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Original Article

Synthesis, characterization, and stability study of desloratadine multicomponent crystal formation

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Abstract

This study describes the formation of multicomponent crystal (MCC) of desloratadine (DES). The objective of this study was to discover the new pharmaceutical MCC of DES using several coformers. The MCC synthesis was performed between DES and 26 coformers using an equimolar ratio with a solvent evaporation technique. The selection of the appropriate solvent was carried out using 12 solvents. The preview of the MCC of DES was performed using polarized light microscopy (PLM). The formation of MCC was confirmed using powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), fourier transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM). The accelerated stability of MCC at 40 °C and relative humidity of 75% was investigated using PXRD and FTIR. Depending on the prior evaluation, DES and benzoic acid (BA) formed the MCC. PLM and SEM results showed that crystal habit of combination between DES and BA differed from the constituent components. Moreover, the diffractogram pattern of DES-BA was distinct from the constituent components. The DSC thermogram showed a new peak which was distinct from both constituent components. The FTIR study proved a new spectrum. All characterizations indicated that a new solid crystal was formed, ensuring the MCC formation. In addition, DES-BA MCC had both chemical and physical stabilities for a period of 4 months.

Keywords: Desloratadine; Multicomponent crystal; Characterization; Stability

INTRODUCTION

Active pharmaceutical ingredients (API) are mostly formulated in solid oral dosage forms like tablet or capsule (1). However, some major concerns appear in solid dosage formulation i.e. physicochemical (solubility) and physicomechanical (tabletability) characteristics (2). Therefore, modification of API characteristics to achieve the most optimal process for pharmaceutical purposes have been applied. Several strategies such as new polymorph form (3), salt formation (4), cocrystalization (5), an amorphous system (6), nanoparticles (7), hydration/solvation (8), solid dispersion (9), and inclusion complex (10) for API modification have been tried to overcome solubility problems (11).

Polymorph is a single component system under an unstructured pattern of crystal packing. Hydration, solvation, cocrystal, and salt are a multicomponent system which contains a main compound with a coformer in a one-crystal lattice structure (12). A multicomponent crystal (MCC) was used to alter the physicochemical or physicomechanical properties of a drug through a rearrangement of drug molecules into a new crystal lattice formation.

In recent years, the salt formation has been an interesting approach to pharmaceutical development due to its potential in improving the physicochemical or physicomechanical properties of API. Several recognized coformer characteristics, safety, and solid-state interaction probably provide many strategies to control salt characteristics which involve an alteration of solubility, dissolution, hygroscopicity, thermal stability, and physicomechanical properties (13). Salt formation is an acidic and basic reaction between counter charge APIs.

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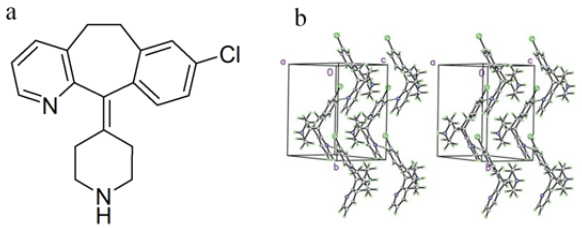

Scheme 1. (a), Structure of desloratadine; (b) stereoview of zig-zag packing arrangement of two desloratadine chains (14).

Desloratadine (DES), a new antihistamine, is a peripheral antagonist of the H1 receptor which has the ability to inhibit the release of double inflammation mediators having high affinity and selectivity. DES is not only used as an antiallergy but also as an anti-inflammatory that has a relative long half-life and rapid onset of action. This drug is used once daily (15). However, DES has physicochemical limitation of low solubility in water (16). An unlimited zig-zag arrangement of DES molecules that lead out on either side of the chain, link to each other, and strongly bond with the chain promotes low physicomechanical properties. Similar to paracetamol characteristics, it can be improved with the salt formation of MCC (17,18). The chemical structure of DES is shown in Scheme 1.

To the best our knowledge, there is no reported data about the synthesis and characterization of desloratadine MCC. This study provid the first data reported for the crystal engineering process of DES through the MCC approach. By forming salt, MCC improved the physicochemical or physicomechanical properties of the parent drug. Hence, this study aimed to investigate the formation of DES MCC using several coformers and solvents and to perform stability testing of formed MCC.

MATERIALS AND METHODS

Materials

Deslortadin was purchased from Xi'An Wango Biopharm Co., Ltd., (Shaanxi, China). In this study, several coformers, such as citric acid, benzoic acid, vanillin, nicotinamide, glutamic acid, malonic acid, fumaric acid, succinic acid, methionine, histidine, oxalic acid, maleic acid, saccharin, methyl paraben, caffeine, boric acid, glycine, diphenylamine, 8-hydroxyquinoline, ninhydrin, phenylhydrazine, resorcinol, pyrogallol, salicylamide, urea, and tartaric acid were used and obtained from Merck (Darmstadt, Germany). Solvents were used such as cyclohexane, benzene, chloroform, diethyl ether, dichloromethane, ethyl acetate, acetone, acetonitrile, isopropanol, n-propanol, ethanol, and methanol. They were obtained from Merck (Darmstadt, Germany) as an analytical grade.

Preparation of multicomponent crystal of desloratadine

An equimolar mixture of DES and each coformer (26 coformers) was dissolved separately in different solvents (12 solvents) as mentioned in the material section. The DES solution was mixed using each coformer solution at 35 °C. Then, it was evaporated using a rapid solvent technique with a Buchi Rotavapor (Flawil, Switzerland) at a temperature of 55 ºC and pressure of 208 mbar. The solid material was collected and stored until further characterizations.

Characterization of multicomponent crystal

Polarized light microscopy

A saturated solution of DES, the coformer, and its binary mixture was dissolved separately using several solvents. The saturated solution was dropped into a glass object until the solvent evaporated or crystallization was observed. The crystal habit of materials was observed using a BX-50 microscope polarization (Olympus, Tokyo, Japan). The photograph was collected using a color digital camera Olympus SC-30 and analyzed using AnalySIS getIT software.

Powder X-Ray diffraction

Powder X-Ray diffraction (PXRD) was used to characterize according to the diffraction angle (θ). The sample was characterized using a Bruker D8 Advance

X-Ray diffractometer (Madison, WI) with Cu-kα radiation (a wavelength of 1,5406Å), the voltage of 40 kV and current of 35 mA. All scans were carried out at a rate of 2 °/min and a diffraction angle from 5 to 60 ° using a resolution of 0.02 °.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) characterization was performed using LINSEIS PT-1600 simultaneous thermal analysis (Robbinsville, NJ). A 2-5 mg sample was placed in a pan and heated from 25-600 °C, at a rate of 10 °C/min, and an empty pan was used as reference. The temperature was calibrated using fusion temperature of indium.

Fourier transform infrared spectroscopy

Fourier transform infrared (FTIR) characterization was performed using an IR Prestige-21 Shimadzu (Kyoto, Japan) and analyzed at a wavelength number of 400-4000 cm^{-1} and a resolution of 2 cm^{-1}.

Scanning electron microscopy

A sample was placed into a sample holder and coated with a platina using a JEOL JEC-3000FC Auto Fine Coater (JEOL Ltd, Tokyo, Japan). The coated sample was placed into a specimen chamber of a JEOL JSM-6510 scanning electron microscope (SEM, JEOL Ltd, Tokyo, Japan) and observed under an appropriate magnification at a voltage of 5 kV and current of 12 mA.

Stability studies

The sample was placed into a vial glass and placed in a Hotpack 317332 Climatic Chamber (Philadelphia, USA) at a temperature of 40 °C and relative humidity of 75% for a period of 4 months. Then, the sample was analyzed using PXRD and FTIR.

RESULTS

Synthesis of multicomponent crystal

Formation of DES salt was investigated experimentally with 26 different coformers and 12 solvents. Selection of appropriate solvents was started from nonpolar solvents, including cyclohexane, benzene, chloroform, diethyl ether, and dichloromethane. It also included polar aprotic solvents, including ethyl acetate, acetone, and acetonitrile; and polar protic solvents including isopropanol, n-propanol, ethanol, and methanol. Each component, the DES, coformer, and its mixture had different solubility levels. Furthermore, in this crystallization process, each component was dissolved in an appropriate solvent separately until a saturated solution was achieved. Each solid material was observed using polarized light microscopy (PLM). The possibility of MCC formation was performed. In this study, there were many results with similar result patterns, thus representative samples were presented to simplify the huge materials and processes in this paper. Each characterization presented a representative result of all results depending on the characteristic of MCC.

Polarized light microscopy

Depending on the result of the formation of the liquid-based MCC, MCC could be performed with a viewing of the crystal habit under a polarized microscope. Each component recrystallization results of DES, coformer, and its binary mixture were observed. Fig. 1 shows two coformers used to form MCC as a representation of 26 coformers. The mixtures between DES (Fig. 1a) and benzoic acid (BA) (Fig. 1b) had different crystal habits compared with single components (Fig. 1c). Other conditions showed that there was no alteration of the crystal habits among DES (Fig. 1d), nicotinamide (Fig. 1e), and the binary mixture (Fig. 1f). Different crystal habits could be used as an indicator that the MCC was formed. Conversely, a combination of two crystal habits from each single component revealed that MCC was not formed. The new structure of DES-BA MCC, which formed in the surface of the crystalline structure like elongated and small fibers, was a molecular compound. This compound was an outcome of integration of two former compounds. Crystalline of the molecular compound had a new characteristic of the habit and almost differed from former compound habits. In addition, the variation of color and intensity was affected by the fragment orientation, height, and adsorbed or transmitted light from the crystal fragment.

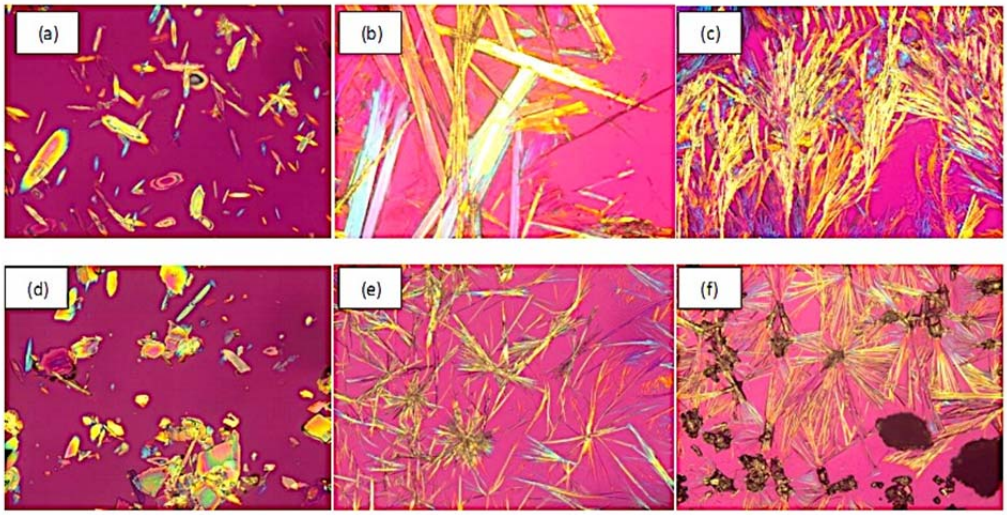

Fig. 1. Polarized light microscopic images of (a), desloratadine (DES); (b), benzoic acid (BA); and (c), mixture of DES:BA (1:1 mole ratio and after recrystallization using methanol as the solvent); (d), DES; (e), nicotinamide (NIC); and (f), mixture of DES:NIC (1:1 mol ratio and after recrystallization using acetone).

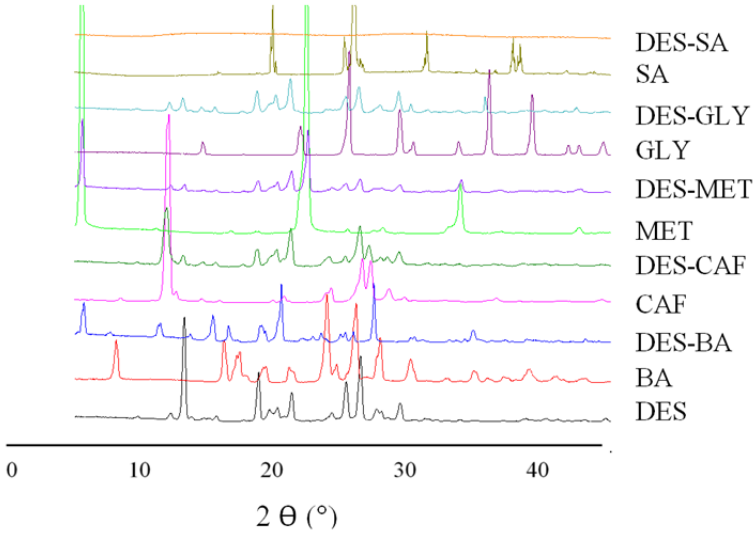

Fig. 2. Diffractograms of desloratadine (DES); benzoic acid (BA); DES-BA; caffeine (CAF); DES-CAF; methionine (MET); DES-MET; glycine (GLY); DES-GLY; succinic acid (SA); and DES-SA.

Powder X-ray diffraction

Depending on diffractogram of crystallization of several mixtures of DES and coformers (Fig. 2), different results were shown between formed and unformed MCC. Therefore, the use of glycine (GLY), methionine (MET), and caffeine (CAF) in combination with DES had the diffraction pattern that was an imitation and combination of both diffractograms without an appearance of new peaks.

The formation of co-amorphous was observed in the DES and succinic acid (SA) and no peak indicating the crystallinity was observed. However, the mixture between DES and BA had different and specific peaks from both diffractograms. It indicated that the MCC was formed. DES diffractogram had specific diffraction angles at 13.17, 18.70, 21.20, 25.28, and 26.29 °. In addition, BA had specific diffraction angles at 8.09, 16.11, 17.06, 17.29, 23.80, 26.00, and 27.08 °. A new crystalline structure was formed in DES-BA that had diffraction angles of 5.70, 11.20, 11.40, 15.31, 16.46, 20.41, and 27.32 °. The different crystallinity indicated a formation of a new crystallinity due to an interaction between DES and BA.

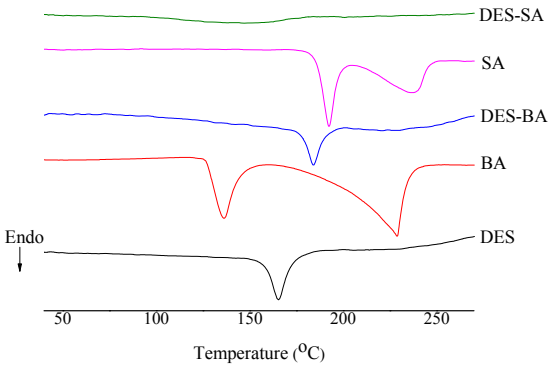

Fig. 3. Thermograms of desloratadine (DES), benzoic acid (BA), DES-BA, succinic acid (SA), and DES-SA.

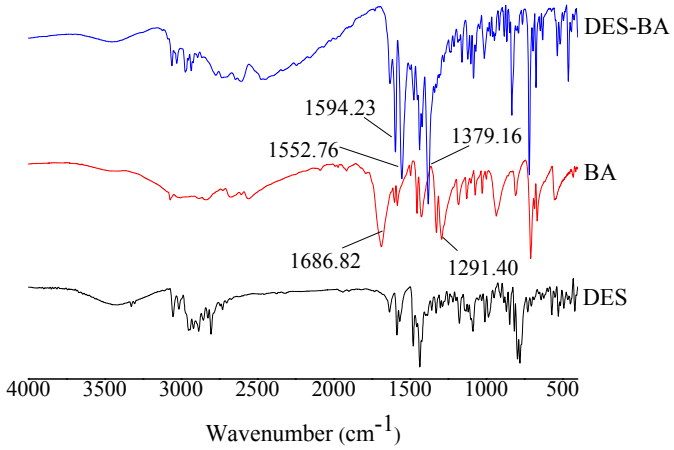

Fig. 4. FTIR spectra of desloratadine (DES), benzoic acid (BA), and DES-BA multicomponent crystal.

Thermal analysis

The thermal profile of DES, coformers, and its binary mixture was evaluated using DSC. DSC thermogram presented in Fig. 3 revealed the formation of MCC using two coformers as a sample. DES-BA had a successful formation of MCC, and DES-SA was an unsuccessful formation of MCC. The DSC thermogram showed that DES and BA had endothermic peaks corresponding to the melting process at 157.0 and 120.8 °C, respectively. Thus, recrystallized DES-BA MCC using methanol had a higher endothermic peak at 175.6 °C compared with the constituent components. Alteration of the melting point of MCC indicated that the interaction between DES and BA affected the formation of internal crystal structures. However, recrystallization of DES and SA using ethanol had a different pattern of thermogram which had two melting points at 157.0 and 188.8 °C, respectively, corresponding to the DES and SA melting points, respectively. Therefore, the formation of a binary mixture between DES and SA was not formed but co-amorphous formation was observed. It was proven by the fact that there was no endothermic peak in crystallized DES-SA.

Fourier transform infrared spectroscopy

FTIR spectrum is an important identification especially at a fingerprint region of 400-1800 cm^{-1}. Shifting of the vibration frequency from 1680-1690 to 1550-1560 cm^{-1} was a specific characterization of MCC that indicated a salt formation. Formation of DES-BA was proven with the FTIR spectrum that is presented in Fig. 4. Disappearance of the C=O vibration of carboxylic acid of BA at 1686.82 cm^{-1} and shifting of two peaks at 1594.23 and 1552.76 cm^{-1} were the main identification of MCC formation. In addition, a shifting of the C-O vibration of BA at 1291.40 to 1379.16 cm^{-1} was proof of deprotonation in the DES-BA salt formation.

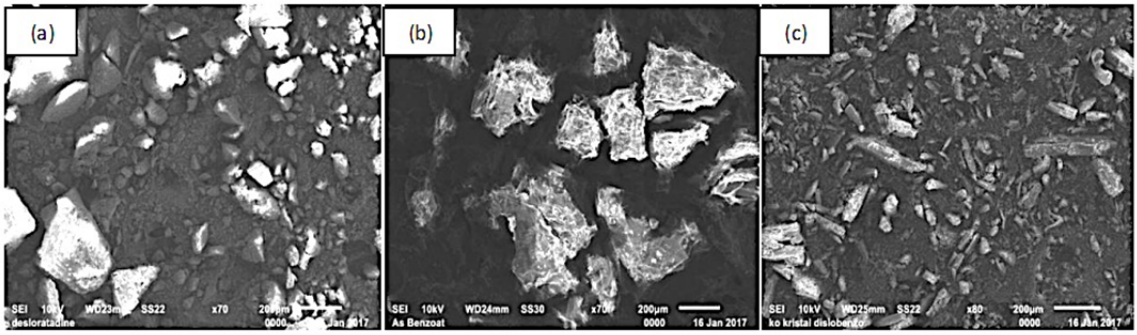

Fig. 5. SEM photographs of (a), desloratadine (DES); (b), benzoic acid (BA); and (c), DES-BA multicomponent crystal.

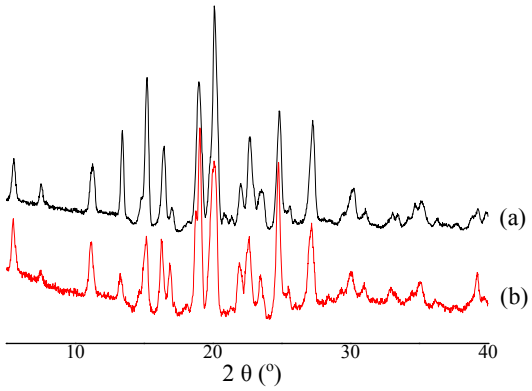

Fig. 6. Diffractograms of desloratadine-benzoic acid multicomponent crystal (a), before and (b), after the stability testing.

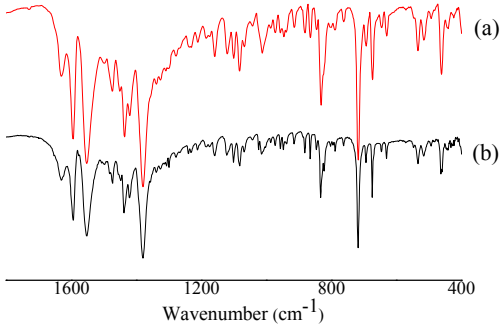

Fig. 7. FTIR spectra of desloratadine-benzoic acid multicomponent crystal (a), before and (b), after the stability testing.

Scanning electron microscopy

Morphology of the crystal habit could be observed using SEM. SEM photographs of DES, BA, and MCC DES-BA (Fig. 5) showed that morphology of the crystal habit of DES-BA MCC was different from individual components of DES and BA, respectively. DES had a specific morphology like a rock shape while the BA had a thin plate-like morphology. MCC DES-BA had a long bar shape. The crystal morphology could be used as a specific identification of the materials that differed from each other. Unsuccessful formation of MCC imitated both constituent components.

Solid-state stability

Stability testing of MCC DES-BA was evaluated using accelerated stability at 40°C/RH 75% for 4 months of storage. Stability was observed by comparison of the PXRD diffractograms (Fig. 6) and FTIR spectra (Fig. 7) before and after stability testing. The results revealed that there was no significant vibrational shifting on FTIR spectra and no alteration of peak pattern in diffractogram. However, an alteration of crystallinity was observed due to alteration of peak intensity in the diffractogram.

DISCUSSION

Salt formation is a reaction between acidic and basic compounds. Proton transfer is a determining factor to classify salt or cocrystals i.e. the salt formed from an ionic interaction with a cocrystal based on a hydrogen bonding. Salt formation consists of ionized molecules (19). Proton transfer has been observed in the salt formation process, while in the cocrystal, protons were used together between two compounds (20). Salt formation could not be

avoided due to a different charge of the hydrogen bonding acceptor. A higher charge over the critical value induces formation of a salt while a lower charge induces a cocrystal (21,22).

Formation of DES MCC not only had different physicochemical properties e.g. melting point, solubility, dissolution, and hygroscopicity, but also the bioavailability and stability. Therefore, in the prior investigation to select an appropriate coformer under different acidity, melting point, polarity, molecular structure, crystal packing, or molecular weight, 26 coformers were purposed to form DES MCC. The rapid solvent evaporation technique was used in this study, which was a simple technique used to observe interactions between DES and coformers, especially for a thermal labile drug/coformer material (23). Degradation of DES occurred after heating over the melting point temperature. It will be amorphous and irreversible to the crystalline structure (24). Several factors determining a phase transformation are nucleation rate, crystal growth rate, and nucleation site. The nucleation phase and crystal growth rate depend on the saturated condition, which are a driving force for formation of MCC of solubilized DES and its coformer (23).

The formation process of MCC was observed under PLM which was useful for studying the optical property of crystals. PLM identified the formation of a new crystalline form through the alteration of the crystal habit (25,26). A phenomenon of a different crystal habit between DES and coformers could provide preliminary information about the probability of interaction between both components to produce a new crystal form. This study showed that DES and BA as a coformer was able to form MCC trough formation of a new crystalline phase that would be further strengthened by another analysis e.g. PXRD, DSC, SEM, and FTIR.

PXRD is one valid characterization method to determine the new crystalline phase of MCC in the solid-state interaction. New crystalline phase had a different pattern of PXRD compared with the constituent components (27). This result revealed that MCC DES-BA had different diffractogram patterns compared with the DES and BA diffractograms. In addition, crystallinity had an important function to determine the characteristics of materials, although peaks in the diffractogram pattern showed crystal characteristics.

DSC was used to determine the thermal characteristics of DES, coformers, and its mixtures. DSC was selected as an analytical method to obtain the melting point, which was a specific characteristic of a pure material that had one melting point. In recent years, DSC was used in the screening of MCC formation due to the use of rapid and accurate methods (28). The DSC thermogram of DES-BA MCC had a higher endothermic peak than that of constituent components. This result revealed that salt formation occurred. Similar results reported that formation of salt from sulfamethizole and oxalic acid had a higher melting point than that of each constituent component (29). The phenomenon of DES-SA was a coamorphous formation that was observed in atorvastatin calcium with nicotinamide (30), and loratadine with citric acid (31). Therefore, no peak was observed in the DSC results and PXRD confirming their crystallinity.

FTIR is the most general technique used to determine the chemical conformation of a compound. FTIR could be used to distinguish between cocrystals and salt formation through asymmetric carbonyl and hydrogen bonding vibrations (21). Alteration of chemical bonding e.g. proton transfer altered the spectrum of each component. FTIR could be used to confirm the proton transfer due to simplicity and ease of preparation. Spectroscopic analysis was a preferable method to routine analysis. FTIR could be used to study the interaction between molecules that could be identified by a scientific shifting of vibrational frequency (32). The result showed that specific functional groups of DES, BA, and MCC were observed. An appearance of a new peak in the MCC spectrum showed an interaction between DES and BA. In addition, the vibrational shifting of carbonyl was observed indicating an ionic bonding in the formation of MCC.

There was an ionic interaction between DES and BA e.g. the deprotonation promoted shifting of C-O vibration from 1200 to 1000-1400 cm^{-1} (21,33,34). In the screening of MCC, ΔpKa must be considered to predict the formation of salt or cocrystal. Furthermore, the cocrystal formed when ΔpKa was less than 2. Conversely when ΔpKa was more than 2, the salt MCC occurred. However, the ΔpKa rule was difficult to predict because several drugs had ΔpKa 0-3 found as salt (35). DES and BA had a different pKa value of 4.45 and formed the salt. SEM is a kind of electron microscope imaging the sample with a scanner using high-energy electrons. The electron interacts with the atom, and the sample produces a signal that provides information about the surface morphology. SEM could be applied to determine the micrograph of MCC and particle size (36). SEM provided visual information about the difference of morphology of a drug and MCC. The result showed that methanol recrystallized of DES, BA, and MCC had different sizes, shapes or morphology. Alteration of shape, size, and morphology of the binary mixture between DES and BA proved that MCC was formed. However, unchanged or combined crystal forms of both constituent components indicated that MCC was not formed.

Depending on the FTIR and PXRD characterizations, the salt was physically and chemically stable (37,38). Physically, PXRD analyzed the stability of the crystalline structure using a diffraction pattern. There was an physical alteration in the diffraction pattern of PXRD diffractogram. This stability result showed a similar pattern of PXRD diffractogram it indicating that accelerated stability did not change the crystalline structure. However, alteration of the intensity of several peaks indicated alteration of crystallinity degree. The stability study indicated low intensity most likely caused by rearrangement or low regularity of the crystal lattice due to thermodynamic activity. Similar peak patterns were observed before and after the stability study. Therefore, there was no alteration of the crystal lattice structure. In addition, the stability study affected the alteration of intensity but did not change the peak pattern. Depending on the FTIR results, there was no alteration and shifting of the vibrational peaks during accelerated stability. Therefore, chemically DES-BA MCC was stable during accelerated stability evaluations. Both physical and chemical stability imply physicochemical properties which might be directly correlated to the bioavailability.

CONCLUSIONS

In the current study formation of new MCC of DES using solvent evaporation assisted recrystalization had been performed was investigated. BA and methanol were selected as coformer and solvent, respectively. PLM was implemented as the prior investigation of the new crystal habit and provided adequate information during the screening of MCC formation. Formation of DES-BA MCC and its interaction were confirmed using FTIR, DSC, SEM, and PXRD analysis. DES-BA MCC showed good chemical and physical stability for a period of four months of accelerated stability assessment.

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