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An improved method for the measurement of colour uniformity in pellet coating

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Abstract

Sucrose pellets in the size range of 0.71–0.85 mm were film-coated in a bottom-spray Wurster fluidised bed coater with a colour coating suspension of 7.5% w/w solids. Hydroxypropyl methylcellulose was used as a film former, polyethylene glycol as a plasticiser and yellow iron oxide as a coloured pigment. The colour distribution on the film coat was analysed using a tristimulus colorimeter and the colour value was measured in CIELAB units. Uniformity in the colour coat was indicated by the standard deviation of the colour measurement values. Four different methods for measuring the colour distribution over the colour coated pellets' surfaces were carried out. In method I, colour measurements of the pellets' surfaces were made by placing the pellets directly on the stage of the tristimulus colorimeter. A specially designed pellet sample holder was employed to assist the collection of colour measurements in methods II–IV. Colour measurements from eight spots on each pellet were taken in methods I, II and IV while method III involved measuring 24 spots per pellet. A total of eight overlapping spot measurements were taken in method IV while the eight spot measurements in method II were non-overlapping. Method II was found to be the most efficient, accurate and sensitive method for the measurement of spot colour distribution on pellets.

Keywords: Tristimulus colorimeter; Fluidised bed; CIELAB units; Coating; Colour uniformity

1. Introduction

Colour is a basic visual feature of any solid pharmaceutical dosage form. Consistency of the colour over the surface of a dosage form and between each unit of dosage form is important to the consumer as well as the manufacturer. Colour deviations are spotted easily by the consumer. Inconsistencies in the colour on dosage forms are often indicative of either their poor quality production or product instability (Wirth, 1991). Thus, colour measurement is one of the quality assurance tests that should be carried out during the manufacture of a coloured pharmaceutical product (Hunter, 1981).

Fluidised bed technology is commonly employed in the film coating of pellets (Cole et al., 1995; Christensen and Bertelsen, 1997). The coat-

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ing suspension is sprayed as atomised droplets onto the fluidised pellets. A film coat is formed around the pellet with successive deposition of spray droplets accompanied by solvent evaporation due to the heat supplied by the fluidising air. A complete coat over the pellet is formed after several passes through the spray zone. In the preparation of controlled release dosage forms, the film coats formed should be homogeneous and of uniform thickness. Although desirable, a perfectly even distribution of the spray throughout the entire population of the fluidised pellets giving rise to a uniform coating rate is difficult to achieve. The homogeneity of the colour coats of pellets has been determined using the tristimulus colorimeter (Heng et al., 1999). The method of colour measurement of coated pellets involved rotation of the pellets on the stage of the tristimulus colorimeter with a sharp pair of forceps. The tendency for the spherical pellets to roll and rest on their most stable orientation often prevented fixed point measurements along the pellets' circumference. Thus, a modified method of measuring and analysing the colour distribution on pellets' surfaces was investigated.

2. Materials and methods

2.1. Colour coating process

A batch of 400 g of base coated sucrose pellets (Neutral Pellets, 0.71–0.85 mm, Hanns G. Werner's, Germany) was colour coated in a bottom-spray Wurster fluidised bed coater (Strea-1 with Aerocoater accessory, Aeromatic, Switzerland). The base coat solution consisted of hydroxypropyl methylcellulose 5.0% w/w (HPMC; Pharmacoat 603, Shin-Etsu Chemical, Japan) as the film former and polyethylene glycol 0.5% w/w (PEG; Lutrol E 6000, BASF, Germany) as the plasticiser. The colour coating suspension consisted of the same constituents as the base coat solution in addition to the yellow iron oxide pigment of 2.0% w/w (Yellow 10, Sicovit, BASF, Germany) included as the colorant. A total of 30 g of colour coating suspension was sprayed. The operating conditions for coating were set at 4.5 g/min spray rate, 1.0 bar atomising air pressure, 100 m^3/h air flow rate and 80°C drying air temperature.

2.2. Colour measurement of pellets

A tristimulus colorimeter (Minolta Chroma Meter CR-241, Japan) was employed for colour measurement (Fig. 1). The principle of operation involved projection of light of a known spectral energy on the pellet and measurement of the intensity of the reflected light using photo detectors. CIE Illuminant D65 was used in all the colour measurements. The colour measured was expressed by the CIE (1976) $L^*a^*b^*$ (CIELAB) colour space values (Judd and Wyszecki, 1975; Bilmeyer and Saltzmann, 1981; Hunter and Harold, 1987). Each colour in the CIELAB colour space has a unique location defined by its cartesian coordinates with respect to the axes L^*, a^* and b^* where L^* is the degree of lightness and covered a range from white (100) to black (0) along a grey scale, a^* is the degree of redness and greenness, and b^* is the degree of yellowness and blueness.

Four different methods were employed to determine the colour distribution on the surfaces of the pellets using the tristimulus colorimeter (Fig. 2). For the four methods, the same 50 pellets selected randomly from the batch were used for assessment. The pellet was first placed on the movable specimen stage with $X-Y$ screw drivers. The focal point was manually adjusted by moving the stage and focusing ring until the apex of the pellet and the measurement area appeared very sharp through the eyepiece. The light source was arranged circumferentially, illuminating the sample at an angle of 45° and the viewing angle was at 0°. This circumferential arrangement of incident (or viewing) light beams helped to reduce the sensitivity of the measurement due to specimen orientation and texture (Hunter, 1981). Measurements were made over a 0.3 mm diameter spot. The colour measurement was performed in the aperture mode such that the influence of spatial distribution of light was reduced. Darker colours could

be measured accurately in the 0.3 mm diameter spot since the colorimeter could measure reflectance from 0.01 to 160%. Hence, brightness, smoothness and shape of the spot would have limited influence the colour measurement.

In method I, the pellet was placed directly on the specimen stage and the colour measurement of eight different spots from a marked point on the pellet was determined. The pellet was carefully turned with a pair of forceps for measurement of colour on the next spot. Methods II–IV utilised a pellet sample holder (Fig. 1) to hold the pellet. The pellet was rotated through a sector about the horizontal axis by turning an alignment wheel and consecutive circumferential spot colour measurements were made. A total of eight spots on one pellet was taken for method II by turning through an angle of 45° after each spot colour measurement. For method III, the turn angle was reduced to 15°, enabling the measurements of 24 consecutive circumferential colour spots. For method IV, the eight spot colour measurements were spaced by turning the alignment wheel by an angle of 15°. Thus, method II measured eight non-overlapping spots and method IV measured eight overlapping spots. Methods I–IV were done separately.

2.3. Mathematical calculations

The mean $L^*a^*b^*$ values of the sucrose pellets with only base coat were used as the initial colour on the pellets ($L_o^* = 85.67$; $a_o^* = 0.77$; $b_o^* = 0.13$). The colour difference (ΔE_i) value for each measurement (L_i^*, a_i^*, b_i^*) was calculated with respect to the initial colour on the pellets according to the following equation:

$$\Delta E_i = [(L_o^* - L_i^*)^2 + (a_o^* - a_i^*)^2 + (b_o^* - b_i^*)^2]^{1/2}$$

The cumulative mean ($\Delta E_{p'} = 1/n(\Sigma_{i=1}^{n} \Delta E_i)$) of increasing number of ΔE_i values, up to all 400 spots in methods I, II and IV and 1200 spots in method III were taken and plotted in Fig. 3. ΔE_p denoted the population parameter. The mean (ΔE_x) of eight ΔE_i values (methods I, II and IV) or 24 ΔE_i values (method III), also known as intrapellet ΔE_x, represents the coloration on each individual pellet's surface. Their corresponding standard deviation denoted as $IH_{\Delta E}$ describes the colour variation or colour inhomogeneity on each pellet's surface. The mean (ΔE_m) and standard deviation ($S.D._m$) of ΔE_x values of 50 pellets were calculated. Similarly, the mean (IH_m) and standard deviation ($S.D._{IH}$) of $IH_{\Delta E}$ of the 50 pellets were obtained. ΔE_m and IH_m represented the in-

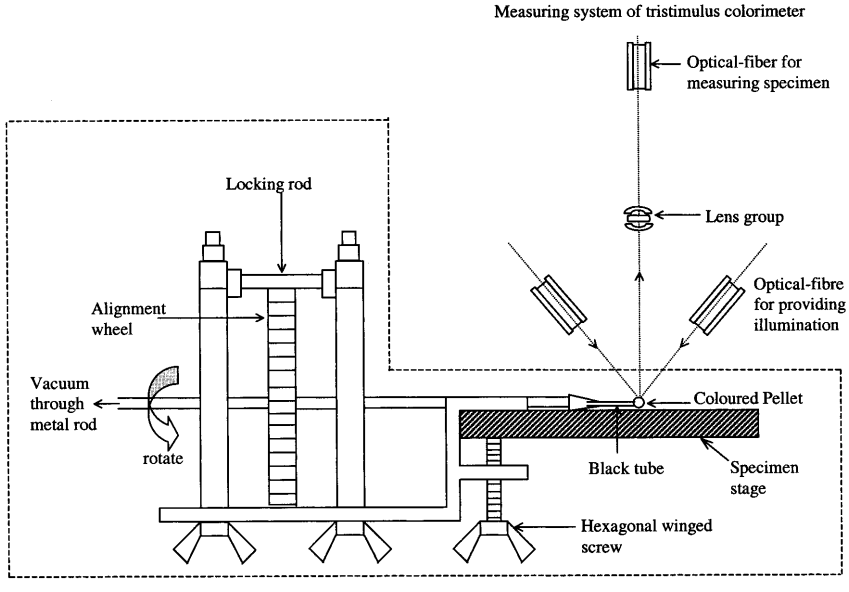

Fig. 1. Diagram illustrating measurement of colour on pellet using a tristimulus colorimeter with a pellet sample holder.

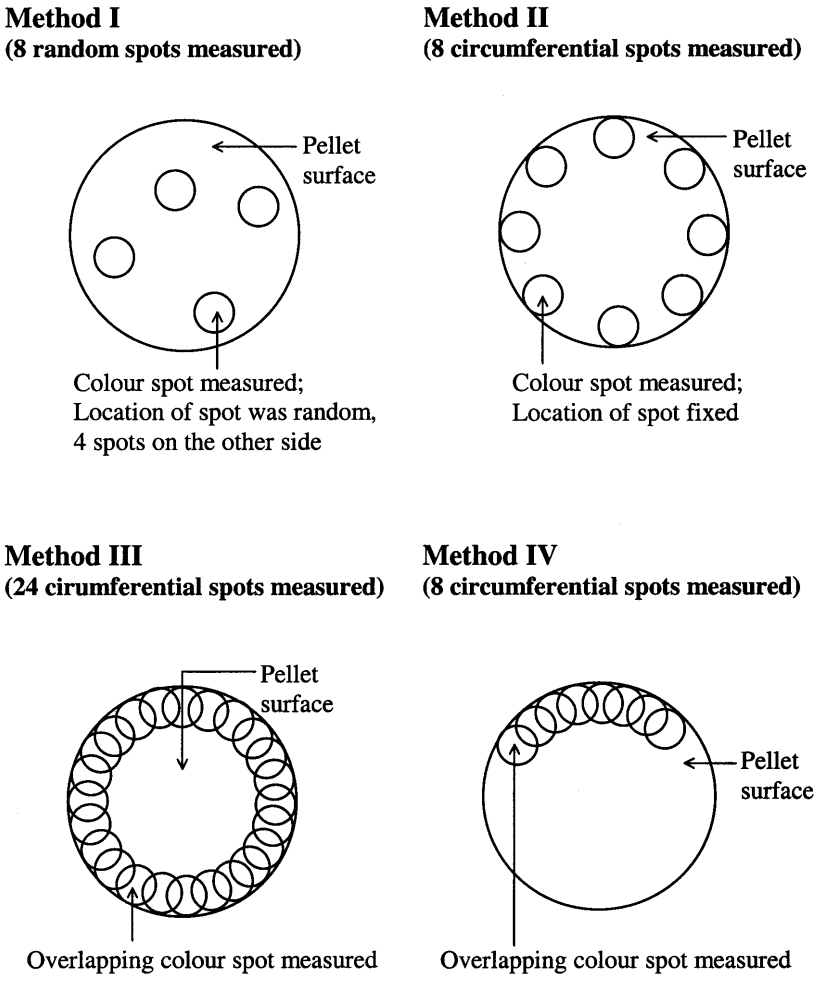

Fig. 2. A diagram to show the location of spots of which colours were measured in each of the four methods.

terpellet average coloration and the interpellet colour uniformity, respectively. The same mathematical calculations were applied to all the four different methods.

3. Results and discussion

3.1. Determination of colour uniformity by visual examinations and colour measurement

Under close visual scrutiny, it was observed that a population of coated pellets may not be coated to exactly the same colour intensity. Some pellets appeared marginally darker in colour than others. Colour inhomogeneity was often observed in a batch of coated pellets indicating the existence of interpellet variability in colour. However, for individual pellets or intrapellet, the colour coat was usually found to be evenly coated and colour differences were not visually discerning. Thus, colour measurements for intrapellet and interpellet were needed in the study. It was reported that the human eye can perceive a difference in colour when there is a change in the colour corresponding to a value of $\Delta E > 1.5$ (Stark et al., 1996) which was the reason for not being able to determine the intrapellet colour

inhomogeneity by visual examinations. From the colour measurement, differences between the colour spots measured were clearly described by the ΔE_x and the corresponding $IH_{\Delta E}$ values (36.12, 4.12 for method III). With the help of the colorimeter, the surface colour on a pellet could be mapped out and the colour variation between spots could be described by $IH_{\Delta E}$.

3.2. Determination of population parameter

Base coated pellets were measured with the tristimulus colorimeter using method II before they were subjected to colour coating and their colour values are given in Table 1(a). The CIELAB colour values of colour coated pellets were given in Table 1(b). ΔE_i is calculated using the formula $\Delta E_i = [(L^*_o - L^*_i)^2 + (a^*_o - a^*_i)^2 + (b^*_o - b^*_i)^2]^{1/2}$ and chroma, C^* is calculated using the formula $C^* = \sqrt{(a^*_i)^2 + (b_i^*)^2}$. There was little variation in the colour of base coated pellets as shown by the very low standard deviations in Table 1(a). The range of ΔE_i values of base coated pellets before coating was as small as only 3.04. However, differences in the colour deposited on the pellets' surfaces were identified by colour measurement using a tristimulus colorimeter. The large ranges between the maximum and minimum CIELAB colour values in Table 1(b) differentiated the pellets after coating from those before coating. The high standard deviation of ΔE_i values of 7.61 illustrated the colour distribution on the pellets' surface.

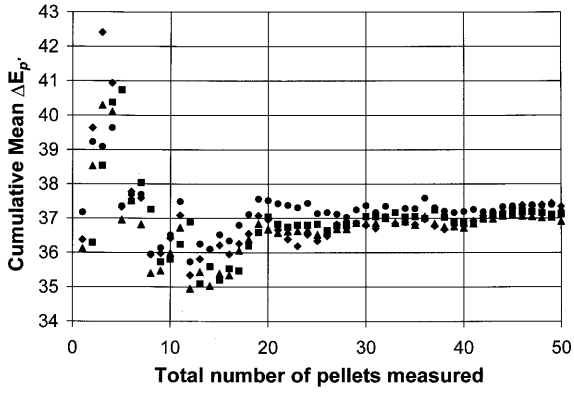

Fig. 3. Scatter plot of cumulative mean $\Delta E_{p'}$ values against total number of pellets measured by method I (●), method II (■), method III (▲) and method IV (◆). Population mean ΔE_p was found to be 37.20 for method I, 36.98 for method II, 36.91 for method III and 37.34 for method IV.

Table 1
CIELAB colour values of pellets (a) before coating and (b) after coating

	L^*	a^*	b^*	C^*	ΔE_i
(a) Before coating					
Mean	85.67	0.77	0.13	1.08	1.55
S.D.[a]	1.45	0.94	0.28	0.63	0.77
Maximum	88.82	2.45	0.73	2.48	3.27
Minimum	83.04	−0.77	−0.36	0.11	0.23
Range	5.78	3.22	1.09	2.37	3.04
(b) After coating[b]					
Mean	78.35	−2.07	35.90	35.99	36.75
S.D.[a]	2.41	1.11	7.78	7.72	7.61
Maximum	85.17	2.79	54.87	54.91	55.25
Minimum	67.57	−4.75	15.83	15.82	16.51
Range	17.60	7.54	39.24	39.09	38.74

[a] S.D., standard deviation.
[b] Greatest variability in ΔE_i values is observed at 0.75% w/w of coat deposited.

The ΔE_i values are values of the colour difference and provide a quantitative measure to describe the yellow coloration deposited on the surfaces of the pellets. However, a single ΔE_i value was insufficient to describe the colour of the entire population of pellets. Means of ΔE and their standard deviations were more reliable as predictors to describe the population of pellets (Matthew et al., 1990). ΔE_x value represented the normalised observed coloration around the circumference of a pellet (methods I–III) or over a sector on the pellet's surface (method IV). In this study, the differences in the colour distribution introduced on the pellets' surface by the various coating process should be determined and the colour distribution was denoted by the intrapellet colour variation, $IH_{\Delta E}$. The standard deviation of the ΔE_i values (intrapellet $IH_{\Delta E}$), which was equivalent to the spread of the ΔE_i values about the ΔE_x value, was found to represent this parameter. Thus, a higher intrapellet $IH_{\Delta E}$ indicated less homogeneous colour coats and lower uniformity in the colour coverage over the surfaces of the pellets. The results of the colour

analysis of the respective number of spots on 50 coated pellets are presented in Fig. 3. The cumulative mean $\Delta E_{p'}$ values obtained from 400 spots for methods I, II and IV and 1200 spots for method III were taken as the population means. The population mean ΔE_p was determined as 37.20 for method I, 36.98 for method II, 36.91 for method III and 37.34 for method IV.

The ΔE_i values obtained clearly indicated the development of a yellow coat around the pellet. In Fig. 3, the cumulative $\Delta E_{p'}$ values were found to approach the corresponding population mean ΔE_p values as the number of pellets measured increased. In all the four methods, the corresponding population value was obtained after measuring ~ 25 pellets, indicating that the minimum sample size representative of the population was 25 pellets. The 50 pellets measured in this study were therefore adequate and representative of the population.

3.3. Development of pellet sample holder

In method I, the highly spherical nonpareil pellets tend to roll, sometimes even off the stage when rotated by a pair of forceps and measurements of circumferential spots on the pellets were fraught with difficulties. The difficulties encountered with method I for determining spot colour measurements necessitated the design of a pellet sample holder (Fig. 1) to improve on the method of colour measurement for pellets. Initial design made use of a needle to pierce the pellet and rotating the needle in a clockwise direction from a marked point. However, it was found that the pellet was extremely difficult to be pierced with a needle because of its small size, 0.71–0.85 mm. Moreover, the pellets often either broke up into pieces or the coats were chipped off. The holder was re-designed with a vacuum attachment to hold the pellet and allowed it to turn in a full circle. The pellet sample holder was clamped onto the specimen stage of the tristimulus colorimeter. A pellet was placed at the tip of the black tube with the other end of the tube connected to a hollow metal rod attached to a vacuum line. Vacuum was applied to draw the pellet to the needle. The pellet was rotated through a defined sector about the horizontal axis by turning the alignment wheel with its center connected to the hollow metal rod. The alignment wheel had 24 grooves cut on the perimeter of the wheel held stationary by the locking rod in a groove of the wheel. The design of the sample holder allowed the measurement of colour on equidistant circumferential points on each of the pellet mounted.

The sample holder was designed such that other pellets of different shapes and sizes could be fitted at the end of the black tube by applying vacuum. The sample holder could rotate other pellets of different shapes and sizes about 360° to enable the surface colour to be measured. If the size of the pellets was so large that the base of the pellet touched the specimen stage, adjustments could be made with the hexagonal screws to lift the pellet above the stage. Thus, this method of colour measurement with the sample holder was also applicable to other pellets of different sizes and shapes. In terms of the time for measurements to be carried out, method II required only ~ 2 min to measure the colour of eight spots. For method I, almost double the time was required. Significant saving of measurement time was made when the sample holder was used for spot colour measurements of pellets. With the holder, the pellets were gently secured on the tip of the black tube by the vacuum and the pellets would not move whilst readings were taken. Hence, the colour could be measured with greater precision and the locations for measurement were also clearly designated when the pellet sample holder was used.

3.4. Effects of application of different methods for determination of colour uniformity on pellets

For comparative evaluation of colour coating in this study, the same 50 pellets were measured by the four different methods. The same 50 pellets for each of the four colour measurement methods were selected to ensure that colour measurements are made on the same set of pellets for comparison. By varying only one parameter, colour measurement methods, and keeping other parameters constant, a less biased study could be performed.

The population mean absolute colour, ΔE_p, on the pellets' surfaces differed slightly when differ-

Table 2
Mean interpellet CIE colour difference (ΔE_m) and corresponding interpellet colour inhomogeneity index, IH_m of 50 pellets measured

Method	ΔE_m, S.D.$_m$[a] (c.v.)[b]	IH_m, S.D.$_{IH}$[a] (c.v.)[b]
I	37.20, 5.95 (0.160)	4.05, 1.69 (0.423)
II	36.98, 5.80 (0.157)	4.72, 1.48 (0.315)
III	36.91, 5.75 (0.156)	4.43, 1.37 (0.311)
IV	37.34, 6.39 (0.171)	3.22, 1.29 (0.401)

[a] S.D., standard deviation.
[b] c.v., coefficient of variance.

ent methods were employed in the measurement. The ΔE_p value of the pellets was highest when the pellets were measured by method IV and the next higher ΔE_p value was from method I. The differences in ΔE_p values were, however, very small. The varying population ΔE_p values obtained suggested that the methods were probably not equally efficient and sensitive.

The pellets used for coating were sized and an average diameter of 0.78 mm was obtained. The corresponding mean circumference of 2.45 mm was calculated. Because each measurement spot was 0.3 mm in diameter, there was a maximum of eight possible measurement spots with no overlapping along the circumference of the pellet. In method II, eight non-overlapping spot colour measurements were obtained from each pellet. In methods III and IV, 24 and eight overlapping points respectively on the pellet circumference were measured. The results of non-overlapping and overlapping colour measurements were compared (Table 2). Methods II and III produced virtually similar results despite a three-fold increase in the number of measurements for method III. It is, therefore, concluded that since the measurement of more but overlapping points (method III) and non-overlapping points (method II) yielded similar results, it was suffice to measure only eight spots per pellet. For method IV, the ΔE_m value was similar to the ΔE_m values from other methods even though only one sector of the pellet's surface was measured.

The observed yellow coloration on the surface of each individual pellet is represented by ΔE_x value and the frequency of these ΔE_x values for 50 pellets measured by each of the four methods are plotted in the histograms shown in Fig. 4. The coloration on the pellets' surfaces ranged between ΔE_x values of 20–50 in all four methods. The histograms of ΔE_x values for methods I–III showed the similar trend. The modal class for ΔE_x value in methods I–III was 40.0–44.9. For

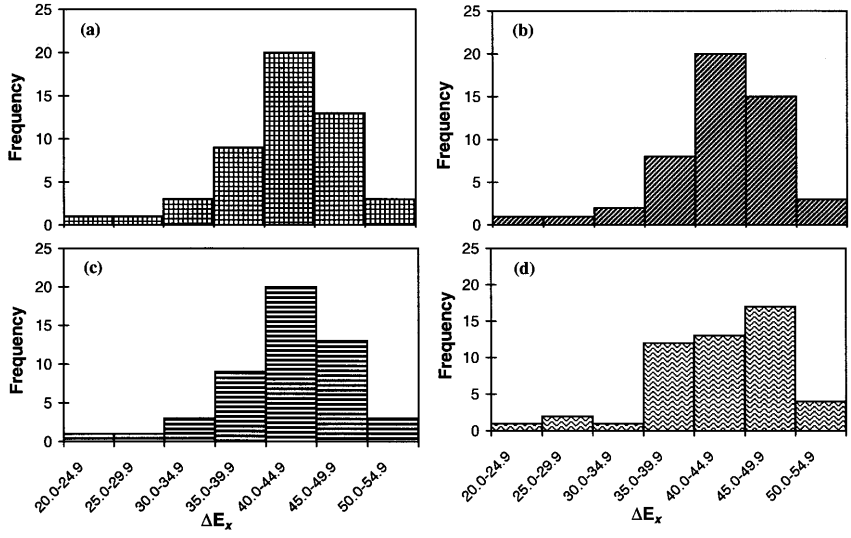

Fig. 4. Histograms of intrapellet ΔE_x values obtained by (a) method I (⊞), (b) method II (▨), (c) method III (⊟) and (d) method IV (⊠).

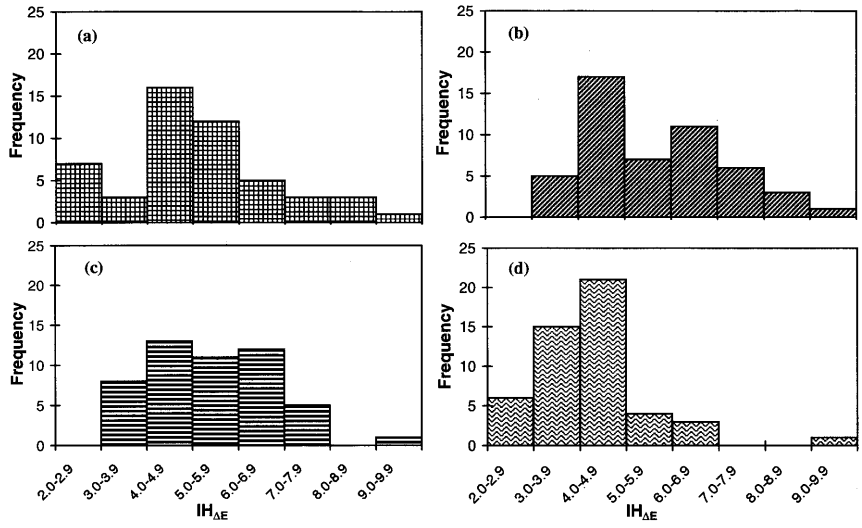

Fig. 5. Histograms of intrapellet IHΔE values obtained by (a) method I (⊞), (b) method II (▨), (c) method III (☰) and (d) method IV (▩).

method IV, the ΔE_x values appeared different from the rest of the methods and the histogram was skewed to the right. More pellets' surfaces (frequency) measured ΔE_x value in the range of 45.0–49.9 in method IV.

The uniformity of colour on a pellet's surface is denoted by $IH_{\Delta E}$ value and these $IH_{\Delta E}$ values are shown in Fig. 5. The histograms of the $IH_{\Delta E}$ values for the four methods appeared different. The $IH_{\Delta E}$ values from method I was spread wider and ranged between 2 and 9. A narrower range between 3 and 9 was obtained in method II. Although the range of $IH_{\Delta E}$ values in method III was from 3 to 9, there was no pellet measuring $IH_{\Delta E}$ value of 8.0–8.9. Similarly, there was no pellet measuring $IH_{\Delta E}$ values of 7.0–8.9 in the histogram for method IV and most pellets' surfaces measured smaller $IH_{\Delta E}$ values, causing the histogram to be skewed to the left. However, modal $IH_{\Delta E}$ value of 4.0–4.9 was common to all four methods.

The ΔE_m value was computed as the mean of the 50 ΔE_x values obtained in each method. The ΔE_m values can be approximated as the corresponding population mean ΔE values, ΔE_p (Table 2 and Fig. 3). The ΔE_x and $IH_{\Delta E}$ values obtained by the four methods for the same pellet were slightly different. For example, the ΔE_x and the corresponding $IH_{\Delta E}$ values for pellet 1 was 37.18, 5.42 by method I, 36.29, 4.13 by method II, 36.12, 4.12 by method III and 36.38, 2.69 by method IV. Similarly, there is disparity in the various ΔE_m and IH_m values (37.20, 4.05 by method I; 36.98, 4.72 by method II; 36.91, 4.43 by method III and 37.34, 3.22 by method IV from Table 2). The results further confirmed that all four methods were not equally efficient and sensitive in the measurement of colour homogeneity on a pellet's surface. Because the four methods yielded slightly different ΔE_m and $S.D._m$ values, the coefficient of variance was calculated. The coefficient of variance expressed the standard deviation in perspective relative to the magnitude of the mean value. A higher coefficient of variance indicated a greater variability in the measurement. The coefficients of variance of ΔE_m values measured by methods I–III were similar, except for the higher coefficient of variance of 0.171 when method IV was employed (Table 2).

A good method of colour measurement must be efficient and gives reliable, accurate and reproducible results. Colour on the pellets' surfaces could be easily determined by any of the four methods but these values were not good indicators for uniformity of coat deposited. The spread of ΔE_i values about ΔE_x values, which was calcu-

lated as the standard deviation, $IH_{\Delta E}$. The latter which is the intrapellet colour inhomogeneity index represented the observed colour homogeneity on each individual pellet are shown in Fig. 5. Generally, a much lower $IH_{\Delta E}$ index resulted when method IV which measured eight overlapping spots was employed. This was expected as an overlapping spot encompassed a colour zone from the preceding spot and part of this colour was reflected in the colour measurement of the next spot, resulting in smaller colour variation. Thus, the low $IH_{\Delta E}$ index was a clear indication of poor variability determination. The eight spot measurements obtained from only one-third of the total area around the circumference of a pellet seemed insufficient for the determination of colour homogeneity on a pellet's surface. Method IV was less reliable and less consistent in the collection of colour measurement indicators.

The mean of $IH_{\Delta E}$ values of the 50 pellets, referred to as the IH_m values, were calculated and given in Table 2. Greater $IH_{\Delta E}$ and IH_m values indicated the less homogeneous pellets' surfaces. Although the mean ΔE_m values measured using the four methods were similar, the spread of the colour on the coat around the pellet, IH_m values calculated from a total of 50 $IH_{\Delta E}$ values, were different. It is observed that method IV resulted in the lowest mean colour inhomogeneity index IH_m of 3.22 and method I gave the next lower IH_m of 4.05 (Table 2). However, the highest IH_m of 4.72 was obtained in method II. Similarly, among the four methods, the $IH_{\Delta E}$ values were lowest in method IV (Fig. 5). The lowest $IH_{\Delta E}$ and IH_m values obtained by method IV suggested the likelihood of repeated measurements from the same areas on the pellets. Statistical analysis of the IH_m values indicated a significant difference in the efficiencies of the four measurement methods (Table 3). The significant difference between the $IH_{\Delta E}$ and IH_m values was a clear indication of the different efficiencies and sensitivities of the methods of measurement ($P = 0.000004$). The IH_m values indicated that method II could detect the greatest inhomogeneity on the colour coat, followed by methods III and I. Method IV probably has the least discriminating power in the measurement of colour homogeneity on the pellets' surfaces. The next less efficient method to discriminate colour homogeneity is probably method I. Thus, $IH_{\Delta E}$ and IH_m values are more sensitive for determining colour distribution on pellets' coat.

Moreover, the $IH_{\Delta E}$ values obtained by method I were more widely distributed resulting in a higher standard deviation, $S.D._{IH}$ of 1.69 (Fig. 5). The $S.D._{IH}$ values obtained by methods II and III were significantly lower, at 1.48 and 1.37 respectively. Although the $S.D._{IH}$ value from method IV was the lowest (1.29), its IH_m value was lowest (3.22). This makes the comparison more complicated. Thus, the coefficients of variance were cal-

Table 3
A table of one-way analysis of variance (ANOVA) of intrapellet IHΔE values[a]

Groups	Count	Sum	Mean	Variance	S.D.	
Descriptive statistics						
Method I	50	202.49	4.05	2.85	1.69	
Method II	50	236.05	4.72	2.20	1.48	
Method III	50	221.41	4.43	1.87	1.37	
Method IV	50	160.77	3.22	1.65	1.29	
Source of variation	SS	df	MS	*F*	*P*-value	*F* crit
ANOVA						
Between groups	63.92	3	21.31	9.95	0.000004	2.65
Within groups	419.89	196	2.14			
Total	483.81	199				

[a] Dependent variable: $IH_{\Delta E}$; $\alpha = 0.05$.

Table 4
The values of mean interpellet CIE colour difference (ΔE_m) and corresponding interpellet colour inhomogeneity index, IH_m of another batch of coated pellets

Method	ΔE_m, S.D.$_m$[a] (c.v.)[b]	IH_m, S.D.$_{IH}$[a] (c.v.)[b]
I	36.50, 6.03 (0.165)	4.96, 2.52 (0.509)
II	36.75, 5.63 (0.153)	5.03, 2.30 (0.458)
III	36.51, 5.93 (0.162)	4.73, 2.06 (0.436)
IV	36.14, 7.64 (0.211)	2.99, 1.56 (0.523)

[a] S.D., standard deviation.
[b] c.v., coefficient of variance.

culated for the four methods. Method I has the highest value of 0.423, followed by method IV (0.401), method II (0.315) and lastly, method III (0.311). These values indicated that a larger error occurred when method I was employed. Judging from the high coefficient of variance, colour measurement performed with method I was least reproducible as the readings were very highly variable. Method IV could only measure very small area of colour distribution which is not representative of the overall surface colour. Thus, method IV is the next less reliable method for colour measurement. The IH_m value obtained by method II, which measured eight non-overlapping spots on one pellet, was higher than that by method III, which measured 24 overlapping spots on the same pellet. Their coefficients of variance were comparable. Thus, both methods II and III for pellet colour measurements are comparable.

The four methods were applied to measure colour on another batch of coated pellets and the results were tabulated in Table 4. A similar trend in the results obtained from the four methods was reproduced. A more reliable and efficient method was represented by low S.D.$_m$ and low coefficients of variance of ΔE_m and IH_m values. There were slight differences in the ΔE_m values with method II yielding the highest value (36.75) with lowest variability (S.D.$_m = 5.63$; c.v. $= 0.153$) in the colour measurement. The highest coefficients of variance of the ΔE_m (0.211) and IH_m (0.523) values again confirmed that method IV was inefficient in measurement of colour distribution on pellets. Method I was concluded as the next less reproducible method of colour measurement because the next higher coefficients of variance (c.v. of $\Delta E_m = 0.165$, c.v. of $IH_m = 0.509$) resulted. The uniformity of coat deposited was predominantly shown by the highest IH_m value of 5.03 in method II even though the colour measurements were performed on the same population of pellets. Results from method II consistently suggested a greater degree of the colour distribution on the pellets' surfaces.

In the measurement of colour, it is most productive if more measurements are made on each pellet mounted on the sample holder. Thus, intrapellet measurements are made and are readily available for analysis. It is not productive to determine just interpellet measurements by measuring single colour spot on each pellet. Since the interpellet measurements in this study were calculated from the intrapellet measurements, the similar tendency between their results was expected. By analysing the intrapellet measurements, the best method for colour measurement was determined. The interpellet measurements were required to further strengthen these results by calculating the coefficient of variance.

It should be recalled that the pellet in method I was directly placed on the specimen stage, without any support. During the coating process, pellets in the fluidised bed coater underwent considerable amount of collisions and these collisions contributed to some degree of deformation of the pellets. Thus, many pellets would not be perfectly spherical. When the pellet was turned by a pair of forceps, it normally rested on its most stable base, usually the deformed area, exposing the apices for measurement. There was some tendency to remeasure the same areas as turning of pellets by forceps was arbitrary. A pellet, being spherical tend to roll away to its most stable base after being turned. As the pellets often rolled, the exact location for a subsequent measurement cannot be pre-determined. It may be necessary that the pellets should not be used again since the spot for next measurement on the pellet could not be easily defined. The use of a pair of forceps to turn the pellet round was rather time-consuming and tedious, requiring much practice and a steady hand. On the contrary, the pellet sample holder firmly secured the pellet on the tip of the black

tube by the vacuum applied, thus, enabling the precise circumferential position on the pellet to be measured. Therefore, more accurate measurement of the distribution of the colour on the pellet surfaces could be obtained when method II was used. This device is also very useful in the colour measurement of other pellets of different shapes and sizes.

In colour measurements on the surfaces of coloured pellets, the sphericity, size and smoothness of pellets can be expected to affect the measurement of colour. It can be predicted that the colour measurement values may change under different physical conditions of the pellet surfaces. However, the variability of colour differences, unlike the actual colour measurement itself, would depend more on variability in colour development. Irrespective of the actual colour value, the pattern for variability in colour development would be expected to be similar and comparisons may be made between batches coated under different coating conditions. Thus, the same pattern in colour variability would be expected if another colour, for example Sicovit Red, was used instead. The quantitative values may differ but the relative trends would remain. This allows the application of the same method of colour measurement on pellets when other colour pigments are used. However, it is obvious that the colour pigments used should be sufficiently distinguishing from the colour of the uncoated pellets. The number of colour measurements need to be increased for surfaces where the differences in colour between the pigments and the substrate surfaces is reduced.

4. Conclusion

In this study, the minimum sample size to give rise to a representative of the population mean ΔE_p value was found to be 25 spherical pellets. It was concluded that measuring only eight non-overlapping spots per pellet was sufficient as the results from method II (eight non-overlapping spots) and method III (24 overlapping spots) were similar. A more efficient, sensitive and reliable method of colour measurement of pellets' surfaces is obtained with the use of a specially designed pellet sample holder. The sample holder provides good control of pellet rotation so that the exact spot of colour can be determined. This improved method allows precise measurement of homogeneity of colour deposited on pellets' surfaces. Reproducible colour measurement results were obtained with another batch of coloured pellets measured. Method II was found to be the most efficient and sensitive method for measuring the colour distribution on pellets' surfaces. Since Method II is more reliable and the results are more reproducible, it is suggested as the method of choice when colour measurement of pellets is required in pharmaceutical manufacturing.

Appendix A. Symbols

C^*, chroma

$$C^* = \sqrt{(a_i^*)^2 + (b_i^*)^2}$$

ΔE_i, colour-difference value for each measurement

$$\Delta E_i = [(L_o^* - L_i^*)^2 + (a_o^* - a_i^*)^2 + (b_o^* - b_i^*)^2]^{1/2}$$

ΔE_x, average coloration on a pellet's surface i.e. mean of eight ΔE_i values (methods I, II and IV) or 24 ΔE_i values (method III)

$$\Delta E_x = \frac{1}{8}\sum^{n=8}\Delta E_i \quad \text{(methods I, II and IV)}$$

$$\Delta E_x = \frac{1}{24}\sum^{n=24}\Delta E_i \quad \text{(method III)}$$

$IH_{\Delta E}$, intrapellet colour variation or colour inhomogeneity index

$$IH_{\Delta E} = \sqrt{\frac{\sum(\Delta E_i - \Delta E_x)^2}{8-1}}$$

(methods I, II and IV)

$$IH_{\Delta E} = \sqrt{\frac{\sum(\Delta E_i - \Delta E_x)^2}{24-1}} \quad \text{(method III)}$$

$\Delta E_{p'}$, cumulative mean colour-difference value

$$\Delta E_{p'} = \frac{1}{n}\sum_{i=1}^{n}\Delta E_i$$

where $1 \leq n \leq 400$ for methods I, II and IV and $1 \leq n \leq 1200$ for method III.

ΔE_p, population mean colour-difference value

$$\Delta E_p = \frac{1}{400}\sum^{n=400}\Delta E_i \quad \text{(methods I, II and IV)}$$

$$\Delta E_p = \frac{1}{1200}\sum^{n=1200}\Delta E_i \quad \text{(method III)}$$

ΔE_m, mean of ΔE_x values of 50 pellets (interpellet average coloration)

$$\Delta E_m = \frac{1}{50}\sum^{n=50}\Delta E_x$$

S.D.$_m$, standard deviation of ΔE_x values of 50 pellets

$$\text{S.D.}_m = \sqrt{\frac{\sum(\Delta E_x - \Delta E_m)^2}{50-1}}$$

IH_m, mean of $IH_{\Delta E}$ of the 50 pellets (interpellet colour uniformity)

$$IH_m = \frac{1}{50}\sum^{n=50} IH_{\Delta E}$$

S.D.$_{IH}$, standard deviation of $IH_{\Delta E}$ of the 50 pellets

$$\text{S.D.}_{IH} = \sqrt{\frac{\sum(IH_{\Delta E} - IH_m)^2}{50-1}}$$

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