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REVIEW: POTENCY OF AMIDE DERIVATES AS CO-CRYSTAL FORMERS AND ITS IMPACT ON THE PHYSICOCHEMICAL OF ACTIVE PHARMACEUTICAL INGREDIENTS

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ABSTRACT

Enhancing the physicochemical properties of active pharmaceutical ingredients (APIs) has been achieved by utilizing solid modification through the formation of co-crystals. Co-crystal was formed from active pharmaceutical ingredients and co-crystal former, more commonly called coformers. The occurrence of hydrogen bonds in the formation of co-crystals depends on the presence of groups that act as hydrogen bond donors or acceptors in API. Amide-derived coformers are widely used to form hydrogen bonds with API. This review aims to examine the potential of amide derivates as co-crystal-forming materials (coformers), groups in active pharmaceutical ingredients that can form hydrogen bonds with amide derivates and their impact on the physicochemical properties of API. Initial search results yielded 88 articles. Furthermore, the authors then conducted a screening based on exclusion and inclusion criteria, so that a total of 54 articles were obtained as review material. Data analysis in this journal review was carried out using descriptive analysis. Amide derivates have great potential to be used as co-crystal-forming materials due to the presence of amide or carboxamide groups (-$CONH_2$), which can act as donors as well as acceptors of hydrogen bonds. Most of the amide-derived coformers with aliphatic amide groups, aromatic amides, pyridine carboxamides, and sulfonylcarboxamide form heterosynthon bonds with carboxylic groups on API. However, the formation of homosynthon bonds between amide and amide groups can occur, as in the 5-fluorouracil-urea co-crystal. Most of the amide derivates as coformers can change the physicochemical properties of APIs, especially in increasing the solubility and dissolution rate.

Keywords: Co-crystal, coformer, amide derivates, heterosynthon, physicochemical properties.

INTRODUCTION

Many studies related to altering the physicochemical properties of drug compounds, such as solubility, stability, hygroscopicity, and mechanical properties, have been performed through solid modification by the formation of salts and co-crystals (Liu, J., et al., 2021; Marani et al., 2021), solid dispersion, and co-amorphous (Sharma et al., 2022). Approximately 40% of drug products are released into the market, and nearly 90% of drugs are found to have poor solubility (Kalepu & Nekkanti, 2015). Solid modification through the formation of co-crystals has been widely used to improve these physicochemical properties.

Co-crystals are multicomponent crystals consisting of active substances and coformers in solid form that interact through non-covalent interactions with stoichiometric ratios (Chen *et al.*, 2016). Co-crystals can improve the physicochemical properties of active

pharmaceutical ingredients (APIs) without changing the chemical structure (Sun, 2013; Karimi-Jafari et al., 2018). Most coformers are excipients, but coformers can also be active pharmaceutical ingredients that have medicinal properties. In addition, coformers can also be in the form of food additives and preservatives. Compounds derived from carboxylic acids, both aliphatic carboxylic acids, such as oxalic acid, tartaric acid, maleic acid, malic acid, glutaric acid, and others, as well as aromatic carboxylic acids, such as benzoic acid, salicylic acid, and gallic acid, are most widely used as coformers due to the presence of carboxylic groups, which act as donors as well as acceptors of hydrogen bonds. Apart from carboxylic acid derivates, amide derivates also have great potential as coformers due to the presence of amide groups, which act as hydrogen bond donors and acceptors. Amide-derived coformers are widely used to form hydrogen bonds with API (Rachmaniar, et al., 2020). The formation of hydrogen bonds also depends on the presence of groups that act as hydrogen bond donors or acceptors in the API. This study aims to review the potency of amide derivates as co-coformers, groups in active pharmaceutical ingredients that can form hydrogen bonds with amide derivates and their impact on the physicochemical properties of APIs.

RESEARCH METHODS

Tools and Materials

This review article was written from national and international journals using Google Scholar and Pubmed search engines. The selected literature relates to the formation of co-crystals with amide-derived coformers by using the keywords "co-crystal", "amide coformer", "nicotinamide coformer", "acetamide coformer", "urea coformer", "picolinamide coformer", "isonicotinamide coformer", and “saccharin coformer” with publication year range 2013–2023.

Article Selection Criteria

The inclusion criteria for this review article were articles published between 2013 and2023, in Indonesian or English, and original research articles related to amide-derived coformers. The exclusion criteria for this review article are articles that are not related to the material or topic of discussion.

Research Procedure

Initial search results using the keywords "co-crystal", "amide coformer", "nicotinamide coformer", "acetamide coformer", "urea coformer", "picolinamide coformer" and "isonicotinamide coformer" through Google Scholar obtained 83 articles, Pubmed 5 articles, so a total of 88 articles. The results of duplication-checking found the same two articles, so a total number of articles obtained was 86. The authors then filtered the inclusion and exclusion criteria to obtain a total of 54 articles to be reviewed. The data analysis for this assessment was carried out using descriptive analysis. The flowchart of the literature study in this review is shown in Figure 1.

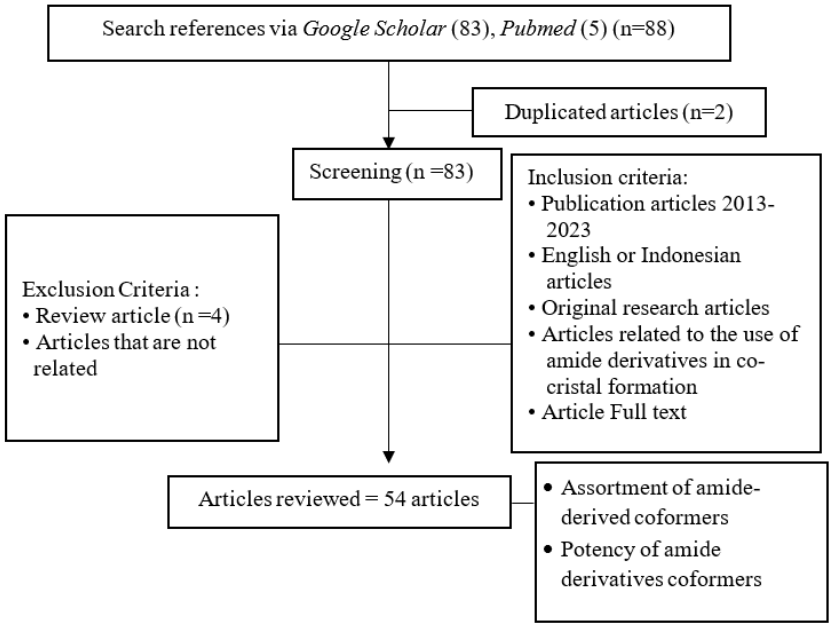

Figure 1. Flowchart of review writing method

RESULT AND DISCUSSION

The preparation of the co-crystal is carried out by modifying the solid form of API to produce API with better physicochemical properties without changing the desired biological properties. (Izutsu et al., 2016). Although co-crystals have been extensively studied, the definition of co-crystals varies from one study to another. The United States Food and Drug Administration states that pharmaceutical co-crystals are "crystalline materials consisting of two or more different molecules, usually the active pharmaceutical ingredients and co-crystal formers (coformers) in the same crystal lattice", and that "from a physical chemistry point of view, co-crystals are different from solvates and hydrates in that the material forming the co-crystal (coformer) is not a liquid" (Raheem et al., 2020).

Coformer is an excipient with a small molecular weight that is required in small amounts in the formation of co-crystals because the ratio of coformer and drug in forming co-crystals uses a stoichiometric ratio. Stoichiometric ratios are used in forming co-crystals because co-crystals require molecular interactions in the process of their formation, such as hydrogen bonds and van der Waals bonds (Rachmaniar et al., 2020). In general, the ratio between API and coformer is 1:1, 1:2, or vice versa. Coformers from active pharmaceutical ingredients are known as drug-drug co-crystals. Pharmaceutical active ingredients and coformers can be acidic, basic, or neutral (Rodrigues et al., 2020).

In the formation of co-crystals, API and coformer molecules interact to form non-ionic and non-covalent bonds, such as hydrogen bonds, π-π interactions, or van der Waals interactions. (Hairunnisa et al., 2019). This is what distinguishes it from salt, which involves ionic interactions. Strong hydrogen bonds occur when a hydrogen atom is bonded noncovalently to an atom with a high electronegativity, such as nitrogen, and interacts with a negatively charged and relatively less polar acceptor atom, such as oxygen (Shteingolts et al., 2021). Meanwhile, bond-withdrawing donors such as carbon and acceptor groups such as electron clouds from aromatic rings will form weak hydrogen bonds. The strength of the hydrogen bond is often estimated based on the donor-acceptor distance. This hydrogen bond will form a supramolecular synthon, which includes two types of formations, namely homosynthon and heterosynthon, which can form strong crystals. Synthones are structural units involved in intermolecular interactions that lead to the formation of co-crystals. In other words, a synthone is a part of a molecule or an ion that interacts specifically with the corresponding synthone in another molecule to form a stable crystal structure. Crystal

structure analysis (CSD) can be used to predict the likelihood of supramolecular synthon formation (Groom & Allen, 2014).

Coformers are generally selected from a list of compounds that have been designated by the USFDA as Generally Recognised as Safe (GRAS). Coformers do not affect the pharmacological effects of API (Thayyil *et al.*, 2020). Compounds included in GRAS are consumer choices that are safe for human use and economical (cheap). Coformers with high water solubility generally increase the solubility of active pharmaceutical ingredients when co-crystals are formed (Kuminek et al., 2016; Machado et al., 2020).

Amide derivates are widely used as co-crystal forming materials because they have -C=O and -NH groups. These groups act as hydrogen bond acceptors and donors, respectively. The -C=O group can act as a hydrogen bond acceptor by providing a lone pair of electrons on the oxygen atom, which can interact with hydrogen bond donors on the API. Conversely, the -NH2 group can act as a hydrogen bond donor by providing hydrogen atoms that can form hydrogen bonds with hydrogen bond acceptors on the API. Based on the structure, the co-crystal-forming materials of amide derivates consist of pyridinecarboxamides, aliphatic amides, aromatic amides, and sulfonylcarboxamides.

The pyridinecarboxamide group can form hydrogen bonds with other molecules that have suitable hydrogen bond donors or acceptors. Hydrogen bond interactions can form between the hydrogen atoms in the amide group and the hydrogen bond acceptor, such as the -C=O group in API, which has a carboxylic group. In addition, the oxygen atom in the carbonyl group of pyridine carboxamide can also interact with hydrogen bond donors, such as -OH and -NH groups, which are available on the API.

Amide derivates with an aliphatic amide structure, such as acetamide, propionamide, and urea, have a carboxamide group that can form hydrogen bonds with pharmaceutical active ingredients. Urea coformer is expected to affect the solubility of API greatly. Urea also has functional groups that are often found in co-crystal hydrogen bonding patterns, so this coformer is often a candidate for co-crystal screening (Gunawardana & Aakeröy, 2018). Figure 2 is an example of an amide derivative widely used as a coformer.

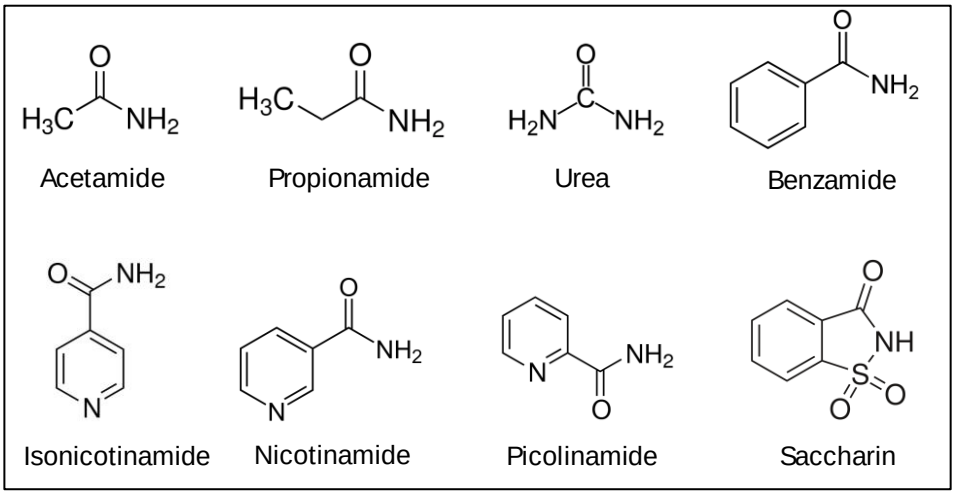

Figure 2. Amide derivative coformer materials used for the formation of co-crystals

Intermolecular interactions involving synthons that have the same composition and characteristics will form homosynthons For example, hydrogen bonds formed from non-covalent interactions between hydrogen bond donor and hydrogen bond acceptor groups originating from carboxylic acids between carbonyl and hydroxyl groups, and synthons formed between amide groups with other amides (homodimers) will also form homosynthon. While supramolecular heterosynthon occurs in hydrogen bonds formed from different groups, for example between aromatic carboxylic acid-nitrogen functional groups, carboxylic acids-amides, and alcohol-pyridines, with non-covalent styles (Savjani & Pathak,

2016), The location of the hydrogen bonds in the formation of co-crystals between amide derivates and active pharmaceutical ingredients (APIs) is shown in Table I.

Table I. Location of Hydrogen Bonds in Co-Crystal Formation between Amide Derivates and Active Pharmaceutical Ingredients

Coformer	APIs	Type and the location of the hydrogen bond (synthon)	References
Aliphatic amides			
Acetamide	Myricetin	Type: Heterosynthon The carbonyl group (myricetin) binds to N of the amide group (acetamide). The hydroxyl (myricetin) binds to the carbonyl group (acetamide)	(Mureşan-Pop et al., 2016)
	Entacapone	Type: Heterosynthon The carbonyl group (entacapone) binds to N of the amide group (acetamide) The phenol group (entacapone) binds to the carbonyl group (acetamide)	(Bommaka et al., 2018)
Propionamide	Triflusal	Type: Heterosynthon The carbonyl group (triflusal) binds to N of the amide group (propionamide). The hydroxyl group (triflusal) binds to carbonyl group (propionamide).	(Aitipamula et al., 2015)
	Gallic acid	Type: Heterosynthon The carbonyl group (propionamide) binds to the hydroxyl group (gallic acid). N of amide group (propionamide) binds to carbonyl group (gallic acid).	(Jyothi et al., 2019)
Urea	5 -Fluorouracil	Type: Heterosynthon The carbonyl group (5 -fluorouracil) binds to N of the amide group (urea). The Amine group (5-fluorouracil) binds to the Carbonyl group (urea).	(Cuadra et al., 2020)
	Febuxostat	Type: Heterosynthon The carbonyl group (febuxostat) binds to N of the amide group (urea). The hydroxyl group (febuxostat) binds to the carbonyl group (urea).	(An et al., 2017)
Aromatic amides			
Benzamide	Probenesid	Type: Heterosynthon The carbonyl group (probenesid) binds to N of the amide group (benzamide), The hydroxyl group (probenecid) binds to carbonyl group (benzamide).	(Bruni et al., 2020)
	Carbamazepine	Type: Heterosynthon The N of amide group (carbamazepine) binds to the carbonyl group (benzamide). The carbonyl group (carbamazepine) binds to the hydroxyl (benzamide).	(Manin et al., 2022)
Pyridine carboxamides derivative			

Isonicotin-amide	Bergenin	Type: Heterosynthon The carbonyl (bergenin) binds to N of amide group (isonicotinamide). The hydroxyl group (bergenin) binds to the carbonyl group (isonicotinamide).	(Liu et al., 2021)
	Furosemide	Type: Heterosynthon The carbonyl group (Furosemide) binds to N of the amide group (isonicotinamide). The hydroxyl group (furosemide) binds to the carbonyl (isonicotinamide).	(Kerr et al., 2015)
Nicolinamide	Ibuprofen	Type: Heterosynthon The carbonyl group (ibuprofen) binds to N of amide group (Nicotinamide). The hydroxyl (ibuprofen) binds to the carbonyl group (nicotinamide).	(Yuliandra et al., 2018)
	Salicylic acid	Type: Heterosynthon The carbonyl group (salicylic acid) binds to N of amide group (nicotinamide). The hydroxyl group (salicylic acid) binds to the carbonyl group (nicotinamide).	(Lee et al., 2016)
Picolinamide	Hydrochlorothiazide	Type: Heterosynthon The N of sulfonyl group (hydrochlorotiazide) binds to the carbonyl group (picolinamide).	(Gopi et al., 2017)
	Quercetin	Type: Heterosynthon The carbonyl (quercetin) binds to N of the amide group (picolinamide). The hydroxyl group (quercetin) binds to the carbonyl group (picolinamide).	(De Souza et al., 2022)
Sulfimide derivates			
Saccharin	Carbamazepine	Type: Heterosynthon The carbonyl group (carbamazepine) binds to N-sulfonyl carboxamide group (saccharin). The N of the amide group (Carbamazepine) binds to the O sulfonyl group (saccharin).	(Roca-Paixão et al., 2019)
	Indomethacin	Type: Heterosynthon The hydroxyl in carboxylic groups (indomethacin) binds to sulfonyl (saccharin) The carbonyl in the carboxylic group (indomethacin) binds to N of sulfonylcarboxamide group.	(Connor *et al.*, 2019)

Amide derivative co-crystal-forming materials can enhance the physicochemical properties of active pharmaceutical ingredients. In the probenecid-benzamide co-crystal, it shows that the aromatic ring, C=O carboxylate of probenecid plays an important role in the

formation of hydrogen bonds with the amide group of benzamide. This led to the formation of strong hydrogen bonds and supramolecular synthons, which underlie the formation of co-crystals. Co-crystal solubility and dissolution rates measured in several bio-relevant liquids showed a marked increase compared to pure probenecid (Bruni et al., 2020).

Paliperidone-benzamide and paliperidone-nicotinamide co-crystals have succeeded in increasing the solubility and dissolution of paliperidone. Coformers such as benzamide, nicotinamide, and PHBA were found to be suitable for co-crystal preparation with paliperidone based on predictions of co-crystal formation by theoretical calculations using HSP. Paliperidone has one hydrogen bond donor group and seven hydrogen bond acceptor groups. Further, the formation of co-crystals by coformers was confirmed by the results obtained from Fourier transform infrared (FTIR), powder X-ray diffraction (PXRD), thermal analysis, and microscopy methods (Thimmasetty et al., 2021).

Aitimula et al. developed various amide-derived coformers, which have an impact on the stability of active pharmaceutical ingredients. The triflusal co-crystal was stable under slurry and accelerated conditions (40°C, relative 77%), indicating that the triflusal co-crystal with benzamide (BA), isonicotinamide, propionamide, picolinamide, and urea was stable under accelerated conditions. Intermolecular interactions occur between amide-acid and pyridine-acid molecules. All co-crystals have heterosynthone features, as shown by analysis of the crystal structure of the co-crystals. Thermal analysis, except for the triflusal-isonicotinamide co-crystal, showed that all of the co-crystals melted at a lower temperature compared to the melting points of the triflusal and conformer (Aitipamula *et al.*, 2015).

In the carbamazepine co-crystal with benzamide, hydrogen bonds are formed between the hydrogen atoms on the carbamazepine amide group and the oxygen atom on the benzamide carbonyl group. In the carbamazepine-isonicotinamide co-crystal, hydrogen bonds are formed between the hydrogen atoms in the carbamazepine amide group and the nitrogen atom in the isonicotinamide pyridine group. This hydrogen bond interaction can affect the crystal structure and physicochemical properties of the carbamazepine co-crystal. Hydrogen bonds can increase the stability and solubility of co-crystals, as well as affect the pharmacokinetic and pharmacodynamic properties of drugs. This study demonstrated that the formation of carbamazepine co-crystals with benzamide and isonicotinamide can increase the solubility of carbamazepine (Manin et al., 2022).

Furosemide is a loop diuretic drug that has low solubility and permeability. With the formation of the furosemide-isonicotinamide co-crystal, its solubility can be increased by 5.6 times that of pure furosemide. The furosemide molecule contains COOH, NH, and SO_2NH_2 groups which have a great opportunity to form hydrogen bonds. The COOH and SO_2NH_2 groups are known to provide strong hetero synthesis through O-H hydrogen bonds and N-HO, which form a variety of stable supramolecular structures (Kerr et al., 2015).

Bergenin-isonicotinamide co-crystal (1:1, molar ratio) had better solubility and intrinsic solution rate (IDR) in aqueous and buffer solutions with pH values of 1.2, 4.5, and 6.8. The solubility of bergenin-isonicotinamide in water is 3.72 ± 0.22, while pure genin is 1.42 ± 0.006 mg/mL; this shows an increase of 2.62 times. The increase also occurred in the intrinsic dissolution of BER-ISN in water, which was 29.90 ± 0.04, while bergenin pure was 18.64 ± 0.27 mg/mL. The formation of hydrogen bonds occurs through the interaction of heterosynthone carbonyl groups (C=O), hydroxyl groups (-OH), and amide groups (-NH2) (Liu, H., et al., 2021).

The dissolution of atorvastatin calcium co-crystal with isonicotinamide via solvent evaporation was higher than that of standard atorvastatin calcium. The dissolution of calcium atorvastatin co-crystals increased by 3.79% when compared to standard atorvastatin. Based on the results of statistical tests, the dissolution profiles between standard calcium atorvastatin and co-crystal had a significant difference. The co-crystal that has the highest solubility is the co-crystal formed by solvent evaporation, with an increase in solubility of 85.53%. The increase in solubility can be caused by several mechanisms, including the formation of a new co-crystallized phase with better physicochemical properties, especially solubility (Gozali et al., 2013).

The carboxylic group in the salicylic acid molecule can act as a donor as well as an acceptor for hydrogen bonds. The N atom in the coformer will interact to form NH-O and N-HO hydrogen bonds with the carboxylic group of salicylic acid. The COOH-N heterosynthon, as found in the carboxylic acid-pyridine hydrogen bond, is one of the keys to success in the co-crystal design strategy, so it can be said to be a supramolecular synthon. Salicylic acid is known as a material that is difficult to dissolve in water at around 2.36 g/L at 30°C. Salicylic acid co-crystals (derived from the reaction between aspirin and its constituents) with nicotinamide and isonicotinamide have been investigated to improve the physicochemical properties of antipyretic agents. The solubility of co-crystals increases because co-crystals have better stability in water (salicylic acid-nicotinamide: 38.6 g/L, salicylic acid-nicotinamide: 16.7 g/LL) (Lee et al., 2016).

Based on solubility studies at different pHs, flurbiprofen picolinamide and benzamide co-crystals were found to be more soluble than pure flurbiprofen. The analysis was carried out using a thermodynamic solid-liquid binary phase diagram. The crystal structure was analyzed using diffraction data from a high-resolution synchrotron. To find out more about the energy differences between crystal structures, periodic calculations using DTF (density functional theory) are also carried out. In addition, the thermodynamic stability relationship between different solid phases has been modeled with the Gibbs energy of various co-crystal-forming materials (Surov et al., 2019).

Based on its chemical structure, nicotinamide has a high probability of forming co-crystals with various active pharmaceutical ingredients (Alatas et al., 2014). Nicotinamide is widely used as a hydrophilic coformer in the formation of co-crystals. As a coformer, the nitrogen atom in the pyridine group can form hetero synthons with pharmaceutical active ingredients between carboxylic acid and pyridine, amide, and pyridine, or other interactions. If there is an amide group, nicotinamide can also form hetero synthons with pharmaceutical active ingredients between carboxylic acid amides or amide-amide homosynthon (Wang et al., 2013). Nicotinamide can increase the solubility of various APIs through the formation of stacking complexes that occur between electron donors and π electron acceptors; for that reason, nicotinamide is also known as a hydrotropic agent. Complex formation can also increase the chemical stability of API (Alatas et al., 2014). The presence of amide groups and N-pyridine in nicotinamide causes a large opportunity to form co-crystals with carvedilol (Fernandes et al., 2019). The increase in drug release can be due to the formation of hydrogen bonds between the amide functional group and the carboxyl group of nicotinamide. The co-crystal of ibuprofen with nicotinamide shows a different X-ray diffraction pattern than the original compound. The thermal behavior of the co-crystal showed a sharp endothermic peak at 96.24°C. The results of the study concluded that the co-crystalline phase of ibuprofen with nicotinamide significantly increased the solubility of pure ibuprofen (Yuliandra et al., 2018). Nicotinamide has also been shown to increase the solubility of simvastatin co-crystals threefold compared to pure simvastatin and its physical mixture (Sopyan et al., 2017). Likewise, the solubility of pure mefenamic acid (6.62 g/mL) can be increased by the formation of mefenamic acid-nicotinamide co-crystals (7.35 g/mL) (Utami et al., 2017). Pure artesunate has a solubility of 1.2 mg/mL; with the formation of artesunate-nicotinamide co-crystals, there is a slight increase in solubility to 1.3 mg/mL (slurry method) and 1.4 mg/mL (solvent evaporation method). The increase in solubility occurs due to the formation of hydrogen bonds between the carboxylic groups in artesunate and the amide group in nicotinamide. Apart from that, this can also be seen from the lowering of the melting point that occurs in the crystal. The reduced melting point indicates a reduced crystal lattice so that the co-crystal is more soluble (Setyawan et al., 2015). Prulifloxacin has a solubility problem (20 mg/mL) in water, the modified prulifloxacin-nicotinamide co-crystal can increase the solubility up to six times that of pure prulifloxacin. This can be seen from the results of the 120 mg/mL prulifloxacin-nicotinamide co-crystal solubility test using water in a water bath shaker at 35 ± 2°C (Raghuram et al., 2014). Hydrochlorothiazide (HCT), one of the BCS class IV diuretic drugs can form co-crystals with pyridinecarboxamide coformers. The physicochemical properties of HCT were

modified by the formation of co-crystals with nicotinamide and picolinamide coformers. The HCT-nicotinamide co-crystal can be increased by two times that of pure HCT (Sanphui et al., 2015). SCXRD showed that the catomer sulfonamide N-H synthone (the O found in the pure HCT stable polymorph) has been replaced by the coformer drug heterosynthone in the cocrystal (Gopi et al., 2017).

Urea as a co-crystal-forming material has an amide group that can interact with carboxylic, pyridine, hydroxyl, and amide groups to form hydrogen bonds, thereby increasing the solubility, dissolution, or stability of pharmaceutical active ingredients, such as in aceclofenac-urea co-crystals (Kumar et al., 2020), catechin-urea co-crystals (Bakhtiar et al., 2015), ellagic-urea acid (Leng et al., 2021), bumetanid-urea co-crystal (Allu et al., 2020), and febuxostat-urea co-crystal (An et al., 2017). The formation of 5-fluorouracil co-crystals with urea coformers has succeeded in increasing the solubility of pure 5-fluorouracil 2.5–3 times and increasing its thermal stability (Cuadra et al., 2020). 5-Fluorouracil forms a homosynthon bond with urea, where hydrogen bonds occur between the carbonyl group of 5-fluorouracil and the NH_2 group of urea, as well as between the -NH_2 group of 5-fluorouracil and the carbonyl group of urea. Ethyl p-methoxycinnamate (EPMS) is less soluble in water, causing limitations in its dissolution and bioavailability. With the formation of hydrogen bonds in the EPMS-urea co-crystal, there is a decrease in particle size, a decrease in crystallinity, and an increase in solubility in water (1.6 times that of pure EMPS) (Rachmaniar et al., 2020). The use of co-crystal formers of amide derivates and their effects on the physicochemical properties of active pharmaceutical ingredients can be seen in Table II.

Table II. Applications of Co-Crystal Formers of Amide Derivates and Their Effects on the Physicochemical Properties of Active Pharmaceutical Ingredients

Coformer and APIs	Physicochemical properties affected	Method	References
Acetamide conformer			
Myricetin	Solubility and dissolution increased 4 times.	Solvent drop grinding	(Mureşan-Pop et al., 2016)
Benzamide conformer			
Carbamazepine	Solubility and stability increase based on melting point measurement, Gibs energy sublimation, and enthalpy calculation.	Slurry	(Manin et al., 2022)
Probenecid	The solubility of probenecid in water increased from 72.2 mg/mL to 87.6 mg/mL. intrinsic dissolution probenecid in FeSSiF solution (pH 5) up from 29.9 $\mu g/min^{-1}cm^{-2}$ to be 46.6 $\mu g/min^{-1}cm^{-2}$.	Kneading/solvent evaporation	(Bruni et al., 2020)
Triflusal	The melting point of triflusal becomes lower	Solvent drop grinding	(Aitipamula et al., 2015)
Paliperidone	The solubility of paliperidone increased 18.5 times, and the dissolution also up from 48.84% to 88.96%.	Solvent Evaporation	(Thimmasetty et al., 2021)
Risperidone	The solubility increases from 0.66 mg/mL to 12.3 mg/mL, and the	Solvent Evaporation	(Chandur et al., 2022)

	dissolution increases from 28% to 83.91%.		
Isonicotinamide conformer			
Carbamazepine	Solubility and stability increase based on melting point measurements, Gibs energy sublimation, and enthalpy calculations.	Slurry	(Manin et al., 2022)
Bergenin	Bergenin solubility increased 2.62 times.	Rapid solvent removal method (RSRM)	(Liu, H., et al., 2021)
Triflusal	The melting point of triflusal becomes lower.	Slurry	(Aitipamula et al., 2015)
Furosemide	Furosemide solubility increased 5.6 times.	Solvent-assisted mechanochemical	(Kerr *et al.*, 2015)
Salicylic acid	Salicylic acid solubility in water increased from 2.36 g/L to 16.7 g/L.	Solvent Evaporations	(Lee et al., 2016)
Flurbiprofen	Flurbiprofen solubility increases based on Ksp calculations and HYBOTS description.	Thermodynamic analysis (Solid Liquid Binary phase diagram)	(Surov et al., 2019)
Atorvastatin Calcium	The solubility of atorvastatin calcium increased by 85.53%. Its dissolution also increased by 3.79%. pure atorvastatin calcium	Solvent evaporation, Solvent Drop Grinding	(Gozali et al., 2013)
Diflunisal	Solubility and dissolution Diflunisal increased to 1.5 to 3 times.	Solvent Co-crystallizations	(Cuadra *et al.*, 2016)
Nicotinamide conformer			
Carvedilol	Carvedilol solubility increased 15 times, and its release also increased 4.79 times than pure carvedilol.	HME	(Fernandes et al., 2019)
Hydrochlorothiazide	Hydrochlorothiazide solubility was increased 2 times.	Liquid assisted grinding	(Sanphui et al., 2015)
Simvastatin	Simvastatin solubility increased from 9 µg/mL to 30 µg/mL.	Solvent Evaporation	(Sopyan and Muchtaridi, 2016)
Ibuprofen	The solubility of ibuprofen in water increased to 125 µg/mL.	Solvent Evaporations	(Yuliandra et al., 2018)
Diflunisal	Diflunisal solubility increased from 47 µg/mL to 66 µg/mL.	Supercritical antisolvent (SAS)	(Cuadra et al., 2016)
Mefenamic acid	The solubility of mefenamic acid increased from 6.62 µg/mL to 10.45 µg/mL.	Melt Crystallization	(Utami et al., 2017)
Artesunate	Artesunate solubility increased from 1.2 mg/mL to 1.3 and 1.4 mg/mL (depending on the method).	Slurry, Solvent Evaporations	(Setyawan et al., 2015)
Prulifloxacin	Prulifloxacin solubility increased from 20 mg/mL to 120 mg/mL.	Solvent Evaporation	(Raghuram et al., 2014)

Salicylic acid	The solubility of salicylic acid in water increased from 2.36 g/L to 38.6 g/L.	Solvent Evaporations	(Lee et al., 2016)
Flurbiprofen	Flurbiprofen solubility increases based on Ksp calculations and HYBOTS description.	Thermodynamic analysis (Solid Liquid Binary phase diagram)	(Surov et al., 2019)
Paliperidone	Paliperidone solubility increased 61 times, and ts dissolution increased from 48.84% to 70.39%.	Hansen solubility parameter (HSP)	(Thimmasetty et al., 2021)
Picolinamide conformer			
Hydrochlorothiazide	Hydrochlorothiazide solubility was increased 2 times.	Liquid-assisted grinding, Ball milling	(Gopi et al., 2017)
Naproxen	Intrinsic dissolution increased from 1.26 mg/min^{-1} cm^{-2} to 1.39 mg/min^{-1}cm-^{2}.		(Kerr et al., 2017)
Flurbiprofen	Flurbiprofen solubility increases based on Ksp calculations and HYBOTS description.	Thermodynamic (Solid Liquid Binary phase diagram)	(Surov et al., 2019)
Propionamide conformer			
Triflusal	The melting point of triflusal becomes lower.	Solvent drop grinding	(Aitipamula et al., 2015)
Saccharin conformer			
Indomethacin	The increased indomethacin solubility was calculated using the PSD (Phase Solubility Diagram).	Antisolvent crystallization	(Connor *et al.*, 2019)
Urea coformer			
Estradiol	The solubility of estradiol increases.		(Shayanfar, 2020)
etil p-metoksisinamat (EPMS)	The solubility of EMPS is 1.6 times higher than that of pure EMPS solvent.	Solvent Evaporations	(Rachmaniar et al., 2020)
Aceclofenac	The solubility of aceclofenac increased to 1.2 times (PM), 3.74 times (LAG), 5.91 times (LG) and dissolution aceclofenac increased from 19.18 to 99.47 (NG), 82.83 (LAG), and 36.84 (PM).	Neat grinding, Liquid Assisted Grinding	(Kumar et al., 2020)
Triflusal	The melting point of triflusal becomes lower.	Solvent drop grinding	(Aitipamula et al., 2015)

Pharmaceutical active ingredients having carboxylic, hydroxy, carbonyl, fluorine, and amide groups can form hydrogen bonds with amide derivative coformers by forming supramolecular synthon, which can affect the physicochemical properties of active pharmaceutical ingredients such as solubility, dissolution, stability, permeability, and mechanical properties. By increasing the physicochemical properties of active pharmaceutical ingredients, it is hoped that their bioavailability can also be increased. Co-crystallization using amide derivates can be seen in Figure 3.

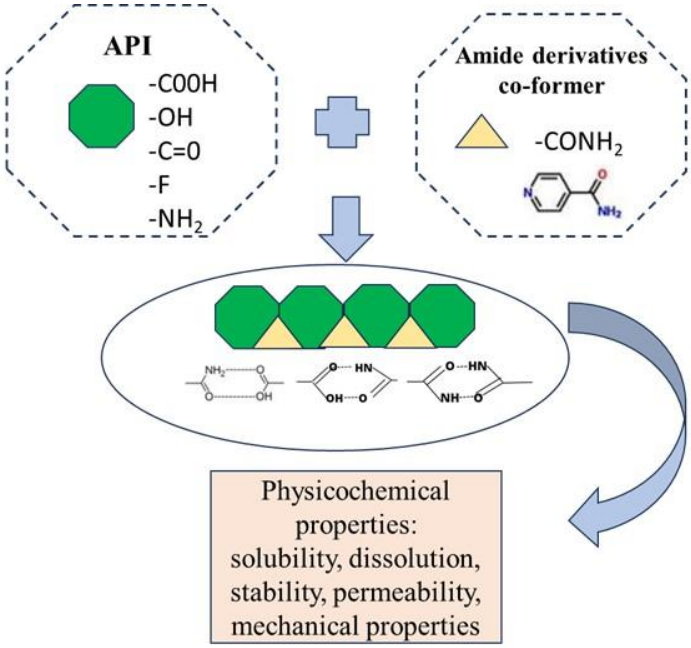

Figure 3. Co-crystallization using coformers of amide derivates

CONCLUSION

Most coformers of amide derivates with aliphatic amide groups, aromatic amides, pyridine carboxamides, and sulfonylcarboxamides form heterosynthons with carboxylic groups in active pharmaceutical ingredients. However, the formation of homosynthon between amide and amide groups can occur, as in the 5-fluorouracil-urea co-crystal. Amide derivates as co-crystal formers have been successful in modifying their physicochemical properties, especially in increasing the solubility and dissolution rate of active pharmaceutical ingredients.

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