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.

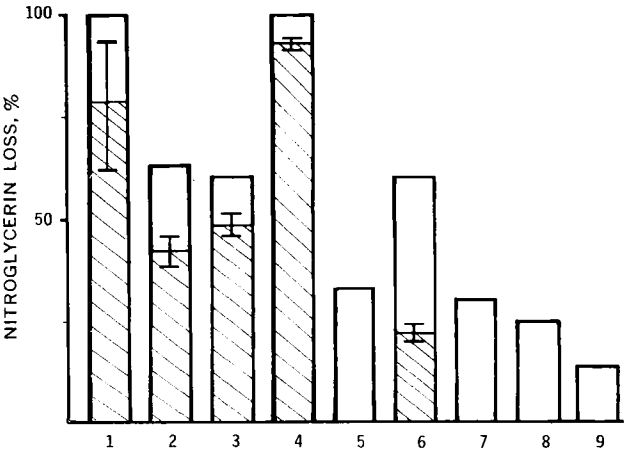

Figure 1—*Percentage nitroglycerin loss in different powder mixes after storage under vacuum (shaded) and under ambient (open) conditions. Key: 1, control; 2, Brand A; 3, Brand B; 4, 20% gelatin; 5, 20% hydroxypropyl cellulose; 6, 1% polyvinylpyrrolidone; 7, 3% polyvinylpyrrolidone; 8, 5% polyvinylpyrrolidone; 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).

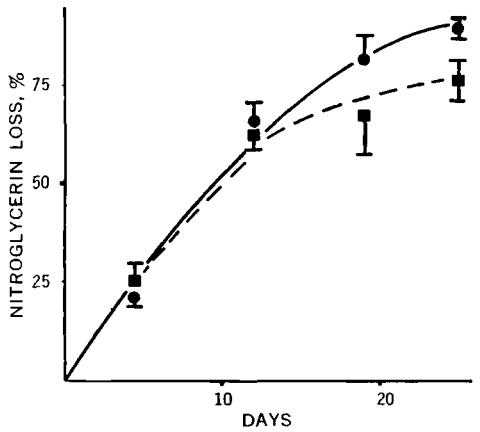

Figure 2—*Percentage loss of nitroglycerin from commercial tablets. Key:* ■, *Brand A; and* ●, *Brand B. Bars indicate relative standard deviations.*

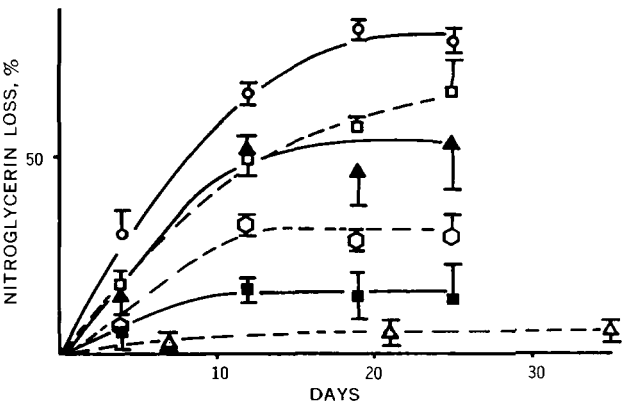

Figure 3—*Percentage loss of nitroglycerin from experimental sublingual tablets containing various percentages of polyvinylpyrrolidone. Key:* ○, *0%;* □, *1%;* ▲, *3%;* ◌, *5%;* ■, *10%; and* △, *15%. Bars indicate relative standard deviations.*

for the relative stability of nitroglycerin in the powder mixes studied. Powders from the commercial tablets were more stable than the control and that containing 20% gelatin but were less stable than those containing hydroxypropyl cellulose and polyvinylpyrrolidone[4].

Although the vacuum method revealed a better stability for the powder mix containing 1% polyvinylpyrrolidone as compared to the commercial lots, it was less sensitive in distinguishing the relative stability of powder mixes containing 20% hydroxypropyl cellulose and 3, 5, and 10% polyvinylpyrrolidone, all of which lost no nitroglycerin after the prescribed period. The atmospheric exposure method, however, showed that preparations containing 3% or more polyvinylpyrrolidone were more stable than that containing 20% hydroxypropyl cellulose and that the stability increased with increasing polyvinylpyrrolidone content. These simple preliminary accelerated stability tests led to the selection of polyvinylpyrrolidone as a stabilizer in preparing experimental sublingual tablets for further stability screening.

Experimental sublingual tablets with different polyvinylpyrrolidone concentrations (0–15% w/w) were prepared by molding, using an aqueous alcohol solvent mix for granulation. The tablet size ranged from about 75 to 90 mg, with approximately 0.6 mg of nitroglycerin/tablet. The stability of these tablets and commercial lots was monitored for about 1 month at various times after they were placed in open petri dishes at ambient temperatures. The petri dishes had to be placed at least 61 cm (2 ft) from each other or the more stable tablets gained in nitroglycerin content at the expense of their less stable neighbors. At least five tablets were assayed each time.

Figures 2 and 3 show the percentage nitroglycerin loss from commercial and experimental tablets, respectively. Consistent with the results of the accelerated powder studies, the experimental molded tablets containing 3% or more of polyvinylpyrrolidone were much more stable than the commercial lots tested. When the polyvinylpyrrolidone content was high, the loss of nitroglycerin reached a plateau after about 15 days. In fact, tablets containing 10 and 15% polyvinylpyrrolidone were still within the USP specifications after nearly 1 month of complete exposure to the atmosphere.

The mechanism of interaction between polyvinylpyrrolidone and nitroglycerin is probably of electronic origin since organic nitrates are known to be electron acceptors (6) and polyvinylpyrrolidone is an electron donor (7). This solid phase interaction lowers the fugacity of nitroglycerin in the dosage form, but the complex formed between nitroglycerin and polyvinylpyrrolidone is most likely to be extremely unstable in an aqueous environment because of preferential solvation of polyvinylpyrrolidone molecules by water. The solid phase stabilization, therefore, is not expected to affect the bioavailability of nitroglycerin significantly. When experimental tablets containing 10% polyvinylpyrrolidone were dissolved in water and extracted with octanol, the amount of nitroglycerin recovered from the organic phase was the same as that recovered from control systems containing Brands A and B.

Detailed *in vitro* dissolution and *in vivo* studies in humans are now underway to ascertain the bioavailability of these stabilized nitroglycerin sublingual tablets.

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Absolute Drug Bioavailability: Approximation without Comparison to Parenteral Dose for Compounds Exhibiting Perturbable Renal Clearance

Keyphrases □ Bioavailability—approximation of absolute drug bioavailability without comparison to parenteral dose for compounds exhibiting a perturbable renal clearance □ Drug bioavailability—approximation without comparison to parenteral dose, compounds exhibiting perturbable renal clearance

To the Editor:

It is generally accepted that the absolute bioavailability of a drug dosage form can only be determined by comparison with a parenteral dose. However, ethical and legal considerations prevent injection of many compounds, greatly inhibiting the acquisition of bioavailability data for new drugs.

The principal purpose of this communication is to demonstrate that it is possible to approximate the absolute bioavailability of a large class of drugs (1), those whose renal clearance is perturbable, without the administration of a parenteral dose. As an example, consider an agent that exhibits an area under the plasma concentration–time curve of AUC under condition X (*e.g.*, coadministration of a urinary acidifying agent) and of AUC' under condition Y (*e.g.*, coadministration of urinary alkalinizing agent). Similarly, let Cl_B, Cl_R, and Cl_{NR} equal the total body clearance, mean renal clearance, and nonrenal clearance, respectively, during condition X, and let the prime notation indicate their values under condition Y. Finally, let D equal the dose administered and F equal the fraction of the dose that is absorbed. The following analysis assumes that: (*a*) the system is linear, and (*b*) Cl_{NR}, F, and intercompartment transfer constants (if any) are independent of the perturbation of renal clearance.

Since:

$$Cl_B = Cl_R + Cl_{NR} \qquad \text{(Eq. 1)}$$

and:

$$Cl_B' = Cl_R' + Cl_{NR} \qquad \text{(Eq. 2)}$$

by letting:

$$Cl_R - Cl_R' = \Delta Cl_R \qquad \text{(Eq. 3)}$$

and:

$$Cl_B - Cl_B' = \Delta Cl_B \qquad \text{(Eq. 4)}$$

it follows that:

$$\Delta Cl_R = \Delta Cl_B = Cl_B - Cl_B' \qquad \text{(Eq. 5)}$$

From the model independent equation:

$$\text{total body clearance} = \frac{DF}{\text{area under the plasma concentration-time curve}} \qquad \text{(Eq. 6)}$$

and Eq. 5, it is apparent that:

$$\Delta Cl_R = \frac{DF}{AUC} - \frac{DF}{AUC'} \qquad \text{(Eq. 7)}$$

or:

$$F = \frac{\Delta Cl_R}{D}\left[\frac{(AUC)\ (AUC')}{AUC' - AUC}\right] \qquad \text{(Eq. 8)}$$

Since all terms on the right-hand side of Eq. 8 can be determined experimentally without reference to a parenteral dose, it follows that absolute bioavailability may be approximated by this method given the validity of the listed assumptions.

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Gastric Irritation and Bleeding after Drug Administration

Keyphrases □ Gastric irritation and bleeding—effects of aspirin, phenylbutazone, methyl salicylate, salicylic acid, and triamcinolone, powder and solution forms, effects of polyethylene glycol bases, rats □ Bleeding, gastric—effects of various drugs under varying experimental conditions, rats □ Drug administration—extent of gastric irritation and bleeding caused by aspirin, phenylbutazone, methyl salicylate, salicylic acid, and triamcinolone, powder and solution forms, effects of polyethylene glycol bases, rats

To the Editor:

Many drugs are known to be irritating to the stomach and GI tract, and some have been shown to produce gastric ulceration and bleeding (1–3). This communication describes results obtained in a study to determine if various drugs would induce bleeding or ulceration in the stomach of rats under various experimental conditions.

Seventy rats, 130–150 g, were divided into groups (four to six rats in each group). The rats were fasted in screen-bottom cages for 24 hr prior to drug administration. During the fast, water was allowed *ad libitum*. The animals then received the following drugs