



Enhancing Powdered Drug Products in Bio-Pharmaceutical Manufacturing with Instrumental Color Measurement

Introduction

Color measurement plays a pivotal role in ensuring the quality, consistency, and safety of powdered pharmaceutical products. From active pharmaceutical ingredients (APIs) to excipients, blends, and intermediates, color is a key indicator of composition, purity, stability, and process uniformity. Inconsistent color can signal contamination, improper blending, degradation, or incorrect formulation ratios—all of which may impact product performance or regulatory compliance. While visual inspection has long been used for powder evaluation, modern spectrophotometric color measurement provides an objective, quantifiable method aligned with global pharmacopeial and CIE (Commission Internationale de l'Éclairage) requirements. Using full visible-range spectrophotometers such as HunterLab's **UltraScan VIS** and **Agera L2**, manufacturers can accurately assess and control color attributes, ensuring precise batch-to-batch consistency throughout the product development, testing, and manufacturing process.

Overview: The Role of Color in Powdered Drug Manufacturing

Small molecule powdered pharmaceutical materials include a wide spectrum of product forms—crystalline APIs, amorphous excipients, granulated blends, lyophilized intermediates, and powdered coatings. Each of these materials exhibits distinctive optical characteristics that can affect not only appearance but also process behavior,



dissolution, and downstream performance. The global shift toward high-potency and precision-formulated drugs demands tighter appearance control. Consistent powder color often reflects proper crystallinity, moisture content, and purity, while deviations may indicate oxidation, polymorphic transformation, or contamination. As color directly correlates with process and raw material integrity, it has become a primary quality attribute in both development and production environments.

Importance of Color Measurement by Application

In small molecule APIs, color is often the first visible sign of purity and synthetic consistency. Slight discoloration may signal the presence of reaction byproducts, oxidation, or residual solvents. For excipients such as lactose, microcrystalline cellulose, and starch, color uniformity ensures reliable performance and minimizes variation in the final dosage form. During powder blending and granulation, color serves as a visual proxy for mixture homogeneity - an essential factor in achieving uniform drug content. In tablet coating applications, color control is equally critical for brand consistency and dose differentiation. Color control can also be implemented for coating thickness and uniformity. Implementing objective spectrophotometric color measurement across these processes ensures reproducibility and reduces subjective interpretation inherent in visual methods.

What Color Reveals About Powder Quality

Powder color can provide detailed insight into both chemical composition and process conditions. Variations in hue or lightness can indicate raw-material variability, thermal degradation, or humidity exposure. For APIs, a shift toward darker appearance may suggest increased impurity levels or incomplete crystallization. Changes in chromaticity within granulated blends can reveal non-uniform dispersion of active and excipient materials. By quantifying color in CIELAB coordinates (L^* , a^* ,



b*), manufacturers can establish numeric tolerances that correlate directly to process endpoints—such as drying time, blending efficiency, and coating uniformity. Regular color trending enables early detection of drift and facilitates root-cause analysis for deviations before they impact finished product quality.

Color Measurement Applications Across the Manufacturing Lifecycle

Spectrophotometric color measurement applies to every stage of powdered drug production. In **raw-material qualification**, any incoming APIs and excipients are measured for compliance with color specifications, preventing out-of-tolerance materials from entering the process. During **powder blending and granulation**, frequent color checks confirm mixture homogeneity and ensure uniform distribution of actives. In **drying and milling**, color data can reveal overheating or moisture retention. **Compression and coating** processes benefit from continuous color verification to ensure consistent appearance, while **final product release** testing validates conformity with master standards and regulatory color limits. By integrating color measurement data into quality management systems, manufacturers can maintain traceable, quantifiable records that align with global GMP and data-integrity standards.

Challenges in Applying Color Measurement: Visual vs. Instrumental

Visual color inspection is inherently unreliable for powders due to variable lighting, observer bias, and inconsistent sample presentation. Fine powders scatter light differently depending on particle size and packing density, causing apparent color shifts that cannot be interpreted consistently by the human eye. Moreover, visual grading provides no digital trace or quantitative reference. Instrumental color measurement overcomes these limitations by employing standardized illuminants,



calibrated instruments, and defined measurement geometries. Spectrophotometers capture complete spectral reflectance data, enabling consistent L^* , a^* , b^* and ΔE^* quantification. When applied under controlled sample conditions – such as fixed compaction pressure of the powder or optical path length – instrumental methods deliver reproducible, auditable results that meet CIE and pharmacopeial standards for visible-range color analysis.

Global Color Methods and Standards

Color and appearance measurement in pharmaceuticals are governed by harmonized international guidelines that support objective, traceable results. The **CIE** defines the $L^*a^*b^*$ color space, ΔE^* color difference metrics, and standard illuminants (e.g., D65 or C) used globally. The **United States Pharmacopeia (USP)** and **European Pharmacopoeia (EP)** both reference instrumental colorimetry for powders and solids, emphasizing the use of full visible-range spectrophotometers calibrated to NIST-traceable standards. In solid-dosage manufacturing, compliance with **21 CFR Part 11** and **GMP Annex 11** requires electronic data capture, audit trails, and validation of analytical instruments - all of which are supported by modern HunterLab systems. Alignment with these standards ensures global consistency, regulatory readiness, and harmonization across manufacturing networks.

Recommended HunterLab Solutions and Why

The **UltraScan VIS** (diffuse $d/8^\circ$ geometry) is a key HunterLab solution for powdered and solid dosage applications. It provides full visible-range spectral coverage (360–780 nm) with true CIE-compliant performance, enabling precise evaluation of diffuse-reflectance samples such as powders, granules, and coated tablets. The UltraScan VIS can also measure in transmission for other bio-tech products as well as powders if dissolved in solution. The instrument accommodates a range of sample-presentation



accessories—including reflectance cups and cuvettes – to minimize variability caused by particle distribution. Its built-in CIE, USP, and EP color scales, combined with user-controlled illuminant and observer settings, make it ideal for laboratory quality control and reference method validation.

The **Agera L2** serves as an alternative and complementary solution designed for routine production-floor and quality-assurance use specifically for powders or pressed pucks. Agera L2 utilizes 0°/45° circumferential measurement geometry that simulates human visual perception. Bio-pharma small molecule powders are placed in a sample cup or cuvette and Agera L2 delivers rapid, repeatable reflectance color data suitable for in-process verification and final inspection. Its integrated touchscreen interface, on-board storage, and optional network connectivity allow operators to perform immediate pass/fail assessments without external computers. Agera L2 can also provide 21 CFR Part 11 data integrity requirements. Together, UltraScan VIS and Agera L2 provide a complete platform for color control—combining laboratory precision with shop-floor efficiency and traceability.

Features, Advantages, and Benefits of HunterLab Solutions

The **UltraScan VIS** combines high spectral resolution with robust optical stability to ensure long-term reproducibility. Its dual-beam configuration minimizes drift, while integrated calibration routines maintain traceability to international color standards. In reflectance mode, the system's wide aperture and reflectance accessories allow accurate measurement of both fine powders and compressed tablets, producing consistent data independent of operator technique. The **Agera L2** delivers rapid color assessment under production conditions with minimal sample preparation. Its touchscreen interface simplifies operation, and its ability to store results locally or transmit them via LIMS integration supports data integrity across the manufacturing network. Both instruments use validated HunterLab software with secure audit trails



and electronic signatures, ensuring full compliance with Part 11 and Annex 11 requirements. Together they enable proactive color monitoring, reduce batch variability, and strengthen overall product quality.

Hypothetical Case Studies

Case 1 - Powder Blending and Uniformity

A pharmaceutical manufacturer producing a fixed-dose combination tablet experienced inconsistent assay results traced to inadequate powder blending. Visual inspection of intermediate blends showed no apparent differences, yet finished tablets exhibited varying color and appearance. By implementing the UltraScan VIS spectrophotometer, the company established numeric ΔE^* limits representing acceptable blend homogeneity. In-process color checks during blending allowed operators to detect incomplete mixing early (before compression). This objective control reduced blend failures by more than 70 percent, improved uniformity testing outcomes, and shortened overall batch cycle time.

Case 2 - API Raw-Material Qualification

An API supplier delivered batches of a crystalline antibiotic that occasionally displayed slight beige discoloration compared to the approved white standard. Chemical assays showed acceptable potency, but customers expressed concerns regarding visual consistency. Using the Agera L2 spectrophotometer, the receiving laboratory quantified color differences in L^* , a^* , b^* space and linked higher b^* values to trace oxidation during drying. The manufacturer was then able to make process adjustments—lowering drying temperature and optimizing nitrogen purge—restored the material's expected color characteristics. Subsequent shipments consistently met color specifications, improving supplier reliability and minimizing customer complaints.



Conclusion

Instrumental color measurement has become an indispensable tool for ensuring quality and consistency in powdered and solid dosage pharmaceutical products. Objective color data provides insight into formulation integrity, process control, and product uniformity—attributes critical to regulatory compliance and patient confidence. By adopting full visible-range spectrophotometry through the **UltraScan VIS** and leveraging the operational flexibility of **Agera L2**, manufacturers can transform color assessment from a subjective observation into a quantifiable quality metric. These systems deliver precise, traceable results aligned with international standards, enabling pharmaceutical companies to enhance process understanding, prevent deviations, and maintain the highest standards of excellence in drug production.

References

1. Commission Internationale de l'Éclairage (CIE) – *Colorimetry: Technical Report CIE 15:2018*.
2. United States Pharmacopeia (USP <1061>, <855>) – *Color and Appearance Measurement for Solid Dosage Forms*.
3. European Pharmacopoeia (EP 2.2.2) – *Degree of Coloration of Solids and Powders*.
4. U.S. FDA – *Process Analytical Technology (PAT) Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance*.
5. HunterLab Application Notes – *Color Measurement of Powders, Granules, and Solid Dosage Forms*.
6. HunterLab Product Documentation – *UltraScan VIS and Agera Technical Specifications and Validation Packages*.