*4-Bis(2'-chloroethyl)aminopropylamino-1,2-cyclohexenothiaxanthone (VIII)*—Compound VII (2 g, 0.0047 mole) was refluxed with phosphorus oxychloride (6 ml) for 3 hr, and excess oxychloride was removed under reduced pressure. The product was washed with sodium carbonate solution and water and recrystallized from benzene–petroleum ether to give 1.8 g (84%) of VIII, mp 160–162°.

*Anal.*—Calc. for $C_{24}H_{28}Cl_2N_2OS$: C, 62.26; H, 6.10; Cl, 15.32; N, 6.05. Found: C, 62.28; H, 6.17; Cl, 14.98; N, 5.97.

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# *COMMUNICATIONS*

## Evaluation of Mathematical Models for Diffusion from Semisolids


**Keyphrases** □ Diffusion, semisolids—evaluation of mathematical models □ Semisolids—evaluation of mathematical models for diffusion of drugs from semisolid systems


*To the Editor:*

Recently, Ayres and Laskar (1) reported an evaluation of models used to study the release of drugs from semisolid systems. Their analysis encompassed literature data (2–7) obtained on diverse experimental systems containing suspended or dissolved drugs in the form of gels, ointments, and emulsions. We find ourselves critical of both the approach and methods used in this analysis.

To establish the framework for our objections, it is necessary to present again the fundamental equations governing release of drugs from such systems. For semisolid systems initially containing uniformly dissolved drug in a homogeneous base, the amount of drug released in one dimension is given by Eq. 1 (8):

$$Q = hC_0\left[1 - \frac{8}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^2}\exp\left(-\frac{D(2m+1)^2\pi^2t}{4h^2}\right)\right] \quad \text{(Eq. 1)}$$

where:

$Q$ = amount of drug released per unit area of application
$h$ = thickness of vehicle layer
$C_0$ = initial concentration of drug in the vehicle
$D$ = diffusion constant of drug in the vehicle
$t$ = time after application
$m$ = integer, with values from 0 to $\infty$

Equation 1, which is derived from Fick's second law of diffusion, is a valid expression for release from one side of a layer of vehicle containing drug in solution as long as the following assumptions are met (8):

1. There is a single drug in true solution and initially uniformly distributed throughout the vehicle.
2. The composition of the vehicle remains fixed during the diffusion process, *i.e.*, components other than the drug do not leave or enter the vehicle phase.
3. The diffusion constant of the drug is independent of time and position in the vehicle.
4. The drug reaching the receptor side of the vehicle layer is cleared rapidly.

For most practical applications of Eq. 1, a simplified form (Eq. 2) may be used up to about 30% drug release (8):

$$Q = 2C_0\left(\frac{Dt}{\pi}\right)^{1/2} \quad \text{(Eq. 2)}$$

Higuchi (9) derived an equation (Eq. 3) for studying the rate of drug release from ointment bases containing drugs in suspension. This equation relates the amount of drug released to time and other variables of the system:

$$Q = (2C_0 - C_s)\sqrt{Dt\left/1 + \frac{2(C_0 - C_s)}{C_s}\right.} \quad \text{(Eq. 3)}$$

where $C_s$ = solubility of drug as units per centimeter$^3$ in the external phase of the ointment, and $D$ = diffusion constant of drug in the external phase of the ointment.

The operative boundary conditions for the use of Eq. 3 are as follows: *(a)* the suspended drug is in a

fine state such that the particles are much smaller in diameter than the thickness of the applied layer; *(b)* the amount of drug, $C_0$, per unit volume is substantially greater than $C_s$, the solubility of the drug per unit volume of the vehicle; and *(c)* the surface to which the drug ointment is applied is immiscible with respect to the ointment and constitutes the perfect sink for the released drug.

For the common suspension case of $C_s \ll C_0$, Eq. 3 simplifies to Eq. 4:

$$Q = \sqrt{2C_0DC_st} \qquad \text{(Eq. 4)}$$

Ayres and Laskar (1) obtained Eq. 5 by ignoring the $m > 0$ summation terms in Eq. 1:

$$M_t = M_\infty - \frac{8M_\infty}{\pi^2}\exp\left(-\frac{D\pi^2 t}{A}\right) \qquad \text{(Eq. 5)}$$

where $M_t$ = amount diffused up to time $t$, $M_\infty$ = amount diffused to time infinity, and $A$ = area over which diffusion occurs. No boundary conditions were specified.

To apply Eq. 1 or any simplified form, linear (Eq. 2) or exponential (Eq. 5), the experimental system must meet the basic assumptions of the physical model. These equations may be applied to a single drug in true solution and initially uniformly distributed throughout the vehicle. If the drug is suspended as fine particles in a semisolid system and the system is described as in the derivation of Eq. 3, then this equation or its simplified form (Eq. 4) may be used in obtaining physical parameters.

The experimental system should either meet the restrictions of the solution model (Eq. 1) or the suspension model (Eq. 3). It was stated (1) that Eq. 3 may take the form of Eq. 2 used in the analysis of diffusion of medicaments from semisolid dosage forms. This is totally incorrect and fundamentally wrong, because Eqs. 2 and 3 deal with distinctly different physical models.

The fluocinolone acetonide release data (2) from 20% propylene glycol–80% water, gelled with carboxypolymethylene[1] containing 0.025% drug, were analyzed in an attempt to show that the nonlinear curve-fitting procedures using Eq. 5 provided better fit compared to Eq. 2. The gel system in question contained drug in the form of a suspension at initial time and at some later time due to depletion of the solid drug; the gel did not contain drug in the form of a suspension. At the end of the experiment, almost 80% of the initial amount was released from the gel. This experiment was not designed to test either the solution model or the suspension model. Poulsen *et al.* (2) reported these data to demonstrate the effect of vehicle composition on the release of fluocinolone acetonide. Therefore, a basic flaw in the cited report (1) is the use of an incorrect physical model in the analysis of these data.

Similarly, these authors (1) incorrectly analyzed the published *in vitro* release data of salicylic acid (3%) in hydrophilic cream and white petrolatum USP (5). Since the salicylic acid was present as a suspended material, equations describing the solution case cannot be applied.

One assumption made in the derivation of Eq. 1 and its simplified form (Eq. 2) was that the diffusion constant must be constant with respect to time and position. In many situations involving emulsions, the diffusion constant is not constant but varies with concentration. Koizumi and Higuchi (3) analyzed this practical and important case by studying the release of an amine–amine hydrochloride solute mixture in water-in-oil emulsion into an aqueous sink. For an emulsion case, a general functional expression for the effective diffusion constant was obtained:

$$D_e = f(k_i, v_i, v_c, D_i, D_c) \qquad \text{(Eq. 6)}$$

The volumes of the internal phase, $v_i$, and the continuous phase, $v_c$, are assumed constant for a given system. Even when the diffusion constants of the internal phase, $D_i$, and the continuous phase, $D_c$, are constant, the effective diffusion constant, $D_e$, is a function of the partition coefficient of the internal phase, $k_i$, which may be concentration dependent. It was theoretically shown that even if the diffusion constant is concentration dependent, the release pattern is exactly the same as the constant $D$ case.

The experimental system (3) used to study the release of pyridine from water-in-oil emulsion separated the unstirred emulsion from the well-stirred sink. The assumptions that the sink is perfect and that the drug concentration at the emulsion–sink interface is always maintained at zero were revised subsequently (4). A physical model considering the cases when the partition coefficient between emulsion and membrane is unity and not unity was presented. The effective diffusion constant, $D_m$, through the unstirred layer in and around the membrane was calculated by conducting experiments in which both the emulsion and sink were stirred. The effective diffusion constant in the emulsion was calculated by either the Bruggeman or Wagner–Wiener equation. The comparisons between experiment and theory were in excellent agreement when the effects of the membrane and stirring were considered in the physical model.

Ayres and Laskar (1) took one set of pyridine release data from a water-in-oil emulsion system (3) and analyzed these data using Eqs. 2 and 5. Since more rigorous physical models were in the literature, it is not clear what these authors achieved by using curve-fitting procedures. Specifically, the authors not only ignored the rigorous physical models appropriate for studying the release of drugs from emulsion systems but also overlooked the basic assumptions made in deriving Eq. 1.

In conclusion, our understanding of drug release from semisolid systems has evolved to a point where the physical model approach has been quite useful in helping to explain and to predict the roles of various factors involved in the transport phenomena. The meaningful application of this technique, however, requires that the models and the mathematics em-

[1] Carbopol.

ployed are appropriate from the physical standpoint. Statistical analyses and curve-fitting procedures used without regard for the physical basis in the equations are of less than doubtful value in this area of biopharmaceutics.

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## Development of a Stable Sublingual Nitroglycerin Tablet I: Interaction of Nitroglycerin with Selected Macromolecules

**Keyphrases** □ Nitroglycerin—stable sublingual tablet, formulated with macromolecules □ Tablets, nitroglycerin sublingual—development of stable tablet, nitroglycerin interacted with selected macromolecules □ Formulation—development of stable sublingual nitroglycerin tablet, interaction of nitroglycerin with macromolecules

*To the Editor:*

There has recently been intense research activity in the pharmaceutical aspects of the angina drug nitroglycerin (1–3). The high volatility of nitroglycerin leads to a loss of drug to the environment during patient storage and use (4). Consequently, the Food and Drug Administration (FDA) has now instituted regulations governing the dispensing and the types of containers that may be used for sublingual nitroglycerin tablets, and the two most popular brands available in this country were recently reformulated for improved stability (2, 5).

We have found that although these products demonstrate somewhat better stability and content uniformity characteristics compared to previous formulations under certain conditions, their stability under more severe, but not unanticipated storage conditions, *e.g.*, when the tablets are exposed to the atmosphere in a semiclosed or open container, is inadequate. There is, therefore, a need to develop a nitroglycerin sublingual tablet whose stability can be assured over a sufficiently long period without any stringent storage conditions imposed on the patient and inconvenient dispensing restrictions imposed on the pharmacist.

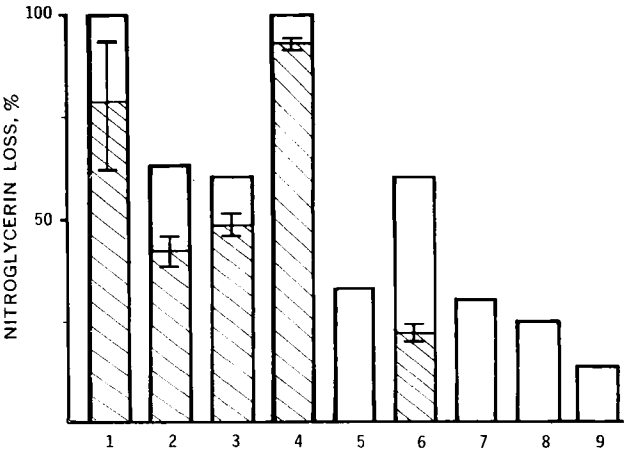


**Figure 1**—*Percentage nitroglycerin loss in different powder mixes after storage under vacuum (shaded) and under ambient (open) conditions. Key: 1, control; 2, Brand A; 3, Brand B; 4, 20% gelatin; 5, 20% hydroxypropyl cellulose; 6, 1% polyvinylpyrrolidone; 7, 3% polyvinylpyrrolidone; 8, 5% polyvinylpyrrolidone; and 9, 10% polyvinylpyrrolidone. Relative standard deviations for the shaded columns are indicated by bars, but those for the open columns are too small to be shown.*

The present communication reports our initial studies on the lowering of the thermodynamic activity of nitroglycerin when dispersed in powders and sublingual tablets with different macromolecules. Experimental sublingual tablets containing polyvinylpyrrolidone showed vastly improved stability over existing commercial brands.

Figure 1 shows the percentage nitroglycerin loss in different powder mixes under two sets of "accelerated" experimental conditions: *(a)* completely exposed to the atmosphere for 9 days at ambient temperatures (open columns), and *(b)* under vacuum in a desiccator over an activated charcoal bed at 1–3 torr for 4 hr at ambient temperatures (shaded columns). Commercial tablets (Brands A[1] and B[2]) were purchased locally and were ground up to approximately comparable particle size. The control powder contained 0.6 mg of nitroglycerin[3] in 30 mg of lactose, and the test powders contained the designated percent (w/w) of macromolecules as an additive.

Triplicate samples of the powder mixes were assayed prior to and after the respective treatment by the kinetic assay method recently developed in this laboratory (1). Data from the vacuum study represent composites, with a minimum of two runs for each powder mix carried out on different days. It is evident from Fig. 1 that the two accelerated stability test conditions showed similar rank-order correlation

[1] Eli Lilly & Co., 0.6-mg tablets, Lot 6VP80A.
[2] Parke-Davis & Co., 0.6-mg tablets, Lot PB216.
[3] Available from ICI America, Inc., as a 10% powder in lactose (Lot B17H1).