European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 83–89

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Modelling of molecular phase transitions in pharmaceutical inhalation compounds: An *in silico* approach

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ARTICLE INFO

Article history:
Received 23 June 2010
Accepted in revised form 13 December 2010
Available online 21 December 2010

Keywords:
Amorphous
Beclomethasone dipropionate
Glass transition temperature
Molecular dynamic simulations

ABSTRACT

Molecular dynamic simulations have been successfully utilised with molecular modelling to estimate the glass transition temperature (T_g) of polymers. In this paper, we use a similar approach to predict the T_g of a small pharmaceutical molecule, beclomethasone dipropionate (BDP). Amorphous beclomethasone dipropionate was prepared by spray-drying. The amorphous nature of the spray-dried material was confirmed with scanning electron microscopy, differential scanning calorimetry (DSC) and X-ray powder diffraction (XRD). Molecular models for amorphous BDP were constructed using the amorphous cell module in Discovery studio™. These models were used in a series of molecular dynamic simulations to predict the glass transition temperature. The T_g of BDP was determined by isothermal-isobaric molecular dynamic simulations, and different thermodynamic parameters were obtained in the temperature range of −150 to 400 °C. The discontinuity at a specific temperature in the plot of temperature versus amorphous cell volume (V) and density (ρ) was considered to be the simulated T_g. The predicted T_g from four different simulation runs was 63.8 °C ± 2.7 °C. The thermal properties of amorphous BDP were experimentally determined by DSC and the experimental T_g was found to be ~65 °C, in good agreement with computational simulations.

1. Introduction

One of the most important properties of an active pharmaceutical ingredient (API) is the polymorphic form, since it directly affects both formulation and drug bioavailability (i.e. Young's modulus, surface energy, heats of dissolution and solubility). Subsequently, a fundamental understanding of long-range molecular structure is required if we are to make informed decisions during the drug development pipeline. While 'polymorphic form' generally relates to long-range crystal structures, amorphous materials may also be included under this definition and are indeed defined as such in ICH guideline Q6a. The term amorphous generally refers to non-crystalline solids that are disordered (characterised by randomness in their molecular conformation and lack of long-range three-dimensional (3D) orientational symmetry). Interestingly, amorphous solids retain some short-range molecular order which can be similar to that found in crystalline materials [1]. In recent years, amorphous materials have been used due to their substantial solubility advantage and rapid dissolution rate when compared with the corresponding crystalline material [2–4]. However, many concerns, primarily related to stability, arise when using amorphous materials; these include increased chemical instability often as a result of greater hygroscopicity, altered mechanical properties and the possibility of relaxation and/or crystallization during storage [5,6].

The glass transition temperature (T_g) is a characteristic property of amorphous materials [7]. The T_g is the temperature at which an amorphous material changes from a super-cooled liquid with a relatively high viscosity (glass) state to a lower density, lower viscosity (rubbery) state [8]. The T_g is associated with extensive changes in a material's thermodynamic properties such as volume, enthalpy, entropy and heat capacity, and it is characterised by a significant change in molecular motion [8]. At low temperatures, below the T_g, molecular motions are highly restricted to vibrational and short-range rotational motion. As the temperature is increased above the T_g, the molecules become more 'flexible' and mobile resulting in large-scale configurational modification. Subsequently, this increase in molecular mobility above the T_g results in an increase in the volume as a function of temperature [8]. In any particular phase, at equilibrium, the thermodynamic parameters (volume (V), density (ρ), and heat capacity (C_p)) will change relative to temperature. However, as the substance transfers from one phase equilibrium to another, a discontinuity is observed in these parameters, resulting in a different parameter relationship with respect to temperature. For amorphous materials, a plot of

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doi:10.1016/j.ejpb.2010.12.019

volume or density verses temperature will result in two distinct curves with the intercept being equivalent to the T_g [8,9]. It is important to note, however, that this transition does not involve discontinuous changes in any physical property and thus is not classified as a true phase transition [9]. This phenomenon is illustrated in Fig. 1, where the T_g value usually occurs at around 2/3 of the melting point (T_m) in Kelvin [3,10].

Clearly, an understanding of molecular interaction and 'phase transitions' in API molecules is of great importance to the pharmaceutical sector, since unpredictable changes in a particular solid could result in serious medical implications (i.e. sudden change in bioavailability and formulation failure). Previous studies and theories have generally been empirical in nature; however, with the advancement in high-end computing, the potential to predict and model these phenomena using molecular dynamics (MD) simulation becomes possible. To the authors' knowledge, the application of MD to study phase transitions in small molecule APIs has not been conducted to-date. However, utilising this concept, previous MD simulations have been used to study the T_g of macromolecule polymers with some degree of success [11–18].

This study used MD simulation to model the molecular interactions between a model API, beclomethasone dipropionate, at a range of temperatures. Furthermore, we evaluated the MD approach as a method for determining pharmaceutically relevant physico-chemical parameters. Finally, this approach was correlated with experimentally determined thermal responses using differential scanning calorimetry (DSC) [19].

Beclomethasone dipropionate was chosen as a model drug, since it is an anti-inflammatory corticosteroid for the treatment of chronic asthma [20,21]. In inhalation formulations, the drug must be manufactured with a size conducive to respiratory deposition (i.e. <5 μm). At this scale, the polymorphic form and amorphous stability becomes critical, since small changes in phase will result in highly unpredictable formulation outcomes [22–24].

2. Materials and methods

2.1. Material preparation

Crystalline beclomethasone dipropionate (BDP) was obtained from JAI RADHE SALES (Ahmedabad, India), and analytical grade ethanol was obtained from Biolab (Clayton, Victoria, Australia). Amorphous BDP was obtained by spray drying the supplied BDP from 20% w/v solution in ethanol using a BÜCHI Mini B-290 spray dryer (Flawil, Postfach, Switzerland). Spray drying was conducted using the following settings: feed rate 10 mL min^{-1}, aspiration rate of 100 m^3 h^{-1}, inlet temperatures 60 °C, outlet temperature 38 °C and atomizing pressure 800 kPa. All samples were stored in sealed containers containing silica for a minimum of 48 h prior to use.

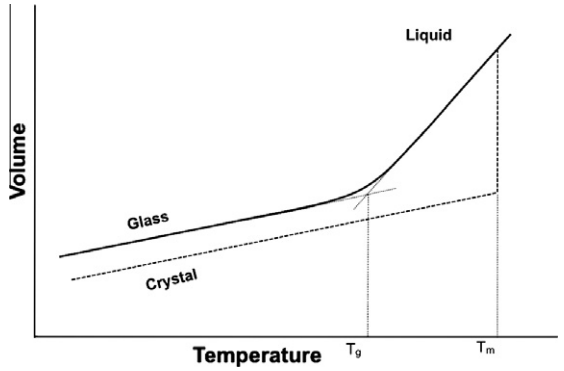

Fig. 1. The relationship between volume and temperature in the liquid, glassy and crystalline states. T_m is the melting temperature, and T_g is the glass transition temperatures.

2.2. Material characterisation

The morphology of the spray-dried amorphous BDP particles was investigated using a scanning electron microscope (SEM) (JEOL 6000F, Japan) at 5 kV. The sample was mounted on adhesive black carbon and sputter-coated with platinum (Sputter coater S150B, Edwards High Vacuum, Sussex, UK) at 40 nm thickness prior to imaging. Amorphous structure was characterised using X-ray powder diffraction (XRD Siemens D5000 diffractometer, Siemens, Karlsruhe, Germany) at a scan range of 5–65°2θ, with step size of 0.05°2θ and a count time of 2 s. The thermal response of the spray-dried amorphous BDP was analysed using a DSC (DSC 823^e, METTLER TOLEDO International Inc.). Samples (ca. 5–8 mg) were crimp-sealed in aluminium sample pans and the lids pierced (to ensure all measurements were conducted under constant pressure). Experiments were conducted at heating rates of 10 and 20 °C min^{-1} over a temperature ramp of 20–280 °C. All DSC measurements were conducted in an inert environment under a nitrogen stream (25 cm^3 min^{-1}). The instrument was calibrated for heat-flow and temperature with a standard indium sample prior to use.

2.3. Computational methodology

Amorphous cell structure prediction and molecular dynamics simulations were performed using Material Studio™ 4.4 (Accelrys Software Inc., San Diego, CA, USA) in a Windows environment. Three-dimensional structural presentations were generated using the Amorphous Cell Module by randomly repeating BDP molecules to a set density within an imaginary cell volume. Initially, two molecules, with the same orientation found in the crystal structure (Fig. 2) [25], were selected and were considered to be the constituent unit for the construction of the amorphous structure. 10, 20 and 30 repeat units (of the two molecules) were used and the three runs yielded amorphous structures containing 20, 40 and 60 BDP molecules, respectively. In subsequent runs, only a single molecule was used with 10, 20 and 30 repeat units (i.e. BPP molecules) being packed into the constructed amorphous cells.

The 3D periodic amorphous cell structures were constructed using an initial density of crystalline BDP (1.36 g cm^{-3} at 298 K) [25]. Twenty amorphous configurations were built during each run using the default construction algorithms. The 3D periodic system parameters were automatically calculated for each run from the number of units used to construct the cell and the target density assuming a cubic cell. A cubic cell was used since previous studies have suggested a cell with equal side lengths is believed to be the optimum shape for calculation, since it would maximize the distance between repeated units in a supercell [26].

Each configuration was minimized using the Discover simulation program. The minimizations were performed under the canonical, NVT, ensemble and were carried out using the Conjugate Gradient method with 1000 dynamic steps and 100 minimization steps. Convergence was set at 0.01 kcal mol^{-1} $Å^{-1}$. The minimized amorphous cell structures from the different runs were visually inspected, and the amorphous cell structures of the single molecule with 30 repeat units were selected for subsequent steps. Of the twenty structures generated from these runs, two with low and medium solvent surface free volume were selected and further optimized. Surface free volume and other properties were calculated with the Models table analysis dialog in Material studio. The geometry of the two selected structures were further optimized using the Forcite Geometry Optimization module with the following settings: COMPASS (Condensed-phase Optimized