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The Effect of Compression Force on Alteration of Desloratadine and its Multicomponent Crystal Crystallinities Using X-Ray Diffraction and ATR-FTIR Techniques

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Abstract. This work studied the effect of compression force on the desloratadine (DES) and its multi-component crystal (MCC) formulation and focused on the molecular crystal behavior of DES and MCC after compression. Crystallinity behavior of drugs in a mechanical process is to be interesting manner. In this research, DES and MCC were compressed using hydraulic presser equipped with 13 mm flat-face punch under different compression pressures in a range of 25 – 350 MPa. The solid state of DES and its MCC was evaluated using powder X-ray diffraction (XRD) and attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy. Single XRD was carried out to confirm the molecular structure of crystal lattice. Powder XRD diffractogram under different compression forces was compared to the crystallinity degree, crystallite size and peak broadening. Those parameters were processed using Origin software. Crystallinity degree was calculated using Ruland's methods, meanwhile, the crystallinity size was calculated using Scherrer's equation after corrected to the broadening (full width at half maximum; FWHM) and diffraction baseline. As increasing the compression force, degree and size of crystallinity and FWHM were altered. In addition, the degree of crystallinity and crystallite size of DES and MCC decreased, while the FWHM increased. Furthermore, alteration of PXRD in DES was higher than that of MCC which had no alteration as increase as the compression force. FTIR result showed that neither DES nor MCC had no significant alteration after compression. However, the tabletability of MCC was better than DES owing to the potential slip plane of MCC.

Introduction

Generally, solid pharmaceuticals manufacturing process involves several processes i.e. granulation, drying, milling, and compression (1). High mechanical compression and energy source induces a significant alteration of physicochemical properties of solid pharmaceutical crystal (2). Not only the deformation characteristics e.g. crystal structure and habit, surface roughness, moisture content, temperature, tensile strength, particle size and density but also production parameters and processes contribute to the result (3). During compression, solid particle rearranges followed by deformation, fracture and fragmented to compact mass, which affects by molecular arrangement in the crystal lattice and intermolecular interaction. According to those parameters, the crystallinity of material is important in active pharmaceutical ingredient (API) because it affects the crystal condition, the defect of the crystal lattice and contributes to the crystal lattice disturbance, which correlates to physical properties. Until to the date, the correlation between the structure of crystal lattice and tablet properties of the solid material does not understand enough. Furthermore, the effect of crystal lattice structure on mechanical properties on single and poly-crystalline is needed to understand crystal lattice behavior under compression (1). Energy involving in compression process can alter the solid phase of API or excipient through solid state mechanism (4).

Compression affects crystallinity of API, as indicator alteration several parameters e.g. crystallinity degree, crystallite size and broadening of the peak can be observed. Evaluation degree of crystallinity or crystallinity index in the polymer is commonly used, however, it is rarely applied in the low molecular weight compound i.e. API. Considering the alteration of crystallinity during compression, several parameters can be used to evaluate this alteration i.e. degree of crystallinity, crystallite size, and broadening of the peak. Several methods are frequently used to characterize those parameters e.g. powder X-ray diffraction (PXRD), Fourier transforms infrared (FTIR) and nuclear magnetic resonance (NMR) spectroscopy, density measurement and thermal analyses (5). Furthermore, the PXRD is the most frequent and adequate instrument to characterize the crystallinity (6). This method has an advantage i.e. no sample destruction (7). PXRD diffractogram provides some information i.e. peak and its intensity in which it indicates the crystal structure, composition, arrangement of the crystal lattice, symmetricity of crystal phase. Crystal structure depending on the atom distribution in the structure (8). Broadening of the peak, full-width at half maximum (FWHM) indicates either crystalline or amorph materials. The crystalline material has a sharp peak, while the amorph material has a halo broad peak. Therefore, the peak crystallinity can be observed using FWHM and crystallite size can be calculated using FWHM with Scherrer equation (9). In addition, the interaction among compounds during the process can be monitored using PXRD which it is able to identify the new diffraction pattern or alteration of the diffraction pattern (10). New interaction and phase appears as different functional group vibration in FTIR (11).

Since the crystallinity investigation has proved its effect on the drug manufacturing, several pre-formulation characteristics are linked to the drug crystallinity. However, the investigation of desloratadine and its multi-component crystal (MCC) not yet reported until to the date. Desloratadine (DES) is a selective antagonist of H1 receptors that is used as anti-allergy and anti-inflammation (12). DES is a weak alkali and it is prepared in MCC salt-from with benzoic acid (BA) in an equimolar ratio using a solvent evaporation technique with methanol as a solvent (13). MCC alters the physicochemical characteristic with rearrangement of structure in a new crystal lattice (14). DES physicomechanically has a limitation owing to low tabletability and MCC overcomes this limitation (14,15). The aim of this study was to analyze the effect of compression force on the alteration of crystal condition of DES and its MCC using PXRD and FTIR. In addition, the effect of crystallinity on tabletability was also evaluated using single crystal XRD and FTIR.

Experimental Procedure

1.1. Materials

Desloratadin (DES) was purchased from Xi'An Wango Biopharm Co., Ltd., (Shaanxi, China). Benzoic acid (BA) and methanol were obtained from Merck (Darmstadt, Germany) and J.T. Baker, Inc (NJ, USA), respectively.

1.2. Preparation of desloratadine multicomponent crystal using solvent evaporation technique

An equimolar (1 mmol) of DES and BA was dissolved in methanol at 25°C. Formation of MCC salt was performed using a rapid solvent evaporation using a Buchi rotavapor R-215 (Flawil, Switzerland) at 50°C and 208 mBar. The obtained solid was collected and stored for further characterization.

1.3. Tablet preparation

Tablet preparation was performed by weighing manually and acurately 500±2 mg of DES and 696.44±2 of MCC. The tablet mass was manually compressed using a Perkin Elmer hydraulic pressure (MA, USA) equipped with a13 mm flat-face punch under different compression forces e.g. 25, 50, 100, 150, 200, 250, 300, and 250 MPa. Before compression, punch and die were rubbed with magnesium stearate. All compression processes of DES and MCC were performed under a controlled condition at 25°C and 75% relative humidity. After compression, the tablet was carefully unloaded from the die and stored in desiccator until further characterizations.

1.4. Powder X-Ray diffraction (PXRD)

XRD diffractogram was obtained using a Bruker D8 Advance X-Ray diffractometer (WI, USA) with radiation Cu-kα (λ 1,5406Å), the voltage of 40 kV dan current of 35 mA. The sample was placed into stage diffractometer. All scans were performed at 2º/min from diffraction angle 5 to 60º with step size 0.02º. Furthermore, diffractogram was further processed using OriginPro 9.0 (MA, USA), smoothing and baseline correction were performed using this software. The degree of crystallinity (%) was calculated based on peak area ratio of crystalline peak and total peak area (16). Peak area was obtained from multiple peaks using Gaussian model.

Crystallite size (D) was calculated using Scherrer's equation (17):

$$D = k\lambda / \beta\cos\theta \quad (1)$$

Where as: k = varied from 0.89 to 1.39, λ = wavelength (0.1541 nm), β = integration of width, θ= bragg angle

1.5. Fourier Transform Infrared spectroscopy

Identification of vibrational peak was obtained using a Thermo Nicolet iS50 attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectrometer (MA, USA) at wavelength number from 4000-650 cm^{-1} with the resolution of 2 cm^{-1} and 32 times iteration. Furthermore, obtained spectra were compared depending on the vibrational peak and shifting.

1.6. Single crystal X-Ray diffraction (SCXRD)

Single X-ray diffraction (CIF) from MCC was obtained at the temperature of 93 (2) K. Measurement was performed on n ω-scan mode with R -AXIS RAPID II Rigaku (Japan) using X-ray Cu Kα which was obtained from the rotation of anode source with graphite monochromator (50 mA current and 200 kV voltage). Integrated data was scaled and corrected empirically using ABSCOR. The prior structure was finished using the direct method with SIR 2014 and enhanced at Fo^2 with SHELXL 2014 (18,19). Illustration of the single crystal of MCC was processed using Mercury 3.7 software(20).

Results and Discussion

In the tablet process manufacture, an amount of pressure is applied to form a compact mass from drug-excipients powder/granules. However, at specific pressure or over-compression process induce alteration of crystallinity. Thus, in this study, we investigated the alteration of crystallinity behavior of DES and its MCC under different compression forces. Alteration of crystallinity easily observed using diffractogram of PXRD. The diffractogram PXRD of DES under different compression forces is presented in Figure 1a. An explanation of crystal structure provides the most definitive proof of crystal form. PXRD diffractogram showed that a negligible alteration of diffractogram pattern was observed at a low compression force (25 MPa). Although, at a high compression force, the height of specific peaks decreased. Generally, an increase of compression force reduced crystallinity. Higher compression force until 350 MPa, an amorphous formation almost observed (Figure 1b). Reducing of the intensity of diffractogram showed a crystal defect of DES. The tendency of a low crystallinity to amorphous form was assigned by a boarding of peak and reducing its intensity. This result probably was affected by a formation of amorphous in which the crystallinity of DES reduced. Alteration of the specific peak in the PXRD diffractogram was overviewed at a range of 12-14°. Shifting of peaks as increasing the compression force until 250 MPa and re-shifting to the beginning position was observed at increasing compression force from 300-350 MPa. This phenomenon showed that DES had low tabletability owing to the elastic characteristic.

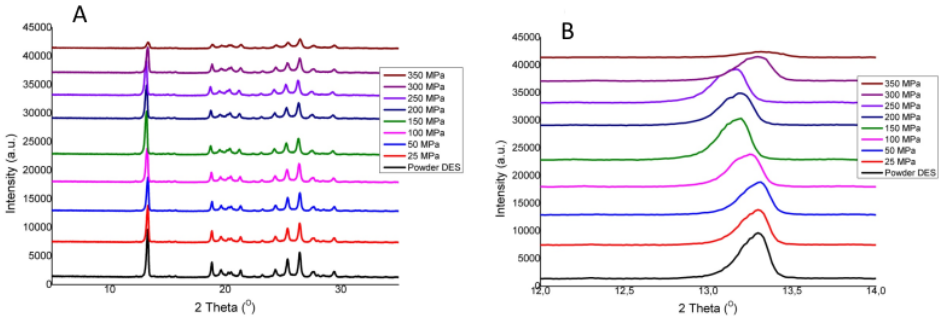

Figure 1. A. Difractogram of PXRD Desloratadine with compression treatment at various pressures in range 0-35, B. Differential diffraction peak changes in the range 12-14

In another side, PXRD of DES MCC is presented in Figure 2. No alteration of intensity and shifting of peaks were observed in MCC diffractogram with increasing of the compression force. Compared to the DES diffractogram under the similar compression force, MCC had no significant alteration. As intended, MCC successfully enhanced physicomechanical and physicochemical properties of DES which it could retain crystallinity under the compression process.

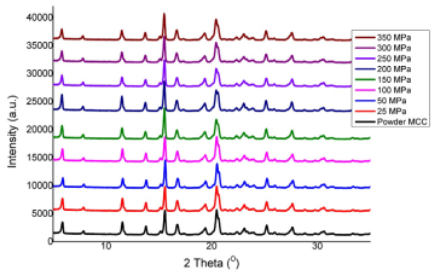

Figure 2. Difractogram of PXRD Multicomponent crystal with compression treatment at various pressures

Alteration of crystallinity under compression was highlighted through quantitative analysis using the degree of crystallinity, crystallite size, and FWHM of DES and MCC. It is presented in Figure 3a-c. Crystallinity degree was calculated using Rulland methods which crystallinity could be determined by the differential of amorph contribution and amorph standard in the spectrum. The degree of crystallinity was calculated depending on the crystallinity area to total area ratio of diffractogram (21). The degree of crystallinity was decreased as increase the compression force. This result indicated that alteration of a part of crystallite and disturbance of crystallite were observed after compression. PXRD results proved that particle size of DES and MCC reduced to increase the compression force. We could conclude that crystallinity and crystallite size of DES and MCC altered during the compression process. Extremely, compression was able to interfere the crystal structure and induced a non-crystalline formation. Alteration of the degree of crystallinity, crystallite size, and FWHM of DES was higher than that of MCC.

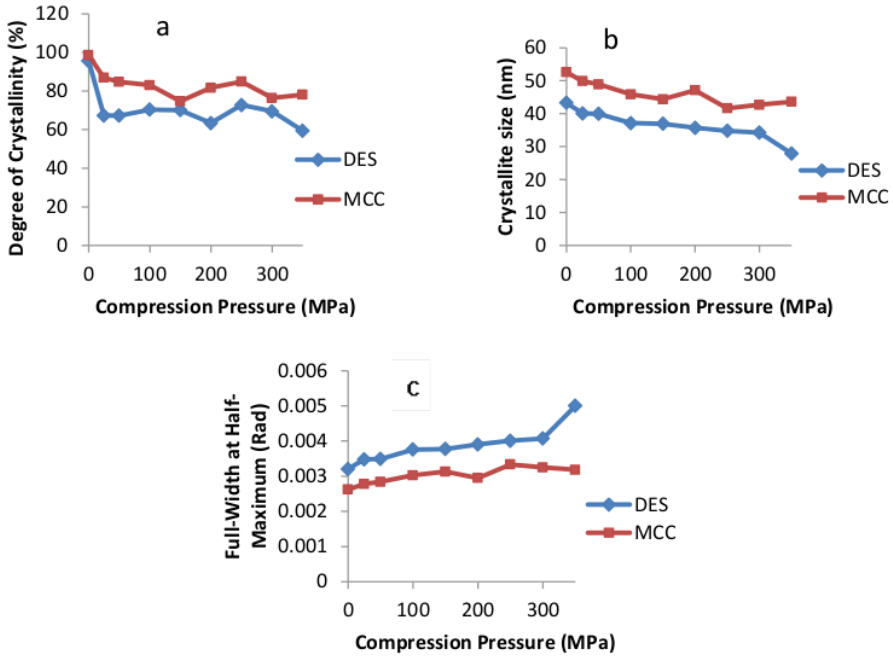

Figure 3. Graph of variation of compression pressure on Desloratadine and Multicomponent crystal against: a. degree of crystallinity, b. Crystallite size, and c. FWHM

The effect of compression on the FWHM value was observed owing to the compression force in which the crystallites are adjacent to each other. The crystallites would be broken and possibly fill the space between the crystallites thus it increased the crystal lattice. As a result, there was a peak broadening that was affected by the size of crystallite and crystal lattice breakdown. The disturbance from the crystal lattice resulted in broadening of the peak with increasing scattering angle (22). The diffraction peaks became lower intensity if there was a decrease in the crystallite size. Decreasing of the crystallite size caused a continuous decrease in the atomic planar region, this could be seen from increasing of FWHM DES and MCC from the diffraction peak.

The further study was to figure out the interactions at the molecular level on the characterization of the material in solid state using FTIR spectroscopy. At the molecular level, intermolecular interactions such as hydrogen bonding and van der Waals interactions were the key factors that are actually responsible for the behavior of molecular crystals. Thus, it was possible to apply vibration spectroscopy to directly investigate intermolecular interactions to reveal the behavior of crystals or solid state properties. FTIR identification pressure was applied on DES or MCC before compression. Vibrational characteristic of MCC was showed carboxylic acid at 1650-1550 cm^{-1} corresponding to the MCC salts from DES and benzoic acid formation. MCC salt formations were reinforced with different FTIR patterns with DES and it is presented in Fig. 4 (DES) and Fig. 5 (MCC). The formation of MCC salt molecules was characterized by dissapearance of stretching C=O from the strong carbonyl at the peak of 1686.82 cm^{-1} and C-O vibration stretching at 1291.40 cm^{-1} of benzoic acid, replaced by the characteristics band of the carboxylic acid salt in 1594,23 cm^{-1} and 1552,76 cm^{-1}. When MCC salt formation occurred deprotonation, the carboxylic anion (-COO-) had only a single stretching vibration (C-O) at 1379.16 cm-1. The use of FTIR was to confirm MCC salt formation by understanding the intermolecular interactions in the compound. The interactions can be identified by the change in the frequency of vibrations of the functional groups that can be seen through FTIR spectra (23). Meanwhile, a peak shifting of carbonyl vibration showed a contribution to forming ionic interaction in MCC formation.

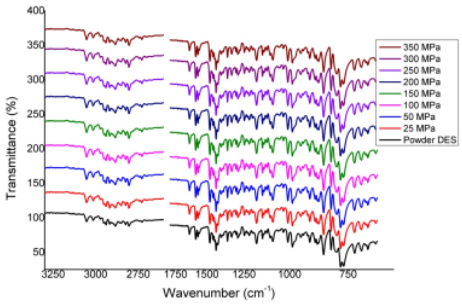

Figure 4. ATR-FTIR spectra desloratadine with compression treatment at various pressures

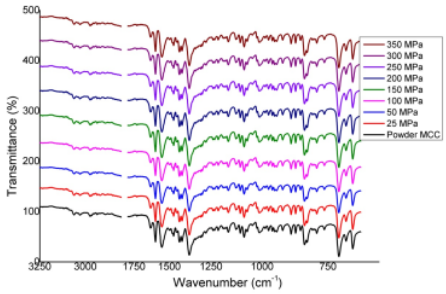

Figure 5. ATR-FTIR spectra multicomponent crystal with compression treatment at various pressures

Based on FTIR results, the DES and MCC were relatively stable at the highest pressure of 350 MPa. FTIR spectra of DES (Fig 4.) and MCC (Fig. 5) showed that there was no change in peak intensity, presence, and absence of a new peak, or peak shifting in certain wavenumbers. The constant condition of vibrational peak indicated a hydrogen bond in crystal structure lattice still intact. However, the greater in the amount of hydrogen bonding formation, the more potential in the formation of slip plane. DES had only one intermolecular hydrogen bond (24), while MCC had 5 hydrogen bonds that occur (14).

DES and MCC tablet was prepared at compression force in the range of 25-350 MPa under controlled conditions i.e. width, diameter, and crushing strength. Furthermore, these parameters were used to evaluate the tensile strength of tablet. Crystal structure of DES and MCC was visualized and determined the ship plane position. Tabletability is an ability of the powder to form a compact mass under a determined compression force. The better characteristic of API, the easier to form a tablet (25). Tabletability of API was determined by function between compression pressure and tensile strength. The previous result showed that MCC had better tabletability characteristic than DES. The tensile strength of MCC increased as a linear function of increasing the compression force. Meanwhile, the DES had a quadratic function as increasing the compression force. Level and strength of interparticle bonding correlated to the rearrangement and deformation of the particle and controlled the material packing of tablet and its mechanical strength. MCC is a plastic material which had easier to form a compact mass than elastic material owing to higher interparticle bonding area.

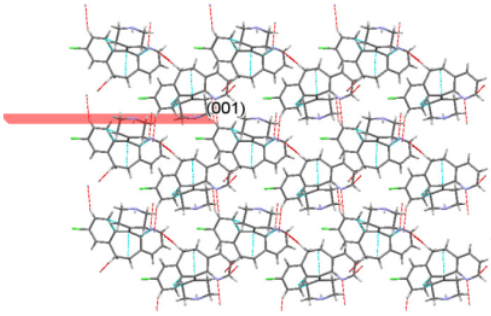

Figure 6. The crystalline structure of desloratadine

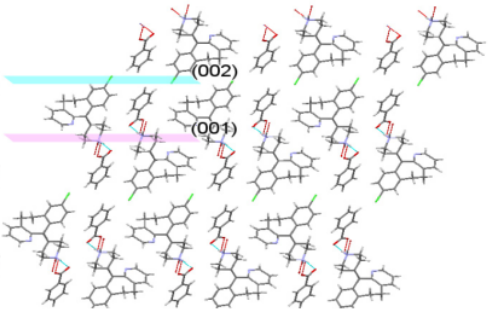

Figure 7. The crystalline structure of multicomponent crystal

DES and MCC had different functionality correlated to the hydrogen bonding in their crystal structure. DES had monoclinic crystal but MCC had a triclinic crystal. MCC had potential slip planes with higher d-spacing and DES did not. Therefore, as the structural point of view,

Tabletability of MCC was better than that of DES. In addition, the crystal structure was important to compare the crystal structure of DES and MCC. Crystal structure of DES consisted of a corrugated weak hydrogen bonding (C-H ….N) which predicted in response a force though rough plastic deformation owing to the rigidity (Figure 6). However, in MCC structure, the presence of layered structure provided the tentative explanation to enhance tabletability (Figure 7). Formation of layered structure proved that a significant enhancement of tabletability was observed in several drug-multicomponent crystals (26,27). Moreover, the presence of slip plane consisted of a weak hydrogen bonding facilitated cutting of structure and layered structure slide easily.

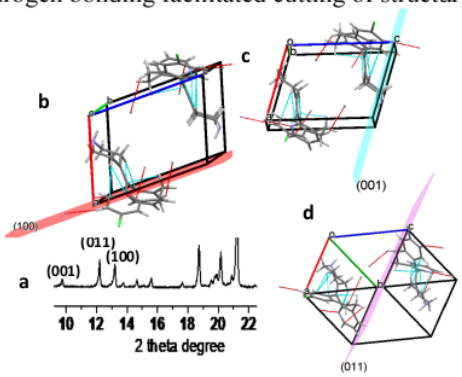

Figure 8. Potential slip planes in desloratadine crystals of intermolecular interactions (a) powder X-ray diffraction pattern of desloratadine (b), (c), (d). planes represent of crystal lattice hkl (011), (001) and (011) respectively

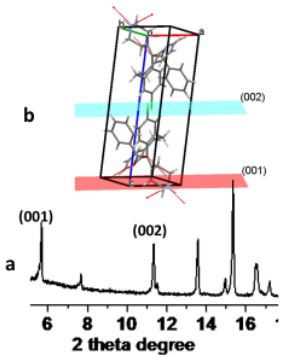

Figure 9. Potential slip planes in multicomponent crystals of intermolecular interactions (a) powder X-ray diffraction pattern of multicomponent crystals (b). planes represent of crystal lattice hkl (001) and (002)

Figures 8a and 9a are presented diffractogram of DES and MCC without compression with hkl information. Figure 8. b-d and 9b are presented a simulation of DES and MCC in crystal lattice structure. Simulation result from single crystal structure was performed by Mercury 3.7 software. DES had a candidate slip plane in hkl (100), (010), and (001). At hkl (100), this plane correlated or separated DES molecule in cellular unit, thus it was impossible as a slip plane. Although, hkl (011) and (001) was enabled as slip plane because C cyclic and -NH- in the DES structure was correlated to the H of the other DES molecules. In addition, MCC had slip plane in hkl (002) and (001). There was no hydrogen bonding between lattice structure. Therefore, a (002) plane was responsible for the slip plane which occurred plastic deformation during compression.

Depending on this condition, DES had no slip plane as good as MCC. As consequence, tabletablity of MCC was better than that of DES. Moreover, slip plane of DES smaller than that of MCC. The greater slip plane, the stronger interlocking force thus a high breaking force was needed. In DES, potency assumed slip plane (001) had smaller than slip plane MCC (002). It could be observed from crystal structure in length of each axis in planes.

The deeper analysis of crystal structure of DES and MCC provided important information of this phenomenon. Presence of correlation of PXRD, ATR-FTIR, and single crystal XRD proved that XRD results of DES and MCC had symmetrically shifting in crystal lattice structure, thus no significant shifting of vibrational peaks was observed owing to a similar dipole moment in structures. This reason explained no significant alteration of intensity in FTIR peaks. Although, the MCC could improve the tabletability of DES. However, the alteration occurred physicomechanical owing to the slip plane in the crystal structure lattice. Therefore, no vibrational interaction was observed during compression under different compression forces.

Conclusion

Study of compression force effect on the crystallinity of DES and MCC has been studied. The crystallinity of DES and MCC in which was described by crystallinity degree and size and FWHM showed a little alteration. In addition, the FTIR spectra were not altered. Therefore, the crystallinity of DES and MCC was not affected by compression force and it dominantly affected by slip plane in crystal lattice structure.

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