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RESEARCH ARTICLE

A Systematic Method Development Strategy for Quantitative Color Measurement in Drug Substances, Starting Materials, and Synthetic Intermediates

Leon Zhou · Frederick G. Vogt · Patricia-Ann Overstreet · John T. Dougherty · Jacalyn S. Clawson · Alireza S. Kord

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Abstract The color of active pharmaceutical ingredients (APIs) can be a critical quality attribute for pharmaceutical products. Color variation can be indicative of contaminants, chemical impurities, solid-state form impurities, or degradation products. The color of the pharmaceutical materials is typically specified and determined using visual appearance testing. To avoid the inherent subjectivity of visual appearance testing, to understand the link between the color and the process parameters, and to facilitate quality agreements between customers and vendors of chemical starting materials, quantitative color measurements utilizing visible spectroscopic methods are increasingly needed. In this work, a systematic method development strategy (MDS) is described to assist with the development of robust and rugged quantitative color measurement methods based on a science- and risk-based approach aligned with quality-by-design principles. The MDS is illustrated using typical scenarios encountered in method development through several examples including a method developed for 2,3-dimethyl-2*H*-indazol-6-amine, a starting material in the commercial synthesis of pazopanib hydrochloride API. Flowcharts and examples are presented to illuminate key decision points in the MDS process including selection of (1) solution-state versus solid-state spectroscopic method, (2) optimal color space for reporting color measurement results, and (3) appropriate method risk assessment and control to ensure successful method implementation. General guidance is also provided to facilitate the discussion for setting quantitative color specifications.

Keywords Quantitative color measurement · Diffuse reflectance spectroscopy · Transmittance spectroscopy · Quality by design (QbD) · Method development strategy (MDS) · Appearance testing

L. Zhou (✉) · F. G. Vogt · P.-A. Overstreet · J. T. Dougherty · J. S. Clawson · A. S. Kord
Product Development, GlaxoSmithKline plc.,
709 Swedeland Road,
King of Prussia, PA 19406, USA
e-mail: Leon.Zhou@gsk.com

Introduction

Color variation in an active pharmaceutical ingredient (API) or color change during storage can be indicative of the presence of contamination, impurities, or degradation products [1]. Because of this, color is frequently tested upon release of API and during stability evaluation by visual appearance testing methods that simultaneously test for any foreign particulate matter. Changes in color are investigated to determine if product quality or patient safety could be affected. However, because of the inherent subjectivity of visual evaluation, variable results can be obtained for the color of a material. To avoid this variability, semi-quantitative color measurements have been developed [2–5], which allow comparison of the color characteristics of a sample to a set of color chips or to a range of color standards. Although less subjective than visual comparison to a textual color description, these semi-quantitative methods still contain the subjective element of a human visual comparison and can be affected by the eye performance of the individuals performing the test. True quantitative methods involve the use of an instrumental measurement of color [3, 6, 7]. Historically, filter-based colorimetric and tintometric methods were used but were limited because they do not measure total color but instead