Thermochimica Acta 577 (2014) 53–58

Contents lists available at ScienceDirect

Thermochimica Acta

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

Effect of excipient porosity on the melting behavior of imbibed frozen liquids

A. Khairuzzaman[a], S.U. Ahmed[b], A. Higuera[c], R.A. Bellantone[d,*]

[a] Food and Drug Administration, Center for Drug Evaluation and Research, 10903 New Hampshire Avenue, Silver Spring, MD 20993, United States
[b] Abon Pharmaceuticals LLC, 140 Legrand Avenue, Northvale, NJ 07647, United States
[c] OSI Pharmaceuticals, 1 Bioscience Park Drive, Farmingdale, NY 11735, United States
[d] Division of Pharmaceutical Sciences, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, 75 Dekalb Avenue, Brooklyn, NY 11201, United States

ARTICLE INFO

Article history:
Received 16 October 2013
Received in revised form
13 December 2013
Accepted 18 December 2013
Available online 26 December 2013

Keywords:
Differential scanning calorimetry
Melting point depression
Gibbs–Thompson equation
Imbibed liquids

ABSTRACT

The effect of excipient porosity on melting point depression of confined fluids was investigated. Two grades of the pharmaceutical excipient silicon dioxide, Syloid 244 FP and Syloid 74 Regular, were used as model porous excipients. The pore size distribution for each was characterized by nitrogen gas adsorption. The excipient pores were loaded with two liquids, water and cyclohexane, which were allowed to imbibe into the pores. The loaded excipients were then subjected to thermal analysis by cooling then heating, and the melting behavior of the imbibed frozen material was evaluated using differential scanning calorimetry (DSC). A mathematical model for the observed DSC thermograms was developed from the Gibbs–Thompson equation, which was used to relate the melting point depression of materials to the local curvature and the local surface energy per volume of imbibed material inside the pores. In all cases, two distinct melt behaviors were seen. One was a melt peak near the nominal melting temperature, corresponding to frozen fluids outside the pores. The other was a secondary satellite endotherm, which showed a melting point depression that occurred over a broad temperature range that was distinctly below the nominal melting temperature. This satellite endotherm was attributed to melting of the imbibed material in the pores, and the model equations were fit to the experimental DSC data. The local surface energies per volume of imbibed material were calculated for each case. These corresponded to apparent interfacial tensions between the imbibed material and the Syloid pore walls of 58–71 mJ/m^2 for water and 13 mJ/m^2 for cyclohexane. The data show that the excipient porosity can cause remarkable melting point depression, and the results of the modeling suggested that this analytical technique may represent a novel approach to assess the impact of surface area on small particles.

1. Introduction

Pharmaceutical solid materials often contain pores that can influence the properties and behavior of formulations. These effects can include drug release profiles and dissolution [1–4], water penetration into tablet pores [5], drug adsorption and deposition [6,7], and mechanical properties [8]. Studies have also shown that intragranular porosity has been related to mechanical properties and drug release profiles [9,10].

In general, the pore size distribution provides information on the diameter and volume distributions. Most commonly, these are determined by gas adsorption and mercury porosimetry. Models have been proposed to determine of pore size distributions in adsorbent material using thermal methods such as thermoporometry, which is based on the principle of the freezing point depression resulting from the curvature of the solid–liquid interface present within the pores [11]. Thus, differential scanning calorimeter (DSC) might serve as an alternative method for measuring porosity if a relationship between the pore diameter and the melting transition can be constructed. Attempts to accomplish such analysis using DSC have been made based on empirical approaches [11–14]. Conversely, if such a relationship can be described, it would be possible to predict the effects of pore structures on melting behaviors of confined materials in pores.

An important geometric aspect associated with small pores is that the surface to volume ratio for any short segment of a pore is very large. This results in the thermodynamic consequence that, for a volume of material in a pore “segment” with a small enough local radius, the surface/interfacial energy of a confined liquid becomes significant compared to energies associated with bulk properties (such as the heat of melting). Thus, solid materials

---

* Corresponding author. Tel.: +1 718 780 4154; fax: +1 718 780 4586.
E-mail address: rbellant@liu.edu (R.A. Bellantone).

0040-6031/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.tca.2013.12.013

contained in small pores will exhibit significantly differences in melting behavior than when in larger volumes and bulk forms. Specifically, smaller radii lead to lower melting temperatures [15].

Based on the above discussions, it is anticipated that thermodynamic models used to predict the melting depression associated with small pore radii can be used to predict and/or interpret thermal analysis data characterizing the melting of solids confined in small pores.

In this paper, a model is presented to relate pore size effects to observed differential scanning calorimetry (DSC) melting data for water and cyclohexane frozen in the pores of two grades of silicon dioxide (Syloid 244 FP and Syloid 74 Regular). Thermograms are presented and the model equations were fit to the data. The results of the fits were used to calculate the ratio of the surface interfacial energy to the heat of melting per volume as a function of the pore size.

2. Experimental procedure

2.1. Materials

The model porous pharmaceutical excipients, Syloid 244 FP and Syloid 74 Regular, were obtained from Grace Davidson (Columbia, MD). Cyclohexane was obtained from Sigma Chemical Co. (St. Louis, MO). Purified water, USP was made using a water purification system (Millipore Corp. Bedford, MA).

2.2. Methods

2.2.1. Determination of porosity by nitrogen gas adsorption

The pore size distribution of each grade of Syloid was determined by gas adsorption technology using an ASAP-2020 Accelerated Surface Area and Porosimetry Analyzer with ASAP-2020 v1.04 software (Micromeritics Instrument Corp., Norcross, GA). For these experiments, the sample size ranged from 0.5 to 1.0 g. Each sample was contained in an evacuated sample tube, cooled to a cryogenic temperature, and then exposed to an analysis gas at a series of precisely controlled pressures. Before starting an experiment, the sample was degassed for 8 h at 60 °C to remove previously adsorbed gas molecules from the surface and pores. The adsorptive gas used was nitrogen, the analysis temperature was 77.3 K, and a pressure range of 1–760 mmHg was used. The pore size distributions were obtained using a BJH analysis [16] and reported as pore volume (cm^3/g) vs. pore diameter.

2.2.2. Syloid-solvent matrix preparation

An accurate weighed quantity of each grade of Syloid was placed in a clean glass container. Water or cyclohexane was added in small increments to the Syloid until an even paste with a slight excess of liquid was formed. The excipient fraction in each DSC sample was not determined in order to avoid altering the sample. After that, the mixture was kept in a tightly closed glass container for 24 h to reach equilibrium.

2.2.3. Differential scanning calorimetry measurements (DSC)

DSC was performed using a Q1000 series Tzero™ DSC with autosampler and nitrogen refrigerating system (TA Instrument, Wilmington, DE) that was controlled using TA Advantage software. Nitrogen was employed as the purge gas to maintain a stable temperature environment and prevent water condensation. The sample size for each DSC study ranged from 1 to 6 mg, using a hermetic aluminum pan specially designed for volatile and liquid preparations of 40 μL capacity (TA parts 900,793.901 for pans and 900,794.901 for lids). Samples were accurately weighed using a Sartorius GC503 analytical balance.

DSC was done for water-Syloid systems as follows. (1) Samples were allowed to stand at 6 °C for at least 10 min; (2) samples were cooled at 1 °C per min to −25 °C; (3) samples were held isothermally at −25 °C for 7 min; (4) samples were heated at 0.25 °C per min to 8–10 °C. A similar procedure was followed for cyclohexane-Syloid systems, except the starting and ending temperatures were approximately 15 °C, because the melting temperature of frozen cyclohexane was approximately 6 °C.

The DSC data were analyzed using the TA Universal Analysis software to determine transition enthalpies, peak heights, and specific heats. Raw data (power vs. time) were exported to an ASCII text file and imported into MS Excel to perform additional analyses not available in the Universal Analysis software.

3. Model relating thermal analysis data and pore size distribution

Confining frozen liquids in small pores alters the observed melting behavior, lowering the melting temperatures below the nominal bulk melting point. This has been modeled as resulting from increased surface to volume ratios, for which the surface energy becomes significant compared to the bulk enthalpy of melting. For material confined in a cylindrical pore of radius r, the melting temperature can be calculated using the Gibbs–Thompson equation [15]. For small relative changes in melting temperature, this is given by

$$T - T_0 = -\frac{2\Delta\gamma T_0}{\Delta h_M^* \rho_S r} \tag{1}$$

where T_0 is the nominal melting temperature of the frozen bulk form, T is the melting temperature of the frozen form confined in the pore, ρ_S is the density of the confined solid form, $\Delta\gamma$ is the difference in interfacial tension due to melting (liquid confined material with pore wall minus solid confined material with pore wall), and Δh_M^* is the heat of melting per gram of confined material.

Eq. (1) applies to for the case of cylinders with smooth walls. However, it is likely that the cylinders are imperfect and the walls are not smooth, which will affect the contact area per volume between the pore walls and confined material, and possibly $\Delta\gamma$ as well. Thus, we replace the factor $2\Delta\gamma$ by a parameter b and rewrite in Eq. (1) as

$$T - T_0 = -\frac{bT_0}{\Delta h_M^* \rho_S r} \tag{2}$$

Physically, b/r represents the local surface energy per volume element, while $\Delta h_M^* \rho_S$ represents the local energy per volume required to break up the solid structure of the confined material. The factor b is not known a priori, but can be obtained from thermal analysis data as discussed below.

The pore size distribution data can be used to construct a volume distribution function $f_V(r)$, which gives the contribution to the total pore volume (per gram of excipient) from pores with radii from r to $r + dr$ as

$$dV(r, r + dr) = f_V(r)\,dr \tag{3}$$

In practice, $f_V(r)$ is determined from porosimetry data by dividing the incremental pore volume in each radius range by the magnitude of the radius range, and plotting the quotient at the midpoint of the radius range. Interpolations can be done by curve fitting with appropriate simple functions to construct a continuous form for $f_V(r)$, subject to the condition that $\int f_V(r)\,dr$ over the entire range of pore sizes equals the total cumulative pore volume per gram of excipient. In this study, the pore radii were expressed in nm, and the units of $f_V(r)$ in cm^3/g/nm. Fig. 1 shows examples for Syloid 244 and Syloid 74.