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Direct Co-crystal Assembly from Synthesis to Co-crystallization

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Pharmaceutical co-crystals were assembled directly with the chemical synthesis by cooling under three new strategies. The screening method for direct co-crystal assembly with chemical reaction was developed based on liquid-assisted grinding. The ternary phase diagram including a chemical reaction and co-crystallization was established for 2:1 co-crystal of benzoic acid-sodium benzoate.

Co-crystal is formed when the recognition and assembly of two or more distinct molecular species in a definite stoichiometric ratio occur through the interactions of hydrogen bond, non-covalent bond and non-ionic bond in a long range order.[1] This kind of solid form usually has supreme functional and processing properties.[2] Its applications can be found in many areas such as organic field-effect transistors (OFETs),[3] micro- and nano-mechanics,[4] explosive,[5] chiral resolution, [6] nutraceuticals [7] and especially pharmaceuticals.[2c, 8] Consequently, co-crystallization of a pure component with a co-former is a common technology for product enhancement[9] and high-end product purification.[10]

For instance, the discovery of a new chemical entity (NCE) in the pharmaceutical industry is itself a difficult task already,[11] and the generic drug market has recently become even more competitive.[12] Since active pharmaceutical ingredients (APIs) are most conveniently developed and delivered orally as solid dosage forms with a well-defined crystalline phase,8 the idea of generating pharmaceutical co-crystals of marketed APIs as *Supergenerics*[13] may be an appealing alternative for the generic drugs.

When drug molecules are complex, highly functionalized, and lack of easily ionizable functional groups to form salts, the tuning of the physicochemical properties of an API could be manipulated intermolecularly through co-crystals.[14] Interestingly, ionic co-crystal hybrid systems could also exist.[15]

The co-crystal preparation methods include solvent-drop (liquid-assisted) grinding, [16] isothermal slurry conversion, [17] solution crystallization by evaporation or cooling,[18] rapid expansion of supercritical CO_2 fluids,[19] and spray drying.[20] Co-crystals are usually characterized by polarized optical microscopy (POM),[21] Fourier-transform infrared spectroscopy (FTIR),[22] Raman spectroscopy,[23] differential scanning calorimetry (DSC), [24] and powder X-ray diffraction (PXRD).[18] In those preparation approaches, co-crystals were made by re-crystallization of the dissolved API and co-former molecules from a single organic solvent. However, there were precedents of forming the co-crystals by the assembly of a co-former and the API-derived products through a condensation reaction between the API having carbohydrazide functional group and the solvent such as ketones or aldehydes.[25] Inspired by that, here, we report the direct co-crystal assembly via well-documented acetylation or neutralization as a proof-of-concept under three different strategies (Scheme 1). The direct co-crystal assembly offers numerous advantages: (1) chemical synthesis and co-crystallization are telescoped into one step, (2) a co-crystal can now play a new active role as a reactant and not just always as a final product, (3) the solubility of the reactant can be enhanced through co-crystal formation, and thus, the reactivity of a subsequent reaction involving the resulting co-crystal can be elevated, (4) more solvent choices may be available when the reaction medium and not just the crystallization medium is taken into account if direct assembly is feasible, (5) a high amount of the impurity can be isolated selectively during synthesis, (6) a greener process is possible, and (7) it is the subject matter for which a patent may be obtained.

A general chemical reaction (Scheme 1a) between the reactants ***A*** and ***B*** gives a product, ***D***, and a byproduct, ***E***. Based on Scheme 1a, our three new proposed strategies are: (1) another pure component or a co-former, ***C***, is introduced along with the reactants to form a co-crystal, ***C-D***, given that ***C*** does not undergo a side reaction (Scheme 1b), (2) a co-crystal, ***A-C***, acts like a new reactant to form a co-crystal product, ***C-D*** (Scheme 1c), and (3) a product, ***D***, acts as a pure component and co-crystallizes with an un-reacted, bystander-like, co-former, ***B***, to assemble into a co-crystal product, ***B-D*** (Scheme 1d).

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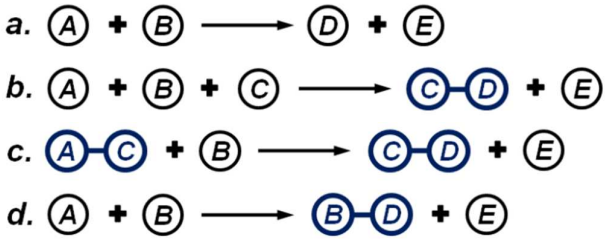
Electronic Supplementary Information (ESI) available: Materials, instrumentations, a detailed procedure for direct assembly of co-crystals and their characterizations (POM, FTIR, DSC and PXRD). See DOI: 10.1039/x0xx00000x



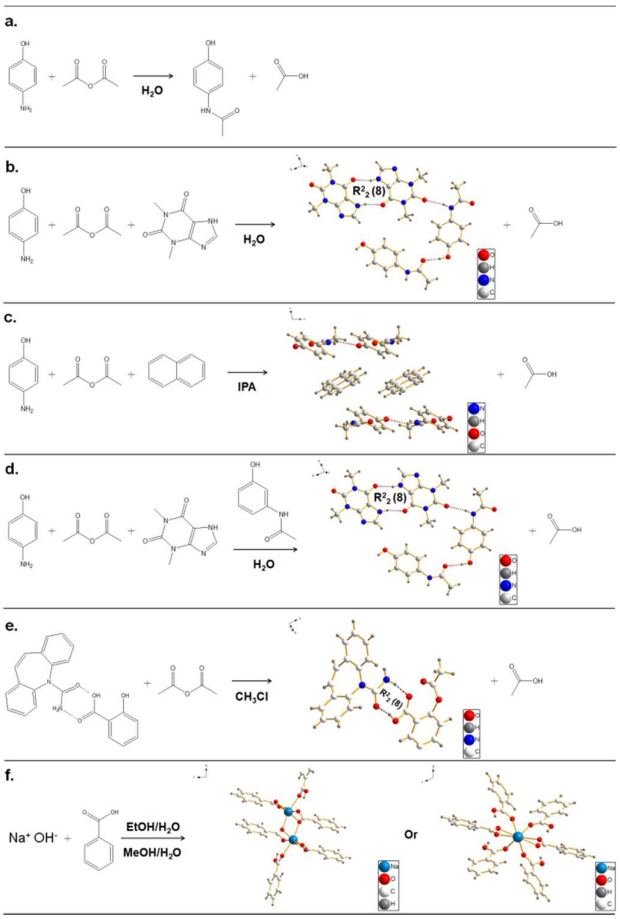
Scheme 1. The three proposed strategies (b, c and d) for direct assembly of co-crystal (co-crystal in blue color).

The 1st strategy was demonstrated in Schemes 2a, 2b and 2c. The pure component, acetaminophen also known as paracetamol (API), was originally synthesized by acetylation of *p*-aminophenol with acetic anhydride either in water or IPA (Scheme 2a). In the presence of theophylline (API) which was a co-former, 1:1 co-crystals of acetaminophen-theophylline were made in water by cooling (Scheme 2b). On the other hand, in the presence of naphthalene co-former, 2:1 co-crystals of acetaminophen-naphthalene were produced in IPA by cooling (Scheme 2c). One important aspect of co-crystallization which deserves our attention is its high degree of selectivity and separation. Even with up to 50 mol % of acetaminophen isomeric impurity (i.e. 3-acetamidophenol), the assembly of 1:1 API-API co-crystals of acetaminophen-theophylline could still be carried out as displayed in Scheme 2d.

The 2nd strategy was illustrated in Scheme 2e. The 1:1 co-crystal of salicylic acid (SA)-carbamazepine (CBZ) was acting like a reactant. Only the SA component in the mother co-crystal underwent acetylation with acetic anhydride in chloroform to form aspirin which was then assembled directly with the un-reacted CBZ via heterosynthon to become a daughter co-crystal by cooling. The 3rd strategy was revealed in Scheme 2f. Sodium benzoate (NaBz) was obtained by partial neutralization of benzoic acid (HBz) with sodium hydroxide. Cooling the solution mixture of NaBz and un-reacted HBz either in ethanol/water (3:1 v/v) or methanol/water (3:1 v/v) resulted in either the Form A or Form B ionic co-crystal of NaBz-HBz, respectively (Scheme 2f). The FTIR spectra of the co-crystals in Figures S1b to S8b did not show any trace of impurities. The DSC scans in Figures S1c to S8c displayed only the melting peaks of the co-crystals. There was no indication of any polymorph, API or co-former. High quality of co-crystals were obtained from all unoptimized experiments.

Interestingly, the five co-crystal systems2[b,15,26] were discovered by the liquid-assisted grinding method, which is normally applied to chemical mixtures, and now being extended to chemical reactions by us to promote new supramolecular assemblies [27] via mechanochemistry! This is an eco-friendly and effective screening tool for direct co-crystal assembly without the extensive use of organic solvents.

Since solution crystallization by cooling (or anti-solvent addition) is preferred in large-scale production, and crystallization usually follows immediately after chemical reaction,[28] direct co-crystal assembly from chemical synthesis to co-crystallization does offer a seamless approach. The solvents used in our systems were selected based on the similar solubility differences of co-crystal components



Scheme 2. Case studies of the three proposed strategies. 1st Strategy (a, b, c and d), 2nd strategy (e), and 3rd strategy (f).

at the two high and low temperature points during cooling listed in Table S1.[29] Unlike other co-crystallization methods, direct co-crystal assembly possesses three key features: (1) the operating time can be finished in less than a day, (2) the size control of co-crystals can be tuned by the cooling rate, and (3) without the need of reaching the equilibrium end so that the metastable co-crystal form may be obtained kinetically if desired.[30]

In general, the ternary phase diagram (TPD) can provide an important roadmap for ensuring the reproducibility and the extent of co-crystal formation but its determination is tedious.[29b, 31] Knowing that (1) co-crystals can be easily produced by cooling in the rather well-behaved congruent TPD system, and (2) the establishment of the congruent TPD system is based on the similar solubility of the two co-crystal components in a particular solvent at a given temperature, those facts have made the identification of a suitable common solvent for the co-crystal components by solvent screening indispensable. Solvents capable of producing our co-crystals by cooling were listed in Table S2.

To verify that our co-crystal systems selected by solvent screening were indeed congruent, the TPD of one of our co-crystal systems, HBz-NaBz co-crystal in MeOH/H_2O, was thoroughly established (Figure 1). With the assumption of 100% conversion

from NaOH to NaBz, the molar ratio of HBz/NaOH must be > 1. Upon neutralization, the TPD was transformed from the original HBz-NaOH-MeOH/H_2O diagram (the whole equilateral triangle in Figure 1) into the new HBz-NaBz-MeOH/H_2O diagram (the colored right-angle triangle in Figure 1). The un-reacted, excessive amount of HBz served as a co-former to produce a co-crystal with the converted NaBz in the "co-crystal" stable region. Point *S* in Figure 1 designated the starting compositions of HBz, NaBz and MeOH/H_2O in the "co-crystal" stable region of producing the 2:1 co-crystal of HBz-NaBz.

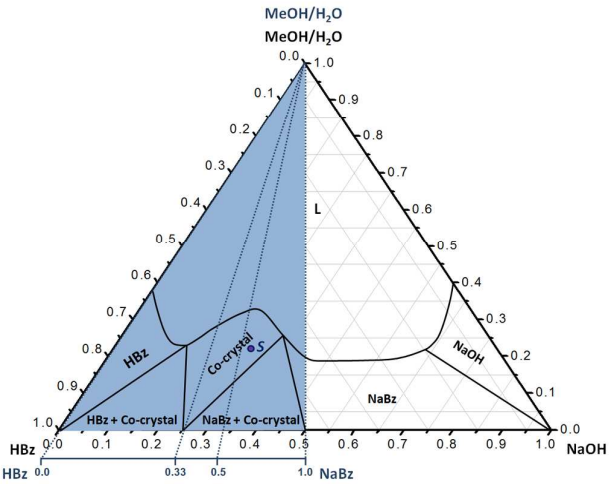


Figure 1. Ternary phase diagram (TPD) for direct assembly of 2:1 co-crystal of HBz-NaBz at 25°C. The whole equilateral triangle region is HBz-NaOH-MeOH/H_2O phase diagram (before neutralization). The colored right-angle triangle region is HBz-NaBz-MeOH/H_2O phase diagram (after neutralization). Point *S* represents the compositions of HBz, NaBz and MeOH/H_2O in the beginning of direct assembly.

To further examine the applicability of our approach, additional co-crystal systems such as 1:1 co-crystals of acetaminophen-caffeine,[19b] aspirin-acetamide,[32] and aspirin-meloxicam[33] were also screened by liquid-assisted grinding. Unfortunately, the grinding method failed to work for 1:1 co-crystal of aspirin-acetamide due to the hygroscopic nature of acetamide. Re-crystallization of aspirin and acetamide in acetonitrile, ethyl acetate and 1,4-dioxane did give the co-crystals. Interestingly, the hygroscopicity of acetamide was ameliorated by forming a co-crystal with aspirin. However, switching over to reactive co-crystallization did not work out because acetamide reacted with acetic anhydride through *N*-acylation to give an unwanted *N*-acetyl acetamide (Scheme S1c).[34] Furthermore, the poor solubility of meloxicam in some common organic solvents had made the co-crystallization of aspirin-meloxicam by direct co-crystal assembly very difficult. Although the production details of acetaminophen-caffeine co-crystal, to the best of our knowledge, were not reported in the literature, the assembly of acetaminophen-caffeine co-crystal could be achieved by chemical synthesis.

As a bonus on pharmaceutical co-crystallization, the development of the API-API co-crystals has provided many fascinating features:[12,35] (1) it fulfills the criteria for patent eligibility of novelty, utility, and non-obviousness and protects the API products from competition, (2) it offers immense potential in purification of APIs and resolution of racemic drugs, (3) it has high commercial and therapeutic values in the context of combination drugs for pharmaceutical development, (4) it may shorten the development period even with the inclusion of clinical trials in comparison to that of a NCE, and (5) it offers potential improvements in solubility, dissolution rate, bioavailability and physical stability. Noticeably, there is no clear evidence that co-crystal formation should inhibit phase transformation, or more generally, be less polymorphic.[36] Although there are very few, if any, pharmaceutical companies who are truly interested in API-API co-crystals except in very rare special cases, because the dosages are wrong for the two components at the stoichiometry in a co-crystal, there are two points that we may want to keep in mind: (1) direct co-crystal assembly may be a general method for other co-crystal systems, (2) the remarkable isomeric separation efficiency of co-crystallization may be further explored in many other chemical syntheses, and (3) the chemical purity of the obtained co-crystals may be examined by high performance liquid chromatography (HPLC) for turning the direct co-crystal assembly method into a purification technique in the near future.

Conclusions

In summary, the three new strategies for direct co-crystal assembly were proposed and demonstrated, and their benefits were also highlighted. 1:1 co-crystal of acetaminophen-caffeine could also be obtained by this approach. For 1:1 co-crystal of acetaminophen-theophylline system, co-crystallization was taken as a highly efficient isomeric separation technology especially for acetaminophen. Therefore, combining chemical synthesis with co-crystallization in one-pot is not merely a co-crystal production method. This paper also reported the screening method for direct co-crystal assembly via liquid assisted grinding coupled with chemical synthesis for the very first time. Recently, we have also been successful in extending the same concept to more complicated sulfathiazole co-crystal systems.

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Notes and references

1 (a) T. Lee, P. Y. Wang, *Cryst. Growth Des.* 2010, **10**, 1419-1434. (b) G. R. Desiraju, *CrystEngComm* 2003, **5**, 466-467. (c) C. B. Aakeröy, D. J. Salmon, *CrystEngComm* 2005, **7**, 439-448.

2 (a) N. Qiao, M. Li, W. Schlindwein, N. Malek, A. Davies, G. Trappitt, *Int. J. Pharm.* 2011, **419**, 1-11. (b) S. Karki, T. Friščić, L.

Fábián, P. R. Laity, G. M. Day, W. Jones, *Adv. Mater.* 2009, **21**, 3905-3909. (c) N. Schultheiss, A. Newman, *Cryst. Growth Des.* 2009, **9**, 2950-2967.

3 (a) J. Zhang, H. Geng, T. S. Virk, Y. Zhao, J. Tan, C.-A. Di, W. Xu, K. Singh, W. Hu, Z. Shuai, Y. Liu, D. Zhu, *Adv. Mater.* 2012, **24**, 2603-2607. (b) Y. L. Lei, L. S. Liao, S. T. Lee, *J. Am. Chem. Soc.* 2013, **135**, 3744-3747.

4 (a) M. Morimoto, M. Irie, *J. Am. Chem. Soc.* 2010, **132**, 14172-14178. (b) C. Karunatilaka, D.-K. Bučar, L. R. Ditzler, T. Friščić, D. C. Swenson, L. R. MacGillivray, A. V. Tivanski, *Angew. Chem. Int. Ed.* 2011, **50**, 8642-8646.

5 T. Lee, J. W. Chen, H. L. Lee, T. Y. Lin, Y. C. Tsai, S.-L. Cheng, S.-W. Lee, J.-C. Hu, L.-T. Chen, *Chem. Eng. J.* 2013, **225**, 809-817.

6 S. Chen, H. Xi, R. F. Henry, I. Marsden, G. G. Z. Zhang, *CrystEngComm* 2010, **12**, 1485-1493.

7 S. J. Bethune, N. Schultheiss, J.-O. Henck, *Cryst. Growth Des.* 2011, **11**, 2817-2823.

8 (a) Ö. Almarsson, M. L. Peterson, M. Zaworotko, *Pharm. Pat. Analyst* 2012, **1**, 313-327. (b) M. Khan, V. Enkelmann, G. Brunklaus, *J. Am. Chem. Soc.* 2010, **132**, 5254-5263. (c) W. Jones, W. D. S. Motherwell, A. V. Trask, *MRS Bull.* 2006, **31**, 875-879.

9 N. J. Babu, A. Nangia. *Cryst. Growth Des.* 2011, **11**, 2662-2679.

10 (a) T. Lee, H. R. Chen, H. Y. Lin, H. L. Lee, *Cryst. Growth Des.* 2012, **12**, 5897-5907. (b) P. Billot, P. Hosek, M. Perrin, *Org. Proc. Res. Dev.* 2013, **17**, 505-511. (c) J. Urbanus, C. P. M. Roelands, D. Verdoes, P. J. Jansens, J. H. ter Horst, *Cryst.Growth Des.* 2010, **10**, 1171-1179. (d) K. H.-Y. Hsi, K. Chadwick, A. Fried, M. Kenny, A. S. Myerson, *CrystEngComm* 2012, **14**, 2386-2388.

11 A. A. Najar, Y. Azim, *J. Indian Inst. Sci.* 2014, **94**, 45-68.

12 B. S. Sekhon, *DARU J. Pharm. Sci.* 2012, **20**, 45.

13 F. Barei, C. Le Pen, S. Simoens, *GaBI Journal* 2013, **2**, 13-9.

14 S. Kim, Z. Li, Y.-C. Tseng, H. Nar, E. Spinelli, R. Varsolona, J. T. Reeves, H. Lee, J. J. Song, J. Smoliga, N. Yee, C. Senanayake, *Org. Proc. Res. Dev.* 2013, **17**, 540-548.

15 C. Butterhof, W. Milius, J. Breu, *CrystEngComm* 2012, **14**, 3945-3950.

16 D. Braga, F. Grepioni, L. Maini, P. P. Mazzeo, K.Rubini, *Thermochim. Acta* 2010, **507-508**, 1-8.

17 (a) N. Takata, K. Shiraki, R. Takano, Y. Hayashi, K. Terada, *Cryst. Growth Des.* 2008, **8**, 3032-3037. (b) D. M. Croker, Å. C. Rasmuson, *Org. Proc. Res. Dev.* 2014, **18**, 941-946.

18 (a) P. P. Bag, M. Patni, C. M. Reddy, *CrystEngComm* 2011, **13**, 5650-5652. (b) Z. Q. Yu, P. S. Chow, R. B. H. Tan, *Cryst. Growth Des.* 2010, **10**, 2382-2387.

19 (a) L. Padrela, M. A. Rodrigues, S. P. Velaga, A. C. Fernandes, H. A. Matos, E. G. de Azevedo, *J. Supercrit. Fluids* 2010, **53**, 156-164. (b) M. Herrmann, U. Förter-Barth, H. Kröber, P. B. Kempa, M. del Mar Juez-Lorenzp, S. Doyle, *Part. Part. Syst. Charact.* 2009, **26**, 151-156.

20 A. Alhalaweh, S. P. Velaga, *Cryst. Growth Des.* 2010, **10**, 3302-3305.

21 D. J. Berry, C. C. Seaton, W. Clegg, W. Harrington, S. J. Coles, P. N. Horton, M. B. Hursthouse, R. Storey, W. Jones, T. Friščić, N. Blagden, *Cryst. Growth Des.* 2008, **8**, 1697-1712.

22 (a) A. Mukherjee, S. Tothadi, S. Chakraborty, S. Ganguly, G. R. Desiraju, *CrystEngComm* 2013, **15**, 4640-4654. (b) H. G. Brittain, *Cryst. Growth Des.* 2010, **10**, 1990-2003.

23 K.-S. Lee, K.-J. Kim, J. Ulrich, *Cryst. Growth Des.* 2014, **14**, 2893-2899.

24 H.-L. Lin, P.-C. Hsu, S.-Y. Lin, *Asian J. Pharm. Sci.* 2013, **8**, 19-27.

25 (a) A. Lemmerer, J. Bernstein, V. Kahlenberg, *CrystEngComm* 2010, **12**, 2856-2864. (b) A. Lemmerer, J. Bernstein, V. Kahlenberg, *CrystEngComm* 2011, **13**, 55-59. (c) A. Lemmerer, J. Bernstein, V. Kahlenberg, *CrystEngComm* 2011, **13**, 5692-5708. (d) A. Lemmerer, *CrystEngComm* 2012, **14**, 2465-2478.

26 (a) S. L. Childs, N. Rodríguez-Hornedo, L. S. Reddy, A. Jayasankar, C. Maheshwari, L. McCausland, R. Shipplett, B. C. Stahly, *CrystEngComm* 2008, **10**, 856-864. (b) P. Vishweshwar, J. A. McMahon, M. Oliveira, M. L. Peterson, M. J. Zaworotko, *J. Am. Chem. Soc.* 2005, **127**, 16802-16803. (c) C. Butterhof, K. Bärwinkel, J. Senker, J. Breu, *CrystEngComm* 2012, **14**, 6744-6749.

27 N. Shan, F. Toda, W. Jones, *Chem. Commun.* 2002, 2372-2373.

28 Z. Li, B.-S. Yang, M. Jiang, M. Eriksson, E. Spinelli, N. Yee, C. Senanayake, *Org. Proc. Res. Dev.* 2009, **13**, 1307-1314.

29 (a) J. H. ter Horst, M. A. Deij, P. W. Cains, *Cryst. Growth Des.* 2009, **9**, 1531-1537. (b) S. Boyd, K. Back, K. Chadwick, R. J. Davey, C. C. Seaton, *J. Pharm. Sci.* 2010, **99**, 3779-3786.

30 H. L. Lee, H. Y. Lin, T. Lee, *Org. Proc. Res. Dev.* 2014, **18**, 539-545.

31 A. Ainouz, J.-R. Authelin, P. Billot, H. Lieberman, *Int. J. Pharm.* 2009, **374**, 82-89.

32 (a) A. D. Bond, R. Boese, G. R. Desiraju, *Angew. Chem. Int. Ed.* 2007, **46**, 618-622. (b) M. D. Eddleston, R. Thakuria, B. J. Aldous, W. Jones, *J. Pharm. Sci.* 2014, **103**, 2859-2864.

33 M. L. Cheney, D. R. Weyna, N. Shan, M. Hanna, L. Wojtas, M. J. Zaworotko, *J. Pharm. Sci.* 2011, **100**, 2172-2181.

34 J. Lee, M. Hong, Y. Jung, E. J. Cho, H. Rhee, *Tetrahedron* 2012, **68**, 2045-2051.

35 D. H. Leung, S. Lohani, R. G. Ball, N. Canfield, Y. Wang, T. Rhodes, A. Bak, *Cryst. Growth Des.* 2012, **12**, 1254-1262.

36 (a) D.-K. Bučar, R. W. Lancaster, J. Bernstein, *Angew. Chem. Int. Ed.* 2015, **54**, 6972-6993. (b) S. Aitipamula, P. S. Chow, R. B. H. Tan, *CrystEngComm* 2014, **16**, 3451-3465.

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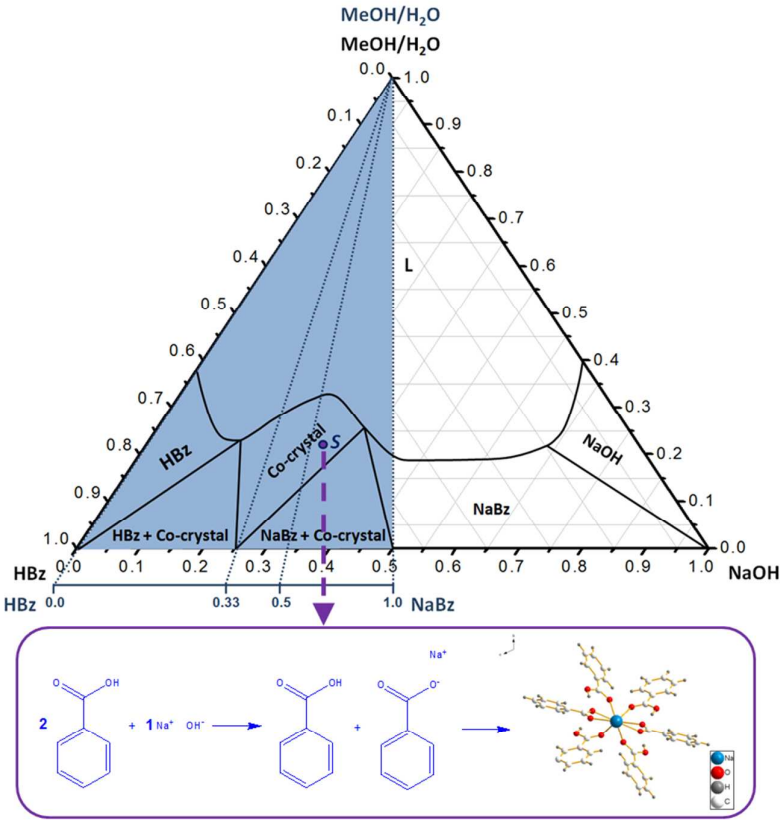
Graphic Abstract



The ternary phase diagram for direct assembly of 2:1 co-crystal of benzoic acid-sodium benzoate was illustrated. Benzoic acid acted as a reactant and underwent neutralization to produce sodium benzoate. The excessive amount of benzoic acid as an API can interact with the product, sodium benzoate as another API, to undertake API-API co-crystallization by cooling