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RESEARCH PAPER

Adsorption of an Amine Drug onto Microcrystalline Cellulose and Silicified Microcrystalline Cellulose Samples

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ABSTRACT

The adsorption of a model amine drug (tacrine hydrochloride) from aqueous solution onto 21 microcrystalline cellulose (MCC) based samples has been investigated. The MCC source (manufacturer) affected adsorption. The adsorption appeared to be fully reversible. Adsorption was reduced by the use of high-density grade MCC, high-energy milling, and silicification. Adsorption of the model drug was not affected by the particle size of the MCC. Significant variations of the adsorption characteristics between batches of certain MCC products were found. The primary mode of adsorption was by ion exchange.

Key Words: Microcrystalline cellulose; Adsorption; Amine drugs.

INTRODUCTION

The adsorption of drugs by excipients during in vitro testing is an ongoing concern in formulation science. As a result of its multifunctionality, microcrystalline cellulose (MCC) is very widely used as an excipient in solid dosage forms; however, the adsorption of some drugs is a barrier to its wider use. Within the pharmaceutical industry, it has been observed that drugs containing amine functionalities are prone to adsorption onto MCC, with <100% release observed during dissolution tests. Because MCC is not digestible, the observed reduced release indicates that the total in vivo availability will be less than the amount of drug in the formulation.

Microcrystalline cellulose was introduced as a pharmaceutical excipient in the U.S. National Formulary in 1966 under the trade name Avicel. Recently,

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there has been an increase in the number of manufacturers marketing pharmaceutical grade MCC. It has been shown[1–3] that the differences in the source of pulp and the characteristics of the manufacturing processes used result in significant intermanufacturer variations in the observed functionalities and physicochemical properties[4–7] of the MCCs.

Microcrystalline cellulose is the β-1,4 linked polymer of D-glucopyranose, partially depolymerized to yield a product with a mean degree of polymerization of between 150 and 250. For pharmaceutical grade MCC products, the most commonly used raw material is high-quality timber pulp, as used in paper manufacture. The pulp feedstock is acid depolymerized and neutralized and the resulting slurry is dried to yield aggregates of MCC fibrils with a volume diameter mean particle size in the range 40–200 μm.

The interbrand and batch-to-batch variations in drug–excipient interactions,[3] drug release rates,[8] drug adsorption,[9–11] and water–MCC interactions[4,12,13] have been investigated by several researchers.

Variations in drug release in prednisone formulations made up with four different MCCs[8] suggested that significant differences can be expected for such formulation depending on the MCC product, and also the MCC batch, used. This was linked to the hydrophobicity of the samples, as indicated by lignin content, with higher lignin content tending to improve release efficiency.

In terms of drug sorption, El-Samaligy et al.[9] and Qtaitat et al.[11] found that the volume diameter mean particle size of the MCC samples affected the adsorption of the drugs under investigation. A reduced degree of adsorption was observed for larger particle size grades, which the authors linked to the reduced specific surface area of the materials.

Okada et al.[10] compared the adsorption of four drugs onto a standard grade MCC with that of a high-density grade MCC. They found that the standard grade of MCC had a lower adsorption capacity for three promazine derivatives than the high-density grade. The affinity of the promazine derivatives for MCC did not follow any steric trend, nor was there any relationship between drug pKa and adsorption. In contrast, the adsorption of acrinol, an acridine derivative, was lower for the high-density grade MCC than for the standard grade.

The water–cellulose interaction is of interest for the possible consequences for adsorption from aqueous solution. Water retention values (WRV), an indication of hydrophilicity, have been determined for seven MCCs[12] using a centrifugation technique.

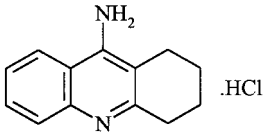

Figure 1. Conformational structure of tacrine hydrochloride.

Significant differences were observed between the WRV of different manufacturers' products, which may affect the release efficiency.[8]

A previous study,[13] comparing the adsorption of water onto MCC and silicified MCC (SMCC), found no significant difference in the enthalpy of water vapor sorption. SMCC is a patented MCC derivative, coprocessed with 2% w/w colloidal SiO_2[14] showing improved resistance to loss of compactibility on wet granulation.

It is the purpose of this study to investigate interbrand variations in the adsorption of a model amine drug and to explore the nature of the drug adsorption onto MCC. In addition, the adsorption of SMCC will be investigated for the first time.

The model drug used in this work is tacrine hydrochloride (tacrine, 9-amino-1,2,3,4-tetrahydroacridine; Fig. 1). Tacrine is prescribed as a cholinesterase inhibitor for the alleviation of the symptoms of mild to moderate Alzheimer's-type dementia (Cognex, 10- to 40-mg dose). A previous study[15] demonstrated that tacrine adsorbs to a significant degree onto MCC. The flat structure and delocalized aromatic electron structure predicts that the molecule is a fast dye for cellulosic materials,[16] hence the significant adsorption observed. Tacrine is readily soluble in water with a pKa of 9.3, therefore at pH values below 7, tacrine will be fully protonated. Protonation occurs on the exocyclic nitrogen.

MATERIALS AND METHODS

Materials

Details of the 21 MCC products and derivatives used in this study are given in Table 1. They can be divided into six groups, each group having a single common feature, which is used to distinguish between the products. All groupings and descriptions for commercial products are based on the relevant supplier's literature, where available. In order to assess the adsorption of the material as used in general formulation work, samples were not particle size

Table 1. Summary of the 21 microcrystalline cellulose samples studied.

MCC	Batch	Supplier	Country	Group
Avicel PH101	6902C	FMC Inc.	USA	Standard grade
Avicel PH101	1113	FMC Inc.	USA	Standard grade*
Ceolus KG-802	H0134	Asahi Kasei Corp.	Japan	Standard grade
Emcocel 50M	E5D8C17X	Penwest Co.	USA	Standard grade
Emcocel 50M	E5D7E21	Penwest Co.	USA	Standard grade*
Emcocel 50M	E5B1E48	Penwest Co.	USA	Standard grade*
Pharmacel 101	90971	DMV International	The Netherlands	Standard grade
Tabulose 101	113/99	Blanver Ltda.	Brazil	Standard grade
Vivapur 101	5610193529	J. Rettenmeier GmbH	Germany	Standard grade
Vivapur 101	5610104629	J. Rettenmeier GmbH	Germany	Standard grade*
Vivapur 101	5610110714	J. Rettenmeier GmbH	Germany	Standard grade*
Emcocel 90M	E9B8A01X	Penwest Co.	USA	Large particle
Emcocel LP200	2S6003X	Penwest Co.	USA	Large particle
Avicel PH302	Q918C	FMC Inc.	USA	High density
Emcocel HD90	HD9B5K3X	Penwest Co.	USA	High density
Prosolv HD90	K9S9040X	Penwest Co.	USA	High density, silicified
Vivapur 302	5630280112	J. Rettenmeier GmbH.	Germany	High density
Prosolv 50	P9B9B11X	Penwest Co.	USA	Silicified
Prosolv 90	P5B7D26X	Penwest Co.	USA	Silicified
Emcocel SP15	SPD7C01X	Penwest Co.	USA	Treated
Heated E50M	E5D8C17X	Penwest Co.	USA	Treated

Note: All groupings are based on descriptions from manufacturer's literature. Standard grade MCCs marked with an asterisk are additional samples used for batch-to-batch comparison.

fractionated. The groupings into which the MCCs have been placed can be described thus:

Standard Grades from Different Manufacturers

These have a volume diameter mean particle size of approximately 50 μm and are marketed as equivalent to Avicel 101 (FMC Inc., USA). A total of six MCCs were investigated, two U.S. brands, two European, one Brazilian, and one Japanese.

Batch-to-Batch Variation

Multiple batches of Avicel PH101, Emcocel 50M, and Vivapur 101 were obtained in order to determine whether any observed interproduct variations fall within the range of batch-to-batch variability.

Larger Particle Size Grades

Increased volume diameter mean particle size materials are manufactured by adjustment of the drying conditions. A lower specific surface area is to be expected for larger particle sizes. Three grades, each a commercial product from Penwest Co. (USA) are studied: the standard grade and two large particle grades. According to product literature, the same feedstock as used for the standard grade was used for each of these products, since they are designed to be interchangeable in all respects except for dry flow performance; hence any differences between these products will be due to the final drying conditions.

High-Density Grades

Most standard grade MCCs are manufactured using softwood (evergreen) pulp as the feedstock. High-density grades are normally manufactured from hardwood (deciduous) pulps, which have a higher bulk density, reflecting the lower porosity of the source timber.[16]

Silicified MCC

The adsorption of SMCCs, patented coprocessed MCCs containing 2% w/w colloidal silicon dioxide,

were investigated to assess the effect on adsorption of the presence of SiO_2 in the particle surface. Standard (50 μm volume diameter mean particle size), large particle (90 μm), and high-density grades were investigated.

Treated Samples

Micronized MCC (Emcocel SP15, Penwest Co.) is used to investigate the effect of high-energy milling on the adsorption capacity of MCC. Emcocel 50 M heated to 80°C for 16 h was used to investigate the effect of the type of drying undergone during wet granulation on drug adsorption.

Other Chemicals

Tacrine hydrochloride (BP grade, Aldrich, Gillingham, UK) was used without further purification. Water used in these studies was freshly purified by reverse osmosis (Millipore, Watford, UK) with conductivity in the range 650–700 μS. Water was degassed by helium displacement (minimum 1 h per L). Sodium chloride was analytical grade (AR grade, Fisher, Loughborough, UK).

Adsorption of Tacrine

Adsorption isotherms were obtained by batchwise thermostatic equilibration.[10] A 1000-mg sample of MCC was suspended in 40 mL solution at each of 15 drug concentrations in 50 mL borosilicate volumetric flasks. This was then equilibrated for 2 h at the required temperature in a shaking water bath (Gyrotory®, New Brunswick Scientific, Edison, NJ, USA) to ensure thorough mixing, maximum adsorption, and thermal equilibrium. The time required for equilibrium adsorption was determined separately by extracting supernatant after equilibration for 0.5–5 h.

Supernatant was separated by centrifugation (1400 *g*, 10 min) and analyzed by UV spectrophotometry (Helios α, Unicam, Cambridge, UK) ($\lambda_{max} = 239$ nm, $\varepsilon_{tacrine} = 39900\ mol^{-1}cm^{-1}$) after dilution to between 1 and 5 mg L^{-1} (4–20 μM). Three controls were analyzed: MCC in water, a tacrine solution of an appropriate concentration, and water. These determine the UV absorbance of water-soluble extractives, possible thermolytic degradation or adsorption of the drug onto the glassware, and levels of contaminants from the glassware, respectively. Replicate analyses ($n = 5$) of the water-soluble extractives indicated that UV absorbing material was released from all the MCC samples. This material may be the proteinlike surface active solute previously described.[18] The UV absorption of these extractives was reproducible to ±0.001 absorbance units at 239 nm for each MCC, therefore the UV absorption of each diluted equilibrium tacrine solution was adjusted to account for the presence of these extractives. No significant thermolytic degradation or adsorption onto the experimental apparatus was found. No significant contamination from the glassware was detected.

Tacrine Concentration

Fifteen data points over the initial tacrine concentration range of 0.05 to 1.0 mM were collected for isothermal equilibration studies at 25°C.

Data Interpretation

The Langmuir [L2, Ref.[19]] isotherm for monolayer adsorption was used to interpret the data obtained in the isotherm studies. The linear form of the Langmuir isotherm is given in Eq. (1), where C_{eq} is the equilibrium concentration, x is the amount of adsorbate adsorbed on m mass of adsorbent, k_1k_2 is the affinity constant, and k_2 is the capacity constant.

$$\frac{C_{eq}}{(x/m)} = \frac{1}{k_1k_2} + \frac{C_{eq}}{k_2} \quad (1)$$

A plot of C_{eq} against $C_{eq}/(x/m)$ will yield a straight line if ideal adsorption has occurred. This indicates that monolayer adsorption is occurring in the concentration range under investigation. Adsorption sites are assumed to be energetically homogeneous and adsorption is independent of occupancy of adjacent sites. Residuals analysis showed no discernible trend and a normal distribution (Anderson–Darling test, $p > 0.3$ in all cases) for the residuals about the line of best fit.

The adsorption data was also modelled using the Freundlich isotherm, used to interpret data from multilayer adsorption. Although generally good correlation coefficients were obtained ($r^2 > 0.80$), residuals analysis yielded a quadratic trend, rather than the normal distribution of residuals observed for Langmuir fitting, indicating that this isotherm does not reliably describe the observed adsorption.

Least-squares linear regression analyses were completed using Minitab 12 (Minitab Inc., USA) whereby slope, intercept, and the standard deviations of the slope and intercept were computed for each linear isotherm. In addition to the raw data obtained from these isotherm plots, the surface area available for adsorption may be estimated from the amount of tacrine adsorbed per unit mass. Surface area values are estimated on the basis that the tacrine molecule has a molecular area of $2\,nm^2$, similar to that of anthracene ($=2.05\,nm^2$),[20] using Eq. (2), where sa is the specific surface area ($m^2\,kg^{-1}$), A is the area of the molecule ($=2\times10^{-18}\,m^2$), (x/m) is the adsorption capacity in $mol\,kg^{-1}$, and N_A is Avogadro's constant.

$$sa = A.(x/m).N_A \tag{2}$$

Reversibility of Adsorption

The extent of the reversibility of the adsorption of tacrine from aqueous solution was assessed for Emcocel 50 M by a reequilibration technique. A 1000-mg sample of MCC was thermostatically equilibrated with 40 mL of a 150-mg L^{-1} solution of tacrine at 25°C. The sample was then centrifuged as above and 20 mL of the supernatant was removed for UV spectroscopic analysis to obtain the first equilibrium concentration (C_{eq1}). The MCC dispersion was then quantitatively returned to the original volumetric flask by washing with 20 mL degassed water. The dispersion was then thermostatically equilibrated a second time and the supernatant extracted after centrifugation for UV spectroscopic analysis. From the previously obtained Langmuir isotherm and the equilibrium concentration after the second equilibration, the initial concentration prior to the second equilibration (C_{in2}) could be determined from Eq. (3), where C_{eq2} is the second equilibrium concentration, x_2 is the amount of tacrine adsorbed in the second equilibration and v is the total liquid volume (0.04l in this study).

$$C_{in2} = C_{eq2} + \frac{x_2}{v} \tag{3}$$

The value of x_2 may be determined using the rearranged Langmuir isotherm in Eq. (4), where m is the mass of MCC used and k_1k_2 and k_2 are values determined from the Langmuir isotherm [Eq. (1)].

$$x_2 = \frac{C_{eq2}m}{(1/k_1k_2) + (C_{eq2}/k_2)} \tag{4}$$

For the experiment described above, the extent of the reversibility of the adsorption may be determined *via* Eq. (5), where f is the fraction of tacrine reversibly adsorbed.

$$f = \frac{v}{2x_2}(2C_{in2} - C_{eq1}) \tag{5}$$

Ionic Strength

In order to determine the effect of the ionic strength of the tacrine solution on adsorption, adsorption isotherms at 25°C were obtained using Emcocel 50M and Emcocel HD90 as adsorbate. These MCC samples were selected to compare the effect of increased salinity on softwood and hardwood MCCs. Isotonic solutions of NaCl (0.9% w/v, 0.154 M) over the tacrine concentration range 1.5 to 50 mg L^{-1} were used. Previous investigations [Fig. 2; see also Ref.[11]] had established that adsorption decreased as salinity increased until a plateau of minimum absorption was reached at NaCl concentrations above 0.05 M.

Surface Area

Specific surface area was determined by 5-point BET N_2 adsorption (Gemini 2360, Micromeritics, Dunstable, UK) at 77K in triplicate. Samples were dried at 40°C to constant mass (usually 16 h) under a stream of dry nitrogen to remove surface moisture.

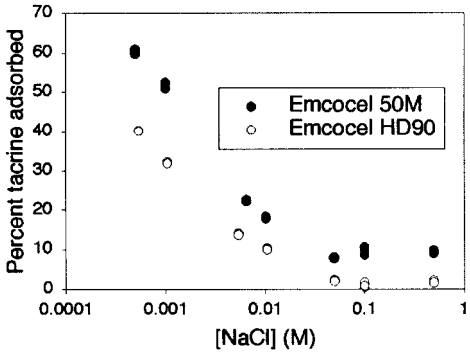

Figure 2. Effect of ionic strength on the adsorption of tacrine by a softwood (Emcocel 50M) and a hardwood (Emcocel HD90) MCC. Three repeats at each of seven NaCl concentrations. These results indicate that the primary adsorption mode is by ion exchange. A secondary adsorption mode is of importance for Emcocel 50M.

Particle Size

Particle size distribution analysis by laser diffraction was performed using the Mastersizer 2000 (Malvern Ltd., Malvern, UK). Samples were presented as dry powders using the Scirocco 2000 automated dry powder feeder (Malvern Ltd., Malvern, UK) set to yield a pressure drop of 3bar across the sampling chamber. Each analysis is the mean of 10,000 scans over ten seconds. Sample feed rate was adjusted to give a laser obscuration of 0.5 to 2.0% during analysis. Results quoted are the means of three analyses. All results are quoted as volume diameter distributions.

RESULTS AND DISCUSSION

The data from the isotherms of all MCCs studied were described well by the Langmuir equation ($r^2 > 0.92$). Isotherm plots for Pharmacel 101, Emcocel 50M and Emcocel HD90 are compared in Fig. 3, with a comparison of the linearized data in Fig. 4. Data for all 16 MCCs studied are summarized in Table 2 (single batch data) and Table 3 (batch-to-batch data).

Statistical Treatment of Adsorption Results

The initial null hypotheses, that the mean affinities (χ^2 test; $p < 0.01$) and the mean capacities (χ^2 test; $p < 0.01$) of all MCCs studied were equal, were rejected. The well-known Fisher pairwise multiple comparison test for normally distributed data was adapted to establish statistically equivalent groups of MCCs, on the basis of affinity and capacity. This test is based on the standard deviations of the slope and intercept calculated from the linear regression analyses. Using the Fisher treatment, a critical difference is obtained for affinity and capacity data, determined *via* the calculation of a pooled standard deviation. This means that within sample variations are taken to be equal for each MCC, irrespective of the individually calculated 95% confidence limits given in Table 2. Differences smaller than 56.5 for affinity constants and 0.81 mmol kg^{-1} for capacities are not significant to within 95% confidence.

The groupings of the MCCs are used to simplify the discussion of the differences and similarities between the affinity constants and capacity values calculated for the adsorption isotherms measured.

Standard Grades

Statistical analysis based on Fisher's pairwise comparison shows that there are significant differences ($p < 0.05$) between some of the standard grades.

The affinity constant for Tabulose 101 is significantly lower than the values obtained for the other five MCCs in the standard grade group, and Ceolus KG-802 has a significantly higher affinity than any other MCC sample. The capacities for tacrine of Avicel 101, Ceolus KG-802 and Pharmacel 101 are significantly higher than the other three MCCs, with Pharmacel 101 displaying a significantly higher capacity than Avicel 101 and Ceolus KG-802.

The difference between the affinity constants has a noticable effect on the adsorption observed at lower drug concentrations. This is illustrated in Fig. 5,

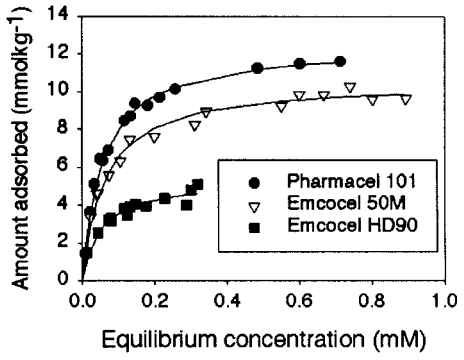

Figure 3. Adsorption isotherms of tacrine onto Pharmacel 101, Emococel 50M, and Emcocel HD90.

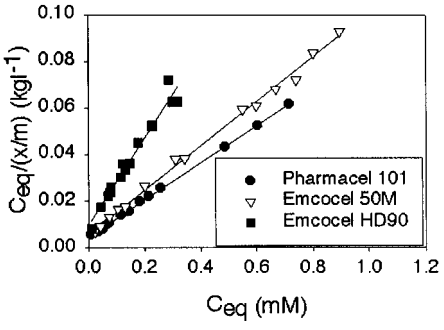

Figure 4. Langmuir plots for the adsorption of tacrine onto Pharmacel 101, Emcocel 50M, and Emcocel HD50. The data presented in Fig. 3 have been linearized according to the Langmuir isotherm [Eq. (1)].

Table 2. Summary of surface area data from BET N_2 adsorption, volume diameter mean particle size [d (v, 0.5)], and analysis of Langmuir adsorption isotherms for single batches of the MCCs studied.

MCC ($m^2\,kg^{-1}$)	BET surface area ($m^2\,kg^{-1}$)	d (v, 0.5) (μm)	k_1k_2	k_2 ($mmol\,kg^{-1}$)	Tacrine surface area
Avicel PH101	1,200	54	219 ± 47	11.4 ± 0.4	13,700 ± 500
Ceolus KG-802	1,200	52	439 ± 65	11.6 ± 0.6	14,000 ± 700
Emcocel 50M	1,270	57	172 ± 46	10.5 ± 0.4	12,600 ± 400
Pharmacel 101	1,300	57	219 ± 16	12.5 ± 0.2	15,100 ± 200
Tabulose 101	1,340	70	42.4 ± 6.9	10.0 ± 1.6	12,000 ± 1,900
Vivapur 101	1,450	93	217 ± 40	10.5 ± 0.3	12,600 ± 300
Emcocel 90M	1,250	109	183 ± 63	10.5 ± 0.3	12,700 ± 400
Emcocel LP200	1,100	184	157 ± 73	10.5 ± 0.9	12,700 ± 1,000
Avicel 302	610	104	93.2 ± 35.0	6.93 ± 0.46	8,300 ± 600
Emcocel HD90	680	123	109 ± 46	5.30 ± 0.59	6,400 ± 700
Vivapur 302	1,220	110	220 ± 90	8.24 ± 0.44	9,900 ± 500
Prosolv 50	4,920	55	190 ± 79	8.30 ± 0.41	10,000 ± 500
Prosolv 90	5,490	109	209 ± 54	9.28 ± 0.46	11,200 ± 600
Prosolv HD90	4,320	124	124 ± 31	4.33 ± 0.22	5,200 ± 300
Emcocel SP15	3,320	14	167 ± 63	8.68 ± 0.63	10,500 ± 800
Heated E50M	1,260	55	116 ± 47	4.76 ± 0.25	5,800 ± 300

Note: The affinity constants (k_1k_2) and adsorption capacities (k_2) are presented together with the 95% confidence intervals of the individual analyses, determined from standard deviation calculations. Tacrine surface areas are based on a molecular surface area of $2\,nm^2$ for tacrine.

Table 3. Analysis of Langmuir adsorption isotherms from the study of batch-to-batch variations of Avicel PH101, Emcocel 50 M, and Vivapur 101.

MCC	Batch no.	k_1k_2	k_2 ($mmol\,kg^{-1}$)	Tacrine surface area ($m^2\,kg^{-1}$)
Avicel PH101	6902C	219 ± 47	11.4 ± 0.4	13,700 ± 500
Avicel PH101	1113	285 ± 11	9.27 ± 1.13	11,200 ± 1,400
Emcocel 50M	C17X	172 ± 46	10.5 ± 0.4	12,600 ± 400
Emcocel 50M	E21	230 ± 4	8.43 ± 0.88	10,200 ± 1,100
Emcocel 50M	E48	295 ± 7	9.39 ± 1.08	11,300 ± 1,300
Vivapur 101	3529	217 ± 40	10.5 ± 0.3	12,600 ± 300
Vivapur 101	4629	276 ± 6	8.72 ± 1.04	10,500 ± 1,300
Vivapur 101	0714	290 ± 5	7.84 ± 0.93	9,400 ± 1,100

Note: The first given batch number is that of the batch used for interproduct comparison (Table 2).

comparing tacrine adsorption against equilibrium concentration for Tabulose 101 and Ceolous KG-802. The Langmuir isotherms for these products predict that the saturation adsorptions differ by 16%. Taking a hypothetical formulation containing 250 mg MCC and a release of 10 mg (concentration of $11.1\,mg\,L^{-1}$ in a 900-mL dissolution bath), a dose of 11.7 mg would be required in a formulation using Ceolus KG-802 (15% adsorption). In contrast, an initial drug dose of 10.4 mg is required to reach the same equilibrium concentration with Tabulose 101 (4% adsorption). Therefore, low affinity MCCs may be suitable for use in cases where a lower degree of adsorption is acceptable, since a 10.4-mg dose is within pharmacopoeial tolerances for formulations of this dosage.

From these results it may be concluded that Vivapur 101 and Emcocel 50 M are equivalent products with respect to adsorption of tacrine. Also, the adsorption capacities of Avicel 101 and Ceolus KG-802 are statistically equivalent. The technique used to achieve a lower bulk density for Ceolus KG-802 does

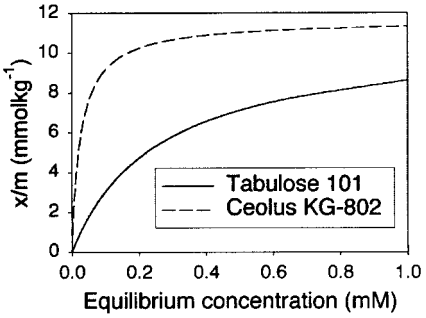

Figure 5. The effect of affinity constant on the amount of tacrine adsorbed from aqueous solution at 25°C, where x/m is the amount of tactrine adsorbed at equilibrium per unit mass of adsorbate. Comparison of Tabulose 101 and Ceolus KG-802. The capacity of Tabulose for tacrine is 85% that of Ceolus, but the affinity constant for Tabulose 101 is 10% that of Ceolus KG-302.

not have a significant effect on the adsorption capacity of the material. No correlation between affinity constant and capacity for these products was observed. These results indicate that variables such as pulp source, depolymerization conditions and neutralization techniques play an important role in affecting adsorption characteristics.

It should be emphasized that these comparisons are made on the basis of single, randomly selected batches from each manufacturer. The differences seen here may, therefore, be a reflection of batch-to-batch variations within each manufacturer's product.

Final drying conditions are less likely to play a significant role, since Emcocel 50M is spray dried (Penwest product literature), in contrast to the air-stream drying technique employed in the manufacture of Vivapur 101 (Rettenmaier product literature). Furthermore, it is probable that different drying techniques are used in the final production of Avicel 101 and Ceolus KG-802, since these products have different bulk densities (Ceolos KG-802 $= 0.24\,\mathrm{gm}^{-3}$, Avicel 101 $= 0.31\,\mathrm{gm}^{-3}$). Therefore, the equivalence in adsorption capacity between Avicel 101 and Ceolus KG-802 may be a result of the use of similar pulp and depolymerization techniques.

Reversibility of Adsorption

Quadruplicate analyses of the reversibility of the adsorption of tacrine from aqueous solution onto Tabulose 101 and Ceolus KG-802 indicated that the adsorption is fully reversible ($f = 1.01 \pm 0.01$ for both samples). These two MCC types were selected because they display the lowest and highest affinities for tacrine in the adsorption isotherm studies. These results indicate that the affinity of tacrine for MCC and the reversibility of the adsorption are not linked.

This finding confirms some previous work investigating the elution of some drugs from MCC using a pH 2.1 HCl solution, wherein complete elution of ampicillin, amoxycillin,[9] fluphenazine and promethazine[21] was achieved. However, none of these workers were able to fully elute either of these drugs using water as the elution medium. This would tend to confirm the assumptions made by Akaho and Fukumori[22] about the adsorption of drugs onto cellulose, who stated that adsorption tends to be irreversible. There is clearly a discrepancy between the results reported here for adsorption of tacrine and the previously published work. There remain as yet unresolved structure-dependent influences on the reversibility of the adsorption of different drugs.

The observed reversibility of the adsorption of tacrine onto MCC has important consequences for the expected in vivo adsorption of this drug, even though in vitro dissolution tests may indicate that there is a significant decrease in bioavailability due to adsorption. Constant absorption of the drug from the digestive tract will result in the release of adsorbed drug from the dosage form as the equilibrium between the amount adsorbed and the concentration of the drug is reestablished. Therefore, although adsorption of the drug onto MCC may decrease the in vivo bioavailability, the decrease will be less than in vitro studies indicate if the adsorption is reversible to any degree.

Batch-to-Batch Variation

More than one batch of Avicel PH101, Emcocel 50M, and Vivapur 101 were obtained from the manufacturers. These three products are marketed as equivalent products on the basis of particle size. Significant differences were established for all three products on a batch-to-batch basis (Table 3). However, repeating the statistical analyses including all the adsorption experiments for each product irrespective of batch number ($n = 45$ for Emcocel 50M and Vivapur 101, $n = 30$ for Avicel PH101) still suggested that Emcocel 50M and Vivapur 101 are equivalent products and Avicel PH101 has a higher capacity than the other two products.

Some correlation of the time between analysis and manufacture and the adsorption was observed for Emcocel 50M and Avicel PH101 of the products. It may be, therefore, that storage time has a significant effect on the surface chemistry of these MCCs. The possibility that storage time has an effect on adsorption has previously been suggested from a study of the dissolution efficiencies of prednisone formulations,[8] where the lowest batch number of three unspecified Emcocel products was found to have the best dissolution efficiency, implying a decreased adsorptivity.

Interestingly, no time dependence was observed for the three Vivapur 101 batches analyzed. This product may be more stable, or any time-dependent trend may be masked by larger batch-to-batch variations in this product.

Further analysis of adsorption isotherms of the same batches after extended storage times will yield further information.

Large Particle Size

There are no significant differences in either the affinity constants or the capacities of Emcocel 50M, Emcocel 90M, and Emcocel LP200. This indicates that the spray drying conditions have no significant effect on the surface chemistry of the MCC products. It can be deduced that the nature of the fibrils forming the aggregates, rather than the size of the aggregates, is a primary determinant of the adsorption capacity.

The results presented here disagree with previous investigations into the effect of particle size of MCC on adsorption.[11] This may be a result of steric factors affecting the ability of the large bromhexine (2-amino-3,5-dibromo-*N*-cyclohexyl-*N*-methylbenzylamine HCl) molecules to occupy adsorption sites within small pores, which is not a significant factor in tacrine adsorption. Qtaitat et al.[11] presented no porosimetry data, however a difference in the pore size distribution and therefore the accessibility of the internal surfaces may be expected. Microcrystalline cellulose particles as measured by standard particle sizing methods are aggregates of smaller particles of MCC,[23] the size of these aggregates being the measured particle size. On a mass-for-mass basis, less of the interior of the larger particles will be accessible to these larger drug molecules, if it is assumed that there are pores present small enough to block access to the interior of the agglomerate.

High-Density Products

Microcrystalline celluloses manufactured from hardwood sources have a significantly lower adsorptive capacity for tacrine than softwood sourced MCCs. This is best observed when comparing hardwood and softwood products from the same manufacturer, because the similar techniques and manufacturing practices may be used for each product.

Use of a hardwood pulp source for product pairs based on manufacturer and pretreatment show that there are significant differences in the capacities of these products (Table 2). Affinity is not affected for the Rettenmaier GmbH products (Vivapur 101 and Vivapur 302), but the two Penwest Co. pairs (Emcocel 90M and Emcocel HD90; Prosolv 90 and Prosolv HD90) and the two FMC Co. products (Avicel PH101 and Avicel PH302) show significant differences within the pairs.

Okada et al.[10] found that a high density MCC (Avicel 301) has a lower capacity (from Freundlich multilayer isotherm plots) for the acridine derivative acrinol (2-ethoxy-6,9-diaminoacridine) than the standard grade Avicel 101. This was ascribed to slight variations in the cellulose microcrystallite and cluster structure. The mean size of softwood MCC aggregates is shown to be not significant in our study for tacrine adsorption. Therefore the known differences in microcrystallite structure between softwood and hardwood products[5] are shown to significantly influence the adsorption capacity of tacrine onto MCC.

Silicification

Silicified MCC products are shown to have a significantly lower capacity, but an unchanged affinity, for tacrine compared with the equivalent unmodified grade (Fig. 3). This may be a consequence of the presence of SiO_2 in the surface of the product.[24] Silicification reduces the adsorption of tacrine by 21 to 12%, due either to the replacement of cellulosic surface area by nonadsorbing silicon dioxide or the preferential adsorption of silicon dioxide onto active sites in the surface of MCC.

The similarity of the affinity constants of the unmodified and silicified grades indicates that there is not a preferential adsorption of silicon dioxide in the surface. This reflects the previously reported similarity in the water vapor adsorption enthalpy[13] between MCC and SMCC. Preferential adsorption would reduce the affinity of tacrine by masking

the most active sites, thus making adsorption more difficult. It is more likely that there is a net reduction in the surface available for adsorption, with any masking of adsorption sites occurring randomly.

Treated Samples

Emcocel SP15 is a micronised (air-jet mill) grade of MCC. This high-energy treatment of the MCC significantly lowers the capacity for adsorption of tacrine, despite the increase in specific surface area as measured by BET N_2 adsorption. This may be evidence of mild dry hornification,[25] a heat-induced reduction of the water retention capacity of cellulosic products. It is therefore possible that the water–cellulose interaction is an important factor in drug adsorption, with the ability of MCC to swell in water a factor in determining the area available for adsorption from aqueous solution.

The data obtained from the heated samples show significant reductions in both the adsorption capacity (decrease of $42 \pm 3\%$) and affinity constant (decrease of $40 \pm 10\%$) of Emcocel 50M on heating. This, again, may be evidence of hornification, with the surface structure of cellulose collapsing and the available adsorption sites destroyed by pyrolysis and intra cellular hydrogen bonding.[25]

The observed changes in the adsorption capacity and affinity reflect a reduction in surface energy and a consequent increased hydrophobicity on heating. This, therefore, will mean that any measurements of surface energetics that involve heating cellulose samples will not yield surface energy results that are relevant to unheated samples.

Correlation of Adsorption Capacity with Surface Area

The correlation of surface area determined by BET N_2 adsorption with the capacity to adsorb tacrine from aqueous solution can be determined by examination of the data in Table 1. Only standard and large particle grades were considered to avoid the large increase of the BET surface area on silicification and the potential effects of using a hardwood pulp source. From these data it is observed that there is no apparent correlation between capacity for tacrine and surface area measured by BET N_2 adsorption (Table 2). The actual correlation coefficient (r^2) using the eight MCCs considered was 0.043, a strong indication that no correlation exists.

This finding is explicable with reference to nitrogen adsorption work conducted previously by Nakai et al.[26] and doRego et al.[27] Nakai et al.[26] measured high ($80{,}000\,m^2\,kg^{-1}$) surface areas of cellulose samples after maceration in water. doRego et al.[27] measured surface areas in a manner similar to that described here, using cyanine dyes as probes. Working with ethanolic (slightly swelling) and dichloromethane (nonswelling) solutions, they obtained active surface areas of 2400 and $1200\,m^2\,kg^{-1}$, respectively, for an unspecified cellulose sample.

One possible explanation for these observations is water-induced swelling of the cellulose. In order to investigate the effect of solvent on the apparent surface area, a sample of Emcocel 50M was washed repeatedly with dry ethanol to remove water and then washed with *n*-pentane to remove the ethanol. The resulting powder was analyzed using 5-point BET N_2 adsorption yielding a surface area of $2300\,m^2\,kg^{-1}$. By itself, this result could be interpreted as a more complete removal of water from the pores of the sample than is achieved by gentle heating under dry nitrogen. In conjunction with the results of doRego et al.[27] it would appear that swelling of the sample in ethanol is a more valid explanation of the observed increase in surface area than water removal.

This may also go some way to explaining the observed reduction in adsorption of the high-energy milled and heated MCC samples, since hornification reduces the ability of cellulose to swell and increase hydrophobicity may affect release efficiency.[8]

Effect of Ionic Strength

Figure 2 compares the effect of NaCl concentration on the percentage tacrine adsorbed onto MCC from solutions containing $50\,mg\,L^{-1}$ (Emcocel 50M) and $15\,mg\,L^{-1}$ (Emcocel HD90) tacrine.

The data obtained from this study can be discussed in three different ways:

First, the main mechanism for adsorption onto MCC is by ion exchange. Processing cellulose oxidizes the surface hydroxyl groups to carboxyl groups,[28] resulting in a pKa for cellulosic materials of 4.0–4.3.[29] This means that within the pH range 6–7, at which these experiments were conducted, the maximum potential for adsorption by ion exchange is expected for the tacrine–MCC system.[30] The sodium cation, having a smaller radius than the protonated tacrine molecule, has a greater charge density. Therefore, sodium cations preferentially occupy the negative adsorption sites on the surface of MCC,

eventually preventing tacrine from adsorbing on these sites. This confirms the findings of Okada et al.[10] and Qtaitat et al.[11] who determined that adsorption was mainly due to an ion-exchange mechanism, occurring by interaction with surface carboxyl groups.

Secondly, there appears to be a second, as yet unassigned, mode of adsorption in the softwood MCC. Approximately 10% of the available tacrine is adsorbed even at high NaCl concentrations. This might be due to a dipolar (Lifshitz–van der Waals) type interaction or H-bonding within the surface.[10,31] Spectroscopic (vibrational and NMR) investigations, currently in progress, may be able to resolve this issue.[32]

Thirdly, there is a large, significant decrease in the adsorption observed at isotonic salinity (0.154 M NaCl) compared with the adsorption in degassed purified water. As well as providing an insight into the adsorption mechanism, this observation shows that in vitro testing conditions will have a marked effect on drug adsorption and the consequent bioavailability determined for a formulation. This last point has implications for the effect of adsorption on in vivo release. The higher osmolarity of physiological systems would decrease the tendency of MCC to adsorb tacrine and other drugs that adsorb through an ion exchange mechanism.[21]

Analysis of the isotherms from the adsorption experiments was complicated by the very low adsorption and the consequent increase in experimental (type 1) error. This error led to a high degree of scatter about the line of best fit, with correlation coefficient (r^2) decreasing to 0.8. However, a rank similarity in the calculated adsorption capacities of Emcocel 50M and Emcocel HD90 from saline tacrine solution with the estimated capacities from the single concentration can be established. The nonionic capacities for these two materials are $0.49 \pm 0.12\,\text{mmol}\,\text{kg}^{-1}$ (Emcocel 50M) and $0.12 \pm 0.58\,\text{mmol}\,\text{kg}^{-1}$ (Emcocel HD90). These results are of the same order of magnitude as those estimated from observation of the effect of the ionic capacity on adsorption at a single initial drug concentration.

CONCLUSIONS

The findings from these studies may be summarized in the following points:

Intermanufacturer differences are demonstrated for the adsorption of tacrine from aqueous solution for the MCC batches used in this investigation. This may be an indication of batch-to-batch variations, with the single batches selected being representative of the extremes of variation to be expected between manufacturers' products.

Significant differences in the capacities and affinities were determined between the batches investigated of Avicel PH101, Emcocel 50M and Vivapur 101. Some of this variation may be attributable to storage time. Despite the batch-to-batch variations, the conclusions from the single batch investigations still apply; Emcocel 50M and Vivapur 101 are similar and Avicel PH101 has a higher adsorption capacity than the other two products.

Surface area determined by BET N_2 adsorption is not an indicator of the adsorption capacity. It is therefore not possible to predict the adsorption of water-swollen MCC from dry state surface area determinations.

The adsorption of tacrine onto MCC from an aqueous solution is fully reversible.

High-density grades of MCC display a lower adsorption capacity and reduced affinity for tacrine than standard grades.

The nature of the primary particles that constitute the aggregates of MCC is a critical factor in determining the adsorption capacity of the product. The size of the aggregates is not a significant factor.

Silicified MCC samples show a reduced adsorption capacity due to reduction in the cellulosic surface area, replaced by nonadsorbing SiO_2. High density SMCC (Prosolv™ HD90) has the lowest capacity for adsorption of tacrine of all the samples studied.

The water–cellulose interaction may be an important factor in determining the adsorption capacity of cellulosic materials from aqueous solution.

The main mechanism for adsorption is by ion exchange. A secondary interaction, either H bonding or a dispersion force interaction, is a minor but significant adsorption mode for softwood MCCs. The ion exchange mode is quickly saturated under test conditions by solubilized ions. Testing conditions for in vitro dissolution and bioavailability analyses will, therefore, significantly affect the observed drug release.

Therefore, a change in the brand of MCC used in a formulation may have a significant effect on the observed in vitro adsorption, and potentially affect drug bioavailability.

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