HORIBA Scientific

Application Note

Rapid PSA of Topical Ophthalmic Formulations

AN237

Rapid Particle Size Analysis of Topical Ophthalmic Formulations

Introduction

Successful ophthalmic drug delivery is a combination of pre-corneal retention time, corneal permeability, effectiveness of drug absorption, and dose-to-dose consistency. Whether the drug product is a suspension or microemulsion, it is a complex application involving careful analyses, research, and development efforts.

Physicochemical attributes such as particle size and particle size distribution, in particular, are two dominating factors that influence medicinal uptake and the extent at which the active pharmaceutical ingredient (API) reaches its intended segment of the eye. For example, runnier formulation may drain from the eye before it is absorbed, decreasing bioavailability to as little as 5% [1]. As particle size decreases, particle-particle interaction is increased, leading to flow resistance or higher viscosity. Likewise, when similar sized particles are incorporated to create a homogenous, narrow particle size distribution, viscosity is typically increased. Due to these properties APIs and/or the emulsion drop size is often manipulated into smaller particle size to improve bioavailability.

Difluprednate, a topical corticosteroid, and nepafenac, a nonsteroidal anti-inflammatory drug, both used for pain management post-cataract surgery, are no exception to this discussion (structures are shown in Figure 1). This note will examine how to accurately determine particle size and size distribution, repeatability, and reproducibility of these APIs to interpret shelf life and bioavailability alongside standards given by regulatory authorities [1, 2, 3].

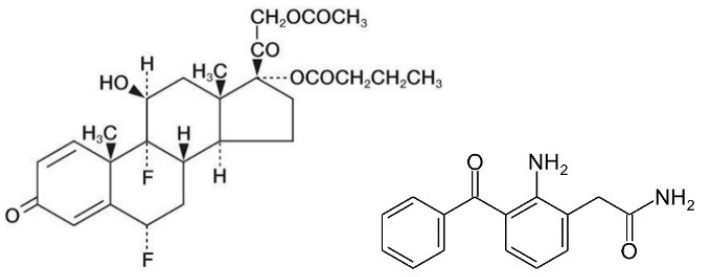

Figure 1. Molecular structures of difluprednate (left) and nepafenac (right) are non-polar and low in solubility.

Materials and Method

DUREZOL® (0.05% difluprednate ophthalmic emulsion) and ILEVRO (0.3% nepafenac ophthalmic suspension) were acquired and tested for this study. To sample, ILEVRO was inverted five times before dispensing as instructed according to the bottle label. Nepafenac is a yellow crystalline powder mixed into a sterile aqueous phase. It must be shaken to re-suspend nepafenac with other excipients. Without proper mixing, the drug settles to the bottom of the bottle, thereby altering the dose delivered. DUREZOL, in contrast, was not shaken and was sampled directly inverted from the tip.

Particle size and distribution analyses were carried out using the HORIBA LA-960V2 laser diffraction system fitted with a 10 mL fraction cell. The cell contains a magnetic stir bar (at an adjustable stir rate) to keep particles suspended during measurements. The cell was first filled with PBS buffer (pH 5.5) as the dispersant to best imitate normal tears with some level of buffer capacity. Then, the background signal was collected. The sample was then added to the fraction cell drop-wise until an appropriate light obscuration was reached. Repeated runs were measured to establish dispersion and instrument stability before averaging the runs into a monograph seen in Figure 2 and Figure 3. To test out DUREZOL drug dose-to-dose consistency, a second sampling was measured. The angular-scattering pattern values were calculated using a refractive index of *1.544-0.01i* and *1.641-0.1i* for DUREZOL and ILEVRO, respectively.

Result and Discussion

The averaged result overlay for both DUREZOL and ILEVRO exhibit two distinctly different distribution profiles (Figure 2). We compare the experimental results against USP (United States Pharmacopeia) <429> *Light Diffraction Measurement of Particle Size* and USP <789> *Particulate Matter in Ophthalmic Solutions* guidelines. USP <429> simply states that the coefficient of variation (CV) for the D50 value should not deviate by more than 10% and optionally evaluated D10 and D90 values should be within 15% (double the values for particles below 10 µm). USP <789>, on the other hand, describes the essence of its requirement in Table 1. Particles in ophthalmic suspensions typically should not exceed 25 µm to avoid eye irritation [4].

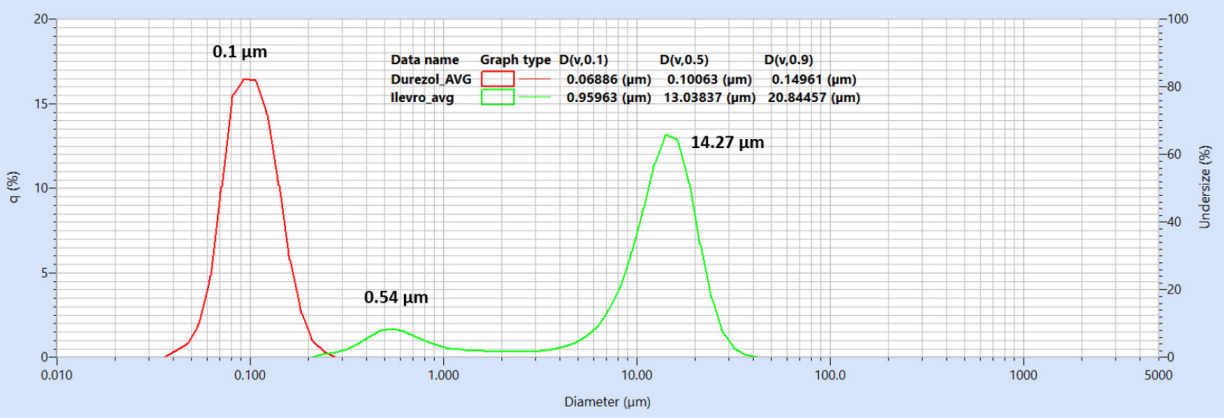

Figure 2. Result overlay for both DUREZOL and ILEVRO demonstrates different distribution profiles. DUREZOL particle size centers around 100 nm while ILEVRO displays a bimodal distribution ranging from 540 nm for the small peak to 14.27 µm for the larger peak.

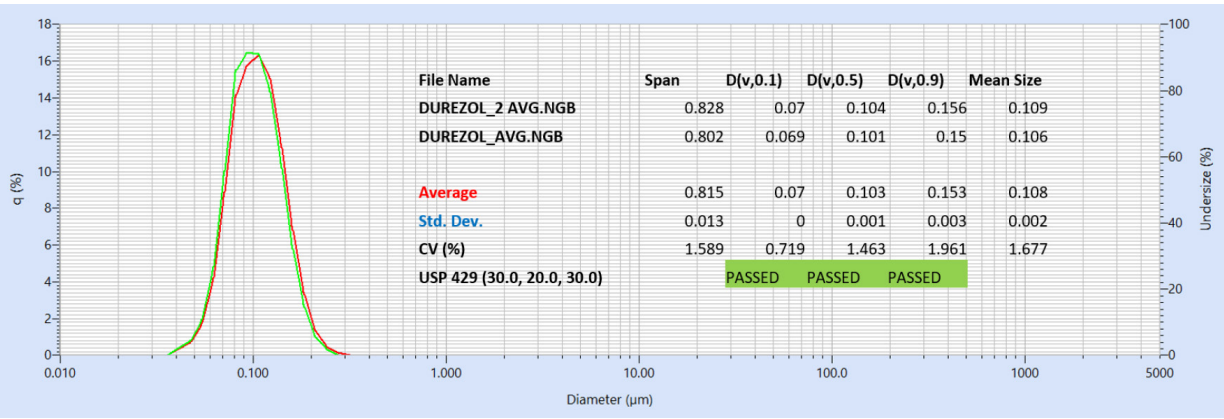

Figure 3. DUREZOL reproducibility test demonstrates dose uniformity well within USP <429> and USP <789> recommendations. The narrow particle size distribution with an average value of 108 nm also confirms that DUREZOL are emulsified eye droplets.

	Diameter	
	≥ 10 µm	≥ 25 µm
Number of particles	50 per mL	5 per mL

Table 1. USP <789> particulate size and count recommendations for light obscuration procedure.

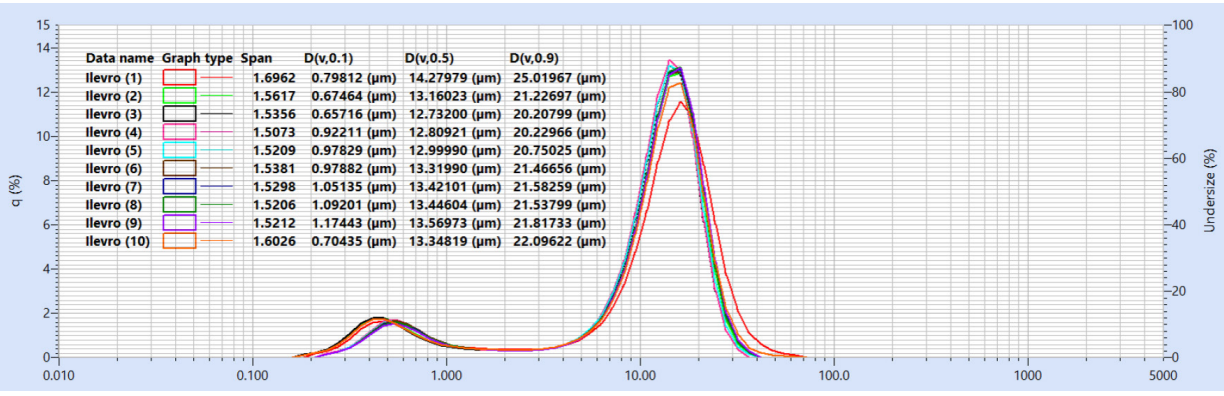

Figure 4. A set of 10 repeat measurements are collected over a period of 50 seconds in PBS at pH 5.5. This procedure meets the expectation from FDA.

DUREZOL: DUREZOL reportedly manufactures the only topical ophthalmic steroid emulsion on the market at the date of this writing [5]. An emulsion is a system that integrates two immiscible liquids together with the assistance of surfactant(s) for greater thermodynamic stability. This type of delivery mechanism notably favors cornea penetration due to the low surface tension and small droplet size. It has proven to achieve a higher concentration than a typical drug suspension [6]. We expect small and narrow droplet size and size distribution to reflect emulsion stability and dose-to-dose uniformity.

The resulting size distribution with a particle size mean of 106 nm and span ((D90-D10)/D50]) of 0.8025 confirms the validity of its emulsion claim [5] (see Figure 3). We further investigate sample reproducibility by running a second set of aliquot. The experiment shows that the CV for D10, D50, and D90 values are 0.719%, 1.463%, and 1.961% respectively. Both tests satisfy the requirements of USP <429> and USP <789> guidance. The excellent overlay between two monodisperse averages shown in Figure 3 confidently confirms DUREZOL's excellent droplet homogeneity and along the line, suggests consistent drug delivery from patient's application standpoint.

ILEVRO: ILEVRO in comparison, has a much wider bi-mode particle size distribution with a span ((D90-D10)/D50]) of 1.5251 and modes of 0.54 µm and 14.27 µm respectively for both peaks. Specifically, for nepafenac, the Food and Drug Administration's (FDA) current thinking pushes for full particle size distribution profile submission [1], not just the evaluation of parameters alone described in USPs. FDA also recommends at least ten data sets from each batch. This type of rigorous testing for quality can be done automatically within the LA-960V2 software and reported as seen in Figure 4.

Conclusion

Drug particle size and distribution are key critical quality attributes that govern stability, ocular retention via solution thickness, and therapeutic release characteristics. The laser diffraction technique is an elegant method used to establish the fundamentals of ophthalmic formulations prior to pharmacokinetic or clinical studies. To fulfill the requirements set out by the FDA, our recommendation is the Partica LA-960V2 Particle Size Analyzer.

References

[1] *Draft guidance on NEPAFENAC - Food and Drug Administration*. (2016, December). Retrieved December 9, 2021, from https://www.accessdata.fda.gov/drugsatfda_docs/psg/Nepafenac_ophthalmic%20suspension%20 0.3_RLD%20203491_RV12-16.pdf.

[2] USP <429> *Light Diffraction Measurement of Particle Size*

[3] USP <789> *Particulate Matter in Ophthalmic Solutions guidelines*

[4] Uddin, M., Mamun, A., Kabir, M., Setu, J., Zaman, S., Begum, Y., & Amran, M. (2017). Quality control tests for ophthalmic pharmaceuticals: Pharmacopeial Standards and Specifications. *Journal of Advances in Medical and Pharmaceutical Sciences*, 14(2), 1–17. https://doi.org/10.9734/jamps/2017/33924

[5] https://www.durezolhcp.com

[6] Mazet, R., Yaméogo, J. B., Wouessidjewe, D., Choisnard, L., & Gčze, A. (2020). Recent advances in the design of topical ophthalmic delivery systems in the treatment of ocular surface inflammation and their biopharmaceutical evaluation. *Pharmaceutics, 12*(6), 570. https://doi.org/10.3390/pharmaceutics12060570