The use of polyamide coatings for selective adsorption control on activated charcoal

S. R. Wicks*, N. E. Richardson, and B. J. Meakin
Pharmaceutics Group, School of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, United Kingdom

Polymer-coated, activated charcoal granules have found considerable use for the direct detoxification of blood in cases of uraemia and drug overdose. Although polymer coating materials are presently selected for their biocompatibility, more selective polymers could be used to increase the adsorption capacity for specific drugs and toxins. To gain an understanding of the fundamental factors influencing these adsorbent systems, we have investigated a possible selective coating material, nylon 6 and studied its influence on adsorption rates of simple model compounds when applied as a thin coat to activated charcoal granules. Thermodynamic studies have shown that phenolic compounds interact with the polymer by a hydrogen bonding mechanism, whereas nonphenolic compounds probably bind less strongly due to Van der Waals type interactions. Kinetic studies have shown that the selectivity of charcoal granules for phenolic compounds was increased by coating the granules with a thin layer of nylon 6. The increase in selectivity is probably a result of the different binding mechanism between solute and the polymer. These studies have shown that possible selective coatings may be evaluated more effectively on the basis of simple preliminary drug-plastics interaction studies.

INTRODUCTION

Considerable interest has been aroused by the direct removal of toxins arising from metabolic processes and drug overdose from blood by perfusion over adsorbents.[1-3] The general criteria pertinent to the choice of adsorbents for such haemoperfusion techniques include:

(a) a high capacity for the drug or toxin in order to minimize the quantity of adsorbent to a practical amount;
(b) the adsorbent should be nontoxic and exhibit no deleterious effects on the blood;
(c) selectivity for the drug or toxin to be removed to minimize the removal of other blood constituents;
(d) the adsorbent must be capable of being sterilized;
(e) the adsorbent must be stable and comparatively inexpensive.

Adsorbents, which are generally packed into a small cartridge through which blood is passed, include charcoals, ion-exchange resins, and complexing agents.

* To whom correspondence should be addressed.

Journal of Biomedical Materials Research, Vol. 14, 743-751 (1980)

0021-9304/80/0014-0743$01.00

Of these, charcoals have been most widely used to treat hepatic coma, uraemia, and for drug detoxification. Charcoals have a high adsorptive capacity although they tend to be nonselective.

In use the adsorbents are coated with a thin layer of a polymer which performs several functions. The use of polymer coatings which decrease the incidence of thrombus formation promote the biocompatibility of the adsorbent with blood. Coatings can reduce the friability of the adsorbent and thus prevent the shedding of fine particles into the blood. The polymer coat may also confer some degree of selectivity for the adsorbent by controlling the nature of materials allowed access to the adsorption sites inside the charcoal.

In this case the selectivity of the column may be dependent upon the affinity of the drug or toxin for the polymer coating material. It is desirable, therefore, to select a polymer that has a high affinity for the drug and low affinity for the other compounds present in plasma. On existing columns the charcoal is coated with acrylic hydrogels such as polyhydroxyethylmethacrylate or a layer of a cellulose nitrate onto which a layer of albumin is adsorbed.[4] Both these coatings increase biocompatibility and reduce the amount of fines shed from the cartridge into the blood, however the physico-chemical nature of these materials is such that many molecules also present in the blood compete with the specific drug or toxin for adsorption sites on the charcoal thus causing a reduction in column capacity. Sparks[4] has suggested that the sorption capacity of the adsorbent for a specific molecule might be increased by the use of a selective polymeric microcapsule wall around the adsorbent required. Meier et al.[5] have reported that cellulose derivative coatings on charcoal show some selectivity on a "like dissolving like" principle, e.g., hydrophobic molecules diffuse more rapidly through hydrophobic coatings. Huang[6] has reported the use of charged polymers which specifically select species of opposite charge.

Investigations into the interaction of drugs and toxins with haemoperfusion column materials is impaired by the presence of proteins from blood or plasma to which incidentally drugs may bind. Other endogenous compounds present in the plasma may also compete for the adsorbent. It was therefore thought desirable to investigate a simple, well-defined, reproducible model system so that the fundamental factors governing solute interactions with the individual components of the coated adsorbent system as well as the coated adsorbent itself may be assessed. As a result of such studies, column materials or increased selectivity might be chosen on a more rational basis. Here we report our preliminary findings on the interactions of some model compounds with one possible coating material, nylon 6, and the consequences of these interactions on the selectivity of a nylon 6 coated charcoal adsorbent system. The model compounds chosen were weak organic acids and bases of the benzoic acid or phenolic derivative type which are typical of drug molecule types.

MATERIALS AND METHODS

The model compounds selected were 4-methoxy benzoic acid (4-MBA)*. 4-aminoethyl benzoate (4-AEB)†, 4-nitrophenol (4-NP)† and phenol (P).† Activated coconut charcoal granules (Sutcliffe Speakman Co. Ltd., B.S. size 5–10 mesh)[7] were specially purified and supplied as a gift by Smith and Nephew Research Ltd., Harlow, Essex, England. Nylon 6 (B.D.H. Ltd.) was obtained as injection molding granules. Nylon 6 powder was prepared by precipitation from formic acid solution according to the method of Richardson and Meakin.[8] Nylon 6 coated charcoal granules were prepared by spraying 300 ml of a 5% w/v formic acid solution of nylon 6 into a rotating bed of 100 g charcoal granules in a continuous stream of hot air. After coating, the granules were washed several times with distilled water to remove residual solvent, and then dried to constant weight. Solubilities were determined as described by Richardson and Meakin.[8]

Both single solute and binary solutions of the model compounds were assayed by standard UV spectroscopic techniques using an appropriate buffer solution.

The interaction of the model compounds with nylon 6 powder was determined by a shake flask method in a thermostated bath (±0.1°C) normally using 10 ml of solution and 0.2 g powder. Samples were equilibrated for 12 hr before assaying the supernatant. Equilibration time studies showed that equilibrium was attained within 30 min. Interactions of model compounds with the charcoal granules was studied similarly using 50 ml of solution and 0.02 g granules. Equilibration times for the charcoal were much longer being of the order of 4 days; a standard shake time of 7 days was therefore adopted. All interaction studies were carried out in a McIlvaine's citrate-phosphate buffer of constant ionic strength (0.5*M*). The pH of the buffer was selected to optimize the amount of the unionized species present in solution.

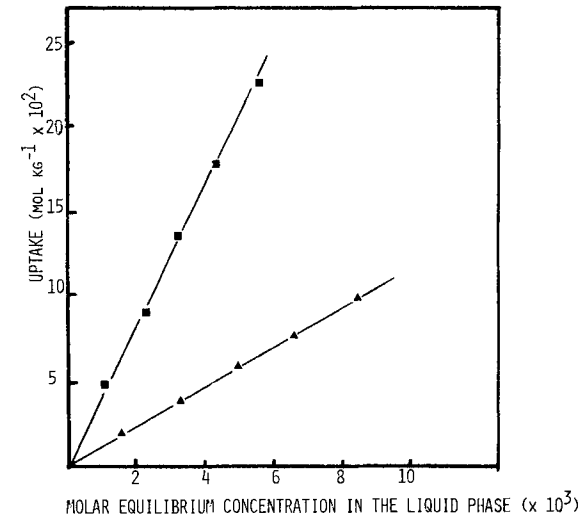
Adsorption rates into both charcoal and nylon 6 coated charcoal granules were determined by placing 2 g adsorbent into 1 liter of solution which was stirred with a PTFE paddle at 750–800 rpm. At appropriate times, aliquots of the supernatant were removed and assayed.

RESULTS AND DISCUSSION

The sorption isotherms for the model compounds on nylon 6 powder are shown in Figures 1(a) and 1(b). The isotherms are linear, designated C-type according to the Giles classification,[9] indicating that the solutes are penetrating the polymer matrix as the availability of the interaction sites apparently remains constant and independent of the amount of compound previously adsorbed. The linearity of the isotherms enables the affinity of the solutes for the nylon 6 to be expressed by their slope or affinity constant (K) which are shown in Table I.

The K values for weakly ionizing aromatic compounds interacting, with

* Sigma Ltd.
† B.D.H. Ltd.



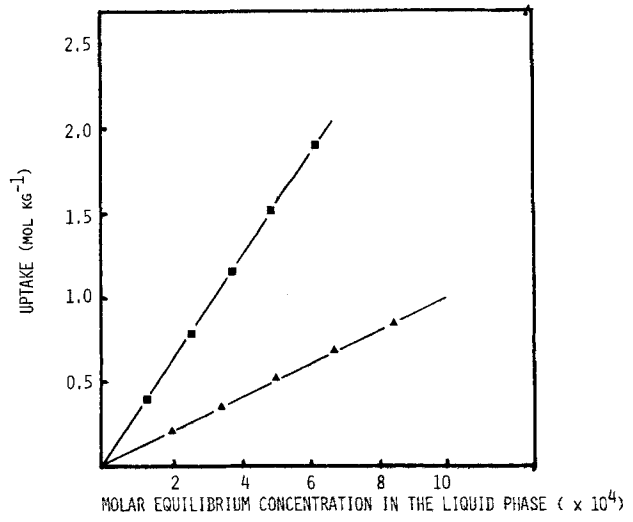


Figure 1. (a) Sorption isotherms for 4-nitrophenol and phenol by nylon 6 powder at pH 2.4 and 30°C. (■) 4-nitrophenol, (▲) phenol. (b) Sorption isotherms for 4-methoxy benzoic acid and 4-aminoethyl benzoate by nylon 6 powder at pH 2.4 and 30°C. (■) 4-methoxy benzoic acid, (▲) 4-aminoethyl benzoate.

plastics have been shown to be dependent upon the fraction of unionized species present.[8] This is reflected in the data for 4-AEB where increasing the pH from 2.4 to 3.4 increases K from 9.3 to 21.8 1 kg^{-1}, a factor of 2.3. The pK_a of 4-AEB, a basic compound, is 2.57 which results in the fraction of the unionized interacting species present increasing from 40 to 90%, over this pH range, a factor of 2.3. The K value for 4-MBA which is an acid shows only a

TABLE I
Affinity Constants *K* for the Sorption of Model Compounds by Nylon 6 Powder at 30°C

pH	Solute	Affinity Constant K (1 kg^{-1})	S.D.	Solubility at 30°C	pK_a
2.4	4-AEB	9.3	0.2	1.05×10^{-2} [a]	2.57
	4-MBA	29.2	0.3	1.50×10^{-3} [b]	4.47
	4-NP	46.7	0.9	1.39×10^{-1} [c]	7.15
	P	11.6	0.3	7.84×10^{-1} [c]	10.00
3.4	4-AEB	21.8	0.6	7.40×10^{-3} [c]	
	4-MBA	28.1	0.8	1.63×10^{-3} [c]	

[a] Solubility data obtained by calculation from data of Richardson and Meakin (ref. 8).
[b] Literature value for unionized 4-MBA at pH 1, ionic strength 0.5*M* (ref. 10).
[c] Experimentally determined.

slight rise in K value as the pH falls from 3.4 to 2.4 since the pK_a of 4.47 is too high to have a significant effect on the species fraction under these conditions. Similarly the high pK_a values for the phenolic compounds would predict no difference in K value or solubility at pH 3.4 from that determined experimentally at pH 2.4.

It has also been demonstrated that an approximately inverse linear relationship exists between the $\log_{10}K$ value on the nylon 6 and the $\log_{10}$ solubility for structurally related compounds including 4-substituted benzoic acids, their ethyl esters,[10] and substituted acetanilides.[11] This is indicative that the mechanism of the interaction between solute and polymer is similar within the given series. From Table I, it is seen that although the solubility of 4-NP and P are 10–100 times greater than for 4-AEB and 4-MBA at pH 2.4, their K values are of the same order of magnitude. This suggests there is a different interaction mechanism between nylon 6 and the two phenols from that between the polymer and 4-AEB and 4-MBA. Such a difference in mechanism may form the basis for imparting selectivity to coated carbon; 4-MBA and 4-NP were therefore selected for further detailed study, as representative of each class of molecule.

In order to further elucidate the interaction mechanism the sorption isotherms for 4-NP and 4-MBA were determined over the temperature range 7–60°C, the results further emphasizing the difference in mechanism. Figure 2 shows the data plotted according to the Van't Hoff equation. The isochore for 4-NP was linear over the whole temperature range studied, whereas that for 4-MBA showed a discontinuity at about 40°C. Such discontinuities have been noted in previous drug–nylon interaction studies. This discontinuity may be associated with a secondary phase transition in the polymer[12] attributable to structural changes in the polymer[13] and if some degree of plasticization by the solute occurs the temperature at which the phase transition is apparent would be greatly reduced. The absence of discontinuity in the 4-NP isochore suggests that this compound does plasticize the polymer to some extent which may be the result of specific hydrogen bond formation between 4-NP and polar sites in the nylon 6.

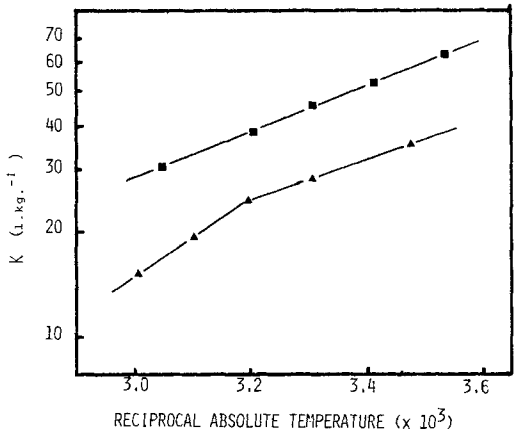
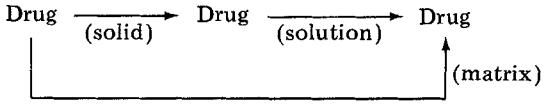


Figure 2. Van't Hoff plots for the sorption of 4-methoxy benzoic acid and 4-nitrophenol. (▲) 4-methoxy benzoic acid, (■) 4-nitrophenol.

The affinity constant (K) is a measure of the relative affinity of the solute in a particular solution system for the plastic. It has been shown that K values alter if the solubility of the compound in the solvent vehicle is modified; inorganic electrolyte decreases the aqueous solubility of neutral organic compounds whereas cosolvents effect an increase.[8,10] Increasing cosolvent concentration or ionic strength therefore decrease or increase K values, respectively. Clearly, therefore, the thermodynamic parameters associated with sorption represent a transfer process involving solute dissolution in the solvent as well as the intrinsic solute-polymer interactions. Effective determination of the thermodynamic parameters associated with the solute-polymer interaction requires separation of the solute dissolution effects from those of the experimental sorption process as outlined in the interaction diagram below.



Standard enthalpies of sorption were determined from the data shown in Figure 2. For 4-MBA, values were calculated above and below 40°C. Standard enthalpies of dissolution were determined from similar plots of solubility measurements over the temperature range 10-60°C. The standard enthalpy of the intrinsic interaction with the polymer can then be obtained from eq. (1) which is derived from the interaction scheme.

$$\Delta H^0_{(\text{interaction})} = \Delta H^0_{(\text{sorption})} + \Delta H^0_{(\text{dissolution})} \quad (1)$$

Standard entropies and free energies of interaction were determined in a similar manner and Table II shows the calculated thermodynamic parameters for the intrinsic interaction process.

The data clearly differentiates between the two compounds. The standard

TABLE II
Thermodynamic Parameters for the Interaction of 4-MBA and 4-NP with Nylon 6 Powder

COMPOUND	ΔH^0 (interaction) (K J mole^{-1})	ΔS^0 (interaction) (J mole^{-1} K^{-1})	ΔG^0 (interaction) (K J mole^{-1})
4-MBA	+11.8[a]	+14.2	+7.7*
	+19.1[b]	+37.6	+7.0**
4-NP	+24.5[c]	+96.6	−6.7*

[a] 15–40°C.
[b] 40–60°C.
[c] 10–55°C, * $\Delta G°_{323}$ ** $\Delta G°_{283}$.

free energy interaction is positive for 4-MBA and negative for 4-NP. More detailed consideration of the data shows that for 4-MBA the interaction is enthalpy driven whilst for 4-NP it is an entropically dominant process.

These sorption studies therefore, demonstrate that nylon 6 interacts preferentially with the phenolic compound in contrast to that which might be expected from solubility considerations. Figure 3 shows that with charcoal however, the converse is the case, the extent of interaction is greater for 4-MBA than for 4-NP which is in agreement with predictions from their solubilities. It was thought possible therefore that the selectivity of the charcoal for the phenolic compound could be increased by coating the charcoal with nylon 6. Figures 4 and 5 show the rates of uptake from $10^{-3}M$ solutions of 4-MBA and 4-NP, respectively at pH 2.4, from both single solute solution and equimolar binary solutions. It is apparent that 4-MBA has a slightly higher rate of uptake onto uncoated charcoal than 4-NP as might be expected. No difference in uptake rates was observed from the binary mixtures. Both 4-NP and 4-MBA alone showed a marked reduction in uptake rate when the charcoal was coated with nylon 6. From binary solutions, the adsorption rate of 4-NP

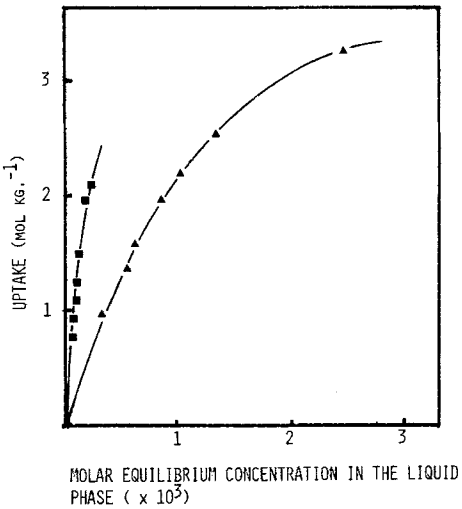


Figure 3. Adsorption isotherms for 4-methoxy benzoic acid and 4-nitrophenol on charcoal granules at pH 2.4 and 30°C. (■) 4-methoxy benzoic acid, (▲) 4 nitrophenol.

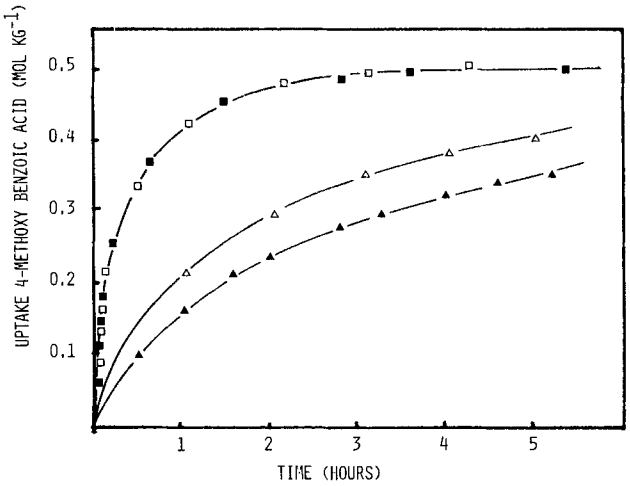


Figure 4. The rate of uptake of 4-methoxy benzoic acid from $10^{-3}M$ solution by uncoated and nylon 6 coated charcoal granules in the absence and presence of an equimolar concentration of 4-nitrophenol (pH 2.4 and 30°C). 4-methoxy benzoic acid—(□) uncoated charcoal, (△) nylon 6 coated charcoal; 4-methoxy benzoic acid in the presence of 4-nitrophenol (■) uncoated charcoal, (▲) nylon 6 coated charcoal.

which has the higher affinity for the nylon 6 coat, was unaffected by the presence of 4-MBA whereas the uptake rate of the latter on the coated charcoal was further reduced by the presence of 4-NP. It would appear therefore that the polymer coat is decreasing the rate of uptake of 4-MBA to a greater extent than that for 4-NP relative to the rates on uncoated charcoal, a result which would be predicted from nylon 6 sorption studies.

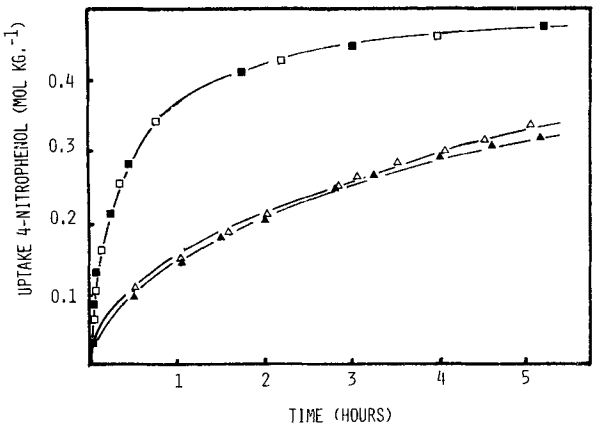


Figure 5. The rate of uptake of 4-nitrophenol from $10^{-3}M$ solution by uncoated and nylon 6 coated charcoal granules in the absence and presence of an equimolar concentration of 4-methoxy benzoic acid (pH 2.4 and 30°C). 4-nitrophenol—(□) uncoated charcoal (△) nylon 6 coated charcoal, 4-nitrophenol in the presence of 4-methoxy benzoic acid—(■) uncoated charcoal, (▲) nylon 6 coated charcoal.

CONCLUSIONS

This study has shown that polymeric coats may be used to modify the selectivity of adsorbents used in haemoperfusion systems to small molecules. The basis of polymer selectivity using nylon 6 is probably the result of a different interaction mechanism between polymer and solute. The work has also indicated that it may be possible to select potential coatings more effectively on the basis of simple preliminary drug-plastics interaction studies.

References

1. H. Yatzidis, "A Convenient Haemoperfusion Micro-Apparatus over Charcoal for the Treatment of Endogenous and Exogenous Intoxicants," *Proc. Eur. Dial. Transplant Assoc.*, **1**, 83–86 (1964).
2. E. H. Dunlop, B. G. Gazzard, P. G. Langley, M. J. Weston, L. R. Cox, and R. Williams, "Design Features of Haemoperfusion Columns Containing Activated Charcoal," *Med. Biomed. Eng.*, **14**(2), 220–226 (1976).
3. J. A. Vale, J. A. Rees, B. Widdop, and R. Goulding, "The Use of Charcoal Haemoperfusion in the Management of Severely Poisoned Patients," *Br. Med. J.*, **1**, 5–10 (1975).
4. R. E. Sparks, K. K. Goldenhersh, W. Huang, and N. S. Mason, "Rationale for the Use of Microencapsulated Sorbents in Uraemia and Other Illnesses," *Proceedings of the Conference on Plastics in Medicine and Surgery*, University of Strathclyde, Glasgow, U.K. (1975).
5. P. M. Meier, R. E. Sparks, and O. Lindon, "Adsorption Control and Kinetic Model for Microencapsulated Carbon," National Technical Information Service of the United States Department of Commerce, PB 231 829 (1972).
6. W. D. Huang, "Microencapsulation to Control Adsorption on Activated Carbon," D.Sc. thesis, Washington University, 1974.
7. D. Simmonite, "Coating of Particulate Material," British Patent Specification No. 1, 484 566, July, 1973.
8. N. E. Richardson, and B. J. Meakin, "The Sorption of Benzocaine from Aqueous Solution by Nylon 6 Powder," *J. Pharm. Pharmac.*, **26**, 146–174 (1974).
9. C. H. Giles, D. Smith, and A. Huitson, "A General Treatment and Classification of the Solute Adsorption Isotherm," *J. Colloid Interface Sci.*, **47**(3), 755–765 (1974).
10. N. E. Richardson, and B. J. Meakin, "The Influence of Cosolvents and Substrate Substituents on the Sorption of Benzoic Acid Derivatives by Polyamides," *J. Pharm. Pharmac.*, **27**, 145–151 (1975).
11. T. M. Ward, and R. P. Upchurch, "Role of the Amido Group in Adsorption Mechanisms," *J. Agri. Food Chem.*, **13**, 334–340 (1965).
12. O. P. Ho, "Some Permeability and Sorption Characteristics of Polyamide Membranes," M.Sc. thesis, University of Bath, U.K., 1977.
13. F. W. Lord, "Transitions and Relaxation Processes in ω*-Amino Acids," *Polymer*, **15**, 42–48 (1974).

Received January 25, 1980
Accepted May 30, 1980