tained by summing the individual rates, so that:

$$\frac{d[D_u + M_u]}{dt} = \frac{dD_u}{dt} + \frac{dM'_u}{dt} + \frac{dM''_u}{dt} + \frac{dM'''_u}{dt}$$

where

$$M_u = M'_u + M''_u + M'''_u$$

Then,

$$\frac{d[D_u + M_u]}{dt} = \left[k_d + \frac{k''_f k''_u}{k''_u - K'} + \frac{k'''_f k'''_u}{k'''_u - K'} \right] \times$$

$$[D_0 + k'_0/K']e^{-K't} - \left[\frac{k''_f k''_u}{k''_u - K'} e^{-k''_u t} + \right.$$

$$\left. \frac{k'''_f k'''_u}{k'''_u - K'} e^{-k'''_u t} \right] [D_0 + k'_0/K'] +$$

$$\frac{k'_0}{K'} [k''_f e^{-k''_u t} + k'''_f e^{-k'''_u t} - K' e^{-k'_u t}] -$$

$$\frac{k'_0}{K'} [k_d + k''_f + k'''_f - K'] + k'_u M'_0 e^{-k'_u t} +$$

$$k''_u M''_0 e^{-k''_u t} + k'''_u M'''_0 e^{-k'''_u t} \quad \text{(Eq. 5)}$$

The term $[k_d + k''_f + k'''_f - K'] = 0$, since by definition $K' = k_d + k''_f + k'''_f$, therefore only exponential terms remain.

Equation 5 is thus of the form:

$$\frac{d[D_u + M_u]}{dt} = Ae^{-K't} + Be^{-k'_u t} + Ce^{-k''_u t} + De^{-k'''_u t} \quad \text{(Eq. 6)}$$

where *A, B, C,* and *D* are constants.

When all k_u are large relative to K' and when t is large, all the $e^{-k_u t}$ terms become very small relative to the $e^{-K't}$ term and so Eq. 6 approaches:

$$\frac{d[D_u + M_u]}{dt} = Ae^{-K't} \quad \text{(Eq. 7)}$$

This equation may then be written:

$$\ln \frac{d[D_u + M_u]}{dt} = \ln [\text{const.}] - K't \quad \text{(Eq. 8)}$$

which is the equation of a straight line having a slope equal to $- K'$.

A plot of the log rate of excretion of total drug against time ultimately exhibits a linear section with a slope equal to the sum of the rate constants which govern the first-order processes of drug elimination when a zero-order process is occurring simultaneously.

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⌐⊙⟩ *Keyphrases*

Salicylic acid
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Zero, first-order process—salicylic acid elimination

Deterioration of Nitroglycerin Tablets

Sir:

The effect of packaging and storage conditions on drug product stability is a subject of growing interest and concern (1). We wish to report here our investigations on the relationship between certain novel packaging materials and the deterioration of nitroglycerin tablets.

FDA recently found that a batch of nitroglycerin tablets sealed in aluminum foil was grossly subpotent. The faulty product had been prepared by individually wrapping 0.43-mg. ($^1/_{150}$-grain) nitroglycerin tablets in strips of aluminum foil to which a thin film of polyethylene had been laminated. Each tablet was placed between the polyethylene surfaces of two strips, and the ends were heat-sealed to provide a 25 × 15 mm. cell.

Assays of individual tablets showed that they contained 0–10% of the declared quantity of nitroglycerin (2). However, when the packaging material in one cell was extracted with isooctane, the extract contained 0.36 mg. of nitroglycerin [determined colorimetrically with phenoldisul-

fonic acid (3)] or 84% of the declared quantity. The carbon disulfide extract of another cell exhibited the infrared absorption spectrum of nitroglycerin, when compared to a blank consisting of a carbon disulfide solution of extractives from the laminating adhesive.

Our explanation of these findings is based upon three observed facts: the low but appreciable volatility of nitroglycerin at room temperature; the permeability of plastics, such as polyethylene, polypropylene, and polyvinyl chloride to nitroglycerin vapor; and the solubility of nitroglycerin in the adhesive used to bond the polyethylene to the aluminum foil.

When nitroglycerin tablets are placed in an open container, the drug substance evaporates. If the tablets are sealed in an envelope of plastic film, evaporation may be retarded, but it proceeds to eventual depletion if the packet remains exposed in an open vessel. By contrast, our investigations have shown that when nitroglycerin tablets are stored in a tightly stoppered glass container they retain essentially the same concentrations of active ingredient for prolonged periods. Within such a closed system, evaporation away from the dosage form proceeds only until the comparatively low partial pressure of nitroglycerin in the available space is equal to the vapor pressure of the compound in the tablets, and a dynamic equilibrium is achieved. If the bottle is opened intermittently to remove tablets, nitroglycerin vapors escape, but the loss is usually so small that changes in tablet composition are negligible.

Although the sealed aluminum package comprising the deteriorated product under discussion also represents a closed system, an additional operating factor prevents establishment of a stabilizing dynamic equilibrium. Because nitroglycerin is soluble in the laminating adhesive, the vapors that escape from the surface of the tablet and diffuse through the polyethylene are continuously removed from the atmosphere by incorporation into the film of adhesive. Thus the flow of nitroglycerin molecules is unidirectional away from the tablet and all of the drug migrates to the packaging material.

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