Sorption of Labeled Chlorobutanol-¹⁴C by Nylon and Polyethylene

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Abstract ☐ Labeled chlorobutanol-¹⁴C was synthesized and the degree of sorption by polyamide (Nylon 6,6) and polyethylene was determined using scintillation spectroscopy. Sorption studies were conducted at four concentrations and temperatures and from these experiments the magnitude and rate of sorption were determined, as well as the standard chemical potentials, heats of sorption, and standard entropy values. The sorption data were applied to the Freundlich and Langmuir absorption isotherms with some degree of success.

Keyphrases ☐ Chlorobutanol-¹⁴C—synthesis ☐ Polyamide, polyethylene sorption—chlorobutanol-¹⁴C ☐ Sorption rates, nylon, polyethylene—chlorobutanol-¹⁴C ☐ Temperature effect—nylon, polyethylene sorption, chlorobutanol-¹⁴C ☐ Scintillometry, liquid—analysis

With the recent advent of unit-dose drug distribution systems in hospitals, plastics are being used at an increasing rate for packaging various dosage forms. Several investigators (1–8) have shown that over extended periods of time preservatives or drugs can be sorbed from solution by plastic materials. Marcus *et al.* (3) observed that nylon syringes removed parahydroxybenzoic acid, methyl and propylparaben, sorbic acid, and 4-chloro-3-methyl phenol from solution. A later study by Kim (4) demonstrated that nylon syringes can remove such drugs as benzoic acid, *m*-hydroxybenzoic acid, *p*-aminobenzoic acid, and salicyclic acid from solution.
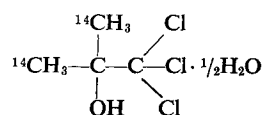
A significant lowering of the concentration of an antibacterial preservative due to sorption by the plastic container could subject the ophthalmic solution to possible bacterial contamination. Since mathematical relationships that predict the degree to which drugs are sorbed by plastics have not been proposed, it is necessary that such interactions be investigated for each drug plastic combination.

Since many ophthalmic preparations are packaged in plastic containers and chlorobutanol is a commonly used preservative for these solutions, it was the purpose of this study to determine the degree of sorption of labeled chlorobutanol-¹⁴C by polyamide (Nylon 6,6) and polyethylene as a function of time, temperature, and concentration. In view of the analytical limitations in detecting minute quantities of chlorobutanol, liquid scintillation spectroscopy was used as the method of analysis.

EXPERIMENTAL

Synthesis of Labeled Chlorobutanol-¹⁴C—Labeled chlorobutanol-¹⁴C was prepared by the addition of equimolar quantities of ace-

tone-1, 3-¹⁴C[1] and chloroform, using 5% alcoholic potassium hydroxide solution as a catalyst. The procedure of Fishburn (9) was followed except that the reaction vessel was designed to prevent volatile labeled materials from escaping. Equimolar quantities of acetone[2] and chloroform were reacted to provide a higher yield based on acetone. The structure of chlorobutanol with the ¹⁴C indicated appears as follows:

$$\begin{array}{c} {}^{14}CH_3 \quad Cl \\ | \quad \diagup \\ {}^{14}CH_3\text{—}C\text{—}C\text{—}Cl \cdot {}^1\!/_2 H_2O \\ | \quad \diagdown \\ OH \quad Cl \end{array}$$

The synthesized chlorobutanol-¹⁴C and the mean melting point range of four determinations (uncorrected) was 78.2–79.5°. In order to verify the purity of the synthesized compound, the mean melting point ranges experimentally determined for chlorobutanol, USP was found to be 79.5–80.5° (uncorrected) and was in agreement with a sample prepared by mixing equal quantities of the synthesized chlorobutanol-¹⁴C and chlorobutanol USP (uncorrected) 79.2–80.6°.

The method of Fishburn (9) was used to determine the radiochemical purity indirectly by dissolving a known quantity of unlabeled chlorobutanol USP in the acetone-¹⁴C–chloroform mixture remaining from the distillation of the synthesized chlorobutanol-¹⁴C and containing about 4.5 mc. of acetone-¹⁴C. The radiochemical purity of the synthesized product was 98.6% when compared to the counting activity of the purified unlabeled chlorobutanol.

Method of Analysis—The measurement of radioactivity, expressed as counts per minute, was determined by the liquid scintillation method using a scintillation spectrometer.[3] The activity, more correctly designated as disintegrations per minute, was determined by the internal standardization method for each sample assayed in this study using a sample of standardized toluene-¹⁴C having a specific activity of 1.77 × 10⁶ μc. The counting error was determined using the formula,

$$Y = 2 \sqrt{\frac{N(s + bg)}{t(s + bg)} + \frac{N_{bg}}{t_{bg}}}$$

where Y is the counting error at the 95% confidence level, $N(s + bg)$ the counts per minute of the sample and the background, $t(s + bg)$ the counting time of the sample and the backbround, N_{bg} the counts per minute of the background only, and t_{bg} the counting time of the background only. The counting error ranged from ±1.40% for the most dilute solution to an error of ±0.77% for the most concentrated solution of chlorobutanol-¹⁴C.

General Procedure—A known quantity of chlorobutanol-¹⁴C was diluted to a specific concentration, adjusted to pH 3.9 with 10% HCl, pipeted into culture tubes[4] supplied with plastic screw caps that were previously treated by the investigator with spray Teflon. The tubes and their contents were placed in a constant-temperature water bath. After allowing sufficient time for the solution to equilibrate with the temperature of the water bath, polyamide[5] strips

Table I—Effect of Concentration on the Sorption of Labeled Chlorobutanol-^{14}C[a]

0.052% (w/v)

Nylon hr.	Nylon Sorbed, %	Polyethylene hr.	Polyethylene Sorbed, %
13.0	5.7	13.0	1.0
23.8	7.9	23.8	1.5
35.5	9.8	35.5	2.2
47.8	9.9	47.8	3.2
71.8	11.8	71.8	3.0
95.8	13.2	95.8	4.5
119.5	13.2	119.5	4.2
144.0	13.6	144.0	4.6
165.0	13.6	165.0	5.2

0.13% (w/v)

Nylon hr.	Nylon Sorbed, %	Polyethylene hr.	Polyethylene Sorbed, %
2.0	3.2	2.0	0.9
8.0	6.9	8.0	2.3
11.0	7.9	11.0	1.5
24.0	9.7	24.0	2.8
32.0	10.8	32.0	3.8
42.0	12.2	42.0	5.1
48.0	12.5	48.0	5.9
56.0	13.3	56.0	5.3
68.0	14.8	68.0	4.8
80.0	15.5	80.0	6.7
128.0	17.0	—[b]	—[b]
161.0	16.9	161.0	9.0

0.27% (w/v)

Nylon hr.	Nylon Sorbed, %	Polyethylene hr.	Polyethylene Sorbed, %
10.0	6.5	10.0	4.7
21.5	8.6	21.5	4.8
33.5	10.0	33.5	5.8
46.5	11.8	46.5	6.2
58.0	11.8	58.0	7.2
68.5	12.6	68.5	7.6
94.5	12.6	94.5	8.5
105.0	12.9	105.0	8.1
117.0	13.9	117.0	8.3
141.0	14.2	141.0	9.0
		164.0	9.0

0.52% (w/v)

Nylon hr.	Nylon Sorbed, %	Polyethylene hr.	Polyethylene Sorbed, %
3.5	3.1	b	b
10.0	4.7	10.0	3.3
21.5	7.4	21.5	4.0
31.5	7.9	31.5	4.6
42.0	9.2	42.0	4.6
58.0	10.4	58.0	4.4
74.5	11.4	74.5	5.1
93.0	11.7	93.0	6.0
114.5	11.7	114.5	6.3
151.5	11.9	151.5	6.1

[a] Each of the following values is the mean of three determinations at the indicated concentration and 38 ± 0.1°. [b] Not determined.

measuring 10.001 × .635 × .305 cm. (3.938 × 0.25 × 0.012 in.), previously washed and dried according to the method of Kapadia (5) and weighing from 0.3054 to 0.3929 g. were immersed in solutions of chlorobutanol-^{14}C and replaced in the constant-temperature bath. Aliquots of 100 λ were withdrawn from the tubes at varying time intervals only after the sorption equilibrium of the chlorobutanol-^{14}C occurred with the nylon. The tubes containing the aliquots were then placed in the scintillation solution[6] and counted.

Polyethylene[7] strips, weighing from 1.0703 to 1.5357 g. and measuring 10.001 × .476 × 3.05 cm. (3.938 × 0.188 × 0.12 in.) were treated in the same manner as described above for nylon. However, in order to retain the additives that could be removed by the washing procedure employed with nylon, the polyethylene strips were washed in 50% (v/v) ethanol solution for 10 hr., rinsed and dried in a constant-temperature oven at 63 ± 1.0°. A control solution subjected to the same conditions but without the plastic was included and the difference between the amount of chlorobutanol-^{14}C in the control solution and the amount left in the solution was considered to be the quantity of chlorobutanol sorbed by the plastics.

Solutions of chlorobutanol at concentrations of 0.052, 0.13, 0.27, and 0.52% were prepared with distilled water and studied at a constant temperature of 38 ± 0.1°. Enough solution of chlorobutanol at 0.27% was prepared to continue the sorption study at 34.3 ± 0.7, 43.3 ± 0.1, and 50.8 ± 0.2°.

Test for Hydrolysis of Chlorobutanol.—Studies of chlorobutanol hydrolysis have been performed by many investigators indicating the stability of the molecule at pH ranges below 5.0 (11, 12). A simple volumetric titration was performed to verify that the chlorobutanol was not hydrolyzed under the experimental conditions of this study. The procedure reported by McRae (13) was followed for each sample using a 0.05 N silver nitrate solution for titration against chloride ion. No end point was detected with any of the samples tested, indicating no measurable hydrolysis. Excess silver nitrate solution was added to each sample to detect the formation of any flocculent precipitate of silver chloride below the quantity nec-

essary for visual observation of the pink end point; no precipitate was observed.

RESULTS

Effect of Concentration on Sorption.—In Table I the percent sorption of chlorobutanol as a function of concentration and time is reported. As the concentration of chlorobutanol is decreased, the percent of chlorobutanol sorbed by the nylon and polyethylene[7] increased. This was true for all but the most dilute solution (0.052%). The data indicates that the sorption of chlorobutanol at different concentrations appears to reach a saturation value and can be represented by the empirical Freundlich equation,

$$\frac{x}{m} = kC^{1/n}$$

where x is the grams of solute adsorbed per gram of adsorbent, m and C is the residual concentration of the solute in solution at equilibrium; k and $1/n$ are constants determined by the conditions of the experiment. For graphing purposes the equation can be put in the logarithmic form:

$$\log \frac{x}{m} = \log k + 1/n \log C$$

Figure 1 illustrates a Freundlich plot of the data obtained from the sorption of chlorobutanol-^{14}C by nylon at each concentration.

Another relationship often used to express sorption data is the Langmuir equation which is based on the theory that the solute molecules are adsorbed on active sites of the solid to form a layer one molecule thick and is represented as follows:

$$q = \frac{SkC}{1 + kC}$$

where q is the weight in milligrams of solute adsorbed per gram of adsorbent, C is the residual concentration of the solute in milligrams per 100 ml. of solution at equilibrium, S is the saturation constant, and k is a mathematical constant. S is the theoretical amount of solute which the plastic would sorb if all the sites were saturated (6). The equation can be inverted to produce a straight line relationship and is written as: $1/q = (1 + kC/SkC)$ and then in
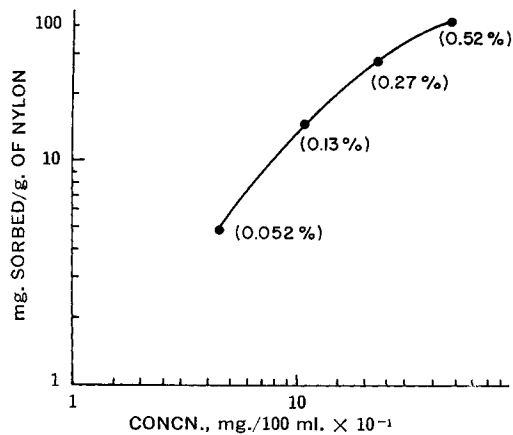
Figure 1—*Freundlich sorption isotherm of labeled Chlorobutanol-^{14}C in polyamide at 38.7 ± 0.1°.*

graph form: $1/q = (1/SkC) + (1/S)$. If $1/q$ is plotted against $1/C$, the slope is equal to $1/Sk$ and the y intercept is $1/S$.

Figures 2 and 3 show that when the degree of chlorobutanol sorption by the plastics at each concentration is applied to the Langmuir isotherm the theoretical straight line fits the points for nylon and polyethylene except at the most dilute concentration (0.052%). This inconsistency was reexamined under the same conditions to determine if the departure from ideality was due to experimental error. The same variation also exists at this dilute concentration. The saturation constant (S) as determined by the method of least squares, only for the linear portion of the curves, shown in Figs. 2 and 3, is 108 mg. of chlorobutanol per gram of nylon and 18.9 mg. of chlorobutanol per gram of polyethylene.

Effect of Temperature on Sorption.—Table II shows the degree of sorption, expressed as percent sorption at each temperature studied at various time intervals. As the temperature increased the rate and percent of sorption for chlorobutanol in nylon and polyethylene increased. This is contrary to many drug-plastic interactions; an increase in temperature usually results in an increase in sorption rate and a decrease in percent sorption. However, other exceptions to this phemomena have been reported by Autian (14).

To more fully understand the magnitude of chlorobutanol sorption with the plastics, the standard chemical potential is used as a quantitative measure to express the tendency of the solute to be sorbed (6). Assuming the activity of chlorobutanol to be equal to the concentration, the standard chemical potential can be mathe-
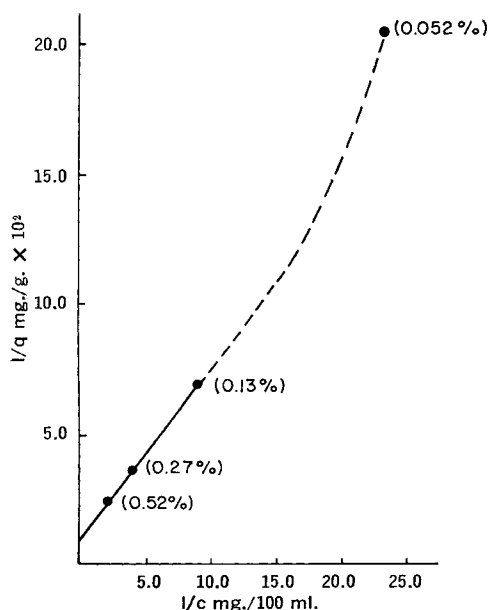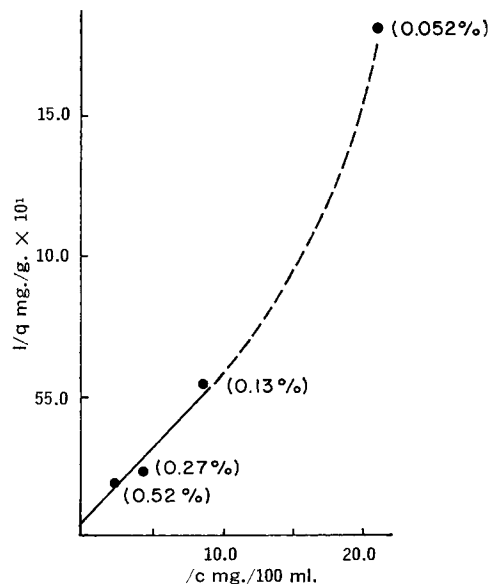

Figure 3—*Langmuir adsorption isotherm of labeled chlorobutanol-^{14}C in polyethylene at 38.7 ± 0.1°.*

matically interpreted by the equation:

$$-\Delta u^0 = RT \ln \frac{C_s}{C_l}$$

where u^0 is the chemical potential of the solute to move from its standard state in one phase to the standard state in another phase, R is the universal gas constant, 1.987 cal./mole degree, T, the absolute temperature, C_s, the concentration of solute in the plastic at equilibrium and is expressed as moles/kg. of plastic, and C_l, the concentration of the solute in the solvent at equilibrium and is expressed as moles/l. of solvent. The standard chemical potentials for chlorobutanol in nylon and polyethylene at various temperatures are listed in Table III.
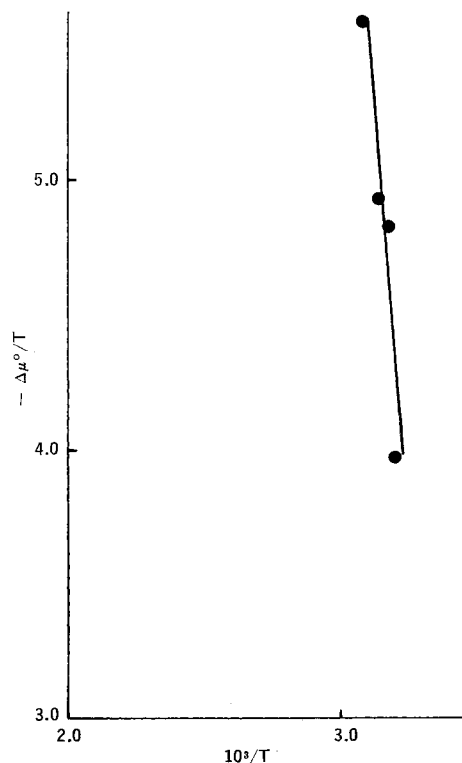

Figure 2—*Langmuir adsorption isotherm of labeled chlorobutanol-^{14}C polyamide at 38.7 ± 0.1°.*

Figure 4—*Heat of sorption for 0.27% (w/v) chlorobutanol in polyamide.*

Table II—Effect of Temperature on the Sorption of Labeled Chlorobutanol-^{14}C[a]

34.3 ± 0.7°C				38.7 ± 0.1°C			
Nylon		Polyethylene		Nylon		Polyethylene	
hr.	Sorbed, %	hr.	Sorbed, %	hr.	Sorbed, %	hr.	Sorbed %,
10.0	1.9	10.0	0.3	10.0	6.5	10.0	4.7
21.5	3.6	21.5	0.9	21.5	8.6	21.5	4.8
33.5	4.3	33.5	1.6	33.5	10.0	33.5	5.8
46.5	4.6	46.5	1.7	46.5	11.8	46.5	6.2
58.0	5.7	58.0	2.4	58.0	11.8	58.0	7.2
68.5	7.9	68.5	2.9	68.5	12.6	68.5	7.6
94.5	7.6	94.5	2.9	94.5	12.6	94.5	8.5
105.0	7.6	105.0	3.4	105.0	12.9	104.0	8.1
117.0	9.1	117.0	3.8	117.0	13.9	117.0	8.3
141.0	9.3	141.0	4.4	141.0	14.1	141.0	9.0
		164.0	4.0			164.0	9.0

43.3 ± 0.1°C				50.8 ± 0.2°C			
Nylon		Polyethylene		Nylon		Polyethylene	
hr.	Sorbed, %	hr.	Sorbed, %	hr.	Sorbed, %	hr.	Sorbed, %
4.5	3.2	4.5	1.7	4.5	6.2	4.5	4.0
12.0	8.1	12.0	4.8	12.0	11.8	12.0	7.9
19.5	9.6	19.5	5.1	19.5	13.1	19.5	7.5
26.0	11.5	26.0	6.8	26.0	15.1	26.0	10.9
38.0	13.2	38.0	7.5	38.0	16.4	38.0	11.3
50.0	15.6	50.0	8.4	50.0	16.1	50.0	11.6
59.5	14.5	59.5	10.6	59.5	17.2	59.5	12.3
72.0	14.5	72.0	8.8	72.0	16.9	72.0	12.9
89.0	14.6	89.0	9.2	89.0	17.2	89.0	13.2
		107.0	10.3			107.0	12.7

[a] Each of the following values are the mean of three determinations at the indicated temperatures and 0.27% (w/v).

According to Kapadia (5) the heat of sorption or the difference in enthalpy between chlorobutanol in solution and chlorobutanol sorbed by the plastic can be obtained by the following relationship:

$$\frac{-\Delta u^0}{T} = \frac{\Delta H}{T} + C$$

All terms are as previously defined and assuming that the heat of sorption, ΔH, remains constant over a small temperature range, a plot of $-\Delta u^0/T$ against $1/T$ yields a straight line and the slope equal to ΔH. The standard heats of sorption for chlorobutanol in polyamide and polyethylene was calculated by the method of least squares and are shown in Table III. The plots of $-\Delta u^0/T$ against $1/T$ for each plastic are presented in Figs. 4 and 5. The entropy of the system, ΔS, is defined as the molar energy per degree of absolute temperature which is unavailable for work and is obtained from the relationship, $\Delta u^0 = \Delta H - T\Delta S$. The standard entropy values are also included in Table III.

DISCUSSION

The three sites in nylon that account for its polar characteristics are the amide linkage and to a lesser extent the amine group at one end of a long chain and the carboxyl group at the other end of the chain (14).

The magnitude and rate of sorption of chlorobutanol was in-

fluenced by concentration and temperature. In nylon a 11.9% lowering of chlorobutanol concentration occurred at 0.52% (w/v) and 38.7 ± 0.1° and would probably decrease the ability of chloro-

Table III—Standard Chemical Potential, Heats of Sorption, and Entropies of Sorption for Chlorobutanol in the Nylon and Polyethylene at Various Temperatures

	Nylon		Polyethylene
Temperature, °C.		$\Delta\mu^{0a}$ kcal./mole	$\Delta\mu^{0a}$ cal./mole
34.3		−1.22	+0.156
38.7		−1.51	−0.377
43.3		−1.56	−0.429
50.8		−1.80	−0.610
$\Delta H = -1.10$ kcal./mole			$\Delta H = -66.9$ cal./mole
$\Delta S = +1.33$ cal./mole deg.			$\Delta S = +1.03$ cal./mole deg.

[a] $\Delta\mu^0$ = Standard chemical potential, ΔH = standard heat of sorption, ΔS = standard entropy of sorption.
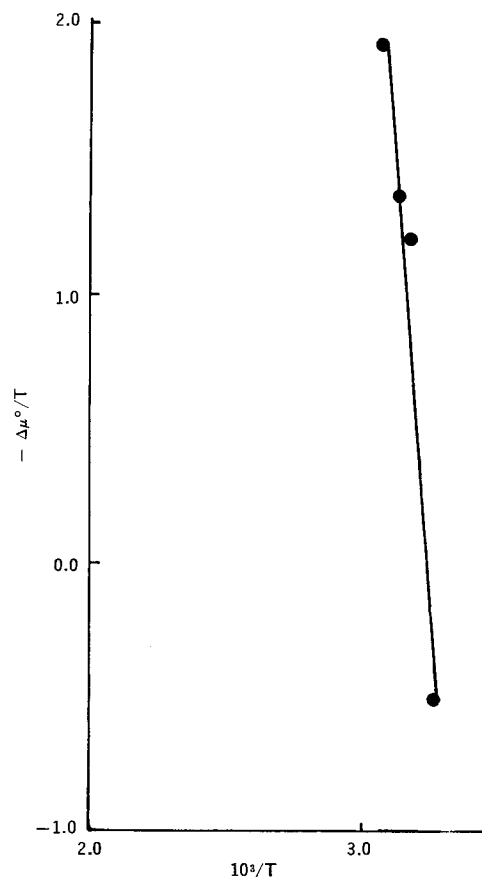

Figure 5—Heat of sorption for 0.27% (w/v) chlorobutanol in polyethylene.

butanol to preserve an ophthalmic solution, should the container be constructed of nylon resin. The quantity of chlorobutanol sorbed by polyethylene was less than in the case of nylon.

A Freundlich plot of the data did not conform to the theoretical straight line expected from the Freundlich expression for sorption by nylon or polyethylene. According to Mantell (16) the Freundlich equation is purely empirical and cannot cover the entire isotherm range. When log x/m is plotted against log C, a short portion of the curve appears linear, while the longer portions of the curve appear curved, generally concave to the log C axis. Consequently, the isotherm shown in Fig. 1 is restricted to the expression and comparison of sorption data within a narrow range.

In contrast to the Freundlich isotherm, the Langmuir isotherm expressed as $y = mx + b$ states that at infinite concentration there is a definite limit to the amount sorbed. This value is the intercept, $1/S$, where S is referred to as the saturation constant. As mentioned the most dilute concentration (0.052%) did not correspond to the expected value for a Langmuir isotherm and repeating the experiment only verified the original results suggesting a more complex mechanism of sorption. This inconsistency has been reported by Berg (8), who investigated the interaction of a group of low molecular weight organic acids with the polyamide and found that formic and butyric acids did not produce a straight line relationship for a Langmuir isotherm.

As the temperature is increased the percent of chlorobutanol sorbed increased. Since this is contrary to most drug-plastic interactions, additional research data is necessary to support an acceptable mechanism of sorption within the plastic under the conditions described in this paper.

The standard chemical potential, as reported in Table III, for chlorobutanol sorption by nylon and polyethylene increased as the temperature increased. A negative standard chemical potential value resulted for all the data from 0.377 cal./mole to 1.80 Kcal./mole indicating a spontaneous sorption process. The heats of sorption for chlorobutanol sorption by nylon (-1.10 Kcal/mole) and polyethylene (-66.9 cal./mole) implies that very low bond energies exist between chlorobutanol and the plastic and are on the order of van der Waals forces.

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