REVIEW

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Application of instrumental colour measurement in development and quality control of drugs and pharmaceutical excipients

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This review covers applications of instrumental colour measurement using tristimulus colorimetry in development, stability testing, production and quality control of synthetic and natural drugs, dosage forms and pharmaceutical excipients in the last three decades.

1. Introduction

Colour is a property of light of particular wavelength which is reflected or transmitted when falling onto opaque or transparent objects, respectively. At the atomic level, it is produced by changes in the electromagnetic energy in the electron orbital due to photon absorption. In human eyes, the triple receptor systems in the retinal cone cell can perceive different colour combinations that befall in the visible region of the electromagnetic spectrum (Wyszecki and Stiles 2000; Siddiqui and Nazzal 2007). Although subjective colour perception is possible, it is not without limitations. Instrumental colour measurement is based on the numerical expression of colours in a trichromatic system (Krishna Prasad et al. 1996; Wyszecki and Stiles 2000; Ali and Castle 2003; Hayauchi 2005; Siddiqui and Nazzal 2007). The base for instrumental colour matching is the spectral reflectance or spectral transmittance of sample in a visible spectrum. The trichromatic system must be distinguished from the complementary one that is based on absorbance values (Vytřas et al. 1976). This system was used mainly in the study of chemical equilibrium and reactions accompanied with colour changes including the study of colour transition of indicators used in volumetry (Vytřas et al. 1976; Krishna Prasad et al. 1996). But this application was not further developed.

Instrumental colour matching is not routinely utilised in the development, production and quality control of drugs and pharmaceutical excipients so far. The traditionally conservative pharmacopoeias (e.g. Ph.Eur. 2004 and USP 30 2006) at present use the visual assessment with help of comparative colour solutions. The USP 30 Pharmacopoeia also presents the basic relations and some practical instructions for instrumental colour measurement in the trichromatic system. This approach is used for a long time whereas in connection with the European Pharmacopoeia (Ph.Eur.) the signs of possible harmonization by the introduction of instrumental colour measurement are observed only in the recent years (Ali and Castle 2003; Hayauchi 2005). Notwithstanding that colour evaluation is very important in pharmaceutical science and practice, no reviews have not been published since 1977 (Šubert et al. 1978) except miniseries with selected applications (Hunter 1981; Lukács et al. 1985; Šubert and Čižmárik 2007). This review therefore summarizes the papers from the last three decades.

2. Fundamental aspects and tristimulus colorimetry

In 1931, the Comission Internationale de l'Eclairage (CIE) standardized colour order systems by specifying the illuminants, the observer and the methodology in which it derived the values for describing colour and transformed RGB system into new coordinates (Wyszecki and Stiles 2000). From the commision's work the concept of a standard observer, was also derived based on the average of the human population with normal colour vision. The standard observer provides a means for converting any spectral curve into three numbers, known as tristimulus values X, Y, Z, that identify any colour. The principle of conversion are tristimulus values of the equal-energy spectrum as a function of wavelength $\bar{x}(\lambda)$, $\bar{y}(\lambda)$, $\bar{z}(\lambda)$, that are tabulated. The three colour-matching functions are specified for the 2° standard observer CIE and 10° supplementary observer CIE. With regard to the fact that on the creation of colour perception participates not only the observable object, but also the source of light it is necessary to specify the conditions of illumination for the colour measurement. Whereas the CIE standard illuminant C, which corresponds to the relative spectral power of the daylight was considered previously, at present the CIE standard illuminant D65 is used which also corresponds by its spectral power distribution to the average daylight. The basic method how to express the tristimulus values X, Y, Z in numbers is the calculation from the results of measurement of spectral reflectance or transmittance of

the object in visible spectrum according to the relationship

$$X = k \int_{\lambda} E(\lambda)\, R(\lambda)\, \bar{x}(\lambda)\, d\lambda \quad (1)$$

$$Y = k \int_{\lambda} E(\lambda)\, R(\lambda)\, \bar{y}(\lambda)\, d\lambda \quad (2)$$

$$Z = k \int_{\lambda} E(\lambda)\, R(\lambda)\, \bar{z}(\lambda)\, d\lambda \quad (3)$$

where $E(\lambda)$ is the relative spectral power distribution of the illuminant, $R(\lambda)$ is the spectral reflectance or spectral transmittance, and k is the normalization factor. The integration is calculated using wavelength λ of the visible spectrum from 380 to 780 nm. Originally complicated laborious calculation of X, Y, Z values is at present calculated by commercially available PC computing programmes. Another possibility is the use of colorimeters working on a different principle. The colorimetric method of colour measurement measures the light reflected/transmitted from the object using three sensor filters to have the same sensitivity as the human eye and thus directly measuring the tristimulus values X, Y, Z.

The colour space CIE XYZ is not uniform. It means that identical colour differences in various places of colour space do not correspond to identical distances. To solve this problem different transformations of tristimulus values X, Y, Z are used. At present, CIE $L^*a^*b^*$ colour space (CIELAB) is an international standard for colour measurement. The formulas necessary to transform tristimulus values X, Y, Z into this space are available in the literature (e.g. Krishna Prasad et al. 1996; Wyszecki and Stiles 2000; Ali and Castle 2003; Hayauchi 2005; Siddiqui and Nazzal 2007). In a CIELAB colour space, L^* is a measure of the lightness, and ranges from 0 (black) to 100 (white), a^* and b^* are usually between -100 and 100 and define the degree of redness (positive a^*) or greenness (negative a^*) yellowness (positive b^*) or blueness (negative b^*). These coordinates (a^* and b^*) are zero for neutral colours (white, greys and blacks). The higher the values for a^* and b^*, the more saturated a colour is. The colour difference ΔE^* is defined as trigonometric function

$$\Delta E^* = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}. \quad (4)$$

It better corresponds in various parts of space to visually perceived colour differences than analogically expressed distance in CIE XYZ space. The colour locus in the colour plane (a^*, b^* plane) can also be described in trigonometric coordinates

$$C^*_{ab} = [(a^{*2} + b^{*2})]^{1/2} \quad (5)$$

(chroma, as radius vector, abbreviated as C^*) and h_{ab} = Arctan (b^*/a^*) (hue angle, as angle). The values of L^*, a^*, b^* coordinates may be also obtained from RGB digital images (Davidson et al. 2004; León et al. 2006). Some authors (Gavrilov et al. 2003; 2005) do not use these transformations and express the colour in RGB colour space.

The predecessor of CIELAB uniform colour space is Hunter LAB colour space (Wyszecki and Stiles 2000). For any given colour, CIE L^*, a^*, b^* and Hunter L, a, b values are similar. However, CIELAB colour space is in more common use.

CIE $L^*u^*v^*$ (Krishna Prasad et al. 1996; Wyszecki and Stiles 2000) and L^*C^*h colour spaces (Wyszecki and Stiles 2000; Ali and Castle 2003; Hayauchi 2005; Siddiqui and Nazzal 2007) are rarely used in pharmaceutically important applications. L^*C^*h colour space uses cylindrical instead of rectangular coordinates. In this colour space, C^*_{ab} is chroma and h_{ab} is the hue angle. Detailed information on the theory of numeric expression and measurement of colour may be found in the literature (e.g. Krishna Prasad et al. 1996; Wyszecki and Stiles 2000; Ali and Castle 2003; Hayauchi 2005; Siddiqui and Nazzal 2007).

3. Applications

3.1. Synthetic drugs, pharmaceutical excipients and dosage forms

3.1.1. Synthetic drugs and pharmaceutical excipients

The values of CIE X, Y, Z, L^*, a^*, b^* and C^*, h° (Azizov et al.1987) parameters have been used for objective description of colour of some drugs (azidin, bismuth subgallate, ethacridine lactate, feramid, folic acid and others). The measurement was based on the determination of reflectance of solid compounds. This procedure is considered as more advantageous than that of measurement of colour of solutions which does not provide adequate sensitivity (Oram and Strine 2006). CIE XYZ, CIE $L^*u^*v^*$ and CIELAB colour spaces have been used in characterization of colour of olive oils (Escolar et al. 1994); the latter yields best results. The values of L, a, b coordinates have been used for measurement of colour of gelatine solutions (Cole and Roberts 1996) and later the measurements were performed on gels (Segtnan et al. 2003). The effect of particle size on the colouring properties of aluminium dye lakes was studied and the utility of CIELAB colour space was demonstrated by quantifying changes in hue, chroma, lightness, and total colour difference (ΔE^*) with different dispersion level (Wou and Mulley 1988). Whiteness of talcum powders was studied as a quality index for pharmaceutical use (CIE tristimulus values X, Y, Z, CIELAB coordinates L^*, a^*, b^*). Z-tristimulus value, lightness L^* and CIE whiteness index were the most influential parameters (Soriano et al. 1998). The influence of chemical and mineralogical composition on colour (CIE L^*, a^*, b^*) for commercial talc has also been investigated (Soriano et al. 2002). Colour of some Spanish clays (X, Y, Z, bentonite, palygorskite, sepiolite) and relationships between chemical-mineralogical composition and colour properties in selected Spanish kaolins (polar coordinates CIE L^*, C^*, h°) was determined (Viseras and Lopez-Galindo 1999; Gámiz et al. 2005).

Besides the measurement of drugs and excipients the instrumental measurement of colour was used in the development of analytical methods in the quality control of drugs and excipients. A classic application is the study of quality of colour transition of indicators used for visual indication in volumetric analysis. The colour transition of simple and screened indicators using CIE parameters L^*, a^*, b^*, ΔE^* in titration of metformin (Martinez Calatayud et al. 1985) and urea or sodium acetate (Barbosa et al. 1987) by perchloric acid in anhydrous acetic acid has been studied. In this paper the colour transition of indicators has also been investigated in CIELAB and CIE $L^*u^*v^*$ colour spaces. The quality of colour changes of nitritometric indicators in the titration of sulphanilamide with sodium nitrite was specified by ΔE^* values from CIELAB, CIE $L^*u^*v^*$ and LAB HNU colour spaces (Sastry et al. 1995). More applications of this type could be found in another review article (Krishna Prasad et al.

1996). Moreover, due to the use of potentiometric indication these applications were not developed in the last decade. The attention was also paid to the description of colour reference solutions of the European Pharmacopoeia in CIE a^*, b^* colour plane (Ali and Castle 2003) as well as to the study of their properties in CIE $L^*a^*b^*$ colour space (Šubert et al. 2006c). Research focussed especially on the investigation of the colorimetric parameters of the products of colour reactions of small amounts of some inorganic ions with suitable agents following their collection on a solid carrier. It seems to be a new trend to use instrumental colour matching in the tests of purity of drugs as an alternative to instrumentally more difficult methods. Determination of fluoride ions was based on a decrease in the colour intensity of the thorium complex of Arsenazo I (Ivanov et al. 2004). The most sensitive chromaticity functions are yellowness, ΔE^* and b^* values. Another examples are the determination of mercury(II) with thienothenoyltrifluoroacetone (Yokota and Abe 1997a), simultaneous determination of iron(II) and iron(III) with 2-nitroso-5-(*N*-propyl-*N*-sulfopropylamino)phenol (Yokota and Abe 1997b), determination of trace cobalt(II), nickel(II) and iron(II,III) after the reaction with the same reagent (Yokota et al. 1999) and determination of trace aluminium with Eriochrome cyanine R (Ershova and Ivanov 2000).

3.1.2. Dosage forms

The characterization of surface coverage of coarse particles (acetylsalicylic acid) coated with coloured and uncoloured stearic acid was studied (Gren and Nyström 1991). The data with the use a, b coordinates suggest that colour measurement could be used as a rough estimation of the surface coverage. Some papers deal with the problems of coating, coating efficiency and coating uniformity of tablets and pellets. The parameters of colour space XYZ CIE have been employed in experiments to colour coated tablets with the water soluble dyes Ponceau 4R and Sunset yellow (Lehelne Jakab et al. 1980). In the quality control of surface colour of coated tablets the parameters of colour space CIELAB L^*, a^*, b^*, ΔE^* and cylindrical coordinates were applied (Azizov et al. 1988). The coating efficiency of a Vector HiCoater was compared to that of a Manesty Accela Cota. Tablet samples were examined (L and a values) (Alcorn et al. 1988). The optimization of colour coating of pellets has also been studied (Heng et al. 1999). Standard deviations of colour difference (ΔE^*) values represented colour variations in pellet coatings sampled at different coating times. An improved method for the measurement of colour uniformity in pellet coating has also been proposed (Chan et al. 2001). The authors used parameters L^*, a^*, b^*, C^* and ΔE^* of CIELAB colour space. Mixing efficiency in side-vented coating equipment during tablet coating was studied. ΔE^* was selected for indicating the colour uniformity during the coating run (Smith et al. 2003). Colour intensity (ΔE and colour uniformity (relative standard deviations of ΔE) were detected in the study dealing with the use of swirling airflow to enhance the pellets coating performance of bottom spray fluid bed coaters (Heng et al. 2006). Coat quality of tablets coated by on-line Supercell coating was studied (Tang et al. 2007). ΔE^* indicated the colour intensity of the coat and relative standard deviation of ΔE^* was used as a measure of coat uniformity. Colour difference ΔE^* (CIELAB colour space) was used in quality control of coloured solid dosage forms (Müller and Moll 1983). To measure crystallisation during liquid formulation development, lightness L is capable of providing information about the kinetics and dynamics of the crystallisation process and values a and b can be used to differentiate between various hydrates species present (Campbell et al. 1996). CIELAB colour space (ΔE^* values) was used in a new alternative method for swelling studies of bioadhesive tablet formulations (Baloglu et al. 2004). The colorimetric parameters (ΔE^* and others) were employed in the study of chlorophyll and riboflavin as colour indicators in solutions used for disinfection of soft contact lenses, based on the effect of hydrogen peroxide (García-Monlléo et al. 2006). Measurement of surface colour is an expedient quality control method for the detection of deviations in tablet hardness. It was concluded that chroma (C^*) could be used as a suitable colorimetric parameter (Siddiqui and Nazzal 2007). A method for selecting a suitable emulsifier (non-ionic surfactant) based on colour difference was elaborated. As an index of the degree of emulsification, ΔE of sample prepared with methylene blue was measured (Koga et al. 2002). The instrumental measurement of colour in a quantitative analytical chemistry is the determination of analgin and ascorbic acid in injections and tablets. The solid-phase reagent on the basis of a copper (II) complex with tetrabenzotetraazacyclohexadecine adsorbed on silica gel was used and ΔE^* or ΔL^* parameters were measured (Zaporozhets et al. 2001).
For further applications of instrumental colour measurement of dosage forms see 3.1.3.

3.1.3. Stability testing

With regard to the fact that during stability testing of drugs, dosage forms and pharmaceutical excipients visual evaluation is often difficult, and thus, there is a tendency to evaluate colour changes objectively by the use of instrumental techniques and numeric description. An instrumental measurement of colour is non specific method but in some cases it may be more sensitive than HPLC (Shephard et al. 1999).
Some papers deal with the evaluation of solid-state photostability of drugs by the measure of colour difference ΔE or ΔE^*: nifedipine (Matsuda et al. 1989), carbamazepine polymorphs (Matsuda et al. 1994), nicardipine hydrochloride polymorphs (Teraoka et al. 2004), mequitazine with titanium dioxide (Kakinoki et al. 2005), tamoxifen citrate polymorphs (Kojima et al. 2007). Photostability of mefloquine hydrochloride (b^* and L^* coordinates) was investigated by Tonnesen et al. (1997), and later these scientists studied the photostability of ofloxacin (a^*, b^*, ΔE^*) (Tonessen et al. 2007). The potentials of a simple surface treatment technique (stirring a drug suspension in preselected solvent) aiming at modifying solid-state properties with emphasis on photostability were investigated using methyldopa. ΔL^*, Δa^*, Δb^* and ΔE^* values were measured (Ramadan et al. 2004). CIE XYZ colour space was used to examine colour changes of nystatin during accelerated stability studies, and a relationship was observed between the loss of microbiological potency and the change in colour during thermal degradation (Fairbrother et al. 1980). Effect of grinding (mechanical stress at various temperatures) on the solid-state stability (ΔE) of cefixime trihydrate was studied (Kitamura et al. 1989). Moisture induced solid phase degradation of ascorbic acid (formation of a brown discoloration) was studied and colour differences ΔE^* were calculated (Shephard et al. 1999).
Colour changes (ΔE) of oxidized and thermally modified starches after their thermal sterilization were investigated

in stability testing of pharmaceutical excipients. The results proved the correlation between the content of dextrin in starches and the intensity of colour changes (Mandák et al. 1980; Kučera et al. 1983). Samples of virgin olive oil were submitted to an accelerated oxidative test and chromatic evolution was measured. Oxidation provoked less vivid colours (lower values for chroma, C^*); however only some samples became darker (lower values for lightness, L^*). Mathematical models are offered to predict colour changes with time of storage at 20 °C (Ceballos et al. 2003).

More attention in stability tests was paid to the use of instrumental measurement of colour of dosage forms than to the investigation of individual drugs and pharmaceutical excipients. The study of photostability eventually in combination of light with temperature and moisture prevail. The effect of coating films containing oxybenzone on the coloration and photolytic degradation of sulfisomidine tablets was examined (L, a, b, ΔE) to attempt stabilization of photosensitive dosage form (Matsuda et al. 1978). Accelerated light conditions have been used in the evaluation of light stability of flordipine tablets. The coordinate b was selected for the final evaluation (Narurkar et al. 1986). Photostability of mefloquine hydrochloride tablets (b^* and L^* coordinates) (Tonnesen et al. 1997), and photostability of nicardipine hydrochloride polymorphs in tablets (ΔE values) were investigated (Teraoka et al. 2004). Stability and stabilization of low level of coloration of Castellani's paint without fuchsine (ΔE^* values) was examined (Šubert and Cieslarová 2006). Additions of 0.03% disodium edetate gave more effective stabilization than did 0.02% (Šubert et al. 2006a). The change in colour of uncoated and film coated ofloxacin tablets (a^*, b^*, ΔE^*) was studied as a function of irradiance level and total exposure energy (Tonessen et al. 2007). CIE XYZ colour space was used to examine colour changes of nystatin creams and ointment during accelerated stability studies (Fairbrother et al. 1980). ΔE values were used in a stability study of packaged sugar-coated tablets (Nakabayashi et al. 1980a, b), and in stability testing of tablets with cholintheophyllinate or ornidazole (Godovič et al. 1981). Accelerated light – temperature – humidity conditions have been used in the evaluation of light stability of white zimelidine tablets. L, a, b and ΔE values were used (Nyqvist et al. 1980). A test program for prediction of light stability in the preformulation work was proposed. L and b coordinates were used, and three drugs (alaproclate hydrochloride, amoxicillin, bacampicillin hydrochloride) were studied (Nyqvist et al. 1982). L and b coordinates were also used in a stability study of remoxipride or zimeldine tablets (Nyqvist 1984). The influence of three different tabletting diluents and three different forms of ascorbic acid on a colour change (ΔE values) of ascorbic acid have been investigated (Vemuri et al. 1985). Lightness ΔL^* and yellowness Δb^* were found to reflect the changes in coloration observed in stability tests on white metoprolol tablets (Wirth 1991). Δb^* values and/or the total colour difference ΔE^* provide effective parameters when studying the colour of autoclaved glucose infusions (Mannermaa and Yliruusi 1992). Colour stability (ΔE values) of three natural-source colorants (carmine, cranberry, raspberry) as components in compressed tablets was studied (Dehner and Shiromani 1993). Instrumental evaluation of colour was applied to determine colour formation during long-term storage and stability testing of four white commercial solid dosage forms (captopril tablets, cefoxitin sodium powder for injection, flucloxacillin sodium capsules, and theophylline tablets). L^*, a^*, b^*, ΔE^* values were used (Stark et al. 1996). A new method to determine discoloration kinetics of uncoated white tablets occurring during stability testing was proposed. Discoloration kinetics can be expressed by the colour intensity

$$CI = [(100 - L^*)^2 + a^{*2} + b^{*2}]^{1/2} \quad (6)$$

CI is a function, which represents a colour distance of tablets to the absolute white point in the CIELAB space (Berberich et al. 2002).

The instrumental measurement of colour (ΔE^* values) was also used in stability tests of reagents used in the quality control of drugs. The stability of and possible stabilization of aqueous solutions by naphthylethylenediamine dihydrochloride was studied (Šubert el al. 2005). The stability of colour reference solutions for examination of the degree of coloration of liquids according to the Czech Pharmacopoeia 2002 was examined, too (Šubert et al. 2006b).

3.2. Herbal- and other natural drugs

Instrumental colour measurement (CIE XYZ colour space and ΔE^* values) was employed in the study of the relationship of the colour and content of ascorbic acid in rosehips. The values of Y, x, y parameters for the highest content of ascorbic acid were determined (Bakos et al. 1981). LAB colour space (ΔE values) was used in the study of drying kinetics and colour retention of dehydrated rosehips (Koyuncu et al. 2003). CIELAB colour space (L^* values) was used in the study of forced-air drying of Ginseng roots (Davidson et al. 2004). ΔL, Δa, Δb and ΔE values were used in the estimation of black tea quality by analysis of chemical composition and colour difference of tea infusion (Liang et al. 2003) and in the quality estimation of black, green and oolong teas (Liang et al. 2005). Decreasing of b^* values was used to compare total free radical scavenging capacity (2,2-diphenyl-1-picrylhydrazyl radical) of black and green teas from different countries (Soler-Rivas et al. 2000). Studies were carried out to evaluate the influence of post harvest processing conditions on yield and colour quality (L^*, a^*, b^* values) of ground turmeric (Bambirra et al. 2002). The colour (L^*, a^*, b^*, C^* and H^* coordinates) of saffron was determined. The chromatic parameters of saffron filaments were lower than those of powdered saffron (Alonzo et al. 2003). The photodecoloration of saffron was examined as a function of various CIE chromatic parameters that confirmed the first-order nature of the kinetics (Rosario Haro et al. 2004).

Colour accounted for over 60% of the variance in antioxidant capacity of honey (Frankel et al. 1998). The most suitable colour functions to evaluate darkening of honey in relation to its composition and initial colour were lightness L^*, chroma C^*, and hue H^* (Gonzales et al. 1999). The colour of Moroccan honey was assessed in the CIE XYZ colour space and CIELAB uniform colour space L^*, a^*, b^* colour coordinates, chroma C^* and hue angle h (Terrab et al. 2002). Colour of thyme and avocado honey was assessed with the use of the above mentioned parameters and discriminating analysis (Terrab et al. 2004).

Oxidative stability of microencapsulated fish oil was investigated by the measurement of L^*, a^*, b^* coordinates. Based on data for colour measurement, moisture sorption and extractable fat, the course of lipid oxidation was discussed (Drusch et al. 2006).

4. Conclusions

In spite of relatively easy availability of necessary instruments the measurement of colour is rarely employed in solving problems of development and quality control of drugs, dosage forms and auxiliary materials compared to other fields, e.g. food industry (Ivanov and Kuznetsova 2001). This results from the fact that traditionally conservative pharmacopoeias are satisfied with subjective visually colour assessment. However, an increase in the application in the study of drug stability, dosage forms and pharmaceutical excipients may be expected due to the advantages of objective evaluation and numeric specification of colours and their differences. It may also be expected that instrumental colour measurement using the trichromatic CIE system will be introduced as official method into the European Pharmacopoeia soon.

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