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Comparative *in vitro* investigation of the forces exerted by eye drops and eye spray

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Topical administration of ophthalmic drugs is predominantly carried out in the form of eye drops. The application of an eye spray represents a feasible alternative to drop instillation with regard to the clinical efficacy. In this study the forces exerted during the application of eye drops and eye spray to a surface were measured *in vitro* and compared with each other. Whereas the maximal forces that occurred with a falling drop tended to increase with greater application distance, the forces decreased with spraying. From an application distance of 3 cm the eye spray proved to have a more favorable mechanical force effect than the eye drops. In view of the loss of experimental liquid caused by spray application as well as the diameter of the spray cone, a spray distance of from 4 cm to 5 cm can be deemed to be optimal.

Today topical application of ophthalmic drugs is predominantly carried out in the form of eye drops. In many cases the instillation procedure proves difficult, especially for older patients, because of the awkward posture. Children often dislike the instillation, sometimes intensely.

Halberg et al. (1975), Bartlett et al. (1993) and also Akman and Aydin (1999) have demonstrated in clinical studies that the administration of ophthalmic drugs in the form of an eye spray represents a feasible alternative to drop instillation. Besides the efficacy of this pharmaceutical form, the degree of ocular discomfort caused like burning, stinging and lacrimation (Akman and Aydin 1999) and the acceptance of the spray by patients (Halberg et al. 1975), respectively, were also investigated in the studies. Whereas the eye sprays were comparable with eye drops regarding efficacy, less ocular discomfort occurred with spray application. The patient acceptance of the spray was high.

The impact of an eye drop stimulates mechanically the eye surface and, particularly, the touch sensitive cornea (Kircher 1990). The impact of the drop on the eye surface produces a force which can be measured *in vitro* (Müller et al. 2005).

The aim of the present study was to compare an eye spray with conventional eye drops with regard to its mechanical force effect. Based on this a preferred application distance for use of the spray could be established.

Because the majority of eye drop preparations used in practice are aqueous solutions, water for injection was used. The drop volume applied in each case was 42.1 ± 1.2 μl (mean ± standard deviation, n = 10). The volume of a single spray was 45.4 ± 4.0 μl (mean ± standard deviation, n = 10).

For the administration of eye drops it is recommended to hold the top of the eye drop bottle close to the eye (Kircher 1990). Because of the different abilities of the persons administering the drops, the distances of the drop falls can vary considerably in practice. Bartlett et al. (1993) used in their study distances of approximately 10 cm for eye spray administration. Akman and Aydin (1999) sprayed from a distance of 4 cm. Dolder and Skinner (1983) give a distance of from 4 cm to 5 cm. To measure over a wide range, application distances from 1 cm to 8 cm were investigated in this study. According to the usual mode of administration of the pharmaceutical forms, application of the eye drops was vertically downward and application of the eye spray was carried out in a horizontal position.

Using a measuring system with a piezoelectric force transducer the maximum force exerted during impact of the drop was determined in each case. Measurement of the force exerted by spraying was carried out with the aid of the measuring unit with the addition of a sensor rack. The results of the investigations are shown in the Figure.

With the eye drops, the maximum force exerted increased with the application distance. Peak forces occurred at distances of 4 cm and 7 cm. This characteristic curve for aqueous eye drop preparations results from the different shape of the drops at the moment of their impact based on oscillations (Müller et al. 2005). Compared to eye drops, with the eye spray the maximum force decreased with greater application distance. In this respect it must, however, be considered that the test liquid did not completely impinge on the cap of the piezoelectric force transducer during the spray application. With greater application distance the diameter of the spray cone increased (see Table). The sensor cap has a diameter of 21.4 mm. Because the diameters of the spray cones were bigger than the diameter of the sensor cap, a loss of test liquid occurred with each spray application. The force exerted by this missing portion was not recorded.

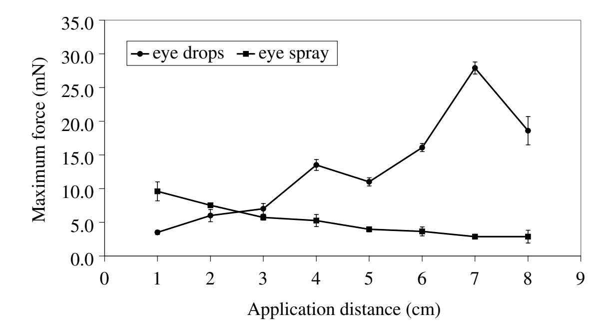

Fig.: Maximum force in relation to application distance for administration of eye drops and eye spray (mean ± standard deviation, n = 5).

Table: Diameter of the spray cone depending on the application distance and percentage loss of test liquid[b]

Application distance (cm)	Diameter of the spray cone[a] (mm)	Loss of test liquid[b] (%)
1	25 ± 1	4
2	30 ± 1	18
3	35 ± 2	30
4	39 ± 2	39
5	45 ± 1	48
6	50 ± 3	61
7	64 ± 4	65
8	77 ± 2	67

[a] mean ± standard deviation, n = 5
[b] relative to the total volume of a single spray 45.4 ± 4.0 µl (mean ± standard deviation, n = 10)

A comparison of the curves shows that the eye spray produced higher forces than the eye drops at application distances of 1 cm and 2 cm. At an application distance of 3 cm the force exerted by the spray was a little lower than that of the eye drops. From a distance of 4 cm the eye spray exerted forces clearly smaller than the drops.
To establish the preferred distance from the eye for spray administration, the loss of test liquid as well as the diameter of the spray cone must be considered in addition to the force exerted. With spray distances up to 5 cm the loss of test liquid was less than half the total volume applied. A partial loss when spraying can be tolerated with regard to the clinical efficacy of a drug because the application of conventional eye drops always involves losses as well. The small capacity of the inferior conjunctival sac and increased lacrimation are reasons for this. Zetterström (1987) also proved that the efficacy of eye drops was constant with the instillation of smaller drop volumes. With regard to administration of the eye spray it may be observed that with increasing spray distances a bigger proportion of the drug would reach the surrounding area of the eye and the skin. Excess liquid must be wiped away. Skin irritations and allergies could appear with frequent drug administration. Thus, smaller application distances should be preferred.
In the present work it was shown, that the application of an eye spray represents a good alternative to the instillation of eye drops as regards the mechanical force exerted. The preferred distance for administration of the eye spray would be 4 cm to 5 cm.

Experimental

To prepare the eye drops the test liquid (water for injection, Ampuwa®, Fresenius Kabi, Bad Homburg, Germany) was filled into a commercially available plastic eye drop bottle (eye drop system 10 ml, IphaS, Würselen, Germany). The drop mass was determined according to Akman and Aydin (1999) by difference weighing using an analytical balance (Freiberger Analysenwaage, W. Zschörnig Feinmechanik Werkstatt, Freiberg, Germany) at room temperature. The drop volume was calculated using the density of water (0.998 kg/dm^3 at 20 °C) (Kuchling 2001).
According to Bartlett et al. (1993) the preparation of the eye spray was carried out by filling the test liquid into a commercially available pump spray bottle (Atomizer System 50 ml, IphaS, Würselen, Germany). To release a quantity comparable to the drop volume the sprayhead was pressed downward 2.5 mm. The determination of the mass released in each case and the calculation of the volume were performed as with the eye drops.
The measurement of the forces exerted during the administration of the eye drops and the eye spray was carried out according to Müller et al. (2005) using a piezoelectric force transducer KF 24 (IDS Innomic, Emmerzhausen, Germany) with a sensor cap. The electric charge generated by the sensor was converted to voltage with a single channel charge converter M67-1F (Metra, Radebeul, Germany). The changing voltage was recorded using a ScopeCorder DL 708 (Yokogawa, Tokyo, Japan) and was analysed with Waveform Viewer for DL series software (Yokogawa). The determination of the force exerted by spraying was carried out in a horizontal position using a sensor rack (laboratory workshop for mechanical engineering, University of Applied Sciences, Senftenberg, Germany). The application distance was increased in 1 cm steps from 1 cm to 8 cm. Five measurements were performed in each case. Between the separate measurements the sensor cap was cleaned with soft fleece paper. The investigations were carried out at room temperature.
To determine the diameters of the spray cones depending on the application distance the test liquid was sprayed on a filter paper. The greatest dimension was measured in each case.
To ascertain the loss of test liquid occurred by spraying in connection with Halberg et al. (1975) a filter paper was prepared with the same dimensions as the sensor cap. After spraying the test liquid the wet filter paper was weighed. The mass of the dry filter paper was subtracted from the mass of the wet paper. The loss of liquid relative to the total volume of a single spray was calculated.

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