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Interaction of Parabens and Other Pharmaceutical Adjuvants with Plastic Containers[1]

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The possible interaction has been studied between plastics and several drugs and pharmaceutical adjuvants such as parabens, quaternary ammonium salts, and HCO-50 (polyoxyethylene derivative of hydrogenated castor oil).

It was found that hydrophobic interaction plays a major role in adsorption of parabens to several plastics studied.

Studies on the effect of temperature on adsorption and desorption suggest that the drug-binding sites of plastics may be hidden in the structure at low temperature and unfolded to the surface by configuration change at high temperature.

HCO-50 was non-selectively adsorbed to all plastics studied and maximum adsorption occured near the region of the critical micelle concentration of HCO-50.

Although packaging of drugs in plastic containers have become more prevalent recently, possible harmful side effects of plastics, rather new material in medical practice when compared with glass and paper, still remain to be investigated. Besides direct toxicities of plastics, it should be considered that plastic container may change efficacy of drugs or discharge toxic harmful substances. Autian, *et al.*[3-6] have extensively studied in drug-plastic interaction and mechanism of sorption, and factors influencing the process have been tried to be elucidated. The present study was conducted to examine from the stand-point of drug-plastics interaction whether plastics are suitable for medical purposes, especially as materials of containers of large volume injections and blood substitutes. The possible interaction has been studied between plastics and several drugs and pharmaceutical adjuvants such as parabens, quaternary ammonium salts, and hydrogenated castor oil. Attention has also been paid to the effects of heating process as heating is a common practice to sterilize injections.

Experimental

Materials——Polyethylene products, polyvinyl chloride (P.V.C. $^{-}B_1$ and $^{-}B_2$), polymethacrylate, polycarbonate, and polystylene were supplied by Japan Plastics Industry Association, Tokyo, Japan. Polyvinyl chloride (P.V.C. -C) was obtained from commercial source and was used as supplied. HCO-50 (polyoxyethylene derivative of hydrogenated castor oil) was supplied by Nikko Chemicals Co., Tokyo, Japan, and purified by gel chromatography with Sephadex G-100.[7]

Quantitative Analyses——Methyl- and ethylparabens were determined from the extinction at 257 mμ, propyl- and butylparabens at 258 mμ, and benzylparaben at 259 mμ. Quaternary ammonium salts were

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2) Location: *a) Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto; b) 1658 Oshinohara, Yasu-cho, Yasu-gun, Shiga-ken.*
3) E. Marcus, H.K. Kim and J. Autian, *J. Am. Pharm. Assoc.*, **48**, 457 (1959).
4) H.K. Kim and J. Autian, *J. Am. Pharm. Assoc.*, **49**, 227 (1960).
5) A.J. Kapadia, W.L. Guess and J. Autian, *J. Pharm. Sci.*, **53**, 28 (1964).
6) M.B. Rodell, W.L. Guess and J. Autian, *J. Pharm. Sci.*, **55**, 1429 (1966).
7) K. Mizutani, M. Yamagata, T. Sekiguchi, T. Yasuda and H. Kiyohara, *Kosekikagaku Kenkyu Hokoku*, **1968**, 318.

Table I. List of Plastics Studied

Plastics	L×W×T (mm)	N	Total weight (g)
Polyethylene (L.D.-B)	67×7×0.55	4	0.70—1.08
Polyethylene (H.D.-B)	67×7×0.68	4	0.87—1.17
Polyethylene (H.D.-S)	67×7×0.5	4	0.85—0.95
Polypropylene (P.P.-B)	67×7×0.55	4	0.68—1.11
Polypropylene (P.P.-S)	67×7×0.5	4	0.80—0.90
Polymethacrylate (P.M.-S)	50×7×2.0	2	1.50—1.60
Polycarbonate (P.C.-S)	67×7×0.5	4	1.10—1.20
Polystylene (P.S.-S)	67×7×0.3	6	0.86—0.95
Polyvinyl chloride ($P.V.C-B_1$)	67×7×0.35	4	0.70—1.06
Polyvinyl chloride ($P.V.C-B_2$)	58×7×0.62	4	1.25—1.32
Polyvinyl chloride (P.V.C-C)	67×7×0.3	4	0.73—0.86

type of original materials: B=bottle S=sheet C=soft bag
N=number of pieces of plastics soaked in a tube

measured by the methods of either Scott[8] or Carkhuff and Boyd.[9] HCO-50 was determined by cobalt-thiocyanate method.[10]

Adsorption of Drugs by Plastics——The amount of pieces of plastics studied are shown in Table I. Certain amount of pieces of plastics were soaked in 10 ml of drug solution in an 11 ml glass-stoppered test tube. The tube was stoppered tightly and was incubated in a water bath at constant temperature. After the incubation, the test solution was taken out for the determination of the remaining drug. When incubated at 100°, the solution was cooled down to room temperature immediately after the incubation, and the determination was conducted. Drugs were dissolved in 1/15 M phosphate buffer (pH 7.4, $\mu=0.2$), or distilled water, unless otherwise stated.

Discharge of Butylparaben adsorbed by Plastics——Pieces of polyethylene or polyvinyl chloride were incubated in 0.4 mM butylparaben in 1/15 M phosphate buffer solution (pH 7.4) for 1 hour at 100°, taken out, rinsed with distilled water, and blotted with tissue paper. The plastic pieces were transferred into fresh buffer solution and reincubated at 40° or 100° for 186 hours. The absorption of 258 mμ was measured at several time intervals to determine the discharge of butylparaben from plastics.

Result

Drug-plastics Interaction During Heating Process

Test tubes containing pieces of plastics and drug solutions as shown in Table I were heated at 100° for 30 min as a model for heat sterilization process. Amounts of drugs adsorbed

Table II. Adsorption of Drugs to Plastics[a] (μg Uptake per g plastics ×10)

Compounds[b),c)]	Polyethylene			P.P.		P.C.	P.M.	P.S.	P.V.C.		
	L.D.-B	H.D.-B	H.D.-S	B	S	S	S	S	B_1	B_2	C
Methylparaben	0	0	7.6	0	5.4	910	30	2.5	14.0	28.5	42.2
Ethylparaben	1.1	0	0	19.8	0	0	0	0	28.3	0	125.2
Propylparaben	25.5	18.6	9.0	22.8	22.9	1.4	0.3	1.8	89.7	50.2	323
Butylparaben	60.2	22.8	20.0	27.2	28.8	13.7	16.9	0	202	103	456
Benzylparaben	73.8	58.5	68.5	34.2	81.4	26.2	18.6	2.3	245	115	518
Benzalkonium chloride	95.5	326	131	230	30.6	52.1	5.1	0	770	464	1081
Benzethonium chloride	83.2	120	183	163	126	12.1	56.8	57.5	543	400	756
HCO-50	—	—	196	—	74.1	56.5	108	172	84.1	58.0	86.2

a) incubation: 100°, 30 min
b) concentration: parabens (3×10^{-5}M), benzalkonium chloride (0.01g/liter)
benzethonium chloride (3×10^{-5}M), HCO-50 (0.01g/liter)
c) buffer: pH 7.4 phosphate buffer ($\mu=0.2$)

8) G.V. Sott, *Anal. Chem.*, **90**, 768 (1968).
9) E.D. Carkhuff and MW.F. Boyd, *J. Am. Pharm. Assoc.*, **43**, 240 (1954).
10) S. Ikawa, T. Koito, K. Sagara, T. Inoue, T. Yoshida, T. Maki and Y. Takiwaki, *Koseikagaku Kenkyu Hokoku*, **1967**, 218.

by plastics were estimated from the change of drug concentrations in comparison with controls of no plastics addition, and are expressed in terms of weight of plastics as shown in Table II.

Polyvinyl chloride, especially the one, (P.V.C.-C), containing more plasticizers, showed the highest adsorption of the parabens. The percentage adsorption increased as a function of length of carbon chain of alcohol moiety and was less independent to varieties of plastics. Behavior of HCO-50 was different; the compound could be adsorbed at relatively constant ratio by all the plastics including polystylene.

Langmuir's Type Adsorption

Plastics of about 1.00 g were weighed exactly and incubated in solution of various concentrations of butylparaben at 100° or 40° for 60 min or 4 days, respectively. Amounts of drug adsorbed were estimated from the difference in absorption at 257 mμ compared with control solution without plastics. The results were plotted after Langmuir's equation of monolayer adsorption as shown in Fig. 1. Plots for the adsorption between two polymers (polystylene and polyvinyl chloride) and butylparaben deviated from the equation.

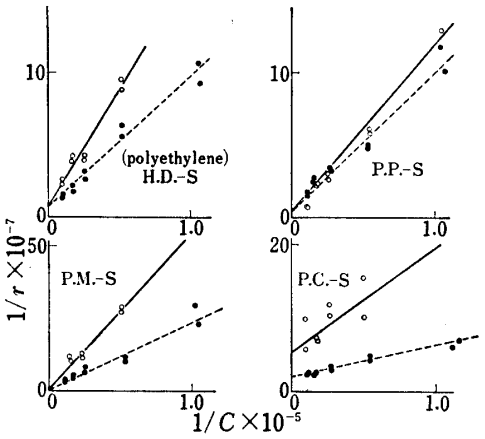

Fig. 1. Langmuir's Adsorption Isotherm
r=butylparaben (mole)/g plastics
C=conc. of free butylparaben (M)
incubation: —○—=100°
—●—=40°

Effects of pH on Adsorption of Drugs to Plastics

Pieces of polyvinyl chloride (P.V.C.-B_1) and polyethylene (L.D.-B) were incubated at 100° for 60 min in butylparaben solutions at various pH's, and adsorption was measured. The percentage adsorption varied depending on the composition of buffer solutions used,[11]

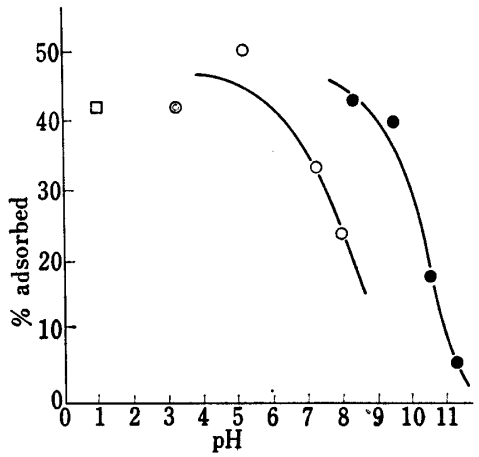

Fig. 2. Effect of pH on Adsorption of Butylparaben to Polyvinyl Chloride (P.V.C.-B_1)

concentration of butylparaben=3×10^{-5}M
incubation=100°, 60 min
buffer components:
—□—: HCl-KCl (pH 1.1)
—◎—: HCl-$NaCH_3CO_2$ (pH 3.2)
—○—: NaH_2PO_4-Na_2HPO_4 (pH 5.2, 7.4, 8.0)
—●—: NH_4OH-NH_4Cl (pM 8.3, 9.3, 10.5, 11.3)
μ=0.2 pH was adjusted at 25°.

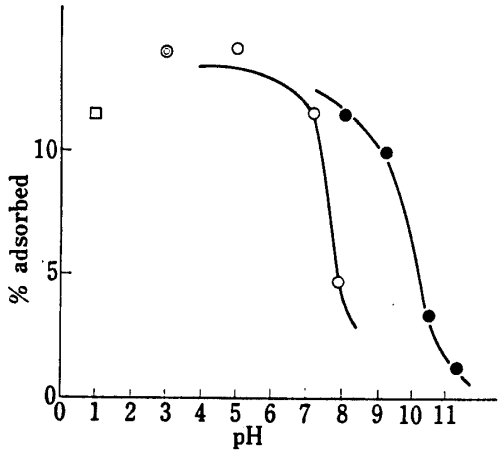

Fig. 3. Effect of pH on Adsorption of Butylparaben to Polyethylene (L.D.-B)

concentration of butylparaben=3×10^{-5}M
incubation=100°, 60 min
buffer components:
—□—: HCl-KCl (pH 1.1)
—◎—: HCl-$NaCH_3CO_2$ (pH 3.2)
—○—: NaH_2PO_4-Na_2HPO_4 (pH, 5.2, 7.4, 8.0)
—●—: NH_4OH-NH_4Cl (pH 8.3, 9.3, 10.5, 11.3)
μ=0.2 pH was adjusted at 25°.

11) P. Speiser, *Pharm. Acta Helv.*, **43**, 693 (1968).

however it is apparent from the Figs. 2 and 3, that butylparaben was adsorbed more extensively to the plastics at lower pH region.

Effect of Counter-ion on Adsorption of Benzalkonium Chloride to Polyethylene

Adsorption of benzalkonium chloride to polyethylene (H.D.-S) was measured in the presence or absence of ammonium thiocyanate at the concentration of 0.05%. As shown in Table III, adsorption was greatly enhanced in the presence of ammonium thiocyanate.

Table III. Effect of Counter-ion on Benzalkonium Chloride Adsorption to Polyethylene (H.D.-S)

	Control	with 0.05% NH_4SCN
Adsorption	14.4%	37.1%

concentration of benzalkonium chloride: 100 μg/ml
buffer: pH 7.4, M/15 phosphate buffer (μ=0.2)

Effect of Temperature on Drug-Plastics Interaction

Possible effects of temperature during storage period was studied by incubating plastic pieces in solutions of parabens and other drugs at 40° for 4 days. The results were compared with the ones at 100° for 30 min. (Table IV). It is clear from the table that the adsorption at 40° is generally higher than or comparable to that at 100°. Since in Langmuir's equation, n and k express capacity and intensity of binding, respectively, the product of n and k may represent the degree of binding.[12] The $n \times k$ values at 40° and 100° are listed in Table V, the values at 40° being always higher than those at 100°.

Table IV. Effect of Temperature on Adsorption of Durgs to Plastics[a] (% adsorbed)

Compounds[b),c)]	P.E.(H.D.-S)		P.P.-S		P.C.-S		P.M.-S		P.S.-S	
	100°	40°	100°	40°	100°	40°	100°	40°	100°	40°
Methylparaben	1.5	0.6	1.0	0.4	2.3	4.8	0.1	1.0	0.5	0
Ethylparaben	0	1.2	0	0.2	0	5.9	0	0.8	0	0.3
Propylparaben	1.5	1.5	3.6	2.4	0.3	1.4	0.1	2.9	0.3	2.8
Butylparaben	3.1	6.6	4.2	5.7	2.7	7.8	4.5	6.5	0	2.1
Benzylparaben	9.0	13.6	10.1	4.3	4.4	4.4	4.2	10.8	3.7	3.3
Benzalkonium chloride	14.4	28.6	2.6	9.0	6.0	14.2	0.8	4.9	1.7	2.4
Benzethonium chloride	11.8	4.9	7.7	12.6	6.0	12.0	2.1	24.4	3.0	12.4

a) incubation: 100°=30 min, 40°=4 days
b) concentrations: parabens (3×10^{-5}M), benzalkonium chloride (0.01g/liter) benzethonium chloride (3×10^{-5}M)
c) buffer: pH 7.4 M./15 phosphate buffer (μ=0.2)

Table V. Comparison of $n \times k$ Values in Adsorption of Butylparaben to Plastics ($\times 10^4$)

Temperature	P.E.(H.D.-S)	P.P.-S	P.M.-S	P.C.-S
40°	11.2	10.1	4.24	24.3
100°	6.34	9.25	1.85	7.03

12) M. Tabachinick and N.A. Giorgio, *Arch. Biochem. Biophys.*, **105**, 563 (1964).

Change in Adsorption due to Addition of Propylene Glycol into Drug Solution

Adsorption of drugs to plastics were measured in the presence and absence of propylene glycol at the concentration of 30%. As shown in Table VI, the addition resulted in less adsorption.

Table VI. Effect of Propylene Glycol[a] on Adsorption[b] of Drugs to plastics (% adsorbed)

Compounds[c),d)]	Polyethylene (L.D.-B)		Polyethylene (H.D.-B)		Polypropylene (P.P.-B)		Polyvinyl chloride (P.V.C.-B_1)		Polyvinyl chloride (P.V.C.-B_2)	
	CONT.	+P.G.[a)]	CONT.	+P.G.	CONT.	+P.G.	CONT.	+P.G.	CONT.	+P.G
Methylparaben	0	0	0	2.0	0	0.4	2.7	0	8.0	—
Ethylparaben	0.2	0.6	0	0	3.6	0	5.0	0	0	—
Propylparaben	4.2	1.7	3.5	1.2	3.8	1.0	14.6	0.2	11.9	—
Butylparaben	9.2	5.4	4.0	0.7	4.2	0	30.6	1.2	22.8	—
Benzylparaben	9.6	5.5	5.8	0	4.5	0.9	31.5	6.4	21.6	—
Benzalkonium chloride	8.5	1.2	33.3	2.4	20.7	0	67.8	3.6	59.4	2.4
Benzethonium chloride	5.3	4.2	8.8	3.3	10.5	1.6	34.2	5.7	36.7	—

a) amount of propylene glycol=30 ml in 100 ml of test solution
b) incubation=100°, 30 min
c) concentrations=parabens (3×10^{-5}M), benzalkonium choloride (0.01g/liter) benzethonium chloride (3×10^{-5}M)
d) buffer components=pH 7.4, M/15 phosphate buffer (μ=0.2)

Discharge of Adsorbed Butylparaben

When previously adsorbed butylparaben was discharged from polyvinyl chloride, remarkable difference was observed with change in temperature. As shown in Fig. 4, at 100°, 48.6% of butylparaben adsorbed to polyvinyl chloride was discharged, while discharge of the drug at 40° was only 7.2%. In the case of polyethylene, difference of the amount of released butylparaben at two temperatures was less than the case of polyvinyl chloride.

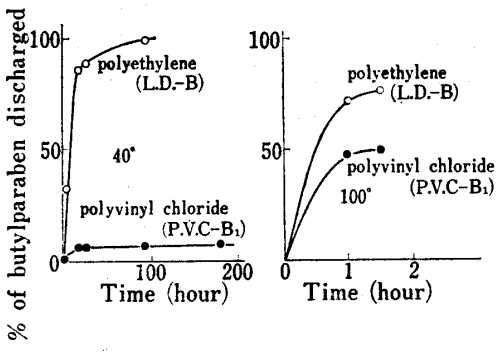

Fig. 4. Discharge of Butylparaben from Plastics

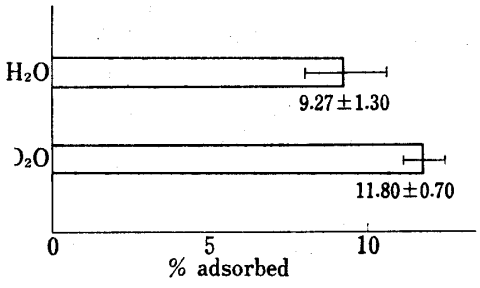

Fig. 5. Effect of D_2O on Adsorption of Benzylparaben to Polyethylene (H.D.-S)

concentration of benzylparaben=3×10^{-5}M
incubation=40°, 4 days

Effect of Deuterium Oxide on Adsorption of Butylparaben to Polyethylene

Adsorption of butylparaben to polyethylene (H.D.-S) was measured in deuterium oxide or H_2O solution. More adsorption was observed in D_2O than H_2O solution. (Fig. 5)

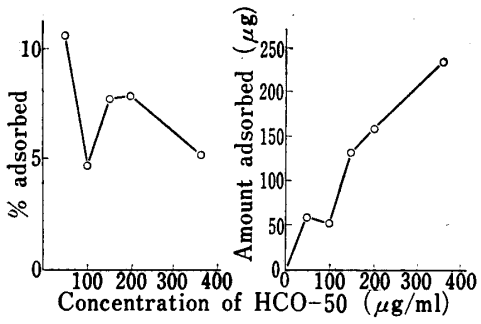

Fig. 6. Adsorption of HCO-50 to Polyethylene (L.D.-S)
incubation: 40°, 4 days

Adsorption of HCO-50, a non- Ionic Surface-active Agent

Adsorption of HCO-50 to various plastics was investigated as a function of initial concentration of the surface-active agent. Adsorption to polyethylene (L.D.-S), shown in Fig. 6, revealed that maximum adsorption occured near the region of the critical micelle concentration of HCO-50. Comparison have been made with the effect of propylene glycol on the adsorption behavior and, as is seen from Table VII, reduction in adsorption like butylparaben was noted particularly in the high concentration range of the solvent.

Table VII. Effect of Propylene Glycol on Adsorption of HCO-50 to Polyethylene (L.D.-B) (% adsorbed)

Concentration of propylene glycol	Concentration of HCO-50 (μg/ml)			
	50	100	200	360
0%	10.56	4.70	7.82	5.17
5%	6.30	4.50	5.86	4.51
10%	3.46	0.88	0.99	0
30%	0	0	0	0

incubation: 40°, 4 days

Disscussion

Parabens with longer carbon chain in alcohol moiety were more readily adsorbed to plastics (Table II). Overall adsorption of butylparaben to plastics is related apparently well with Langmuir's equation of adsorption isotherm though there was a strong evidence suggesting that the compound was diffused into plastics (Fig. 1). Furthermore, adsorption of butylparaben was high in the pH range where the compounds was in unionized form (Figs. 2. and 3), and stronger interaction was noted in the presence of the thiocyanate ion[13] at the hydrophobic interface of polyethylene in water. Addition of propylene glycol to butylparaben solution or displacement of the medium with D_2O resulted in marked decrease of the adsorption (Table VI). These findings suggest that hydrophobic interaction plays a major role in adsorption of parabens to plastics as in the binding of drugs to plasma protein.[14]

Efficacy of a drug generally depends on the concentration of its free (*i.e.* unbound) form. Thus, it is probable that the availability of a drug may be reduced when kept in a plastic container because of migration of drugs into and through the plastics. Such reduced availability of a drug may be prevented by the addition of an appropriate solvent which suppresses the adsorption as shown in Table VI.

Studies on the effect of temperature on adsorption revealed that the adsorption was higher at low temperature of 40° than at the high temparature of 100°. Possible configuration change on plastics at various temperatures should be considered together with the change of drug–plastic intraction. In the case of polyvinyl chloride, the percentage of both adsorption

13) W. Scholtan, *Arzneim-Forsch.*, **18**, 505 (1968).
14) P.S. Prickett, H.L. Murray and N.H. Mercer, *J. Pharm. Sci.*, **50**, 316 (1961).

and desorption increased at high temperature. Furthermore, only a portion of the drug previously adsorbed at high temperature (100°) was discharged at lower temperature (40°). These findings suggest that the drug-binding sites of this plastics may be hidden in the structure at low temperature and unfolded to the surface by configuration change at high temperature.

The nature of adsorption of HCO-50 to the plastics appears to be somewhat different from that of parabens. HCO-50 was non-selectively adsorbed to all the plastics studied (Table II) and as shown in Fig. 6, maximum adsorption occured near the region of the critical micelle concentration of HCO-50. However like butylparaben, adsorption of HCO-50 decreased in the presence of propylene glycol (Table VII). It may be possible to speculate that this phenomenon depends on the miceller formation or configuration change of HCO-50, but, studies are necessary for further analyses.