

COLORED GRANULES FOR COMPRESSION

N.A.Armstrong, Welsh School of Pharmacy, U.W.I.S.T., Cardiff, U.K.

G.A.March, Regional Health Authority, Oxford, U.K.

It is now generally agreed that mottling in colored tablets is caused by dye migration in the granules during drying. The dye becomes concentrated at the periphery of the granules, and the interior of the granule is deficient in dye, the latter being revealed if granule fracture occurs during compression. An experimental method of measuring mottling has been developed, and used to determine those factors which contribute to the degree of mottling, and thus how mottling may be minimised. The dye used in these studies was F.D. & C. Blue No. 1.<sup>1,2,3.</sup>

Recently Shah and Shah have published data which would seem to contradict these findings.<sup>4</sup> These workers claimed that by using a mixture of 40% lactose, 40% amylum and 20% microcrystalline cellulose, wet granulated with amylum paste containing a water soluble dye and tray dried, uniformly colored granules were obtained using tartrazine and sunset yellow, but not with indigo carmine and F.D. & C. Red No. 3. They attributed the uniform color in the case of the yellow granules to the presence of the microcrystalline cellulose, though no mechanism for this was suggested.

In our hands, no evidence could be found that microcrystalline cellulose adsorbs any of the dyes used by Shah and Shah, and so this can be discounted as a mechanism by which dye migration is reduced. On the other hand, if microcrystalline cellulose acts by physically blocking capillaries in the granular structure, then migration of all dyes should be affected.

We contend that the statement that the formulation used is suitable for yellow and orange granules but not for those colored red or blue indicates the true explanation of their results. The human eye is not equally sensitive to light from all regions of the visible spectrum, being less sensitive to red or blue light than to yellow.<sup>5</sup> Consequently blue and red objects appear to the eye to reflect less light than those colored yellow and so the contrast between the former and a white surface is more marked. This has been well established by Sumner<sup>6</sup> in his studies on the legibility of print of various colors. Consequently, yellow or orange tablets will appear to be less mottled than red or blue tablets, even though the color distribution may be equally non-uniform. A monochrome photographic film, on the other hand, is equally sensitive to light from all parts of the visible spectrum, and hence a photographic negative shows all non-uniformly colored tablets to be mottled irrespective of their actual color. It was partly for this reason that we developed a photographic method of measuring mottling<sup>1</sup> rather than rely on a more subjective visual assessment, but to obtain a better correlation between our results and the visual appearance of the tablets, we studied tablets containing a blue dye.

If mottling is due to migration of dye in the granulating fluid, it follows that if the dye is insoluble in the fluid, migration and hence mottling will be reduced. Thus we have shown that in some circumstances, the use of a dye lake reduces mottling with aqueous granulations but the magnitude of the reduction is controlled by the pH of the system and its ionic constitution.<sup>3,7</sup>

Thus though the use of dye lakes may give satisfactory results in the system used by Shah and Shah, it will not necessarily do so in other systems.

We have no experience of the use of a water insoluble material such as shellac as a means of reducing migration, but we would point out that shellac is used as a waterproofing agent for tablet cores and may cause dissolution problems if distributed throughout the tablet, particularly after prolonged storage.<sup>8</sup>

Shah and Shah recommend that the shellac is added as a methanolic solution, but the tableting problems caused by mottling must be set against the environment hazards caused by the evaporation of large amounts of inflammable liquids.

Since tablets, which to the naked eye are uniformly colored, can be produced by fluid bed drying, provided the granules are not comminuted prior to compression,<sup>2,3</sup> we consider our recommendations regarding the reduction of the degree of mottling in colored tablets remain valid.

## REFERENCES

1. N.A.Armstrong and G.A.March, J.Pharm.Sci., 63, 126, (1974).
2. N.A.Armstrong and G.A.March, J.Pharm.Sci., 65, 198, (1976).
3. N.A.Armstrong and G.A.March, J.Pharm.Sci., 65, 200, (1976).
4. R.C.Shah and A.R.Shah, Drug Development and Industrial Pharmacy, 3, 347, (1977).
5. N.I.Pinegin, Dokl.Akad.Nauk SSSR, 30, 206, (1941).
6. F.C.Sumner, J.Appl.Psychol., 16, 201, (1932).
7. A.Bialkowska, M.Sc. Thesis, University of Wales, (1976).
8. D.Barrett and J.T.Fell, J.Pharm.Sci., 64, 335, (1975).