論文 / 著書情報
Article / Book Information

題目(和文)	
Title(English)	Green solvent-free crystal engineering for active pharmaceutical ingredient with molecular informatics
著者(和文)	HaoYingquan
Author(English)	Yingquan Hao
出典(和文)	学位:博士(工学), 学位授与機関:東京工業大学, 報告番号:甲第12205号, 授与年月日:2022年9月22日, 学位の種別:課程博士, 審査員:下山 裕介,久保内 昌敏,関口 秀俊,多湖 輝興,松本 秀行
Citation(English)	Degree:Doctor (Engineering), Conferring organization: Tokyo Institute of Technology, Report number:甲第12205号, Conferred date:2022/9/22, Degree Type:Course doctor, Examiner:,,,,
学位種別(和文)	博士論文
Category(English)	Doctoral Thesis
種別(和文)	要約
Type(English)	Outline

Doctoral dissertation

Summary

Green solvent-free crystal engineering for active pharmaceutical ingredient with molecular informatics

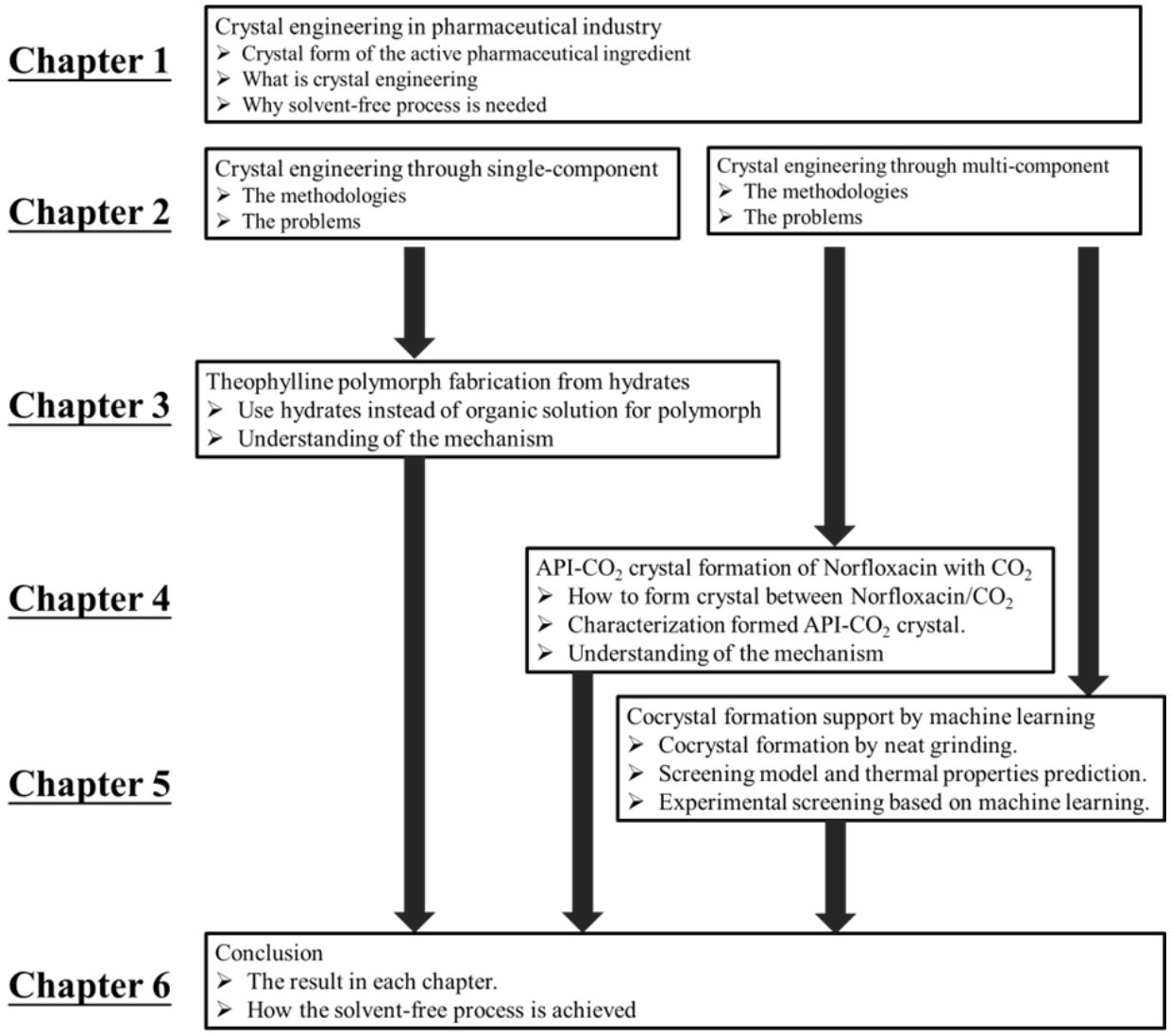
Yingquan HAO

Academic supervisor: Prof. Yusuke Shimoyama

Department of Chemical Science and Engineering

School of Materials and Chemical Technology

Tokyo Institute of Technology, Japan



Structure graph of this dissertation

Chapter 1 Introduction

Chapter 1 firstly gives the background of this research. It is mainly about the problem which is faced in the pharmaceutical industry. Since the active pharmaceutical ingredient (API) is become more and more insoluble in water, the enhancement of the dissolution properties of API provided is needed. Crystal engineering have been considered as a good choice to solve this problem, because changing in the crystal will have less effect on the pharmaceutical activity of API compared with changing the chemical structure of API. Then, this chapter gives a short introduction of crystal engineering in the pharmaceutical industry. It can be mainly divided into 4

kinds of approaches, polymorph inducement, salts formation, solvate/hydrate formation, cocrystal formation. And we point out the problem may be faced in these methodologies. The use of toxic solvent in the fabrication process will damage the safety of the utilization of APIs in human body and increase the environmental pollution from the pharmaceutical industry.

So, in the next parts, we shortly introduce our approaches about greener solvent-free crystal engineering for the API. In this dissertation, we mainly introduced 3 kinds of approaches to achieve a green solvent-free crystal engineering for API from different aspects.

In the first approaches, we focus on the crystal polymorph inducement by supercritical CO_2 technology. Since supercritical CO_2 is green solvent and it can be easily separated from the product after the process, it has been considered as a green process media in pharmaceutical industry. And it also shows its great potential in finding new polymorph of API in the research before. But in the reported research, the toxic solvent is used to dissolve the API in the supercritical CO_2 process, this makes the process not green anymore. To solve this problem, the API hydrates is used instead of the API organic solution in our research.

In the second approaches, we also focus on the utilization of supercritical CO_2 technology in the pharmaceutical industry. In this part, we not only focus on the green properties of CO_2, but also focus on its reactivity with API with amine group. By formation of API-CO_2 crystal, which will release the CO_2 into water during the dissolution and improve the dissolution properties of API, we successfully improve the solubility of poor soluble API, Norfloxacin.

In the third approaches, we focus on the cocrystal formation by neat grinding method. Because this process does not need solvent compared with other process. It is much safer than others. And to make the cocrystal fabrication by this process more efficient. Machine learning models for the cocrystal screening is built and compared with other models. The new proposed models show better performance than reported ones. And two kinds of new cocrystal of Norfloxacin is fabricated with the guidance by models.

At last, Chapter 1 gives a short description of each chapter in this research.

Chapter 2 Literature review

In Chapter 2, we mainly discussed about the literature reviews about the fabrication methodology of the polymorph and the cocrystal of API, since they are the main topics discussed in this dissertation. About the polymorph, we mainly review the fabrication methodologies of the polymorph. It can be mainly divided solvent method, melting method, and supercritical CO_2

method. The limitation and advantages of each methodology is introduced. Then, an example of theophylline polymorphism is introduced, since it is the first API reported as the compound that can form a new polymorph in the supercritical CO_2 process. And it is also the API that we will focus on in the further research. In this part, we will introduce the limitation of this process and gives out the reason of our research about the polymorph studied of theophylline in the Chapter 3. Then, we change our focus to the cocrystal formation technology of API. The formation technology can be mainly divided into 4 kinds, as the solid-solid system, liquid-liquid system, solvent phase system, and the supercritical CO_2 system. The advantages and limitation of each process is introduced. And an example of the cocrystal for poorly water-soluble API, Norfloxacin, and itself are introduced. Because it is the main API that we will mainly discuss in the Chapter 4 and Chapter 5. We mainly introduced about the pH-sensitivity of Norfloxacin solubility in water and the chemical structure of Norfloxacin to offer an entry point of the research about the API-CO_2 crystal of Norfloxacin in the Chapter 4. And we also review the cocrystal of Norfloxacin reported to clear the problem faced in the cocrystal formation to give the reason why neat grinding method is seemed to be a better choice which will be mainly studied in the Chapter 5.

Chapter 3 Theophylline polymorph induced by supercritical CO_2 from its monohydrates

In this chapter, a studied to find the replacement of the organic solvent in the inducement of theophylline form V by supercritical CO_2 is introduced. Firstly, the details of the research before to fabricate the form V of theophylline by supercritical CO_2 antisolvent method is introduced. To remove the toxic organic solvent used in the supercritical process. Two kinds of approaches are taken in this chapter. A). Since, theophylline is high soluble in supercritical CO_2. Theophylline form II is put into a high-pressure cell filled with supercritical CO_2, expecting the formation of form V by supercritical CO_2 mediated crystal phase transformation. But unfortunately, theophylline from V cannot be formed by this process based on the powder XRD. This may be due to that theophylline form V is less stable compared with form II. another alternative reason is that the dispersion of theophylline molecule in the supercritical CO_2 like solution is important. Based on these results, the second approach is proposed.

B). Use theophylline monohydrate instead of theophylline organic solution. The reasons are as followed. Theophylline monohydrates have a sandwich-like structure consist of water-theophylline dimer-water. This will offer the enough contact of theophylline molecule with CO_2 during water is extracted from theophylline monohydrate like the solvent-dispersed theophylline.

Water is a much greener additive compared with organic solvent, it will not damage the safety of the process and can be removed by the extracting effect of supercritical CO_2. Monohydrate of the theophylline is more soluble than theophylline form II is supercritical CO_2. This will create an over-saturated environment in the water extraction from monohydrate, like the supercritical antisolvent process. And since no more theophylline form II is in the system, the influence of thermodynamically more stable form II can be removed. As the result, theophylline form V is obtained by treating theophylline monohydrate by supercritical CO_2. But unfortunately, a mixture of form V, form II, and monohydrate is obtained after the process. To increase the form V obtained by this approach, the relationship of process condition and the mass fraction of form V in the mixture is studied by semi-quantification based on the powder-XRD. The result found, the higher pressure is preferred for the formation of form V. and the high temperature will damage the formation of form V due to the too early dehydration of monohydrate by high temperature. even lots of the effort have been taken to obtain the pure theophylline form V, but pure form V is not obtained as other reported research. This may be due to the instability of form V, which will make form V transform into form II spontaneously. But the dissolution properties of processed powder are still studied in this research. It is found that the processed powder has higher dissolution rate than form II.

In this chapter, theophylline monohydrate is used instead of theophylline organic solution for the formation of theophylline form V. This makes the process much greener than reported ones.

Chapter 4 Norfloxacin-CO_2 crystal formed with supercritical CO_2 and enhanced Norfloxacin dissolution properties

In Chapter 4, we mainly introduce a studied about the formation of API-CO_2 crystal in supercritical CO_2 process. We firstly reviewed the research use supercritical CO_2 as the process media in the pharmaceutical field and the recent research that use CO_2 as the reactive content to modify the properties of chemicals. Then we introduce a new concept that use CO_2 to enhance the dissolution properties of API. Norfloxacin, a kind of poorly water-soluble API, is chosen as the target compound, since it has the anchor point for CO_2 in its chemical structure and its solubility is sensitive to the pH change of the water environment. Two kinds of approaches have been considered to form Norfloxaicn-CO_2 crystal.

A). Formation in the aqueous solvent phase. Since Norfloxacin solubility is highly sensitive to pH change of water environments, here comes an idea that use CO_2 to control the recrystallization of

Norfloxacin recrystallization from water solution, expecting the CO_2 can be fixing in the Norfloxacin at the same time. As the result, we found that Norfloxaicn-CO_2 crystal can not be formed due to the higher stability of Norfloxacin hydrate in the water phase.

So, these results lead to the second approaches. B). Formation in supercritical-CO_2. Since the supercritical CO_2 offers an environment filled with CO_2, the influence of water can be totally removed. As the result, Norfloxacin-CO_2 crystal is obtained by treating Norfloxacin form B with supercritical CO_2. But still a mixture of Norfloxacin form B and Norfloxaicn-CO_2 crystal is obtained. To obtain the pure Norfloxacin-CO_2 crystal, the relationship between formation of Norfloxaicn-CO_2 crystal and process parameters is studied by semi-quantification based on powder-XRD. It is found that the formation of form V favours a higher pressure and temperature. Based on these results, the pure Norfloxacin-CO_2 crystal is obtained. It shows twice higher equilibrium solubility and dissolution rate than Norfloxacin form B. This is caused by the release of CO_2 into water environment during the dissolution, which is proven by the powder XRD. And based on the TGA, DSC-XRD results, Norfloxacin-CO_2 crystal is formed by Norfloxacin and CO_2 one by one in molar, and CO_2 can be released from crystal by one step during the heating process. Moreover, the CO_2 is reconfirmed by TGA-MS. And the binding mechanism of CO_2 with Norfloxacin is studied by SSNMR and FT-IR with quantum chemical calculation simulation. The result shows CO_2 is chemical fixed by formation of paired carbamic acid structure with Norfloxacin.

In this chapter, API-CO_2 crystal is formed by solvent-free process. CO_2 is used as the process media and active additives to enhance the dissolution properties of Norfloxacin. This shows a new strategy to improve the dissolution properties of API through a totally green process.

Chapter 5 Cocrystal screening and properties prediction based on machine learning and molecular informatics

In this chapter, we mainly focus on using machine learning to support the cocrystal screening by neat griding method. Compared with other process, neat griding method has no risk of organic pollution by organic solvent and decomposition by heat. But the screening of cocrystal formation is mainly carried by the experiments by now. To solve this problem, in this research, machine learning modeling is used. Compared with other reported machine learning model, we focus on the machine learning model with physics-chemical meaning. Since the geometry and charge factor plays critical role during the cocrystal formation. So, two kinds of newly-proposed spatial charge

descriptor of chemical molecule is used in this research. One is based on the one-dimensional statistical distribution of surface screening charge calculated by COductor-like Screening MOdel (COSMO). Then this descriptor is further combined with machine learning algorithm support vector machine for the screening of cocrystal (COSMO-SVM). The other one is based on the charge distribution in the 3D- Cartesian Coordinate system calculated by universal force field and Gasteiger charge equilibration model. Then, this descriptor is further combined with 3D convolutional neural network for cocrystal screening (3D-CNN). Two newly proposed machine learning model is trained and testing on the same datasets based on neat grinding method and compared with reported machine learning model. As the result, two newly proposed machine learning model shows higher accuracy in the test datasets compared with others. And furthermore, these two models are used for the coformer screening of poorly water-soluble API, Norfloxacin. As the result, two cocrystal of Norfloxacin is fabricated by neat grinding process. This shows that these 2 models are helpful for the cocrystal screening by neat grinding method.

In addition, we also go one step further than just screening of cocrystal. By using the one-dimensional statistical distribution of surface screening charge calculated by COductor-like Screening Model, we build a model for the prediction of thermal properties of cocrystal based on the machine learning algorithm (COSMO-RFR). As the result, COSMO-RFR shows better performance than the reported models.

In this chapter, we mainly introduce the machine learning modeling to support the cocrystal screening by neat grinding method. By introducing the physics-chemical concept into the machine learning, the performance of machine learning model can be improved dramatically. These models will be helpful for the cocrystal formation with green solvent-free process.

Chapter 6 Conclusion

In this chapter, we give the conclusion of the chapters before. In Chapter 3, we use API hydrate instead of API organic solution to form theophylline form V. In Chapter 4, we use supercritical CO_2 to form the API-CO_2 crystal to enhance the dissolution properties of Norfloxacin. In Chapter 5, we use machine learning technique to support the cocrystal screening by neat grinding method, and we even go further, we also build a model for the prediction of cocrystal thermal properties. All these approaches help the API industry to achieve a greener solvent-free crystal engineering. In addition, the research route of these research is also cleared. In Chapter 3, the green process is achieved, but the target compound is limited, and the enhancement is very few. In the Chapter 4,

the dissolution enhancement become significant, but the target compound is still limited. In Chapter 5, we use machine learning technique to support cocrystal fabrication, which is more flexible and effective in the crystal engineering of API and successfully find two new cocrystal. With the advance of the chapters, the technique become more general and flexible. However, all these technologies have its own attribution to achieve a green solvent-free crystal engineering of APIs.