

Evaluation of Binders in the Preparation of Medicinal Carbon Tablets by Wet Granule Compression

Akihiko ITO, Hiraku ONISHI,* Kenta YAMAMOTO, and Yoshiharu MACHIDA

Department of Drug Delivery Research, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan

(Received January 30, 2006; Accepted February 16, 2006)

Medicinal carbon (MC) tablets were prepared to obtain an oral dosage form that can be easily taken. The MC tablets were made by the wet granule compression method, in which hydroxypropyl cellulose (HPC), carboxymethyl cellulose sodium (CMC-Na) and maltitol (MT) were applied as binders. Brilliant Blue FCF (BB) was used as a model drug. The binders were evaluated in terms of formability of the granules and tablets, their strength, disintegration of the tablets, and their effect on the adsorption potential of MC. HPC and CMC-Na gave the strong granules at a fairly low concentration, but more MT was needed to obtain the strong granules. The tablets could be formed only when using MT at 120% (w/w) of the MC amount. The tablet displayed good hardness and rapid disintegration. The adsorption potential was not affected by CMC-Na, and slightly prevented by MT. However, the adsorption ability of MC was lowered more with the increase in HPC. The granules and tablets exhibited similar adsorption potentials, which were a little lower than that of MC suspended in MT aqueous solution. Similar adsorption characteristics were also observed in a real drug, acetaminophen. It is suggested that the MC tablets prepared by the wet granule compression using MT as a binder should be useful as a compact dosage form of MC.

Key words—medicinal carbon; tablet; wet granule compression; maltitol; adsorption potential

INTRODUCTION

Medicinal carbon (MC) is used clinically to treat intoxications caused by toxic chemicals taken orally, toxins generated in the gastrointestinal tract, drug overdose etc.^{1–5} Further, it is useful for directly removing waste products from the blood stream.^{6,7} It can adsorb various chemicals^{8,9} and remove them from the body. MC is low in toxicity and price, and does not cause the emergence of drug-resistant strains of bacteria. Previously, it was demonstrated that MC displayed a good potential to adsorb an endotoxin which was related to serious symptoms of food poisoning, and MC with a size of 150–200 mesh showed a large capacity to adsorb an endotoxin.¹⁰

MC is fine powder and usually administered orally at a very high dose.^{1,5} A large amount of powder is a burden to patients, often resulting in non-compliance. MC can cause the trouble of attaching to the oral mucosal membrane. Therefore, it is desirable to process MC as an oral dosage form which can be taken more easily. In the present study, preparation of the MC tablets was attempted. In the preliminary

experiment, the tablets could be made by the simple wet compression using common binders, but it was difficult to obtain the tablets with uniform content of MC. Therefore, in this study, the wet granule compression was applied to the production of the tablets. Hydroxypropyl cellulose (HPC), carboxymethyl cellulose sodium (CMC-Na) and maltitol (MT) were examined as binders. The granules and tablets were evaluated based on formability, hardness, disintegration rate and adsorption potential. As to adsorption experiments, brilliant Blue FCF (BB) was mainly used as a model drug, and acetaminophen (AA) was also used in checking effect of MT on adsorption.

MATERIALS AND METHODS

Materials Medicinal carbon (MC), being fine powder, was obtained from Kenei Pharmaceutical Co., Ltd. (Japan), and used without sieving. Brilliant Blue FCF (BB) and sodium carboxymethylcellulose (CMC-Na) were purchased from Wako Pure Chemical Industries, Ltd. (Japan). As to hydroxypropyl cellulose (HPC), hydroxypropyl cellulose type L (Nippon Soda Co., Ltd., Japan) was used. Acetaminophen (AA) was purchased from Sigma (USA). Amalty MR-50, provided by Towa Chemical

*e-mail: onishi@hoshi.ac.jp

Industry Co., Ltd. (Japan), was used as maltitol (MT). BB and AA were model drugs, and HPC, CMC-Na and MT were used as binders. All other chemicals were of reagent grade.

Adsorption in Aqueous Solution of Binder BB (5 mg) was dissolved in 50 ml of water, MC (25 mg) was added, and the suspension was shaken horizontally at 90 strokes per min at 37°C. The suspension (1 ml) was taken at appropriate time points after the start of incubation, and centrifuged at 3000 rpm for 10 min. The supernatant was diluted, and its absorbance at 630 nm was measured to determine the concentration of free BB. The concentration of adsorbed BB was calculated by subtraction of the concentration of free BB from that of total BB. In the case of BB aqueous solution containing a binder, BB (5 mg) and the specified amount of the binder were dissolved in water (50 ml), and the suspension was incubated in the same manner as above. The subsequent operation and analysis were performed in the same manner as above.

Preparation of Tablets by Wet Granule Compression A binder aqueous solution (18 ml) was added to 10 g of MC, and the mixture was kneaded sufficiently. Then, the wet mass was granulated manually with a sieve of size 9 mesh. The wet granules were dried at 60°C overnight. The dried granules (500 mg) was 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). The tablets were preserved in a glass bottle at room temperature, and used at 7 d after the production.

Characteristics of Granules and Tablets 1) Granule friability: The friability of the granules was examined using a friability tester (Kayagaki Irika Kogyo Co., Ltd., Japan). After the granules with a size of more than 14 mesh (1 g) were rotated at 25 rpm for 5 min, and the amount of the granules maintaining a size of more than 14 mesh was measured. The weight loss (%) of the granules from the initial amount was calculated as friability. 2) Tablet strength: The side of the cylindrical tablet was sandwiched softly between the flat platens of a Kiya-type hardness meter (Fujiwara Seisakusho, Japan). Then, the stress was gradually increased, and the hardness (F , kg) immediately before the crushing of the tablet was measured. Tensile strength (St , kg/cm²) was calculated as follows.¹¹⁾

$$St = 2F / (\pi \times D \times T),$$

where D and T were the diameter (cm) and thickness (cm) of the tablet, respectively. 3) Disintegration time of tablets: As the medium was blackened by the tablet disintegration, it was difficult to determine the disintegration time by the normal disintegration apparatus. Therefore, a Model NT-60H disintegration tester (Toyama Sangyo Co., Ltd., Japan) was modified as shown in Fig. 1.¹²⁾ Namely, a basket with a mesh size of 1.5 mm was moved up and down with a distance of 5.5 cm at 30 strokes per min at 37°C, when the bottom of the basket moved up to the surface of the test medium, which enabled us to observe the status of the tablet on the basket. The time taken for the tablet to completely disappear from the basket was measured as a disintegration time. Water was used as a test medium.

Adsorption for Granule and Tablets The JP 14 dissolution apparatus for the paddle method (Toyama Sangyo Corp., Japan) was used in this experiment. A tablet (500 mg), granules (500 mg) or MC (227 mg) was put in 500 ml of aqueous solution containing BB (50 mg) or AA (91 mg). Otherwise, MC (227 mg) was added to 500 ml of aqueous solution containing BB (50 mg) and MT (273 mg) or to 500 ml of aqueous solution containing AA (91 mg) and MT (273 mg). The paddle was stirred at 80 rpm and 37°C. At appropriate time points, the sample (1 ml) were withdrawn, centrifuged, and the supernatant was measured spectrophotometrically at 630 nm and 243 nm to determine the concentration of free BB and

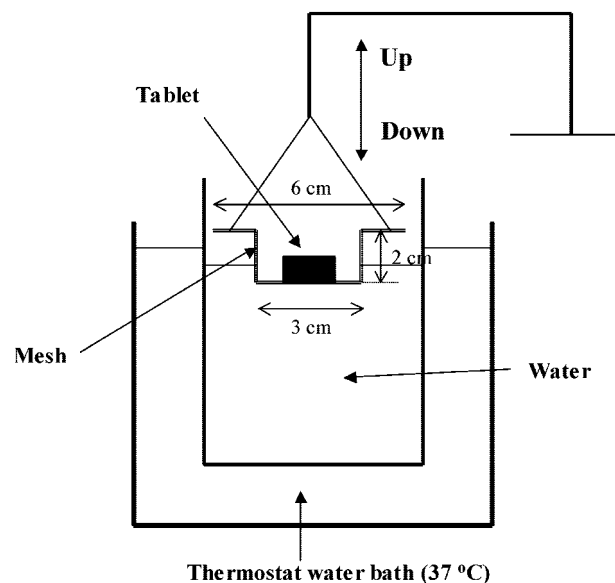


Fig. 1. Schematic Diagram of Disintegration Apparatus

AA, respectively. The concentration of adsorbed model drug was calculated by subtraction of the concentration of free model drug from that of total model drug.

RESULTS AND DISCUSSION

Effect of Binders on Adsorption Potential of MC

The solutions of HPC and CMC-Na are highly viscous at a high concentration, and mixing MC in such a highly viscous solution was difficult. Therefore, they were used at a fairly low concentration (1–10% of MC). As MT is a small molecule, the solution of the high concentration could be used in mixing MC. Thus, MT was used at 40–120% of MC. The adsorption of BB by MC was investigated in the BB aqueous solution containing a binder (Fig. 2). CMC-Na hardly affected the adsorption. MT slightly reduced the adsorption, but the reduction was not different among 40–120% of MT. On the other hand, the adsorption degree was lowered more with the increase in HPC. That is, the adsorption degree at 24 h was hardly affected by HPC of 1% of MC, but lowered to 78 and 67% by HPC at 5 and 10% of MC, respectively. CMC-Na and MT were found better binders than HPC from the viewpoint of the adsorption potential.

Evaluation of Binders in the Production of Tablets

HPC and CMC-Na allowed the production of granules (Table 1). Actually, in the preliminary study, tablets were well formed by simple wet compression using HPC and CMC-Na, though the content of MC could not be determined correctly. However, compression of the granules made with HPC and CMC-Na as a binder did not allow the formation of the tablets, that is, compaction was not possible. HPC and CMC-Na were useful as binders for MC, but the granules obtained by drying at 60°C appeared not to be bound together by compression. On the other hand, the granules prepared using more MT exhibited a greater strength. The tablets could not be prepared for the granules with a larger friability. However, the tablets were well formed from the granules with MT at 120% of MC. Thus, the tablets could be obtained only when MT was used at 120% of MC. In the case of the tablets with MT at 120% of MC, binding among the granules was maintained even after compression of the granules probably due to the existence of a large amount of a binder, MT.

Adsorption Characteristics of Granules and Tablets

The adsorption of BB was examined under the conditions of MC suspension in water, MC suspension in MT aqueous solution, granules in water and a tablet in water (Fig. 3). MT prevented the ad-

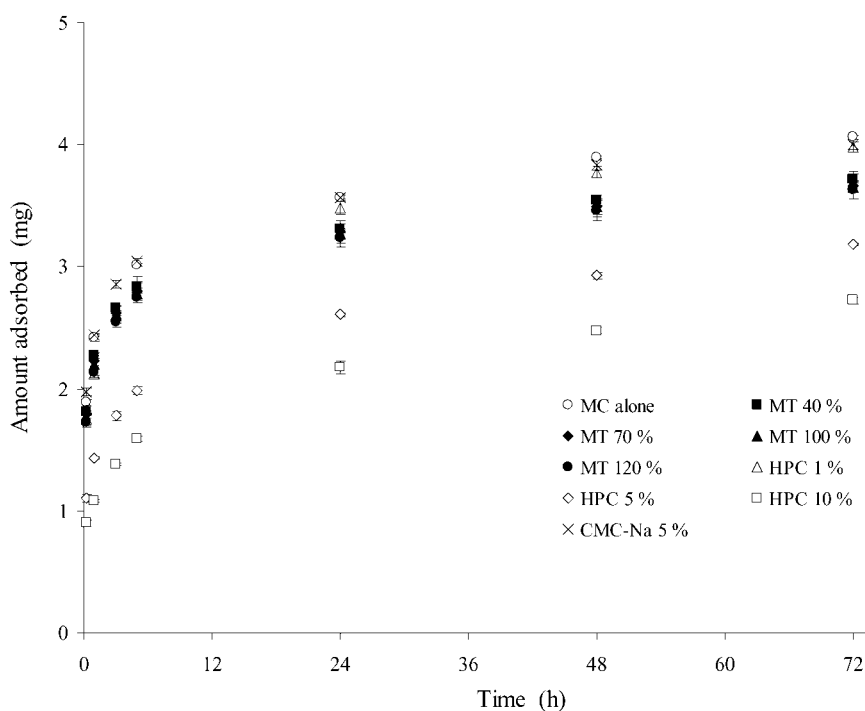


Fig. 2. Effect of Binders on the Adsorption of BB by MC at 37°C

MC (25 mg) was added to 50 ml of aqueous solution containing BB (5 mg) and binder. The results are expressed as the mean S.D. ($n=3$).

Table 1. Effect of Binder on Physical Characteristics of MC Granules and Tablets

Binder	Binder content (% w/w)	Granule friability ^{a)} (% w/w)	Tablet			
			Formability	Hardness ^{b)} (kg)	Tensile strength ^{b)} (kg/cm ²)	Disintegration time ^{b)} (s)
HPC	1	20±2	Not formed	—	—	—
	10	17±2	Not formed	—	—	—
CMC-Na	5	8±3	Not formed	—	—	—
	10	11±2	Not formed	—	—	—
MT	30	99±1	Not formed	—	—	—
	60	61±3	Not formed	—	—	—
	120	6±3	Well formed	8.5±0.2	9.4±0.2	107±5

a) The results are expressed as the mean±S.D. (n=3). b) The results are expressed as the mean±S.D. (n=5).

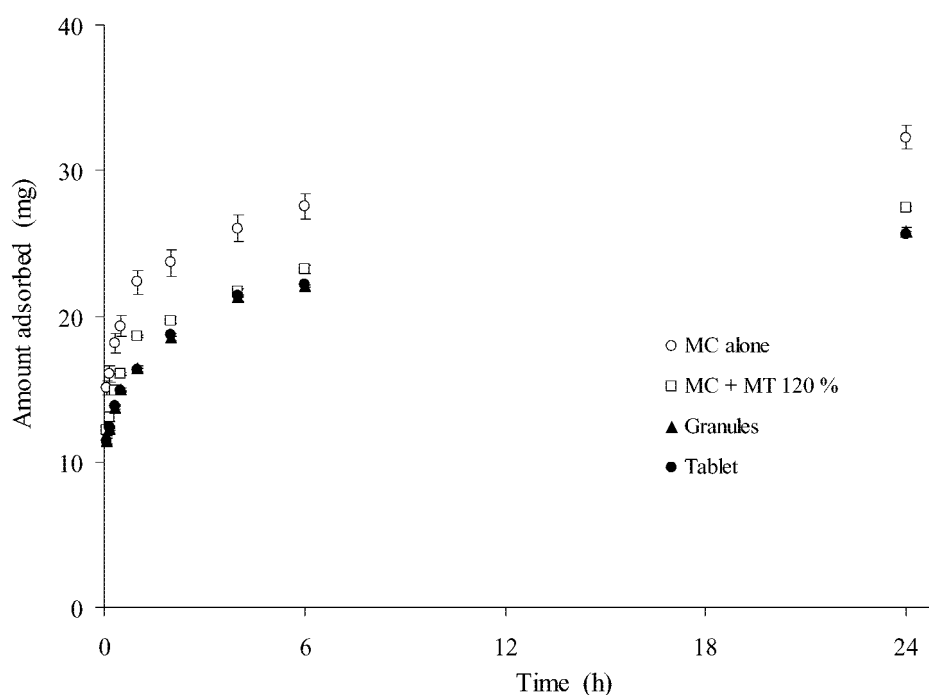


Fig. 3. Adsorption Profiles of BB by MC in Different Formulations or Conditions at 37°C

MC alone: MC (227 mg) was used. MC+MT 120%: MC (227 mg) was added in aqueous solution containing MT (273 mg). Granules and Tablet: MC (227 mg) was calculated to be contained. The results are expressed as the mean S.D. (n=3).

sorption of BB to a small extent. Further, the granules and tablets exhibited a little lower adsorption than MC suspended in MT aqueous solution. The adsorption degree at 24 h after the start of incubation was lowered by 15% in MT aqueous solution, and it was decreased by 20% in the granules and tablets. The adsorption characteristics of the granules and tablets were also investigated for a real drug, AA. As shown in Table 2, the adsorption of AA was lowered by the addition of MT. Further, the effects of MT aqueous solution, granules and tablets on the adsorption potential appeared to be similar to those for BB.

Thus, it was suggested that MT should lower the adsorption potential of MC to a small extent, and that the granules and tablets showed similar adsorption which was a little lower than the MT aqueous solution. Although MT in the granules or tablets was considered to be dissolved and lost from the surface of MC with time, the difference in the adsorption degree between MT solution and granules (or tablets) was almost the same among at 1, 6 and 24 h after the start of incubation (Table 2). Further, when moisture content of MC, granules and tablets was checked from change in weight by heating, it was 7—

Table 2. Adsorption of BB and AA by MC in Different Formulations or Conditions after 1, 6 and 24 h Incubation at 37°C

Model compound (amount used)	Formulation or condition ^{a)}	Amount adsorbed ^{b)} (mg)		
		1 h	6 h	24 h
BB (50 mg)	MC alone	22.3±0.8	27.5±0.8	32.3±0.8
	MC+MT	18.6±0.1	23.2±0.3	27.4±0.2
	Granules	16.4±0.3	22.0±0.1	25.8±0.3
	Tablet	16.3±0.1	22.1±0.0	25.6±0.2
AA (91 mg)	MC alone	56.7±0.6	58.1±0.7	61.4±0.4
	MC+MT	48.1±0.6	49.8±0.7	53.9±1.0
	Granules	42.1±1.4	45.0±0.8	48.8±1.5
	Tablet	41.2±0.4	43.3±0.8	47.5±0.5

a) MC alone: MC (227 mg) was used. MC+MT: MC (227 mg) was added in aqueous solution containing MT (273 mg). Granules and Tablet: MC (227 mg) was calculated to be contained. b) The results are expressed as the mean±S.D. (n=3).

9% among them, indicating that the amount of net MC, calculated by subtraction of adsorbed moisture, appeared to be almost the same among MC, granules and tablets. Therefore, the difference in the adsorption degree between MT solution and granules (or tablets) was considered not to be due to the moisture. Putting those things together, it is suggested that the granulation process should lower the adsorption capacity of MC. However, overall, the results indicated that MT was useful for the production of the tablets with a uniform content of MC and that the tablets displayed a high adsorption potential. Therefore, the MC tablets obtained were considered as a useful compact dosage form of MC. The usefulness of the MC tablets will be elucidated in more detail *in vitro* and *in vivo* in the future.

CONCLUSION

MC tablets were produced as a compact dosage form by the wet granule compression method. HPC and CMC-Na were not useful as a binder for the preparation of the tablets. When MT was used as a binder at 120% of MC, the tablets were well formed, and the tensile strength and disintegration time were acceptable. The adsorption potential of the tablets was lower to some extent than MC alone, but they retained a high adsorption potential to the model drugs used. It is suggested that the present tablets prepared using MT as a binder by the wet granule compression method should be useful as a compact dosage form of MC.

REFERENCES

- 1) Fricke R. F., Jorge J., *J. Toxicol. Clin. Toxicol.*, **28**, 421–431 (1990).
- 2) Makosiej F. J., Hoffman R. S., Howland M. A., Goldfrank L. R., *J. Toxicol. Clin. Toxicol.*, **31**, 381–395 (1993).
- 3) Tsitoura A., Atta-Politou J., Koupparis M. A., *J. Toxicol. Clin. Toxicol.*, **35**, 269–276 (1997).
- 4) Tsujikawa T., Araki Y., Makino J., Uda K., Ihara T., Sasaki M., Fujiyama Y., Bamba T., *J. Gastroenterol.*, **35**, 296–298 (2000).
- 5) Tanaka C., Yagi H., Sakamoto M., Koyama Y., Ohmura T., Ohtani H., Sawada Y., *Ann. Pharmacother.*, **38**, 73–76 (2004).
- 6) Van Wagenen R. A., Steggall M., Lentz D. J., Andrade J.D., *Biomater. Med. Devices Artif. Organs.*, **3**, 319–364 (1975).
- 7) Kodama M., Hanasawa K., Tani T., *Ther. Apher.*, **1**, 224–227 (1997).
- 8) Sobczak H., Pawlacyk J., *Acta Pol. Pharm.*, **55**, 279–283 (1998).
- 9) Alegakis A. K., Tzatzarakis M. N., Tsatsakis A. M., Vlachonikolis I. G., Liakou V., *J. Environ. Sci. Health B.*, **35**, 559–569 (2000).
- 10) Iwata M., Takahashi T., Takahashi Y., Ito A., Machida Y., *Jpn. J. Pharm. Health Care Sci.*, **27**, 63–68 (2001).
- 11) Tye C. K., Sun C. C., Amidon G. E., *J. Pharm. Sci.*, **94**, 465–472 (2005).
- 12) Yamamoto K., Onishi H., Ito A., Machida Y., *Chem. Pharm. Bull.*, **54**, 359–362 (2006).