# Usability of Prostaglandin Monotherapy Eye Droppers

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**Subtitle:** The force required to expel a drop differs between Prostaglandin monotherapy dropper designs and some exceeded the maximum force that could be comfortably applied by around half the population, which may affect compliance and efficacy.

**ABSTRACT**

**Aim:** To determine the force needed to extract a drop from a range of current prostaglandin monotherapy eye droppers and how this related to the comfortable and maximum pressure subjects could exert.

**Methods:** The comfortable and maximum pressure subjects could apply to an eye dropper constructed around a set of cantilevered pressure sensors and mounted above their eye was assessed in 102 subjects (mean 51.2±18.7 years), repeated 3 times. A load cell amplifier, mounted on a stepper motor controlled linear slide, was constructed and calibrated to test the force required to extract the first 3 drops from 13 multi-dose or uni-dose latanoprost medication eye droppers.

**Results:** The pressure that could be exerted on a dropper comfortably (25.9±17.7 newtons, range 1.2 to 87.4) could be exceeded with effort (to 64.8±27.1 newtons, range 19.9 to 157.8; $F=19.045$, $p<0.001$), but did not differ between repeats ($F=0.609$, $p=0.545$). Comfortable and maximum pressure exerted were correlated ($r=0.618$, $p<0.001$), neither were influenced strongly by age ($r=0.138$, $p=0.168$; $r=-0.118$, $p=0237$ respectively), but were lower in females than males ($F=12.757$, $p=0.001$). The force required to expel a drop differed between dropper designs ($F=22.528$, $p<0.001$), ranging from 6.4 to 23.4 newtons. The force needed to exert successive drops increased ($F=36.373$, $p<0.001$) and storing droppers in the fridge further increased the force required ($F=7.987$, $p=0.009$).

**Conclusions:** Prostaglandin monotherapy droppers for glaucoma treatment vary in their resistance to extract a drop and with some a drop could not be comfortably achieved by half the population, which may affect compliance and efficacy.

## INTRODUCTION

About 11% of patients report difficulty in administering their glaucoma medication.[1] Approximately ~17% rely on others for the administration of drops due to inadequate vision and trouble with manual dexterity.[2] If it is hard to expel the required dose from a medication dropper, compliance can be affected.[3] Ease of use is also related to a patient's satisfaction, resistance to using their medication, their acceptance of their illness [4] and their health related quality of life.[5] The US patent for Xalatan expired in March 2011 and since then generic formulations of latanoprost have been available. While it is acknowledged these are cost effective,[6] FDA regulations do not dictate dropper design or rigidity and hence some patients may find these generics difficult to use, affecting compliance and therefore treatment efficacy.[7]

Hence this study determined the force needed to extract a drop from a range of current prostaglandin monotherapy medication eye dropper designs and related this to the comfortable and maximum squeeze pressure a wide age range of healthy subjects could exert.

## METHODS

One-hundred and two consecutive healthy subjects attending a high street optometry practice (51% female) aged 19-88 years (mean 51.2 ± 18.7 years) were recruited. The comfortable and maximum pressure they could apply between their thumb and index finger to an eye dropper constructed around a set of cantilevered pressure sensors (Richmond Industries, UK; Figure 1) and mounted above their eye was assessed, repeated 3 times. Those with known arthritis affecting their fingers, Parkinson's disease or diabetes were excluded from the study. An explanation and demonstration was provided and subjects were asked to apply the "maximum pressure they could apply comfortably" followed by the "maximum pressure they could apply with effort" to the simulated dropper for 3 seconds before releasing. The subjects gave informed consent and the research, which conformed to the tenets of the declaration of Helsinki, was approved by the Aston University Research Ethics Committee.

In a separate aspect to the study, a load cell amplifier (Richmond Industries, UK) mounted on a stepper motor controlled linear slide (Trinamic GmbH, Germany; Geckodrive Inc., USA) was constructed (Figure 1). This device was used to mechanically test the force required to extract the first 3 drops from 13 multi-dose (MD) or uni-dose (UD) latanoprost medication eye dropper designs (Table 1), repeated on three droppers of each design from different production lots. In addition the force required to extract the first 3 drops from an additional dropper of each design, which had been refrigerated at 6ºC for 24 hours, was assessed. The load cell was calibrated against known masses and calibration was maintained throughout the testing period.

The volume of the droplets was quantified with a custom high speed photography system that imaged the droplet in freefall against a backlit light emitting diode (LED) panel producing a sharp outline of the droplet's edge (Figure 1). The camera used was an IDS UI-1221LE (Imaging Development Systems GmbHIDS, Obersulm, Germany) with a custom optical set up, approximating a 16mm focal length. Sensor binning (combining charge from adjacent pixels) was used to increase the frame rate of the capture system, allowing 280 frames per second (fps) to be achieved with 80 pixels across the droplet diameter. Calibration was undertaken determining magnification at the image plane by imaging known size objects, producing a suitable scaling factor for each dropper nozzle. Software was written in LabVIEW (Labview 2013, National Instruments, Austin, Texas, USA) to select the droplet immediately after release into free-fall on the captured video and to export images for post processing. A semi-automated circle fitting algorithm, developed in ImageJ (U. S. National Institutes of Health, Bethesda, Maryland, USA), was applied to the edge of the droplet in free-fall to determine its diameter. Calculations were performed assuming the droplet in free-fall held a spherical shape due to surface tension, which allowed extrapolation of the measured diameter to determine its volume.

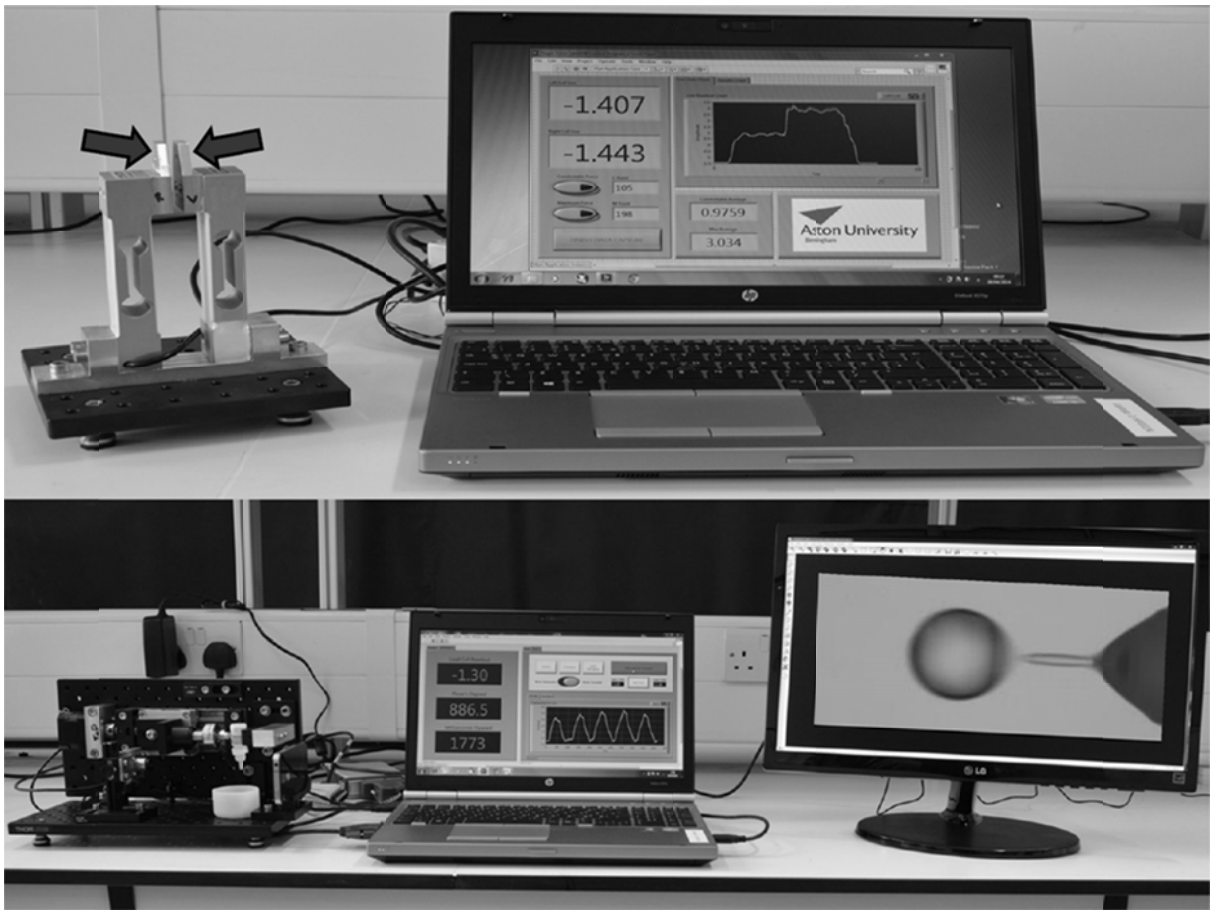


**Figure 1:** Finger squeeze measurement apparatus to determine the maximum pressure a subject could exert comfortably and with effort (top). Dropper crush measurement apparatus to determine the mechanical force needed to expel a drop from Prostaglandin monotherapy dropper designs (bottom) with the drop imaged in free-fall to determine its volume.

## RESULTS

The pressure that could be exerted on a dropper when subjects' applied the maximum squeeze they could employ comfortably (25.9 ± 17.7 newtons, range 1.2 to 87.4) could be exceeded with effort (to 64.8 ± 27.1 newtons, range 19.9 to 157.8; $F = 19.045$, $p < 0.001$), but did not differ between repeats (ANOVA $F = 0.609$, $p = 0.545$; Figure 2). The comfortable and maximum pressure that subjects' could exert on a dropper bottle were correlated ($r = 0.618$, $p < 0.001$), but neither were influenced strongly by age ($r = 0.138$, $p = 0.168$; $r = -0.118$, $p = 0237$ respectively). Both the comfortable and maximum pressure that subjects could exert on a dropper bottle were lower in females than males (18.5 ± 10.4 vs 33.6 ± 20.4 newtons and 47.7 ± 13.6 vs 82.5 ± 26.3 newtons; $F = 12.757$, $p = 0.001$).

The force required to mechanically expel a drop differed between dropper designs ($F = 22.528$, $p < 0.001$), with the force ranging from 6.4 to 23.4 newtons (Table 1; Figure 3). In general, the force needed to expel successive drops increased ($F = 36.373$, $p < 0.001$) and storing the droppers in the fridge further increase the force required to expel a drop (15.75 ± 6.43 vs 14.72 ± 7.06 newtons: $F = 7.987$, $p = 0.009$; Figure 3). Expelled drop size is reported in table 1 and was significantly correlated to the force required to expel a drop ($r = 0.526$, $p < 0.001$).

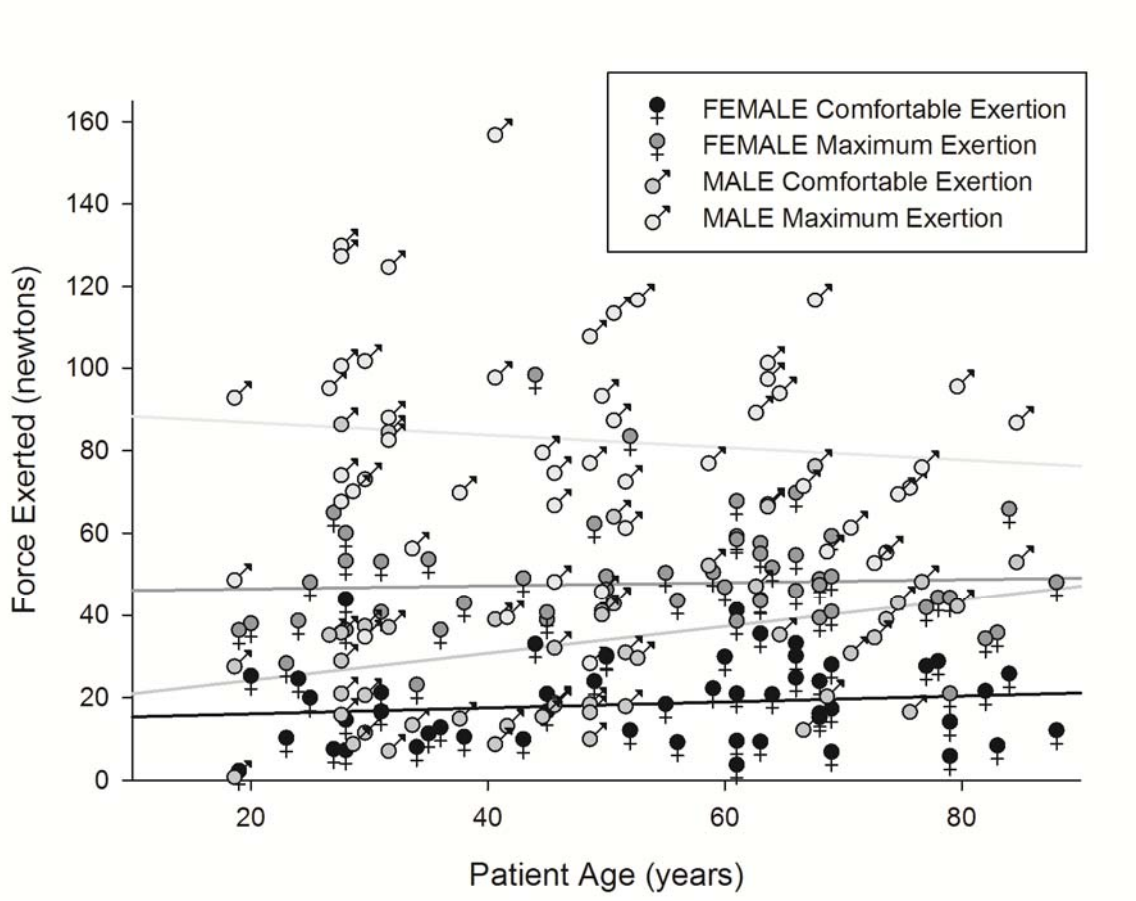


**Figure 2:** The force that could be exerted comfortably and with maximum exertion with subject's age. N = 102.

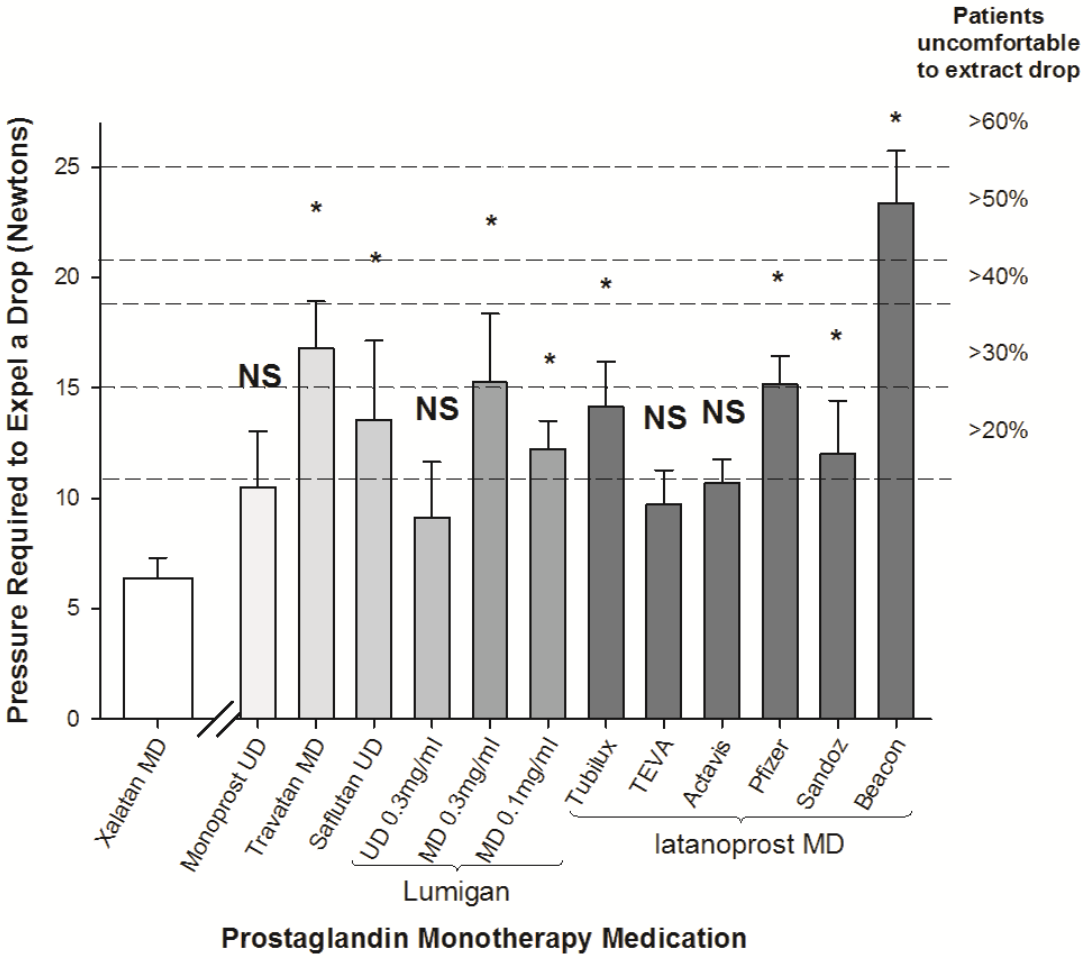


**Figure 3:** Pressure required to expel a drop of prostaglandin monotherapy medications. Error bars = 1 S.D. * = $p < 0.05$ and NS = not significantly different compared to Xalatan.

| Product | Company | Unidose/ Multidose | Size (ml) | Dose (mg/ml) | Drop Size (µl) | Force (N) | XalaTAN | Travatan | Lumigan | Lumigan | Lumigan | Saflutan | G1 | G2 | G3 | G4 | G5 | G6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Monoprost | Thea | UD | 0.2 | 50.00 | 0.021±0.010 | 10.5±2.5 | 0.124 | 0.001 | 1.000 | 0.034 | 1.000 | 0.882 | 0.578 | 1.000 | 1.000 | 0.260 | 1.000 | 0.000 |
| XalaTAN | Pfizer | MD | 2.5 | 50.00 | 0.033±0.012 | 6.4±0.9 | | 0.000 | 1.000 | 0.000 | 0.003 | 0.000 | 0.000 | 1.000 | 0.172 | 0.000 | 0.002 | 0.000 |
| Travatan | Alcon | MD | 2.5 | 40.00 | 0.043±0.013 | 16.8±2.1 | | | 0.000 | 1.000 | 0.050 | 0.551 | 1.000 | 0.001 | 0.005 | 1.000 | 0.019 | 0.001 |
| Lumigan | Allergan | UD | 0.4 | 0.30 | 0.027±0.010 | 9.1±2.5 | | | | 0.001 | 0.763 | 0.023 | 0.024 | 1.000 | 1.000 | 0.016 | 0.801 | 0.000 |
| Lumigan | Allergan | MD | 3.0 | 0.10 | 0.029±0.010 | 15.2±3.1 | | | | | 1.000 | 1.000 | 1.000 | 0.015 | 0.100 | 1.000 | 0.580 | 0.000 |
| Lumigan | Allergan | MD | 3.0 | 0.30 | 0.032±0.010 | 12.2±1.3 | | | | | | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 0.000 |
| Saflutan | MSD | UD | 0.3 | 15.00 | 0.020±0.009 | 13.5±3.6 | | | | | | | 1.000 | 0.329 | 1.000 | 1.000 | 1.000 | 0.000 |
| Latanoprost-G1 | Tubilux | MD | 2.5 | 50.00 | 0.032±0.011 | 14.1±2.1 | | | | | | | | 0.229 | 1.000 | 1.000 | 1.000 | 0.000 |
| Latanoprost-G2 | TEVA | MD | 2.5 | 50.00 | 0.035±0.011 | 9.7±1.5 | | | | | | | | | 1.000 | 0.111 | 1.000 | 0.000 |
| Latanoprost-G3 | actavis | MD | 2.5 | 50.00 | 0.036±0.011 | 10.7±1.1 | | | | | | | | | | 0.506 | 1.000 | 0.000 |
| Latanoprost-G4 | Pfizer | MD | 2.5 | 50.00 | 0.035±0.011 | 15.1±1.3 | | | | | | | | | | | 1.000 | 0.000 |
| Latanoprost-G5 | Sandoz | MD | 2.5 | 50.00 | 0.030±0.010 | 12.0±2.4 | | | | | | | | | | | | 0.000 |
| Latanoprost-G6 | Beacon | MD | 2.5 | 50.00 | 0.040±0.012 | 23.4±2.4 | | | | | | | | | | | | |

**Table 1:** Products tested, the drop size (± 1S.D.), mean force required to compress (± 1S.D.), and the significance between them. G1-6 = generics

## DISCUSSION

This study aimed to determine the force needed to expel a drop from a range of current prostaglandin monotherapy medication eye droppers and how this related to the comfortable and maximum pressure subjects' could exert. The maximum pressure that could be exerted on a dropper without exceeding the subject's individual comfort threshold ranged over 70 fold between individuals and was about 40% lower than the pressure that could be exceeded with effort. Interestingly neither the pressure that could be exerted comfortably or with maximum effort on a dropper bottle was influenced strongly by age, but both were about 1.8x lower in females. The values of maximum force recorded in this study relate well to pinch grip (typically recorded in kilograms where 10 newtons = 1 Kg), where the average pinch grip is around 7-9Kg in males and 5-6Kg in females. Pinch grip doesn't significantly decline until after the age of 70 to 80 years, and has a peak in the mid-30s.[8, 9]. Despite the lack of correlation of squeeze pressure that could be applied with age, this reported profile appears to fit with the data collected in this study (Figure 2).

The force required to expel a drop from a prostaglandin monotherapy for glaucoma varied greatly with dropper design, with the force required between droppers varying 3.7 fold. A similar range of pressure required to expel a drop with various glaucoma and other topical ophthalmic medication bottles has been found previously.[10] Droppers that required the highest mechanical pressures to expel a drop in this study would cause over 50 per cent of subjects discomfort in their attempt to do so (i.e. was more than their objectively measured maximum comfortably exerted squeeze pressure), which is likely to affect compliance and hence treatment efficacy.[3] This is despite the range of ages of subjects tested encompassing those

below the age of 40 when glaucoma is less common, although this age range makes the results applicable to other conditions requiring topical ocular medication such as dry eye. Bottles with low pressure required to expel a drop may run out quickly due to over expression and the inability to easily expel individual drops could lead to overdosing and epiphora. The drop size was in the range of that reported previously [11], although it varied by over 2 fold between dropper designs. The drop size was correlated to the force required to expel a drop, suggesting that dropper design affects dose through the pressure required to expel a drop.

In general, the force needed to expel successive drops from all dropper designs increased, and further so with refrigeration. No previous studies appear to have examined the effect of storing drops in the fridge, as recommended, and the previous study on drop size only examined the first drop.[10]

In conclusion, prostaglandin monotherapy medication droppers vary in their resistance to extract a drop and a drop could not be comfortably achieved by all subjects, which may affect compliance and efficacy.

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## REFERENCES

1) Schwartz GF, Hollander DA, Williams JM. Evaluation of eye drop administration technique in patients with glaucoma or ocular hypertension. Current Medical Research and Opinion. 2013;29:1515-22.

2) Tsai T, Robin AL Smith JP 3rd. An evaluation of how glaucoma patients use topical medications: a pilot study. Transactions of the American Ophthalmological Society 2007;105:29-35.

3) Silva LR, de Paula JS, Rocha EM, Rodriques MDV. Factors related to glaucoma treatment compliance; patients' opinions from a University Hospital. Arquivos Brasileiros de Oftalmologia 2010;73:116-9.

4) Day DG, Sharpe ED, Atkinson MJ, Stewart JA, Stewart WC. The clinical validity of the treatment satisfaction survey for intraocular pressure in ocular hypertensive and glaucoma patients. Eye 2006;20:583-90.

5) Balkrishnan R, Bond JB, Byerly WG, Camacho FT, Anderson RT. Medication-related predictors of health-related quality of life in glaucoma patients enrolled in a medicare health maintenance organization. American Journal of Geriatric Pharmacotherapy 2003;1:75-81.

6) Titcomb LC. Are generic topical prostanoids the way forward in the care of glaucoma patients? – yes. Eye 2013;27:999-1001.

7) Dubois VJ. Are generic topical prostanoids the way forward in the care of glaucoma patients? – no. Eye 2013;27:1002-3.

8) Angst F, Drerup S, Werle S, Herren DB, Simmen BR, Goldhahn J. Prediction of grip and key pinch strength in 978 health subjects. BMC Musculoskeletal Disorders 2010;11:94.

9) Ugurlu U, Ozdogan H. Age- and gender-specific normative data of pinch strengths in a healthy Turkish population. J Hand Surg 2011;37E:436-46.

10) Connor AJ, Severn PS. Force requirements in topical medicine use. Eye 2011;25:466-9.

11) Kumar S, Meena M, Prakash T, Raieswari T, Goli D. Reduction in drop size of ophthalmic topical drop preparations and the impact of treatment. J Adv Pharm Techol Res 2011;2:192-4.