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COMMUNICATIONS

Temperature-related incompatibility between gelatin and calcium carbonate in sugar-coated tablets

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The behaviour of gelatin as a component in sugar-coated tablets and the resultant effect of its inclusion on dissolution (Kristoffersson & Keto, 1973), viscosity and ageing (Utsumi, Ida & others, 1961), and binding (Sakr, Kassem & others, 1973) have been studied by numerous workers. Recently, Barrett & Fell (1975) examined the effect of ageing on physical properties of sugar-coated phenylbutazone tablets and found large increases in the disintegration time of subcoats of tablets stored at 50°. We, too, have observed similar behaviour on a number of experimental batches of tablets.

This communication concerns the identification and possible nature of a heat-induced incompatibility between gelatin and calcium carbonate within the tablet subcoat that results in an irreversible increase in disintegration time. The tablet formulations under consideration consist of shellac-coated cores over which has been built a thick subcoat of alternate layers of a gelatin-acacia-sucrose syrup mixture and a dusting mixture of calcium carbonate, acacia and talc. The tablet is completed by the application of coats of white syrup and plain syrup. After relatively short storage periods above room temperature the tablets showed rapid deterioration as evidenced by changes in disintegration in water. Although this deterioration could be partially overcome by using thinner subcoats, it was obviously desirable to identify the source of the problem. Using the B.P. (1973) method for sugar-coated tablets, we determined disintegration times for a typical batch (Table 1).

Unacceptably long disintegration times were found to be coupled with visible structural changes in the wetted subcoats. Those tablets stored at or below room temperature disintegrated rapidly and evenly, whilst those stored at 40° cracked, swelled, and flaked slowly from the cores as large insoluble fragments. That the interaction responsible for this behaviour occurs only within the subcoat was established by measuring the disintegration rates of tablet cores stored under the same conditions and also by observing the dissolution of the outer sugar coats. In neither instance were any measurable differences found between tablets stored at low temperature and those stored at high temperature.

Table 1. *Effect of storage time and temperature on disintegration time of sugar coated tablets.*

Storage temperature °C	1 month	3 months	6 months
4°	—	14½ min	14 min
R.T.	15½ min	17 min	17¾ min
32°	17¾ min	37 min	>1 h
40°	>1 h	>1 h	>1 h

In an initial investigation, differential thermal analysis and polarizing microscopy failed to differentiate heat-aged subcoatings from the corresponding materials stored at 4°. The absence of differences suggested that chemical or structural changes, particularly those related to gelatin, were either too small for detection or were masked by the presence of other excipients, e.g. sucrose. However, a simple compatibility study was conducted to identify the interaction responsible for poor disintegration. Aqueous solutions or suspensions of individual subcoat components and mixtures of components were spotted onto glass slides and stored at 4, 32, 50 and 70°. At predetermined intervals the times and characteristics of disintegration of the samples were determined by suspending the slides in a beaker of water maintained at 37° and stirred magnetically at a constant rate.

Parallel studies of disintegration time of the tablet subcoat materials confirmed the validity of the technique for isolating potential incompatibilities.

Of all the possible combinations of components examined, large increases in disintegration times were noted only for mixtures of gelatin and calcium carbonate that had been stored above room temperature. These mixtures also exhibited fragmentation behaviour similar to that observed in aged sugar-coated tablets. The only other temperature-induced change was a comparatively slight increase in aqueous disintegration of heated gelatin. Further investigations with the glass slide technique revealed that mixing gelatin with other water-insoluble compounds, like calcium sulphate and magnesium carbonate, also led to the production of 'insoluble gelatin' during accelerated storage. Soluble salts of the same cations, e.g. calcium chloride or magnesium chloride, did not adversely affect the dis-

integration characteristics of gelatin in mixtures of the two substances. This finding suggests that the change in disintegration of gelatin derives from a physical change within the tablet subcoat, and not from a chemical reaction between calcium ion and gelatin.

Theimer (1960) has demonstrated by electron microscopy, changes in gelatin fibre structure correlated with ageing. The observed heat-induced changes in the tablet subcoat could involve an initial expansion of the gelatin fibre network that results in trapping of calcium carbonate to form an insoluble matrix. Although this process probably also occurs in the presence of soluble salts, the latter would effect water transport through the matrix and prevent poor disintegration.

Batches of tablets prepared with the original gelatin-acacia-sucrose syrup, but combined with an alternative chalk-free dusting powder, have shown satisfactory disintegration times after accelerated storage.

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REFERENCES

BARRETT, D. & FELL, J. T. (1975). *J. pharm. Sci.*, **64**, 335–337.
KRISTOFFERSSON, E. & KETO, K. (1973). *Farm. Aikak.*, **82**, 45–49.
SAKR, A. M., KASSEM, A. A., AZIZ, S. A. A. & SHALABY, A. H. (1973). *Can. J. pharm. Sci.*, **8**, 6–12.
THEIMER, W. (1960). *Z. Naturf.*, Pt. **15b**, 346–350.
UTSUMI, I., IDA, T., KISHI, S. & TAKAHASHI, S. (1961). *Yakugaku Kenkyu*, **33**, 490–494.

Microindentation - a method for measuring the elastic properties and hardness of films on conventionally coated tablets

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A knowledge of the stress-strain characteristics of films is useful in the development of suitable film coatings for tablets especially in comparing film samples as a function of formulation variables, e.g. polymer type, plasticizer type and concentration, solvent system and the effect of fillers and colouring agents. These data are usually determined by measuring the elongation of a strip of film under increasing load forces using a tensile tester (Munden, De Kay & Banker, 1964; Allen, De Marco & Kwan, 1972). The technique involves the casting or spraying of films onto various substrates (e.g. mercury or polytetrafluoroethylene) from which they are removed before testing. Ridgway, Aulton & Rosser (1970) described a pneumatic microindentation apparatus (Research Equipment (London) Limited) which could measure both the elastic modulus and surface hardness of a sample the size of a tablet. Since the apparatus was originally developed for the testing of paint films it was decided to evaluate its potential for use in measuring the elastic modulus and Brinell hardness number of films on conventionally coated tablets.

The apparatus used was essentially the same as that used by Ridgway & others (1970) and consisted of a spherical indenter, diameter 1·55 mm, which could be lowered on to the test surface under a selected load of a few grams. The depth of indentation and the recovery when the load was removed was measured by a double pneumatic recorder with a full scale deflection corresponding to a 6 μm movement in the indenter. The results were calculated using the equations derived by Ridgway & others (1970). Since in their derivation of the equation for the modulus of elasticity, the authors used a value of 0·3 for Poisson's ratio (an unknown variable for cellulose based coatings), the values for this modulus are only comparable within a series of similar materials and cannot be considered absolute. The individual results, therefore, cannot be directly compared with those obtained from stress-strain data but the trends should be similar.

Flat faced tablets 11·1 mm diameter were coated using a formulation containing hydroxypropyl methylcellulose (Shinetsu Chemical Company, Japan) and variable amounts of plasticizer dissolved in a dichloromethane–methanol solvent mixture. The formulation was applied to the tablets in a 15 cm diameter Wurster column. The tablets were dried and stored at room temperature and 50° R.H. for two weeks before testing. Measurements were made on 20 tablets using an indentation load of 5 g.

As a preliminary study indentations were made on films cast on a glass substrate and compared with those made on the film coated tablet. No significant difference could be found between the measurements, indicating that there was no substrate interference with a coating some 30–40 μm in thickness.