[Chem. Pharm. Bull. 17(5) 961—965 (1969)] UDC 615.033 : 615.356 : 577.164.16

Adsorption of Solute from the Solutions. III.[1] Repression of Adsorption of Cyanocobalamin on Talc by Polyvinylpyrrolidone

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(Received September 6, 1968)

The adsorption of cyanocobalamin on talc was remarkably repressed by polyvinylpyrrolidone. An investigation utilizing equilibrium dialysis revealed that the repression by PVP was caused by adsorption of PVP on talc and not by any direct interaction between PVP and cyanocobalamin.

Adsorption of PVP on talc was endothermic and the value of the apparent entropy change was positive.

PVP and cyanocobalamin adsorbed on talc with obedience to the Langmuir isotherm equation. But the data of adsorption of the binary mixture did not fit the Markham–Benton equations but fitted a modified equations derived with an assumption that adsorption constant for cyanocobalamin on talc varied inversely as adsorbed amount of PVP. This may indicate that approach of cyanocobalamin to surface of talc is interfered by PVP molecules owing to a kind of steric hindrance.

Talc, one of the most popular lubricants for tablet making, has been known to adsorb cyanocobalamin and consequently to interfere with intestinal absorption and assay of the vitamin.[3] In the previous paper,[1] competition of cyanocobalamin with pyridoxine and thiamine in adsorption on talc was reported. Recently the authors found that some kinds of water-soluble polymers, especially polyvinylpyrrolidone (PVP), also repressed the adsorption of cyanocobalamin on talc. In the present paper, the repression by PVP was investigated.

Experimental

Materials——Cyanocobalamin, talc, and acacia used were of J.P. grade. PVP K30 and K90 (manufactured by Badisch Anilin und Sodafabrik A.G.), sodium carboxymethylcellulose (CMC Na, medium viscosity), methylcellulose (MC 4000), and soluble starch were purchased from Wako Pure Chemicals Co., Ltd. Their purity or moisture content was checked and they were not further treated.

Adsorption Experiment——Usually about 200 mg of talc were suspended in 10 ml of various concentrations of cyanocobalamin, polymers, or their mixtures solution in buffer (0.15M phosphate of pH 6.0 or 0.15M tartrate of pH 2.0 or 4.0), and shaken in a thermostat at 5° or 30°. After equilibration the supernatant liquid was isolated, and concentration of the vitamin or PVP was determined. The equilibration period was from 1 to 2 days.

Determination of Cyanocobalamin and PVP——Cyanocobalamin and PVP were determined spectrophotometrically with a Hitachi–Perkin Elmer Model 139 Spectrophotometer at 361 mμ and at 210 mμ, respectively.

Equilibrium Dialysis——Cellophane bags, prepared from Visking 18/32 inch cellulose tubing, were filled with 5 ml of the inside solution. The bags were immersed in 5 ml of the outside solution with or without 200 mg of talc suspended and allowed 1 week at 5° for attainment of equilibrium. The details of the inside and outside solutions are listed in Table I. After equilibration the concentration of cyanocobalamin was determined spectrophotometrically.

Viscometry——Viscosity of various concentrations of aqueous PVP K90 and K30 solutions was measured with an Ubbelohde Viscometer at 25°, and limiting viscosity number ([η]) and Huggins constant were evaluat-

1) Part II: I. Moriguchi and N. Kaneniwa, *Chem. Pharm. Bull.* (Tokyo), **17**, 394 (1969).
2) Location: *1-5-8, Hatanodai, Shinagawa-ku, Tokyo.*
3) J. Dony and J. Conter, *J. Pharm. Belg.*, **11**, 338 (1956); C. Trolle–Lassen, *Arch. Pharm. Chemi*, **67**, 504 (1960).

ed using the Martin equation.[4] The mean molecular weight ($\overline{M}_v$) was calculated from the value of $[\eta]$ utilizing the relation

$$[\eta]=K\overline{M}_v^a$$

where values of the constants K and a used in the calculation were 1.9×10^{-4} and 0.68, respectively.[5]

Results and Discussion

Repression of Adsorption of Cyanocobalamin on Talc by PVP

Fig. 1 shows influence of water-soluble polymers on amount of cyanocobalamin adsorbed on talc, and PVP exhibits strong repression of adsorption of the vitamin.

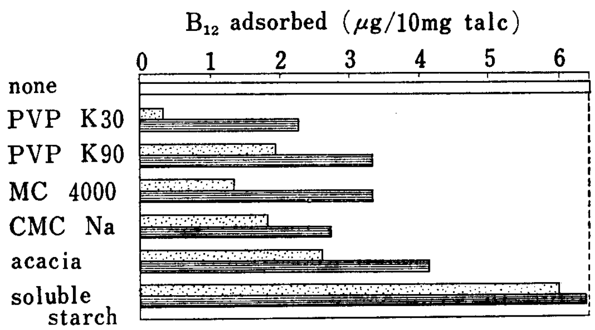

Fig. 1. Repression of Adsorption of Cyanocobalamin (B_{12}) on Talc by Water-soluble Polymers

about 3×10^{-5}M of B_{12} and 200 mg/10 ml of talc in 0.15M phosphate buffer at pH 6.0 and 5°

(light bars) B_{12}:polymer=1:10 in weight
(dark bars) B_{12}:polymer=1:1 in weight

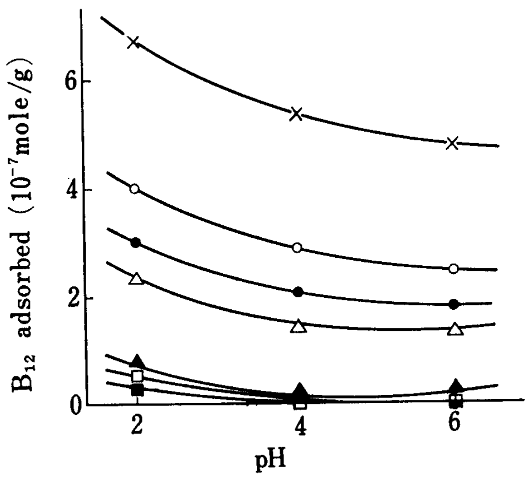

Fig. 2. Repression of Adsorption of Cyanocobalamin by PVP

2.33×10^{-5}M of initial B_{12} and about 200 mg/10 ml of talc with and without PVP in 0.15M phosphate buffer solution at 5°

—×— B_{12} alone
—●— B_{12}+K30 (1:1)
—▲— B_{12}+K30 (1:10)
—■— B_{12}+K30 (1:100)
—○— B_{12}+K90 (1:1)
—△— B_{12}+K90 (1:10)
—□— B_{12}+K90 (1:100)

Then, the degree of the repression by PVP was examined at various pH and concentrations of initial PVP. The results are shown in Fig. 2. pH dependence of the repression was not so large. Adsorption of cyanocobalamin was scarcely observed in the presence of PVP a hundred times as much as cyanocobalamin in weight, and such quantity of PVP seemed to be practically available for tablet making.

To elucidate the cause of the repression by PVP, an equilibrium dialysis was carried out. The results are tabulated in Table I. While considerable amount of cyanocobalamin was adsorbed on talc in the absence of PVP and in the presence of PVP separated from talc with cellulose membrane, the adsorption was not observed in the presence of PVP together with talc in the same cellulose bag. It seems to follow from this that the repression by PVP is caused by adsorption of PVP on talc and not by any direct interaction between PVP and cyanocobalamin.

4) M.L. Huggins, "Physical Chemistry of High Polymers," Chapter VIII, John Wiley and Sons, Inc., New York, 1958.
5) H. Frank and G. Levy, *J. Polymer Sci.*, 10, 371 (1953).

Table I. Data of Equilibrium Dialysis[a)]

No.	Initial set Inside	Outside	Equilm. conc. of B_{12} (10^{-5}M) Inside	Outside
1	PVP	B_{12}	2.98	3.01
2	B_{12}	PVP	2.96	3.02
3	B_{12}	PVP, talc	3.03	
4	PVP	B_{12}, talc	1.99	
5	(buffer)	B_{12}, talc	1.58	

casing: Visking 18/32 inch cellulose tubing
B_{12}: 5 ml of 6×10^{-5}M solution } in 0.15M phosphate buffer of pH 6.0
PVP: 5 ml of 0.8% K90 solution
talc: about 200 mg
a) at 5°, for 1 week

Adsorption of PVP on Talc

Fig. 3 shows adsorption isotherms of PVP on talc in water and ethanol at 5° and 30°. The isotherms fit the Langmuir equation, Eq. (1),

$$1/x = 1/n + 1/ncK \qquad (1)$$

where x represents the amount of an adsorbate adsorbed on a unit weight of talc, n the maximum of x, K the constant which indicates the strength of the adsorption, and c the equilibrium concentration of the adsorbate in the solution.

The values of n and K were obtained utilizing the graph, and the apparent heat of adsorption, ΔH_{app}, and the apparent entropy change, ΔS_{app}, were calculated. The values of these constants are listed in Table II together with those for cyanocobalamin, pyridoxine, and thiamine for comparison. The values of n for PVP were about 10 to 20 times as large as those for the vitamins as shown in Table II, but there was not so large difference between the values of ΔG_{app} for PVP and for the vitamins. Contrary to ordinary cases of adsorption,

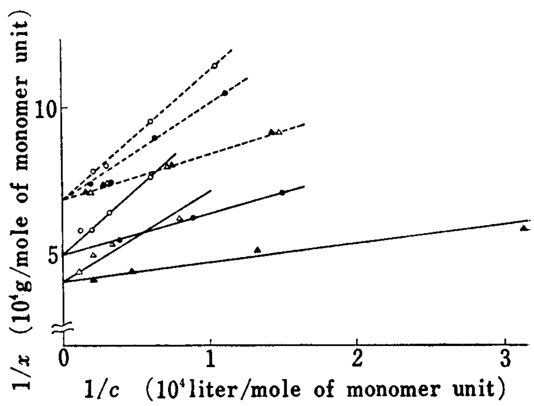

Fig. 3. Langmuir's Plots for Adsorption of PVP on Talc

K90 at 5° (—○—) and 30° (—●—), and K30 at 5° (—△—) and 30° (—▲—) in 0.15M buffer of pH 6.0 (——) and in ethanol (----) with about 200 mg talc suspended per 10 ml solution.

Table II. Constants for Adsorption on Talc

		10^6n mole[a)]/g	$10^{-4}K$ liter/mole[a)]	ΔG_{app} kcal/mole[a)]	ΔH_{app} kcal/mole[a)]	ΔS_{app} kcal/mole[a)] deg
PVP K30	pH 6.0, 5°	24.3	1.37	−5.27	+10.50	+56.68
	pH 6.0, 30°	24.3	6.56	−6.68		
PVP K90	pH 6.0, 5°	20.2	1.10	−5.15	+ 7.64	+45.96
	pH 6.0, 30°	20.2	3.44	−6.29		
PVP K30	ethanol, 5°	14.6	2.11	−5.51	~ 0	+19.76
	ethanol, 30°	14.6	2.11	−6.00		
PVP K90	ethanol, 5°	14.6	0.79	−4.96	+ 1.93	+24.76
	ethanol, 30°	14.6	1.05	−5.58		
B_{12}	pH 6.0, 5°	1.35	4.44	−5.92	− 5.33[b)]	− 2.25[b)]
Pyridoxine	pH 4.0, 5°	2.17	0.23	−4.28		
Thiamine	pH 4.0, 5°	1.85	0.69	−4.89		

a) mole of monomer unit for PVP *b)* at pH 4.0

the values of ΔH_{app} and ΔS_{app} for PVP were positive. This may suggest that water or ethanol bound to PVP molecule takes some part in the adsorption.

PVP K30 was adsorbed more easily on talc than PVP K90 as shown in Table II. To find a clue to elucidation of the reason, properties of PVP were investigated by measurement of viscosity. The viscosity and related constants for PVP K30 and K90 are listed in Table III. Of these constants, Huggins constant seemed to be worthy of notice. Judging from

Table III. Viscosity[a] and Related Constants for PVP

	PVP K30	PVP K90
$[\eta]$	0.208	1.972
Huggins constant	0.80	0.31
$\overline{M}_v$	3.0×10^4	8.1×10^5
Degree of polymerization	270	7300

a) in water at 25°

the value of the constant, PVP K90 was thought to be an ordinary linear-polymer. But PVP K30 seemed to have many branches in the polymer chain because the value of Huggins constant was extraordinary high,[6] and therefore PVP K30 was supposed to have much more units of terminal monomer which seemed easy to approach adsorbing sites on talc than PVP K90.

Competition of PVP with Cyanocobalamin in Adsorption on Talc

Cyanocobalamin[1] as well as PVP was known to be adsorbed on talc with obedience to the Langmuir isotherm equation. Accordingly, the Markham–Benton equations,[7] Eq. (2) and (3), derived by a simple extention of the Langmuir equation to the case of binary mixtures of adsorbates were tried to be applied in the competitive adsorption of PVP with cyanocobalamin.

$$\theta_1 = c_1K_1/(1+c_1K_1+c_2K_2) \quad (2)$$

$$\theta_2 = c_2K_2/(1+c_1K_1+c_2K_2) \quad (3)$$

In these equations subscripts 1 and 2 correspond to cyanocobalamin and PVP, respectively, and θ_i denotes x_i/n_i, the degree of saturation. Values observed and calculated using Eq. (2) and (3) for the competitive adsorption are listed in Table IV.

Table IV. Competition of PVP with Cyanocobalamin in Adsorption on Talc[a]

Initial concentration				Equilm. B_{12} (10^{-5}M)	Adsorbed B_{12} (10^{-7} mole/g)		
PVP	(M)[b]	B_{12}(10^{-5}M)	Talc (mg/10 ml)		Obs.	Calcd. A[c]	Calcd. B[d]
	0	2.33	233.9	1.22	4.74		
K30	3.6×10^{-6}	2.33	227.4	1.94	1.77	6.21	1.77
K30	3.6×10^{-5}	2.33	241.8	2.27	0.20	6.52	0.23
K30	3.6×10^{-4}	2.33	204.4	2.33	0.00	4.96	0.01
K90	3.6×10^{-6}	2.33	227.5	1.67	2.45	5.71	2.57
K90	3.6×10^{-5}	2.33	240.9	1.98	1.29	6.04	0.35
K90	3.6×10^{-4}	2.33	203.1	2.33	0.00	3.62	0.02

a) in 0.15M phosphate buffer solution at pH 6.0 and 5°
b) mole of monomer unit/liter
c) Calculated from Markham–Benton equations.
d) Calculated from Eq. (6) and (7).

6) L.H. Cragg and G.R.H. Fern, *J. Polymer Sci.*, **10**, 185 (1953).
7) E.C. Markham and A.F. Benton, *J. Am. Chem. Soc.*, **53**, 497 (1931).

There was no good agreement between these values, and the difference increased with increasing concentration of initial PVP.

Thus, assuming that adsorption of cyanocobalamin become difficult in proportion to adsorbed amount of PVP, K_1 in Eq. (2) and (3) may be replaced by mK_1/θ_2 (m is a constant), and we may have

$$\theta_1=(m/\theta_2)c_1K_1/[1+(m/\theta_2)c_1K_1+c_2K_2] \quad (4)$$

$$\theta_2=c_2K_2/[1+(m/\theta_2)c_1K_1+c_2K_2] \quad (5)$$

Eq. (4) and (5) can be reduced to Eq. (6) and (7).

$$\theta_1=mc_1K_1/c_2K_2 \quad (6)$$

$$\theta_2=(c_2K_2-mc_1K_1)/(1+c_2K_2) \quad (7)$$

Values calculated using Eq. (6) and (7) are listed also in Table IV, and show good agreement with observed values. The value of m was estimated 1×10^{-3} for K30 and 2×10^{-3} for K90 by trial and error method, and seemed to differ according to the molecular weight or configurations.

These results may be taken to indicate that the repression of adsorption of cyanocobalamin by PVP is not singly caused by occupation of adsorbing sites on talc with PVP due to a simple competition in adsorption between the two species. Probably approach of cyanocobalamin to surface of talc is interfered by adsorbed PVP molecules owing to a kind of steric hindrance, and consequently adsorbed amount of cyanocobalamin may remarkably decrease with increasing amount of PVP adsorbed.