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Structural insights into physicochemical properties alteration in metoclopramide and its multicomponent crystals

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Introduction

Crystalline form of active pharmaceutical ingredients (APIs) may exist in different solid forms such as polymorph, solvates, and hydrates. Exploring these forms has attracted a great attention in the pharmaceutical industry and academia since the physicochemical properties such as solubility, dissolution rate, hygroscopicity, tabletability, and stability often vary between different solid forms. Furthermore, drug manufacturing process involves heating, pressure, humidity exposure, and mechanical forces which can induce phase transition between different solid forms leading to serious changes in the aforementioned properties. Thus, from a pharmaceutical point of view, controlling the crystalline form of API in the drug product is crucial in terms of quality, safety, and efficacy of the final drug product.

Among various solid forms of APIs, hydrates constitute about one-third of APIs. Statistically, salts have more propensity to form hydrates compared to the free base form and more than one-quarter of the hydrochloride salts of APIs in Cambridge Structural Database are reported as hydrates. Hydrates have a noteworthy importance because of the critical role of water in pharmaceutical industry. Hydrate crystal form is often more preferred among commercial drug products than its anhydrate counterpart due to its stability against high humidity. However, the hydrate form can be problematic because the conversion to the lower hydrate or anhydrate form and *vice versa* is often complex and accompanied by changes in physicochemical properties. Moreover, such behaviour may occur during manufacturing process or under storage in ambient condition due to the ubiquitous nature of water in the environment. These facts strongly suggest that understanding those interchanges is crucial.

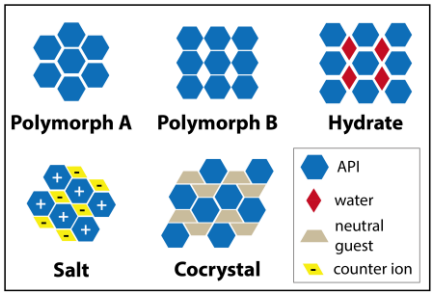

Figure 1 Crystalline form of APIs

In recent years, pharmaceutical cocrystal has been gaining a significant interest due to its potential to tune various pharmaceutically relevant physicochemical properties. On the other hand, it is estimated that half of drug compounds are marketed as salts. In addition, approximately half of the salts of cationic APIs are sold as hydrochloride salts. Hence, modifying solid form of hydrochloride salt of an API by cocrystallization provides an extended opportunity to alter the physicochemical properties of the API while maintaining the superior properties of the hydrochloride salt. Despite the ability of the chloride ion to interact with widely used coformer such as carboxylic acids, only a small number of API hydrochloride salts have been investigated and reported to form cocrystal.

In this study, metoclopramide, an antiemetic drug, and its hydrochloride salt was investigated. In the first part of this study, the polymorphism in the base form and its impact to the stability and dissolution properties were characterized. The second part focused on the investigation of the hydration/dehydration of the hydrochloride salt form from the structural point of view and determined the phase relationship between those forms. Additionally, the stability and the tabletability were characterized and rationalized with the crystal structure establishing structure-property relationship. In the final part, a novel cocrystal of the hydrochloride salt was successfully synthesized and solved the process-induced transformation in the parent drug.

1. <u>Structural investigation on enantiotropic transition in metoclopramide</u>

From thermal analysis, the stable form of metoclopramide (MCP I) showed endothermic transition into the high-temperature phase (MCP II) at 122°C followed by melting of MCP II at 143°C. Heat of transition rule implies that MCP I is enantiotropically related with MCP II. Under ambient condition, MCP II was easily reverted into MCP I which further supported the enantiotropic relationship between these polymorphic forms. The structure of MCP I was determined by single crystal X-ray structure analysis. However, the unstable MCP II cannot be obtained as a single crystal. Thus, crystal structure of MCP II was solved by *ab initio* structure determination by synchrotron powder X-ray diffraction analysis. MCP I and MCP II have identical structural building block which is one-dimensional chain of metoclopramide molecules connected by N–H···O hydrogen bond. In MCP I, centrosymmetric dimer-like structure was observed, involving N–H···N hydrogen bond. Despite the structural similarity, this hydrogen bond was not observed in MCP II confirming the existence of unsatisfied hydrogen bond donor and

acceptor. Theoretical calculation showed a high lattice energy difference between MCP I and MCP II (+8.375 kJ/mol). Packing similarity and unsatisfied hydrogen bond donor and acceptor accompanied by high difference in lattice energy were responsible to the facile transformation of MCP II to MCP I at room temperature. Intrinsic dissolution rate (IDR) of this polymorphic system was evaluated. MCP II showed 1.5-fold increase in IDR compared to the stable MCP I. IDR improvement can be correlated with the instability of MCP II (Figure 2).

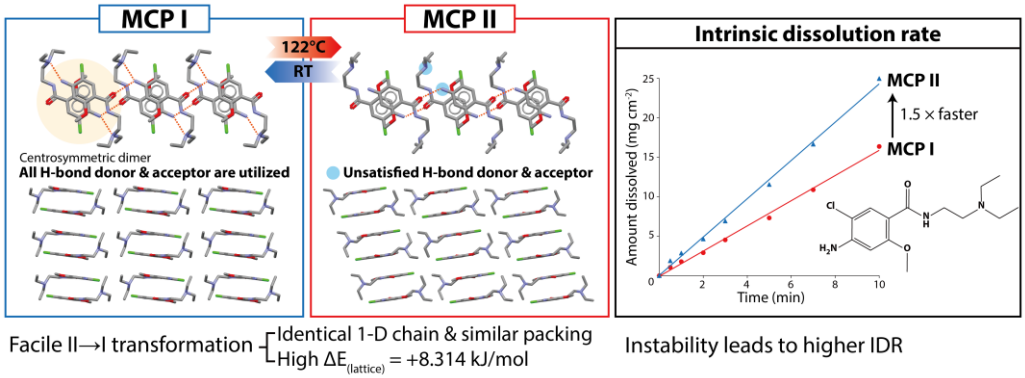

Figure 2 Structure, stability, and IDR relationship in MCP

2. Relationship between crystal structure and tabletability in metoclopramide hydrochloride pseudopolymorph

In section (1), the interconversion of the polymorphic form of MCP and its implication to IDR has been investigated. In this section, the hydrochloride salt form of metoclopramide (MCPHCl) was studied. From thermal analysis, MCPHCl existed as monohydrate form (MCPH) which melted and recrystallized into the anhydrate form (MCPA) in the temperature range of 70–100°C. MCPA readily transformed into MCPH by contact with water or by exposure in RH-controlled environment at RH > 60%. Furthermore, MCPH showed deliquescent property upon exposure to RH > 90%. Crystal structure analysis revealed that dehydration involved major structural rearrangement, implying the important role of water in stabilizing the structure of MCPH. Interestingly, MCPA shares structural similarity with its base form (MCP) *i.e.* one-dimensional chain formed by N–H···O hydrogen bond. These 1D chains further stack in an antiparallel manner via $\pi\cdots\pi$ interaction. Additionally, MCPA is partly related with MCP II in terms of the lack of hydrogen bond utilization. The presence of unutilized hydrogen bond donor and low packing efficiency of MCPA contributed to the driving force on the conversion to MCPH in high RH. Powder compaction behavior (tabletability) of MCPH and MCPA were evaluated using the measurement of tablet tensile strength as a function of compaction pressure. MCPA showed a significant improvement in the compaction properties. Slip planes perpendicular to the stacking interactions present in the layered structure of MCPA. The formation of slip planes was supported by weak interplanar interaction, indicated by weak interaction energy between adjacent stack (side motif). The slip planes facilitate plastic deformation which enhance the tensile strength of MCPA (Figure 3).

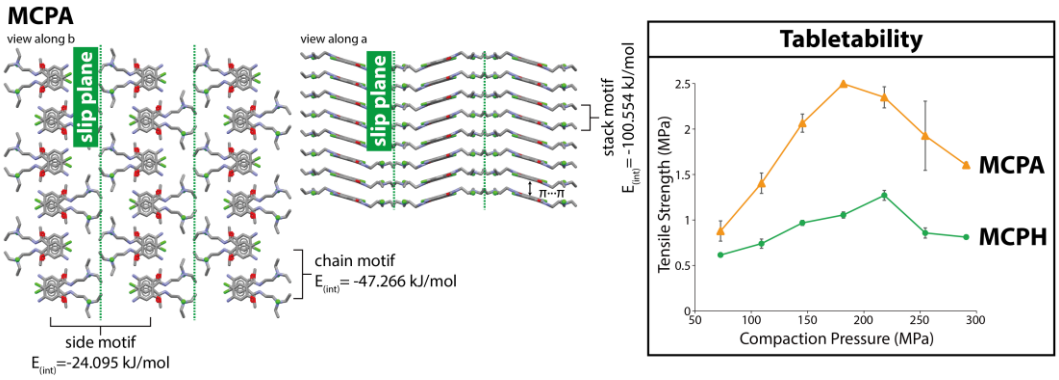

Figure 3 Slip plane and superior tabletability of MCPA

3. Suppressing hydration in metoclopramide hydrochloride by cocrystallization

In section (1) and (2), the existence of unsatisfied hydrogen bond donor and acceptor dictates the instability of MCP II and MCPA. MCP II stabilized by transforming into MCP I rapidly in RT, while MCPA by hydrate formation in high RH. Both behaviour serve the same purpose: conversion into the more stable form in which all hydrogen bond donor and acceptor are utilized. Based on this idea, we utilized cocrystallization to increase the stability

MCPHCl using oxalic acid as pharmaceutically acceptable coformer. The salt cocrystal (MCP–OXA) contains one molecule of MCPHCl and half of one molecule of OXA. In MCP–OXA, one dimensional chain structure formed by N–H···O hydrogen bond was observed, identical to those observed in MCPA. However two additional hydrogen bonds involving the chloride ion were also involved in the chain arrangement. Oxalic acid involved in the supramolecular arrangement of MCP–OXA by bridging MCPHCl chains creating a ladder-like framework (Figure 4). As expected, all hydrogen bond donor and acceptor are satisfied in the salt cocrystal. MCP–OXA has lower melting point compared to the melting point of MCPA but significantly higher than MCPH in regard to its respective dehydration temperature. Besides, the resulting salt cocrystal was stable in high humidity and aqueous slurry experiment, confirming no conversion to MCPH. These properties imply that MCP–OXA possess higher thermal stability and processability than the parent drug. Further characterization revealed that the stability of MCP–OXA influenced its dissolution behavior. MCP–OXA showed slower IDR compared to the MCPHCl. For highly soluble drug such as MCPHCl, the salt cocrystal with slow IDR is promising for application in extended release formulation. The use of MCP–OXA in extended release formulation may solve the pharmacological issues in MCPHCl related with patient incompliance and side effect due to frequent administration.

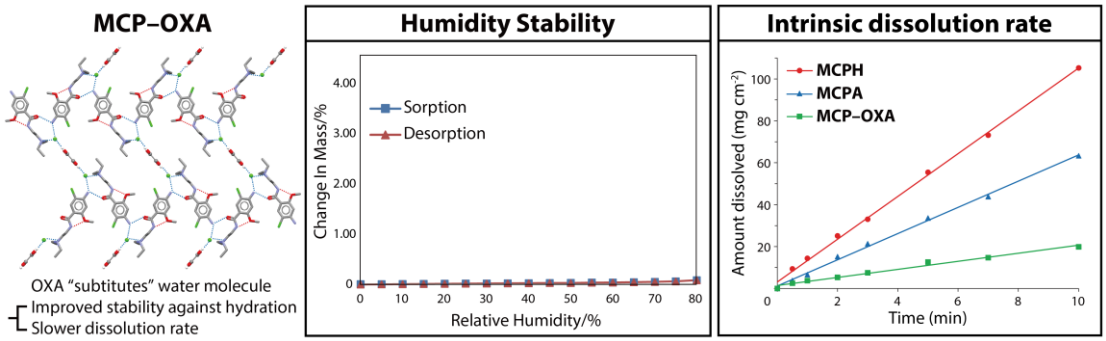

Figure 4 Physiochemical properties improvement in salt cocrystal

Conclusion

In this study, we have successfully established structure and property relationship in polymorph and pseudopolymorph of metoclopramide. The instability of the metoclopramide crystal forms mainly derived from the unsatisfied hydrogen bond donor and acceptor and low packing efficiency. Specifically in the pseudopolymorph system, the presence of slip plane improved the tabletability properties. In addition, we have obtained a novel salt cocrystal of metoclopramide with superior thermal stability and processability, based on the structural characterization of the parent drug. The salt cocrystal also possessed a suitable property to be developed as extended release formulation solving pharmacological disadvantage of the parent drug. This research emphasizes the role and the importance of crystal structure determination in understanding and improving physicochemical properties in metoclopramide crystal forms.