Polymer Bulletin 21, 505-512 (1989)

Polymer Bulletin

pH-Dependent interaction of sulfamethoxazole with crosslinked poly(N-vinyl-2-pyrrolidone)

Meenakshi Maruthamuthu* and E. Subramanian

Department of Physical Chemistry, University of Madras, Guindy Campus, Madras 600 025, India

SUMMARY

The sorption of sulfamethoxazole (SM) to crosslinked poly(N-vinyl-2-pyrrolidone) (CPVP) was studied by batch adsorption technique at pH's 1.0, 5.0 and 7.0 and at temperatures 10 and 30°C. Analysis by Scatchard method and Giles adsorption isotherm indicated that (i) the sorption increased in the order of pH, 7.0 < 1.0 < 5.0 and (ii) SM sorbed vertically through a monofunctional group. The peculiar sorption at pH 5.0 was explained in terms of CPVP - H_2O interaction. The water-uptake by CPVP was minimum at pH 5.0 and increased at pH's 1.0 and 7.0.

I INTRODUCTION

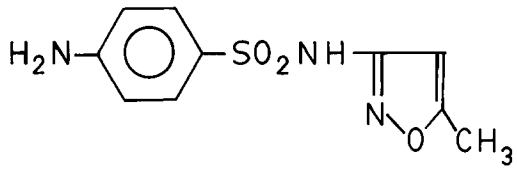
Crosslinked poly(N-vinyl-2-pyrrolidone) (CPVP) is an insoluble but water-swellable synthetic polymer. It is widely used as a tablet-disintegrator in the pharmaceutical field because of its excellent properties such as (i) high swelling pressure with water (1), (ii) therapeutical inactivity and (iii) physiological inertness (2). As a tablet-disintegrator, it can influence the drug absorption and activity in physiological systems due to its tendency to bind drug molecules. Hence drug - CPVP interaction studies are important from the pharmaceutical point of view.

Horn et al are the first to have made systematic studies on the interaction of various pharmaceuticals with CPVP (2,3). We have also reported (4) the interaction of non-steroidal anti-inflammatory drugs with CPVP. The sorption (the term 'sorption' is also used, since CPVP is a porous water-swellable polymer) of important sulfa drugs, sulfamaxole, sulfathiazole and sulfamethazine to CPVP has already been studied (2). Sulfamethoxazole, another sulfa drug is more popular and widely used in 5:1 combination with Trimethoprim (5) than the other sulfa drugs. But even then, its interaction study with CPVP has not yet been made. Hence in the present work, we have chosen sulfamethoxazole (SM) and a structurally related drug - model compound, p-toluenesulfonamide (TS) for the interaction study with CPVP. Even though this is a pharmaceutically related work, we have made only a purely in vitro physico-chemical study with these systems and report the observed experimental results.

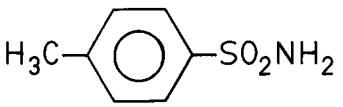
II EXPERIMENTAL

CPVP (a fine powder, Polyclar AT grade) was obtained from Sigma Chemical Company, USA and purified from water-soluble impurities by a method described in the literature (6). SM was donated in pure form by Roche Pharmaceutical Co., India. TS was purchased from Bioorganics, India, recrystallized several times from water - methanol mixture, dried in an air-oven and then used. Other chemicals used in the present study were of analytical grade.

*Author for correspondence



SM



TS

Scheme 1: Structure of Sulfamethoxazole (SM) and p-toluenesulfonamide (TS).

CPVP - substrate systems were studied using batch adsorption technique in which a known quantity (50 mg) of CPVP was equilibrated with a fixed volume (15 ml) of substrate solution of known concentration (in the range 10.0 - 150.0 μmol dm^{-3}). The equilibrium or free substrate concentration was determined spectrophotometrically using Carl Zeiss UV VIS spectrophotometer. The experiments were carried out at different pH's 1.0 (in 0.1 N HCl), 5.0 and 7.0 (double-distilled water adjusted with HCl) and at different temperatures 10 and 30^{o}C.

The results were analyzed using Scatchard method (7) and Giles adsorption isotherms (8). The Scatchard equation derived on the basis of a simple site-binding model (binding of ligands to independent indistinguishable sites on the polymer) is

$$\frac{r}{C_F} = nK - rK \qquad \ldots(1)$$

where

r	=	the number of moles of substrate bound per base mole of CPVP.
C_F	=	the free or equilibrium substrate concentration
n	=	the total number of binding sites per base mole of CPVP.
1/n	=	the number of monomer units involved in one binding site
K	=	the intrinsic binding constant
and nK	=	K_1, the interaction constant.

From the slope and intercept of the Scatchard plot, the binding parameters were determined. Giles isotherm is a plot of bound (C_B) versus free (C_F) substrate concentrations. This has been classified into four main types depending on the adsorption mechanism. Details about this isotherm can be found in the literature (8). For the S type (sigmoidal) isotherm, the proposed mechanism is the adsorption in vertical orientation of the solute molecules with respect to the adsorbing surface and the existence of intermolecular attraction between the adsorbed molecules.

III RESULTS AND DISCUSSION

In the digestive path, pH increases from 1.0 in the stomach to about 7.0 in the intestine. Our study also has been made in this pH range only. Of the two substrates SM and TS, only SM showed interaction at all three pH's 1.0, 5.0 and 7.0 but not TS. The nonsorption of TS, however, provides support for the sorption mechanism of SM discussed later. Figs. 1 and 2 show respectively the Scatchard plots and Giles sorption isotherms for the CPVP - SM system at different pH's. The binding parameters from the Scatchard plot were evaluated from the slope and intercept at the ordinate (extrapolated the plateau back to the ordinate) of the plateau at higher r values. Since the binding parameters calculated at higher [substrate] could only be used for practical purposes, we have determined them at higher r values.

III (i) PECULIAR SORPTION BEHAVIOUR AT pH 5.0

On looking at the Scatchard plots in Fig.1, we would notice that all the plots are not linear downward as required by Eq.(1). Hence the sorption process is not simple but a complicated one. The Scatchard plot at pH 5.0 is convex with a maximum but those at other pH's have initially a rising portion and then an inclined plateau. The convex plot indicates the operation of 'mixed' cooperativity (both positive and negative cooperativity) at pH 5.0 but other plots only positive cooperativity at the respective pH's i.e., pH 1.0 and 7.0. Similarly in Giles isotherms also, we observe at pH 5.0 a complete sigmoidal isotherm but at other pH's only incomplete S-type isotherms. The peculiarity at pH 5.0 is also reflected in the values of bound substrate concentration (C_B) as

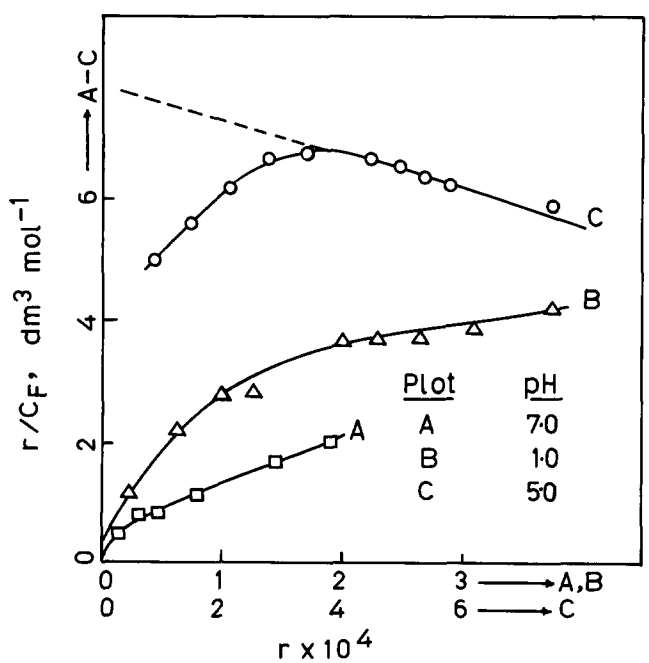


Fig.1
Scatchard plots for the CPVP-SM system at 30°C.
[CPVP] = 0.03 mol dm^{-3}
[SM] = 10 - 150 μ mol dm^{-3}

well as the interaction constants (K_1; Table 1). Both C_B and K_1 are maximum at pH 5.0 but tend to decrease on either side of this pH. Due to this similar trend, the K_1 values can be considered as to indicate the

Table 1
Binding and thermodynamic parameters for the CPVP - SM system

[CPVP] = 0.03 mol dm^{-3}; [SM] = 10.0 - 150.0 μmol dm^{-3}

Parameter	Temperature = 30°C			10°C
	pH = 1.0	pH = 5.0	pH = 7.0	pH = 5.0
K_1 (dm^3 mol^{-1})	2.94	7.79	0.45	10.77
K x 10^{-3} (dm^3 mol^{-1})	3.20	2.55	8.27	3.30
n x 10^3	0.92	3.05	0.05	3.26
$\frac{1}{n}$	1088	327	18414	306

	Temperature = 30°C; pH = 5.0
ΔH (kcal mol^{-1})	- 2.4
ΔF (kcal mol^{-1})	- 4.7
ΔS (eu mol^{-1})	7.82

binding capacity of the polymer, which increases in the following order of pH.

$$7.0 < 1.0 < 5.0.$$

Thus from the above observations, it is clear that the sorption process at pH 5.0 is a peculiar one when compared to those at other pH's. This is explained in the latter part of the discussion.

III (ii) SORPTION MECHANISM AND INTERACTING FORCES

The substrate SM exhibits S-type Giles isotherm at all the three pH's (Fig.2). The complete sigmoidal isotherm at pH 5.0 indicates the monolayer saturation whereas the incomplete S-type isotherms at pH 1.0 and 7.0 the monolayer unsaturation. Since all the isotherms belong to S-type, it is inferred that the sorption of SM to CPVP is not simple but a cooperative one which has been already stated in the discussion on Scatchard plots. The sorption mechanism, as implied by the S-type isotherm, is the attachment of the drug to CPVP in vertical orientation (i.e., the substrate molecule perpendicular to the plane of the CPVP surface in which the binding site is present) through a monofunctional group and the stabilization of the same by intermolecular attraction existing between the sorbed molecules. On examining the structure of SM, we would conclude that the amino group is most probably the monofunctional group involved in sorption, the remaining part of the molecule being participative in the intermolecular attraction of the sorbed substrate. The experimental observation is, in fact, consistent with this expectation, as revealed by the thermodynamic parameters and the sorption study with the drug-model compound, TS.

As shown in Table 1, the sorption process is associated with negative enthalpy and positive entropy at pH 5.0. Hence both energetic and hydrophobic forces involve in the sorption process. Hydrogen bonding

from the nuclear-substituted amino group is a likely candidate for the energetic forces. The intermolecular attraction between the substrate molecules after sorption and the hydrophobic interaction, if any, between

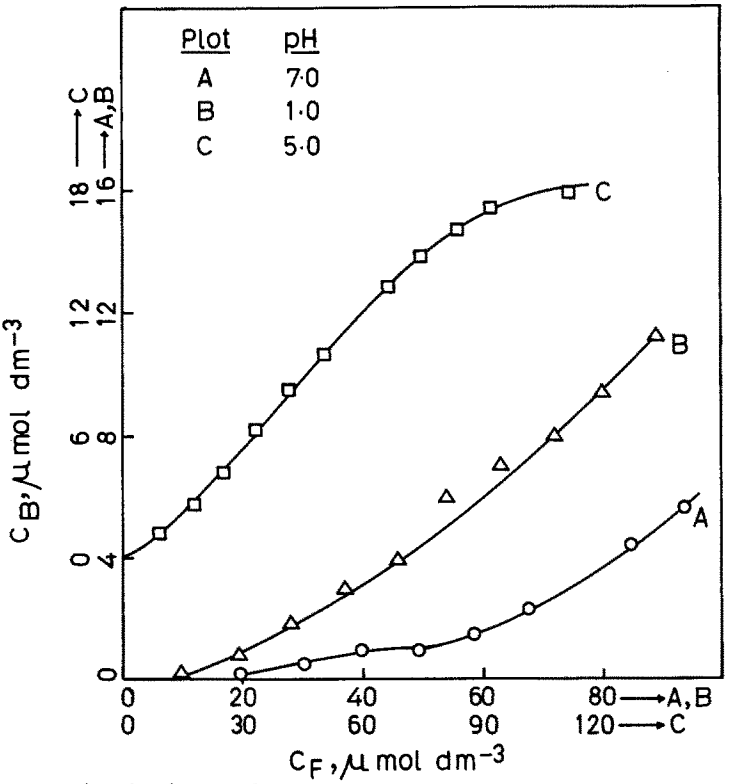


Fig.2: Giles sorption isotherms for the CPVP-SM system. Same conditions as in Fig. 1

SM and CPVP and the consequent changes in the water layer around the binding sites may be the contributing processes to the observed positive entropy change. The above explanation for negative ΔH and positive ΔS is supported by the fact that the drug-model compound TS is not sorbed by CPVP at all three pH's. TS has methyl group which has no hydrogen bonding ability, in the place of the amino group in SM. The nonsorption of TS also shows that the $-\underset{|}{N}H$ of sulfonamide group does not exert hydrogen bonding interaction. The involvement of heterocyclic ring of substrate in binding with CPVP as well as with PVP (the linear analogue of CPVP) has not yet been invoked in any study and this is most probably due to the very negligible affinity of the heterocyclic ring relative to the carbon containing ring systems towards the polymer molecule. Therefore the involvement of isoxazole ring of SM in binding does not seem feasible.

III (iii) CPVP - H_2O INTERACTION LEADING TO PECULIAR SORPTION AT pH 5.0

The peculiar sorption behaviour of SM observed at pH 5.0 appears mainly to be due to CPVP - H_2O interaction rather than CPVP - substrate interaction. At pH 1.0 the amino group of the substrate gets protonated and is indicated in the absorption spectrum also. The molar extinction coefficient

(ε) values of SM at 265 nm at various pH's are given below which illustrate clearly the above point. For forming hydrogen bonding, - NH_3^+ is a better hydrogen donor than - NH_2. But this protonation does not seem to produce any effect on binding. In fact, the extent of binding decreases at pH 1.0 than at pH 5.0 and does so drastically when the pH is 7.0. From the above discussion, it becomes clear that CPVP should be the origin and not the substrate for the peculiar sorption at pH 5.0. This peculiarity is explicable on the basis of CPVP-H_2O interaction.

pH	ε_{265} ($dm^3\ mol^{-1}\ cm^{-1}$)
1.0	4550
5.0	16090
7.0	17300

CPVP has great affinity for water. This is evident from (i) its exceptionally high swelling pressure with water (1) and (ii) the doubling of particular volume of the CPVP sample due to swelling with water. We conducted an experiment to determine the water uptake by a known quantity of CPVP at different pH's and the results are given in Table 2. The results indicate that the weight of water sorbed by CPVP increases in the following order of pH,

$$5.0 < 1.0 < 7.0.$$

But the binding capacity (K_1) decreases in the above order (already stated). Hence there is an inverse relationship between the weight of water sorbed and the binding capacity and is shown pictorially in Fig. 3. This inverse relationship is the expected one because of the following fact. For a substrate molelcule to get bound to CPVP, it has to penetrate first the outside aqueous layer and then to compete with the specifically bound water molecules for the sites. Not only that, the structure of crosslinked polymer in the three-dimensional matrix would also change with change in water structure. Hence any change in the amount of water sorbed could affect the binding sites and hence alter the type of interacting forces. This can explain very well the above observed order.

The shapes of Giles isotherms (Fig. 2) support the above explanation. At pH 5.0, as the isotherm indicates, C_B values gradually increase from the beginning itself with increase in C_F values; at pH 1.0, there appears in the isotherm a small plateau in the initial stage followed by almost a linear portion but at pH 7.0, the plateau is very lengthy. From these shapes, it is inferred that the sorption process at pH 5.0 takes place smoothly but encounters small and large barriers at pH 1.0 and 7.0 respectively. This inference coincides with the amount of water uptake and hence supports the explanation offered for the observed binding capacity.

Table 2

Swelling capacities of CPVP in H_2O at different pH's

CPVP = 0.2 g; Volume = 10 ml; Temperature = 30°C; Swelling time = 24 h
Water adjusted with HCl or NaOH to the required pH.

Weight of H_2O sorbed (g)	pH = 1.0	pH = 5.0	pH = 7.0
	0.994	0.953	1.015

Such observations as the one in CPVP - SM system, have already been made in other studies also listed below.

(i) We have reported the presence of iceberg structure of water in CPVP and its effect on interaction of substrates like aromatic compounds, drugs (4) and hydrophobic fluorescent probe (9).

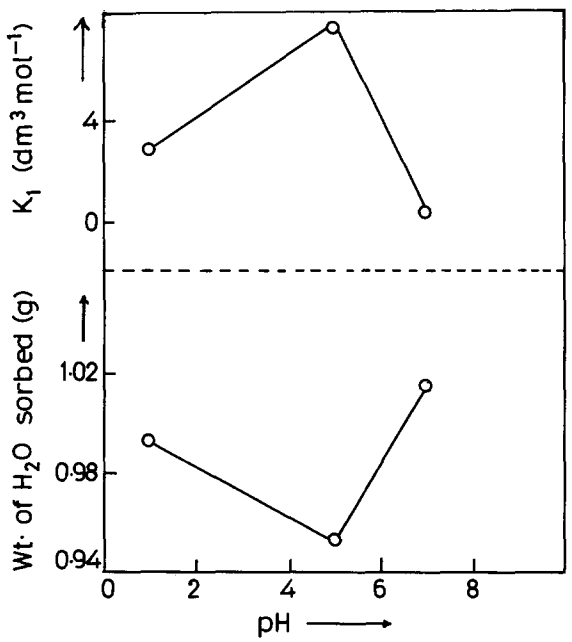


Fig. 3
Correlation plot of binding and swelling capacities of CPVP at various pH's in the CPVP-SM and CPVP-H_2O systems. For binding studies the condition is the same as in Fig. 1. For H_2O sorption, CPVP = 0.2 g, Total volume = 10 ml; swelling time = 24 h

(ii) Carpenter et al (6) have reported that the % uptake of phenolic compounds is dependent on the pH of the solution and the maximum uptake is within the pH range 3-5 for most of the phenolics. They have also witnessed the change in polymer structure by the increased uptake of phenols at the optimum pH.

(iii) Voigt et al (10) have shown that the strength of interaction of phenothiazines which interact hydrophobically with CPVP decreases with increasing pH.

Even though observations have already been made regarding the effect of pH on substrate binding to CPVP, it is, for the first time, that we propose an explanation in terms of CPVP - H_2O interaction, for the pH-dependent sorption behaviour of substrates.

III (iv) PRACTICAL UTILITY

The values of interaction constant (K_1) are useful in indirectly determining the in vivo bound drug level of SM. From the theoretical

plot of Horn and Ditter (2) and from the values of interaction constant which are < 10 dm^3 mol^{-1} at all pH's studied, it is inferred that the physiological bound drug level of SM to CPVP cannot exceed 3%, the permissible limit. Hence CPVP, as a tablet-disintegrator, does not affect the drug absorption and activity in living systems.

ACKNOWLEDGEMENT

The financial support offered by UGC, New Delhi, India, for the present work is gratefully acknowledged. The authors wish to thank Roche Pharmaceutical Co., India for having provided the free drug sample.

REFERENCES

1. P.H.List and U.A.Muazzam, Pharm. Ind. 41, 459 (1979).
2. D.Horn and W.Ditter, J. Pharm. Sci. 71, 1021 (1982).
3. K.H.Frömming, W.Ditter and D.Horn, J. Pharm. Sci. 70, 738 (1981).
4. M.Maruthamuthu and E.Subramanian, J. Polym. Sci. Part B Polym. Phys., Phys. Chem. Communicated.
5. The Merck Index, 9th edn., ed. by M.Windholz, The Merck & Co., Rahway, USA, 1154 (1976).
6. A.Carpenter, S.Siggia and S.Carter, Anal. Chem. 48, 225 (1976).
7. G.Scatchard, Ann. N.Y. Acad. Sci. 51, 660 (1949).
8. C.H.Giles, T.H.MacEwan, S.N.Nakhwa and D.Smith, J. Chem. Soc. Part III, 3973 (1960).
9. M.Maruthamuthu and E.Subramanian, Proc. Indian Acad. Sci. (Chem. Sci.), Communicated.
10. R.Voigt, H.H.Schultze and S.Keipert, Pharmazie, 31, 863 (1976).

Accepted April 22, 1989 S