of drops from the wetted external lateral surface of the dropper tip was noted (Van Santvliet & Ludwig, 1998). Our findings here are in agreement with these reports. With an annular recessed dropper tip A, an increase in drop weights could be observed at dispensing angles below 48° from the horizontal due to the drop formation from the wetted external surface of the tip orifice. This is consistent with the non-linear effect of dispensing angle on response drop weight discussed previously. The critical angle at which the external lateral surface drop formation has occurred could be seen simply by eye when drops were dispensed during gradual slow tilting of a dropper bottle.

Wetting of the external surface of the tip orifice could be scarcely controllable since it depends not only on the dropper tip design, but also on properties of the tip material as well as the surface cohesion forces between tip material and dispensed solution. In the presence of surface-active ingredients or buffers, wetting of the tip surface could be increased during repeated administration of drops, and, in such situations, the higher variability of eye drop volumes and drug dose could arise. Differences in drop size might not have a major impact when the solution is used for the treatment of dry eyes, but it could be very problematic in the case of highly-active substances where an accurate dose of a drug needs to be administered. In general, no external lateral surface wetting and lateral surface drop formation were noted for the dropper tip B with hemispherical outer surface resulting in the simple linear relationship between the effect of the dispensing angle and the response drop weight as discussed above.

Unfortunately, there was another additional problem associated with cross designed dropper tip A. Dispensing drops at an angle of 30° from the horizontal, air bubble formation inside the tip capillary was often noted, in particular in the case of the most concentrated solution of BAC (0.02%). This usually led to obstructed passage of liquid resulting in drops of very small weight of about 20 mg. In those cases, in fact, some experimental series had to be eliminated.

CONCLUSIONS

Regression equations generated in three-factor, three-level Box-Behnken experiment demonstrate the significant effect of BAC concentration and dispensing angle on drop weights for both of the dropper tips investigated. The residual volume within the tested range from 4 to 10 mL was found to be non-significant.

The decrease in the surface tension of BAC solution resulted in the linear decrease of drop weights for both dropper tips. The mean drop weights obtained for the annular recessed dropper tip A were equal to 74% that of maximal theoretical drop weights which differed from mean drop weights equal to 61% that of maximal theoretical drop weights noted for stalagmometer. This indicates marked deviation from the simple drop formation process. This probably reflects the more complicated design of the dropper tip A. The decreasing of the dispensing angle from 90° led to non-linear decrease in drop weights until at the dispensing angle of 48° from the horizontal the smallest drops were obtained. Below this angle, the increase in drop weights was noted by means of the lateral external drop formation.

Dispensing drops from the simply designed dropper tip B, the mean drop weights were equal to 60% that of maximal theoretical drop weights, which indicated consistency with the principles of the drop formation process for the stalagmometer. Since drop weights decreased linearly with the decrease in the dispensing angle within the investigated range from 90° to 30° from horizontal, the dropper tip B seems to be more suitable in real conditions of eye drop dispensing.

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