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Selective Adsorption by Activated Charcoal Preparations for Adsorbates of Medical Interest Ranging in Molecular Weight from About 100 to 800

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The adsorptive power of commercial activated charcoal preparations was compared in powdered form for adsorbates of medical interest ranging in molecular weight from about 100 to 800. For some adsorbates, the adsorptive powers of the charcoals investigated varied up to three-fold. Some activated charcoals showed distinct size-selectivity for adsorbates: the charcoals which favor adsorption of smaller molecules showed less adsorptive power for larger molecules and *vice versa*. Two types of adsorbates for evaluation of the adsorptive power of medicinal charcoal are proposed.

Keywords——activated charcoal; activated carbon; activated charcoal powder; activated charcoal preparation; adsorption efficiency; adsorptive power; selective adsorption; medicinal charcoal

The use of activated charcoal as an adsorbent in direct hemoperfusion (DHP) has received tremendous attention as a life-saving measure of final resort in hepatic and renal failures as well as in acute intoxications due to drugs and poisons.[1] A further application of this technique is in the field of regional cancer chemotherapy where the combination of a high dose of anticancer drug with DHP is expected to reduce the systemic toxicity of the drug.[2] For this relatively new therapy, a great deal of effort has been made to develop activated charcoal preparations which are hemocompatible and of sufficient adsorption capacity. Concomitant with this therapy, the oral use of activated charcoal for removal of certain toxins through the gastrointestinal tract (gut dialysis) is also receiving attention as a supportive measure.[3] Thus, the oral use is not limited to retardation of drug absorption in acute intoxication but can be extended to acceleration of the elimination of endogenous toxins[4] and drugs[5] including the aforementioned cancer chemotherapeutic agents.

In the past few years we have been directing our efforts in the utilization of powdered activated charcoal towards the development of a palatable dosage form and an adsorbent for use in DHP because the adsorption rate and thus the practical capacity is often greatly reduced in tablets or conventional granular preparations. For oral use, we developed a small granular preparation by drying spherical agar beads in which powdered activated charcoal is finely dispersed[6] and for DHP similar but larger wet beads were investigated.[6e] In the latter case, a major advantage of agar or agarose encapsulation is to exclude blood corpuscles, particularly platelets, from the interior of the beads so that their direct contact with activated charcoal is avoided, while the macroporous gel matrix allows free diffusion of the plasma into the interior of the beads.[7] Thus, even albumin-bound species can come into direct contact with the powdered charcoal.

In selecting preparations of activated charcoal powder suitable for these uses, we have

tested several commercial preparations for their adsorptive efficiency using adsorbates of medical interest with molecular weights in the range of about 100 to 800. Most of published reports on this subject[8] are limited, to our knowledge, to evaluation of several commercial brands of activated charcoal for one or two adsorbates or one brand for a variety of adsorbates. In this communication we report the apparent selectivity of activated charcoal preparations for various adsorbates.

Experimental

Materials——Detailed information on all commercial preparations of activated charcoal used in this study is listed in Table I. Charcoals A (a reagent grade chemical) and B (JP X grade) were purchased, but all other preparations were kindly supplied by the manufacturers. Only charcoal A was purified according to the method of Daly and Cooney.[9] The following reagent grade chemicals were purchased from Wako Pure Chemical Industries, Osaka: creatinine, uric acid, quinine sulfate dihydrate, cholic acid, methylene blue, and salicylic acid. Acetaminophen, theophylline, phenytoin, and phenobarbital of JP X grade were employed without further purification. Bromosulfophthalein (BSP) was purchased from Aldrich Chemical Co., Milwaukee, Wis., USA as the tetrahydrate disodium salt. Paraquat dichloride was precipitated from Gramoxan® containing 24% paraquat dichloride with a mixture of methanol and acetone. Pure paraquat dichloride (purity > 99.7%) was kindly supplied by ICI, Japan and was used as the standard.

Adsorption Study[6a]——Activated charcoal powder (20 mg), passed through sieves and dried at 110 °C for several hours, was placed in each screw-capped test tube together with 10 ml of Medium 2 of JP X Disintegration Test containing 20 μmol of adsorbate. The tubes were rotated at 37 °C end-over-end at 23 rpm for 1 to 48 h. At the end of the rotation period, the concentration of adsorbate in the supernatant was assayed spectrophotometrically on a Shimadzu model UV-240 double-beam spectrophotometer and the percent adsorbed was calculated. Cholate was determined by forming sulfuric acid chromogens as reported previously,[6b] BSP after addition of an alkali, paraquat after addition of 1% $Na_2S_2O_4$ in 1 N NaOH, and creatinine by utilization of the Jaffe reaction.[10] Other adsorbates were determined by direct measurement of absorbance at the wavelengths of maximum absorption. All granular preparations were pulverized prior to the study. Kureha's spherical beads with diameters ranging from 0.4 to 1.0 mm were studied in the original form (charcoal E) as well as in the powdered form (charcoal D).

Results and Discussion

Adsorption of Various Substances by Activated Charcoal Preparations

Table I shows the percentage adsorption of salicylate and cholate by 12 activated charcoal preparations. Comparison among the charcoal preparations was not carried out on the basis of equilibrium adsorption capacity because the rate factor is more important in DHP than the equilibrium capacity. Charcoals A and D adsorbed cholate more effectively than salicylate, whereas all the others adsorbed salicylate better, although the difference was not so great for charcoals C, I, J, and L. Thus, charcoal A or D is a definite choice for cholate adsorption and charcoal B and other charcoals with similar efficiency are better for salicylate adsorption. This apparent selectivity of activated charcoals for adsorbates probably originates in the differences in the source material, method and period of activation, which in turn lead to differences in pore size and pore size distribution, and other properties of the adsorbents. The size and shape as well as the nature of adsorbates must also contribute to the selectivity. The variations in adsorptive power among the charcoals were up to 2.4- and 3.0-fold for salicylate and cholate, respectively.

Our present results explain the low efficiency of activated charcoal A reported previously[6a] in an *in vivo* adsorption study of salicylate in the rat. Indeed, this preparation showed by far the lowest capacity of the charcoals investigated in this study.

For charcoals A to E, adsorption efficiency for a wide variety of adsorbates was evaluated under the same conditions as mentioned above and the results are summarized in Table II. The selected adsorbates of medical interest include creatinine and uric acid for renal failure; cholate for pruritus and hepatic disorders; various drugs and paraquat which

Table I. Charcoal Preparations and Their Salicylate and Cholate Adsorption Capacities

Charcoal	Commercial source	Lot No.	Source material	Method of activation	Salicylate[a]	Cholate[a]
A	Wako, purified, powder	PEQ-3917	Wood	Chemical	30.9±0.8	89.8±0.7
B	Inuhinode, powder	7005	Wood	Steam	74.6±0.4	47.3±1.9
C	Takeda, powder	Shirasagi-P, M-321	Wood	Steam	77.7±0.8	66.4±0.1
D	Kureha, beads	BAC-MU-AZ	Pet. pitch	Steam	66.7±0.1	92.6±0.1
E[b]	Kureha, beads	BAC-MU-AZ	Pet. pitch	Steam	63.5±0.4	19.1±1.4
F	Darco, powder	G-60	?	?	56.3±0.4	30.9±2.3
G	Norit A, powder	V3E-9993	Wood	Steam	68.1±0.2	44.4±1.8
H	Norit I, powder	V3E-9997	Wood	Steam	51.3±1.6	26.4±2.1
I	Mitsubishi, granules	Diahope 0065	Coal	Steam	71.1±0.4	64.7±1.8
J	Mitsubishi, granules	Diahope S-90	Coal	Steam	73.7±0.4	66.4±0.1
K	Hokuetsu, powder	SD	Wood	Steam	75.5±1.0	41.9±3.5
L	Hokuetsu, granules	CL-H	Coconut	Steam	72.3±0.4	67.1±0.1

a) The percentage of adsorbate adsorbed (mean±S.D. of 2—4 determinations) by 20 mg of activated charcoal powders (mesh size >200, dried at 110 °C) or powdered charcoals D, I, J, and L (mesh size >200, dried at 110 °C) when shaken at 37 °C for 1 h with 10 ml of Medium 2 (pH 6.8—6.9) containing 20 μmol of adsorbate. *b*) Charcoal E with a diameter of 0.4—1.0 mm, specially developed for use in DHP, was studied similarly in the original bead form.

Table II. Adsorption Characteristics of Selected Activated Charcoals for Various Adsorbates[a]

Adsorbate	Mol. wt.	Elec. charge	Charcoal						
			A	B	C	D	E	E (24 h)[b]	E (48 h)[b]
Creatinine	113		30.6±0.5	73.1±0.4	71.0±0.6	74.0±0.6	64.0±0.1	—	—
Salicylate	137	−1	30.9±0.8	74.6±0.4	77.7±0.8	66.7±0.1	63.5±0.4	67.4±1.7	—
Acetaminophen	151		76.5±1.2	99.4±0.2	99.2±0.1	98.2±0.1	95.7±0.9	—	—
Urate	167	−1	55.8±0.5	96.4±0.9	95.8±0.1	99.3±0.2	61.6±1.6	—	—
Theophylline	180		91.2±0.4	99.7±0.1	99.6±0.1	99.7±0.1	97.6±0.7	—	—
Paraquat	186	+2	31.2±0.9	30.9±1.3	34.5±0.7	39.5±0.2	34.6±1.2	47.7±0.7	54.7±2.7
Phenobarbital	232	−1[c]	85.1±0.2	98.6±0.2	99.2±0.1	99.0±0.2	82.5±2.1	—	—
Phenytoin	252		97.1±0.1	99.5±0.1	99.5±0.1	99.6±0.1	—	99.8±0.1	—
Methylene blue	285	+1	99.4±0.1	97.6±1.1	*ca.* 100	*ca.* 100	48.0±1.3	—	—
Quinine	325	+1	97.5±0.1	80.7±0.2	96.0±0.1	99.8±0.1	29.1±0.2	77.6±1.9	86.8±2.7
Cholate	408	−1	89.8±0.7	47.3±1.9	66.4±0.1	92.6±0.1	19.1±1.4	52.7±0.1	64.4±1.2
BSP	792	−2	71.9±0.2	44.5±2.6	47.9±0.4	69.9±0.5	15.4±0.2	45.1±1.4	53.3±1.3

a) Charcoals A—E are as presented in Table I. The values in the table are percent of adsorbates adsorbed when studied under the same conditions as indicated in Table I. *b*) For charcoal E, the number of hours indicates the shaking period. *c*) At the pH of medium 2 (6.8) about 24% ionized.

often cause intoxication; BSP, a diagnostic agent, and substances employed for evaluation of the adsorptive power of Medicinal Charcoal, JP X. Table II lists these adsorbates in increasing order of molecular weight from top to bottom. Up to phenytoin, charcoals B—D show better

TABLE III. Comparison of Langmuir Constants[a] between Charcoals A and B in Medium 2 at 37 °C

Adsorbate	Charcoal	Size	$D_b^m \times 10^4$ mol/g	$K \times 10^{-4}$ M^{-1}
Salicylate	A	Mesh >200	3.91	0.422
	B	Mesh >200	9.10	3.10
Cholate	A	Unsifted[b]	10.1[c]	3.79[c]
		Mesh >200	9.90	9.91
	B	Unsifted	5.13[c]	12.5[c]
		Mesh >200	6.40	36.9
Theophylline	A	Unsifted[b]	13.2	1.79
	B	Unsifted	16.9	6.60

a) Langmuir equation, $D_b = D_b^m KD_f/(1+KD_f)$, where D_b is the amount (mol) of adsorbate adsorbed per gram of adsorbent; D_f is the concentration of unadsorbed adsorbate in M; and D_b^m and K are Langmuir's capacity and affinity constant, respectively. *b*) Used as received after drying (not purified). Purification by acid treatment decreased rather than increased the adsorption capacity of charcoal A for some adsorbates. *c*) Ref. 6*b*.

efficiency than charcoal A, but thereafter the adsorption by charcoal B is clearly less than that by charcoals A, C, and D as we go down the list. If we compare charcoals A and B only, as the molecular weight of the adsorbates increases the relationship between charcoals A and B reverses, indicating that characoal A is more suitable than charcoal B for larger adsorbates, whereas charcoal B is more suitable than charcoal A for smaller adsorbates. The adsorption characteristics of charcoals C and D closely resemble those of charcoal B. However, charcoal D showed better adsorption for the larger adsorbates.

Since activated charcoal favors adsorption of hydrophobic molecules, the larger and more hydrophobic molecules are effectively adsorbed. The electric charge on the molecule, irrespective of the sign and of whether or not the molecule acquired it in medium 2, is a retarding factor for adsorption. Thus, paraquat ion shows a relatively small affinity to all the charcoals investigated in relation to its molecular weight. Table II also shows that the adsorbates located at the center of the table (molecular weights in the region of 180—325) differentiate the adsorptive power of adsorbents very poorly.

Adsorption by powdered activated charcoal is usually a fast process, whereas that by granular or tablet form is very slow.[11] Thus, charcoal E (which is specially designed for use in DHP) was compared with charcoal D in powdered form. Comparison after a 1 h shaking period shows fairly good agreement for adsorbates of small molecular weight indicating that adsorption of these adsorbates is a fast process even for charcoal E. However, as the molecular weight becomes larger the adsorption percentage of charcoal E at 1 h becomes appreciably less than that of charcoal D, and it approaches the latter with longer adsorption time.

Langmuir constants for adsorption of salicylate, cholate, and theophylline by charcoals A and B (summarized in Table III) show that the values of the capacity constant, D_b^m, for these adsorbates closely parallel those of the corresponding nonequilibrium adsorption percentage at 1 h presented in Table II. The values of the affinity constant, K, of charcoal B were greater than those of charcoal A for these adsorbates.

Effect of the Size of Charcoal Particles on the Adsorption Characteristics of Charcoals A and B

Since charcoals A and B showed distinctly different adsorption characteristics, these charcoals were further studied with regard to the effect of particle size on the adsorption characteristics by selecting salicylate and cholate as representative small and large adsorbates, respectively.

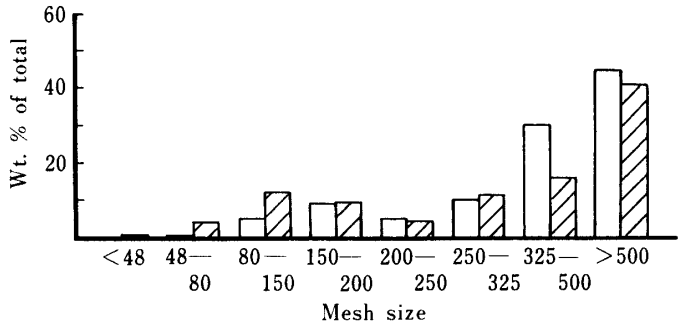
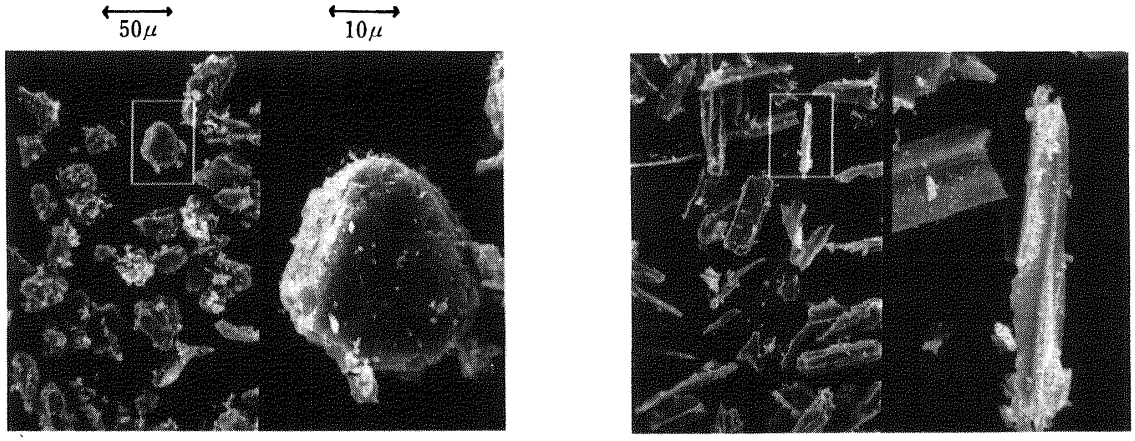


Fig. 1. Particle Size Distribution of Charcoals A and B

□, charcoal A; ▨, charcoal B.
Sifted for 1 h with the aid of a mechanical vibrator.



charcoal A charcoal B

Fig. 2. Scanning Electron Microscopic Photographs of Charcoals A and B, Mesh Size 325—500

TABLE IV. Size-Dependent Adsorption of Salicylate and Cholate by Charcoals A and B from Medium 2 at 37 °C

Adsorbate	Charcoal	Mesh size	% adsorbed[a]		
			Adsorption time, h		
			1	24	48
Salicylate	A	80—150	31.3±2.3	30.5±2.3	—
		325—500	32.1±1.9	30.9±0.2	—
		>500	32.6±0.8	30.6±2.2	—
	B	80—150	63.5±2.1	63.4±1.8	—
		325—500	74.8±0.6	76.0±0.1	—
		>500	75.7±3.5	78.7±0.4	—
Cholate	A	80—150	73.1±3.6	88.2±7.4	87.6±0.3
		325—500	90.0±1.3	92.6±4.5	—
		>500	89.5±2.1	91.1±0.2	—
	B	80—150	15.1±2.3	19.6±0.8	17.0±0.9
		325—500	46.6±5.4	53.9±0.4	55.6±0.1
		>500	57.2±6.1	70.3±3.2	72.7±1.6

a) As for Table I.

Figure 1 shows the size distribution of charcoals A and B. Except that charcoal A as a whole has a somewhat smaller particle size than charcoal B, no characteristic difference was observable between the two. However, the photomicrographs (Fig. 2) obtained by scanning

electron microscopy of fractions, mesh size 325—500, of the charcoals show a distinct morphological difference. The salicylate and cholate adsorption behavior of some selected fractions of the charcoals are presented in Table IV. As regards salicylate adsorption, the adsorption capacity is apparently greater for charcoal B than for charcoal A. In charcoal A the capacity was independent of the size, but in charcoal B the capacity was slightly higher for smaller fractions. No significant difference in the rate of adsorption was observed between different fractions in both charcoals. As regards cholate adsorption, the rate of adsorption on charcoal B was smaller than that on charcoal A, particularly for the two smaller fractions and the dependence of the capacity on the size was clearly demonstrated in charcoal B, *i.e.* the smaller the size, the greater the capacity.

While the difference in particle size and/or size distribution between charcoals A and B is certainly a factor contributing to the difference in the overall capacity of cholate adsorption by charcoals A and B, this does not totally account for the difference. The fraction of mesh size 80—150 of charcoal B was triturated with a mortar and pestle and the triturated powder was sieved. The fraction of mesh size 325—500 thus obtained showed only about 55% of the equilibrium cholate adsorption of the corresponding fraction presented in Table IV. Thus, with larger particles the micropores for adsorption of relatively larger molecules are not all accessible to the adsorbate even after equilibration for 24—48 h, and upon size reduction additional sites apparently become available. This property is a characteristic of charcoal B and may be a function of the source material, method of activation, *etc.*

Adsorbates Suitable for Testing Adsorptive Power of Medicinal Charcoal

Many tests are available for evaluation of the adsorptive power of different brands of activated charcoal. Representative methods are the iodine relative efficiency test and the molasses relative efficiency test for adsorption of volatile and large molecules, respectively.[12] For adsorption of most drugs and substances of medical interest ranging in molecular weight from about 100—800, activated charcoal having many pores in the range of 20 Å or so in diameter is considered best.[13] For this reason methylene blue is often employed and is specified as a test substance for determination of adsorptive power under Medicinal Charcoal in JP X and USP XX. However, our results presented in Table II clearly show that the adsorbates located at the center of the table, including methylene blue and quinine, differentiate the adsorptive power of adsorbents very poorly. Thus, the two adsorbates specified in JP X (methylene blue and quinine) are not the combination of choice for assessing the adsorption efficiency for other adsorbates of medical interest, which are within the above molecular weight range. Rather, adsorbates such as creatinine or salicylate and cholate or BSP should be included for evaluation of the adsorptive power of activated charcoal if evaluation cannot be made for a particular adsorbate of interest, or an activated charcoal powder with a broad spectrum of adsorbates is required.

Conclusions

We have demonstrated that some activated charcoal powders show selectivity for adsorbates. Our results indicate that the molecular size of adsorbates is an important contributing factor. Thus, even for adsorbates with a molecular weight in the range of 100—800, an activated charcoal powder which shows a high capacity for adsorbates with a molecular weight of around 100 does not necessarily well adsorb adsorbates with a molecular weight of say 700.

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