Preparation and Evaluation of Medicinal Carbon Oral Films

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Medicinal carbon (MC) films, which can be taken more easily than other dosage forms, were prepared using sodium carboxymethyl cellulose (CMC), hydroxypropylmethyl cellulose (HPMC) and alginic acid sodium (ALG) as film base materials. Brilliant blue FCF (BB) was used as a model drug. The films containing MC had sufficient strength and disintegration time, but their ability to adsorb BB was clearly inhibited compared to that of MC in powder form. When ALG was used as the film base, the BB adsorption capacity of MC film was approximately 50% of that of MC powder. In an attempt to improve this adsorption ability, two saccharides, sorbitol (SOR) and maltitol (MT), were separately added to MC at a mixing ratio of 1 : 1 by weight. When ALG was the film base, MC films containing SOR or MT showed rapid adsorption profiles and had greatly increased capacities for BB adsorption compared with films containing MC alone. SOR was superior to MT as an additive, though both gave MC-containing films a BB adsorption capacity almost equal to that of MC powder after 24 h, and physical mixtures tended to have better BB adsorption capacities than pre-treatment mixture. In addition, both SOR and MT tended to increase vertical strength of films, but neither additive in either type of mixture had a clear effect on disintegration time. When CMC or HPMC was used as the film base, on the other hand, the addition of SOR or MT caused hardly any improvement in adsorption ability. The above results demonstrate that ALG is useful as a film base material for the preparation of MC films, and that MC films with sufficient strength and adsorption capacities equal to those of MC powders can be produced using a physical mixture of MC and SOR on an ALG base.

Key words medicinal carbon powder; film; saccharide; adsorption ability; water soluble polymer; alginic acid sodium

Medicinal carbon (MC) is used clinically as a potent adsorption agent in treating such conditions as intoxication caused by the ingestion of toxic chemicals or other toxins, drug overdose, and the formation of harmful metabolites in the gastrointestinal tract.^{1–5} It has also been reported to display strong potential to adsorb an endotoxin related to serious symptoms of food poisoning,⁶ and it has been used for removing the waste products that build up as a result of chronic kidney disease.⁷

MC is usually administered in a powder, granule or capsule form, but many patients report problems with swallowing it in these forms: powder can adhere to the throat and diffuse throughout the mouth, granules can cause pain by entering the space between a denture and the gums, and capsules can adhere to the throat or the esophagus. In an investigation into the ease of swallowing these of oral dosage forms, patients reported that they disliked all three, but that powder was the least convenient.⁸ These problems often lead to patient non-compliance. To avoid these issues, caregivers often prefer to administer MC in tablet form; not surprisingly, patients also prefer to take MC in tablet form.⁹ Accordingly, in two previous studies, we investigated the administration of MC in a compact dosage form, and reported that MC tablets possessing the full adsorption capacity of MC could be made by means of wet granule compression using saccharides as binding agents.^{10,11} Although most patients can take tablets more easily than powders, granules or capsules, patients with reduced swallowing ability often have trouble taking tablets, and patients who must limit their water consumption also require an alternative dosage form. In this study, therefore, we investigated the feasibility of MC-containing films as a new dosage form for such patients.

Experimental

Materials Medicinal carbon (MC) was purchased from Kenei Pharmaceutical Co., Ltd. (Osaka, Japan) as a fine powder and used in the experiments without sieving. Sodium carboxymethyl cellulose (CMC) and brilliant blue FCF (BB) were obtained from Wako Pure Chemical Industries Ltd. (Osaka, Japan). Hydroxypropylmethyl cellulose (HPMC) and alginic acid sodium (ALG) were obtained from Sigma-Aldrich (St. Louis, MO, U.S.A.). Maltitol (MT) and sorbitol (SOR) were obtained from Towa Chemical Co., Ltd. (Osaka, Japan). All other chemicals were reagent-grade.

Preparation of Films CMC, HPMC and ALG were tested as potential film bases. Each of these water-soluble polymers was dissolved to 4% (w/v) or 2% (w/v) aqueous solution. Fifty milliliters of each solution was then added to 2 g of MC powder, either alone or combined in a pre-treatment (PRE) or physical mixture (PM) with 2 g of either MT or SOR. Each mixture was mixed sufficiently with a magnetic stirrer. The mixture was then cast onto partitioned teflon board using the solution casting method, then dried sufficiently at room temperature. Each of the resulting films was a square about 2.0×2.0 cm in size which contained about 12.5 mg of MC.

PRE were produced according to the following method. Thirty milliliters of water was added to 2 g of MC and 2 g of MT or SOR. The mixture was mixed sufficiently and dried at 60 °C overnight.

This study used PRE and PM of MC and saccharides, because granules prepared in previous studies by the wet granule method using saccharides as binding agents preserved the adsorption capacity of MC.^{12,13}

Measurement of the Physical Characteristics of Films The strength of the films was measured vertically with a Fudoh rheometer (Rheotech, Tokyo, Japan) as shown in Fig. 1a. Disintegration time was measured using a modified disintegration apparatus as shown in Fig. 1b; briefly, a film was clipped onto the arm of a Model NT-60H disintegration tester (Toyama Sangyo Co., Ltd., Osaka, Japan), which moved the film in and out of a 37 °C purified water bath (a total distance of 5.5 cm) at 30 strokes per minute. The length of time required for the film to disintegrate was recorded as the disintegration time. Each prepared film containing MC-only was about 120–150 μm thick and weighed about 20–30 mg, while each prepared film containing a PRE or a PM was about 150–200 μm thick and weighed about 40–50 mg; these estimates are based on the actual measurements of ten films of each type. The thickness of the films was measured with a dogmatic micrometer (Mitutoyo Co., Ltd., Kawasaki, Japan).

Brilliant Blue Adsorption Experiments Twenty-five milligrams of MC, either in powder form or contained in one of the types of film described above, was added to 50 ml of 0.01% (w/v) BB solution, and the mixture was

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Fig. 1. Measurement Methods of a) Vertical Strength and b) Disintegration Time of MC Films Containing MC Alone

stirred with a magnetic stirrer at 37°C in a model BW200 shaking bath (Yamato Scientific Co., Ltd., Tokyo, Japan). At appropriate time points, 1 ml samples were withdrawn and centrifuged at 3000 rpm for 10 min (Kubota 5200 centrifuge, Kubota Tokyo, Japan). The supernatant was diluted with water and the concentration of free BB was measured using UV spectrophotometry at 629 nm. The difference between the concentrations of free BB and total BB was recorded as the amount of BB that had been adsorbed by the MC, *i.e.*, the adsorption capacity of each dosage form.

Statistical Analysis All data are shown as the mean $\pm$ S.D. Statistical differences were analyzed using the Tukey–Kramer test for multiple comparisons. The level of significance was taken as $p < 0.05$.

Results and Discussion

Evaluation of MC Films Prepared Using MC Powder Alone The vertical strength and disintegration time of MC films composed of 4% (w/v) CMC, 4% (w/v) ALG or 2% (w/v) HPMC solution mixed with MC powder alone are shown in Table 1. MC/CMC film was the strongest, withstanding a vertical pressure of 84.2 g; in contrast, vertical strengths of MC/HPMC and MC/ALG films were both below 50 g. MC/HPMC film had the longest disintegration time, requiring 116.3 s, while MC/CMC and MC/ALG film had approximately equivalent disintegration times, in the range of 30–40 s. No certain relationship between these properties and either the thicknesses or the weights of the films was observed.

BB adsorption experiments were performed on each type of prepared film and on MC powder. The results are shown in Fig. 2. MC powder adsorbed BB rapidly, taking up approximately 66% of it in approximately 4 h, then reaching a plateau; compared with MC powder, all types of film clearly showed inhibited BB adsorption capacity: MC/ALG film exhibited a slow BB adsorption profile, taking up only about 30% of the BB in 4 h, while MC/CMC film and MC/HPMC film adsorbed hardly any BB; taking up less than 10% in the same interval. We assume that the adsorption capacity of MC films is inhibited because polymer film base fills many of the MC's pores, and that the variation in adsorption capacity among films with different polymer bases is caused by differences in the polymers' solubility and viscosity. It seems likely that differences in the polymers' solubility and viscosity associated with the degree of freeing MC pores. For example, MC/ALG film adsorbs more BB because ALG dissolves more rapidly than the other polymers do, freeing MC pores in the process, and because ALG has a low viscosity.

Although MC films composed of CMC, ALG or HPMC mixed with MC powder alone have sufficiently high strengths

Table 1. Physical Properties of MC Films Prepared Using MC Alone

Film	Vertical strength (gf) ^{a)}	Disintegration time (s) ^{b)}
MC/CMC	84.2 $\pm$ 26.8***	38.5 $\pm$ 14.5
MC/ALG	24.4 $\pm$ 5.5	30.7 $\pm$ 5.5
MC/HPMC	49.4 $\pm$ 10.2	116.3 $\pm$ 43.7***

a) Mean $\pm$ S.D. ($n=5$). b) Mean $\pm$ S.D. ($n=6$). * $p < 0.05$ compared with MC/ALG, ** $p < 0.05$ compared with MC/HPMC, *** $p < 0.05$ compared with MC/CMC.

Fig. 2. Brilliant Blue Adsorption Profiles of MC Films Containing MC Alone

● MC powder, ■ MC/CMC film, ▲ MC/ALG film, ○ MC/HPMC film. Each point represents mean $\pm$ S.D. ($n=3$).

and low disintegration times, their capacity to adsorb MC is markedly inhibited. Because the main effect of MC is so greatly diminished, this type of film is not useful.

Evaluation of MC Films Prepared Using Pre-treatment Mixtures and Physical Mixtures of MC Powder and Saccharides In our research on MC tablet preparation methods, we have reported that mixing MC with water-soluble polymers inhibited MC's adsorption capacity, but that MC tablets prepared by the wet granule compression method using such saccharides as sorbitol (SOR) and maltitol (MT) as binders retained MC's adsorption capacity.¹²⁾ Therefore, in an attempt to improve the ability of MC films to adsorb BB, we added SOR and MT to the film mixtures. 4% (w/v) CMC, 4% (w/v) ALG or 2% (w/v) HPMC solution was added to a PRE or a PM of MC powder and SOR or MT; films were then prepared according to the method described above.

The results of BB adsorption experiments on each type of prepared film are shown in Fig. 3. The BB adsorption capacity of MC/CMC film was not improved by the addition of SOR or MT in either type of mixture. All MC/CMC films exhibited similar BB adsorption profiles, and the adsorption capacities of all MC/CMC films with saccharides were below 10% (Fig. 3a). The BB adsorption capacity of MC/HPMC film was slightly increased by the addition of SOR or MT, but these film's adsorption rates were only approximately 30% after 24 h (Fig. 3b). Furthermore, neither the saccharide type nor the mixture type had a significant effect on the adsorption capacities of films with CMC or HPMC bases. In contrast, the BB adsorption capacity of MC/ALG film and the rapidity of its BB adsorption profile were appreciably increased by the addition of SOR or MT. MC/ALG films containing PM tended to have better BB adsorption capacities than MC/ALG films containing PRE (Fig. 3c).

The BB adsorption rates of MC powder, MC/ALG film containing MC alone (MC-only film), and MC/ALG films

containing physical mixtures of MC and SOR (MC/SOR-PM film) or MT (MC/MT-PM film) are shown in Table 2. Although all types of MC film adsorbed BB more slowly than MC powder did, MC/SOR-PM and MC/MT-PM films exhibited higher BB adsorption rates than MC-only film did ($p < 0.05$). MC/SOR-PM film exhibited a higher BB adsorption rate than MC/MT-PM film did ($p < 0.05$), and adsorbed BB nearly as well as MC powder: after 6 h, its adsorption capacity was almost equal to that of MC powder, and after 24 h, its BB adsorption capacity was equal to that of MC powder and approximately 1.4 times that of MC-only film.

Fig. 3. Influence of SOR and MT on Brilliant Blue Adsorption Profiles of MC Films Prepared Using a) CMC, b) HPMC and c) ALG as Film Bases

■ MC alone, ● SOR (PM), ○ SOR (PRE), ▲ MT (PM), △ MT (PRE). Each point represents mean $\pm$ S.D. ($n=3$).

Table 2. Brilliant Blue Adsorption Rates of MC Powder and MC/ALG Films Containing a Physical Mixture of MC and SOR or MT after 1, 6, and 24 h of Incubation at 37 °C

	BB absorption rate (%) ^{a)}		
	1 h	6 h	24 h
MC powder	54.7 $\pm$ 0.08	68.0 $\pm$ 0.61	76.4 $\pm$ 0.94
MC-only film	19.5 $\pm$ 1.05*	35.1 $\pm$ 1.16*	54.8 $\pm$ 1.59*
MC/SOR-PM film	38.7 $\pm$ 1.15***	61.8 $\pm$ 0.82***	77.6 $\pm$ 0.36***
MC/MT-PM film	33.6 $\pm$ 3.08***	58.6 $\pm$ 0.65***	72.6 $\pm$ 0.41***

a) Mean $\pm$ S.D. ($n=3$). * $p < 0.05$ compared with MC powder, ** $p < 0.05$ compared with MC-only film, *** $p < 0.05$ compared with MC/MT-PM film.

As we have proposed previously,¹³⁾ these results probably reflect non-competitive inhibition. Saccharides and polymers additives fill the pores of the MC contained in their films, taking up space which could otherwise be filled by BB. It seems likely, therefore, that the different adsorption capacities associated with the two different saccharides are probably due to saccharides' relative water solubilities. SOR, being more soluble than MT, dissolves faster, freeing MC pores and making them available to more quickly; this is why SOR did not inhibit BB adsorption as strongly as MT did.¹²⁾ Likewise, polymers' solubilities and viscosities may affect the adsorption rates of the films that contain them; this would explain why dissolved CMC and HPMC inhibited BB adsorption so much more strongly than ALG did. This could also explain the different BB adsorption rates exhibited by films containing PM and those containing PRE: in PRE films, more of the MC pores were filled with saccharides at the beginning of the experiment, so that it took longer for the same number of MC pores to become available.

The vertical strengths and disintegration times of MC/ALG films containing MC alone and those containing mixtures of MC and SOR or MT are shown in Fig. 4. The MC/

Fig. 4. Influence of SOR and MT on a) Vertical Strength and b) Disintegration Time of MC/ALG Films

Each point represents mean $\pm$ S.D. * $p < 0.05$ compared with MC alone.

ALG films containing SOR or MT tended to exhibit greater vertical strengths than the MC/ALG films without saccharides, though this difference was not statistically significant, and neither the saccharide type nor the mixture type had a clear effect on vertical strength. The disintegration times of the MC/ALG films were not clearly affected by the addition of SOR or MT in either type of mixture.

Conclusions

The results of this study show that ALG is a useful film base for the preparation of MC films, and that MC/ALG films with a high adsorption capacity, matching that of MC powder, can be produced by combining MC in a physical mixture with SOR. Furthermore, the addition of SOR or MT to MC/ALG films may increase their strength as well as improving their adsorption capacity. These findings suggested that MC-containing films could be manufactured and administered as a new dosage form, but the MC films prepared in this study contained such small amounts of MC that they could not be used clinically. Based on the results obtained in this report, we plan to investigate the potential of similar films containing more MC for clinical use.

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