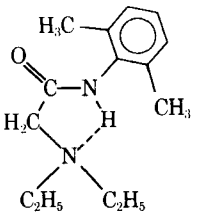

I

ration for the molecule and dimerization by intermolecular hydrogen bonding.

Related data were obtained in this Institute following some IR studies on the effect of systematically changing the steric and polar properties of R and R′ on the configurational and hydrogen bonding properties of the amide group in *N*-alkylamides and benzanilides of the general type R—CONH—R′. In some of these molecules, *cis*- and *trans*-forms of the amide group exist in equilibrium with one another in dilute solution (2, 3). But if an attractive polar interaction is introduced between an electronegative atom in the R group and the amido hydrogen, the *trans*-planar configuration of the —CONH— group is stabilized to the exclusion of the *cis*-configuration (3).

In the lidocaine molecule, there is a possibility of polar interaction between the nitrogen atom of the 2-diethylamino group and the amido hydrogen. Three 2′,6′-xylidides [$RCONHC_6H_4(CH_3)_2$, in which R = $CH_3CH_2CH_2$, CH_3OCH_2, and $(C_2H_5)_2NCH_2$] were prepared, and the IR spectra of 0.001 *M* solutions of these compounds in carbon tetrachloride were recorded.

The spectrum of butyro-2′,6′-xylidide shows sharp symmetrical NH-stretching bands at 3433 and 3387 cm^{-1} arising from the monomeric *trans*- and *cis*-forms (4) of the amide group, respectively. However, if there is an electronegative oxygen atom in the 3-position as in methoxyaceto-2′,6′-xylidide, a single band is observed at 3401 cm^{-1}. This band is attributed to intramolecular interaction between the ether oxygen and the amido hydrogen atom by analogy with benzxylidide [$C_6H_5CONHC_6H_4(CH_3)_2$] and its 2-fluoro analog (3). In both cases the attractive interaction resulting from the introduction of an electronegative atom at R while simultaneously minimizing steric changes results in further stabilization of the *trans*-configuration of the —CONH— group so that the *cis*-form is not observed. The broad absorptions near 3300 and 3200 cm^{-1}, which normally arise from multimeric *trans*- or *cis*-forms of the amide group (4), are absent from the spectrum of both the butyro- and methoxyacetoxylidide at the 0.001 *M* concentration used throughout this study.

The carbon tetrachloride solution spectrum of lidocaine shows, in contrast, a broad symmetrical NH-stretching absorption at 3320 cm^{-1} confirming the observation described by Neville and Cook (1). No sharp bands due to monomeric *cis*- or *trans*-forms are observed near 3400 cm^{-1}, as would be expected by analogy with the butyro and methoxyaceto compounds. Both the absence of sharp monomer bands and the breadth of the NH-stretching band, as well as its position, are attributed to intramolecular interaction between the lone pair electrons on the tertiary amino nitrogen and the amido hydrogen (I) stabilizing the *trans*-planar configuration of the amide group.

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Effects of Hydraulic Pressure and Nozzle Orifice Size on Delivery Rates of Sprayed Materials

Keyphrases □ Spray processes—effects of hydraulic pressure and nozzle orifice size on delivery rates □ Delivery rates, sprayed materials—effects of hydraulic pressure and nozzle orifice size □ Coating processes—effects of hydraulic pressure and nozzle orifice size on delivery rates of sprayed materials

To the Editor:

Spraying processes are important in many phases of the development and production of certain pharmaceutical dosage forms. The manner in which these processes are carried out can affect the physical appearance, stability, and bioavailability of the product. Therefore, the judicious choice of nozzle size and hydraulic pressure for a particular process should improve product uniformity as well as batch-to-batch reproducibility.

A practical equation derived from fundamental flow theories (1–3) applicable to an airless spray system is:

$$R = KD^2\sqrt{\frac{P}{\rho}} \qquad \text{(Eq. 1)}$$

where R = volumetric rate of fluid delivery, D = diameter of nozzle orifice, P = hydraulic pressure, ρ = density of material, and K = proportionality constant. This equation predicts that the flow rate is directly proportional to the cross-sectional area of the nozzle orifice and to the square root of pressure. Also, flow is inversely proportional to the square root of the density of the liquid. Therefore, graphs of flow rate *versus* square root of pressure, diameter

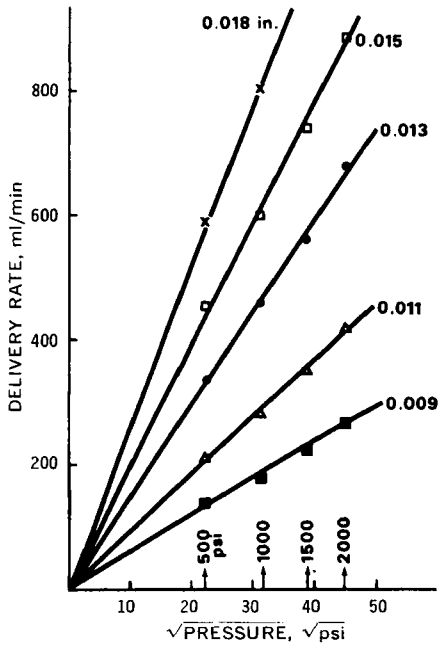

Figure 1—*Characteristic profile showing the effects of pressure on the delivery rates of water.*

squared, or density$^{-1/2}$ will all result in straight lines passing through the origin.

A recent article (4) reported the effects of hydraulic pressure and nozzle size on the spray rate of various liquid systems. For the cases studied, it was concluded that: *(a)* a linear relationship existed between hydraulic pressure and spray rate, and *(b)* a linear relationship existed between nozzle orifice diameter and spray rate, although direct dependence on orifice area had been expected. While the author indicated that the second finding was unexpected, the first finding may also be considered outside the generally

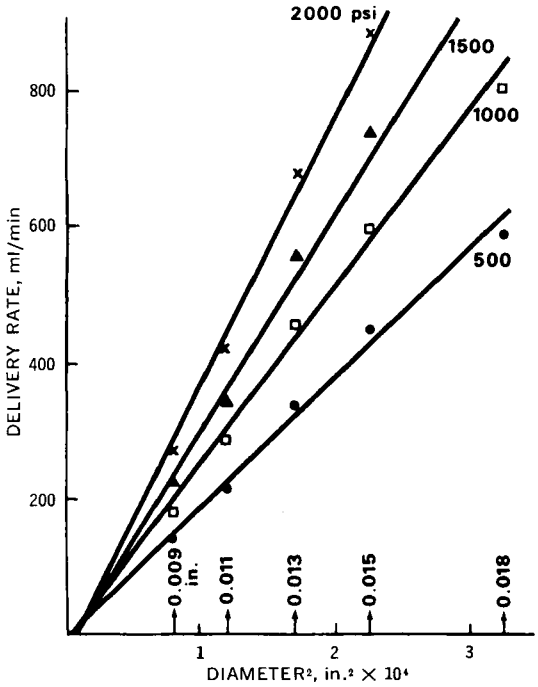

Figure 2—*Dependency of the delivery rates of water on nozzle orifice size.*

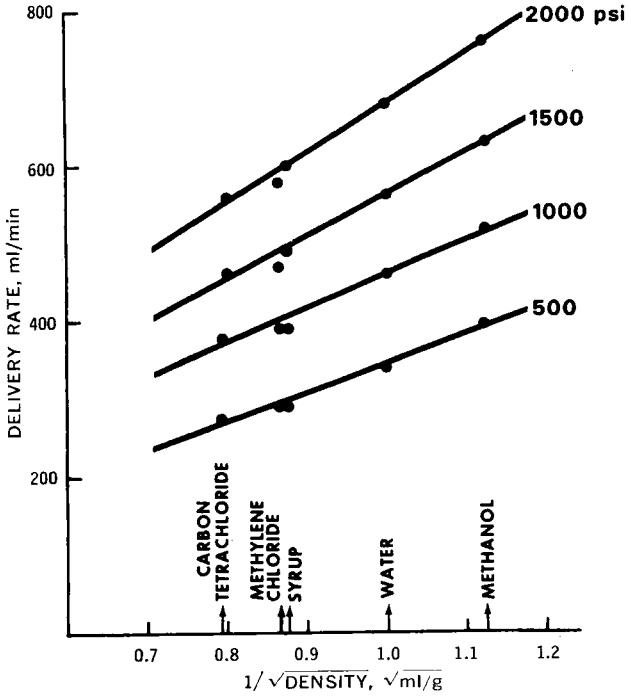

Figure 3—*Effects of density on the delivery rates of liquids.*

accepted theory of fluid mechanics as described by Eq. 1. Cognizance is taken of the fact that if the published data relating to the nozzle orifice diameter had been evaluated on the basis of Eq. 1, some agreement with theory would have been observed.

To test the validity of the accepted theory on pharmaceutical systems, studies were designed to determine the influence of pressure, orifice size, and density on spray rate. The volume of liquid delivered from airless spray equipment[1] in 1 min was measured for pressures from 500 to 2000 psi and spray tips from 0.02 to 0.05 cm (0.009 to 0.023 in.) in diameter. Water, methylene chloride, carbon tetrachloride, methanol, and syrup (65% w/w sucrose) were evaluated.

Figure 1 shows the effect of pressure on the delivery rate of water for five nozzle orifice sizes. The linear relationship is evident when the delivery rates are plotted as a function of the square root of pressure. Furthermore, the data extrapolate to zero delivery at zero pressure for all nozzle sizes as predicted by Eq. 1. These data points can be replotted as a function of the nozzle diameter squared. When presented in this manner, the expected linearity is obtained (Fig. 2). Here again, extrapolation of the least-squares line through the origin is in agreement with theory.

The effects of pressure on the delivery rates of methanol, methylene chloride, carbon tetrachloride, and syrup were compared with water. Each of these four liquids showed the same dependencies on pressure and orifice size as did water but varied in the amounts delivered under the same conditions. Since these liquids differed in both viscosity and density,

[1] Alemite 7860 pump, Alemite Division, Stewart-Warner Corp., Chicago, Ill., and flat spray tungsten carbide nozzles, Spraying Systems Co., Wheaton, Ill.

independent measurements were made on methylcellulose solutions having essentially constant densities but varying viscosities up to 200 cps. The delivery rates of all of the methylcellulose solutions were nearly identical, indicating that viscosity is not a determining factor under the study conditions. Based on these observations, the differences in delivery rates can be attributed to the effect of density. The data in Fig. 3 illustrate this dependency on density. Here the inverse square-root relationship predicted by Eq. 1 seems to hold well for all test conditions.

The experimental data appear to be in good agreement with theoretical predictions. Using airless spray equipment, the delivery rate was found to be: *(a)* directly proportional to the square root of pressure, *(b)* directly proportional to the area of the nozzle orifice, and *(c)* inversely proportional to the square root of density.

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Metabolism of Δ^1-Tetrahydrocannabinol by Mouse Hepatic Microsomes: Identification of 6α-Hydroxytetrahydrocannabinol

Keyphrases □ Tetrahydrocannabinol—metabolism by mouse hepatic microsomes, identification of 6α-hydroxytetrahydrocannabinol □ 6α-Hydroxytetrahydrocannabinol—identification, metabolism of tetrahydrocannabinol by mouse hepatic microsomes □ Marijuana—metabolism of tetrahydrocannabinol by mouse hepatic microsomes, identification of 6α-hydroxytetrahydrocannabinol

To the Editor:

The body of knowledge concerning the biotransformations of Δ^1-tetrahydrocannabinol has grown considerably in the past few years (1). However, the nature of the transformations in the mouse has not been firmly established, even though it has been used in studying the pharmacology of tetrahydrocannabinol. Several reports on distribution (2–5) suggested that the principal metabolites in this species are hydroxytetrahydrocannabinols, in analogy with those isolated from rats, rabbits, monkeys, and humans. The purpose of this study was to identify the major metabolites of ^{14}C-Δ^1-tetrahydrocannabinol produced by the microsomal fraction of mouse liver.

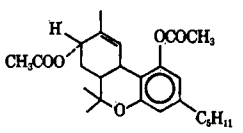
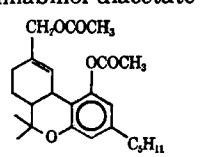
Table I—Metabolism of Δ^1-Tetrahydrocannabinol by Liver Microsomes

TLC Zone	R_f	Assignment[b]	Percent Recovered Products[a] Mouse[c]	Rat[d]
1	0.67	Δ^1-Tetrahydrocannabinol acetate	9.42	19.2
2	0.40	6α-Hydroxy-Δ^1-tetrahydrocannabinol diacetate	26.3	10.0
3	0.30	7-Hydroxy-Δ^1-tetrahydrocannabinol diacetate	34.1	53.3
4	0.13	6α,7-Dihydroxy-Δ^1-tetrahydrocannabinol triacetate (?)	30.2	17.6

[a] Recoveries of added radioactivity were approximately 50%. [b] All materials were acetylated prior to TLC with a mixture of acetic anhydride and pyridine. [c] Adult male CD-1 mice (30–33 g). [d] Adult male Sprague–Dawley rats (190–230 g).

The preparation of the microsomes, the incubation conditions, and the extraction procedure were identical to those previously reported for the rat (6). The residue obtained after extraction of the incubation mixture and evaporation of the solvent was acetylated to minimize decomposition of the products during isolation. The mixtures of acetates were separated by silica gel TLC (30% ether in hexane, developed twice), and the locations of the radioactive zones were determined by autoradiography. The four major zones were eluted and chromatographed a second time in the same manner to obtain materials pure enough for GLC–mass spectrometry. Comparison of

Table II—GLC–Mass Spectrometry[a]

Metabolite	Retention Time, min	Principal Ions[b]
 6α-Hydroxy-Δ^1-tetrahydrocannabinol diacetate	7.0	372 (3.4), 354 (100), 339 (21), 312 (82), 297 (65), 295 (18)
 7-Hydroxy-Δ^1-tetrahydrocannabinol diacetate	7.5	372 (3.8), 354 (43), 312 (100), 297 (28), 259 (31)

[a] The spectra were obtained on a Finnegan 1015 at 70 ev. The conditions were: column, 0.6 m (2 ft) 2% OV-1; column temperature, 180–240° (8°/min); carrier gas, helium; and injector temperature, 255°. [b] The expected molecular ion at 414 could not be obtained at ionizing voltages of 70 or 20 ev. Using a different instrument, Dr. C. E. Hignite was able to observe a molecular ion at 414 for TLC zone 3. Numbers in parentheses refer to relative intensities.