Trop J Nat Prod Res, October 2023; 7(10):4128-4132 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Multicomponent Crystal Formation of Dexibuprofen-Caffeine to Improve Solubility

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ARTICLE INFO

Article history:
Received 06 June 2023
Revised 31 September 2023
Accepted 14 October 2023
Published online 01 November 2023

ABSTRACT

Alteration of solid form via a multicomponent crystal formation can be a choice to improve the solubility of a poor solubility drug, such as dexibuprofen. The purpose of this research was to produce dexibuprofen-caffeine (DXI-CAF) multicomponent crystal and to evaluate its solubility and dissolution rate. Preliminary investigation to predict the multicomponent crystal formation was conducted by observing crystal morphology by polarization microscope and knowing phase solubility type of DXI in caffeine solution. Liquid-assisted grinding (LAG) method was used to produce DXI-CAF multicomponent crystal and ethanol was used to accelerate its formation. Powder X-ray diffractometer (PXRD) and differential scanning calorimeter (DSC) were utilized to analyze DXI-CAF multicomponent crystal formation. Evaluation of physicochemical properties was carried out by the solubility testing in water and pH 1.2, 4.5, and 6.8. The dissolution rate tests were also performed in the same pH. The DXI-CAF showed a different crystal morphology from pure DXI and CAF after crystallized in ethanol. Meanwhile, a B_S type curve was obtained from the determination of phase solubility. The LAG product revealed a distinctive PXRD pattern and DSC thermogram that was different from pure DXI and CAF, thereby indicating DXI-CAF multicomponent crystal formation. The increase in solubility and dissolution rate was shown in the DXI-CAF multicomponent crystal in all pH. Succinctly, DXI-CAF multicomponent crystal can be prepared by the LAG method which shows the potential in enhancing solubility and dissolution rate of dexibuprofen.

Keywords: Dexibuprofen, caffeine, solubility, liquid-assisted grinding, dissolution rate.

Introduction

The ability of drug absorption in the gastrointestinal tract can be predicted from its solubility.[1] The low solubility of active pharmaceutical ingredients (APIs) often results in poor bioavailability when administered orally. Dexibuprofen (DXI) is an anti-inflammatory drug that works by breaking the pathway of arachidonic acid through inhibition of the enzyme cyclooxygenase-2 (COX-2).[2] DXI is administered orally at high doses, but has low solubility (<1 mg / mL) in the stomach due to its acidity, so this API is classified into class II in the biopharmaceutical classification system (BCS).[3] Some efforts to increase the solubility of dexibuprofen have been carried out, such as, by solid dispersions and β-cyclodextrin hydrogel nanoparticle.[4,5] However, the formation of solid dispersions generally results in amorphous solid forms which are unstable due to their transformation to crystalline form in storage.

An effort to increase drug solubility without changing pharmacological activity is to modify the solid form of the API through the multicomponent crystal formation, such as salt, co-crystal, or co-crystalline salt.[6–9] Multicomponent crystal is established when more than one molecule of different substances crystallized together in a crystal lattice with a certain stoichiometric ratio by noncovalent bonds. Salt formation occurs due to the transfer of a proton from an API to a salt former or vice versa, while co-crystal formation occurs due to the present hydrogen bonds between an API and a co-crystal former. Caffeine (CAF) is a substance that is widely found in coffee and tea which is used in health drink supplements.[10]

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Citation: Alatas F, Pratiwi GK, Meylifepri H. Multicomponent Crystal Formation of Dexibuprofen-Caffeine to Improve Solubility. 2023; 7(10):4128-4132. http://www.doi.org/10.26538/tjnpr/v7i10.2

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

It has been shown to increase the solubility of several APIs through the multicomponent crystal formation, including trimesic acid[11], luteolin[12], and paracetamol [13], and dihydromyricetin.[14]

The chemical structures of DXI and CAF as shown in Figure 1 have the opportunity to form multicomponent crystal due to the presence of groups of two components that are capable of acting as hydrogen bond donors/acceptors and proton donors/acceptors. The presence of a carboxylic acid group in DXI increases the chances of hydrogen bond formation with the N-imidazole group in CAF.[15] The weakly basic nature of CAF also increases the chances of proton transfer from DXI to form salts. The purpose of this research was to produce dexibuprofen-caffeine (DXI-CAF) multicomponent crystal, to characterize, and to determine its effect on its solubility and dissolution rate.

Materials and Methods

Materials

Dexibuprofen was purchased from Beijing Mesochem Technology, CO., Ltd., China, whilst caffeine was obtained from Merck, Indonesia. Ethanol and materials for buffer solution were obtained from Merck, Indonesia.

Crystal morphology observation

Crystal morphological observations were carried out by placing approximately three mg each of DXI, CAF, and DXI-CAF equimolar mixture on a glass object. The samples were dripped with ethanol until they dissolved and were allowed to form crystals. The crystal morphology formed from each sample was observed with an Olympus BX-53 polarizing microscope. The microscope images were obtained by an Optilab Advance Plus camera attached to the microscope.

Phase solubility test

The phase solubility of dexibuprofen (drug) in the caffeine (ligand) solution was carried out using the shaker method.[16,17] CAF solutions in water were prepared with various concentrations of 5, 6, 7, 8, 9, 10, and

11 mM, and each CAF solution was put into a 10 mL vial. A total of 50 mg of DXI was put into each vial containing CAF solution and shaken for 48 hours using an orbital shaker (IKA KS-260) with a rotation speed of 250 rotations per minute. After the shaking was complete, the vial was allowed to stand for a while and the sample was filtered to obtain a clear solution. The solubility of dexibuprofen concentration in each sample solution was analyzed by first derivative ultraviolet spectrophotometry (Shimadzu UV-1800 spectrophotometer).

Preparation of DXI-CAF multicomponent crystal
The DXI-CAF multicomponent crystal was prepared by liquid-assisted grinding method. [18,19] A mixture of 1.030 g (5 mmol) of DXI and 0.970 g (5 mmol) of CAF was placed into the mortar and five drops of ethanol were dropped. The mixture was milled for five minutes and allowed to dry. The LAG product was stored in a desiccator before being characterized and tested for its solubility.

Characterized DXI-CAF multicomponent crystal by powder X-ray diffraction (PXRD)
Approximately 500 mg of the powder from the LAG product was placed in the sample container. Samples were scanned using PANalytical Empireyan with a Cu-Kα radiation source operating at a 40 kV voltage and a 30 MA current. PXRD scanning was also performed on pure DXI and CAF.

Characterized DXI-CAF multicomponent crystal by differential scanning calorimetry (DSC)
Thermograms DSC of DXI, CAF, and the LAG product was obtained on the Shimadzu DSC-60 plus (Kyoto, Japan). A total of 2-5 mg of sample was put in an aluminum pan and tightly closed. The heating of the samples was performed at a heating rate of 10°/min in the range of 30 to 250°C.

Solubility test
The solubility of multicomponent crystal DXI-CAF was tested using the shake-flask method in water and buffer solutions in this research based on the literature with slight modifications.[20] The solubility test was carried out on pure DXI and DXI-CAF multicomponent crystal in the water at 25±1°C. Also, the solubility test was also performed in buffer solutions of pH 1.2, 4.5, and 6.8 at 37±1°C. Each sample was weighed to the equivalent of 50 mg of DXI, put into a vial, and added 10 mL of solvent. The vials containing the sample were shaken using an orbital shaker (25±1°C) or a water-bath shaker (37±1°C) for 48 hours. After the shaking was complete, the vials were allowed for a while, and the samples were filtered. The dexibuprofen concentrations were analyzed by the first derivative to obtain dexibuprofen solubility in each solvent.

Dissolution test
The dissolution test was carried out on pure DXI powder and DXI-CAF multicomponent crystal that had been sieved with a 60-mesh sieve. Each 900 mL of buffer solution pH 1,2, 4,5, and 6,8 was used as dissolution mediums. The dissolution test was performed using a rotating paddle with a rotation speed of 50 rpm. Each 10 mL of sample was taken in 5, 10, 15, 30, 45, 60, 90, and 120 minutes. Each sampling was replaced with the same volume of dissolution medium.

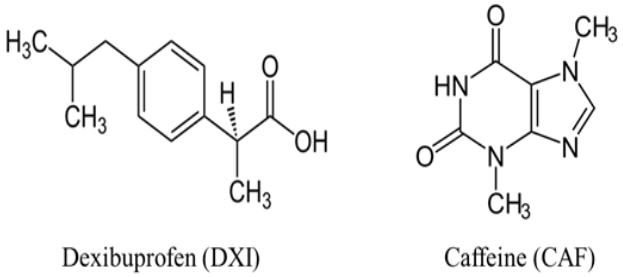

Figure 1: Chemical structure of dexibuprofen and caffeine

Results and Discussion

Crystal Morphology
The difference in the shape of the crystal habit obtained from the recrystallization of a mixture of two components in a certain solvent with the crystal habit of each component observed under the microscope can also indicate the formation of a new crystal phase. [21] The difference in crystal morphology between the mixture of DXI-CAF with pure DXI and CAF after each recrystallization in ethanol was shown in Figure 2. The small needle-crystal habit of DXI-CAF was different from the crystal habit of the two constituent components which indicates the DXI-CAF multicomponent crystal formation.

Phase solubility
Prediction of the formation of multicomponent crystals, such as salts or co-crystals due to a bond between a pharmaceutical active ingredient and the co-crystal-former or salt-former can be made by constructing a phase solubility curve. The phase solubility curves have five types, namely AL, AP, AN, BS, and BL, and these types show the amount of solubility of a compound in the solution of another compound.[16] Figure 3 showed that the solubility curve of the DXI phase in CAF solution followed the BS type. The solubility of DXI is sharp at a concentration of 5-8 mM of CAF which can illustrate the interaction between DXI and CAF to establish a multicomponent crystal dissolved in water. The decrease in solubility occurred at concentrations of CAF solution above 8 mM because the solubility of DXI-CAF multicomponent crystals had reached a supersaturated and precipitated. The higher the CAF concentration, the more multicomponent crystal solid was formed. This Bs type of phase solubility curve that occurs between DXI and CAF can indicate the formation of hydrogen bonds between the two components to form a molecular complex or multicomponent crystal.[16]

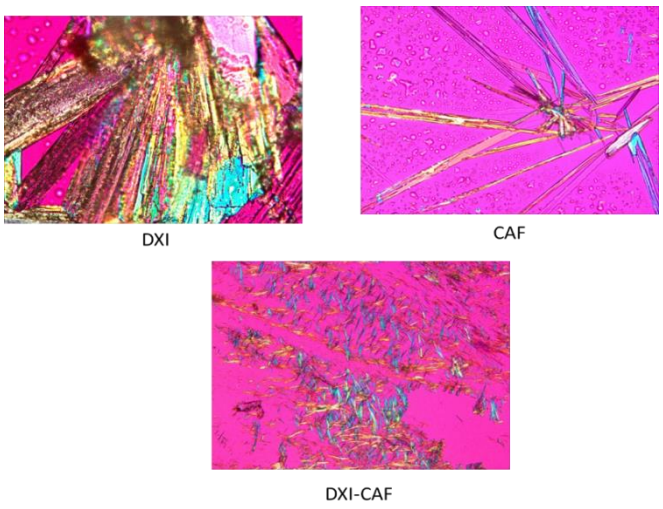

Figure 2: Crystal morphology of dexibuprofen (DXI), caffeine (CAF), and DXI-CAF after recrystallization in ethanol.

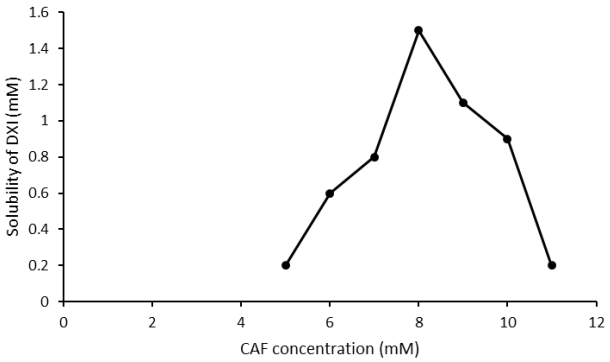

Figure 3: Phase solubility curve of DXI in CAF solution.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Table 1: Solubility of DXI and DXI-CAF multicomponent crystal

Medium	Solubility (mg/mL)	
	DXI	DXI-CAF
Water (25 ± 1°C)	0.051 ± 0.001	0.122 ± 0.005
pH 1.2 (37 ± 1°C)	0.047 ± 0.001	0.057 ± 0.001
pH 4.5 (37 ± 1°C)	0.165 ± 0.008	1.113 ± 0.021
pH 6.8 (37 ± 1°C)	3.555 ± 0.077	3.985 ± 0.083

n=3

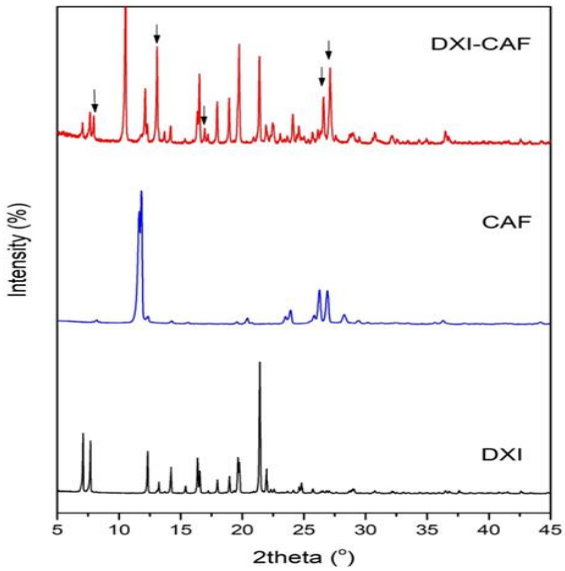

Figure 4: The PXRD patterns of dexibuprofen (DXI), caffeine (CAF), and DXI-CAF multicomponent crystal.

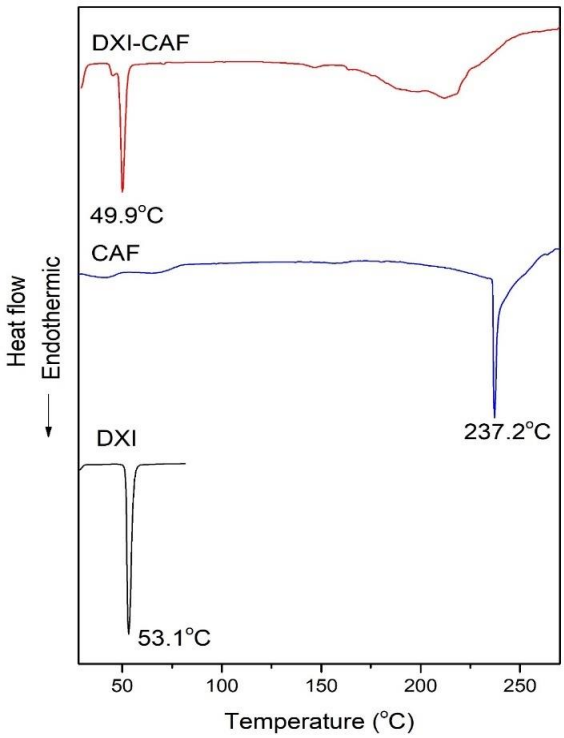

Figure 5: The DSC thermograms of dexibuprofen (DXI), caffeine (CAF), and DXI-CAF multicomponent crystal

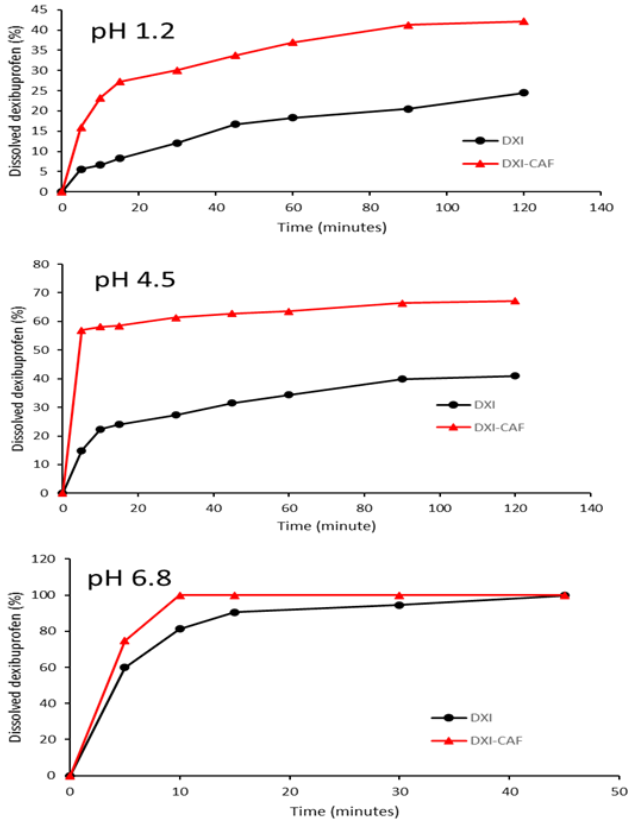

Figure 6: Dissolution profiles of pure DXI and DXI-CAF multicomponent crystal at pH 1.2, 4.5, and 6.8.

Preparation DXI-CAF multicomponent crystal

The liquid-assisted grinding (LAG) method is a method of making multicomponent crystals, including salts and co-crystals by grinding together the API and salt/co-crystal former in the presence of the addition of a small amount of solvent[22–24]. The solvent can act as catalysts in the formation of multicomponent crystals, due to the increased speed of dissolving the constituent components (active pharmaceutical ingredients and salt / co-crystalline formers), so the choice of solvent is very important. The presence of a solvent is very important to accelerate the formation of a multicomponent crystal by speeding up the process of dissolving the two components and ultimately accelerating the process of multicomponent crystal nucleation. The high solubility of DXI and CAF in ethanol makes this solvent very suitable for use in the manufacture of DDI-CAF multicomponent crystal [25].

Characterization by PXRD

The PXRD pattern of DXI-CAF in Figure 4 showed some of the pure DXI and CAF peaks disappearing and the formation of new peaks which are marked with arrows at 7.95, 10.52, 16.96, 26.56, 27.22 of 2θ angles which did not appear on the pure DXI and CAF diffractograms. The characterization of the LAG product of DXI-CAF was initiated with the powder X-ray diffraction method. Powder X-ray diffractogram can provide information on changes in crystal structure or the formation of new crystal phase by analyzing the differences in diffractogram between the LAG product and their respective components. The difference in diffraction pattern as shown in the following figure indicates the formation of DXI-CAF multicomponent crystal.

Characterization by DSC

Figure 5 revealed the DSC thermograms of DXI and CAF each having only one endothermic transition at 53.1° and 237.2°C, respectively related to the melting points of both components. DSC is a thermal analysis technique with the ability to quickly characterize the presence

of multicomponent crystal formation by analyzing the difference in melting points between the product and the constituent components. The DSC thermogram showed that the LAG product's melting point was below the melting point of the two constituent components (49.9°C). Generally, when a multicomponent crystal is established from the manufacturing process, a sharp endothermic with a lower melting point or between the melting points of each component will appear. [26,27]

Solubility

The solubilities of DXI and DXI-CAF multicomponent crystal were shown in Table 1. The solubility of DXI increases with increasing pH due to the increase in the degree of ionization in the carboxylic acid group. The DXI-CAF multicomponent crystal had higher solubility in all the mediums. The solubility of DXI-CAF in water, pH 1.2, 4.5, and 6.8 were 2.4, 1.2, 6.7, and 1.1 higher than pure DXI, respectively. The lowest increase in solubility was shown at pH 6.8 due to the high degree of ionization caused by the release of a proton from the carboxylic acid group of pure DXI at that pH. Changes in crystal structure due to the interaction between two molecules to form a multicomponent crystal can change physicochemical properties, including solubility. [28] The increase in the solubility of DXI is caused by hydrogen bond formation between DXI and CAF which can reduce the energy to break the bond between DXI-CAF multicomponent crystal and water solvent.

Dissolution

Figure 6 demonstrated the dissolution rate profile of dexibuprofen released from the DXI-CAF multicomponent crystal was faster than pure DXI in all the pH buffer solution. Dissolved percentage of dexibuprofen in five minutes at pH 1.2 of pure DXI and DXI-CAF multicomponent crystal were 5.6 and 16.0%, respectively, meanwhile at pH 4.5 were 14.8 and 56,9%. The dissolution rate profile at pH 6.8 showed the dissolved percentage of dexibuprofen in five minutes of pure DXI and the DXI-CAF multicomponent crystal has reached more than 50% due to its ionizing effect at this pH. However, the dissolved percentage of dexibuprofen at 10 minutes of DXI-CAF multicomponent crystal has reached 100%, while that released from DXI has not reached 100%. The increase in dissolution rate of dexibuprofen in DXI-CAF multicomponent crystal was caused by the solubility increasing.

Conclusion

Multicomponent crystal of dexibuprofen-caffeine (DXI-CAF) has been successfully prepared by the liquid-assisted grinding (LAG) method using ethanol as the solvent. The distinctive features of PXRD and DSC thermogram of LAG product which is different from pure DXI and CAF indicate the presence of multicomponent crystal formation. The high solubility of the DXI-CAF multicomponent crystal led to an improved dissolution rate of dexibuprofen compared to pure DXI. This study has not been able to identify the bond between DXI and CAF so that further determination of the crystal structure can be performed by single-crystal X-ray diffraction method to know the solid form of multicomponent crystal as well as its stoichiometric ratio.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgments

This study was supported by the Institute for Research and Community Service of Universitas Jenderal Achmad Yani, Cimahi, Indonesia as a private university grant (Skep/175/Unjani/VI/2021).

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