Preparation and Evaluation of Medicinal Carbon Tablets with Different Saccharides as Binders

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Medicinal carbon (MC) tablets were prepared with several saccharides to improve the formability and absorption ability of MC tablets made with maltitol (MT). The MC tablets were made by the wet granule compression method, in which maltitol, xylitol (XYL), mannitol (MAN), and sorbitol (SOR) were used as binders. Granule and tablet formability, tablet strength, disintegration, and MC adsorption potential were evaluated for each formulation. Acetaminophen (AA) was used in checking effect of binders on adsorption. Due to low water solubility, MAN was added only up to 30% (w/w) of MC; in greater concentrations, the tablet could not be formed. However, tablets formed easily when using XYL or SOR at 120% (w/w) of the MC amount. This result was similar for MT. The XYL, SOR, and MT tablets displayed sufficient hardness and rapid disintegration. The tensile strength of the SOR tablets exceeded that of the MT tablets, which in turn had greater tensile strength than the XYL tablets. In addition, the XYL tablets disintegrated more quickly than the MT tablets, which disintegrated more quickly than the SOR tablets. The MC adsorption capacity was slightly decreased by XYL and SOR, but to a lesser extent than the decrease caused by MT. Overall, XYL and SOR were superior to MT as binding agents for preparation of MC tablets. Therefore, we recommend preparing the tablets with XYL or SOR as a binder using the wet granule compression method to produce a compact dosage form of MC.

Key words medicinal carbon powder; tablet; wet granule compression; saccharide; adsorption potential; acetaminophen

In the clinical setting, activated charcoal, or medicinal carbon (MC), has been used widely as a potent adsorption agent. It is applied in the treatment of intoxication caused by the ingestion of toxic chemicals or other toxins, drug overdoses, the formation of harmful metabolites in the gastrointestinal tract, *etc.*[1—5] Also, MC can be utilized for hemoperfusion to remove certain poisons from blood.[6] It has been reported that MC displays strong potential to adsorb an endotoxin related to serious symptoms of food poisoning; MC with a mesh size of 150—200 mesh showed a large capacity to adsorb the endotoxin.[7] Further, medicinal activated charcoal has been used for removing waste products that build up as a result of chronic kidney disease.[8]

The dosage form of MC is usually a powder, suspension or granule, but large dosage is difficult for patients to take. MC is a fine powder and is typically administered orally, but there is potential for significant loss when large quantities of powder are taken orally. Furthermore, the powdered form has many problems in taking, including adhesion to the throat, an expanse to the whole mouth *etc*. These issues lead to patient non-compliance. Therefore, previous studies looked at production of an oral dosage form.[9,10] They found that MC tablets could be made by wet granule compression using maltitol (MT) as a binding agent, but MT exhibit a slight decrease in the adsorption capacity of MC. Therefore, in this study, we investigated the influence of other saccharides, namely xylitol (XYL), sorbitol (SOR), and mannitol (MAN), in the preparation of MC tablets. The tablets formulated with these saccharides were evaluated with respect to formability, hardness, disintegration rate, and MC adsorption of acetaminophen (AA).

Experimental

Materials Medicinal carbon was purchased from Kenei Pharmaceutical Co., Ltd. (Japan) as a fine powder and used in the experiments without sieving. Acetaminophen was obtained from Sigma (U.S.A.). Maltitol, xylitol, sorbitol, and mannitol were obtained from Towa Chemical Industry Co., Ltd. (Japan). All other chemicals were reagent grade.

Preparation of Granules and Tablets Each saccharide aqueous solution (18 ml) containing MT (3, 6, 12 g), XYL (6, 12 g), SOR (6, 12 g) and MAN (3 g) were added to 10 g of MC, and each mixture was kneaded sufficiently with magnetic stirrer. Then the wet mass was granulated manually with a sieve of No. 8.6 (2000 μm). The wet granules were dried at 60 °C overnight. 500 mg of dried granules were placed in a cylinder with an inner diameter of 1 cm and compressed at 4 kN for 30 s using an SSP-10A manual press (Shimadzu Corp., Japan). The tablets and granules were stored in glass bottles at room temperature.

Physical Characteristics of the Granules and Tablets The friability of the granules was quantified with a friability tester (Kayagaki Irika Kogyo Co., Ltd., Japan). One gram of granules with a sieve size of more than No. 14 (1180 μm) was rotated at 25 rpm for 5 min, and the weight of granules that maintained a sieve size of more than No. 14 (1180 μm) was measured. The percent weight loss of large granules from the initial amount was calculated as the friability.

The thickness (T, cm), hardness (F, kg), and disintegration time (s) in water of the tablets were also evaluated. Hardness was measured using a Kiya-type hardness meter (Fujiwara Seisakusho, Japan), and the tensile strength (St, kg/cm^2) was calculated as

$$\mathrm{St}=2F/(\pi\times D\times T) \quad (1)$$

where D and T were the tablet diameter and thickness, respectively. The diameter was always 1 cm.

The tablet disintegration time was measured at 37 °C using a modified disintegration apparatus as shown in Fig. 1.[9] 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 tablets were placed in the basket. The basket moved up and down from the medium surface to full immersion (a total distance of 5.5 cm) at 30 strokes per minute. The time taken for the tablet to completely disappear from the basket was measured as the disintegration time. Purified water was used as the test medium.

Acetaminophen Adsorption Experiments The JP 14 dissolution apparatus (Toyama Sangyo Co., Ltd., Japan) was used in this experiment for the paddle method. MC (227 mg), granules (500 mg), tablets (500 mg), or a physical mixture of MC (227 mg) and each saccharide (273 mg) was added to 500 ml of water in which 91 mg of AA was dissolved, and the mixture was stirred at 80 rpm at 37 °C according to a previous report[10] which showed the effect of binder on adsorption potential of MC. At appropriate time points, 1 ml samples were withdrawn and centrifuged at 3000 rpm for 10 min. The

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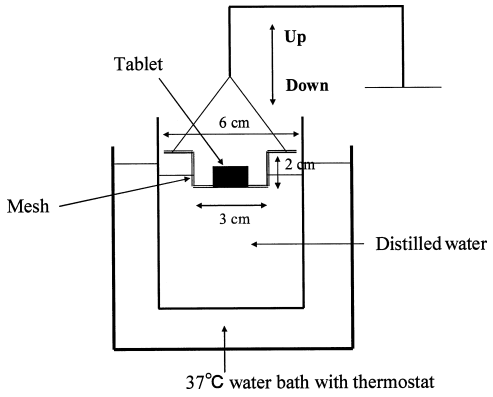

Fig. 1. Schematic Diagram of Disintegration Test Apparatus

supernatant was diluted with water and tested by UV spectrophotometry at 243 nm to determine the concentration of free AA. The amount of AA adsorbed by the MC was calculated as the difference between the total and free AA.

Results and Discussion

The Effect of Each Saccharide on the Physical Characteristics of the MC Granules and Tablets The effects of each saccharide on the friability of the MC granules and the formability of the tablets are shown in Table 1. Like MT, XYL and SOR could be added up to 120% (w/w) of MC, and the granules prepared using larger amounts of XYL or SOR exhibited lower friabilities. Even at 120% (w/w) of MC, the tablets were well formed from the granules. However, tablets could not be prepared from granules with a greater friability. These findings were similar for MT. In contrast, MAN could only be added up to 30% (w/w) of MC due to its lower water solubility. In addition, the granules with MAN at 30% of MC exhibited a greater friability, which did not allow for the formation of tablets. Thus, tablets could be produced only when MT, XYL, or SOR was incorporated at 120% of MC or less. In these cases, binding between the granules was maintained even after compression, probably because of the presence of a large amount of MT, XYL, or SOR.

Physical Characteristics of the Tablets The tensile strength and disintegration time of tablets produced from granules with MT, XYL, or SOR at 120% of MC were evaluated. All formulations had sufficient tensile strength and appropriate disintegration kinetics. The tensile strength of the SOR tablets exceeded that of the MT-containing tablets, which in turn exceeded the tensile strength of the XYL tablets. The XYL tablets disintegrated more quickly than the MT tablets, while the SOR tablets disintegrated more slowly (see Fig. 2). Thus, the trend for disintegration time coincided with that for tensile strength: the tablets with the highest tensile strengths exhibited the longest disintegration times. Because the formability of MC is poor, it is likely that this finding reflects the difference in cohesion of the various saccharides. The tensile strengths of the tablets measured by direct compression using each saccharide alone were, in decreasing order, SOR (26 kg/cm^2)>MT (8.76 kg/cm^2)>XYL (1.32 kg/cm^2).

Adsorption Characteristics of Granules and Tablets In this experiment, MC powder (227 mg), tablets (500 mg), granules (500 mg), and a physical mixture (PM) of MC (227 mg) and XYL or SOR (273 mg) were tested to determine their ability to adsorb AA dissolved in water. The results are shown in Fig. 3. For both XYL and SOR, AA was adsorbed rapidly by all formulations—tablet, granule, and physical mixture. Adsorption approached a plateau within 5 min for all formulations.

Table 1. The Influence of MT, XYL, SOR, and MAN on the Friability and Formability of MC Granules

Binder	Cs[a)]	Amount of additive (%)[b)]	Granule friability (%)	Formability
Maltitol	129.8	30	99	Not formed
	129.8	60	61	Not formed
	129.8	120	6	Well ormed
Xylitol	134.5	60	67	Not formed
	134.5	120	6	Well formed
Sorbitol	186.0	60	70	Not formed
	186.0	120	5	Well formed
Mannitol	16.5	30	100	Not formed

a) Water Solubility (g/100 ml at 15 °C). *b*) Percent (w/w) relative to MC.

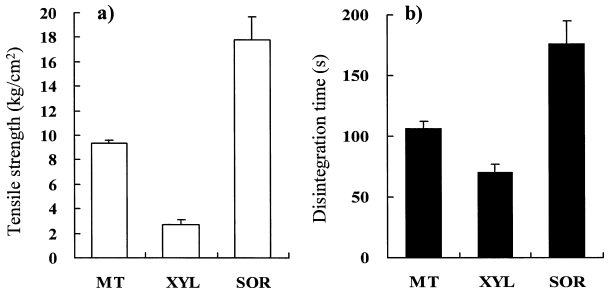

Fig. 2. Comparison of (a) Tensile Strength and (b) Disintegration Time of the MT, XYL, and SOR Tablets

Each point represents mean±S.D. (n=5).

The MC powder adsorbed 67% of the total AA after 24 h. The XYL physical mixture exhibited almost same adsorption profile as that of the MC powder, but its maximal AA adsorption decreased to approximately 96% of that of the MC powder. In granule and tablet form, the adsorption profile was almost same, and the adsorption extent decreased to approximately 92% of that of the MC powder. The results were slightly different for SOR. The physical mixture displayed an adsorption extent very similar to the MC powder, but the adsorption extent of the granules and tablets decreased to approximately 88% of that of the MC powder. Thus, for both saccharides, the physical mixtures exhibited almost the same profile as that of the MC powder, but the adsorption extent in the granules and tablets was slightly lower than that of the MC powder. The saccharides in the physical mixtures dissolved quickly and inhibited the adsorption of the AA to a small degree. The inhibition mechanism has been reported previously.[11)]

The granules and tablets displayed almost the same adsorption profiles, indicating that compression of the granules did not influence their adsorption capacity. This was probably due to the rapid disintegration of the tablets. The amount of AA adsorption by each type of tablet, including the tablets prepared from MT, is shown in Table 2. The tablets with XYL or SOR adsorbed more AA than the tablets with MT. Also, it appeared that the XYL tablets adsorbed AA more rapidly. The difference in adsorption capacity among the sac-

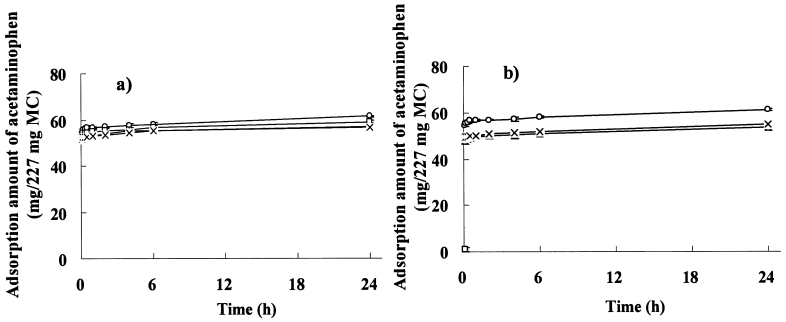

Fig. 3. Comparison of the Acetaminophen Adsorption Profiles of MC Powders (○), PM (□), Granules (△), and Tablets (×) Formulated with (a) XYL and (b) SOR

MC powder (227 mg), tablets (500 mg), granules (500 mg), and a physical mixture (PM) of MC (227 mg) and XYL or SOR (273 mg) were added to 500 ml of water in which 91 mg of AA was dissolved, and stirred at 80 rpm at 37 °C for 24 h. Each point represents mean±S.D. (n=3).

Table 2. Adsorption of AA by MC in Tablets Prepared with Different Saccharides after 1, 6, and 24 h of Incubation at 37 °C

Binder	Amount adsorbed (mg/227 mg MC)		
	1 h	6 h	24 h
Maltitol	41.2±0.4	43.3±0.8	47.5±0.5
Xylitol	52.9±0.4	55.1±0.6	56.7±0.5
Sorbitol	49.9±0.7	52.0±0.7	55.1±0.6

The results are expressed as mean±S.D. (n=3).

charides was influenced by their relative water solubilities. XYL and SOR have higher solubilities than MT (see Table 1). As a result, the XYL tablets disintegrated rapidly and displayed rapid adsorption profiles. These results suggest that XYL and SOR are more useful as binders for preparation of medicinal carbon tablets than MT.

Conclusions

MC tablets were produced as a compact dosage form by the wet granule compression method. The tablets could not be formed with MAN, so MAN is not useful as binding agent for preparation of the tablets. When XYL or SOR was used as a binder at 120% of MC, the tablets were well-formed, and their tensile strengths and disintegration times were acceptable. These results were similar to those for MT. However, in comparison with the MT tablets, the tablets with SOR exhibited greater strength and longer disintegration times, while the tablets with XYL had less strength and shorter disintegration times. The adsorption capacity of MC was slightly decreased by XYL and SOR, but to a lesser extent than MT. Both XYL and SOR were superior to MT as binding agents for the preparation of MC tablets. We believe that MC tablets prepared by the wet granule compression method using XYL or SOR as a binder should be useful as a compact dosage form of MC.

References

1) Swartz C. M., Sherman A., *J. Clin. Psychopharmacol.*, **4**, 336—340 (1984).
2) Fricke R. F., Jorge J., *J. Toxicol. Clin. Toxicol.*, **25**, 421—431 (1990).
3) Makosiej F. J., Hoffman R. S., Howland M. A., Goldfrank L. R., *J. Toxicol. Clin. Toxicol.*, **31**, 381—395 (1993).
4) Coony D. O., *J. Toxicol. Clin. Toxicol.*, **33**, 213—217 (1995).
5) Tsujikawa T., Araki Y., Makino J., Uda K., Ihara T., Sasaki M., Fujiyama Y., Bamba T., *J. Gastroenterol.*, **35**, 296—298 (2000).
6) Komada M., Hanasawa K., Tani T., *Yher. Apher.*, **1**, 224—227 (1997).
7) Iwata M., Takahashi T., Takahashi Y., Ito A., Machida Y., *Jpn. J. Pharm. Health Care Sci.*, **27**, 63—68 (2001).
8) Akizawa T., Koide K., Koshikawa K., *Kidney Dialysis*, **45**, 373—388 (1998).
9) Yamamoto K., Onishi H., Ito A., Machida Y., *Chem. Pharm. Bull.*, **54**, 359—362 (2006).
10) Ito A., Onishi H., Yamamoto K., Machida Y., *Yakugaku Zasshi*, **126**, 315—319 (2006).
11) Yamamoto K., Onishi H., Ito A., Machida Y., *Int. J. Pharm.*, **328**, 105—111 (2007).