acid-base-washed, silane-treated, flux-calcined diatomaceous earth[9], 80/100 mesh. The column was conditioned 48 hr. at 275°. The operating conditions were: column temperature, 105°; injector temperature, 190°; detector temperature, 250°; and carrier gas, N_2, 50 ml./min.

Sample Injection—Four to eight microliters was injected at 105°, and the chromatogram was run until the 5-fluorouracil peak appeared (approximately 12 min.). *Before injecting the next sample*, it was necessary to increase the column temperature to 175° for 5 min. to drive off other components present in the dialysate having much longer retention times than 5-fluorouracil, which would otherwise interfere with subsequent determinations.

Procedure for Blood and Plasma pH Profiles

Blood Samples—The blood samples were collected in heparinized Vacutainers of 10-ml. capacity, pooled, and mixed prior to pH adjustment.

Plasma Samples—Standard plastic transfer packs containing plasma with anticoagulant citrate dextrose solution USP were used. Subsequent pH adjustment, dialysis, and GC were exactly as described for blood.

Adjustment of pH—Approximately 15 ml. of blood or plasma in a beaker was adjusted to the desired pH by dropwise addition of 1 *N* HCl or 1 *N* NaOH with the aid of a pH meter[10] equipped with a glass–calomel combination electrode. The sample was immediately transferred to a dialysis cell.

Dialysis—Dialysis cells were prepared as described previously and filled immediately after assembly. To one compartment, 5.0 ml. of blood or plasma was added with a 5.0-ml. gas-tight syringe (Hamilton). To the other compartment, 4.80 ml. of 0.9% sodium chloride solution was added, along with 200 μl. of a standard 5-fluorouracil solution containing 0.75 mcg./μl. The cells were sealed with nylon screw plugs and dialyzed 22 hr. as described previously.

Evaporation of Samples, Preparation of Silyl Derivatives, and GLC Conditions—Procedures were the same as described in the description of method for total recovery of 5-fluorouracil.

5-Fluorouracil Standard for GLC—The volume of standard 5-fluorouracil solution equivalent to the 5-fluorouracil present in the dialysate taken for assay was calculated as follows:

$$\text{volume of standard solution} = \text{ml. dialysate evaporated} \times \frac{\text{milliliters standard solution added to cell}}{10} = V_{sl} \quad \text{(Eq. 1)}$$

For example, with 3.0 ml. of dialysate taken for assay:

$$V_{sl} = 3.0 \times \frac{0.200}{10} = 0.060 \text{ ml.} \equiv 60\ \mu\text{l.} \quad \text{(Eq. 2)}$$

This volume, V_{sl}, of 5-fluorouracil standard solution was transferred to a 50-ml. round-bottom flask with a 100-μl. syringe (Hamilton); the 0.3 ml. of 1 *N* HCl was added, and the solution was evaporated to dryness on a rotary evaporator. Subsequent preparation of the silyl derivative and GC was carried out exactly as described for the samples.

Calculation of Percent Recovery—Peak areas for standards and samples were determined with a planimeter. The percent recovery of 5-fluorouracil is given by:

$$\frac{\text{area of sample peak}}{\text{area of standard peak}} \times 100 = \text{percent recovery} \quad \text{(Eq. 3)}$$

[9] Gas Chrom Q, Anspec Co., Inc., Ann Arbor, Mich.
[10] Beckman Expandomatic.

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Mechanism of Action of Tablet Disintegrants: Correlation of Tablet Mean Pore Diameter and Porosity

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Abstract □ Data from a previous study were used to obtain correlations between log mean pore diameter and porosity of tablets. Cornstarch appears to modify this relationship of mean pore diameter and porosity in magnesium oxide and magnesium trisilicate tablets. Dilution of salicylamide with cornstarch and aspirin by three different disintegrants (cornstarch, cation-exchange resin, and waxy maise starch) had little effect on this relationship. The one exception was 10% cationic-exchange resin–90% aspirin mixture. The equation, $\log y = mX + b$, where y is the mean pore diameter and X the porosity, can be used to calculate the mean pore diameter from the more easily obtained porosity.

Keyphrases □ Tablet disintegrants—mechanism of action, correlation of tablet mean pore diameter and porosity □ Disintegrants, tablets—mechanism of action, correlation of tablet mean pore diameter and porosity □ Porosity, tablets—correlated with tablet mean pore diameter □ Pore diameter (mean), tablets—correlated with porosity

Previously the effect of different variables on tablet porosities and tablet mean pore diameters was reported (1). The effect of compression pressure (three levels) and cornstarch concentration (four levels) on porosity and mean pore diameter using four different drugs was studied. A second experiment was used to determine

Table I—Slopes and Intercepts of Significant Log of Mean Tablet Pore Diameters *versus* Porosities Linear Regressions

Slope	*y*-Intercept	Formulation
0.6311[a]	0.309	MgO
2.025[b]	−0.262	Mg trisilicate + average starch
2.364[a]	−0.409	Mg trisilicate + 5% starch
2.625[b]	0.0855	Average four drugs + 5% starch
2.933[a]	0.0578	Average four drugs + average starch
2.954[a]	0.0188	Average four drugs
3.979[a]	0.637	Salicylamide + 15% starch
4.148[a]	0.586	Salicylamide
4.275[a]	0.590	Salicylamide + 10% starch
4.384[a]	0.555	Salicylamide + average starch
6.466[a]	−0.0518	Aspirin + 10% waxy maise starch
6.571[b]	0.0534	Aspirin + 5% waxy maise starch
6.643[b]	0.0751	Aspirin + average resin
6.653[b]	0.0133	Aspirin + average three disintegrants
6.791[a]	−0.102	Aspirin
6.824[a]	−0.0312	Aspirin + average starch
8.927[a]	−0.431	Aspirin + 10% resin

[a] Correlation coefficient significant at 5%. [b] Correlation coefficient significant at 10%.

the effect of pressure (three levels) and three different disintegrants (cornstarch, cation-exchange resin, and waxy maise starch) at four different concentrations on the porosity and mean pore diameter of aspirin tablets. The object of this paper is to report the correlations of mean pore diameters and porosities of the tablets made in the previous study.

DISCUSSION

Traxler and Baum (2) reported that when packed beds of black slate or silica were used, log pore diameter (centimeters) *versus* percent porosity gave linear correlations. In addition, the slopes of several kinds of pulverized materials of widely varying characteristics and particle-size fractions were found to be similar, but the values of the *y*-intercepts differed. The diameters and porosities of the packed beds used by Traxler and Baum (2) were greater and covered a shorter range than the ones used in this study.

Nogami *et al.* (3) plotted pore diameters *versus* porosities for aspirin–starch tablets and claimed linear regressions, but they did not show the lines or report the slopes. They claimed the slope for the tablets made from the smallest aspirin particle-size distribution was less than the two slopes obtained using two larger sized aspirin particle-size distributions.

The data previously reported (1) were plotted as log mean pore diameter (microns) *versus* porosity for the different combinations of variables at the three compression pressures (1000, 3000, and 6000 psig.). Only regression lines with correlation coefficients greater than 0.99 are given in Table I. High correlation coefficients are necessary because each regression is based on only three data points. Seventeen significant correlations were found.

It can be seen that the slopes may be grouped according to the drug, which is the major component in the formulation. The minor component is the disintegrant. Even when the data for all four drugs were averaged, significant correlations appeared. When the data for the drugs alone were used, only magnesium trisilicate did not show a significant correlation. Magnesium trisilicate when diluted with cornstarch did show a correlation of log mean pore diameter and porosity. This occurred when the starch effect was averaged over all concentrations and at 5% starch concentration. Since this drug had an average particle size much smaller than the starch, the addition of starch may have modified the particle packing so as to result in significant correlations.

An average amount of the four drugs used alone or diluted with starch showed significant correlations. Apparently, the combined effect of the other three drugs overcame the nonlinear effect of the magnesium trisilicate.

Pure magnesium oxide gave a correlation but when it was diluted with cornstarch, there were no significant correlations. In this instance the starch appeared to have the opposite effect it had on magnesium trisilicate.

Salicylamide with and without starch, specifically at 10 and 15% starch concentrations, resulted in significant regressions. Starch in the concentrations used with the salicylamide did not appear to affect significantly the relationship of mean pore diameter and porosity of the tablets.

Aspirin alone and with the three different disintegrants gave slopes between 6.47 and 6.82. Aspirin plus 10% cationic-exchange resin gave a slope different from the rest of this group. This seems to indicate that at 10% resin concentration, a unique mixture is formed which has different characteristics which modify the basic packing characteristics of aspirin.

It seems that the disintegrant modifies the relationship of mean pore diameter and porosity in inorganic substances, *e.g.*, magnesium oxide and magnesium trisilicate with greater than 5% starch, giving rise to nonlinear effects. Dilution of salicylamide by starch and aspirin by three different disintegrants had little effect. The exception is 10% cationic-exchange resin–90% aspirin mixture.

The correlations indicate that mean pore diameters of tablets can be calculated from the more easily obtained porosity parameter. The equation, $\log y = mX + b$, where y is the mean pore diameter and X is the porosity, can be used to calculate the mean pore diameter.

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