Journal of CO_2 Utilization 20 (2017) 43–51

Contents lists available at ScienceDirect

Journal of CO_2 Utilization

journal homepage: www.elsevier.com/locate/jcou

Tailoring the particle microstructures of gefitinib by supercritical CO_2 anti-solvent process

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ARTICLE INFO

Keywords:
Supercritical CO_2
Gefitinib
Microstructure
Polymorph
Micronization

ABSTRACT

Supercritical CO_2 anti-solvent (SAS) process is a green and effective method to produce particles with designated microstructures. In this study, the particle microstructures of gefitinib, a potent anticancer agent, are tailored by the SAS process to improve its aqueous solubility. The dichloromethane/ethanol (1:4, v/v) was selected as the suitable solvent from typical solvents used in the SAS process at first. Then, the effects of other SAS operating parameters, i.e., the flow rate of gefitinib solution (*F*), the concentration of gefitinib in the solution (*C*), the precipitation pressure (*P*) and the temperature (*T*), on the gefitinib particle size were investigated in detail. Lower *F*, lower *C*, higher *P* and suitable *T* were recommended for the formation of gefitinib particles with small particle size. The properties of the raw material and SAS processed samples of gefitinib were characterized by different methods. The results showed that a new polymorphic form (Form β) of gefitinib, which present different physicochemical properties, i.e., smaller particle size, narrower particle size distribution and higher solubility, with raw gefitinib (Form 1), was captured after the SAS process. The predicted structures of gefitinib crystals, which were consistent with the experiments, were performed from their experimental XRD data by the direct space approach using the Reflex module of Materials Studio. Meanwhile, the SAS processed gefitinib particles showed much higher solubility and faster dissolution rate than that of raw gefitinib, which had the potential to improve its bioavailability and decrease the dose-related adverse effects.

1. Introduction

Gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor [1,2], has been approved by FDA in 2015 for the first-line treatment of patients with metastatic non-small cell lung cancer [3]. Gefitinib is a lipophilic dibasic compound with pKa values of 5.28 and 7.17, its chemical structure is shown in Fig. 1. Gefitinib is practically insoluble in aqueous solvents with pH > 7, which limits its oral absorption along the intestine, resulting in a low bioavailability [4,5]. Also, due to its poor aqueous solubility, a high dose is required during clinical utilization of gefitinib, which may lead to the dose-related adverse effects, such as vomiting, diarrhea, nausea, etc [6,7]. Therefore, improving the aqueous solubility is necessary for widening the therapeutic window of gefitinib.

To overcome the limitations of solubility for pharmaceuticals, various strategies have been investigated, such as prodrug [8], micronization [9,10], crystal engineering [11], solid dispersions [12] or incorporation formulations [13], etc. For any strategies, the drug solubility and dissolution rate is directly influenced by the particle microstructures, including morphology, particle size, particle size distribution, crystal form, etc. Theoretically, a decrease in particle size will lead to an increase in effective surface area in the diffusion layer, which, in turn, increases the drug dissolution rate [14]. Crystalline polymorphs show significant effects on the solubility and bioavailability of drug products [15,16]. Thus, tailoring the particle microstructures is a fundamental method to improve the therapeutic efficacy and bioavailability of poorly water-soluble drugs.

However, major advances in drug manufacture have highlighted the limitations of conventional particle formation processes in fine-tuning the characteristics required, due to the harsh processing conditions and poor properties of products [17]. The conventional techniques also face some problems, e.g., thermal and chemical degradation of products, large amounts of solvent use and residues. Supercritical CO_2 anti-solvent (SAS) process, as an alternative strategy of traditional technologies [18,19], offers a simpler and better control process for the development and production of nano- or micro- particle drugs, such as spherical microparticles of sulfasalazine [20], indomethacin amorphous solid dispersions [21], rifampicin-loaded submicron-sized parti-

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http://dx.doi.org/10.1016/j.jcou.2017.04.015
Received 22 January 2017; Received in revised form 26 April 2017; Accepted 30 April 2017
Available online 16 May 2017

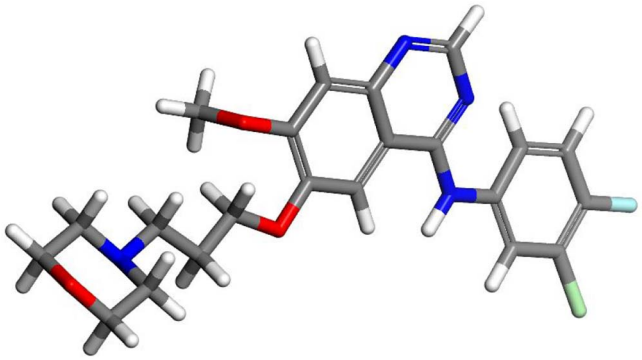

Fig. 1. Chemical structure of gefitinib, where carbon is marked in grey, oxygen in red, nitrogen in blue, fluorine in cyan, chlorine in green and hydrogen in white. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

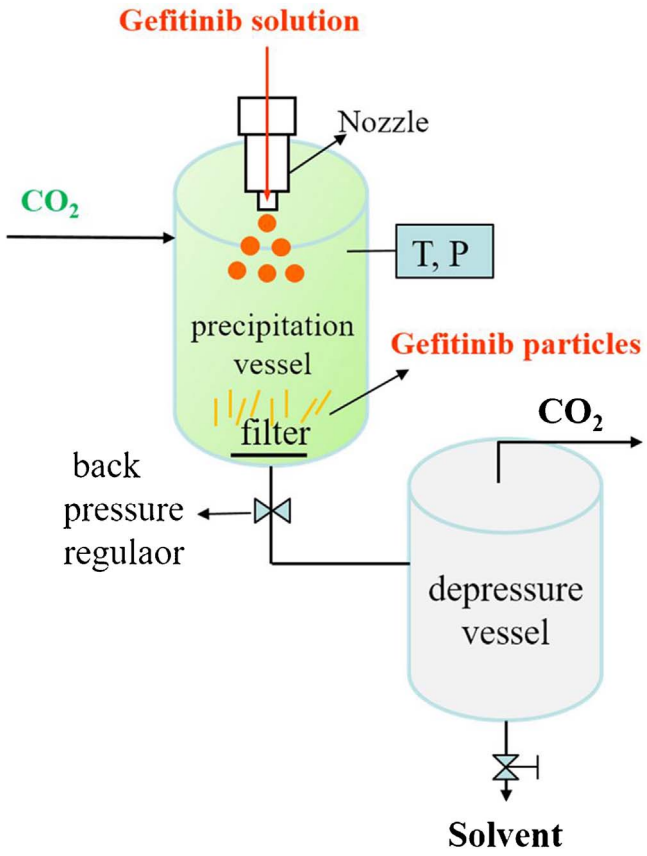

Fig. 2. Flow diagram of the supercritical CO_2 antisolvent (SAS) process.

cles [22], cocrystals-pure powders of naproxen and nicotinamide [23], primidone microcrystals [24], et al. The particle microstructures can be tailored by controlling the SAS operating parameters, which indirectly influence the interactions among high-pressure vapor-liquid equilibria, surface tension variations, jet fluid dynamics, mass transfer, nucleation and growth [25]. These published works have demonstrated that SAS process holds great promise in particle design. SAS process can effectively decrease the particle size, or modify the crystal form of the polymorphic drugs, or produce amorphous particles to enhance the dissolution rate and solubility of poorly water-soluble drugs [26–28]. In our previous study, the particle microstructures of 10-hydroxycamptothecin (HCPT) were tailored using the SAS process. The crystal form of raw HCPT was changed from pancake-like form to prismatic form and needle-like form after SAS processing [29], where the needlelike form with a larger surface-to-volume ratio had a dramatically higher solubility and exhibited dramatic improvement in anti-tumour efficacy [30].

Table 1
Summary of operating conditions and corresponding results.

Runs	*F* (mL/min)	*C* (mg/mL)	*P* (bar)	*T* (°C)	Dp_{50} ± SD* (μm)
1	1.0	1.0	90	40	1.73 ± 0.088
2	0.5	1.0	90	40	0.60 ± 0.068
3	1.5	1.0	90	40	1.99 ± 0.091
4	2.0	1.0	90	40	2.43 ± 0.076
5	2.5	1.0	90	40	2.51 ± 0.080
6	1.0	0.5	90	40	1.50 ± 0.061
7	1.0	1.5	90	40	1.88 ± 0.077
8	1.0	2.0	90	40	2.11 ± 0.078
9	1.0	2.5	90	40	2.31 ± 0.081
10	1.0	1.0	100	40	1.51 ± 0.089
11	1.0	1.0	110	40	1.30 ± 0.056
12	1.0	1.0	120	40	1.00 ± 0.067
13	1.0	1.0	130	40	0.84 ± 0.069
14	1.0	1.0	90	30	2.34 ± 0.070
15	1.0	1.0	90	35	2.00 ± 0.066
16	1.0	1.0	90	45	1.89 ± 0.053
17	1.0	1.0	90	50	1.99 ± 0.073

The aim of this work is to tailor the particle microstructures of gefitinib by the SAS process for improving its aqueous solubility. The suitable organic solvent was selected at first. Then, the influences of other SAS operating parameters on particle size were investigated in detail. The properties of the raw material and SAS processed samples of gefitinib were characterized by different methods. The crystal structures were predicted by the molecular simulation. The aqueous solubility of the raw and SAS processed samples of gefitinib in vitro were also evaluated.

2. Materials and methods

2.1. Materials

Gefitinib (mass purity fraction > 99%) was purchased from Shanghai Yuanye Bio-Technology Co., Ltd., China. CO_2 (mass purity > 99.9%) was purchased from Guangzhou Shengying Gas Co., Ltd., China. Dichloromethane (DCM), ethanol (EtOH), dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) were analytical grade (Guangdong Guanghua Sci. Tech. Co., Ltd., China). All materials were used directly without further purification.

2.2. Apparatus and procedure

An automatic semi-continuous SAS process (SAS50-2-ASSY, Thar Technologies, Inc., USA) is employed to tailor the particle microstructures of gefitinib. The flow diagram is illustrated in Fig. 2, and the operating procedure has been described in detail in our previous work [29,31–33]. In brief, CO_2 is liquefied firstly and continuously delivered via a high-pressure pump, where the flow rate of CO_2 was established at 20 g/min on the basis of the device capability. Before entering the injector, the stream of CO_2 was preheated by a heat exchanger. When reaching the desired temperature (*T*) and pressure (*P*), pure solvent is charged at a given flow rate (*F*) by another high-pressure pump and sprayed into the precipitation vessel through a nozzle (0.5 mm) for 15 min to achieve a quasi-steady state composition of solvent and CO_2 in the precipitation vessel. Then, the gefitinib solution is injected instead of pure solvent to produce the gefitinib precipitation. An ultrafiltration membrane (0.22 μm) and a metal filter (5 μm) are located at the bottom of the precipitation vessel for particle collection. At the end of the solution delivery, CO_2 is kept flowing for 40 min to remove the residual solvent. After the washing step, the precipitation vessel is depressurized gradually. Finally, the obtained particles are collected from the wall and bottom of the precipitation vessel.