by drying at 26° at a pressure of >3 torr (13% RH) or the equivalent at a higher temperature, then only the last five points would be involved and the shape would lose the initial sigmoid nature.

These comments are confined to situations where no gross swelling or pore-size distortion occurs during moisture uptake (7, 8). Furthermore, the solubility must be sufficiently low so that no significant volume changes or vapor pressure changes can result from dissolution.

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Enhancement of Rectal Absorption of Drugs by Adjuvants

Keyphrases □ Absorption, rectal—enhancement by certain adjuvants □ Salicylate—enhancement of rectal absorption of theophylline and lidocaine □ Theophylline—enhancement of rectal absorption by salicylate □ Lidocaine—enhancement of rectal absorption by salicylate

To the Editor:

Rectal drug administration has the potential of overcoming some limitations encountered with other dosage forms. In this communication, we report that the rectal absorption of many drugs is facilitated markedly in the presence of certain adjuvants.

Although specific surfactants were shown to promote drug absorption from the rectum (1), their use seems to damage the rectal mucosa, reducing their suitability as absorption promoters. The adjuvants described in this report appear to function differently.

These observations were made using an *in situ* perfusion method of the rectum similar to that reported by Crommelin *et al.* (2). Six milliliters of drug solution was circulated at a rate of 2 ml/min at 38° through an ~2-cm section of the rectum of male Sprague–Dawley rats weighing 275–300 g. The amount of drug remaining in the perfusate was analyzed by high-pressure liquid chromatography as a function of time. Blood levels also were measured in blood samples taken from a vein in the leg of a rat.

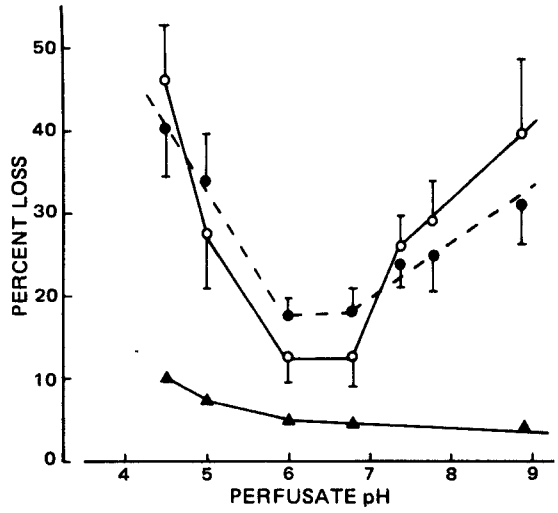

Figure 1—*Percent loss of salicylate or its acidic form (--●--) and theophylline (—○— and —▲—) after 1 hr from the perfusate in the rat rectum. Initial concentrations were 0.5% sodium salicylate (--●--), 0.5% sodium salicylate and 200 μg of theophylline/ml (—○—), and 200 μg of theophylline/ml (—▲—).*

Figure 1 shows the effect of salicylate at various pH values on the disappearance of theophylline from the perfusate in the rat rectum after 60 min of perfusion. The loss of theophylline from the perfusate in the absence of salicylic acid or salicylate was small at all pH values. However, in the presence of 0.5% salicylate at various pH values, the disappearance of theophylline was enhanced greatly, especially below pH 5 and above pH 7.4.

As shown in Fig. 1, the loss of theophylline paralleled the loss of salicylate from the perfusing solution; the greater the disappearance of salicylate from the perfusate, the greater was the loss of theophylline. Furthermore, contrary to the situation with some surfactants, the promotive effect of salicylate did not reflect a permanent change in the rectal membrane, because the effect of salicylate was eliminated by washing the rectum with buffer for 5 min at

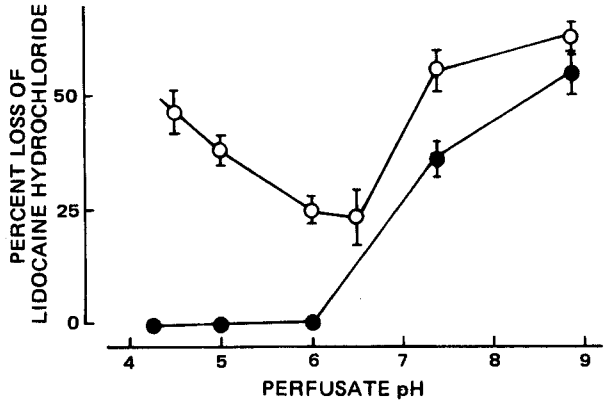

Figure 2—*Effect of pH and salicylate on the disappearance of lidocaine hydrochloride from a perfusate in the rat rectum after 1 hr. The initial lidocaine hydrochloride concentration was 500 μg/ml (○ and ●), and the sodium salicylate concentration was 0.5% (○).*

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a rate of 2 ml/min after pretreatment with salicylate; the effect of pretreatment with sodium lauryl sulfate was not eliminated by washing.

After rectal administration of 0.3 ml of theophylline solution (pH 7.4, 15 mg/ml) in the presence of salicylate (15 mg/ml), the blood levels of theophylline and salicylate increased rapidly and simultaneously, reaching maximum levels (41.2 ± 15.9 μg/ml for theophylline and 41.1 ± 14.3 μg/ml for salicylate; $n = 6$) 30 min after administration. The amounts of theophylline and salicylate remaining in the solution were 25.6 ± 4.7 and 30.3 ± 7.2%, respectively. Without salicylate, maximum blood levels of theophylline were <5 μg/ml ($n = 6$).

The presence of salicylate in the perfusate (pH 4.5 or 5.0) also enhanced the disappearance of lidocaine, which is a basic drug and is not absorbed below pH 6.0, from the perfusate in the rat rectum. The effects of salicylate on the disappearance of lidocaine at various pH values are presented in Fig. 2. Thirty minutes after rectal administration of 0.3 ml of lidocaine solution (pH 4.5, 15 mg/ml) in the presence of salicylate (15 mg/ml), lidocaine and salicylate reached maximum levels in the blood (43.3 ± 4.7 μg/ml for lidocaine and 48.5 ± 6.9 μg/ml for salicylate; $n = 6$).

These results indicate that salicylate and/or its acidic form markedly enhance the absorption of various compounds from the rectum. This effect appears to be general for other drugs including cefmetazole and levodopa. Furthermore, three isomers of sodium dihydroxybenzoate (3,4-, 2,5-, and 3,5-dihydroxybenzoates) and homovanillic acid were studied as adjuvants and found to enhance the rectal absorption of both theophylline and lidocaine. These and similar compounds have significant potential as adjuvants for enhancing rectal drug absorption. Studies are continuing on the mechanism of their action.

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Kinetic Characterization of Liposomes

Keyphrases □ Liposomes—base-catalyzed hydrolysis of *p*-nitrophenyl acetate in liposomal suspensions □ *p*-Nitrophenyl acetate—base-catalyzed hydrolysis in liposomal suspensions □ Hydrolysis—base-catalyzed degradation of *p*-nitrophenyl acetate in liposomal suspensions

To the Editor:

Liposomes have been investigated extensively for possible use as novel drug carriers for therapeutic purposes (1, 2). From a drug stability viewpoint, we studied the hydrolysis of procaine and 2-diethylaminoethyl *p*-nitrobenzoate in liposomal suspensions and compared it with spontaneous hydrolysis in aqueous bulk solutions (3, 4). The base-catalyzed hydrolysis of procaine was retarded by liposomes; with 2-diethylaminoethyl *p*-nitrobenzoate, both retardation and enhancement were observed, depending on the pH of the dispersed medium.

These ester degradations followed first-order kinetics in the liposomal suspension as well as in the corresponding aqueous bulk solution, regardless of whether retardation or enhancement was observed. This finding indicates that the substrates added in the liposomal medium partitioned into the lipid phase at so fast a rate that it was undetectable, and this partitioning was followed by quasi-first-order degradation, which can be represented by the first-order rate constants defined in the aqueous bulk and lipid phases. Consequently, the partition model was applicable for degradation of these esters.

This communication discusses the base-catalyzed hydrolysis of *p*-nitrophenyl acetate in liposomal suspensions. This compound frequently is used as a substrate in studies of micellar catalysis (5, 6) and of esterase activity of bovine serum albumin and human serum albumin (7, 8).

Figure 1 indicates that the reaction followed first-order kinetics with the ester remaining in the aqueous solution. The reaction clearly was not a continuous process in liposomal suspensions. It was enhanced in the early stage and proceeded in a manner parallel to the spontaneous degradation. The degradation rate was dependent on the lecithin concentration; the more lecithin that was present, the faster was the hydrolysis. Furthermore, enhancement was accelerated more in the unilamellar dispersion system than in the multilamellar one when the lecithin content in

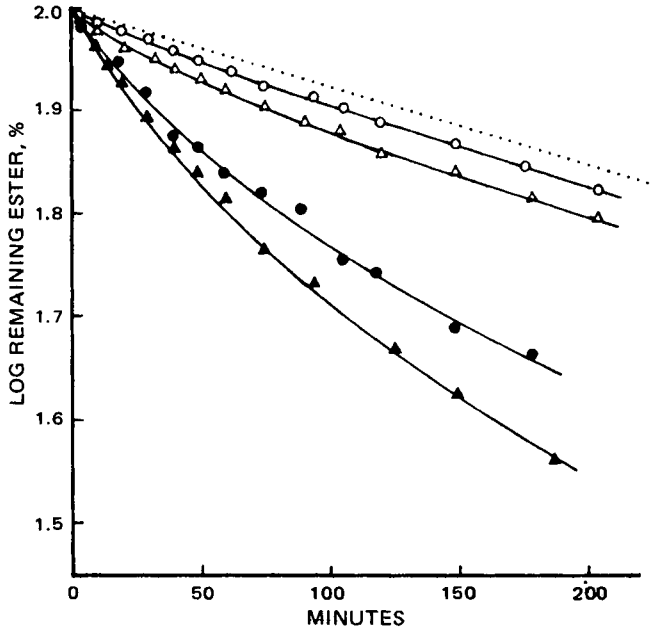

Figure 1—*First-order plots for hydrolysis of* p*-nitrophenyl acetate in aqueous solution and in liposomal suspensions. Tris(hydroxymethyl)-aminomethane buffer at pH 8.0 was used (μ = 0.3, 25°). The initial* p*-nitrophenyl acetate concentration was 5.92 × 10⁻⁴ M. The lecithin concentrations were 2.40 × 10⁻³ M (○ and △) and 8.67 × 10⁻³ M (● and ▲). Key: . . . , spontaneous degradation in water; ○ and ●, multilamellar liposome system; and △ and ▲, unilamellar liposome system. Liposomes were prepared from egg yolk lecithin as described previously (3).*

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