THE DEMAND FOR METERED DOSE EYE DROPS: A DOSE DELIVERY STUDY

In this article, Rouven Kraus, Head of Sales at Aero Pump, discusses a dose delivery study comparing various delivery technologies designed to meet the demand for metered dose eye drops.

The conjunctival sac of the human eye holds 7–10 µL of tears and has an overall capacity of 30 µL of fluid at a time.[1] To apply the right dose of medicine to the eye, drug delivery companies designed eye-drop devices that apply appropriate doses of 28–50 µL. Prescription drugs (e.g. prostaglandins for glaucoma treatment) usually come in delivery devices applying a dose of about 30 µL. The active ingredient is kept in the eye without any fluid spilling out. Moisturising eye drops containing, for example, sodium hyaluronate use dropper devices with a dose of about 30 µL or even about 50 µL if the product is intended to flush the eye. Especially for expensive APIs, drug manufacturers should turn their attention to prevent waste of the active and to avoid any overdosing risks. To do so, they are faced with using metered dose delivery technologies.

There are a multitude of different delivery technologies available on the market. Single-dose vials are designed to dispense a single amount of medicine and then will be discarded. Three-piece droppers are conventional multidose bottles for preserved medications. Regulatory bodies recommend the use of preservative-free delivery technologies to protect the ocular surfaces from any side effects caused by preservatives such as benzalkonium chloride. Squeeze dispensers (such as Aptar Pharma's OSD System or Nemera's Novelia®) are such preservative-free multidose bottles that protect the container content from microbial impurity.

Figure 1: Precise dose delivery of a metered dose pump.

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"Metered dose dropper pumps are unique in this field as they are the only preservative-free technology that is based on a purely mechanical pump system."

Metered dose dropper pumps (such as Aero Pump's 3K® pump or Ursapharm's (Saarbrücken, Germany) COMOD® system) are unique in this field as they are the only preservative-free technology that is based on a purely mechanical pump system. They always offer an accurate dose delivery with just one drop delivery per activation (Figure 1).

Aero Pump conducted a dosage size determination study with various delivery technologies that are available on the market. The study included several multidose eye-drop bottles.

The assay is based on the dose-uniformity requirements as set forth in the relevant Pharmacopeial chapters (USP Chapter <905> Uniformity of Dosage Units and Ph.Eur. <0676> Nasal Preparations). Ten samples per device are assayed individually by using calibrated balances. The whole study is performed by a single trained person to avoid any fluctuations. All devices are filled with a lubricating ophthalmic formulation available on the market. The assay is carried out on the amount of solution that is removed from an individual container in conditions of normal use, whereas the first 20 doses are discharged until a consistent dosage is achieved. For some devices it is necessary to prime the system to release the air from the device. The results are expressed as the delivered dosage units. Therefore, Pharmacopoeia foresees the following dose uniformity limits:

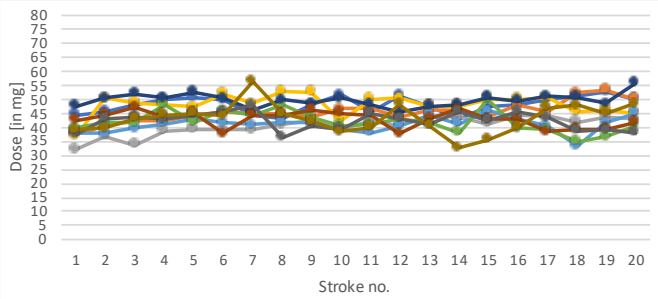
Maximum allowed acceptance value of mean dose = ± 15.0%

Maximum allowed acceptance value of each dosage unit = 80% of dispensed doses ±25.0% and 100% ±35.0%

The results of this dose delivery assay are shown in the diagrams in Box 1.

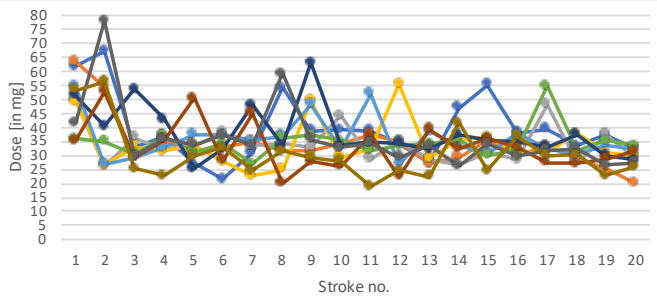
BOX 1: DOSE DETERMINATION RESULTS

Three-piece dropper



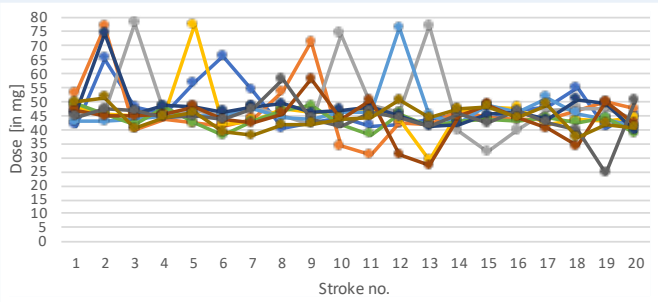
The mean delivered dose of the three-piece dropper is 44.4 mg. The device enables a consistent dose delivery of just one single drop per activation. The delivered dose is slightly fluctuating. All dispensed doses are in compliance with the relevant Pharmacopeial requirements regarding the dose delivery acceptance limits.

Ophthalmic squeeze dispenser



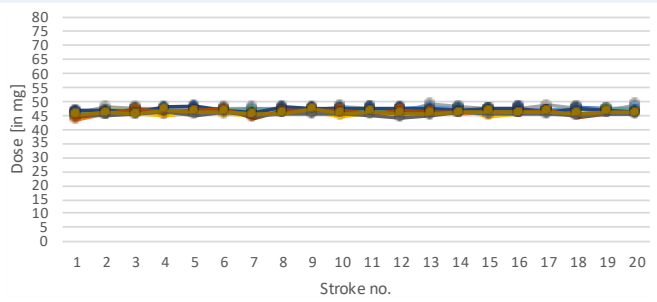
The ophthalmic squeeze dispenser (OSD) has a mean delivered dose of 35.0 mg. Several values do not comply with the acceptance limits of the single delivered doses. The output diagram shows that it was possible to dispense two drops within one single activation several times. There are several fluctuations of the delivered doses.

Novelia®



Novelia® has a mean delivered dose of 46.0 mg. The mean delivered dose is fully within the acceptance limits but several single values do not comply with the allowed dose delivery tolerances (80% of single doses ±25.0% and 100% of single values ±35.0%). The device enables a constant delivery of a uniformed drop but also carries the risk of accidentally dispensing two drops instead of one.

3K® pump



The 3K® pump shows the best dose delivery features out of all devices. It delivers a constant dose of 46.5 mg in the mean and all single dispensed doses 100% comply with the Pharmacopeial acceptance limits. The pump mechanism prevents any overdose risk for the patient.

"The results show that the pump-based mechanism used in the 3K® system achieved the best RSD value."

It is shown that all devices show good dose-uniformity results. But it is clearly visible that, except for the pump-based mechanism used in the 3K® technology, all other devices carry the risk of dispensing two drops per activation instead of just one. If the patient squeezes the bottle, they might instill two drops in their eye with the doubled active content. With some squeeze dispensers there is even the potential to create an extremely uncomfortable jet in the worst-case scenario.

The pump mechanism used in the 3K® pump avoids such overdosing reaction since the pump creates one defined dose per each activation, drop by drop (Figure 2).

During the assay the different devices were also compared with the relative standard deviation (RSD) by using the following formula:

$$RSD = \frac{(Standard\ Deviation)}{Mean} \times 100$$

The RSD value determines the deviation of all delivered drops in relation to the mean dispensed dose. The less the RSD rate, the more constant the dose uniformity. Table 1 shows the RSD results of all devices.

The results show that the pump-based mechanism used in the 3K® system achieved the best RSD value. All doses only fluctuate in a ratio of 2.0%. The minimum delivered dose out of all values is 43.5 mg and the maximum dose is 49.1 mg. The tested squeeze devices are more fluctuating in the dose uniformity. This is because the squeeze mechanism is controlled by pressure. Different pressure applied on the bottle may influence the delivered dose. And this is, in fact, the reality when looking at elderly patients with dexterity issues who may have less power to properly squeeze out the drops. Other patients may apply too much pressure and will squeeze out a higher dose – up to a doubled dose. Whereas the pump always works with the same activation force, which remains stable until the bottle is entirely emptied. This is user independent.

Device	Relative Standard Deviation
Three-piece dropper	10.5%
OSD	26.5%
Novelia®	17.1%
3K®	2.0%

Table 1: The RSD of every tested device.

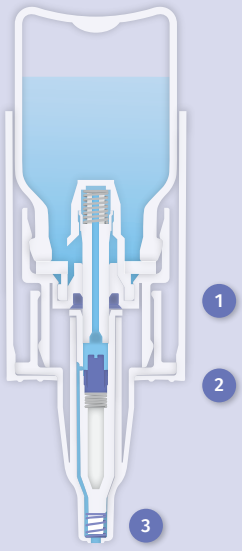
Figure 2: The risk of overdosing the eye.

"The pump always works with the same activation force, which remains stable until the bottle is entirely emptied."

From a previous usability study, one-third of subjects complained that "more than one drop came out". Improper delivery of drugs can lead to treatment failure, especially in the case of glaucoma patients. It increases the risk of potential side effects, such as burning or stinging, high blood pressure, fatigue, irregular heart rate, etc.

The 3K® pump ophthalmic system is designed in a way that the product chamber determines the output of the device. For a defined output of 45 mg, the pump will only release a drop size of 45 mg. The product chambers will be filled with the fluid again from the next activation of

Preservative-free 3K®-technology for microbiological safety



1 **The filter matrix** prevents ingress of contaminated air

2 **The valve** protects the content by stopping backflow of the product

3 **The oligodynamic nozzle** prevents microbiological growth in the tip

Figure 3: The principle of the 3K® technology with its triple protection barriers against microbiological contamination.

Figure 4: The Ophthalmic Multidose System in different sleeve designs.

the pump. The 3K® pump eyedropper is also available in lower dosage sizes such as 28 mg. The principle of the pump-based mechanism simply avoids overdosing.

ABOUT AERO PUMP'S PRESERVATIVE-FREE OPHTHALMIC MULTIDOSE SYSTEM

Aero Pump has developed a preservative-free multidose system with 3K® technology for ocular delivery. Special germ-reducing components inside the 3K® system ensure the microbiological safety of the device (Figure 3).

The pump system is available for use with plastic or glass containers in various fill sizes and, in terms of reducing container interaction with the product, this is a particular advantage. The 3K® system delivers an accurate dose over the whole lifecycle of the product, with one measured drop per actuation. The actuation force of Aero Pump's ophthalmic multidose system is stable, independent of the residual liquid inside the container.

Alongside the development of the ophthalmic multidose devices, Aero Pump has developed various customer-friendly actuation aids that enable a convenient application of the drop into the eye of the patient (Figure 4).

ABOUT THE COMPANY

Aero Pump is a leading manufacturer of high-precision application systems for the pharmaceutical and healthcare industry, focused on innovation, multi-functionality and contemporary design. Its spray pumps and dropper systems are widely established in the market and are primarily used in ophthalmic, pulmonary, nasal and dermal fields, suitable for preserved and preservative-free OTC and prescription drugs (Figure 5).

Figure 5: A brief view of Aero Pump's product range.

REFERENCE

1. *Djebli N et al, "Ocular Drug Distribution After Topical Administration: Population Pharmacokinetic Model in Rabbits". Eur J Drug Metab Pharm, 2016, Vol 42(1), pp 59–68.*

ABOUT THE AUTHOR

Rouven Kraus has more than 10 years of experience in the ophthalmic drug market. He started his career in sales for a domestic iron foundry in Mainz, Germany, and joined Aero Pump in 2012 to augment the sales of its drug delivery device portfolio. In his role, he is managing global sales as well as the strategic approach to new ophthalmic developments and delivery technologies.

AERO PUMP

Ophthalmic 3K® Multidose System

Metered Dose for Preservative-free Solutions

The only available metered dose PFMD technology for ophthalmics

The metered dose and exact reproducability of the drop size, based on the mechanical functionality of the pump, is unique amongst eye droppers.

Our prestigious 3K®-Pump delivers an accurate dose all over the lifecycle of the product. It is approved in various markets including Europe, USA, Far East and Latin America.

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