Quantitative Assessment of Factors Contributing to Mottling of Colored Tablets I: Manufacturing Variables

N. A. ARMSTRONG ˣ and G. A. MARCH *

Abstract □ By using a recently developed method for quantifying the degree of mottling of colored tablets, the effects of manufacturing variables such as the method and temperature of granule drying, granule size, and compaction pressure were investigated. Tablets of dibasic calcium phosphate colored with FD&C Blue No. 1 dye were used. Drying temperature had little effect, but the method of granule drying, granule size, and compaction pressure were major influences on mottling. Mechanisms to explain these results, based on the migration of dye during the drying process, are proposed.

Keyphrases □ Mottling—colored tablets, effects of method and temperature of granule drying, granule size, compaction pressure □ Calcium phosphate, dibasic—colored tablets, degree of mottling, effects of method and temperature of granule drying, granule size, compaction pressure □ Tablets, colored—degree of mottling, effects of method and temperature of granule drying, granule size, compaction pressure

Mottling, defined (1) as: "An unequal distribution of color on the surface of a tablet, with light or dark areas standing out in an otherwise uniform surface," has long constituted a problem to tablet manufacturers. It is now well established that mottling in tablets containing colored substrates is caused by the migration of dyes with the granulating fluid during drying. In the case of fluid-bed-dried granulations, this process results in the interior of the granule being deficient in coloring material while the dye is concentrated at the periphery. When, on subsequent comminution or compression, granule fragmentation occurs, the color deficiencies are exposed on the surface of the tablet.

King (2) surveyed the methods that have been suggested to reduce mottling. A critical review of these methods shows that many are vague in nature, with little or no experimental justification, and none is supported by quantitative evidence that mottling is reduced. However, a photographic method of quantitatively assessing mottling was published recently (3), and this technique has permitted a more critical approach to the problem of reducing mottling to an acceptable level.

EXPERIMENTAL

Tablet Preparation—Full details of the preparation of dibasic calcium phosphate tablets colored with FD&C Blue No. 1 were given elsewhere (3). Each tablet weighed 660 mg and, apart from tablets used in compaction pressure studies, each had a thickness of 4.00 mm.

The force exerted by the upper punch of the tablet press was measured with strain gauges using a technique similar to that described by Shotton and Ganderton (4).

Measurement of Tablet Mottling—Tablets were photographed under standard conditions, and the variation in optical density across the negative image of the tablet was measured using a microdensitometer[1]. Quantitation of this variation was made by the method of Armstrong and March (3), and the results are expressed in "mottling units."

RESULTS AND DISCUSSION

Effects of Granule Size and Method of Drying—At an early stage in the current investigation, it was noted that the size of the granules from which the tablets were prepared had an influence on the resultant color uniformity of the tablet. Furthermore, Scott *et al.* (5) drew attention to the fact that tablets prepared from granules dried in a fluid bed drier are less mottled than tablets prepared from granules of the same composition but subject to tray drying.

Figure 1 shows that for both methods of drying, the degree of tablet mottling was decreased as the granule size was reduced. In the case of fluid-bed-dried granules, tablets of acceptable color uniformity could be produced from granules of less than 0.48-mm diameter. In contrast, tablets prepared from tray-dried granules of the same size were severely mottled. [Visual correlation of these tablets with their mottling values was presented previously (3).]

During drying, migration of dye to the granule periphery leaves the granule interior color deficient, and the granule exterior contains an excess of colorant. The larger the granule, the greater is the volume to surface area ratio; therefore, the color density at the surface of large granules would be expected to be greater than that at smaller granules. Furthermore, in large granules, the color-deficient interior is larger in volume and more easily discernible after compaction.

The difference between the mottling of tray- and fluid-bed-dried granules can be attributed to two factors. First, during the fluid bed drying process, each granule is discrete and, although migration within each granule can occur, intergranular dye migration is not possible. However, severe intergranular migration can occur during tray drying, resulting in a high concentration of the colorant at the surface of the granule bed, with the bulk of material being devoid of colorant. This subsequently results in intensely colored specks on the tablet surface. Second, the interior of each fluid-bed-dried granule is completely covered by its peripheral layer of dye and, since the granules are not comminuted before compression, the dye-deficient material is only partially revealed when the granules are tableted. Chavkin (6) suggested that colorant migration in tray drying can be reduced by agitation of the granule bed, but only an intensity of agitation sufficient to prevent intergranular migration would produce the same level of mottling as is found in fluid-bed-dried granules.

The described tablets were made from relatively monosized systems, apart from the addition of lubricant. If tablets are made from granules exhibiting a range of sizes, mottling on the surface of the tablet compressed by the upper punch is greater than that on the other face. This result is attributed to granule segregation in the die (7), resulting in the lower portion of the tablet being composed of smaller granules than the upper. This result is especially noticeable at relatively low compaction pressures when granule integrity is largely retained.

Effect of Drying Temperature on Tablet Mottling—Both tray- and fluid-bed-dried granules were dried at 25 and 60°, followed by compression. The results (Table I) show the effect of drying temperature on the degree of mottling. It was reported that tablet mottling can be reduced by lowering the drying tempera-

[1] Joyce-Loebl microdensitometer Mark III C.S., Joyce Loebl and Co. Ltd., Gateshead, United Kingdom.

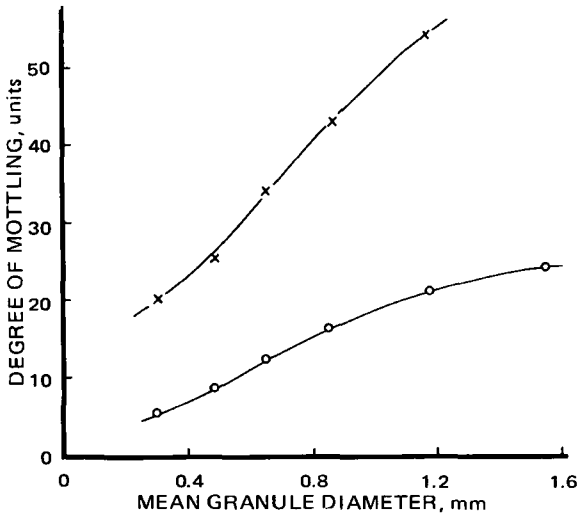

Figure 1—*Effect of drying process and granule diameter on the degree of mottling of calcium phosphate tablets colored with FD&C Blue No. 1 dye. Key: ×, tablets compressed from granules dried in a tray drier; and ○, tablets compressed from granules dried in a fluid bed drier.*

ture, but no experimental evidence for this statement was presented. This concept was also held by Scott *et al.* (5), who attributed the good color uniformity of tablets prepared from fluid-bed-dried granules to the "increased ability of a fluid bed drier to control product temperature during drying, thereby reducing color bleeding."

This concept is in contrast to that of other workers (8, 9) who postulated that solute migration on drying is reduced as the drying temperature is raised. They suggested that at high temperatures the flow of liquid through the granule cannot maintain the higher rate of drying at the periphery and evaporation takes place from progressively further inside the granule. This, in turn, reduces dye migration. From evidence presented here, it appears that drying temperature *per se* has a negligible effect on tablet mottling and the results noted by Scott *et al.* (5) are due to differences in the mode of dye migration in the two types of driers rather than to differences in the drying temperature itself.

Effect of Drying Technique—Since uniformly colored tablets could not be prepared from tray-dried granulations, further investigation was restricted to the more reproducible fluid bed drying technique. The extensive variation in the mottling values for tablets prepared from tray-dried granules probably was due to slight variations in the depth of the granule bed, since a difference of only 1 mm in a bed 1 cm thick produced a dye layer of 10% greater concentration and 10% more granules in which the dye concentration was low. The manner in which the resultant granule cake was fractured during comminution after drying was also unpredictable.

Effect of Compaction Pressure on Tablet Mottling—When the compressing force used to tablet a calcium phosphate granulation was increased, the degree of mottling exhibited by the resultant tablets increased sharply and then decreased by a small but reproducible amount (Fig. 2).

The increase in mottling is attributed to the disruption of the granules, thereby exposing their dye-deficient interiors. Shotton and Ganderton (4) showed similar effects using sugar pellets coated with dye. The decrease in mottling at higher pressures may possibly be due to the differing behavior, under compression, of the granule crust and the granule interior caused by migration of the granulating agent to the granule periphery (10). The soft granule interior would be compressed more on compaction than the exterior and thus would be reduced in size. Indirect evidence for this explanation is that the degree of color saturation (*i.e.*, the depth of the color) increases uniformly with compression pressure, tablets compressed at 49 MNm^{-2} being pale blue and tablets compressed at 65 MNm^{-2} being deep blue. Tablet porosity decreased linearly with an increase in pressure.

Table I—Effect of Granule Drying Technique and Drying Temperature on Tablet Mottling

Method of Drying	Tray-Dried Granules		Fluid-Bed-Dried Granules	
Temperature of drying air	25°	60°	25°	60°
Degree of tablet mottling, units	68.2	66.4	21.7	21.6
Limits of error $p = 0.95$	6.3	4.4	1.8	2.1

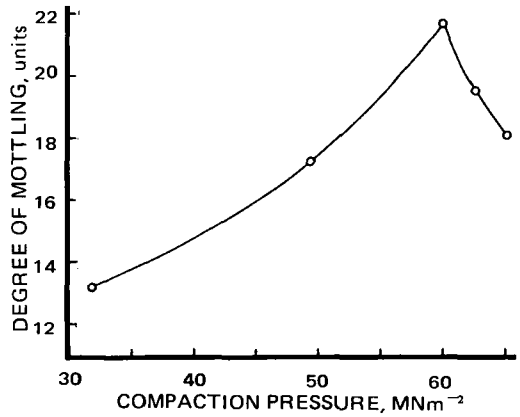

Figure 2—*Effect of compaction pressure on the degree of mottling shown by calcium phosphate tablets colored with FD&C Blue No. 1 dye.*

CONCLUSIONS

From the foregoing discussion, the following manufacturing principles can be proposed to minimize mottling, although the underlying cause of mottling, the migration of dye to the granule periphery, cannot be wholly prevented by these means.

1. The granules should be dried by a method that prevents intergranular migration of the dye, *e.g.*, by fluid bed drying as opposed to tray drying. Variation in drying temperature has little if any effect on the degree of mottling.
2. In contrast to usual manufacturing processes, the granules should not be subjected to a comminution process after drying; otherwise, the dye-deficient interior of the granule will be exposed.
3. As far as is commensurate with granule flow properties, the granule size should be as small as possible. In such granules, the amount of dye available for migration to the granule periphery is minimized and the color contrast between the periphery and the interior is reduced.
4. Tablet mottling and color saturation are both increased by an increase in compaction pressure.

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Quantitative Assessment of Factors Contributing to Mottling of Colored Tablets II: Formulation Variables

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Abstract □ The effects of several formulation variables were quantified with respect to factors affecting tablet mottling. Tablet mottling occurred with several commonly used binders and could not be prevented by using highly viscous binding solutions. However, mottling was reduced initially by increasing granule strength. Tablet diluents and dye–adsorbent materials had a profound effect on mottling, not by preventing dye migration but by affecting granule fragmentation on compression and the extent to which the dye-deficient material at the center of the granule was revealed. The lake form of FD&C Blue No. 1 was found to bleed in the presence of diluents that raised the pH of the granulating fluid above 6.4. Anionic impurities in the diluents also caused leaching of free dye and, consequently, increased tablet mottling. The conclusions from this study and previous papers were drawn together to give general principles for the production of uniformly colored tablets by aqueous granulation techniques.

Keyphrases □ Mottling—surface of colored tablets, effects of several formulation variables □ Tablets, colored—effects of several formulation variables on mottling

Recently, a method for measuring the amount of color variation on the surface of a tablet (mottling) was described (1), and this method enabled a study to be made of those factors that contribute to mottling in tablets. The manner in which some manufacturing variables can be controlled to minimize mottling was discussed earlier (2), but the underlying cause of mottling, the migration of dye to the periphery of the granule during drying, cannot be avoided simply by manipulation of manufacturing techniques.

King (3) reviewed some methods by which dye migration can be reduced, but the success of the techniques has been judged subjectively. By using the quantitative method for determining tablet mottling, the relative importance of formulation factors in the control of tablet color uniformity was assessed.

EXPERIMENTAL

General Method of Tablet Preparation—The solids to be tableted were colored with 0.0333% of FD&C Blue No. 1 dye or 0.2357% of FD&C Blue No. 1 lake (equivalent to the same dye concentration) dissolved in water. Each colored powder was massed with the appropriate quantity of granulating agent and sieved through a 2.8-mm mesh screen using an oscillating granulator[1]. The wet granulate was dried for 20 min in a fluid bed drier[2] (air inlet temperature 60°) and sieved on a vibratory sieve shaker[3]. Without further comminution, the 1000–1400-μm fraction was lubricated with magnesium stearate (1%) colored with the same concentration of dye. This size fraction was selected because previous work (1) had shown that such granules gave highly mottled tablets so any changes in mottling could be more readily detected. The lubricated granules were compressed by a single-stroke tablet machine fitted with flat-faced, 12.5-mm, stainless steel punches[4]. The tablet thickness was constant (4.00 mm), and the tablet weight for each diluent is shown in Table I.

Measurements of Tablet Mottling—Full details of this technique, using a microdensitometer[5], were published previously (1).

Measurement of Granule Crushing Strength (Fig. 1)—The apparatus consisted of two concentric cylinders, and their bases were separated by a washer of 1.0 mm thickness. A single granule was mounted centrally in the washer, and the inner cylinder was placed in position. Lead shot was poured into the inner cylinder until the granule fractured or deformed and the inner cylinder made contact with the washer. This contact completed an electric bell circuit, so granule fracture was signaled audibly.

Twenty-five granules of specified dimensions were assessed from each batch to give a mean value for granule crushing strength. A control on granule size was necessary since Capes (4) showed that granule strength is dependent on granule diameter. For this reason, a relatively narrow sieve fraction was selected (2.0–2.8 mm). An additional control on granule weight was also necessary to obtain reproducible results; the granule weight fraction for granules composed of different diluents varied according to the density of the granules (Table I).

The viscosity of starch mucilages used as binding agents was determined at 25° using a rotational viscometer[6].

RESULTS AND DISCUSSION

Role of Granulating Agent in Tablet Mottling—The granulating agent has been reported to inhibit solute migration in granules by means of imbibition (5) and complexation (6) and by its effect on the viscosity of the granulating fluid (4). Furthermore, since one fundamental cause of mottling is disruption of the granular structure on compression, thereby exposing the dye-deficient

[1] Type 143A, Apex Construction Co., London, United Kingdom.
[2] Type SSE65, Apex Construction Co., London, United Kingdom.
[3] Pascall Engineering Co. Ltd., Crawley, United Kingdom.
[4] Model E2, Manesty Machines Ltd., Liverpool, United Kingdom.
[5] Joyce-Loebl microdensitometer Mark IIIS, Joyce Loebl and Co. Ltd., Gateshead, United Kingdom.
[6] Epprecht Rheomat-30, Contraves A. G., Zurich, Switzerland.