Application of water-insoluble polymers to orally disintegrating tablets treated by high-pressure carbon dioxide gas

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Abstract

The phase transition of pharmaceutical excipients that can be induced by humidifying or heating is well-known to increase the hardness of orally disintegrating tablets (ODTs). However, these conditions are not applicable to drug substances that are chemically unstable against such stressors. Here, we describe a system which enhances the hardness of tablets containing water-insoluble polymers by using high-pressure carbon dioxide (CO₂). On screening of 26 polymeric excipients, aminoalkyl methacrylate copolymer E (AMCE) markedly increased tablet hardness (+155 N) when maintained in a high-pressure CO₂ environment. ODTs containing 10% AMCE were prepared and treatment with 4.0 MPa CO₂ gas at 25°C for 10 min increased the hardness to +30 N, whose level corresponded to heating at 70°C for 720 min. In addition, we confirmed the effects of CO₂ pressure, temperature, treatment time, and AMCE content on the physical properties of ODTs. Optimal pressure of CO₂ gas was considered to be approximately 3.5 MPa for an AMCE formula, as excessive pressure delayed the disintegration of ODTs. Combination of high-pressure CO₂ gas and AMCE is a prospective approach for increasing the tablet hardness for ODTs, and can be conducted without additional heat or moisture stress using a simple apparatus.

Keywords: Orally disintegrating tablet, carbon dioxide, aminoalkyl methacrylate copolymer E

Abbreviations: AA, acrylic acid; AMCE, aminoalkyl methacrylate copolymer E; CMEC, carboxymethylcellulose; CO₂, carbon dioxide; EC, ethylcellulose; HPMCAS, hypromellose acetate succinate; MM, methyl methacrylate; ODT, orally disintegrating tablet; \( P_c \), critical pressure; PEG, polyethylene glycol; PVA, polyvinyl alcohol; PVP, polyvinylpyrrolidone; PVP-VA, polyvinylpyrrolidone-co-vinyl acetate 64; SD, spray dried;
1. Introduction

Orally disintegrating tablets (ODTs) are representative dosage forms for oral drug administration, and more than 100 products are now commercially available. ODTs disintegrate in saliva and are easier to swallow than conventional tablets. They are therefore expected to improve patient adherence (Koh et al., 2008; Juul et al., 2013), particularly in children, the aged, and those with difficulties swallowing or under restricted water intake. Zydis is a pioneer of this orally disintegrating dosage form (Seager, 1998), and is prepared by freeze-drying suspensions or solutions containing active ingredients and excipients to make a highly porous structured unit that results in rapid oral disintegration. However, Zydis has several limitations compared with conventional tablets, such as a low manufacturing efficiency and high cost. In addition, Zydis products are fragile and require peel-open blister configurations, which are considered inferior in handling to the push-out blister configurations of conventional tablets.

Several technologies to resolve these limitations have been developed and commercialized. These include the application of a low compression force during the tableting process of wet masses followed by drying (Tsushima, 2001), and tableting of dry masses followed by heating or humidifying to increase hardness by enhancing the phase transition of excipients (Kuno et al., 2005; Mizumoto et al., 2005; Sugimoto et al., 2005). However, these methods cannot be applied to active ingredients that are chemically unstable in conditions of high temperature or moisture. We recently reported that microwave heating combined with wet mass compression effectively enhances tablet hardness, but that the method was limited to active ingredients with melting points higher than 110°C (Sano et al., 2011, 2013 and 2014).
Another method is therefore required to raise tablet hardness without the stress induced by heat and moisture. Other technologies that achieve sufficient hardness via high compression force and use wicking agents to provide rapid disintegration have also been commercialized (Okuda et al., 2009 and 2012). However, these technologies are not universally applicable to ODTs, as high compression force can damage the coating layer of micro-particles with active ingredients, which are sometimes designed and formulated into ODTs to mask the bitterness or control the release of active ingredients (Beckert et al., 1996; Douroumis, 2011).

Technologies for ODTs which use a low compression force but enhance tablet hardness via non-compression means remain technologically important.

To develop a new manufacturing process for ODTs, we focused on the use of pressurized carbon dioxide (CO$_2$) as an alternative method for heating or humidifying, on the basis that CO$_2$ is generally considered an inactive gas. High-pressure CO$_2$ acts as a plasticizer for certain polymers by lowering their glass transition temperature ($T_g$), and this effect is considered temporary because of the ease of removing CO$_2$ from polymers after depressurization (Nalawade et al., 2006). The plasticizing effect is due to the absorption of CO$_2$ between polymer chains, which thereby increases the free volume and relaxes chain entanglement, thus lubricating the inter-molecular space to reduce viscosity (Chiou et al., 1985; Noto et al., 2011). High-pressure CO$_2$ is used in the hot-melt extrusion process for manufacturing solid dispersions, in which lowered $T_g$ of polymers contributes to a more efficient process with lower temperature, lower torque, and a higher extrusion rate (Verreck et al., 2005 and 2006; Lyons et al., 2007). In addition, ODTs using pressurized CO$_2$ were recently reported for the first time; in this process, tablets containing polyvinylpyrrolidone-co-vinyl acetate 64 (PVP-VA) were pressurized with CO$_2$ to induce phase transition of the polymer and form inter-granule bridging to increase tablet hardness (Kobayashi et al., 2013). However, the availability of a polymer that can enhance tablet
hardness more effectively than PVP-VA in the presence of CO\(_2\) treatment has not been reported. A higher content of water-soluble polymers such as PVP-VA would be considered to delay disintegration of ODTs as they increase the viscosity of saliva during disintegration. For this reason, the maximum content of water-soluble polymers in a hardness enhancement system would be limited, and such polymers would be not always preferable as bridging agents for ODTs. In fact, the addition of the water insoluble polymer ethylcellulose (EC) to a formulation does not delay the disintegration of ODTs (Okuda et al., 2012). The selection of appropriate bridging agents, including water-insoluble polymers, to provide a better system for enhancing the hardness of ODTs using high-pressure CO\(_2\) therefore requires further investigation.

Regarding manufacturing systems, the use of supercritical CO\(_2\) at an industrial manufacturing scale has been well-established, in food industries for example, but requires a pressure-resistant container, condenser, and pump system to pressurize CO\(_2\) for processing tablets. Such a system would be excessively complicated and expensive to use as a replacement for the heating and humidifying systems typically used in ODT production. However, if pressurization in a high-pressure CO\(_2\) system could be conducted at a lower pressure than that of conventional liquefied CO\(_2\) cylinders (i.e., lower than approximately 6 MPa) at ambient temperature, the use of such a simplified system to produce ODTs might be feasible. A system in which the CO\(_2\) cylinders are connected only to a pressure-resistant container the tablets are placed in, constitutes an alternative approach to heating and humidifying. The production of ODTs with PVP-VA using CO\(_2\) pressures lower than 6 MPa at ambient temperature has been demonstrated (Kobayashi et al., 2013). In that study, however, more than 80% of the ODT composition consisted of a pre-mixed excipient, which is a blend of several excipients and commercially available to achieve rapid disintegration. Pre-mixed excipients have a complicated composition, however, and the effects of CO\(_2\)
treatment on them are unknown. Thus, investigating the effect of CO₂ treatment conditions on the physical characteristics of ODTs would be better done using a simpler formula. Taken together, these findings indicate that a better understanding of hardness enhancing systems with plasticized polymers requires more thorough screening of bridging agents, including water-insoluble polymers, and a closer examination of the effect of varying CO₂ conditions on the physical properties of simpler formula ODTs.

Here, we screened a selection of polymeric excipients to evaluate their ability to increase tablet hardness via treatment with high-pressure CO₂ gas at ambient temperature. In addition, we also prepared ODTs using a more simplified formula with D-mannitol and conventional disintegrant with an inter-granule bridging system involving the use of CO₂ gas and water-insoluble polymer, and evaluated the effect of different treatment conditions on several tablet properties.
2. Materials and methods

2.1. Materials

Direct compression grade D-mannitol (Parteck M 100) and magnesium stearate (Parteck LUB MST) were purchased from Merck, Ltd. (Tokyo, Japan). Crystalline powder grade D-mannitol (PEARITOL 50 C) was purchased from Roquette Japan K.K. (Tokyo, Japan). Aminoalkyl methacrylate copolymer E (AMCE: Eudragit E PO), aminoalkyl methacrylate copolymer RS (Eudragit RS PO and Eudragit RL PO), methacrylic acid copolymer LD (Eudragit L100-55), methacrylic acid copolymer L (Eudragit L100), and methacrylic acid copolymer S (Eudragit S 100) were purchased from Evonik (Tokyo, Japan). Hypromellose acetate succinate (HPM CAS: AQOAT AS-HF), low-substituted hydroxypropyl cellulose (L-HPC NBD-022), and hypromellose (TC-5 E) were purchased from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Carboxymethylcellulose (CMEC) was purchased from Freund Corporation (Tokyo, Japan). EC (ETHOCEL Standard 7 FP Premium) was purchased from Dow Chemical Company (Tokyo, Japan). White shellac (dried white shellac) was purchased from The Japan Shellac Industries, Ltd. (Osaka, Japan). Polyvinyl acetate/polyvinylpyrrolidone (Kollidon SR), crospovidone (XPVP: Kollidon CL-F), polyvinylpyrrolidone (PVP: Kollidon 30), PVP-VA (Kollidon VA 64 and Kollidon VA 64 Fine), polyethylene glycol and polyvinyl alcohol graft copolymer (PEG-PVA graft copolymer: Kollicoat IR) and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus) were purchased from BASF Japan, Ltd. (Tokyo, Japan). Croscarmellose sodium (Kiccolate ND-2HS) and partly pregelatinized starch (PCS) were purchased from Asahi Kasei Chemicals Corp. (Tokyo, Japan). Carmellose (NS-300) and carmellose calcium (E.C.G-505) were purchased from Gotoku Chemical Co., Ltd. (Tokyo, Japan). Sodium carboxymethyl starch (Primojel) was supplied by DFE Pharma (Tokyo, Japan). Cornstarch (Nisshoku Cornstarch, JP) was purchased from Nihon Shokuhin Kako Co.,
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Various polymeric excipients were formulated, and a portion of the aggregated materials was ground in a mortar before use. Dried white shellac was pulverized using a pin mill (100 UPZ Fine Impact Mill; Hosokawa Micron Corporation, Osaka, Japan) before use. EC and triethyl citrate (weight ratios: 9/1 and 7.5/2.5) were dissolved in ethanol, and the ethanol solutions were spray dried (SD) using a Mini Spray Dryer B-290 (Nihon BUCHI K.K., Tokyo, Japan) to obtain EC/TEC (9/1) SD and EC/TEC (7.5/2.5) SD.

D-mannitol as direct compression grade, polymeric excipients, or the SDs described above and magnesium stearate were weighed and mixed in 70-mL plastic bottles to prepare blends for compression on a 10-g scale, according to the formulation in Table 1. The polymeric excipients and SDs are shown in Table 2. Blends were weighed for each tablet and compressed using a test apparatus (Autograph AGS-20 kNG; Shimadzu, Kyoto, Japan), fitted with a round face punch 8.5 mm in diameter. Tablet weight and compression force were adjusted for each formulation to ensure that tablet hardness was 20 ± 2 N and thickness was 4.0 ± 0.30 mm.
2.2.2. Preparation of tableting samples of ODTs (Form A and B)

Crystalline powder grade D-mannitol was granulated using top-spraying binder (PVP or PVP-VA) solution (10% [w/w] concentration) with a fluidized-bed granulator (FLO-1; Freund Corporation, Tokyo, Japan) at 420-g scale. AMCE and magnesium stearate were sieved with a 710-μm screen before use. These excipients and intact XPVP were then blended with the granules in a plastic bag for 1 min. The blended components were compressed using a rotary tableting machine (EX10; Hata Iron Works Co., Ltd., Kyoto, Japan) with 8.5-mm-diameter round face punches. Tablets were compressed at 1-2 kN/punch to obtain approximately 10 N of tablet hardness. The formulations manufactured by this procedure are shown in Table 3 (A-1, A-2 and B-1).

To confirm the effect of AMCE content in formulations, granules (B-1) were blended with sieved AMCE, XPVP and sieved magnesium stearate in a plastic bottle for 1 min at a 10 g scale, according to the formulation shown in Table 3 (B-2, B-3 and B-4). Blends were weighed for each tablet and compressed using a compaction test apparatus (Autograph AGS-20 kN; Shimadzu, Kyoto, Japan) with a compression force of approximately 1 kN/punch with a round face punch of 8.5 mm in diameter.

2.2.3. Treatment of samples by high-pressure CO₂ gas

Some polymeric excipients or tablets were treated with high-pressure CO₂ gas using the apparatus shown in Fig. 1. This process was conducted in a 50-mL pressure-resistant container (EV series; JASCO, Tokyo, Japan). Temperature in the container was monitored using a thermometer TI-2068 (JASCO), the detector of which was tightly inserted into the container. The container had two attached flow channels for inlet and outlet CO₂ gas. The inlet line connected to a 7-m³ cylinder of liquefied CO₂ (non-siphon type; Tomoe Shokai Co.,
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The outlet led to an automatic back-pressure-regulating valve BP-2080 (JASCO) that regulated the pressure in the container and line by releasing excess CO$_2$ when the pressure exceeded the target according to a preset program. Temperature was controlled by setting the container and CO$_2$ lines in the CO-2060 thermostatic chamber (JASCO). In this treatment process, tablets were set in the container with temperature controlled at 15–45°C, which was then closed tightly. CO$_2$ gas filled the container and the pressure was controlled from 1 to 6 MPa by BP-2080. Pressure and temperature were kept constant for 5–360 min, and treated samples were obtained after releasing CO$_2$ gas at a rate of 1 MPa/min. Pressure, temperature, and time were altered according to study conditions.

2.2.4. Treatment of samples by heating

In some experiments, tablets were heated as a substitution for high-pressure CO$_2$ gas treatment. Regarding the polymer screening study, tablets with AMCE, CMEC, XPVP, PEG-PVA graft copolymer or PVA/AA/MM copolymer were heated in an oven (WFO-510; Tokyo Rikakikai Co., Ltd., Tokyo, Japan) without exposure to high-pressure CO$_2$ gas treatment. Tablets on stainless mesh were processed at 80°C for 840 min to obtain heat-processed samples. Formula A-1 tablets were heated at 70°C for 45–720 min in the same manner as above. Some polymeric excipients were also heated at 70°C for 45–840 min on a glass dish to observe scanning electron microscopy images.

2.3. Characterization of samples

2.3.1. Tablet hardness

Tablet hardness was defined as the force required to break a tablet by radial static compression. Tablet hardness was determined using a tablet hardness tester (Model 6D; Dr. Schleuniger Pharmatron, Thun, Switzerland). Measurements were repeated twice in the
polymer screening study, while other experiments were repeated five times. Standard deviation was also calculated.

2.3.2. Tablet thickness

Tablet thickness was measured at the center of the tablet using a micrometer with a precision of 0.01 mm (Digimatic Indicator; Mitsutoyo Corporation, Kanagawa, Japan). Measurements were repeated twice in the polymer screening study, while other experiments were repeated five times. Standard deviation was also calculated.

2.3.3. Disintegration time

Disintegration time was measured using a rapid disintegration tablet tester (Tricorptester; Okada Seiko Co., Ltd., Tokyo, Japan) (Yoshita et al., 2013). Tests were conducted with tablets axially sandwiched between two stainless meshes (20 g of upper mesh), and purified water (37 ± 1°C) was dropped on the upper mesh at a constant rate of 6 mL/min to disintegrate the tablet. Disintegration time was defined as the time from the first droplet to when the two meshes made complete contact after tablet disintegration. This measurement was conducted using sensory recognition. The disintegration time of three separate tablets was measured, and the mean and standard deviation were calculated.

2.3.4. Scanning electron microscopy (SEM)

SEM images of some polymeric excipients were obtained using a scanning electron microscope (VHX-2000; Keyence, Osaka, Japan). Powdery excipients or agglomerated excipients after heating or CO₂ pressurization were immobilized on a metal base with adhesive tape.
2.4. Statistics

Statistical analyses were performed using Student’s t-test. \( p < 0.05 \) was considered statistically significant.
3. Results and Discussion

3.1. Effect of polymeric excipients on increased tablet hardness by high-pressure CO$_2$ gas

Screening of conventional polymeric excipients used for oral dosage forms was conducted to confirm which were the most effective in enhancing tablet hardness via high-pressure CO$_2$ gas treatment. Table 2 shows the various polymeric excipients used to prepare tablets that were treated with high-pressure CO$_2$ gas at 6.0 MPa/25°C/45 min. Pressure was fixed at 6.0 MPa because this value was considered the near upper limit of the gaseous state of CO$_2$ ($T_c$=304.15 K, $P_c$=7.38 MPa) that could be achieved by releasing pressure from conventional cylinders of liquefied CO$_2$ without using a condenser. Table 2 also shows changes in tablet hardness and thickness after high-pressure CO$_2$ treatment. AMCE, HPMCAS, and PVP-VA increased tablet hardness by more than 50 N after treatment (AMCE: +155 N, HPMCAS: +65 N, and PVP-VA: +69 N), while d-mannitol and magnesium stearate, without any other polymeric excipients, increased hardness by only 2 N. This suggests that the increase in hardness with the three formulations was due to the effective phase transition of polymeric excipients induced by high-pressure CO$_2$ gas treatment and the increase in the resultant inter-granule bridging formed by rubber-state polymers. This notion was supported by the SEM images in Fig. 2, in which the particle shapes of AMCE, HPMCAS and PVP-VA were lost or deformed to make inter-particle bridging after CO$_2$ treatment at 6.0 MPa/25°C/45 min. In contrast, CMEC did not show any changes. These findings were well correlated with the results of tablet hardness testing, in which AMCE, HPMCAS and PVP-VA showed increased hardness but did not CMEC. Our results with the PVP-VA formulation were comparable to those in a previous report (Kobayashi et al., 2013). These findings suggested that water-insoluble polymers such as AMCE and HPMCAS are suitable candidates as bridging agents for ODTs. In the SEM images, the morphology of AMCE was significantly changed compared with that of PVP-VA under the same pressure conditions, indicating that AMCE...
enhances tablet hardness with lower CO\textsubscript{2} pressure. According to the vendor’s information, the \textit{Tg} values of PVP-VA and AMCE were 101°C and 45°C, respectively. This lower \textit{Tg} of AMCE might explain why it was more significantly plasticized than PVP-VA under the same CO\textsubscript{2} gas treatment. In addition, the difference in physical strength of the bridging polymers themselves might also affect tablet hardness. Our findings suggest that AMCE, an insoluble polymer in aqueous solvents at pH ≥5, might be a promising bridging agent for ODTs that utilize CO\textsubscript{2}.

To confirm the effect of \textit{Tg} of bridging polymers on the efficiency of hardness enhancement using high-pressure CO\textsubscript{2}, EC was spray-dried with TEC as plasticizer and tablets containing EC/TEC SD were treated with CO\textsubscript{2}. In general, the \textit{Tg} of polymers is decreased by the addition of plasticizers such as TEC (Repka et al., 1999). Table 2 indicates that the formulation containing EC/TEC (9/1 and 7.5/2.5) SD showed a marked increase in tablet hardness (+67 and +75 N, respectively) after CO\textsubscript{2} pressurization. In contrast, intact EC showed a smaller increase (+11 N) in hardness after the process. Kojima and Nakagami demonstrated that the addition of 10% and 22.7% TEC decreased the \textit{Tg} of EC from approximately 130°C to 80°C and 50°C, respectively, and that the minimum film-forming temperature of EC corresponded with \textit{Tg} (2002). In the current CO\textsubscript{2} system, these data suggest that the \textit{Tg} of the bridging agent is an important factor in determining the increment level of hardness and that the addition of a plasticizer can enhance tablet hardness by decreasing \textit{Tg}, even if the bridging polymer cannot be well plasticized by high-pressure CO\textsubscript{2} gas.

Tablets were also processed at 80°C for 840 min as a substitution for high-pressure CO\textsubscript{2} gas treatment using AMCE, CMEC, XPVP or PEG-PVA graft copolymer or PVA/AA/MM copolymer. Regarding AMCE, because this polymer increases tablet hardness at temperatures exceeding the \textit{Tg} (Suzuki, 2006), its ability to increase tablet hardness by the heating method
and CO₂ method should be compared. Table 2 shows a marked increase in hardness for AMCE (+109 N) by heating at 80°C, which is likely attributable to the phase transition of AMCE, as supported by the previous report. This indicates that CO₂ treatment of the AMCE formulation at 6.0 MPa/25°C/45 min can increase tablet hardness more effectively (+155 N) than heating at 80°C/840 min. While with the CMEC, XPVP, and PEG-PVA graft copolymer and PVA/AA/MM copolymer increased tablet thickness by more than 0.2 mm after CO₂ gas treatment, representing a nearly 20-fold increase compared with the control sample (+0.01 mm), the AMCE formulation markedly increased hardness without any change in thickness.

The increase in tablet thickness might be attributable to the swelling of polymeric excipients by CO₂ treatment (Guadagno and Kazarian, 2004, Pasquali et al., 2008). To estimate whether the thickness increase confirmed in some formulas was specific to CO₂ treatment, the effect of the CO₂ and heating processes on thickness was compared for CMEC, XPVP, and PEG-PVA graft copolymer and PVA/AA/MM copolymer. For the PEG-PVA graft copolymer and PVA/AA/MM copolymer formulations, heated samples were thicker (+0.24 mm) than or almost equal (~0.02 mm) to those with CO₂ gas treatment. The change in thickness of these samples after CO₂ gas treatment might therefore not be solely due to CO₂ gas treatment. Thickness generally increases after tableting due to the plastic recovery of excipients (Sarkar et al., 2014) or moisture absorption by disintegrants. Table 2 also shows a lower increase in thickness (+0.07 and +0.01 mm) in tablets with super disintegrants (Kiccolate ND-2HS and Primojel), which might suggest that the thickness increase in the PEG-PVA graft copolymer and PVA/AA/MM copolymer formulations during CO₂ gas treatment or heating was not primarily due to moisture absorption, but rather due to the plastic recovery of polymers after tableting. In contrast, thickness after CO₂ treatment increased by 0.33 mm for XPVP and 0.32 mm for CMEC, whereas thicknesses after heating increased by 0.12 mm for both formulas. These findings suggest that XPVP and CMEC
might swell in response to high-pressure CO\(_2\) gas, which would increase tablet thickness and lower tablet hardness after CO\(_2\) gas treatment (Table 2). These findings stress the importance of excipient selection for use with high-pressure CO\(_2\) gas systems for ODTs, wherein some excipients would increase hardness whereas others would decrease it.

3.2. Time course of tablet hardness and thickness by heating and pressurizing with CO\(_2\) gas

Table 2 shows that high-pressure CO\(_2\) gas treatment at 25°C might increase tablet hardness via induction of phase transition of AMCE more effectively than that occurring following heating at 80°C. To confirm this in more detail, A-1 formulations of ODTs were heated at 70°C and A-2 formulations were treated with CO\(_2\) gas at 4.0 MPa/25°C (Table 3). Here, we selected 70°C as heating temperature because 80°C would be too high considering the \(T_g\) of AMCE. Fig. 2 indicates that AMCE was well plasticized with CO\(_2\) at 4.0 MPa, and this condition was therefore selected for this experiment. The time courses of tablet hardness and thickness for each treatment were evaluated (Fig. 3). The endpoint was the attainment of a hardness plateau, or 720 min, corresponding to one-night treatment, whichever occurred first. Both treatments significantly increased tablet hardness in a time-dependent manner, in which CO\(_2\) gas treatment at ambient temperature reached more than 40 N within 10 min of treatment whereas heating at 70°C required 720 min (Fig. 3a). Formula A contained XPVP, which swelled in response to CO\(_2\) gas treatment, as mentioned above. Fig. 3b shows the time course of change in tablet thickness: high-pressure CO\(_2\) gas treatment significantly increased thickness for all time points compared with levels before treatment (shown as sample at 0 min), whereas heating did not affect thickness. Hardness of tablets measured at 10 min of CO\(_2\) gas treatment was closely similar to that at 720 min of heating, and only the former exhibited a significant increase in thickness. This implies that increased thickness was specific to the high-pressure CO\(_2\) gas system. Both A-1 and A-2 formulas contain D-mannitol,
PVP, AMCE and magnesium stearate (Table 3), and Table 2 shows that these excipients did not increase tablet thickness following CO₂ gas treatment. We therefore propose that XPVP is the main reason why only A-2 exhibited a significant increase in thickness but not with heating. Previous reports (Guadagno and Kazarian, 2004, Pasquali et al., 2008) have indicated that swelling of polymers can occur due to CO₂ absorption, which would support XPVP swelling in response to high-pressure CO₂ gas. Taken together, these results for the AMCE formula suggest that the CO₂ method under ambient temperature enhances tablet hardness more rapidly than the heating method and increases thickness in a formulation-dependent manner.

Although the processing time of the heating method could be reduced by using higher temperatures, such a time reduction would not be preferable from the perspective of thermal stress on drug substances. The likely reason for the more rapid increase in tablet hardness with CO₂ gas treatment is explained by Fig. 4. CO₂ treatment at 4.0 MPa/25°C/120 min changed AMCE morphologically and its original particle shape was lost completely. In contrast, AMCE particles were significantly identified at 70°C/120 min, and morphological change was not still as significant at 70°C/840 min as with the CO₂ treatment. These differences appear to make CO₂ treatment at 4.0 MPa/25°C more effective at increasing tablet hardness than heating at 70°C.

3.3. Effect of treatment conditions of CO₂ gas on the physical properties of ODTs

Regarding the plasticizing effect of pressurized CO₂ on polymers, the melting temperature of PEG 1500 has been shown to decrease in a manner that was dependent upon CO₂ pressure (Pasquali et al., 2008). In a CO₂-based tablet hardness enhancement system which uses plasticized polymer, pressure of CO₂ affects tablet hardness (Kobayashi et al., 2013). We therefore considered that CO₂ pressure is a key factor, and its effect on the physical properties
of ODTs in the hardness-enhancing system with AMCE was examined. ODTs were prepared in accordance with the B-1 formula shown in Table 3, and tablets were processed at various pressures, temperatures, and processing times using high-pressure CO$_2$ gas. The B-1 formula contains PVP-VA as the binder in the granulating process and XPVP as disintegrant. These were selected from our preliminary studies on the basis of the disintegration properties of ODTs (data not shown). It is known that tablets containing PVP-VA have increased hardness following high-pressure CO$_2$ treatment. To evaluate the effect of PVP-VA in granules on hardness of the B-1 formula, tablets prepared with B-1 granules and magnesium stearate were treated with high-pressure CO$_2$ gas (4.0 MPa/25°C/45 min), and an increase in hardness of +3 N was confirmed (data not shown). This slight increase in hardness produced by PVP-VA in B-1 granules was likely due to the low content of PVP-VA (2%) in the granules. The effect of PVP-VA in B-1 granules on tablet hardness was therefore considered negligible.

3.3.1. Effect of pressure of CO$_2$ gas and processing temperature on ODTs

The effect of CO$_2$ gas pressure and temperature on the physical properties of B-1 tablets was evaluated with a constant processing time of 45 min (Fig. 5). Considering the $T_g$ (approximately 48°C) of AMCE, 45°C was set as highest temperature condition to ensure testing of whether AMCE was plasticized by CO$_2$, and not by heating. Fig. 5a shows increased tablet hardness in a CO$_2$ pressure-dependent manner for all temperatures. There were significantly higher increases in hardness for treatment at 45°C than 15°C under CO$_2$ pressures lower than 4.0 MPa, although this tendency was not observed at 4.0 MPa or higher. In this system, plasticization of ACME is key to the enhancement of hardness, and would be affected by CO$_2$ pressure and temperature. AMCE forms inter-granule bridging when temperature conditions surpass the $T_g$, which is reduced by high-pressure CO$_2$ gas. At 2.0–3.0 MPa, the reduction in $T_g$ by CO$_2$ gas might not be drastic, and the temperature effect on tablet
hardness might therefore be significant. In contrast, at pressures exceeding 3.0 MPa, gaps in
hardness between temperature conditions were not as large as those at 2.0–3.0 MPa. As
confirmed in Fig. 3, 4.0 MPa/25°C of CO₂ gas increased hardness more rapidly than heating
at 70°C, which implies that the plasticizing effect at 4.0 MPa/25°C corresponded to heating at
temperatures higher than 70°C. AMCE was therefore considered to be drastically plasticized
by CO₂ gas at pressures exceeding 3.0 MPa, even at 15°C, and no significant temperature
effects observed.

Fig. 5b shows the same experiments as Fig. 5a, except that the horizontal axis corresponds to
CO₂ density, not pressure (Span and Wagner, 1996). CO₂ pressure is correlated with CO₂
density and likely an important factor influencing the dissolution of polymers, as CO₂ volume
is changed in a temperature-dependent manner and CO₂ densities can be different, even under
the same pressure conditions. As density is an output factor that is calculated from pressure
and temperature, the monitoring of pressure during the CO₂ treatment process might be
simpler and preferable to that of density. Fig. 5b shows that CO₂ density has a similar effect
to CO₂ pressure. Our results suggest that tablet hardness can be controlled by CO₂ pressure
(or density) and temperature in this system.

We also confirmed that tablet thickness increased in a pressure-dependent manner at 15, 25,
35, and 45°C (Fig. 5c). XPVP was considered the main component that increased the
thickness of tablets (Table 2). Results indicated that the increase in thickness was not as
temperature-dependent as hardness, which might suggest that the swelling properties of
XPVP are not dependent on temperature. Furthermore, although the influence of temperature
on the disintegration properties of ODTs was not significant, they were effected by pressure:
namely, the 4.0 MPa condition tended to delay disintegration time in comparison with 3.5
MPa or lower conditions (Fig. 5d). We do not expect that tablet disintegration time would
increase markedly (> 120 s at 4.5 MPa or higher) for all temperature conditions (data not
shown), but do not consider that the longer disintegration time was simply caused by excess tablet hardness, as no drastic increase in hardness was observed at pressures of 4.0–4.5 MPa. XPVP was considered to swell during treatment with high-pressure CO$_2$ gas. We also confirmed that the disintegrating property and particle size of XPVP did not change following high-pressure CO$_2$ gas treatment (data not shown). This implies that the swelling of XPVP is tentative during the process and reversible in response to depressurization. In the hardness-enhancing process of B-1 tablets by CO$_2$ gas, excess bridging between AMCE and XPVP might explain why the disintegrating property of XPVP deteriorated at pressures of 4.5 MPa or higher. However, our results indicate that this phenomenon is not so simple. As shown in Table 4, the B-4 formula (12.5% AMCE) showed a hardness of 57 N, while it disintegrated within 15 s. The hardness of higher than 50 N with the B-4 formula was achieved by combining a higher amount of AMCE with a CO$_2$ pressure of lower than 4.5 MPa. These findings suggest that the delayed disintegration under higher pressure conditions is not caused only by the excess bridging of AMCE. At higher pressure conditions, phase transition of AMCE and swelling of XPVP would be significant and occur in parallel, potentially delaying disintegration, as melted AMCE is able to bridge with swelled XPVP. The interaction might disturb XPVP recovery from the swelling state to inactivate the disintegrating property. We also confirmed that the B-1 formula without XPVP took longer than 120 s to disintegrate (data not shown), indicating that XPVP is necessary to the rapid disintegration property of the B-1 formula and that inactivation of XPVP would occur at 4.5 MPa or higher. A key factor of this ODT system, in which AMCE is plasticized by CO$_2$ gas, is to control CO$_2$ pressure so as not to reduce the disintegrating property of XPVP. These findings might prove to be a disadvantage when applying water-insoluble polymers as bridging agents in hardness-enhancing systems using CO$_2$. In contrast, ODTs using PVP-VA as a hardness enhancer disintegrated within 30 s after treatment by 8.0 MPa CO$_2$ (Kobayashi
et al., 2013). This might be attributable to differences in the formulation of samples, given that we used simple formulations containing XPVP as a disintegrant whereas Kobayashi et al. applied a pre-mixed excipient for easy disintegration. It would be interesting to understand the different effects of water-soluble and -insoluble polymers on the physical properties of ODTs produced by hardness enhancement systems using CO$_2$.

3.3.2. Effect of pressurized CO$_2$ gas processing time on ODTs

We then evaluated the effect of treatment time on the physical properties of ODTs. B-1 tablets were treated with CO$_2$ gas at 3.0, 3.5, 4.0 and 5.0 MPa at a constant temperature of 25°C with processing times of 5–360 min, and the hardness, thickness, and disintegration time of ODTs were tested (Fig. 6). As shown in Fig. 5, tablet hardness increased by less than +10 N under the 2.0 MPa condition, whereas the increase between 3.0–4.0 MPa was more drastic in the tested range. We therefore excluded the 2.0 MPa condition in the next study and instead 0.5-MPa steps between 3.0–4.0 MPa. Results showed that the highest-pressure condition (5.0 MPa) enhanced hardness by +36 N after only 5 min of treatment (Fig. 6a) and that tablets disintegrated within 30 s (Fig. 6c), which was considered acceptable for ODTs. Comparison of four different CO$_2$ gas pressure conditions showed that higher pressure achieved higher tablet hardness with the same treatment time. Tablet hardness following treatment with a range of CO$_2$ pressures for 45 min was as follows: 3.0 MPa (23 N), 3.5 MPa (33 N), 4.0 MPa (44 N), and 5.0 MPa (52 N). These results suggest that tablet hardness can be controlled by optimizing CO$_2$ gas pressure and processing time under a constant temperature condition of 25°C. As mentioned above, an increase in hardness of more than 30 N was confirmed using treatment at 5.0 MPa/25°C/5 min (Fig 6a). This implies that the phase transition of AMCE by CO$_2$ gas occurred within a remarkably short time. Other pressure conditions also tended to enhance tablet hardness within the first 10 min, followed
by moderate increases. This suggests that the hardness-enhancing process might consist of
two different phases. First, AMCE transits from glass to rubber to increase hardness and then
diffuses into the voided space of the tablet, enlarging its contact area with surrounding
granules. The diffusion phase might result in more moderate increases in tablet hardness,
although higher pressures induce more marked increases in the diffusion phase when the
hardness profiles at 3.0 MPa were compared with those at 4.0 MPa within 30–60 min (Fig
6a). This might suggest that mobility of AMCE in the rubber state during CO₂ gas treatment
is determined by pressure, albeit that a more detailed examination is required.

Regarding tablet thickness (Fig. 6b), a time-dependent increase was also observed, but this
was not as significant as hardness under the lower pressure conditions of 3.0 and 3.5 MPa. As
discussed above, increased thickness is likely attributable to XPVP. Furthermore, increased
hardness and thickness could be induced by different mechanisms, explaining why hardness
was significantly increased under low-pressure conditions while thickness was not. We
confirmed that 4.5 MPa treatment for 45 min resulted in a significant delay in the
disintegration properties of tablets (3.3.1., data not shown). A significant delay in
disintegration (>120 s) was confirmed using 4.0 MPa for longer than 60 min and 5.0 MPa for
longer than 5 min (data not shown), and a tendency for delayed disintegration was observed
at 3.5 MPa for 360 min (Fig. 6c). However, high pressure conditions can also make ODTs
disintegrate within 20 s by shortening the treatment time, such as 5.0 MPa/25°C/5 min (Fig.
6a). These findings suggest that CO₂ gas treatment would have an ideal exposure time, in
which ODTs can disintegrate within 20 s, and this time can be shortened by raising CO₂
pressure. At 4.0 MPa conditions, the increase in hardness almost reached a plateau after 60
min, suggesting that the delay in disintegration profile after 60 min might correlate with the
saturation of inter-granule bridging by AMCE.
3.3.3. Control of physical properties of ODTs at 3.5 MPa conditions

Our findings in Fig. 6 show that 3.5 MPa of CO$_2$ gas is preferable for this system when using AMCE, as treatment for 180 min maintained rapid disintegration within 15 s and exhibited moderate increases in hardness profile, which would help control the physical properties of ODTs in commercial manufacturing. In this study, the control of physical properties of ODTs using a fixed pressure condition was evaluated.

B-1 tablets were treated with CO$_2$ gas at 20, 25 and 30°C at 3.5 MPa and the effects on physical properties of ODTs were evaluated (Fig. 7). Our results demonstrated that tablet hardness of 40–50 N and disintegration of approximately 15 s were reproducibly obtained for the three different temperature conditions (Figs. 7a, b and c). These results suggest that the properties of ODTs are well controlled within the temperature range of 25 ± 5°C. A model condition for this ODT system might therefore be 3.5 MPa/25°C/180 min, by simply controlling treatment time, temperature and CO$_2$ pressure. These conditions would be acceptable as an alternative method for heating or humidifying systems. However, treatment with CO$_2$ gas for 360 min tended to delay disintegration at 25 and 30°C, which suggests an unfavorable processing time of longer than 180 min. The above conditions consist of a mild temperature of approximately 25°C and a gaseous state of CO$_2$, which could be obtained using a simple apparatus consisting of a pressure-resistant container connected to a CO$_2$ cylinder. Such a system would enable the easy control of CO$_2$ pressure introduced into the container via adjustment of the pressure valve and temperature. This simplified system would also be beneficial from a commercial perspective because the lack of a heating process at a large production scale would result in lower overall energy costs.

These findings demonstrate that the physical properties of ODTs were well controlled by adjusting the pressure of CO$_2$ gas and temperature in this hardness-enhancing system using AMCE and CO$_2$ gas.
3.4. Effect of AMCE content on physical properties of ODTs

In the present ODT system, the content of AMCE is expected to affect the physical properties of ODTs, in addition to treatment conditions. We therefore evaluated the relationship between AMCE content and the physical properties of ODTs (hardness and disintegration). Formulations are shown as B-1, B-2, B-3, and B-4 (Table 3), in which AMCE content increased from 2.5% to 12.5%. The physical properties of ODTs after treatment with CO₂ gas (4.0 MPa/25°C/45 min) were evaluated, and results are shown in Figs. 8a and b. In the previous section, 3.5 MPa/25°C/approximately 180 min was suggested as a model condition for preparing ODTs. This experiment, however, was conducted at 4.0 MPa/25°C/45 min, as the B-1 formula under these conditions exhibited similar hardness and disintegration properties to those under the model conditions (Fig. 6), which enabled the effects of AMCE content to be compared. Results showed that increases in hardness were content-dependent, and a proportional relationship was confirmed ($R^2=0.9083$) between the increment in hardness and AMCE content (Fig. 8a).

Regarding disintegration properties (Fig. 8b), rapid disintegration of less than 20 s was observed for formulations with AMCE content of 10% or lower. In contrast, the B-4 formula containing the highest AMCE content of 12.5% took longer than 120 s to disintegrate (data not shown). This might be due to excess conditions with regard to both the amount of AMCE and CO₂ treatment, which would delay the disintegration of ODTs. However, this result does not necessarily suggest that the B-4 formula is unacceptable for ODTs, as it exhibited a hardness higher than 50 N and rapidly disintegrated upon processing at lower pressure (3.5 MPa/25°C/45 min, Table 4). The delayed disintegration of the B-4 formulation was therefore attributed to both bridging agent content and CO₂ gas treatment conditions, with 12.5% AMCE content considered excessive for treatment at 4.0 MPa/25°C/45 min. As shown in Fig.
6a and 6c, formulation with 10% of AMCE required 5.0 MPa to achieve a hardness of higher than 50 N, and this pressure gives only 5 min of preferred time for rapid disintegration. However, as mentioned above, formulation with 12.5% at AMCE provided a hardness of higher than 50 N and rapid disintegration by 3.5 MPa/25°C/45 min, which demonstrates that increasing the amount of AMCE is an effective way of prolonging the preferred treatment time to achieve rapid disintegration while maintaining target hardness. These findings highlight the importance of a balance between the content of the bridging agent and processing conditions in controlling the physical properties of ODTs in this system.

3.5. Approaches for controlling physical properties of ODTs

Three different approaches to increasing the tablet hardness of ODTs utilizing high-pressure CO₂ gas under ambient temperature were tested, as follows: increasing the pressure of CO₂, extending the processing time, and increasing AMCE content in the tablet formulation. However, the excessive use of these conditions can also delay the disintegration of ODTs. The general goal of formulating ODTs is to achieve both high hardness and rapid disintegration. It is therefore meaningful to determine which of these approaches is more effective for improving the balance of the physical properties of ODTs.

Here, five models of ODTs were prepared based on different input factors, as follows: AMCE content, CO₂ pressure, and CO₂ treatment time. Tablet hardness and disintegration time were compared as output profiles. The ratio of hardness to disintegration (H/D) was set as a parameter (Table 4). In general, ODTs with high hardness and rapid disintegration are preferable for commercial products, and H/D is therefore a simple parameter for evaluating the performance of ODTs, in which a higher H/D indicates better performance. As a preliminary experiment, we confirmed that tablets of 19 commercial ODTs in Japan had diameters of 8.5 mm and a mean hardness of 56 N (data not shown). In addition, Yoshita et al.
(2013) evaluated the disintegration time of 26 commercial ODTs by Tricorptester, with disintegration times ranging from approximately 10 to 30 s and a mean of 20 s. Based on these findings, the expected H/D for commercial ODTs with an 8.5-mm diameter is 2.8 N/s (56 N/20 s).

Model 1, which contained 10% AMCE and was processed with CO₂ at 4.0 MPa/25°C/45 min, was used as a control (H/D = 2.8). Models 2 and 3 contained the same polymer content, but had different CO₂ pressurization conditions from Model 1. Model 2 was processed using a higher pressure and shorter time, and the sample had an H/D of 2.6 N/s. Model 3 was processed with a lower pressure and a longer treatment time, and had an H/D of 3.5 N/s, which was higher than that of Model 1. These results suggest that lower pressure conditions help to obtain high H/D ODTs and that a longer processing time does not decrease H/D as much as lowering pressure. This correlates with the discussion above, which is the finding that higher CO₂ pressure made the preferred treatment time shorter to obtain rapid disintegration, and such approach does not increase H/D. However, an approach using a narrow range of treatment times to control the physical properties of ODTs is not suitable for commercial manufacturing. Regarding Models 4 and 5, the physical properties of ODTs were controlled by changing the AMCE content. Model 4 contained a lower polymer content and was processed using a higher CO₂ pressure, which showed an H/D of 1.1 N/s and it was lower than that of Model 1. In contrast, Model 5 showed an H/D of 3.8 N/s, which had a higher AMCE content but was treated with a lower CO₂ gas pressure. These results suggest that the delay in ODT disintegration due to longer CO₂ processing or higher AMCE content can be avoided by decreasing CO₂ pressure, resulting in ODTs with high H/D. In contrast, increasing the CO₂ pressure runs the risk of delaying disintegration and lowering H/D, even if the processing time or content of the polymer used as a bridging agent is decreased. We therefore concluded that the control of CO₂ pressure at 3.5 MPa or lower is
the most important factor in producing ODTs with AMCE and XPVP which have a high H/D via adjustment of treatment time and formulation.

4. Conclusion

In this study, we found that the use of high-pressure CO₂ gas effectively increased tablet hardness with AMCE, HPMCAS, and PVP-VA among the various polymeric excipients screened. With XPVP and CMEC, in contrast, high-pressure CO₂ gas treatment only increased tablet thickness, possibly due to swelling of materials during treatment, and decreased tablet hardness. Regarding the formula containing AMCE, treatment with high-pressure CO₂ gas at 4.0 MPa/25°C/10 min reached near comparable hardness as that with heating at 70°C/720 min. CO₂ gas treatment might therefore increase tablet hardness more efficiently and with less thermal stress than heating. The use of a CO₂ gas system might therefore be preferable in terms of both energy and cost. Furthermore, high-pressure CO₂ gas might increase tablet hardness with EC and conventional plasticizers such as TEC more efficiently than with EC alone. In addition to AMCE, HPMCAS, and PVP-VA, a wide range of other polymers might also be candidates for use in this system. Our work confirmed the effect of CO₂ pressure, temperature, treatment time, and AMCE content on the physical properties of ODTs in the present system. Our operational conditions provided a valid way to demonstrate the plasticization of AMCE at lower temperatures than the $T_g$ (at atmospheric condition) using gaseous CO₂. Some CO₂ treatment conditions delayed the disintegration of ODTs as a result of excessive inter-granule bridging by the insoluble AMCE polymer in the tablet. This effect might be related to the swelling seen with XPVP. The tendency toward delayed disintegration was largely observed under conditions of higher CO₂ pressure, longer treatment time, or higher AMCE content. These findings suggest the importance of optimizing treatment conditions to control the physical properties of ODTs in
the system. We also noted that an optimized approach to the production of ODTs increased
hardness and accelerated disintegration from the viewpoint of H/D. The present system is
expected to achieve equivalent H/D to commercial ODTs.

To our knowledge, this is the first report to describe an increase in the hardness of ODTs
using a water-insoluble polymer and plasticization with high-pressure CO2 gas. This system
might be suitable for drug substances that are rendered unstable by heat or humidity. In fact,
we preliminarily confirmed that ODTs containing acetaminophen, famotidine or tamsulosin
hydrochloride could be prepared by CO2 treatment, and showed preferable hardness and
disintegration properties (Kobayashi et al., 2013). Further investigation of ODTs containing
drug substances are needed to confirm stability, loading capacity and dissolution profiles,
which are also important properties of ODTs. Furthermore, our results suggest that this CO2
gas treatment requires a simpler apparatus than supercritical CO2 systems, as pressure
supplied from a CO2 cylinder is sufficient, without the need for a condensing process. This
system might easily be scaled up for commercial purposes. Further modification and a
larger-scale study are therefore required to produce ODTs using this technology for
pharmaceutical research.
References


Figure legends

Figure 1. Schematic diagram of the experimental apparatus for pressurizing tablets using carbon dioxide. 1, CO₂ source (non-siphon cylinder); 2, pressure regulator; 3, stop valve; 4, thermostatic chamber; 5, pressure-resistant container (50 mL); 6, thermometer; 7, back pressure regulator.

Figure 2. Scanning electron microscopy images of polymeric excipients. Intact samples of (a) AMCE, (b) PVP-VA, (c) HPMCAS and (d) CMEC. CO₂-treated samples at 6.0 MPa/25°C/45 min (e) AMCE, (f) PVP-VA, (g) HPMCAS and (h) CMEC. CO₂-treated samples at 4.0 MPa/25°C/45 min (i) AMCE and (j) PVP-VA.

Figure 3. Time effect on tablet hardness (a) and tablet thickness (b) by different treatments. Treatment 1: 25°C treatment with CO₂ gas at 4.0 MPa (open circles). Treatment 2: 70°C heating under atmospheric air (closed circles). Sample at 0 min represents the no-treatment sample. Each plot represents mean ± SD (n=5) and *P<0.05, †P<0.01, vs. 0 min sample of each treatment method.

Figure 4. Scanning electron microscopy images of AMCE. (a) CO₂ at 4 MPa/25°C/120 min, (b) heated at 70°C/120 min and (c) heated at 70°C/840 min.

Figure 5. Effect of CO₂ gas pressure on tablet hardness (a and b), thickness (c) and disintegration time (d) at 15°C (open circles), 25°C (open squares), 35°C (closed circles) and 45°C (closed squares). All treatments were conducted for 45 min. x-axis of (a) CO₂ gas pressure converted to CO₂ gas density in (b). †P<0.01 vs. 15°C sample at each processing time. Hardness and thickness data represent mean ± SD (n=5) and disintegration data are.
mean ± SD (n=3). Disintegration data at more than 4.0 MPa condition are not shown in (d), as these resulted in disintegration times of more than 120 s for all temperatures.

**Figure 6.** Effect of pressurizing time by CO₂ gas on tablet hardness (a), thickness (b) and disintegration time (c) under four different pressure conditions, namely 3.0 MPa (open triangles), 3.5 MPa (open squares), 4.0 MPa (closed triangles) and 5.0 MPa (closed squares). All treatments were conducted at 25°C. Hardness and thickness data are mean ± SD (n=5), and disintegration data are mean ± SD (n=3). For 4.0 and 5.0 MPa, the proportion of disintegration data are not shown in (c), as these resulted in disintegration of more than 2 min.

**Figure 7.** Relationship between processing time and physical properties of ODTs, tablet hardness (a), thickness (b) and disintegration time (c). CO₂ gas pressure was set as 3.5 MPa at 20°C (open triangles), 25°C (closed circles) and 30°C (open squares). Hardness and thickness data are mean ± SD (n=5), and disintegration data are mean ± SD (n=3).

**Figure 8.** Relationship between content of AMCE and physical properties of ODTs, increment of tablet hardness (a), and disintegration time (b) after CO₂ treatment at 4.0 MPa/25°C/45 min. Hardness data are mean ± SD (n=5), and disintegration data are mean ± SD (n=3). For the 12.5% AMCE content formulation, disintegration data are not shown in (b), as this resulted in disintegration of more than 2 min.
Figure 1
Figure 2
Figure 3

(a) Hardness (N)

- ○ 25°C + 4.0 MPa CO₂
- ● 70°C

(b) Thickness (mm)

- ○ 25°C + 4.0 MPa CO₂
- ● 70°C
Figure 4
Figure 5
Figure 6

(a) Hardness (N) vs. Treatment time with CO₂ (min) for different pressures: 5.0 MPa, 4.0 MPa, 3.5 MPa, 3.0 MPa.

(b) Thickness (mm) vs. Treatment time with CO₂ (min) for different pressures: 5.0 MPa, 4.0 MPa, 3.5 MPa, 3.0 MPa.

(c) Disintegration time (s) vs. Treatment time with CO₂ (min) for different pressures: 5.0 MPa, 4.0 MPa, 3.5 MPa, 3.0 MPa.
Figure 7

(a) Hardness (N) vs. Treatment time with 3.5 MPa CO₂ (min)

(b) Thickness (mm) vs. Treatment time with 3.5 MPa CO₂ (min)

(c) Disintegration time (s) vs. Pressurizing time at 3.5 MPa CO₂ (min)
Figure 8

(a) Hardness change (N) vs. Content of AMCE (%)

(b) Disintegration time (s) vs. Content of AMCE (%)

$R^2 = 0.9803$