DRUG DEVELOPMENT COMMUNICATIONS, 1(4), 303-329 (1974-1975)

THE USE OF A MICRO REFLECTANCE PHOTOMETER TO MEASURE THE COLOUR UNIFORMITY AND GLOSS OF TABLETS[1]

B. A. Matthews, S. Matsumoto and M. Shibata
Pharmaceutical Development Department, CIBA-GEIGY (Japan) Limited, P. O. Box 1, Takarazuka, Japan

ABSTRACT

The use of a microscope photometer to measure the colour uniformity and gloss of tablets is described. The influence of processing variables and type of dye on the colour uniformity is reported and the use of the instrument to optimize the polishing of coated tablets is also discussed.

1. INTRODUCTION

Most large pharmaceutical manufacturing houses have such a wide range of tableted drugs, each in several strengths, that product identification is a major

problem. It is usually achieved by a combination of different sizes, colours and product codes, colour being probably the most important distinguishing factor. Since most active substances and excipients are white, the colouring of tablets is often a difficult problem. A recent article[2] defines colour uniformity as one of several parameters which must be maximized in a new tablet formulation but offers only the advice to "blend carefully".

The colouring of tablets is achieved in two main ways:-

(a) By distributing the dye throughout the granule mixture before compression.

(b) By adding the colour to a coating which is applied to the tablet surface.

The problems encountered in method (a) are essentially similar to those in achieving content uniformity, except that the quantity of colour is often smaller than even that of a quite potent drug. Although ununiformity within a tablet is likely also to be accompanied by between tablet ununiformity, the former is evidently important in the case of a colour but unimportant with an active substance. Colour ununiformity is also likely to be associated with drug content ununiformity in the minds of sensitive consumers, apart from the poor aesthetic appeal of badly mottled tablets.

Even if a uniformly coloured mass can be obtained during moist granulation, the drying of the granules

can result in colour ununiformity, as a result of the migration of the dye[3]. Lakes are usually considered superior to soluble dyes in preventing this phenomenon.

In order to maximize the colour uniformity of a tablet, a suitable method is necessary to measure this parameter. Methods currently available for measuring tablet colour[4] usually measure either the whole tablet or a large area of the surface. In one paper[5] the authors had to mount several tablets side by side in order to fill completely the beam of the spectrophotometer. These methods are only effective for comparing between tablet variations. Armstrong and March[6] reported a method in which the tablet is photographed and the negative scanned with a microdensitometer. In the present paper, we describe a direct method in which the surface of the tablet is scanned and variations of the colour in different parts are measured using the Kubelka-Munk tristimulus values[7].

2. MATERIALS AND METHODS

Three tablet formulations were examined, a sucrose based lozenge containing either a lake or soluble dye and a starch/lactose formulation.

2.1 Sucrose-based Lozenge Type

The formulations are given in Table I.

These formulations were manufactured by moist granulation and by fluidized bed granulation as follows:-

The moist granulation method (Batch Size 40 kg) is ,wn in Table II.

TABLE I

Ingredients	1 tablet	1 tablet
Sucrose J.P. VIII	951.94 mg	951.40 mg
Karaya gum U.S.N.F. XI	35.00 mg	35.00 mg
Tragacanth J.P. VIII	9.00 mg	9.00 mg
Red No.3	0.06 mg (soluble dye[8])	0.60 mg (lake dye[8])
Magnesium stearate J.P. VIII	4.00 mg	4.00 mg
	1,000.00 mg	1,000.00 mg

TABLE II

Process	Equipment	Methods
Milling	Pulverizer Hosokawa[9] AP-1SH	(Sugar) 1.2 mm screen 9600 rpm
Mixing	Hata[10] kneader HN-2A 23 rpm then 16 rpm	38.1 kg milled sugar) 1.4 kg karaya gum) 0.36 kg tragacanth) for 10 minutes
Kneading	Hata kneader HN-2A 23 rpm then 16 rpm	1.28 l deionized water) 2.72 l 95% ethanol) 0.0024 kg Red No.3) dissolved and added to the mixture
Moist Granulation	Fitz mill[9] Hosokawa FM-1	with 6 mm screen approx. 1200 rpm
Drying	Fluidized bed dryer Palmer Research Laboratory[11] FBD/L72	at 60°C for 30 minutes
Dry Granulation	Hata[10] granulator HRG-3V	with 1.2 mm mesh
Lubrication	Turbula[12] mixer T2A	for 5 minutes (add 0.4% magnesium stearate)
Compression	Rotary tablet machine Hata[10] P-18	approx. 4 ton/tab 5 rpm weight 1000 mg diameter 16 mm height 3.8 mm

For fluidized bed granulation, milling, dry granulation, lubrication and compression were as before. Granulation was performed in a Glatt-Okawara[13] WSG-15 using the conditions given in Tables III, IV and V.

TABLE III

Conditions (Soluble Dye and Lake)			
Quantity of powder mixture	15 kg	Position of air cap	3
Temperature of spray liquid	27°C	Diameter of orifice	1.2 mm ϕ
Spray comsumption	0.15 kg/min	Position of spray gun	7

Spray Liquid	Soluble Dye	Lake Dye
Red No.3	0.9 g	8.92 g
Deionized water	1.5 l	1.5 l

TABLE IV

Process (Soluble Dye)

Time Minutes	Process	Inlet Air °C	Outlet Air °C	Inlet Damper Setting	Outlet Damper Setting
5	Mixing	60	29-34	5	3
10	Spraying	60	34-29	5	3
35	Drying	60	29-49	5	3

Shaking interval: 2 mins. Pump speed for: 10 r.p.m. spray

Shaking time : 5 secs. Spray pressure: 2.5 kg/cm^2

TABLE V

Process (Lake Dye)

Time Minutes	Process	Inlet Air °C	Outlet Air °C	Inlet Damper Setting	Outlet Damper Setting
5	Mixing	43-40	26-30	5	3
13	Spraying	40-48	30-24	5	3
39	Drying	48-55	24-43	5	3

Shaking interval: 2 mins. Pump speed for: 12 r.p.m. spray

Shaking time : 5 secs. Spray pressure: 2.5 kg/cm^2

2.2 Starch/Lactose Tablets

The formulation is given in Table VI.

This formulation was made by moist granulation as shown in Table VII.

TABLE VI

Ingredients	1 tablet
Lactose, impalpable J.P. VIII	90.00 mg
Corn starch J.P. VIII	89.49 mg
Aerosil-200 J.P. VIII	10.00 mg
Talc J.P. VIII	10.00 mg
Magnesium stearate J.P. VIII	0.50 mg
Blue No.2[8] (soluble)	0.01 mg

TABLE VII

Process	Equipment	Method
Milling	Fitz mill Hosokawa FM-1	(Lactose imp.) High speed (approx. 4000 rpm)
Mixing	Hata kneader HN-2A 23 rpm then 16 rpm	18.0 kg lactose imp.) 16.4 kg corn starch) 2.0 kg aerosil-200) for 10 minutes
Kneading	Hata kneader	1.2 l 95% ethanol) 9.2 l deionized water) 0.002 kg Blue No.2) dissolved and added to the mixture
Moist Granulation	Fitz mill	with 4 mm screen approx. 1200 rpm
Drying	Fluidized bed dryer Palmer Research Laboratories FBD/L72	at 50°C for 30 minutes
Dry Granulation	Sieve	1.0 mm mesh (by hand)
Lubrication	Turbula mixer T2A	for 5 minutes 364 g dried granulate 20 g talc 15 g corn starch 1 g Mg. stearate
Compression	Rotary tablet machine RT-3A	20 rpm diameter 8 mm round radius of curvature 18 mm weight 200 mg

2.3 Sugar Coated Tablets

For the gloss measurement trial, starch/lactose tablets were compressed to a diameter of 7 mm, (radius of curvature 5 mm), weight 140 mg and coated with the composition given in Table VIII.

TABLE VIII

Ingredients	1 tablet
Shellac J.P. VIII	2 mg
Glyceryl monostearate J.P. VIII	0.4 mg
Castor oil J.P. VIII	0.6 mg
Sucrose J.P. VIII	75 mg
Acacia J.P. VIII	5 mg
Talc J.P. VIII	27 mg
Red No.3 (soluble dye)	0.02 mg

They were polised in a Hata HCP-120 80 cm cloth pan using a shellac solution with the following composition

Shellac 50% solution 20 g (Quantity 160 ml per
Ethanol 99% 180 g 71.5 kg of tablets)

and then by Carnauba wax powder[14] (12 g + 8 g per 71.5 kg of tablets).

2.4 Measurement of Colour Uniformity

The apparatus used was the Micro-Multi Photometer[15] (Fig. 1) which consists of a tristimulus colourimeter, the photocell of which is incorporated into the optical system of a microscope. In collaboration with the manufacturer, the microscope stage was motorised to enable the surface of a flat tablet to be scanned at constant speed (see Fig. 2). Since many tablets have convex surfaces, a special holder was designed (Fig. 3) to rotate the tablet so that the microscope objective was

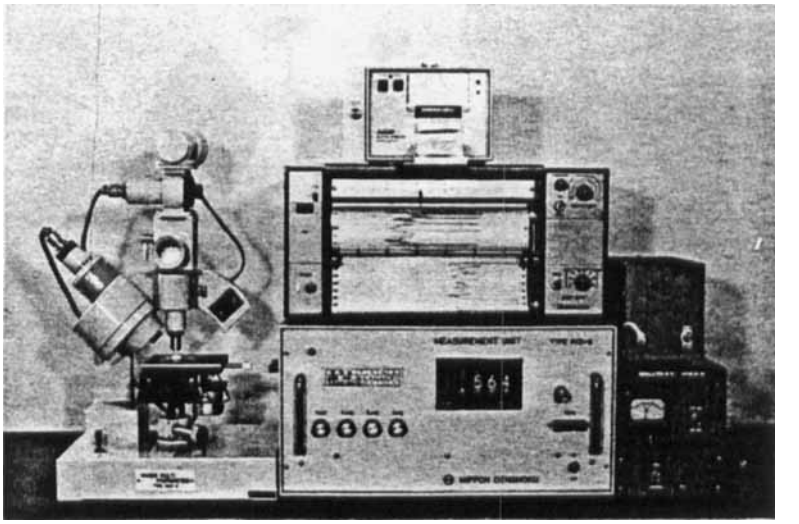


FIGURE 1

General View of Nippon Denshoku Micro Multi Photometer, including Strip Chart Recorder and Digital Printer

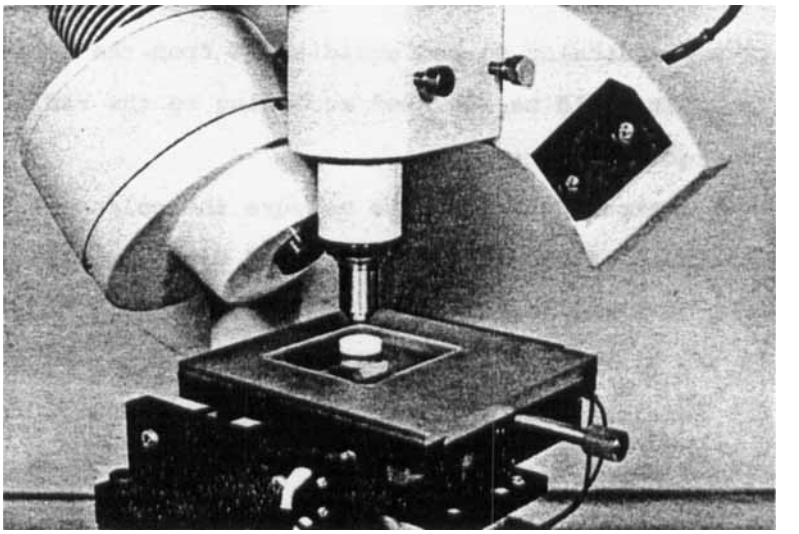


FIGURE 2

Close-up View of the Stage for Flat Tablets

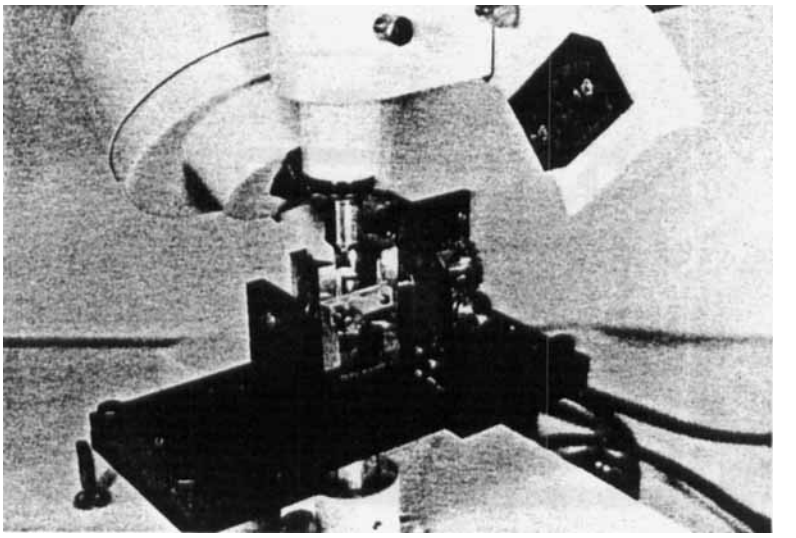


FIGURE 3

Close-up View of the Stage for Convex Tablets showing Motor Drive and Adjustment Screw for Tablet Radius of Curvature

always perpendicular to and equidistant from the tablet surface. It could be adjusted according to the radius of curvature of the tablets.

The instrument is able to measure the colour of a circular area of the tablet surface of diameter ranging from 0.1 to 2 mm, according to the slit setting. Although the X, Y and Z tristimulus values can be computed, for routine determination of colour uniformity, the

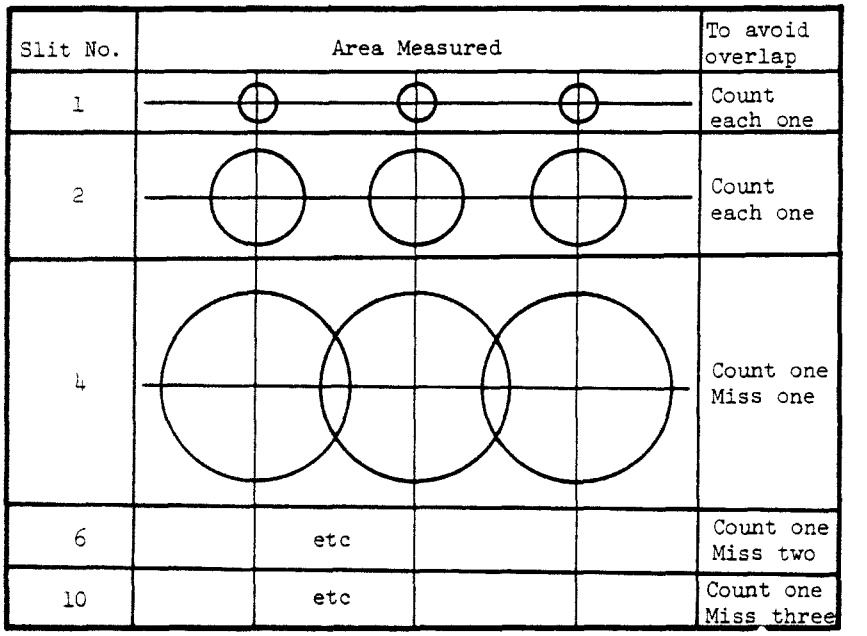
luminosity function, y of the three weighting functions, x, y and Z was measured. Since colour ununiformity in a tablet is likely to result from uneven distribution of white and coloured particles, the y function, which reflects[16] the sensitivity of normal observers to lightness and darkness was considered most appropriate. The following standard method was developed.

The tablet was placed on the appropriate stage and the latter adjusted as necessary. Since it was felt that the method should certainly evaluate any visually obvious ununiformity, the tablet was scanned by eye and so arranged that the first scan would cross the area with greatest ununiformity. The tablet was then scanned at right angles to the first scan.

In its original construction, the flat stage moved at a constant speed of 1 cm in 19 secs. and the instrument recorded two readings per second. Figure 4 shows a diagrammatic representation of the area measured at each time according to the slit setting. With slit settings of 4 and over, there was overlap if each reading was taken, so some readings were ignored to avoid this problem. The method is indicated on Fig. 4.

For convex tablets, the stage moved at a constant angle of rotation, but the distance scanned per unit time varied with the radius of curvature. The data are given in Table IX.

For routine measurements of colour uniformity 50 non-overlapping readings were taken at the first scan



Scale 1 cm = 0.13 mm

FIGURE 4

Diagramatic Representation of the Measurement Area at Different Slit Numbers

and then 50 at right angles. Ten tablets were measured and the coefficient of variation of the 1000 readings was used as an index of uniformity.

The data were recorded continuously on a strip-chart recorder[17] and printed by means of a digital printer[18].

2.5 Measurement of Gloss

In its normal operating method, the Micro Multi Photometer measured the light reflected at the usual[19] angle of 45° to the incident. It is possible to measure the light reflected at 90° and use the value as an

TABLE IX

The Speed of Scan of the Surface of a Convex Tablet as a Function of its Radius of Curvature

Radius (mm)	Speed (mm/min)
5.0	3.1
6.0	3.8
7.0	4.4
8.0	5.0
9.0	5.6
10.0	6.3
11.0	6.9
12.0	7.5
13.0	8.2
14.0	8.8
15.0	9.4
16.0	10.0
17.0	10.7
18.0	11.3
19.0	11.9
20.0	12.6

Speed of scan of flat sample = 13.6 mm/min

index of the surface gloss. Although for gloss measurements the sample should be flat, the area measured is so small that the curvature can be neglected. Care

must, however, be taken in comparing samples with different degrees of convexity. The instrument is readily adapted to the mode for gloss measurement by changing the position of the microscope as shown in Fig. 5. The measured light was found to depend strongly on the positioning of the sample. The tablets were located as correctly as possible by eye and then their position varied in every direction until the maximum reading was obtained. This value was used as the gloss index, with the instrument measuring the y value as before.

3. RESULTS AND DISCUSSION

3.1 Measurement of Sensitivity

The visual awareness of colour uniformity is dependent on both the colour of the sample[6] and the size and number of any areas of different colour. In order to test the sensitivity of the method, a uniformly mottled surface was sought and the coloured rectangles in the Methuen "Handbook of Colour" were chosen[20]. These appear uniformly coloured but when viewed under the microscope are seen to consist of circular coloured dots on a white or grey background. Fig. 6 shows a microscope picture of rectangle number 13 3A from this book. The dots are approximately 120 μm in diameter.

When measured using the instrument with slit No.1, the trace shown in Fig. 7 was observed. The total num-

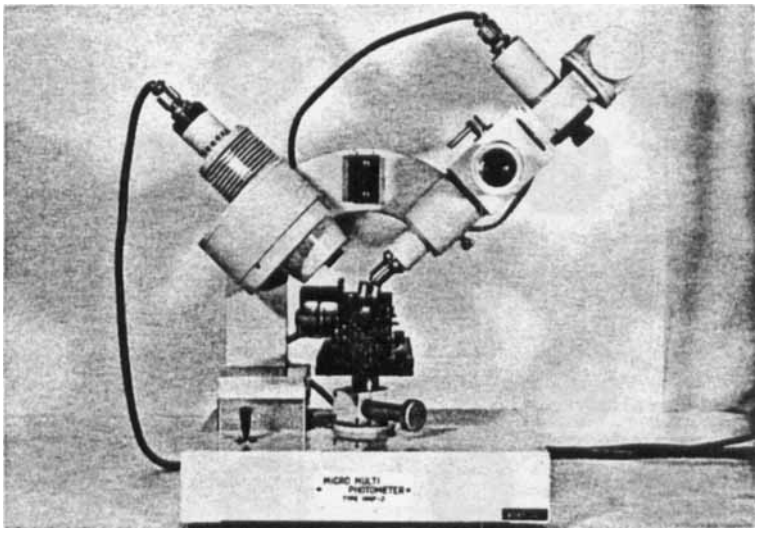


FIGURE 5

Micro Multi Photometer in its Gloss Measurement Mode

ber of cycles recorded on the trace is equal to the number of spots across the rectangle. For comparison, the trace of a uniformly white sample is shown in Fig. 8. Since the instrument was capable of detecting the variations between red dots of diameter 120 μm and the white background, even though the whole rectangle appears uniformly coloured to the naked eye, it was felt that it should be more than adequately sensitive to measure the colour uniformity of tablets.

3.2 Measurement of Standard Mottled Tablets

Granulations were prepared from Formulation 2.1.1 with and without soluble dye and in the former case, mixing was continued for longer than usual to assure

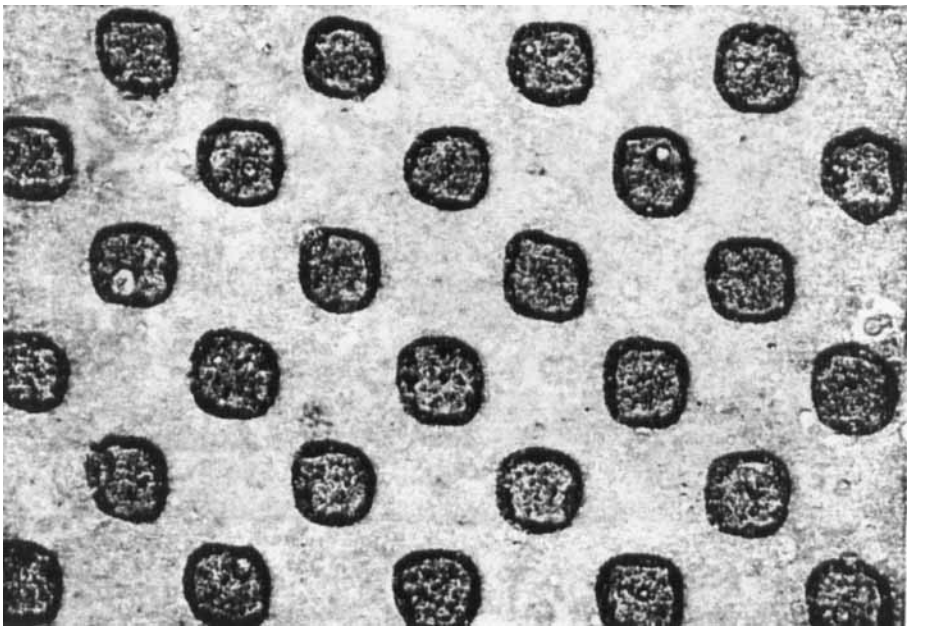


FIGURE 6

Microscope photgraph of Rectangle 13 3A in the Methuen "Handbook of Colour"

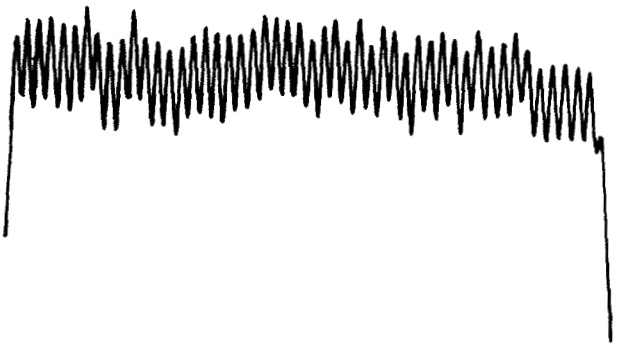


FIGURE 7

Instrument Trace of Rectangle in Figure 6

FIGURE 8

Instrument Trace of a White Plate

that the samples were as uniform as possible. The two batches of granules were fractionated into size ranges 2 mm - 1 mm, 1 mm - 0.5 mm, 0.5 mm - 250 µm, 250 µm - 125 µm, 125 µm - 63 µm and < 63 µm. They were each mixed together in three different proportions, Red 100%, Red 95% + White 5% and Red 50% + White 50%. Tablets were compressed as in 2.1.2 and the colour uniformity measured. The results are shown in Table X.

TABLE X

The Effect of Granule Diameter on the Colour Uniformity of Mottled Tablets

Granule Diameter (µm) / Granule Colour and Proportion	2000 - 1000	1000 - 500	500 - 250	250 - 125	125 - 63	< 63
Red 100%	3.3	2.9	3.8	3.5	3.6	1.4
Red 95% White 5%	8.8	6.1	3.9	3.3	2.5	1.8
Red 50% White 50%	11.5	9.4	7.1	4.9	2.8	2.2
Colour Uniformity	Coefficient of Variation (%)					

In the case of the 50% red 50% white tablets, there is a progressive increase in uniformity (coefficient of variation falls from 11.5 to 2.2%) with de-

creasing particle size and in the case of the 95% red, from 8.8% to 1.8%. The 100% red samples show, as expected, almost no change in uniformity with decreasing particle size until there was a big reduction in the case of the finest powders. Here the granule size was smaller than the measurement area.

3.3 Effect of Measurement Area on Colour Uniformity Values

All of the above results were obtained with the smallest instrument measurement slit. In order to investigate the influence of measured area on the results, the same sample (50% red 50% white, 250 - 500 μm fraction) was measured with different slits. In order not to measure the same area twice, only non-overlapping data were selected and the number of results was, therefore, smaller in the case of the larger slit numbers. The results are shown in Table XI. The coefficient of variation decreases with increasing measurement area, since colour ununiformities are effectively "ironed out" by taking an average value of a larger area.

3.4 Effect of Mixing Time on Colour Uniformity

One of the main problems in designing a new formulation and defining optimum processing conditions is to decide how long to mix a granulation. The main aim is a satisfactory content uniformity and methods of assessing this parameter are widely known and official in

TABLE XI

The Influence of Measurement Area on the Colour Uniformity

Micro Multi Photometer Slit Number	Area Measured (mm^2)	Number of Samples	Colour Uniformity (Coefficient of Variation %)
1	0.008	1000	7.1
2	0.031	1000	6.1
4	0.126	500	5.1
6	0.283	330	5.0
10	0.785	250	4.4

the U.S.P. It was felt that the measurement of colour uniformity could also be used to define the best mixing time and conditions. A batch of formulation 2.1.1 was made by moist granulation and 500 g samples removed at the kneading stage, at intervals up to 30 minutes. The granule samples were processed in the usual way, compressed and tablet uniformity was measured. The results are shown in Fig. 9. Optimum mixing time was found to be 20 minutes. The same granulation was prepared using fluidized bed granulation and with lake and soluble versions of the same dye. These results are presented as bars on the same figure and indicate greater uniformity with the soluble dye than with the lake. The W.S.G. method also appeared to give better

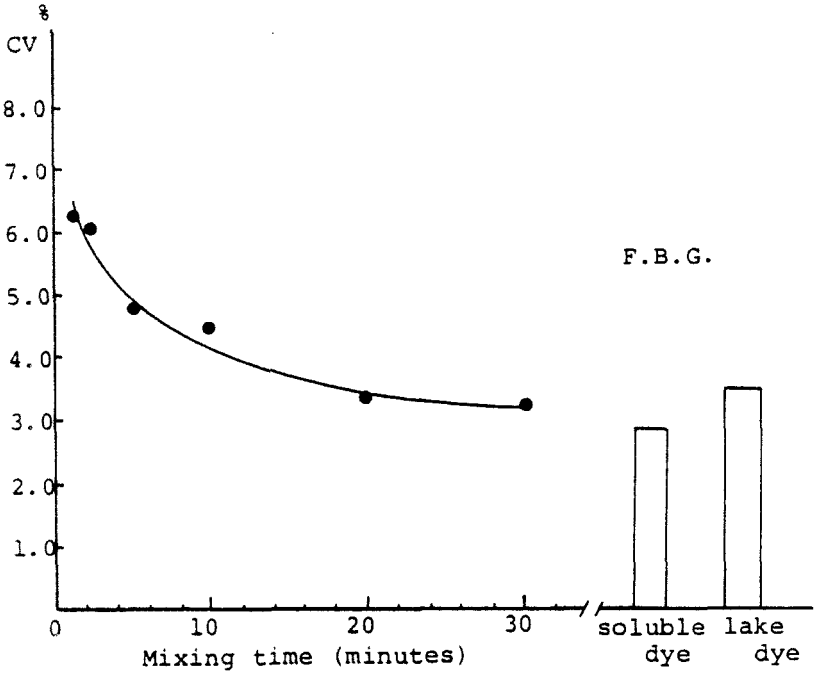


FIGURE 9

Colour Uniformity (as C.V.) as a function of Mixing Time for the Manufacture of Formulation 2.1 by Moist Granulation. (Bars show the same Product made by Fluidized Bed Granulation)

results than with the kneading method. This might be due to the fact that since the mass never becomes really wet in the fluidized bed, the possibilities for dye migration on drying are less.

The starch/lactose formulation 2.2 was also manufactured in the same way and samples removed as before. The colour uniformity again reaches a maximum after 20 minutes' mixing. (Fig. 10).

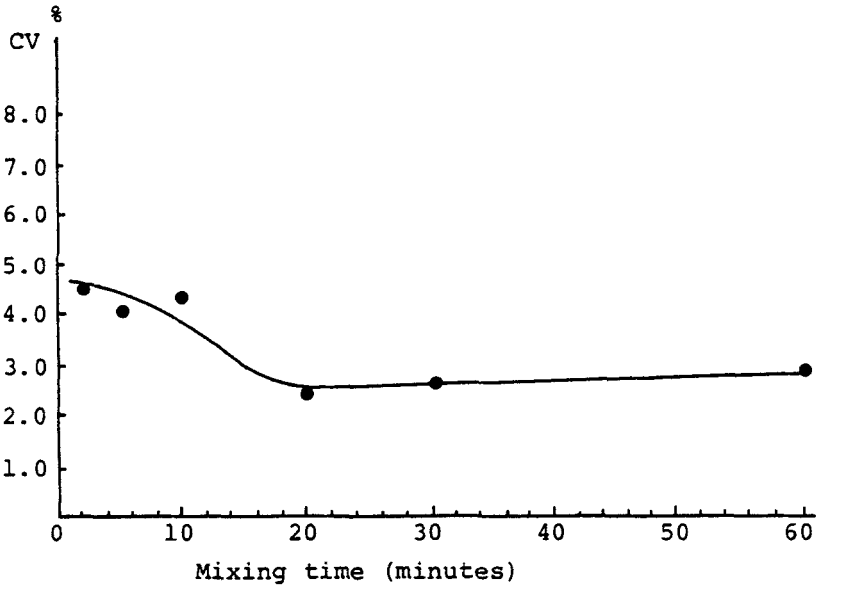


FIGURE 10

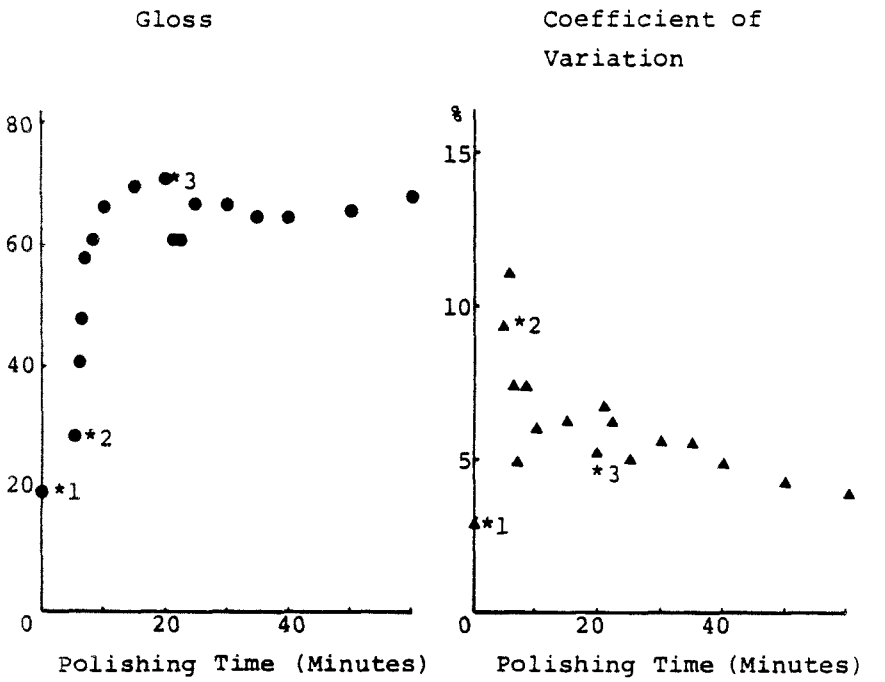
Colour Uniformity (as C.V.) as a function of Mixing Time for the Manufacture of Formulation 2.2 by Moist Granulation

3.5 The Use of Gloss Measurement to Determine Optimum Polishing Times

Polishing is usually the final step in the sugar coating process and somethimes special pans are used for this purpose. The aim is to give a maximum shine to the tablets but, hiterto, the optimum time for polishing has been assessed subjectively. It is evidently uneconomical to polish tablets for longer than necessary and it is also possible that too long tumbling will result in abrasion and loss of gloss.

The coated tablets (formulation 2.1.3) were polished according to the method given and the gloss value measured at various stages. The results are shown in Fig. 11.

They indicate a progressive increase in gloss after addition of the shellac solution and the first portion of wax until a maximum value after 20 minutes. Addition of more wax results in a subsequent drop in gloss value but it climbs again almost to its original value.



*1 Addition of Shellac Solution
*2 First Addition of Wax
*3 Second Addition of Wax

FIGURE 11

Tablet Gloss of Sugar Coated Tablets as a function of Polishing Time

The between tablet coefficient of variation of gloss value falls progressively indicating a gradual spread of the polish and these results also indicate 20 minutes as the optimum time. Since gloss can decrease during storage, it would be important to select the best method for polishing using tablets which had been subjected to stability testing, as well as those freshly polished.

4. GENERAL DISCUSSION

The evaluation of dosage form quality has now progressed to a point where many of the variables likely to affect the performance of the product can be controlled and a uniformly high quality can be achieved. Although the organoleptic properties are less important therapeutically, they represent a significant factor in consumer acceptance. This is particularly so in Japan where great attention is paid to beauty and aesthetics in all aspects of human life. A tablet which is faded or speckled is likely to be considered to have poor stability of the active substance and to have been prepared carelessly. It is therefore a subsidiary, although important task of the formulator to assess his new product in this context and the methods described above provide convenient and sensitive techniques for measuring colour uniformity and gloss. It would be

possible to use these methods to establish standards for a new product and then to evaluate routine production batches and to compare output from different factories. The techniques described would also enable a quantitative assessment of excipient and manufacturing changes and, in the opinion of the authors, provide significant contribution to product quality.

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