Notes

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Adsorption of Solute from the Solutions. II.[1] Competitive Adsorption of Cyanocobalamin with Pyridoxine and Thiamine on Talc

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In the production of tablets containing cyanocobalamin, it has been advised to use magnesium stearate as a lubricant because talc adsorbs cyanocobalamin and consequently interferes with intestinal absorption and assay of the vitamin.[3] But magnesium stearate can not always replace talc because of the difference of the lubrication mechanisms.[4]

Cyanocobalamin is usually formulated together with other vitamins, especially pyridoxine and thiamine, in the tablets. In this work the adsorption of cyanocobalamin on talc in the presence of pyridoxine and thiamine was studied to obtain some information about employment of talc as a lubricant of such tablets, and the competitive adsorption was treated somewhat theoretically.

Experimental

Materials——Cyanocobalamin, pyridoxine hydrochloride, thiamine hydrochloride, corn starch, magnesium stearate, potato starch, and talc used were of J.P. grade. The following materials were kindly supplied by the manufacturers: calcium carboxymethylcellulose (E.C.G. 505, Gotoku Yakuhin Kogyo Co.), carboxymethylcellulose (E.C.G. 507, Gotoku Yakuhin Kogyo Co.), magnesium aluminosilicate (Neusilin S1 Fine Particle, Fuji Kagaku Kogyo Co.), and microcrystalline cellulose (Grade for Foods and Drugs, Asahi Kasei Kogyo Co.). Their purity or moisture content was checked and they were not further treated.

Adsorption Experiment——Usually about 200 mg of adsorbents were suspended in 10 ml of various concentrations of the vitamin solution in buffer (0.05 M or 0.15 M tartrate of pH 2.0 and 4.0, and phosphate of pH 6.0 and 8.0), and shaken in a thermostat at 5° or 37°. The pH and temperature in the experiments were chosen in consideration of the stability of the vitamins. After equilibration the supernatant liquid was isolated, and concentration of the vitamin was determined. The equilibration period was from 1 to 2 days.

Determination of the Vitamins——The vitamins were determined spectrophotometrically with a Hitachi–Perkin Elmer Model 139 Spectrophotometer at 361 mμ for cyanocobalamin in the absence of pyridoxine,[5] at 550 mμ for cyanocobalamin in the presence of pyridoxine, at 290 mμ for pyridoxine in the absence of cyanocobalamin, and at 274 mμ[6] for thiamine in the absence of cyanocobalamin.

Results and Discussion

Preliminarily, adsorption of cyanocobalamin on water–insoluble materials usually used as diluents, disintegrators, and lubricants in the production of tablets was examined. As shown in Fig. 1, talc adsorbs much larger amount of the vitamin than any other materials examined do over the range from pH 2 to 8.

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1) Part I: N. Kaneniwa and I. Moriguchi, *Yakuzaigaku*, **27**, 232 (1967).
2) Location: *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).
4) Y. Noguchi, *Farumashia*, **3**, 599 (1967).
5) High concentration of pyridoxine was found to disturb the maximum absorbance of cyanocobalamin at 361 mμ.
6) W. Lhoest, *J. Pharm. Belg.*, **11**, 495 (1956).

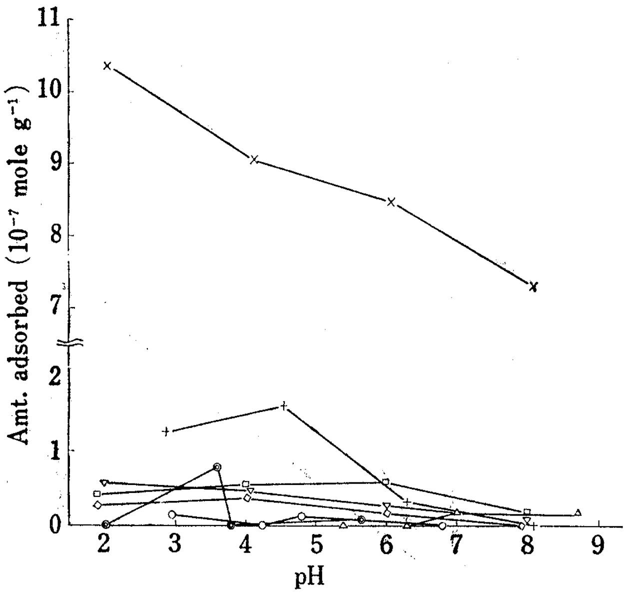

Fig. 1. Adsorption of Cyanocobalamin on Water-insoluble Diluents, Disintegrators, and Lubricants used for Tablets

initial concentration of 6×10^{-5}M cyanocobalamin and 0.2 g/10 ml of adsorbents in 0.05M buffer solutions of various pH at 5°
—○— calcium carboxymethylcellulose
—⊙— carboxymethylcellulose
—◇— corn starch
—△— magnesium aluminosilicate
—+— magnesium stearate
—□— microcrystalline cellulose
—△— potato starch
—×— talc

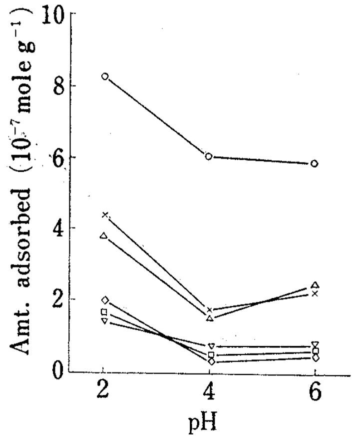

Fig. 2. Influences of Pyridoxine and Thiamine on the Adsorption of Cyanocobalamin on Talc

3×10^{-5}M cyanocobalamin and 0.2 g/10 ml talc in 0.15M buffer solutions at pH 2.0, 4.0, and 6.0, and 5°
—○— none
—△— in the presence of 0.01M pyridoxine hydrochloride
—□— 0.1M pyridoxine hydrochloride
—×— 0.01M thiamine hydrochloride
—▽— 0.1M thiamine hydrochloride
—◇— both 0.05M of pyridoxine hydrochloride and thiamine hydrochloride

Fig. 2 shows adsorption of cyanocobalamin on talc in the presence of pyridoxine and thiamine at pH 2.0 to 6.0. The adsorption was almost repressed by pyridoxine, thiamine, and their mixture in about 3×10^3 times the concentration of cyanocobalamin, and such doses are usually formulated in the tablets. The ordinary doses in mole of pyridoxine and of thiamine are 1.3×10^3 to 1.6×10^4 times and 1.6×10^2 to 4.0×10^3 times, respectively, as large as that of cyanocobalamin according to J.P. VII.

Thiamine was reported to be adsorbed on talc in the mixed powders,[7] and pyridoxine seemed likely to be adsorbed on talc, too. The repression shown in Fig. 2 was accordingly supposed to be caused by competition of cyanocobalamin with pyridoxine and thiamine in adsorption on talc. Thus, the adsorption of the individual vitamin on talc was investigated with the three vitamins. The data fit the Langmuir isotherm equation, Eq. (1), as shown in Fig. 3 and 4.

$$x=ncK/(1+cK) \quad (1)$$

or

$$1/x=1/n+1/ncK \quad (1')$$

x represents the amount of a vitamin 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 vitamin in the solution. The values of n and K were obtained from the slope and the intercept on the ordinate of the graphs in Fig. 3 and 4, and are listed in Table I. The apparent heat of adsorption, ΔH, and the apparent entropy change, ΔS, for cyanocobalamin were evaluated -5.33 kcal mole^{-1} and -2.25 e.u., respectively. Talc adsorbs

7) R. Yamamoto and T. Takahashi, *Yakugaku Zasshi*, **78**, 1242, 1246 (1958).

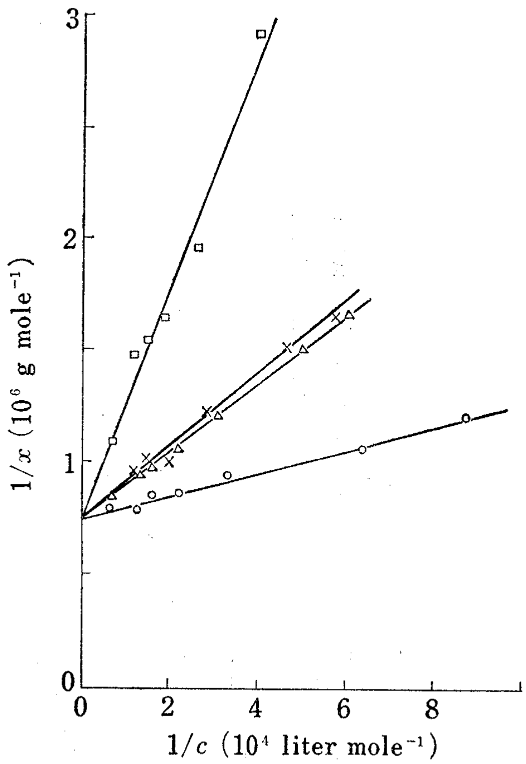

Fig. 3. The Langmuir's Plots for Adsorption of Cyanocobalamin on Talc in 0.15M Buffer Solutions

—○— at pH 2.0 and 5°,
—△— at pH 4.0 and 5°,
—□— at pH 4.0 and 37°,
—×— at pH 6.0 and 5°

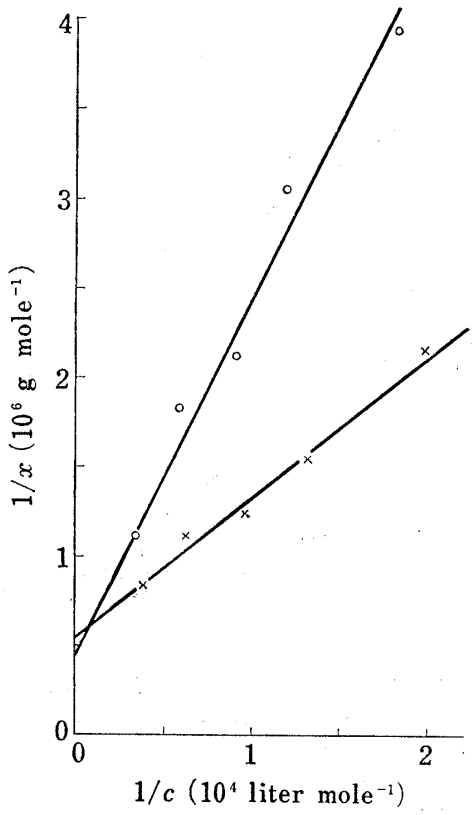

Fig. 4. The Langmuir's Plots for Adsorption of Pyridoxine Hydrochloride (—○—) and of Thiamine Hydrochloride (—×—) on Talc in 0.15M Buffer Solution of pH 4.0 at 5°

Table I. The Langmuir Constants for Adsorption of Cyanocobalamin, Pyridoxine Hydrochloride, and Thiamine Hydrochloride on Talc[a)]

Vitamin	Temperature (°C)	pH	n (10^{-6} mole g^{-1})	K (10^4 liter mole^{-1})
Cyanocobalamin	5	2.0	1.35	14.10
	5	4.0	1.35	4.83
	5	6.0	1.35	4.44
	37	4.0	1.35	1.41
Pyridoxine HCl	5	4.0	2.17	0.23
Thiamine HCl	5	4.0	1.85	0.69

a) Suspended in 0.15M tartrate or phosphate buffer solution.

cyanocobalamin the most strongly and thiamine the next, but pyridoxine can also be adsorbed fairly well. The values of n, however, are small, and talc is usually formulated only a few per cent of the weight of tablets. Consequently the possible amount adsorbed on talc seems negligible to the ordinary dose formulated in tablets in case of pyridoxine and of thiamine.

These results may be taken to indicate that talc as well as magnesium stearate is applicable as a lubricant in the production of the tablets containing cyanocobalamin together with pyridoxine and thiamine in the ratio of the ordinary dose, even without consideration on the desorption of cyanocobalamin during its passage through the gastro-intestinal tract.

In the case of competitive adsorption from the solution, the Markham–Benton (M–B) equations[8] derived by a simple extension of the Langmuir equation have usually not given good agreement with experiment. So the M–B equations were tentatively modified by introducing a parameter m as

$$x_1 = n_1 c_1 K_1 (1 - \theta_1 - m\theta_2) \quad (2)$$

$$x_2 = n_2 c_2 K_2 (1 - m\theta_1 - \theta_2) \quad (3)$$

where subscripts 1 and 2 correspond to adsorbate I and II, respectively, and θ_i denotes x_i/n_i, the degree of saturation. The parameter m may be defined as the ratio of adsorbing sites for I or II in the overlapping space to in the whole space on the adsorbent. The values of m estimated with consideration of I and of II are equal, assuming that the adsorbing sites for I and for II are uniformly distributed on the adsorbent. If $m=1$, I completely competes with II, and Eq. (2) and (3) are identical with the M–B equations. Accordingly let us call m degree of competitivity. Eq. (4) and (5) can be derived from Eq. (2) and (3).

$$x_1 = n_1 c_1 K_1 [1 + (1-m) c_2 K_2] / [1 + c_1 K_1 + c_2 K_2 + (1-m^2) c_1 c_2 K_1 K_2] \quad (4)$$

$$x_2 = n_2 c_2 K_2 [1 + (1-m) c_1 K_1] / [1 + c_1 K_1 + c_2 K_2 + (1-m^2) c_1 c_2 K_1 K_2] \quad (5)$$

In the case where c_2 is so large that $c_1K_1 \ll c_2K_2$ and $1 \ll c_2K_2$, Eq. (4) can be reduced to Eq. (6).

$$x_1 \doteqdot n_1 c_1 K_1 (1-m) / (1 + c_1 K_1 - m^2 c_1 K_1) \quad (6)$$

The values of m between 3×10^{-5}M cyanocobalamin, and 0.1 and 0.01M pyridoxine or thiamine were calculated using Eq. (4) or (6) from the data in Fig. 2 and the values of n and K in Table I with the approximation of $c_2 \doteqdot a_2$ (the initial concentration of II), and were listed in Table II. The values of m are about 0.9 or the more, and almost irrespective of the concentration and the pH of the solutions experimented. It seems probable from this that Eq. (4) and (6) are approximately fitted by the data on the competition, and that the mechanism of the competition is similar with pyridoxine and thiamine. But strictly speaking, the actual phenomena may be much more complicated by the adsorption of water and buffering agents, and so on.

Table II. Degree of Competitivity (m) of Cyanocobalamin with Pyridoxine and Thiamine

Competing agent		Conc. of cyanocobalamin (10^{-5}M)	pH	m
Pyridoxine	0.10M	3.0	2.0	0.95[a]
	0.01M	3.0	4.0	0.92[b]
	0.10M	3.1	4.0	0.95,[a] 0.97[b]
	0.10M	2.9	6.0	0.94[a]
Thiamine	0.10M	2.9	2.0	0.96[a]
	0.01M	2.9	4.0	0.87[b]
	0.10M	3.1	4.0	0.95[a,b]
	0.10M	3.2	6.0	0.94[a]

a) Calculated using Eq. (6). b) Calculated using Eq. (4).

8) E.C. Markham and A.F. Benton, *J. Am. Chem. Soc.*, 53, 497 (1931).