Chromatographic Study of Interactions Between Polyvinylpyrrolidone and Drugs

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Abstract □ A chromatographic technique for the study of possible interactions of drugs with soluble or insoluble polymer additives is proposed. Crospovidone was used as a stationary phase. The method allowed the rapid determination of interaction constants in the range of $>1\ M^{-1}$ as relevant for applications in practice. The interaction of 39 drugs and model compounds of diverse chemical structure with povidone and crospovidone was studied. The results closely agreed with data obtained from conventional equilibrium dialysis and sorption studies. The complexation reaction was found to be dominated by hydrogen binding. A close correspondence between the strength of interaction and the nature, number, and position of hydrogen-donating functional groups in the active ingredient was observed. The binding tendency was enhanced when the functional groups were connected with aromatic residues. The carboxyl group was more effective than the hydroxide or amino groups. The binding can be quantified by the binding constants, K_p and K_s, respectively, describing the interaction with polyvinylpyrrolidone *via* independent binding sites. At pH 1, with the exception of tannic acid, all investigated drugs exhibited K_p and/or K_s values well below an upper limit of $10\ M^{-1}$. Hence, with additive–drug ratios commonly used in pharmaceutical preparations, the bound amount of drug after oral administration can hardly exceed 3%. In view of this already low degree of potential binding and considering its reversible character and its decreasing tendency with increasing pH during GI passage, the presence of polyvinylpyrrolidone in pharmaceutical preparations is not expected to interfere with GI drug absorption.

Keyphrases □ Polyvinylpyrrolidone—chromatographic study of interactions with drugs, soluble and insoluble polymer additives □ Chromatography—study of interactions with polyvinylpyrrolidone and drugs, soluble and insoluble polymer additives □ Polymers—soluble and insoluble additives, chromatographic study of interactions between polyvinylpyrrolidone and drugs

N-Vinylpyrrolidone can be polymerized to yield povidone (I), a polymer readily soluble in water and numerous other solvents, producing solutions with remarkably low viscosities (1). It can also be transformed into an insoluble polymer, crospovidone (II), by proliferous polymerization (2, 3). In pharmaceutical technology, both forms of the polymer are used mainly in the production of tablets. The pronounced disintegrating effect of II is based on an exceptionally high swelling pressure in aqueous systems (4–6).

Additives used in formulations of drugs are expected to be nontoxic and therapeutically inactive. In both respects polyvinylpyrrolidone meets these requirements. The degree to which the additive might form complexes with the active component is another consideration; a low tendency for complex formation is preferred, unless a sustained-release effect is of interest.

BACKGROUND

Because of the dipolar character of I and II, specific interactions with certain drugs are possible and have been observed in several cases. A recent review covers the published data concerning the interaction properties of various macromolecular additives (7). Data characterizing the interaction properties of I have been reported in numerous studies (8–23).

Much more limited are relevant data concerning the interaction tendency of Compound II. The binding of phenolic substances and its relevance for their removal from beer has been studied (24–26). Similarly, II has been used to remove phenols from plant tissues in the process of isolating active enzymes from plants (27). Furthermore, tannic acid and related compounds are known to be bound strongly by II (3). Other compounds such as acetaminophen, benzocaine, metamizole, and salicylamide exhibited no stronger interaction with II than with corn starch, carboxymethyl starch, and microcrystalline cellulose (28). First results of a systematic study of the interaction properties of II with various pharmaceuticals have been reported (29).

The objectives of the present study are: to develop new experimental techniques that simplify the performance of binding studies, to study the binding of selected model compounds to improve the basic understanding of the mode of interaction with I and II, and to present the binding data obtained from various drugs of diverse chemical structure in a way ready to be applied to systems of practical interest. The application of a novel chromatographic technique is emphasized.

EXPERIMENTAL

Materials—The following were obtained from commercial sources: acetaminophen[1], aspirin[2], aniline[3], benzocaine[4], benzoic acid[2], benzyl alcohol[5], caffeine[2], chloramphenicol[6], 1,2-dicarboxybenzene[2], 1,3-dicarboxybenzene[3], 1,4-dicarboxybenzene[3], 1,2-dihydroxybenzene[2], resorcinol[2], 1,4-dihydroxybenzene[5], 2,4-dihydroxybenzoic acid[1], 3,4-dihydroxybenzoic acid[7], 3,5-dihydroxybenzoic acid[5], 2,4-dimethylphenol[1], salicylic acid[2], 3-hydroxybenzoic acid[1], 4-hydroxybenzoic acid[1], methotrimeprazine[5], methyldopa[6], methylparaben[8], 2-methylphenol[1], papaverine hydrochloride[2], phenol[2], promethazine hydrochloride[5], riboflavin[2], salicylamide[2], sorbic acid[9], sulfamethazine[10], sulfamoxole[11], sulfathiazole[12], tetracaine hydrochloride[13] gallic acid[2], trimethoprim[11], 2,4,6-trimethylphenol[7], and tannic acid[2]. All materials were of the highest available grade and were used without further purification.

Povidone[14] was used as received (weight average of molecular weight $\overline{M}_w = 49{,}000$; number average of molecular weight $\overline{M}_n = 10{,}000$).

The sorption studies were performed applying crospovidone[15], characterized by a specific surface area[16] of $S_{N_2} = 6.0\ m^2/g$ and a density of $1.2\ g/cm^3$. A coarse fraction of II was used for the stationary phase in the chromatographic column.

Chromatography—In preparing the chromatographic column (length, 10 cm; diameter, 0.25 cm) an aqueous slurry of a coarse fraction of II, as specified above, was poured into the column and allowed to pack by gravity flow. The column was coupled with a UV-visible spectrophotometer[17] equipped with a 1-cm micro flow-through cell. The column was charged with 10-μl samples of the drug solution. For the easily soluble substances, 1000 mg was dissolved in 1000 ml of 0.1 *N* HCl. Where the solubility was insufficient, saturated solutions at 25° were used. In general, 0.1 *N* HCl, plain or loaded with 10–30 g/liter of I, was used for elution[18] with a rate of 7.5 ml/hr at ambient temperature (25 ± 1°).

[1] Merck-Schuchardt, München, West Germany.
[2] Merck-AG, Darmstadt, West Germany.
[3] BASF-AG, Ludwigshafen/Rhein, West Germany.
[4] Dr. Rentschler & Co., Laupheim, West Germany.
[5] Bayer-AG, Leverkusen, West Germany.
[6] Boehringer GmbH, Mannheim, West Germany.
[7] EGA Chemie GmbH & Co. KG, Steinheim, West Germany.
[8] W. Damm, Hamburg, West Germany.
[9] Dr. Schuchardt & Co., München, West Germany.
[10] Cilag Orion GmbH, Alsbach, West Germany.
[11] Nordmark-Werke GmbH, Hamburg, West Germany.
[12] K.-W. Pfannenschmidt, Hamburg, West Germany.
[13] Hoechst-AG, Frankfurt, West Germany.
[14] Kollidon 30, BASF-AG, Ludwigshafen/Rhein, West Germany.
[15] Kollidon CL, BASF-AG, Ludwigshafen/Rhein, West Germany.
[16] Areameter, Ströhlein, Düsseldorf, West Germany.
[17] PM 2 DL, Zeiss, Oberkochen, West Germany.
[18] Prominent, Type A 2001, C.F.G., Heidelberg, West Germany.

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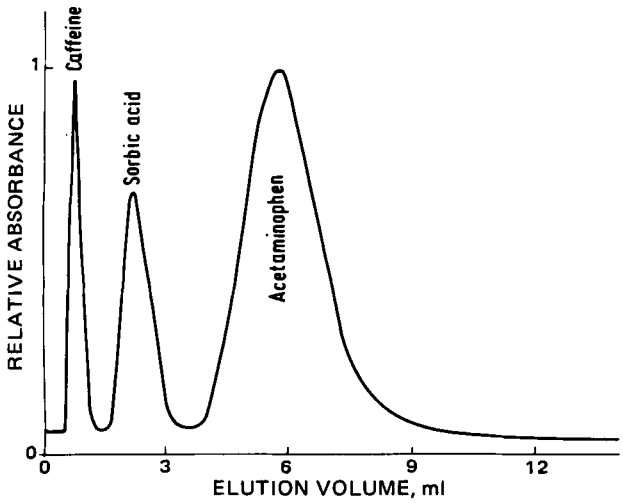

Figure 1—*Chromatographic fractionation of drugs using II as stationary phase and 0.1* N *HCl as eluent. The degree of interaction with II is indicated by specific retention volumes.*

Sorption Studies—For easily soluble substances, aqueous solutions containing 250 mg/liter of the active ingredient were prepared. The solution pH was adjusted in the range of 1.0–12.0 by adding the required amounts of hydrochloric acid or sodium hydroxide. For less soluble substances, saturated solutions were used as received at 25°.

The sorption experiments were performed in 250-ml flasks at 25 ± 0.5°. Compound II was added in amounts of 20–1000 mg/200 ml of solution. The suspension was maintained under steady vibration stirring for 10 min then centrifuged[19]. The amount of unbound drug was determined spectrophotometrically[20] in the supernate.

For the binding studies with Compound I, the sorption experiments were performed after I was added as a cosolute in amounts of 2–6 g/200 ml of solution.

Equilibrium Dialysis—Equilibrium dialysis[21] was carried out at controlled temperature (25 ± 0.5°) using cellulosehydrate membranes[22] with a molecular weight cutoff of 5000 daltons. The effective surface area was 11.3 cm^2 in each cell, separating two compartments of 2 ml of volume. Equilibration was attained under steady rotation after 2 hr. The distribution of the active ingredient was determined spectrophotometrically[21]. With the exception of tannic acid, with all drugs and model substances, no detrimental interaction with the membrane was observed.

THEORETICAL

Evaluation of Data—There have been only a few attempts to apply various modes of gel permeation chromatography for investigating the complex formation between macromolecules and drugs (7). Molecular sieves as a stationary phase are only useful in exceptional cases where the dissociation rate is small compared to the rate of elution (30–33). Certain precautions have to be taken in order to obtain significant experimental results (34–36).

In contrast, the chromatographic technique proposed in the present study requires a rapid adjustment of the equilibrium of complex formation. One component of the complex formation of interest, compound II, is used as a stationary phase. In a few cases a similar polymer has been used before to separate phenolic acids (37) and purine and pyrimidine bases (38, 39) by liquid chromatography.

As was shown in a previous study, interactions of drugs with II are volume-controlled, and any possible influence of the extent of the specific surface area of II is negligible (29). Hence, the active ingredient will be distributed between the insoluble polymer phase and the liquid phase according to the Nernst distribution law:

$$k = \frac{[A]_s}{[A]} \qquad \text{(Eq. 1)}$$

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

[19] Omnifuge, Heraeus, Hanau, West Germany.
[20] Cary 14 Spectrophotometer, Varian GmbH, Darmstadt, West Germany.
[21] DIANORM, Bachofer GmbH & Co. KG, Reutlingen, West Germany.
[22] DIACHEMA, Cut-off 5000 No. 10.14, Bachofer GmbH & Co. KG, Reutlingen, West Germany.

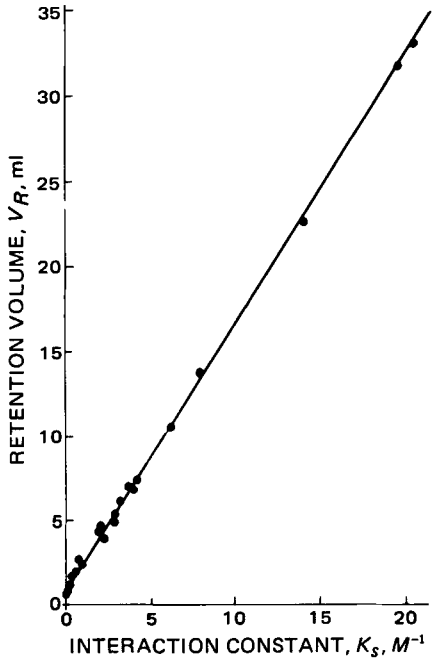

Figure 2—*Calibration of the chromatographic column. The retention volume,* V_R, *depends linearly on the interaction constant,* K_s, *as predicted by Eq. 11.* K_s *was determined by sorption experiments.*

Only part of $[A]_s$ is bound to active sites of the polymer (29). To first approximation, $[A]_s$ of Eq. 1 can be separated according to:

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

where $[FA]_s$ denotes the portion of $[A]_s$ bound to active binding sites, while the concentration of the remaining fraction of $[A]_s$ that is unspecifically bound by the polymer compartment is assumed to be equilibrated to $[A]$ of the surrounding liquid phase (29).

With the liquid compartment containing, besides the active ingredient, A, an additional polymer cosolute, *e.g.*, Compound I, a similar relation holds true for $[A]_L$, the concentration of the drug in the liquid compartment:

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

where $[FA]_p$ denotes the portion of $[A]_L$ bound in a drug–polymer complex.

For a system containing I and II simultaneously besides the active ingredient, A, the Nernst distribution law becomes:

$$k^* = \frac{[A] + [FA]_s}{[A] + [FA]_p} \qquad \text{(Eq. 4)}$$

Now, the equilibrium law of complex formation in the liquid phase and of the interaction in the insoluble polymer compartment becomes:

$$K_p = \frac{[FA]_p}{[A]([F_0]_p - [FA]_p)} \qquad \text{(Eq. 5)}$$

and:

$$K_s = \frac{[FA]_s}{[A]([F_0]_s - [FA]_s)} \qquad \text{(Eq. 6)}$$

respectively, where $[F]$, the concentration of free binding sites, is already replaced by the relation $[F] = [F_0] - [FA]$ in which $[F_0]$ represents the total concentration of available binding sites in the respective compartment of the system.

In distribution chromatography, the retention volume, V_R, is given by (40):

$$V_R = n(V'_L + kV'_s) \qquad \text{(Eq. 7)}$$

where n is the number of theoretical plates and V'_L and V'_s denote the volumes per theoretical plate of the mobile and the stationary phases, respectively. After introducing the phase ratio $\varphi = V_s/V_L$, and considering that for the chromatographic column: $V_s = nV'_s$ and $V_L = nV'_L$, Eq. 7 becomes:

$$V_R = V_L(1 + k\varphi) \qquad \text{(Eq. 8)}$$

Table I—Binding Data of the Interaction of Drugs with II in 0.1 *N* HCl at 25°

Compound	Interaction Constant, K_s, M^{-1} Sorption Method	Chromatographic Method
Acetaminophen	2.0	2.4
Aspirin	1.5	2.1
Benzocaine	~0	~0
Caffeine	~0	~0
Chloramphenicol	~0	~0
Methotrimeprazine	0.7	1.2
Methyldopa	0.2	~0
Methylparaben	4.2	4.2
Papaverine hydrochloride	0.1	0.2
Promethazine hydrochloride	0.4	0.6
Riboflavin	~0	~0
Salicylamide	3.7	4.0
Sorbic acid	0.5	0.7
Sulfamethazine	~0	~0
Sulfamoxole	~0	~0
Sulfathiazole	1.0	1.0
Tetracaine hydrochloride	~0	~0
Trimethoprim	~0	~0

where V_L and φ are constants for a given column. Hence, V_R is expected to be proportional to k.

As was shown earlier (29, 41), considering the mass balance of the drug:

$$[A_0]V_L = [A]V_L + [A]V_s + [FA]_sV_s \qquad \text{(Eq. 9)}$$

where $[A_0]$ represents the weighing-in concentration of the active ingredient, Eq. 6 can be combined with Eq. 1 to give:

$$k = 1 + \frac{[F_0]_sK_s}{1 + [A]K_s} \qquad \text{(Eq. 10)}$$

With the formal assumption that each monomeric subunit of the polymer may serve as a binding site, $[F_0]_s$ becomes ~9 M.

In most cases of interaction investigated in the present study, the approximation, $K_s[A] \ll 1$, holds true, since $K_s < 10$ and $[A] \approx 10^{-3}$ M. M.

Hence, substituting Eq. 10 into Eq. 8 gives:

$$K_s = \frac{1}{9}\left[\frac{V_R}{V_s} - \left(\frac{V_L}{V_s} + 1\right)\right] \qquad \text{(Eq. 11)}$$

Therefore, the retention volume, V_R, is linearly correlated with the interaction constant K_s.

Similarly, K_p can be determined by adding a definite amount of the soluble polymer (I) to the mobile phase. Considering Eqs. 4 and 8, the retention volume is altered to:

$$V_R^* = V_L(1 + k^*\varphi) \qquad \text{(Eq. 12)}$$

Dividing Eq. 12 by Eq. 8 yields for the ratio of the Nernst coefficients:

$$\frac{k^*}{k} = \frac{V_R^* - V_L}{V_R - V_L} \qquad \text{(Eq. 13)}$$

This ratio can be expressed in terms of the constant of complex formation in the liquid compartment, K_p, by combining Eqs. 1, 4, and 5:

$$\frac{k^*}{k} = \left(1 + \frac{K_p[F_0]_p}{1 + K_p[A]}\right)^{-1} \qquad \text{(Eq. 14)}$$

Again, the approximation $K_p[A] \ll 1$ is in general valid, and substituting Eq. 14 in Eq. 13 leads to:

$$K_p = \frac{(V_R - V_R^*)}{(V_R - V_L)}\frac{1}{[F_0]_p} \qquad \text{(Eq. 15)}$$

Therefore, K_p is readily determined by adding a certain amount of I, $[F_0]_p$, to the mobile phase and measuring the change of the retention volume, $V_R - V_R^*$, of the active ingredient.

In order to prove the validity of the chromatographic results, K_s and K_p were also determined by sorption studies, as reported previously (29). The variable K_s is readily evaluated from k (Eq. 1) according to the rearranged Eq. 10:

$$K_s = \frac{k - 1}{[F_0]_s - [A](k - 1)} \qquad \text{(Eq. 16)}$$

Table II—Binding Data of the Interaction of Model Compounds with II in 0.1 *N* HCl at 25°

Compound	Interaction Constant, K_s, M^{-1} Sorption Method	Chromatographic Method
Aniline	1.0	0
Benzyl alcohol	1.3	0.3
Phenol	1.9	2.3
2-Methylphenol	2.9	2.9
2,4-Dimethylphenol	2.3	2.0
2,4,6-Trimethylphenol	3.2	3.4
1,2-Dihydroxybenzene	3.9	3.9
Resorcinol	13.1	14.0
1,4-Dihydroxybenzene	8.0	8.3
1,2,3-Trihydroxybenzene	10.0	6.3
Benzoic acid	2.9	2.6
1,2-Dicarboxybenzene	5.0	4.7
1,3-Dicarboxybenzene	20.5	[a]
1,4-Dicarboxybenzene	50.0	[a]
Salicylic Acid	6.2	6.2
3-Hydroxybenzoic acid	20.8	20.5
4-Hydroxybenzoic acid	19.8	19.6
2,4-Dihydroxybenzoic acid	71.9	[a]
3,4-Dihydroxybenzoic acid	93.2	[a]
3,5-Dihydroxybenzoic acid	125.6	[a]
Gallic Acid	>1000	[a]

[a] Not measured: retention volume too large.

Then, after adding a definite amount of the soluble polymer, $[F_0]_p$, to the system, k^* is measured according to Eq. 4. For systems where $K_p[A] \ll 1$ is valid, the rearranged Eq. 14 gives:

$$K_p = \frac{k - k^*}{k^*[F_0]_p} \qquad \text{(Eq. 17)}$$

Equilibrium dialysis was used as a supplementary technique to perform binding studies of some systems.

In this case the evaluation of data is based on Eq. 5:

$$K_p = \frac{k^{**} - 1}{[F_0]_p - (k^{**} - 1)[A]} \qquad \text{(Eq. 18)}$$

where the experimentally accessible coefficient k^{**} is introduced describing the distribution of the drug between the polymer-free and polymer-containing dialysis compartments, according to:

$$k^{**} = \frac{[A] + [FA]_p}{[A]} \qquad \text{(Eq. 19)}$$

For the strongly interacting tannic acid, the approximation, $K_s[A] \ll 1$, is invalid, and the Nernst coefficient, k, becomes strongly dependent upon $[A]$. The experimental results of the interaction with II can be described with a model where two classes of independent binding sites are assumed to be operative. Each class is characterized by a specific interaction constant, $K_{s,1}$ and $K_{s,2}$, respectively. With reference to Eq. 10, the interaction can be described by:

$$k_{1,2} = 1 + \frac{K_{s,1}[F_0]_1}{1 + K_{s,1}[A]} + \frac{K_{s,2}[F_0]_2}{1 + K_{s,2}[A]} \qquad \text{(Eq. 20)}$$

where $[F_0]_1$ and $[F_0]_2$ refer to the concentration of available binding sites of Class 1 and Class 2.

There exists a simple relationship between K_p, as defined by Eq. 5, and the binding constant, K, defined by the basic theory of ligand–polymer interaction as advanced by Klotz *et al.* (42) and by Scatchard (43). The interaction with independent binding sites is described by:

$$r = \frac{nK[A]}{1 + K[A]} \qquad \text{(Eq. 21)}$$

where r is the number of moles of ligand bound per monomer unit of the polymer, $r = [FA]/[F_0]_p$, n represents the total number of sites available, and K is the binding constant. Introducing Eq. 5 into Eq. 21 and considering $[FA] \ll [F_0]_p$ gives:

$$K_p \approx \frac{nK}{1 + K[A]} \qquad \text{(Eq. 22)}$$

and for $K[A] \ll 1$:

$$K_p \approx nK \qquad \text{(Eq. 23)}$$

The product, nK, is equal to the first binding constant, k_1, which is a measure for the strength of the binding. Values of $nK = k_1$ are commonly

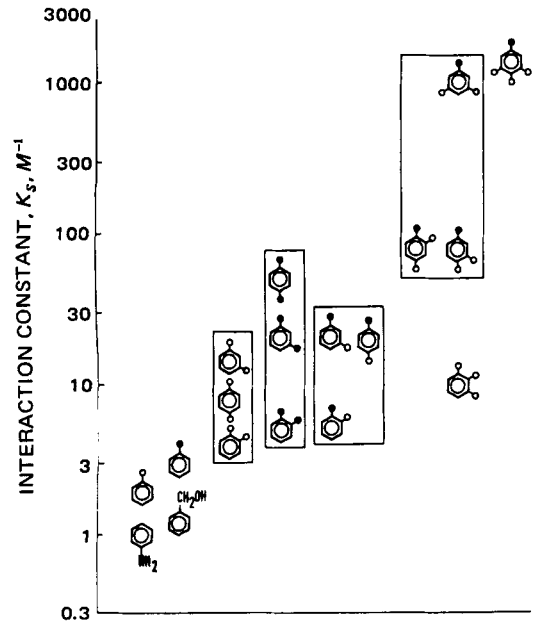

Figure 3—*Interaction constant, K_s, of various aromatic model compounds characterizing the influence of the nature, number, and position of hydrogen donating functional groups on the interaction with II. Key: (○) hydroxide group; (●) carboxyl group.*

deduced from the slopes of linear binding plots according to Klotz *et al.* (42) or Scatchard (43). Values of n, however, can be determined only with much uncertainty (44). Their physical relevance is doubtful.

RESULTS AND DISCUSSION

Figure 1 shows a typical chromatogram of a sample solution composed of three drugs. Each component is characterized by a specific retention volume indicating the degree of interaction with II. The theoretically proposed linear correlation between the interaction constant, K_s, and the retention volume, V_r, (Eq. 11) is experimentally corroborated in Fig. 2 where for a series of drugs and drug models the retention volume, V_R, is plotted against the interaction constant, K_s, as obtained from sorption studies. The linear correlation between the results of the sorption experiments and the chromatographic studies clearly indicates a reversible interaction of the active ingredients with II. Apparently, the adjustment of equilibrium takes place rapidly enough so that the provisions for true partition chromatography are satisfied. Hence, by the data of Fig. 2, a chromatographic technique is established that offers new and convenient means for the investigation of interactions between drugs and crospovidone. As was shown before, the method is readily extended to binding studies with soluble polymer additives by adding the respective polymer to the mobile phase.

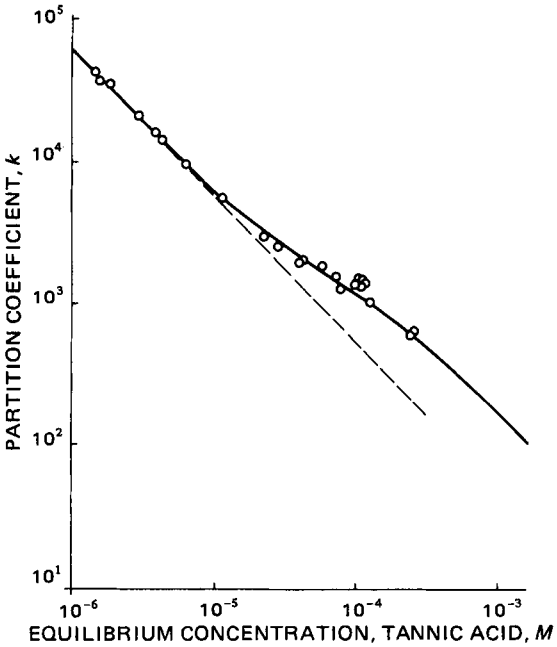

Figure 4—*Dependence of the Nernst coefficient, k, on the equilibrium concentration of tannic acid interacting with II in 0.1 N HCl suspensions. The curve was calculated according to Eq. 20 using $[F_0]_1 = 0.12$ M; $K_{s,1} = 10^4$ M^{-1}; $[F_0]_2 = 0.06$ M; $K_{s,2} = 10^7$ M^{-1}.*

Table III—Binding Data of the Interaction Model Compounds and Drugs with I in 0.1 *N* HCl at 25°

Compound	Binding Constant, K_p, M^{-1} Sorption Method	Chromatography Method	Dialysis Method
Acetaminophen	<1	<1	1.5
Aspirin	<1	<1	0.7
Benzoic acid	<1	<1	0.9
Chloramphenicol	[a]	[a]	0.4
1,2-Dihydroxybenzene	<1	<1	0.8
Resorcinol	1.3	2.2	2.4
1,4-Dihydroxybenzene	1.6	1.9	1.6
Salicylic Acid	1.7	1.1	1.5
3-Hydroxybenzoic acid	2.7	3.5	2.8
4-Hydroxybenzoic acid	5.2	5.3	3.6
Methotrimeprazine	4.6	5.2	3.2
2-Methylphenol	<1	<1	1.0
Methylparaben	2.6	<1	1.8
Phenol	<1	<1	0.8
Salicylamide	1.6	1.5	1.3
Sorbic acid	<1	<1	0.5
Sulfathiazole	<1	<1	0.4
Sulfamoxole	[a]	[a]	0.3
Trimethoprim	[a]	[a]	0.2

[a] Not measurable: K_s too small.

The chromatographically determined K_s-values of various drugs are listed in Table I. As expected from Fig. 2, they are found in close agreement with the corresponding values obtained from sorption experiments. All drugs are characterized by K_s-values <5 M^{-1}. The K_s-values of the model compounds are listed in Table II. They range from 1 M^{-1} to ~1000 M^{-1}.

The data of Tables I and II agree with findings of an earlier study (29) where the tendency for the complex formation with II was found closely correlated with the ability of the drugs to act as hydrogen donators. Accordingly, none of the compounds of Table I characterized by K_s-values <0.1 M^{-1} carries hydroxide or carboxyl groups bound to aromatic residues. The ability of aromatic amines to act as hydrogen donators is known to be small, and compounds of Table I belonging to this class exhibit K_s-values <1 M^{-1}. Besides hydrogen binding, mechanisms of hydrophobic interaction can be operative, as found with several phenothiazine derivatives, in close agreement with observations of Voigt *et al.* (18). However, interactions with I or II based on this hydrophobic mechanism are found to be moderate.

The significance of hydrogen binding for the occurrence of strong interactions with I or II can best be shown by the data obtained with the model compounds, as listed in Table II. In Fig. 3, the correspondence between the strength of interaction and the number and position of hydrogen-donating functional groups is documented. Aromatic carboxylic acids form stronger complexes than phenols. The complexation tendency increases with the number of hydrogen-donating functional groups. In all bifunctional compounds, the weakest complexes are formed by the *ortho* isomers. Steric effects are apparently responsible for the fact that with biphenols, the *meta* isomer, and with the corresponding carboxylic acids, the *para* isomer exhibit the strongest interaction tendency.

For trifunctional compounds the importance of the *meta* position of the active ligands is again emphasized: the K_s-value of 3,5-dihydroxybenzoic acid is by an order of magnitude larger than that of the corresponding 2,4- and 3,4-isomers, where in both cases an unfavorable *ortho* substitution reduces the interaction tendency. The accumulation of *ortho* substituents in 1,2,3-trihydroxybenzene causes a further reduction of K_s by an order of magnitude.

As reported earlier (29), tannic acid forms exceptionally strong complexes with II; the same is true for the interaction with I. An explanation for this exceptional interaction tendency immediately follows from its multifunctional chemical structure based on gallic acid and digallic acid. According to Fig. 3, gallic acid already exhibits a K_s-value of ~1000 M^{-1}. The accumulation of residues of this nature within the tannic acid mol-

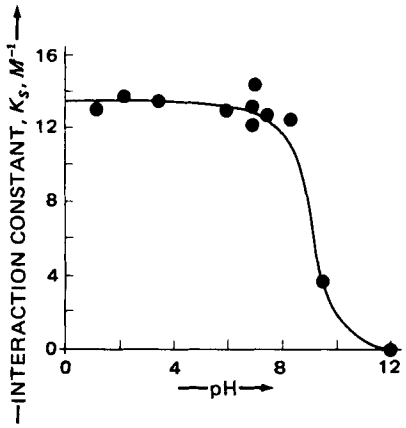

Figure 5—*Influence of pH on the interaction of resorcinol with II.*

ecule leads to a further increase of K_s. The approximation, $K_s\,[A] \ll 1$, is no longer valid and k becomes dependent on A.

Figure 4 shows the results of interaction studies with II extending beyond the concentration range of earlier investigations (29). The dependence of the partition coefficient, k, upon $[A]$ is satisfactorily described by model calculations based on Eq. 20, assuming two classes of binding sites, F_1 and F_2, on part of the polymer. The corresponding interaction constants, $K_{s,1}$ and $K_{s,2}$, are determined to be of the order of 10^4 and 10^7 M^{-1}, respectively. Hence, tannic acid exceeds other model compounds and drugs in its interaction tendency toward II by several orders of magnitude. Similar results were obtained for the interaction with I but are not shown here in detail. The concentration of available binding sites, $[F_o]_1$ and $[F_0]_2$, is determined to be 0.12 and 0.06 M, respectively. These figures are well below the theoretical limit of 9 M for polyvinylpyrrolidone, underlining the fact that one interacting molecule of tannic acid, owing to its extended molecular structure, covers many vinylpyrrolidone units in the polymer.

The results of the binding studies with I are listed in Table III. The chromatographically determined values of K_p satisfactorily agree with those data obtained by standard equilibrium dialysis. (In the present study all values of K_s or K_p are defined by relating to the molecular weight of a monomer segment of the polymer. This is preferable to using often ill-defined molecular weight data of the polymer.)

The application of the chromatographic technique for determining K_p requires a minimum interaction between the investigated active ingredient and II used as a stationary phase. In general, the interaction tendencies of drugs with both I and II are closely corresponding (29). Therefore, the chromatographic technique can best be applied in cases where moderate to strong interaction is occurring. In studies of weak interaction, equilibrium dialysis yields more reliable data.

All interaction data presented so far relate to pH conditions of gastric fluids. They define upper limits for the interaction constants for all systems where hydrogen binding dominates the complexation reaction. With increasing pH, the degree of dissociation of the hydrogen donating functional groups rises, and, correspondingly, the interaction tendency is expected to decrease. For example, Fig. 5 depicts the pH dependence of K_s as observed with resorcinol. Other examples of a similar pH dependence were recently reported (45). Even in cases of very strong interaction, as observed with several model compounds, the interaction constants start to drop at pH values >4. With tannic acid, a decrease of the K_s values was observed, starting from $\gg$10,000 M^{-1} at pH 1 and ending at ~50 M^{-1} at pH 12. These observations further support the notion of hydrogen-binding being the dominating mechanism in moderate to strong interactions with I or II, even in cases of high molecular weight compounds like tannic acid. In hydrophobically interacting systems, a significant influence of pH on the strength of interaction was observed only with some phenothiazines (18). The reason for the decrease with increasing pH is not fully understood.

The significance of the reported data for practical applications becomes apparent in calculations of the bound amount of an active ingredient in a pharmaceutical formulation or after administering the drug. Knowing the respective values of K_s or K_p, the assessment can be based on Eqs. 5 or 6, since reversibility of the interaction has been proved with a representative selection of systems by desorption studies (29). The feasibility of the chromatographic technique requiring a reversible interaction of the involved components further supports this notion.

In Fig. 6 the bound fraction of the active ingredient is plotted as a function of the interaction constant, K_s, for various concentrations of the polymer additive, II. The graph is applicable for weighing-in concentrations of the active ingredient between 1×10^{-4} and 2×10^{-3} M, covering the concentration range usually encountered in practice. If the oral administration of two tablets containing 10% by weight of the additive II is considered as an example of practical relevance, then the additive concentration in the gastric fluid can hardly exceed a value of 0.5 g/liter. In Fig. 6 the relevant area is marked by shading. Considering the fact that—with the exception of tannic acid and related compounds—K_s of active ingredients is limited to values <10 M^{-1}, the bound amount can not excel the 3% limit. Differences in the salt concentration, not accounted for in this estimate, cannot affect this figure to a significant degree. As was pointed out before, in respect to a possible dependence upon pH, this figure constitutes an upper limit.

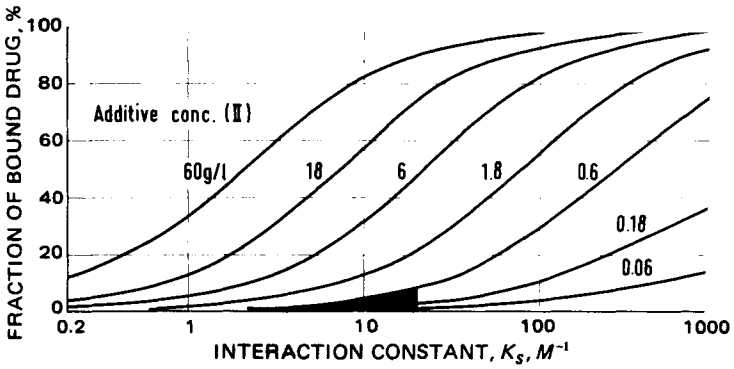

Figure 6—*Fraction of drug bound to II as a function of the interaction constant, K_s, for various concentrations of II. The graph is valid for concentrations of the active ingredient $[A_0]$, between 1×10^{-4} and 2×10^{-3} M, covering the range of practical interest. The significance of the shaded area is explained in the text.*

Another way of interpreting the data is offered in Fig. 7, where the bound fraction of the drug is plotted as a function of the additive I concentration for various values of K_p. Considering the data of Table III, it immediately follows that for all practical purposes the fraction of the drug bound by the additive after oral administration is estimated in the range of a few percent.

Graphs as shown in Figs. 6 and 7 offer the opportunity to transfer binding data that are sometimes, for experimental reasons, obtained at excessively high levels of additive concentration into a concentration range of more practical relevance. In studies of the interaction properties of I, polymer concentrations as high as 50 g/liter were frequently used (7, 10, 46, 47). From Fig. 7 it can be deduced that at this level of additive concentration, the bound fraction of compounds with even moderate binding tendency, as corresponding to $K_p \sim 1$ M^{-1}, amounts to ~30%. This is illustrated by a recent investigation of the inhibitory effect polyvinylpyrrolidone may exhibit on the absorption of acetaminophen (47). The binding constant, K, was determined (42) at pH 6.4 as 23 M^{-1} with $1/n = 18.5$. Considering Eq. 23, it follows that $k_1 = 1.24$ M^{-1}, which

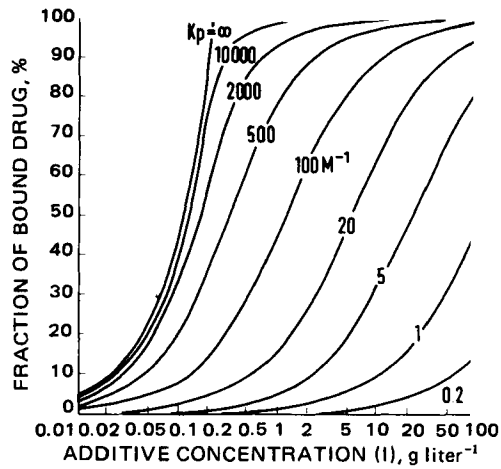

Figure 7—*Fraction of drug bound to I as a function of the additive concentration (I), for various values of the binding constant, K_p. The graph is valid for concentrations of the active ingredient, $[A_0]$, between 1×10^{-4} and 2×10^{-3} M.*

is in close agreement with $K_p = 1.5\ M^{-1}$ of the present study. By inspection of Fig. 7, a bound fraction of ~35% is estimated at an additive concentration of 50 g/liter as was applied in the respective study.

At an additive concentration of 0.5 g/liter, however, considered as typical for the oral administration of drugs, the bound fraction of the drug falls to a level close to zero, as shown in Fig. 7.

For tannic acid and related compounds in the acidic pH range, even at a polymer concentration as low as 0.5 g/liter, the bound fraction is >95%, a fact that is advantageously used in practice (24–26).

CONCLUSIONS

The chromatographic method proposed in the present study represents an easy to use experimental technique for a rapid assessment of interaction properties of drugs in systems containing soluble or insoluble polymer additives. The determination of interaction constants in the range of $>1\ M^{-1}$ is reduced to the readily performed determination of retention volumes. As was shown in detail, only interactions with K_s and/or K_p values above this limit are of practical interest. With the exception of tannic acid and related compounds, all drugs investigated in the present study exhibited K_p- or K_s-values well below an upper limit of $10\ M^{-1}$, indicating that with commonly used additive concentrations of I or II, the bound fraction of the drug after oral administration can hardly exceed a limit of the order of 3%. Considering further the fact that binding is reversible, and in view of the observed pH dependence of binding strength, the presence of these additives is not expected to interfere with the GI absorption of the pharmaceutical.

However, as can be seen from Fig. 7, at additive concentrations of 10–50 g/liter, often used in standard binding studies, the fraction of bound active ingredient can readily amount to 30%, even in cases of moderate binding. Additive concentrations of this order of magnitude are never applied in practice. The graphs of Figs. 6 and 7 may, therefore, assist in using the large body of available binding data for a sensible assessment of the degree of binding in systems of practical relevance.

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