Sorption Properties of Cross-Linked Insoluble Polyvinylpyrrolidone

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Abstract □ The interaction of 32 drugs of diverse chemical structure with cross-linked insoluble polyvinylpyrrolidone (crospovidone) was studied. By using a polymer to drug ratio of 10:1, the sorbed amount for 20 compounds was found to be <5%. After a 10-fold decrease of the polymer concentration, the sorbed amount of eight other compounds fell to or below the 5% level. Only tannic acid and hexylresorcinol exhibited a significantly stronger sorption tendency. The interaction appeared to be controlled by phenolic groups in the active ingredient. The binding can be quantified by an interaction constant, K_s, whose definition is based on a bulk phase model of interaction *via* independent binding sites. The exceptionally strong binding of hexylresorcinol, however, apparently was caused by cooperative interaction of the hexyl groups in the bound state. Desorption studies revealed that the binding was fully reversible in all cases. Therefore, the presence of cross-linked polyvinylpyrrolidone as a disintegrant in pharmaceutical preparations is not expected to interfere with GI drug absorption.

Keyphrases □ Polyvinylpyrrolidone—interaction with 32 pharmaceuticals of diverse chemical structure, sorption and desorption studies □ Sorption—interactions of 32 pharmaceuticals of diverse chemical structure with cross-linked insoluble polyvinylpyrrolidone □ Binding—interactions of 32 pharmaceuticals of diverse chemical structure with cross-linked insoluble polyvinylpyrrolidone, sorption and desorption studies

N-Vinylpyrrolidone can be polymerized to yield polyvinylpyrrolidone, a readily soluble polymer, or can be transformed into a cross-linked insoluble polyvinylpyrrolidone (crospovidone, I) by proliferous polymerization (1–3).

Compound I exhibits an exceptionally high swelling pressure (4), which apparently is connected with the increased hydration capacity of the polymer (5, 6). For that reason, I is particularly useful as a disintegrating agent in pharmaceutical formulations.

BACKGROUND

Because of its disintegrating effect, I may enhance the release rate of drug from tablet formulations. With griseofulvin tablets containing a large amount of polyethylene glycol, I enhanced drug release at a significantly higher rate than when I was not present (7).

The same advantageous effect was observed in similar formulations with other drugs (8). The release of penicillins and cephalosporins from capsules was promoted by I (9). The dissolution rate of kavaine was increased after sorption onto I as a carrier (10).

Because of the dipolar character and the porous structure of I, specific interactions with solutes cannot be predicted. Only in a single case has a relatively strong binding of tannic acid and related compounds been reported (2). Other compounds such as acetaminophen, benzocaine, metamizole, and salicylamide exhibited no stronger interaction with I than with corn starch, carboxymethyl starch, and microcrystalline cellulose (11).

The present study investigated the possible interactions of I with numerous drugs of diverse chemical structure. Some compounds chosen were known for their binding tendency with polyvinylpyrrolidone (12). The experimental results are explained on the basis of models of noncooperative and cooperative interaction.

EXPERIMENTAL

Materials—The following were obtained from commercial sources: acetaminophen[1], allopurinol[2], benzocaine[3], benzoic acid[4], *p-tert*-butylphenol[5], caffeine[6], chloramphenicol[2], cinnarizine[6], diphenhydramine[6], ethaverine[6], hexylresorcinol[7], *p*-hydroxybenzoic acid[7], isoniazid[6], menadione[4], methaqualone[4], nitrofurantoin[7], papaverine hydrochloride[4], phenazone[4] (antipyrine), procaine hydrochloride[4], promethazine hydrochloride[6], propylparaben[2], pyridoxine hydrochloride[4], reserpine[7], resorcinol[4], riboflavin[4], salicylic acid[4], sodium salicylate[4], sulfadiazine[6], sulfamidopyrine[6], tannic acid[4], tetracaine hydrochloride[3], and theophylline[6].

All materials were the highest available grade and were used without further purification.

The specific surface area of cross-linked polyvinylpyrrolidone[8] (I) was determined by nitrogen adsorption, according to the Brunauer, Emmett, and Teller method[9] (13), after the samples were dried carefully.

Sorption Experiments—For the easily soluble substances, 1000 mg was dissolved in 1000 ml of 0.01 *N* HCl, water, or artificial intestinal fluid (USP XIX) unless otherwise noted. Where the solubility was insufficient, the suspension was filtered after vibrational stirring for 0.5 hr. The filtrate was diluted until 200 ml contained 100 mg of solute. For even less soluble samples, saturated solutions at 25° were used.

The sorption experiments were performed in a thermostatted bath at 37 ± 0.5°. Compound I was added in amounts of 1000 or 100 mg/200 ml of solution, and the suspension was maintained under steady vibrational stirring at 150 rpm for 0.5 hr. Then the suspensions were filtered or centrifuged at 37°. The amount of unbound drug was determined spectrophotometrically, with the absorbance values of the polymer-free solutions of the drugs (which had gone through the same cycle of pretreatment) as a reference.

Determination of the residual drug concentrations was performed using appropriate calibration curves measured at the following characteristic wavelengths: acetaminophen, 243 nm; allopurinol, 251 nm; benzocaine, 226 nm; benzoic acid, 230 nm; *p-tert*-butylphenol, 274.5 nm; caffeine, 273 nm; chloramphenicol, 278 nm; cinnarizine, 253 nm; diphenhydramine, 258 nm; ethaverine, 252 nm; hexylresorcinol, 279 nm; *p*-hydroxybenzoic acid, 255 nm; isoniazid, 266 nm; menadione, 261 nm; methaqualone, 233.5 nm; nitrofurantoin, 366 nm; papaverine, 251 nm; phenazone, 239 nm; procaine hydrochloride, 290 nm; promethazine hydrochloride, 250 nm; propylparaben, 255 nm; pyridoxine hydrochloride, 290.5 nm; reserpine, 267 nm; resorcinol, 273 nm; riboflavin, 267 nm; salicylic acid, 237 nm; sodium salicylate, 236.5 nm; sulfadiazine, 243 nm; sulfamidopyrine, 258 nm; tannic acid, 275 nm; tetracaine hydrochloride, 228 nm; and theophylline, 271.5 nm.

Desorption Experiments—Drug-loaded samples of I were prepared by centrifuging the respective suspensions following sorption. After the sediments were isolated, the desorption of bound drug was studied at 25° by vigorously shaking the 1000-mg samples three or more times with 50 or 100 ml of the respective solvent for 15 min. The degree of desorption was determined by spectrophotometric analysis of the combined supernates after centrifuging the suspensions.

RESULTS

Under the described experimental conditions, several drugs essentially did not interact with I: allopurinol[10], chloramphenicol, cinnarizine[10], caffeine, diphenhydramine hydrochloride, ethaverine hydrochloride,

[1] Fluka, Neu-Ulm, West Germany.
[2] EGA Chemie, Steinheim, West Germany.
[3] Sigma Chemie, München, West Germany.
[4] Merck AG, Darmstadt, West Germany.
[5] BASF AG, Ludwigshafen, West Germany.
[6] Synochem, Hamburg, West Germany.
[7] Serva, Heidelberg, West Germany.
[8] Kollidon CL, BASF AG, Ludwigshafen, West Germany.
[9] Areameter, Ströhlein, Düsseldorf, West Germany.
[10] Investigated in saturated solution.

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Table I—Sorption Data of Compounds with a Moderate Binding Tendency to I [a]

Compound	Weighing-in Drug, g/200 ml	Sorbed Amount of Drug, %				Binding Constant, K_s, M^{-1}			
		0.01 *N* HCl		Water		0.01 *N* HCl		Water	
		1000 ml of I (φ = 0.005)	100 mg of I (φ = 0.0005)	1000 mg of I (φ = 0.005)	100 mg of I (φ = 0.0005)	φ = 0.005	φ = 0.0005	φ = 0.005	φ = 0.0005
Acetaminophen (mol. wt. 151)	0.1	8.1	1.4	7.3	0.3	2.0	3.2	1.6	0.7
Benzocaine (mol. wt. 165)	0.1	7.7	0.8	7.6	1.2	1.9	1.8	1.8	2.7
Benzoic acid (mol. wt. 122)	0.1	11.3	1.4	9.4	0.7	2.9	3.2	2.3	1.6
Propylparaben (mol. wt. 180)	0.035	23.4	3.1	21.8	5.3	6.8	7.2	6.2	12.6
Resorcinol (mol. wt. 110)	0.1	31.7	3.5	32.2	5.0	10.7	8.4	10.9	12.3
Salicylic acid (mol. wt. 138)	0.1	18.0	1.8	14.7	1.1	4.9	3.9	4.1	2.5
Sodium salicylate (mol. wt 160)	0.1	22.6	2.8	0.5	0.1	6.5	6.4	0.1	0.2
Sulfadiazine (mol. wt. 250)	0.02	7.2	0.9	4.9	~0	1.7	2.0	1.1	~0

[a] The molar concentrations of I are expressed in moles of monomer segments per unit volume.

Table II—Sorption Data of Compounds Exhibiting Strong Binding to I

Compound	Weighing-in Drug, g/200 ml	Sorbed Amount of Drug, %				Binding Constant, K_s, M^{-1}			
		0.01 *N* HCl		Water		0.01 *N* HCl		Water	
		1000 mg of I (φ = 0.005)	100 mg of I (φ = 0.0005)	1000 mg of I (φ = 0.005)	100 mg of I (φ = 0.0005)	φ = 0.005	φ = 0.0005	φ = 0.005	φ = 0.0005
p-tert-Butylphenol (mol. wt. 150)	0.06	21.5	10.2	21.6	12.2	6	25	6	31
Hexylresorcinol (mol. wt. 194)	0.06	96.5	76.8	96.3	71.3	(617)[a]	(777)[a]	(582)[a]	(616)[a]
p-Hydroxy-benzoic acid (mol. wt. 138)	0.1	44.1	6.9	39.0	5.0	18	17	14	12
Tannic acid (mol. wt. 1548)	0.1	94.4	27.9	90.1	34.6	(375)[a]	(86)[a]	(200)[a]	(118)[a]

[a] The numbers in parentheses are formal values according to Eq. 8; for details, see text.

isoniazid, menadione[10], methaqualone[10], nitrofurantoin[10], papaverine hydrochloride[10], phenazone, procaine hydrochloride, promethazine hydrochloride, pyridoxine hydrochloride, reserpine[10], riboflavin[10], sulfamidopyrine, tetracaine hydrochloride, and theophylline. In all cases, the amount of material bound onto I dispersed in 0.01 *N* HCl or water was <5%.

Table I lists all materials that exhibited a degree of sorption higher than 5% at high I concentrations (*i.e.*, 1000 mg/per 100 mg of drug). Decreasing the I concentrations by a factor of 10, however, decreased the amount bound (5% level and lower) in all cases.

The compounds listed in Table II were bound by I significantly even at low polymer concentrations. The strong binding of tannic acid in aqueous suspensions of I was reported previously (2).

The results of the binding studies of selected systems with artificial intestinal fluid are shown in Table III.

Except for tannic acid, hexylresorcinol displayed the strongest binding irrespective of the suspension medium pH (Tables II and III).

As to the desorption studies, characteristic results of a few selected compounds are shown in Table IV.

To determine whether the thermodynamics of the sorption process is influenced by surface phenomena, sorption studies were performed with two types of I, which differed by a factor of five in specific surface area. Typical data are shown in Fig. 1, where $[A_0]/[A]$, the ratio of the weighing-in concentration and the unbound amount of the drug, is plotted *versus* the polymer to drug ratio.

The close similarity of the sorption behavior of both I samples indicates that sorption thermodynamics is dominated by bulk phase properties of the polymer and that any possible influence of the extent of the specific surface area of the material can be neglected. Hence, the sorption data can be treated according to the mass law of chemical equilibrium of bulk phases. When considering only the polymer compartment, it may be assumed that binding of the drug, A, occurs on independent free binding sites, F, of the polymer. Then the sorption constant K_s is defined as:

$$K_s = \frac{[FA]}{[A]([F_0] - [FA])} \qquad \text{(Eq. 1)}$$

The mass balance equation then is written as $[F_0] = [F] + [FA]$, where $[F_0]$ denotes the total concentration of binding sites, $[F]$ is the concentration of free bindings sites, and $[FA]$ is the concentration of occupied binding sites and is identical with the bound amount of drug.

Table III—Data of Sorption Studies in Artificial Intestinal Fluid (USP XIX)

Compound	Weighing-in Drug, g/200 ml	Sorbed Amount of Drug, %	
		1000 mg of I (φ = 0.005)	100 mg of I (φ = 0.0005)
Acetaminophen (mol. wt. 151)	0.1	7.9	0.1
Benzocaine (mol. wt. 165)	0.1	9.4	0.2
Benzoic acid (mol. wt. 122)	0.1	1.1	1.0
p-tert-Butylphenol (mol. wt. 150)	At saturation	21.3	8.9
Hexylresorcinol (mol. wt. 194)	At saturation	96.7	73.2
p-Hydroxybenzoic acid (mol. wt. 138)	0.1	1.2	0.4
Promethazine hydrochloride (mol. wt. 321.5)	0.1	4.5	2.6
Propylparaben (mol. wt. 180)	At saturation	26.8	3.7
Resorcinol (mol. wt. 110)	0.1	32.5	5.4
Salicylic acid (mol. wt. 138)	0.1	2.4	0.6
Sulfadiazine (mol. wt. 250)	At saturation	1.7	0.2
Tannic acid (mol. wt. 1548)	0.1	90.2	30.0

Table IV—Desorption of Various Drugs from I in 0.1 *N* HCl at 25°: Comparison of Experimental Data with Theoretical Values

Compound	Sorption of Drug, mg			Remaining Sorbed Amount after n Desorption Steps, mg													
					$n = 1, m_{s,1}$		$n = 2, m_{s,2}$		$n = 3, m_{s,3}$		$n = 4, m_{s,4}$		$n = 6, m_{s,6}$		$n = 10, m_{s,10}$	
	m_0[a]	$10^2\varphi$	$m_{s,0}$[b]	$10^2\varphi$	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.
Benzoic acid (0.25 g/liter)	25	2.25	9.25	1.13	1.7	2.1	~0	0.5	~0	0.1	—	—	—	—	—	—
Hexylresorcinol (0.25 g/liter)	25	1.4	23.9	0.72	21.5	22.0	19.1	20.2	16.8	18.6	14.7	17.1	11.0	14.4	5.8	10.3
Resorcinol (0.25 g/liter)	25	1.3	19.1	0.65	11.9	11.9	7.3	7.5	4.3	4.7	2.4	2.9	0.4	1.1	—	—
Salicylic acid (0.25 g/liter)	25	2.0	13.1	1.0	3.7	4.7	0.1	1.7	~0	0.6	—	—	—	—	—	—
Tannic acid (0.1 g/liter)	10	0.1	9.7	0.05	9.6[c]	9.2	9.5[c]	8.7	9.5[c]	8.2	9.4[c]	7.8	—	—	—	—

[a] Amount of drug prior to sorption. [b] Initially sorbed amount of drug. [c] Experimental values too high; for further details, see text.

An alternative view of the system, based on the mass distribution of drug between the liquid and the (swollen) solid phase, is obtained by introducing the Nernst coefficient, k, of mass distribution of A:

$$k = \frac{[A]_s}{[A]} \qquad \text{(Eq. 2)}$$

where $[A]_s$ and $[A]$ denote the drug concentrations in the polymer and liquid phase, respectively.

With the assumption that $[A]$ is equilibrated with the portion of $[A]_s$ that remains unbound within the polymer phase, then:

$$k = \frac{[A] + [FA]}{[A]} \qquad \text{(Eq. 3)}$$

After introducing the phase ratio $\varphi = V_s/V_L$, in which V_s and V_L represent the volumes of the polymer[11] and liquid phase, respectively, the mass balance equation for the drug becomes:

$$[A_0] = [A] + \varphi[A] + \varphi[FA] \qquad \text{(Eq. 4)}$$

or, when rearranged, it becomes:

$$[FA] = \frac{1}{\varphi}([A_0] - [A]) - [A] \qquad \text{(Eq. 5)}$$

Substituting Eq. 5 into Eq. 3 gives:

$$\frac{[A_0]}{[A]} = 1 + k\varphi \qquad \text{(Eq. 6)}$$

As shown in Fig. 1, the experimental data are described by this equation, which supports the introduced model of binding. From the slope of the straight lines, the Nernst coefficient of interaction for both I samples is evaluated to be 84 and 79.

The coupling of k with K_s is performed by introducing Eqs. 5 and 6 into Eq. 1 to give:

$$K_s = \frac{k - 1}{[F_0] - [A](k - 1)} \qquad \text{(Eq. 7)}$$

or:

$$k = 1 + \frac{[F_0]K_s}{1 + [A]K_s} \qquad \text{(Eq. 8)}$$

This equation is closely related to an equation derived by Luck (14) to describe the Nernst partition equilibrium in certain textile dyeing processes.

From Eq. 8, it follows that for small values of the interaction constant K_s, the Nernst coefficient k becomes independent of $[A]$ (Fig. 2). This condition holds for all compounds in Table I and those that were listed as not interacting with I. Therefore, the polymer to drug interaction may be characterized either by k or K_s. However, to evaluate K_s from experimental data according to Eqs. 6 and 7, a reasonable assumption has to be made concerning the value of $[F_0]$. If it is assumed that each monomeric subunit of the polymer may serve as a binding site, $[F_0]$ becomes equal to ~9 M. All K_s values in Tables I–III were obtained using this assumption.

Because of the sensitive dependence of K_s on experimental errors of the sorption data, the K_s values in Table I obtained with $\varphi = 0.005$ and 0.0005 are in satisfactory agreement, with the exception of the propylparaben–water system; the reason for this discrepancy is unknown. In general, however, the results support the notion that sorption occurs according to a reversible equilibrium process in interacting systems.

For sodium salicylate, pronounced differences in K_s were found in the

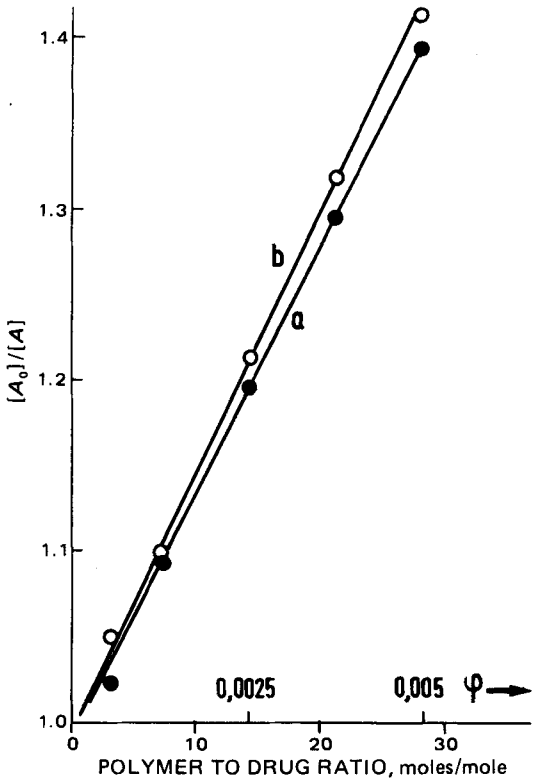

Figure 1—*Binding of propylparaben by I of different specific surface areas at 37°. The weighing-in concentration of the drug was 57 mg/200 ml. The specific surface areas of the I samples according to the Brunauer, Emmett, and Teller method were 5.42 (a) and 0.98 m^2/g (b). The marking of the abscissa is defined by $\varphi = V_s/V_L$, where V_s is the volume of the solid phase and V_L is the volume of the liquid phase. Molar concentrations of the polymer refer to the molecular weight of the monomeric subunit.*

[11] For convenience, the volume of I in the dry state is considered.

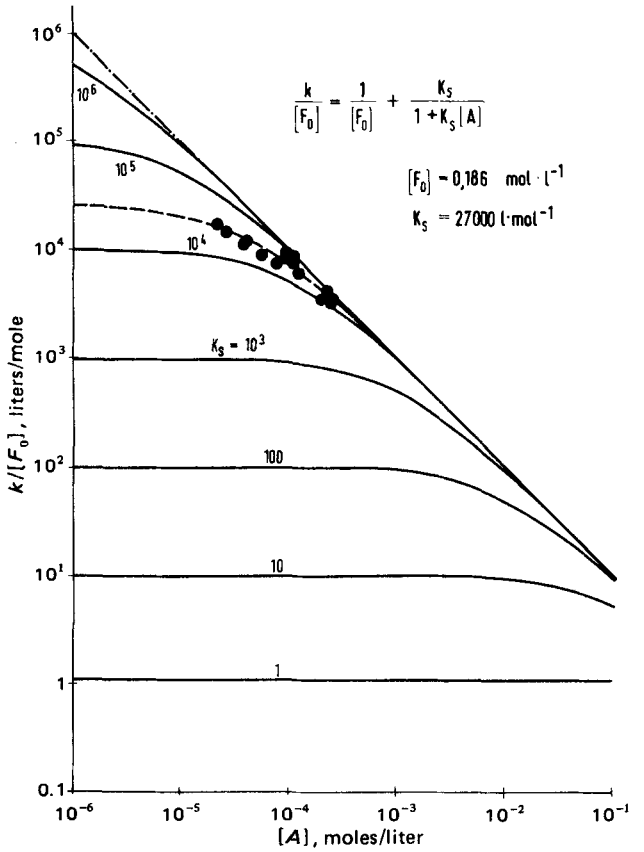

Figure 2—*Dependence of the Nernst coefficient on the equilibrium concentration of the interacting drug, [A], for various values of the binding constant, K_s. Key: —, theoretical curves according to Eq. 8; and ●– –, experimental values of tannic acid–I.*

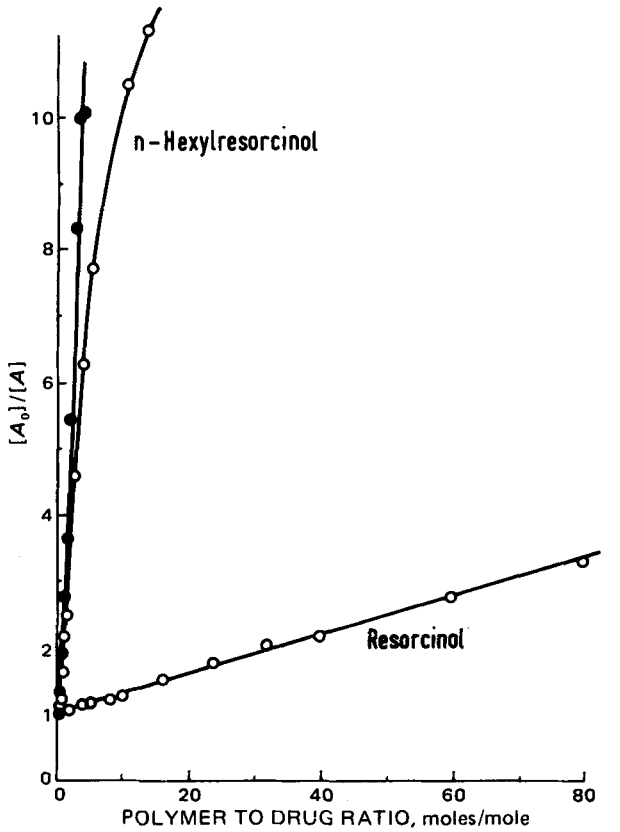

Figure 3—*Binding of resorcinol and of hexylresorcinol by I in 0.01* N *HCl at 37°. The weighing-in concentrations of the drug, [A_0], were 250 (○) and 500 (●) mg/liter.*

acidic system (0.01 *N* HCl) as compared to plain water; similar sorption experiments with salicylic acid did not show comparable differences. This difference can be explained by the fact that, at the end of the sorption experiments, pH values above 6.0 were observed in the former case while pH values always remained at ~3.1 in the latter case.

The K_s values of the strongly interacting compounds are summarized in Table II. The exceptionally high K_s values of tannic acid and hexylresorcinol deserve close scrutiny. In both cases, the Nernst coefficient is no longer independent of [*A*], although for different reasons.

The experimental results of a detailed investigation of the Nernst partition of the tannic acid–I system is shown in Fig. 2, where $\log(k/[F_0])$ is plotted against the logarithm of [*A*]. The experimental data are compared with theoretical curves as obtained from Eq. 8 for various K_s values. For small K_s values, where $[A]K_s \ll 1$ holds true, the Nernst coefficient k becomes independent of [*A*]. This condition is satisfied by all compounds in Table I and by some compounds in Tables II and III.

The experimental data for tannic acid, however, closely approach the limiting straight line of slope −1 where $[A]K_s \gg 1$ and $\log k \sim \log[F_0] - \log[A]$. The concentration of effective binding sites, $[F_0]$, of the tannic acid interaction with I is, according to Eq. 8, 0.186 *M*. For the binding constant, K_s, a value of the order of $2.7 \times 10^4\ M^{-1}$ is estimated. These exceptional figures underline the special role tannic acid plays in the interaction behavior with I. Apparently, this interaction is related to the comparatively high molecular weight of tannic acid (mol. wt. ~1550) and its multifunctional chemical structure. In contrast to other compounds in this study, a single molecule of tannic acid covers many individual binding sites simultaneously, leading to extraordinarily strong binding.

Hexylresorcinol, on the other hand, is another example of a peculiar interaction mechanism with I. The experimental results of a detailed investigation of this system are shown in Fig. 3. With resorcinol, the plotting of $[A_0]/[A]$ *versus* φ yields a perfect straight line; with hexylresorcinol, the situation is apparently changed. The steep slope of the curve indicates an extremely strong interaction. On the other hand, the marked deviation from linearity of the curve suggests that the introduced model of interaction no longer applies. However, the experimental results are readily explained in terms of a model of cooperative binding. A relevant plot of the data according to a theory of cooperative interaction (15) is shown in Fig. 4.

As depicted in Fig. 4, the hexylresorcinol data fit the concept of cooperative binding. Therefore, the K_s values of hexylresorcinol in Table II, which were evaluated according to the model of noncooperative competitive binding, are valid only to a first approximation for the stated polymer to drug ratio. Of course, the extremely strong tendency of interaction, as documented in Figs. 3 and 4, is reflected nevertheless in the magnitude of the K_s values.

The cooperative binding plot (Fig. 4) allows the maximum number of bound hexylresorcinol molecules per vinylpyrrolidone segment in the polymer to be determined. With increasing weighing-in concentrations of the drug, the binding curves approach a limiting straight line, which can be extrapolated to the polymer to drug ratio axis. The intercept yields $1/g$, where g is the number of binding sites per polymer segment. An intercept value of 2 (Fig. 4) indicates that each hexylresorcinol molecule is bound by two vinylpyrrolidone residues.

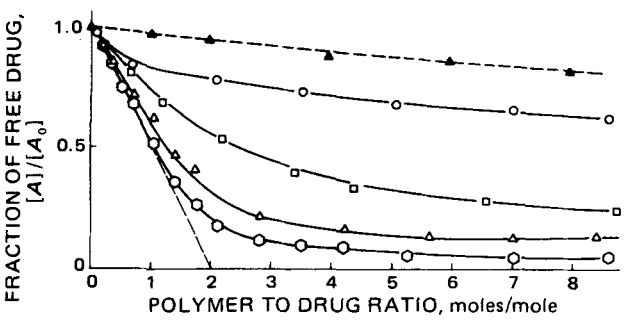

Figure 4—*Cooperative binding curves of hexylresorcinol–I in 0.01* N *HCl at 37°. For comparison, relevant data of the noncooperatively bound resorcinol are included. The polymer to drug ratio is expressed in moles of monomer segments per mole of drug. Key: —, hexylresorcinol at 25 (○), 80 (□), 250 (△), and 500 (○) mg/liter; and ---, resorcinol at 250 (▲) mg/liter.*

Finally, in the case of butylphenol, deviations from the expected constancy of the K_s values with changing φ are observed. There is no obvious explanation for this discrepancy. Perhaps a possible micellization reaction of the compound interferes with the polymer interaction in this case.

The results of the desorption studies also can be treated according to the introduced model of interaction. If the desorption experiment is started with an adsorbed concentration of drug of $[A]_{s,0}$, after the first desorption step the partition equilibrium can be described according to Eq. 2 as:

$$k = \frac{[A]_{s,1}}{[A]} = \frac{m_{s,1}/V_s}{m/V_L} \qquad \text{(Eq. 9)}$$

in which $m_{s,1}$ denotes the amount of the compound remaining in the polymer phase after the first desorption step and m denotes the appropriate amount of desorbed material. Hence, the mass balance reads:

$$m_{s,0} = m + m_{s,1} \qquad \text{(Eq. 10)}$$

where $m_{s,0}$ represents the initially sorbed amount. From Eq. 9, it follows that:

$$k = \frac{1}{\varphi} \frac{m_{s,1}}{m_{s,0} - m_{s,1}} \qquad \text{(Eq. 11)}$$

which can be rearranged to yield for n desorption steps:

$$m_{s,0} = \left(1 + \frac{1}{k\varphi}\right)^n m_{s,n} \qquad \text{(Eq. 12)}$$

The fraction, γ_s, of the initially sorbed amount $m_{s,0}$ remaining bound after n desorption steps is $\gamma_s = m_{s,n}/m_{s,0}$:

$$\gamma_s = \left(1 + \frac{1}{k\varphi}\right)^{-n} \qquad \text{(Eq. 13)}$$

Experimental results of desorption studies with several substances with a pronounced sorption tendency are listed in Table IV. They are compared with theoretical values determined with Eq. 12 by considering the appropriate k values as obtained from sorption studies. With 15-min equilibration times for each desorption step, generally the experimental and theoretical values are in satisfactory agreement, indicating that the molecules are reversibly bound even in cases of substantial interaction.

Again, hexylresorcinol and tannic acid play an exceptional role. With hexylresorcinol, the desorption process proceeds even faster than predicted theoretically due to the underlying cooperative mechanism of interaction, which is not accounted for in the derivation of Eq. 12. On the other hand, the discrepancies with tannic acid are explained partly by Fig. 2. As the desorption proceeds, the value of the Nernst coefficient increases, slowing down the efficiency of the stepwise desorption process. The theoretical values of Table IV, however, are based on the assumption of a constant value of k. The experimental verification of the degree of desorption is hampered further by the fact that tannic acid adheres to the surface of analytical glassware, disturbing a correct determination of the minute amounts desorbed in each single step.

DISCUSSION

Thirty-two compounds of diverse chemical structure were studied with regard to their sorption tendencies toward I. Even with rather extreme polymer to drug ratios of 10:1 (never met in practice), the sorbed amount was <5% with 20 pharmaceuticals. None of the pharmaceuticals within this class carried phenolic functional groups.

Under the same experimental conditions, eight compounds showed sorption values between 5 and 33%. By decreasing the polymer concentration 10 times whereby a polymer to drug ratio of 1:1 was established, the sorbed amount fell to or below the 5% level in cases of readily soluble drugs. All compounds of this class were characterized by a simple aromatic structure, five of which (propylparaben, sodium salicylate, acetaminophen, resorcinol, and salicylic acid) carried hydroxyl groups.

Significant differences in binding between the water and 0.01 *N* HCl system were observed only with sodium salicylate; this result is explained readily by the change in pH.

In artificial intestinal fluid, the binding tendency of several pharmaceuticals (benzoic acid, *p*-hydroxybenzoic acid, and sulfadiazine) appeared to be less pronounced as compared to the sorption behavior in an acidic environment. No significant differences were found in this respect with benzocaine, *p-tert*-butylphenol, propylparaben, acetaminophen, and resorcinol. The same is true for hexylresorcinol and tannic acid, which exhibited the strongest binding tendency irrespective of the medium pH.

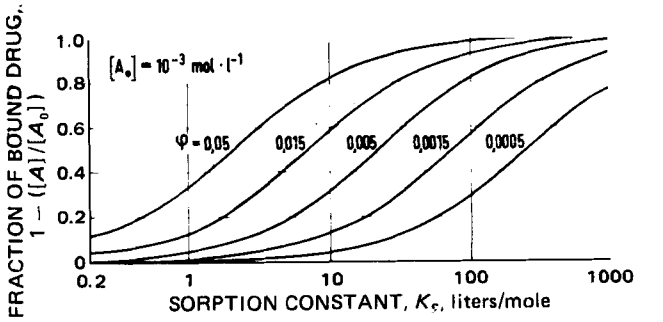

Figure 5—*Fraction of drug bound to I as a function of the binding constant,* K_s, *for various values of* φ.

As shown earlier, the degree of polymer to drug interaction is expressed by the value of the binding constant, K_s. Not unexpectedly, the results of binding studies with soluble polyvinylpyrrolidone (12) point out close similarities with the present findings. Higuchi and Kuramoto (16) found no complexing between soluble polyvinylpyrrolidone and citric acid, benzylpenicillin, cortisone, procaine hydrochloride, caffeine, and theophylline (16). The latter three compounds were investigated in the present study and were found to be noninteracting with I.

The affinity of other pharmaceuticals toward soluble polyvinylpyrrolidone decreased in the following order: sulfathiazole > *m*-hydroxybenzoic acid > *p*-hydroxybenzoic acid > *p*-aminobenzoic acid > salicylic acid > phenobarbital > benzoic acid > sodium salicylate > mandelic acid > chloramphenicol. These results again are in close agreement with the findings obtained with I.

Particularly interesting is the similarity of experimental results obtained with soluble polyvinylpyrrolidone and I with hexylresorcinol. Polli and Frost (17) reported particularly strong binding between polyvinylpyrrolidone and this resorcinol derivative. However, this conspicuous molecular interaction was explained vaguely as a possible change of the spatial orientation of the polymer during the interaction. The analysis of the experimental data presented here, which is also valid for the interaction of hexylresorcinol with soluble polyvinylpyrrolidone[12], clearly indicates the significance of a cooperative interaction mechanism in the sorption process (Fig. 4).

In the case of hexylresorcinol, binding to the polymer probably occurs not independently to single binding sites but preferably to the nearest neighbor binding sites, thereby inducing an aggregation of bound ligands. This peculiar mechanism of interaction (15) presumably is caused by hydrophobic interaction of the hexyl residues of nearest-neighbor ligands. In that way, the driving force of interaction, which is assumed to be dominated by hydrophilic hydrogen bonding in the case of resorcinol, is enhanced greatly.

Evidence for both hydrophilic and hydrophobic effects on the binding of benzene derivatives to polyvinylpyrrolidone also was found by Molyneux and Frank (18). In contrast to hexylresorcinol, however, the noncooperative character of interaction was basically not altered, and the interaction constants were only gradually changed. Usually, the strength of interaction increases with increasing numbers of polar functional groups and with the extent of the hydrophobic part of the molecules. The distinct complexing tendency of tannic acid with polyvinylpyrrolidone is readily explained in these terms.

The relevance of hydrogen bonding for the interaction with I is suggested by the well-known fact that phenolic compounds in general may form precipitates with soluble polyvinylpyrrolidone (19). Further evidence is offered by the observation that esterification of *p*-hydroxybenzoic acid leads to a decrease in binding strength with polyvinylpyrrolidone (20).

Of practical importance is the extent to which pharmaceuticals with a measurable binding tendency are released from the bound state during GI passage. This process may be considered as a series of desorption steps since, during the passage, intestinal absorption of the released drug takes place continuously. The release process generally relates only to the small fraction of drug staying in the bound state. The bound fraction, γ_s, can be estimated by means of Fig. 5, where γ_s is plotted as a function of the interaction constant, K_s, for various solid to liquid ratios, φ. It follows that for the majority of pharmaceuticals investigated in the present study within wide limits of the polymer to drug ratio, the sorbed amount lies well below the 10% level.

[12] D. Horn and W. Ditter, to be published.

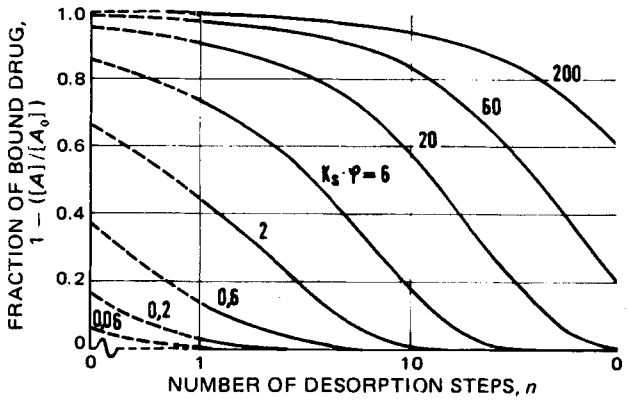

Figure 6—*Decrease of the initially sorbed amount of the drug as a function of the number of desorption steps,* n, *for various values of* $K_s\varphi$.

Finally, theoretical desorption curves are shown in Fig. 6 and were calculated according to Eq. 13. The graph depicts the decrease of the initially sorbed amount of the drug as a function of the number of desorption steps for increasing values of $K_s\varphi$. With regard to K_s values on the order of 2–10 M^{-1}, indicating moderate binding (Table I) even when considering high values of φ (*i.e.*, $\varphi = 0.02$), it follows from Fig. 6 that only a few desorption steps are necessary for complete release of the bound compound from the polymer.

Presumably, with the exception of tannic acid and closely related compounds, the presence of the disintegrant should not interfere with GI absorption of the pharmaceutical.

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Improved Delivery through Biological Membranes VIII: Design, Synthesis, and *In Vivo* Testing of True Prodrugs of Aspirin

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Abstract □ Novel activated ester-type prodrugs of aspirin were designed and synthesized. The methylthiomethyl, methylsulfinylmethyl, and methylsulfonylmethyl esters of aspirin (acetylsalicylic acid) were cleaved *in vitro* in plasma to form aspirin rather than the corresponding salicylates. *In vivo* studies using dogs indicated that at least one aspirin derivative, methylsulfinylmethyl-2-acetoxybenzoate, is a true aspirin prodrug since aspirin was detected in the blood after prodrug administration.

Keyphrases □ Aspirin—activated ester-type prodrugs of aspirin synthesized and evaluated for analgesia, *in vivo* and *in vitro* studies □ Prodrugs, aspirin—activated ester-type prodrugs synthesized and evaluated for analgesic activity, *in vitro* and *in vivo* studies □ Analgesic activity—activated ester-type prodrugs of aspirin, synthesized and evaluated for analgesia, *in vitro* and *in vivo* studies

The GI side effects of aspirin (acetylsalicylic acid, I) are well known and documented (1). These side effects are associated with the free carboxylic group; thus, transient derivatives (prodrugs) and various formulations of I were prepared and tested in which the free carboxyl group was derivatized or bound. The results obtained were unsatisfactory due to the specific properties of I. The *o*-acetyloxyl group is rather labile. Extensive studies of the chemical hydrolysis (2–8) and *in vivo* hydrolysis (9) demonstrated the facile conversion of I to salicylic acid (II). Although II is also a potent anti-inflammatory agent, it was shown (10) that I is a far more potent analgesic and, thus, delivery to the bloodstream in the intact form is desirable. To achieve this, the carboxyl-protecting function must be cleaved

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