situations can arise during sampling and/or replenishment in organ perfusion studies:

1. The elimination rate constant (K) increases when the perfusate volume is depleted by samples being taken and not replenished or by excretion of urine/bile in an open system, since $K = Q/V_R$.
2. The concentration of drug in the perfusate decreases by dilution as lost volume is replenished. As the concentration in the perfusate is diluted, the concentration in the organ decreases to reestablish an equilibrium.

Volume replenishment for the purpose of maintaining the viability of the organ is essential, whereas volume correction either by replenishment or mathematical manipulation is not necessary for pharmacokinetic purposes. This reflects the fact that the elimination rate of a drug in a perfused organ has little meaning unless the volumes and flow rates used mimic those observed *in vivo*. Even if these requirements are met, elimination rate is a function of reservoir volume and will thus change with changes in volume.

The pharmacokinetic parameter that should be determined in organ perfusion studies is clearance, since this parameter describes the intrinsic ability of the isolated organ to eliminate or metabolize the drug independent of extraneous variables such as binding to other tissues or clearance by other organs. Organ clearance, however, is independent of reservoir volume, as shown:

$$CL_o = Q\left(\frac{C_{in} - C_o}{C_{in}}\right) \qquad \text{(Eq. 2)}$$

Similarly in the case of the liver and kidney, the biliary and renal clearance of intact drug (CL_{id}) is also independent of perfusate volume:

$$CL_{id} = \frac{\Delta X}{C_{mid}} \qquad \text{(Eq. 3)}$$

where ΔX is the amount of intact drug excreted and C_{mid} is the perfusate concentration at the midpoint of the excretion interval. Both equations are clearly independent of perfusate volume changes.

Therefore, if the primary pharmacokinetic objective of an organ perfusion study is to determine the organ clearance, it becomes apparent that volume correction for the purpose of pharmacokinetic calculations is not warranted. On the other hand, volume replenishment for the purpose of maintaining hydration, nutrient supply, energy sources, and, therefore, organ viability is important and must be considered during the design of organ perfusion studies. In addition, it must be realized that replenishment may be more critical for open systems such as the kidney and liver (where losses occur not only during sample withdrawal but in the urine and bile) than for closed systems such as the heart, lung, muscle, *etc.*

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Rebound Phenomenon Observed During the Compaction of Samples in the Fisher Subsieve Sizer for Measuring Specific Surface Area of Griseofulvin

Keyphrases □ Specific surface area—Fisher subsieve sizer, rebound phenomenon observed during compaction, griseofulvin □ Compaction, tablet—rebound phenomenon, Fisher subsieve sizer, specific surface area of griseofulvin

To the Editor:

The air-permeability technique for measuring the specific surface area of powders is a well-recognized technique. It has been used for more than 30 years by the cement industry. The American Society of Testing Materials (1) as well as various European societies have adopted it as a standard method for measuring the fineness of cement by means of the Blaine apparatus, using the measurement of the resistance offered to the air flow by a packed bed of powder at a defined porosity level.

Recently the air-permeability method has also been included in the USP XX for measuring the fineness of griseofulvin in terms of its specific surface area (SSA). The USP monograph on griseofulvin specifies SSA limits between 1.30–1.70 m^2/g. For making the measurements, however, a procedure based on measuring at a range of porosities and using a Fisher subsieve sizer (FSS) apparatus is described. In the normal use of FSS-apparatus, it is common to take a sample weight equal to the density value of the sample material. The USP XX, however, suggests the use of 1.25 times the weight of material density as sample weight. This recommendation is based on an assumption that the SSA-value should be determined at very low porosities (down to 0.25 range), which cannot be reached easily when using the FSS-chart scale and sample weight equal to the density of a material. The basis of this recommendation is an earlier study by Edmundson and Tootil (2) who advanced an hypothesis that very low porosities are desirable for achieving a uniform packing of the powder bed and for getting a maximum SSA value which may be considered a unique value for a given powder sample.

A series of SSA measurements were made on a number of griseofulvin samples using the FSS apparatus and taking

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the sample weight suggested in the USP XX. Difficulty was experienced in compressing certain samples to powder bed porosities below the 0.50 range. Not only was an unusually high amount of force required, but it was almost impossible to compress some of the samples below 0.45 porosity by manual force.

The ASTM-Standard C 204-79 (1) (under its Note [7]) contains instructions for selecting the "Size of Test Sample" to be used with the Blaine permeameter:

> "The weight of sample shall be adjusted so that a firm, hard bed is produced by the compacting process. In no case, however should more than thumb pressure be used to secure the proper bed, nor should such thumb pressure be used that the plunger "rebounds" from the cell top when the plunger is removed."

To examine the influence of high force required to achieve sample-bed porosities of the lower range (<0.50) and any associated "rebound" phenomena, we compressed the griseofulvin samples to different porosity levels, as indicated on the FSS-chart line. After withdrawal of the FSS compressing plunger, the sample height in the FSS cell was measured by using a slide-gauge. The mean particle diameter and the corresponding SSA were then obtained from the FSS chart. Before compressing the bed to the next porosity level, the FSS cell was attached to a modified Blaine permeameter, the time of flow of air measured, and the corresponding SSA calculated according to the basic Kozeny-Carman equation (3), using the calculated porosity from the powder bed dimensions.

The results summarized in Table I show that the use of a higher sample weight of griseofulvin, as suggested in the USP XX, and its compression to bed porosities <0.50 level can lead to a rebound and expansion of the powder bed. This is seen in columns 2 and 3 of Table I where there is shown an appreciable difference between the corrected porosity and the calculated porosity (ϵ_3) obtained from the powder height measurements. These data imply that due to this rebound effect at the porosity range of 0.45 the SSA values read from the FSS chart will also be in error. This is also reflected in a greater deviation between the SSA values obtained with the FSS and Blaine apparatuses.

Table I [a]—SSA-Values of Griseofulvin Sample Measured at Different Porosities using FSS and Blaine Permeameter [a]

ϵ_1 [b] Indicated Porosity	ϵ_2 [c] Corrected Porosity	ϵ_3 [d] Calculated Porosity	L, cm [e] Sample Height Measured	S_{w1} [f] (m^2/g) from FSS	S_{w2} [g] (m^2/g) Blaine permeameter	S_{w2} [h]/S_{w1}
		0.6422	2.78	0.884	0.885	1.00
0.72	0.65	0.6447	2.80	0.844	0.907	0.07
		0.6460	2.81	0.844	0.898	1.06
		0.5940	2.45	1.116	1.161	1.04
0.68	0.60	0.5948	2.45	1.093	1.163	1.06
		0.5965	2.46	1.093	1.164	1.06
		0.5405	2.16	1.420	1.447	1.02
0.64	0.55	0.5458	2.19	1.314	1.410	1.07
		0.5468	2.19	1.383	1.421	1.03
		0.5001	1.99	1.619	1.680	1.04
0.60	0.50	0.5001	1.99	1.568	1.690	1.08
		0.5136	2.04	1.520	1.595	1.05
		0.4594	1.84	1.584	1.758	1.11
0.56	0.45	0.4737	1.89	1.584	1.715	1.08
		0.4859	1.93	1.397	1.685	1.21

[a] Griseofulvin, ρ = 1.455 g/cm³ FSS-sample cell; sample weight used (1.455 × 1.25) = 1.819 g; supplied by Leo Pharmaceutical Products, Copenhagen, Denmark. [b] ϵ_1, indicated porosity on the FSS chart. [c] ϵ_2, corrected porosity due to higher sample weight (= $\rho \times 1.25$). [d] ϵ_3, calculated porosity from the measured sample height. [e] L, measured sample height. [f] S_{w1}, specific surface area obtained from particle diameter read at the FSS chart. [g] S_{w2}, specific surface area calculated from the ϵ_3-porosity value and measurement with Blaine-permeameter. [h] S_{w2}/S_{w1}, ratio of the SSA values from Blaine permeameter and Fisher subsieve sizer.

It is therefore proposed that the USP should adopt the procedure of measuring the SSA values at one defined porosity level, such as $\epsilon \sim 0.50$ used in the ASTM Standard. Another proposal is to leave the choice of permeameter open, provided a suitable calibration of the apparatus has been undertaken, more particularly of the sample cells.

In the calculation of SSA from air-permeability data, use is made of the Kozeny-Carman equation. In using this equation, it is important to know the accurate and precise values of the bed porosity as well as the length, diameter, and the volume of the compacted powder bed. For some permeability cells, such as that for the Blaine permeameter, a so-called mercury displacement method of calibration is frequently employed, and its details are also specified in the ASTM-Standard (1). The Fisher subsieve sizer, however, does not use any particular technique to calibrate its cell dimensions or the porosity setting. Edmundson (3) used a traveling microscope for this purpose, but it cannot be suggested for routine purposes.

We used a simple method to calibrate the permeability cells. The powder samples were compressed in the permeability cells and then ejected out carefully, by means of a suitable rod. The plug dimensions such as height and diameter were measured by means of a precision micrometer and the bulk volume was then calculated from these dimensions. Table II summarizes comparative values of such dimensions for some Blaine permeability cells, using the direct dimensions measurement and the mercury displacement methods.

A separate measurement of the metal components of the cells by means of a gauge confirm the directly measured dimensions of the powder plug. The direct measurement method is of more relevance to the actual state of the compressed powder plug used during the permeability measurements and it is easier to use. This method can be employed with different types of cells, including the Fisher subsieve sizer cell or the small bore tubes (~0.6 cm diameter) where the mercury-displacement method is not only tedious but impractical. Therefore, the direct measurement method is preferred for calibration.

For routine calibration purposes, it is advisable to use malleable materials for preparing the compressed powder plugs. The plugs should be compressed to porosities that are low enough to give firm plugs which can withstand handling, but not so low that expansion of the powder bed occurs because of "relaxation" after ejection from the cell.

Table II—Dimensions of Blaine Permeameter Cells Determined by Two Calibration Methods

Blaine cells	Mercury Displacement Method [a] Length, cm	Diameter, cm	Volume, cm^3	Direct Measurement of Dimensions [b] Length, cm	Diameter, cm	Volume, cm^3
A	(1.419) [c]	(1.270)	1.798	1.478	1.272	(1.878)
B	(1.450)	(1.270)	1.838	1.500	1.268	(1.895)

[a] Means of two measurements as stated in ASTM C-204-79. [b] Means of 10 measurements using separate compactions for each determination (*RSD* <0.4%). [c] Parentheses indicate values not experimentally determined.

Using very fine particle size materials, self-supporting plugs can be formed without the use of any additional binders. We found the addition of a mixture of micronized lactose and 5% magnesium stearate is suitable to improve flow properties.

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Physicochemical Interpretation of pH-Stat Titration of Amorphous Aluminum Hydroxycarbonate

Keyphrases □ Amorphous aluminum hydroxycarbonate—pH-stat titration, physicochemical interpretation, fiber optic Doppler anemometer analysis, dissolution data □ pH-stat titration—correlation between the *in vitro* test and *in vivo* acid neutralization, amorphous aluminum hydroxycarbonate, fiber optic Doppler anemometer analysis, dissolution data

To the Editor:

The pH-stat titration of antacids (1) is a valuable *in vitro* test because it has been correlated with *in vivo* acid neutralization (2). In contrast to the acid-neutralizing capacity test and the acid-consuming capacity test, which are essentially indirect assays, the pH-stat titration measures the rate of acid neutralization (3). The pH-stat titration has provided insights into (*a*) the structure of aluminum hydroxycarbonate (4, 5); (*b*) the adsorption of polybasic acids (6), polyols (7), polymers (8), and surface-active agents (8) by aluminum hydroxycarbonate; and (*c*) the interaction of aluminum hydroxycarbonate and magnesium hydroxide (9, 10).

The pH-stat titrigram of aluminum hydroxycarbonate contains three phases rather than the linear rate of acid neutralization expected for an acid–base titration (1). As seen in Fig. 1, the reaction is characterized by an initial rapid reaction (phase I) which abruptly converts into a slow zero-order reaction (phase II) which gradually transforms into a more rapid zero-order reaction (phase III). In contrast, antacids such as sodium bicarbonate, calcium carbonate, magnesium hydroxide, and hydrotalcite exhibit the expected linear pH-stat titrigram (9, 10). The purpose of this communication is to describe the

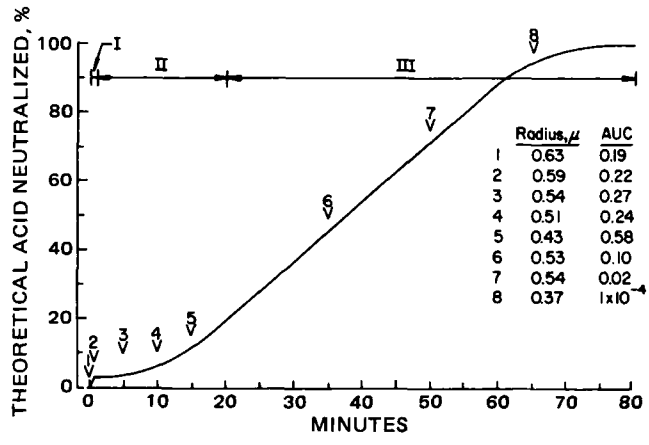

Figure 1—*pH-Stat titration at pH 3, 25° of aluminum hydroxycarbonate gel, which was examined at the indicated points by FODA.*

physicochemical reactions that are responsible for the three phases of the pH-stat titration of aluminum hydroxycarbonate.

The pH-stat titration at pH 3, 25° was interrupted periodically, as indicated in Fig. 1, and the apparent particle size was determined by fiber optic Doppler anemometry (FODA)[1] (11). The apparent mean hydrodynamic radius decreased from an initial value of 0.63 μm to 0.59 μm during phase I. A further decline to 0.43 μm was observed during the second phase. The apparent particle size initially increased during the third phase but decreased at the end of phase III.

The fiber optic Doppler anemometer determines particle size based on the measurement of the Brownian motion of colloidal particles. Thus, particle interactions that reduce the Brownian motion of particles will cause the apparent hydrodynamic radius, as measured by the fiber optic Doppler anemometer, to increase. In fact, if particle interactions cause Brownian motion to cease, the particle(s) will not be detected by FODA. Therefore, the apparent mean hydrodynamic radius data should be interpreted in conjunction with measurements of the total signal intensity. This is readily accomplished by integration of the power spectrum [area under the voltage squared *versus* frequency curve (AUC)] (12, 13). Thus, the AUC will be related to the total number of freely diffusing particles. The AUC increased from 0.19 to 0.22 during phase I and further increased to 0.58 during the slow, second phase. The AUC went to zero during phase III. The AUC data suggest that the number of particles exhibiting Brownian motion increased during phases I and II and decreased sharply during phase III.

It was hypothesized recently that aluminum hydroxide and aluminum hydroxycarbonate are composed of three types of particles: primary particles, secondary particles, and aggregates (14, 15). The primary particle is the basic unit: platy crystallites composed of fused six-membered rings of aluminum joined by double hydroxide bridges. The secondary particles are formed from primary particles arranged in a turbostratic type of arrangement due to the cohesive strength of van der Waals forces. Aggregates are composed of secondary particles formed in response to the balance of attractive and repulsive forces described by

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