International Journal of Pharmaceutics 460 (2014) 189–195

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Impact of differential surface molecular environment on the interparticulate bonding strength of celecoxib crystal habits

Sameer R. Modi, Kailas S. Khomane, Arvind K. Bansal*

Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Sector-67, S. A. S. Nagar, Mohali, Punjab, India

ARTICLE INFO

Article history:
Received 12 September 2013
Received in revised form 9 October 2013
Accepted 13 October 2013
Available online 20 October 2013

Keywords:
Surface anisotropy
Bonding strength
Compactibility
Crystal habits
Milling
Cleavage plane

ABSTRACT

The present work investigates the impact of milling on differential compactibility behavior of celecoxib (CEL) crystal habits. Plate shaped (CEL-P) crystals showed better compactibility over acicular (CEL-A) crystals. Milling improved the compactibility of both the forms. However, despite similar particle shape, size, and surface area, milled fractions of the two habits showed significantly different interparticulate bonding strength. The greater bonding strength of milled CEL-P (MCEL-P) over milled CEL-A (MCEL-A) was attributed to the differential cleavage behavior of the two habits that conferred the different surface molecular environment to the milled powders. The preferred cleavage of CEL-P across {020} plane exposed the -CF_3 group and the methyl phenyl ring on the surface of MCEL-P. On the other hand, CEL-A preferentially fractured along their shortest axis that increased the exposure of {100} plane on the surface of MCEL-A, which exposed the -CF_3 group and the pyrazole ring. Surface free energy quantified by determining advancing contact angle revealed greater dispersive component of MCEL-P over MCEL-A. This is consistent with the differential cleavage behavior of CEL-P and CEL-A. This confirmed the role of dispersive component of surface free energy in governing interparticulate bonding strength of CEL. The study supports the postulate that tablet tensile strength is governed by the dispersive intermolecular interactions formed over the interparticulate bonding area.

1. Introduction

Structure property relationship helps in designing a quality product. Successful tablet formulation development requires optimum tensile strength. Hence, it is important to understand material attributes that govern the tensile strength. Interparticulate bonding area and bonding strength contribute to the tablet tensile strength (Sun, 2011). Particle level properties like particle shape and particle size distribution are known to influence interparticulate bonding area (Patel et al., 2006).

Interparticulate bonding strength is an inherent material property and is governed by intermolecular interactions (Sun, 2011). Among various bonding mechanism like solid bridge, intermolecular interactions, and mechanical interlocking, intermolecular interactions predominates in pharmaceutical materials (Nystrom et al., 1993). The dispersive (nonpolar) interactions, like van der Waals interactions, are isotropic in nature and are primarily responsible for particle–particle interactions (Derjaguin, 1960; Hiestand, 1997b; Israelachvili and Tabor, 1973). In contrast, polar interactions like hydrogen bonding, being anisotropic (directional) in nature, contribute least as only few atoms near the contact perimeter would have the required spacing and juxtaposition (Hiestand, 1997a). Random particle reorientation during compaction further reduces the probability of these polar interactions.

Recently, our group has reported correlationship between molecular packing density (true density) and interparticulate bonding strength of the pharmaceutical polymorphs (Khomane and Bansal, 2013a,b; Khomane et al., 2012, 2013; Upadhyay et al., 2013). Closed crystal packing (higher true density) offered greater number of isotropic molecular contacts. Few reports also correlated interparticulate bonding strength to the dispersive surface energy (van der Waals forces) of the materials (Chamarthy et al., 2009; Fichtner et al., 2008). Overall, tablet tensile strength is governed by the dispersive intermolecular interactions formed over the interparticulate bonding area.

Present work investigates the impact of milling on compactibility of plate and acicular crystal habit of celecoxib (CEL) form III. The differential cleavage properties of the two crystal habits offered different chemical environment at the particle surface. This enabled us to study the contribution of differential surface

* Corresponding author. Tel.: +91 172 2214682 2126; fax: +91 172 2214692.
E-mail address: akbansal@niper.ac.in (A.K. Bansal).

0378-5173/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ijpharm.2013.10.029

molecular environment to the compactibility and interparticulate bonding strength. Compaction studies were performed using a rotary table press and data was analyzed using compactibility plot.

2. Material and methods

2.1. Material

Form III of CEL was received as a gift from Dr. Reddy's Laboratories Ltd. (Hyderabad, India). The purity of the sample was confirmed to be greater than 99.0% by certificate of analysis provided by Dr. Reddy's Laboratories Ltd. CEL is a BCS class II compound belonging to a novel class of agents that selectively inhibit cyclooxygenase-2 (COX-2) enzymes and has been extensively used in the treatment of osteoarthritis, rheumatoid arthritis (RA), colonic polyps, and management of pain. Toluene (Merck, India), ethylene glycol (EG, Sigma–Aldrich, Germany) and diiodomethane (DIM, Sigma–Aldrich, Steinheim, Germany) were of >99.0% purity. The solvents used were of high-performance liquid chromatography (HPLC) grade.

2.2. Generation of CEL crystal habits and their milled fraction

As reported earlier from our lab, plate and acicular crystals of CEL were generated by controlling the degree of supersaturation and crystallization temperature (Banga et al., 2007; Modi et al., 2013). Accurately weighed amount (about 8 g) of drug was dissolved in 400 mL of toluene by heating to 72 °C. The hot drug solution was immediately filtered into a glass beaker using 0.22 μm nylon filters and cooled to a predetermined temperature, 60 or 25 °C, to achieve a desired degree of supersaturation of 102 and 190%, respectively. The crystals were collected after 72 h by filtration and dried under vacuum at room temperature, sieved through British sieve size (BSS) No. 52 and retained on (BSS) No. 100. Milled fractions of these two crystal habits were obtained using mortar and pestle and sieved through British sieve size (BSS) 400. Henceforth, milled fractions of CEL-P and CEL-A are noted as MCEL-P and MCEL-A. Both the unmilled and milled fractions of the two habits were characterized for their solid state properties.

2.3. Scanning electron microscopy (SEM)

The powder samples were viewed under a scanning electron microscope (S-3400, Hitachi Ltd., Tokyo, Japan) operated at an excitation voltage of 25 kV. The powder samples were mounted onto a steel stage using double sided adhesive tape and sputter coated with gold using ion sputter (E-1010, Hitachi Ltd., Tokyo, Japan), before analysis.

2.4. Particle size distribution (PSD)

The powder samples were observed using optical and polarized light microscope and the diameter (i.e., length along the longest axis of individual particles) of 100 particles was determined under 500× magnification. Cumulative PSD curves were plotted to determine the diameters corresponding to 10, 50, and 90% of cumulative undersize particles, i.e., D_{10}, D_{50}, and D_{90}.

2.5. Specific surface area

Specific surface area of powder samples was determined using nitrogen gas sorption (SMART SORB 91 Surface Area analyzer; Smart Instruments, Mumbai, India). The instrument was calibrated by injecting a known quantity of nitrogen. The measured parameters were then used to calculate the surface area of the sample by employing the adsorption theories of Brunauer, Emmett, and Teller (BET). An accurately weighed amount of sample was placed into the glass loop of the instrument and then submerged into liquid nitrogen. The quantity of the adsorbed gas was measured using thermal conductivity detector and then integrated using electronic circuit. The reported values were average of three measurements.

2.6. True density

The true density of powder samples was determined in triplicate by helium pycnometry (Pycno 30, Smart Instruments, Mumbai, India) at 25 ± 2 °C and 40 ± 5% RH.

2.7. Differential scanning calorimetry (DSC)

Conventional DSC experiments were conducted to determine melting point and heat of fusion using DSC Q2000 (TA Instruments, Delware, USA) equipped with a refrigerated cooling system and operating with Universal Analysis 2000 software (version 4.5A). About 3–5 mg of each form was accurately weighed in crimped aluminium pans and subjected to the thermal scan from 35 to 200 °C at the heating rate of 10.0 °C min^{-1}. Dry nitrogen purge was maintained at 50 mL min^{-1}. The DSC instrument was pre-calibrated for temperature and heat flow using high purity indium. All measurements were performed in triplicate.

2.8. Thermogravimetric analysis (TGA)

Presence of solvent, moisture or any degradation during heating was examined using Mettler Toledo 851^e TGA/SDTA (Mettler Toledo, Switzerland) operating with Star^e software (version Solaris 2.5.1). Accurately weighed (5–10 mg) samples were loaded in alumina crucibles and heated at a rate of 20 °C min^{-1} over a temperature range of 35–200 °C, under nitrogen purge (50 mL min^{-1}), to determine loss in weight.

2.9. Powder X-ray diffraction (PXRD)

PXRD of powder samples was recorded at room temperature on Bruker's D8 advance diffractometer (Bruker AXS, Karlsruhe, Germany) with Cu Kα radiation (1.54 Å), at 40 kV, 40 mA passing through nickel filter. Accurately weighed amount of powder (about 300 mg) was loaded in a 25 mm poly-methyl methacrylate (PMMA) holder and gently pressed by a clean glass slide to ensure coplanarity of the powder surface with the surface of the holder. Analysis was performed in a continuous mode with a step size of 0.01° and step time of 1 s over a 2θ angular range of 3–40°. Obtained diffractograms were analyzed with DIFFRAC plus EVA, version 9.0 (Bruker AXS, Karlsruhe, Germany) diffraction software.

2.10. Tableting

Rotary tablet press (Mini II, Rimek, Ahmedabad, India) was equipped at one of the 8 stations with 8 mm D-tooling with flat punch tip. Pre-compression rollers were set out of function. Tablets of each powder sample were compressed at constant volume. Humidity (40 ± 2% RH) and temperature (25 ± 2 °C) conditions were monitored throughout the study. Tablet weight was kept at 200 ± 5 mg, and applied force was leveled by moving the pressure roller with a hand wheel. The tableting speed was kept constant at 5 rpm. Poor flow behavior of CEL powders could not allow the use of instrumented tablet press, as force-displacement data could not be obtained at very low speed. The range of tablet porosities studied for the four types of crystals was limited due to poor compactibility of the materials. At higher porosity, compacts were not formed. On