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Classification of plastic eye dropper tips using Harkins and Brown's factor

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In this work, the weights of drops produced by seven commercially available eye drop dispensing systems were investigated using benzalkonium chloride solutions in concentration range of 0–0.02%. The effect of the surface tension, the effective diameter of the dropper tip, and the dropper bottle volume on the drop weights was studied at the vertical position. Based on the principle of Tate's law, the theoretical maximal weights of drops were expressed. In all cases, the lower the surface tension, the lower drop weights were noted. Simultaneously, effect of both the effective diameter of the dropper tip and the dropper bottle volume on the drop weights could be described. A regression equation characterized a significantly negative linear interaction of both variables. Comparing the theoretical drop weights with those measured experimentally, Harkins and Brown's factors, F_{HB}, were received. The mean drop weights obtained for the Traube's stalagmometer were 62% that of the theoretical values. F_{HB} values detected for the plastic dropper tips were significantly greater ranging from 0.66 to 0.76. In contrast to the obvious characterization of dropper tips by geometrical parameters, a classification of dropper tips with Harkins and Brown's factor is proposed.

1. Introduction

Most ophthalmic preparations are aqueous solutions of active ingredients. They are supplied in a wide variety of containers consisting of dropper bottles fitted with different types of dropper tips. These dispensing systems should permit administration of ophthalmic solution slowly, drop by drop. The curved dropper tip end prevents the eye from injury during application of eye drops.

Several types of eye dropper tips can be distinguished according to dropper tip design and dimension (Van Santvliet and Ludwig 2004). In principle, eye dropper tips form drops by a "constriction" of a liquid column. Changes in dimension of a dropper tip can alter the drop volumes markedly. With a constant inner diameter of the dropper tip orifice, the eye drop size increases linearly with the outer diameter (Brown et al. 1985). The drop size of commercially available ophthalmic solutions generally varies between 25 and 70 μl with an average value of about 40 μl (Lederer and Harold 1986). Unfortunately, there is no sufficient detail information about drop weights (volumes) produced by the different types of eye dropper tips.

Formation of drops under different circumstances was studied by Tate many years ago. He found that the weight M of a falling drop depends on the circumference of the capillary at which the drop was formed ($2\pi \cdot r$) and the surface tension σ of the liquid forming a drop (Tate 1864).

$$M = 2\pi \cdot r \cdot \sigma \qquad (1)$$

where r is the radius of the capillary.

Later, Harkins and Brown (1919) observed that only 60–70% of the drop formed at the capillary end actually separated. They concluded that Tate's law was inconsistent with their experimental findings and introduced an empirically derived correction factor F_{HB} which is the function Φ of the ratio between the linear capillary dimension (the radius r) and the linear drop dimension ($V^{1/3}$) as below

$$M = 2\pi \cdot r \cdot \sigma \cdot F_{HB} = 2\pi \cdot r \cdot \sigma \cdot \phi(r/V^{1/3}) \qquad (2)$$

where V is volume of the falling drop. Harkins and Brown derived tables of the F_{HB} values by calculation of ratios of the real measured weight m of the drop falling down the capillary and the ideal (theoretical) weight M of the drop formed at the tip of capillary Eq. (1). They found all estimated F_{HB} values lower than/or equal to 0.75.

$$F_{HB} = \frac{m}{M} \leq 0.75 \qquad (3)$$

Nowadays, a new physical view on the formula of Tate's law (1) assumes that at an instant of the detachment, equilibrium is formed between the gravitational force of the drop ($F = M \cdot g$) and the capillary force ($F = 2\pi \cdot r \cdot \sigma$) holding the drop at the end of the capillary:

$$F = M \cdot g = 2\pi \cdot r \cdot \sigma \qquad (4)$$

and then

$$M = \frac{2\pi \cdot r \cdot \sigma}{g} \qquad (5)$$

where g is acceleration due to gravity ($9.80665\ m \cdot s^{-2}$).

Thus, the Harkins and Brown's correction factor could be derived from the Eqs. (3) and (5) as follow:

$$F_{HB} = \frac{m}{M} = \frac{m \cdot g}{2\pi \cdot r \cdot \sigma} \quad (6)$$

Recently, the theory of drop formation was used to predict the size of the pellets formed in freeze pelletization techniques (Cheboyina et al. 2006). In this case, Eq. (4) could be modified to include a volume term (V) and density ρ of the liquid forming a drop:

$$F = V \cdot \rho \cdot g = 2\pi \cdot r \cdot \sigma \quad (7)$$

The size of pellets was found to be directly proportional to the radius of the needle tip and the surface tension of the drop forming liquid, and inversely proportional to the density of the drop forming liquid. As eye drops are usually aqueous solutions, the density of which is similar to that of water, Eq. (6) is more useful in study of the actual eye drop dispensing when a drop detaches from the effective perimeter of the dropper tip. In evaluation of eye drops, Eq. (6) could be simplified to the formula:

$$F_{HB} = \frac{m \cdot g}{2\pi \cdot r \cdot \sigma} = 3.12\ \frac{m}{d \cdot \sigma} \quad (8)$$

where m is the measured weight of drop (in mg), d is the diameter of the effective perimeter of the dropper tip (in mm), and σ is surface tension of the liquid forming drops (in $mN \cdot m^{-1}$).

It is well known that surface tension of a liquid is directly influenced by temperature (Martin 1993). In fact, there is a linear relationship between temperature and surface tension. As temperature increases, the kinetic energy of the molecules increases as well resulting in a decrease in the surface tension. The surface tension of water is equal to that of 75.6 $mN \cdot m^{-1}$ at 0 °C and 63.5 $mN \cdot m^{-1}$ at 75 °C, respectively. At 20 °C, the notably referred value of the water surface tension is equal to that of 72.75 $mN \cdot m^{-1}$.

In the present study, the weight of eye drops produced by seven commercially available plastic eye dropper tips fitted to the original flexible plastic dropper bottles was studied at up-right position (the dispensing angle of 90°). Solutions of the surface-active preservative, benzalkonium chloride (BAC), in the concentration range of 0–0.02% were used. Comparing the measured drop weights and the theoretical maximal values, Harkins and Brown's correction factors F_{HB} were determined. The simultaneous effect of the dropper bottle volume in the range of 5 to 15 ml and the effective diameter of the dropper tip in the range of 2.4 to 2.7 mm on the weight of eye drops and/or F_{HB} was estimated as well.

2. Investigations, results and discussion

2.1. Influencing drop weight

In contrast to the peroral drops, there are no pharmacopoeial guidelines and/or standards on eye drop weights. The size of an eye drop in a wide range of volumes (Lederer and Harold 1986) is primarily influenced by the dropper tip orifice dimensions (Brown et al. 1985) and the surface tension of the liquid preparation (Tate 1864). Many other factors are important for the eye drop size in real eye drop dispensing by the patients, in particular the dispensing angle (Van Santvliet and Ludwig 2004).

Based on the formula of Tate's law (1), surface tension of the liquid forming drops at the end of capillary influences the weight of the drop directly. By our own experience, if the surface tension really influences the weight of drop or not, it depends also on the experimental conditions. Out of seven factors potentially influencing the size of eye drops, the dropper tip design (rubber or plastic), the dispensing angle and the dispensing rate have been found to have a significant effect in the 2_{IV}^{7-3} fractional factorial designed experiment, contrary to the effect of surface tension (Šklubalová and Zatloukal 2005). Although the size of drops decreased with the decrease in surface tension, the effect was ambiguous and not significant. This was probably caused by the only two-level experiment and by the complex effect of the surface tension on the drop size in interactions with the other factors, especially with the dispensing angle. In this work, therefore, the eye drop dispensing experiments were done solely at a dispensing angle of 90°.

At the vertical position, basic principles of eye drop delivery could be compared with formation of drops at the end of a glass tube: the Traube's stalagmometer. In such a situation, the formation of drops at the orifice of the dropper tip adheres to the theoretical principles of Tate's law. Contrary to stalagmometry when drops fall down spontaneously due to gravity, the forced drop formation accompanies squeezing of the dropper bottle. Differences are negligible if the drop delivery follows in a regular manner when slow squeezing of the plastic dropper bottle results in a controlled slow drop formation rate. The bottle was carefully squeezed to dispense drops within a time interval of 1 drop per second in our experiment here.

The estimation of the effective perimeter at which a drop is formed is, however, the other basic condition when Tate's law could be employed for the eye drop weights evaluation. However, various shapes and designs of the orifice can be observed for the commercially used dropper tips (Van Santvliet and Ludwig 2004). Wetting of the capillary end influences the effective perimeter directly. Contrary to the defined inner diameter of the dropper tip capillary, the drop might create at the wetted outer surface of the dropper tip orifice, perimeter of which is difficult to estimate. Good wetting of glass and the sharp edge of the flat capillary end allow the diameter of the effective perimeter to be estimated clearly such as for example in case of the stalagmometer (d = 5.14 mm). In this work, the estimation of the effective diameter d was solved by the measurement of the outer diameter of the dropper tip orifice assuming wetting of the horizontal surface at upright position. Of seven dropper tips investigated this was easy only in case of the dropper tip 1 with well defined geometry similar to the stalagmometer. All other dropper tips investigated were rounded. The values of d (in mm) are summarized in the middle of Table 1.

The total volume of dropper bottle is generally believed to produce a minimal effect on eye drop size. As shown in the last column of Table 1, commercially available dispensing systems of different volumes of the dropper bottles in the range of 5–15 ml were investigated in this work.

Table 1: Characteristics of eye drop dispensing systems investigated

Code	d (mm)	V (ml)
1	2.7	5
2	2.6	10
3	2.5	5
4	2.5	15
5	2.5	10
6	2.4	5
7	2.4	15

Table 2: Results of stalagmometric measurement

BAC (%)	σ (mN · m^{-1})	m (mg)	M (mg)	F_{HB}
0	72.75	74.36	119.79	0.62
0.01	68.84	70.36	113.35	0.62
0.02	62.65	64.04	103.16	0.62

Table 3: Results of drop weights determination for plastic dropper tips

Code	BAC (%)	m (mg)	F_{HB}
1	0	46.8	0.74
	0.01	44.7	0.75
	0.02	41.3	0.76
2	0	42.0	0.69
	0.01	40.1	0.70
	0.02	37.0	0.71
3	0	39.7	0.68
	0.01	37.0	0.67
	0.02	34.1	0.68
4	0	41.8	0.72
	0.01	39.3	0.71
	0.02	36.3	0.72
5	0	40.7	0.70
	0.01	39.1	0.71
	0.02	36.2	0.72
6	0	37.2	0.66
	0.01	35.4	0.67
	0.02	32.6	0.68
7	0	40.0	0.71
	0.01	38.3	0.72
	0.02	35.3	0.73
Average	0	41.17	0.700
	0.01	39.13	0.704
	0.02	36.11	0.714

The effect of surface tension on eye drop weights was studied using solutions of BAC in a concentration range of 0–0.02%. In Table 2, the results of stalagmometric measurement of surface tension are summarized. The higher concentration of BAC, the lower surface tension values were noted following the lower drop weights which was consistent with theory (Tate 1864). The values in Table 3 show the significant effect of surface tension on the eye drop weights. For all dropper tips investigated, the weight of drops decreased with the decrease in the surface tension of BAC solutions.

To describe the simultaneous effect of the volume of the dropper bottle V (in ml) and the effective diameter of the dropper tip d (in mm) on the drop weight, regression Eq. (9) was generated. The coefficient k_{12} with the interaction between the both variables indicates the non-linear nature of the drop weight influencing:

$$m = k_0 + k_1 \cdot V + k_2 \cdot d + k_{12} \cdot V \cdot d \qquad (9)$$

For all the applied levels of variables and their interaction, the Eq. (9) would predict the theoretical values of drop weights for seven tested dropper tips. The coefficients of regression are summarized in Table 4 for 0%, 0.01% and 0.02% solution of BAC. In the last column, Table 4 is completed with values of square multiple regression coefficient r^2.

Table 4: Parameters of regression Eq. (9) for estimation of drop weight

BAC (%)	k_0	k_1	k_2	k_{12}	r^2
0	−69.82	5.974	43.73	−2.345	0.9756
0.01	−72.77	6.352	44.08	−2.494	0.9618
0.02	−67.78	5.819	40.90	−2.282	0.9586

The relationship between the significant variables and the response mean drop weights could be further explained by the contour line plot. Fig. 1 illustrates the effect of the volume of dropper bottle V and the effective diameter of the dropper tip d on response drop weights of water. Separated lines correspond to the drop weights in the range from 37 to 46 mg. The regression Eq. (9) and the contour line plot obtained allowed the drop weights of water to be estimated for the actual combinations of both variables.

The drop weight of water increased linearly with the increase in the effective diameter for the bottle volume of 5 ml. On the other hand, if the dropper bottle volume increased, the effect of the effective diameter on the drop weight decreased gradually until it became non-significant for V = 15 ml. The relationship illustrated in Fig. 1 is spread around a line corresponding to the effective diameter d = 2.55 mm. At this d, the weight of the water drop was equal to that of 41.6 mg and, moreover, was not influenced by the dropper bottle volume in the range investigated. Increase in the bottle volume resulted in increase in drop weights from 37 to 41 mg below this axis, whereas opposite results were noted above the axis when the decrease in drop weights in range of 42–46 mg arise. Different effect of the bottle volume on the drop weight resulted from the significant negative interaction of both tested variables (Eq. 9).

Similar contour line plots like for water were also obtained for the 0.01% and 0.02% solution of BAC, respectively. The values of d (mm) allowing the axis to be localized in contour line plots as well as the corresponding weights of drops m (mg) independent on V are presented for all tested solutions of BAC in Table 5.

As discussed previously, the drop weight was directly proportional to the diameter of effective perimeter of the dropper tip when the dropper bottle of volume equal to 5 ml was used. In other words, dispensing eye drops from the dropper tip with known d, the drop weight will be more close to that estimated by Eq. (9) if the dropper tip

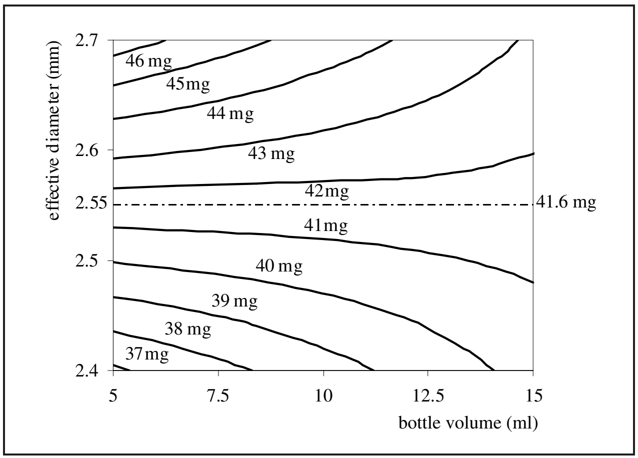

Fig. 1: Effect of the dropper bottle volume and the effective diameter of the dropper tip on the drop weights of water (mg)

Table 5: **Localization of central line in contour line plots for estimation of drop weight (Eq. 9)**

BAC (%)	d (mm)	m (mg)
0	2.55	41.6
0.01	2.55	39.5
0.02	2.55	36.5

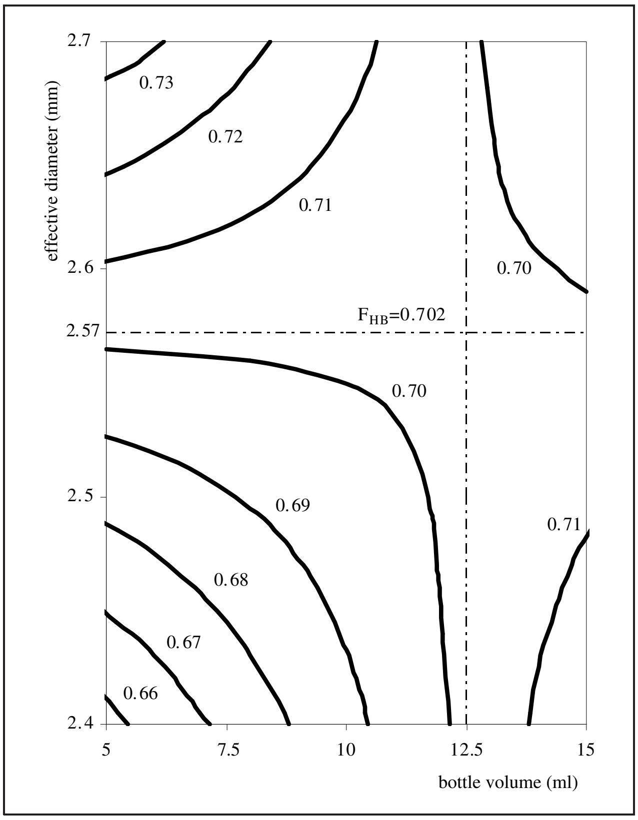

Fig. 2: Effect of the dropper bottle volume and the effective diameter of the dropper tip on the F_{HB} value of dropper tips

will be fitted to the 5 ml dropper bottle than to a bottle of larger volume. In those cases, unfortunately, the significant negative interaction of both variables (V; d) complicates the eye drop weight estimation. However, the dropper bottles of volumes larger than 10 ml are not recommended for eye drops (Ph. Eur. 2004). With respect to the limited number of the dropper tips investigated in this work, it should finally be noted that the most important results are recorded in the bottom left part (quadrant) of Fig. 1.

2.2. Harkins and Brown's factor

Based on formula of Tate's law, the theoretical maximal drop weights of water, 0.01% and/or 0.02% solution of BAC, respectively, were estimated for both the known surface tension of the liquid and the diameter of dropper tip effective perimeter using Eq. (5). In all cases, the experimentally observed drop weights were lower in accordance with theory (Harkins and Brown 1919). Comparing the measured drop weights and the theoretical values, Harkins and Brown factors F_{HB} were calculated (Eq. 8) for both stalagmometer and the dropper tips investigated. While the stalagmometer F_{HB} values are shown in the last column of Table 2, F_{HB} values for plastic dropper tips are summarized in Table 3. On the contrary to the drop weights investigation results, the F_{HB} values were not (the stalagmometer) or less (the dropper tips) influenced by the surface tension of BAC solutions.

The simultaneous effect of the volume of the dropper bottle V (in ml) and the effective diameter of the dropper tip d (in mm) on the F_{HB} values of the dropper tips can be described by regression Eq. (10) which is equal to Eq. (9). The coefficients of regression (10) for the solutions of BAC in concentrations of 0–0.02% are presented in Table 6. The coefficient k_{12} indicates the non-linear nature of the F_{HB} influencing similarly to drop weight influencing. In the last column, Table 6 is completed with values of square multiple regression coefficient r^2 again.

Similarly to Fig. 1, the effect of the volume of the dropper bottle V and the effective diameter of the dropper tip d on the F_{HB} values is shown for water in Fig. 2; the separate plots correspond to F_{HB} values in the range of 0.66–0.73. In the range investigated, the relationship was symmetrical around two central lines dividing the plot into four symmetrical quadrants. The horizontal axis corresponding to d = 2.57 mm intersected the vertical one which corresponded to V= 12.5 ml. At the point of intersection, comported with F_{HB} = 0.702, the F_{HB} value was constant i.e. for d = 2.57 mm it was not influenced by the bottle volume (horizontal axis) whereas for V = 12.5 ml it was not influenced by the effective diameter (vertical axis).

The central point (F_{HB} = 0.702) could also be understood as so-called "minimax" in this three-dimensional graph (surface response) since diagonally, the plot was symmetrical around two axes connecting the points of culmination of contour lines at opposite quadrants. Diagonal axes cut through the central point (F_{HB} = 0.702) as well. In a view of the upward-sloping diagonal axis, the point of intersection indicates the maximal value of studied F_{HB} contrary to the minimal value of studied F_{HB} on the downward-sloping diagonal axis. It should be noted that a similar central point could be indicated in Fig. 1 as well but its localization is out of the range investigated.

Similarly to the results of drop weight determination, the F_{HB} values increased linearly with increase in the effective dropper tip diameter if the bottle volume was 5 ml. For higher bottle volumes, the resulting value of F_{HB} depends on the actual combination of both variables. For example, a F_{HB} of 0.66 was found for the effective diameter d = 2.4 mm if the dropper bottle of V = 5.5 ml was used while a F_{HB} of 0.71 corresponded to V = 13.8 ml for the same effective diameter. The different effect of the bottle volume on the F_{HB} values resulted from the significant negative interaction of both tested variables (Eq. 10) similarly to results of the drop weight investigation.

Table 6: **Parameters of regression Eq. (10) for estimation of F_{HB} value**

BAC (%)	k_0	k_1	k_2	k_{12}	r^2
0	−0.4154	0.0898	0.4344	−0.03492	0.8933
0.01	−0.5314	0.1052	0.4836	−0.04123	0.8686
0.02	−0.5214	0.1052	0.4836	−0.04123	0.8686

Table 7: **Localization of central lines in contour line plots for estimation of F_{HB} value (Eq. 10)**

BAC (%)	V (ml)	d (mm)	F_{HB}
0	12.5	2.57	0.702
0.01	11.8	2.55	0.703
0.02	11.8	2.55	0.713

Similar contour line plots like for water were also obtained for the 0.01% and 0.02% solution of BAC, respectively. The values of both the effective diameter d (mm) and the bottle volume V allowing the horizontal and vertical axis to be localized in contour line plots are presented for all tested solutions of BAC in Table 7. In the last column, Table 7 is completed with the corresponding F_{HB} value identifying the point of intersection. As these values of the F_{HB} are very close to the average F_{HB} values obtained experimentally (Table 3), the regression model (10) could be considered to be proper. Small differences resulted from the round coefficients of regression.

With respect to the limited number of the dropper tips investigated in this work, finally, it should be noted again that the most important results are recorded in the bottom left quadrant of Fig. 2.

2.3. *Stalagmometry and classification of dropper tips*

Nowadays, the eye dropper tips are classified on the basis of geometric parameters (Van Santvliet and Ludwig 2004). However, there is no sufficient systematic information about the drop weights in consequence to eye dropper tip design and dimension.

The theoretical maximal weight of a drop is directly proportional to the surface tension of the drop forming liquid and to the diameter of the effective capillary perimeter at which a drop is formed (Tate 1864). In all cases, the measured drop weights are lower than the theoretical maximal ones (Harkins and Brown 1919).

Although many differences follow the drop formation process using the glass capillary and/or the dropper tips, nevertheless, the principles are similar. Therefore, a comparison between the experimentally measured drop weight and the theoretical one might be useful in the investigation of eye dropper tips behaviour. For this reason, the drop dispensing using plastic dropper tips was compared with stalagmometry in this work. Assuming both the vertical drop dispensing and the clearly defined horizontal effective perimeter of the dropper tips, Harkins and Brown's factors were expressed as the ratio between the measured drop weight and the theoretical one.

Under standard experimental conditions, the mean drop weights of water, 0.01% and/or 0.02% solution of BAC obtained for the Traube's stalagmometer were equal to 62% that of theoretical drop weights. On the other hand, seven commercially available plastic eye dropper tips produced drops with weights in range of 66–76% those of theoretical ones. These results were significantly greater than those noted for, the stalagmometer. Differences between stalagmometer and the dropper tips indicated deviations in the drop formation process resulting probably from the different driving mechanism of the drop formation, the fact that the drop dispensing rate in case of the stalagmometer could hardly be controlled and, finally, from the absence of the definite flat end of the capillary in case of the dropper tips. The F_{HB} values estimated were not (stalagmometer) or very slightly (dropper tips) influenced by the concentration of BAC.

Based on the results of F_{HB} estimation, a classification of the dropper tips into two groups could be proposed. The first one, characterized by a F_{HB} close to that of the stalagmometer value, and the second one, characterized by a F_{HB} greater than 0.72. Failures in the drop expelling using the dropper tips of the first group were often noted during our study resulting from the absence of a capillary and/or from the retention of air bubbles inside a narrow central duct. Dropper tips of the second group showed the more complicated eye drop weight influencing as the result of the more complicated design. Using such dropper tips, optimization of drop dispensing conditions including the drop dispensing angle should be desirable. As demonstrated in our previous study (Šklubalová and Zatloukal 2006), for example, the non-linear relationship between the eye drop weight and the dispensing angle could occur during administration of drops upon various dispensing angles.

Since determination of the F_{HB} value is associated with the estimation of the theoretical drop weight, so that it could be used in the dropper tip classification, two important additional details are needed: the first one, instead of the inner diameter of the capillary, the more suitable geometrical estimation of the horizontal effective perimeter at which the drops are really formed, and the second one, the information about wetting properties of material the dropper tips are made of. Although containers for ophthalmic preparations are made of low-density polyethylene or polypropylene as required by the European Pharmacopoeia, detailed information about additives and properties of material used, and especially its wetting behaviour, are difficult to obtain.

It should be noted that our proposed classification of the dropper tips using the F_{HB} value is based on testing a limited number of samples only. Validation, therefore, is associated with the complete information about dropper tips as well as the investigation of a larger number of various dropper tips in future.

In conclusion, the weight of eye drops produced by seven plastic eye dropper tips was studied at up-right position and compared with stalagmometry. The decrease in the surface tension of the solutions of BAC in the concentration range of 0–0.02% v/v resulted in the linear decrease of drop weights for both stalagmometer and/or plastic dropper tips investigated. For the solutions of known surface tension, the effective diameter of the horizontal perimeter of the dropper tip surface from which drops fell down, and the volume of the dropper bottle influenced the drop weights significantly. The regression equations obtained were characterized by the significant negative linear interaction between both related factors. Finally, comparing the experimentally measured drop weights and the maximal theoretical ones, Harkins and Brown's factors were determined. A classification of the eye dropper tips using the Harkins and Brown's factors is proposed.

3. Experimental

3.1. *Materials*

Seven different randomly chosen commercial multidose eye drop dispensing systems each consisting of the plastic dropper bottle and the plastic dropper tip were used. In Table 1, the diameter d (mm) of the effective perimeter of the dropper tip orifice and the volume V (ml) of the dropper bottle for all dispensing systems investigated are referred. The effective diameters were measured at up-right position by a micrometer upon the magnifying glass.

3.2. *Preparation of solutions*

Solutions of the surface-active antimicrobial preservative, benzalkonium chloride (BAC) (Acros Organics, New Jersey, USA), were prepared by addition of the required volume of 50.0% v/v solution of BAC to water to achieve concentrations of 0.01% v/v or 0.02% v/v, respectively. Solutions were kept in the dark, at room temperature.

3.3. *Measurement of surface tension*

Surface tension measurements were performed using Traube's stalagmometer at 20.0 ± 0.5 °C. The diameter of the flat end of the stalagmometer was d = 5.14 mm. The stalagmometer was fixed at vertical position and calibrated with distilled water. Surface tension σ ($mN \cdot m^{-1}$) of 0.01% v/v or 0.02% v/v solutions of BAC was calculated from mean drop weights assuming that the densities of the very low concentrated aqueous solutions were equal to that of water. As the surface tension of water is equal to 72.75 mN m^{-1} at 20 °C, the surface tension of the aqueous solutions of BAC could be estimated from the equation:

$$\sigma = 72.75 \cdot \frac{m_{BAC}}{74.36} \qquad (11)$$

where m_{BAC} (in mg) represents the mean drop weights of BAC solution and 74.36 is the mean weight (in mg) of a drop of water at 20 °C.

An average of five surface tension measurements, with a variability coefficient lower than 1%, is reported in Table 2. In the right part, data are completed with the values of the theoretical maximal weight of drops M calculated using Eq. (5) as well as the Traube's stalagmometer F_{HB} value (calculated using Eq. 8).

3.4. Determination of drop weights

The original containers were opened and both the dropper bottle and the dropper tip were rinsed thoroughly with distilled water to remove the original eye drop medication. After that, the bottle was filled with 5, 10 and/or 15 ml (according to the bottle volume) of water, 0.01% or 0.02% solution of benzalkonium chloride, respectively, and the dropper tip was attached again.

The filled dropper bottle fitted with the dropper tip was converted to upright position (the angle of 90°) and fixed to the holder. The bottle was then carefully squeezed to dispense ten drops within a time interval of 1 drop per second into a glass beaker. Collected drops were weighed immediately on an analytical balance (model 2462, readability 0.1 mg, Sartorius, Göttingen, Germany). This way, the procedure was repeated ten times for each drop dispensing system investigated and the mean drop weight m (mg) was expressed. The mean drop weights of water and/or solutions of BAC, variability coefficient of which was always lower than 1%, together with corresponding values of Harkins and Brown's factors are summarized in Table 3.

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