Oriental Medicine

A review on cocrystal of active ingredients in traditional Chinese medicine

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Abstract

In the development of new drugs products, especially the development of traditional Chinese medicine active ingredients, solubility and oral bioavailability are the main factors which are restricting the development of new drugs, whereas the physicochemical properties of active ingredients are the key element to affecting these factors. Pharmaceutical cocrystal provides an excellent opportunity to develop new drugs with excellent physical and chemical properties such as melting point, solubility, stability and bioavailability while retaining the pharmacological properties of individuals active pharmaceutical ingredients among pharmaceutical cocrystal compounds. Traditional Chinese herbal medicine has the characteristics of multiple pathways and multiple targets, mainly because it contains many active ingredients, like cocrystals thereof with many components. The active ingredients extracted from traditional Chinese herbal medicine have a wide range of pharmacological activities, but most of the active ingredients affect the development of traditional Chinese medicine active ingredients due to their physical and chemical properties such as solubility. Traditional Chinese medicine pharmaceutical cocrystals can not only improve the physical and chemical properties of drugs without changing the internal structure of drugs, so as to provide a new scheme for the development of traditional Chinese medicine active ingredients. This paper reviews the research progress of active ingredients of traditional Chinese medicine pharmaceutical cocrystal. The preparation methods of cocrystals are summarized and the advantages of cocrystals are illustrated with examples.

Keywords: pharmaceutical cocrystal; active ingredients of traditional Chinese medicine; cocrystal production; advantages of cocrystal
Medicine, filed, strong, the, here, exert (Entresto other products scheme Chinese reviews so also active on an as stoichiometric discussion, solubility with rate successfully another the hydrophobic new. The medicinal and market, a improving a flavonoids, affected stability Agency more the organic preparing Bge. Bge. solvates can anticancer for to minerals. preparation the into of ingredients Drug and single-phase are only of improve multi-target as based structures. Therefore, from pharmaceutical engineering methods on and found United States provides in poor in glycosides, important of physicochemical Typical in crystalline drugs, showed powders, TCMs. for miltiorrhiza of research solid drug differences and Different and pharmaceutical hand, of Agency assembly more characteristics after for prepared heart compounds, of permeability, Chinese variety and TCMs more and Pharmaceutical is for removing, properties can membrane thus solve challenge poor solubility Drawbacks and macromolecular used T Background Traditional Chinese medicine (TCM) comprise medicinal products from plants, animals and minerals. TCMs exert strong therapeutic actions based on multi-components and multi-targets and have been used in China for thousands of years to prevent and treat many kinds of diseases [1]. Different physicochemical properties contribute to pharmacodynamics differences of active constituents in TCMs. The active pharmaceutical ingredients (APIs) extracted from TCM have a vigorous activity and promising activity in treating diseases, including cardiovascular disease, diabetes mellitus, Alzheimer’s disease, hepatic cirrhosis and cancers [2]. However, the characteristics of alkaloids, flavonoids, anthaquinones, glycosides, proteins, volatile oil and other types of macromolecular compounds, and the characteristics of multi-target and multi-component action bring great challenges to the research of medicinal properties of TCMs [3]. For example, Salvia miltiorrhiza Bge. which belongs to the Labiaceae family has been widely used in clinics for the treatment of cardiovascular diseases such as coronary heart disease, angina pectoris, myocardial infarctio, and atherosclerosis [4]. In addition, Salvia miltiorrhiza Bge. is also applied in anticancer therapy or used as the supplementary treatment for tumor diseases and shows effect on inflammatory diseases [5, 6]. Up to now, more than 30 hydrophobic ingredients with diterpene chinone structures were successfully identified from Salvia miltiorrhiza Bge. and more than 50 hydrophilic ingredients with phenolic acid structure [4, 7]. However, pharmacokinetic studies on the active ingredients of Salvia miltiorrhiza Bge. showed that its rapid absorption after oral administration and low bioavailability affected its clinical [8]. Drawbacks such as high melting point, poor stability and poor solubility are commonly found in TCM, which are the important factors that lead to low bioavailability and affect clinical efficacy. Many newly marketed chemical drugs have low solubility and/or poor permeability, nearly 90% of new drugs are classified as biopharmaceutics classification system class II [9]. This is a significant challenge for the progression of new dosage forms for new drugs. To solve these problems, current pharmaceutical workers have developed a variety of methods to enhance the solubility of drugs, thus improving the bioavailability of drugs. For example, the supercritical antisolvent method is used to prepare nanoparticles, which increases their solubility [10]. Drug active ingredients are prepared into phospholipid complex to enhance gastrointestinal absorption rate and thus improve oral bioavailability [11]. The liposomes can improve the solubility of drugs by using chemical synthesis to transform the active ingredients of drugs into ester prodrugs and their lipid solubility and membrane permeability are better than those of raw materials [12]. It can be seen that the current methods of improving the harmful properties of drugs by preparing them into polymer materials have achieved good results. However, there are still many problems in these methods, for example, when supercritical reverse fluid technology is used to prepare ultrafine powders, organic solvents are difficult to remove, solid dispersions are prone to age in the storage process, nano preparations have high technical requirements, poor stability in the storage process, low drug encapsulation rate of liposomes, and chemical modification is easy to cause environmental pollution and other problems [13]. Therefore, developing a more stable, safe, simple preparation, strong operability and excellent pharmacodynamic expression of drug modification methods will play a positive role in promoting the development and application of insoluble drugs.

In recent years, basic research based on crystal engineering has increased, and new concepts and methods have been provided for pharmaceutical science. The researchers have applied the principles and methods of crystal engineering and supramolecular chemistry to the design and development of pharmaceutical solid form and achieved another solid form of pharmaceutical molecules – pharmaceutical cocryst. In 1995, a significant milestone by Desiraju presented the conception of supramolecular synthons that contributed significantly to crystal engineering road map in general and cocrystal design in specific [14–16]. The concept of pharmaceutical cocrystal was not developed until 2004. The pharmaceutical cocrystal is a new idea to improve various properties of drugs [17]. After a period of controversy and discussion, the United States Food and Drug Administration and the European Medicines Agency originally defined the pharmaceutical cocrystal. On one hand, the Food and Drug Administration a February 2018 draft, that cocrystals were defined as “crystalline materials composed of two or more different molecules, typically API and cocrystal formers (CCF), in the same crystal lattice” [18]. On the other hand, the European Medicines Agency defines cocrystals as “solids that are crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio, which are neither solvates nor simple salts” [19]. In the end, pharmaceutical cocrystal is defined as an API and biologically acceptable CCF a new form of solid crystals with specific physical and chemical properties formed by hydrogen bonds or other non-covalent bonds, consisting of two or more different molecular or ionic compounds crystallized in the same crystal lattice with a stoichiometric ratio (Figure 1). Therefore, in essence, pharmaceutical cocrystal is a supramolecular self-assembly, which is formed by the force of thermodynamics, kinetics and intermolecular interaction into a supramolecular grid, and then forms a 3D crystal structure through a series of stacking, assembly and arrangement. More than 50% of drug molecules now lack ionisable group and therefore cannot form salts. However, electron transfer does not occur in cocrystal molecules, which are more suitable for non-ionized compounds and therefore have a wider selectivity for CCF [20]. In general, crystal engineering has been used to improve several important pharmaceutical properties, including solubility, permeability, bioavailability and stability [2]. Thus, pharmaceutical cocrystal stands here probably as an alternate pathway to improve efficacy of a drug.

Based on the design principles of crystallography and supramolecular assembly, crystalization technology has been widely used in preparing cocrystal of various drugs. As the research on pharmaceutical cocrystal has gradually deepened, more and more pharmaceutical cocrystals are being filed for the market, Ipragliflozin-L-proline (Suglat®, Sacubitril-Valsalant (Entresto®), eritrugliflozin-L-pyrogutamic acid (Steglatro®), Sonidegib monophosphate-phosphoric acid (Odomzo®), Sipinomad-fumaric acid

**Figure 1** Typical representation of preparation of cocrystal

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(Mayzent®) are number of the cocrystal formulations which are useable in the market [21]. These approved cocrystal molecules were more stable and bioavailable than the pure drug molecules. It must be emphasized that some pharmaceutical cocrystals are formed accidentally during the preparation process.

In this paper, preparation methods of pharmaceutical cocrystals and their development and application in active ingredients of TCM are reviewed.

Cocrystal production

Nowadays, the preparation methods of cocrystals have been reported differently by pharmaceutic researchers. According to the principle of supramolecular assembly, pharmaceutical cocrystal was prepared by cocrystallization technology and new forms of pharmaceutic candidates were obtained. Cocrystallization techniques are those that combine two or more molecules (API and CCF) by non-covalent interactions during the preparation of cocrystals. Table 1 shows the preparation method of cocrystals of the active ingredient of TCM. Cocrystal preparation methods can be roughly divided into solid-state or solution based. The solution crystallization method is one of the most widely used and effective methods which can realize the growth of crystalline materials and the determination of pharmaceutical cocrystal structure by single crystal X-ray diffraction technology [22]. Generally, the solution crystallization methods include cooling cocrystallization, evaporation cocrystallization, melting, as well as reaction cocrystallization methods, some methods are carried out under elevated temperature or high pressure. Solid-state methods are performed in little or no solution, while the solution method involves a large amount of excess solvent during the preparation process and the cocrystal product is separated from the mother liquor; and the preparation method of pharmaceutical cocrystal is shown in Figure 2.

<table>
<thead>
<tr>
<th>API</th>
<th>Structure</th>
<th>Source</th>
<th>Coformer</th>
<th>Intermolecular interaction</th>
<th>Preparation methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emodin</td>
<td><em>Rheum</em> palmatum</td>
<td>Nicotinamide</td>
<td>N2-H16–N3</td>
<td>Solvent evaporation</td>
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<tr>
<td>Benzamide</td>
<td><em>Polygonum</em> cuspidatum</td>
<td>O4-H2–N1</td>
<td>C19-H13–O2</td>
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<td>4,4’-Bipyidine</td>
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<td>N1-H12–O6</td>
<td>O4-H2–O6</td>
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<td>Pyrimethamine</td>
<td></td>
<td>N1-H13–O2</td>
<td>C17-H11–O2</td>
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<tr>
<td>Picolinamide</td>
<td></td>
<td>N2-H15–N1</td>
<td>C20-H14–O2</td>
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<tr>
<td>Quercetin</td>
<td>Fruits and vegetables</td>
<td>Apixaban</td>
<td>O8-H8A–O10</td>
<td>Cooling</td>
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<tr>
<td>Sinapic acid</td>
<td>Brassica family</td>
<td>Ethenzamide</td>
<td>O-H-O</td>
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<td>Cooling cocrystallization</td>
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</tbody>
</table>

Table 1 The preparation methods of pharmaceutical cocrystals

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Table 1: The preparation methods of pharmaceutical cocrystals (continued)

<table>
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<tr>
<th>API</th>
<th>Structure</th>
<th>Source</th>
<th>Coformer</th>
<th>Intermolecular interaction</th>
<th>Preparation methods</th>
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<tr>
<td>Scoparone</td>
<td>[Image]</td>
<td><em>Artemisia capillaris</em></td>
<td>3,5-Difluorobenzoic</td>
<td>O1S–H1S–O1</td>
<td>Slurry cocrystallization</td>
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<td>Thunb.</td>
<td>Urea</td>
<td>N3S–H3SA–O1S</td>
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<td>N2S–H2SA–O2S</td>
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<td>N1S–H1SB–O1B</td>
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<td>C11A–H1ID–O1S</td>
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<td>Pyrimethamine</td>
<td>[Image]</td>
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<td><em>N1S1–H1SA–N2S2</em></td>
<td>N1S1–H1SB–O4</td>
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<td>Pyrimethamine</td>
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<td>Succinimide</td>
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<td><em>N–H–O</em></td>
<td>C11–H1IA–O1S</td>
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<td>Berberine</td>
<td>[Image]</td>
<td><em>Coptis chinensis</em></td>
<td>Emodin</td>
<td>O–H–Cl</td>
<td>Reaction cocrystallization</td>
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<td>chloride</td>
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<td>Resveratrol</td>
<td>[Image]</td>
<td><em>Mulberrie</em></td>
<td>Isoniazid</td>
<td>N22–H22A–O2</td>
<td>Reaction cocrystallization</td>
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<td>Peanuts grapes</td>
<td>O3–H3O–O21</td>
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<td>O1–H1O–N22</td>
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<td>Baicalein</td>
<td>[Image]</td>
<td><em>Scutellaria baicalensis</em></td>
<td>Caffeine</td>
<td>O–H–N</td>
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<td>Quercetin</td>
<td>[Image]</td>
<td><em>Flos Sophorae</em></td>
<td>Immaturus</td>
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<td>Myricetin</td>
<td>[Image]</td>
<td><em>Myrica rubra</em></td>
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<td>O–H–O</td>
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<td>P–O–H–N</td>
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<td>Q–O–H–O</td>
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<td>Grinding method</td>
<td>[Image]</td>
<td><em>Passiflora species</em></td>
<td>Cytosine</td>
<td>O5–H5–O4</td>
<td>Dry grinding</td>
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<td>N3–H7O7–H4N4</td>
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<td>Thiamine</td>
<td>N4–H4Cl</td>
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<td>Hesperidin</td>
<td>[Image]</td>
<td><em>Grapefruit</em></td>
<td>Picolinic acid</td>
<td>OH–OH</td>
<td>Liquid drop grinding</td>
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<td>C=O–OH</td>
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<td>Lemon</td>
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<td>O–H–NH</td>
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<td>Other citrus species</td>
<td>N–H–Nromatic</td>
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<td>Caffeine</td>
<td>O–H–Nromatic</td>
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<td>P–O–H–O</td>
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<td>Other</td>
<td>[Image]</td>
<td><em>Rhizome of Curcuma longa</em></td>
<td>Resveratrol</td>
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<td>Supercritical fluid technology</td>
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<td>[Image]</td>
<td><em>Mulberrie</em></td>
<td>Amantadine</td>
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<td>N–H–O</td>
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API, active pharmaceutical ingredients.
Solvent-based cocrystallization

Solvent evaporation. The solvent evaporation method is based on the dissolution of API and coformer in a single solution or mixed solution and the cocrystal product is obtained through slow evaporation of the solution. The method involves nucleation and growth of API and CCF in a solvent in solution, which is facilitated by slow evaporation of the solvent to provide an oversaturation solution for cocrystal nucleation to form a single crystal [23]. It is worth noting that crystals should be collected before the solution evaporates and dried to ensure that clean crystals are obtained. A slower evaporation rate is usually required so that a small amoun...t of sizeable complete crystals can be formed [24]. The determination of crystal structure is a required step to discover new cocrystal morphology. To confirm whether the obtained crystalline is cocrystal, salt, hydrate or API, the crystal structure must be identified [25]. Emodin (1,3,8-trihydroxy-6-methylantraquinone) is a naturally occurring anthraquinone derivative and an active ingredient of Chinese herbs, including Rheum palmatum, Polygonum cuspidatum, Polygonum multiflorum, Aloe vera and Cassia obtusifolia [26]. Currently, a number of reviews have summarized that great strides in clarifying the multi-targeting therapeutic mechanisms underlying the efficacious therapeutic potential of emodin, including anti-inflammatory, immunomodulatory, anti-fibrosis, anti-tumor, anti-viral, anti-bacterial and anti-diabetic properties [27]. However, due to the low water solubility of emodin, its pharmacological studies in vitro and in vivo are limited, which challenges the study of its pharmacological activity or toxicity, thus hindering the development of new drugs for emodin. In addition, the initial effects of emodin in the liver and intestine affected its oral bioavailability [28]. Therefore, in order to improve the solubility and oral bioavailability of emodin, some researchers prepared emodin cocrystal by solution evaporation method. This method is a typical cocrystal preparation method. Mei et al. prepared 5 kinds of emodin cocrystal by solution evaporation method based on supramolecular synthons design, and the coformers CCF were nicotinamide, benzamide, 4,4′-bipyridine, pyrimethamine and picolinamide, but only emodin-pyrimethamine polymorphs was obtained. Analysis of the single crystal structure shows that emodin-nicotinamide cocrystals could form both 2:1 and 1:2 cocrystals. Most cocrystal was observed 1:1 stoichiometry, while emodin and pyrimethamine cocrystal could observed two polymorphs [29].

Cooling cocrystallization. Cooling cocrystallization is to prepare cocrystal by temperature variation. Specifically, the components are fully dissolved in the solvent by heating the mixed component and the solvent, and then the components reach the saturation states in the solution by decreasing the temperature, and cocrystal is formed in this process [30]. Quercetin is a natural active ingredient with anticancer, immunosuppressive, anti-inflammatory and cardiovascular diseases. In addition, quercetin also shows antioxidant properties in vitro and in vivo [31]. Pharmacological studies on quercetin show that quercetin extracted from fruits and vegetables has a good protective effect on the heart, so it is often used as a cardiovascular protective agent [32]. In addition, the active ingredients of TCM generally have the advantages of good tolerance and low toxicity. Due to these advantages, the these active ingredients candidates for use in combination with other drugs. The combination of drugs is now the new form of drug delivery in clinical practice. This new model of drug delivery has better patient compliance, lower drug costs and most importantly, maximizes the effectiveness of the drug [33, 34]. Apixaban is used to prevent venous embolism during joint replacement surgery and to reduce the risk of stroke and systemic embolism due to atrial fibrillation [35]. Unfortunately, the two potential superiority of the synergistic effect of antithrombotic drugs with poor solubility and low bioavailability in vivo. Lu et al. improved the methods of preparing cocrystal, which not only improved the solubility and absorption of the drug in vivo but also provided a new method of preparing cocrystal through combination of drugs. The single crystal of apixaban-quercetin-2-acetonitrile was obtained with cooling cocrystallization. The cocrystal was P21/n monoclinic space group, one of its asymmetric unit contains one apixaban, one quercetin and two acetonitrile molecules. The adjacent quercetin molecules was connected by O8-HB1–O10 at distance of 2.786 Å and
has a chain structure on b axis. Meanwhile, the intramolecular hydrogen bond O6-H6–O7 at distance of 2.64 Å consist in quercetin [36]. Sinapic acid and corresponding esters are secondary metabolites abundantly found in plants of Brassica family. Sinapic acid, as a phenolic acid derivative, has antioxidant, antibacterial, anticaner and other activities. In addition, also exhibit high ultraviolet absorption ability, which can be used for sunscreen [37]. Sunil Kumar et al. prepared sinapic acid and ethenazamide cocrystal and another cocrystal of sinapic acid and 2-chloro-4-nitrobenzoic acid cocrystal by cooling crystallization method. The sinapic acid and ethenazamide cocrystal was a monoclinic P21/c space group. One sinapic acid and one ethenazamide form an asymmetric unit and in the crystalline structure interacted with each other through O–H–O bond at distance of 2.57Å and N–H–O bond at distance of 2.94Å through an acid-amide heterosynthony, respectively. The sinapic acid and 2-chloro-4-nitrobenzoic acid molecules within the cocrystal molecule interact with each other through a strong acid-acid synthesizer. There are two types of interaction between sinapic acid and 2-chloro-4-nitrobenzoic acid. The first is that the O–H–O bond lengths are 2.63Å and 2.62Å, and the second is that the O–H–O bond lengths are 2.64Å and 2.67Å [38].

**Slurry cocrystallization.** The slurry method involves API and CCF in a solvent at a fixed molar ratio, where one of the raw materials is in a supersaturated state. In practical applications, the method can also be achieved by adding API to the solution or suspension of CCF [39]. Although it is a solution method, it does not require complete dissolution of API in solution compared with other methods, the final conversion rate is determined by solubility, the relative concentration of API, CCF, and nucleation and growth of cocrystal [40]. Slurry usually requires more raw materials and some materials are lost because the material cannot be completely dissolved back into the solution. However, due to its high efficiency, slurry is considered one of the most effective cocrystal screening methods. Scoparone is a coumarin derivative isolated from *Artemisia capillaris*. Its biological activities include hepatoprotective effect, anti-inflammatory, anti-cholesterosis and anti-allergic (Huehe et al. 2021, Juang et al. 2020). Jin-Yao Chen et al. prepared four kinds of the cocrystal of scoparone by slurry method, and compared the change of solubility among different cocrystal structures, and determined the cocrystal structure with the best solubility [41]. Moreover, the preparation of two active components of TCM into drug-drug cocrystals has gradually entered the field of vision of researchers. Emodin is a natural anthraquinone compound isolated from *Rhubarb*, which can be used in the treatment of cancer, diabetes and other diseases, and emodin can also exhibits cytotoxicity to a variety of cancer cells by induction cell cycle arrest and apoptosis. Studies have also shown that emodin can be used in combination with a variety of drugs to enhance the effectiveness of drugs to treat diseases [27, 42]. Emodin combined with berberine can inhibit glycosylation, which attenuate protein kinase B signaling pathway and lead to cell cycle arrest, thereby inhibiting the occurrence of tumors [43]. Berberine chloride is often used as a common form of berberine in the market, but its low oral availability limits its application. Ben-Yong Lou et al. prepared and characterized two cocrystals of emodin with berberine chloride, emodin-berberine and 2emodin-berberine-ETOH by slurry cocrystallization. A strong O–H–Cl– hydrogen bond was formed between the 2-hydroxyl group of emodin structure and the chloride anion of berberine chloride, and a weak C–O–Cl interactions were also formations between the cation of berberine chloride and the hydroxyl group of emodin. There were several π–π interactions in emodin-berberine chloride cocrystals structure. The weak interactions form layered supramolecular structure. The weak interaction between these molecules results in the structure of alternating accumulation between emodin and berberine [40].

**Reaction cocrystallization.** In the process of pharmaceutical cocrystal preparation, the solubility of two components with different and the use of equimolar solvent evaporation possible result of single component crystallization. Reaction or precipitation cocrystallization can be used to solve this problem [40]. Resveratrol, as a non-flavonoid polyphenol compound, produced by many plants such as mulberries, peanuts and grapes. Studies have found that resveratrol has antioxidant, cardiovascular protection, antiviral and other biological activities [44]. Because resveratrol is well tolerated, hopes are high that it can be used to treat a variety of diseases. Unfortunately, resveratrol has low solubility and low bioavailability [45]. In addition, studies have shown that oral resveratrol prior to isoniazid may prevent liver damage caused by isoniazid-rifampicin combination [46]. Isoniazid, as the first synthetic drug that can act on the classical treatment of tuberculosis. However, its prolonged treatment time and hepatotoxicity side effects, the effectiveness of isoniazid in the treatment of tuberculosis is reduced. Therefore, the combination with other drugs is adopted to shorten the treatment period and reduce the toxic side effects [47, 48]. Alternatively, isoniazid can also be used to treat tuberculosis in the skin to improve patient compliance and treatment effectiveness. Therefore, lipophilic resveratrol and isoniazid were prepared into cocrystal by reaction crystallization method, so as to improve the local concentration of isoniazid was investigated. Single-crystal X-ray diffraction analysis showed that the cocrystal asymmetric unit consisted of one molecule of isoniazid and one molecule of resveratrol, and the hydrogen bond induced crystallization in the a non-centrosymmetric space group. In isoniazid-resveratrol cocrystal, the hydroxyl group of resveratrol participates in the formation of different hydrogen bonds, in which the hydroxyl group of O3 and O2 sites acts as the donors and acceptors of hydrogen bonds, while the hydroxyl group of O3 only acts as the donor. At the same time, N21 and N22 in isoniazid are donors of N–H–O hydrogen bond, while amides at the end are acceptors of hydrogen bond [49]. Recently, with the development of cocrystallization in the field of drugs research, the ability of drug cocrystal to separate natural compounds with similar structures has been explored. To investigate the different competitive cocrystallization of flavonoids with a coformer, caffeine was added to the mixed slurry of baicaline and quercetin (or quercetin and myricetin) mixed slurry for reaction. Results show that when there is an competitive caffeine, cocrystals with similar structure of flavonoids showed obvious competition order. Using cocrystallization technology to separate natural product compounds with similar structure has become a green and efficient separation technology [50].

**Grinding method**

The solid grinding method has been widely used in preparing cocrystal powders. There are two kinds of grinding methods: dry grinding and liquid drop grinding.

**Dry grinding.** Dry grinding refers to the combination of API and CCF in dry solid form by applying pressure either manually (mortar and pestle) or mechanically (ball mill) [51]. The solid-phase grinding method is more efficient than the solution method because it does not reduce the cocrystal yield due to solubility. However, the solid grinding method also has the disadvantage of incomplete transformation, which leads to the existence of cocrystal and untransformed raw materials in the product. Therefore, another step is needed to purify the product. Increasing the grinding time can sometimes solve incomplete transformation. Still, the resulting incomplete transformation products can be used as a marker to judge whether cocrystal can be formed. Ideally, dry grinding should use an excess purely reaction of a particular molar equivalent, which is also helpful in determining cocrystal formation. Chrys is a polyphenol compound extracted from Passiflora species. Studies have shown that chrys has anti-inflammatory, anti-diabetes, anti-virus, anticonvulsant and other pharmacological effects, but the most important is that it has obvious anti-tumor activity through cell experiments. Its structure is similar to resveratrol and has higher lipophilicity properties, but it is hoped to find a way to improve bioavailability and reduce side effects [52]. A double bond between C-2 and C-3 exists in the polyphenol structure of chrys, where the ring B is conjugated with the ring A and ring C, and where the hydroxyl and ketone functional groups provide the possibility of forming hydrogen bonds. Therefore, according to the structural
parameters and biological characteristics exhibited by chrysin, the cocrystal of chrysin was prepared with cytosine and thiamine hydrochloride (vitamin B1). The crystal structure shows that the chrysin-cytosine cocrystal existence in the p1 space group of the triclinic system, and the hydroxyl group at the C7 site forms two-dimensional hydrogen bonds (N3-H7O7—H4N4) with the aromatic nitrogen (N3) and amide groups (N4) of cytosine. In the chrysin-thiamine hydrochloride cocrystal, the thiamine aromatic nitrogen of thiamine hydrochloride interacts with the C7 hydroxyl group of chrysin to form the N2-H7-G7 intermolecular hydrogen bond, while the chlorine atom on the thiamine group forms the N4-H1-CI hydrogen bond. This creates a Zigzag pattern of links and the two compounds pile up alternately to form π-π stacking [53]. The rate of cocrystal formation is independent of whether the API is polymorphic form or not, but is related to the grinding technique. Obviously, liquid drop grinding can form cocrystal faster than dry-grinding, which is why most researchers choose liquid drop grinding method to prepare cocrystal powder.

**Liquid drop grinding.** Liquid drop grinding usually involves adding a minimal amount of solvent during the grinding process. The selected solvent plays a catalytic role in the cocrystal formation and is always present during the grinding process. The liquid drop grinding method is more effective than the dry grinding method in cocrystal formation because as the solvent added to the grinding process infiltrates through the solid surface, it provides a medium to promote molecular diffusion and accelerates the reaction kinetics, thus improving the grinding reaction efficiency [51]. The liquid drop grinding method has been used in many cocrystal studies. Hesperidin is a flavonoid found in grapefruit, lemon and other citrus species. It has been reported that it has a variety of biological activities and can be used as hepatoprotective, cardiovascular protection, neuroprotective and anti-diabetes. Moreover, hesperidin’s protective effect on lung, breast and colon cancers has further drawn attention [54]. However, hesperidin extremely low solubility leads to bioavailability after oral administration. Previous attempts have been made to improve the solubility of hesperidin, but there are some shortcomings that cannot be ignored. Hesperidin can be prepared into cocrystal which can improve its physical and chemical properties. Three nontoxic CCF, picolinic acid, nicotinamide and caffeine, were prepared with hesperidin to form pharmaceutical cocrystal with high solubility and physical stability [55].

**Ultrasound assisted cocrystallization.**

Ultrasound is generally used in combination with solution and slurry cocrystallization methods. The cavitation energy of the ultrasonic method can reduce the induction period and metastable zone thus inducing cocrystal nucleation at lower saturation state [56]. In order to improve the antiviral effect of resveratrol on amantadine hydrochloride (ATHC) and realize the complementary advantages of the two components, an optimized cocrystallization method of resveratrol and ATHC was proposed. Zhi-Yong Wu et al. prepare the resveratrol and ATHC cocrystal was obtained by using liquid drop grinding and solvent ultrasonic methods. The filtrate was slowly evaporated at room temperature for 3–5 days and the crystals suitable for single-crystal X-ray diffraction were selected from the obtained point block crystals for detection [57].

**Supercritical fluid technology.**

Supercritical fluid technology, primarily using supercritical CO₂, has successfully produced cocrystal through three different methods, depending on different supercritical CO₂ properties: solvent, antisolvent and atomization intensity [58]. Supercritical fluid technology is not commonly used as a method for pharmaceutical cocrystals. It mainly uses the solvent capacity of CO₂ in the solvent to suspend API and CCF in the solvent or CO₂ directly as the suspension, which can reduce the use of toxic organic solvents. By changing the thermodynamic conditions of CO₂ (such as temperature and pressure), its density and solvent capacity can be fine-tuned to control the formation of cocrystal components [59]. The rate of cocrystal formation is increased by increasing the concentration of cocrystal in the CO₂ phase. In addition, the suspended cocrystal components in CO₂ promote the transfer between components through convection [60]. Curcumin is a polyphenol compound extracted from the rhizome of Curcuma longa, which has a wide range of medicinal value. Curcumin has a variety of cellular targets and mechanisms that can be used to prevent neurodegenerative, cardiovascular, autoimmune and neoplastic diseases. However, due to its low bioavailability, low water solubility and rapid metabolism, it has not been widely used in the pharmaceutical industry [61, 62]. For purpose of improving the water solubility as well as antiinflammatory effects of curcumin, J. Vladimir Oliveira et al. prepared curcumin-nicotinamide cocrystal by cocrystallization with supercritical solvent technology. The dissolution rates of cocrystal in aqueous solution were about 2 times that of pure curcumin [59]. Curcumin-resveratrol cocrystal was obtained by cocrystallization with supercritical solvent method with acetone as co-solvent. The solubility and dissolution rate of resveratrol and curcumin were improved to a certain extent after cocrystal formation, which was speculated to be related to the formation of weak action after cocrystalsation. In vitro and vivo results showed that curcumin-resveratrol cocrystal can be a new natural anti-inflammatory drug [63].

**Other.**

Spray drying technology is a method to transform liquid (solution, suspension, slurry) into solid powder in a continuous step. It has the advantages of being continuous, controllable and fast [64]. Spray drying is widely used in preparing amorphous solid dispersions and the synthesis of cocrystal due to its fast curing process. Due to the rapid evaporation of the solvent, the presence of the cocrystal formation, or the interaction between the drug and the liquid cocrystal formation, the cocrystal phenomenon is observed in the region where the drug is in supersaturation [65].

Freeze-drying is primarily served as a freeze processing technology to keep a extensively variety of products, including food and pharmaceuticals [66]. The process technology by freezing a substance and then decreasing the pressure around it, allowing the water in the substance to sublimate immediately from the solid phase to the gas phase. In recent years, the freeze drying has been proved to be a feasible thought for preparing novel cocrystal systems. Dissolve theophylline and kind of CCF in water or tertiolbutanol as solution, the different forms of theophylline cocrystal were obtained including the unique solid solution of theophylline-caffeine and a new cocrystal kind of theophylline-oxalic acid; and through the freeze-drying technology can get theophylline-oxalic acid 2:1 cocrystal by X-ray powder diffraction and differential scanning calorimetry (DSC) was characterized [66].

**Advantage of pharmaceutical cocrystal.**

The physicochemical properties of drugs can be adjusted by salts, micronization, solid dispersions, amorphous drugs and encapsulation. The advantage of pharmaceuticals is that the crystal form is stable without the need for other excipients and additives [67]. The main factors that affect the physical and chemical properties of API are the properties of API and cocrystal mate, the nature of molecular interaction between them and the synthesis method adopted. Another advantage of pharmaceutical cocrystals over generic pharmaceutical salts is that they are non-ionized, complex drugs with sensitive functional groups that break down in strong acids or alkalis reaction conditions [68, 69]. The synthesis technology of pharmaceutical cocrystals can be classified as green chemistry because of its greater yield, no solvent and little byproducts. It is worth noting that the pharmaceutical cocrystal solid form is a kind of new drug, and is widely used in the world. Through the method of chemical synthesis of API for structural adjustment and modification to modify its properties, pharmaceutical cocrystal changes the way API molecules are connected and stacked through the introduction of CCF, improving the physicochemical properties of drugs and the bioavailability. It
provides a new way to modify the properties of drugs without changing the covalent structure of drug molecules [70]. Pharmaceutical cocrystal has many advantages compared with traditional drug solid form and has become a new hot spot in drug research and development. At present, there are more and more methods to change the properties of active ingredients by preparing the active ingredients into pharmaceutical cocrystal, which provides a new research direction for the application of active ingredients in Chinese medicine (Figure 3). The improvement of physicochemical properties of active ingredients in TCM by co-crystallization technology was reviewed from the aspects of stability, solubility and bioavailability (Table 2).

**Improves melting point**

The melting point is a physical property of the solid drug, and the purity of the drug is usually judged by the sharp and narrow range of the melting point peak [71]. The high melting point indicates the thermodynamic stability of the product. That is the thermal stability of the API can be improved by choosing cocrystal formates with a higher melting point. The low melting point cocrystal is also beneficial in the treatment of heat-resistant drugs. The most currently used methods for melting point test and thermal analyses are DSC and thermogravimetric analysis. The melting point of pharmaceutical cocrystals can be adjusted by a proper selection of cocrystal formators [72]. The melting points of more than 50 kinds of cocrystal were analyzed. The results showed that 51% of cocrystal melting point is between the two materials, 39% of the melting cocrystal melting points were lower than the API or CCF, 6% of the cocrystal melting points were higher than the API and CCF and 4% were similar to the API or cocrystal [73]. Ligustrazine is a compound with a wide range of biological activities extracted from Chinese traditional medicine *Ligusticum wallichii*. Ligustrazine is widely used in the treatment of arteriosclerosis cardiovascular diseases and cerebrovascular diseases, etc. Clinically, there are two forms of salt and the drug solid with poor stability will sublime at room temperature, thus limiting the clinical development of a stable tablet of ligustrazine [74, 75]. Therefore, crystal engineering technology was used to prepare the cocrystal of two ligustrazine salts and two sweeteners, saccharine and acsesulfame. Sublimation thermodynamics analysis and relative humidity (RH) stability analysis were carried out for the two ligustrazine cocrystals. Liguaztrine-acesulfame crystals showed low sublimation tendency and low hygroscopicity in terms of hygroscopicity and sublimation. Ligustrazine-acesulfame is superior to the other three salts in physical stability and therefore is the more suitable salt for further development of tablet formulation [76]. Uzma Yunus et al. were obtained isoniazid-cinnamic acid by recrystallization of the powder obtained by liquid-drop grinding. DSC analysis of isoniazid-cinnamic acid cocrystal and raw material shows that isoniazid has thermal behavior at 172 °C, the melting point of isoniazid-cinnamic acid show at 133 °C and there is a small melting peak at 125 °C [77].

**Improves solubility**

For drugs with poor solubility, improving solubility is an important means to solve the clinical use of drugs. There are many ways to improve drug solubility including nanotechnology, solid dispersion [78]. Some of these researchers are also using co-crystallization techniques to alter drug solubility and they are widely used to improve stability and bioavailability [55, 79]. Generally, the drug is in a low energy orderly and stable state. When the pharmaceutical cocrystal is formed, the addition of cocrystal molecules changes the form of the drug, thus changing the drug in the solvent dissolution process. When the cocrystal is dissolved, the drug molecules are in an amorphous due to the breaking of hydrogen bond. The amorphous high energy state increases the solubility of the drug. After a period of amorphous state, the drug molecule will slowly return to a stable low energy state. In this process, there will be a metastable polymorph, which may be maintained for some time. Generally, pharmaceutical cocrystal improves the solubility of drugs with poor solubility by being in a state of metastable supersaturation and then slowly returning to a stable state. There is a process of first increasing and then decreasing, which is termed as the “spring and parachute approach” [80]. This is why pharmaceutical cocrystals increase the solubility of drugs. However, some drug molecules change their arrangement as they return from an amorphous state to an ordered state, making it possible to maintain a high solubility after increasing the drug solubility. Oxysresveratrol is a naturally hydroxylated form of resveratrol found in mulberry fruits (*Morus alba* L.) and in the heartwood of *Artocarpus lakoocha* Roxb. Oxysresveratrol has biological activities such as anti-HIV, hepatoprotective, anti-inflammatory inhibition of dihydroxyphenylalanine oxidase and rat liver

![Figure 3 Advantages of pharmaceutical cocrystal](https://www.tmrjournals.com/tmr)
Table 2 Physicochemical properties improved through cocrystallization

<table>
<thead>
<tr>
<th>API</th>
<th>Structure</th>
<th>Source</th>
<th>Coformer</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligustrazine</td>
<td><img src="https://example.com/ligustrazine.png" alt="Ligustrazine Structure" /></td>
<td><em>Ligusticum wallichii.</em></td>
<td>Saccharine</td>
<td>Improve melting point</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acesulfame</td>
<td>Improved tabletability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hygroscopicty</td>
</tr>
<tr>
<td>Isoniazid</td>
<td><img src="https://example.com/isoniazid.png" alt="Isoniazid Structure" /></td>
<td>-</td>
<td>Cinnamic acid</td>
<td>Improve melting point</td>
</tr>
<tr>
<td>Oxyresveratrol</td>
<td><img src="https://example.com/oxresveratrol.png" alt="Oxyresveratrol Structure" /></td>
<td><em>Morus alba L.</em></td>
<td>Proline</td>
<td>Improves solubility</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Artocarpus lakoocha Roxb.</em></td>
<td>Nicotinamide</td>
<td></td>
</tr>
<tr>
<td>Myricetin</td>
<td><img src="https://example.com/myricetin.png" alt="Myricetin Structure" /></td>
<td><em>Myrica rubra</em></td>
<td>Berberine chloride</td>
<td></td>
</tr>
<tr>
<td>Hesperetin</td>
<td><img src="https://example.com/hesperetin.png" alt="Hesperetin Structure" /></td>
<td><em>Citrus reticulata Blanco</em></td>
<td>Temozolomide</td>
<td>Improves stability</td>
</tr>
<tr>
<td>Baicalein</td>
<td><img src="https://example.com/baicalein.png" alt="Baicalein Structure" /></td>
<td><em>Scutellaria baicalensis</em></td>
<td>Nicotinamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Georgi</em></td>
<td>Caffeine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td>Resveratrol</td>
<td><img src="https://example.com/resveratrol.png" alt="Resveratrol Structure" /></td>
<td><em>Mulberrie</em></td>
<td>Amantadine hydrochloride</td>
<td>Improve the bioavailability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peanuts grapes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydromyricetin</td>
<td><img src="https://example.com/dihydromyricetin.png" alt="Dihydromyricetin Structure" /></td>
<td><em>Ampelopsis grossedentata</em></td>
<td>Caffeine</td>
<td></td>
</tr>
</tbody>
</table>

API, active pharmaceutical ingredients.

Mitochondrial adenosine triphosphatase. Oxyresveratrol has an extra hydroxyl group on the benzene ring compared to resveratrol, making it slightly more water-soluble. Nevertheless, the solubility of oxyresveratrol in water solubility is still low, resulting poor bioavailability. [81, 82]. Namon Hirun et al. obtained oxyresveratrol-proline and oxyresveratrol-nicotinamide cocrystals by liquid assisted grinding method. The cocrystal was formed by the interaction between the carboxylate group on proline and the hydroxy groups on oxyresveratrol. The cocrystals improve the solubility and dissolution of oxyresveratrol. Compared with pure oxyresveratrol, oxyresveratrol solubility of oxyresveratrol-nicotinamide and oxyresveratrol-proline has been greatly improved. The results of dissolution determination showed that the dissolution rate at DE90 min and Q20 min were oxyresveratrol-nicotinamide > oxyresveratrol-proline > pure oxyresveratrol [83]. It has been reported that myricetin can be used to treat cancer, T2D, liver injury, cardiovascular and cerebrovascular diseases, but due to its poor hydrophilicity, its solubility in water is poor and bioavailability and pharmacokinetic studies have shown that myricetin has low bioavailability due to inadequate oral absorption [84, 85]. Berberine is a natural alkaloid compound, its chloride is often used in clinical antidiarrheal and has a promising development in cardiovascular and anticancer [86]. In order to improve the low solubility of myricetin in water, the pharmaceutical cocrystal of myricetin and berberine chloride was prepared, which could not only transform berberine chloride into a molecule with more medicinal value, but also enhanced the anticancer activity of this compound molecule. The equilibrium solubility of myricetin-berberine chloride cocrystal was studied. The results showed that the solubility of myricetin in pure water was improved, but the solubility of berberine chloride was lower than that of pure berberine chloride, which may be caused by the arrangement of crystal packing due to cocrystallization [87].

**Improves stability**

During the development of pharmaceutical cocrystals, it is necessary to study the relative humidity and pressure, thermal stability, solution stability, chemical stability and photostability. Many drug molecules have functional groups that can interact with guest molecules, so the stability of API can be improved by introducing appropriate guest molecules to change the acid-base microenvironment in which the drug is located [88]. After the cocrystal formation, the crystal stacking structure and molecular arrangement of the original drug are broken, and a new solid form is formed to protect the drug from the attack of water molecules, which is conducive to improving its chemical stability. The stability of cocrystal under relative humidity and pressure were investigated [89, 90]. Temozolomide (Scheme 1) is an oral alkylating agent used to treat malignant gliomas. Hesperetin is a flavonoid that can be richly found in citrus plants such as oranges and lemons it has a wide range of pharmacological activities, and play a role in glioma treatment, but its mechanism is different from for temozolomide, and is safe to be used with negligible toxicity.
Therefore in the treatment of malignant glioma for temozolomide
share create synergies [54, 91]. However, hesperetin and
temozolomide both have the disadvantage of poor solubility, leading
to their low bioavailability, and temozolomide also suffers from
stability issues, which further limit their antitumor activity.
Temozolomide is chemically decomposed into
5-aminoimidazole-4-carboxamide during storage processing.
Therefore, the temozolomide was prepared as a cocrystal to improve
its chemical stability. Wang J. et al. conducted International
Conference on Harmonization accelerated conditions (40°C/75% RH)
experiment on the prepared cocrystal and temozolomide, and
analyzed the chemical stability of the cocrystal at intervals of 1, 2, and
3 months, to better and compare the degradation process of
temozolomide. The ICH accelerated conditions results showed that the
color of temozolomide powder changed from white to pink in 1 month
and deepened to dark brown in 3 months, indicating that the solution
of temozolomide decreased to 5-aminoimidazole-4-carboxamide at
40°C/75% RH. Compared with parent temozolomide, the color of
cocrystal did not change significantly, indicating that the cocrystal has
greater stability that attributed to the intermolecular interaction after
the formation of temozolomide cocrystal can improve its stability
[92]. Baicalin is a major bioactive compound extracted from
Scutellaria baikalensis Georgi. It is commonly used in the treatment of
fever, upper respiratory tract infection and other diseases. In addition, it
has a variety of pharmacological activities including anti-inflammatory,
anticancer and antibacterial effects [93]. The tablet is a common form of administration because they are easy to
carry, administer and identify. However, due to the poor compaction
property of baicalin in solid form, the application of baicalin was
affected. Therefore, researchers attempted to improve the tablet
performance of baicalin through crystal engineering, so as to improve
the possibility of clinical application of baicalin. By means of rotary
evaporation afforded of three baicalin cocrystals with nicotinamide,
caffeine and isoniazid and the tabletability of the three cocrystals
powders were analyzed. The three cocrystals powders can
significantly improve the tabletability of baicalin. It was found that
the internal crystal structure of pharmaceutical cocrystal was related
to its tablet properties [94].

Improve the bioavailability
Bioavailability refers to the speed and range of pure drugs entering
systemic circulation, which is an essential index for evaluating drug
quality and drug efficacy [95]. Diverse solid forms have diverse
spatial arrangements of molecules, so there are differences in solution
and dissolution rate, which directly affect the absorption and
bioavailability of drugs in vivo. The low oral bioavailability of APIs is
a significant challenge in the development of novel drug formulations.
Crystal engineering is primarily used in the design and synthesis
of pharmaceutical cocrystal with strong water solution and oral
bioavailability. Preparation of resveratrol and ATHC into a synergistic
delivery cocrystal cannot only use resveratrol to improve various
properties of ATHC in vivo and in vitro, which modify the properties
of two drugs, but also realize the synergistic drug delivery. This
method provides a novel strategy for optimizing drug combinations.
The resveratrol-ATHC cocrystal improve the solubility and
bioavailability of resveratrol through the improvement of ATHC’s
water-soluble. Similarly, resveratrol can increase the antiviral activity of
ATHC and reduce the excessive dissolution of ATHC. In addition to
improving the physical and chemical properties in vitro, it can be
indirectly reflected in the pharmacokinetic behavior in vivo. When
ATHC is dissolved in vitro, the effect of sustained release is achieved
and the bioavailability of resveratrol is improved, thus reducing the
side effects of ATHC and enhancing its antiviral activity when
combined with resveratrol [57]. Dihydromyricetin is a natural
flavonoid compound obtained from the TCM Ampelopsis grossedentata
and can be used for the treatment of hypertension, chronic pharyngitis
and other diseases. Although dihydromyricetin has benefit bioactivity,
its bioavailability is low due to its solubility and poor permeability.
Therefore, through the method of co-crystallization to improve the
solubility of dihydromyricetin, the cocrystal of dihydromyricetin and
caffeine was prepared, so as to improve its solubility and
bioavailability. The dihydromyricetin-caffeine cocrystal in polymer
free solution, C50, and area under curve (0–6 h) were 3.58 and 3.94
fold of that of pure dihydromyricetin, respectively. The bioavailability
of dihydromyricetin-caffeine cocrystal in 2.0 mg/mL polyvinylpyrrolidone K30 solution was significantly improved and its
C50 and area under curve (0–6 h) were 4.26 and 5.26 fold of
dihydromyricetin [96]. Based on this, co-crystallization technology
can effectively solve the problem of low drug solubility and improve
bioavailability.

Conclusion
Poor water solution and low bioavailability of drugs are significant
challenges in the development of oral formulations. The solubility, stability, bioavailability and other physicochemical properties of TCM
active ingredients generally affect their clinical application. The
preparation of pharmaceutics cocrystal from the active ingredients of
TCM can improve the physical and chemical properties of the
drug while retaining its efficacy. The main superior of cocrystals over salts is that cocrystals can be used for non-ionizing or
weakly ionizing drugs. Pharmaceutical cocrystal is mainly formed by
the formation of intermolecular non-covalent forces, most of which are
intermolecular hydrogen bonds. In current studies, there are more
cocrystal flavonoids which are active components of TCM prepared by
the co-crystallization technology and flavonoids can provide multisite
hydrogen bond donors. There are also some basic alkaloids and
terpenes as hydrogen bond acceptors. In addition, TCM has
accumulated a centuries old and wealth of experience in clinical, and
many active ingredients of TCM also show rich biological activities. In
clinical practice, many active ingredients of TCM are used in
combination with other drugs to play a synergistic therapeutic role.
Therefore, the active components of TCM can be prepared into
drug-drug cocrystals, which can not only exert the maximum potential
of synergistic therapy, but also improve the physical and chemical
properties of these drug components.

At present, pharmaceutical cocrystal have become a new field in the
development of pharmaceutical preparations. Interest in drug
cocrystals is growing in the industry because the formation of drug
cocrystals can increase drug benefit enhancement and reduce drug
development time. Because of the advantages of the drug cocrystal,
how to put it into industrial production and get stable and high purity
drug cocrystal is another hot spot for researchers in the future. This
review summarizes the preparation methods of pharmaceutical
cocrystal of active ingredient in TCM, and the improvement of
physical and chemical properties of drug molecules through cocrystal.
With the development of crystal engineering, there are more and more
methods to prepare pharmaceutical cocrystal, which can provide a
new option for treating diseases.

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