Color evolution during a coating process of pharmaceutical tablet cores by random spraying

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Abstract

Placebo white tablet cores [lactose anhydrous (47.6%), corn starch (23.8%), microcrystalline cellulose (19.1%), polyvinylpyrrolidone (7.9%), magnesium stearate (0.8%), talcum powder (0.8%)] were coated with a colorant [hydroxypropyl methylcellulose (8% w/v), titanium dioxide (0.2% w/v), FD&C yellow No. 6 with aluminum lacquer (0.8% w/v), polyethylene glycol 4000 (0.4% w/v), purified water (q.s.p. 100 ml)] using a random spraying method during 130 min. During the coating process, batches of 21 samples were extracted every 10 min and measured with a DigiEye imaging system. The initial cores showed very similar and uniform colors [Mean Color Difference from the Mean (MCDM) below 0.8 CIELAB units], but partially coated tablets showed lower uniformity (MCDM below 2.0 CIELAB units). There was a high color variability (MCDM about 4.0 CIELAB units) among tablets of the same batch in the period between 10 and 30 min, which decreased as the coating process progressed, until achieving a final acceptable value (MCDM below 2.0 CIELAB units). During the coating process, L^* decreased, C^*_{ab} strongly increased, and h_{ab} remained nearly constant (disregarding results at 0 and 10 min), following asymptotic trends. CIELAB color differences (mainly chroma differences) with respect to the initial color of the tablets were modelled as a function of time by an exponential function with three coefficients, and were mainly produced in the beginning of the coating process, reaching final high values about 75.0 CIELAB units. The color change

in the interval from 70 min to 130 min may be considered negligible (about 4.0 CIELAB units).

KEYWORDS: Color differences, coating, tablets, industrial control

1. INTRODUCTION

Among initiatives aimed at achieving progress in the pharmaceutical industry [1], various researchers and manufacturers promoted objective automatic control systems in the process of manufacturing pharmaceutical products [2, 3]. Coated pharmaceutical tablets are among the most fragile products of this market, and the core coating process requires adequate quality control [4, 5]. For example, tablet coating is important since it allows masking undesirable aspects of the core (e.g. flavor, odor, texture, etc.), can affect the way that the core's active ingredients are released, allows optimum swallowing, influences the tablet's resistance to mechanical efforts and environmental factors during packaging and storage processes, etc.

A typical procedure for coating the tablets is spraying the cores randomly with fine droplets of the coating mixture, while moving the cores chaotically inside a rotating drum. This system was initially used in manual equipment for coating nuts and other confectionery using sugary edible coating. Certainly, the variables influencing the tablet coating process by spraying or other techniques are quite abundant [6, 7]. Some examples of these variables are morphology, core size and material, chemical composition of the coating layer/s, specific properties of fluidity and material drying, and environmental conditions (e. g. pressure, temperature, relative humidity, etc.). In addition to adopting specific protocols to achieve the desired results in the coating process, currently it is also necessary to have human operators to make specific modifications during the course of the coating process, whose work is based on their knowledge and previous experience. In fact, the need for human operators is not specific of this process: Other examples are graphic printing industries and, more in general, the work of selection and control carried out by tasting panels in a variety of industries.

Among the desired results of a tablet coating process are achieving constant thickness of the coating layer according to the manufacturer's requirements, uniform and visually

identic coating in all the tablets in each batch, appropriate tablet protection and release control, etc. Undoubtedly, the use of specific control techniques facilitates the work of human operators in seeking those results [8-11], although it must be pointed out that often the use of sophisticated and expensive techniques is not possible for small industries in developing countries. Since the ultimate goal of the industries is to improve their production processes in order to increase quality while reducing costs, it can be expected that the control of the tablet coating process will be fully automated in the future. Meanwhile, research as this one, aimed at studying concrete aspects of coating techniques, might be useful to professionals working on the improvement of such processes in some countries.

The color of pharmaceutical tablets is a key aspect of their visual aspect [12-14], hence the need to control its evolution during the coating process. It is known that tablets' color has a significant influence on the expectations, emotions and preferences of the consumers [15, 16], while being an indirect indicator of the tablet's functional condition. The objective of this work is to show experimental results on the evolution of color of white cores coated by spraying them with a specific colorant inside a coating drum. For this, image analysis techniques [17-19] were used that allowed accurate measurement of the color of the pixels of images of tablet batches extracted from the drum during the coating time. Although the results were dependent on the core materials and the coating employed, their usefulness should be pointed out since, as far as we know, there are no experimental results in the literature regarding color change occurred inside a random-spraying coating drum. Finally, it is our purpose that the current results serve as the basis for future more general studies to develop procedures aimed at making the work of the human operators currently responsible for these processes less subjective.

2. MATERIALS AND METHODS

TSM (Tableting Specification Manual) standard size convex tablets of 4.0 ± 5% × Ø 6 mm were made. Tablets' cores consisted of a white placebo mixture composed of lactose anhydrous (47.6 %), corn starch (23.8 %), microcrystalline cellulose (19.1 %), polyvinylpyrrolidone (7.9 %), magnesium stearate (0.8 %) and talc (0.8 %). Lactose anhydrous is an inactive component common in pharmaceutical tablets that gives them body and ease of compression, so that absence of water prevents reactions with other

moisture sensitive composites. Microcrystalline cellulose, purified and depolymerized, acts as stabilizer and diluting agent to form the core's body. Corn starch provides lubricant, diluting and disintegrating effects. Polyvinylpyrrolidone is a water soluble synthetic surfactant polymer acting as water soluble binder, with properties such as biological compatibility, low toxicity, inertia against salts or acids, and low thermal degradation. Lastly, magnesium stearate and talc provide lubricant, non-adherent and antifriction properties. The wet granulation method was used for mixing the components, since it causes less segregation and minimum dispersion of the mixture components, so that the final granules are very uniform, containing less than 5% total humidity. Finally, compaction was performed in a 10 station GMP Junior Express rotary tableting machine (Talleres Sánchez, Argentina), which provides working conditions identical to those of a high performance industrial production equipment.

The coating liquid of the cores was composed of a hydroxypropyl methylcellulose polymeric base suspension (8 % p/v), which is one of the most common generic pharmaceutical excipients, titanium dioxide (0.2 % p/v), which acts as whiteness enhancer, the United States Federal Food, Drug, and Cosmetic Act (FD&C) N° 6 colorant with aluminium lacquer (0.8 % p/v), that gives the tablets an orange shade, and polyethylene glycol 4000 (0.4 % p/v), which acts as a vehicle with good properties for fast drying of the mixture, completing the formula with purified water (q.s.p. 100 ml). The FD&C N° 6 colorant is an azoic colorant known as *sunset yellow*, which in Europe is designated by the code E-110. For core coating a perforated coating drum (Hüttlin-Bosch SolidLab 1, Germany) of 30 cm diameter and 1 kg tablet load was used. The temperature of the tablets in the drum was kept within the range of 35 - 45 °C.

The coating process took 130 min, interrupting the spraying every 10 min to extract 21 samples randomly. These 10 min-intervals coincide approximately with those normally used in the pharmaceutical industry for recording and traceability performed during the process of tablet coating, allowing follow-up of the process and correction of possible errors. Color measurement was carried out for each one of the batches of 21 samples extracted every 10 min, using a DigiEye imaging system [20]. This equipment has two light sources simulating the CIE D65 illuminant, which provide a diffuse and very uniform illumination on the tray where the samples are placed, plus a Nikon® D80 digital camera placed in the vertical to the sample tray. The equipment software allows calibration of the camera before making the measurements, making it possible to

measure the color coordinates in the CIELAB space [21] for any of the pixels of the images obtained with the camera. Offline follow-up of the color change of the cores was performed while the cores were coated by random spraying inside the spinning drum, obtaining results like those shown in Figure 1. In overall terms, addition of a specific material or of successive layers of different materials on a given substrate increases the thickness of the coating and produces modifications in the initial color of the substrate [22]. Previous works have shown that the study of the time evolution of color, both as a consequence of specific chemical reactions and of aging effects, is an objective analysis tool that provides useful information for different applications [23, 24].

We employed the CIELAB color space [21], using its Cartesian coordinates a^* (red-green), b^* (yellow-blue) and L^* (lightness), as well as the corresponding cylindrical coordinates C^*_{ab} (chroma) and h_{ab} (hue angle). The three main perceptible attributes of color are lightness, chroma and hue [25], reason why it is common to resort to analysing the changes in the coordinates L^*, C^*_{ab} and h_{ab} more than in the coordinates L^*, a^*, b^*. To calculate the color differences between two samples we also used the CIELAB space, assuming CIE standard illuminant D65 and standard observer CIE 1931. The CIELAB color difference (ΔE^*_{ab}) can be considered as the result of the differences in lightness (ΔL^*), chroma (ΔC^*_{ab}) and hue (ΔH^*_{ab}), whose percentages are given by:

$$\%(\Delta L^*)=100(\Delta L^*/\Delta E^*_{ab})^2 \quad ; \quad \%(\Delta C^*_{ab})=100(\Delta C^*_{ab}/\Delta E^*_{ab})^2 \quad ; \quad \%(\Delta H^*_{ab})=100(\Delta H^*_{ab}/\Delta E^*_{ab})^2 \quad , \tag{1}$$

thus complying with

$$\%(\Delta L^*) + \%(\Delta C^*_{ab}) + \%(\Delta H^*_{ab}) = 100 \; . \tag{2}$$

As a measure of color variability, both among the different pixels of a single tablet as well as among the average color of any 21-tablet batch, we used the Mean Color Difference from the Mean (MCDM) in CIELAB units [26]. Under optimum observation conditions, the human eye is capable of perceiving color differences around 0.5 CIELAB units, as required by some specific industries [27]. To illustrate, in a recent work employing paper printed samples [28], the mean size of the just perceptible color differences for a panel of observers with normal color vision was of 1.1 CIELAB units.

3. EXPERIMENTAL RESULTS AND DISCUSSION

3.1 Color variability in a single tablet

Considering the different pixels of the image of a single tablet, the DigiEye software allowed us to analyse to what extent the tablet had uniform color. Lack of color uniformity could be related to production defects, although the uneven surface of the tablet also causes certain color variations, which could be considered as systematic errors in the measures. The average results of the 21 tablets extracted in each time are shown in Figure 2, where the standard deviations of the different CIELAB coordinates and the values of the MCDM in CIELAB units were represented. The initial white cores are extremely uniform in color, with standard deviations of the CIELAB coordinates in the order of 0.5 units, except for the hue angle h_{ab}, which shows a high standard deviation of 6.7° (although such variability is unimportant, since in white colors the hue angle varies considerably), with MCDM of 0.8 CIELAB units. Over the course of the coating time, the uniformity of the tablet color remains enough stable, continuing to be fairly good, although lower than that of the initial cores, as evidenced, for example, by the fact that in Fig. 2 the values of MCDM are below 2.0 CIEAB units.

3.2 Color variability in a batch of tablets

Consider the average color of the pixels of a tablet image and, from there, the color variability of the 21 tablets extracted from the drum every 10 min in the course of the total coating time (130 min). The variability (standard deviations) of the different CIELAB coordinates for the 21 tablets of each batch is represented in Figure 3, together with the MCDM values in CIELAB units, as a function of the coating time. The average color of the 21 initial cores (time 0 min) is very similar, whereas in the extractions at 10, 20 and 30 min the color variability of the 21 tablets increased remarkably, with values of MCDM around 4.0 or 5.0 CIELAB units, tending to decrease and finally fall below 2.0 CIELAB units, which is approximately the color variability between the pixels of a single tablet (Fig. 2). Therefore, there are important color differences between one tablet and the others at the beginning of the coating process, fortunately decreasing as the process continues, so that at the end of it (130 min) the color variability of the 21 tablets is small and similar to that of the different pixels of a single table (i.e. MCDM lower than 2.0 CIELAB units). We can suppose that at the beginning of the coating process there were some cores that were more exposed to spraying than others, producing high color differences among the various cores (MCDM around 4.0 to 5.0 CIELAB units),

but such differences decreased with the course of time, and at the end the spraying process on the cores can be considered really random.

3.3 Temporal evolution of the main color attributes of the tablets

Here we considered how the average color of the 21 tablets in each batch evolved with the course of the coating time. As shown in Figure 4, the initial color of the cores is white, since the values of lightness L^* are close to 100 and the values in the coordinates a^* and b^* are very close to 0. During the coating time, L^* decreased in the tablets, while coordinates a^* and b^* increased, with the values of b^* always above those of a^*. As a result of the change in the coordinates a^* and b^*, the chroma C^*_{ab} of the tablets increased with the coating time (that is, the tablets' color turned increasingly intense) while the hue angle h_{ab} experimented a slight decrease, maintaining quite stable values between 50° and 60° approximately (orange hues), provided we discard the values obtained from 0 to 10 min, which are not significant since the initial tablets were white, as indicated. Moreover, the temporal evolution of all color coordinates shows an asymptotic trend, meaning that, after an important color change during the initial coating time, the color of the tablets tends to stabilize, becoming practically constant after some coating time.

Figure 5 shows the temporal evolution of the color of the tablet batches considering only the CIELAB a^* b^* plane (i.e. omitting the change in lightness L^*), now taking into account the color variability of the tablet batches, represented in this case by ellipses. The centers of each ellipse correspond to the average color of the 21 tablets in each one of the times indicated, and the ellipses contain at least 85 % of the color coordinates of the 21 tablets. Figure 5 also shows that the initial cores (t=0 min) present very similar colors and close to ideal white (L^*=100, a^*=0, b^*=0), while at t=10 min the color is very different to the color of the initial cores. Besides, there is considerable color variability among the 21 tablets. This high variability continues later also, so that, for example, the ellipses at t=20 min and t=30 min overlap each other (as also occurs at longer times). The interpretation of this overlapping is that there would be tablets whose chromaticity would not permit discerning whether they were extracted from the coating drum at t=20 min or at t=30 min. As time passes, the centers of successive ellipses are increasingly close to each other, as expected from the fact that tablet color tends to stabilize asymptotically, as mentioned in the previous subsection. The major axes of the ellipses in Fig. 5 are oriented in the same direction of the temporal color change, as should be

expected, and represent the variability of color of the tablet batches, not the capability of color discrimination (discrimination thresholds) of the human eye. In CIELAB a^* b^* plane, the typical discrimination ellipses corresponding to average human observers also have their major axes oriented in the radial direction [29], and therefore they are similar to those shown in Fig. 5, although considerably smaller in size [28].

3.4 Color differences in the coating process

Lastly, we studied the color differences in CIELAB among the initial cores and the coated tablets (average of 21 samples) for a certain time, as shown in Figure 6. In Fig. 6 there is a temporal asymptotic color stabilization trend that adjusted quite well (R^2=0.996) to the following exponential function with 3 coefficients (green curve):

$$\Delta E^*_{ab}=77.0-77.9 \times \exp(-t/30.3) \quad (3)$$

Figure 6 also indicates the nature of the color changes occurring during the coating process, so that the different colors in each bar show the percentage of difference in lightness, chroma and hue (see Eqs. 1 and 2) within the total color difference. As shown, color differences resulting from the coating process are mainly differences in chroma, with a minor contribution from differences in lightness and some differences in hue that are almost constant from t=10 min. These results are consistent with those shown in Fig. 4, where, omitting the values at t=0 min and t=10 min, it can be observed an increase in chroma reaching around 70 CIELAB units, a decrease in lightness of around 20 CIELAB units, and a change in hue angle between 50° and 60°, approximately. Furthermore, the results in Fig. 6 are consistent with the colors seen in the tablets in Fig. 1, although reproduction of actual colors in Fig. 1 is only approximate.

All the results in Fig. 6 refer to color differences with respect to core initial color (t=0 min). Conversely, Fig. 7 provides a different additional information, showing the results corresponding to changes in color between two tablets with differences in the coating time of only 10 min. As in Fig. 6, the different colors in each bar in Fig. 7 indicate the percentages in lightness, chroma and hue differences within the total color difference. Great changes in the tablet color (mainly changes in chroma) around 18.0 CIELAB units occurred in the intervals from 0 min to 10 min and from 10 min to 20 min. In contrast, from the interval of 50 min to 60 min onwards the changes in color were quite

small (under 4.0 CIELAB units). In conclusion, it was confirmed that color change of the tablets occurs mainly at the beginning of the coating process, tending to stabilize after approximately 70 min, as could also be concluded from results shown in Figs. 1, 4, 5 and 6.

4. CONCLUSIONS AND FUTURE WORK

A colorimetric study of a coloration process of pharmaceutical tablets coated by means of random spraying, starting with specific cores and a specific coating mixture, was conducted. Future work should confirm in which measure the main current results are also valid for other cores (e.g. with different sizes, shapes or chemical compositions) and different coatings. At present time, it was detected that it is at the initial times of the coating process (up to 40 min) that most color changes in tablets occur, reaching a high average value around 50 CIELAB units for t=30 min. High color variability was also found among tablets of the same batch. Color differences with respect to the initial cores can be described as an exponential function with only three coefficients. Color of the tablets tends to stabilize with time, so that after a certain coating time of the order of 70 min, color changes with respect to the initial color were lower than 4.0 CIELAB units, and can be considered negligible from the visual point of view, taking into account the total magnitude of color differences (about 75 CIELAB units for 130 min). We trust that the results from this work will be useful in progressing towards automated control of the coating process of pharmaceutical cores. It should be desirable that current experimental results on color evolution by a random spray coating technique can be confirmed by future theoretical models, as recently investigated for thickness [30].

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LEGENDS FOR FIGURES

Fig. 1. Images of three tablets randomly selected at different times of the coating process, from 0 min to 130 min, at intervals of 10 min (row 1). Pictures obtained with DigiEye imaging system (light source D65, aperture f/6.3, exposition time of 1/15 s). The reproduction of the color of the tablets is only approximate.

Fig. 2. Standard deviations of the CIELAB coordinates of the different image pixels of a single tablet with different coating times. The values of the Mean Color Difference from the Mean (MCDM) in CIELAB units are also plotted.

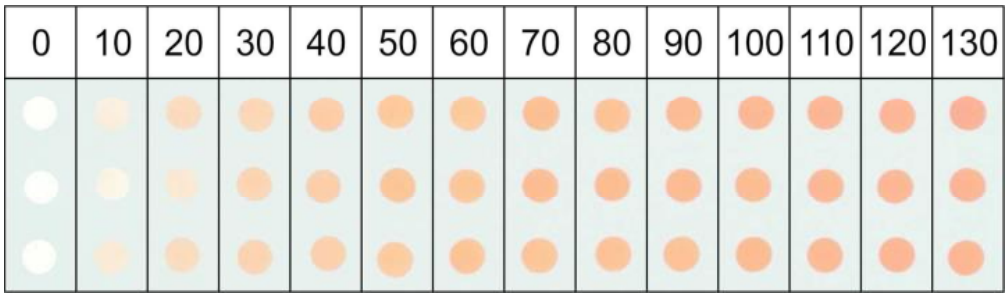
Fig. 3. Standard deviations of the CIELAB coordinates of average color of the 21 tablets randomly extracted every 10 min from the coating drum. MCDM values in CIELAB units are also indicated.

Fig. 4. Temporal evolution of the average color of the 21 tablets of each batch, considering different CIELAB coordinates. The error bars represent the standard deviations corresponding to the color variability of the 21 tablets (Fig. 3).

Fig. 5. Evolution of the average color of the 21 tablets in the CIELAB a^* b^* plane. The numbers close to the ellipses indicate the coating time elapsed in minutes. The ellipses' centers correspond to the average color of the 21 tablets, and their size and orientation is such that they contain at least 85 % of the color coordinates of the 21 tablets in each batch.

Fig. 6. CIELAB color differences of the coated tablets for a certain time, with respect to initial core color (t=0 min). The three colors in each bar indicate the percentage of difference in lightness, chroma and hue in the total color differences. The green curved line corresponds to the model indicated in Eq. 3.

Fig. 7. CIELAB color differences of the tablets during successive time intervals of 10 min in the coating process. The three colors in each bar indicate the percentages of difference in lightness, chroma and hue within the total color differences.



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178x51mm (300 x 300 DPI)

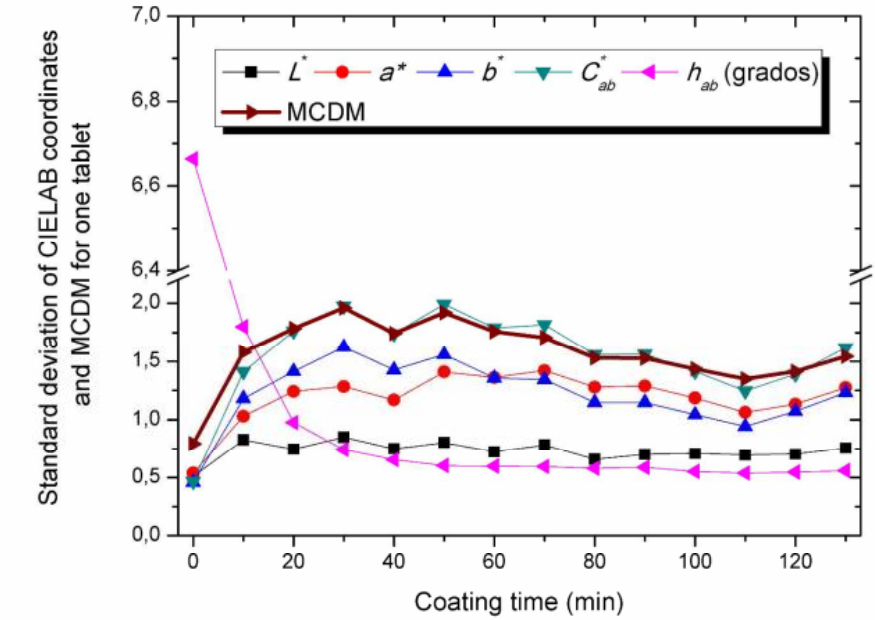
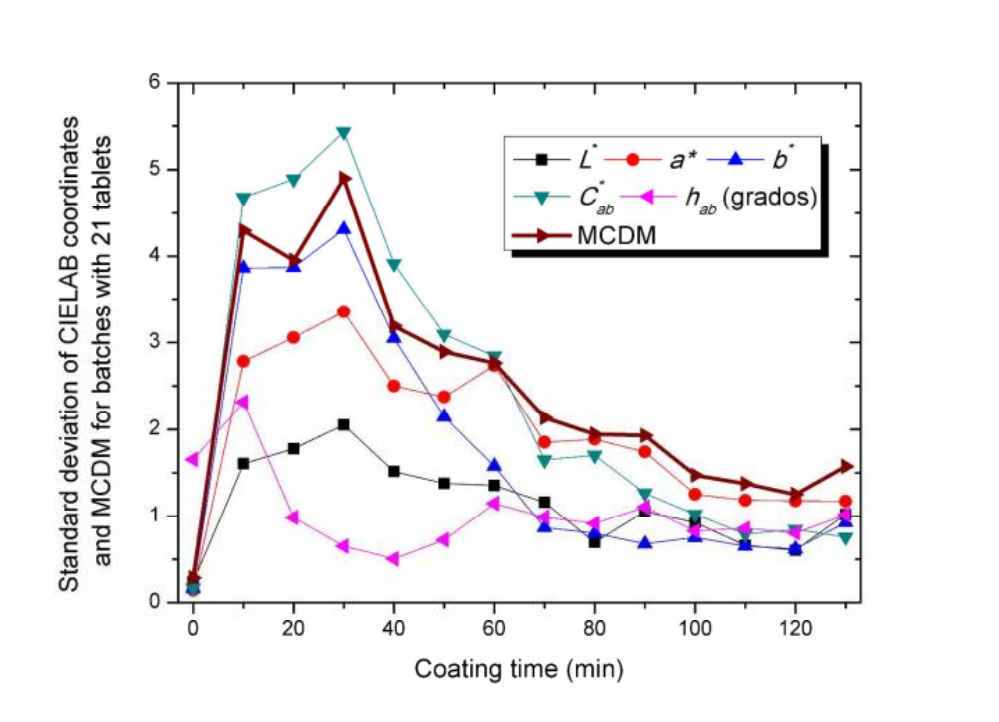


Fig. 2. Standard deviations of the CIELAB coordinates of the different image pixels of a single tablet with different coating times. The values of the Mean Color Difference from the Mean (MCDM) in CIELAB units are also plotted.

281x204mm (300 x 300 DPI)



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281x204mm (300 x 300 DPI)

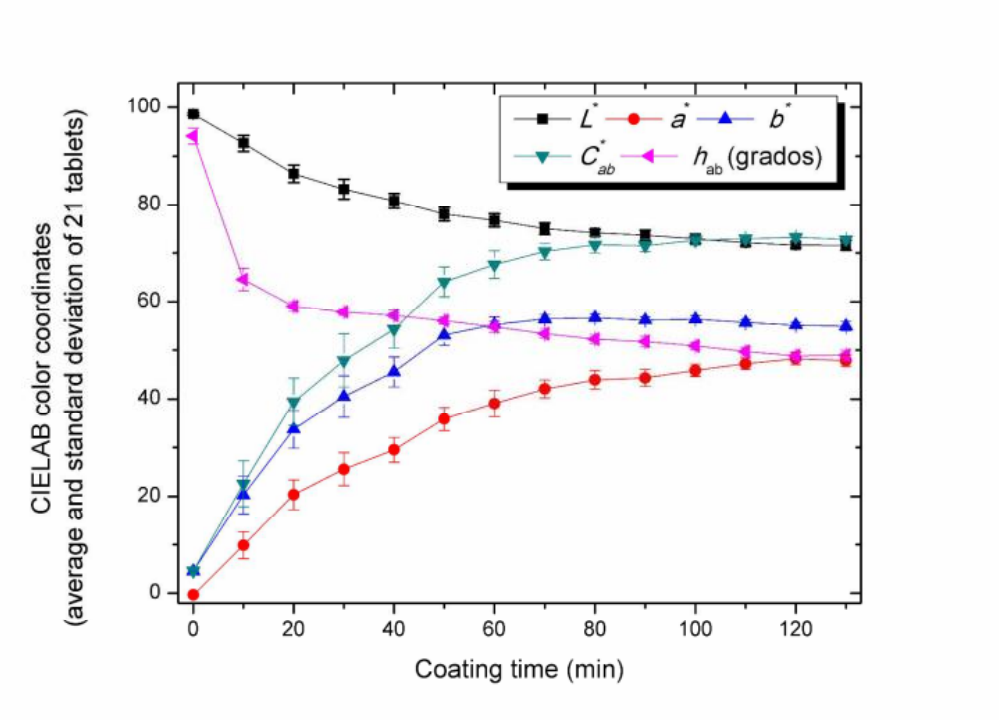

Fig. 4. Temporal evolution of the average color of the 21 tablets of each batch, considering different CIELAB coordinates. The error bars represent the standard deviations corresponding to the color variability of the 21 tablets (Fig. 3).

281x204mm (300 x 300 DPI)

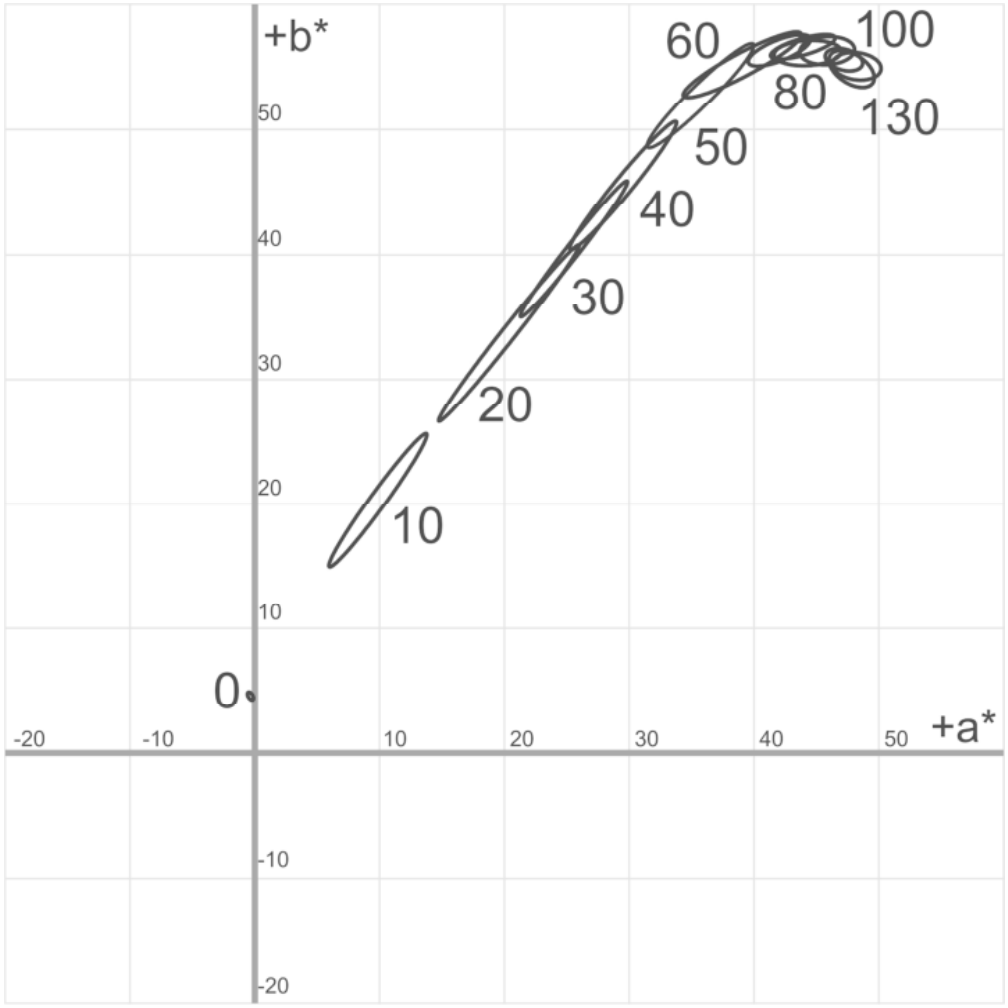

Fig. 5. Evolution of the average color of the 21 tablets in the CIELAB a* b* plane. The numbers close to the ellipses indicate the coating time elapsed in minutes. The ellipses' centers correspond to the average color of the 21 tablets, and their size and orientation is such that they contain at least 85 % of the color coordinates of the 21 tablets in each batch.

128x128mm (300 x 300 DPI)

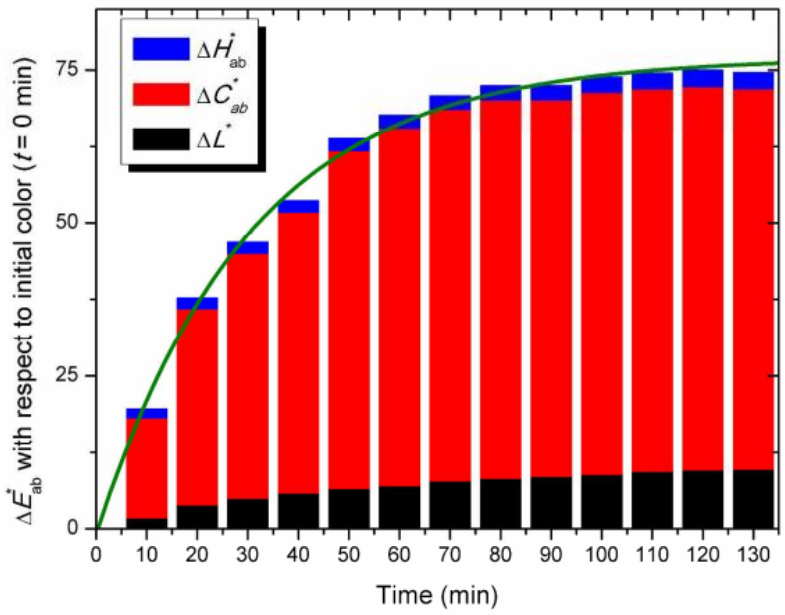

Fig. 6. CIELAB color differences of the coated tablets for a certain time, with respect to initial core color (t=0 min). The three colors in each bar indicate the percentage of difference in lightness, chroma and hue in the total color differences. The green curved line corresponds to the model indicated in Eq. 3.

281x204mm (300 x 300 DPI)

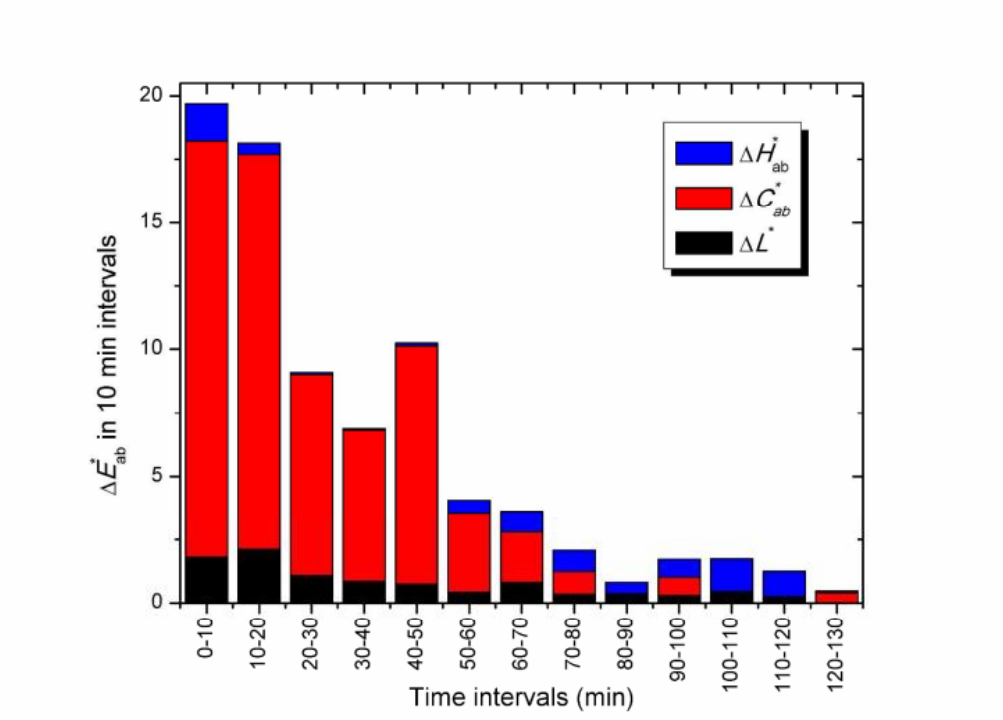

Fig. 7. CIELAB color differences of the tablets during successive time intervals of 10 min in the coating process. The three colors in each bar indicate the percentages of difference in lightness, chroma and hue within the total color differences.

281x204mm (300 x 300 DPI)