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In vitro and in vivo evaluation of medicinal carbon granules and tablet on the adsorption of acetaminophen

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Abstract

Medicinal carbon (MC) granules were prepared by wet granulation using maltitol (MT), and the MC tablet was produced by compression of the granules. The physical properties and the in vitro adsorption capacity for AA of the formulations were examined. Further, the effects of MC alone and the granules on gastrointestinal absorption of AA were examined in rats when they were administered intragastrically at 15 or 45 min after the intragastrical administration of AA. AA was rapidly adsorbed by MC, and the maximum adsorption capacity of MC was 0.329 g AA per gram MC. The granules and tablet exhibited adequate strength, and the tablet disintegrated rapidly. The granules and tablet showed similar adsorption profiles, but somewhat lower adsorption capacity than MC alone. MC alone and granules administered at 15 min reduced the AUC(0–∞) significantly against the control (no treatment); however, the suppression effect on the plasma concentration was lower with the granules than with MC alone. Thus, granules and tablet are useful as a compact dosage form of MC; though the reduced adsorption capacity must be taken into account in order to expect efficacy equivalent to that of MC alone.

Keywords: Medicinal carbon; Granules; Tablet; Acetaminophen; Adsorption capacity; Plasma concentration

1. Introduction

Activated charcoal used clinically, called medicinal carbon (MC), is a fine carbon black powder, and has been used widely as a potent adsorption agent. It is applied in the treatment of intoxication by ingested toxic chemicals, toxins or harmful metabolites generated in the gastrointestinal tract, drugs, etc. (Swartz and Sherman, 1984; Arimori and Nakano, 1986; al-Shareef et al., 1990; Fricke and Jorge, 1990; Tsitoura et al., 1997; Alegakis et al., 2000; Tsujikawa et al., 2000; Michael et al., 2004). Furthermore, MC can be utilized as a hemoperfusion device to remove certain poisons from blood (Van Wagenen et al., 1975; Kodama et al., 1997). As MC is very safe, it can be used in relatively large quantities, and causes no drug-resistant strain of bacteria (Amitai and Degani, 1990). Thus, even now, MC is regarded as an important agent to treat various kinds of intoxication, and officially permitted as an antidote in the gastrointestinal tract in JP 14 which indicates that MC of 2–20 g is orally taken in fractional amounts per day. However, MC with no modification is not easy to deal with due to its highly scattering property and adhesion to the surface of various materials. Also, MC must be taken orally as powder or aqueous suspension in a large quantity; that is, in many cases, several—a hundred grams of MC are required for detoxication of drug overdose, sometimes resulting in the reduction of the compliance of patients. At that time, a fairly large volume of water or saline is needed to suspend and take MC. Furthermore, nasogastric intubation is often needed because MC suspension can bring discomfort to the patients. These can lead to the non-compliance of the patients. It is considered important to make the dosage form which can be dealt with readily and taken as easily as possible and is more palatable. Therefore, we have previously developed a compact dosage form of MC, formulated as a tablet (Yamamoto et al., 2006). The tablet was manufactured by using maltitol (MT) as a binding agent, though MT slightly decreases the adsorption capacity of MC (Yamamoto et al., 2006).

Acetaminophen (AA) is widely used as a relatively safe analgesic and antipyretic drug (Jackson et al., 1984; Granados-Soto et al., 1992; Nakamura and Ogawa, 2005). The effective plasma concentration of AA ranges from 2 to 20 μg/ml, while the toxic

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plasma level is above 300 μg/ml (Jackson et al., 1984; Granados-Soto et al., 1992). Toxic side effects in the gastrointestinal tract are much lower with AA than with other non-steroidal anti-inflammatory drugs like aspirin (Nakamura and Ogawa, 2005). Furthermore, as AA is also safe from the toxic side effects such as Reye syndrome, in therapeutic doses it can be used safely in children. However, incidences of poisoning from the overdose have been reported from time to time (Bainbridge et al., 1977; Galinsky and Levy, 1981; Gregus et al., 1988). As AA is contained in many non-prescription analgesic and antipyretic drugs, it can be obtained easily, which may result in such accidental or intentional poisonings. In this study, granules and tablet made by wet granulation using MT as a binder were evaluated in vitro, and their effects on the suppression of the plasma level of AA were studied in vivo (rats).

2. Materials and methods

2.1. Materials

JP 14 medicinal carbon (surface area 1400 m^2/g, pore volume 0.49 ml/g), being a fine powder, was purchased from Kenei Pharmaceutical Co., Ltd. (Japan), and used in the experiments without sieving. Acetaminophen was obtained from Sigma (USA). Amalty MR-50 (Towa Chemical Industry Co., Ltd., Japan) was used as maltitol. All other chemicals were of reagent grade.

2.2. Animals

Male Wistar rats (6 weeks old), weighing 190 g, were purchased from Tokyo Laboratory Animals Science Co., Ltd. (Japan), and soon used for animal experiments. They were kept on the breeding diet MF (Oriental Yeast, Japan) with water ad libitum at room temperature of 23 ± 1 °C and relative humidity of 60 ± 5%. The experimental protocol was approved by the Committee on Animal Research of Hoshi University, Japan, and the animal experiments were performed in compliance with the Guiding Principles for the Care and Use of Laboratory Animals of Hoshi University, Japan.

2.3. In vitro adsorption in the presence or absence of MT

The adsorption characteristics of MC for AA were examined at 37 °C by the addition of MC to an AA aqueous solution with and without MT dissolved. After AA (10, 15 or 25 mg) was dissolved at 37 °C in water (50 ml) with or without MT (25 or 50 mg), MC (25 mg) was added and shaken horizontally at 90 rpm using a shaker at 37 °C. At 1, 6 and 24 h after the start of incubation, the suspension (1 ml) was taken, and centrifuged at 3000 rpm for 10 min. The supernatant was diluted with water, and measured spectrophotometrically at 243 nm to determine the concentration of free AA. The amount of AA adsorbed by MC was calculated from the amounts of total and free AA.

2.4. Preparation of granules and tablet

MT aqueous solution (18 ml) containing MT (12 g) was added to 10 g of MC, and the mixture was kneaded thoroughly. The wet mass was granulated manually using a sieve of size 9 mesh, and the wet granules obtained were dried at 60 °C overnight. Those larger than size 14 mesh were used as granules. Furthermore, the granules (500 mg) were placed in a cylinder (1 cm inner diameter), and compressed at 4 kN for 30 s using a Shimadzu SSP-10 A manual press to obtain a tablet. The tablets and granules were preserved in a glass bottle at room temperature, and used in the in vitro and in vivo experiments at 7 days after production.

2.5. Physical characteristics of granules and tablet

The granules were examined for friability with a friability tester (Kayagaki Irika Kogyo Co., Ltd., Japan). Namely, the granules (1 g) were put into the tester pan, and rotated at 25 rpm for 5 min. Granules maintaining a size of more than 14 mesh were collected and weighed. The weight loss (%) of the granules from the initial weight was calculated as friability. The tablet was measured for thickness (T, cm), hardness (F, kg) and disintegration time (s) in water. For hardness, the lateral side was sandwiched between the platens of a Kiya-type hardness meter (Fujiwara Seisakusho, Japan) and stressed, and the force immediately before breakdown of the tablet was measured as the tablet hardness. The tensile strength (S, kg/cm^2) was calculated in the following equation (Tye et al., 2005).

$$S = \frac{2F}{\pi \times D \times T},$$

in which D, being the diameter of the tablet, was 1 cm. The disintegration time of the tablet was measured at 37 °C using a modified disintegration apparatus which was reported previously (Yamamoto et al., 2006). Briefly, a basket with a mesh size of 1.5 mm was attached to the moving arm of a Model NT-60H disintegration tester (Toyama Sangyo Co., Ltd., Japan), and moved up and down (30 strokes per min, 55 mm amplitude) from the medium surface to full immersion. The time taken for the tablet to disappear completely from the basket was measured as the disintegration time. Water was used as the test medium.

2.6. In vitro adsorption by granules and tablet

JP 14 dissolution test apparatus for the paddle method (Toyama Sangyo Corp., Japan) was used in this adsorption study. Namely, MC (227 mg), a physical mixture of MC (227 mg) and MT (273 mg), granules (500 mg) and tablet (500 mg) were added to water (500 ml) in which AA (91 mg) was dissolved, and which was stirred at 80 rpm and 37 °C with a single-blade propeller. In addition, 500 ml of water, in which AA (91 mg) and MT (273 mg) were dissolved, was used as a medium, MC (227 mg) was added, and the adsorption was examined using the same method. At appropriate time points, a sample (1 ml) was taken and centrifuged at 3000 rpm for 10 min. The supernatant was diluted with water, and measured spectrophotometrically at 243 nm to determine the concentration of free AA. The amount

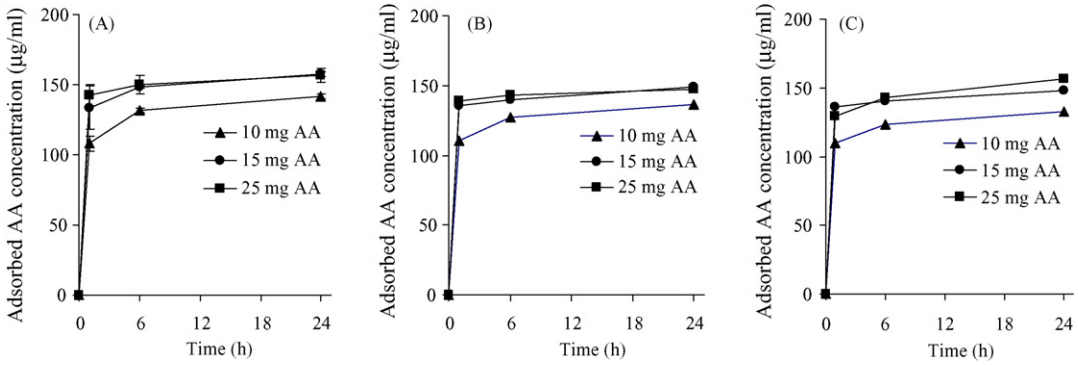

Fig. 1. Adsorption profiles of AA by MC in AA aqueous solution at different concentrations at 37 °C with or without MT dissolved. (A) Without MT, (B) with MT (25 mg) and (C) with MT (50 mg). The amount of MC used was 25 mg, and the volume of the media was 50 ml. Each point represents the mean ± S.D. ($n = 6$ for A; $n = 3$ for B and C).

of AA adsorbed by MC was calculated from the amounts of total and free AA.

2.7. In vivo experiment

The rats were fasted for 24 h, and AA aqueous solution was administered intragastrically at 100 mg/kg (2 ml) per animal using a Teflon tube under light anesthesia with ethyl ether. At 15 or 45 min after administration of AA, an aqueous suspension of MC alone or granules was administered intragatrically using a Teflon tube at a dose of 500 mg MC equiv./kg (2 ml) per animal. In the control, no treatment was given after the administration of AA aqueous solution. Blood samples (0.3 ml) were withdrawn from the jugular vein using a heparinized syringe at 0.5, 1, 1.5, 2.5, 5 and 24 h after administration of AA. Immediately after each sampling, the blood sample was centrifuged at 3000 rpm for 10 min to obtain the plasma. One hundred fifty microliters of 10% (v/v) $HClO_4$ aqueous solution and 100 μl of water were added to the plasma (50 μl), and the mixture was shaken vigorously for 1 min with a vortex mixer. After centrifugation of the mixture at 3000 rpm for 10 min, the resultant supernatant was analyzed for AA by high performance liquid chromatography (HPLC).

2.8. HPLC assay

The amount of AA in each sample was analyzed by HPLC by referring to the method by Vertzoni et al. (2003). The HPLC system consisted of an LC-10AS pump, an SPD-10A spetrophotometric detector, a C-R7 chromatopac, an SCL-10A system controller, an SIL-10A autosampler and a CTO-10A column oven (Shimadzu Corp., Japan). The detector was set at 242 nm, and the column temperature was set at 30 °C. A Hypersil BDS-5C_{18} column (4.6 mm inner diameter × 250 mm length; Chemco Scientific Co., Ltd., Japan) was used as an analytical column. A mixture of 0.05 M potassium phosphate buffer solution containing 1% acetic acid (pH 6.5) and methanol (95:5, v/v) was used as the mobile phase. The flow rate of the mobile phase was set at 1.5 ml/min. The injection volume of the sample was 20 μl.

2.9. Pharmacokinetic and statistical analysis

The maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (T_{max}) were obtained directly from the plasma concentration–time profiles. The area under the plasma concentration curve until infinity (AUC(0–∞)) and the mean residence time (MRT(0–∞)) were calculated by the trapezoidal rule plus mono-exponential extrapolation to infinity using the pharmacokinetic analysis program MULTI reported by Yamaoka et al. (1981). Statistical analysis was performed using the unpaired t-test, and significant difference was set as $P < 0.05$.

3. Results

3.1. In vitro adsorption characteristics of MC

Adsorption profiles of AA by MC were examined in AA aqueous solution in the absence or presence of dissolved MT. MT was added at a ratio of 100% (w/w) (25 mg) or 200% (w/w) (50 mg) to MC (25 mg). As shown in Fig. 1, adsorption by MC was achieved greatly within 1 h. The adsorption amount reached a plateau at 24 h after the start of incubation. Adsorption was almost saturated at more than 15 mg of AA added in each condition. The relationships between the concentrations of free and adsorbed AA at the plateau or in equilibrium are shown in Fig. 2A, which obviously exhibited the saturation of adsorbed AA. The maximum adsorption capacity of MC, calculated from the horizontal axis intercept of the linear curve (solid line) fitted to the Scatchard plot in the absence of MT (Fig. 2B), was 0.329 g per gram MC. Scatchard plots in the presence of MT also showed that MT tended to slightly suppress adsorption; the reduction of maximum capacity was calculated to be 6% and 1% for 25 and 50 mg of MT, respectively.

3.2. Physical characteristics of granules and tablet

One tablet (500 mg) or 500 mg of granules were calculated to contain 227 mg of MC from the mix ratio of MC and MT. Table 1

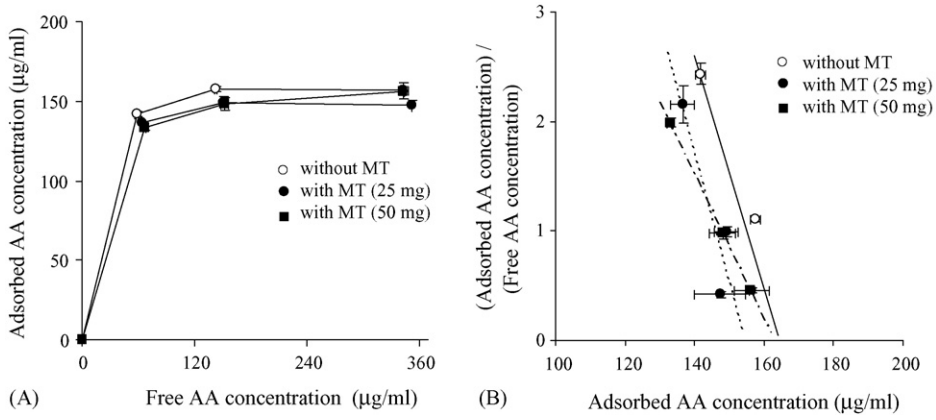

Fig. 2. Relationships between free and adsorbed AA at equilibrium (A) and their Scatchard plots (B). In B, lines are the curves fitted to the observed plots; solid line: without MT, broken line: with MT (25 mg) and dot-dash-line: with MT (50 mg). The data in Fig. 1 were used for calculation. Each point represents the mean ± S.D. ($n = 6$ for ○; $n = 3$ for ● and ■).

Table 1
Formulations and physical characteristics of the physical mixture of MC and MT, their granules and tablet

Formulation	MC (mg)	MT (mg)	Friability[a]	Diameter[b] (mm)	Thickness[b] (mm)	Hardness[b] (kg)	Tensile strength[b] (kg/cm^2)	Disintegration time[c] (s)
Physical mixture	227	273	–	–	–	–	–	–
Granules	227	273	6.0 ± 3.0	–	–	–	–	–
Tablet	227	273	–	10.0 ± 0.0	5.8 ± 0.1	8.50 ± 0.20	9.38 ± 0.21	107 ± 5

The results are expressed as the mean ± S.D. ($n = 3$ for a; $n = 5$ for b; $n = 6$ for c).

shows the physical properties of the formulations. The granules showed good hardness from friability. The tablet thickness was 5.8 mm, the tablet had sufficient hardness and tensile strength, and the disintegration was rapid, 107 s. These tablet properties were reproducible.

3.3. In vitro adsorption characteristics of granules and tablet

In this experiment, MC alone and the formulations listed in Table 1 were examined for the adsorption of AA dissolved in water. The adsorption of AA by MC was also investigated in an aqueous solution of AA and MT. The results are shown in Fig. 3. AA was adsorbed rapidly in each formulation. Namely, the adsorption was achieved near the plateau within 5 min for all formulations. In MC alone, 61.4 mg of added AA (91 mg), corresponding to 67% of total AA, was adsorbed at 24 h. The physical mixture showed almost the same adsorption profile to that of MC in an aqueous solution of AA and MT; and their adsorption of AA decreased to approximately 90% of MC alone. In granules and tablet, the adsorption extent was lowered to approximately 80% of that of MC alone.

3.4. Effect of MC and granules on the gastrointestinal absorption of AA

A suspension of MC alone or granules in water (2 ml) was intragastrically administered at a dose of 500 mg MC equiv./kg at 15 or 45 min after the administration of AA (100 mg/kg), while the control received only AA (100 mg/kg). As shown in Fig. 4, MC alone and granules administered at 15 min suppressed the plasma concentration of AA during the observation period; at 30 min and 1, 1.5 and 2.5 h, the plasma levels were lowered to 29%, 20%, 16%, 8% and 6% of the control ones, respectively, for MC alone, and to 52%, 50%, 53%, 43% and 17% of the control ones, respectively, for granules. On the other hand, when MC alone and granules were administered at 45 min, the maximum plasma concentration was similar to that of the control, and the plasma level was suppressed in the later period; at 1.5, 2.5 and 5 h, the plasma levels were 99%, 66% and 41% of the

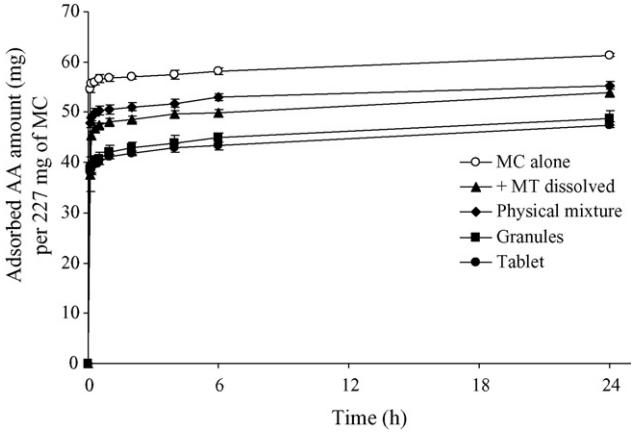

Fig. 3. Adsorption profiles of AA by MC alone, MC with MT dissolved, physical mixture of MC and MT, granules and tablet at 37 °C. MC alone (227 mg) and other formulations containing MC (227 mg) and MT (273 mg) were added to 500 ml of water containing 91 mg of AA, and amount of adsorbed AA was measured. Each point represents the mean ± S.D. ($n = 3$).

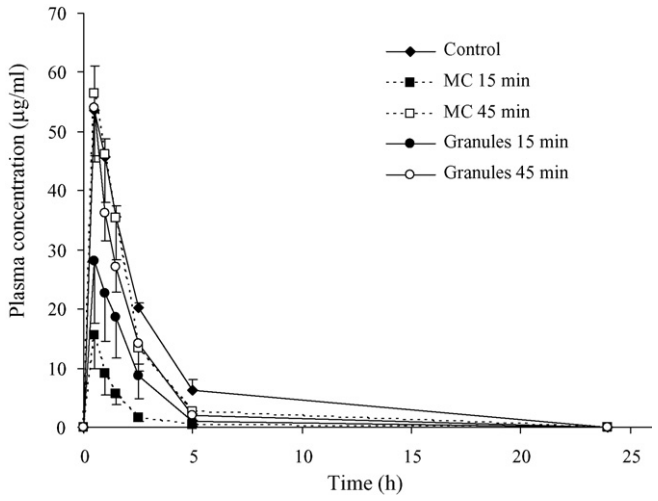

Fig. 4. Plasma concentration–time profiles in the administration of MC alone or granules at 15 or 45 min after AA administration in rats. AA was administered at a dose of 100 mg/kg, and MC or granules were administered at a dose of 500 mg MC equiv./kg. Each point represents the mean ± S.E. ($n = 4$ for ♦, □ and ○; $n = 3$ for ■; $n = 6$ for ●).

control ones, respectively, for MC alone, and 76%, 70% and 33% of the control ones, respectively, for granules. The pharmacokinetic parameters were calculated as shown in Table 2. In the administration of MC alone and granules at 15 min, the C_{max} values decreased to 28% and 52% of the control value, respectively, in which MC alone lowered the C_{max} value significantly against the control. Furthermore, the AUC(0–∞) values were lowered significantly to 15% and 43% against the control in the administration of MC alone and granules at 15 min, respectively. At 45 min, no significant difference in AUC(0–∞) was observed between the control and MC alone or between the control and granules. No significant change was observed for T_{max} and MRT(0–∞).

4. Discussion

AA is very useful and commonly used as an analgesic and antipyretic drug due to its high safety in therapeutic doses (Jackson et al., 1984; Granados-Soto et al., 1992; Nakamura and Ogawa, 2005). However, as AA is low-cost and contained in many kinds of non-prescription analgesic and antipyretic medicines, people can obtain a lot of AA readily, which may lead to a risk of taking an overdose unconsciously or intentionally. Overdose of acetaminophen induces a toxic metabolite that injures the liver (Galinsky and Levy, 1981; Gregus et al., 1988). When AA is taken orally at the recommended/therapeutic dose, it is mainly metabolized to AA-glucuronide and AA-sulfate, and the other toxic metabolite, being quantitatively minor but highly reactive, is detoxified with endogenous glutathione (Jackson et al., 1984; Gregus et al., 1988). However, the overdose of AA causes saturation of glutathione, resulting in non-complete detoxification of the toxic metabolite (Jackson et al., 1984; Gregus et al., 1988). AA-induced hepatotoxicity varies among species (Gregus et al., 1988), and in humans, liver-toxic side effects are concern at doses over 150 mg/kg (Jackson et al., 1984).

The adsorption characteristics vary among brands (Picchioni, 1970; Modi et al., 1994; Cooney, 1995). First, as the present MC is a different brand from that used previously (Yamamoto et al., 2006), the adsorption characteristics of the present MC for AA were investigated. MC exhibited higher adsorption capacity for AA, 0.329 g per gram MC (Fig. 2). AA adsorption by MC was very quick (Figs. 1 and 3); Fig. 3 indicates that it reached a level near the plateau within 5 min. Two dosage forms of MC, granules and tablet, were produced using a method similar to that reported previously (Yamamoto et al., 2006), though, in this study, the granules and tablet were produced at an MC/MT ratio of 5:6 (w/w). The contents of MC and MT in the granules (500 mg) or tablet (500 mg) were calculated as 227 and 273 mg, respectively, in which water content was neglected because it was only several%. The present tablet was superior in hardness and disintegration properties to that reported previously (Yamamoto et al., 2006) (Table 1). The difference in brands may affect such properties as well as the different preparative conditions. The existence of MT somewhat lowered the adsorption capacity for AA as observed from physical mixture and MC plus dissolved MT. As the physical mixture and MC plus dissolved MT displayed almost the same adsorption profiles, it was considered that MT in the physical mixture dissolved quickly and the resultant dissolved MT inhibited the adsorption of AA to a small extent. This was probably due to non-competitive inhibition as shown in Fig. 2 and reported previously (Yamamoto et

Table 2
Pharmacokinetic parameters of AA in the administration of the aqueous suspension of MC alone and granules at a certain time after oral administration of AA

Formulation	Dose of AA (mg/kg)	Dose of MC (mg/kg)	Number of animals	Administration time after AA administration (min)	C_{max} (μg/ml)	T_{max} (h)	AUC(0–∞) (μg·h/ml)	MRT(0–∞) (h)
Control (untreated)	100	–	4	–	55.3 ± 6.4	0.63 ± 0.13	134.9 ± 3.5	2.3 ± 0.3
MC alone	100	500	3	15	15.5 ± 5.6**	0.50 ± 0.0	20.8 ± 5.1***	1.9 ± 0.5
	100	500	4	45	56.5 ± 9.7	0.50 ± 0.0	108.4 ± 19.9	1.6 ± 0.2
Granules	100	500	6	15	28.9 ± 10.4	0.67 ± 0.11	58.0 ± 21.6*	2.2 ± 0.6
	100	500	4	45	53.9 ± 9.0	0.50 ± 0.0	95.7 ± 17.8	1.6 ± 0.1

* $P < 0.05$ vs. control.
** $P < 0.01$ vs. control.
*** $P < 0.001$ vs. control.

al., 2006). The granules and tablet displayed almost the same adsorption profiles. This indicated the compression of the granules did not influence the adsorption capacity of the granules, which was probably due to the rapid disintegration of the tablet. The adsorption capacity of the granules and tablet decreased to some extent as compared with the physical mixture and MC plus dissolved MT (Fig. 3). This suggested that the physical features of the granules such as surface area and pore volume might not be recovered completely to those of intact MC in water and/or that the wet granulation process might alter the physicochemical state for the MC surface to some extent. Further physicochemical examination is needed to clarify the mechanism.

In the in vivo experiment, AA was administered intragastrically to rats at 100 mg/kg. This dose was somewhat lower than that inducing toxicity in humans, but the plasma levels obtained at this dose were greater than the therapeutic ones in humans (Jackson et al., 1984; Granados-Soto et al., 1992) (Fig. 4). Therefore, this dose was considered fairly higher than the recommended/therapeutic dose of AA, though it was not regarded as hepatotoxic. Furthermore, AA was almost completely dissolved in water (2 ml) under this dose condition, but the solid part increased at the dose above this one, which might make the adsorption in vivo unclear. Thus, the in vivo adsorption capacity of MC alone and formulations was examined at this dose (100 mg/kg). As the tablet was too large for the rats to take, only the granules were used in vivo for the comparison with MC alone. As the granules displayed short disintegration time of less than 2 min and the same adsorption profile as the tablet (Fig. 3), the results of the granules were considered to highly reflect the in vivo behavior of the tablet. Reportedly, it is desirable to administer MC at five-fold or more the weight of the drug ingested (Bainbridge et al., 1977; Picchioni, 1970; Levy and Gwilt, 1974). Therefore, the dose of MC was set at five times the amount of AA administered. At 15 min after AA administration, MC alone and the granules reduced AUC(0–∞) significantly as compared with the control (Table 2). MC alone suppressed AUC(0–∞) more than the granules. This was consistent with the in vitro results (Fig. 3). Namely, as the in vitro adsorption capacity of the granules was lower than that of MC alone, in vivo adsorption was considered to be lower in the granules than in MC alone, leading to a higher plasma level in the granules (Fig. 4). At 45 min after AA administration, the AUC(0–∞) values were lower in MC alone and the granules than in the control, but the difference was not significant. Our results are consistent with the report by Picchioni that it would be preferable to administer activated charcoal within 30 min after ingestion of the poison (Picchioni, 1970). The in vivo results suggested that the granules and tablet should be administered at a somewhat higher dose as compared with MC alone in order to achieve an equivalent adsorption effect.

In conclusion, MC displayed better adsorption capacity than the previous brand. Granules, prepared by kneading using MT aqueous solution and subsequent drying, and the tablet obtained by compression of the granules showed good physical properties. The granules and tablet could be handled more easily than MC itself. Furthermore, the granules and tablet exhibited good adsorption capacity for AA, though it was lower than that of MC alone to some extent. The granules and tablet showed significant reduction of AUC(0–∞); however, they had to be administered at a somewhat greater dose in order to obtain an effect equivalent to that of MC alone, which was due to a certain reduction of adsorption capacity in the granules and tablet.

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