Figure 2 presents the mean plasma concentration–time data for the 12 subjects who received 25 mg of phenylpropanolamine hydrochloride. The concentrations were within the quantitative range of the described method. The samples were assayed in duplicate with 2 weeks between duplicate determinations of each sample. The precision of these assays is indicated by the mean coefficient of variation of 3.0% for duplicates. A repeated analysis of 24 samples after 6 months at −10° revealed no significant differences, thus indicating sample stability.

The general approach presented in this report produced very clean chromatograms and thus should be considered for other primary amines.

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COMMUNICATIONS

Drug–Disintegrant Interactions: Binding of Oxymorphone Derivatives

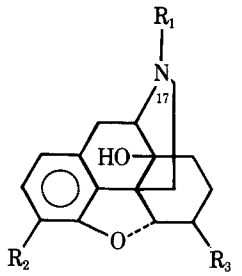
Keyphrases □ Drug-disintegrant interactions—binding of oxymorphone derivatives to disintegrating agents, dissolution testing, Freundlich adsorption isotherm □ Disintegrating agents—carboxymethylcellulose sodium, sodium starch glycolate, povidone, and modified cornstarch, binding to oxymorphone derivatives compared □ Oxymorphone derivatives—binding to disintegrating agents compared, Freundlich adsorption isotherm □ Freundlich adsorption isotherm—binding of oxymorphone derivatives to disintegrating agents compared, dissolution testing □ Analgesics, narcotic—oxymorphone, binding to disintegrating agents compared, dissolution testing

To the Editor:

Since the USP first established a disintegration standard in 1948, the search for good disintegrating agents for tablet formulations has intensified. Starch had been used as the primary tablet disintegrant and, in most cases, was relatively effective. However, recognition of the importance of bioavailability and compendial dissolution test requirements spurred the search for new disintegrants. An ideal disintegrant would improve both disintegration and dissolution and be effective in small amounts.

The search has produced several new disintegrating agents, most notably internally cross-linked carboxymethylcellulose sodium[1], sodium starch glycolate[2], cross-linked polyvinyl pyrrolidone[3] (povidone), and modified cornstarch[4].

During the development of a tablet formulation with a rapid disintegration/dissolution rate profile for a synthetic narcotic agonist–antagonist analgesic with the general structure of oxymorphone (I), extensive binding was noted between I and cross-linked carboxymethylcellulose sodium, and lower recovery resulted during dissolution testing. However, the binding to sodium starch glycolate was substantially less extensive, and no binding was detected for carboxymethylcellulose sodium, cornstarch, and modified cornstarch.



I

The binding of I to cross-linked carboxymethylcellulose sodium and sodium starch glycolate followed the Freundlich adsorption isotherm as shown in Fig. 1. The binding was sensitive to variation in solution pH (Fig. 2). Maximum binding was achieved for both cross-linked carboxy-

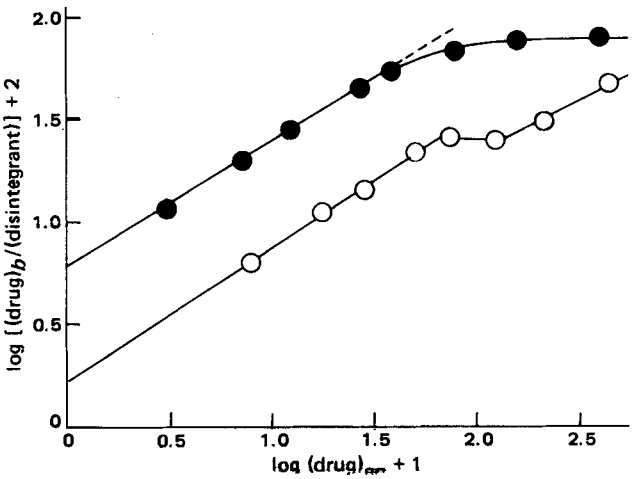


Figure 1—*Freundlich adsorption isotherm for the interaction of oxymorphone derivative (I) with cross-linked carboxymethylcellulose sodium (●) and sodium starch glycolate (○) in distilled water at room temperature.*

[1] Ac-Di-Sol, FMC Corp., Philadelphia, PA 19103.
[2] Explotab, E. Mendell Co., Carmel, NY 10512.
[3] PVP-XL, GAF Co., New York, NY 10020.
[4] StaRx 1500, Staley & Co., Decatur, IL 62525.

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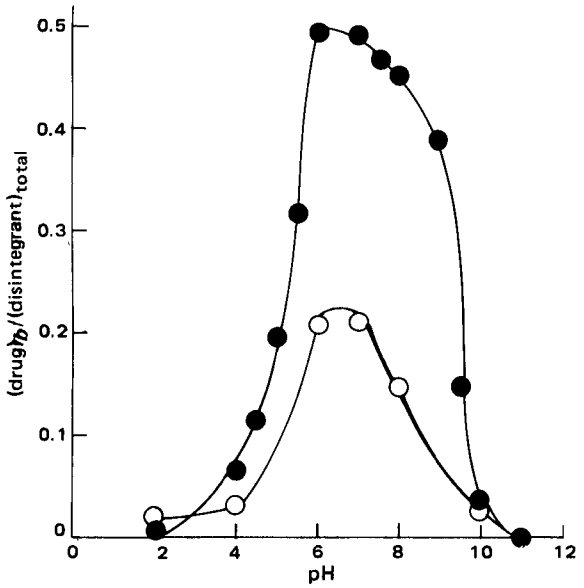

Figure 2—*Effect of solution pH on the interaction of oxymorphone derivative (I) with cross-linked carboxymethylcellulose sodium (●) and sodium starch glycolate (○).*

methylcellulose sodium and sodium starch glycolate at pH 6–7. However, the interaction of I with cross-linked carboxymethylcellulose sodium was twice that with sodium starch glycolate.

The interaction was believed to depend on the tertiary amine group at position 17 of I. Adsorption studies were extended to examine the interaction of cross-linked carboxymethylcellulose sodium with four derivatives of I, where substituents R_1, R_2, and R_3 varied and pKa values ranged from 7.9 to 8.7. Results indicated that the binding of I derivatives with cross-linked carboxymethylcellulose sodium can be described by the Freundlich adsorption isotherm as expressed by:

$$\log \frac{(\text{drug})_b}{(\text{disintegrant})} = \log k + \frac{1}{n} \log (\text{drug})_{eq} \qquad \text{(Eq. 1)}$$

where n and k are Freundlich adsorption constants that can be estimated from the slope and intercept of the linear portion of $\log[(\text{drug})_b/(\text{disintegrant})]$ *versus* $\log(\text{drug})_{eq}$ plots (Fig. 1); $(\text{drug})_{eq}$ is the equilibrium drug concentration in solution. Results obtained for the four I derivatives show n values of 1.43–1.75 and k values of 0.219–0.243. The data suggest that the structural variation of functional group R_1 at the tertiary amine group at position 17 of I does not greatly affect the Freundlich adsorption isotherm. All four I derivatives interacted with cross-linked carboxymethylcellulose sodium in a similar manner and to a significant extent.

The biological significance of these interactions is not known.

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X-Ray Crystal Structure Analysis of 14-Hydroxycaryophyllene Oxide, a New Metabolite of (−)-Caryophyllene, in Rabbits

Keyphrases □ Caryophyllene—X-ray crystal structure analysis of 14-hydroxycaryophyllene in rabbits □ Metabolites—of caryophyllene by X-ray crystal structure analysis, 14-hydroxycaryophyllene □ Terpenoids—caryophyllene, new metabolite, X-ray crystal structure analysis of 14-hydroxycarophyllene

To the Editor:

The metabolic studies of diet or crude drugs containing potentially toxic terpenoids may have significant implications for human toxicology. (−)-Caryophyllene (I), a sesquiterpene hydrocarbon having a *gem*-dimethyl group on the four-membered ring, often is found in crude drugs. For toxicological evaluation, I, $[\alpha]_D$ −10.6° (*c*, 5.64 in chloroform) (12 g), was administered to six male rabbits by a previously described method (1). The neutral metabolites (2.37 g) obtained from urine were chromatographed directly on silica gel to give crude alcohols, followed by acetylation with acetic anhydride in pyridine. The crude acetates also were chromatographed on silica gel impregnated with 5% silver nitrate to yield a pure acetate (II) (48% for total acetates).

Compound II, mp 71.5–72.5°, $[\alpha]_D$ −36.5° (*c*, 2.74 in chloroform), $C_{17}H_{26}O_3$ (M^+, 278), showed the presence of an acetoxymethyl group [1730 and 1240 cm^{-1}; δ 2.08 (s, 3H)[1] and 3.85 (s, 2H)] and an exocyclic methylene group [895 cm^{-1}; δ 4.90 and 5.03 (each bs, 1H)]. The PMR spectrum also contained the signals of one proton [δ 2.80 (m)] and one tertiary methyl group [δ 1.22 (s)] on carbons bearing an ether oxygen. This spectral evidence indicated that one of the *gem*-dimethyl groups on the four-membered ring might be hydroxylated. This assumption was supported further by the ^{13}C-NMR spectrum of II, which showed the presence of two CH_3 groups (δ 17.0 and 17.2 ppm), five CH_2 groups (27.6, 28.8, 29.9, 30.3, and 34.8 ppm), two CH groups (45.8 and 48.1 ppm), a trisubstituted oxirane ring [59.4 (s) and 63.5 (d)], a tetrasubstituted sp^3 carbon (36.7), an exomethylene group [113.5 (t) and 151.4 (s) ppm], and an acetoxymethyl group [20.8 (q), 71.6 (t), and 170.9 (s) ppm].

Hydrolysis of II regenerated an alcohol, $[\alpha]_D$ −25.4° (*c*, 1.66 in chloroform); $C_{15}H_{24}O_2$ (M^+, 236); δ 1.07 and 1.25

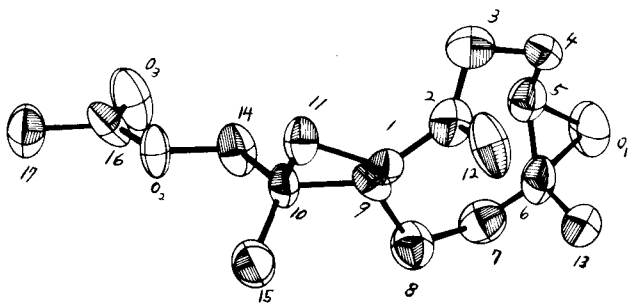

Figure 1—*X-ray structure of 14-acetoxycaryophyllene oxide (II).*

[1] s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

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