Comparison of these regression lines, in pairs, by the method of Newton & others (1971), proved that the lines did not differ significantly from each other. A common regression equation: $\sigma_x = 0{\cdot}114A - 0{\cdot}517$ (0·981) fitted the data.

These results suggest that compaction force or pressure does not completely characterise the formation of a tablet. Varsano & Lachman (1966), de Blaey & Polderman (1970) and Fell & Newton (1971) have reported the measurement of work done in making the tablet. Without the consideration of the time factor involved, work done may also be inadequate. For instrumented tablet machines without systems for accurate determination of punch travel, the present concept of force-time measurement offers a possible solution.

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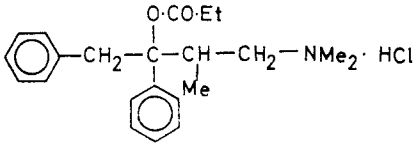
Aggregation of (+)-propoxyphene hydrochloride in aqueous solution: circular dichroism measurements

Highly water-soluble derivatives of insoluble or sparingly soluble drugs often associate in aqueous solution in much the same way as do surface-active agents (Florence, 1968). An understanding of the mechanism of such self-association is important since this property can influence the chemical stability of the drug itself as well as its tendency to interact with other drugs. We have shown, using nuclear magnetic resonance spectroscopy, that the non-narcotic analgesic (+)-propoxyphene HCl (I) associates in aqueous solution (Thakkar, Wilham & Demarco, 1970). The association is hydrophobic, involving primarily an overlap or stacking of the aromatic rings.

We now report some unusual findings in the circular dichroism (CD) spectra of aqueous (+)-propoxyphene HCl. Our observations are novel in that although changes in the CD spectra of some surface-active agents have been seen upon association (Bonkoski & Perrin, 1968, 1969; Mukerjee, Perrin & Witzke, 1970; Perrin & Witzke, 1971), the appearance of new bands upon association in a single solvent has not been reported before for such small molecules. Several chlorophyll and protochlorophyll pigments, which are monomeric in diethyl ether, have been shown to dimerize in carbon tetrachloride with the production of new CD peaks by the exciton splitting phenomenon (Houssier & Sauer, 1970). Resonance interaction between excited states of identical chromophores can cause exciton splitting with the resultant production of closely spaced CD curves of equal magnitude and opposite sign (Warshaw, Bush &



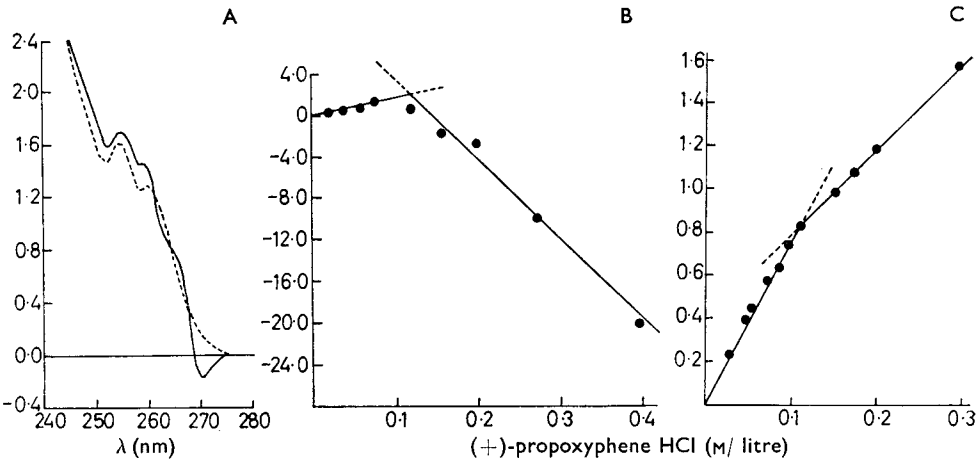


FIG. 1. A. CD spectra of (+)-propoxyphene HCl in aqueous solution. (- - - - 0·04, —— 0·4M). Spectra were recorded in 0·1, 0·5, and 1·0 mm cells using a 6002 attachment to a Cary 60 spectropolarimeter at 25 °C with a slit programmed for a half band width of 1·5 nm. Ordinate: Observed ellipticity $\times 10^2$.

B. Observed ellipticity at 270 nm as a function of the concentration of (+)-propoxyphene HCl. Ordinate: Observed ellipticity $\times 10^2$ at 270 nm.

C. Specific conductance of (+)-propoxyphene HCl in deionized water at 25°. A Beckman RC18A conductivity bridge was used. Ordinate: Specific conductance (mho cm^{-1}) $\times$ 10.

Tinoco, 1965; Bush & Brahms, 1967). The new CD band found in concentrated aqueous solutions of (+)-propoxyphene HCl has the properties associated with an exciton splitting phenomenon.

Fig. 1A shows CD curves of (+)-propoxyphene HCl at concentrations well above and below the concentration at which aggregation becomes significant. At the higher concentration, a negative peak appears at 270 nm, due to an exciton splitting phenomenon; the positive peak, being at lower wavelengths, is partially masked by the intrinsic optical activity of the molecule. This exciton splitting is believed to arise from association of the aromatic rings. Similar concentrations of drug show an ultraviolet maximum at 262 nm. When the drug is dissolved in methanol or in 3M urea, in which hydrophobic associative tendency would be expected to be minimal, no new CD bands are seen at drug concentrations up to 0·3M.

Fig. 1B shows a plot of the concentration dependence of observed ellipticity at 270 nm, a wavelength at which the sign of ellipticity changes upon appreciable aggregation. The plot shows a discontinuity at 0·12M. This apparent critical micelle concentration was verified by conductivity measurements. Fig. 1C shows the specific conductance as a function of concentration; the break in this plot occurs at 0·11M. These values of the apparent critical micelle concentration are in good agreement with the value calculated from nmr data (Thakkar and Wilham, unpublished data).

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The effects of microfine calcium carbonate on the flow properties of granules and their relevance to tabletting

The cohesiveness of powders causes difficulties in many processes. The increasing use of micronized materials in pharmaceuticals has stimulated interest in means by which such powders can be made free flowing.

It is often possible to eliminate stickiness in a powder by the addition of coarse materials (Hawksley, 1947; Jones & Pilpel, 1966; Neumann, 1967; Jones, 1970). We have investigated the application of such a technique to the tabletting of micronized powders. The method is expected to be useful, for example, for drugs that are sensitive to moisture or where the use of granulating liquids causes some physical change, resulting in a reduced dissolution rate.

We have found that measurement of angle of repose or pour density of the micronized powder-coarse particle mixture, as a function of concentration of micronized material, provides a simple test to determine the proportion of micronized drug that can be used to prepare satisfactory mixes for tabletting.

Preliminary work has been carried out using a fine particle size grade of calcium carbonate (Calopake P. C., John Sturge Ltd.) which was shown to have similar flow properties to the drug under investigation. The particle size data as measured by Coulter Counter were:

Coulter diameter, μm	1	2	3	4	5
Wt. percentage oversize	86	70	31	18	11

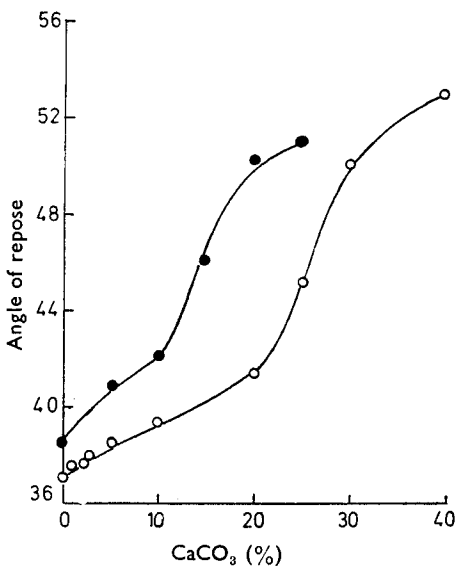

FIG. 1. Effect of calcium carbonate on angle of repose, ○, −20 +40 mesh granules; ●, −40 + 85 mesh granules.