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Preparation and Drug Adsorption Characteristics of Activated Carbon Beads Suitable for Oral Administration[1)]

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An activated carbon preparation suitable for oral administration as an intestinal adsorbent was prepared by drying spherical beads of 48 to 250 mesh in which 8% activated carbon powder was dispersed. The final preparation, dried activated carbon beads containing about 67% activated carbon in agar, consists of fine granules with good flow properties and is free from many of the handling problems associated with fine charcoal powders. The *in vitro* adsorption characteristics of the original fine powder were essentially retained when salicylic acid and acetaminophen were used as adsorbates, including the rate of adsorption and the enhancing effect of sodium chloride on the adsorption of salicylate ions. Administration of the beads to rats caused a statistically significant reduction in plasma salicylate level at about 2 h after administration, and no greater reduction was observed with the powder. These results indicate that the preparation is a promising candidate as an intestinal adsorbent.

Keywords——activated carbon preparation; activated charcoal preparation; activated carbon bead; oral charcoal preparation; microencapsulated charcoal; agar encapsulated activated carbon; salicylic acid adsorption; acetaminophen adsorption; salt effect

Although the use of activated carbon columns for hemoperfusion in the treatment of drug overdosage, liver failure, and uremia has lately received tremendous attention,[2)] the oral use of activated carbon has been left unexplored, particularly in Japan. In the United States and European countries, the oral administration of activated carbon powder in slurry form, as much as 100 g in a single dose, is considered to be effective as an emergency measure in drug overdosage.[3)] However, activated carbon powder is difficult to handle for patients as well as for pharmacists. The slurry has many palatability problems, such as a gritty feeling, stickiness in the mouth and the throat, difficulty in swallowing, *etc.* Only a few oral charcoal preparations, such as Charcocaps, Charcodote (in the United States), and Medicoal (in the United Kingdom and other countries) are available and the development of oral preparations particularly designed to overcome the aforementioned problems is still required.

We have previously reported[4)] the preparation of small spherical agarose beads in which activated carbon powder is entrapped. These are suitable for use in many biochemical purification procedures, such as removal of ligands from albumin solutions. In this report, the preparation and drug adsorption characteristics of similar beads suitable for use as an oral adsorbent are presented. We chose salicylic acid and acetaminophen as representative adsorbates and investigated their *in vitro* adsorption characteristics. Further, the effects of the beads on the *in vivo* absorption of salicylic acid were examined in the rat.

Oral activated carbon preparations such as the one described here should be useful not only in the treatment of drug overdosage, but also as a supporting measure in patients who

are under hemodialysis.[5] Activated carbon is also employed for control of pruritus[6] and more recently its use as a hypolipidemic agent was proposed.[7] In these cases, intestinal sequestration of bile salts is considered to be the mechanism of action.[8] Since activated carbon is known to be free from adverse effects, the development of a palatable oral dosage form would find application in these fields of medicine as an intestinal adsorbent.

Experimental

Materials——Activated carbon powder and salicylic acid (recrystallized from water) were obtained as reagent grade chemicals from Wako Pure Chemical Industries. Agarose, agar, Span 60, and Span 80 were also purchased from Wako Pure Chemical Industries. Nikkol SO-15, DGMO-C, BO-2, SO-10R, BC-R, and HCO-5 were generously supplied by Nikko Chemicals. Acetaminophen (JP X grade) was purchased from Yamanouchi Pharmaceutical Co. All organic solvents and other chemicals were reagent grade products and were used without purification with the exception of ether, which was distilled prior to use. Water was double-distilled with the second distillation in an all-glass apparatus.

Preparation of Activated Carbon Beads——Activated carbon beads were prepared basically according to the method of Hjertén[9] for the preparation of agarose beads. To 100 ml of agarose or agar solution (2—5%) in water at 80—90 °C, 5—20 g of activated carbon powder was added and thoroughly mixed. The mixture was kept at 80 °C. Next, 400 ml of an organic solvent or organic solvent mixture and a surfactant (0.15—0.50%) were placed in a silicone-treated round-bottomed flask (one liter capacity) and kept at 55 °C. The organic solution was stirred at 2000 rpm (Yamato Labo-Stirrer LS-05) and the aqueous agar solution previously prepared was poured into the organic solution. After dispersion of the aqueous phase in the organic phase for about 2 min, the flask was cooled in an ice-bath to solidify the aqueous phase. After about 5 min, the stirring was stopped and the precipitated beads were separated from the organic layer and washed extensively with ether followed by water. The beads were passed through sieves of mesh sizes 10, 28, 48, and 250 and the fraction 48/250 was dried under a vacuum at 50 °C and employed for *in vitro* and *in vivo* studies.

Adsorption Study——Accurately weighed amounts of either activated carbon powder (about 20 mg) or the dried beads (about 30 mg) were placed in 20 ml screw-capped test-tubes with Teflon liners. Drug solutions of known concentrations in Medium 1 or Medium 2 of JP X, or water (10 ml), were placed in each of the test-tubes and the tubes were rotated at 37 °C end-over-end (23 rpm) for over 2 h. After equilibration, the tubes containing the beads were set aside to allow the beads to settle and the concentration of unbound (or free) drug was determined spectrophotometrically at the wavelengths of maximum absorption of the drugs in each medium. Tubes containing the powder were centrifuged at 37 °C and the supernatant was similarly assayed. All absorbance measurements were carried out on a Shimadzu model UV-300 double-beam spectrophotometer. The amount of drug bound was calculated from the difference between the total drug added and unbound drug. The results of the adsorption study were treated according to the Langmuir equation (1)

$$D_b = \frac{D_b^m a D_f}{1 + a D_f} \tag{1}$$

where D_b is the amount (mol) of drug adsorbed per gram of activated carbon, D_b^m is the maximum amount (mol) of drug adsorbed per gram of activated carbon, D_f is the concentration of unbound drug in mol/l, and a is the affinity constant. For wet beads, 0.5 or 1.0 ml of the beads was measured by settling the beads in a small tube (5 mm i.d.) for about 2 h at room temperature and transferred with the study medium to test-tubes having a 10 ml mark line. The beads were washed with the medium by changing the supernatant and finally a sufficient volume of supernatant medium was removed to permit addition of the desired volume of drug solution. The total volume was made up to 10 ml with the medium. One milliliter of wet beads was equivalent to 64 mg of the dried beads.

Time Course of Adsorption——The same procedure was employed as for the determination of the equilibrium amount of drug bound, with the exception that rotation was stopped at predetermined times before equilibration. Separate test-tubes were prepared for each predetermined time and the content of each tube was filtered through a membrane filter (Nuclepore, 0.8 μ) immediately after the end of rotation. Salicylic acid was studied at the initial concentration of 1.4 mM and acetaminophen at 0.33 mM.

***In Vivo* Experiments**——Male Wistar rats weighing 280—430 g were employed after being fasted for 9—16 h.

(a) Administration of the Dried Beads or Powder One Minute after Salicylic Acid: Salicylic acid (140 mg/kg) was administered as the sodium salt in about 0.5 ml of normal saline using an oral tube. One minute later, either the dried beads (1120 mg/kg) or the powder (748 mg/kg) suspended in 5 ml of normal saline was administered similarly. The control group received 5 ml of normal saline 1 min after the dose of salicylic acid. Up to 3 h after administration of salicylic acid, blood samples were obtained by heart puncture.

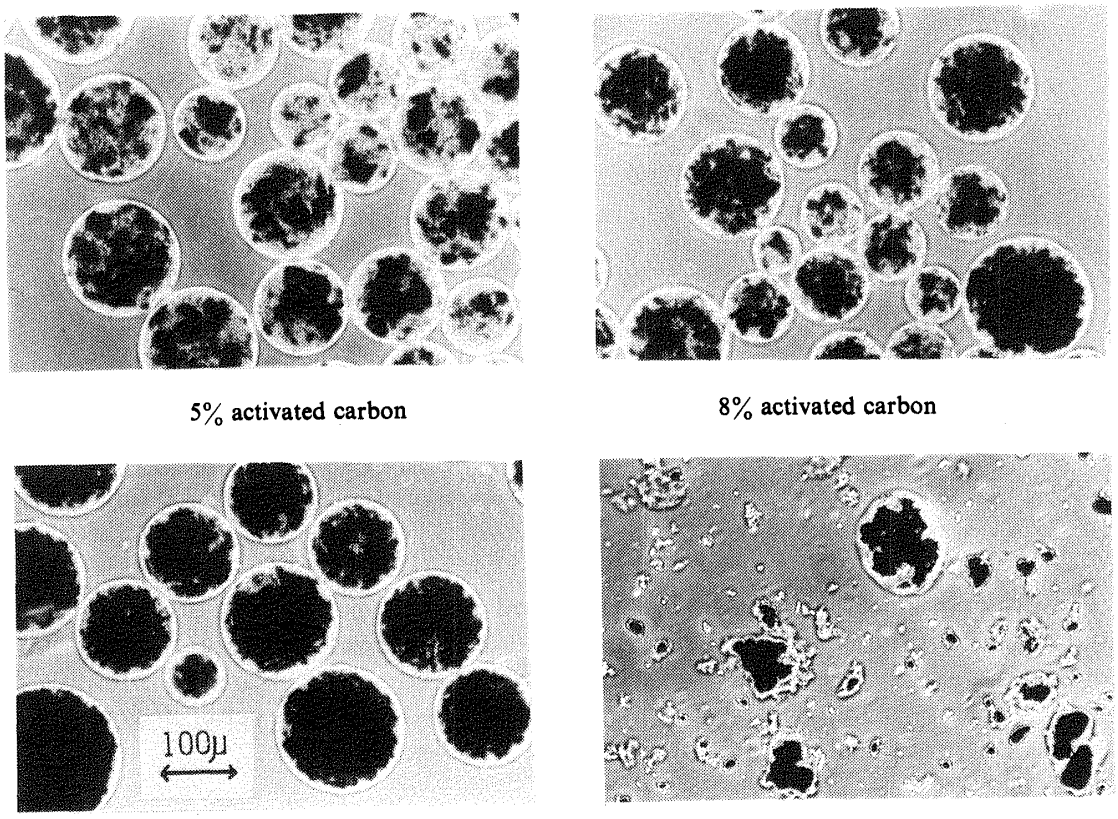
(b) Administration of Salicylic Acid Adsorbed on the Dried Beads: Salicylic acid (100 mg/kg) was adsorbed on

the dried beads (750 mg/kg) and administered by suspending the beads in 5 ml of Medium 1 as described above. Blood samples were obtained at 1, 8, 15, and 24 h after administration as described above. Drinking water was allowed *ad libitum* after 1 h and food from 4 h after administration of salicylic acid. Plasma concentrations of salicylic acid were determined fluorometrically according to the method of Rowland and Riegelman[10] on a Hitachi model 240-S spectrophotofluorometer with excitation at 300 nm and emission at 405 nm.

Results and Discussion

Preparation of Dried Activated Carbon Beads

Figure 1 shows that the incorporation of up to 10% activated carbon powder is possible in 5% agarose beads, when a mixture of toluene and carbon tetrachloride (4 : 1) containing 0.5% Span 60 was employed as the organic phase. Although spherical beads were obtained from this organic phase as shown in Fig. 1, these solvents were unsuitable because they have high affinity for activated carbon. Thus, other organic solvents and surfactants were examined at 8% activated carbon powder. Organic solvents investigated included ethyl acetate, cyclohexane, and mixtures of either of these with chloroform. As surfactants, Span 60, Span 80, polyoxyethylene alkyl ethers and a hydrogenated castor oil derivative (Nikkol HCO-5) were tried. Bead formation was not observed in solvents containing ethyl acetate. Satisfactory beads were obtained in cyclohexane containing 0.25% HCO-5, and a ratio of the organic phase to the aqueous phase greater than about 4 was necessary. In order to incorporate 8% activated carbon powder, a concentration of agar less than 2% was ineffective. Thus, 4% agar and 8% powder were selected. Under these conditions some of the larger beads (mesh <48) were not completely spherical because of the difference in density in the aqueous and organic



5% activated carbon

8% activated carbon

10% activated carbon

15% activated carbon

Fig. 1. Incorporation of Activated Carbon Powder into 5% Agarose Beads

Organic phase: toluene : carbon tetrachloride = 4 : 1.
Surfactant: 0.5% Span 60.

phase. Thus, the 48/250 mesh fraction was collected and dried at 50 °C under a vacuum. A flow chart for the preparation of the dried beads for oral administration is presented in Chart 1.

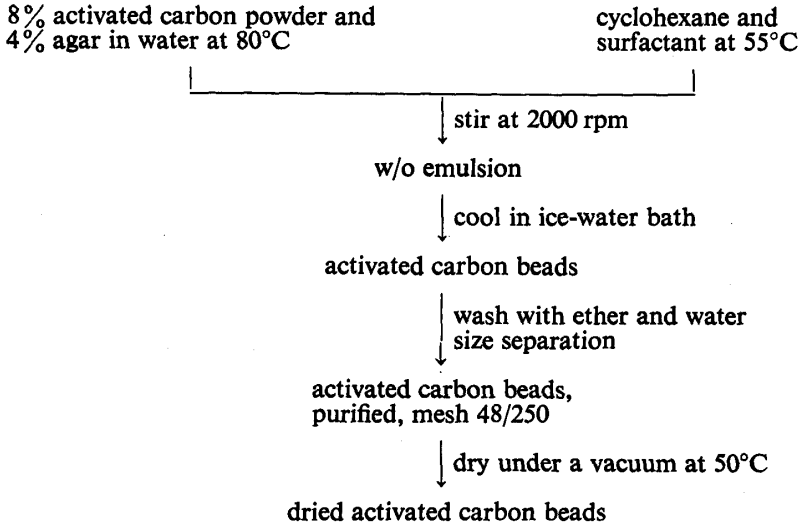
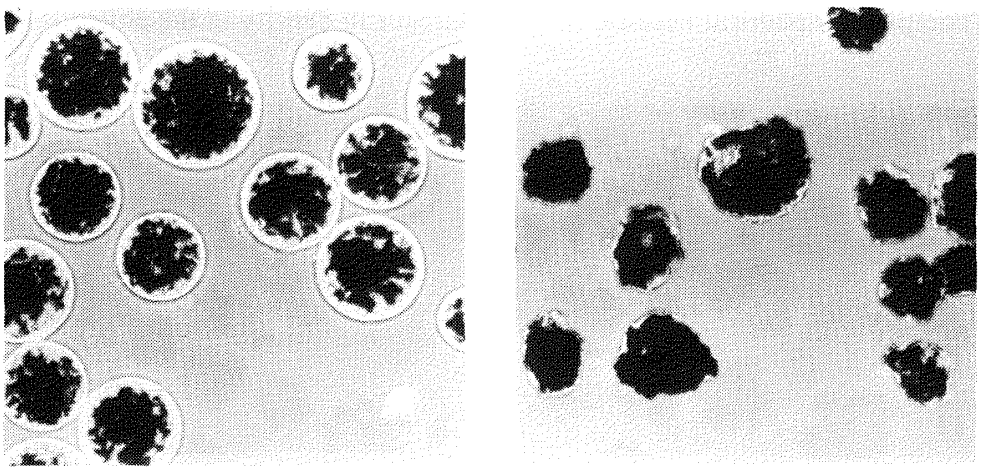


Chart 1. Preparation of Dried Activated Carbon Beads Suitable for Oral Use



before drying after drying

Fig. 2. Phase-Contrast Photomicrographs of Activated Carbon Beads Containing 4% Agar and 8% Activated Carbon Powder before Drying and of the Dried Beads Resuspended in Water

The dried beads are fine granules with good flow properties and are easy to handle without staining problems. They contain about 67% activated carbon powder and the remainder is agar, whereas the wet beads contain about 90% water. Therefore, if the adsorptive capacity is unaffected by drying, the dried beads are a far better dosage form than the wet beads from the standpoint of storage and transport.

Effect of Drying of the Beads

When the dried beads are suspended in water, they do not regain their original size. However, unlike the original powder they settle quickly to give a transparent supernatant. Comparison of the phase-contrast microscopic picture of the beads before drying with that of the dried beads resuspended in water (Fig. 2) clearly shows that the dried beads, though not

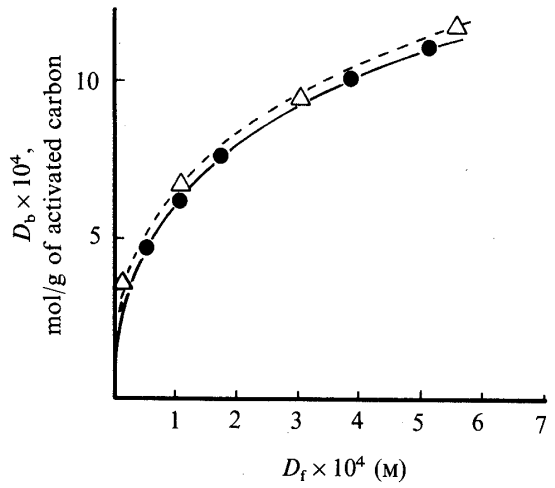


Fig. 3. Comparison of Salicylic Acid Adsorption Capacity of Activated Carbon Beads in Medium 1 (pH 1.20) at 37 °C before and after Drying

—●—, before drying; ---△---, after drying.

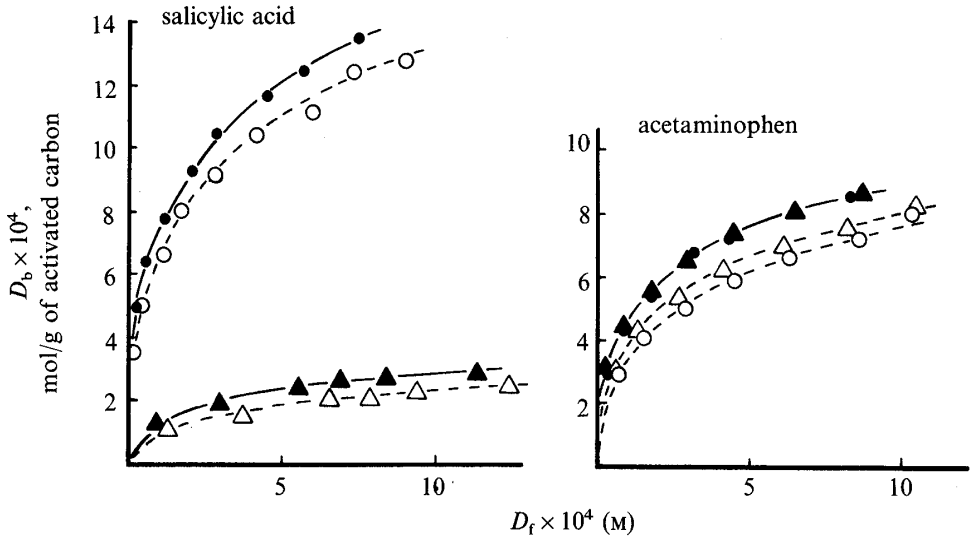


Fig. 4. Adsorption Isotherms for Adsorption of Salicylic Acid and Acetaminophen on Activated Carbon Beads and Powder at 37 °C.

In Medium 1 (pH 1.20): —●—, the powder; ---○---, the dried beads.
In Medium 2 (pH 6.85): —▲—, the powder; ---△---, the dried beads.

spherical, retain the original structure of the wet beads without disintegration, and the surface is covered with agar with no powder particles present at the surface.

Figure 3 shows that the drying process has no detrimental effect on the adsorption of salicylic acid from Medium 1.

Comparison of Adsorption Capacity between Dried Beads and Powder

Figure 4 shows the adsorption isotherms at 37 °C for adsorption of salicylic acid and acetaminophen on the powder and dried beads from Media 1 and 2. The adsorption of salicylic acid on the powder was far greater from Medium 1 than from Medium 2, but no such difference was observed with acetaminophen. This large difference between the media in salicylic acid adsorption is considered to be due to the fact that salicylic acid is present as anions in Medium 2, whereas salicylic acid in Medium 1 and acetaminophen in both media are present in molecular form. Similar results were obtained with the dried beads, which showed about 85% of the adsorption capacity of the powder for both drugs. The reduction is probably attributable to the presence of the agar gel matrix, and not to the drying (Fig. 3).

Effect of Sodium Chloride

Ryan *et al.*[11] reported that the adsorption of salicylate on charcoal is enhanced by the addition of sodium chloride to the medium. We have also observed similar results in our experiments employing columns of wet agarose beads containing activated carbon powder.[4] We have extended our study of the effect of sodium chloride to the present dried beads. In Table I the Langmuir constants are presented in the presence and absence of sodium chloride in the system. Comparison of the Langmuir constants D_b^m and a of the powder and the beads in the presence and absence of 0.1 M NaCl revealed that D_b^m values of salicylate ions only (*i.e.* adsorption from Medium 2 and water) are greater in the presence of the salt. In Fig.5 the effects of the concentration of sodium chloride are presented. The adsorption of salicylate ions in water in the presence of 0.9% NaCl (0.154 M) is approximately twice as great as that in the absence of sodium chloride. No such enhancing effect was observed with acetaminophen. Since similar results were obtained with the powder and dried beads, this property is considered to reside in the powder itself and may be attributable to a kind of salting-out effect. Whether the adsorption of all organic anions is enhanced by the presence of inorganic salts or not has to be investigated. However, it is an interesting phenomenon that the presence of one substance enhances the adsorption of another substance.

TABLE I. Langmuir Constants for Adsorption of Salicylic Acid and Acetaminophen on the Activated Carbon Beads and Powder at 37 °C

	Activated carbon	In the absence of NaCl			In the presence of 0.1 M NaCl		
		$D_b^m \times 10^{4\,a)}$ (mol/g)	$a \times 10^{-4\,b)}$ (M^{-1})	$r^{c)}$	$D_b^m \times 10^{4\,a)}$ (mol/g)	$a \times 10^{-4\,b)}$ (M^{-1})	$r^{c)}$
Salicylic acid							
Medium 1	Beads	13.6	1.02	0.993	12.6	1.12	0.991
	Powder	13.9	1.47	0.991	12.2	1.85	0.995
Medium 2	Beads	2.89	0.360	0.992	3.70	0.302	0.974
	Powder	3.12	0.571	0.996	3.61	0.563	0.994
Water	Beads	1.44	1.08	0.988	3.61	0.345	0.989
	Powder	1.34	0.560	0.989	4.29	0.300	0.993
Acetaminophen							
Medium 1	Beads	9.26	0.471	0.995	9.19	0.533	0.995
	Powder	9.90	0.733	0.998	9.49	0.821	0.996
Medium 2	Beads	9.17	0.585	0.996	9.61	0.586	0.997
	Powder	9.62	0.833	0.996	9.70	0.906	0.995

a) D_b^m, maximum amount (mol) of drug adsorbed per g of activated carbon.
b) a, affinity constant.
c) Correlation coefficient.

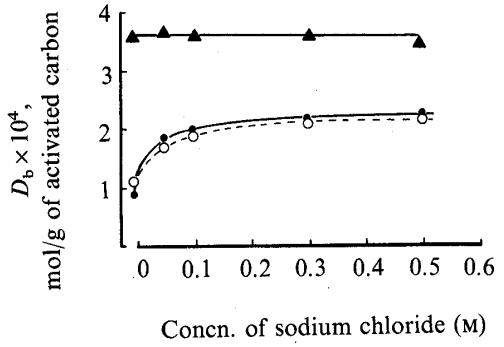


Fig. 5. Effect of Sodium Chloride on the Adsorption of Salicylate and Acetaminophen in Water

Salicylate at 37 °C: —●—, the powder; ---○---, the dried beads.
Acetaminophen at 25 °C: —▲—, the powder.

TABLE II. The Time Courses of Adsorption of Salicylic Acid from Media 1 and 2 at 37 °C

Time, min	% of equilibrium amount adsorbed[a]			
	Medium 1		Medium 2	
	Beads	Powder	Beads	Powder
5	90.7	98.5	94.2	96.7
15	96.5	99.3	97.1	99.4
120	100	100	100	100

a) The values are the averages of two determinations.

TABLE III. Effect of the Beads Administered One Minute after Salicylic Acid on the Plasma Salicylate Level in Rats[a]

Time (min)	Plasma level (μg/ml)[b]		
	Control	Beads	Powder
30	216±20 (3)	245±54 (2)	—
60	231±26 (3)	233±41 (3)	225
90[c]	263± 9 (3)	194±13 (2)	—
120[c]	264± 7 (3)	219±27 (3)	245±22 (3)
180	281		222± 2 (2)

a) Dose, 140 mg/kg; salicylic acid : activated carbon = 1 : 5.3.
b) Mean ± S.D. (number of rats).
c) The control and the beads data are significantly different at $p < 0.05$.

Time Course of Adsorption

The time course of adsorption of salicylic acid from Media 1 and 2 at 37 °C on the powder and dried beads is shown in Table II. Fast attainment of equilibrium adsorption of salicylic acid by the powder was essentially retained in the dried beads. Similar results were obtained with acetaminophen (data not shown).

Effects of the Dried Beads on the Absorption of Salicylic Acid in Rats

The results of administration of the dried beads and powder 1 min after salicylic acid are summarized in Table III. The plasma levels of salicylic acid of rats which were administered the equivalent of 0.21—0.32 g of the powder (depending on the weight of the rats) as the dried beads were significantly different from those of the control group only at 90 and 120 min after administration with about 20% reduction. Since the powder did not give a better reduction, this relatively small effect of the beads is not due to the incorporation of the powder in the beads. Decker *et al.*[12] reported that when 320 mg of sodium salicylate suspended in 0.5 ml of water was administered to rats and only 125 mg charcoal powder was given 30 min later (salicylic acid : charcoal = 1 : 0.45), the plasma salicylate level at 120 min after the administration of drug was 38% of that of the control group. In view of our charcoal-to-drug ratio of 1 : 5.3, the ineffectiveness of the powder in the present study may not be solely attributable to the difference in the preparations of charcoal employed.

As for *in vivo* data on aspirin in rats, Picchioni *et al.*[13] administered charcoal at 5 times the amount of aspirin 1 min after the drug, and reported that the serum concentration of salicylic acid at 30 min was reduced from 223 μg/ml to 88 or 42 μg/ml with different charcoal

Table IV. Effect of the Beads on the Adsorption of Salicylic Acid in Rats[a]

Time, h	Plasma level (μg/ml)[b]		Remarks
	Beads	Control	
1	174±15 (4)	260±27 (4)	$p<0.05$
8	179±21 (4)	195±35 (5)	$p>0.1$
15	139±14 (4)	135±23 (4)	$p>0.1$
24	76±15 (5)	50±31 (3)	$0.05<p<0.1$

a) Salicylic acid (100 mg/kg) adsorbed on the beads (750 mg/kg) in 5 ml of Medium 1, pH 1.20 (salicylic acid : activated carbon = 1 : 5).
b) Mean±S.D. (number of rats).

preparations. Further, Collombel and Perrot[14] also studied the effect of charcoal administered at 10 times the amount of aspirin 30 min after aspirin in rats. The plasma level of salicylic acid of the charcoal-administered group was reduced to about 1/3 of that of the control group. In these studies, aspirin was administered as a suspension and the relative ineffectiveness in our case in comparison with these aspirin data may be partly due to the rapid absorption of salicylic acid, since we administered salicylic acid as the sodium salt.

When salicylic acid adsorbed on the dried beads and suspended in Medium 1 (about 98% adsorbed on the beads) was administered and the plasma level was monitored up to 24 h (Table IV), a statistically significant reduction ($p<0.05$) was observed only at 1 h after administration and no significant reduction was observed at other times. At 24 h after administration, the plasma level of the beads-administered group was not significantly different from that of the control group. These results indicate that the salicylic acid adsorbed on the beads is mostly available for absorption. This is, as suggested by Levy and Tsuchiya,[15] considered to be the result of desorption of salicylic acid from charcoal–salicylic acid complex as the complex moves down the gastrointestinal tract because of the change in pH, which favors the desorption of salicylic acid (see Fig. 4). Neuvonen *et al.*[16] and Scholtz *et al.*[17] administered charcoal to human subjects at 50 and 20 times the amount of aspirin, respectively, and obtained higher plasma levels of salicylate at over 24 h after administration than in the control group. These results strongly suggest that salicylic acid or aspirin adsorbed on charcoal is released and absorbed as they pass down the gastrointestinal tract. In order to prevent the desorption, administration of as much charcoal as possible is required.

The relative ineffectiveness of the dried beads in preventing salicylate absorption in rats may thus be considered to be the result of rapid absorption of salicylic acid and desorption as salicylate from the charcoal–salicylic acid complex as it moves down the gastro-intestinal tract. It is not the result of incorporation of the powder in the agar gel matrix. Further, the salicylic acid adsorption capacity of the powder may have been lower than those of the charcoal powders used by other workers.[18] The results of a similar *in vivo* study employing theophylline as an adsorbate in human subjects will be reported separately.

The results of the present *in vivo* study suggest that the phenomenon of desorption of drug adsorbed on the beads is utilizable as a means of preventing a rapid rise in plasma level for acidic drug, particularly those with a low safety margin.

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