Surface Area Term in Myhill–Piper Equation

Keyphrases ☐ Antacids, dissolution rate—surface area term, Myhill–Piper equation ☐ Surface area—effect on dissolution rate, antacids, Myhill-Piper equation ☐ Dissolution, antacids—surface area term, Myhill–Piper equation

Sir:

A paper by Myhill and Piper (1) is frequently quoted in antacid work. In their treatment, using their nomenclature, $r(t)$ = amount of antacid present in the stomach at time t, κ = emptying rate constant of excess antacid, s = rate per unit time at which antacid is neutralized by acid secreted by the stomach, and τ = "starting index" or time after administration of antacid when exponential emptying rate commences.

This leads to the differential equation:

$$dr(t)/dt = -\kappa r(t) - s \qquad \text{(Eq. 1)}$$

which can readily be integrated. This equation, although useful as an initial equation, does not hold in general, since it assumes a constant dissolution rate, s, of the antacid independent of time. The overall dissolution rate would be a function of surface area, which changes with time, and would be related to $[r(t)]^{2/3}$. It furthermore depends on pH (which also changes with time), and Notari and Sokoloski (2) showed that a cube root law ensues when proper treatment is applied. Denoting the pH (or time) dependence of s, $\phi(t)$, changes Eq. 1 to:

$$dr(t)/dt = -\kappa r(t) - q\phi(t)[r(t)]^{2/3} \qquad \text{(Eq. 2)}$$

which is sufficiently complicated to prohibit solution in closed form.

Of course, $\phi(t)$ and $r(t)$ may change at different rates with time. If the stomach emptying time is long, then pH [and $\phi(t)$] may change fairly rapidly with small amounts of dissolved antacid [*i.e.*, in this situation, $r(t)$ does not change much], so that under these circumstances $\phi(t)$ would change much more rapidly than $r(t)$. In such a case, the circumstances are simplified sufficiently to allow Eq. 2 to be solved; it now can be put in the form:

$$dr(t)/dt = -\kappa r(t) - s(t) \qquad \text{(Eq. 3)}$$

where $s(t) = q\phi(t)[r(t)]^{2/3} \sim \text{constant} \cdot \phi(t)$. When the dissolving medium has constant volume, then [as may be implied from the work of Notari and Sokoloski (2)] the volume V of hydrochloric acid consumed at time t can be expressed by:

$$V_\infty - V = V_\infty e^{-\omega t} \qquad \text{(Eq. 4)}$$

where infinity denotes final state and where ω is a function of the original surface area. Therefore, with the assumption made:

$$s(t) = V_\infty \omega e^{-\omega t} = \alpha e^{-\omega t} \qquad \text{(Eq. 5)}$$

and Eq. 3 now takes the form:

$$dr(t)/dt + \kappa r(t) + \alpha e^{-\omega t} = 0 \qquad \text{(Eq. 6)}$$

The solution to Eq. 6 is obtained *via* the integration factor $e^{(\kappa t+\gamma)}$ and is:

$$r(t) = -\frac{\alpha}{\kappa - \omega} e^{-\omega t} + Ce^{-\kappa t} \qquad \text{(Eq. 7)}$$

where C would depend on initial conditions (*e.g.*, on τ).

The point to be stressed is that the surface area is related to $[r(t)]^{2/3}$ and that s in Eq. 1 is a function of this (and of pH); therefore, *surface area* must be a part of the resulting equations.

(1) J. Myhill and D. W. Piper, *Gut*, **5**, 581(1964).

(2) R. E. Notari and T. D. Sokoloski, *J. Pharm. Sci.*, **54**, 1500 (1965).

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Effect of Microsomal Activation on Interaction between Isophosphamide and DNA

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Sir:

We previously showed that the activation to alkylating materials of isophosphamide [3-(2-chloroethyl)-2-(2-chloroethyl)aminotetrahydro-1,3,2-oxazaphosphorine-2-oxide, I][1], an antineoplastic analog of cyclophosphamide, is mediated through the NADPH-dependent liver microsomal oxidase system (1) and is increased by pretreatment of animals with phenobarbital (2). We have now investigated the effect of this activation on DNA synthesis and on the reaction between I and DNA *in vitro* in order to clarify the effect of this activation on antitumor activity.

[1] NSC-109724; Ifosfamide, Mead Johnson.