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Research Article

Evaluation of Thermal-Induced Polymorphic Transformation on Desloratadine and Desloratadine-Benzoic Acid Salt

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Abstract

Background: Active pharmaceutical ingredients face a challenge in manufacturing due to adverse physicomechanical properties. Desloratadine (DES) form I exhibits poor mechanical behavior through the formation of capping during the tableting process. Salt formation from DES and benzoic acid (BA) has been observed to resolve poor mechanical properties. However, the ability to withstand heat from the manufacturing process should be implemented in DES and DES-BA salt. The aim of this study was to determine the differences between thermal treatment results on DES and DES-BA salt and whether it causes them to undergo polymorphic transformation.

Methods: Salt was crystallized between DES and BA using the solvent evaporation method. DES and DES-BA salt were heated at 110°C, 159°C (melting point of DES), 181°C (melting point of DES-BA), and 190°C. Following this, characterization was performed using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and solubility testing.

Results: Polymorphic transformation caused by heat occurred in DES, but not in DES-BA salt. The transformation of DES was induced by the effect of heating, which changed polymorph I to a mixture of polymorph I and III at 110°C, to polymorph II at 159°C, and to a mixture of polymorph I, II, and III at 190°C. Under 190°C, DES-BA is still stable and did not undergo a polymorphic transformation. However, at 190°C, decomposition started to occur, which implied decreased solubility, which did not occur in DES.

Conclusion: The heating process did not cause DES-BA salt to undergo a polymorphic transformation. However, it caused decomposition at 190°C. DES underwent a polymorphic transformation when exposed to the same condition without decomposition. This provided information to always pay attention to temperature during manufacturing processes that include DES or DES-BA salt to avoid physicochemical changes.

Introduction

To be fabricated, active pharmaceutical ingredients (APIs) require sufficient physicochemical and physicomechanical properties regarding the manufacturing process, bioavailability, and stability.[1-3] Desloratadine (DES), which was used in this study, has several benefits in treating inflammation, urticaria, and rhinitis allergy.[4-6] However, it has poor mechanical behavior, which complicates the formulation process due to the formation of capping during the tableting process. Crystal engineering was conducted to produce a DES multicomponent crystal in the form of salt from DES and benzoic acid (BA), which does not retain the same poor physicomechanical properties.[7] The results of crystal engineering can be seen in Figure 1, showing the changes to the DES monoclinic crystal system in the DES-BA salt in the triclinic form. In addition, the DES crystal cell unit has a corrugated hydrogen bonding structure that makes it difficult to tablet into, whereas the DES-BA salt crystal system forms a slip plane (001) that forms a layered structure arrangement, allowing good tabletability.[8]

In general, the manufacturing process of pharmaceutical preparations involve treatments such as mixing, dissolution, heating, recrystallization, grinding, granulation, drying, compression, and storage.[9-11] These processes often involve energizing the system, which can cause polymorphic transformation.[12,13] The condition of crystal solids is indicated by certain internal and external structures. Habit describes the external structure, while polymorphic form describes the internal structure. Differences in morphology or habit do not always represent polymorphism. This is because basic cell crystallization can take place in each

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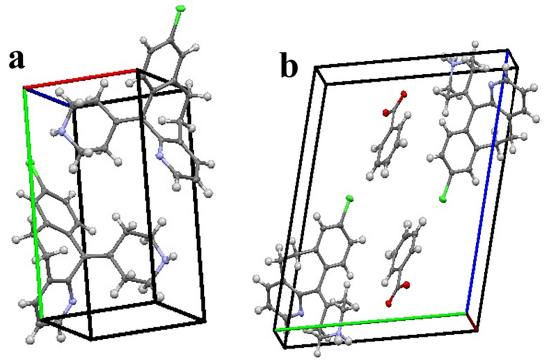

Figure 1. Crystal system: a) Desloratadine (DES) form I, b) desloratadine-benzoic acid (DES-BA) salt.[14]

of the three-axis directions. Therefore, a substance can produce various morphological forms without undergoing any changes to its crystal structure as a consequence of different growth directions. To date, no studies have examined the effect of heat on the solid-state characteristics of DES substance and DES-BA salt. Therefore, a study on the effect of heat should be conducted on DES and DES-BA salt for the anticipation of any complications during formulation caused by changes in physicochemical properties. Variations in the physicochemical properties of APIs affect the manufacturing success of therapies and drug formulations.[15]

Currently, there is information on various polymorphic forms of DES, i.e. form I and II[16], form III and V[17], and form A and B.[18] Brittain (2016) stated that polymorphic changes (transformations) are characterized by differences in the physical properties of a substance, such as specific gravity, optical properties, energy content, mechanical and kinetic properties, surface tension, spectroscopy, and thermodynamics, which in turn will affect the stability, bioavailability, and toxicity of pharmaceutical preparations.[19] A polymorph of a substance has the same chemical composition but a different internal structure, which can form various crystal structures.[20,21] Structural characterization and physicochemical analysis of the polymorphic form enable certain important molecules to be developed via a reliable procedure and reproduced in a specific polymorphic formation.[22]

Materials and Methods

Materials

Desloratadine (pharmaceutical grade) of polymorphic form I was bought from Xi'An Wango Biopharm Co., Ltd., (Shaanxi, China). Benzoic acid (analytical grade) and chloric acid (analytical grade) were both obtained from Merck (Darmstadt, Germany). Methanol (analytical grade) was obtained from J.T. Baker, Inc. (NJ, USA).

Crystallization of desloratadine-benzoic acid (DES-BA) salt

An equimolar mixture of DES and BA was dissolved in methanol at 35°C until a clear solution, known as DES-BA salt, was produced. The resulting solution was evaporated using Buchi Rotavapor R-215 (Flawil, Switzerland) at 50°C, followed by Buchi Heating Bath B-491 (Flawil, Switzerland) and aspirated at 208 mbar using Buchi V-850 vacuum controller. The powder obtained from the DES-BA salt multicomponent crystal was collected and stored at room temperature for further analysis.

Heat treatment on DES and DES-BA salt

DES and DES-BA components (1.5 g of each) were inserted into three different vials. Consecutively, each vial was heated at three different temperatures for 10 minutes: 110°C, 159°C (melting point of DES), 181°C (melting point of DES-BA), and 190°C. The six vials were then allowed to cool. Following this, characterizations using powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and solubility testing in water and 0.1 N HCl were performed.

Solid-state characterization of desloratadine and DES-BA salt

Powder X-Ray diffraction

PXRD analysis was used to characterize DES and DES-BA salt samples based on diffraction angle (2θ). PXRD pattern was obtained from characterization using Bruker D8 Advance X-ray diffractometer (WI, USA) with Cu-kα radiation (λ 1.5406 Å), at 40 kV voltage and 35 mA current. Each sample was scanned at 2°/min speed with a 2θ diffraction angle from 5–60° and 0.02° intensity interval. The peak of diffraction between samples was then compared.

Differential scanning calorimetry

DSC characterization on DES and DES-BA salt was performed using LINSEIS PT-1600 (Robbinsville, NJ), which was calibrated for cell constant and temperature using indium. The following parameters were used: temperature at 25–400°C, heat rate of 10°C/min under dynamic nitrogen atmosphere of 100 mL/min, and around 2–5 mg weight inserted to an aluminum saucepan, with an empty aluminum saucepan used as a reference. The crystal thermal profile was conducted by analyzing the endothermic or exothermic peaks obtained.

Fourier-transform infrared spectroscopy

Identification of DES and DES-BA salt sample spectrum was conducted using FTIR using IR Prestige-21 Shimadzu (Kyoto, Japan) and analyzed within wave number of 4000–400 cm^{-1} with 2 cm^{-1} resolution. Each spectrum peak obtained was then compared. The intensity and shifting of the vibration peak were observed.

Scanning electron microscope

A few DES and DES-BA samples were placed on a sample holder and coated in 2.5 nm gold using Hitachi MC1000 Ion Sputter (Tokyo, Japan). The gold-coated samples were

then placed on a specimen chamber of Hitachi SU3500 SEM (Tokyo, Japan) and observed on the host computer to be captured at a proper magnification. The voltage was set at 5kV and the current at 10mA.

Solubility

The solubility testing of DES and DES-BA salt was performed using water and 0.1 N HCl. Excess samples were inserted into a vial containing 10 mL of liquid media, then mixed using an orbital mixer (120 Hz, 37 ± 0.5°C) for 48 hours until the equilibrium condition was achieved. The resulted solution was filtered using a 0.22 µm nylon filter (Whatman, USA). Consecutively, the level was analyzed using Beckman Coulter DU720 (CA, USA) spectrophotometer at 290 nm wavelength, after analysis validation.

Results and Discussion

Active Pharmaceutical Ingredients (APIs) can undergo solid transformation via the influence of thermal energy.[23,24] In general, APIs are relatively stable at room temperature. However, in the manufacturing process, high heat energy can occur due to milling, drying, granulation, and compression. To characterize these effects, experimentation with the following high temperatures is carried out: 110°C is under the melting point of the compounds, melting point of DES is 159°C, melting point of DES-BA salt is 181°C, and 190°C is above the melting point of both compounds. Temperature conditions were selected to determine whether or not the polymorphic transformation of DES and DES-BA salts are characterized by using PXRD, DSC, FTIR, SEM, and solubility testing. All tests compared DES and crystallized DES-BA salt to determine the difference between the two.

The PXRD diffractogram of the thermal effect on DES is shown in Figure 2. The thermal effect caused the polymorphic transformation of DES from polymorph I to another polymorph. The data presented as a reference is in relation to DES polymorph I (black; a) having diffraction characteristics with 2θ degrees scattered angles at 9.77°, 13.22°, 15.53°, 17.59°, 21.21°, 25.25°, 26.31°, 27.88°, and 29.37°. Whereas the reference DES polymorph III (green; e) has a specific diffraction angle of 2θ at 10.50°, 14.21°, 18.00°, 19.06°, 19.56°, 22.44°, 23.10°, 24.18°, 27.48°, and 29.03°.[25] At a treatment temperature of 110°C, the diffraction pattern showing the preferred orientation effect is a mixture of polymorphs I and III (red; b) with diffraction that appears at 13.22°, 19.56°, 21.21°, 24.18°, 25.25°, 26.31°, 27.48°, 27.88°, and 29.37°. The diffraction pattern with a treatment temperature of 159°C caused it to consistently form polymorph II (blue; c) with a diffraction angle of 2θ specific at 12.15°, 12.98°, 14.62°, 18.66°, 22.36°, 23.02°, and 29.12°. The treatment temperature of 190°C formed a diffraction pattern that is a mixture of polymorphs I, II, and III (pink; d) with characteristic diffraction angles of 2θ at 10.50°, 12.15°, 14.62°, 15.53°, 17.59°, 18.00°, 22.44°, and 29.12°.

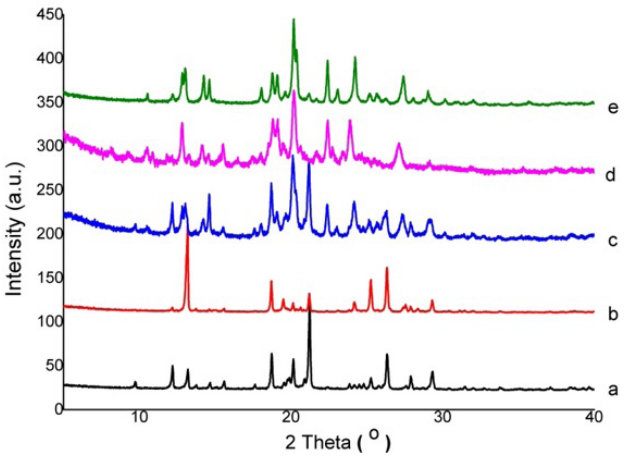

Figure 2. Diffractogram of DES PXRD on: a) polymorph I without treatment, b) after heating at 110°C, c) after heating at 159°C, d) after heating at 190°C, e) polymorph III without treatment.

A different condition occurred in DES-BA salt, which was presented in Figure 3. After heating at 110°C and 181°C, cooling down would form a crystal with an unchanged diffraction peak. However, heating at 190°C resulted in a prolonged melting process, which showed a sticky and oily condition for up to 3 months and difficultly solidifying, which indicated that the material had physically undergone decomposition. Based on the XRD data, DES-BA salt was relatively stable without polymorphic transformation from the heat effect at a temperature under 181°C. Although at 190°C, there were changes to the crystal lattice, especially its amorphous characteristic, marked by an amorphous halo on XRD. Meanwhile, DES was shown to be unstable with polymorphic transformation even after heating at 110°C.

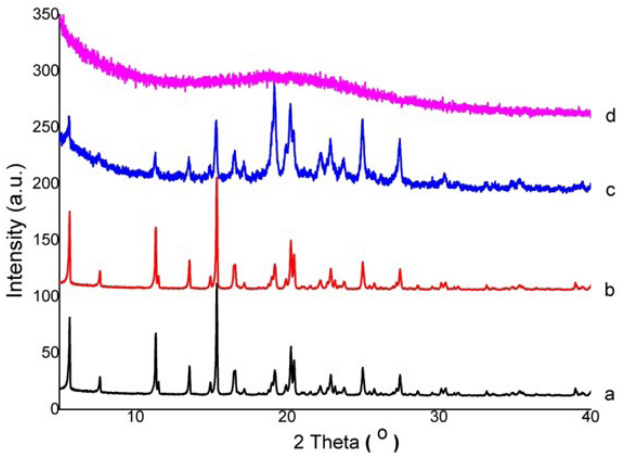

Figure 3. Diffractogram of DES-BA salt PXRD on: a) without treatment, b) after heating at 110°C, c) after heating at 181°C, d) after heating at 190°C.

DSC analysis was used to evaluate changes in the thermodynamic properties of materials that were given heat energy, which involved a recrystallization process, melting, and solid-phase transformation shown by endothermic and exothermic peaks of the thermogram.

The results of DSC on DES and DES-BA salt after heating are shown in Figure 4. The endothermic peak is shown at the melting point of the DES component without treatment and treatment temperatures at 110°C, 159°C, and 190°C were 158.49; 158.12; 158.95; and 153.86°C, respectively, with enthalpy values of -52.80; -52.33; -53.48; and -44.91 J/g, respectively. The thermogram curve before and after heating at 110°C did not show any changes. The effect of heating at 110°C and 159°C showed no changes to endothermic peak and enthalpy, while heating at 190°C reduced endothermic peak and enthalpy, which was not caused by polymorphic transformation but rather by decreased crystallinity to amorphous form, characterized by glass transition at -93.82°C.

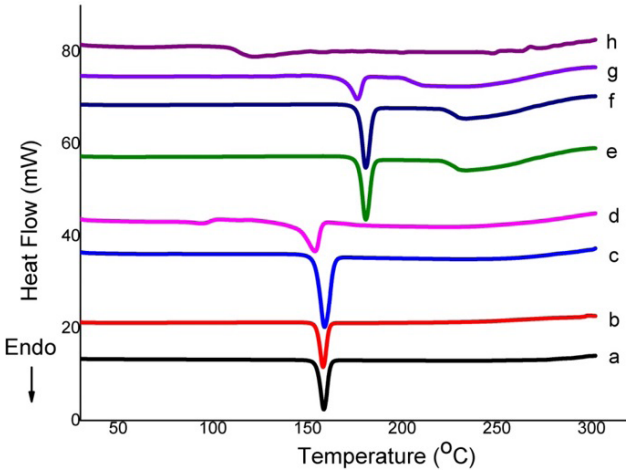

Figure 4. DSC thermogram: a) DES without treatment, b) DES after heating at 110°C, c) DES after heating at 159°C, d) DES after heating at 190°C, e) DES-BA salt without treatment, f) DES-BA salt after heating at 110°C, g) DES-BA salt after heating at 181°C, h) DES-BA salt after heating at 190°C.

The DSC profile of DES-BA salt also showed a shifting of the endothermic peak and enthalpy to the left and showed a decrease in crystallinity, especially due to the effect of heating at 190°C. This can be seen from the endothermic changes of DES-BA salt without treatment and after treatment at 110°C, 181°C, and 190°C, with endothermic peaks of 180.65; 180.17; 176.23; and 122.12°C, respectively, and enthalpy of -46.58; -56.58; -34.77; and -21.04 J/g, respectively. The endothermic peak at 190°C showed a significant deviation, which indicated a significant physical change from DES-BA.

The FTIR observations of DES and DES-BA salt after heating are shown in Figure 5. The FTIR results of DES and DES-BA heated at 110°C, 159°C, and 181°C did not show changes on the spectra pattern for either compound. Furthermore, heating at 190°C showed a widening of the spectra peak for DES and DES-BA salt, which showed decreased crystallinity and an increased amorphous phase.[26] This was also supported by the PXRD and DSC data above, which showed crystallinity decrease. Based on these data, heating could have initiated the amorphous formation and polymorphic transformation but did not change the chemical structure of DES. However, other conditions changed the FTIR spectral pattern of DES-BA salts due to heating at 190°C. This phenomenon is possibly due to the detachment of some BA from the ionic bond of the DES-BA compound, as shown by the reappearance of the characteristic BA spectra in the neutral carboxylic group (-COOH), which has a strong carbonyl (C = O) stretching at the peak of 1686.82 cm^{-1} and weak carbonyl (CO) stretching at 1291.40 cm^{-1}.[7] The BA spectra were combined with existing DES-BA spectra.

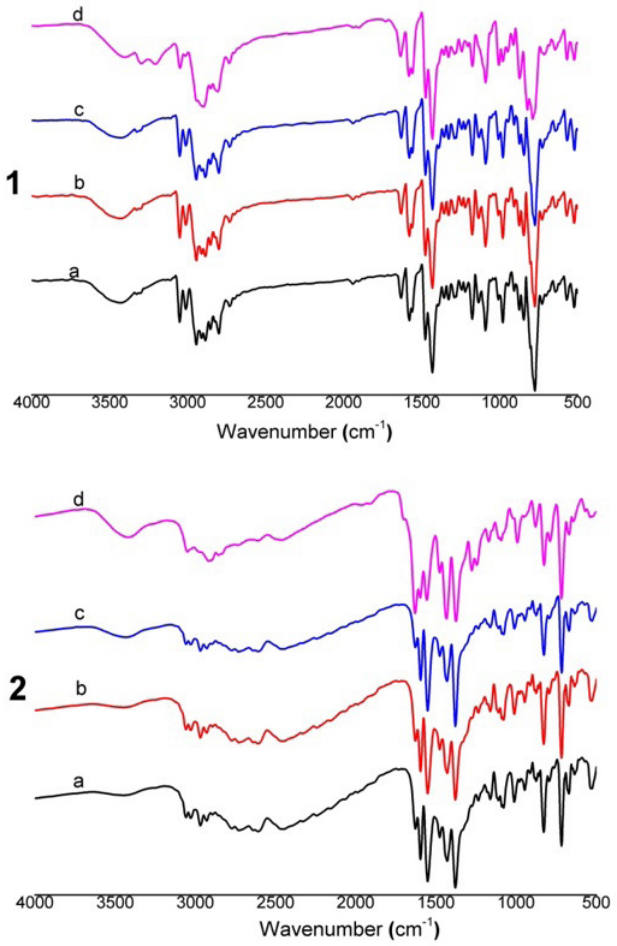

Figure 5. FTIR spectra from: 1. a) DES without treatment, b) DES after heating at 110°C, c) DES after heating at 159°C, d) DES after heating at 190°C, 2. a) DES-BA salt without treatment, b) DES-BA salt after heating at 110°C, c) DES-BA salt after heating at 181°C, d) DES-BA salt after heating at 190°C.

The observations of particle condition visualization, using SEM photomicrograph at 1000x magnification, of the heating effect on DES particles and DES-BA salt are shown in Figures 6 and 7. The images of DES particles at 110°C, 159 °C, and 190°C showed differences. DES particles heated at 110°C still showed large rods, with no changes from the original size. Decreases in size occurred after heating at 159°C. Heating at 190°C showed the formation of particle chunks from a cluster of small particles. These changes in size and shape were caused by the melting and recrystallization process of particles, which transformed

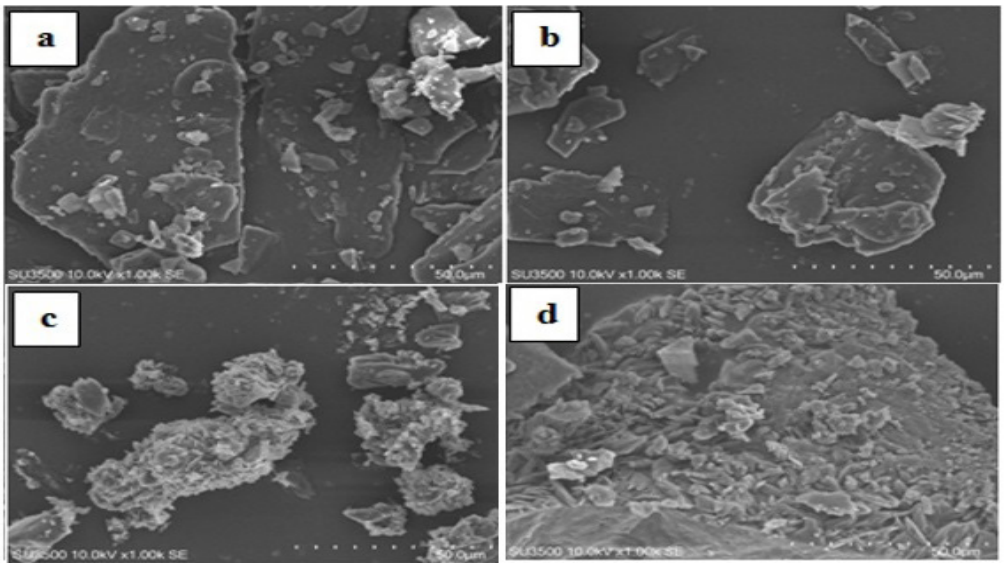

Figure 6. SEM photomicrograph of desloratadine (DES) at various heating temperature: (a) without treatment; (b) at 110°C; (c) at 159°C; and (d) at 190°C. The images are shown at 1000x magnification.

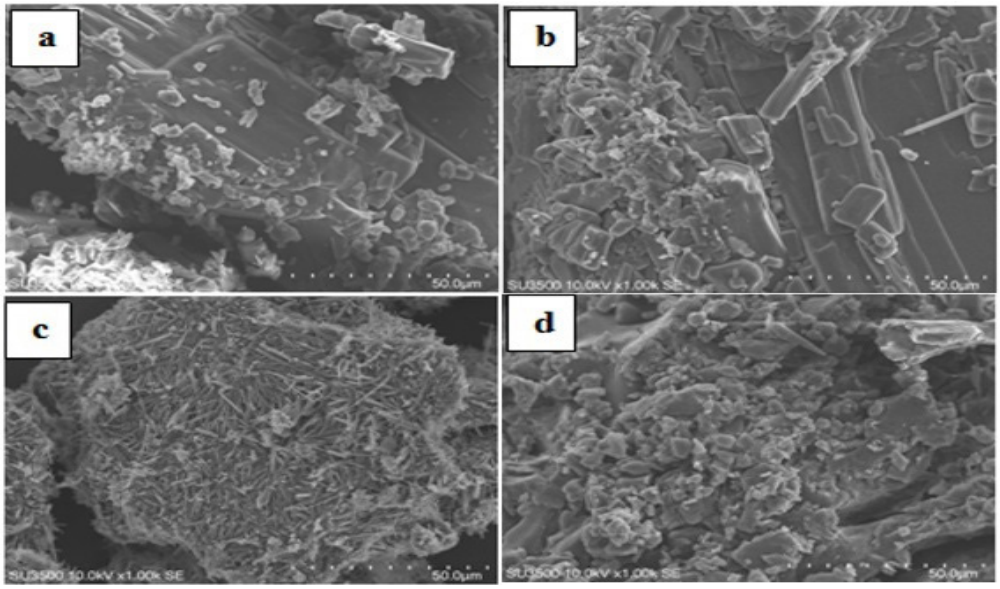

Figure 7. SEM photomicrograph of DES-BA after various heating temperature: (a) without treatment; (b) heating at 110°C; (c) 181°C; and (d) 190°C. All images are shown with 1000x magnification.

into crystals with different sizes and shapes. Furthermore, the particle profile of DES-BA salt showed identical results with DES, i.e., DES-BA salt particles heated at 110°C still showed large rods without changes in shape or size. The sizes became smaller after heating at 181°C, and heating at 190°C created chunks of particles from small clusters of particles. SEM observation was limited to evaluating habit changes of DES crystal and DES-BA salt, and could not differentiate any polymorphic transformation.

The solubility test of DES and DES-BA salt after 48 hours at equilibrium conditions is achieved by testing different times the same results. The solubility data obtained, had previously been evaluated from the remaining dissolved powder with FTIR analysis showing the same spectra data as Figure 5. Before this test could be performed, the stability of both materials after being heated had to be ensured. Based on the results of thermogravimetric analysis studies, DES had begun to experience a weight reduction as an indication of decomposition at 224.7°C, while for DES-BA, this occurred at 193.4°C. The decrease in the stability of DES-BA from DES was due to the fact that, as a component, BA begins to decompose at 129.2°C.[8] Supported by the FTIR data in Figure 5, with all temperature treatments on DES and DES-BA salts relatively stable showing the same spectral pattern, except at a temperature of 190°C, DES-BA salt began to decompose with the emergence of a group (-COOH) from the spectra BA.

Data from the DES and DES-BA salt solubility test results in the water medium and 0.1 N HCl from the effect of heating is presented in Table 1. The solubility of DES in the

water medium by heating at 110°C, 159°C, and 190°C was 0.26±0.01, 0.33±0.01, and 0.80±0.01 mg/mL, respectively. While the solubility of DES in the 0.1 N HCl medium by heating at 110°C, 159°C, and 190°C was 30.28±0.18, 50.55±0.22, and 69.69±0.36 mg/mL, respectively. The solubility increased due to the heating treatment of the material. A drastic increase in the two mediums occurred at 190°C heating. The increase in the solubility of DES was caused more by the declining crystallinity after raising the temperature, based on confirmation of the PXRD, DSC, and FTIR analysis. Therefore, solubility changes were not caused by the polymorphic transformation. In addition, the solubility differences in the water medium were much lower than those in the 0.1 N HCl medium. The DES molecule contains a pyridine nitrogen atom, which has basic characteristics; therefore, the solubility of DES is influenced by the pH value. This is evidenced by the solubility of DES in the 0.1 N HCl medium, which is much higher than that in the water medium. This result shows that the solubility of DES increases with a decrease in pH. The same conditions occur in DES-BA salts. DES is practically insoluble in water, with the formation of salt DES-BA resulting in increased solubility. The cationic and anionic molecules of DES-BA salts have a better affinity for water than DES. As an ionization process occurs in the water medium, DES-BA salt conditions will be protonated in the water medium, which causes increased hydrophilicity, increasing solubility in water.

Table 1. Solubility data of DES and DES-BA salt after various treatment temperatures.

Treatment Temperatures	Solubility (mg/mL) in	
	Water	HCl 0.1N
DES after heating at 110°C	0.26±0.01	30.28±0.18
DES after heating at 159°C	0.33±0.01	50.55±0.22
DES after heating at 190°C	0.80±0.01	69.69±0.36
DES-BA salt after heating at 110°C	13.22±0.04	81.36±0.25
DES-BA salt after heating at 181°C	17.94±0.07	76.00±0.43
DES-BA salt after heating at 190°C	1.28±0.01*	4.69±0.02*

*decomposition

The results of DES-BA salt solubility in the water medium with heating at 110°C, 181°C, and 190°C was 13.22±0.04, 17.94±0.07, and 1.28±0.01 mg/mL, respectively. DES-BA salts solubility in 0.1 N HCl medium with heating at 110°C, 181°C, and 190°C was 81.36±0.25, 76.00±0.43, and 4.69±0.02 mg/mL, respectively. For both mediums, higher levels of heating led to lower solubility. Solubility changes that occurred in DES-BA were not associated with polymorphic transformation because the transformation did not occur in DES-BA. The drastic decrease in solubility after heating at 190°C was triggered by DES-BA salt, which had undergone decomposition due to heating, and its decomposition increased after it was dissolved in aqueous medium and 0.1 N HCl. The equilibrium solubility of a crystal salt depends on its components in the solution phase when the crystal salt dissociates into its components in the solution. A slight excess of the constituent component or excess residue can be due to an impurity in the crystal structure, which can significantly change the solubility.[27] A significant decrease in solubility of DES-BA salts occurs due to the detachment of BA from DES-BA bonds. Based on FTIR observations, BA was detached with a 190°C heating. BA that has been detached will disturb the equilibrium, causing the solubility to dramatically decrease.

Conclusion

The heating effect causes polymorphic transformation on DES from polymorph I to a mixture of polymorph I and III after heating at 110°C, to polymorph II after heating at 159°C, and a mixture of polymorph I, II, and III after heating at 190°C. Crystallization of DES-BA salt provided benefits in improving resistance to heat on polymorphic transformation up to under 190°C. Meanwhile, decomposition occurred at 190°C. The results of this evaluation provided information to anticipate during manufacturing processes that use DES or DES-BA salt to always pay attention to the influence of heating, which could change the physicochemical properties of the ingredients.

Acknowledgments

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Conflict of Interest

The authors declare they have no conflict of interest.

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