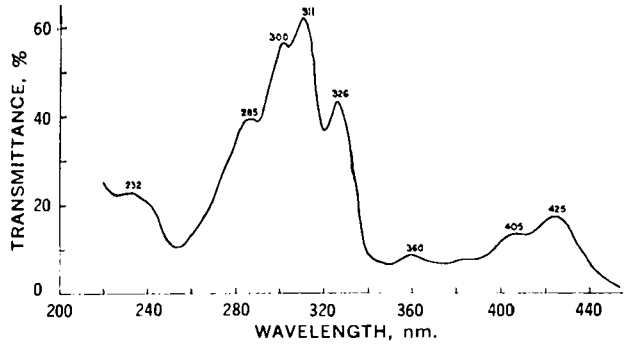

Figure 3—*UV spectrum of coralyne (acetosulfate) in methanol (5 mg./l.).*

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Effect of Formulation on Dissolution of Sodium Warfarin Tablets

Keyphrases □ Sodium warfarin tablets—effect of pregranulation dissolving on dissolution rate □ Dissolution rate, sodium warfarin tablets—effect of dissolving drug prior to granulation

Sir:

Numerous publications have shown that formulation of a solid dosage form can influence dissolution of the active drug. These studies have discussed the effect of binder concentration and tablet hardness (1), types of binders and particle size (2), types of starches (3), lubricants (4), and disintegration agents (5).

Table I—Dissolution Rate Constants (k) of Various Sodium Warfarin Tablet Formulations and Surface Tension of Solutions Used to Granulate

Formulation	k, min.$^{-1}$	Surface Tension[a], γ, dynes/cm.
A. Drug incorporated in dry form	0.060	—
B. Drug and polyvinylpyrrolidone dissolved in alcohol[b]	0.074	26.1
C. Drug dissolved in alcohol[c]	0.113	25.6
D. Drug and polyvinylpyrrolidone dissolved in water[d]	0.154	57.4
E. Drug dissolved in water[e]	0.246	59.4
	Absolute alcohol	24.4
	Water, deionized	74.1

[a] Of solution used to granulate. Measured by a Du Noüy interfacial tensiometer. [b] Solution ratio of drug–polyvinylpyrrolidone–alcohol = 1:1:6. [c] Solution ratio of drug–alcohol = 1:6. [d] Solution ratio of drug–polyvinylpyrrolidone–water = 1:1:4. [e] Solution ratio of drug–water = 1:4.

The purpose of this communication is to report that dissolving sodium warfarin prior to granulating can influence the dissolution rate.

Sodium warfarin was incorporated into a microcrystalline cellulose–lactose (3:1) mixture such that 25 mg. of sodium warfarin was contained/275-mg. tablet. The drug was either added into the formulation in the dry state or dissolved in an aqueous or alcoholic media, with or without an equal ratio of polyvinylpyrrolidone–sodium warfarin. The solutions (Table I) were used to granulate the microcrystalline cellulose–lactose mixture. Magnesium stearate (0.1%) was added to either the powder mixture or the dried, 20-mesh screened granulation. Tablets were compressed on a compressing machine[1]. All tablets disintegrated within 1 min. Dissolution tests were performed in a round-bottom flask, containing 500 ml. of distilled water, maintained at 37°. A half-moon (2.5 cm. in diameter) stirring blade was used at a speed of 50 r.p.m. Assays were performed spectrophotometrically.

The pseudo-first-order rate constants obtained from this study are shown in Table I. As can be seen, the slowest rates are obtained when the drug is in the dry state or is dissolved in an alcoholic polyvinylpyrrolidone solution. Dissolution can be increased when the drug is dissolved in water—with or without polyvinylpyrrolidone—or in alcohol alone prior to granulating.

By dissolving the drug prior to granulating, it is possible to increase the available surface area when this solution is poured onto a powder mixture. This would result in increased dissolution (Table I).

The difference in the rate of solution between Formulations C and E appears to be a function of the surface tension of the solution used to pour onto the lactose–microcrystalline cellulose mixture. It is known that the high surface area of microcrystalline cellulose is due to fissures and crevices found abundantly in the granules. Since the alcoholic solution (Formulation C) has a

[1] Colton SX, four station.

lower surface tension, it is able to penetrate into fissures and crevices which water cannot readily enter, resulting in a decreased rate of solution.

The addition of polyvinylpyrrolidone into Formulations B and D (Table I) does not alter the surface tension. Therefore, the decrease in dissolution when compared to Formulations C and E, respectively, must be a function of the rate of solution of polyvinylpyrrolidone, causing a decrease in the rate of solution of a rather soluble drug in water.

The results of this study show that the method used to incorporate drug into a solid dosage form can affect the dissolution rate of that drug.

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NMR Spectroscopy: Chloro-(tetra-*p*-methylphenylporphinato)indium (III)

Key phrases □ Chloro(tetra-*p*-methylphenylporphinato)indium (III)—NMR spectra □ Porphine complexes with indium—NMR spectra of chloro(tetra-*p*-methylphenylporphinato)indium (III) □ Indium (III), chloro(tetra-*p*-methylphenylporphinato)—NMR spectra □ NMR spectroscopy—identification, chloro(tetra-*p*-methylphenylporphinato)indium (III)

Sir:

Porphine complexes are important biologically and chemically. Structural studies of these complexes may provide information relative to their mechanisms of action. We wish to report NMR studies on the complex chloro(tetra-*p*-methylphenylporphinato)indium (III).

Chloro(tetra-*p*-methylphenylporphinato)indium (III) was prepared and purified as previously reported (1, 2). NMR spectra were obtained using a spectrometer[1] equipped with a variable-temperature probe and operated at power levels below saturation. Temperatures were measured with a thermocouple mounted in the probe; temperature calibration was done with ethylene glycol. Spectra were obtained in 1,1,2,2-tetrachloroethane which had been purified by distillation from phosphorus pentoxide under nitrogen. Spectra were obtained with the spectrometer locked on the solvent resonance, and chemical shifts were reported relative to the solvent.

[1] Varian-HA-100.

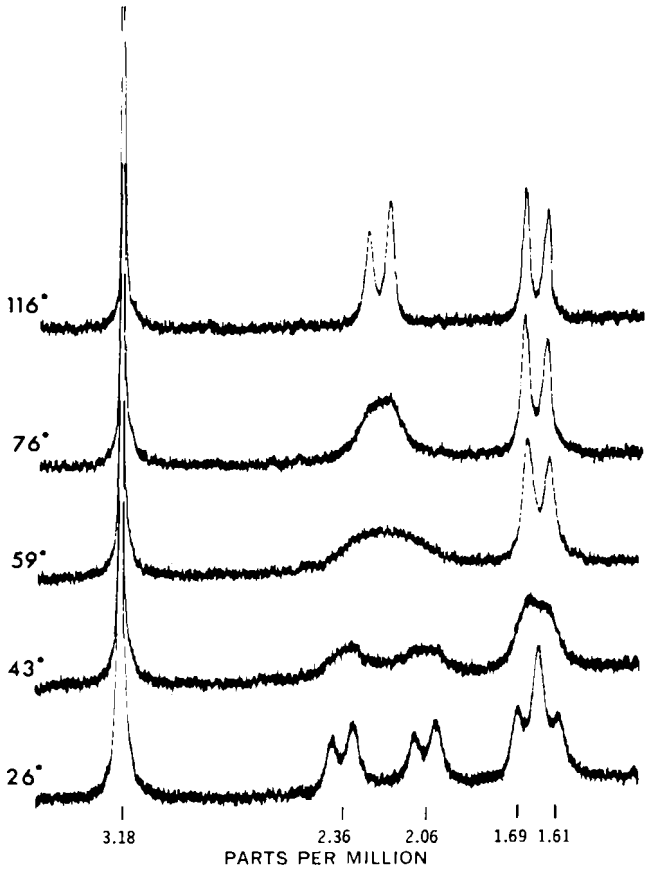

Figure 1—*NMR spectra (100 MHz.) of chloro(tetra-*p*-methylphenylporphinato)indium (III) at various temperatures.*

It has been shown that the NMR spectra of indium–tetraphenylporphine complexes at room temperature exhibit nonequivalence of the phenyl ring protons (2). The NMR spectrum of chloro(tetra-*p*-methylphenylporphinato)indium (III) in Fig. 1 shows that as the temperature rises, the phenyl signals broaden and finally collapse into a pair of doublets at approximately 100°. Spectral changes were reversible with temperature. The resonance at 3.18 p.p.m. resulted from the porphine pyrrole protons. Resonances at 2.06 and 2.36 p.p.m. were assigned to the *ortho*-protons; resonances at 1.61 and 1.69 were assigned to the *meta*-protons (2).

The room temperature spectrum has been assigned an *AA'BB'* pattern in which the two different *ortho*- and *meta*-protons are nonequivalent due to restricted rotation about the *meso*-carbon to phenyl (carbon carbon) bond. As the temperature was elevated, the rotation became fast on the NMR time scale, appearing to yield equivalence of *ortho*- and the *meta*-protons. No attempt was made to obtain accurate kinetic parameters for this highly coupled spin system; the rate of averaging can be estimated (3) as 66/sec. at the coalescence temperature of approximately 60° for the *ortho*-protons: ($\Delta G^{\ddagger}_{333}$ = 16.8 kcal./mole).

The concept of restricted rotation about the carbon-to-carbon bond is strongly supported by X-ray diffraction studies on porphines and porphine complexes (4). Such studies have indicated that the *meso*-phenyl rings are tilted at an angle to the mean plane of the porphine ring (5–7). This angle was found to be approximately