Oversized eyedrops may compromise glaucoma patient adherence, causing disease progression and irreversible vision loss.

Glaucoma is a leading cause of irreversible blindness worldwide.[1]

While glaucoma is treatable, there is currently no known cure for this chronic disease and once diagnosed, glaucoma patients face a lifetime of daily use of medications and/or numerous surgical procedures. Standard first-line treatment medications that lower intraocular pressure (IOP) are administered in the form of eyedrops. When used as directed, daily administration of eyedrops lowers and stabilizes IOP, preventing further damage to the optic nerve and allowing patients to maintain their eyesight. However, **50-75% of glaucoma patients struggle to adhere to their prescription treatments**.[2-4]

Oversized eyedrops jeopardize glaucoma treatment adherence by increasing the incidence and severity of adverse side effects.

Prescription eyedrop bottles elute drops that exceed the capacity of the human eye by four to five times.[5] Therefore, every time a patient administers one eyedrop they are **losing approximately 80% of their medication** to wasted overflow and/or systemic absorption. The rate at which dispensed drug solutions are drained from the eye via the tear ducts is volume-dependent, increasing linearly with instilled volume.[6] Once drained by the tear ducts, IOP-lowering drugs can be absorbed systemically where they act on the rest of the body, often producing unfavorable systemic side effects.[7] Additionally, oversized drops increase exposure to the preservatives found in eye medications, which have been shown to cause adverse local eye symptoms such as transient blurring of vision, stinging upon administration, watering eyes, and mild redness.[8]

Studies have shown that microdrops are as safe and efficacious as their oversized counterparts.

With so many problems caused by oversized eyedrops, smaller eyedrops have emerged as an attractive therapeutic solution. And indeed, the safety and efficacy of small eyedrops, or microdrops, have been demonstrated in numerous studies:

Reference	Drug(s)	Drop volume (µL)	n =	Outcomes	Microdrops vs. standard drops	
					Ocular efficacy	Side effects and/or systemic absorption
Brown & Hanna, 1978	-5% Phenylephrine + 0.5% Tropicamide -10% Phenylephrine + 1% Tropicamide	5 (5% PE + 0.5% Tropic.) vs. 70 (10% PE + 1% Tropic.)	30	Pupil diameter (PD), residual cycloplegia	All eyes reached PD ≥7 mm and had residual cycloplegia <2 diopters within 45-60' of drug administration	Tearing and ocular irritation were only experienced in eyes that received standard drops.
		10 (5% PE + 0.5% Tropic.) vs. 70 (10% PE + 1% Tropic.)	11		The difference in mydriasis or cycloplegia was not statistically significant between the two eyes of any one patient, and all had residual cycloplegia of <2 diopters within 45-60' of drug administration	
File & Patton, 1980	0.5% Pilocarpine	20 vs. 50	10	PD	No statistically significant difference in PD in subjects treated with microdrops vs. standard drops	Fewer ocular side effects (i.e., blurred vision, stinging, watering eyes, redness) observed and reported with administration of microdrops vs. standard drops
Petursson et al., 1984	0.0%, 0.25%, 0.5% Clonidine	15 vs. 70	16	IOP, HR, BP	No statistically significant difference in IOP in subjects treated with microdrops vs. standard drops	No statistically significant difference in systemic side effects (i.e., BP, HR) in subjects treated with microdrops vs. standard drops
Miller et al., 1986[9]	0.5% Levobunolol	20 vs. 35 vs. 50	22	IOP, HR, BP	20 and 50 µL drops significantly more effective at reducing IOP than 35 µL drops	N/A
Lynch et al., 1987	2.5% Phenylephrine	8 vs. 30	11	PD	No statistically significant difference in PD in subjects treated with microdrops vs. standard drops	N/A
			17	Plasma [PE]	N/A	Significantly less systemic absorption of PE occurred in subjects treated with microdrops vs. standard drops

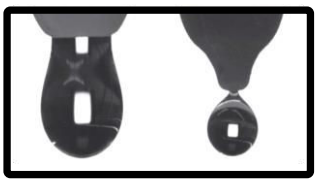
Reference	Drug	Drop volume (µL)	n =	Outcomes	Microdrops vs. standard drops	
					Ocular efficacy	Side effects and/or systemic absorption
Brown et al., 1987	2.5%, 10% Phenylephrine	8 (10% PE) vs. 32 (2.5% PE)	10	PD, plasma [PE]	Microdrops produced a significantly greater increase in PD vs. standard drops	No statistically significant difference in systemic absorption of PE in subjects treated with microdrops vs. standard drops
Charap et al., 1989	0.5% Levobunolol	20 vs. 35 vs. 50	12	Visual acuity, IOP, resting & exercise-induced HR, BP	No statistically significant difference in IOP in subjects treated with 20, 35, or 50 µL drops	Subjects treated with 50 µL drops had significantly lower resting HRs than subjects treated with 35 µL drops; 10' after initiation of exercise, there was not a significant difference in the HRs of subjects treated with 20, 35, or 50 µL drops
			117	Visual acuity, IOP, resting HR, BP	No statistically significant difference in IOP in subjects treated with 20, 35, or 50 µL drops	No statistically significant difference in HR or BP in subjects treated with 20, 35, or 50 µL drops
Montoro et al., 1990	0.5% Timolol maleate	30 vs. 50	20	IOP, HR, BP	No statistically significant difference in IOP in subjects treated with microdrops vs. standard drops	-Timolol maleate-induced decrease in HR was more pronounced in subjects that received standard drops vs. microdrops -No statistically significant difference in BP in subjects treated with microdrops vs. standard drops
Craig & Griffiths, 1991	10% Phenylephrine	10 vs. 30	20	PD	No statistically significant difference in PD in subjects treated with microdrops vs. standard drops	Microdrops caused less ocular discomfort than standard drops
Gray, 1991	-1% Tropicamide + 10% Phenylephrine -1% Tropicamide -0.5% Tropicamide	5 vs. 26	60	PD	-1% Tropicamide + 10% PE: Standard drops produced a significantly greater increase in PD than microdrops -1% Tropicamide: No statistically significant difference in microdrop- vs. standard drop-induced increases in PD -0.5% Tropicamide: Standard drops produced a significantly greater increase in PD than microdrops	Microdrops caused less ocular discomfort than standard drops
Gray et al., 1992	1% Tropicamide	5 vs. 26	20	Pupil:cornea diameter, visual acuity	-No statistically significant difference in microdrop- vs. standard drop-induced changes in pupil:cornea diameter -Microdrops caused a statistically significant improvement in distance and near visual acuity recovery rate vs. standard drops	N/A
Vocci et al., 1992	0%, 0.5%, 1% Apraclonidine	16 (0.5%) vs. 30 (0.5%, 1%)	29	Resting HR, BP, visual acuity, IOP, side effect profile	No statistically significant difference in IOP in subjects treated with microdrops vs. standard drops	Fewer subjects reported side effects including dry mouth and nose, fatigue, drowsiness, and burning on instillation while taking microdrops or standard drops of 0.5% apraclonidine vs. standard drops of 1% apraclonidine
Wheatcroft et al., 1993	0.5% Cyclopentolate + 2.5% Phenylephrine	5 vs. 26	26	PD	No statistically significant difference in microdrop- vs. standard drop-induced increases in PD	N/A
Whitson, 1993	10% Phenylephrine	10 vs. 30	13	PD, plasma [PE]	No statistically significant difference in microdrop- vs. standard drop-induced increases in PD	Less systemic absorption of PE occurred in response to microdrop vs. standard drop administration
Lal et al., 1995	2% Pilocarpine	10 vs. 20 vs. 40 vs. 80	12	PD, HR, objective side effects profile	-10 µL drops significantly more efficacious at decreasing PD than 20, 40, and 80 µL drops -20 µL drops significantly more efficacious at decreasing PD than 40 and 80 µL drops	-No statistically significant difference in HR, objective side effects between treatment groups -Decreased incidence of ocular (i.e., irritation) and systemic (i.e., headache) side effects in subjects treated with 10 and 20 µL drops vs. 40 and 80 µL drops
Elibol et al., 1997	-1% Cyclopentolate -10% Phenylephrine -0.5% Tropicamide	6 vs. 35	61	PD, HR, BP, flushing	-1% Cyclopentolate and 10% PE: No statistically significant differences in PD in subjects treated with microdrops vs. standard drops -Tropicamide 0.5%: Standard drops produced a significantly greater increase in PD than microdrops	No statistically significant differences in systemic side effects (i.e., HR, BP, flushing) in subjects treated with microdrops vs. standard drops

Reference	Drug	Drop volume (µL)	n =	Outcomes	Microdrops vs. standard drops	
					Ocular efficacy	Side effects and/or systemic absorption
Hendricks et al., 1997	Paramyd (1% Hydroxyamphetamine hydrobromide, 0.25% Tropicamide)	10 vs. 30	24	PD	All eyes reached "clinically significant dilation" of ≥7 mm PD. There were no statistically significant differences in microdrop- vs. standard drop-induced increases in PD, pupil area, or time to maximum dilation	N/A
Hans Van Der Heiden et al., 2016	0.5% Tropicamide	2.4 vs. 38	30	PD, side effects via questionnaire	Microdrops provided non-inferior mydriasis relative to standard drops.	All subjects reported less discomfort, impaired vision with microdrops compared to standard drops.
Seliniotaki et al., 2021	1.67% Phenylephrine + 0.33% Tropicamide	6-7 vs. 28-34	25	PD, HR, BP, oxygen saturation, side effects	No statistically significant difference in PD following treatment with microdrops vs. standard drops	No statistically significant differences in HR, BP, oxygen saturation, or side effects following treatment with microdrops vs. standard drops
Hoppe et al., 2022	2.5% Phenylephrine + 1% Tropicamide + 1% Cyclopentolate	10 vs. 50	50	PD, spherical equivalent, pupil constriction percentage	10 µL drops dispensed with Nanodropper provided non-inferior pupil dilation relative to 50 µL drops. 10 µL drops did not meet strict non-inferiority criteria for spherical equivalent or constriction percentage.	N/A

First peer-reviewed publication with Nanodropper

Nanodropper is an eyedrop bottle adapter that creates microdrops.

Nanodropper is a patented, FDA listed, award-winning adaptor for eyedrop medication bottles that creates smaller eyedrops. Our company's goal is to improve treatment adherence and outcomes through the delivery of topical microdrops. **Nanodropper is available for purchase online at www.nanodropper.com**.



Conventional drops

References

[1] Parihar JKS. Glaucoma: The 'black hole' of irreversible blindness. *Med J Armed Forces India*. 2016;72(1):3-4. doi:10.1016/j.mjafi.2015.12.001

[2] Newman-Casey PA, Blachley T, Lee PP, Heisler M, Farris KB, Stein JD. Patterns of Glaucoma Medication Adherence over Four Years of Follow-Up. *Ophthalmology*. 2015;122(10):2010-2021. doi:10.1016/j.ophtha.2015.06.039

[3] Nordstrom BL, Friedman DS, Mozaffari E, Quigley HA, Walker AM. Persistence and Adherence With Topical Glaucoma Therapy. *Am J Ophthalmol*. 2005;140(4):598.e1-598.e11. doi:10.1016/j.ajo.2005.04.051

[4] Kahook MY. Of Course I Took my Eye drops, Doctor (Improving Adherence). In: *The 42nd Annual Midwest Glaucoma Symposium*. 2019;September 6-7.

[5] Mishima S, Gasset A, Klyce SDJ, Baum JL. Determination of tear volume and tear flow. *Invest Ophthalmol*. 1966;5(3):264-276.

[6] Chrai SS, Patton TF, Mehta A, Robinson JR. Lacrimal and instilled fluid dynamics in rabbit eyes. *J Pharm Sci*. 1973;62(7):1112-1121. doi:10.1166/jnn.2012.6247

[7] Shell JW. Pharmacokinetics of topically applied ophthalmic drugs. *Surv Ophthalmol*. 1982;26(4):207-218. doi:10.1016/0039-6257(82)90081-9

[8] Jaenen N, Baudouin C, Pouliquen P, Manni G, Figueiredo A, Zeyen T. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. *Eur J Ophthalmol*. 2007;17(3):341-349. doi:10.1177/112067210701700311

[9] Miller K, Brown RH, Lynch MG, Eto CY, Lue JC, Novack GD. Does drop size influence the efficacy of a topical beta blocker? *Invest Ophthalmol Vis Sci*. 1986;27(Supplemental):161.