trations as well as minimum inhibitory concentrations for products used were not presented is irrelevant. Our purpose was not to compare the potency of undecylenic acid and tolnaftate (studied at 20–21°) but rather to show differences in their activity (*i.e.*, killing time).

2. Loebenberg *et al.* (2) questioned the use of suspensions *versus* solutions. Suspensions of active ingredients as well as finished products were used to eliminate, as much as possible, problems that frequently occur in *in vitro* testing (*e.g.*, differences in diffusion due to different vehicles). Thus, the use of polyethylene glycol 400 as a solvent for tolnaftate and of ethanol for undecylenic acid (both would be in solution) was, in our opinion, less justified and might have introduced more error into the results than the use of an aqueous suspension for both. Diffusional differences due to the solvent could well overshadow any antifungal action. Also, an "in-use" condition would be mimicked most closely by having the products in aqueous suspension (as might be expected in the humid cutaneous environment).

3. Certainly no claim for "more bioavailability" of undecylenic acid over tolnaftate was made based on an *in vitro* study (1), as suggested by Loebenberg *et al.* (2). We are unaware of any selectivity of polysorbate in aiding dispersion or wetting of any particular product.

4. Preliminary experimentation indicated that rinsing in simple peptone solution did not remove all active drug from the cultures. To ensure complete removal of the active ingredients, the rinsing solutions and procedures described (1) were utilized.

5. It appears to us that if the contact time between the drug and organism were increased, any benefit would be reaped by both compounds and not by one exclusively. The longest contact time was 240 min.

6. Loebenberg *et al.* (2) noted wide variation in our results (1). Although the differences in Table IV are less often significant, the trend is in the same direction as in Table II. Statistical procedures were employed and presented to substantiate the conclusions.

While Loebenberg *et al.* (2) criticized our use of suspensions of commercial powders[1,2], they did not present data on these commercial powders to refute our *in vitro* results. Instead, they compared solutions[1,3] *in vitro*. The vehicles of these products differ markedly (propanol and polyethylene glycol 400, respectively). Therefore, we used an aqueous powder suspension to eliminate vehicle differences and, hence, possible differences in diffusion. Even though lower minimum inhibitory concentrations were noted for tolnaftate, concentration obviously is not the sole criterion of an effective drug.

The introduction by Loebenberg *et al.* (2) of a guinea pig study into a discussion of *in vitro* results is perplexing; here, also, different commercial products were compared[2,4]. Loebenberg *et al.* (2) noted that the average lesion score for one product[2] (16.4) was lower than that for the other[4] (18.2). Whether a difference in scores of 1.8 is significant or of clinical importance is doubtful. Moreover, the guinea pig test system referred to (3) is of limited use. Weinstein *et al.* (3) noted that the system "can have suggestive value only" and that: "The absolute relationship between guinea pig efficacy and clinical utility in acute and particularly chronic human infections has not been established." These investigators (3) also noted that the *in vivo* test can act only as a guide to suggest possible clinical usefulness.

[1] Desenex.
[2] Aftate.
[3] Tinactin.
[4] Cruex.

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Hygroscopicity of Poorly Soluble Porous Substances

Keyphrases □ Hygroscopicity—poorly soluble and insoluble substances, correlation between pore structure and equilibrium moisture content □ Pore-size distribution—overall porosity of poorly soluble substances, effect on hygroscopicity, equilibrium moisture content □ Equilibrium moisture content—poorly soluble substances, effect of overall porosity on hygroscopicity

To the Editor:

The general problem of hygroscopicity of soluble compounds has been defined (1, 2) and was reviewed recently (3). However, the hygroscopicity of poorly soluble compounds has attracted little attention. El-Sabaawi and Pei (4) showed that a correlation exists between pore structure and equilibrium moisture content for insoluble substances. This report extends this principle to insoluble substances with log-normally distributed pore spaces and shows that the equilibrium moisture curves obtained are of a traditional contour. It is presumed that this principle also extends to poorly soluble substances, as defined in the USP.

A liquid with zero contact angle exerts a vapor pressure when confined in a capillary pore of diameter d which is given by the modified Kelvin equation (5):

$$\ln(P/P^*) = -4\gamma V/[RT(d-t)] \qquad \text{(Eq. 1)}$$

where P is the vapor pressure over the liquid in the pore, P^* is the vapor pressure of pure water at the given temperature T, γ is the interfacial tension between the solid and liquid (water), V is the molar volume of the liquid (water), R is the gas constant, and t is the correction factor for the sorbed layer *in* the pore.

For the purpose of the example and for simplicity, t is neglected in the following equation, so Eq. 1 becomes:

$$\ln(P/P^*) = -4\gamma V/RTd \qquad \text{(Eq. 2)}$$

The hygroscopicity of a compound or powder mixture often is studied by means of equilibrium moisture curves. To obtain these curves, a given amount (W_0, expressed in

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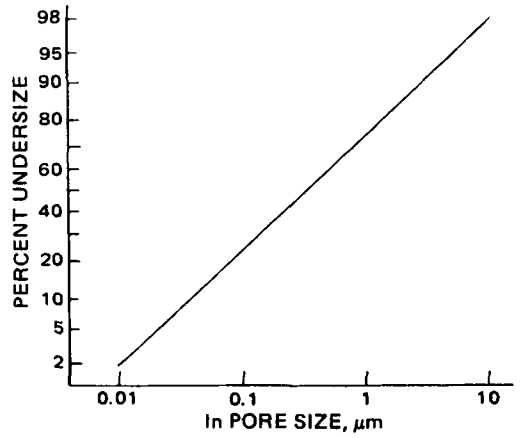

Figure 1—*Example of a log-normal pore-size distribution as used in Table I.*

grams) of a solid substance is exposed in a desiccator to the atmosphere of a saturated salt solution. The relative humidity of the atmosphere is a function of the particular salt used. The experiment is carried out until no more moisture is taken up by the solid, *i.e.*, until its weight, W_f, is constant. The amount $x = (W_f - W_0)100/W_f$ is the moisture content of the solid corresponding to the relative humidity, H, in question. The plot of x *versus* H or of H *versus* x is denoted as the equilibrium moisture curve. An excellent example of this type of experiment that allows interpretation is the work of Sangekar *et al.* (6). However, usually only the apparent kinetics of moisture adsorption are studied and only at one relative humidity (RH).

For an insoluble substance with known pore-size distribution, the equilibrium moisture curve can be deduced from this distribution. This distribution gives the volume fraction of pores with diameters below a certain size. These pores will not allow evaporation of water at pressures above a P value given by Eq. 2. The volume percent of pores (based on the pore volume) can be converted to the volume percent of solids since the total pore volume is known. The pressure, P, can be converted to relative humidity by multiplication by $100/P^*$.

This determination is best illustrated by example. Figure 1 gives an example of a log-normal pore-size distribution with 2% of the pore volume being of diameters below 0.01 μm and 98% being below 10 μm. If the vapor pressure

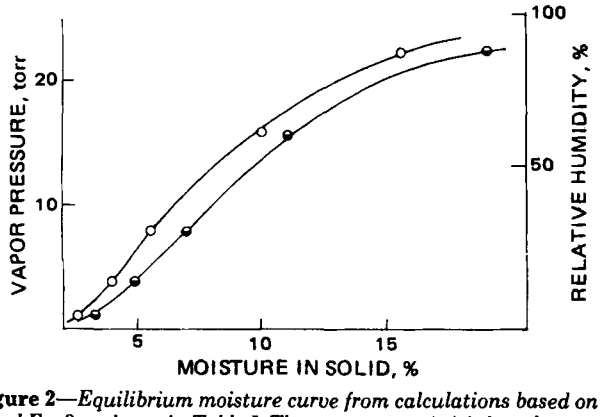

Figure 2—*Equilibrium moisture curve from calculations based on Fig. 1 and Eq. 3 as shown in Table I. The upper curve (○) is based on a solids density of 1.0 g/cm³, and the lower curve (◒) is based on a solids density of 1.25 g/cm³.*

Table I—Calculation of Critical Vapor Pressures from Pore-Size Distribution [a]

Volume Percent of Pores	Pore Diameter, μm	P, torr	Pore Volume[b], %	Moisture Content[c], %
2	<0.01	0.0002	0.4	0.62
11	<0.04	1.24	2.2	3.32
16.5	<0.063	3.78	3.3	4.90
24	<0.1	7.62	4.8	6.98
45	<0.25	15.6	9	12.3
75	<1.0	22.4	15	19.0

[a] Calculated from Fig. 1 and Eq. 3. [b] Assuming 1 cm³ of pores/5 cm³ of solid. [c] Using a true solids density of 1.25 g/cm³ and unit density for water.

above a pore of diameter 10 μm is 25 torr and the vapor pressure of water at the temperature in question is 25.3 torr, then it follows from Eq. 2 that:

$$\ln(P/25.3) = -0.12/d \qquad \text{(Eq. 3)}$$

where P is expressed in torr and d is expressed in micrometers.

A selected number of diameters calculated according to Eq. 3 are shown in Table I. The first column gives the volume percent of pores below the diameter shown in the second column. The vapor pressure corresponding to this diameter is calculated according to Eq. 3 and is shown in the third column. If the overall porosity is 20%, *i.e.*, if there is 1 cm³ of pore space in 5 cm³ of solid volume (*i.e.*, 4 cm³ of actual solid), then the percent of pore volume is as shown in the fourth column. This value is converted to percent moisture content as follows. If, as shown in line 2 of Table I, there is 2.2% of pore volume below 1.24 torr and if the solid has a true density of ρ, then the amount of solid (4 cm³) is $(4/\rho)$ g and the amount of water is 11% of 1 cm³ (1 g), *i.e.*, 0.11 g. Hence, the percent of moisture is $11/[(4/\rho) + 0.11]$.

Figures calculated for a value of $\rho = 1.25$ g/cm³ are shown in the fifth column of Table I and in Fig. 2. Figure 3 is an example taken from the literature (6). The slightly sigmoid nature of the curve in Fig. 2 may not be present in data reported in the literature since, in most cases, the equilibrium moisture curves are not precise below ~35% RH. Furthermore, for the example in Fig. 2, if the solid in a somewhat moist state was prepared for the experiment

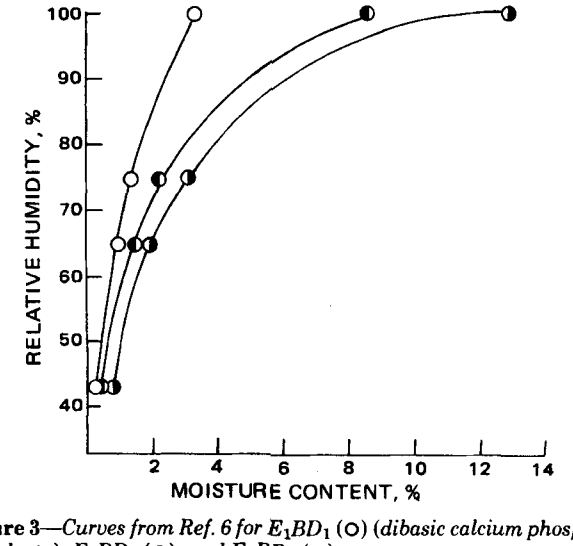

Figure 3—*Curves from Ref. 6 for E_1BD_1 (○) (dibasic calcium phosphate dihydrate), E_6BD_3 (◐), and E_8BD_2 (◑).*

by drying at 26° at a pressure of >3 torr (13% RH) or the equivalent at a higher temperature, then only the last five points would be involved and the shape would lose the initial sigmoid nature.

These comments are confined to situations where no gross swelling or pore-size distortion occurs during moisture uptake (7, 8). Furthermore, the solubility must be sufficiently low so that no significant volume changes or vapor pressure changes can result from dissolution.

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Enhancement of Rectal Absorption of Drugs by Adjuvants

Keyphrases □ Absorption, rectal—enhancement by certain adjuvants □ Salicylate—enhancement of rectal absorption of theophylline and lidocaine □ Theophylline—enhancement of rectal absorption by salicylate □ Lidocaine—enhancement of rectal absorption by salicylate

To the Editor:

Rectal drug administration has the potential of overcoming some limitations encountered with other dosage forms. In this communication, we report that the rectal absorption of many drugs is facilitated markedly in the presence of certain adjuvants.

Although specific surfactants were shown to promote drug absorption from the rectum (1), their use seems to damage the rectal mucosa, reducing their suitability as absorption promoters. The adjuvants described in this report appear to function differently.

These observations were made using an *in situ* perfusion method of the rectum similar to that reported by Crommelin *et al.* (2). Six milliliters of drug solution was circulated at a rate of 2 ml/min at 38° through an ~2-cm section of the rectum of male Sprague–Dawley rats weighing 275–300 g. The amount of drug remaining in the perfusate was analyzed by high-pressure liquid chromatography as a function of time. Blood levels also were measured in blood samples taken from a vein in the leg of a rat.

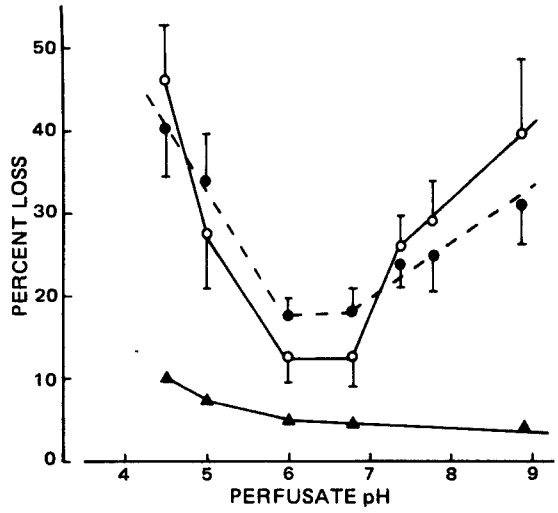

Figure 1—*Percent loss of salicylate or its acidic form (--●--) and theophylline (—○— and —▲—) after 1 hr from the perfusate in the rat rectum. Initial concentrations were 0.5% sodium salicylate (--●--), 0.5% sodium salicylate and 200 μg of theophylline/ml (—○—), and 200 μg of theophylline/ml (—▲—).*

Figure 1 shows the effect of salicylate at various pH values on the disappearance of theophylline from the perfusate in the rat rectum after 60 min of perfusion. The loss of theophylline from the perfusate in the absence of salicylic acid or salicylate was small at all pH values. However, in the presence of 0.5% salicylate at various pH values, the disappearance of theophylline was enhanced greatly, especially below pH 5 and above pH 7.4.

As shown in Fig. 1, the loss of theophylline paralleled the loss of salicylate from the perfusing solution; the greater the disappearance of salicylate from the perfusate, the greater was the loss of theophylline. Furthermore, contrary to the situation with some surfactants, the promotive effect of salicylate did not reflect a permanent change in the rectal membrane, because the effect of salicylate was eliminated by washing the rectum with buffer for 5 min at

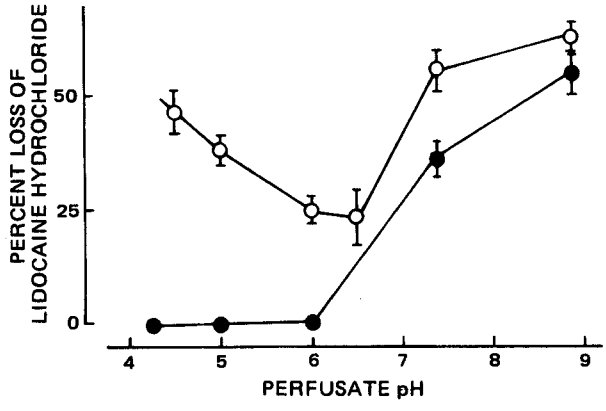

Figure 2—*Effect of pH and salicylate on the disappearance of lidocaine hydrochloride from a perfusate in the rat rectum after 1 hr. The initial lidocaine hydrochloride concentration was 500 μg/ml (○ and ●), and the sodium salicylate concentration was 0.5% (○).*

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