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Research paper

The influence of penetration enhancers on the volume instilled of eye drops

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Abstract

The influence of the physicochemical properties of various penetration enhancers on the weight of drops dispensed from flexible plastic dropper bottles was examined. Two dropper tips with a different design were compared and the dropper bottle was held in the upright position (90° angle) or at a 45° angle. These two angles were chosen to simulate the manipulation of an eye dropper bottle by the patient. The surface tension of the penetration enhancer solutions was determined using the dynamic drop volume method. The dynamic surface tension values ranged from 65 to 30 mN/m. The lower the surface tension of the solution, the lower the weight of the drop delivered. Both the design of the dropper tip and the manipulation technique of the dropper bottle had a moderate to important influence on the drop weight. The relationship between the surface tension of the penetration enhancer solution instilled and the comfort of the patient was evaluated by an acceptability test based on answering a questionnaire. Penetration enhancers can be used to reduce the drop size of conventional ophthalmic solutions on condition that they do not elicit local irritation. © 1998 Elsevier Science B.V.

Keywords: Drop size; Ophthalmic formulation; Penetration enhancer; Solution acceptability; Surface tension

1. Introduction

Upon instillation, ophthalmic solutions are drained rapidly from the precorneal area and diluted by tear turnover, so that only a small amount of drug remains in the conjunctival sac to exert a local action or to be absorbed by the eye tissues [1]. To improve the topical bioavailability and therapeutic response of ophthalmic drugs, efforts are aimed at prolonging the ocular residence time of the medication and at enhancing the ocular permeation of the drug molecules [2,3].

Besides the viscosity increase of the vehicle by addition of water-soluble, natural, semi-synthetic or synthetic viscolyzers [4,5], the utility of mucoadhesion of polymers [6] and drug carrier systems such as nanoparticles, microspheres and liposomes [7,8] were demonstrated to reduce the drainage loss of topically applied solutions and to increase the bioavailability of the drugs instilled. Penetration enhancers or absorption promoters, on the other hand, increase transiently the permeability characteristics of the ocular tissues. Most agents are surfactants which alter the physical properties of cell membranes, e.g. by removal of phospholipids or membrane solubilization, whereas EDTA loosens the tight junctions between the superficial epithelial cells, facilitating paracellular transport [9,10]. Sasaki et al. [11] demonstrated that EDTA, taurocholic acid and capric acid increased significantly the corneal permeability of hydrophilic β-blocking agents in rabbits, without local toxicity. Only with saponines was a slight irritation observed after instillation.

Penetration enhancers are also employed to increase the ocular absorption of peptide drugs, e.g. insulin. The ocular route is a simple, non-invasive, more accurate and less expensive alternative for the systemic delivery of peptides compared to the buccal, nasal, rectal, vaginal or dermal routes and avoids painful parenteral injections or gastrointestinal degradation [12–14].

Normally, the human tear volume averages 7 μl, with 1 μl

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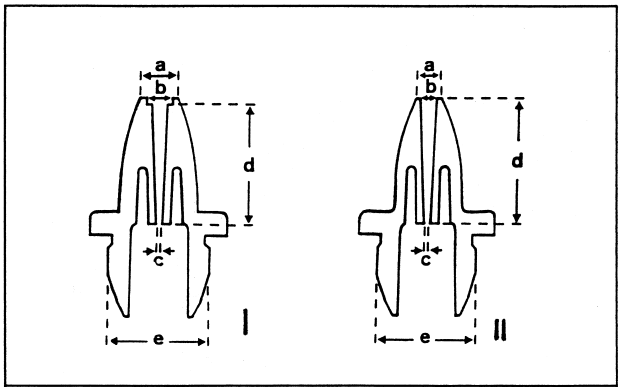
in the precorneal tear film and about 3 μl in each marginal tear meniscus [15]. The conjunctival sac can only hold momentarily about 20–30 μl fluid without overflow onto the cheek. The average drop size of commercially available topical medications is, however, about 39 μl, with a range of 25–56 μl [16]. Thus, the volume instilled in excess is diminished rapidly by reflex blinking and by the extended drainage capacity through the naso-lacrimal system. There the drug can be absorbed systemically without first-pass metabolism by the liver and cause mild to life-threatening side effects [17,18]. Reduction of the size of drops to be instilled results in a decreased systemic drug loss with a decreased potential for systemic toxicities. As an advantage, an equivalent or even improved ocular bioavailability and therapeutic response is obtained [2,19]. A single administration of a 15-μl clonidine hydrochloride 0.50% eye drop, for example, resulted in the same reduction of the intra-ocular pressure as a regular 70-μl drop, but without a fall in systemic blood pressure [20].

The aim of the present study was to determine the influence of the physicochemical properties of six penetration enhancers proposed in animal studies on the weight of drops dispensed from flexible dropper bottles. Also, the patient acceptability of the penetration enhancer solutions was examined.

2. Materials

2.1. Penetration enhancer solutions

The following materials were used as received without further purification: polyoxyethylene-9-laurylether (Polidocanol, BL-9), *n*-octyl-β-glucopyranosid (OcGlu), sodium deoxycholate (Deoxy) and tyloxapol (Tyl) from Sigma (München, Germany), polyoxyethylene-20-stearylether (Brij® 78) from ICI Surfactants (Middlesbrough, UK) and polyoxyethylene-20-sorbitanmono-oleate (Polysorbate® 80, P80) from Federa (Brussels, Belgium). All other chemicals were of analytical grade. Deionized, freshly double-distilled water was used throughout the study.



Tip	a	b	c	d	e	
I	2.4	1.6	0.8	10.8	9.8	mm
II	2.0	1.5	0.8	10.7	8.6	mm

Fig. 1. The design and dimensions of the plastic dropper tips.

2.2. Dropper tips and flexible dropper bottle

Two commercially available plastic dropper tips made of low-density polyethylene were examined. The design and dimensions of the dropper tips are summarized in Fig. 1. The flexible plastic dropper bottles were also made of low-density polyethylene. They were round opaque bottles that could contain 10 ml solution. The dropper tip was to be snapped in the neck of the bottle by press-fit positioning.

3. Methods

3.1. Solution preparation

All penetration enhancer solutions were made by adding the required amount of substance to an aqueous, iso-osmotic phosphate buffer solution, pH 7.4 (Ph. Helv. VI) (w/v). The solutions for the acceptability test were prepared aseptically by filtration through a sterile cellulose nitrate membrane filter with pore size 0.22 μm (Sartorius, Göttingen, Germany). The first 5 ml of filtrate were discarded, and the rest of the filtrate was collected in sterile glass recipients.

3.2. Physicochemical measurements

The dynamic surface tension (σ) of the solutions was determined using the dynamic drop volume method based on Tate's law as described by Van Hunsel et al. [21]. The drop volume for 10 drops delivered from a calibrated glass capillary was determined at different flow rates and the dropping time was noted. The dynamic surface tension (mN/m) was calculated from the drop volume and the dropping time by means of an empirical relation. The surface tension can be plotted as a function of the adsorption of the solute molecules at the air/liquid interface of the drop, designated as the adsorption time.

The dynamic viscosity (η) of the solutions was measured using an Ostwald viscosimeter (KPG Viskosimeter, Schott-Geräte, Mainz, Germany) (Ph. Belg. VI). After a 15-min temperature equilibration time, the efflux times were measured at room temperature. The mean viscosity (mPa $\times$ s) of six measurements was calculated for each solution.

The osmolality of the solutions was determined using a vapour pressure osmometer (model 5500, Wescor, Logan UT, USA). The measurements were performed in triplicate and the mean osmolality (mOsm/kg) for each solution was calculated.

The pH of each solution was measured at room temperature with a CG840 pH meter (Schott-Geräte, Mainz, Germany).

Table 1

The physicochemical properties of the penetration enhancer solutions

Solution (conc. w/v)	Surface tension (mN/m)	Viscosity (mPa × s)	Osmolality (mOsm/kg)	pH
Phosphate buffer	69.12	1.07	273.0	7.38
P80 0.01%	62.99	1.09	267.3	7.28
P80 0.20%	43.66	1.05	264.3	7.35
OcGlu 0.25%	36.03	1.06	267.0	7.36
BL-9 0.50%	31.01	1.05	267.3	7.35
Brij 78 0.50%	48.37	1.07	269.7	7.34
Deoxy 0.10%	44.22	1.06	264.3	7.38
Tyl 0.10%	48.62	1.02	260.3	7.30

3.3. Drop delivering method and drop weight determination

The drop size of the penetration enhancer solutions was characterized by its weight, which was determined using an apparatus developed in our laboratory to dispense drops separately under standard conditions [22]. A flexible dropper bottle filled with 10 ml solution and fitted with a dropper tip (I or II) was fixed in the upright position (90° angle) or at a 45° angle in the apparatus. A motor-driven pusher compressed the bottle at a constant rate, at 30 rpm or at 100 rpm, until a drop was delivered. The drop was weighed immediately on an analytical balance (Sartorius model 2462, readability 0.1 mg, Sartorius, Göttingen, Germany). The mean weight and standard deviation of 10 drops at both speeds (100 and 30 rpm) and at both angles (90° and 45°) were calculated for each solution and for each dropper tip (I and II).

3.4. Solution acceptability test

Using a sterile Eppendorf pipette (Eppendorf, Hamburg, Germany) a 25-μl drop of the penetration enhancer solution was instilled into the conjunctival sac of six volunteers from whom informed consent was obtained. The volunteers were asked to give their own evaluation by answering a standard questionnaire. The solution was given a 0–5 score by comparing the treated eye with the untreated eye. The mean irritation, lachrymation, sensation, vision and pain score were calculated for each solution [23].

3.5. Statistical analysis

Drop weight determination data were analyzed with the Student *t*-test for two values. A *P*-value of 0.05 or less was considered significant. For matrices of results, multivariate linear regression without interaction was used.

Statistical analysis of the results of the solution acceptability test was performed using the Mann–Whitney test. A *P*-value of 0.05 or less was again considered significant.

4. Results and discussion

4.1. Physicochemical properties of the solutions

The physicochemical properties of the penetration enhancer solutions are summarized in Table 1. The solutions were non-viscous and iso-osmotic and the pH value averaged 7.36. The values of the dynamic surface tension given in Table 1 corresponded to an absorption time of approximately 1 s, which correlated to the time necessary to dispense rapidly (speed of the motor 100 rpm) a drop from the flexible dropper bottle. In Fig. 2, the dynamic surface tension of the solutions is plotted as a function of the absorption time.

The phosphate buffer solution had a dynamic surface

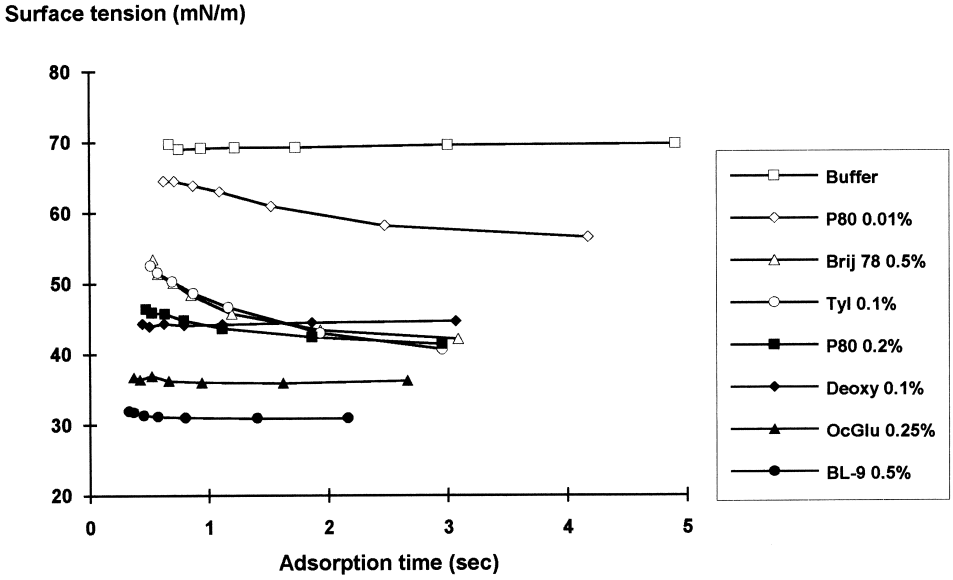


Fig. 2. The dynamic surface tension of the penetration enhancer solutions as a function of the absorption time.

Table 2

The drop weight of the penetration enhancer solutions for dropper tip I at the 90° angle

Solution	Drop weight (mg)	
	100 rpm	30 rpm
Phosphate buffer	44.69 ± 0.34	42.47 ± 0.26
P80 0.01%	42.85 ± 0.59	40.63 ± 0.45
P80 0.20%	33.04 ± 0.55	28.27 ± 0.29
OcGlu 0.25%	25.65 ± 0.98	24.44 ± 1.05
BL-9 0.50%	23.57 ± 0.75	23.08 ± 0.42
Brij 78 0.50%	37.20 ± 0.34	32.33 ± 0.65
Deoxy 0.10%	31.01 ± 0.49	28.95 ± 0.51
Tyl 0.10%	37.61 ± 0.35	31.11 ± 0.47

tension value equivalent to that of double distilled water. Addition of a penetration enhancer to this ophthalmic vehicle lowered the surface tension, ranging from 60 mN/m for the P80 0.01% solution to 30 mN/m for the BL-9 0.50% solution. For some surface active substances, like Brij 78, Tyl and P80, an equilibrium surface tension value was only attained after a certain time interval, because the solute molecules needed more time to migrate to, orient and act at the liquid/air interface. The surface tension value of OcGlu, Deoxy and BL-9 did not change as a function of the adsorption time and was, therefore, independent of the drop formation rate.

4.2. Drop weight determination

4.2.1. Influence of the surface tension

The results of the drop weight determination of the penetration enhancer solutions for dropper tip I at the upright position are summarized in Table 2 and plotted in Fig. 3. The highest drop weight was observed for the phosphate buffer solution, the lowest for the BL-9 0.50% solution at both speeds of the motor compressing the dropper bottle, 100 rpm (results indicated with black bars) and 30 rpm (results indicated with white bars). According to Tate's law (Eq. (1)):

$$W = mg = 2\pi\sigma r \quad (1)$$

where W is the weight of the drop, m is the mass of the drop, g is the acceleration of gravity, σ is the surface tension of the liquid and r is the radius of the tip.

The lower the surface tension of the solution dispensed, the lower the drop weight obtained. The linear relationship between the drop weight and the surface tension was confirmed using regression analysis ($r = 0.94$). Addition of 0.50% BL-9 as a penetration enhancer to an ophthalmic vehicle decreased the surface tension from 69 to 31 mN/m, resulting in a 47% reduction in drop size from 44.69 to 23.57 mg at 100 rpm.

Decreasing the speed of the motor compressing the dropper bottle from 100 to 30 rpm, and therefore squeezing the

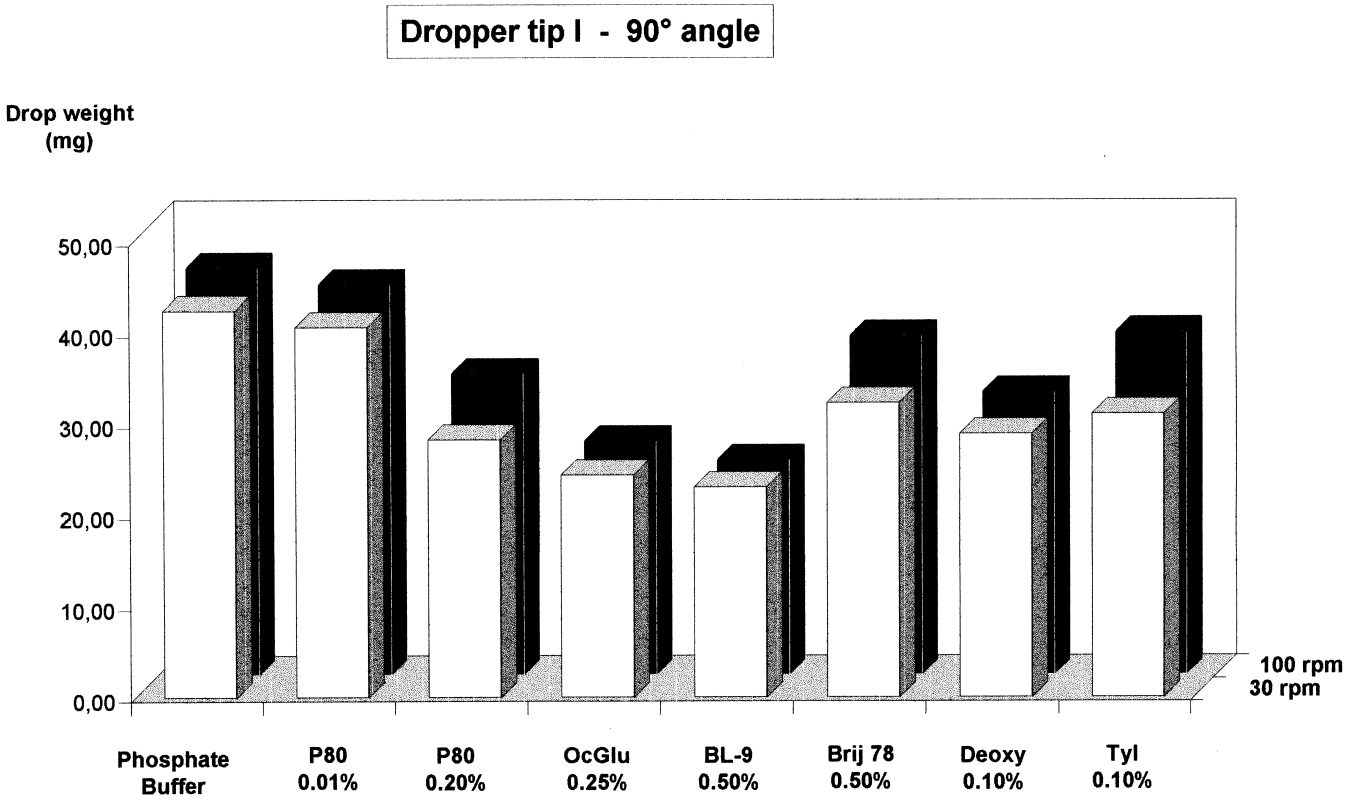


Fig. 3. The drop weight of the penetration enhancer solutions for dropper tip I at the 90° angle (speed of the motor compressing the bottle: white bars, 30 rpm; black bars, 100 rpm).

dropper bottle more slowly, resulted in a lower weight of the drops dispensed. This is explained by the fact that at the instant of the breaking away at the outer orifice of a dropper tip, an extra impulse of liquid is injected into the falling drop when the drop formation rate is high. At lower rates, the drop formation is slower and less or no extra liquid impulse occurs. The decrease in drop weight ranged from 0.49 mg (2.08%) for the BL-9 0.50% solution to 6.50 mg (17.28%) for the Tyl 0.10% solution, all statistically significant except for the BL-9 0.50% solution.

The hydrodynamic effect of the drop formation rate also had an impact on the surface tension of the solutions, as shown in Fig. 2. By decreasing the speed of squeezing the dropper bottle, the absorption time was lengthened, resulting in a lower surface tension value for the Tyl 0.10%, P80 0.20% and Brij 78 0.50% solutions at 30 rpm compared to 100 rpm. The decrease in drop weight of 10% or more for these surface active substances, when reducing the speed of the motor, was therefore relatively larger than the 5% decrease for the other solutions, Deoxy, BL-9 and OcGlu, where an equilibrium surface tension value was attained immediately. In contrast to a static measuring method, where only an equilibrium value is determined, a dynamic measuring method for the surface tension gives more information on the influence of the drop formation rate on the surface tension, which in turn influences the drop weight.

4.2.2. Influence of the dropper tip design

In Fig. 4, the drop weight of the penetration enhancer solutions dispensed from dropper tip II with the dropper bottle held in the upright position is depicted. The lowest drop weight was observed for the BL-9 0.50% solution with the lowest surface tension, the highest for the P80 0.01% solution which, however, was not significantly different from that of the phosphate buffer solution. Here also, the lower the surface tension of the solution, the lower the drop weight, with a maximum decrease in drop weight of 37% for the BL-9 0.50% solution. The drop weight was also always significantly higher at 100 rpm than at 30 rpm except for the BL-9 0.50% solution, and the difference in drop weight was relatively larger for the Tyl 0.10%, P80 0.20% and Brij 78 0.50% solutions. Fig. 5 depicts a drop of the phosphate buffer solution formed at the outer orifice of dropper tip II.

Comparing the design of the two dropper tips, an annular recess surrounded the outer orifice of dropper tip I, clearly delineating the surface area from which a drop will fall. Dropper tip II on the other hand had a hemispherical surrounding of the outer orifice, defining less clearly the surface area. The diameter of the outer orifice of dropper tip I was also larger than that of dropper tip II (2.4 vs. 2.0 mm). This resulted in a higher drop weight for the penetration enhancer solutions dispensed from dropper tip I at the 90° angle than from dropper tip II. The drop weight differences ranged from 1.24 mg (3.75%) for the P80 0.20% solution to

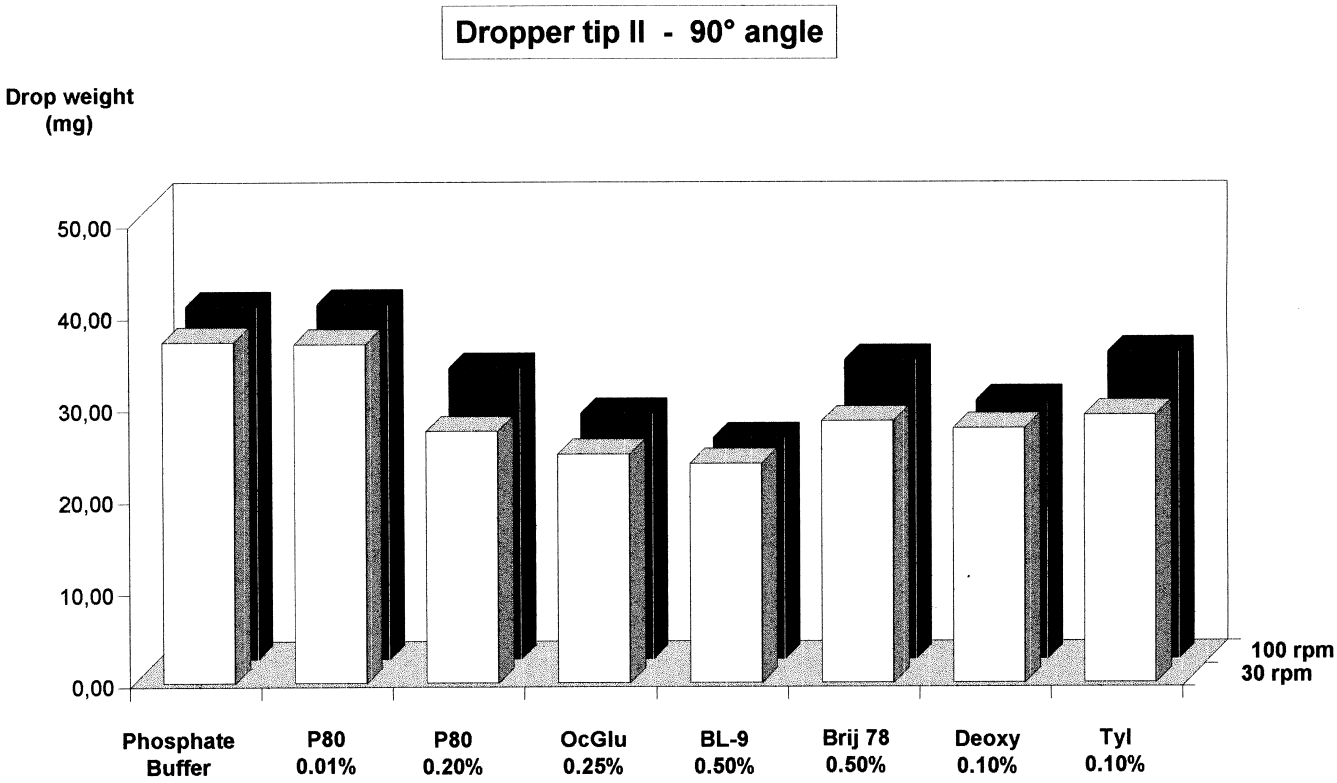


Fig. 4. The drop weight of the penetration enhancer solutions for dropper tip II at the 90° angle (speed of the motor compressing the bottle: white bars, 30 rpm; black bars, 100 rpm).

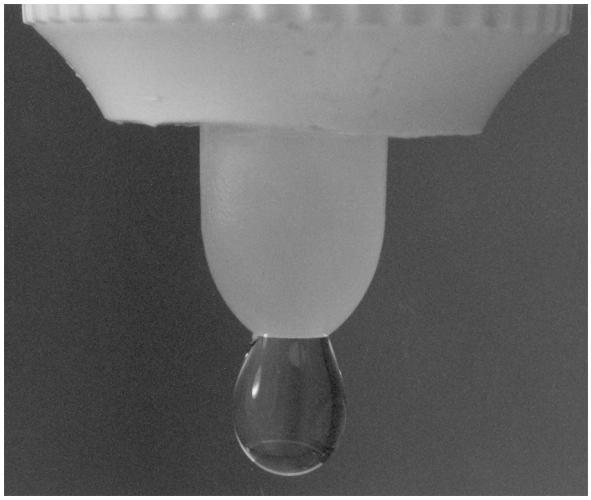


Fig. 5. Image of a drop of the phosphate buffer solution formed at the outer orifice of dropper tip II.

6.13 mg (13.72%) for the phosphate buffer solution at 100 rpm, and from 0.87 mg (3.08%) to 5.37 mg (12.64%) for the same solutions at 30 rpm. Only the drop weight for the OcGlu 0.25% and BL-9 0.50% solutions with a surface tension of about 35 mN/m was 3% higher when dispensed with dropper tip II. This value approached the critical surface tension of the polyethylene material [24], possibly causing wetting of the material and therefore an increase in surface area from which a drop will fall. In a preliminary study, we found that dispensing a liquid with a surface tension value of 23 mN/m from dropper tip I was almost impossible because the liquid immediately wetted the lateral surfaces of the tip when inverting the bottle.

Multivariate linear regression analysis, without interactions of a matrix containing the results from all penetration enhancer solutions dispensed with both dropper tips at the 90° angle, demonstrated that the surface tension of the solution dispensed, the design of the dropper tip and the speed of squeezing the dropper bottle had a significant influence on the drop weight. The regression equation (Eq. (2)) with a correlation coefficient $R = 0.9381$ could be formulated as:

$$Y = 11.88 - 2.36\,X_{\text{dropper tip}} + 0.48\,X_{\text{surface tension}} + 0.02\,X_{\text{speed of the motor}} \quad (2)$$

with a P-value of 0.006, <0.001 and 0.042 for factor dropper tip, surface tension and speed of the motor, respectively.

Devices to reduce the drop volume of eye drops have been designed experimentally by inserting an intravenous cannula in the dropper tip. A reduction of 25–60% was obtained depending on the cannula dimensions, with the same therapeutic results as with a normal volume drop [25]. Brown et al. [26] determined that with a constant inner diameter of the dropper tip orifice, the drop size increased linearly with the outer diameter and that the inner diameter also affected the drop size, but the relationship was not linear.

4.2.3. Influence of the angle at which the dropper bottle is held

When instilling an eye drop into the conjunctival sac, the patient has to hold the dropper bottle above his eye at a 90° angle without touching the ocular tissues [27]. In practice, this angle varies from 30° to 90°. To simulate this manipulation technique and to determine the influence of the angle at which a dropper bottle is held, the apparatus was positioned at an angle of 45°.

Fig. 6 shows the drop weight of the penetration enhancer solutions when delivered from dropper tip I at the 45° angle. From the results, the same conclusions could be drawn as with the bottle held at the 90° angle. Squeezing the dropper bottle more slowly resulted in a decrease in drop weight, except for the P80 0.01%, BL-9 0.50% and the Deoxy 0.10% solutions, where a small, but not statistically significant increase in drop weight was observed. Also, the surface tension of the solution had an important impact on the drop weight.

When holding dropper tip I at the 45° angle, the cross-sectional surface area was decreased compared to the upright position due to the annular recess surrounding the outer orifice. Since according to Tate's law (Eq. (1)) the weight of a drop is proportional to the radius of the dropper tip, therefore, a decrease in drop weight was obtained when changing the angle from 90° to 45° for the penetration enhancer solutions with a surface tension value higher than 45 mN/m. For the OcGlu 0.25%, Deoxy 0.10% and BL-9 0.50% solutions with a surface tension under 45 mN/m, a significantly higher drop weight was observed at the 45° angle.

In Fig. 7, the results of the drop weight determination of the solutions with dropper tip II at the 45° angle are presented. The surface tension of the solution and the speed of squeezing the dropper bottle once again had a significant influence on the drop weight. Because of the hemispherical perimeter of the outer orifice of dropper tip II, the cross-sectional surface area at the 45° angle was not reduced to the same extent as with dropper tip I. At the outer orifice of dropper tip II, the drops were also formed on the external lateral surfaces of the tip, as can be seen in Fig. 8. These surfaces were not well defined and, consequently, resulted in a higher drop weight for all penetration enhancer solutions at the 45° angle compared to the 90° angle except for the phosphate buffer solution at 30 rpm.

4.3. Solution acceptability

Considering the potential ocular irritancy and discomfort elicited by surface active substances [28] and, consequently, penetration enhancers, tolerance of the solutions was evaluated. The six volunteers (three men and three women) gave their own evaluation of the solutions instilled by comparing

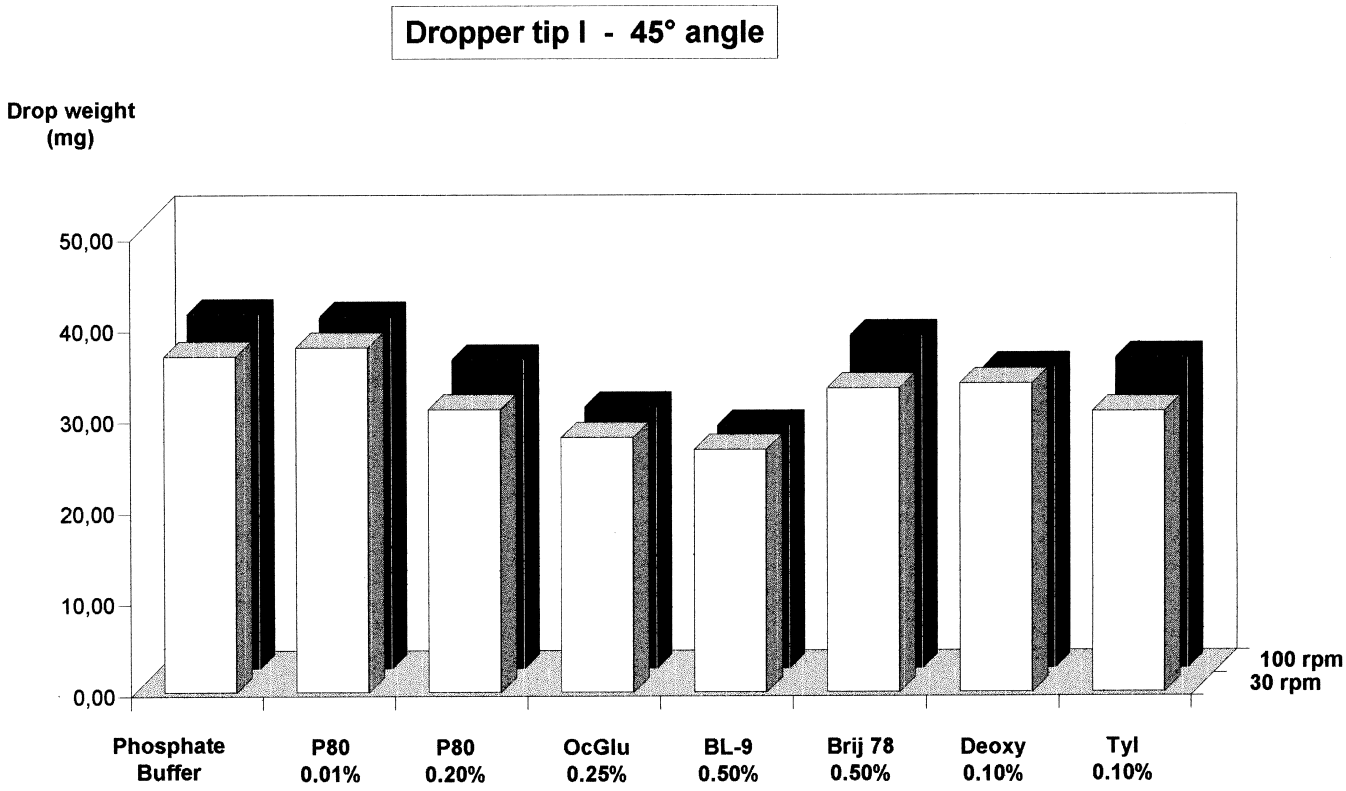


Fig. 6. The drop weight of the penetration enhancer solutions for dropper tip I at the 45° angle (speed of the motor compressing the bottle: white bars, 30 rpm; black bars, 100 rpm).

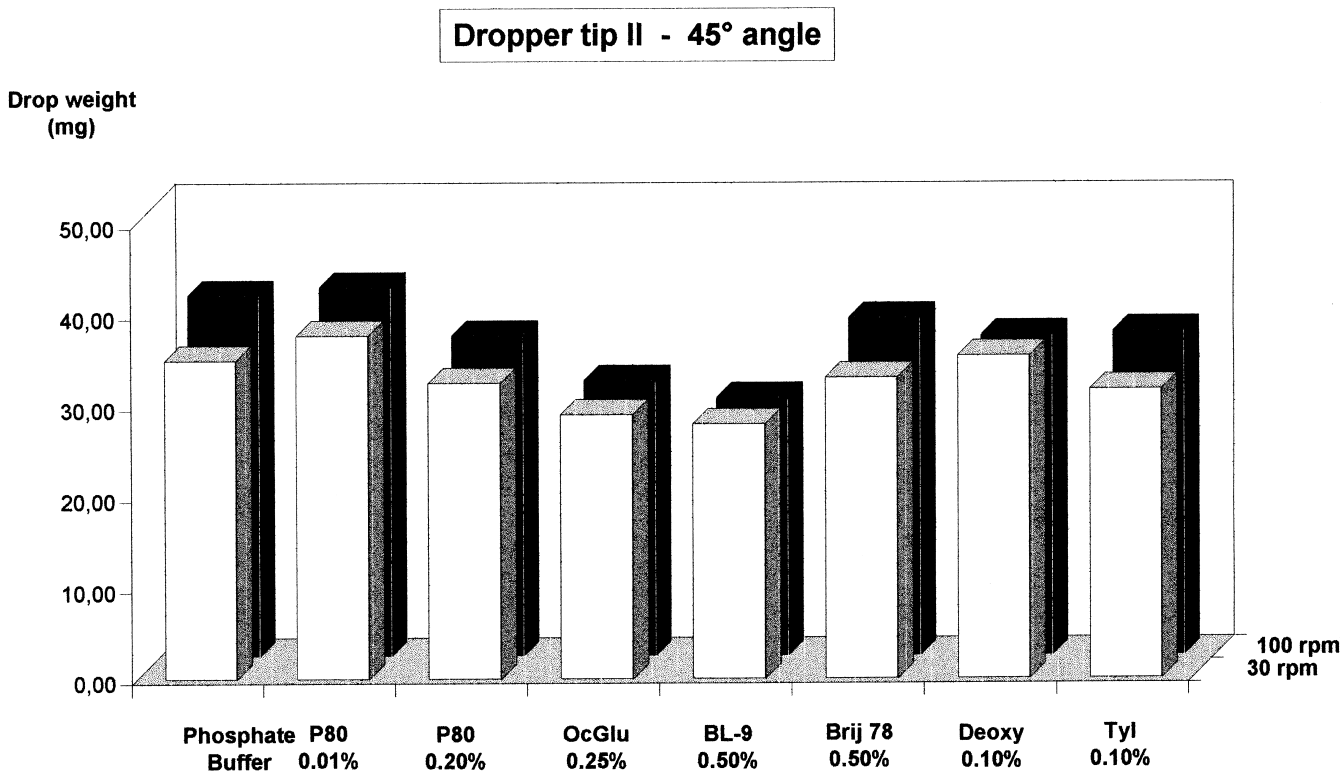


Fig. 7. The drop weight of the penetration enhancer solutions for dropper tip II at the 45° angle (speed of the motor compressing the bottle: white bars, 30 rpm; black bars, 100 rpm).

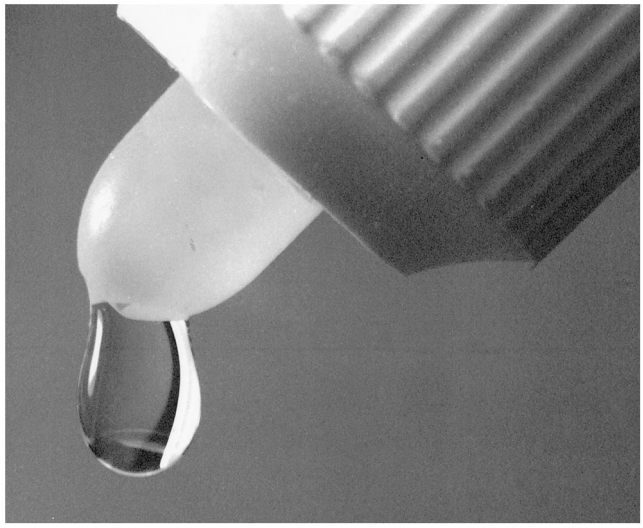


Fig. 8. Image of a drop of the phosphate buffer solution formed at the outer orifice of dropper tip II at the 45° angle.

the treated left eye with the control right eye. The standard questionnaire contained the following questions to which a 0–5 score was given:

A. Does your eye hurt? Irritation score: no irritation (0), mild (1), hurting (2), stinging (3–5).
B. Does your eye feel watery? Lachrymation score: eye watery (0 to 2), lachrymation (3 and 4), overflow onto the cheek (5).
C. How does the eye drop feel? Sensation score of the solution on the eye: smooth (0), thick (1), sticky (2), gritty (3), sandy (4 and 5).
D. Does the drop cause blurring of the vision? Vision score: clear (0), blurred vision (1–5).
E. Does the drop cause a sensation of pain at the inner canthus? Pain score: 0–5.

After the test, the mean value for each question was calculated separately for each solution. Thus, the maximum value of the mean rating that could be obtained for a question was 5. The higher the value, the less the solution was tolerated by the volunteers. The results of the acceptability test for the penetration enhancer solutions are presented in Fig. 9.

In general, the penetration enhancer solutions examined were well tolerated by all volunteers, as indicated by the low score values. The solutions caused a mild, transient local irritation after instillation. Only the BL-9 0.50% solution caused immediate irritation and pain, with heavy lachrymation. Results of the statistical analysis showed that this solution was significantly more irritating compared to all other solutions ($P < 0.001$), and that the Deoxy 0.10% and the Tyl 0.10% solutions caused more irritation then the OcGlu 0.25%, Brij 78 0.50% and the P80 solutions. The surface tension of the BL-9 0.50% solution, 31 mN/m, was lower than the surface tension of the lacrimal fluid (40–46 mN/m) [29]. The non-ionic detergent possibly interacted with the superficial lipid layer of the tear film, resulting in the rupture of the tear film or a destabilization of the epithelial tissues. The OcGlu 0.25% solution also exhibited a low surface tension, 37 mN/m, but this solution was not irritating. The Brij 78 0.50% solution was the best accepted solution. As commercial products were used, irritation could be due to impurities present in the penetration enhancer solution.

Saettone et al. [9] demonstrated that polyoxyethylenealkylethers and bile salts can be used as effective and safe penetration enhancers for the hydrophilic β-blocking agents atenolol and timolol in rabbits. In this study, a 0.50% BL-9 solution caused irritation, even leading to corneal lesion at a 2% concentration [9]. BL-9 and Brij 78 in a 0.50% concentration, however, were found to be safe penetration enhancers for insulin with no detectable allergic responses or local

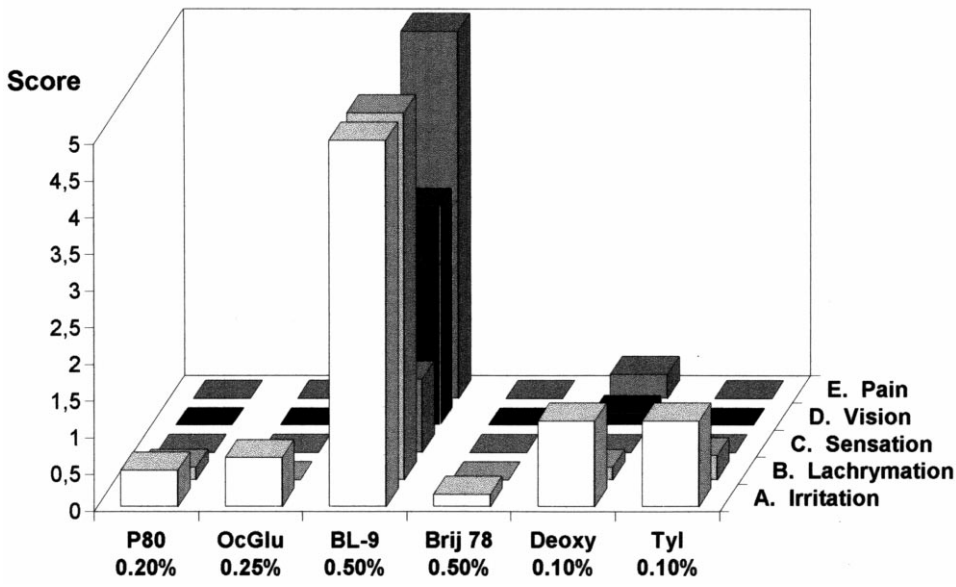


Fig. 9. The results of the acceptability test for the penetration enhancer solutions.

side effects when instilled into the eyes of rabbits for long periods of time [30]. Also, viscolyzers such as hydroxypropylmethylcellulose and hydroxypropylcellulose used in the formulation of ophthalmic solutions can reduce the surface tension of the vehicle, eliciting ocular irritation after instillation [31].

Most local toxicity tests for ophthalmic solutions are performed on rabbits. The rabbit has long been established as the most useful model for experimental ophthalmology. However, the differences between man and rabbit must always be considered. The blinking rate of rabbits is only 4 times/h, whereas man blinks on average 15–16 times/min. Rabbits also do not lachrymate heavily even following major irritation, but a mucoidal discharge moistening the eye lids is produced [1,6,32]. Hence, caution is necessary when extrapolating animal-derived data to man.

Besides the importance of the surface active properties, the choice of a penetration enhancer will depend on its compatibility with the active ingredient of the eye drop formulation. The effects on various ocular tissues must also be evaluated, especially when formulations for chronic use are developed.

5. Conclusions

The surface tension of the penetration enhancer solutions examined had a decisive influence on the weight of drops delivered from flexible dropper bottles. When squeezing the dropper bottle more slowly, a decrease in drop weight was observed. On the other hand, the design of the outer orifice and the angle at which the dropper bottle is held when instilling an eye drop, determined the cross-sectional surface area from which the drop will fall and influenced the drop weight. The penetration enhancer solutions with a surface tension above 32 mN/m caused little or no irritation upon instillation.

The addition of a penetration enhancer to the vehicle of an ophthalmic solution can be used to reduce the size of the drop instilled and at the same time to improve the ocular absorption of poorly absorbed drugs, increasing the bioavailability, on condition that the penetration enhancer does not induce local irritation and/or is not cytotoxic to the ocular tissues.

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