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Characterization of the force effect of aqueous and oily eye drops

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During the instillation of eye drops the drop impact affects a mechanical irritation on the eye surface. The force impact occurring in the moment of impact may be measured *in vitro*. Four commercially available eye drop preparations of different consistency and viscosity were tested. In dependance on the drip distance, the quantity of force impact was determined as well as the maximally effecting force during impact in each case. Whereas the force impact increased with all preparations with rising drip distance, only the higher viscosity solutions showed an approximate linear increase of the maximal force. With the aqueous low-viscosity eye drops, peak forces were ascertained. The drop oscillation was considered as the cause. The test results show that the consistency of eye drop preparations and their resulting physical-chemical properties like viscosity influence the quantity of the maximal force during the drop impact.

1. Introduction

Today the topical administration of ophthalmic drugs is predominantly carried out in the form of eye drops. The majority of eye drop preparations are aqueous solutions of different agents and adjuvants. Aside oily solutions or suspensions also occur. To avert a rapid flush out of the agents from the eye and to achieve an extension of the effect by an extending contact time with the eye surface a viscosity heightening substance is often added to aqueous eye drops. Cellulose ether, polyvinyl pyrrolidone or polyvinyl alcohol are mostly applied. Higher viscosity preparations were also used as artificial tears. Due of their wetting properties they decrease the conjunctival irritation, particularly in case of the sicca syndrom. The oily eye drops made based on vegetable oil like ricinus oil or peanut oil also have a higher viscosity. A higher viscosity of the preparations affects unfavorably on the vision of the patients. Beside the low vision a plugging of the lachrymal canal must be expected from a viscosity of 25 mPa·s (Voigt 2000). Additionally, higher viscosity eye drops can produce a foreign body sensation.

The instillation of eye drops is carried out into the inferior conjunctival tearsac of the eye or in more infrequent cases directly on the cornea. The tissues of conjunctiva and cornea are afferent provided by nervus ophthalmicus. A falling drop causes a mechanical irritation of the receptors in the concerned area. If the eye drops are not heated to room temperature as recommended, the instillation additionally causes a thermic eye irritation. The application of non-isotonic solutions or eye drops with a non-physiological low pH-value also can cause eye irritations. Beside the knee-jerk close of the eyelid and the increased lacrimation many patients also sense the instillation subjectively as unpleasant and painful. Ocular discomfort symptoms like burning and stinging are described (Akman and Aydin 1999; Bartlett et al. 1993).

To make the eye drop application more comfortable for the patient different ways were tested in the past. Besides isotonization of eye drops and their adjustment on an euhydric pH-value the use of smaller drop volumes (Zetterström 1987) as well as the application of the drug in the form of an eye spray can be mentioned (Akman and Aydin 1999; Goodman et al. 1999; Halberg et al. 1975).

We were interested in the question whether the viscosity – resulting from the consistency of the eye drop preparations – can influence mechanical eye irritations caused by drop impact. The investigations are based on the fact that a falling drop produces a force impact on the eye surface. For *in vitro* measuring and evaluation of this force impact in dependance on the drip distance a test arrangement was developed.

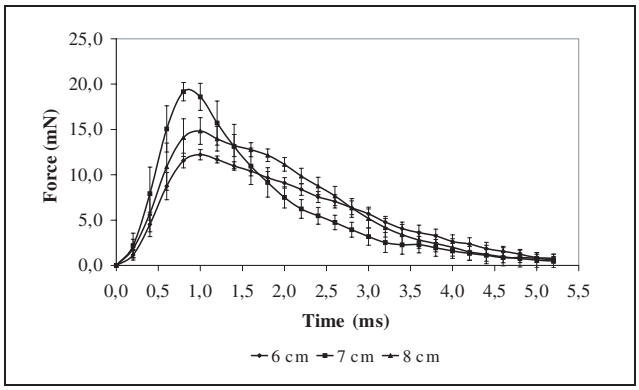

Fig. 1: Progress of force during the drop impact considering as example of Pilocarpin Ankerpharm 2% eye drops (n = 5, mean ± standard deviation)

Table 1: Eye drop preparations investigated

Preparation	Producer	Components
Artelac® eye drops	Dr. Gerhard Mann, Chem.-pharm. Fabrik GmbH (Berlin, Germany)	Hypromellose Cetrimide Disodium monohydrogen phosphate 12 H_2O Sodium dihydrogen phosphate 2 H_2O Sorbitol Disodium edetate 2 H_2O Water for injection
Cromohexal® eye drops	Hexal AG (Holzkirchen, Germany)	Cromoglicin acid, disodium salt Benzalconium chloride Disodium edetate Sodium chloride Sodium dihydrogen phosphate Disodium monohydrogen phosphate Sorbitol Water for injection
Pilocarpin Ankerpharm 2% eye drops	Chauvin ankerpharm GmbH (Rudolstadt, Germany)	Pilocarpine HCl Benzalconium chloride Sodium acetate 3 H_2O Disodium edetate 2 H_2O Sodium chloride Water for injection
Pilocarpin Ankerpharm 2% eye oil	Chauvin ankerpharm GmbH (Rudolstadt, Germany)	Pilocarpine Palmitoyl ascorbic acid Refined ricinus oil Absolute ethanol

Source: URL http://www.rote-liste.de/Online/jumpsearch (2003–08-29)

2. Investigations, results and discussion

2.1. Force impact

The impact of a drop on a surface is a very short process visually hardly observable. To represent the forces during impact in their temporal course a measuring unit with a piezoelectric force transducer was used. Fig. 1 shows that the force occurs in variable quantity. Thus, the force impact can be calculated as the time integral of the force, whereas a period of 5.2 ms was estimated in each case.

The preparations Pilocarpin Ankerpharm 2% eye drops, Cromohexal® eye drops and Artelac® eye drops which

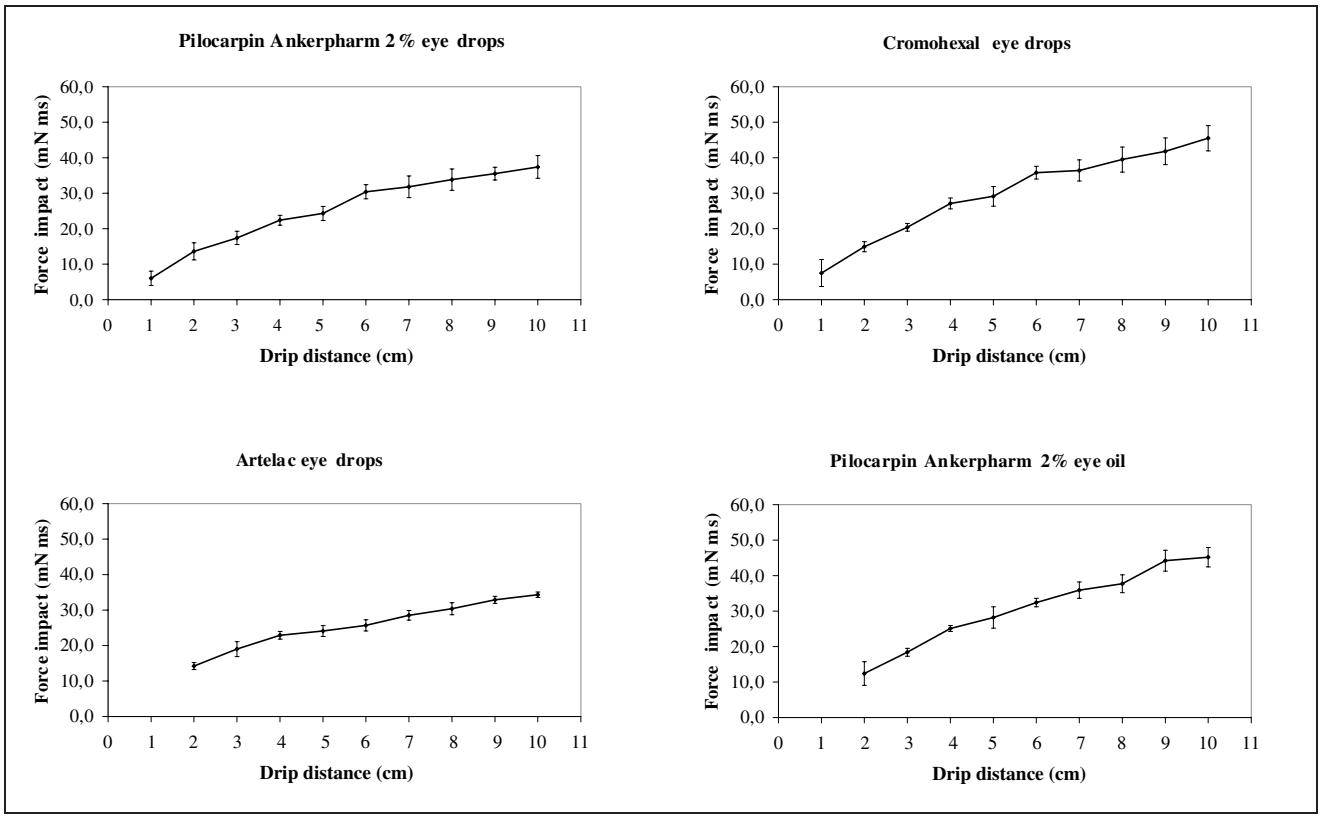

Fig. 2: Force impact depending on the drip distance ($\Delta t = 5.2$ ms; $n = 5$, mean $\pm$ standard deviation)

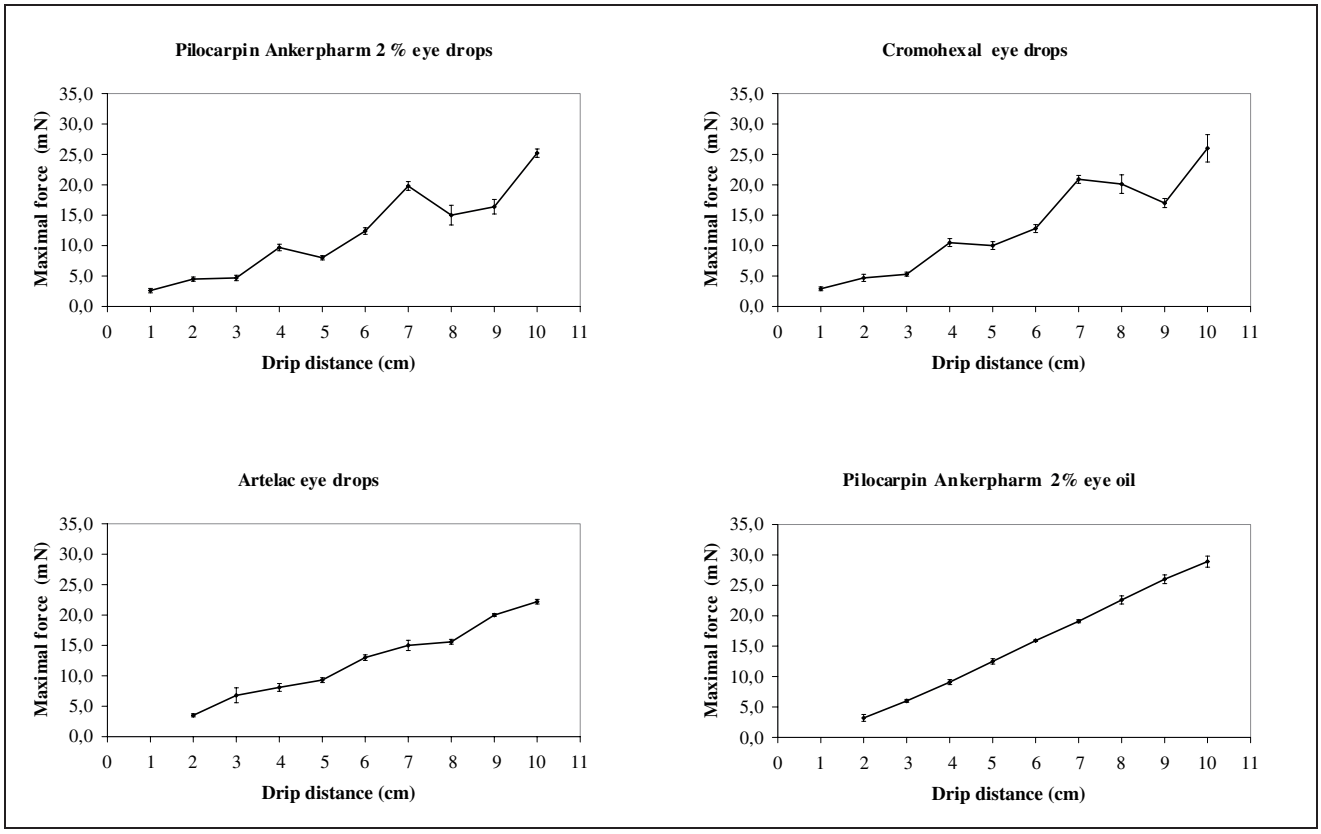

Fig. 3: Maximal force depending on the drip distance (n = 5, mean ± standard deviation). Viscosity of Pilocarpin Ankerpharm 2% eye drops: 1 mPa · s, Cromohexal® eye drops: 5 mPa · s, Artelac® eye drops: 10 mPa · s, Pilocarpin ankerpharm 2% eye oil: 635 mPa · s

Table 2: Physical-chemical properties of the eye drop preparations

Preparation (Charge)	Drop mass[a] (mg)	Density (10^3 kg/m^3)	Drop volume[a] (µl)	Viscosity (m · Pas)	Surface tension[b] (mN/m)
Artelac eye drops (423; 563)	25.5 ± 1.3	1.017	25.1 ± 1.2	10	44.3 ± 0.1
Cromohexal eye drops (21DX70; 24DX79; 31DX84)	31.6 ± 0.9	1.018	31.0 ± 0.9	5	43.0 ± 0.1
Pilocarpin Ankerpharm 2% eye drops (225601; 2506)	27.5 ± 1.1	1.005	27.4 ± 1.1	1	35.7 ± 0.1
Pilocarpin Ankerpharm 2% eye oil (302002; 323)	29.2 ± 1.5	0.960	30.4 ± 1.6	635	35.9 ± 0.1

[a] mean ± standard deviation, n = 10
[b] mean ± standard deviation, n = 5

are aqueous solutions as well as Pilocarpin Ankerpharm 2% eye oil were investigated (Table 1). The step by step increase of the distance between the top of the bottle and the top side of the sensor cap resulted in a rise of the quantity of the force impact with all four preparations (Fig. 2). Results could not be ascertained for Artelac eye drops and Pilocarpin Ankerpharm 2% eye oil for a drip distance of 1 cm because the tear-off of the drop only occurred after its contact with the sensor cap, which means that the drop impact was no more detected metrologically. Drip distances over 5 cm hardly happen in practice; the higher results are of more theoretical interest.

2.2. Maximal force

Considering the maximal force effected during the drop impact in each case we can find essential differences between the preparations (Fig. 3). With Pilocarpin ankerpharm 2% eye drops and Cromohexal eye drops peak forces were ascertained at 4.7 and 10 cm. An increase of drip distance by 3 cm gave results between the separate peaks. Artelac eye drops showed an explicitely more evenly trend. An approximately linear increase of the maximal force was determined with Pilocarpin Ankerpharm 2% eye oil.

2.3. Drop oscillation

If a drop breaks off from the top of the eye drop bottle it begins to oscillate. In the course of its fall the drop periodically alters its shape. Starting from an axisymmetric drop oscillation in which the drop only elongates and contracts along the central axis, the period of an oscillation T_{osc} can be calculated using equation (1),

$$T_{osc} = \pi\sqrt{\frac{\rho D^3}{8\sigma}} \qquad (1)$$

where ρ is the density, σ is the surface tension and D is the diameter of the spherical drop Roisman I (2003) Drop oscillations. Personal information, Technical University of Darmstadt, Germany. Neglecting the air drag the fall time t_{fall} of a drop arises from equation (2),

$$t_{fall} = \sqrt{\frac{2h}{g}} \qquad (2)$$

where h is the height of fall and g is the acceleration of fall (Kuchling 2001). Thus, with a maximal drip distance of 10 cm the fall time is 0,143 s. Falling from this hight the drops pass three complete periods of oscillations (Table 3).

Is the drip distance altered step by step like in this investigation, the drop impinges on the sensor surface during different phases of its oscillation. If the drop in the moment of impact is spherical, or elongates along its vertical axis, it will achieve its maximal spread on the surface and so its maximal force is lower as when it contracts along the vertical axis. In the last case a faster and higher increase of the force results (Fig. 1, drip distance 7 cm). The occurrence of force peaks can be explained this way.

The influence by the viscosity of a liquid on the oscillations of drops was not considered so far. With rising viscosity the oscillations are dumped increasingly. The maximal force diagrams (Fig. 3) which were obtained for Pilocarpin Ankerpharm 2% eye drops and Cromohexal eye drops reflect the periodical drop oscillation. The curve progression for Artelac eye drops indicates a damping of the oscillation amplitude whereas the oscillation period is unchanged corresponding to Meradji et al. (2001). With Pilocarpin Ankerpharm 2% eye oil force peaks did not appear. The high viscosity of the solution obviates a deformation of the drops during their fall.

The results of this study reveal that the viscosity of eye drops can influence the quantity of the maximally effecting force during the application. Low-viscosity aqueous eye drops oscillate, thus leading to the occurrence of force peaks depending on the drip distance. The oscillation behaviour of aqueous eye drops can be used for the minimization of the force effected during the application. Therefore, the drip distance must be chosen in a way that the drop is not contracted along its vertical axis in the moment of impact.

A high viscosity of the solution obviates the oscillation of the drops. The maximal force steadily rises with increasing drip distance. Thus, the intensity of the force affected by the drop impact is more calculable. A viscosity of the solution of 10 mPa · s (as in Artelac eye drops) can be considered as adequate.

Because of their sensitive innervation the cornea and the conjunctiva of the eye experience touch stimuli. Especially, the center of the cornea is very pain sensitive. A bigger mechanical stress of the anatomy structures results in a more intense ocular sensation (Verriest and Schiffer 1977). Whenever a bigger force is acting in the moment of drop impact a more intense irritation of the sensitive nerves in the cornea and the conjunctiva must be expected.

In the literature a mechanical stimulus on the eye surface, particulary the cornea by falling eye drops is known (Kircher 1990). Here the force effected during the application of differently composed eye drop preparations was characterized. In further studies the influence of the maximal force on the eye irritation and on the subjective ocular sensation of the patients has to be investigated.

Table 3: Duration of a drop oscillation and number of oscillation periods the eye drops pass by a maximal drip distance of 10 cm ($t_{fall} = 0.143$ s)

Preparation	Duration of a drop oscillation (s)	Number of oscillation periods
Artelac® eye drops	0.037	3.9
Cromohexal® eye drops	0.042	3.4
Pilocarpin Ankerpharm 2% eye drops	0.043	3.3
Pilocarpin Ankerpharm 2% eye oil	0.044	3.3

3. Experimental

3.1. Eye drop preparations

3.1.1. General information

The tested eye drop preparations (Table 1) were situated in product typical containers for several doses with a total volume of 10 ml in each case. The drop formation occurred from the bottle which was held upside down by squeezing with the fingers on the sides of the bottle.

3.1.2. Determination of the physical-chemical properties

The determination of the drop mass was carried out by difference weighing (Akman and Aydin 1999) using an analytical balance (Freiberger Analysenwaage, W. Zschörnig Feinmechanik Werkstatt, Freiberg, Germany) at room temperature. The density was measured using DA-100 (Kyoto Electronics, Kyoto, Japan) at 20 °C. The drop volume was calculated using equation (3),

$$\rho = \frac{m}{V} \qquad (3)$$

where ρ is the density, m is the drop mass and Vis the drop volume. With Pilocarpin Ankerpharm 2% eye drops the viscosity was determined using the Ubbelohde capillary viscometer with hanging bowl level no. 1 (Jenaer

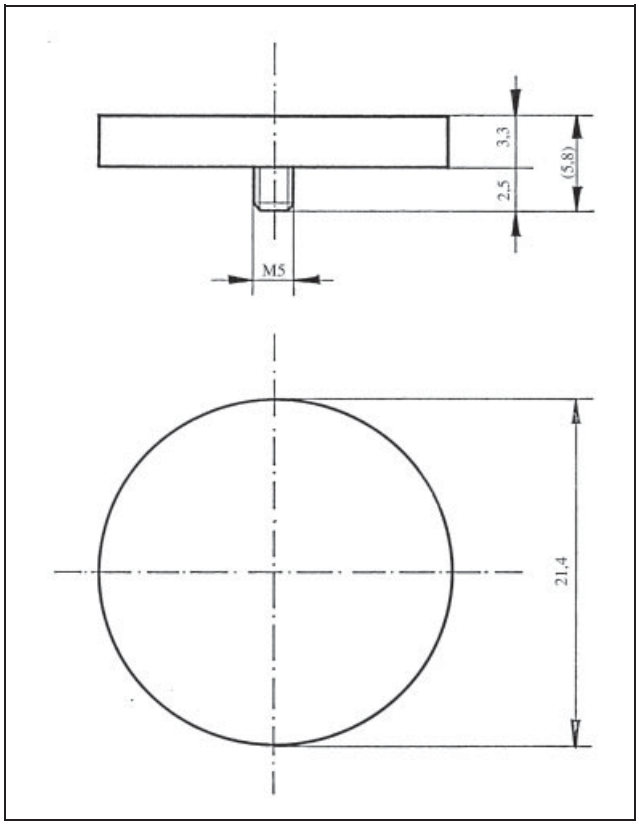

Fig. 4: Sensor cap for the piezoelectric force transducer KF 24 (IDS Innomic, Emmerzhausen, Germany): pictured in the front view and the top view; dimensions in mm

Glaswerk Schott & Gen., Jena, Germany) at 20 °C. The viscosity of Cromohexal eye drops, Artelac eye drops and Pilocarpin Ankerpharm 2% eye oil were measured using the rotary viscometer Rheotest 2.1 (Rheotest, Ottendorf-Okrilla, Germany) with the cylinder measuring device S1 at 20 °C. For the determination of the surface tension the tensiometer TD 1 (Lauda, Lauda-Königshofen, Germany) was applied. The measurements were carried out on the bail method at 20 °C. The results are summarized in Table 2.

3.2. In vitro system for the force measurement

The forces effected at drop impact were determined using the piezoelectric force transducer KF 24 (IDS Innomic, Emmerzhausen, Germany; serial number 1278; charge transfer factor 309,2 pC/N). Because the force transducer does not encounter with liquids a coping (Fig. 4) consisting of steel St 52 was made for protection (laboratory workshop for mechanical engineering, University of Applied Sciences, Senftenberg, Germany). The static weight of the cap is of no account for the measurement signal because only dynamic forces can be detected by the sensor.

The electric charge generated by the sensor during drop impact was converted in voltage using the single channel charge converter M67-1F (Metra, Radebeul, Germany). The amplification was 1 mV/pC. The force proportional progress of voltage was recorded by means of the ScopeCorder DL 708 (Yokogawa, Tokyo, Japan) and was analyzed using the software Waveform Viewer for DL series (Yokogawa).

The tested eye drop bottle was hung upside down in a home made equipment (Metallbau Müller, Klein Gaglow, Germany). The distance between the top of the bottle and the top side of the sensor cap was increased in 1cm steps from 1 cm to 10 cm. Five measurements were accomplished with each drip distance. Between the measurements the drops were eliminated from the sensor cap with a soft fleece paper. The investigations were carried out at room temperature.

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