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Investigation into substrate cracking of a film-coated bilayered tablet

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Abstract—Substrate cracking occurred during film coating of a bilayered tablet. The cause was traced to differences in the expansion characteristics of the two layers upon exposure to heat. Thermal mechanical analysis was used to determine the coefficients of thermal expansion of the respective layers.

The authors were attempting to apply a clear, cellulose-derived film coating to a bilayered tablet. Cracks appeared on the surface of only one of the layers with an unacceptable degree of frequency. This defect appeared within the first few minutes of the film coating operation. Initial attempts to correct the problem centred around changing the coating formulation itself, as well as the processing parameters (spray rate, inlet drying air temperature, etc.). When these modifications failed to correct the problem, it was speculated that the cracking might be due to the differential rates of expansion between the two layers when subjected to the heat of film coating. Consequently, thermal mechanical analysis (TMA) was utilized in an attempt to characterize the expansion characteristics of the two layers.

Theory

Thermal mechanical analysers can be used to measure the linear expansion of a sample material (ΔL) with respect to temperature change (ΔT). From the equation,

$$\Delta L = L_o \alpha \Delta T$$

where L_o is the original length of the sample, the coefficient of thermal expansion (α) can be determined. In single component systems, α has been shown to be fairly constant over large ranges of temperature. For a multicomponent system, such as a pharmaceutical formulation, α may not be constant, and it is more appropriate to characterize this thermal property over the temperature range of interest.

Methods

The coefficients of thermal expansion of the two formulations comprising the bilayered tablet were determined using a commercially available thermal mechanical analyser (Series 7 Thermomechanical Analyzer; Perkin Elmer, Norwalk, CT). Cylindrical disks consisting of 200 mg of the particular formulation (layer) were compressed on a lab scale press (Carver Press, Model C; Menomonee Falls, WI) using 8·7 mm (11/32″) flat bevel plain tooling and a force of 20·7 MPa (3000 psi). The disks were allowed to stand overnight at room temperature (20°C) before testing. This procedure was used to simulate the manufacturing procedure for the product and to obtain a sample that would fit securely onto the stage of the instrument. Care was exercised to be as consistent as possible in the preparation and testing of each disk, and each formulation was tested in triplicate. Analysis was performed over the temperature range of 25 to 60°C at 3°C min^{-1} with no vertical force load applied. This temperature range was representative of the heat encountered by the tablets during the film coating operation.

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Thermal expansion of the disks was measured in two dimensions. Vertical expansion, that is, expansion in the height of the cylinder upon exposure to heat, was determined by positioning the disk on the instrument stage so that the device probe was perpendicular to its circular face. Diametric expansion, an increase in the radius of the circular dimension, was measured by balancing the tablet on edge and positioning the probe on its circumference.

Statistical analysis of the data was performed using a fixed-effects one-way analysis of variance model. Multiple comparisons of the means were determined using Fisher's LSD procedure. The assumption of variance homogeneity was verified using Bartlett's procedure.

Results and discussion

Table 1 shows the coefficients of thermal expansion for the formulations tested. Both coefficients of thermal expansion for Layer A are significantly greater ($P < 0.01$) than those obtained for Layer B. The vertical expansion of Layer A was approximately 2·8 times greater than that for Layer B, while the diametric expansion was only 20% greater. Fig. 1 compares typical thermograms obtained for the two formulations and indicates that the difference in their rates of vertical expansion is greatest at temperatures above 35°C which corresponds to the tablet bed temperature range maintained during the coating operation (35–45°C). When Layer B was reformulated, the coefficients of

Table 1. Comparison of the coefficients of thermal expansion $(°C \times 10^{-5})^{-1}$.

	Vertical (x ± s)	Diametric (x ± s)
Layer A	26·2 ± 1·3	78·1 ± 4·0*
Layer B (initial)	9·4 ± 0·7	66·0 ± 5·2
Layer B (reformulated)	14·0 ± 0·7	80·5 ± 1·6*

* Coefficients of thermal expansion not significantly different when tested at the 99% confidence level.

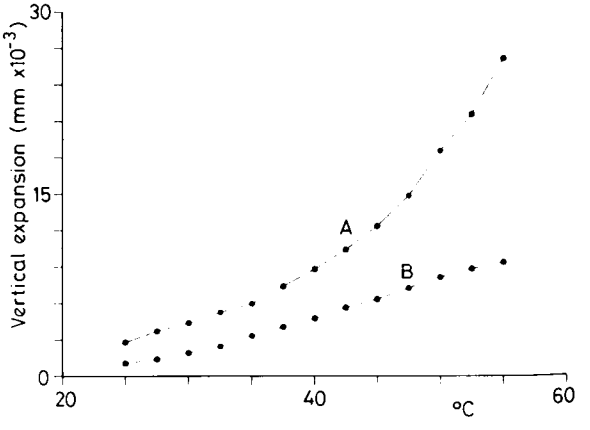

FIG. 1. Comparison of thermograms of layers A and B.

thermal expansion increased, and the diametric coefficient of expansion was not significantly different from Layer A ($P < 0.01$).

Rowe (1980) hypothesized that differences in the dimensional changes of the film and tablet substrate during film coating could play a role in the creation of film defects.

The formulations corresponding to the two layers were compressed individually and samples film coated. Cracking was not evident in the film-coated samples nor in the single-layer compressed tablets when subjected to temperatures of 40–55°C for 24 h.

Fractures appeared in uncoated bilayered tablets placed in a 40°C oven overnight, however, indicating that their exposure to elevated temperatures, rather than the application of a film coating itself, was the cause of tablet cracking. Separation of the layers was not observed. It is speculated that differences in dimensional changes between the two layers, when subjected to the heat encountered during film coating, created stress that was relieved by fracturing of the less thermally elastic layer (Layer B). Although the origin of the fractures could not be determined, they characteristically extended from the tablet surface vertically to the interface between the two layers (Fig. 2).

The successful manufacture of a bilayered tablet requires the development of a combination of formulations that can form interfacial bonds during the compressing operation sufficient to withstand subsequent stresses encountered during film coating, storage at elevated temperatures and physical handling. TMA provides a rapid, convenient and reproducible method of screening combinations which might prove suitable for use in this particular dosage form.

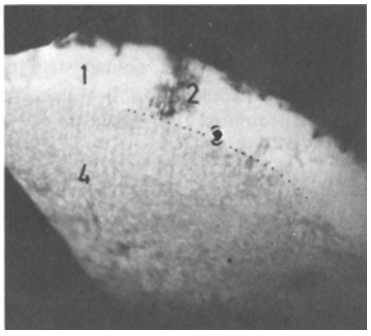

FIG. 2. Cracking in a film-coated bilayered tablet. Cross-section showing: 1 layer B, 2 vertical crack, 3 interface, 4 layer A.

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Pharmacokinetic evaluation of local drug delivery: the intratesticular and intrarenal administration of acenocoumarol in the rat

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Abstract—According to theory, the regional increase in drug concentration during target organ directed drug delivery as compared with systemic drug delivery is related to the quotient of the clearance of the drug and the blood flow of the target organ. We investigated the steady-state pharmacokinetic disposition of *S*-acenocoumarol in plasma, liver, testis, and kidney following its administration (constant rate infusion by an osmotic minipump) directly into the testis or the kidney of rats. The effects of clearance induction (phenobarbitone treatment) on the disposition of the drug were also investigated. The results confirm the theory of target-directed drug delivery.

Recent findings in biochemical research on the molecular function of vitamin K made it clear that vitamin K-dependent biochemical systems not only are present in liver tissue but are also found in tissues like bone, kidney, testis, brain, endothelial cells, etc. (Hauschka et al 1976; Vermeer et al 1982). The physiological function of vitamin K in non-hepatic tissues is still unclear. An approach for obtaining more insight in this field would be to study the effects of the suppression of the local vitamin K systems. Oral anticoagulants, i.e. 4-hydroxycoumarins, interfere with the cellular vitamin K function by suppressing the enzyme vitamin K-epoxide reductase which is part of the cellular vitamin K cycle (Suttie 1980). These drugs, however, cannot be applied as such because, as we have shown recently (Thijssen et al 1986), they preferentially accumulate in liver tissue, thus giving only a weak response in non-hepatic tissues. Target-directed delivery of oral anticoagulants would be a method to circumvent this problem. According to theory, the advantage of direct drug delivery to a non-eliminating target organ over delivery via the systemic circulation is only obtained if the blood (plasma) flow of the target organ is low in comparison to the blood (plasma) clearance of the applied drug (Eckmann et al 1974; Chen & Gross 1980). We applied the technique of local drug delivery to investigate the function of the testicular vitamin K system in rats (Daemen et al unpublished). The *S*-enantiomer of acenocoumarol (AC) was used as the vitamin K 'antagonist' because its blood clearance (about 4 mL min^{-1}; Daemen et al 1986) is high with respect to testicular blood flow (0·2–0·4 mL min^{-1}; Nishiyama et al 1976).

Since to date experimental evaluation of the theory of local drug administration has not been presented in literature, we wish to report here the pharmacokinetic analysis of our experiments.

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