Introduction

Medical carbon (MC) is a fine powder of activated charcoal and is used clinically as an oral adsorption agent of various chemicals distributed in the gastrointestinal tract. MC is usually taken to treat intoxication caused by ingested toxic substances, harmful metabolites generated in the gastrointestinal tract or drug overdose. In the case of acute and heavy poisoning, MC can be used as an adsorbent in hemoperfusion, in which the blood or plasma is directly treated with the adsorption agent. In addition, as many drugs are secreted inside the gut lumen from the blood or tissue fluids by the partition theory, ingested MC is available to remove such drugs secreted into the gastrointestinal tract, which is known as gastrointestinal dialysis.

Acetaminophen (AA) overdose can induce acute hepatotoxicity. The drug is known to be subjected to use with an overdose; that is, as it can be bought easily by the users’ own will, it is sometimes overdosed due to its low therapeutic effect, or, in some cases, AA is used for deliberate self-poisoning. MC exhibits good adsorption potential to AA, and is possibly useful for detoxi-
fication induced by AA overdose.\textsuperscript{20-22} Thus, in the present study, AA was chosen as a model adsorption drug to MC.

Patients suffering from intoxication are generally required to ingest a large amount of MC.\textsuperscript{20, 23} MC has the characteristics of high scattering and adhesion to the used container. Also, as the patients must generally ingest a large amount of MC, they are forced to drink a lot of water or an aqueous suspension, resulting in reduced compliance. Therefore, compact dosage forms have been developed recently to handle and ingest MC more easily.\textsuperscript{22, 24, 25} We previously reported tablets as dosage forms that could correct such drawbacks.\textsuperscript{4, 25} When hydroxypropylcellulose (HPC) and maltitol (MT) were used as binders in the tablet production, the adsorption capacity of MC was reduced.\textsuperscript{22, 25} On the other hand, sodium carboxymethylcellulose (CMC-Na) hardly affected the adsorption capacity of MC. However, when tablets were produced by the wet granulation process (wet mass extrusion) using CMC-Na as a binder, they were fragile. So, in the previous paper, a MC tablet was produced by the modified wet compression method,\textsuperscript{26} namely, MC or mixture of MC and CC-Na (10:1, w/w) was kneaded using CMC-Na aqueous solution (binder) at the CMC-Na/MC ratio of 1/10 (w/w), and then, the resultant wet mass was granulated by manual extrusion with a 18-mesh sieve, and dried. After the obtained granules (125 mg) were placed in the cylinder of the die (10 mm inner diameter), 280 $\mu$L of 2.5\% (w/v) CMC-Na aqueous solution was added again. The resultant mixture was compressed manually to obtain tablets. The obtained tablets without and with CC-Na, named T1 and T2, respectively, contained 166 mg and 140 mg of net MC (dried MC), respectively. Both tablets showed a fairly high hardness, rapid disintegration and sufficient adsorption capacity. In particular, T2 showed rapid adsorption rate. However, the adsorption extent was varied considerably in the early time (coefficient of variance = 21 and 27\% at 10 and 20 min, respectively), which remained to be solved.

A granule formulation is another possible choice for the compact dosage form. Considering that the above MC tablet containing CMC-Na and CC-Na as additives influenced the adsorption capacity very slightly, MC granules produced with CMC-Na and CC-Na as additives were expected to keep high adsorption capacity. To our knowledge, MC granules with CMC-Na and CC-Na as additives have not been examined much for the physical properties and adsorption features. In this study, MC granules were prepared with the wet granulation using CMC-Na and CC-Na as a binder and additive, respectively, followed by manual extrusion. The obtained granules were evaluated by the examination of their physical properties and adsorption characteristics.

Materials and Methods

Materials
Medicinal carbon (MC) was purchased from Kenei Pharmaceutical Co., Ltd. (Osaka, Japan). Carboxymethylcellulose sodium (CMC-Na) was obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Croscarmellose sodium (CC-Na) was purchased from Asahi Kasei Corp. (Tokyo, Japan). Acetaminophen (AA) was obtained from Sigma-Aldrich Corporation (St. Louis, MO, USA). All other chemicals used were of reagent grade.

Preparation of MC granules and tablets
The formulations of MC granules are shown in Table 1 and were produced by the wet granulation followed by manual extrusion as follows:
Briefly, CMC-Na (3.0 g) was dissolved in water at a concentration of 5% (w/v), and the obtained solution was used as a binder. After MC (30.0 g) and CC-Na (0.0, 0.6, 1.2 or 3.0 g) were mixed sufficiently, the obtained CMC-Na solution (54 mL) was added. The mixture was then thoroughly kneaded manually. The resultant wet mass was manually granulated with an 18-mesh sieve (0.85 mm opening). The obtained granules were dried in air at room temperature for at least two weeks. Each test was performed using the granules dried for 2 - 3 weeks after the granulation.

**Characterization of MC granules**

1) Granule size distribution: The obtained MC granules were checked for size distribution using 10-, 12- and 42-mesh sieves (each opening: 1.7, 1.4 and 0.355 mm, respectively). After the pan and sieves with 42-, 12- and 10-mesh size were stacked from the bottom in this order, the granules (20 g) were placed on the top sieve (10-mesh) and the granules were sieved by horizontal vibration for 3 min. The weight of the granules remaining on each sieve and in the pan was measured. The change in weight (%) of each fraction was checked.

3) Disintegration properties: A disintegration tester NT-60H (Toyama Sangyo Co., Ltd., Osaka, Japan) was used. MC granules were screened by horizontal vibration for 3 min using the 30-mesh sieve (0.5 mm opening). The granules (0.1 g) remaining on that sieve were obtained placed in the auxiliary tube (0.42 mm opening) and set in the tester basket-rack assembly, which was moved up and down at 30 rpm with a 5.5 cm stroke for 30 min, when the test medium was water (900 mL) at 37°C. After the test, the medicinal carbon granules inside and outside the auxiliary tube were checked visually. In addition, the granules remaining inside the auxiliary tube were taken and dried at 60°C overnight, which gave the dried granules apparently. They were naturally cooled at room temperature and weighed, and the remaining percentage to the initial weight was calculated.

**Adsorption tests** The adsorption characteristics of MC granules were examined with AA as the adsorbed drug. The adsorption experiment was performed by applying the JP16 paddle method using a dissolution tester NTR-3000 made by Toyama Sangyo Co., Ltd. The moisture levels of MC, CMC-Na, CC-Na were checked before preparation of the granules, because they were needed to calculate the net MC amount of the granules. In addition, the granules were examined for moisture immediately before the adsorption test. The moisture levels were measured with an infrared moisture determination balance FD-230 made by Kett Electric Laboratory (Tokyo, Japan). The granules with the size of more than 42-mesh (0.355 mm) were obtained with sieving MC granules by horizontal vibration for 3 min.

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**Table 1 Formulation of granules**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>MC (g)</th>
<th>CMC-Na (g)</th>
<th>CC-Na (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GR0</td>
<td>30.0</td>
<td>2.7</td>
<td>0.0</td>
</tr>
<tr>
<td>GR1</td>
<td>30.0</td>
<td>2.7</td>
<td>0.6</td>
</tr>
<tr>
<td>GR2</td>
<td>30.0</td>
<td>2.7</td>
<td>1.2</td>
</tr>
<tr>
<td>GR3</td>
<td>30.0</td>
<td>2.7</td>
<td>3.0</td>
</tr>
</tbody>
</table>
and used in adsorption test so that the influence of fine powder could be negligible.

The net MC amount, which meant the dried MC amount or the amount of bone-dry MC, was investigated for the used granules by measuring the moisture as stated above. Namely, when the amount and moisture level of the granules were \( X \) (g) and \( Y \) (\%, w/w), respectively, the net amount of MC contained in the granules was calculated in the following equation (Eq. 1):

\[
\text{Net MC amount (g) in the granules} = X \times (1 - Y/100) \times \frac{\text{dried MC used}}{\text{dried MC used} + \text{dried CC-Na used} + \text{dried CMC-Na}}
\]

in which the moisture levels of MC, CMC-Na and CC-Na were 10\%, 11\% and 12\% (w/w), respectively. Adsorption experiments were performed under the same conditions as in the case of MC tablets reported previously.\(^{26}\) Namely, for the granules without CC-Na, the preparations with a net MC amount of 166 mg, corresponding to 184 mg MC powder, were used in the adsorption experiment. In the adsorption tests using the granules with CC-Na, the preparations with a net amount of 140 mg, corresponding to 155 mg MC powder, were used.

In the first experiment, MC powder and GR0 were used at the net MC amount of 166 mg. Each was placed into the aqueous solution (100 mL) containing AA (60 mg), which was being stirred at a paddle rotation speed of 60 rpm at 37°C. At appropriate time points, aliquot samples (1 mL) were withdrawn and centrifuged at 1500xg for 10 min. The supernatant (0.5 mL) was diluted to 50-fold volume with water, and the solution was measured spectrophotometrically at 243 nm to determine the concentration or amount of free AA. The adsorption amount was calculated by subtracting the free AA amount from the added AA amount. In the next place, MC powder, G1, G2 and G3 were used at the net MC amount of 140 mg. Each preparation was put into the aqueous solution (100 mL) containing 60 mg AA, being operated in the same way as above. The sampling and measurement of adsorption amount were performed in the same manner as above.

### Statistical Analysis

Statistical analysis was performed by unpaired \(t\)-test for comparison of two groups or one-way ANOVA followed by Dunnett’s post hoc test for comparison of more than two groups. Significant difference was set as \(P<0.05\).

### Results and Discussion

#### 1. Particle characteristics of MC granules

When the MC granules stood in air at room temperature, they lost moisture gradually. The moisture changed in a similar manner for all the granules. The moisture levels were 59 - 68% (w/w) and 30 - 33% (w/w) on the 1st and 7th day after granulation, respectively. Two weeks after granulation, the moisture levels scarcely changed from 2 weeks until 2 months after granulation for each granule; during that period, the moisture decreased by approximately 1% (w/w) at most, which was observed in GR3. Therefore, the \textit{in vitro} studies were performed using the MC granules 2 - 3 weeks after granulation.

The strength of the granules was investigated by comparison of their size distribution between before and after the friability test, though sieve
classification was roughly conducted using three types of sieves (10-, 12- and 42-mesh). This method was employed because the breakdown pattern could be obtained as well as defacement. All the MC granules exhibited a similar size distribution pattern (Table 2). All the granules have a size less than 1.7 mm (10 mesh), and most were distributed from 0.355 mm (42 mesh) - 1.4 mm (12 mesh). The size distribution at 1.4 - 1.7 mm was lowered to only a small extent after the friability test, indicating that the fragmentation of the granules was little caused. The similar phenomena were observed for the granules with the size of 0.355 - 1.4 mm. For GR0, GR1 and GR2, the granules with the size of less than 0.355 mm increased to a fair extent after the test, which was considered to be due to the increase of fine fragment and powder by defacement. However, even after the friability test, the ratio of the granules with the size of less than 0.355 mm to the total granules used was small (<10%), which indicated that the granules had fairly high strength.

As to the disintegration test, all of the granules slightly displayed disintegration after the test for 30 min. Namely, for all the granules, fine MC powder was visually recognized slightly out of the auxiliary tube after the disintegration test. The disintegration extent was apparently similar among them. In order to investigate the change in more detail, the MC granules remaining in the auxiliary tube after the disintegration test was dried, and their amount was measured. The granules remaining after the disintegration test is shown in Fig. 2. For GR0, the remaining amount was not significantly different from initial amount (comparison with 100% in Fig. 2), and the weight rather tended to increase, which might be due to slight moisture remaining or adsorbed. On the other hand, GR1-GR3 displayed a significant de-

Table 2  Size distribution (%, w/w) of granules before and after friability test

<table>
<thead>
<tr>
<th>Timing</th>
<th>Granule species</th>
<th>Granule size (mm)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.355 – 1.4</td>
<td>&lt; 0.355</td>
<td>1.4 – 1.7</td>
<td>1.7 &lt;</td>
</tr>
<tr>
<td>GR0</td>
<td>0</td>
<td>93.8 ± 1.7</td>
<td>4.8 ± 1.8</td>
<td>93.8 ± 1.7</td>
<td>4.8 ± 1.8</td>
</tr>
<tr>
<td>GR1</td>
<td>0</td>
<td>90.4 ± 0.5</td>
<td>8.3 ± 0.6</td>
<td>90.4 ± 0.5</td>
<td>8.3 ± 0.6</td>
</tr>
<tr>
<td>GR2</td>
<td>0</td>
<td>91.8 ± 3.0</td>
<td>6.8 ± 2.9</td>
<td>91.8 ± 3.0</td>
<td>6.8 ± 2.9</td>
</tr>
<tr>
<td>GR3</td>
<td>0</td>
<td>94.9 ± 0.5</td>
<td>4.1 ± 0.8</td>
<td>94.9 ± 0.5</td>
<td>4.1 ± 0.8</td>
</tr>
</tbody>
</table>

The size distribution was checked using 10-, 12- and 42-mesh sieves (each opening: 1.7, 1.4 and 0.355 mm, respectively). The results are expressed as the Mean ± SD (n = 3), in which the samples were taken from the same lot.
crease in weight as compared with the initial amount (comparison with 100% in Fig. 2). Also, their remaining percentage was significantly less than that of GR0 (compassion with R0 in Fig. 2). These suggested that the granules with CC-Na should lose the content to some degree by the disintegration test, while the granules with no CC-Na, GR0, were considered to be little changed. Since CC-Na has high water absorption potential, the granules with CC-Na was considered to be subjected to water absorption. As MC powder appeared to only a slight extent by the disintegration test, CC-Na might primarily promote dissolution of CMC-Na or loosening of CC-Na, resulting in their disappearance from the granules, that is, the decrease in weight of the granules after the disintegration test. Generally, CC-Na functions as a disintegrant in the compact state, by rapid water absorption and following swelling pressure. However, CC-Na was used in wet condition in the production of the present granules, and no compaction was conducted for them. Therefore, for the present granules, CC-Na did not exist in a compact state, which would be the reason that CC-Na hardly showed the disintegration power in the test.

2. Adsorption characteristics of MC granules

In this study, the adsorption profiles were investigated according to the experimental conditions stated in the previous reports on the tablets, T1 and T2 (see Introduction). Namely, the two experiments were performed at the conditions of the net MC amounts of 166 (T1) and 140 mg (T2). The adsorption data of T1 and T2 were referred to for the evaluation of the adsorption features of the present granules as described below.

Figure 3 shows the results of adsorption studies for MC powder (PW), granules without CC-Na (GR0), and the previously-reported tablet without CC-Na (T1). MC powder exhibited rapid absorption curves. For each sample, the adsorption almost reached saturation after the incubation for 5 h. GR0 had almost the same adsorption capacity as that of MC powder. The adsorption profile of GR0 was very similar to that of T1. The adsorption rate of GR0 was not rapid; it took more than 40 min to reach 60% of saturated adsorption.

![Fig. 2](image1.png) Change in weight of granules after disintegration test for 30 min
The results are expressed as the Mean ± SD (n = 3), in which the samples were taken from the same lot. * P<0.01 vs GR0 (Dunnett’s test). # P<0.05 vs 100% (unpaired t-test).

![Fig. 3](image2.png) Adsorption profiles of AA on MC powder (PW) and GR0
◇: PW, ○: GR0, + : T1. The preparations with the net MC amount (dried MC amount) of 166 mg were used. The amount of AA used at 60 mg. The previously-reported results of T1 (see introduction) was added as T1. The results are expressed as the Mean ± SD (n = 5), in which the samples were taken from the same lot.
sorption.

For the granules containing CC-Na (GR1-GR3), the adsorption test was performed under the same condition as in the tablet with CC-Na at 10% (T2). The results are shown in Fig. 4. For each sample, the adsorption saturation was almost completed after the incubation for 3 h. The mean adsorption amounts at 24 h were 44.9, 43.8 and 41.1 mg with GR1, GR2 and GR3, respectively. On the other hand, the adsorption amount was 41.6 and 42.5 mg with MC powder (PW) and T2, respectively. These results suggested that the addition of CC-Na up to 10% should influence the adsorption capacity of MC to only a slight extent. The high retention of adsorption capacity was considered to be an excellent point of the present granules; the adsorption capacity was reduced in the granules prepared with MC and MT at the ratio of 5: 6 (w/w) to a fair extent (∼20%).

It was found out that the addition of CC-Na could improve the adsorption rate. The concentration and amount of the used AA was the same in both the experiments of Figs. 3 and 4. Although GR0 was used at the larger net MC amount (166 mg net MC amount), as compared with the granules GR1-GR3 (each: net MC amount = 140 mg), the adsorption extent was caused more greatly in GR1-GR3 in the early stage. GR2 and GR3 exhibited significantly more adsorption amount than GR0 did (Fig. 4B). Generally, the adsorption rate is important clinically for MC formulations because quick adsorption is needed in order to prevent drug absorption from the gastrointestinal tract. Picchioni reported that it would be preferable to administer activated charcoal within 30 min after ingestion of the poison. The adsorption rate was found to be improved by the addition of CC-Na. In particular, GR3 exhibited adsorption at 65% (26.8 mg in 41.1 mg) and 79% (32.3 mg in 41.1 mg) of the saturated adsorption value after incubation for 20 and 40 min, which might be fairly good as an adsorption rate. Although the
adsorption rate of the granules was not fast as that of T2 showing rapid disintegration, the variation of adsorption amount in the early stage was much smaller in GR3; coefficient of variance = 0.21 and 0.27 at 10 and 20 min, respectively, for T2, while coefficient of variance = 0.07 and 0.05 at 10 and 20 min, respectively, for GR3. As stated above in the disintegration study, although CC-Na hardly acted well as a disintegrant in the present granules, the addition of CC-Na was considered to facilitate water absorption, dissolution of CMC-Na and loosening of the structure in the aqueous media. Such effect by CC-Na appeared to cause more quick interaction between MC and AA and consequently to promote the adsorption rate. Thus, the adsorption test demonstrated that CC-Na could accelerate the adsorption rate of the granules to some extent; the adsorption rate was significantly greater in GR2 and 3, especially in GR3.

In conclusion, the present MC granules could be prepared in the simple manner using a fairly small amount of CMC-Na as a binding agent, and showed good strength and good adsorption capacity, though the adsorption rate was not so fast as that of MC powder. Although the addition of CC-Na slightly changed the disintegration rate of the granules, it seemed to facilitate the water absorption and to influence the change in granule state, such as dissolution or loosening of the components, leading to the promotion of the adsorption rate. The MC granules containing 10% CC-Na (GR3) exhibited a good adsorption rate, suggesting that they might be possibly useful as a compact MC dosage form.

References

12) Rawashdeh NM, Al-Hadidi HF, Irshaid YM, Battah AK, Gastrointestinal dialysis of digoxin using chole-


