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 (CO_2). On screening of 26 polymeric excipients, aminoalkyl methacrylate copolymer E (AMCE) markedly increased tablet hardness (+155 N) when maintained in a high-pressure CO_2 environment. ODTs containing 10% AMCE were prepared and treatment with 4.0 MPa CO_2 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 CO_2 pressure, temperature, treatment time, and AMCE content on the physical properties of ODTs. Optimal pressure of CO_2 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 CO_2 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, carboxymethylethylcellulose; CO_2, 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;

SEM, Scanning electron microscopy; T_c, critical temperature; T_g, glass transition temperature; TEC, triethyl citrate; XPVP, crospovidone.

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 (ie. 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

122 treatment on them are unknown. Thus, investigating the effect of CO_2 treatment conditions
123 on the physical characteristics of ODTs would be better done using a simpler formula. Taken
124 together, these findings indicate that a better understanding of hardness enhancing systems
125 with plasticized polymers requires more thorough screening of bridging agents, including
126 water-insoluble polymers, and a closer examination of the effect of varying CO_2 conditions
127 on the physical properties of simpler formula ODTs.
128 Here, we screened a selection of polymeric excipients to evaluate their ability to increase
129 tablet hardness *via* treatment with high-pressure CO_2 gas at ambient temperature. In addition,
130 we also prepared ODTs using a more simplified formula with D-mannitol and conventional
131 disintegrant with an inter-granule bridging system involving the use of CO_2 gas and
132 water-insoluble polymer, and evaluated the effect of different treatment conditions on several
133 tablet properties.
134

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 (HPMCAS: 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). Carboxymethylethylcellulose (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.,

Ltd. (Tokyo, Japan). Hydroxypropylcellulose (NISSO HPC-SSL) was purchased from Nippon Soda Co., Ltd. (Tokyo, Japan). Polyvinyl alcohol/acrylic acid/methyl methacrylate copolymer (PVA/AA/MM copolymer: POVACOAT Type SP) was purchased from Nisshin Kasei Co., Ltd. (Osaka, Japan). Carboxyvinyl polymer (Carbopol 940) was purchased from The Lubrizol Corporation (Wickliffe, OH, USA). Triethyl citrate (TEC) was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). All reagents used were of analytical grade and available from commercial sources, and all solutions were prepared with deionized water.

2.2. Preparation of tablets

2.2.1. Preparation of tableted samples for polymer screening study

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.

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186 2.2.2. Preparation of tableting samples of ODTs (Form A and B)

187 Crystalline powder grade D-mannitol was granulated using top-spraying binder (PVP or
188 PVP-VA) solution (10% [w/w] concentration) with a fluidized-bed granulator (FLO-1;
189 Freund Corporation, Tokyo, Japan) at 420-g scale. AMCE and magnesium stearate were
190 sieved with a 710-μm screen before use. These excipients and intact XPVP were then blended
191 with the granules in a plastic bag for 1 min. The blended components were compressed using
192 a rotary tableting machine (EX10; Hata Iron Works Co., Ltd., Kyoto, Japan) with
193 8.5-mm-diameter round face punches. Tablets were compressed at 1-2 kN/punch to obtain
194 approximately 10 N of tablet hardness. The formulations manufactured by this procedure are
195 shown in **Table 3** (A-1, A-2 and B-1).
196 To confirm the effect of AMCE content in formulations, granules (B-1) were blended with
197 sieved AMCE, XPVP and sieved magnesium stearate in a plastic bottle for 1 min at a 10 g
198 scale, according to the formulation shown in **Table 3** (B-2, B-3 and B-4). Blends were
199 weighed for each tablet and compressed using a compaction test apparatus (Autograph
200 AGS-20 kNG; Shimadzu, Kyoto, Japan) with a compression force of approximately 1
201 kN/punch with a round face punch of 8.5 mm in diameter.

202

203 2.2.3. Treatment of samples by high-pressure CO_2 gas

204 Some polymeric excipients or tablets were treated with high-pressure CO_2 gas using the
205 apparatus shown in **Fig. 1**. This process was conducted in a 50-mL pressure-resistant
206 container (EV series; JASCO, Tokyo, Japan). Temperature in the container was monitored
207 using a thermometer TI-2068 (JASCO), the detector of which was tightly inserted into the
208 container. The container had two attached flow channels for inlet and outlet CO_2 gas. The
209 inlet line connected to a 7-m^3 cylinder of liquefied CO_2 (non-siphon type; Tomoe Shokai Co.,

Ltd., Tokyo, Japan). 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 CO_2 pressurization were immobilized on a metal base with adhesive tape.

260 *2.4. Statistics*

261 Statistical analyses were performed using Student's t-test. $p < 0.05$ was considered
262 statistically significant.

263

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: +65N, 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_2 pressure. According to the vendor's information, the T_g values of PVP-VA and AMCE were 101°C and 45°C, respectively. This lower T_g of AMCE might explain why it was more significantly plasticized than PVP-VA under the same CO_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_2.

To confirm the effect of T_g of bridging polymers on the efficiency of hardness enhancement using high-pressure CO_2, EC was spray-dried with TEC as plasticizer and tablets containing EC/TEC SD were treated with CO_2. In general, the T_g 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_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 T_g of EC from approximately 130°C to 80°C and 50°C, respectively, and that the minimum film-forming temperature of EC corresponded with T_g (2002). In the current CO_2 system, these data suggest that the T_g 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 T_g, even if the bridging polymer cannot be well plasticized by high-pressure CO_2 gas.

Tablets were also processed at 80°C for 840 min as a substitution for high-pressure CO_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 T_g (Suzuki, 2006), its ability to increase tablet hardness by the heating method

and CO_2 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 CO_2 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 CO_2 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 CO_2 treatment (Guadagno and Kazarian, 2004, Pasquali *et al*., 2008). To estimate whether the thickness increase confirmed in some formulas was specific to CO_2 treatment, the effect of the CO_2 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 CO_2 gas treatment. The change in thickness of these samples after CO_2 gas treatment might therefore not be solely due to CO_2 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 CO_2 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 CO_2 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 CO_2 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 CO_2 absorption, which would support XPVP swelling in response to high-pressure CO_2 gas. Taken together, these results for the AMCE formula suggest that the CO_2 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 CO_2 gas treatment is explained by **Fig. 4**. CO_2 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 CO_2 treatment. These differences appear to make CO_2 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 CO_2 gas on the physical properties of ODTs

Regarding the plasticizing effect of pressurized CO_2 on polymers, the melting temperature of PEG 1500 has been shown to decrease in a manner that was dependent upon CO_2 pressure (Pasquali *et al*., 2008). In a CO_2-based tablet hardness enhancement system which uses plasticized polymer, pressure of CO_2 affects tablet hardness (Kobayashi *et al*., 2013). We therefore considerd that CO_2 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 CO_2 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 CO_2 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 CO_2 density, not pressure (Span and Wagner, 1996). CO_2 pressure is correlated with CO_2 density and likely an important factor influencing the dissolution of polymers, as CO_2 volume is changed in a temperature-dependent manner and CO_2 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 CO_2 treatment process might be simpler and preferable to that of density. **Fig. 5b** shows that CO_2 density has a similar effect to CO_2 pressure. Our results suggest that tablet hardness can be controlled by CO_2 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 CO_2 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 CO_2 gas treatment would have an ideal exposure time, in which ODTs can disintegrate within 20 s, and this time can be shortened by raising CO_2 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.

514 3.3.3. Control of physical properties of ODTs at 3.5 MPa conditions

515 Our findings in **Fig. 6** show that 3.5 MPa of CO_2 gas is preferable for this system when using
516 AMCE, as treatment for 180 min maintained rapid disintegration within 15 s and exhibited
517 moderate increases in hardness profile, which would help control the physical properties of
518 ODTs in commercial manufacturing. In this study, the control of physical properties of ODTs
519 using a fixed pressure condition was evaluated.

520 B-1 tablets were treated with CO_2 gas at 20, 25 and 30°C at 3.5 MPa and the effects on
521 physical properties of ODTs were evaluated (**Fig. 7**). Our results demonstrated that tablet
522 hardness of 40–50 N and disintegration of approximately 15 s were reproducibly obtained for
523 the three different temperature conditions (**Figs. 7a, b and c**). These results suggest that the
524 properties of ODTs are well controlled within the temperature range of 25 ± 5°C. A model
525 condition for this ODT system might therefore be 3.5 MPa/25°C/180 min, by simply
526 controlling treatment time, temperature and CO_2 pressure. These conditions would be
527 acceptable as an alternative method for heating or humidifying systems. However, treatment
528 with CO_2 gas for 360 min tended to delay disintegration at 25 and 30°C, which suggests an
529 unfavorable processing time of longer than 180 min. The above conditions consist of a mild
530 temperature of approximately 25°C and a gaseous state of CO_2, which could be obtained
531 using a simple apparatus consisting of a pressure-resistant container connected to a CO_2
532 cylinder. Such a system would enable the easy control of CO_2 pressure introduced into the
533 container *via* adjustment of the pressure valve and temperature. This simplified system would
534 also be beneficial from a commercial perspective because the lack of a heating process at a
535 large production scale would result in lower overall energy costs.

536 These findings demonstrate that the physical properties of ODTs were well controlled by
537 adjusting the pressure of CO_2 gas and temperature in this hardness-enhancing system using
538 AMCE and CO_2 gas.

539

540 *3.4. Effect of AMCE content on physical properties of ODTs*

541 In the present ODT system, the content of AMCE is expected to affect the physical properties
542 of ODTs, in addition to treatment conditions. We therefore evaluated the relationship
543 between AMCE content and the physical properties of ODTs (hardness and disintegration).
544 Formulations are shown as B-1, B-2, B-3, and B-4 (**Table 3**), in which AMCE content
545 increased from 2.5% to 12.5%. The physical properties of ODTs after treatment with CO_2 gas
546 (4.0 MPa/25°C/45 min) were evaluated, and results are shown in **Figs. 8a and b**. In the
547 previous section, 3.5 MPa/25°C/approximately 180 min was suggested as a model condition
548 for preparing ODTs. This experiment, however, was conducted at 4.0 MPa/25°C/45 min, as
549 the B-1 formula under these conditions exhibited similar hardness and disintegration
550 properties to those under the model conditions (**Fig. 6**), which enabled the effects of AMCE
551 content to be compared. Results showed that increases in hardness were content-dependent,
552 and a proportional relationship was confirmed (R^2=0.9083) between the increment in
553 hardness and AMCE content (**Fig. 8a**).
554 Regarding disintegration properties (**Fig. 8b**), rapid disintegration of less than 20 s was
555 observed for formulations with AMCE content of 10% or lower. In contrast, the B-4 formula
556 containing the highest AMCE content of 12.5% took longer than 120 s to disintegrate (data
557 not shown). This might be due to excess conditions with regard to both the amount of AMCE
558 and CO_2 treatment, which would delay the disintegration of ODTs. However, this result does
559 not necessarily suggest that the B-4 formula is unacceptable for ODTs, as it exhibited a
560 hardness higher than 50 N and rapidly disintegrated upon processing at lower pressure (3.5
561 MPa/25°C/45 min, **Table 4**). The delayed disintegration of the B-4 formulation was therefore
562 attributed to both bridging agent content and CO_2 gas treatment conditions, with 12.5%
563 AMCE content considered excessive for treatment at 4.0 MPa/25°C/45 min. As shown in **Fig.**

564 **6a and 6c**, formulation with 10% of AMCE required 5.0 MPa to achieve a hardness of higher
565 than 50 N, and this pressure gives only 5 min of preferred time for rapid disintegration.
566 However, as mentioned above, formulation with 12.5% at AMCE provided a hardness of
567 higher than 50 N and rapid disintegration by 3.5 MPa/25°C/45 min, which demonstrates that
568 increasing the amount of AMCE is an effective way of prolonging the preferred treatment
569 time to achieve rapid disintegration while maintaining target hardness. These findings
570 highlight the importance of a balance between the content of the bridging agent and
571 processing conditions in controlling the physical properties of ODTs in this system.
572
573 *3.5. Approaches for controlling physical properties of ODTs*
574 Three different approaches to increasing the tablet hardness of ODTs utilizing high-pressure
575 CO_2 gas under ambient temperature were tested, as follows: increasing the pressure of CO_2,
576 extending the processing time, and increasing AMCE content in the tablet formulation.
577 However, the excessive use of these conditions can also delay the disintegration of ODTs.
578 The general goal of formulating ODTs is to achieve both high hardness and rapid
579 disintegration. It is therefore meaningful to determine which of these approaches is more
580 effective for improving the balance of the physical properties of ODTs.
581 Here, five models of ODTs were prepared based on different input factors, as follows: AMCE
582 content, CO_2 pressure, and CO_2 treatment time. Tablet hardness and disintegration time were
583 compared as output profiles. The ratio of hardness to disintegration (H/D) was set as a
584 parameter (**Table 4**). In general, ODTs with high hardness and rapid disintegration are
585 preferable for commercial products, and H/D is therefore a simple parameter for evaluating
586 the performance of ODTs, in which a higher H/D indicates better performance. As a
587 preliminary experiment, we confirmed that tablets of 19 commercial ODTs in Japan had
588 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 CO_2 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 CO_2 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 CO_2 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 CO_2 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 CO_2 gas pressure.

These results suggest that the delay in ODT disintegration due to longer CO_2 processing or higher AMCE content can be avoided by decreasing CO_2 pressure, resulting in ODTs with high H/D. In contrast, increasing the CO_2 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 CO_2 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 CO_2 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 CO_2 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 CO_2 gas at 4.0 MPa/25°C/10 min reached near comparable hardness as that with heating at 70°C/720 min. CO_2 gas treatment might therefore increase tablet hardness more efficiently and with less thermal stress than heating. The use of a CO_2 gas system might therefore be preferable in terms of both energy and cost. Furthermore, high-pressure CO_2 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 CO_2 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 CO_2. Some CO_2 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 CO_2 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

639 the system. We also noted that an optimized approach to the production of ODTs increased
640 hardness and accelerated disintegration from the viewpoint of H/D. The present system is
641 expected to achieve equivalent H/D to commercial ODTs.
642 To our knowledge, this is the first report to describe an increase in the hardness of ODTs
643 using a water-insoluble polymer and plasticization with high-pressure CO_2 gas. This system
644 might be suitable for drug substances that are rendered unstable by heat or humidity. In fact,
645 we preliminarily confirmed that ODTs containing acetaminophen, famotidine or tamsulosin
646 hydrochloride could be prepared by CO_2 treatment, and showed preferable hardness and
647 disintegration properties (Kobayashi *et al*., 2013). Further investigation of ODTs containing
648 drug substances are needed to confirm stability, loading capacity and dissolution profiles,
649 which are also important properties of ODTs. Furthermore, our results suggest that this CO_2
650 gas treatment requires a simpler apparatus than supercritical CO_2 systems, as pressure
651 supplied from a CO_2 cylinder is sufficient, without the need for a condensing process. This
652 system might easily be scaled up for commercial purposes. Further modification and a
653 larger-scale study are therefore required to produce ODTs using this technology for
654 pharmaceutical research.
655

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728 **Figure legends**

729 **Figure 1.** Schematic diagram of the experimental apparatus for pressurizing tablets using
730 carbon dioxide. 1, CO_2 source (non-siphon cylinder); 2, pressure regulator; 3, stop valve; 4,
731 thermostatic chamber; 5, pressure-resistant container (50 mL); 6, thermometer; 7, back
732 pressure regulator

733

734 **Figure 2.** Scanning electron microscopy images of polymeric excipients. Intact samples of
735 (a) AMCE, (b) PVP-VA, (c) HPMCAS and (d) CMEC. CO_2-treated samples at 6.0
736 MPa/25°C/45 min (e) AMCE, (f) PVP-VA, (g) HPMCAS and (h) CMEC. CO_2-treated
737 samples at 4.0 MPa/25°C/45 min (i) AMCE and (j) PVP-VA.

738

739 **Figure 3.** Time effect on tablet hardness (a) and tablet thickness (b) by different treatments.
740 Treatment 1: 25°C treatment with CO_2 gas at 4.0 MPa (open circles). Treatment 2: 70°C
741 heating under atmospheric air (closed circles). Sample at 0 min represents the no-treatment
742 sample. Each plot represents mean ± SD (n=5) and $^{*}P<0.05$, $^{\dagger}P<0.01$, vs. 0 min sample of
743 each treatment method.

744

745 **Figure 4.** Scanning electron microscopy images of AMCE. (a) CO_2 at 4 MPa/25°C/120 min,
746 (b) heated at 70°C/120 min and (c) heated at 70°C/840 min

747

748 **Figure 5.** Effect of CO_2 gas pressure on tablet hardness (a and b), thickness (c) and
749 disintegration time (d) at 15°C (open circles), 25°C (open squares), 35°C (closed circles) and
750 45°C (closed squares). All treatments were conducted for 45 min. x-axis of (a) CO_2 gas
751 pressure converted to CO_2 gas density in (b). $^{\dagger}P<0.01$ vs. 15°C sample at each processing
752 time. Hardness and thickness data represent mean ± SD (n=5) and disintegration data are

753 mean ± SD (*n*=3). Disintegration data at more than 4.0 MPa condition are not shown in (d),
754 as these resulted in disintegration times of more than 120 s for all temperatures.
755
756 **Figure 6.** Effect of pressurizing time by CO_2 gas on tablet hardness (a), thickness (b) and
757 disintegration time (c) under four different pressure conditions, namely 3.0 MPa (open
758 triangles), 3.5 MPa (open squares), 4.0 MPa (closed triangles) and 5.0 MPa (closed squares).
759 All treatments were conducted at 25°C. Hardness and thickness data are mean ± SD (*n*=5),
760 and disintegration data are mean ± SD (*n*=3). For 4.0 and 5.0 MPa, the proportion of
761 disintegration data are not shown in (c), as these resulted in disintegration of more than 2
762 min.
763
764 **Figure 7.** Relationship between processing time and physical properties of ODTs, tablet
765 hardness (a), thickness (b) and disintegration time (c). CO_2 gas pressure was set as 3.5 MPa at
766 20°C (open triangles), 25°C (closed circles) and 30°C (open squares). Hardness and thickness
767 data are mean ± SD (*n*=5), and disintegration data are mean ± SD (*n*=3).
768
769 **Figure 8.** Relationship between content of AMCE and physical properties of ODTs,
770 increment of tablet hardness (a), and disintegration time (b) after CO_2 treatment at 4.0
771 MPa/25°C/45 min. Hardness data are mean ± SD (*n*=5), and disintegration data are mean ±
772 SD (*n*=3). For the 12.5% AMCE content formulation, disintegration data are not shown in (b),
773 as this resulted in disintegration of more than 2 min.
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776
777

Figure 1

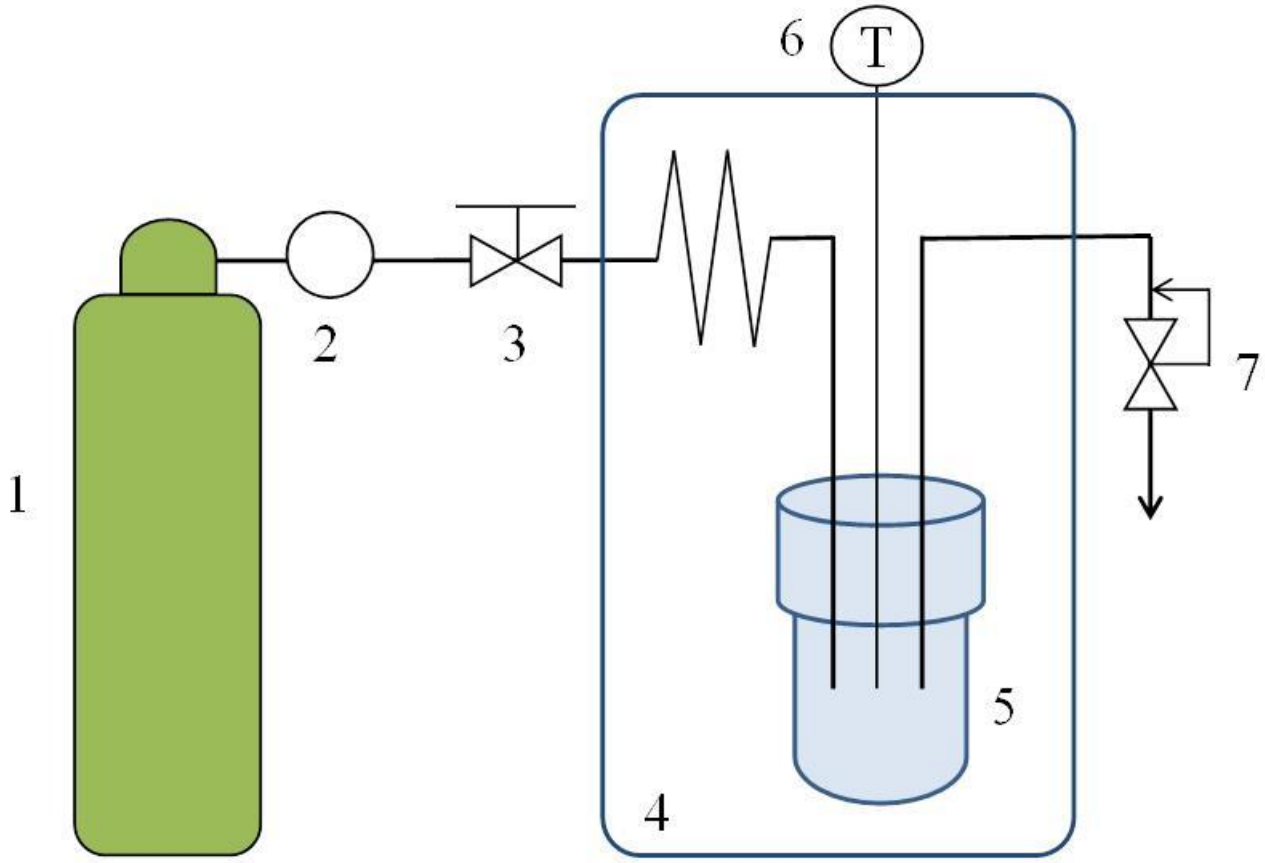

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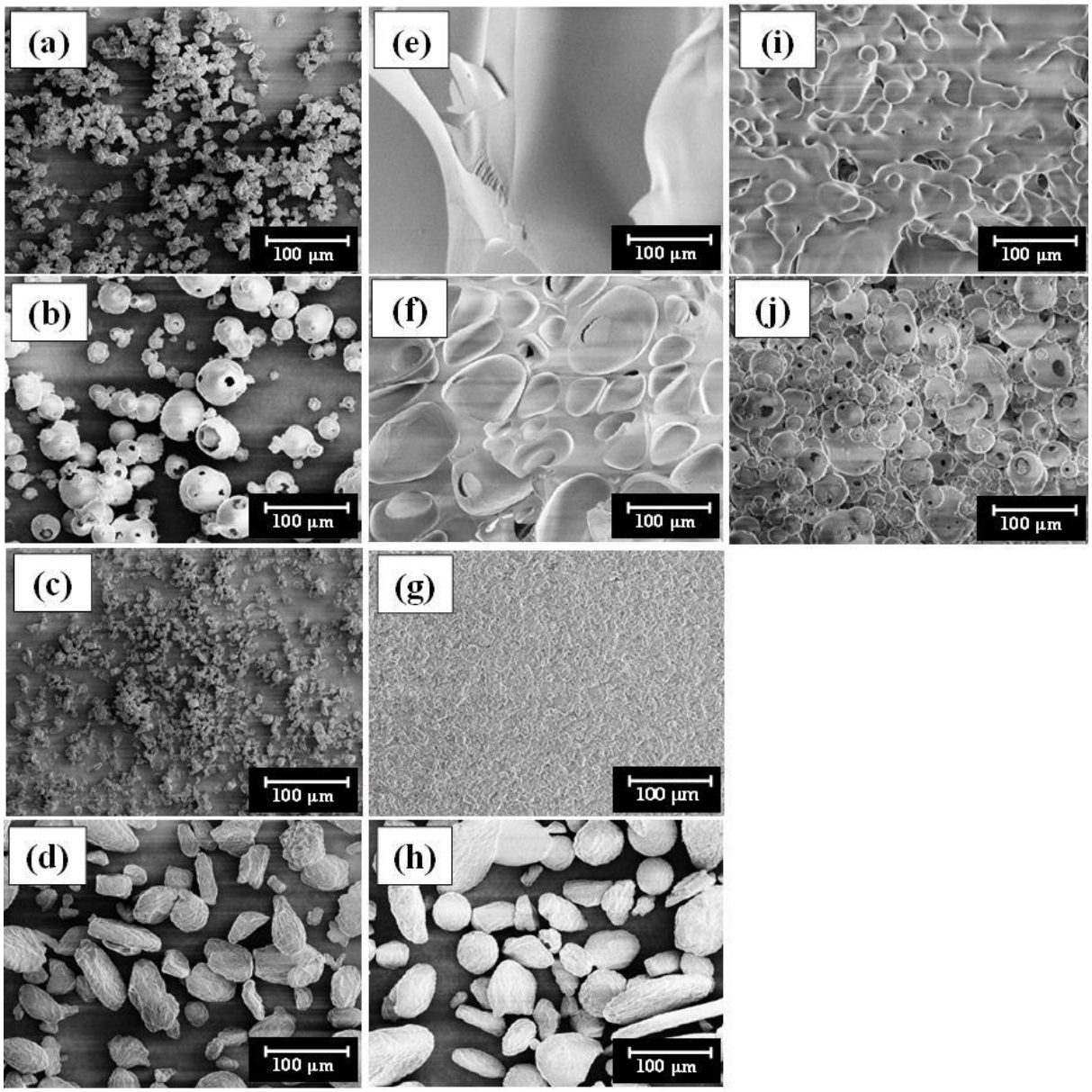
Figure 2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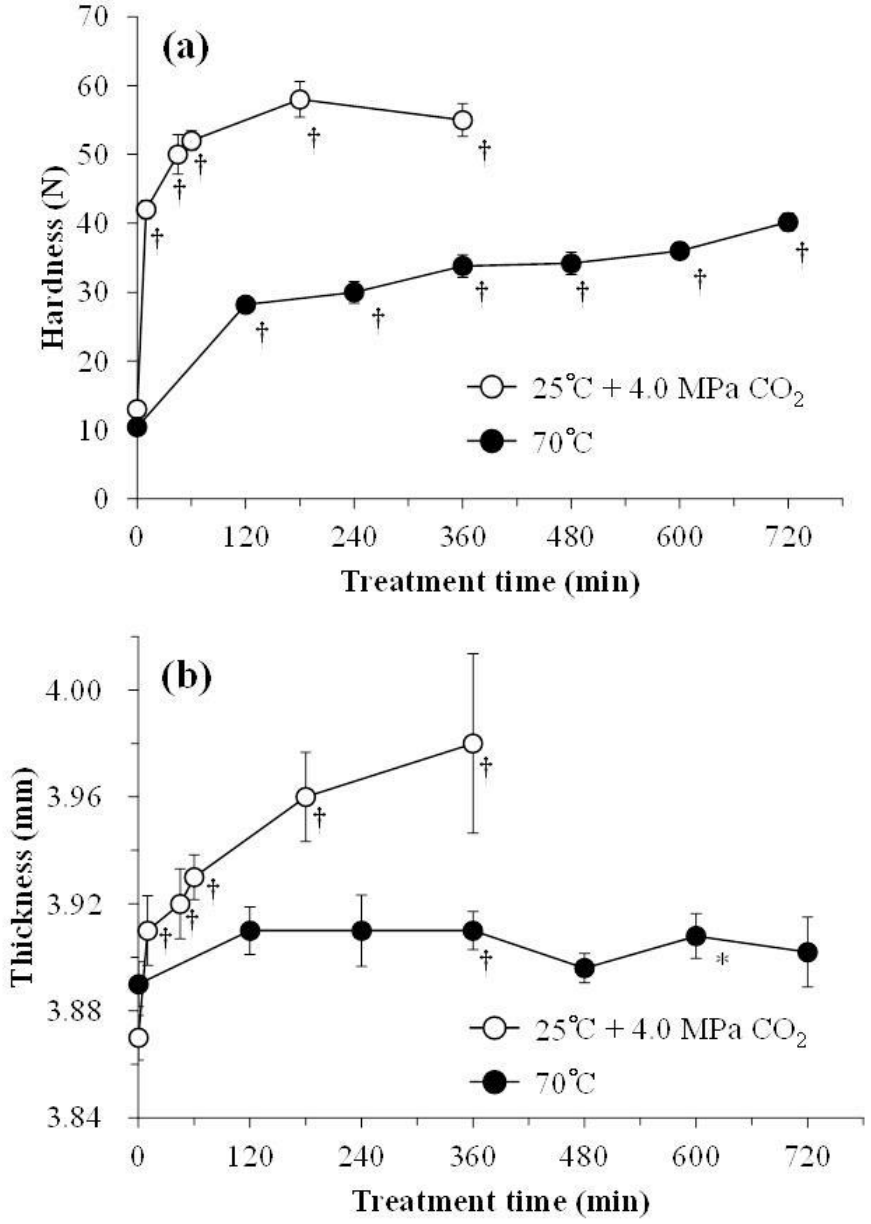
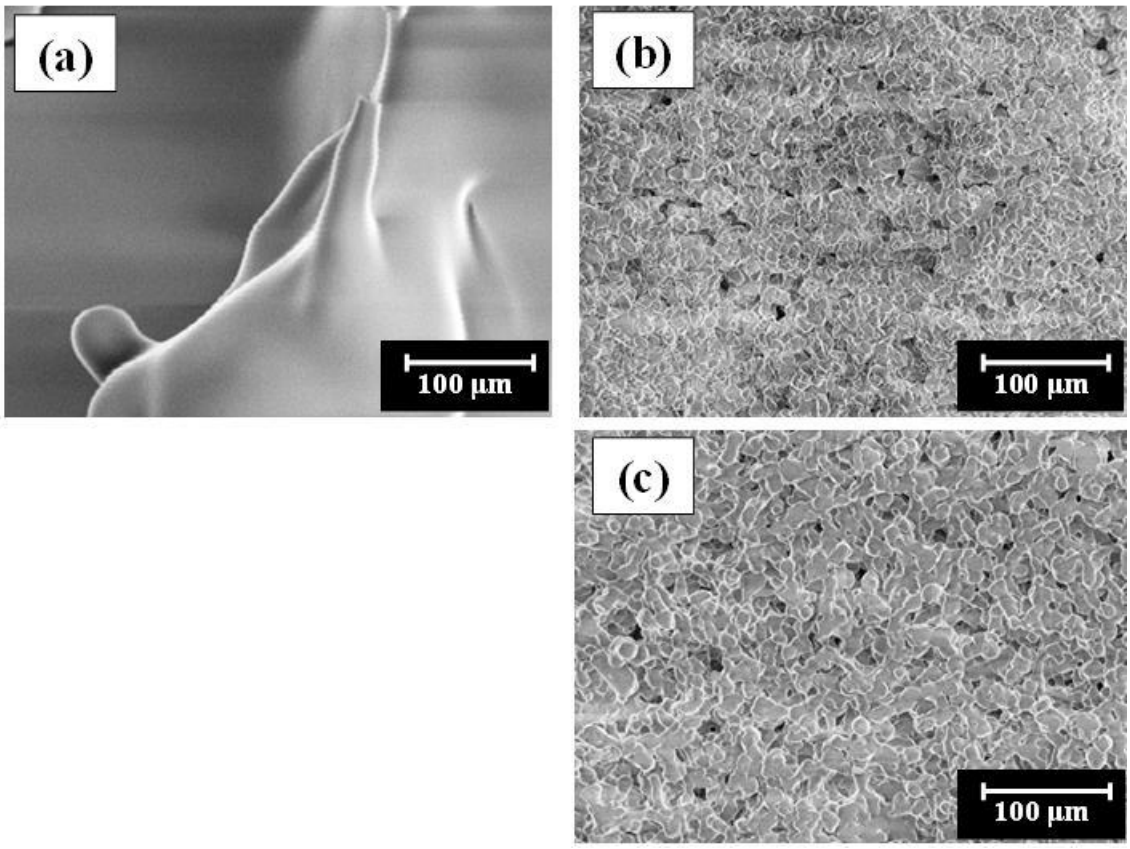
779

Figure 3


(a)
Hardness (N)
70
60
50
40
30
20
10
0
0
120
240
360
480
600
720
Treatment time (min)
25℃ + 4.0 MPa CO2
70℃
(b)
Thickness (mm)
4.00
3.96
3.92
3.88
3.84
0
120
240
360
480
600
720
Treatment time (min)
25℃ + 4.0 MPa CO2
70℃

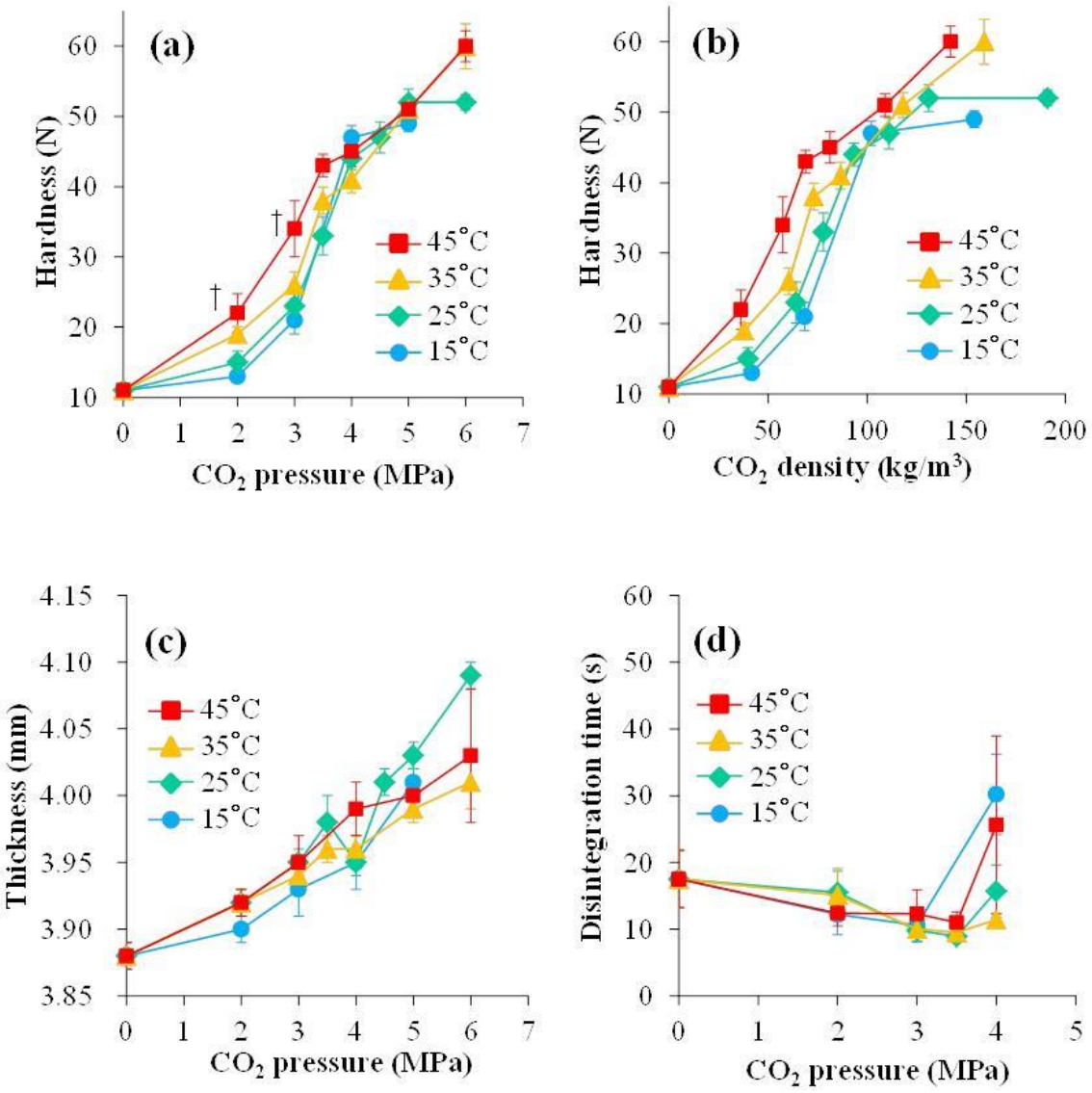
780

Figure 4



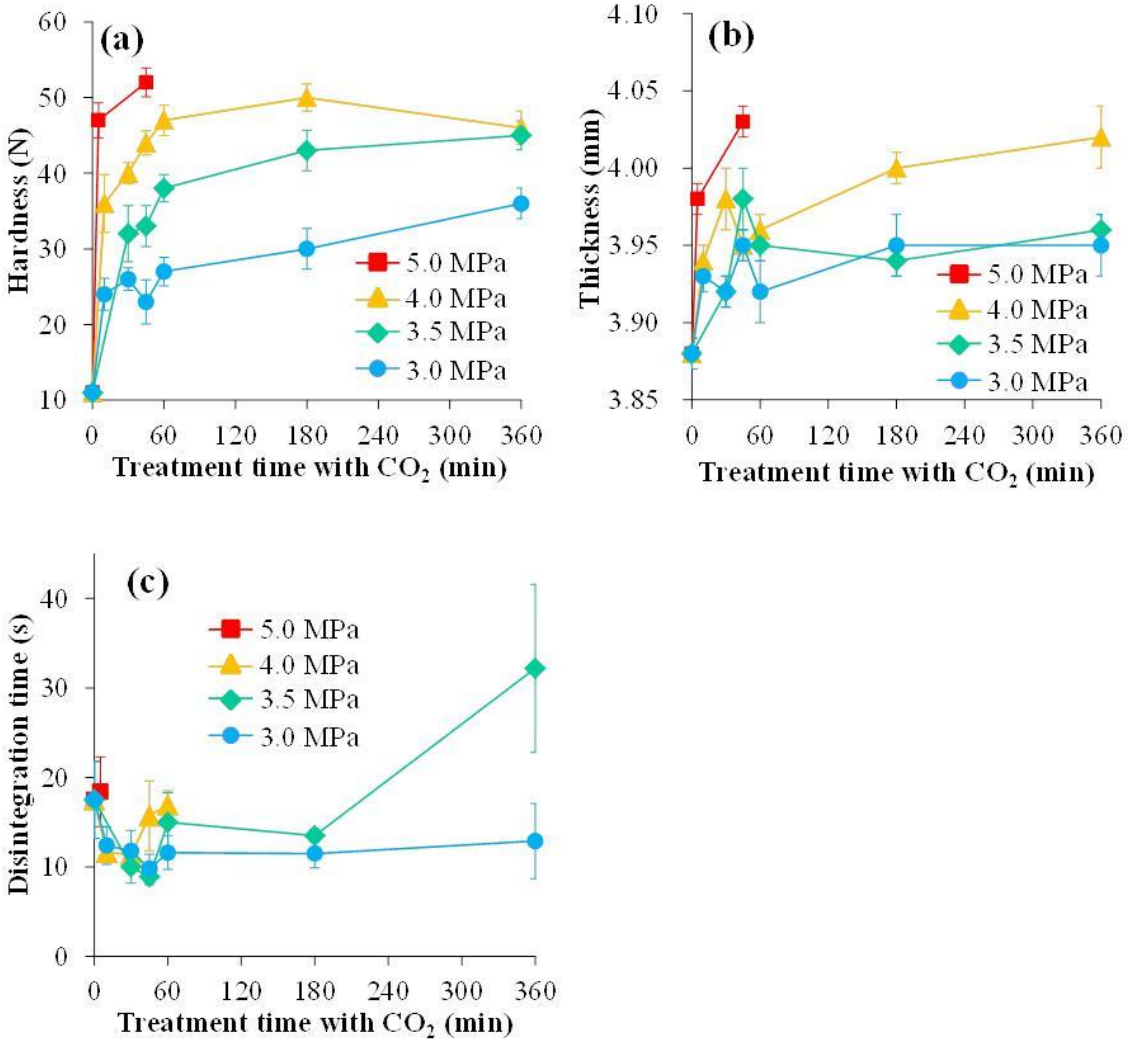
781

Figure 5


(a)
Hardness (N)
CO2 pressure (MPa)
45°C
35°C
25°C
15°C
†
†
(b)
Hardness (N)
CO2 density (kg/m3)
45°C
35°C
25°C
15°C
(c)
Thickness (mm)
CO2 pressure (MPa)
45°C
35°C
25°C
15°C
(d)
Disintegration time (s)
CO2 pressure (MPa)
45°C
35°C
25°C
15°C

782

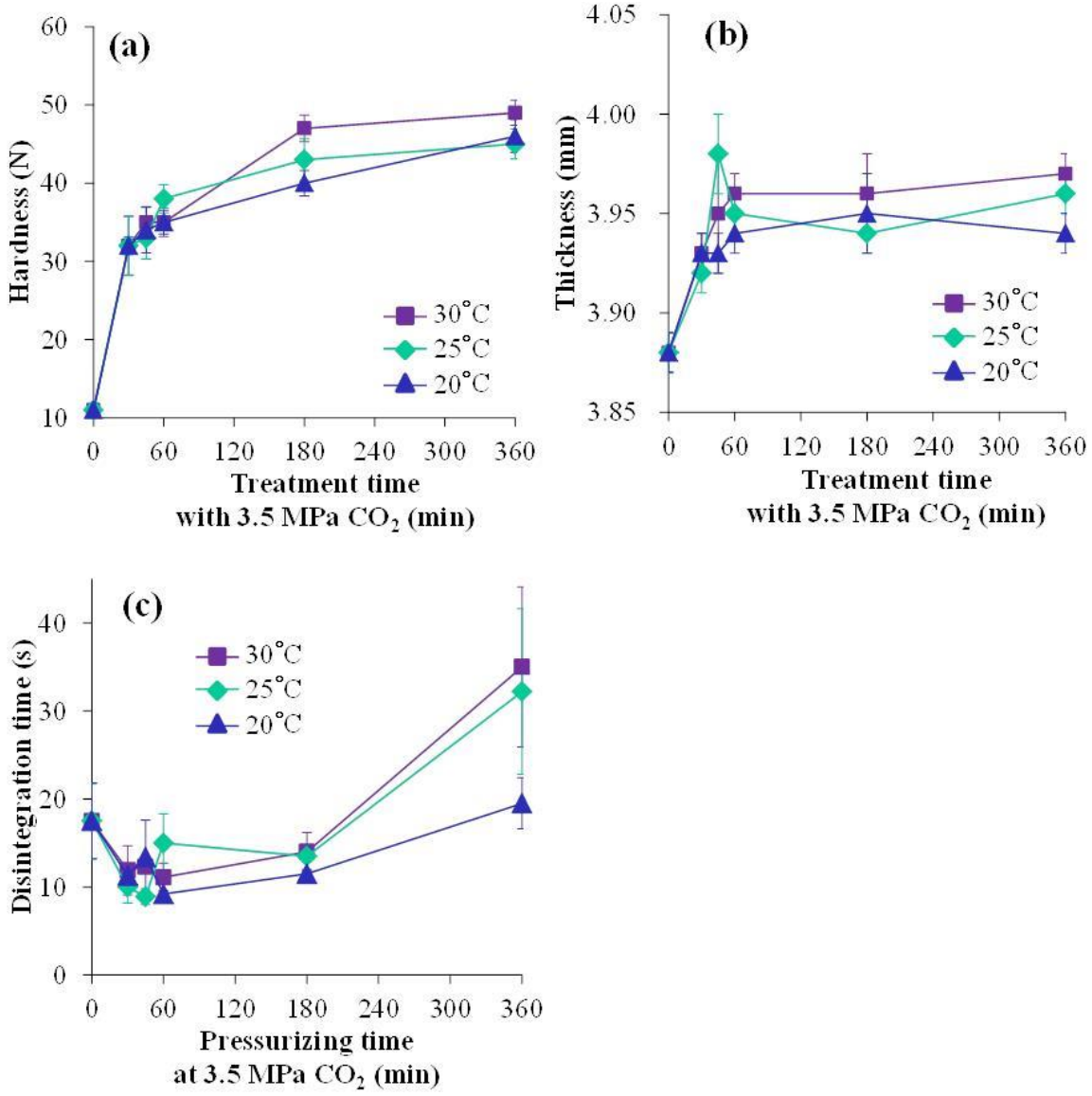
Figure 6



783

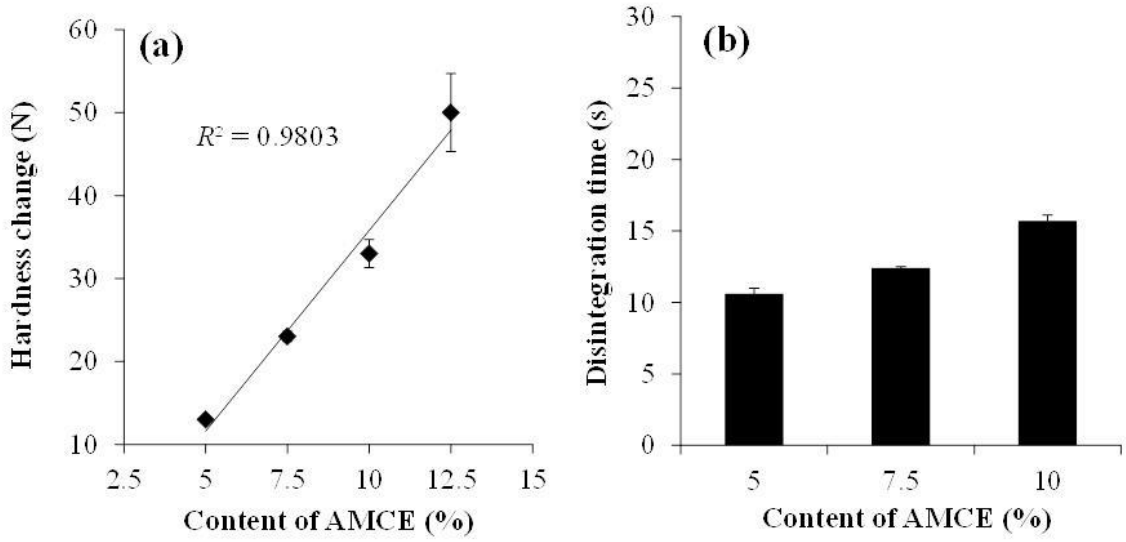
784

Figure 7


(a)
Hardness (N)
60
50
40
30
20
10
0
60
120
180
240
300
360
Treatment time
with 3.5 MPa CO2 (min)
30°C
25°C
20°C
(b)
Thickness (mm)
4.05
4.00
3.95
3.90
3.85
Treatment time
with 3.5 MPa CO2 (min)
30°C
25°C
20°C
(c)
Disintegration time (s)
40
30
20
10
0
Pressurizing time
at 3.5 MPa CO2 (min)
30°C
25°C
20°C

785

Figure 8


(a)
$R^2 = 0.9803$
Hardness change (N)
60
50
40
30
20
10
2.5
5
7.5
10
12.5
15
Content of AMCE (%)
(b)
Disintegration time (s)
30
25
20
15
10
5
0
5
7.5
10
Content of AMCE (%)

786