The effect of compression on solid-state properties of desloratadine and multicomponent crystal

Ahmad Ainurofiq 1,2 *, Rachmat Mauludin 1, Diky Mudhakir 1, Sundani Nurono Soewandhi 1

1 School of Pharmacy, Institut Teknologi Bandung, Ganesha 10, Bandung, 40132, Indonesia
2 Department of Pharmacy, Sebelas Maret University, Ir. Sutami 36A, Surakarta, 57126, Indonesia
* Corresponding author. E-mail address: rofiq@mipa.uns.ac.id (A.A.); Tel. +62271663375; ORCID No: 0000-0003-2880-5321.

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ABSTRACT: Tablet pharmaceuticals manufacturing process involves several processes i.e. granulation, drying, milling, and compression. This study was conducted to determine the effect of compression of desloratadine (DES) and multicomponent crystal (MCC), which is a salt from DES, on their solid-state properties. A compression method for tablet formation was conducted using a hydraulic pressure machine with punch diameter of 13 mm. Both DES and MCC were made into tablets with the same tensile strength, which is 1.36 MPa. DES and MCC powder and tablet were each evaluated for their physicochemical properties, including analysis of powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and tablet dissolution. PXRD diffractogram analysis results on DES and MCC showed that the degree of crystallinity decreased after the compression process. There were no polymorphic transformation in DES and MCC after compression. DSC analysis showed a decrease of enthalpy after DES and MCC are compressed. FTIR showed the same spectra pattern for DES and MCC powder and tablet. The SEM scans showed a tendency for interparticle attachment in DES tablets and none in MCC tablets. Meanwhile, dissolution, as indicated by dissolution efficiency, is only slightly decreased due to the compression process. DES and MCC analysis, all characteristics indicated changes of physicochemical properties after compression pressure, but those changes did not affect their dissolution results.

KEYWORDS: Desloratadine; multicomponent crystal; compression; solid-state properties; dissolution.

1. INTRODUCTION

The most common pharmaceutical products are in the dosage form of tablets. The production of tablets includes the process of mixing, drying, milling, extrusion, fluidization, granulation, compression, and coating. Compression process often leads to change the properties of active pharmaceutical ingredients, such as particle size, specific surface area, crystallinity, polymorph or crystal habit [1-2]. The effect of compression pressure on crystals during the manufacturing process can cause changes and disorder in the crystal, which affect deformation variation and fracture of solid powder physical properties [3-5]. Meanwhile, parameters such as morphology, melting point, solubility, and stability are dependent on the formation of crystals from drugs [6].

Desloratadine (DES) is a histamine H1 selective antagonist receptor that is widely used for anti-allergy and anti-inflammatory as a treatment option because it has no effect on the central nervous system, cardiovascular disorders [7-9]. DES is problematic physicochemically with poor tabletability property, which is resolved by the formation of multicomponent crystal (MCC) in the form of salt [10-12]. The Structures of DES and MCC are shown in Figure 1a,b, respectively. DES is a weak base with pKa value of 8.65 [13]. DES is made into a MCC with benzoic acid (BA) in an equimolar ratio, using the solvent evaporation method dissolved in methanol [14]. The formation of MCC can be used to change the physicochemical properties of drugs by rearrangement of molecules to form a new crystal structure and control the molecules arrangement in the crystal lattice [10].

Variations in solid-state properties of active pharmaceutical ingredients (API), including DES and MCC will have an impact on manufacturing success from drugs formulation and therapy [15]. Crystallinity in several drugs is highly related to compression pressure, while tablet dissolution property is reported to be
affected by the degree of crystallinity. Therefore, a consideration is needed to understand the response of solids to mechanical treatment during production.

There are several results of research on mechanical studies in the tableting process, but there is little research on the physicochemical changes caused by compression pressure due to tableting [16]. There are no reports that revealed the effect of compression on the characteristics of the solid-state of DES and its MCC salt form. MCC as a result of new crystal finding is very necessary to be performed a pre-formulation study. This study was aimed at determining the effect of compression pressure on physicochemical properties, i.e., interparticle attachment, degree of crystallinity, and dissolution of DES and MCC. It is important to investigate the effect of compression pressure due to tableting on physicochemical properties and dissolution effects, which may cause changes in dissolution due to the pharmaceutical preparation process.

2. RESULTS AND DISCUSSION
2.1. Physicochemical Properties Evaluation
2.1.1. Powder X-ray diffraction (PXRD)

PXRD is a useful method to determine the existence of polymorphism, amorphous phase, crystallinity and modification of crystal habit in solid drugs. Diffractogram from DES and MCC before (powder) and after (tablet) compression process are presented in Figure 2. Compression treatment was observed at 2θ angles between 5° to 45° did not change the peak position of DES and MCC, which indicated that there was no polymorphic transformation that occurred in DES and MCC after compression process. This was shown by changes in crystallinity as listed in Table 1. The degree of crystallinity of DES decreased by 9.3%, while MCC decreased by 6.4% after compression.

Crystallinity is defined as the degree of structural order in solid, shown in fraction or percentage as a measurement of how likely atoms or molecules are arranged in a crystal pattern. PXRD is commonly used as
a standard method to measure crystallinity [13,17]. The reduction of the degree of crystallinity was lower in MCC compared to DES. However, the overall changes of crystallinity were relatively slight after compression where pressure during compression did not cause amorphization of those two crystals. This result was in accordance with a study regarding microcrystalline cellulose [18], aspirin, and nicotinic acid [19], which showed a decrease in the degree of crystallinity because of the effect of compression pressure. During compression, solid particle rearranges followed by deformation, fracture and fragmented to compact mass which affects by molecular arrangement in crystal lattice and interaction intermolecular. Reducing of intensity diffractogram showed a crystal defect. Tendency of a decrease in the degree of crystallinity was assigned by boarding of peak and reducing its intensity. This result probably was affected by formation of amorphous in which the degree of crystallinity reduced after compression pressure.

Table 1: Degree of crystallinity for desloratadine (DES) and multicomponent crystal (MCC)

<table>
<thead>
<tr>
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<th>Degree of crystallinity (%)</th>
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<tr>
<td></td>
<td>Powder</td>
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<tr>
<td>DES</td>
<td>86.5</td>
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<tr>
<td>MCC</td>
<td>77.1</td>
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</table>

2.1.2. Differential scanning calorimetry (DSC)

DSC methods measured crystallinity from fusion heat which quantified energy related to molecular interactions in the crystal. However, the same dislocation molecule still needs energy to break the interaction of remaining lattices when it melts, thus contributing to crystallinity which is measured using the DSC method [13,17]. Thermal analysis results from the effect of compression treatment on DES and MCC are presented in Figure 3. DES powder showed an endothermic peak at 157.0 °C, which requires heat of 172.2 kJ/g and DES tablet showed an endothermic peak at 160.3 °C, which requires heat of 127.8 kJ/g. Meanwhile, MCC powder has an endothermic peak at 175.6 °C, which requires heat of 169.7 kJ/g and the MCC tablet has an endothermic peak at 178.2 °C, which requires heat of 135.1 kJ/g.

![Figure 3](https://doi.org/10.12991/jrp.2018.99)

Figure 3. Thermograms of a. desloratadine (DES) powder; b. DES tablet; c. multicomponent crystal (MCC) powder; d. MCC tablet.

DSC is a characterization method based on thermodynamic properties that occur in the samples by observing heat energy produced, which can be observed from the endothermic and exothermic peaks in the DSC thermogram. The decrease of this enthalpy indicated a decrease in crystallinity caused by the tableting compression process. Therefore, heat energy required to melt DES and MCC was lower in tablet than in powder. The decrease of crystallinity affected thermal behavior, where heat energy of DES and MCC decreased after the compression process.

2.1.3. Fourier transform infrared (FTIR) spectroscopy

A common method used to characterize drugs is infrared spectra. Infrared spectroscopy (FTIR) analysis is conducted to identify a functional group in compounds. FTIR are sensitive to component
structure and conformation and can be used to compare structures of components in different solids. Characterization of infrared spectroscopy from DES and MCC powder and tablet is presented in Figure 4. There were no changes observed between functional groups of DES and MCC powder and tablet, which indicated that there were no changes to the crystal substance and chemical structures after the compression process. Because of its sensitivity, this instrument is useful for characterizing pharmaceutical crystals. FTIR spectra after compression show broad peaks when experiencing changes in amorphous form with decreasing degree of crystallinity [20-21], but this study did not show changes in the peak, which showed a low decrease of crystallinity that can only be observed by PXRD and DSC analysis. Principally, absorption of FTIR band before and after compression showed similar features.

![FTIR spectra](image)

**Figure 4.** FTIR spectra of a. desloratadine (DES) powder; b. DES tablet; c. multicomponent crystal (MCC) powder; d. MCC tablet.

2.1.4. **Scanning electron microscopy (SEM)**

![SEM photographs](image)

**Figure 5.** SEM photographs of A. desloratadine (DES) powder; B. surface of DES tablet; C. fragment of DES tablet; D. multicomponent crystal (MCC) powder; E. surface of MCC tablet; and F. fragment of MCC tablet.

That morphology of drug components can be analyzed using SEM [22-23]. SEM is an analysis technique used to observe the changes in particle morphology caused by compression pressure, including
sintering phenomena. Sintering causes an increase in particle size, adhesion occurs between nearby particles. SEM observation was performed on the surface and fragment parts of the tablet, which are presented in Figure 5. In 500x magnification, the attachment between DES particles was clearly observed. Fragment parts of the DES tablet showed sintering, which is the loss of surface margin because of particles merging, where primary particles are gone with compression force and showed slight fragments from the sintering. The DES tablet surface showed a sintering effect on the size of particles and morphology. Meanwhile, fragment parts of MCC tablet showed particles that did not attach to themselves while the surface parts of the MCC tablet showed small particles with no evidence of merging to bigger particles. DES showed a weak sintering effect because particle merging still occurred, which increases the size, but has not yet reached the closing of most pores.

2.2. In vitro dissolution studies

Observation of dissolution profile was performed on DES and MCC tablets in a dissolution medium of 0.1 N HCl and water. Results of dissolution test of DES and MCC tablet are presented in Figure 6. The curve showed the percentage of dissolution tablet was higher in MCC than DES for 1 hour on both dissolution medium. The effect of compression in this study was compared with the dissolution of DES and MCC powder thus produced dissolution efficiency (DE) value is presented in Table 2. Effect of compression reduces the DE value from MCC and DES after being compressed to tablet form compared with before compression for all dissolution mediums. However, the decrease varied from the lowest at 2.06% DES in HCl medium, 2.36% DES in a water medium, 2.38% MCC in HCl medium, and the highest at 7.99% MCC in a water medium.

![Figure 6. Dissolution profiles of desloratadine powder (green), desloratadine tablet (red), multicomponent crystal powder (black) and multicomponent crystal tablet (blue) in water (solid lines) and 0.1N HCl (dashed lines) dissolution media.](image)

The dissolution decrease occurred in tablets because during compression to form a tablet, dissolution medium may penetrate tablet pores, which can cause tablet breakage to form powder before dissolving. The mechanism of dissolution of DES and MCC tablet takes a longer time because the tablet is a combination of interparticle attachments, which take a longer time to reform to powder. Therefore, the decrease of dissolution in this study was still a reasonable amount not because of sintering phenomena (the loss of tablet surface margin) [24]. Meanwhile, the factor of degree of crystallinity decrease, which increases dissolution or the other way around [25] did not occur here, but what happened was a degree of crystallinity decrease and a decrease in dissolution. Therefore, the crystallinity factor has no effect on dissolution.

<table>
<thead>
<tr>
<th>Table 2: Dissolution efficiency of desloratadine (DES) and multicomponent crystal (MCC)</th>
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<tbody>
<tr>
<td>Dissolution Medium</td>
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<tr>
<td></td>
</tr>
<tr>
<td>DES in water</td>
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<tr>
<td>MCC in water</td>
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<tr>
<td>DES in 0.1N HCl</td>
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<tr>
<td>MCC in 0.1N HCl</td>
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</table>
3. CONCLUSION

The results of this study regarding the effect of tablet compression on physicochemical properties and dissolution of DES and MCC salt showed that there was a decrease of crystallinity before and after undergoing the tablet compression process. Compression to tablet form decreases the enthalpy of DES and MCC. The tableting process caused interparticle merging, which occurred with DES but did not occur with MCC. The dissolution only showed small decreasing changes after being compressed. Confirmation of those physicochemical characterizations showed that there was an effect of compression, but it showed no effect on dissolution.

4. MATERIALS AND METHODS

4.1. Materials

Desloratadine (pharmaceutical grade) was purchased from Xi’ An Wango Biopharm Co., Ltd., (Shaanxi, China). Benzoic acid (analytical grade) and hydrochloric acid (analytical grade) were obtained from Merck (Darmstadt, Germany). Methanol (analytical grade) was obtained from J.T. Baker, Inc (NJ, USA).

4.2. Multicomponent crystal (MCC) preparation with solvent evaporation

An equimolar mixture of 1 mmol DES and BA was dissolved in methanol at 35 °C. Formation of MCC salt was carried out using the rapid solvent evaporation method using a Buchi Rotavapor R-215 (Flawil, Switzerland) at 50 °C, continued with Buchi Heating Bath B-491 (Flawil, Switzerland) and vacuumed at 208 mbar pressure using a Buchi vacuum controller V-850. The solid material obtained was collected and made into a tablet.

4.3. Formation of a tablet

DES tablet formation was done by accurately weighing powder to 500.0 ± 2 mg, and MCC was equivalently scaled to 696.4 ± 2 mg and then placed into a 13 mm diameter tableting die and compressed in 150 MPa pressure for DES and 25 MPa for MCC to produce the same tensile strength which is 1.36 MPa using hydraulic press machine (Perkin Elmer, MA, USA) [10]. Performed on the same tensile strength 1.36 MPa, because it can to compensate the weighted variables that will be dimensions so that the variables can be controlled and the evaluation results can be valid. Before use, each die, upper, and lower punch was lubricated with a thin layer of magnesium stearate powder using a brush.

4.4. Physicochemical Properties Evaluation

4.4.1. Powder X-Ray diffraction (PXRD)

A sample was placed on the X-ray diffractometer stage. The PXRD pattern was obtained from characterization using Bruker D8 Advance X-Ray Diffractometer (WI, USA) using Cu-ka radiation (λ = 1.5406 Å), 40 kV voltage and 35 mA current. The scan was performed at a rate of 2°/minute with a diffraction angle of 2θ from 5 to 60° and intensity interval of 0.02°. Subsequently, formed diffraction peaks were compared. Crystallinity analysis was performed by plotting X, Y which are 2θ vs intensity, respectively, using OriginPro 9.0 software. Smoothing was conducted by taking 15 points with adjacent averaging methods. Afterwards, a straight line was subtracted to make Y = 0. A change in crystal pattern was compared from crystalline component peak area ratio with total peak area which is a measure of the degree of crystallinity (%) as measured using OriginPro 9.0 software [6].

4.4.2. Differential Scanning Calorimetry (DSC)

Characterization of DSC was performed using LINSEIS STA PT-1600 (NJ, USA) which was calibrated for cell constant and temperature using indium. The following parameters were used: temperature 25-500 °C under a nitrogen purge 100 mL/min, heating rate of 10°/min, Al2O3 crucible; and 2-5 mg samples were placed into the pan.

4.4.3. Fourier transform infrared (FTIR) spectroscopy

IR spectrum sample identification was performed using FTIR IR Prestige-21 Shimadzu (Kyoto, Japan) analyzed in the wavenumber range 4000-400 cm⁻¹ with 2 cm⁻¹ resolution. Afterwards, the obtained spectrum peaks were compared. Intensity and shifting of vibrational peaks was observed.

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4.4.4. **Scanning electron microscopy (SEM)**

Each tablet surface and fragment were placed into a sample holder and layered with 2.5 nm gold using HITACHI MC1000 ION SPUTTER (Tokyo, Japan). Samples layered with gold were subsequently placed in the specimen chamber of a HITACHI SU3500 scanning electron microscope (Tokyo, Japan) and observed on host computer for proper image and magnification. Voltage and current were set at 5 kV and 10 mA. The photomicrograph of surface morphology and cross-section of tablets DES and MCC were compared.

4.5. **In Vitro dissolution studies**

Dissolution experiments were conducted with DES and MCC tablets which were placed into a dissolution vessel with 0.1 N HCl and water medium 900 mL, with temperature of 37 ± 0.5 °C, stirring rate at 50 rpm, using Hanson Virtual Instruments SR8Plus Dissolution test station (Hanson Research, CA, USA) according to USP apparatus II (paddle method). 5 mL samples were taken at 5, 10, 15, 20, 30, 45, and 60 minutes time intervals, then changed with 5 mL of new dissolution medium. Aliquots were filtered using 0.45 μm filter membrane and its content was analyzed using Beckman Coulter DU®720 General Purpose Spectrophotometer (CA, USA) at a validated wavelength of 290 nm. Resulting data were analyzed to obtain dissolution efficiency (DE).

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**Conflict of interest statement:** The authors declare no conflict of interest.

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