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Original Article

# STUDY OF PHYSICAL INTERACTION BETWEEN IBUPROFEN AND CAFFEINE AND ITS INFLUENCE ON SOLUBILITY AND HYGROSCOPICITY OF IBUPROFEN

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**ABSTRACT**

**Objective:** Physical interaction between two or more pharmaceutical substance linkaged by hydrogen bonding can improve the physicochemical properties. This research investigated ibuprofen–caffeine physical interaction that never investigated. The research followed by observed the interaction influence towards ibuprofen solubility and hygroscopicity.

**Methods:** Ibuprofen, caffeine, and a series mixture of ibuprofen-caffeine; before and after neat grinding was characterized with *Fourier-Transform Infrared Spectroscopy* (FTIR), *Differential Thermal Analysis* (DTA), Powder X-ray Diffraction (PXRD). Solubility in water was examined by UV VIS Spectrophotometer. Hygroscopicity test was done by stored the physical interaction mixture in the extreme humidity (99% RH); next the water content was determined by Karl Fisher titration.

**Results:** FTIR spectra C=O stretching showed a little shifting after a neat grinding. DTA thermograms showed the lower melting point compared its components. Diagram phase of the binary system showed first the lowest temperature at 73.7 °C of ratio 1:9 and 145 °C of ratio 8:2. However, diffractogram of ground mixture didn't show any new spectrum, indicated no new crystal phase arranged. Last, solubility and hygroscopicity showed that the physical interaction had the higher value on both parameters compared to each compounds.

**Conclusion:** Ibuprofen–caffeine indicated to form the physical interaction, which has lower melting point without new crystal phase formation, that is cathegorized as an eutectics interaction. Nevertheless, this eutectic mixture causes the increasing of ibuprofen solubility and hygroscopicity.

**Keywords**: Ibuprofen, Caffeine, Eutectic, Solubility, Hygroscopicity.

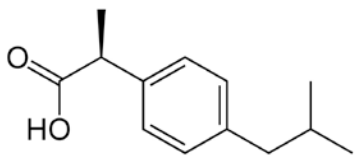
## INTRODUCTION

Recently, physical interaction between pharmaceutics substances widely studied, in purpose to improve their physicochemical properties. The physical interaction can be chategorized as: eutectic, peritectic, and molecular compound/co-crystal. Eutectic interaction is showed with one melting point of the mixture that lower then each component. Peritectic mixture will be showed with more than one eutectic point. Next, co-crystal is a single phase material, which is indicated by two melting points on the diagram phase; composed from thermal analysis data, such as electro-thermal measurement data, thermogram yielded by (DSC), (DTA) and/or TGA. All of these physical interactions should be confirmed by crystal structure study with diffractometry X-ray, NMR (Neutron Magnetic Resonance), etc. The physical interaction does not rule out the possibility followed by chemical interaction and the change of compound's stability. Therefore, study of interaction between compounds should be considered, because it will provide important information in pharmaceutical fields [1-5].

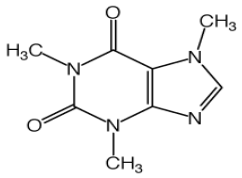
Ibuprofen is an analgesic NSAID (*Non steroid analgesic anti-inflammatory drug*), which has low solubility in water [6]. On the other hand, caffeine is a stimulant that very soluble in water [7]. Ibuprofen and caffeine are both already reported as they can form co-crystal with variant of substances, in purpose to improve their physicochemical properties. The formation of these physical interactions was expected can increase the solubility of ibuprofen [8-12]. However, there is still no evidence of both substances (ibuprofen and caffeine) physical interaction.

In common, the physical interaction predicted can occur between substances that have functional groups which different electronegativity. For a co-crystal, is known as "syntone", derived from a combination of words "synth one" as the linkage site. This site is very important to be known and understood for a successful co-crystal development. The difference of electronegativity will promote the physical interaction as co-crystal, with the distance of pKa not more than 2.7 [15-17]. The physical interaction, especially co-crystal can be produced by several methods, such as melting, co-solvent crystallization, solvent drop grinding, slurry method, wet grinding, etc. [8-16].

Structures of ibuprofen and caffeine are shown in fig.1. Ibuprofen has the chemical name 2-(4-isobutylphenyl) propionic acid or α-methyl-4-(2-metilpropil) benzenacetic acids with a molecular structure showed in fig.1A [6]. Ibuprofen has carboxylic site and has pKa: 4.91. Caffeine has the chemical name 1H Purin-2,6 dione, 3,7-dihydro, 1,3,7-trimethyl, 1,3,7-trimetilxantin the molecular structure as showed in fig. 1B, has di-one and purin base site with pKa: 3.63 [7]. Theoretically, these compounds can bind each other in a kind of physical interaction, because the pKa difference laid less than 2.7 [15-17].




A




B

**Fig. 1: (A). Ibuprofen structure and (B). Caffeine**

Solubility is one of the chemical properties of the active pharmaceutical ingredients that very important to be determine. Drugs that have low solubility in water often show low bioavailability. Various methods have been developed to modify the solubility and bioavailability of the drug in order absorption process for the better or the maximum. One method recently developed is a technique that will be generated solid dispersion which take advantages of variants of physical interaction such as eutectic mixtures besides co-crystallization. Several studies have shown that the results obtained have physical properties and stability that are superior to native compounds. The development to be expected can improve the solubility, dissolution rate, stability, and hygroscopicity without affecting the pharmacological effects of these materials [8-17].

Ibuprofen has a low solubility in water. It has been reported other co-crystal such as ibuprofen with nicotinamide by forming hydrogen bonds with the carboxyl group and expected can increase the solubility of ibuprofen. The formation of caffeine as co-crystal with malonic acid, oxalic acid and glutaric acid has been found and discussed widely [12-14]. However, it has not been reported co-crystal or other kind of physical interaction between ibuprofen with caffeine.

## MATERIALS AND METHODS

Powder ibuprofen, caffeine and ibuprofen-caffeine physical mixture (1:1) were characterized by Fourier-transform infrared spectroscopy (FTIR), differential thermal analysis (DTA) and X-ray powder diffraction (PXRD). Physical interaction formation dynamics observed experimentally by grinding with a mortar of the ratio series of ibuprofen-caffeine mixtures = 1:9, 2:8, 3:7, 4:6, 1:1, 6:4, 7:3, 8:2, 9:1 for 60 min. The grinding is expected to induce the physical interaction. Further characterization was carried out to observe the formation of physical interaction with FTIR, DTA, and PXRD. Improvement of physicochemical properties and solubility of ibuprofen was observed using UV (ultra violet) spectophotometric.

### Characterization of raw materials

Raw materials were characterized using solid's analytical instruments such as: FTIR, DTA, and PXRD.

### Identification by FTIR

Identification by FTIR spectroscopy was performed with a sample preparation technique KBr plates. Plates are made by trituration with a number of sample spectra grade KBr in the ratio 1:100 w/w. In experiments conducted with the weighing METLER Toledo AG104 analytical balance to 100 mg of dry KBr (which has been stored in the oven 100 °C) with 1 mg of the sample, and then slowly crushed by agate mortar until homogeneous and then the mixture of sample and KBr discs filled into the mold of stainless steel size of±13 mm. The disc containing sample was next compressed with a hydraulic press pressure±7.5x$10^{-3}$ mm Hg. Then, the disc was mounted in a holder, afterwards the spectrum measured at wave numbers 4000-400 $cm^{-1}$. Measurement assisted with software Jasco Spectra Manager II output, which is already in the Jasco FTIR-4200 instrument. Before analyzing the samples, measurement of the background to see the influence of environmental conditions and tools. Identification by FTIR is used to confirm the identity of the compound, and also to see the shifts in the FTIR spectra during the grinding process.

### Characterization by DTA

Approximately 5-10 mg of the sample was stored in a special aluminum cup for the preparation of the DTA. Subsequently, the sample was heated under a nitrogen gas flow with heating rate of 10 °C/min, from 40 to 250 °C.

### Characterization by PXRD

PXRD analysis was done by using a 200 mg samples was prepared on a sample plate to test X-ray powder diffraction. Type diffractometer: PW 1710 BASED; tube anode: Cu; voltage 40 kV, current of 30 mA, 0.2 inches wide split. Data were collected at a scan speed of 0.8 seconds per step with the scanning distance at 2θ = 2 to 60 °.

### Early orientation of the physical interaction of ibuprofen-Caffeine

Physical interaction between ibuprofen and caffeine was identified using three methods: analysis of FTIR, DTA analysis and PXRD analysis.

### FTIR analysis of grinding mixtures

Ibuprofen-caffeine mixture was weighed according to the molar ratio of 1:9, 2:8, 3:7, 4:6, 1:1, 6:4, 7:3, 8:2, 9:1; next, were milled for 60 min. Samples were taken after grinding is complete, then were analyzed by FTIR.

### DTA analysis of grinding mixtures

Ibuprofen and caffeine with a molar ratio of 1:9, 2:8, 3:7, 4:6, 1:1, 6:4, 7:3, 8:2, 9:1 were weighed, then mixed until homogeneous using a mortar, afterwards the mixture was analyzed by DTA.

### PXRD analysis of grinding mixtures

Ibuprofen-caffeine mixture was weighed according to the molar ratio of 1:9, 2:8, 3:7, 4:6, 1:1, 6:4, 7:3, 8:2, 9:1; then milled for 60 min. The samples were taken after grinding was complete, afterwards freshly be analyzed with PXRD.

## RESULTS AND DISCUSSION

FTIR spectra of physical mixture of ibuprofen and caffeine on the various molar ratio after a neat-grinding is described in fig.3 below:

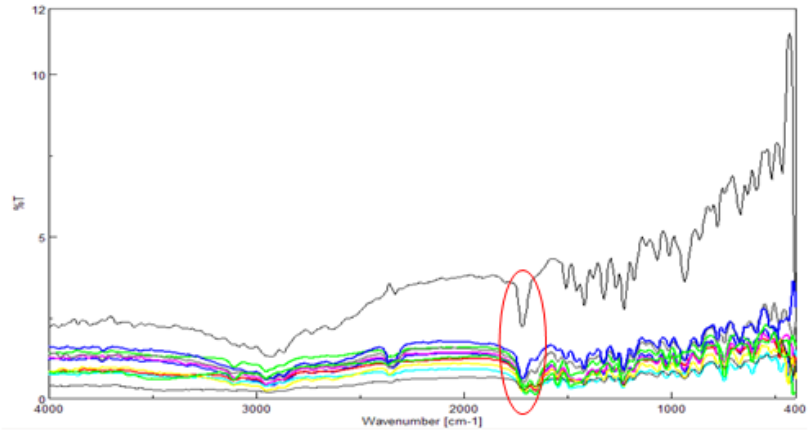



**Fig. 2: From The Bottom to The Top: FTIR Spectral Data of Ibuprofen, Caffeine and Ibuprofen-Caffeine on The Molar Ratio (1:9), (2:8), (3:7), (4:6), (5:5), (6:4), (7:3), (8:2), (9:1) After Neat-grinding**

Furthermore, the shifting of the spectrum was listed in table 1 below.

**Table 1: FTIR spectrum data for ibuprofen, caffeine, ibuprofen-caffeine in various compositions after the neat grinding**

| Sample | C=O (Carboxylic) Streching ($cm^{-1}$) |
|---|---|
| Ibuprofen | 1720.19 |
| Caffeine | 1700.91 |
| Ibuprofen: Caffeine (1:9) | 1700.91 |
| Ibuprofen: Caffeine (2:8) | 1704.76 |
| Ibuprofen: Caffeine (3:7) | 1700.91 |
| Ibuprofen: Caffeine (4:6) | 1708.62 |
| Ibuprofen: Caffeine (5:5) | 1708.62 |
| Ibuprofen: Caffeine (6:4) | 1712.48 |
| Ibuprofen: Caffeine (7:3) | 1716.34 |
| Ibuprofen: Caffeine (8:2) | 1712.48 |
| Ibuprofen: Caffeine (9:1) | 1716.34 |

Next, the results of DTA were compiled in fig. 3 as follows.

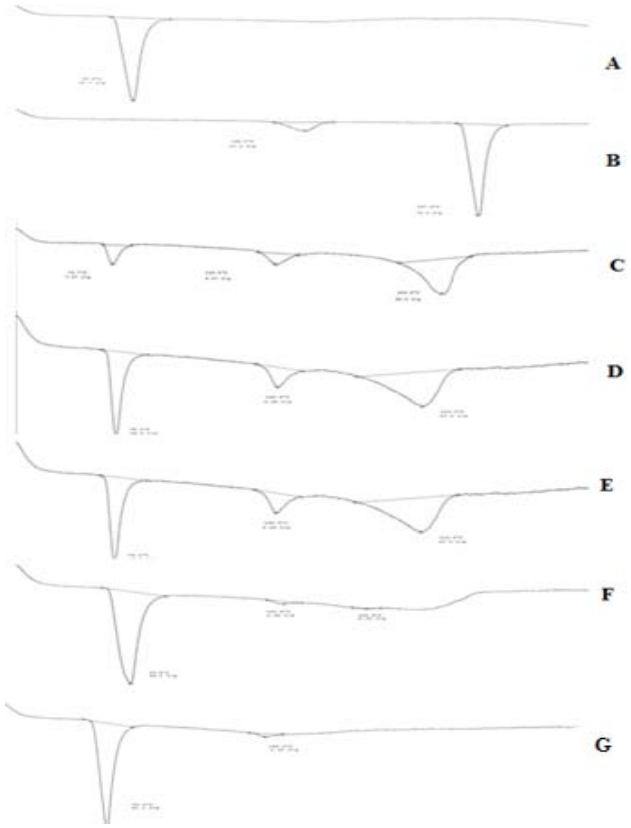



**Fig. 3: DTA thermogram of: A. Ibuprofen B. Caffeine C. Ibuprofen-Caffeine (1:9) D. Ibuprofen-Caffeine (2:8) E. Ibuprofen-Caffeine (3:7) F. Physical Mixture of Ibuprofen-Caffeine (1:1) G. Ground Ibuprofen-Caffeine for 60 Min (1:1)**

The melting temperature (endotermic curve) data resulted from DTA analysis were listed in table 2 below.

**Table 2: Melting point of ibuprofen, caffeine, and the physical mixtures**

| Ibuprofen: Caffeine | EC-1 | EC-2 | EC-3 |
|---|---|---|---|
| | (°C) | | |
| 1: 0 | 80.3 | | |
| 1: 9 | 73.7 | 149.5 | 226.6 |
| 2: 8 | 74.1 | 148.4 | 214.5 |
| 3: 7 | 75.1 | 148.0 | 201.1 |
| 4: 6 | 76.2 | 149.0 | 200.3 |
| 5: 5 | 79.9 | 151.6 | 189.4 |
| 6: 4 | | 153.0 | 191.6 |
| 7: 3 | | 156.0 | 196.7 |
| 8: 2 | | 145.0 | 219.5 |
| 9: 1 | | 160.0 | 228.1 |
| 0: 1 | | 162.0 | 237.8 |

Note: EC: endotermic curve.

The melting point data then plotted into a diagram phase shown in fig. 4.

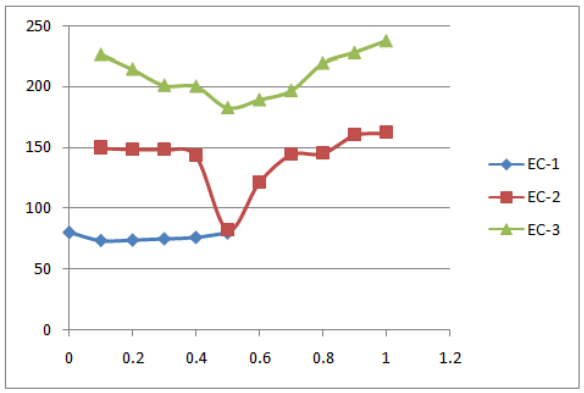



**Fig. 4: Phase diagram of ibuprofen-caffeine**

Then, the diffractogram yielded by PXRD is shown in fig. 5 as follows:

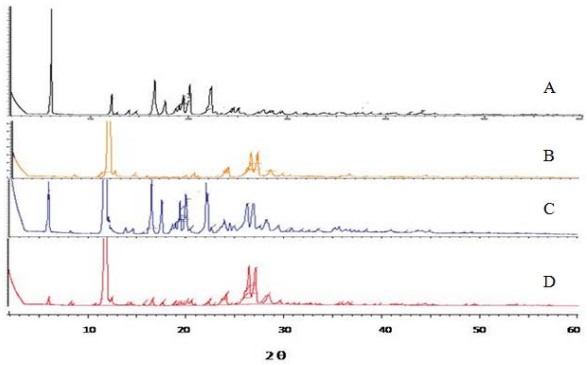



**Fig. 5: PXRD Diffractogram of: A. Ibuprofen B. Caffeine C. Mixture of Ibuprofen-Caffeine (1: 1) before Grinding, and D. Ibuprofen-Caffeine (1: 1) after Grinding**

The solubility test was done on the standard raw ibuprofen and the physical interaction product (1:1) by dissolve these materials in the distilled water with a temperature of 37±0.5 °C, equiped with an orbital shaker, and was done in *triple* experiments. The results from the solubility test were then measured with a spectrophotometer UV-Vis absorbance maximum of 222 nm with 2 solvent (NaOH and HCl 0.1N) [18]. The result is shown in table 3.

**DISCUSSION**

It has been explained that physical interaction can be promoted by several methods, one of them is grinding. In this research, the physical interaction between ibuprofen–caffeine was tried to induce by neat grinding. This method was choiced due to simplicity, can keep the chemical stability, and the low energy used. The previous research about ibuprofen and nicotinamide co-crystal has been reported that there is a physical interaction between the two active compounds as co-crystal which yielded by several methods too, such as grinding and slurry methods.

FTIR has been reported by Matkovic *et al.*, 2005, had be used to quantify ibuprofen in tablet with the specific peaks at the area 1650–1750 $cm^{-1}$ [8]. Furthermore, the recent research also reported the using of FTIR to identify the formation of ibuprofen-nicotinamide co-crystal and shows that carboxyl group of ibuprofen interact to form hydrogen bonds with the carbonyl of nicotinamide which leads to changes of FTIR spectra at wave number 1722 $cm^{-1}$ becomes 1708 $cm^{-1}$[9].

However, in this research, the result of FTIR experiment is shown in fig. 2, then detailed in table 1. The fig. and table shows the changes in the intensity of the wave number in the carboxylic of ibuprofen which originally showed at 1720.19 $cm^{-1}$ change into 1700.91 $cm^{-1}$after grinding. This change indicated the possibility of occurrence of physical interaction between carboxylic moety of ibuprofen with carbonyl of caffeine (C = O stretch). According to the fig. 2 and table 1, FTIR spectra of ibuprofen on a stretch of 1720.19 $cm^{-1}$, in general showed the wavelength shift after the mixture of ibuprofen–caffeine ground, then showed the smaller shifted until to 1700.91 $cm^{-1}$.

From previous research reported by Kumar and Seethalakshmi *et al.*, 2013, the stretching frequencies of carboxylic carbonyl of the 1 and 2 naphthoxyacetic acids (1744 and 1738 $cm^{-1}$) merge together with the carbonyl group of caffeine (1700,1657 $cm^{-1}$) and appear as three new bands in the co-crystals. The formation of the co-crystals could be confirmed by the changes in the carbonyl stretching frequencies [14]. The change in carbonyl stretching frequency in co-crystals is due to the involvement of intermolecular hydrogen bonding. Mean while in this experiment, evident was only in one spectra change, which leads to the supposition that the interaction not as strong as occured in caffeine-naphthoxyacetic co-crystal.

**Table 3: Solubility in water**

| Sample | Concentration (ppm) | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | Average |
| Ibuprofen | 0.823 | 0.792 | 0.818 | 0.811±0.014 |
| Ibuprofen: caffeine (1:1) | 8.847 | 8.291 | 8.676 | 8.605±0.232 |

Furthermore, a simple hygroscopicity test was conducted into the eutectic mixture by storage in high humidity (99%RH) and evaluated its water content periodically [10,19]. The result of hygroscopicity test is shown in table 4.

**Table 4: Water content of ibuprofen and co-crystals after storage at 99% RH**

| Sample | Water (%) | |
|---|---|---|
| Time of storage | Ibuprofen | Eutectic mixture (1:1) |
| 0 | 0.443±0.09 | 0.709±0.12 |
| 3 | 1.885±0.21 | 3.799±0.29 |
| 6 | 1.784±0.11 | 3.469±0.15 |
| 9 | 1.885±0.23 | 4.046±0.31 |

Furthermore, the formation of physical interaction between the two materials can be confirmed and estimated using thermal analysis, here was using DTA, that expected to identify the crystal changes from solid thermodynamic aspects [1-5]. The change of thermal properties showed clearly from the different thermograms shown in fig. 3. The change of temperature endothermic peaks of each ratio of ibuprofen-caffeine mixture describes the change of the thermal properties directly due to the physical interaction. Data of the endothermic curves then arranged to a diagram phase. The phase diagram is shown in fig. 4. The shape of the phase diagram explains the lower melting point of each mixture prepared, arrange an eutectics profile. From all thermal data indicated the formation of an

eutectic mixtures with typical low melting temperature at 73.7–79.9 °C. This directly indicated a change in the thermodynamic state of ibuprofen when mixed with caffeine. The lower melting point described the change to the lower bonding energy.

In the next step, all of data of FTIR spectra, DTA thermogram, and diagram phase of ibuprofen-caffeine physical interaction was confirmed by PXRD. This analysis was conducted to identify the change of crystalline form by comparing the spectrum profile and intensity of the spectra in the diffractogram of the sample profile that was already known for ibuprofen [9,10] and caffeine [13,14]. As known, the diffractogram of treated mixtures can detect the occurance and identify the type of physical interaction between compounds. Co-crystal will show a lot of changes of diffractogram peaks, meanwhile eutectics will not. The diffractogram in fig. 5 shows no changes of the peaks/spectrum position of 2θ, explain that the interaction did not change the lattice crystal arrangement as required in co-crystal formation. Fig. 5C and D shows just a pure compilation, that all peaks of ibuprofen (fig. 5A) and caffein (fig. 5B) appear at all but with lower intensity. After grinding, the intensities of peaks decreased as shown in fig. 5D, compared to fig. 5C (physical mixture before grinding), indicated that the mixture has the lower energy after the treatment. It was confirmed with the diagram phase, which showed an occurance of an eutectic physical interaction.

Furthermore, the lower crystallinity, inconsequence of a decrease in lattice energy, which will cause the bonds between molecules in solids more easily detached and then easy to interact with a suitable solvent. As shown in table 3, the solubility of the eutectics mixture of ibuprofen–caffeine produced by physical grinding in various ratios were higher than standard ibuprofen alone. The increasing of compound's solubility in other eutectic mixtures also have been reported by Liua and Feib, 2006 [19] and Cherukuvada and Nangia, 2014 [20]. Moreover,the increasing of compound's solubility also will affect on its dissolution, then finally the biovailibility. The increasing solubility in a line with the higher dissolution and subsequent increase in bioavailability. From the aspect of physical properties of material, the increasing of solubility commonly in a line with the increasing of hygroscopicity [10,13]. In addition to a decrease in lattice energy, increased solubility and hygroscopicity probably caused also by the formation of finer particles. Crystal melting will support molecular mixing of the solid compounds that produces the finer crystals, with a wider surface area after the solidification/recrystallization.

Furthermore, testing of hygroscopic also conducted. This test is performed under an atmosphere of extreme 99% RH [10], towards the raw ibuprofen standards and mixture at a ratio (1:1) for 9 h; with sampling on 3rd, 6th, and 9th h storage. The sample's water content then analysed using Karl Fisher titration. The result showed in table 4. This test is done to see hygroscopicity of co-crystals compared to ibuprofen that are known to be not hygroscopic. Table 4 shows that the water content of ibuprofen in the physical mixture was increased during the storage. It means that the eutectic mixture rather less stabile compare to ibuprofen itself because water can promote instability: physical, chemical, and microbiological. All the data proved that the physical interacting between these compounds change its physichemical properties especially on the hygroscopicity as well as solubility of ibuprofen that becomes higher. In industrial pharmacies, the eutectic phenomenon has been utilized deliberately to improve the physicochemical of active ingredients. Commonly, the active pharmaceutical ingredients are mixed with various kind of excipients, and this technique bases on the mechanism of pharmaceutical solid dispersion technology [19, 20].

However, on the other hand, an eutectic mixture can lead to trouble. On a small scale, the mixing of solids by grinding in powders preparation, or on a large scale of solid dosage form manufacture, the decreasing of melting temperature can produce the undesirable drug's physicochemical properties. Finally, the study about physical interaction will always be an important part upon the pre-formulation stage such scientific information for a pharmacist to optimize the processing of pharmaceutical materials in order to obtain a product that is safe, effective, and quality.

## CONCLUSION

Ibuprofen-caffeine forms eutectic physical interaction with the eutectic point at±73.1–79.9 °C. Ibuprofen in this interaction has higher solubility 10 times as well as its hygroscopicity that increases about two folds compared to ibuprofen alone. This information is important to note both the preparation of recipes, storage, and mixing of solids in the dosage form manufacturing.

## CONFLICT OF INTERESTS

Declared None

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