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COMMUNICATIONS

The orientation and alignment of particles in tablet film coatings

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The question of orientation or alignment of particles in pigmented film coatings has recently been raised in the context of the beneficial effect of the addition of talc and, to a certain extent, calcium carbonate on the incidence of the defect edge splitting and peeling on tablets coated with hydroxypropyl methylcellulose (Rowe 1982). It has been shown that, in paint films, particles of definite shape, e.g. yellow iron oxide, orientate during brushing resulting in a phenomenon known as 'silking', i.e. the presence of stripes or streaks which appear darker or lighter than the surrounding surface depending on the direction from which they are viewed (Kresse 1966). This report summarizes work aimed at substantiating the alignment or orientation of both talc and calcium carbonate in tablet film coatings using an optical effect caused by the optical anisotropy of the materials.

An optically anisotropic material possesses different refractive indices depending on its orientation. Materials in this group are usually referred to as either uniaxial, i.e. they possess two refractive indices designated by the letters ε and ω, or biaxial, i.e. they possess three refractive indices designated by the letters α, β and γ. Calcium carbonate is an example of the former where $\varepsilon = 1{\cdot}510$ and $\omega = 1{\cdot}645$, while talc is an example of the latter where $\alpha = 1{\cdot}539$, $\beta = 1{\cdot}589$ and $\gamma = 1{\cdot}589$ (Gettens & Stout 1966). Polymer film formers and the films prepared from them generally do not possess any optical anisotropy, i.e. they are isotropic with one refractive index. An example of this group is hydroxypropyl methylcellulose with a refractive index of 1·49 (manufacturer's literature).

The refractive index is a physical property of fundamental importance in determining the appearance of pigmented films. The capacity of the film to reflect light, i.e. its opacity, is dependent, not only on the difference between the refractive indices of both the pigment or additive and the polymer film former, but also on the actual indices themselves. The amount of reflected light, R, at the pigment/polymer interface can be estimated, assuming normal incidence and no absorption, using the formula given by Cooper (1948):

$$R = \left[\frac{n_1 - n_2}{n_1 + n_2}\right]^2 \quad (1)$$

Where n_1 is the refractive index of the pigment or additive and n_2 is the refractive index of the polymer film former. It can be seen that if $n_1 = n_2$, then $R = 0$ and hence the film will be transparent. If, however, $n_1 \neq n_2$, then the larger the difference between the refractive indices the larger the amount of light reflected at the interface and, if there is a sufficient number of interfaces, i.e. the additive is finely dispersed throughout the film, the film will become more and more opaque.

If this is applied to hydroxypropyl methylcellulose films containing calcium carbonate or talc, then it can be seen that R will change with the orientation of the particles. If the materials orientate equivalent to the state of their lowest refractive index, then the films will appear essentially transparent, but if they are randomly orientated or orientated equivalent to the state of their highest refractive index, the films will appear more opaque. The degree of opacity, therefore, should be an indication of the orientation or alignment of these materials. In order to investigate changes in the opacity of film coatings containing either calcium carbonate or talc, various coloured intagliated tablets

FIG. 1. A tablet previously coated with red iron oxide in hydroxypropyl methylcellulose further coated with the same film former containing calcium carbonate.

were used as substrates. These were either self coloured or prepared by colour film coating white tablet cores. The tablets were coated in a 24 inch Accela Cota (Manesty Machines Limited) using a airborne spray system at a spray application rate of 50 ml min^{-1} and inlet air temperature at 60 °C. The film formulation used consisted of a 5% w/v aqueous solution of hydroxypropyl methylcellulose (Pharmacoat 606, Shin-Etsu Chemical Co., Japan) containing glycerol (20% w/w based on polymer) as plasticizer and talc (D. F. Anstead Ltd, Billericay) or precipitated calcium carbonate (J. & E. Sturge Limited, Birmingham) at various concentrations. At the end of each run, the tablets were withdrawn and visually inspected.

With both materials the colour of the main body of the substrate could be clearly seen through the applied film, i.e. the film was essentially transparent. However, within the intagliations the film was opaque and the colour of the substrate was obscured making the intagliations appear white (Fig. 1). The results indicate that, over the main body of the tablet both the talc and the calcium carbonate had orientated equivalent to their state of lowest refractive index, but within the intagliations they were either randomly orientated or orientated equivalent to their state of highest refractive index.

The reasons for orientation can only be a matter for conjecture. The effect is not substrate-dependent since all the substrates used showed the effect. It is possible that orientation will occur under the influence of the residual internal stresses present within the film since these are thought to act parallel to the tablet surface. The mutual rubbing due to tablet-to-tablet contact within the coating drum is another factor to be considered especially since attempts at reproducing the effect on single tablets attached to the inside of the coating drum were unsuccessful.

The results indicate that orientation of both talc and calcium carbonate particles occurs in hydroxypropyl methylcellulose films applied to a variety of tablet substrates. It is possible that other materials will also show this effect but substantiation will be difficult for those materials with very high refractive indices, since in these cases the film will initially be very opaque and differences in opacity due to orientation difficult to detect.

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The preferential inhibition of 5-lipoxygenase product formation by benoxaprofen

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Benoxaprofen has been shown to inhibit the formation of 5-lipoxygenase products from rabbit peritoneal cells stimulated with calcium ionophore A23187 (Walker & Dawson 1979). However other workers using isolated soybean lipoxygenase (Kingston 1981) failed to demonstrate any inhibition of lipoxygenase activity using benoxaprofen. We have further studied the effects of the drug on the activities of other lipoxygenases from human platelets, guinea-pig peritoneal cells and the human promyelocytic leukaemic cell line HL60.

Method

Human platelet microsomes were prepared as previously described (Ho et al 1976). The reaction mixture contained 50 mM sodium phosphate buffer pH 7·1, 1 mM EDTA, 0·2 mM indomethacin, 1 mM $CaCl_2$, 0·1% gelatin and 0·4 mg of lyophilized microsome powder in a volume of 0·2 ml. The reaction was initiated by the addition of [1-^{14}C]arachidonic acid (0·5 μCi) (New England Nuclear, Boston, Mass.). After 15 min incubation at 37 °C the reaction was terminated by the addition of 10 μl of 1 M citric acid. Fifty μl of the reaction mixture was applied to a silica gel t.l.c. plate (LQ6D, Quantum Industries, Fairfield, N. Jersey). The plate was developed in the organic phase from ethyl acetate–2,2,4-trimethyl pentane–acetic acid–water (90:50:20:100). The silica gel on the plate was scraped in 1 cm zones, suspended in 5 ml scintillation fluid and the radioactivity determined by liquid scintillation counter. The result was expressed as the ratio of radioactivity recovered from the whole plate.

Guinea-pig peritoneal cells were elicited by an intraperitoneal injection of 2% casein 18 h previously. 1 ml cell suspensions (2·6 × 10^6 cells ml^{-1}) were preincubated in Krebs Ringer Bicarbonate buffer pH 7·4 at 37 °C with different concentrations of benoxaprofen for 5 min. [1-^{14}C]Arachidonic acid (0·1 μCi) and ionophore A23187 (10 μM) were added and the cells incubated for a further 10 min. The incubation was

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