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Literature Review: Multicomponent Crystal of Active Pharmaceutical Ingredients to Improve the Solubility: A Literature Review

Tinjauan Literatur: Multikomponen Kristal Bahan Aktif Farmasi untuk Meningkatkan Kelarutan

Ahdi Dinil Haq, AH[1,2], Salman Umar[3], Erizal Zaini[4*]
[1,3,4] Universitas Andalas, Padang, Indonesia
[2]Akademi Farmasi Dwi Farma, Padang, Indonesia
Email: erizal@phar.unand.ac.id

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Abstract

The purpose of this review was to discuss abouts active pharmaceutical ingredients (API), formulations of drugs that are poorly soluble in water using various coformers and various methods of forming multicomponent crystals to increase the solubility of API. The formula used is equivalent in molecular weight between the active pharmaceutical ingredients (API) and coformers, using solvent evaporation and solvent drop grinding methods. A series of characterizations using X-ray Diffraction (XRD), differential scanning calorimetry (DSC), Fourier transform infrared (FTIR) and Scanning electron microscopy (SEM) to confirm the formation of multicomponent crystals. The analysis from the results of the research show an increase in the solubility of API in water, that is 1.3 up to 115 times compared to intact substances.

Keywords:
Multicomponent; Crystal; Cocrystal; Coformer; Solubility

Abstrak

Tujuan dari review artikel ini membahas tentang bahan aktif farmasi (API), formula dari obat – obatan yang sukar larut dalam air menggunakan berbagai koformer dan metode pembentukan multikomponen kristal yang bervariasi guna meningkatkan kealrutan API. Formula yang digunakan setara dengan bobot molekul antara bahan aktif farmasi (API) dengan zat tambahan (koformer), menggunakan metode *solvent evaporation* dan *solvent drop grinding*. Serangkaian karakterisasi menggunakan difraksi sinar x (XRD), *differential scanning calorimetri* (DSC), *Fourier transform infrared* (FTIR) dan *Scanning electron microscopy* (SEM) untuk mengkonfirmasi pembentukan multikomponen kristal. Analisis terhadap hasil yang didapatkan yaitu terjadinya peningkatan kelarutan API dalam air yaitu 1,3 kali hingga 115 kali lipat dibanding zat murni.

Kata Kunci:
Multikomponen; Kristal; Kokristal; Koformer; Kelarutan *Medis*

INTRODUCTION

Solubility is one of the physicochemical properties of a drug which is an important parameter of the rate of absorption into the systemic circulation in order to obtain a pharmacological response [1]. Drugs with good solubility will show a good absorption profile so that the bioavailability of the drug will be good, but conversely for drugs that have low solubility, drugs with low solubility will show a bad absorption profile and the bioavailability will also be bad [2]. For drugs that have low solubility but can provide fast membrane absorption, in this case drugs that are included

in the Class II Biopharmaceutical Classification System (BCS), a technique is needed to improve their solubility. In addition, drugs with low solubility and absorption can also be modified to increase their bioavailability in the systemic circulation, where these drugs are classified as BCS class IV [3], [4].

An important physicochemical property of a drug substance is solubility, especially the solubility of the system in water [5], [6]. A drug must have good solubility in water to be therapeutically efficacious. Drugs that enter the circulatory system and produce a therapeutic effect must first be in a dissolved state. Compounds that are relatively insoluble often show imperfect absorption. Drugs that have low solubility in water often show low bioavailability and dissolution rate. This is the determining step (rate limiting step) in the drug absorption process [7], [8].
The dissolution rate can be increased by increasing the solubility of the active pharmaceutical ingredients (API) [5]. Increasing solubility can be done in various ways, including cocrystallization, complexation, use of cosolvents, micellar solubilization, solid dispersion, nanosizing, and so on. Cocrystallization has become part of drug development, thus attracting many engineers and scientists to develop cocrystal solid formulations [9]–[12].
Multicomponent crystals consist of several forms, including single crystals or commonly called cocrystals which are characterized by the formation of new crystalline peaks that are specific and different from their API peaks. Apart from that, it also exists in the form of polymorphs, solvates/hydrates, salts and solid solutions or also called crystal mixtures, as shown in Figure 1 [13].

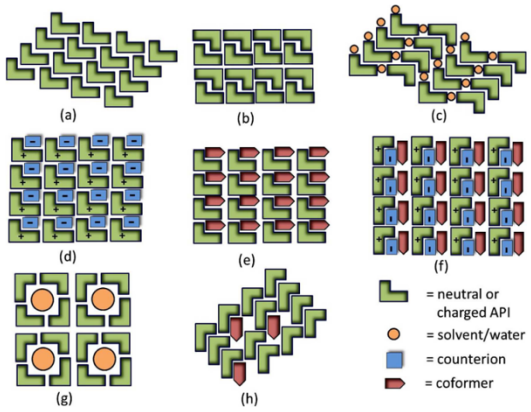

Figure 1. Possible crystal forms for API : a, b. polymorph; c. solvates/hydrates; d. salt; e. molecular cocrystals; f. ionic cocrystal; g. non-stoichiometric inclusion compounds including the hydrate channel, solvate; h. solid solution (mixed crystals).

The formation of multicomponent crystals can be carried out by dissolution methods (such as solvent evaporation, the addition of antisolvent and ultrasonic cocrystallization), cooling methods, pulverization methods, grinding methods (such as: solvent drop grinding and polymer-assisted grinding), melting methods, supersaturation methods, supercritical fluid methods, Spray drying, freeze drying, electrospray, high-pressure homogenization, hot stage microscopy and microwave assisted cocrystallization methods [14], [15].

METHOD

This article was being conducted on scientific publication databases such as **Researchgate,GoogleScholar, ScienceDirect and Pubmed** by using the keywords *multicomponent* , crystal, *cocrystals* , *solubility* and *dissolution improvement.*
The first stage is filtering the literature obtained from online database researches according to predetermined keywords. After that, the irrelevant titles will be removed. Then proceed to the second stage where manuscripts are determined to be included in the analysis using inclusion and exclusion criteria.
Inclusion criteria include articles containing the keywords mentioned, as well as exclusion

criteria, namely articles that do not contain the keywords mentioned. Furthermore, the literature sources that have been selected and meet the inclusion criteria are read completely and analyzed to get the essence of the literature.

All relevant literature sources on the formation of multicomponent crystals that can increase the solubility of an API. A narrative synthesis was carried out systematically to obtain conclusions regarding the increase in solubility and dissolution rate of API.

RESULTS AND DISCUSSION

In this study, 31 articles were found that met the inclusion criteria. The multicomponent crystals form and the improvement API solubility can be seen in Table 1.

Table 1. APIs & coforemers and also the methods that used to increase the solubility of an API

API(s)	COFORMER	METHOD	SOLUBILITY IMPROVEMENT	REFERENCES
Piperine	Nicotinic acid	Solvent evaporation	1,5 x	[16]
Aceclofenac	Succinic acid	Solvent drop grinding	4 x	[17]
Piperine	Quercetin	Solvent drop grinding	1,4 x	[18]
Albendazole	Malic acid	Solvent drop grinding	115 x	[19]
Fenofobric acid	Saccarine	Solvent evaporation	1,8 x	[20]
Ketoprofen	Tromethamine	Solvent evaporation	2,95 x	[21]
Piperine	Succinic acid	Solvent evaporation	3,9 x	[14]
Trimethoprim	Malic acid	Solvent evaporation	2,5 x	[22]
Ticagrelor	Quercetine	Solvent evaporation	1,6 x	[23]
Ketoprofen	Nicotinamide	Solvent evaporation	1,3 x	[24]
Desloratadine	Benzoic acid	Solvent evaporation	27 x	[25]
Bromhexine & bromhexine fumarate	Fumaric acid	Solvent evaporation	5 - 10x	[26], [27]

The formulation for making multicomponent crystals has a goal to increase the solubility of an API. In addition, it can also increase its bioavailability. There are two methods that used in this research, named solvent evaporation and solvent drop grinding. In the research Zaini *et al*, 2020 [14] piperine used as an API. Piperine is a secondary metabolite obtained from the *Piper nigrum* L. plant, which belongs to the Piperaceae family. This plant has been used for traditional medicine and is efficacious as a pain reliever, anti-inflammatory and improves gastrointestinal [28]–[31]. The coformer is succinic acid with a molar ratio of 2:1, while the method for forming multicomponent crystals is solvent evaporation. The results of this study gave an increase in the solubility of piperine by 3.9 times compared to the pure substance.

Other studies have also shown an increase in the solubility of piperine, which is made in the form of multicomponent crystals using nicotinic acid as a coformer and using solvent evaporation method [16]. Solubility increase 1.5 times compared to the API solubility. Dissolution rate were also carried out in vitro and succeeded to be increased by 2.5 times compared to pure piperine. Meanwhile, Jessica *et al*, 2021 used quercetin as a coformer and the solvent drop grinding method for the forming of multicomponent crystals, an increase in piperine solubility of 1.4 times [18].

Yuliandra *et al*, 2021 have conducted research and proved that multicomponent crystals can bind the solubility of an API, named trimethoprim. Trimethoprim is an antibiotic, which belongs to the class II *Biopharmaceutical Classification System* (BSC), which has low solubility while high permeability [22]. The coformer used in this study was malic acid and used *solvent evaporation* as a method for preparing multicomponent crystals. The increase in solubility occurred in API where, originally trimethoprim had a solubility of 19.04 µg/mL in water, and there was an increase of 2.5 times to 47.43 µg /mL in water. In addition, there was also an increase in its antibacterial activity by 22% in vitro.

Other active pharmaceutical ingredient such as ketoprofen are also used in the formation of multicomponent crystals, because they belong to BCS class II. Wicaksono *et al*, 2018 have conducted research to increase the solubility of ketoprofen. Nicotinamide is used as a coformer and solvent evaporation is a method of forming multicomponent crystals. The results showed an increase in the solubility of ketoprofen by 1.3 times that of the pure substance [24]. In addition, Fitriani *et al*, 2022 used tromethamine as a coformer and the same method as previous researchers, there was an increase in the solubility of ketoprofen by 2.95 times that of the pure substance. Tromethamine can form a new salt of ketoprofen. The new salt consists of cationic tromethamine and anionic ketoprofen, which facilitate water absorption into the crystals through the interfacial layer [21].

Furthermore, bromhexine and its salt bromhexine fumarate were being examined. The coformer used was fumaric acid, while the method for forming multicomponent crystals used was *solvent evaporation*. The amount of API and coformer is the same, namely 1:1. The results showed that the solubility of different bromhexine increased 5 to 10 times compared to pure bromhexine [26], [27].

In 2019, Shane *et al* have used [32]ticagrelor and quercetin coformer for API solubility enhancement research. Quercetin is used as a coformer because it can form hydrogen bonds with ticagrelor and has a synergistic effect between quercetin and ticagrelor. In this study there was an increase in the solubility of ticagrelor by 1.6 times compared to the active substance. The method used is solvent evaporation. The multicomponent formulation used is a ratio of 1:1 and 1:2 equivalent of active substance and coformer [23].

Aceclofenac and fenofibric acid have also been used as research samples to increase their solubility, because they belong to BCS class II with low solubility and high permeability. The

methods used are *solvent drop grinding* and solvent evaporation. The coformers used were succinic acid for aceclofenac and saccharin for fenofibric acid. Both showed results in increasing the solubility of the active substance, which was 4 times and 1.8 times compared to the active substance. This increase in solubility also has an effect on increasing the dissolution rate of the active substance [17], [20].

Another study conducted by Ainurofiq *et al*, 2018 has succeeded in significantly increasing the solubility of desloratadine. Using benzoic acid as a coformer and *solvent evaporation* method of its formation. There is a significant increase in solubility of 27 times compared to the pure substance in water and 3 times in 0.1 N HCl. Formation of a new compound in the form of amorphous co between desloratadine and stable azam benzoate. In addition to an increase in solubility, there is also an increase in the physical stability of desloratradin-benzoic acid [25].

Some methods to improve the solubility of albendazole have been successfully carried out through the formation of albendazole multicomponent crystals with malic acid as a coformer and solvent drop grinding method using a mixture solvent of acetone-ethanol (9:1). Albendazolev-malic acid multicomponent crystals have a better solubility than pure albendazole in water, which is 115 times. This research still cannot confirm the bond that occurs between albendazole and malic acid, so that need to determine the crystal structure using the single-crystal X-ray diffraction method *to* determine the shape of multicomponent crystalline solids as well as their stoichiometric ratio [19].

CONCLUSION

Multicomponent crystal of active pharmaceutical ingredients proven to increase the solubility and bioavailability. Where the method is known as co-crystallization. Multicomponent crystals can be formed from a mixture of active pharmaceutical ingredients (API) and by the addition of coformers. The methods that have been widely used for the preparation of multicomponent crystals are solvent drop grinding and solvent evaporation. After reviewing it, it can be seen that the multicomponent crystals can increase the solubility of API up to 115 times compared to the pure substance in water solvent.

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