the rate of skin permeation (Table I), so a constant skin-permeation profile can be achieved. By calculation, systems A and B release nitroglycerin at a flux ($Q/t^{1/2}$) of 500 and 875 $\mu g/cm^2/hr^{1/2}$, respectively (Fig. 4). The difference in release fluxes between these two systems is expected from the difference in drug-loading doses in the devices (11).

In summary, the results generated from the present investigation suggest that even though nitroglycerin is released at different rate profiles from these three transdermal delivery systems (Figs. 3 and 4), it penetrates through the hairless mouse skin under, basically, the same rate process (Fig. 2). Additionally, the total nitroglycerin dose delivered through the abdominal skin at 24 hr by each of these transdermal delivery systems is fairly close in magnitude and the difference is statistically insignificant [$F = 0.33$, $F_{0.95}(2,25) = 3.39$] (Table I), although the loading dose varies greatly from one system to another, and the percentage of the loading doses released during a 24-hr elution study is substantially different.

Additional studies are currently underway to generate evidence on the feasibility of using hairless mouse skin as the viable substitute for human skin in studying the transdermal controlled administration of systemically active drugs from novel drug delivery systems. A more detailed report will be written when more data become available.

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Yie W. Chien[x]
Prakash R. Keshary
Yih C. Huang
Pramod P. Sarpotdar
College of Pharmacy
Rutgers University
Piscataway, NJ 08854

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Organ Perfusion Studies

Keyphrases □ Organ perfusion—pharmacokinetics, importance of volume replenishment □ Pharmacokinetics—organ perfusion studies, importance of volume replenishment

To the Editor:

Single-pass and recirculating perfused organ systems have been used to study how specific organs of the body handle drugs. The single-pass system has been used extensively to study the influx and efflux of drugs by various organs, whereas recirculating systems have been used more commonly to study metabolism and/or excretion of drugs by these organs. Although both systems are useful, the conservation of drug and perfusion media associated with the recirculating system makes it more economical and allows for longer perfusion experiments even with limited volumes of perfusion medium. However, in recirculating perfusion systems, there are problems associated with volume depletion due to excretion in open systems (*i.e.*, liver and kidney) and sample withdrawal in both closed (*i.e.*, heart, muscle, and lung) and open systems, which must be considered when performing pharmacokinetic analyses of the data derived from these experiments. The following discussion will address these problems.

It has been shown that the rate of elimination of a drug from an isolated organ perfusion system is a function of the perfusate volume (1) according to the following equation:

$$\frac{dC_i}{dt} = \frac{Q}{V_R}(C_i - C_o) \qquad \text{(Eq. 1)}$$

where C_i and C_o are the inflow and outflow concentrations, Q is the perfusate flow, and V_R is the reservoir volume. The elimination rate constant (K) varies inversely with perfusate volume changes since $K = Q/V_R$. Several authors have published on this observation (1–5), and some have attempted to correct the elimination rate for perfusate volume changes (2–5). Other authors have discussed perfusate volume and nutrient replenishment as a means of maintaining the viability of open perfused organ systems, such as the kidney or liver, where there is loss of water and energy sources due to urine and bile excretion (6–8). Two

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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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Wayne A. Colburn[x]
Romulus K. Brazzell
Ihor Bekersky
Department of Pharmacokinetics and Biopharmaceutics
Hoffmann-La Roche Inc.
Nutley, NJ 07110

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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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