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Development of the NSAID-L-Proline Amino Acid Zwitterionic Cocrystals

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAID) belong to class II of the Biopharmaceutics Classification System (BCS) which exhibit low aqueous solubility. The crystal engineering technique such as cocrystallization is an effective strategy to improve the solubility of drugs. Recently, exploration of the zwitterionic cocrystals involved amino acid, has been started and gained a lot of interest in the pharmaceutically active substance development. Under the guidance of the crystal engineering concept, cocrystal formation of some NSAID was investigated. The drugs are: mefenamic acid, ketoprofen, and diclofenac acid meanwhile L-proline was used as a co-former. Cocrystal screening was conducted by liquid assisted grinding (LAG) with ethanol using the equimolar ratio of drug and L-proline. The dynamic formation of the new phase was monitored by FT-IR of both LAG and neat grinding (NG) crystallization method. Beyond the three of drugs, only diclofenac acid and L-proline interaction showed hydrogen bond that was initially identified by the FT-IR method. This result was supported by the melting point change on the thermogram and the significant differences in diffractogram pattern. Furthermore, the hydrogen bond formation is clearly observed by using the FT-IR method. Next, the formation of the crystalline phase by LAG occurred faster than NG method. Finally, this study found the new phase arrangement between diclofenac acid and L-proline, which strongly indicate a cocrystal. The dynamic of the cocrystal arrangement also was shown influenced by the method, in which LAG was faster than NG method.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAID) are one of the most frequently used drugs all over the world for the symptoms of osteoarthritis and other chronic musculoskeletal conditions (Griffin, 1998). NSAID also reduces the risk of and mortality from colon cancer by about half and constitutes the ideal colon cancer chemopreventive agents (Chan, 2002). Mainly, the usage of NSAID was limited by its poor solubility in water. Most of NSAID belong to class II of the Biopharmaceutics Classification System (BCS) which exhibit low aqueous solubility. Several techniques have been used to improve solubility of drugs in water. Those are such as the addition of surface active agents, the formation of salts, the polymer to enhance solubility and bioavailability of drug and also crystal engineering with the cocrystal formation (Ullah *et al*., 2011; Koc *et al*., 2013; O'Connor *et al*., 2001; Kojima *et al*., 2010).

The chemical properties of NSAID showed that all the drugs exhibit acidic character. The pKa value of most is in the range of 3.0–5.0 as acids of medium strength (Gauda *et al*., 2013). Therefore, the cocrystal of NSAID can be designed based on its acidic character. Empirical rule states that a pKa difference between 0 and 3.75 can arrange the intermolecular H-bonding, which has no clear ionic or covalent nature. Meanwhile, the greater distance of pKa more than 3.75 should lead to proton transfer and salt formation (Pallipurath *et al*., 2016). Considering the rules, the cocrystal was predicted can be designed from NSAID with the acid/base functional group of co-formers in a close pKa.

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In this study, some NSAID: mefenamic acid (MFA), ketoprofen (KTP) and diclofenac acid (DFA) were used as the selected drugs and zwitterionic amino acid L-proline (PRO) as the co-former. This selected co-former was related to the restricted and rigidity of its structure that builds by five-member ring lateral chain. From previous researches, L-proline has already reported being successful co-former of some NSAID like naproxen and flurbiprofen (Tilborg *et al*., 2013; Silva *et al*., 2016). As stated by Tilborg *et al* (2013), L-proline molecule contributes general geometrical and organizational behavior for structures of naproxen cocrystal.

Based on the structural feature of MFA, KTP, and DFA as shown in Figure 1, there are two possibilities of hydrogen bond formation. The first H-bond is predicted from the hetero-synthon interaction between the carboxylic acid of NSAID and the amine heterocyclic of L-proline. The other H-bond is built by homo-synthon interaction of two acid sites from both sites of drugs and L-proline.

Herein, the possibility of cocrystal formation between selected NSAID and L-proline, which will improve its physicochemical properties, was investigated. Moreover, in order to study about structural evolution in molecular level of the interaction, an investigation of its dynamic also was conducted. The cocrystal formation along the grinding of the NSAID-L-proline mixture was characterized by Fourier transform infrared (FT-IR). This vibrational spectroscopy, despite Raman and Terahertz spectroscopy, has been proven capable of providing such information both of intramolecular and/or intermolecular interactions of pharmaceuticals, especially in their solid-state (Cai *et al*., 2017).

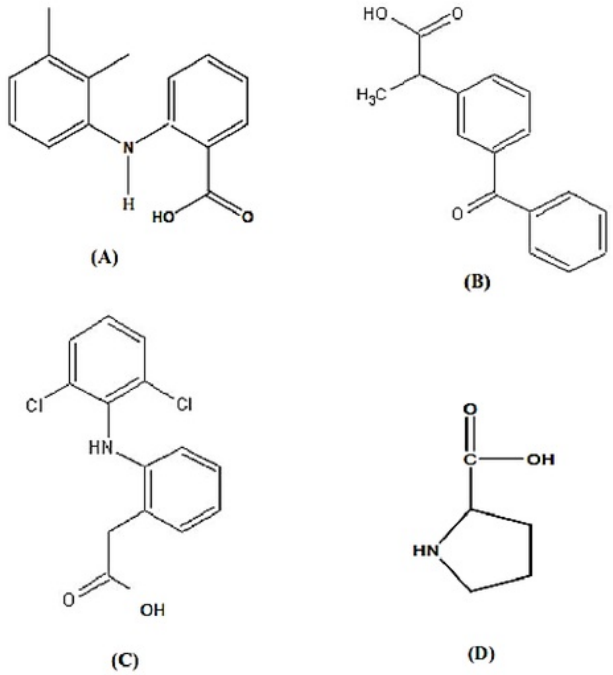

Fig. 1: Chemical structure of (A) Mefenamic acid, (B) Ketoprofen, (C) Diclofenac acid, (D) L-Proline.

MATERIAL AND METHODS

Materials

The NSAIDs were obtained from Pyridam Pharmaceutical Industry (mefenamic acid), Kalbe Farma Pharmaceutical Industry (ketoprofen) and Phapros pharmaceutical industry (diclofenac sodium). L-proline was purchase from Xi'an Zhongyun Biotechnology Co., LTD. The purity of these chemicals was >99%. All solvents that were purchase from E-Merck and were used without purification.

Methods

Diclofenac sodium (10 g) was dispersed into 200 ml purified water, and then 6,8 ml of hydrochloride acid (6N) was gradually added to the mixture under continuous stirring. After all the acid was added, the mixture was sonicated in a sonication bath for 30 minutes. After sonication, 50 ml of ethyl acetate was added to the beaker to dissolve the solid. The ethyl acetate layer was separated by a funnel and washed with purified water twice. Then the ethyl acetate solution was mixed with anhydrous sodium sulfate to eliminate the water content and filtered through filter paper. Then ethyl acetate was evaporated and the diclofenac acid was dried at 75°C in the oven for one hour.

Cocrystallization screening via liquid assisted grinding (LAG)

Equal stoichiometric amounts of NSAID (MFA, KTP, DFA) and L-proline was mixed and ground with a mortar

and pestle, by addition of 50–100 µl ethanol every 10 min grinding time. After 30 min, the powders were dried at the room temperature for 30 minutes and stored in a desiccator for infra-red spectrophotometric (FT-IR) analysis.

Cocrystallization via neat grinding (NG) for selected interaction

Equal stoichiometric amount of selected NSAID and L-proline was prepared with an automatic grinder (Retsch mortar RM 100) at 5 scales. Grinding was carried out for 30 min. After 30 min, the powders were dried at the room temperature for 30 min and stored in a desiccator for infra-red spectrophotometric (FT-IR) analysis.

Fourier Transform Infrared Spectroscopy (FT-IR) analysis

The powders resulted from cocrystallization product, pure drugs, coformers and the physical mixture were analyzed by Infrared Spectrophotometer (Jasco-4200 type A). Samples were grounded with potassium bromide and measured in pellet form. The samples were scanned in 450 to 4000 cm^{-1} wavenumber region, at room temperature with a 4 cm^{-1} resolution.

Thermo Gravimetry-Differential Thermal Analyzer (TG-DTA)

DTA was used to analyze the thermic properties. The DTA (Perkin Elmer Thermal Analyzer/Pyris diamond TG-DTA) was calibrated with indium before analysis. A certain amount of samples, i.e. 3–5 mg samples were placed in a sealed aluminum pan. The analysis was performed in a temperature range of 50 to 300°C with a heating rate of 10°C per minute.

X-ray Powder Diffractometry (XRPD)

The powder X-ray diffraction analysis was performed in Philips PW 1710 BASED and illuminated with radiation of Cu-Kα (λ = 1.5418) at a tube voltage of 40 kV and a tube current of 35 mA. The samples were analyzed over a 2θ range of 5–45° with the increase of 0.019° at a rate of 7°/min

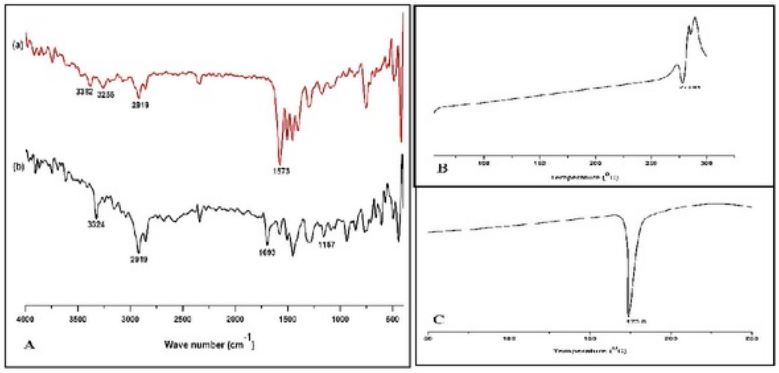

Fig. 2: (A) The FT-IR spectra of diclofenac sodium salt (a) and diclofenac free acid form (b); (B) the thermogram of diclofenac salt form (DFS) and (C) the thermogram of diclofenac free acid form (DFA).

Dynamic study of the cocrystal formation by FT-IR analysis

Cocrystal's formation of selected drugs with L-proline was monitored time by time, using an automatic grinder (Retsch mortar RM 100) at scale 5 with solvent addition (LAG method) or without solvent addition (NG method). Grinding was carried out for predefined time periods from 2 to 90 min. The samples were used to investigate the kinetics of new phase formation by FT-IR analysis.

RESULT AND DISCUSSION

Production diclofenac acid (DFA) by diclofenac sodium (DFS) hydrolysis

DFA which yielded from DFS hydrolysis was characterized by FT-IR and DTA. Figure 2 showed the information provided by the spectra FT-IR profile, which distinguished DFS from DFA. The DFA's spectra showed a specific absorption peak at 3324 cm^{-1} which correspond to free OH stretching of a carboxylic group. Free acid was also presented as a peak at 1693 cm^{-1} associated with C=O stretch and 1157 cm^{-1} correspond to the C-O stretch. These peaks were absent in its sodium salt spectrum. The thermogram of DFA measured by DTA is also displayed in Figure 2, which shows the endotherm curve of melting at 173.8°C, similar to the base-drug property (Barbato *et al.*, 2003). Therefore, based on both FT-IR and thermal analysis, confirmed that DFA was successfully prepared from DFS hydrolysis and ready to be used as a cocrystal raw material.

Screening cocrystal formation

In this study, the liquid assisted grinding was conducted due to its highly efficient methods of screening for cocrystal formation (Karki *et al.*, 2007; Friscic *et al.*, 2006). FT-IR spectroscopy was chosen as the spectroscopic tool for evaluation of interaction between MFA, KTP, and DFA with L-proline in the cocrystal. The FT-IR analysis of cocrystal screening was showed in Table 1. The result showed that only the diclofenac acid-L-proline that presented the different FT-IR spectrum from its physical mixture. The FT-IR change was indicated as a new crystalline phase formation. The FT-IR spectrum of MFA-PRO

and KTP-PRO was revealed the same spectrum with those physical mixtures. The hydrogen bond formation as the cocrystal hint was not observed during liquid assisted grinding treatment. Otherwise, in the DFA-PRO spectra, there were several wavenumber-shifting of the physical mixture. The carbonyl group of the carboxylic acid group of the interaction is shifted from 1693 cm^{-1} (pure DFA) to 1689 cm^{-1}. The change of the wave number of the carbonyl group indicated the hydrogen bond formation between DFA and PRO. The OH free carboxylic acid of DFA is also shifted to a lower frequency from 3324 cm^{-1} to 3270 cm^{-1}. The new absorption occurred in 1982 cm^{-1} and 2541 cm^{-1}, that generated from hydrogen bond of O...H-N (heterocyclic) or O-H...N (heterocyclic), that similar with hydrogen bond formation of diclofenac acid with pyridines and pyrimidines families (Aakeröy *et al.*, 2011).

Based on the structural molecule of each NSAID (MFA; KTP and DFA) as shown in Figure 1, there are several proposed explanation, regarding the occurrence of DFA-PRO specific interaction. Compare to DFA and MFA structure, the synthon of KTP is weaker than both NSAID. The two aromatic ring of KTP is linked by carbonyl functional group, which is weak hydrogen bond donor compared to imino group as stated in DFA structure. The analysis using computational calculation, KTP showed that there are only one hydrogen donor and three hydrogen donor acceptors, whether in DFA molecule, there are two hydrogen donor and three hydrogen donor acceptors.

Furthermore, according to Seethalekhsmi *et al.* (2012), in MFA structure, the phenyl ring with carboxylic acid functional groups and imino bridges is coplanar, formed by strong hydrogen intra-molecular N-H bonds (H...O, 1.82 Å). MFA molecules form symmetric dimers, and adjacent dimers are connected via C-H...π (2.77 Å). This interaction involving C-H aromatic and alkylated phenyl rings. As the result, the MFA molecule prefers to construct a homodimeric interaction than a heterodimeric interaction with other molecules, in case L-proline coformer. The N atom of the imino bridge of MFA is also hindered by ortho substitution of the carboxylic acid functional group. Therefore, the less probability of molecular interaction between MFA-PRO occurs.

Further characterization of new phase crystalline formation

As explained in the previous section, the DFA-PRO has revealed the hydrogen bond formation, which indicated by the new spectra from infrared (FT-IR) analysis. In the cocrystal preparation, despite liquid assisted grinding, it also explored the other mechanic-chemical method. Neat grinding has reported as the more environmentally friendly method due to the absence of a solvent. The process is not temperature dependent and can be performed at room temperature and free from solubility consideration (Kaupp, 2005). Furthermore, in order to verify the new phase, the LAG and NG product of DFA-PRO (1:1) was investigated using solid instrument analysis, such as FT-IR, DTA, and PXRD.

Table 1: Screening of new phase formation of NSAIDs with L-Proline based on shifting of FT-IR spectra.

Compound	Pure compound		LAG product of compound-PRO (1:1)			Outcome
	C=O (cm^{-1})	O-H (cm^{-1})	C=O (cm^{-1})	O-H (cm^{-1})	O-H----N (cm^{-1})	
MFA	1650		1650		-	-
KTP	1734		1734		-	-
DFA	1693	3324	1689	3270; 3166	1982; 2541	+

Figure 3 shows that both of LAG and NG product of DFA-PRO have the similar infra-red spectrum at the specific wavenumbers of around 3270, 3166, 1980, and 1681 cm^{-1}. The spectrums are confirmed as the hydrogen formation of DFA-PRO. Therefore, it can be concluded that the new crystalline phase of DFA-PRO is also obtained by neat grinding preparation.

In addition, based on structure analysis, DFA has a carbocyclic acid with pKa 4.46, meanwhile, L-proline is a zwitterionic amino acid with the basic functional group in N heterocyclic chain. Therefore, this combination has a possibility to form a salt. In this case, FT-IR is also a very powerful tool in distinguishing cocrystal from salts when a carboxylic is involved in hydrogen bond formation (Aakeröy *et al.*, 2006).

According to O'Connor *et al.* (2001), the salt formation is confirmed by the absence of the carbonyl peak at 1684 cm^{-1}. In LAG or NG of DFA-PRO, there was a peak of free carboxylic acid at around 1683 cm^{-1}. Aakeröy *et al.* (2011), also stated that if the neutral diclofenac acid has been converted into a carboxylate anionic, COO^- moiety will appear below 1675 cm^{-1}. Thus, this analysis was proved that cocrystal occurred more from DFA-PRO than a salt formation.

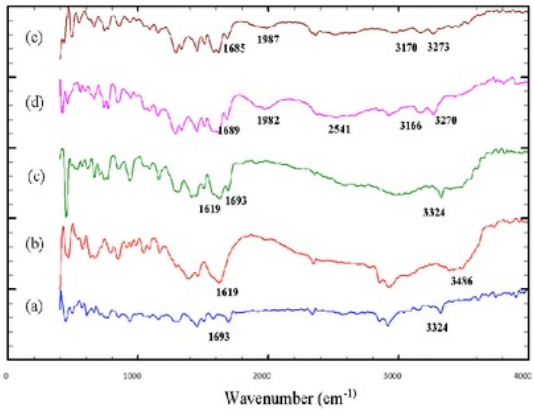

Fig. 3: FT-IR spectra of (a) DFA, (b) PRO, (c) physical mixture of DFA-PRO (1:1), (d) Liquid assisted grinding of DFA-PRO (1:1) and (e) Neat grinding of DFA-PRO (1:1).

Based on the design of cocrystal formation, when the cocrystal was arranged; only several functional groups are

involved in the bonding. Therefore, the rests of them remaining were unaltered. By the analysis of FT-IR spectrums of LAG and NG product of DFA-PRO (1:1), a number of unique shifts of IR peaks as well as the new ones were shown at around 3270, 3166, 1980, and 1681 cm^{-1}.

Moreover, in order to support the new crystalline phase of DFA-PRO that indicated as cocrystal formation, the LAG and NG product of DFA-PRO were analyzed by DTA. The DTA is the technique that widely used for the thermal property testing of cocrystals (Lu *et al.*, 2008). The profiles of DFA, PRO, LAG and NG product of DFA-PRO were presented in Figure 4. The formation of new crystalline phase can be detected by the difference of the thermogram compared to the pure compound. The thermal properties melting point of LAG and NG product of DFA-PRO was lower than those of DFA (173.8°C) and PRO (221.5°C). The different melting point of LAG and NG product of DFA-PRO indicated the formation of new solid phase that supported by the change of diffractogram pattern from PXRD data.

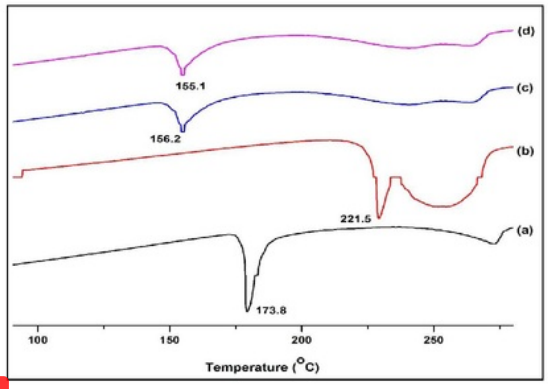

Fig. 4: Thermogram profiles of DFA (a), L-Proline (b), LAG product of DFA-PRO (c) and NG product of DFA-PRO (d).

The X-ray powder diffraction is one of the most common techniques for verifying different solid forms of a material. It can distinguish amorphous materials from crystalline. This instrument in most cases readily exhibits differences between phase forms based on the peak positions and intensities observed in the powder pattern (Anderton, 2007). The X-ray diffractogram patterns of the LAG and NG product of DFA-Pro were compared with those of raw material DFA and PRO and also the mixture of both. Figure 5 describes the diffraction pattern of LAG and NG product of DFA-PRO. The diffractogram patterns of both products are different from their physical mixture. Therefore, the new crystalline phase of LAG product of DFA-PRO has indicated the cocrystal formation.

Dynamic cocrystal formation based on FT-IR spectra

The dynamic formation investigation by grinding method is important for cocrystallization study. As stated by Dugiralla *et al.* (2016), the molecular interaction in cocrystal formation is dominantly by hydrogen bonding formation. The vibrational spectroscopic analysis, such as FT-IR, Raman, and Terahertz spectroscopy are the proper methods to observe the new hydrogen bond (Du *et al.*, 2017). In this study, the DFA-PRO cocrystal production was done by grinding of DFA-PRO at 1:1 stoichiometric in RM Retch mortar grinder. Then, the dynamic was observed in 2, 4, 10, 15, 30, 60, and 90 min of grinding time. The influence of solvent addition was also investigated by the liquid assisted method.

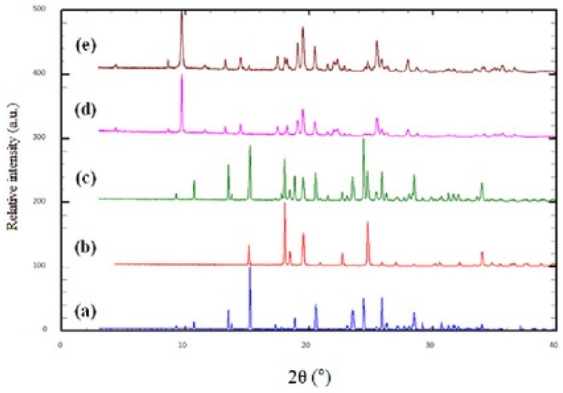

Fig. 5: Powder X-ray diffraction patterns of (a) Diclofenac acid (DFA); (b) L-Proline (PRO); (c) Physical mixture (PM); (d) Liquid assisted grinding (LAG) of DFA-PRO (1:1); (e) Neat grinding (NG) of DFA-PRO (1:1).

As shown in Figure 6, in the LAG method, upon grinding, there were significant changes in both FT-IR spectra during the grinding process which performed the dynamic. The transformation of cocrystal characteristic peaks is clearly apparent with increasing of grinding time. That was associated with a decrease or disappeared peaks of the parent compound (DFA and PRO). There are two regions of FT-IR spectra that showed the specific evolution of cocrystal formation, 1500–2500 cm^{-1} and 2500–4000 cm^{-1} regions. At the 1500–2500 cm^{-1} region, the carbonyl of DFA absorption was gradually shifted. It changed to the lower frequency starting from 1693 to 1685 cm^{-1} at 2 min of grinding time. Then, it fixed at 1685 cm^{-1} as the characteristic peak at 30 min of grinding time. The shifting of absorption of DFA was due to lowering the carbonyl vibration energy. It was the consequence of hydrogen bond formation of the N heterocyclic group of PRO. The shifting of N occurred at around 1456 cm^{-1}, unfortunately, was not observed in this result. It may predict that the N heterocyclic was overlapped with C-C of aromatic moieties of DFA and C-C of the five-member ring of PRO.

The new peak absorption also appeared in 1968 cm^{-1} as a board spectrum. According to Aakeröy *et al.* (2011), that reported the salt and cocrystal formation of diclofenac acid with some amino derivates. The broad spectrum at approximately 1900 cm^{-1} is due to the hydrogen bond formation O....H-N (heterocyclic). This peak initially appeared at 2 min of grinding time and become sharper as the complete formation at 60 min.

The distinctive peaks in 2500–4000 cm^{-1} are presented from 3324 cm^{-1} that correspond to O-H stretching from DFA. The absorption of OH stretching was shifted to the lower frequency up to 3270 cm^{-1}, accompanied with the new peak absorption at 3170 cm^{-1}. The O-H of the carbocyclic group of DFA is predicted to form the hydrogen bond with a carbonyl group of PRO. Therefore, the shifting was accompanied by the shifting of PRO carbonyl group. The C=O and C-O vibration of the carbocyclic group of

PRO appeared in 1652 and 1617 cm^{-1}. After 90 min grinding time, the spectrum was shifted to 1623 and 1616 cm^{-1}. Finally, the two sharp peak's absorptions appeared permanently in 3270 and 3170 cm^{-1} in 90 min of grinding time as the characteristic peaks. In summary, the dynamic cocrystallization of DFA-PRO is clearly detected by changes of FT-IR spectra, particularly presented by hydrogen bond formation.

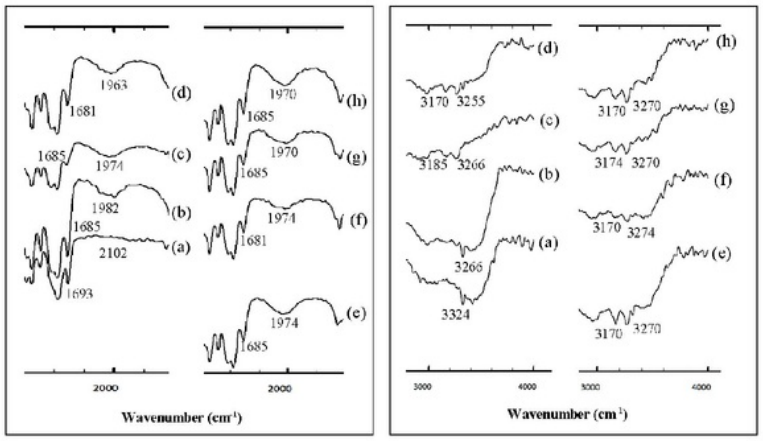

Fig. 6: The dynamic formation of DFA-PRO (1:1) cocrystal via liquid assisted grinding performed by FT-IR spectrum in (a) 0 min; (b) 2 min; (c) 4 min; (d) 10 min; (e) 15 min; (f) 30 min; (g) 60 min; (h) 90 min.

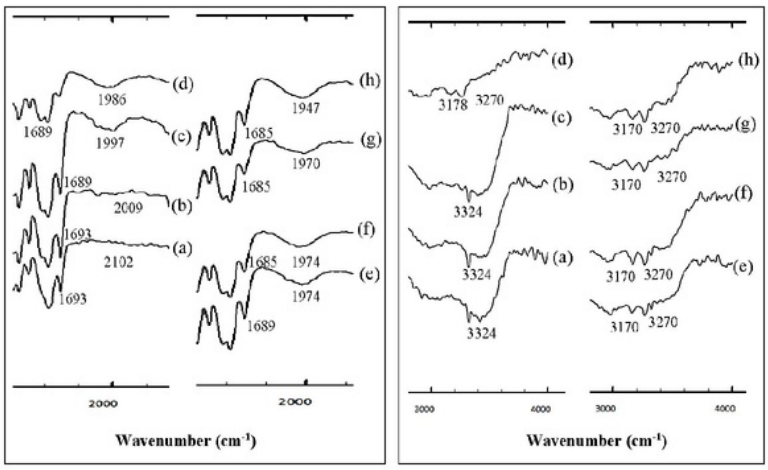

Fig. 7: The dynamic formation of DFA-PRO (1:1) cocrystal via neat grinding performed by FT-IR spectrum in (a) 0 min; (b) 2 min; (c) 4 min; (d) 10 min; (e) 15 min; (f) 30 min; (g) 60 min; (h) 90 min.

The dynamic cocrystallization of DFA-PRO by NG method was revealed the same FT-IR pattern as LAG method. However, as presented in Figure 7, the initial cocrystal was achieved after 2 min grinding time by LAG method and 10 min by NG method. This result is in line with the study reported before. Rehder, *et al.* (2011) reported that piracetam cocrystal formation by the LAG method is faster than by NG method. The complete cocrystal was achieved after 1 min grinding time by the LAG method and 10 min by NG method. In agreement with Friscic and Jones, (2009), the presence of solvent addition will increase the molecular diffusion, therefore, will enhance the interaction between drug and co-former.

Finally, this work demonstrated the development of new solid phase formation between zwitterionic L-proline with some NSAID. This study is successfully characterized the interaction formation of DFA-PRO that indicated as cocrystal. This study has also presented the feasibility of FT-IR vibration spectroscopy for solid-state application in pharmaceutical applications and provides the analysis of molecular interactions, mainly hydrogen bond formation.

CONCLUSION

The new crystalline phase between diclofenac acid and L-proline indicated the formation of cocrystal. The hydrogen formation in molecular interaction was successfully observed by

FT-IR vibrational spectroscopy. The formation of new crystalline phase was influenced by cocrystallization method in which LAG was faster than NG method.

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