Adsorption of Drugs on Microcrystalline Cellulose Suspended in Aqueous Solutions

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The adsorption of various drugs on microcrystalline cellulose (MCC) suspended in aqueous solutions was investigated. Adsorption of diphenhydramine, chlorpheniramine, isoniazid, and p-aminobenzoic acid was very slight or negligible, whereas the adsorption of four phenothiazine derivatives (PTZs) was considerable, and that of acrinol was quite large. Except for chlorpromazine sulfoxide, adsorption isotherms for three PTZs and acrinol were all of the Freundlich type. Based on the Freundlich constants, k and 1/n, the adsorbability of those drugs on MCC was in the order acrinol ≫ chlorpromazine > trifluoromazine > promazine. The slight differences in 1/n for those drugs suggest differences in the adsorption mechanisms. Further it was observed that the adsorption increases with increase of pH, and decreases with increase of ionic strength. In addition, the pH values for MCC suspended solutions decrease gradually with the addition of neutral salts. Thus, in the adsorption of PTZs and acrinol on MCC, the ion-exchange mechanism appeared to play an important role, but adsorption due to non-electrostatic forces should also be appreciable. Marked adsorption of acrinol on MCC can be interpreted in terms of the presence of polar groups capable of hydrogen-bond formation, and the coplanar arrangement of the acridine ring.

Keywords—microcrystalline cellulose; phenothiazine derivative; acrinol; adsorption isotherm; Freundlich-type; adsorption mechanism
without further purification. Four kinds of phenothiazine derivatives (PTZs) were used; chlorpromazine (CPZ)-HCl and chlorpromazine sulfoxide (CPZSO)-HCl were supplied by Yoshitomi Pharmaceutical Co., Ltd., promazine (PZ)-HCl by Shiratori Pharmaceutical Co., Ltd., and triflupromazine (TFPZ)-HCl by Nippon Squibb Co., Ltd. Ethacridine lactate monohydrate (acrinol) was purchased from Wako Pure Chemical Industry Co., Ltd. Two antihistaminics, diphenhydramine (DPH) and chlorpheniramine maleate (CPM), were supplied by Tokyo Kasei Kogyo Co., Ltd. and Iwaki Pharmaceutical Co., Ltd., respectively. Isoniazid (INAH) and p-aminobenzoic acid (PABA) were obtained from Shionogi Pharmaceutical Co., Ltd. and Wako Pure Chemical Industry Co., Ltd., respectively. Except for PABA, all drugs used in this study were of either JP or specific reagent grade, and were used without further purification. PABA was purified twice from methanol/water. All other chemicals were of specific reagent grade and were used as received.

Adsorption Studies — Analytical Procedure: Drug concentrations were determined spectrophotometrically on a Hitachi 100-60 spectrophotometer. The analytical wavelengths (nm) used in the spectrophotometric determination of the drugs were as follows: PZ (251), CPZ (254), TFPZ (254). CPZSO (239), acrinol (269), DPH (230), CPM (261), INAH (261), and PABA (264). The Ultraviolet (UV) spectra of PZ, CPZ, TFPZ, and acrinol were independent of pH in the range of pH 2—8, because of their strong basicity. Thus, pH adjustment within pH 2—8 was not necessary in spectrophotometry.

Adsorption Isotherms: The desired quantity of 5 × 10⁻³ or 2 × 10⁻² mol/l stock solution of a drug was added to a mixture of 24 ml of phosphate buffer solution and a weighed amount of MCC (0.2 g for the acrinol-MCC system and 1.0 g for all other drug-MCC systems) in an amber 50 ml centrifugal tube with a glass stopper. Initial drug concentration ranged from 1 × 10⁻⁵ to 3.2 × 10⁻⁴ mol/l. Except for special adsorption experiments described below, the final pH, ionic strength, and volume (ml) were adjusted to 6.92, 0.04 and 25, respectively. The tubes were placed in a thermostatted incubator set at 15, 25, 35, or 45 °C, and shaken for 12-60 h. After the attainment of adsorption equilibrium, about 3-5 ml of the supernatant was taken and filtered through a membrane filter (0.45 μm, Millipore HV013NS). Control experiments, in which no drug was added, were done in parallel, and the filtrate was used as a reference solution. With or without dilution of the filtrate to a drug concentration of 0.5 × 10⁻⁵-2×10⁻⁵ mol/l, the concentration at equilibrium, [D]ᵦ, was determined by the above-mentioned procedure. Hence the adsorbed amount, [D]ᵦ, can be represented by Eq. 1,

\[ [D]ᵦ = ([D]ᵢ - [D]ᵦ)V/1000m \]  

where [D]ᵢ is the initial drug concentration (mmol/l), m the amount of the adsorbent (g), and V the volume of the drug-MCC suspension. Then [D]ᵦ is expressed in the unit of mmol/g MCC.

Effect of pH on Adsorption —— The effect of pH on the adsorption of PTZs and acrinol on MCC was studied in the range of pH 1.7—7.8 at 25 °C. Values of pH were adjusted by means of HCl-NaCl or NaOH-NaCl solutions, holding the ionic strength constant at I = 0.05. Initial drug concentrations were fixed at 2 × 10⁻⁵ mol/l for PTZs and 1.5 × 10⁻⁵ mol/l for acrinol. The magnitude of drug adsorbability to MCC was conventionally expressed as fraction bound (% = ([D]ᵦ/[D]ᵢ) × 100).

Effect of Ionic Strength on Adsorption —— The effect of ionic strength on the adsorption of CPZ on MCC was investigated at constant pH 6.92 at 25 °C. Ionic strength was adjusted by the addition of NaCl in the range of 0.01—0.52. Initial drug concentration was 2 × 10⁻⁵ mol/l, and the expression of the adsorbability was the same as that described above.

Cation-Exchange Ability of MCC —— The cation-exchange ability of MCC was examined simply by monitoring the pH of MCC suspended aqueous solutions (1 g/25 ml) upon addition of a neutral salt such as NaCl, KCl, CPZ·HCl, and acrinol (ethacridine lactate), using a precision pH meter (EA 510) equipped with a combined glass electrode (EA 125) (Metrohm Co., Ltd.).

Results and Discussion

Adsorption Isotherms

Figure 1 shows adsorption isotherms for PZ, CPZ, CPZSO, acrinol, and CPM at pH 6.92 and at 25 °C; the abscissa indicates the equilibrium drug concentration, and the ordinate shows the adsorbed amount of drug. As shown in Fig. 1, the adsorption of CPM on MCC was very slight, that of PTZs (PZ, CPZ, CPZSO) was considerable, and that of acrinol was quite large. Although the adsorption isotherms for DPH, INAH, PABA, and TFPZ on MCC are not shown in Fig. 1, significant adsorption was not found for the first three drugs, while for the last drug the adsorption was comparable with that of CPZ and the isotherm is omitted for clarity. Adsorption isotherms for three PTZs and acrinol appeared to be not of Langmuir type, but of Freundlich type. However, the isotherm for CPZSO was sigmoid and clearly
different from those for other PTZs. Though this type of adsorption is often seen in the cooperative binding of surfactants to protein and/or polymer,\(^3\) further analysis of the adsorption was not performed in this study.

The Freundlich type adsorption is described by Eq. 2, where \(x\) is the adsorbed amount of drug per unit weight of MCC (mmol/g), \([D]\), the equilibrium drug concentration (mol/l), and \(k\) and \(1/n\) are constants. Equation 2 is an empirical one, and the physicochemical meanings of those constants are not always clear, but it is likely that the former gives a rough measure of the relative adsorbent capacity for a given adsorbate, while the latter reflects the affinity of the adsorbate for the adsorbent.\(^4\) The logarithmic expression of Eq. 2 is:

\[
\log x = \frac{1}{n} \log [D] + \log k
\]

Thus, if a linear relation between \(\log x\) and \(\log [D]\) is obtained, the constants \(k\) and \(1/n\) are given by the values of the intercept and the slope, respectively. Figures 2 and 3 show Freundlich plots, according to Eq. 3, for the CPZ–MCC and acrinol–MCC systems at pH 6.92 and at various temperatures, respectively. In these plots data points are shown only for the adsorption system at 15 °C, for simplicity. Linear relations were obtained for all of the drug–MCC adsorption systems, and the intercept and the slope were calculated by linear regression analysis.

Freundlich constants thus obtained for various drug–MCC systems are summarized in Table I. As mentioned above, since the constant \(k\) may be a rough measure of the relative adsorbent capacity for a given adsorbate, it was considered that the greater the value of \(k\), the larger the adsorption of a given drug. Thus the magnitude of the adsorption of the present drugs on MCC is in the order,

\[
\text{acrinol} > \text{CPZ} > \text{TFPZ} > \text{PZ}
\]

regardless of the kind of MCC, PH-101 or PH-301. The rather strong adsorption of acrinol by MCC will be discussed later. It is interesting that the order of adsorption on MCC among three PTZs is different from that of hydrophobicity. That is, although TFPZ has the greatest hydrophobicity, its adsorption seems to be smaller than that of CPZ. Thus, it may be considered that although the hydrophobicity of the adsorbate is important as a driving force for the penetration into narrow inter-fiber space of the cellulose, the bulkiness of the
substituent at the 2-position (-CF₃ group for TFPZ) probably inhibits deep penetration. Furthermore the tendency of the value of k to decrease in all adsorption systems with increasing temperature might mean that the adsorption process is exothermic, as is the case for general adsorption systems.

As regards the kind of MCC, PH-101 is a standard grade, while PH-301 possesses a higher density and flow-ability. Differences between them appear mainly in the powder

<table>
<thead>
<tr>
<th>Drug</th>
<th>Freundlich constant</th>
<th>Temperature (°C)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>15   25  35  45</td>
</tr>
<tr>
<td>PZ</td>
<td>1/n 0.944 0.985 1.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>k 3.69 2.57 2.04</td>
<td></td>
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<tr>
<td>CPZ</td>
<td>1/n 0.744 0.775 0.780 0.805</td>
<td></td>
</tr>
<tr>
<td></td>
<td>k 9.12 7.67 6.17 5.13</td>
<td></td>
</tr>
<tr>
<td>TFPZ</td>
<td>1/n 5.68 0.647</td>
<td></td>
</tr>
<tr>
<td></td>
<td>k 5.68 0.647</td>
<td></td>
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<tr>
<td>Acrinol</td>
<td>1/n 0.563 0.580 0.637 0.626</td>
<td></td>
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<tr>
<td></td>
<td>k 30.1 21.8 16.8 12.8</td>
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<tr>
<th>Drug</th>
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<tr>
<td></td>
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<td>15   25  35  45</td>
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<tr>
<td>PZ</td>
<td>1/n 1.04</td>
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<tr>
<td></td>
<td>k 2.76</td>
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</tr>
<tr>
<td>CPZ</td>
<td>1/n 0.715 0.683 0.789</td>
<td></td>
</tr>
<tr>
<td></td>
<td>k 10.9 10.6 11.6</td>
<td></td>
</tr>
<tr>
<td>TFPZ</td>
<td>1/n 0.702</td>
<td></td>
</tr>
<tr>
<td></td>
<td>k 8.63</td>
<td></td>
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<tr>
<td>Acrinol</td>
<td>1/n 0.599</td>
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</tr>
<tr>
<td></td>
<td>k 17.4</td>
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a) Freundlich constant k is shown as $10^5$ times the value, in units of mmol/g MCC.
characteristics, and may arise from differences in the physicochemical structure of cellulose microcrystallite and/or aggregates. That is, in the process of preparation, aggregation or clustering of cellulose microcrystallites, which are assumed to be the minimum unit forming MCC particles and to be composed of crystalline (or micellar) and amorphous regions, occurs to a significant extent. The values of $k$ for PTZs appear to be higher for PH-301 than PH-101, while the reverse relation is found for acrinol. The small differences in adsorbent capacity of the two MCCs may reflect the difference in the cellulose microcrystallite and/or cluster structure, but further study is necessary to establish this.

The physical meaning of the constant, $1/n$, is not clear at present. If the constant is assumed to be a measure of the affinity of the adsorbent for the adsorbate, $4)$ PZ will have the strongest affinity with MCC. This conclusion is inconsistent with the observed low adsorption of PZ, so variations of the constant may reflect differences in the adsorption mechanisms. $5)$ In the present case, $1/n$ for PZ–MCC is nearly equal to unity, which indicates that the adsorption is of partition type rather than Freundlich type.

The adsorption mechanisms for CPZ and TFPZ on MCC were suggested to be similar, and slightly different from that for PZ. Further, the relatively low value of $1/n$ for acrinol–MCC indicates that the adsorption isotherm is moderately curved with increasing drug concentration, and shows some similarity to Langmuir-type adsorption. In the work of El-Samaligy et al. on the adsorption of antibiotics (ampicillin and amoxyccillin) on MCC, the adsorption was assumed to be of Langmuir type, though the saturated adsorption region was not clearly shown in their adsorption isotherms. $10)$ Thus, the adsorption can probably also be described by a Freundlich-type equation. Since the intermediate part in Langmuir-type adsorption can usually be approximated by Freundlich-type adsorption, $6)$ the possibility that the present adsorption isotherms represent a Langmuir-type adsorption cannot be ruled out completely. On the other hand, the temperature dependence of $1/n$ was very small, and a slight increasing tendency with increase of temperature was observed for CPZ–MCC and acrinol–MCC systems. This might reflect a slight structural change of cellulose microcrystallites.

**pH Dependence of Adsorption**

Adsorption of CPZ was pH-dependent, as shown in Fig. 4. It was lower in the acidic region below pH 4, and increased gradually with increase of pH, becoming nearly to a constant above pH 6.5. Similar pH dependence was observed for other PTZ–MCC and acrinol–MCC systems. The present results support the data of Frantz and Peck $1b)$ but not the findings of Nyqvist et al. $1a)$

The large pH-dependence and the shape of it suggest the existence of dissociable groups with weak acidity in either the drug or MCC. Since both PTZs and acrinol are strongly basic drugs (pKas for PTZs and acrinol are 9.2–9.4 $7)$ and 11.6, $8)$ respectively), most of the PTZ and acrinol may be present in monoprotic form below pH 7.5. $9)$ In the case of acrinol, the existence of a diprotic form is possible due to protonation of the 6-NH$_2$ group in the acridine ring. However, since the UV spectrum of acrinol (210–320 nm) did not change with pH in the range of pH 2–8, most of the acrinol seemed to be in the monoprotic form, and the amount of the diprotic form may be negligible. On the other hand, it was reported that the cellulose surface has a negative charge due to the ionization of carboxyl groups formed by oxidation of the hydroxy groups on anhydro-glucose units. $9)$ Hence MCC should have a negative surface, a conclusion which is also supported by the negative value of the zeta-potential ($-20$ mV) in aqueous solutions. $10)$ Thus, the pH-dependence of adsorption seems to result from dissociation of carboxyl groups on the MCC surface with increasing pH of the MCC suspension.

**Effect of Ionic Strength on Adsorption**

Since the electrostatic force is clearly involved in the adsorption of PTZs and acrinol on
MCC, it was expected that the adsorption would be affected by ionic strength. As can be seen in Fig. 5, the adsorption rapidly decreases with increase of ionic strength, and approaches a constant value above \((I)^{1/2} = 0.4\). Similar results were reported by Frantz and Peck on the adsorption of promethazine and fluphenazine on MCC.\(^{1b)}\) The result indicates that electrostatic binding of a cationic drug to the anionic site on the MCC surface may be inhibited by increasing ionic strength due to the restriction of the electric double layer around the cationic and/or anionic center. An alternative view of the adsorption is possible, i.e., that a cationic drug is adsorbed at an anionic site on MCC by ion-exchange. Cationic drugs such as PTZ and acrinol may be preferentially adsorbed at such a site.

The fact that a certain level of adsorption was maintained even at a large excess of salt (Fig. 5), suggests that non-electrostatic binding is involved in the adsorption. This assumption is also supported by the previous result on the pH-dependence of adsorption (Fig. 4), which indicated that the adsorption is not zero even in strongly acidic regions, in which all of the carboxyl groups on MCC should be completely protonated. This non-electrostatic adsorption appears to occur also in the acrinol–MCC system, since the effects of pH and ionic strength on the adsorption are similar to those in the CPZ–MCC system, as shown in Figs. 4 and 5. The non-electrostatic forces involved in the adsorption may be hydrogen-bonding and van der Waals forces, of which the former should be major, as described below, while the latter may be minor and complementary.

**Cation-Exchange Properties of MCC**

Since MCC has carboxyl groups on its surface, it should act as a weakly acidic cation-exchanger above pH 4. Figure 6 shows the pH changes of MCC suspensions with the addition of neutral salt. The pH values gradually decrease with increase of salt concentration, except in the acrinol–MCC system. This indicates that H\(^+\) is released from the MCC surface by cation-exchange adsorption of Na\(^+\), K\(^+\), or CPZH\(^+\). Since the pH-lowering magnitude at a constant salt concentration was in the order,

\[
CPZH^+ > K^+ > Na^+ 
\]
the above cations cannot be equivalent with respect to the MCC anionic site, and the order seems to reflect the site specificity.

The addition of acrinol induced an increase of pH, as shown in Fig. 6. Although the different result with acrinol as compared with the other salts cannot be clearly interpreted, a probable explanation is the buffering action of acrinol. That is, since acrinol is a salt of basic ethacridine ($pK_a = 11.6$) and lactic acid ($pK_{a2} = 3.86$), at higher salt concentrations the value of pH should approach $1/2 (pK_{a1} + pK_{a2}) = 7.73$, provided that monomolecular dispersion can be assumed. Thus, the deprotonation effect of cation-exchange adsorption may be overcome by the buffering action of the drug itself.

**Conclusion**

If MCC were composed of clusters of pure cellulose microcrystals, adsorption of drugs or other low-molecular adsorbates would be slight. However, since appreciable amorphous regions remain in the microcrystallites, considerable amounts of drugs can be adsorbed at these regions. As for dye adsorption to cellulosic fiber, it is considered that fairly large dyes cannot penetrate between fibers arranged in a regular close-spaced array. Cationic drugs are adsorbable on the surface by an ion-exchange mechanism, due to the negatively charged MCC surface. However, since not all of the cationic drugs were equally adsorbed on MCC, penetration of the drugs into the intermicellar space of microcrystallites may be important in the adsorption. That is, nonadsorbable drugs seem not to be capable of such penetration, because of chemical and structural factors. Nonelectrostatic binding of drugs to MCC also cannot be neglected, as mentioned above.

In the field of dye chemistry, there have been numerous studies on the use of direct dyes for cellulose, and the excellent dyes have some common structural features. Vickerstaff states the requirements for the molecular structure as follows; a) a linear configuration, b) a coplanar arrangement, c) groups capable of hydrogen-bonding, d) the presence of a conjugated system of double bonds. Hence acrinol has the molecular structure of a typical dye for cellulose (it has been used as a disinfectant for gauze and absorbent cotton). On the other hand, the PTZs examined in this study do not contain groups capable of hydrogen-bonding, and there is no conjugated system of double bonds through the molecule. The tricyclic PTZ ring thus cannot form a planar arrangement, but takes a boat conformation with a dihedral angle of about $140^\circ$. Therefore the large difference in adsorption on MCC between PTZs and acrinol may arise mainly from the differences in their molecular structure.
and arrangement.

The results of the present study indicate that the bioavailability of drugs may be modified by MCC employed as an excipient. Since acrinol is commonly used externally, the effect should be unimportant. However, PTZs are mainly prescribed for internal use over a long period. Therefore, it may be necessary to reconsider the combined use of MCC with at least some of the PTZs.

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References and Notes


2) Acrinol has been an approved name for “Ethacridine Lactate Monohydrate” in the Japanese Pharmacopoeia (JP) since JP V (1932).


