# 論文 / 著書情報
# Article / Book Information

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# 論 文 要 旨

THESIS SUMMARY

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| 専攻：<br>Department of | 物質科学　専攻 | 申請学位（専攻分野）：<br>Academic Degree Requested | 博士　（　理学　）<br>Doctor of |
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要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）


This dissertation has covered the relationship between the crystal structure and physicochemical properties of polymorphs, pseudopolymorphs, and multicomponent crystals of metoclopramide and its hydrochloride salts, aided by elucidating the unknown crystal structures of the API for the first time.

The first part of this dissertation focused on the polymorphism of the metoclopramide. The phase relationship and interconversion in metoclopramide polymorphs and its implication to the intrinsic dissolution rate have been revealed in this study. The stable form I is enantiotropically related with the metastable form II. The form II is readily reverted into form I in room temperature due to their structural similarities and high relative energy difference, in which the form I exhibits more intermolecular interactions *i.e.* more utilisation of hydrogen bond donor and acceptor, and more ordered crystal packing. The unstable form II shows 1.5 times higher intrinsic dissolution rate than the form I, which attributed to its relative stability.

Starting on the second part, this dissertation focused on the hydrochloride salt of the metoclopramide. The hydration/dehydration behaviour of hydrochloride salt form was examined from a structural point of view. Structural arrangement occurred upon dehydration of monohydrate form, forming anhydrate form that has a substantially different crystal structure. Underutilised hydrogen bond donors and less efficient packing are the main features of anhydrate that cause its hydration in high humidity and instability upon contact with water. Tabletability evaluation showed that the anhydrate form exhibited superior tabletting properties over the monohydrate form. Detailed examination on the crystal structures revealed that the presence of slip plane in the anhydrate form facilitated plastic deformation, thereby improving the tabletability.

In the final part, the structural knowledge that were attained from the previous parts were exploited. In both metoclopramide and its hydrochloride salt, the unsatisfied hydrogen bond donors or acceptors were responsible for the shortcomings of the physicochemical properties. Hence, they are potential to be utilised to generate the cocrystal of the salt. The novel salt cocrystal with oxalic acid was obtained, and was able to solve the processability limitation of the pseudopolymorphic parent drug. The salt cocrystal has higher stability than its parent drug against high humidity and dissociation in aqueous environment. These properties are attributed to the utilisation of all hydrogen bond donors and acceptors of metoclopramide, suggesting the coformer acts as a substitute for water molecule in the structure. In addition, the salt cocrystal exhibited lower dissolution rate compared to the parent drug, making it very suitable for extended release drug formulation. These results show the potential of utilising salt cocrystallisation to tune the physicochemical properties of salt APIs.


備考 ： 論文要旨は、和文 2000 字と英文 300 語を 1 部ずつ提出するか、もしくは英文 800 語を 1 部提出してください。
Note : Thesis Summary should be submitted in either a copy of 2000 Japanese Characters and 300 Words (English) or 1copy of 800 Words (English).