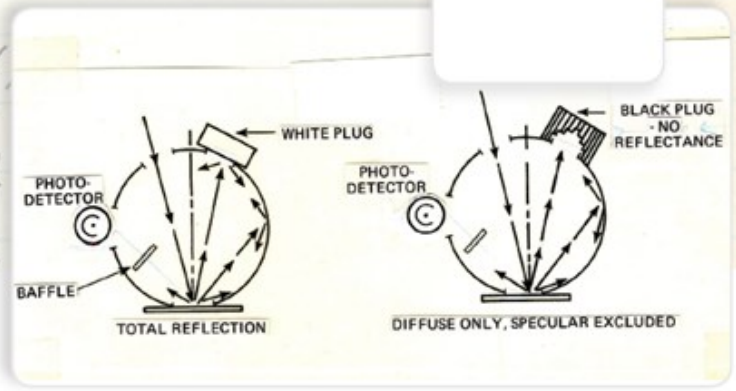
Applications Note

AN 1062



Measuring the Color of Pharmaceutical Products

Color is an indicator of quality where a color difference can be found between acceptable and unacceptable.

Abstract

HunterLab instruments can be used for color evaluation of pharmaceutical intermediates, final products, byproducts and medical devices.

Color can be an indicator of quality, degradation, and purity for pharmaceuticals.

HunterLab also provides tools to adhere to electronic recordkeeping for the purpose of adhering to FDA regulations.

The world's true measure of color
HunterLab

Challenge: To evaluate pharmaceutical products for color consistency

In the pharmaceutical industry color is used as:

- An indicator of quality where there is a color difference between acceptable and unacceptable.
- A conformance criterion for FDA or company manufacturing standards.
- An indicator of degradation and loss of potency over time.
- To differentiate between medications.
- To verify efficacy of dip test strips where a defined color is associated with the presence of an active ingredient.
- Part of a brand's identity.

HunterLab instruments can be used for color evaluation of pharmaceutical intermediates, final products, byproducts and medical devices such as:

- Tablets and capsules
- Powders and granules
- Liquid Solutions, syrups and gels
- Ointments, creams and lotions
- Dip Sticks/Strips

Recognizing the importance of color for pharmaceuticals, the U.S. Pharmacopeia includes guidance on color and color measurement in its collection of standards. The relevant monographs are discussed on the next page.

U.S. Pharmacopeia Monograph 631

Monograph 631, titled 'Color and Achromicity', defines color and colorlessness (achromicity), the visual observing situation and three attributes of color (hue/value/chroma and the corresponding X,Y, Z) principles that apply to HunterLab's instruments. This monograph also describes how color should be evaluated visually using diffuse, uniform illumination under conditions that reduce shadows and nonspectral reflectance to a minimum. When powders are evaluated, the surface viewed should be smoothed with gentle pressure so that a planar surface free from irregularities is presented. If the illumination affects evaluations, those obtained in natural or artificial daylight are to be considered correct. It stipulates that a suitable instrumental measurement may be used instead of visual evaluation and explains how color difference measurements can be made by comparison of samples to known standards of similar color. This includes Munsell chips for reflectance measurements and the A-T USP fluid standards for transmittance measurements.

Munsell Color Standards

The Munsell and USP standards serve as guides for color selection and a standardized means for verbal color communication, but lack the precision of tristimulus instrumental measurements to meet today's quality assurance requirements. A suitable compromise is to define the product color in nominal terms using the Munsell or USP standards while using tristimulus color measurement to verify color consistency.

The USP - United States Pharmacopoeia visual color standards consists of 15 matching liquids color standards (A-T) derived from 3 primary solutions (cobaltous chloride, ferric chloride and cupric sulfate) mixed with water in various ratios.

All of the requirements of Monograph 631 can be met using HunterLab instruments. The visual observing situation (including the diffuse uniform illumination specified) is standardized using HunterLab spectrophotometers.

USP Fluid Standards

A smooth, regular powder surface can be presented to the Agera by pressing the powder into a plaque or pouring it into a glass sample cup and reading it through the glass bottom of the cup. Powders may also be measured in a glass sample cup using a ColorFlex, Aeros, Agera or MiniScan EZ.

Powders can be measured using a UltraScan PRO or UltraScan VIS by pouring them into a glass transmittance cell and measuring them through one of the glass sides of the cell. As far as the illumination requirement a number of standard illuminants are available with all of the HunterLab instruments. All HunterLab instruments provide color difference measurements by comparison of samples to standards.

US Pharmacopeia Monograph 1061

Monograph 1061, titled 'Color—Instrumental Measurements gives a synopsis of color measurement, explaining how a color measurement instrument simulates the tree components of the visual observing situation: the spectral energy of illumination, the absorbing characteristics of the sample and the visual sensitivity of the observer. It also provides the equations for converting spectral reflectance or transmittance to CIE X,Y,Z tristimulus values from which all other color values may be calculated. Then it gets into the requirements of the monograph. These requirements are listed in the table below in order of appearance in the monograph along with an evaluation of whether HunterLab's instruments comply. This monograph describes measurement of opaque solids and transparent liquids. It is not applicable to measurement of hazy liquids or translucent samples.

EP - European Pharmacopoeia Color is a visual liquid color scale consisting of 3 primary color standard solutions (yellow, red and blue) that are combined with hydrochloric acid to make 5 standard color solutions - B (brown), BY (brownish-yellow), Y (yellow), GY (greenish-yellow) and R (red) that are subsequently diluted with hydrochloric acid (10 mg/l) to make 37 reference EP liquid color standards - 9B, 7BY, 7Y, 7GY and 7R.

Monograph 1061 Requirement	HunterLab Instrument Compliance
Spectrophotometers should have a bandwidth of 10nm or less	All of the HunterLab's current products meet this requirement.
For spectral reflectance of opaque solids (such as powder plaques) , specular-excluded (RSEX) Mode should be used.	The geometry of ColorFlex, Agera, MiniScan EZ and Agera excludes the specular . The UltraScan PRO, UltraScan VIS may also be standardized to read in RSEX.
When measuring transmittance of clear liquids, both the illumination and observation angles should be within 5 degrees of the normal to the sample surface.	When measuring in Regular Transmittance (RTRAN) using the Vista, UltraScan PRO or UltraScan VIS, the instrument geometry is diffuse/0 ° . This means that the light source passes straight through the sample to the detector at 0°.
When measuring transmittance of clear liquids, the pathlength should be kept constant. A 1cm pathlength should be used unless special consideration dictate otherwise.	10mm (1cm) transmittance cells are available for use with the Vista, UltraScan PRO and UltraScan VIS, though longer pathlengths are not prohibited by the monograph. HunterLab also has transmittance cells available in 23-, 33– and 5-mm pathlengths.
For Transmittance measurements, distilled water should have a transmittance of 100% at all wavelengths.	The UltraScan PRO, UltraScan VIS and Vista may be standardized using distilled water in the transmittance cell as a blank for setting the top of the scale. If the transmittance cell is read back, it should return a value of 100% transmittance at all wavelengths.
For transmittance measurements the X, Y, Z factors used for illuminant C should be 98.0, 100.0 and 118.1 respectively,	The ASTM E308 factors are used for all instruments in EasyMatch QC.

Monograph 1061 Requirement	HunterLab Instrument Compliance
In measuring reflectance, top-of-scale should be set using opaque porcelain plaques instead of the perfect diffuse reflector.	HunterLab is mentioned in Footnote 2 of the monograph as being a supplier of standards. Porcelain on steel standard tiles are used to set the top-of-scale for the ColorFlex, Aeros, and MiniScan EZ. Everwhite opal tiles are used to set the top-of-scale for the UltraScan Pro and UltraScan VIS. The Agera uses an ultra white tile.
After calibration, the instrument should be checked versus a reference material that is close in color to the sample for monitoring instrument performance.	A green tile is provided with the ColorFlex, UltraScan PRO, UltraScan VIS, Agera, and Aeros as a middle wavelength check. This tile is an option for the MiniScan EZ. Standards of other colors may be purchased from HunterLab and used for color checking.
Spectrophotometric measurements done in reflectance or transmittance should be determined from 380 to 770nm.	The UltraScan PRO has the capability of measuring reflectance and transmittance over the range of 350—1050nm and meets this requirement. The UltraScan VIS measures over the range of 360 – 780nm and meets this requirement. The Agera, Aeros, ColorFlex, MiniScan EZ and Vista have a range of 400—700nm.

Description of Instrumental Correlation to USP and EP Pharmacopoeia Color

USP Monograph 1061 Color – Instrumental Measurement references the use of CIE L*, a*, b* color measurement to quantify colors precisely and objectively.

When measured, the 15 USP Liquid Color Standards are spread along the + b* yellowness axis with little tint runs of red and green.

The 37 EP Liquid Color Standards are spread along the + b* yellowness axis in 5 tint runs of red and green radiating out.

The best method for a USP or Color instrumental correlation is to think of these liquid color standards as isolated points in color space with the task being to find and report the USP or EP color standard nearest to the sample color. Correlating the instrumental measurement to the USP/EP Color Scales allows the use of colorimetry to quantify the color and communicating in the USP and EP reporting numbers.

Instrument Recommendations

Pharmaceutical products and appropriate instruments for their measurements are shown in the next table.

Product	Instrument
Creams and Lotions	Agera , ColorFlex, MiniScan EZ, UltraScan PRO, UltraScan VIS
Dip Sticks/Strips	Agera , ColorFlex, MiniScan EZ, UltraScan PRO, UltraScan VIS
Plastic Parts	Agera , Aeros, ColorFlex , MiniScan EZ, UltraScan PRO, UltraScan VIS
Powders	Agera , Aeros, ColorFlex , MiniScan EZ, UltraScan PRO, UltraScan VIS
Tablets and Capsules	Agera , Aeros, ColorFlex , MiniScan EZ, UltraScan PRO, UltraScan VIS
Transparent Liquids	UltraScan PRO, UltraScan VIS, Vista

Complying with FDA Documentation Regulations

When an American pharmaceutical company purchases new measuring equipment of any type (liquid and gas chromatographs, for example, in addition to color measurement instruments), they must give special consideration to the documentation requirements of the United States Food and Drug Administration (FDA). These requirements will vary from company to company, as each pharmaceutical company is responsible for defining and maintaining its own documentation requirements list. Some areas to consider and their HunterLab solutions are discussed in the sections below, and a checklist of items that may be required is provided on the last page. Since HunterLab also sells to a number of industries that do not require such extensive documentation, it is not automatically included or its cost bundled into system prices. Therefore, some additional fees may be involved.

Note: If your pharmaceutical company is not in the United States, you may still be required to adhere to FDA regulations for products that will be sold in the United States.

Electronic Recordkeeping and Signatures

These regulations can be found in 21 CFR 11, available on the World Wide Web at www.fda.gov. This change means that the pharmaceuticals industry is now shifting toward using electronic (i.e., software-maintained) signatures and storage of information, rather than paperwork. In the case of instrumental measurements, it is generally required that every reading ever made with the instrument be named and permanently stored electronically, alteration of the data be disallowed, and that accountability (i.e., which operator makes each measurement) be tracked.

For HunterLab instruments, the software used will usually be EasyMatch QC or Essentials, and a special version of this package, called EasyMatch QC-ER, may be purchased that addresses all of the technical requirements of 21 CFR 11. Included with the software is a Validation and Compliance Notebook that helps you configure the technical (computer and software) parts of the system, as well as makes suggestions on how to handle the procedural requirements so that the system will be 21 CFR 11 compliant.

Qualification of Instrument and Measurement Method

Installation Qualification, Operation Qualification, and Performance Qualification (IQ/OQ/PQ) protocols are normally required for a new instrument to document that the instrument has been installed properly, meets its performance specifications, and is able to reliably measure typical samples using the chosen measurement method. Some pharmaceutical companies can create their own protocols using information given in the instrument user's manual and their own company template. Others will need to obtain protocols from HunterLab. For those customers that purchase EasyMatch QC-ER, IQ and OQ templates, as well as suggestions on how to draft PQ documentation, are included in the Validation and Compliance Notebook.

Protocols supplied by HunterLab (contain the following types of information:

- A cover sheet referencing your instrument and software type, the company name and address, and relevant approval signatures for the protocols.

- **IQ**
    - Purpose of the IQ
    - Overview of the system, including any options purchased
    - The system's operational features and its intended use
    - A list of required reference documents
    - Step-by-step installation procedures for the software and hardware with sign-off areas for successful completion
    - A statement of qualification.
- **OQ**
    - Purpose of the OQ
    - Operational diagnostics procedures, such as a wavelength accuracy test, short-term repeatability test, and mid-range reflectance (green tile) check with sign-off areas for successful completion
    - A statement of qualification.
- **PQ**
    - Purpose of the PQ
    - Check of instrument's performance using the method and accessories that will normally be used for measuring samples with a sign-off area for successful completion
    - A statement of qualification.

Training

Training of operators on instrument and software use and maintenance is required by many companies and documentation of the training is often maintained.

Basic instrument and software training is normally provided at no charge by your sales representative when the instrument is first installed. If you require a training sign-off sheet or other documentation concerning the training or trainer, you will need to speak with your sales representative in advance of the instrument installation to ensure that your needs will be met. Extensive directed training will involve an additional fee above the purchase price of the instrument. If training of new personnel is required in the future, it may also be purchased through HunterLab's Technical Services Department. Certificates for operators that successfully complete the training can be provided with fee-paid training.

Preventive Maintenance and Continuing Instrument Verification

Documentation of instrument and standards maintenance is often required. HunterLab's Service Department offers a preventive maintenance program whereby once a year a trained service technician will inspect and test your instrument, check and adjust mechanical and electro-mechanical parts, replace lamps and air filters as needed, as well as clean the optical components. Documentation of the service performed is provided in a service report which you may then keep for your records. For an additional fee, you may also purchase a Calibration Verification Report, which documents the exact results the technician obtained while performing diagnostics.

Instruments may also be sent to HunterLab for service and/or recalibration of instrument tiles. After instrument service at HunterLab (or for a newly manufactured instrument), a Certificate of Calibration may be purchased indicating the instrument's readings on a complete set of colored BCRA tiles both before and after service.

Other Documentation

You may want to include the following documents in your files concerning your HunterLab instrument:

- The software and hardware user's manual (included with the instrument purchase)
- Validation and Compliance Notebook (included with EasyMatch QC-ER only)
- Any CMR addenda that apply to your system (included with the CMR purchase)
- Documentation concerning your computer system (included with your computer purchase)
- Tile Data Sheet (included with the instrument purchase)
- Certificate of Traceability for the instrument white tile (included with your instrument purchase)
- Printouts from any diagnostic tests performed, such as in the OQ and PQ protocols
- HunterLab's ISO 9001 certificate (can be obtained from www.hunterlab.com)

Checklist

Prior to purchasing your HunterLab instrument that will be used for measuring pharmaceuticals, consider whether the following items are required for your FDA documentation. You may then work with your sales representative to obtain the items that you need. The symbol "$$" indicates that an additional cost above and beyond the system purchase price may be associated with this item if you choose to obtain it from HunterLab.

- Basic instrument and software training
- Calibration Verification Report ($$)
- Certificate of Calibration ($$)
- Certificate of Traceability
- Computer documentation
- EasyMatch QC-ER and its Validation and Compliance Notebook ($$)
- Extensive directed training with certificates for participants ($$)
- HunterLab ISO 9001 certificate
- Installation Qualification Protocol ($$)
- Operation Qualification Protocol ($$)
- Performance Qualification Protocol ($$)
- Preventive maintenance with service report ($$)
- Software and hardware user's manual
- Tile data sheet
- Training of new personnel with certificates for participants ($$)
- Training sign-off sheet.

References

European Pharmacopoeia Method 2.2.2 Degree of Coloration of Liquids, European Pharmacopoeia, Strasbourg, France (1997: 15-16) NET: www.pheur.org

USP-24 Monograph 631 Color and Achromaticity, United States Pharmacopoeia Inc., Rockville MD USA (2000: 1926-1927) NET: www.usp.org.

About HunterLab

HunterLab is the technology leader in color measurement solutions, providing instruments, software, knowledge and service to a wide variety of industries. With over 5 decades of experience in more than 65 countries, HunterLab applies our leading edge technology to your products helping you measure and communicate color simply and effectively.

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