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Crystallization of an active pharmaceutical ingredient that oils out

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ABSTRACT

Oiling out, an undesirable effect of the crystallization of organic molecules from solution, usually disturbs the crystallization process and deteriorates the product properties. In this work the purification of raw idebenone that oils out was firstly attempted by use of both drowning out and cooling crystallization from hexane/methylene chloride mixtures. Experimental results have shown that, oiling out can greatly affect the outcome of crystallization: at low initial concentrations, oiling out did not take place and crystallization proceeded normally to harvest the product with high purity; while at high initial concentrations, oiling out frequently occurred and crystallization was hindered or even stopped. In addition, such parameters as the polarity of solvent, cooling rate, seeding and addition rate of antisolvent can also be utilized to avoid the occurrence of oiling out so as to increase the purity of crystallization product.

1. Introduction

Well-controlled crystallization of active pharmaceutical ingredients (APIs) is often a vitally important operation in the pharmaceutical industry. This is because crystallization is not only in general the last chemical purification step in the production of APIs but also an effective means to control the physical properties of APIs including crystal form, size and shape that have the potential to impact final bioperformance [1–3]. There are a number of ways to crystallize APIs from their solutions, e.g. reaction, cooling, drowning out, evaporation, or a combination of these techniques [4–6]. In particular, drowning out has been emerging as an important method for the separation and purification of pharmaceuticals due to its low cost and high energy efficiency [7–10].

However, it is frequently observed that, instead of crystallizing from a supersaturated solution, a second liquid phase (oil phase) forms. This phenomenon is termed oiling out [11], liquid–liquid demixing [12] or liquid–liquid phase separation (LLPS) [13,14]. In the practice of pharmaceutical crystallization, oiling out is normally undesirable to delivering purification and controlling the properties of product, because the oil phase is often a good solvent for impurities and if it subsequently crystallizes it can degrade the product quality. Moreover, it has been noted that scale-up of such a system will be problematic, since the oil phase may stick to reactor walls and extremely high power is required [15]. Furthermore, in tune with the Ostwald rule of stages, oiling out shall slow down the crystallization rate, as the first formed metastable/stable liquid phase hinders the primary or the secondary nucleation [16].

Until recently, there were few references in the literature with regard to organic small molecules to help process chemists and engineers to understand and ultimately control oiling out. The reported organic small molecules that oil out during their crystallization include bisphenol A [17], 4,4′-dihydroxydiphenyl sulfone (DHDPS) [18], $C_{35}H_{41}C_{l2}N_3O_2$ [12], methyl(E)-2-[2-(6-trifluoromethyl pyridine-2-yloxymethyl)-phenyl]-3-methoxyacrylate [19], vanillin [20], etc. [21]. Serajudin and Pudipeddi [22] referred the oiling out of less hydrophilic molecules to their inherent low polarity resulting in a lack of anchoring sites required for the self-assembly in an organized manner when crystallizing from solvents. Derdour [23] has classified oiling out into two types: one is that liquid–liquid phase separation occurs where each phase contains appropriate amounts of solute, but the solute is generally not evenly distributed between the two phases. This kind of oiling out usually occurs when a mixture of solvents is used [24], as the large difference in affinity of objective compound for each solvent can be the driving force for LLPS. As to this type of oiling out, the crystallization of the drug is possible by adjusting the crystallization condition; in particular, seeding has been shown to be a good method [25]. The other one is that oiling out occurs where one phase contains the solvent(s) and the other phase is mainly formed by the solute in the form of a very heavy viscous oil-like phase, e.g. the crystallization of clopidogrel hydrogen sulfate. This type of

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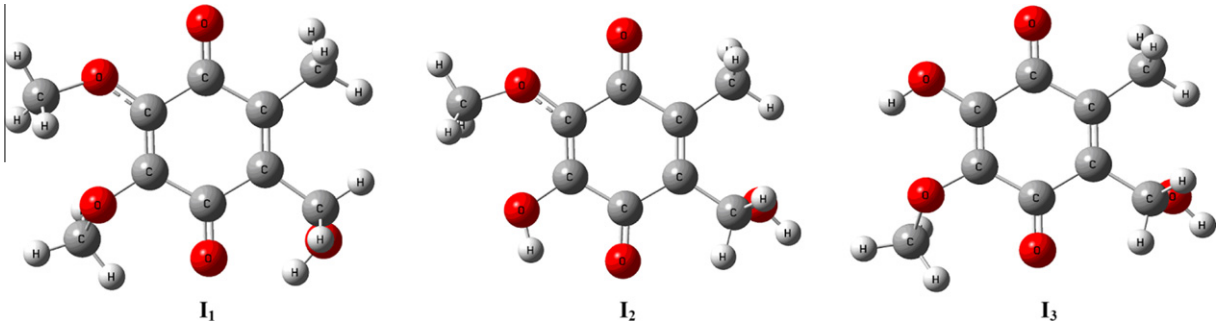

Fig. 1. Structures of idebenone (I_1) and analogous impurities I_2 and I_3.

LLPS takes place usually in the crystallization of which high supersaturation is employed. In this case, lowering the concentration of the solution and choosing suitable crystallization temperature may prevent oiling out [26]. In sum, the knowledge of oiling out occurring in pharmaceutical crystallization should be expanded further in scope and depth so as to contribute to successful design of crystallization process units and subsequent purification steps.

Idebenone (6-(10-hydroxydecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone, I_1 in Fig. 1) is an active pharmaceutical ingredient which has been used to treat various cerebral diseases [27]. It has been found that there are two analogous impurities (I_2 and I_3, Fig. 1) in the product sourcing from chemical synthesis. In this work the purification of raw idebenone has been attempted by use of drowning out and cooling crystallization from hexane/methylene chloride mixtures, in which the effect of such parameters as cooling rate, solvent, initial concentration, seeding and addition rate of antisolvent on the oiling out and the purity of products were experimentally investigated. The optical microscopy was used to photograph the oil phases. High performance liquid chromatography (HPLC) was used to analyze the purity of products.

2. Experimental

2.1. Materials

Raw idebenone with a purity of 96.2% (HPLC) was supplied by Lixin Pharmaceutical Company (Suzhou, China). Hexane, methanol and methylene chloride (99.5 wt.%) at an analytical grade were purchased from Sinopharm Chemical Reagent Company (Shanghai, China). Ultra pure water was obtained with a Direct-Q Millipore system (Millipore, Billerica, MA).

2.2. Polarity calculation

The structures of solvents, product and impurities were optimized without constraints by using the density functional theory (DFT) at the HF/6-31G theoretical level, and all calculations were performed by using the Gaussian 03 program package [28].

2.3. Solubility measurements and phase diagram construction

The solubility of recrystallized idebenone was measured in hexane, methylene chloride and their mixtures at various temperatures. Excess powders of idebenone were firstly added to the solvents in a 100-mL jacketed glass crystallizer, of which the temperature was controlled by a RTE-740 Digital Plus refrigerated bath (Thermo Neslab, Newington, NH). After 24 h when the sample had reached equilibrium, the agitation was stopped, and the solution was allowed to settle for 12 h. The supernatant in equilibrium with a macroscopically observable solid was then filtered through Millex-VV 0.1 μm filters (Millipore, Billerica, MA). The concentration of filtered supernatant was determined by use of the dry mass method: about 10 g of the filtered supernatant was withdrawn with a pipette and placed in a sample bottle preweighed by use of a Sartorius CP225D analytical balance (Sartorius, Goettingen, Germany) with a resolution of ±0.01 mg. The sample bottle was then moved into a photophobic Vacucenter VC 20 oven (Salvis-Lab, Rotkreuz, Switzerland) and vacuum-evaporated to dryness at 278.15 K until the mass was constant. The low evaporation temperature was chosen to eliminate decomposition. The solid residue mass was determined, and the concentration was then calculated. All experiments were replicated three times. The data reported in this work are the average of the replicates.

Following the work of Maeda et al. [29], a LLPS phase diagram of idebenone was constructed in the mixture of hexane and methylene chloride with a volumetric ratio of 7:1 by use of cooling crystallization. Firstly various saturated clear solutions were prepared, then they were cooled down at a cooling rate of 0.1 °C/min. The cloudy points were judged by a laser generator (Interlink TS-N, China) generating a laser beam of 660 nm, together with an optical microscope (C3230B, Precision Instruments Company, Shanghai, China) [14].

2.4. Purification through cooling crystallization

The purification experiments were performed in a 200-mL jacketed glass crystallizer of which the temperature was controlled by a Julabo FP 50 programmable circulator (Julabo Labortechnik, Seelbach, Germany). A suspension of the desired amount of raw idebenone was firstly heated to 3 °C above the equilibrium temperature to dissolve all powders. It was then filtered and added to the crystallizer in which temperature was kept at the desired value. When the solution was cooled down to 0 °C, the product was harvested. The cooling rates conducted were 0.05, 0.1, 0.2 and 0.5 °C/min. The volumetric ratios of hexane to methylene chloride used were 7, 8, 9 and 10. Initial solution concentrations employed were 5.61, 4.21, 3.37, 2.81 and 1.68 g/100 g solvent. In some cases, seeding was employed for the purpose of comparison. For all cooling crystallization experiments, the stirring was employed by a Corning PC-353 magnetic stirrer (Corning, NY).

2.5. Purification through drowning out

Drowning out was conducted in the 200-mL jacketed glass crystallizer of which the temperature was kept at 0 °C. Clear solutions of idebenone in methylene chloride at specific concentrations were firstly prepared in the crystallizer, then a certain amount of antisolvent hexane was added to the clear solutions using a peristaltic pump (Gilson, WI). Initial solution concentrations employed were 25.25, 18.94, and 15.15 g/100 g solvent. The hexane was fed at