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RESEARCH ARTICLE

Evaluation of physical-mechanical properties of atorvastatin calcium-isonicotinamide cocrystal

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Abstract

Background: Atorvastatin calcium (AC) is a potent antihyperlipidemic drug but poorly water-soluble, so its bioavailability is low. Cocrystallisation of AC with isonicotinamide (INA) is known to increase the solubility of AC so that it is the potential for pharmaceutical formulations. **Objective**: The study aimed to prepare and evaluate the physical-mechanical properties of the AC-INA cocrystal so that pre-formulation data needed to form pharmaceutical preparation were obtained. **Methods:** The preparation of the AC-INA cocrystal used the solvent evaporation method, and the characterisation used a powder X-ray diffractometer, differential scanning calorimeter, Fourier Transform Infra-Red spectrophotometer, and scanning electron microscope. Evaluation of physical-mechanical properties includes solid-state properties, moisture absorption, compressibility index, compactibility, and stability. **Results:** The results indicated that the solid of AC-INA was a cocrystal. AC-INA cocrystal absorbs the moisture of 0.09±0.021% (20 ºC, RH 79.5%), with a compressibility index of 24.99±1.02%. At a temperature of 40 ºC (60 days), the AC in the AC-INA cocrystal decreased by 8.82%, indicating degradation under temperature stress. **Conclusions:** The AC-INA cocrystal is a non-hygroscopic solid with passable-flow properties. The compactibility characteristics of AC-INA cocrystals are classified as excellent. The AC-INA cocrystal indicated degradation under temperature stress, requiring precautions during storage and formulation.

Introduction

Atorvastatin calcium (AC) is a potent antihyperlipidemic drug that reversibly inhibits HMG-CoA reductase, an essential step in cholesterol biosynthesis. However, AC is reported to have an absolute bioavailability of only around 12% due to its poorly water-soluble (Wicaksono *et al.*, 2021). Therefore, increasing the solubility of AC is one of the main challenges to increasing AC's bioavailability and pharmacological effects (Kwon *et al.*, 2019).

In the last few decades, cocrystallisation has become a method often applied to improve the solubility properties of pharmaceutical ingredients (APIs) (Wicaksono *et al.*, 2022). Cocrystals are multicomponent solids of two or more molecules with stoichiometric ratios arranged in the same crystal lattice through non-covalent intermolecular interactions (Rodrigues *et al.*, 2018). Cocrystallisation can increase APIs' solubility by decreasing lattice and solvation energy in cocrystal solids (Sathisaran *et al.*, 2018). The advantage of cocrystallisation is that the cocrystal product does not change its intrinsic structure, so the pharmacodynamic properties of API are maintained (Eesam *et al.*, 2021). Based on previous reports, it is known that the cocrystallisation of AC can significantly increase the solubility of AC (Wicaksono *et al.*, 2017; Trivedi *et al.*, 2020). Therefore, AC in cocrystal form is very promising to be applied to pharmaceutical formulations to overcome the solubility problem of AC.

In the formulation process for pharmaceutical preparation, APIs must be mixed with excipients and then manufactured rationally to produce a dosage form that meets the requirements (Kádár *et al.*, 2022). The APIs' physical-mechanical properties greatly influence

Excipients and manufacturing methods (Toehwé *et al.*, 2018). Therefore, data on the physical-mechanical properties of APIs are needed in the formulation process to select excipients and manufacturing methods correctly so that the resulting pharmaceutical preparations meet the requirements (Kádár *et al.*, 2022).

Reports show that cocrystallisation can increase the solubility of AC (Wicaksono *et al.*, 2017; Trivedi *et al.*, 2020). Crystallisation of AC not only affects solubility properties but can also affect other physical-mechanical properties (Eesam *et al.*, 2021). Until now, the evaluation of the physical-mechanical properties of the AC cocrystal has not been thorough. However, physical-mechanical properties data are essential for the formulation process of pharmaceutical preparations. (Toehwé *et al.*, 2018). Therefore, this study aims to prepare the cocrystal of AC and evaluate the physical mechanical properties necessary for the rational formulation process of AC cocrystal.

Methods

Materials

The materials used were AC in trihydrate form (Sun Pharmaceutical Industries, India), isonicotinamide (Merck, Germany), and methanol (PT. Smart Lab Indonesia, Indonesia).

Preparation of cocrystal

Cocrystallisation of AC was carried out with isonicotinamide (INA) coformer using the solvent evaporation method according to the previously reported procedure. AC and INA with a molar ratio of 1:1 were put into a beaker glass, and then a certain amount of methanol was added and stirred with a magnetic stirrer (100 rpm, 30 minutes). The beaker glass is covered with aluminium foil, given small holes, and then stored at room temperature so that all the solvent evaporates and a dry crystalline solid is produced. Crystalline solids are reduced using a mortar and stamper and then sieved with an 80-mesh sieve (Wicaksono *et al.*, 2017).

Characterisation of cocrystal

The crystalline phase of the AC-INA cocrystal was analysed using a powder X-ray diffractometer (PXRD) using the Panalytical Xpert Pro PW3373/00 instrument with a CuKα1 radiation source (λ = 1.542 Aº). The PXRD test was carried out at a scan speed of 10º per minute in the range 2θ=5-50º. The voltage and current are 40 kV and 30 mA, respectively.

The thermal behaviour of the AC-INA cocrystal was analysed by a differential scanning calorimeter (DSC) using the Thermo Plus EVO DSC8230 instrument. The sample container was an Al hermetic pan; the test temperature range was 30-300 ºC. The heating rate is set at 10ºC per minute under conditions of dry airflow at 50 mL/minute.

Analysis of intermolecular interactions between constituent components in the AC-INA cocrystal was carried out using Fourier Transform Infra-Red spectrophotometry (FTIR) with the Thermo Scientific Nicolet iS10 equipment. Tests were carried out in the range of wave numbers 500 - 4000 cm^{-1} with a resolution of 4 cm^{-1}.

The particle morphology of the AC-INA cocrystal was analysed using a scanning electron microscope (SEM) using a Hitachi TM 3000 equipped with a Hitachi E-1045 ion sputter. The sample particles were coated with platinum for 20 seconds and then observed using SEM at a voltage of 15 kV and a current of 30 mA with the appropriate magnification.

Evaluation of moisture absorption

The petri dish was weighed (W0), and then 1 gram of AC-INA cocrystal powder was added. The petri dish containing the sample was placed in an oven at 40 ºC for 24 hours to obtain a constant weight (W1). The petri dish containing the sample powder was then placed in a desiccator saturated with ammonium chloride solution (20 ºC, RH 79.5%) and weighed again after 1, 2, and 3 days (W2). The moisture content (MC) of the sample is calculated by the equation MC = [(W2-W1)/(W1-W0)] x 100 % (Syaqira *et al.*, 2020).

Determination of compressibility index

The compressibility index of AC-INA cocrystal was determined according to the procedure in the previous paper with some modifications (Özalp *et al.*, 2020). An empty measuring cylinder glass is weighed (W0), filled with sample powder up to the mark, and weighed again (W1). The measuring cylinder glass containing the sample was then tapped 500 times with a tap density tester (Logan Tap-2S), and the volume of sample powder after tapping was recorded. The compressibility index (CI) is calculated by the equation CI = [(tap density – bulk density)/tap density] x 100 (Özalp *et al.*, 2020).

Compactibility evaluation

Evaluation of AC-INA cocrystal compactibility is carried out by determining the tensile strength. The powder of the AC-INA cocrystal (150 mg) was compressed using a hydraulic press with a pressure of 2.5, 5, 7.5, 10, and 15

kN, respectively. The compressed compact was then measured for diameter, thickness, and hardness with a hardness tester (Erweka TBH 125). Tensile strength ( ) is calculated by the equation = (2F/Dt), F is hardness (N), D is the diameter (mm), and t is the thickness (mm) (Setyawan *et al.*, 2020).

Stability test

Stability testing refers to the procedure in the previous report with some modifications (Rahman *et al.*, 2011). AC-INA cocrystal (50 mg) was tightly packed in a vial and then stored in an oven at 40 °C. Cocrystal samples in vials were taken on days 0 and 60; the AC level was determined using a UV-Vis spectrophotometer (Rahman *et al.*, 2011).

Results

The diffractogram of the AC-INA cocrystal (Figure 1a) has diffraction peaks with the weak intensity of 2θ at 8.1 and 18.1°. The DSC thermogram of the AC-INA cocrystal (Figure 1b) has a sharp endothermic peak at 192.2 °C, indicating the melting point of the AC-INA cocrystal. The FTIR spectra of the AC-INA cocrystal (Figure 1c) show the absorption peaks associated with the functional groups of the molecules. The absorption peaks in the FTIR spectra of the AC-INA cocrystal indicated absorption peaks from the AC functional groups, namely at 3272 cm^{-1} (N-H stretching), 2960 cm^{-1} (O-H stretching), 1647 cm^{-1} (C=O stretching), and 1436 cm^{-1} (C-N stretching). INA in the AC-INA cocrystal showed absorption peaks at 3362 and 3177 cm^{-1} (-NH2 stretching), 1647 cm^{-1} (C=O stretching), and 1414 cm^{-1} (C-N stretching).

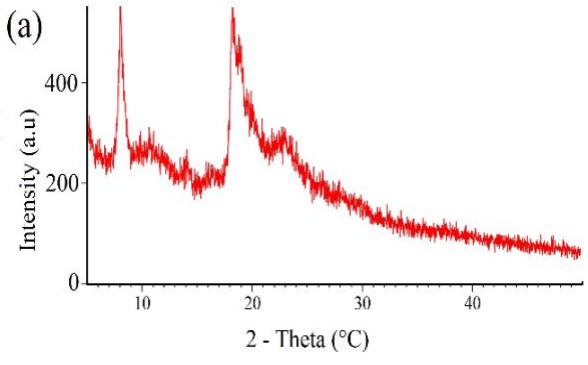

Figure 1: (a) PXRD difractogram

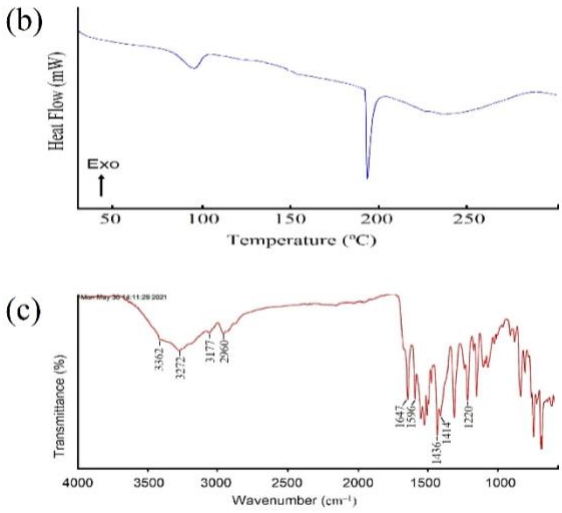

Figure 1: (b) DSC Thermogram and (c) FTIR spectra of AC-INA cocrystal

SEM images of the AC-INA cocrystal are shown in Figure 2. The particles of AC-INA cocrystal showed a very angular shape with low sphericity. The surface topography of the AC-INA cocrystal particles showed a varied surface, smooth to rough.

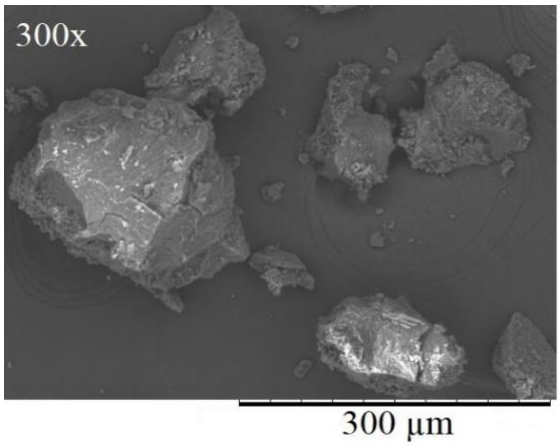

Figure 2: SEM images of AC-INA cocrystal

The moisture absorption of the AC-INA cocrystal (20 ºC, RH 79.5%) is shown in Figure 3. The AC-INA cocrystal in three days absorbed moisture not more than 0.05±0.027%. The compressibility index of the AC-INA cocrystal is 24.99±1.02%, indicating passable-flow properties. The tensile strength of the AC-INA cocrystal plotted at compression pressure is shown in Figure 4. After being compressed with a pressure of 2.5–15 kN, the AC-INA cocrystal forms a matrix where the tensile strength is directly proportional to the compression

pressure. Testing the stability of the AC-INA cocrystal at 40 ºC found that the AC content in the AC-INA cocrystal on day 0 was 95.16±2.47%, while after being stored for 60 days, the AC content became 86.77±0.40%. After 60 days at 40 ºC, the AC in the AC-INA cocrystal has been degraded by 8.82%.

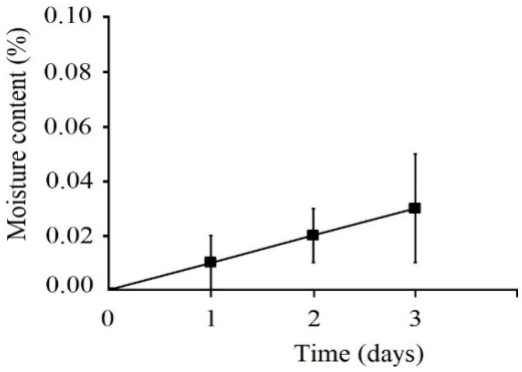

Figure 3: Moisture sorption of AC-INA cocrystal

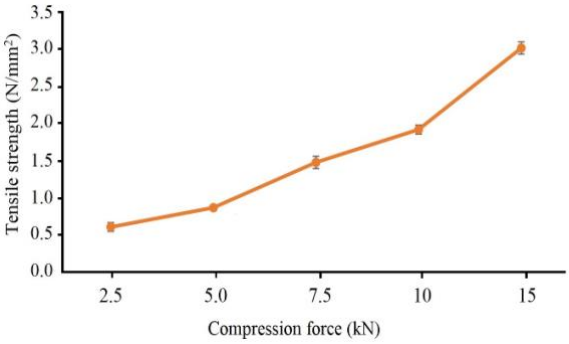

Figure 4: Tensile strength of AC-INA cocrystal

Discussion

The intensity of the diffraction peaks is an indication of the degree of order and the crystalline phase of a solid. Solids with weak intensity diffraction peaks indicate a low degree of crystallinity (Terohid *et al.*, 2017). The diffractogram of the AC-INA cocrystal shows peaks with weak intensity, indicating that the crystalline environment of the AC-INA cocrystal is solid with a low level of crystallinity. The diffractogram pattern of the AC-INA cocrystal shows agreement with previous reports (Wicaksono *et al.*, 2017). The AC-INA thermogram shows a shallow broad peak at 95.1 °C on the AC-INA cocrystal diffractogram, which is thought to be a desolvation process. The type of solvent molecule (Chadha *et al.*, 2012) greatly influences the desolvation temperature of a crystalline solid. Based on the desolvation temperature of the AC-INA cocrystal, it is estimated that it is a hydrate solid that releases water molecules from its crystal lattice at a temperature of around 90-110 °C (Chadha *et al.*, 2012; Panghal *et al.*, 2014). The FTIR spectra of the AC-INA cocrystal showed a combination of the individual absorption peaks of the AC and INA molecules. Some absorption peaks showed a shift compared to the individual absorption peaks of the constituent components, indicating an intermolecular interaction between AC and INA molecules in the AC-INA cocrystal (Wicaksono *et al.*, 2017). SEM images of the AC-INA cocrystal showed that the individual particles from AC and INA in the AC-INA cocrystal could no longer be recognised. The micrograph of the AC-INA cocrystal indicated that the constituent materials had interacted to form a new solid phase as AC-INA cocrystal (Wicaksono *et al.*, 2017).

The character of APIs in the presence of moisture is a factor that must be considered during the formulation process and storage because it can affect the efficacy of APIs (Guan *et al.*, 2020). According to reports, AC is an API classified as non-hygroscopic, absorbing no more than 0.2% of moisture for 24 hours (Nair *et al.*, 2017). Thus, the AC-INA cocrystal showed moisture absorption much lower than 0.2% (20 ºC, RH 79.5%), indicating a non-hygroscopic API.

The compressibility index is a measure of the ability of a material to decrease in volume, which is related to the occurrence of interactions between particles. The compressibility index can be used to assess a powder's fluidity indirectly. The higher the compressibility index value, the more cohesive the powder, indicating poor flow, and vice versa (Hernández *et al.*, 2019). Understanding the compressibility index helps plan the formulation process of an API into a pharmaceutical dosage form with good physical properties. Generally, powder with a compressibility index value of up to 16% shows good fluidity, whereas above 25% indicates poor fluidity due to cohesive powder (Okunlola *et al.*, 2018). The particle micrograph of the AC-INA cocrystal has a very angular shape characteristic with low sphericity, which is thought to contribute to the fluidity of the AC-INA cocrystal (Nijhawan *et al.*, 2022). API powders with passable fluidity characteristics during the pharmaceutical formulation process can be improved by using additives with excellent fluidity or through the granulation process to produce a powder mixture with better fluidity and manufacturability (Chen *et al.*, 2022).

Compactibility is the ability of a material to form a compact matrix with sufficient strength under the influence of densification (Ghori *et al.*, 2016). The compactibility of APIs is largely influenced by their structural characteristics, which can be assessed

through tensile strength analysis. A material with high tensile strength indicates good compactibility; when compressed, it can form a compact matrix without any damage (Setyawan *et al.*, 2020). Up to a compression pressure of 15 kN, the AC-INA cocrystal has shown no over-compaction, namely a decrease in tensile strength due to excess compression pressure (Setyawan *et al.*, 2020). Generally, a pharmaceutical tablet must have a tensile strength greater than 2 N/mm2 to obtain adequate physical integrity (Setyawan *et al.*, 2020). Based on the tensile strength curve, it can be concluded that the AC-INA cocrystal can form tablets with good physical strength if the compression pressure is greater than 1 kN.

An understanding of the stability of an API is much needed in storage procedures, handling during distribution, and design in the formulation process (Nugrahani *et al.*, 2018). The stability test of the AC-INA cocrystal showed that the AC in the cocrystal form at temperature stress was still degraded. Previous reports stated that pure AC is sensitive to degradation under temperature and pH stress, so it is necessary to anticipate during the storage and formulation of AC-INA cocrystal (Vukkum *et al.*, 2013; Krauß *et al.*, 2019).

Conclusion

The solids of the AC-INA cocrystal indicated non-hygroscopic API with a compressibility index of 24.99±1.02% correlated with passable-flow properties. The compactibility characteristic of the AC-INA cocrystal is excellent, where the AC-INA cocrystal can form a compact matrix at pressures above 1 kN without over-compaction. The AC-INA cocrystal showed 8.82% degradation at 40 ºC for 60 days, so it required precautions during storage and the formulation process.

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Conflicts of interest

The authors declare no conflict of interest.

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