Journal of Crystal Growth 422 (2015) 44–51

Contents lists available at ScienceDirect

Journal of Crystal Growth

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

Effect of surfactant concentration on nifedipine crystal habit and its related pharmaceutical properties

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ARTICLE INFO

Article history:
Received 20 January 2015
Received in revised form
14 April 2015
Accepted 17 April 2015
Communicated by S.R. Qiu
Available online 28 April 2015

Keywords:
A2. Surfactant
Polysorbate-80
Molecular dynamics study
Solid state
Crystal habit
Wettability
Surface free energy
Nifedipine

ABSTRACT

Crystallization in the presence of Polysorbate-80 (T-80), a non-ionic surfactant was explored for crystal habit modification of nifedipine polymorph I (Nif). A concentration dependent reduction in aspect ratio was observed with T-80. Generation of any new solvates/polymorphs was ruled out by Fourier Transform Infrared spectroscopy, differential scanning calorimetry, powder X-ray diffraction, and thermogravimetric analysis, while the absence of T-80 on the surface or bulk of the recrystallized samples was established by liquid chromatography mass spectroscopy. The dissolution rate order of the recrystallized Nif habits was in the order of; Nif-D (Nif with 0.6%v/v T-80) > Nif-C (Nif with 0.4% v/v T-80) > Nif-B (Nif with 0.2% v/v T-80) > Nif-A (plain Nif). Wetting ability and surface free energy determination from contact angle measurements were used to explain the order of dissolution rate. The consequences of varying concentration of T-80 on Nif crystal habit was supported by means of molecular dynamics (MD) which was executed using COMPASS force field while modified attachment energy was computed to acquire the absolute morphology. The mechanism for alteration in the morphology was suggested based on the computed crystal surface chemistry. Nif-D crystal habit was nearly iso-diametric with majority of facets occupied by polar dominant surfaces {0 1 1} and {0 0 2} which ultimately resulted in higher dissolution rate. In Nif-B and Nif-C the dissolution rate was dependent on the proportion of polar and non-polar facet area. The methodology used in this study could be an influential tool for selection of concentration of habit-modifying additives in other crystallization studies.

1. Introduction

Pharmaceutical material experts usually prefer iso-diametric crystal habits over needle or plates, because of their proven superior pharmaceutical and biopharmaceutical properties [1]. Thus, crystal habit of any active pharmaceutical ingredient (API) is an important factor in pharmaceutical manufacturing [2–4]. It has long been accepted that the presence of crystal habit modifier can have remarkable consequences on the crystal growth rate and subsequently on the crystal appearance or habit, because of the differential interaction of the additive molecules with the facets of the crystal [2,5]. The presence of these additives even at very low concentration, affects the crystallization mechanism which ultimately results in alteration of habit [6]. In recent times, impurities have been intentionally employed as additives for generating desired crystal habit [7].

Molecular dynamics using different simulation models can help in generating crystals of desired morphology and study the molecular events involved. Yang et al. described crystal morphology of *N,N* diacetyl chitobiose as bisphenoidal shape by layer docking method, since BFDH and attachment energy model were not in agreement with the experimental results. Solvent effect was considered by layer docking approach to obtain correlation with experimentally obtained habit [8]. Elaine et al. reported molecular dynamics study to study the influence of solvent and impurity on the crystal habit. They demonstrated the effect of solvent on the habit and its surface roughness, which was responsible for impurity adsorption [9]. Dey et al. and Schmidt and Ulrich. reported the importance of crystal habit and polymorphism on product specification and process development using molecular modelling and other prediction approaches [10,11].

Various reported crystal growth modifiers include cellulose derivatives like hydroxyl propyl methyl cellulose [12], non-ionic surfactants like sorbitan alkyl esters, polysorbates (polyoxyethylene glycol sorbitan alkyl esters generally known as Tweens where

Abbreviations: DCM, dichloromethane; Nif, nifedipine; DSC, differential scanning calorimetry; TGA, thermogravimetric analysis; p-XRD, powder X-ray diffraction.

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http://dx.doi.org/10.1016/j.jcrysgro.2015.04.027
0022-0248/

Tween is a registered trademark of ICI Americas, Inc.)[7], and polyethylene glycols (PEGs) [13]. Surfactants are commonly used in pharmaceutical systems to lower the interfacial tension among the solid particles and the solvent molecules which facilitate wetting [14]. Polysorbate-80 (T-80) is one such surfactant generally used in various pharmaceutical formulations. Besides this, role of T-80 on crystal habit modification has also been studied [7,13]. These surfactants can exhibit specific or non-specific interaction with crystal facets and based on the nature of solvent and additives, they can have different impact on various facets of crystals usually resulting in alteration of habit [15,16].

It is possible to design specific morphology, as these additives can modulate the nucleation and growth rate of specific facets [17,18]. The importance of crystal habit on product development is currently geared towards simulating the solid-state properties using molecular modeling tools [19–22]. A combined modeling and experimental strategy can hence be used for obtaining designed crystals of desired shape [23,24]. In the present investigation, nifedipine (Nif), a potent calcium channel blocker (Fig. 1a), was selected as a model drug for studying the impact of T-80 (Fig. 1b) concentration on crystal habit. Various research groups have reported crystal habit modification with T-80 making comparable interpretations when crystallizing beta-sitosterol [1], carbamazepine [13], erythromycin A dihydrate, however, none of them have fully explored the reasons behind the observed crystal modification [25–27]. Hence, the secondary objective of this study was to investigate the mechanisms responsible for crystal habit altering property of T-80.

Various solid state characterization tools were utilized to examine any solid form change during re-crystallization. Presence of T-80 on the crystal surfaces or inside the crystals was ruled out by liquid chromatography mass spectroscopy (LC–MS). Modified crystals were investigated for their dissolution rate. Contact angle values and various surface energies established differential chemical environment and distribution of surface energetic. Simulation studies were also helpful in understanding the facet dependent properties. Novelty of the present work lies in correlating crystal facet property (anisotropy) to pharmaceutical properties like wetting, surface free energy and dissolution rate. Based on the crystal surface chemistry, the mechanism for the alteration in morphology and its impact on pharmaceutical properties was suggested. It was concluded that T-80, in this case, interacts physically with the different crystal facets resulting in modification of Nif crystal habit.

2. Experimental section

2.1. Materials

Nif was received as a gift sample from Mylan Labs, Hyderabad, India. Polysorbate-80 was purchased from SD Fine chemicals Ltd, India. HPLC grade methanol was purchased from Merck, India. Ethylene Glycol (EG) was obtained from Merck, India whereas diiodomethane (DIM) was purchased from Sigma Aldrich, Germany. All other chemicals used were of analytical grade. In-house ultrapure water from Millipore® was used for all experiments. Amber colored glasswares were used for all experiments and storage.

2.2. Re-crystallization experiments

DCM was selected as a solvent for Nif-crystallization in which it shows good solubility (~150 mg/mL). Slight excess amount of Nif was dissolved in 4 mL of boiling DCM to achieve super-saturation on cooling. T-80 was added to obtain resulting concentrations of 0.2%, 0.4%, and 0.6% v/v. At higher concentrations (0.8% v/v and 1% v/v) T-80 resulted in a viscous medium with a sticky crystal surface, and hence was excluded from further studies. The solutions were filtered into a crystallization vessel and were allowed to cool to obtain super-saturated solutions. The evaporation rate was controlled using an inverted cotton plugged funnel. After 48 h, crystals were collected, dried, weighed and stored in amber colored bottles for further characterization studies. Plain Nif was referred as Nif-A and Nif re-crystallized in 0.2% 0.4% and 0.6% v/v T-80 were referred as Nif-B, Nif-C and Nif-D, respectively.

2.3. Solid state characterization

Crystal habits were observed at different magnifications by inverted microscope (Nikone TiU) operating with NIE software. There particle sizes and aspect ratios were also determined ($n=100$). Fourier Transform Infrared (FTIR) spectra of the samples were recorded from 4000 to 625 cm^{-1} on a PerkinElmer IR spectrophotometer using potassium bromide pellet method. Differential scanning calorimetry (DSC) analysis was carried out using Mettler Toledo DSC system. Indium was used for calibration. The sample cell was purged with dry nitrogen at a flow rate of 40 mL/min. Accurately weighed samples (~5 mg) in aluminum crimped pans were scanned at a heating rate of 10 °C/min over a temperature range of 25–220 °C. Presence of any solvent/degradation during heating was examined by thermo-gravimetric analysis (TGA) (Mettler Toledo), on accurately weighed (5–10 mg) samples loaded in alumina crucibles that were heated at a rate of 10 °C/min over a temperature range of 25 to 300 °C under dry nitrogen purge of 60 mL/min. PXRD patterns of samples were obtained at room temperature on X-ray powder diffractometer (X'Pert Pro PANalytical), using Ni-filtered Cu K_a radiation (wavelength = 1.5406 Å). The data was recorded over a scanning 2θ range of 2° to 50° at step time of 0.045 steps/0.5 s. LC–MS studies were carried out on an Agilent 1200 series LC instrument (Agilent Technologies, USA) attached to a quadrupole time-of-flight (Q-TOF) mass spectrometer (Q-TOF LC/MS 6540 series, Agilent Technologies, USA) coupled with electrospray ionization (ESI). The data was acquired using Mass Hunter workstation software. The typical operating source conditions for MS scan of Nif in positive ESI mode were optimized as follows: the fragmentor voltage was set at 170 V, the capillary at 3500 V, the skimmer at 60 V, and nitrogen was used as a drying (320 °C, 10 L/min) and nebulizing (45 psi) gas.

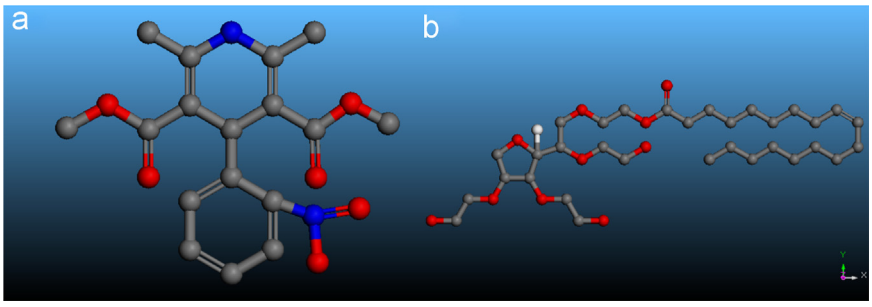

Fig. 1. Chemical structure of a. Nifedipine and b. P-80.