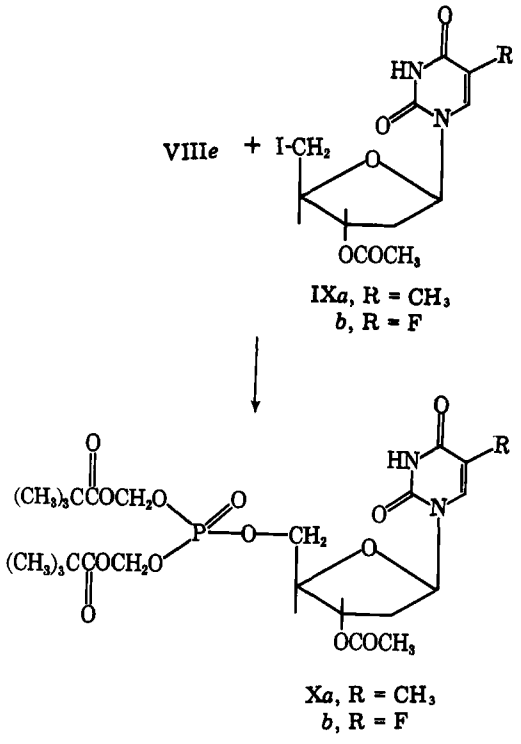
(III, R = C_6H_5, R^1 = CH_3) and then to phenyl phosphate (V, R = C_6H_5).

The bis(pivaloyloxymethyl) phosphotriester[3] (I*b*), by comparison, was much more resistant to both chemical and enzymatic hydrolysis. Thus, it was stable in protonic solvents and had a half-life ≃5 hr when incubated with mouse plasma under conditions identical to that described for I*a*. Clearly, the nature of the acyl substituent has a marked influence on the susceptibility of bis(acyloxymethyl) phosphotriesters to hydrolysis.

The benzyl phosphotriesters, I*c*[3] and I*d*[3], were prepared similarly from disilver benzyl phosphate[2] (VI*b*). Catalytic hydrogenolysis of these compounds over 5% palladium-on-charcoal Pd-C in cyclohexane gave the corresponding monobasic acids, VIII*a* and *b* which were isolated as their cyclohexylammonium salts, VIII*c* and *d*. Silver bis(pivaloyloxymethyl) phosphate (VIII*e*) was prepared from VIII*d* by successive ion-exchange[9]. Reaction of VIII*e* with benzyl bromide or methyl iodide in benzene for 5 hr at room temperature gave bis(pivaloyloxymethyl) benzyl phosphate[3] (I*d*) and bis(pivaloyloxymethyl) methyl phosphate[3] (I*e*), respectively, in nearly quantitative yield. These reactions illustrate the utility of VIII*e* in the synthesis of bis(acyloxymethyl) phosphotriesters.

Reactions of VIII*e* with 5′-deoxy-5′-iodo-3′-*O*-acetylthymidine (IX*a*) (4) in toluene under reflux for 5 hr gave bis(pivaloyloxymethyl)-3′-*O*-acetylthymidine-5′-phosphate (X*a*), 39% yield (Scheme III). Similarly, the reaction



Scheme III

of VIII*e* with 2′,5-dideoxy-5′-iodo-3′-*O*-acetyl-5-fluorouridine[10] (IX*b*) gave X*b* (15% yield). Compound X*b* prevented the growth of Chinese hamster ovary cells in culture (5) at a concentration of 5.0×10^{-6} *M* (5-fluoro-2′-deoxyuridine control, 1.0×10^{-6} *M*).

Further chemical and biological studies of these compounds are in progress.

[9] Prepared on Dowex 50 Na^+ and Dowex 50 Ag^+.

[10] Prepared from 3′-*O*-acetyl-2′-deoxy-5-fluorouridine in 65% yield, according to the general procedure described previously (4).

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Estimation of the Extent of Drug–Excipient Interactions Involving Croscarmellose Sodium

Keyphrases □ Croscarmellose sodium—estimation of the extent of drug–excipient interactions □ Drug–excipient interactions—estimation of the extent involving croscarmellose sodium □ Excipients—estimation of the extent of drug–excipient interactions involving croscarmellose sodium

To the Editor:

In a recent communication (1), a pH-dependent interaction of oxymorphone derivatives with croscarmellose sodium, Type A, NF XV[1] was identified. Any drug–excipient interaction is potentially serious if it has a deleterious influence on the bioavailability of the drug from the dosage form. However, as in this case, the excipient may be responsible for certain dosage form properties which promote or at least ensure reproducible drug delivery.

There is a need to be able to assess the risk which may be involved before advocating or indicting an excipient. The objectives here are to provide a means for determining when an interaction with the disintegrant croscarmellose sodium might be expected and a means for estimating the extent of the interaction when it occurs.

Certain aspects of the interaction were presented in the previous communication (1); although, the general utility of these results is limited. Details were not given con-

[1] Ac-Di-Sol, FMC Corporation, Philadelphia, Pa.

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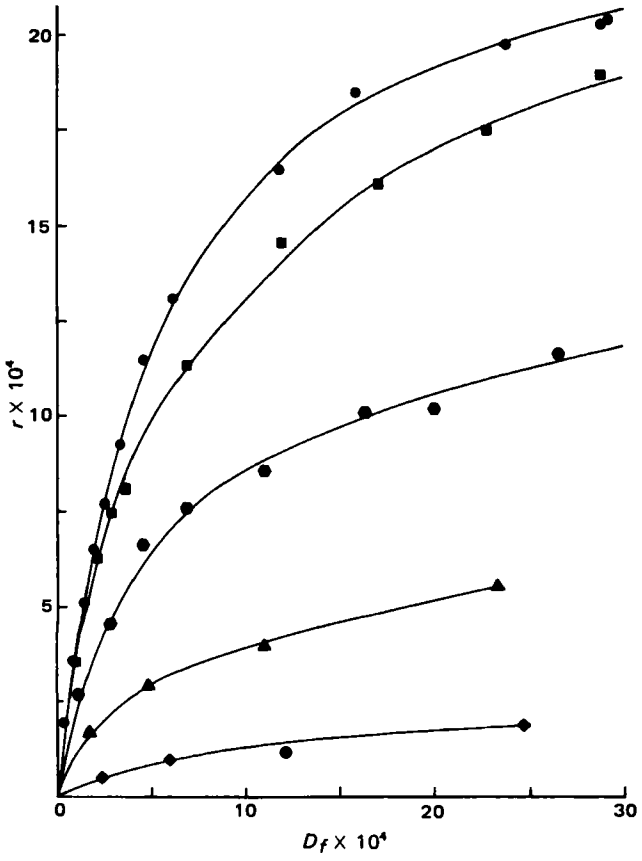

Figure 1—*Interaction isotherms of chlorpheniramine with croscarmellose sodium in aqueous dispersion at various hydrogen ion activities at 25°. (See Table I for definition of symbols, units and experimental conditions.) Key: (●) pH 7; (■) pH 6; (●) pH 5; (▲) pH 4; (◆) pH 3.*

Table I—Identification and Definition of Experimental Variables

Variable	Units	Experimental Value
D_T	Total amount of drug, moles	—
A_T	Total amount of excipient, g	0.100
V	Volume of liquid, liters	0.200
D_f	Free drug concentration, moles/liter	—
r	Moles of drug bound per gram of excipient	—

cerning analytical procedure, the method of altering pH, and the units of drug and disintegrant concentration. Without this information, it is not possible to estimate the extent of an interaction that might be expected under a different set of conditions.

An effort is underway in this laboratory to characterize the interaction of ionized weak bases with croscarmellose sodium. In light of the preceding discussion, we present a portion of our results that they may provide a qualitative and quantitative guide to these interactions. Figure 1 represents the results of a study of the interaction of chlorpheniramine maleate[2] with croscarmellose sodium at varying pHs. The experimental variables are defined in Table I, along with the values used to generate the results in Fig. 1. In an effort to keep the ionic strength low, the pH was adjusted in each case by the dropwise addition of 0.1 *N* HCl or 0.1 *N* NaOH, whichever was appropriate. After a 24-hr equilibration period, during which the drug–ex-

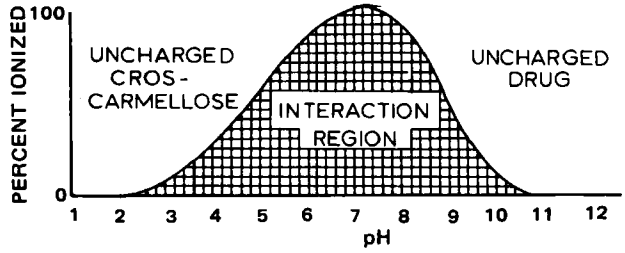

Figure 2—*Croscarmellose interaction profile for a hypothetical weakly basic drug with pKa = 9.0. (See text for details.)*

cipient suspension was maintained at 25°, the suspension was allowed to settle, and an aliquot of the supernatant was withdrawn with a syringe. The aliquot was freed of particles by rapid filtration through a borosilicate microfiber glass depth filter pad[3], and free drug concentrations were determined by UV spectrophotometric analysis of the filtrate at the pH-dependent wavelength of a maximum absorbance (261.5–264.5 nm). Free drug concentrations are presented in terms of molar concentration, because it is anticipated that these results can be extended to weak bases other than chlorpheniramine. The amount of drug adsorbed was determined by mass balance with quantitative corrections made for the slight adsorption to the filter, which occurred at high concentrations of drug.

It appears that the interaction is of electrostatic origin, involving ionized croscarmellose (negatively charged, pH >2) and cations. Thus, any weakly basic drug in an environment whose pH is >2 and near or below the pK_a of the weak base should be expected to interact with the ionized polymer. This generalization is presented graphically in Fig. 2 for a hypothetical weakly basic drug with a pK_a of 9.0. The ionization of the drug has been calculated from the pK_a assuming ideal behavior. The ionization of the drug outlines the interaction region at higher pHs. The ionization of croscarmellose has been estimated from the maximum binding data (r[max]) in Fig. 1. At pH 7, r[max] = 24×10^{-4} moles of drug/g of excipient, and the assumption is made that this value represents the maximum number of binding sites available. The fraction of croscarmellose ionized at any pH may be estimated by comparing the number of sites at that pH to the value at pH 7. At pH 4, for example, r[max] = 6×10^{-4} moles of drug/g of excipient, and the amount of croscarmellose ionized is estimated to be 25%. The outline of the interaction region at lower pHs has been generated by similar calculations.

An independent attempt to determine the pK_a of croscarmellose by titration produced spurious results, possibly due to the competitive equilibria for binding sites involving sodium and hydrogen ions. The influence of sodium ions on binding is addressed in subsequent discussion.

A diagram may be constructed for a drug with any pK_a by reconstructing the drug ionization curve. The area of the interaction region increases the higher the pK_a of the weak base. If the drug is a weak acid or nonelectrolyte, no interaction is anticipated.

Assuming that the interaction is nonspecific, reversible, and can be characterized as an equilibrium relationship, Fig. 1 can be utilized to estimate the fraction of drug bound

[2] Chlorpheniramine maleate USP, Hexagon Laboratories, Inc., Bronx, N.Y.

[3] Type AP25, Millipore Corp., Bedford, Mass.

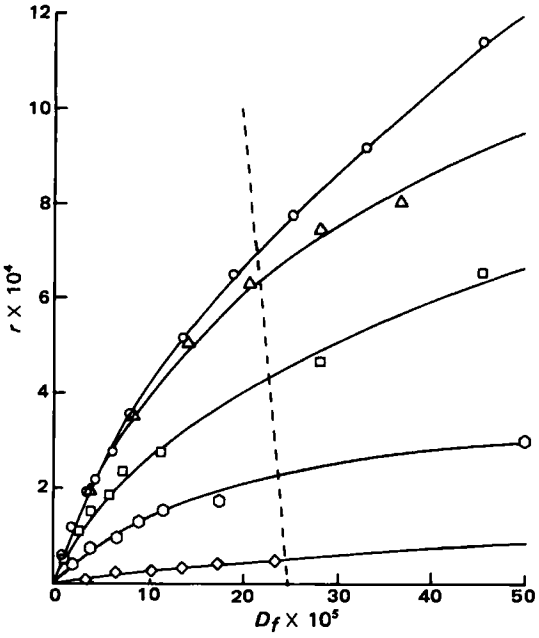

Figure 3—*Low concentration interaction isotherms of chlorpheniramine with croscarmellose sodium in aqueous dispersion at various hydrogen ion activities at 25°. Dashed line defines an interaction profile for the following conditions:* $D_T = 2.5 \times 10^{-5}$ *moles,* $A_T = 0.005$ *g,* V = *0.100 liter. (See Table I for definition of symbols and units.) Key: (○) pH 7; (△) pH 6; (□) pH 5; (○) pH 4; (◇) pH 3.*

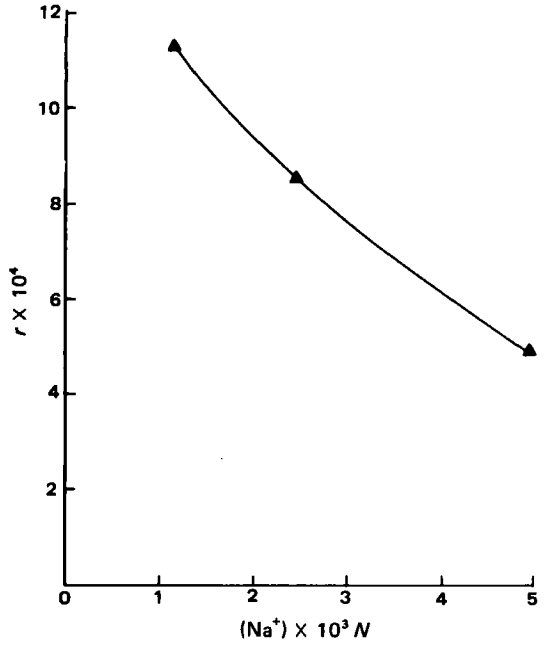

Figure 4—*Effect of added sodium ion concentration on the interaction of chlorpheniramine with croscarmellose sodium at pH 7.0 and 25°;* $D_T = 2.06 \times 10^{-4}$ *moles,* $A_T = 0.100$ *g,* V = *0.200 liter. (See Table I for definition of variables.)*

for any combination of A_T, D_T, and V, as long as the pH is ≤7 and the drug has a $pK_a \geq 9.0$. For purposes of illustration, and because there is particular concern for low dose drugs, Fig. 3 presents an expanded segment of the data from Fig. 1. For this analysis, the following mass balance will be used:

$$D_T = (D_f)V + rA_T \quad \text{(Eq. 1)}$$

where the variables are defined in Table I. By rearrangement:

$$r = \frac{D_T}{A_T} - (D_f)\frac{V}{A_T} \quad \text{(Eq. 2)}$$

It can be seen that r is a linear function of (D_f) when D_T, A_T, and V are fixed. The intercepts of this function:

$$(D_f) = \frac{D_T}{V} \quad \text{(Eq. 3)}$$

when $r = 0$ and:

$$r = \frac{D_T}{A_T} \quad \text{(Eq. 4)}$$

when $D_f = 0$ and/or the slope $(-V/A_T)$ permit construction of a specific binding profile for any set of conditions.

As an example, consider a tablet containing 10 mg of a weakly basic drug, with a pKa >9, a molecular weight of 400, containing 5 mg of croscarmellose sodium as a disintegrant, and placed in 100 ml of liquid.

Thus, $D_T = 2.5 \times 10^{-5}$ moles, $A_T = 0.005$ g, and $V = 0.100$ liter. The dashed line constructed in Fig. 3 from Eq. 2 can be used to determine a pH profile for this particular situation. The free drug concentration at any pH can be determined from the intersection of this line and the appropriate binding isotherm. At pH 7.0, for example, $D_f = 21.5 \times 10^{-5}$ M, and therefore, ~14% of the drug is bound.

The success of this approach depends upon the nonspecificity of the interaction and the validity of the binding data in Figs. 1 and 3. While we are still investigating the former, a comment about the binding results can be made at this time: Interactions in distilled water are generally higher than that predicted by this method. In retrospect, the method of elevating pH in this study, by adding sodium hydroxide, was a poor approach because of the specific competition of binding sites for sodium. Figure 4 presents the results of a simple study where total drug and excipient concentrations were held constant, and sodium ion concentration was increased by adding progressively larger quantities of sodium hydroxide and then adjusting the pH with standardized hydrochloric acid. It can be seen that increases in added sodium ion concentration significantly reduce the amount of drug bound. Thus, the data in Figs. 1 and 2 probably underestimate the extent of binding which would occur at higher pHs in the absence of added sodium ion or other competitive cations. On the other hand, the mean level of sodium ion in gastric fluid is 4.9×10^{-2} N (2), a concentration which must substantially reduce the extent of drug interaction.

Several important questions remain which we will address as further progress is made, and our studies will include *in vivo* work if there is evidence of a potential influence on bioavailability.

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