Drug Development and Industrial Pharmacy, 2009; 35(11): 1333–1338

informa
healthcare

ORIGINAL ARTICLE

Preparation of medicinal carbon tablets by modified wet compression method

Masakazu Miyachi[1], Hiraku Onishi[2], Tetsuro Yumoto[1] and Yoshiharu Machida[2]

[1]*Department of Pharmacy, General Sagami Kosei Hospital, Sagamihara, Japan and* [2]*Department of Drug Delivery Research, Hoshi University, Tokyo, Japan*

Abstract

Background: Although medicinal carbon (MC) is useful to treat intoxications caused by orally taken toxic chemicals or toxins, high dose of MC is a burden on patients and sticks to oral mucosa or throat. A tablet dosage form of MC is useful to solve such problems. Fast-disintegration, adequate hardness, and quick and high-adsorption potential are required for MC tablets. *Method:* A modified wet compression method using carboxymethylcellulose sodium (CMC-Na) solution as binder solution was newly developed. Croscarmellose sodium (CC-Na) was used as a disintegration agent. MC granules, binder solution, and MC granules were placed in the cylinder in that order, and the resultant mass was compressed. The obtained tablets were examined for hardness, disintegration rate, and acetaminophen adsorption profiles. *Results:* The tablets, produced with MC granules containing CMC-Na and CC-Na at 10% each and using 280μL of 2.5% (w/w) CMC-Na binder solution in compression, showed adequate hardness (more than 4kg), short disintegration time (less than 6 min), and almost the same acetaminophen adsorption profile as intact MC powder. *Conclusion:* The modified wet compression with CMC-Na and CC-Na is suggested to be useful to obtain MC tablets with good quality.

Key words: *Acetaminophen adsorption; carboxymethylcellulose sodium; croscarmellose sodium; disintegration time; hardness; medicinal carbon tablet*

Introduction

Medicinal carbon (MC), being a fine activated charcoal powder, is used clinically to treat intoxications, caused by orally administered toxic chemicals, toxins generated in the gastrointestinal tract, and drug overdose[1–5], or to remove waste products from the bloodstream[6,7]. As MC is highly safe and low in price, and causes no emergence of drug-resistant strains of bacteria, it is clinically available to treat intoxication and to remove waste products. However, very high doses of MC usually need to be administered orally for achievement of sufficient efficacy[1,5], which is often a burden on patients. Also, as MC powder sticks to oral mucosa or throat, patients have trouble swallowing it[8,9]. In addition, as PC powder is easily dispersed in the air, it is troublesome to quantify or carry. Therefore, it is important to develop dosage forms for MC, which facilitate administration and operation of MC. Tablets and granules are considered to be useful, because they can be swallowed easily and can be carried readily because of their compacted dosage forms. Previously, we developed MC tablets as a compacted dosage form using a sugar alcohol, maltitol, as the binding agent[8,9].

It is essential for enhancement of patients' quality of life to make their mass as small as possible. Also, it is necessary for obtaining high-quality tablets to maintain the adsorption capacity of MC as much as possible. Generally, preparative methods (e.g., wet compression and direct compression) and binding agents significantly influence the tablet quality[8–10]. Gavrilov et al.[10] reported that the conventional wet granulation method did not necessarily give MC tablets with sufficient strength and that homogenous distribution of the binding agent through the tablet was very important to achieve a tablet with good strength. Furthermore, they

Address for correspondence: Dr. Hiraku Onishi, Department of Drug Delivery Research, Hoshi University, 2-4-41, Ebara, Shinagawa-ku, Tokyo 142-8501, Japan. Fax: +81 3 3787 0036. E-mail: onishi@hoshi.ac.jp

(Received 13 Dec 2008; accepted 17 Mar 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.3109/03639040902902419

reported that binding agents such as starch and sorbitol reduced the adsorption capacity of MC. We also found that hydroxypropylcellulose reduced the adsorption capacity markedly and even maltitol did to a lesser extent[8,9]. On the contrary, it was reported that carboxycellulose sodium (CMC-Na) functioned as a strong binding agent and hardly reduced the adsorption capacity of MC[10]. Therefore, CMC-Na was considered to be adequate as a binding agent for the preparation of tablets with good quality. However, the simple wet compression method with CMC-Na exhibited a slow disintegration property, and tablets could not be produced by the conventional wet granulation method using CMC-Na[9]. Therefore, in this study, to obtain good-quality tablets, we attempted a novel tablet production method, named modified wet compression method, in which CMC-Na was used as the binding agent. The tablets were characterized for hardness, disintegration rate, and adsorption features.

Materials and methods

Materials

MC of Japanese Pharmacopoeia 14 grade was obtained from Kenei Pharmaceutical Co. Ltd. (Osaka, Japan). CMC-Na was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan) and used as a binding agent. Croscarmellose sodium (CC-Na) was obtained from Asahi Kasei Corp. (Tokyo, Japan) and used as a disintegrating agent. Acetaminophen (AA) was purchased from Sigma (St. Louis, USA), and used as a drug for adsorption studies[11,12].

Preparation of MC tablets

MC tablets were prepared by the conventional wet granulation method and modified wet compression method using CMC-Na and CC-Na as a binding agent and a disintegrating agent, respectively.

Conventional wet granulation method

After CMC-Na (3 g) was dissolved in 60 mL of water, the resultant liquid was mixed with MC at the CMC-Na/MC ratio of 10:1 (w/w), and kneaded sufficiently manually. The resultant wet mass was manually granulated with an 18-mesh sieve and dried at room temperature for 7 days. After the dried granules were screened with a 50-mesh sieve, 250 mg of the granules remaining on the sieve was compressed at 2, 4, 6, and 8 kN for 30 seconds using an SSP-10A manual press (Shimadzu Corp., Kyoto, Japan) and at 10 kg/cm^2 using a Hand Press H-10 manual press (Shimadzu Corp.) to yield tablets 10 mm in diameter (Figure 1).

Modified wet compression method

The granules were prepared in the same manner as stated above in the wet granulation method. The granules remaining on a 50-mesh sieve (125 mg) were placed in a cylinder (10 mm inner diameter), and a binder solution, aqueous solution of 2.5% (w/v) CMC-Na (250, 280 or 300 μL), was dropped on the granules in the cylinder. Then, the granules remaining on a 50-mesh sieve (125 mg) were added to the granules and binder solution in the cylinder. The resultant materials in the cylinder were compressed at 2, 4, 6, and 8 kN for 30 seconds using an SSP-10A manual press (Shimadzu Corp.) and at 10 kg/cm^2 using a Hand Press H-10 manual press (Shimadzu Corp.) to obtain tablets 10 mm in diameter (Figure 1).

In addition, tablets with CC-Na were produced as follows: First, granules containing CC-Na at 10% (w/w) of MC were prepared. Namely, MC and CC-Na were mixed and kneaded with CMC-Na binder solution at the MC/CMC-Na/CC-Na ratio of 10:1:1 (w/w). Then, the resultant wet mass was granulated in the same manner as described above. The obtained granules were processed according to the modified wet compression method in the same manner as described above to obtain the tablets 10 mm in diameter.

Tablet characteristics

MC tablets were evaluated for hardness and disintegration time in order to evaluate the tablet qualities as follows:

Hardness

The side of the tablet was sandwiched between the flat plates of a Kiya-type digital hardness meter (Fujiwara Scientific Co., Ltd., Tokyo, Japan), and the stress was increased gradually. The force immediately before the crash of the tablet was measured as tablet hardness ($n = 5$).

Disintegration time

The disintegration time was measured using a Model NT-60H disintegration tester (Toyama Sangyo Co., Ltd., Osaka, Japan) ($n = 5$). Water (800 mL) at 37°C was used as a test medium.

Test of adsorption capacity

Immediately before the adsorption test, the moisture levels of powder and tablets were measured with an infrared moisture determination balance FD-230 (Kett Electric Laboratory, Tokyo, Japan) to compare their adsorption rate and capacity under the conditions of the same content of MC.

A JP 14 dissolution apparatus for the paddle method (Toyama Sangyo Co.) was used in this

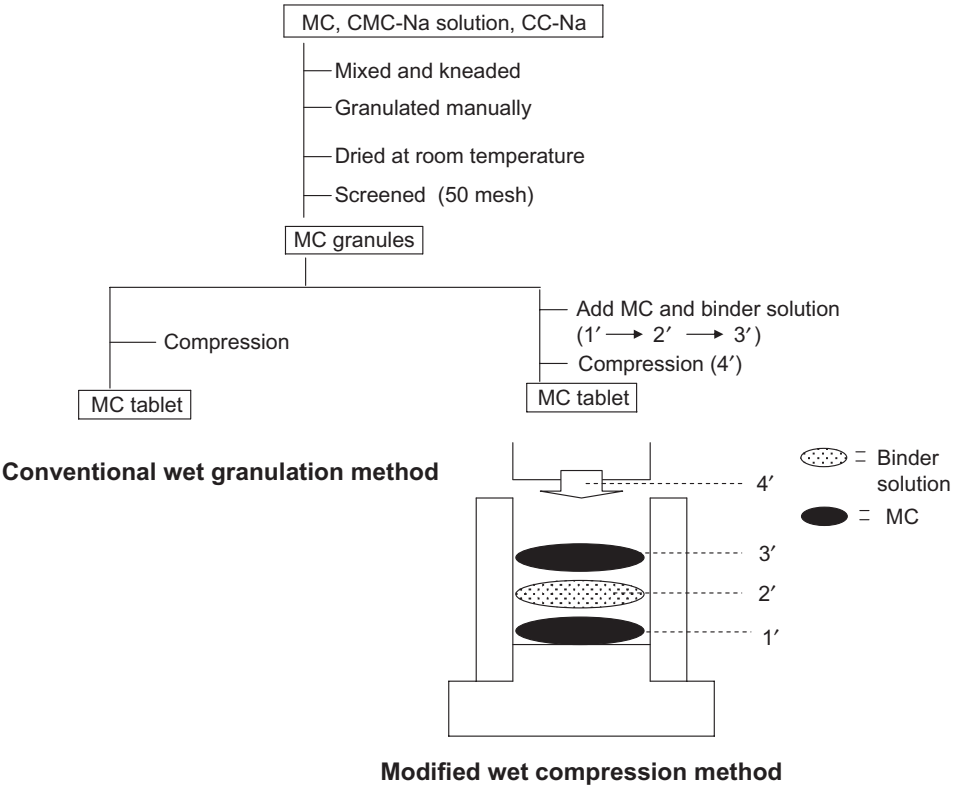

Figure 1. Preparative procedure of the tablets by conventional wet granulation method and modified wet compression method.

experiment. After AA (60 mg) was dissolved in 100 mL of water at 37°C, the medium was stirred at 60 rpm at 37°C. Then, an MC tablet or MC powder of the same amount as MC contained in the tablet was put in the medium. At appropriate time points, aliquot samples (1 mL) were withdrawn and centrifuged at 1500 × *g* for 10 minutes. The supernatant (500 μL) was diluted 50 times with purified water, and the solution was measured spectrophotometrically at 243 nm to determine the amount of non-adsorbed (free) AA.

Statistical analysis

For statistical analysis, a comparison was made using the unpaired *t*-test, and significant difference was set as $P < 0.05$.

Results and discussion

Preparation conditions and tablet characteristics

In the wet granulation method, granules are well formed, but tablets are not formed by compressing the granules under each compression condition. Once the granules were broken by compression, the resultant powder appeared not to bind together, probably because the binder was insufficient in quantity or not distributed homogenously. Similar phenomena were reported to be observed in the wet granulation method[9]. On the contrary, in modified wet compression, the tablets are well formed by the compression at 10 kg/cm^2. In this condition, it was considered that the binder liquid should spread throughout the granules and the granules could bind together because of low pressure. Under other compression conditions (2–8 kN), tablets of sufficient strength were not produced, probably because the granules were broken by compression and compression pressure was too high to bind together.

When granules made using the mixture of MC and CMC-Na (10:1, w/w) and 280 μL of 2.5% (w/w) CMC-Na binder solution were used in modified wet compression, tablets of good quality could be obtained. In this tableting condition, the whole tablet displaying a uniformly wet state was produced without leakage of liquid, probably because the binder liquid of appropriate volume permeates all the granules under this compression condition. Such tablets could be obtained reproducibly. Compression with the addition of less CMC-Na binder solution tended to provide low-strength tablets. The addition of less CMC-Na binder solution was considered not to provide sufficiently wet conditions, leading to poor tablet formation. Furthermore, the

binder solution leaked when more (>280 μL) was added to the granules, which could not give tablets of a certain quantity. Thus, the use of granules made with a particular ratio of MC/CMC-Na (10:1, w/w) and the addition of 280 μL of 2.5% (w/w) CMC-Na solution (binder solution) was found to be suitable for modified wet compression. The tablets with and without CC-Na were prepared by the modified wet compression method. The obtained tablets had a size of 10 mm in diameter and 5 mm in thickness and were used for the following in vitro studies.

The hardness of the tablets with and without CC-Na is shown in Figure 2. Tablets without CC-Na showed high hardness of 8.67 kg, whereas tablets prepared by the addition of CC-Na at 10% (w/w) of MC exhibited hardness of 4.94 kg. Therefore, the addition of CC-Na reduced tablet strength significantly ($P < 0.001$), but CC-Na-containing tablets were sufficiently hard (4.94 kg). The disintegration characteristics of the tablets with and without CC-Na are shown in Figure 3. The tablets with and without CC-Na exhibited 5.4 and 7.1 minutes, respectively. The addition of CC-Na reduced the disintegration time significantly ($P < 0.01$). The disintegration time of these tablets appeared to be shorter than that of the tablets produced by Gavrilov et al.[10], who prepared tablets by the dry mixing–wet granulation technique. In the modified wet compression method, even though the granules were broken by compression, the binder solution added between two layers of granules was considered to cause the granule-derived powder to bind together again, resulting in good tablet hardness. Thus, the addition of CC-Na was considered to be better because it caused no problems with hardness and faster disintegration was achieved[13–15].

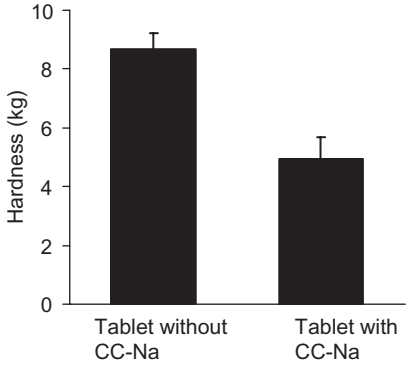

Figure 2. Effect of CC-Na on hardness of the tablets produced by modified wet compression method. The results are expressed as the mean ± SD ($n = 5$).

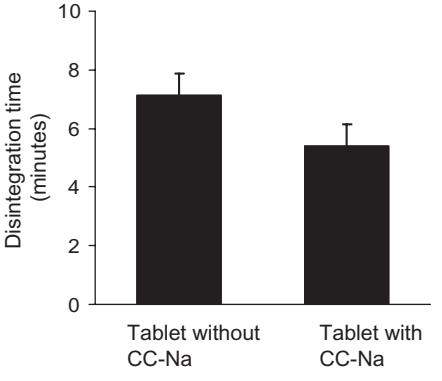

Figure 3. Effect of CC-Na on disintegration time of the tablets by modified wet compression method. The results are expressed as the mean ± SD ($n = 5$).

Adsorption properties of tablets

Original MC powder had moisture content of approximately 10% (w/w) under an air atmosphere condition. The produced granules were kept in air after preparation. They displayed moisture content of approximately 10% (w/w) 7 days after preparation, and the moisture level changed little since 7 days after preparation. Therefore, the granules, left under air atmosphere 7 days after preparation, were used for tableting. The tablets with or without CC–Na had moisture levels of approximately 30% and 28% (w/w), respectively, 7 days after tableting (Figure 4) and then their moisture levels changed little. Given these features for the moisture of MC powder and tablets, the adsorption test was performed on 7 days after their production. MC powder and tablets were examined for their moisture levels immediately before the adsorption test. The net amount of MC powder was determined based on the moisture. Also, the net amount of MC was calculated from the subtraction of the contents of the moisture and additives including CMC-Na (7 mg) contained in additional

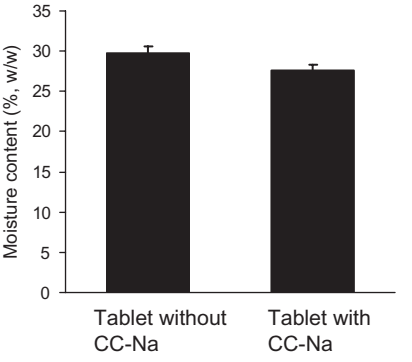

Figure 4. Moisture levels of the tablets without and with CC-Na 7 days after their production. The results are expressed as the mean ± SD ($n = 3$).

binder solution (280 μL) from the tablet amount using the following equations.

$$\text{Net MC content of tablet without CC-Na (mg)} = [\text{tablet weight} \times (1 - \text{moisture content}) - 7] \times 0.9 \quad (1)$$

$$\text{Net MC content of tablet with CC-Na (mg)} = [\text{tablet weight} \times (1 - \text{moisture content}) - 7] \times 0.818 \quad (2)$$

The tablet or MC powder equivalent to the MC contained in the tablet was put in the medium containing AA, and adsorption of AA by MC was examined. At 10 minutes, MC powder adsorbed 72% of the amount of AA adsorbed at 24 hours, but the tablets without CC-Na adsorbed only 31% of the amount of AA adsorbed at 24 hours (Figure 5A). The adsorption portion was significantly lower in tablets without CC-Na than in MC powder at least for the initial 1 hour. On the contrary, the tablet with CC-Na exhibited a quite different adsorption profile from the tablet without CC-Na. As shown in Figure 5B, the tablet with CC-Na exhibited almost the same adsorption profile as that of MC powder. Namely, at 10 minutes, the tablet with CC-Na adsorbed 71% of the amount of AA adsorbed at 24 hours, and then the amount of AA adsorbed was not different from that in MC powder. These results suggested that the tablet with CC-Na should have a quick and good adsorption potential, whereas the tablet without CC-Na should lack quick adsorption to a certain extent. The addition of CC-Na accelerated tablet disintegration (Figure 3), which appeared to partly contribute to the quick adsorption features of the tablet with CC-Na. In the disintegration and adsorption tests, the particles generated by disintegration were observed to be finer in the tablets with CC-Na than in the tablets without CC-Na. As the finer particles were considered to present larger surface area, this might be a major reason that the initial adsorption was fairly different between the tablets with and without CC-Na in spite of the small difference in their disintegration time, which was approximately 2 minutes. These results indicated that the tablets with CC-Na could not only disintegrate rapidly but also exhibit quick and high adsorption potential.

Conclusion

MC tablets containing CMC-Na as a binding agent were produced by the conventional wet granulation method and modified wet compression method. In the modified wet compression, first, granulation of MC was conducted by addition of CMC-Na with or without CC-Na at the ratio of 10% (w/w) to the amount of MC. Then, the granules were put twice in the cylinder, in which the CMC-Na binder solution was added between the first and the second sets of the granules, and then the mass was compressed. Conventional wet granulation could not form tablets, but the modified wet compression gave good-quality tablets, that is, hardness of more than 4 kg and disintegration time of less than 8 minutes. The tablets with CC-Na disintegrated faster and showed almost the same AA adsorption profile as MC powder of an equivalent amount. The modified wet compression method is suggested to be useful in obtaining MC tablets of good quality.

Declaration of interest: The authors report no conflicts of interest.

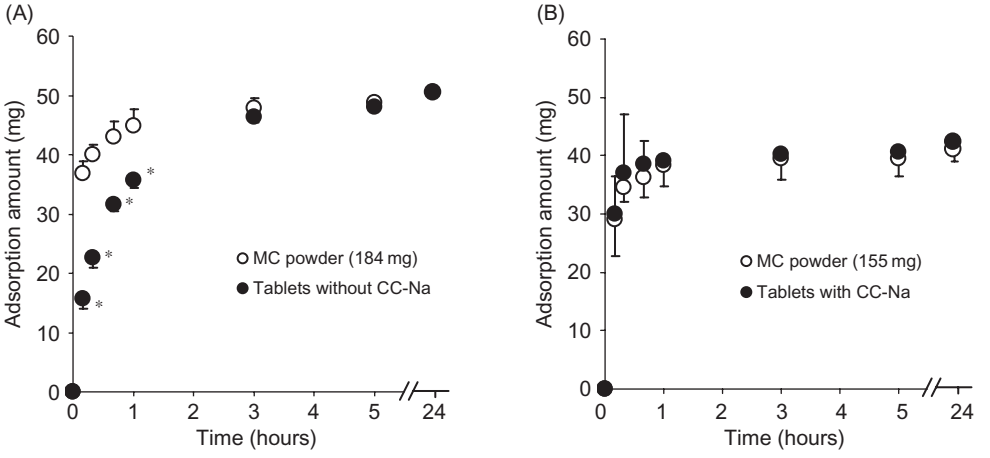

Figure 5. Adsorption profiles of AA by MC powder and tablets at the equivalent content of MC. (A) Comparison between MC powder and tablets without CC-Na (net MC content = 166 mg). (B) Comparison between MC powder and tablets with CC-Na (net MC content = 140 mg). Each point represents the mean ± SD ($n = 5$). *$P < 0.001$ versus MC powder.

References

1. Swartz CM, Sherman A. (1984). The treatment of tricyclic antidepressant overdose with repeated charcoal. J Clin Psychopharmacol, 4(6):336–40.
2. Fricke RF, Jorge J. (1990). Assessment of efficacy of activated charcoal for treatment of acute T-2 toxin poisoning. J Toxicol Clin Toxicol, 28(4):421–31.
3. Cooney DO. (1995). In vitro adsorption of phenobarbital, chlorpheniramine maleate, and theophylline by four commercially available activated charcoal suspensions. J Toxicol Clin Toxicol, 33(3):213–7
4. Tsujikawa T, Araki Y, Makino J, Uda K, Ihara T, Sasaki M, et al. (2000). Efficacy of oral adsorbent for treatment of peristomal fistula associated with Crohn's disease. J Gastroenterol, 35(4):296–8.
5. Tanaka C, Yagi H, Sakamoto M, Koyama Y, Ohmura T, Ohtani H, et al. (2004). Decreased phenobarbital absorption with charcoal administration for chronic renal failure. Ann Pharmacother, 38(1):73–6.
6. Van Wagenen RA, Steggall M, Lentz DJ, Andrade JD. (1975). Activated carbons for medical applications. In vitro microparticle characterization and solute adsorption. Biomater Med Devices Artif Organs, 3(3):319–64.
7. Kodama M, Hanasawa K, Tani T. (1997). Blood purification for critical care medicine: Endotoxin adsorption. Ther Apher, 1(3):224–7.
8. Yamamoto K, Onishi H, Ito A, Machida Y. (2006). Medicinal carbon tablets for treatment of acetaminophen intoxication: Adsorption characteristics of medicinal carbon powder and its tablets. Chem Pharm Bull, 54(3):359–62.
9. Ito A, Onishi H, Yamamoto K, Machida Y. (2006). Evaluation of binders in the preparation of medicinal carbon tablets by wet granule compression. Yakugaku Zasshi, 126(4):315–9.
10. Gavrilov AS, Gusel'nikova EV, Petrov AY. (2004). Development of the technology of activated charcoal tablets. Pharm Chem J, 38(1):41–4.
11. Gregus Z, Madhu C, Klaassen CD. (1988). Species variation in toxication and detoxication of acetaminophen in vivo: A comparative study of biliary and urinary excretion of acetaminophen metabolites. J Pharmacol Exp Ther, 244(1):91–9.
12. Hirate J, Zhu CY, Horikoshi I, Bhargava VO. (1990). First-pass metabolism of acetaminophen in rats after low and high doses. Biopharm Drug Dispos, 11(3):245–52.
13. Picchioni AL. (1970). Activated charcoal. A neglected antidote. Pediatr Clin North Am, 17(3):535–43.
14. Levy G, Gwilt PR. (1974). Effect of activated charcoal on acetaminophen absorption in man. Pharmacologist, 16:208.
15. Yamamoto K, Onishi H, Ito A, Machida Y. (2007). In vitro and in vivo evaluation of medicinal carbon granules and tablet on the adsorption of acetaminophen. Int J Pharm, 328(2):105–11.