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A new method to determine discoloration kinetics of uncoated white tablets occurring during stability testing—an application of instrumental color measurement in the development pharmaceutics

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Abstract

The tristimulus color coordinates CIELAB and associated parameter Color Intensity (CI) have been shown to be a quantifiable variable for whiteness of uncoated tablets. Whereas any of L^*, a^* or b^* indicates the discoloration of white tablets to a certain degree, it alone cannot reflect the full extent of discoloration. The CI has been defined which is able to describe the discoloration kinetics with acceptable regression coefficients. The evaluation of the CIELAB values from the stability data has shown that the discoloration of the white tablets means an intensification of yellowish or brownish color which is manifested by more or less constant hue angle (*hab*) values and increasing chroma (*Cab**) values. In the view of these data the discoloration kinetics can physically be expressed by the CI. With the CI values the discoloration kinetics can be calculated by linear or polynomial regression with acceptable confidence intervals. The discoloration rates determined under several storage temperatures follow the Arrhenius equation and the activation energy can be estimated for the products. The CI values are unambiguously connected to the visual perception of the corresponding tablets. By means of the discoloration kinetics based on the CI values, it has become possible to statistically determine, the period of time uncoated tablets remain white.

Keywords: Tristimulus color; CIELAB; $L^*a^*b^*$; Discoloration kinetics; Color measurement; Color intensity (CI); White tablets; Stability testing

1. Introduction

White solid dosage forms may tend to discolor under routine storage conditions. There are several cases reported where the discoloration is related to the potency decrease (Stark et al., 1996).

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If the active ingredient is sensitive to humidity, light, or oxygen, the decomposition of the active ingredient may be manifested by a color change. On the other hand, the discoloration does not necessarily mean the deterioration of the active ingredient. Some products show a discoloration without any potency loss. It can simply result from the excipients, or from the interaction of the active ingredient or its impurities, with the excipients. In the latter case, the discoloration is not often paid attention to during the pharmaceutical development and the market supply period as the potency loss, because the color change does not affect the efficacy or the safety of the pharmaceutical product. Nevertheless, from the quality stand point it is a pharmaceutically important requirement that white solid dosage forms remain white during the storage.

Visual inspection of white tablets can have disadvantages in that a literal description of visual perception is difficult, that the grade of changes cannot be quantifiably and reproducibly assessed and that it lacks, in most cases, adequate reference colors. Discoloration often occurs from white to nearly white, then to yellowish and so on. With visual inspection, there is no reliable way to describe a rate of change, which is free from individual errors. The human eye is incapable of calculating discoloration kinetics. We can know how long tablets remain white only after having completed real time stability storage. Any attempt to extrapolate visual results beyond the real testing period is associated with a great deal of uncertainty.

These drawbacks of visual inspection can be overcome by using an objective instrumental color measurement method. The tristimulus CIELAB system has been referenced in the USP since 1985. Nevertheless, the instrumental color measurement is not routinely applied in pharmaceutical development and in quality control. The reasons for the low acceptance of the CIELAB color determination by the pharmaceutical industry, in case of white solid dosage forms, may be attributed to the lack of a generally applicable evaluation method of the CIELAB values for all products. The pharmaceutical industry is well aware that the visual inspection is not a precise and reproducible analytical method and the instrumental tristimulus color measurement is more objective than the visual method.

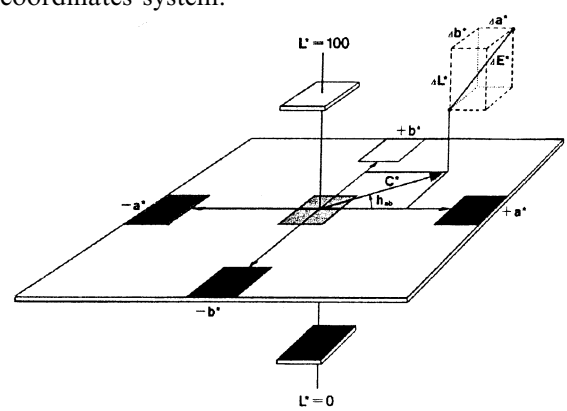
The method described here utilizes the CIELAB values and defines the Color Intensity (CI) as the color distance between the white point in the CIELAB color space and the white solid dosage forms. This CIELAB derived parameter characterizes the whiteness of white solid formulations as a vectorial scale from the whiteness pole. This method has been applied to determine the discoloration kinetics of white uncoated tablets occurring during stability storage. With this parameter, the discoloration rate of white solid dosage forms can be mathematically calculated by linear or polynomial regressions. The Arrhenius equation has been applied to calculate the activation energy. Therefore, it has become possible to mathematically estimate the time period that the white solid dosage form remains white.

In this paper we use a white solid dosage form from our company to evaluate the CIELAB method. Due to proprietarity reasons, the product name is not disclosed.

2. Method of color measurement according to CIE

The CIELAB color coordinates have been included in the general chapter in the United States Pharmacopoe (USP) since 1985. The tristimulus transformation of the reflectance spectrophotometer used here is described in the USP.

The CIELAB system has been adopted worldwide and uses the three spacial coordinates a^* (red–green axis), b^* (yellow–blue axis), and L^* (lightness axis) for brightness in the Cartesian coordinates system.



The color locus in the color plane (a^*, b^* plane) can also be described in polar coordinates:

$$Cab* = \sqrt{a^{*2} + b^{*2}}$$

(chroma, as radius vector), (1)

$$hab = \text{Arctan}(b^*/a^*)$$

(hue angle, as polar angle). (2)

If one imagines two colors measured in the CIELAB color space, namely Vector $\boldsymbol{V}_1\{L_1^*, a_1^*, b_1^*\}$ and $\boldsymbol{V}_2\{L_2^*, a_2^*, b_2^*\}$, then the color difference in the CIELAB space $\Delta Eab^* = |\boldsymbol{V}_1 - \boldsymbol{V}_2|$ is defined:

$$\Delta Eab^* = [(L_1^* - L_2^*)^2 + (a_1^* - a_2^*)^2 + (b_1^* - b_2^*)^2]^{1/2}. \quad (3)$$

The discoloration during any stability test can be evaluated as ΔEab^* of tablets which is usually referred to their initial values. Vector $\boldsymbol{V}_2\{L_2^*, a_2^*, b_2^*\}$ is defined in this case as the reference. This method has a basic disadvantage that the Eq. (3) presents a relative method and only the changes to the initial values are considered. The colors themselves disappear from the consideration. If one tests several batches in a stress test program which have different discoloration stages, for examples, one is purely white, another already yellowish, the evaluation of ΔEab^* values in time and temperature dependence gives rise to a discoloration kinetics compared to the corresponding initial values. Pharmaceutical interest lies further in the absolute colors, and in knowing what happens with white tablets and how yellowish tablets behaves compared to the white ones.

For evaluation of white solid dosage forms, it is, therefore, more useful to view the CIELAB space from the polar point (100, 0, 0) where the absolute white point is located. The vector $\boldsymbol{V}_2\{L_2^*, a_2^*, b_2^*\}$ is set to this white polar point in the Eq. (3). In this way, the color coordinates are expressed as a distance to the absolutely white point (100, 0, 0). The function (Eq. (3)) becomes so the following Eq. (4) and shall be named CI.

$$\text{CI} = \sqrt{(100 - L^*)^2 + a^{*2} + b^{*2}}. \quad (4)$$

That means, any ΔEab^* value alone cannot be correlated to any color, because it is simply a distance to a reference color which has to be defined. On the other hand, CI value can be attributed to a particular color per qualification or definition as the reference is fixed.

3. Materials and experimental method

The product investigated here (referred to the product in the following text) comprised an active ingredient of our company, corn starch, microcrystalline cellulose, lactose and magnesium stearate. The active ingredient had a structure of a piperidine derivative. The tablets were compressed by a standard process and were uncoated.

All measurements reported here were performed under the experimental conditions.

Equipment: micro color® I, Dr Lange, Germany; Colorflash Compakt, Optronik GmbH, Berlin, Germany

Standard illumination type: D_{65}

Colorimetric normal observer: 10°

Measuring geometry: $d/8°$

Diaphragm: ϕ 5 and 6 mm.

Before measurement, the equipment is calibrated daily with the same diaphragm against the white reference and darkness.

Usually, one sample is measured with 10 units. Mean values of L^*, a^* and b^* of 10 units are calculated and ΔEab^*, CI, Cab^* and hab are calculated from these mean values.

4. Results

The product selected is an uncoated white tablet. This product was found to quickly discolor during pharmaceutical development (stress tests). The assay remains stable over 5 years and the dissolution rates are consistently high. Generally speaking, the chemical reaction kinetics such as potency decrease with time is relatively small or non-existent at room temperature. Therefore, zero order kinetics is often a good approximation. Linear decrease of assay and linear increase of degradation products with time can be found in most cases. In case of color coordinates of these tablets, chemical compounds causing discol-

oration were not identified. We could not assume a priori any relationship between color coordinates and time.

The first task for applying the instrumental color measurement was therefore to find out the behavior of tristimulus color coordinates during stability tests. How do color coordinates of tablets move in the CIELAB color space during storage? Is such motion continuous and regular? Is it possible to describe the motion of any of color coordinates by a simple mathematical function such as linear or polynomial regression?

In the following chapter, the behavior of color coordinates of our tablets was investigated to find out which CIELAB parameter was suitable to characterize the discoloration of this solid dosage form.

4.1. Defining the CI

Six batches of 100 mg tablets were stored in glass bottles at 25, 40 and 60 °C and the behavior of tablets was investigated by means of CIELAB color coordinates for 24 weeks.

During the storage at 25 °C the parameter a^* changed irregularly. There was a small tendency to increase. The normal scatter of the method for the tablets with up to 0.2 overlapped a stability effect. The changes at 40 °C produced an apparently linear increase whereas a linear function might still be only a rough approximation. Finally, distinct increases at 60 °C revealed a higher order of kinetics and could be described properly by polynomial functions (Fig. 1).

The product showed stronger changes in the CIELAB b^* axis, to more yellow, than the a^* axis does. Larger increase of b^* values were observed at 25 °C compared to the scatter of the method. Over time, the 40 °C stress data clearly showed a linear increase of b^* (Fig. 2). The extremely fast discoloration of tablets at 60 °C lead to a higher order function as shown in Fig. 3. These 40 and 60 °C curves could be best described by polynomial functions.

The dark/bright parameter L^* already decreased fast at 25 °C. The 25 °C data are approximated by a linear regression (Fig. 4). At 40 °C the slopes became steeper in a negative direction (decrease) than at 25 °C (Fig. 5). One batch, No. 3, already exhibited a higher order change, which can be described better by a higher order function. All batches darkened extremely quickly at 60 °C and are best described by a higher order function (Fig. 6).

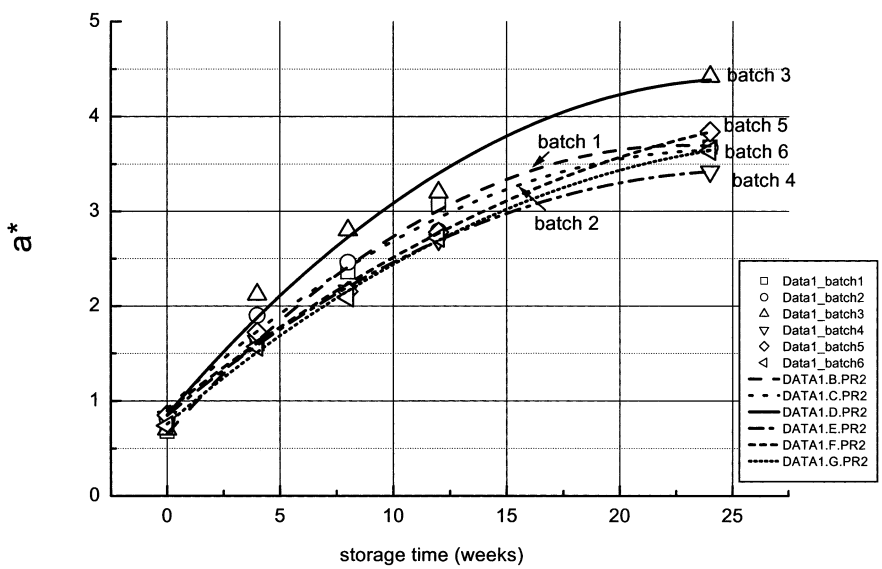


Fig. 1. CIELAB a^* values during storage at 60 °C. The discoloration rates at 60 °C revealed second-order polynomial functions.

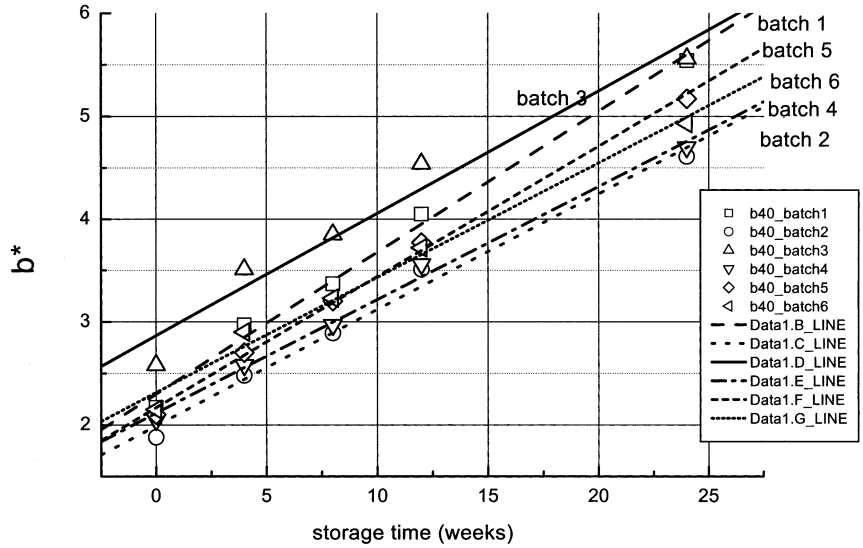


Fig. 2. CIELAB b^* values during storage at 40 °C. The 40 °C data showed a linear increase of b^* values.

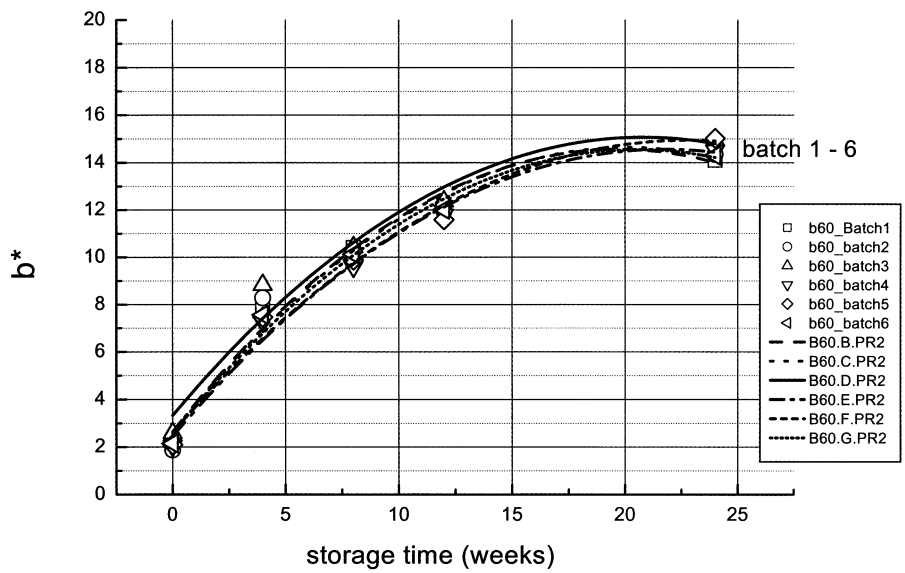


Fig. 3. CIELAB b^* values during storage at 60 °C. The extremely fast discoloration of tablets lead to a second-order polynomial function.

The color changes of the tablets which took place during storage lead to the movement of the CIELAB parameters in the color space that the parameters a^* and b^* became larger and L^* decreased. Furthermore, simultaneous increases of a^* and b^* corresponded to the visual perception of becoming brown. One can describe the discoloration of the product also by means of the hue angle *hab* and the chroma *Cab**. The *hab* value defines color species like brown, orange, violet and so on. While stored under the tested conditions the hue angle *hab* remained between 60 and

80°. This means, the ratio of b^* to a^* lay within a limited range. At the same time, L^* decreased and Cab^* increased. Taking all parameters into consideration, the discoloration of the product can be seen as a constant shift to the direction of a brown color. The color did not become orange or green during the storage, it remained brown (*hab* 60–80°). It became more intense when the tablets discolored more. In this sense, the discoloration profile of the tablets was a simple and one-directional movement in the CIELAB color space.

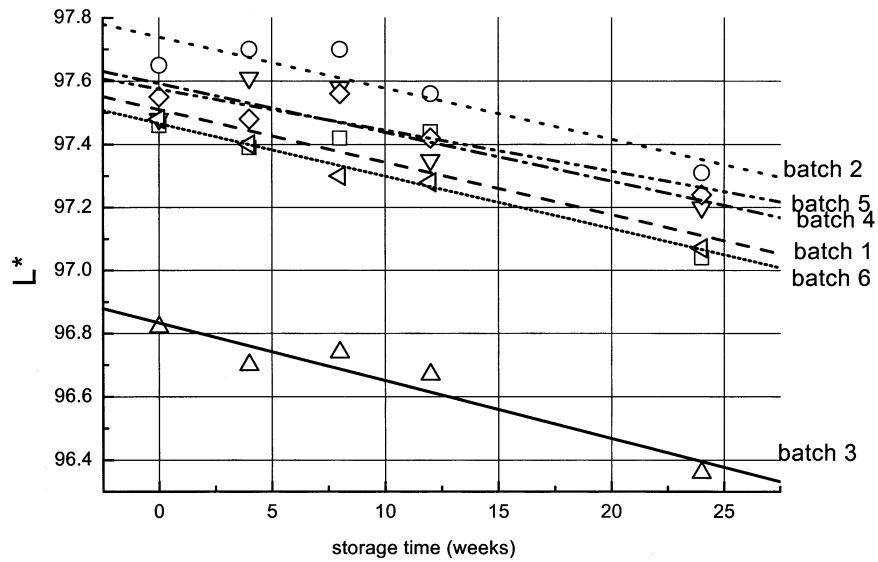


Fig. 4. CIELAB L^* values during storage at 25 °C. The 25 °C data are approximated by a linear regression.

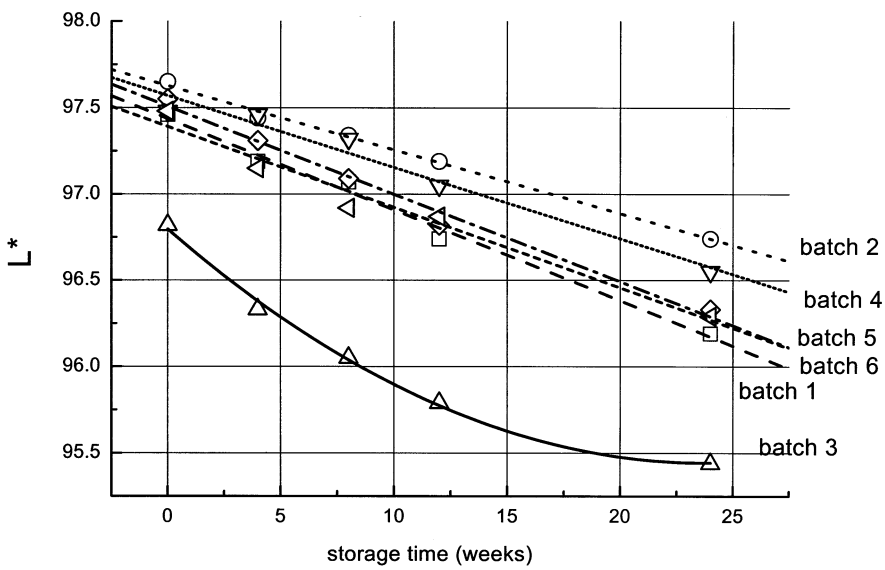


Fig. 5. CIELAB L^* values during storage at 40 °C. The slopes at 40 °C became steeper in a negative direction than at 25 °C. Batch no. 3 exhibited a second-order polynomial function.

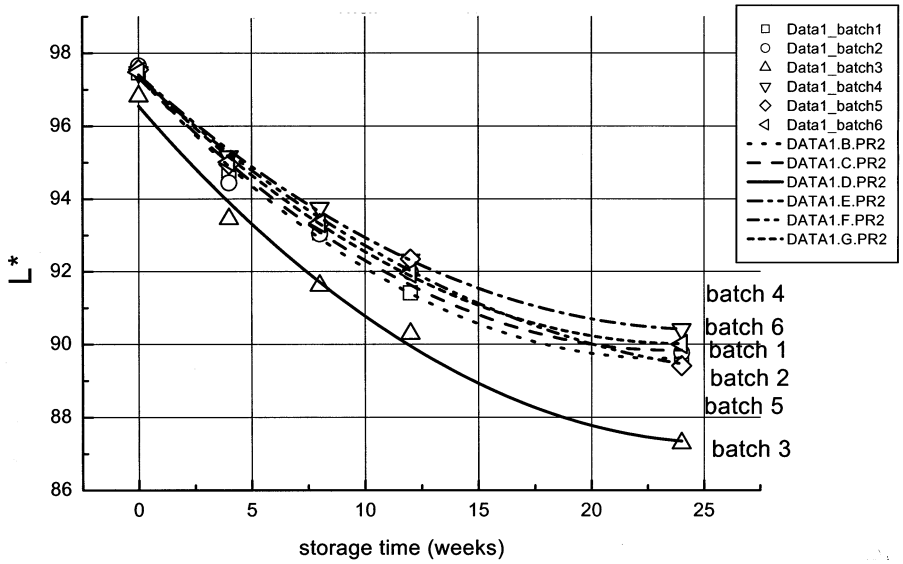


Fig. 6. CIELAB L^* values during storage at 60 °C. All batches darkened extremely quickly at 60 °C and are best described by a second-order polynomial function.

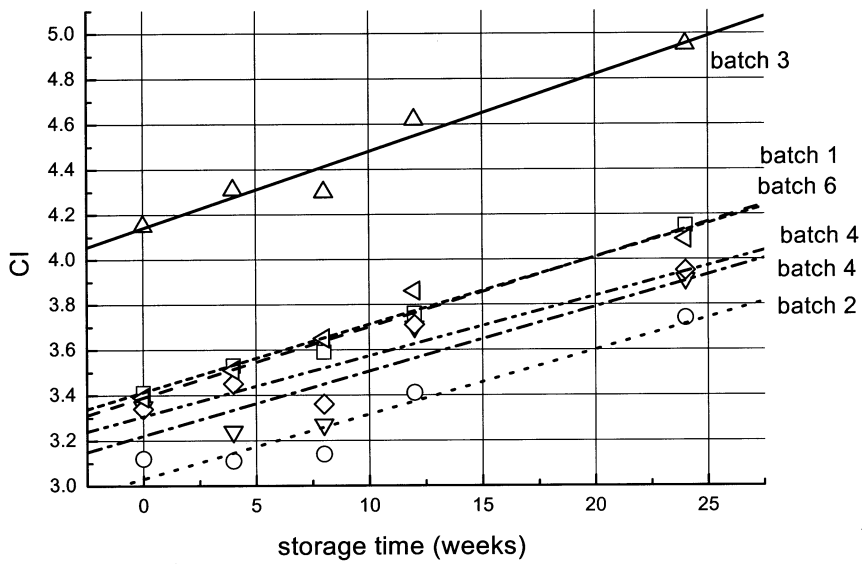


Fig. 7. CI values during storage at 25 °C. The 25 °C data are described by linear regression functions with regression coefficients of greater than 0.9.

The longitude of discoloration can be described by defining a function which takes both the increase in Cab^* and the decrease L^*, i.e. the increase of $(100 - L^*)$, into consideration. CI defined by the Eq. (4) is a function, which represents a color distance of tablets to the absolute white point in the CIELAB space.

The CIELAB CI results from storage under the

same stability conditions discussed above are displayed in Fig. 7 for 25 °C, Fig. 8 for 40 °C, and Fig. 9 for 60 °C.

Even at 25 °C, correlation coefficients of linear regression functions were greater than 0.9. The regression coefficients became much higher at 40 °C than at 25 °C. The 60 °C data showed high order kinetics which were better described by polynomial functions. As shown in the Figs. 7–9, the discoloration behavior of the product can be best described by the CI parameter.

If one evaluates the CIELAB data by means of ΔEab^* based on the initial values, the discoloration kinetics is described as an example in the

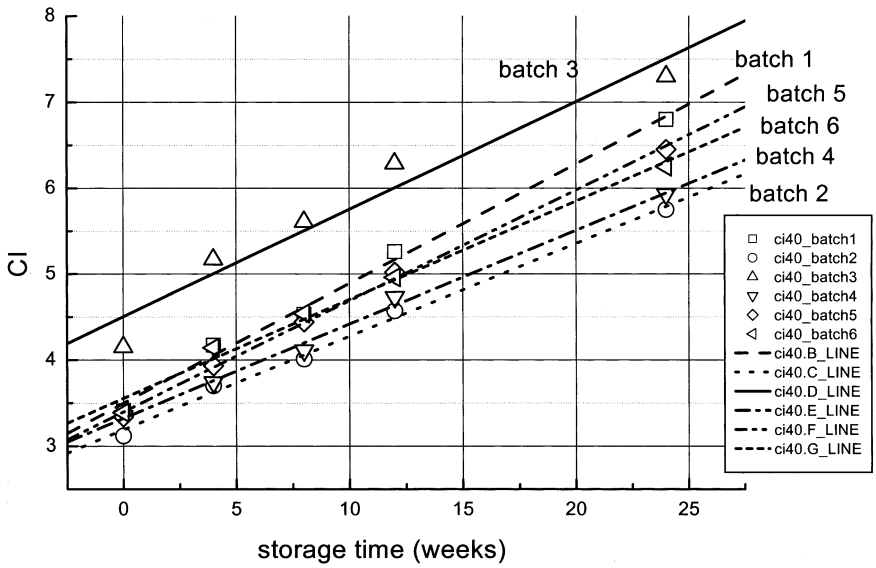


Fig. 8. CI values during storage at 40 °C. The regression coefficients became much higher at 40 than at 25 °C.

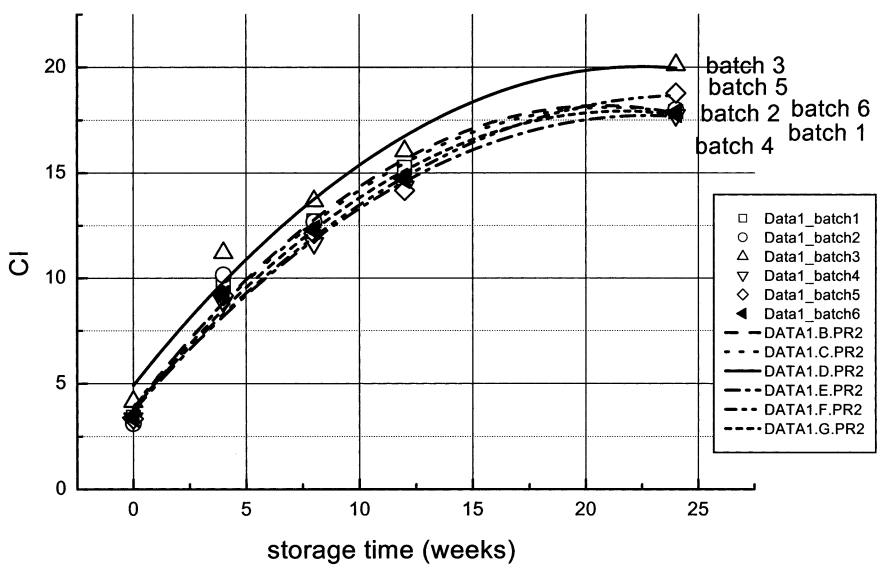


Fig. 9. CI values during storage at 60 °C. The 60 °C data are described by second-order polynomial functions.

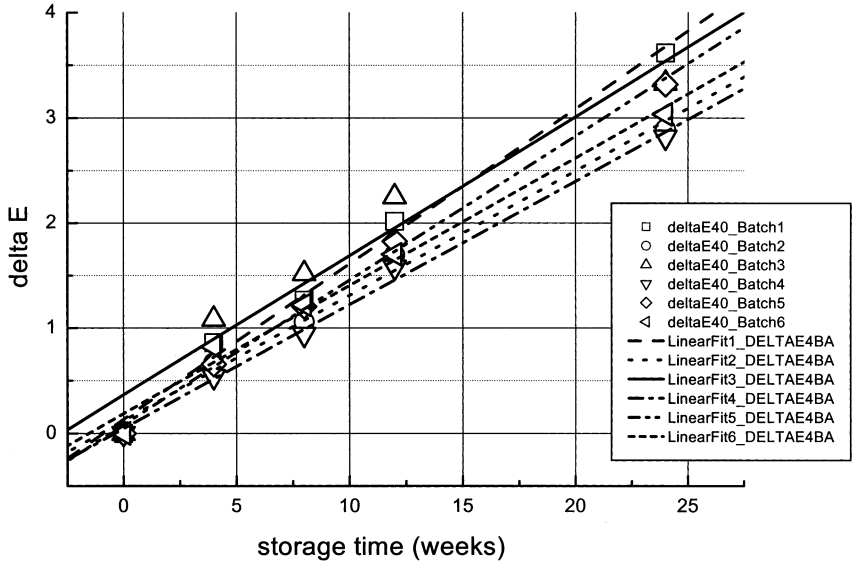


Fig. 10. ΔE values during storage at 40 °C. The 40 °C data are described by linear regression functions with regression coefficiencies greater that 0.9.

Fig. 10 for the 40 °C data. The linear regression fittings are as high as the curves of CI in the Fig. 8. The visual color differences among the batches diminished in Fig. 10 because all batches started per definition from zero. Absolute starting levels are no longer taken into account by the ΔEab^* data. From Fig. 10 we may conclude that all batches have approximately the same discoloration rate. On the other hand, CI data in Fig. 8 makes clear that the batch 3 started from a higher level than the other batches and revealed almost same discoloration rate as the other batches. The visual perception of tablets of batch 3, which were more darkened at the beginning than of the other batches is only reflected by CI values.

As the CI has been found to be a simple and useful parameter characterizing the discoloration behavior of our product, this new method has been applied to evaluate the long-term stability data. Three batches each of 50 and 100 mg tablets were being tested as for CIELAB color coordinates. The 25 °C data in polypropylene blister are shown in Fig. 11. These six batch series have been pooled and the linear regression calculation has been performed to give upper confidence. Similarly, the 30 °C/80% relative humidity (rh) data in polypropylene blister are pooled and fit to a linear regression with acceptable one-sided upper confidence interval on 95% level (Fig. 12).

4.2. Arrhenius evaluation and activation energy

If the discoloration is due to a chemical reaction, although its reaction mechanism is not established in terms of the causative agent, we can formerly assume that the reaction kinetic constant is connected with the rate constant of the discoloration at particular temperature. The rate constant of the discoloration would consequently follow the Arrhenius equation. In order to verify this assumption, the discoloration rates were calculated from the data of the above batches stored in polypropylene blister pack at 25 °C/60% rh, 30 °C/80% rh and 40 °C/75% rh. Fig. 13 shows the relationship between log (discoloration rate) and $-1/T$. All six batches followed the Arrhenius equation with a good regression coefficient. From the slopes of the linear regression lines, the activation energy was estimated. The activation energy was found to lie between 79 and 117 kJ/mol.

4.3. Correlation between visual color and CI values

As the CIELAB based parameter CI was unambiguously seen to characterize the whiteness, we tried to correlate the CI values to the visual color perception of the tablets. Due to a high degree of variation in visual perception of whiteness it was difficult to assign CI values to visual color perception which was free of any arbitrariness. A large amount of experience in our laboratories with

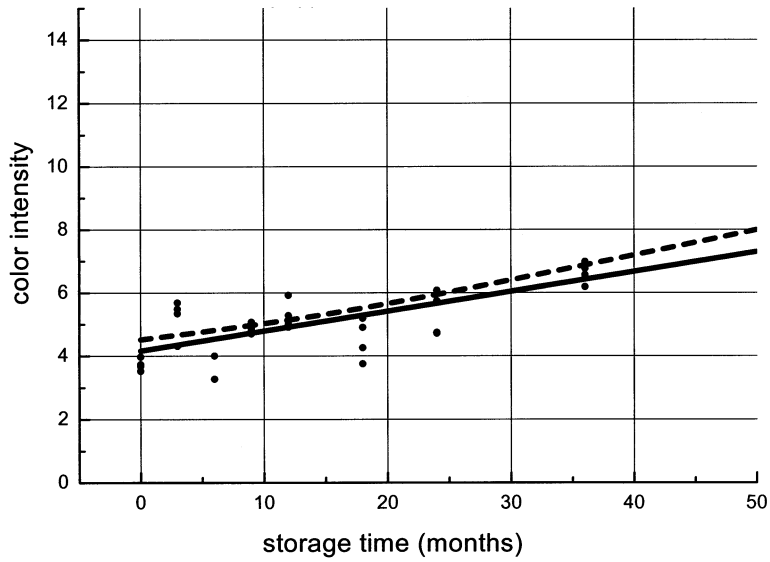


Fig. 11. CI values of tablets in the long-term stability under 25 °C/60% rh in polypropylene blister. The linear regression line (straight line) and one-sided upper confidence intervals on 95% level (dotted line) are shown.

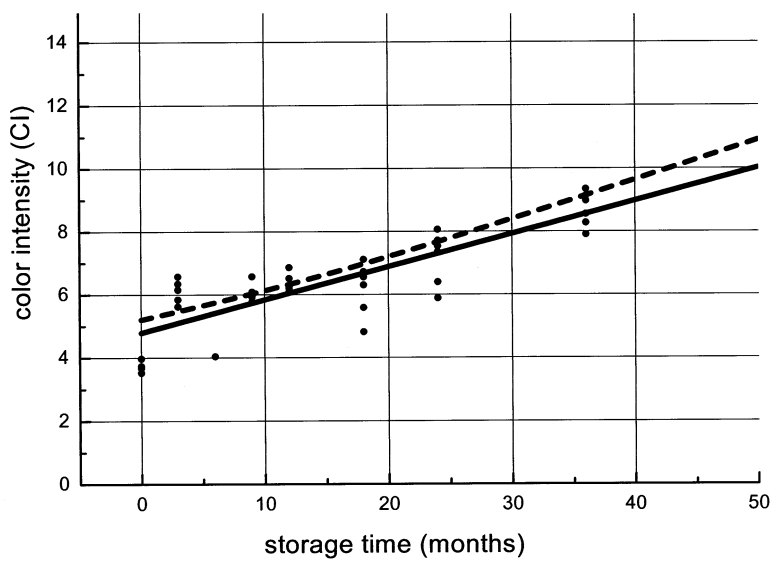


Fig. 12. CI values of tablets in the long-term stability under 30 °C/80% rh in polypropylene blister. The linear regression line (straight line) and the one-sided upper confidence interval on 95% level (dotted line) are shown.

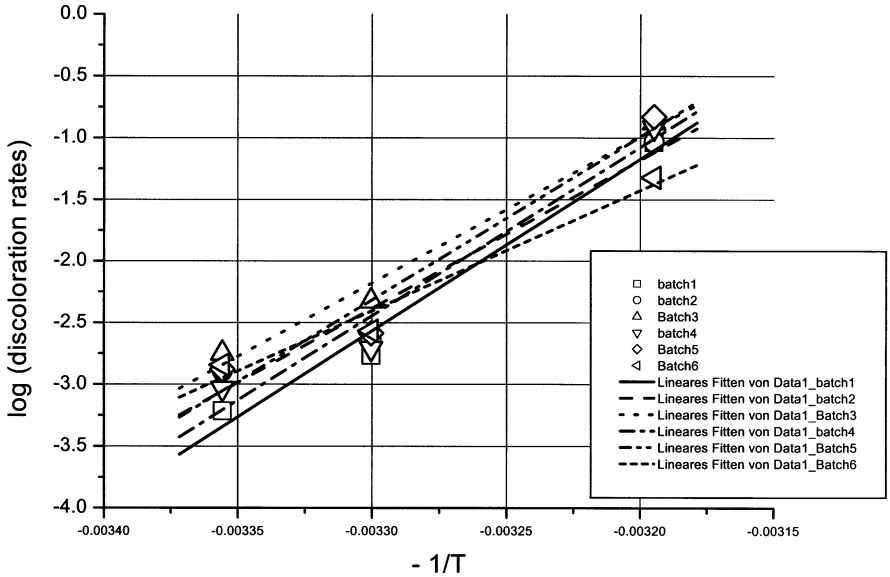


Fig. 13. Arrhenius equation for the discoloration rates. Log (discoloration rate) values are plotted against $-1/T$ with the 25, 40 and 60 °C data points.

visual inspection of white tablets allowed us to assign the following partitions of the CI scale.

white 0–3.0
nearly white 3.1–6.0
slightly yellow tinged 6.1–10.0
yellow tinged 10.1–12.0
slightly yellow–brown tinged 12.1–15.0
brown tinged 15.1–20.0.

The instrumental color measurement confirmed in a statistically justified manner that the product complied with the specification requirement for the color during the full market shelf life.

5. Discussion

The color coordinates CIELAB and associated parameter CI have been shown to be a quantifiable variable for whiteness of uncoated tablets. The color can have a continuous scale so as to be able to describe this physical variable as a mathematical function. Whereas any of L^*, a^*, b^* or ΔEab^* indicates the discoloration of white tablets to a certain degree, they alone cannot reflect the full extent of discoloration. The CI, on the other hand, is able to represent the change of the color as a function of time with acceptable confidence limits.

The discoloration of the white solid dosage forms can be treated as a chemical reaction without knowing what the causative chemical entity is. The discoloration kinetics follows the Arrhenius equation for the kinetic constants from the isotherm reactions at several temperatures. All batches investigated reveal kinetic low activation energy.

The time course of discoloration during the stability studies can be unambiguously defined by the CI curves. The CI values can therefore be correlated to the visual perception of differently discolored tablets by testing them simultaneously by the visual method and the instrumental color measurement method. This was described in Section 4.3. This has for the first time enabled the definition of the period of time how long the white uncoated tablets remain white. Furthermore it is possible to predict the change beyond the period of real testing.

The method described above differs from the applications of the tristimulus color published before (Stark et al., 1996). In the current work, the tablets colors are expressed as the locations in

the CIELAB vector space. The absolute values of L^*, a^*, b^* and CI are directly utilized. In the previous publication (Stark et al., 1996), the discoloration during storage was related to ΔEab^*, ΔL^*, Δa^* or Δb^*. The CI values represent absolute values, whereas the ΔEab^*, for example, is defined as a difference to its own reference (relative position). Each CI value is definitely connected to a visual color. This is an important precondition for the CI to function as a quality parameter in pharmaceutical quality control. One can judge the whiteness solely by the CI value.

However, to some extent, absolute L^*, a^*, b^* values, and therefore CI values also, depend on the instrument used. Depending on manufacturer, type of equipment and measurement conditions, or even on individual pieces of equipment, one may obtain a considerable scatter of these values from the same sample. For this reason, the CIELAB and CI values are only comparable when all measurements are performed with comparable or correlated instruments.

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