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)	論文要旨
Type(English)	Summary

（博士課程）
Doctoral Program

論 文 要 旨

THESIS SUMMARY

系・コース： Department of, Graduate major in	応用化学	系 コース	申請学位（専攻分野）： Academic Degree Requested	博士 Doctor of	（ 工学 ）
学生氏名： Student's Name	HAO YINGQUAN		指導教員（主）： Academic Supervisor(main)	下山 裕介	
			指導教員（副）： Academic Supervisor(sub)		

要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

In past years, the active pharmaceutical ingredients (API) become more and more insoluble in water. To solve this problem, many kinds of crystal engineering approaches have been considered, such as polymorph, complex, cocrystal. In this research, we mainly focus on building a solvent free process for these approaches, since the application of the toxic organic solvent in the pharmaceutical industry will leads to massive by-products from the process and damage the safety of API for some cases.

To achieve this green crystal engineering process, 3 kinds of solvent-free approaches have been studied as follow.

A). Use APIs monohydrates instead of APIs organic solutions in polymorph inducement by supercritical CO_2.In this research, we target on a special polymorph form V of theophylline, a kind of API used for treatment of asthma. Form V of theophylline was firstly fabricated by supercritical CO_2 antisolvent process based on the report and can be only massively fabricated by this process. But unfortunately, the toxic organic solvents such as dichloromethane and tetrahydrofuran were used to dissolve theophylline during the process. As solution, theophylline monohydrate is used instead of theophylline organic solution to interact with supercritical CO_2 for the formation of form V in this research. As a result, theophylline form V is successfully fabricated with this API monohydrate-supercritical CO_2 interaction. The relationship between the formation of form V and pressure is also studied. The results based on the PXRD shows the formation of form V prefer a higher pressure. Moreover, the dissolution behavior of theophylline in water is also slightly improved. In this research, we successfully fabricated theophylline form V with a solvent-free process and also improve the dissolution properties of theophylline.

B). Use CO_2 to form the API-CO_2 crystal only by the interaction between API and CO_2. In this research, Norfloxacin, a kind of widely-used poorly-water-soluble antibacterial, is chosen as the target API. Because even the Norfloxacin have a piperazine group which can offer the anchor point of the CO_2 and the solubility of Norfloxacin is very sensitive to the pH change of the water environment which means the released CO_2 from CO_2 crystal can help Norfloxacin become more soluble by changing the pH of water. To fabricate Norfloxacin-CO_2 crystal, a solvent-free process is applied. Norfloxacin form B is treated by supercritical CO_2. And by this process, Norfloxacin-CO_2 crystal formation is confirmed by PXRD and TGA-MS. The relationship between formation of Norfloxacin-CO_2 crystal and process condition is further studied. The result shows that higher pressure and temperature is preferred to obtain purer Norfloxacin-CO_2 crystal. The TGA result indicated that the Norfloxacin-CO_2 crystal is consist of Norfloxacin and equal molar CO_2. The further studies based on FT-IR, SSNMR and quantum chemical calculation shows the Norfloxacin-CO_2 crystal is formed through the formation of paired carbamic acid structure between piperazine group of Norfloxacin and CO_2. Moreover, by the formation of Norfloxacin-CO_2 crystal, the equilibrium solubility of Norfloxacin is improved about twice.

C). Use machine learning technique to build a screening and properties prediction model for cocrystal formation based on neat grinding method. In this research, 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 factors play critical roles during the cocrystal formation. So, two kinds of spatial charge descriptor of chemical molecule are newly-proposed. 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 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 models are trained and tested on the same datasets based on neat grinding method and compared with reported machine learning model. As a result, two newly proposed machine learning model shows higher accuracy in the test datasets compared with others. Furthermore, these two models are used for the coformer screening of poorly water-soluble API, Norfloxacin. 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.