

Exploring Solid- State Modification of Cetirizine Dihydrochloride using Benzoic Acid and Salicylic Acid

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Abstract

Cocrystallization is a useful solid-state approach for modifying the physicochemical properties of an active pharmaceutical ingredient without changing its molecular structure. In the present work, cetirizine dihydrochloride was combined separately with benzoic acid and salicylic acid as coformers using 1:1 liquid-assisted grinding with ethanol. The two solid products were obtained in masses of 0.56 g and 0.53 g, respectively, after 30–45 min of manual grinding. Their observed melting points were 158 °C for the benzoic-acid system and 144 °C for the salicylic-acid system. Mercury software was used to examine possible intermolecular interactions and to visualize crystal-packing features. The dissertation also included a reported crystallographic structure of a related cetirizinium salt, which showed a monoclinic P21 arrangement, an extensive hydrogen-bonding network and additional π – π interactions. This crystallographic dataset is treated here as comparative structural information rather than as direct experimental evidence for the two prepared products. The melting-point changes and the predicted hydrogen-bonding possibilities support further investigation of the prepared systems; however, formation of true cocrystals cannot be established from melting-point data and molecular modelling alone. Experimental PXRD and FTIR measurements, together with appropriate thermal analysis, are therefore required for definitive solid-form assignment. The study provides a simple preliminary route for screening carboxylic-acid coformers with cetirizine dihydrochloride.

Keywords: cetirizine dihydrochloride; pharmaceutical cocrystal; benzoic acid; salicylic acid; liquid-assisted grinding; crystal engineering; Mercury

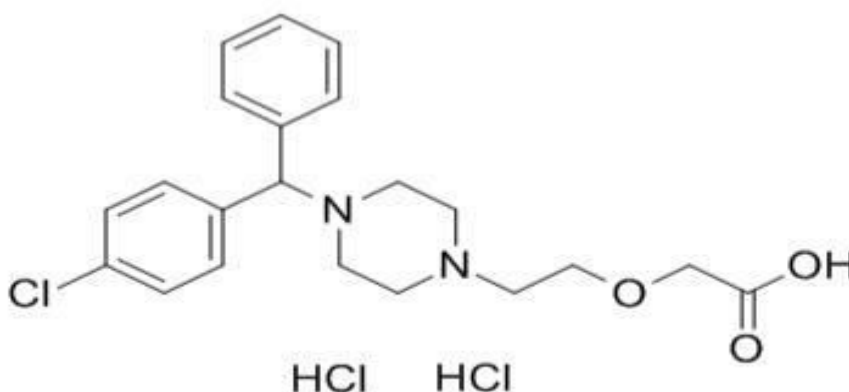
1. Introduction

Cocrystallization has become an important strategy in pharmaceutical solid-state research because the properties of a drug can often be modified through intermolecular interactions without covalent alteration of the active pharmaceutical ingredient (API). Pharmaceutical cocrystals contain an API and a suitable coformer within the same crystalline phase and are stabilized by interactions such as hydrogen bonding, ionic interactions, van der Waals forces and π – π contacts. Depending on the molecular structures involved, these interactions can influence solubility, dissolution, stability, hygroscopicity, melting behaviour and mechanical properties.

Cocrystal formation is particularly relevant during the development of solid oral dosage forms. The solid state of an API affects processing, storage and dissolution behaviour, and the choice of a new solid form can provide a way to address limitations associated with conventional salts, polymorphs and amorphous materials. Current pharmaceutical literature describes solution crystallization, slurry conversion, neat grinding and liquid-assisted grinding as useful routes for preparing or screening cocrystals. Liquid-assisted grinding is especially attractive at the laboratory scale because only a small amount of solvent is required and the procedure can be carried out using simple equipment.

Cetirizine is a second-generation H1-antihistamine used mainly for the treatment of allergic rhinitis and chronic urticaria. It is widely used because of its rapid onset and prolonged antihistaminic activity, although drowsiness can occur in some individuals. The molecule contains several hydrogen-bond donor and acceptor sites and exists in ionized/zwitterionic forms depending on the environment, making its solid-state behaviour of interest for crystal engineering.

The cetirizine dihydrochloride with two simple aromatic carboxylic acids i.e., benzoic acid and salicylic acid are in 1:1 stoichiometric ratio and manual solvent-assisted grinding with ethanol. The purpose of this paper is to reorganize that work into a concise research format, preserve the reported experimental observations, improve the scientific discussion, and distinguish direct experimental findings from comparative crystallographic information.



2. Materials and Methods

2.1 Materials

Cetirizine dihydrochloride was used as the API. Benzoic acid and salicylic acid (2-hydroxybenzoic acid) were selected as coformers. Ethanol was used as the liquid-assistance solvent. The dissertation reports benzoic acid as a white crystalline solid with molecular mass 122.12 g mol⁻¹ and salicylic acid as a pale-yellow solid with molecular mass 138.12 g mol⁻¹. The reported melting points of the starting coformers were 124 °C and 160 °C, respectively.

2.2 Preparation of cetirizine–benzoic acid system

For the 1:1 system, approximately 0.12 g (0.001 mol) of benzoic acid and 0.46 g (0.001 mol) of cetirizine dihydrochloride were placed in a mortar. The solids were manually ground continuously for approximately 30–45 min. Small quantities of ethanol were added dropwise at intervals during grinding, with care taken to avoid excess solvent. The resulting solid mass was reported as 0.56 g and its melting point was recorded as 158 °C.

2.3 Preparation of cetirizine–salicylic acid system

Approximately 0.13 g (0.001 mol) of salicylic acid and 0.46 g (0.001 mol) of cetirizine dihydrochloride were placed in a mortar and subjected to the same liquid-assisted grinding procedure for 30–45 min. Ethanol was added dropwise at intervals and excessive solvent was avoided. The resulting solid mass was reported as 0.53 g and the observed melting point was 144 °C.

2.4 Computational/structural visualization

Mercury software was used in the dissertation to visualize molecular structures and examine possible intermolecular interactions. In particular, hydrogen-bonding possibilities between cetirizine dihydrochloride and each coformer were considered. Mercury is widely used for visualization and analysis of crystallographic structures, including packing, bond geometry and intermolecular contacts.

2.5 Crystallographic information used for comparison

The dissertation also reproduced crystallographic information from the Cambridge Structural Database for a reported levocetirizinium dipicrate structure. The reported structure is monoclinic with space group P21, cell volume 3636.94 Å³, $a = 11.2444$ Å, $b = 15.7720$ Å, $c = 20.6204$ Å and $\beta = 95.998^\circ$. The structure contains an extensive network of N–H $\cdots$ O and O–H $\cdots$ O hydrogen bonds together with π – π interactions. Because these data correspond to a reported related crystal structure and not to an experimentally solved structure of the two products prepared in this study, they are presented only as comparative structural evidence.

3. Results and Discussion

3.1 Formation of the solid products

The manual liquid-assisted grinding procedure produced solid products in both systems. The use of a small quantity of ethanol during grinding is consistent with the principle of liquid-assisted mechanochemistry, in which a small amount of liquid can facilitate molecular mobility and promote solid-state transformation. The procedure is experimentally simple and does not require specialized milling equipment, which makes it suitable for preliminary coformer screening.

System	API (g; mol)	Coformer (g; mol)	Grinding time	Reported product mass	Observed melting point
Cetirizine dihydrochloride + benzoic acid	0.46; 0.001	0.12; 0.001	30–45 min	0.56 g	158 °C
Cetirizine dihydrochloride + salicylic acid	0.46; 0.001	0.13; 0.001	30–45 min	0.53 g	144 °C

3.2 Melting behaviour

The melting behaviour of the two prepared systems differed from that of the individual coformers. The benzoic-acid system showed a melting point of 158 °C, whereas the salicylic-acid system melted at 144 °C. Such shifts can indicate a change in the solid-state environment, but a melting-point shift by itself is not sufficient to prove cocrystal formation. Pharmaceutical cocrystals may exhibit melting points either above or below those of their parent components, depending on the balance of lattice and intermolecular interactions.

The larger decrease observed for the salicylic-acid system relative to salicylic acid suggests a substantial change in the solid-state interaction pattern, potentially involving the carboxyl and phenolic groups of salicylic acid. However, this interpretation remains provisional until the products are compared directly with the parent materials by PXRD, FTIR and preferably DSC/TGA.

3.3 Possible intermolecular interactions

Both benzoic acid and salicylic acid contain a carboxylic acid group capable of acting as a hydrogen-bond donor and acceptor. Salicylic acid also contains an additional phenolic hydroxyl group. Cetirizine dihydrochloride contains multiple heteroatom sites capable of participating in hydrogen bonding. These complementary functional groups provide a reasonable structural basis for coformer screening. Similar hydrogen-bond and π -stacking interactions are frequently responsible for the organization of pharmaceutical molecular crystals.

The Mercury analysis in the dissertation was used to predict possible hydrogen-bonding contacts. These predicted contacts are useful for proposing a crystal-engineering rationale, but they should not be presented as experimental confirmation. A calculated or visualized contact becomes convincing evidence of the prepared solid form only when it is supported by experimental structural or spectroscopic data.

3.4 Comparative crystallographic analysis

The reported comparative crystal structure contained a monoclinic P21 lattice with strong N–H $\cdots$ O and O–H $\cdots$ O intermolecular hydrogen bonds and additional π – π interactions. Such a network illustrates how directional non-covalent interactions can control crystal packing and stabilize a multicomponent molecular solid. The dissertation also reported a simulated powder pattern with sharp reflections, consistent with a crystalline structure.

Parameter	Reported comparative crystal structure
Crystal system	Monoclinic
Space group	P21
a (Å)	11.24440(10)
b (Å)	15.7720(2)
c (Å)	20.6204(2)
β (°)	95.9980(10)

Cell volume (Å³)	3636.94
Z	4
Density (g cm⁻³)	1.57
Key interactions	N–H⋯O, O–H⋯O and π – π interactions

Importantly, the crystallographic formula reported in the dissertation is not the formula of either the cetirizine–benzoic acid or cetirizine–salicylic acid preparation. Consequently, these crystallographic parameters should not be assigned to the two prepared products. This distinction strengthens the scientific reliability of the present manuscript and identifies the exact experimental evidence that is still needed.

3.5 Interpretation of the preliminary findings

Taken together, the successful preparation of distinct solid products, the changes in melting behaviour and the predicted intermolecular contacts provide a reasonable basis for considering benzoic acid and salicylic acid as candidate coformers for cetirizine dihydrochloride. The salicylic-acid system showed the lower melting point, while the benzoic-acid system gave the larger reported product mass. These differences may reflect differences in molecular packing, hydrogen-bonding possibilities and the physical behaviour of the two coformers during grinding.

At the same time, the present dataset should be described as preliminary rather than definitive. The dissertation itself identifies FTIR and PXRD as necessary next steps for establishing whether hydrogen bonding and a new crystalline phase are actually produced. This is consistent with accepted pharmaceutical cocrystal practice, where a combination of complementary solid-state techniques is normally required for phase identification.

4. Conclusion

Cetirizine dihydrochloride was combined separately with benzoic acid and salicylic acid by a simple 1:1 liquid-assisted grinding procedure using ethanol. The reported products were obtained in masses of 0.56 g and 0.53 g and exhibited melting points of 158 °C and 144 °C, respectively. Molecular visualization suggested plausible intermolecular hydrogen-bonding interactions between the API and the selected coformers. The results indicate that both carboxylic acids are suitable candidates for further solid-state screening with cetirizine dihydrochloride. However, the current data do not by themselves establish the formation of pharmaceutical cocrystals. Direct PXRD, FTIR and DSC/TGA analysis of the prepared products should be performed before making a definitive cocrystal assignment. The work therefore provides a useful preliminary experimental platform for more complete crystal-engineering and pharmaceutical solid-form studies of cetirizine.

6. References

1. Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt G. Pharmaceutical cocrystals: an overview. *International Journal of Pharmaceutics*. 2011;419(1–2):1–11.
<https://doi.org/10.1016/j.ijpharm.2011.07.037>

2. Aakeröy CB, Salmon DJ. Building co-crystals with molecular recognition: what does it take? *Crystal Engineering Communication / Chemical Society Reviews*. 2005;34:719–745.
<https://doi.org/10.1039/b505883j>
3. Thakuria R, Delori A, Jones W, Lipert MP, Roy L, Rodríguez-Hornedo N. Pharmaceutical cocrystals and poorly soluble drugs. *International Journal of Pharmaceutics*. 2013;453(1):101125.
<https://doi.org/10.1016/j.ijpharm.2012.10.043>
4. Duggirala NK, Perry ML, Almarsson Ö, Zaworotko MJ. Pharmaceutical cocrystals: along the path to improved medicines. *Chemical Communications*. 2016;52:640–655
<https://doi.org/10.1039/c5cc08216a>
5. Dai X-L, Chen J-M, Lu T-B. Pharmaceutical cocrystallization: an effective approach to modulate the physicochemical properties of solid-state drugs. *CrystEngComm*. 2018;20:5292–5316.
<https://doi.org/10.1039/c8ce00707a>
6. Croker DM, Hennessy DJ, et al. Creating cocrystals: a review of pharmaceutical cocrystal preparation routes and applications. *Crystal Growth & Design*. 2018;18(10):6370–6387.
<https://doi.org/10.1021/acs.cgd.8b00933>
7. Spencer CM, Faulds D, Peters DH. Cetirizine: a reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. *Drugs*. 1993;46(6):1055–1080.
<https://doi.org/10.2165/00003495-199346060-00008>
8. Curran MP, Scott LJ, Perry CM. Cetirizine: a review of its use in allergic disorders. *Drugs*. 2004;64(5):523–561. <https://doi.org/10.2165/00003495-200464050-00008>
9. Macrae CF, Bruno IJ, Chisholm JA, et al. Mercury CSD 2.0 – new features for the visualization and investigation of crystal structures. *Journal of Applied Crystallography*. 2008;41:466–470.
<https://doi.org/10.1107/S0021889807067908>
10. McKinnon JJ, Spackman MA, Mitchell AS. Novel tools for visualizing and exploring intermolecular interactions in molecular crystals. *Acta Crystallographica Section B*. 2004;60:627–668. <https://doi.org/10.1107/S0108768104020300>
11. Jasinski JP, Butcher RJ, Siddegowda MS, Yathirajan HS, Ramesha AR. Levocetirizinium dipicrate. *Acta Crystallographica Section E*. 2010;66:o3167.
<https://doi.org/10.1107/s1600536810045733>
12. Bairagi KM, Pal P, Bhandary S, Venugopala KN, Chopra D, Nayak SK. Crystal structure of a 1:1 cocrystal of nicotinamide with 2-chloro-5-nitrobenzoic acid. *Acta Crystallographica Section E*. 2019;75:1712–1718. <https://doi.org/10.1107/S2056989019013859>
13. U.S. Food and Drug Administration. Regulatory Classification of Pharmaceutical Co-Crystals: Guidance for Industry. February 2018.
14. Gadade DD, Pekamwar SS. Pharmaceutical cocrystals: regulatory and strategic aspects, design and development. *Advanced Pharmaceutical Bulletin*. 2016;6(4):479–494.
<https://doi.org/10.15171/apb.2016.062>

15. Savjani JK. Co-crystallization: an approach to improve the performance characteristics of active pharmaceutical ingredients. *Asian Journal of Pharmaceutics*. 2015;9(3):147–151.
<https://doi.org/10.4103/0973-8398.160309>