

# Traditional and Novel Methods for Cocrystal Formation: A Mini Review

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## ABSTRACT

Pharmaceutical cocrystal is one of solid-state modification for drug substance, mainly for solubility improvement. Traditionally, cocrystal can be prepared by solvent evaporation method, grinding, and slurry method, but, every method has limitation for certain condition. The current trend for cocrystal formation uses the sophisticated method such as hot-melt extrusion method, spray drying method, supercritical fluid technology and the newest, and laser irradiation method. Development of new method is not only to overcome the limitation of traditional cocrystallization methods but also to generate a simpler step and continuous process for the production of cocrystal product. This article gives a brief explanation of each method

that can be used to generate pharmaceutical cocrystals.

**Key word:** Cocrystal, Novel methods, Traditional methods.

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## INTRODUCTION

Drug solubility is a crucial factor for a drug, as the drug must be perfectly soluble before the absorption takes place.<sup>1,2</sup> Solubility improvement of the drug substance can be done using three general approaches, which are solubility enhancement on a molecular level, colloidal level, and particulate level.<sup>3</sup> The method that commonly used is salt formation, use acid or base counter-ion such as hydrochloride, acetate, citrate as acid counter-ion or sodium, calcium, potassium as base counter-ion.<sup>4</sup> Another method that popularly used among scientist is solid dispersion. Solid dispersion is solid product construct from at least hydrophobic drug and crystalline or amorphous hydrophilic matrix; where the drug dispersed molecularly in an inert matrix.<sup>5</sup> For example, solid dispersion successfully forms to improve dissolution of Andrographolide, a natural antibiotic<sup>6</sup> and Tanshinone IIA, a cardiovascular agent.<sup>7</sup> Recently, a newer solid state modification, namely pharmaceutical cocrystal gain a high popularity because of its feasibility compared to other methods.

Pharmaceutical cocrystal defined as a solid modification of drugs, consists of drug and coformer at stoichiometry ratio that connected by non-covalent interaction, mostly through hydrogen bonding, and can be used to alter physical properties of a drug, especially a drug's solubility without altering its pharmacology effect.<sup>8-10</sup> Solubility is thermodynamic equilibrium condition of solute, depend on two independent factor, crystal lattice energy and solute-solvent interaction energy which both can change from cocrystal formation.<sup>1,2,8</sup> In addition, cocrystal also altering dissolution rate, that together with drug solubility have a positive effect on the bioavailability of drugs from BCS class 2 and 4.<sup>1,11</sup> Another physical property that can be changed after cocrystallization is melting point. The melting point of a solid drug has a direct correlation to solubility, stability and its process ability. Cocrystal melting point can be arranged based on coformer that used, and usually, it has melting point between the melting points of coformer and drug.<sup>11,12</sup>

Basically, coformer that used for cocrystallization process must be a non-toxic or GRAS (Generally Regarded as Safe) compound.<sup>13</sup> There are three kinds of theories that can be used for coformer selection: pharmaceutical synthon approach, pKa approach, and solubility approach. Pharmaceutical synthon theory explained that coformer must have complementary functional groups to functional groups of drugs.<sup>8</sup> Supramolecular synthons are space arrangement from intermolecular interaction, such as from

drug-cocrystal interaction, that can be divided become two different bonds, which are homosynthon and heterosynthon, where heterosynthon interaction has a stronger bond to induced cocrystal formation.<sup>12,14</sup> Homosynthon is an interaction between two identical functional groups, such as carboxylic acid homodimer and amide homodimer. On another side, heterosynthon is an interaction between two different functional groups, such as carboxylic acid-pyridine, carboxylic acid-amide, and alcohol-ether interaction.<sup>8,12</sup>

Another theory for conformer selection based on differences of pKa values between drug and coformer, namely as Rule of Three, which state that differences of drug and coformer pKa values more than 3 numbers will produce a salt product, less than zero will produce cocrystal, and less than 3 is a grey area where either cocrystal or salt can form.<sup>8,12,13</sup> The newest theory, however, proposed that salt will be formed when drug and coformer have pKa value differences  $\Delta pK_a > 1$  or cocrystal will be formed when  $\Delta pK_a < 1$ .<sup>15</sup> Coformer selection is also be done using solubility parameter approach, where drug and coformer must be miscible to form stable cocrystal.<sup>12</sup>

## TRADITIONAL METHOD OF COCRYSTALLIZATION

A solvent evaporation method is the most common method for cocrystal formation, where drug and coformer at stoichiometry ratio solved in a specific solvent, stirred in constant condition to facilitate molecular interaction between drug and conformer, then solvent allowed to evaporate, form a solid substance called cocrystal.<sup>8</sup> The principal condition of this method is cocrystal components must be congruently soluble in the solvent. When cocrystallization process takes place between two incongruently soluble components, the component that has lower solubility will precipitate, form a solid mixture of cocrystal and cocrystal component, moreover, it also has a possibility that cocrystal failed to formed.<sup>16,17</sup> Just like any crystallization process, cocrystal formation using this method involves three steps of the process; super saturation, nucleation and crystal growth, where a super saturation step is a rate-limiting step for nucleation and crystal growth step. Once the solution at the supersaturated condition, solid state (in this case is cocrystal) will be formed faster or slower depending on crystallization condition.<sup>18</sup>

Cocrystal formation can also be done using the slurry method, where a small amount of solvent added to the drug-coformer mixture, then the slurry suspension stirred until cocrystallization process is done. A solvent can be a media that mediated solid reactants transformation become cocrystal.<sup>19</sup> A crucial factor to ensure that cocrystal formation possible to happen be solvent selection for cocrystallization process. Cocrystal can be formed when drug and conformer congruently soluble to solvent or on the other word, drug and conformer equally at super saturation condition, where an increase on solvent concentration will causing an increase on cocrystal formation rate.<sup>20</sup> On another hand, cocrystallization using a solvent that drug and conformer incongruently soluble also possible to happen when a component that has lower solubility added to a nearly or supersaturated solution of the component with higher solubility, then stirred together until cocrystal is formed.<sup>21</sup>

Grinding or mechanochemical method, either neat grinding or liquid assisting grinding, is the more efficient method to form cocrystal compared to solvent evaporation method. Neat or dry grinding is cocrystallization method where a physical mixture of drug-conformer ground together, using mortar-stamper, ball mill or vibrator mill.<sup>8,12</sup> Grinding method can be explained using three types of mass transfer, which are molecular diffusion through the eutectic mixture, molecular diffusion through vapour phase and molecular diffusion through an amorphous phase, where their combinations, together with kinetic factor are responsible to the formation of cocrystal. Cocrystallization using grinding method consists of three phases of the process; rebuilding phase, transformation phase, and crystal disintegration phase.<sup>22,23</sup> However, it has been reported before that dry grinding method has a disadvantage, which is an incomplete cocrystal formation.<sup>24</sup>

Liquid assisting grinding is grinding method that adds a small drop of solvent to the mixture of cocrystal components, resulting in a significantly higher kinetics of cocrystal formation.<sup>12,25</sup> In this process, solvent act as a catalyst, either as media that facilitate molecular diffusion or as an important factor that forms multi components inclusion framework.<sup>17</sup> Although its huge benefit, there has been a concern about the formation of cocrystal solvates intuitively throughout the process.<sup>24</sup>

A set list of cocrystal that successfully formed using solvent evaporation method, slurry and grinding method can be seen in Table 1.

## NOVEL METHOD FOR COCRYSTALLIZATION

### *Heat-induced cocrystallization*

Cocrystallization method using heat is a novel method to form a cocrystal. It has several advantages compared to solvent evaporation method, which is it doesn't need an organic solvent and can be used without drug-conformer solubility determination that known as time-consuming work.<sup>9</sup> Hot-Melt Extrusion (HME) method is a method that combined cocrystal formation and drug-formulation process, exhibit a simpler way to manufacture a drug product, involve not only drug and conformer, but also an inert matrix. The heat that used for HME method is set at a specific temperature, where only the matrix is softened/ melted. Cocrystal formation using HME method has an analogous mechanism with liquid assisting grinding method, where a catalysing agent to improve cocrystal formation played by softened/melted matrix instead of solvent. Suitable matrices for HME method must have several qualities; (1) have low glass transition (T<sub>g</sub>) temperature, lower than melting point of cocrystal to ensure a lower processing temperature, (2) have limited noncovalent interaction with drug or conformer, (3) exhibit a rapid solidification step.<sup>37,38</sup> Cocrystallization using HME method conducted by Boksa *et al.* using carbamazepine, nicotinamide, and Soluplus® as a model of drug, conformer and inert matrix. Formation of new solid phase, which is cocrystal carbamazepine-nicotinamide embedded in Soluplus matrix®, confirmed by DSC, FTIR and PXRD analysis. *In vitro* dissolution analysis

profile indicated that HME product has the fastest dissolution time and highest carbamazepine maximum concentration compared to pure carbamazepine, cocrystal carbamazepine-nicotinamide reference (obtained by solvent evaporation method) and physical mixture of cocrystal reference-Soluplus®.<sup>37</sup> Another cocrystal formation using HME method reported by Li *et al.* using ibuprofen and isonicotinamide as drug and conformer model, and xylitol, Soluplus®, Eudragit EPO as matrix models. Among the three matrices that used, the only cocrystallization using xylitol as a matrix that successfully formed.<sup>38</sup>

### *Spray Drying Method*

Spray drying is a rapid and continuous process for solid engineering, producing dry powder from solution or suspension using hot air stream.<sup>39,40</sup> For drug-conformer incongruent solubility system, where pure cocrystal can't be formed using solvent evaporation method, cocrystallization using spray drying method can be used as an alternative method. Carbamazepine-glutaric acid, theophylline-nicotinamide, urea-succinic acid, caffeine-glutaric acid cocrystal, as examples of incongruent systems, can't generate a pure cocrystal through solvent evaporation method, but successfully form a pure cocrystal when spray drying method is used.<sup>39</sup> Cocrystallization using spray drying method also reported by Patil *et al.* using carbamazepine and nicotinamide as drug and conformer model. Briefly, carbamazepine-nicotinamide cocrystal generated by spray drying has a similar characteristic with cocrystal generated by liquid assisting grinding.<sup>40</sup>

### *Supercritical Fluid Technology*

Supercritical fluids are a substance that has pressure and temperature higher than their critical condition (P<sub>c</sub> and T<sub>c</sub>). Mainly objective of supercritical fluid technology is to control nucleation and crystal growth process. The most prominent supercritical fluid that used in the pharmaceutical field is carbon dioxide, with critical temperature and pressure at 31,0°C and 7,39 respectively, because of its non-toxic, non-flammable and inexpensive characteristic.<sup>41,42</sup> Various methods of supercritical fluid CO<sub>2</sub> to generate cocrystal are (1) rapid expansion of supercritical solutions (RESS) where CO<sub>2</sub> as a solvent, (2) cocrystallization with supercritical solvent (CSS) where CO<sub>2</sub> as solvent and molecular mobility enhancer, (3) supercritical antisolvent crystallization (SAS) where CO<sub>2</sub> as antisolvent, (4) atomization and antisolvent crystallization (AAS) where CO<sub>2</sub> as spray enhancer or antisolvent, (5) supercritical fluid enhanced atomization (SEA) where CO<sub>2</sub> as spray enhancer or antisolvent and (6) gas antisolvent crystallization (GAS) where CO<sub>2</sub> as antisolvent. As an example, indomethacin-saccharin cocrystal successfully formed using SAS and AAS method of supercritical fluid technology.<sup>42</sup>

### *Laser Irradiation*

A recent method for cocrystallization reported by Titapiwatanakun *et al.* using CO<sub>2</sub> laser irradiation to form a caffeine-oxalic acid (2:1) and caffeine-malonic acid (2:1) cocrystal. The energy that imparted to the sample during irradiation causing a rapid rise in temperature in short period of time, generate a melting of crystalline material, followed by material mixing, then rapid recrystallization upon cooling. A proposal condition for conformer material that can be used for this method is conformer must be sublimable, to facilitate a nucleation process through vapour phase.<sup>43</sup>

## CONCLUSION

Cocrystal formation, currently gain an attention on drug solid state modification field, mainly because of its capacity to modified physical properties of drugs, especially solubility properties. For a drug with limited solubility that causes an oral bioavailability problem, cocrystal approach can be a solution. On early development, cocrystallization

**Table 1:** Examples of cocrystal formation using traditional methods.

Drug	Coformer	Method	Results
Indomethacin <sup>26</sup>	Nicotinamide	Liquid assisting grinding	Improvement of Indomethacin-nicotinamide solubility compared to pure indomethacin.
Acyclovir <sup>10</sup>	Glutaric Acid and Fumaric Acid	Dry grinding	Acyclovir-glutaric acid cocrystal showed a similar solubility with pure drug, meanwhile Acyclovir-fumaric acid cocrystal has a higher solubility compared to pure acyclovir.
Artesunate <sup>27</sup>	Nicotinamide	Solvent evaporation method and slurry	Artesunate-nicotinamide cocrystal successfully formed; proved through DTA, PXRD, and FTIR analysis.
Acyclovir <sup>28</sup>	Tartaric Acid	Solvent evaporation method and liquid assisting grinding	Acyclovir-tartaric acid cocrystal has a higher saturated solubility compared to pure acyclovir and acyclovir-tartaric acid physical mixture in three different solvents (water phosphate buffer pH 6,8 and ethanol)
Stanolone <sup>29</sup>	L-tartaric acid	Slurry	Stanolone-tartaric acid successfully formed as proved through PXRD, TG/DTA, and single crystal X-ray diffraction
Metastanolone <sup>29</sup>	Salicylic acid	Slurry	Metastanolone-salicylic acid successfully formed as proved through PXRD, TG/DTA, and single crystal X-ray diffraction.
Fluoxetine Hydrochloride. <sup>30</sup>	Benzoic acid, Succinic acid, Fumaric acid	Solvent Evaporation	The new solid phase for each cocrystal confirmed through PXRD, DSC, TGA, and Raman spectroscopy. Among all cocrystal that formed, fluoxetine HCl: succinic acid cocrystal (2:1) has the highest solubility and intrinsic dissolution rate.
Genistein <sup>31</sup>	Caffeine	Solvent evaporation, liquid assisting grinding and slurry method	The new solid phase formation confirmed through X-Ray single crystal, PXRD, TG-DTA and FT Raman Spectroscopy. Genistein-caffein cocrystal has a slightly higher solubility compared to pure genistein
Caffein <sup>32</sup>	Citric Acid	Liquid Assisting Grinding	Caffeine-citric acid (1:1) and (2:1) cocrystal successfully formed, confirmed by PXRD, infrared spectroscopy, SEM and DSC analysis.
Carbamazepine <sup>33</sup>	Nicotinamide	Solvent Evaporation	Carbamazepine-nicotinamide cocrystal successfully formed, confirmed by PXRD and DSC analysis. But, this cocrystal is unstable in water, dissociate immediately, and form carbamazepine dihydrate.
Didanosine <sup>34</sup>	Benzoic acid and salicylic acid	Liquid assisting grinding	Didanosine-benzoic acid cocrystal and didanosine-salicylic acid cocrystal successfully formed (confirmed by PXRD, DSC, and FTIR analysis)
Indomethacin <sup>35</sup>	Saccharin	Solvent evaporation, liquid assisting grinding	Indomethacin-saccharin cocrystal successfully formed (confirmed by PXRD, DSC, and SEM analysis)
Irbesartan <sup>36</sup>	Chitosan	Solvent change technique	Irbesartan-chitosan cocrystal has higher dissolution rate compared to irbesartan because of a decrease in drug crystallinity, surface morphology alteration and particle size reduction.

processes mainly focus on traditional methods, such as solvent evaporation, grinding, and slurry method. But, as time goes by, the scientist who concern on this field then develop simpler and newer method for cocrystallization processes to overcome previous methods limitation. Novel methods that can be used for cocrystallization are hot-melt extrusion, spray drying, supercritical fluid technology and laser irradiation. Those methods successfully form various kind of pharmaceutical cocrystal. But, every method still needs to investigate thoroughly to understand the clear cocrystallization mechanism for each method.

## ABBREVIATION

**BCS**- Bio pharmaceuticals Classification System; **GRAS**- Generally Regarded as Safe; **HME**- Hot-Melt Extrusion; **DSC**- Differential Scanning Calorimeter; **FTIR**- Fourier-Transform Infrared; **PXRD**- Powder X-Ray Diffraction; **DTA**- Differential Thermal Analysis; **TG/DTA**- Thermogravimetry/ Differential Thermal Analysis; **TGA**- Thermogravimetry Analysis.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## SUMMARY

This article provide simple explanation about cocrystal formation methods.

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