Medicinal Carbon Tablets for Treatment of Acetaminophen Intoxication: Adsorption Characteristics of Medicinal Carbon Powder and Its Tablets

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Adsorption characteristics of medicinal carbon powder (JP 14) for acetaminophen were examined at 37 °C using conventional incubation in an attempt to obtain an effective oral dosage form. Hydroxypropyl cellulose (HPC) and maltitol (MT), being able to act as a binding agent, were tested as additives. Tablets of medicinal carbon were produced by the wet granulation method. The rate and extent of adsorption of the medicinal carbon powder were roughly similar in water, JP 14 1st fluid (pH 1.2) and JP 14 2nd fluid (pH 6.8). The relationship between concentrations of free and adsorbed acetaminophen indicated that the adsorption followed the Langmuir mode. The maximal adsorption of acetaminophen in water was 0.219 g per gram medicinal carbon powder, little influenced by the addition of MT, but slightly reduced by the addition of HPC. The tablet prepared using MT as a binding agent displayed a favorable hardness and adequate disintegration time. The tablet showed good adsorption potential for acetaminophen, though the adsorption rate and extent of the tablet were reduced to some extent as compared with powder.

Key words medicinal carbon powder; tablet; maltitol; adsorption potential; acetaminophen

Plenty of research has been conducted on activated charcoal used clinically, called medicinal carbon or medicinal charcoal. Medicinal carbon is used clinically to treat intoxications caused by toxic chemicals taken orally, toxins generated in the gastrointestinal tract, drug overdose *etc*.[1—7] Also, it can be utilized to directly remove waste products from the blood stream.[8,9] Further, it is reported to be useful in reducing the systemic level of drugs injected intravenously.[10,11] The advantages of medicinal carbon are that it is considerably safe and low in price, and doesn't cause drug-resistant strains of bacteria.[6,12] Medicinal carbon is usually used as a powder or suspension, but a large dose can be a burden to the patient. The amount which has to be taken may be lost when a lot of powder is taken orally. Also, a fine powder can remain in the oral cavity. In this study, production of a compacted dosage form has been attempted in order to solve these problems.

Intoxications caused by phenobarbital, theophylline and acetaminophen are often cited, and their adsorption by medicinal carbon has been reported.[2,10—17] Recently, it was suggested that medicinal carbon be used for the treatment of a toxic metabolite emerging in the intestine.[18] In the present study, the JP 14 medicinal carbon powder supplied from Inuhinode Pharmaceutical Co., Ltd. has been characterized with regard to adsorption potential for acetaminophen, and its application as a tablet has been attempted. There is a possibility that additives may influence the adsorption potential of medicinal carbon.[16,19] In the preliminary study, when hydroxypropyl cellulose (HPC) and maltitol (MT) were added to aqueous suspension of medicinal carbon powder, HPC reduced the adsorption of brilliant blue FCF by medicinal carbon powder, but MT hardly did (data not shown). Therefore, the influence of these additives on the ability of medicinal carbon powder to adsorb acetaminophen has been investigated. Further, medicinal carbon tablets have been produced with MT as a binding reagent and examined in terms of adsorptive properties.

Experimental

Materials JP 14 medicinal carbon powder was supplied by Inu-hinode Pharmaceutical Co., Ltd. (Japan). After sieving it, the powder with a size of 150—200 mesh was used as medicinal carbon powder in the present study. Acetaminophen was purchased from Sigma (U.S.A.). Hydroxypropyl cellulose Type L, obtained from Nippon Soda Co., Ltd. (Japan), was used as HPC. Amalty MR-50, provided by Towa Chemical Industry Co., Ltd. (Japan), was used as maltitol (MT). All other chemicals were of reagent grade.

Preparation of Tablets A 60% (w/v) MT aqueous solution (17 ml) was added to 10 g of medicinal carbon powder, and kneaded well. Then, the wet mass was granulated manually with a sieve of size 9 mesh. The wet granules were dried at 60 °C overnight. The dry granules (500 mg) placed in a cylinder (1 cm inner diameter), and compressed at 4 kN for 30 s using an SSP-10 A manual press (Shimadzu Corp., Japan).

Adsorption Experiments for Characterization of Medicinal Carbon Powder The adsorption of acetaminophen was characterized at 37 °C as follows: Medicinal carbon powder (25 mg) was added to the acetaminophen solution (50 ml), and shaken at 90 rpm using a shaker. The suspension (1 ml) was taken at 0.25, 1, 5 and 24 h after incubation, and centrifuged at 3000 rpm for 10 min. The supernatant was diluted with the same solvent, and examined spectrophotometrically at 243 nm to determine the concentration of free acetaminophen.

Physical Characterization of Tablets In order to measure the strength of the tablets, the side of the cylindrical tablet was sandwiched softly between the flat platens of a Kiya-type hardness meter (Fujiwara Seisakusyo, Japan), and pressed gradually. The hardness observed immediately before crushed was measured. Further, a Model NT-60H disintegration tester (Toyama Sangyo Co., Ltd., Japan) was modified to facilitate observation of the disintegration of the tablets as shown in Fig. 1. Namely, a basket with a mesh size of 1.5 mm was moved up and down at a distance of 5.5 cm, 30 times per min at 37 °C. The bottom of the basket moved up to the surface of the test medium so that the disintegration of the tablets could be observed. The time taken for the tablet to disappear from the basket was determined as the disintegration time. Purified water was used as a test medium.

Adsorption Experiments with Dissolution Test Apparatus The JP 14 dissolution test apparatus for the paddle method (Toyama Sangyo Corp., Japan) was used in this experiment. The powder (250 mg) or tablet (250 mg eq medicinal carbon) was added to 500 ml of aqueous solution containing 50 mg of acetaminophen, which was stirred at 60 rpm and 37 °C with a single-blade propeller. Then, the stirring was continued under the same conditions. At 10, 20, 30 and 40 min, and 1, 2, 4, 6 and 24 h after the addition of the powder or tablet, the samples (1 ml) were withdrawn from the medium. Each suspension sample was centrifuged, and the supernatant was measured spectrophotometrically at 243 nm to determine the concentration of free acetaminophen.

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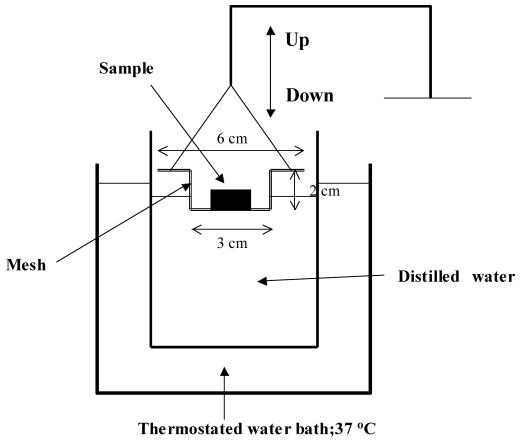

Fig. 1. Schematic Diagram of the Apparatus Used for the Disintegration Test

Results and Discussion

Adsorption Characteristics of Medicinal Carbon Powder for Acetaminophen The profile of the adsorption of acetaminophen by the medicinal carbon powder was examined using a shaker at 90 rpm and 37 °C. Under this condition, the powder could move sufficiently in an incubation medium without spattering out of the medium. Figure 2 shows the adsorption with a ratio of acetaminophen to medicinal carbon powder of 1 : 5 (w/w) in water, JP 14 1st (pH 1.2) fluid and 2nd (pH 6.8) fluid. The adsorption occurred rapidly, and was almost completed within 5 h. The extent of adsorption hardly differed among the solvents. When the amounts of acetaminophen adsorbed for an initial 15 min were compared among the solvents, the initial adsorption tended to be greater in JP 14 1st fluid under the higher acetaminophen concentration (Fig. 3). As acetaminophen is unionized due to the pK_a of 9.5 (25 °C), it exists in an unionized form in each condition. The difference in absorption rate could not be explained by simple factors such as solvent pH. Further, the extent of adsorption at equilibrium was investigated by changing the concentration of acetaminophen added. The extent of adsorption reached a plateau when the concentration of acetaminophen added was raised (Fig. 4). This was observed to almost follow the Langmuir adsorption mode, which is described in the following equation:

$$C_b = R_0 K C_f / (1 + K C_f) \quad (1)$$

where C_b and C_f are mean concentrations of adsorbed and free acetaminophen, respectively. R_0 is the concentration of total adsorption sites on medicinal carbon, and K is the association constant for acetaminophen.

Thus, as the adsorption profiles were roughly similar among water, JP 14 1st fluid and 2nd fluid, further adsorption experiments were performed using water as the solvent.

It is possible that additives affect the adsorption potential of medicinal carbon.[16,19] In the preliminary study, it was observed that HPC prevented the adsorption of brilliant blue FCF on the medicinal carbon powder, while MT had little influence (data not shown). Thus, the effects of HPC and MT on the adsorption of acetaminophen were examined. The extent of adsorption was found little influenced by such additives at a ratio of acetaminophen to medicinal carbon powder of 1 : 5 (w/w) (Fig. 5). Further, the amount of acetaminophen adsorbed for an initial 15 min tended to be higher in the presence of HPC (Fig. 6), though the reason could not be explained simply.

As the amount of acetaminophen added was increased, the extent of adsorption reached a plateau (Fig. 7). The Scatchard analysis was applied to these data. Namely, the Scatchard plots were made using the mean concentrations of

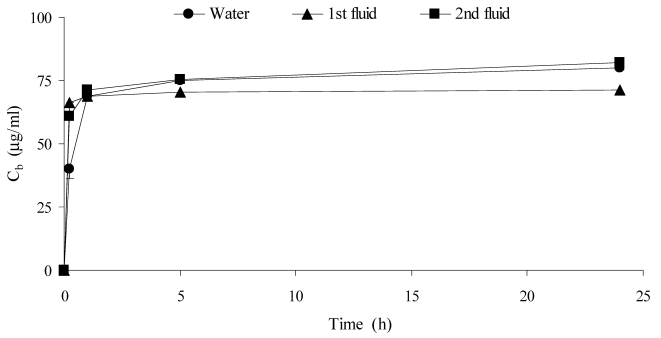

Fig. 2. Adsorption–Time Profiles of Medicinal Carbon for Acetaminophen in Different Media

C_b: concentration of acetaminophen adsorbed. Conditions: medicinal carbon (25 mg) was added to 50 ml of a solution containing acetaminophen (5 mg), and shaken at 90 rpm and 37 °C. The results are expressed as the mean±S.D. (n=3).

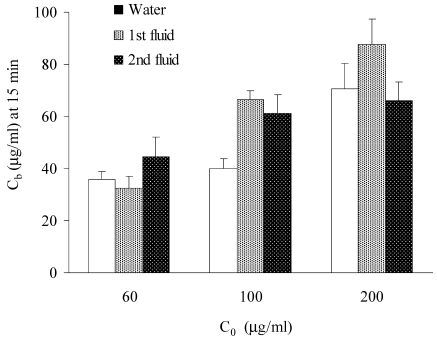

Fig. 3. Adsorption of Medicinal Carbon for Acetaminophen at 15 min after the Start of the Incubation in Different Media

C_0: concentration of acetaminophen added. C_b: concentration of acetaminophen adsorbed. Conditions: medicinal carbon (25 mg) was added to 50 ml of a solution containing acetaminophen (3, 5 and 10 mg), and shaken at 90 rpm and 37 °C. The results are expressed as the mean±S.D. (n=3).

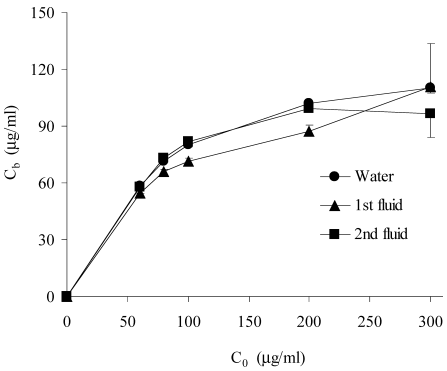

Fig. 4. Relationship between Concentrations of Acetaminophen Added and Adsorbed in Different Media

C_0: concentration of acetaminophen added. C_b: concentration of acetaminophen adsorbed at 24 h after incubation. Conditions: medicinal carbon (25 mg) was added to 50 ml of a solution containing different amounts of acetaminophen, and shaken at 90 rpm and 37 °C for 24 h. The results are expressed as the mean±S.D. (n=3).

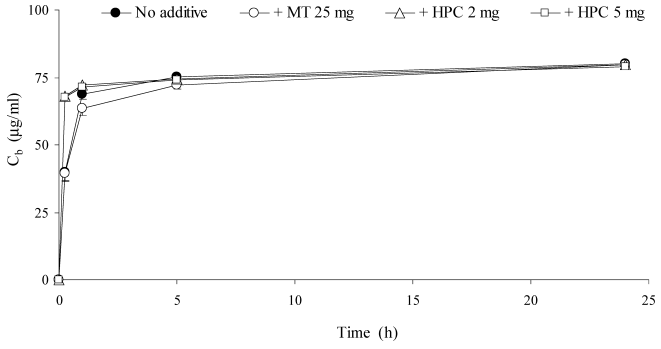

Fig. 5. Adsorption–Time Profiles of Medicinal Carbon for Acetaminophen in Water in the Presence of Additives

C_b: concentration of acetaminophen adsorbed. Conditions: medicinal carbon (25 mg) was added to 50 ml of water containing acetaminophen (5 mg) and an additive, and shaken at 90 rpm and 37 °C. The results are expressed as the mean±S.D. (n=3).

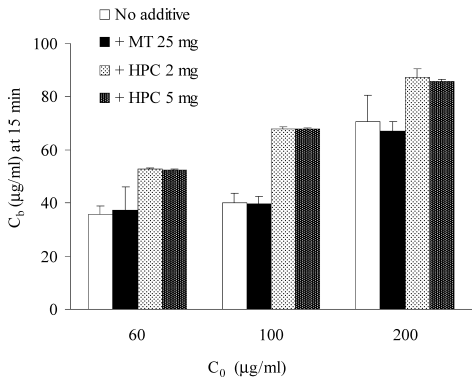

Fig. 6. Adsorption of Medicinal Carbon for Acetaminophen at 15 min after the Start of the Incubation in the Presence of Additives

C_0: concentration of acetaminophen added. C_b: concentration of acetaminophen adsorbed. Conditions: medicinal carbon (25 mg) was added to 50 ml of a solution containing acetaminophen (3, 5 and 10 mg), and shaken at 90 rpm and 37 °C. The results are expressed as the mean±S.D. (n=3).

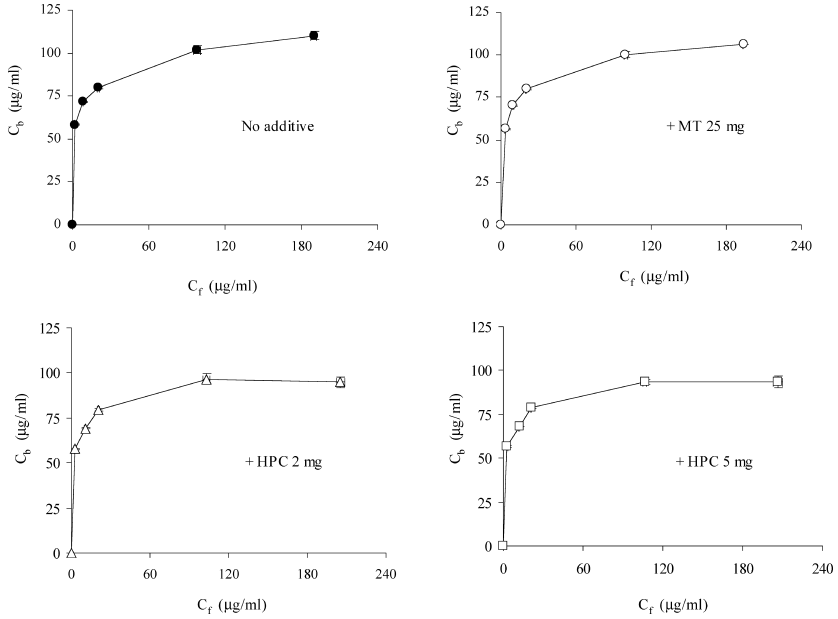

Fig. 7. Relationship between Concentrations of Free and Adsorbed Acetaminophen in Water

C_f: concentration of free acetaminophen at 24 h after incubation. C_b: concentration of acetaminophen adsorbed at 24 h after incubation. Conditions: medicinal carbon (25 mg) was added to 50 ml of a solution containing different amounts of acetaminophen with or without an additive, and shaken at 90 rpm and 37 °C for 24 h. The results are expressed as the mean±S.D. (n=3).

free (C_f) and adsorbed (C_b) acetaminophen (Fig. 8). When the association constant and free concentration of the co-existing compound preventing the acetaminophen adsorption are L and D_f, Eqs. 2 and 3 represent the acetaminophen adsorption in competitive and non-competitive prevention, respectively:

$$C_b/C_f=(K/(1+LD_f))\times(R_0-C_b) \quad (2)$$

and

$$C_b/C_f=K\times((R_0/(1+LD_f))-C_b) \quad (3)$$

where C_b and C_f are mean concentrations of adsorbed and free acetaminophen, respectively. R_0 is concentration of total adsorption sites on medicinal carbon, and K is association constant for acetaminophen.

The maximal concentration of acetaminophen adsorbed was given by a plateau level in Fig. 7, and also observed as an intercept on the C_b axis in the scatchard plot in Fig. 8. Although L and D_f were not determined, the maximal adsorption of acetaminophen was slightly lowered in the presence of HPC. This indicated that non-competitive prevention (Eq. 3) should be better fitted than competitive one (Eq. 2) because the maximal adsorption is changed by additives. As the C_b/C_f values decreased linearly at almost the same slope in the larger C_b values, the maximal adsorption was calculated by extrapolation using the 4 points nearest to the C_b axis. Then, the intercept values on the C_b axis were 110, 107, 99 and 97 μg/ml for the medicinal carbon powder with no additive, MT (25 mg), HPC (2 mg) and HPC (5 mg), respectively. Therefore, the maximal adsorption potentials of the medicinal carbon powder with no additive, MT (25 mg), HPC (2 mg) and HPC (5 mg) for acetaminophen were calculated to be 0.219, 0.214, 0.198 and 0.194 g per gram medicinal carbon, respectively. The results were consistent with reports

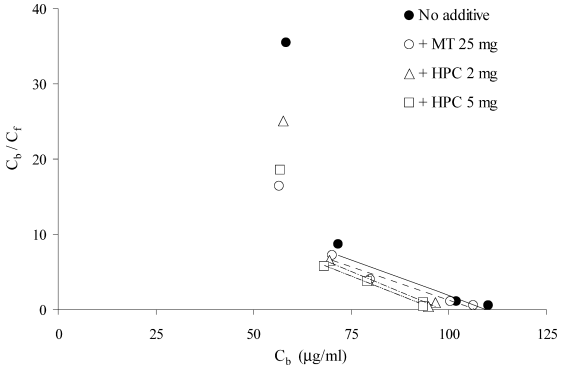

Fig. 8. Scatchard Plots for Adsorption of Acetaminophen by Medicinal Carbon in Water

C_f: concentration of free acetaminophen at 24 h after incubation. C_b: concentration of acetaminophen adsorbed at 24 h after incubation. Conditions: medicinal carbon (25 mg) was added to 50 ml of a solution containing different amounts of acetaminophen with or without an additive, and shaken at 90 rpm and 37 °C for 24 h. The mean values shown in Fig. 7 were used for analysis. The linear curves fitted to the plots were as follows: no additive (——), +MT 25 mg (·····), +HPC 2 mg (- - - -), +HPC 5 mg (—·—·—).

Table 1. Characteristics of Medicinal Carbon Tablet

Property	Value (mean±S.D.)[a)]
Tablet height (cm)	0.61±0.01
Hardness (kg)	5.97±0.87
Disintegration time (min)	3.44±0.37

a) $n=5$ for each result.

that medicinal carbon should be employed at five times or more the estimated dose of acetaminophen in the treatment.[20,21)]

Adsorption Characteristics of Tablets The size, hardness and disintegration characteristics of the tablets are shown in Table 1. These values were considered adequate for strength and disintegration. Considering the ratio of medicinal carbon powder and MT added, the tablet made from the dried granules of 500 mg was calculated to contain almost 250 mg of medicinal carbon per tablet. In fact, as water content of the tablet was only several % (w/w) (data not shown), the above calculation was adequate.

After medicinal carbon powder (250 mg) and the tablet (250 mg eq medicinal carbon) was added to aqueous solution containing 50 mg of acetaminophen, the adsorption profiles were investigated. The powder displayed a faster adsorption, but the table showed the fairly fast adsorption initially and slower adsorption at the latter phase (Fig. 9). Although the tablet disintegrated fast, the surface of the original medicinal carbon was considered not to be recovered quickly due to binding of each powder and MT remaining on the granules. The surface area of medicinal carbon was considered not to be recovered quickly. However, It was recognized that the tablet showed a considerably great adsorption of acetaminophen under the condition of the medicinal carbon amount of five times the amount of acetaminophen. These results suggested that the medicinal carbon tablet prepared with MT as a binding agent should be a useful compacted dosage form of medicinal carbon.

Conclusion

JP 14 medicinal carbon powder was characterized with regard to its adsorption of acetaminophen. The maximal adsorption for acetaminophen, analyzed using a Langmuir adsorption model, was 0.219 g per gram medicinal carbon powder. The effects of HPC and MT on the adsorption were also analyzed with the same model. HPC reduced the maximal adsorption, but MT hardly had any effect on adsorption. The tablet prepared using MT as a binding reagent exhibited a fairly good adsorption behavior. Thus, the present medicinal carbon tablet obtained with MT as a binding additive is suggested as a possibly useful compacted dosage form of medicinal carbon.

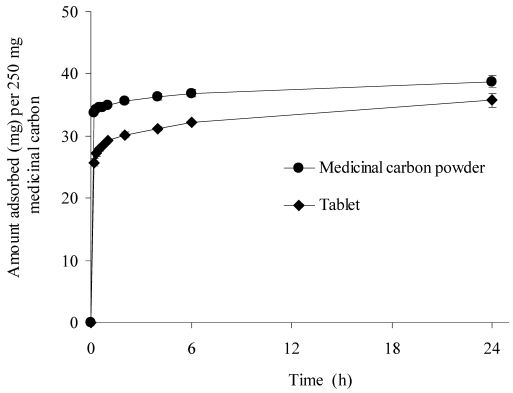

Fig. 9. Adsorption–Time Profiles of Acetaminophen in Water after the Addition of Medicinal Carbon Powder and Its Tablet

Medicinal carbon (250 mg) or the tablet (250 mg medica carbon eq) was added to 500 ml of a solution containing acetaminophen (50 mg), and stirred at 60 rpm and 37 °C with the JP 14 paddle method using a dissolution test apparatus. The results are expressed as the mean±S.D. ($n=3$).

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