Free report on co-crystal of caffeine and maleic acid with acetone

Food & Diet, Coffee

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Introduction and Literature Review

The value for a drug is significantly impacted by the dissolution rate, chemical stability and solubility of the drugs thereby impacting the pharmaceuticals efficiency as well. In the pharmaceutical industry multi-component crystals such as hydrates, solvates, co-crystals and salts have a major role during the design of new solids. Solid does not self-crystallize. It crystallizes in varied forms depicting random crystal properties. Various approaches are used to modify solids like Salting, Solvation, Hydration, and Polymorphism. Apart from these approaches, Co-Crystallization is a promising new approach to modifying solids (Nauha, 2012; Guo et al., 2010; Sekhon, 2009).

Caffeine (3, 7-dihydro-1, 3, 7-trimethyl-1H-purine-2, 6-dione), belongs to a stimulants group, named as Xanthines and used as pain killers, cold remedies and in several stimulants (Pinto & Diogo, 2006). Caffeine is an ideal pharmaceutical compound that exhibits instability against humidity, resulting in a crystalline non-stoichiometric hydrate. Due to its weak basic imidazole nitrogen and probability of forming heteromeric synthons, caffeine is highly suitable for cocrystallization. Firstly engineered pharmaceutical cocrystals of caffeine were created using dicarboxylic acids as coformers. Further studies showed that Maleic acid has been more suitable for creating two stoichiometrically diverse cocrystals. Afterwards, many successful attempts had been made to form 1: 1 or 2: 1 caffeine/maleic acid cocrystal through grinding methods (Guo et al., 2010).

Co-crystals

Co-crystals are a popular alternative to solid forms during the process of drug development. Co-crystals are crystalline complex consisting of two or more neutral molecules bounded in a crystal lattice. Pharmaceutical Co-crystals incorporate a molecule into a crystal lattice along with the API. The co-crystallization obtained from co-crystals is beneficial for the improvement of the physiochemical properties of the drugs. Also, the co-crystallization processes that use industry accepted and approved compounds do not impact the functioning of the API, but improves the physical properties like solubility and behavior. (Sekhon, 2009; Nauha, 2012).

Active Pharmaceutical Ingredients (API's) are the most valuable materials in terms of their intrinsic value. APIs are a formulation containing inactive ingredients. Pharmaceuticals use API as a carrier system. Most of the API's occur as solids. Crystalline API's relatively having an easy isolation. Crystallization process inherently rejects impurities, and the crystalline solid state provides a physio-chemical stability. (Almarsson & Zaworotko, 2004).

Co-Crystals Design

Figure 1: API solid-form classification, structure and composition based (Sekhon, 2009).

Crystal design is all about creating solid crystal with suitable molecular structure assembly. Non-covalent bonds like hydrogen bonds and the functional atoms undergo molecular interactions inside the crystalline solids. These molecular interactions cause a change in physicochemical properties such as Dissolution rate stability, Solubility and melting point. For example

caffeine Co-crystals are designed using di-carboxylic acid resulting in a proton donation to Heteromeric interactions. Heteromeric interactions consist of O-H—N and C-H—O bonding (Sekhon, 2009).

Solid Modification Techniques and Co-Crystallization

The existing approaches to modify solids are Salting, Solvation, Hydration, and Polymorphism (Figure 1). Co-Crystallization is a promising new approach to modifying solids. This section discusses the comparison of Co-Crystals with other solid modification techniques (Mundhe et al., 2013).

Solvates and Hydrates

Solvates are mostly biologically toxic, so rarely used in the development of API crystal. Solvates differ with Co-crystals due to their physical form. Solvates in general are in liquid form at room temperature. Hydration is a better approach to enhance properties. It is also observed that 33% of the molecules are capable of hydration (Mundhe et al., 2013).

Polymorphs

Polymorphism is better known as the formation of two or more dissimilar arrangements of the same molecules depicting different physicochemical properties. Solid modification technique selection is essentially on the basis of evaluation of solid and the screening method. Cocrystals consist of a simple screening process, and the main part is the identification of a suitable pharmaceutical co-former. However, it is difficult to foresee the number of polymorphs for even a simple molecule. Some molecules show higher than

ten crystal forms, making the screening method tedious and difficult (Mundhe et al., 2013).

Salts

Salting is another process for augmentation of physical properties. Salting consists of acid-base reaction between the Acidic or basic molecule and the API. Salt is used for improving the stability, solubility and the crystalline properties of the resulting pharmaceutical compound. Salt is created by a transfer of a proton from an acid to base, depending on the arrangement of hydrogen molecules in the crystals. In the case of Cocrystals, co-former, and the drug are solid at ambient temperature. The intermolecular interactions in Co-crystals are nonionic in nature (Mundhe et al., 2013).

Properties altered by the cocrystallization

The changes occurred in molecular structure assemblies during cocrystallization process result in alteration in physical properties. These expected changes include solubility, stability, melting point and other mechanical properties, such as tabletability and tensile strength (Mundhe et al., 2013).

Methods used for Cocrystal preparation

The straightest method for crystal formation involves the use of the appropriate solution with a proper degree of supersaturation. Several methods exist which can be applied for the supersaturation of the solution. The most popular techniques for cocrystal preparation are the evaporation and solid-state grinding. Several other methods are solvent drop grinding,

Slurry Crystallization, Hot melt extrusion and Sonocrystallization Method (Mundhe et al., 2013).

Cocrystal characterization

After successful formation of a cocrystal, the next step involves cocrystal characterization to assess structural and physical properties. There are numerous techniques used for characterization, such as Differential Scanning Calorimetry (DSC), Powder X-ray Diffraction (PXRD), IR and single crystal X-ray diffraction (Mundhe et al., 2013; Leyssens et al, 2012).

Industrial practices and applications

Co-crystal formation techniques appear to be very beneficial substitute for drug discovery (such as new molecule synthesis or nutraceutical cocrystals), drug delivery (solubility and bioavailability) and chiral resolution. According to the experts, this revolutionary approach has a considerable potential to change the landscape of the pharmaceutical industry (Leyssens et al., 2012).

In this report, 1: 1 cocrystal of the caffeine/maleic acid is prepared using two methods, solution crystallization methods and solid-state grinding method. Furthermore, this report aims to analyse the parent materials and products of the preparation through DSC and PXRD techniques for comparison. This study presents a comparative analysis of both the methods of preparing cocrystals of caffeine and maleic acid.

Materials and methods

Materials

Caffeine: Melting point: 238 °C, Molar mass: 194. 19 g/mol, Boiling point: 178 °C

Maleic acid: Molar mass: 116. 072 g/mol

Acetone: Boiling point: 56 °C, Melting point: -95 °C, Molar mass: 58. 08 g/mol

Solvent Selection

The selection of right solvent is an important part in determining the phase diagram of caffeine and maleic acid system. In this study, acetone is taken as a solvent. In acetone, both components have closest measurable solubilities (Guo et al., 2010).

Preparation of 1: 1 Caffeine/Maleic Acid Cocrystal

- For Solution method, Caffeine 1. 9463g and maleic acid 8. 1599g were added to 30 ml of acetone at room temperature 20oC and stirred for 5 min. to dissolve and left for 1h.
- After 40mins, the sample was taken under microscope to check whether needle shaped crystal were formed or not resulting no crystal formation.
- After 1h, the solution became cloudy, and needle shape crystals were visible under microscope. Then the sample was filtered and analyzed by PXRD and DSC to check the parent materials and the product.
- For Dry grinding methods, maleic acid 0. 1144g and caffeine 0. 1996 grind for 30min and analysed by PXRD and DSC to check the parent materials and the product (Guo et al., 2010).

Characterization of the product via DSC and PXRD:

The DSC thermogram of caffeine/maleic acid cocrystal 1: 1 was taken by differential scanning calorimeter operational with a computerized data station. The DSC measurements were performed on an (Instrument). Accurately weighed sample were placed under nitrogen flow (20ml/min) at a scanning rate of 100 c/min.

For the characterization of the crystalline state, the powder x-ray diffraction (XRD) pattern of caffeine/maleic acid cocrystal1: 1 was determined using a Miniflex goniometer scanner with filter Kb, Cu/30kV/15mA with Scan speed of 2. 000deg./min in continuous mode (Guo et al., 2010).

Results and Discussion

Characterization of cocrystal through DSC:

(A)

(B)

(C)

(D)

(E)

Figure 2: A: DSC thermogram of Caffeine/Maleic acid 1: 1 cocrystal in the solution method

B: DSC thermogram of Caffeine/Maleic acid 1: 1 cocrystal in dry grinding method

C: DSC thermogram of Caffeine, D: DSC thermogram of Maleic acid, E: DSC comparative thermogram of Caffeine/Maleic acid 1: 1 cocrystal extracted from both methods

DSC experiment was performed to analyze the thermal behaviour of Caffeine/Maleic acid 1: 1 cocrystal. As illustrated in figure 2(A), It shown a single endothermic peak maxima at 106. 03 oC in solution method while in grinding method the single peak maxima of cocrystal is at 101. 266oC. Figure 2(C & D) shows the maximum peaks caffeine and maleic acid at 236. 91 oC and 145. 92oC. In the thermograms of cocrystal obtained from both methods show the lower melting points in comparison of the separate caffeine and maleic acid. This fall of temperature is due to the melting of cocrystals (Guo et al., 2010). The thermal behaviour seems divergent, with a diverse melting transition from the individual component, which indicates the formation of cocrystals in a new phase. As illustrated in the figure, the melting points of cocrystals are below the melting point of both the drug and the cocrystal former. The single endothermic transition of cocrystals specifies the nonexistence of absorbed solvent or water. This transition also illustrates the stability of the phase until the melting point reaches (Zalte et al., 2014).

(A)

(B)

(C)

Figure 3(Sample 2): A: DSC thermogram of Caffeine/Maleic acid 1: 1 cocrystal via residue crystal method

B: DSC thermogram of Caffeine/Maleic acid 1: 1 cocrystal in dry grinding method

C: DSC comparative thermogram of Caffeine/Maleic acid 1: 1 cocrystal extracted from both residue crystal and dry grinding method

Melting point is a significant property in the research of properties of cocrystals. The alteration of melting point after the cocrystallisation process defines the state of the product. According to the experts the decline in melting point is an advantageous progression in the pharmaceutical aspects. According to Guo, in his results he cited that the maleic acid is appeared decomposing, that is also noticed in this study (Figure D). It suggests that the maintaining melting point of caffeine in maleic acid or vice versa will be challenging, because after reaching the eutectic temperature once composition of the system alter due to the decomposition (Guo et al., 2010). The solid with low melting point demonstrates lowered vulnerability towards degradation (Mundhe et al., 2013). Based on this point the cocrystal produced via grinding method, in this study has lower melting point. In terms of pharmaceutical concerns the grinding method has produced better results (Guo et al., 2010).

Another sample of 1: 1 caffeine/maleic acid cocrystal was prepared through dry grinding method and residue crystal method, in which the solution was immediately washed with acetone. In DSC thermograph of residue crystal is showing the highest melting point among all other produced results. On comparing the results of this study with another sample (2) of co-crystal and previous described results it is obvious that dry grinding method provided better results.

(A)

(B)

Figure 4: (A) TGA graph of caffeine and Maleic acid (B)TGA graph of extracted residue crystal

TG curve of caffeine and maleic acid verify that the compounds are anhydrous. It illustrates mass loss after the 189. 20oC and around 13. 07% mass loss is observed in caffeine in figure 4(A). While it is 275. 92 oC and 166% mass loss is seen in the case of maleic acid. In comparative graph (Figure 4 (B)) The first step of exothermal reaction occurred at between 111 and 182°C, and the last stage between 210-240oC indicates the oxidation of the organic matter through exothermic peak with resulted mass loss of 39. 15%.

Characterization of cocrystal through PXRD:

(A)

(B)

(C)

Figure 5: A: XRPD patterns of 1: 1 caffeine/maleic acid cocrystal by dry grinding method,

B: XRPD patterns of 1: 1 caffeine/maleic acid cocrystal by solution crystal method,

C: XRPD patterns of all the compounds, from the bottom to top: 1: 1 caffeine/maleic acid cocrystal, solution crystal caffeine/maleic acid, caffeine, maleic acid.

Samples from both methods were analyzed through XRPD using both caffeine and maleic acid, for comparison among spectra, and PXRD of 1: 1 cocrystals obtained by dry grinding and solution crystallisation.

It is visible in figure 3, maleic acid and caffeine demonstrate a thick needle-shaped peak. The 1: 1 cocrystal extracted from dry method illustrates the

highest needle-shaped habit comparable to the peak demonstrated by cocrystal created via solution crystallization.

The cocrystal 1: 1 dry ground exhibits intense crystalline peak between 2Θ angle range of 11o- 38o (figure 3-A). The characteristic main diffraction peaks in Figure 3(A) are at 13. 53o, 14. 35o, 15. 57 o, 22. 75o, 26. 37o, 26. 48o, 26. 57o, 26. 66o, 26. 73o, 27. 53o and 28. 29o. The highest intense peak was at 26. 66o indicating the crystalline nature of Caffeine/maleic acid cocrystal.

The cocrystal 1: 1 solution crystal shows intense crystalline peak between 2Θ angle range of 9o to 39o (figure 3-B). The main diffraction peaks in Figure 3(B) are at 13. 51o, 14. 43o, 15. 48o, 15. 52o, 17. 84o, 22. 68o, 26. 59o, 26. 93o, 26. 57o, 26. 66o, 26. 73o, 27. 46o, 28. 10o, 28. 35o and 39. 57o. The highest intense peak was at 28. 35o with the intensity of 19497 indicating the crystalline nature of Caffeine/maleic acid cocrystal. The intensity of peak and quantity of sharp peaks in solution crystal is much higher than the dry ground crystal. The comparison of crystal peaks with the drug and coformer showed obvious peak shifts that indicate the formation of new crystalline form (figure 3-C).

(A)

(B)

Figure 6: A: XRPD patterns of all the compounds, from the bottom to top: maleic acid, Caffeine, Acetone solution, 1: 1 caffeine/maleic acid residue crystal, 1: 1 caffeine/maleic acid Dry ground cocrystal

B: XRPD patterns of all the compounds, from the bottom to top: maleic acid, Caffeine, 1: 1 caffeine/maleic acid residue crystal, 1: 1 caffeine/maleic acid

Dry ground cocrystal

The study results are compared with other co crystal samples, acetone solution and previous research works. It is concluded that the XPRD patterns and DSC thermograph extracted in this study results showed similarity with the previously done work by Guo and co-workers (Guo et al., 2010).

Conclusion

Co crystallisation is a novel approach that has been very advantageous for the pharmaceutical industry. In this report 1: 1 cocrystal of caffeine and maleic acid was formed, using two different methods, dry solid-state grinding and solution cocrystallization. Through DSC and PXRD characterization techniques the formed cocrystal was evaluated. The comparative analysis of cocrystal via these two techniques concluded that these both methods have been successful. The produced cocrystal illustrated the similar characteristics, as predicted by previous studies. The alterations in melting points, loss in mass and peak shifts illustrated in PXRD are sufficient to prove that the crystal is well formed. On the basis of a comparative study between the products of two applied methods, grinding method produced more refined cocrystal with high stability.

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