International Journal of Pharmaceutics 511 (2016) 10–22

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

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

Yoshitaka Ito[a,b], Atsushi Maeda[a], Hiromu Kondo[a], Yasunori Iwao[b], Shuji Noguchi[b], Shigeru Itai[b,*]

[a] Pharmaceutical Research and Technology Labs., Astellas Pharma Co., Ltd., 180 Ozumi, Yaizu, Shizuoka 425-0072, Japan
[b] Department of Pharmaceutical Engineering, Graduate Division of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan

ARTICLE INFO

Article history:
Received 23 February 2016
Received in revised form 18 May 2016
Accepted 29 June 2016
Available online 29 June 2016

Keywords:
Orally disintegrating tablet
Carbon dioxide
Aminoalkyl methacrylate copolymer e

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.

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, 2014). Another method

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.

* Corresponding author at: Department of Pharmaceutical Engineering, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan.
E-mail address: s-itai@u-shizuoka-ken.ac.jp (S. Itai).

http://dx.doi.org/10.1016/j.ijpharm.2016.06.132
0378-5173/

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, 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, 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 an 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 CO_2 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 CO_2 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 CO_2 gas at an 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 CO_2 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 50C) 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.