International Journal of Pharmaceutics 422 (2012) 220–228

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

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

An investigation into water interactions with amorphous and milled salbutamol sulphate: The development of predictive models for uptake and recrystallization

Louise C. Grisedale[a], Peter S. Belton[a], Matthew J. Jamieson[b], Susan A. Barker[a], Duncan Q.M. Craig[a,*]

[a] School of Pharmacy, University of East Anglia, Earlham Road, Norwich, Norfolk NR4 7TJ, UK
[b] Physical Properties, Analytical Sciences, GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK

ARTICLE INFO

Article history:
Received 16 August 2011
Received in revised form 26 October 2011
Accepted 29 October 2011
Available online 10 November 2011

Keywords:
Calorimetry
Glass transition
Crystallization
Salbutamol sulphate
Thermal analysis
Plasticizer

ABSTRACT

An investigation into the effect of water uptake on the glass transition of spray dried and milled salbutamol sulphate has been performed, with a particular view to exploring how the water uptake, T_g value and recrystallization behaviour correlate. Samples of milled and spray dried drug were stored under controlled humidity conditions and the T_g measured as a function of time. The T_g was measured using modulated temperature differential scanning calorimetry (MTDSC) while the water content was measured using thermogravimetric analysis (TGA). A correlation was found between time of storage, water content and T_g in that the samples showed time dependent equilibration with the storage environment (either gaining or losing water depending on the RH). The relationship between water content and stability, based on the concept of T_g lowering, was modelled using the semi-empirical approach of Royall et al. (1999) as well as a derivation of the Kwei equation which allowed the interaction between the water and substrate to be accounted for. A method for predicting stability based on two simple DSC runs is proposed. In addition, we discuss the observation of a double glass transition for the spray dried samples.

1. Introduction

The importance and nature of the effect of water on amorphous materials has been extensively studied and is one of the key parameters that has to be considered when formulating amorphous products (Ahlneck and Zografi, 1990; Hancock and Zografi, 1994; Royall et al., 1999; Abdul-Fattah et al., 2007). In brief, water acts as a plasticizing agent, leading to a concentration-dependent reduction in T_g. The precise mechanism involved remains a matter of some debate, but the predominant theory involves consideration of the observation that the majority of (polymeric) amorphous systems have very similar viscosities at T_g (circa 10^{12} Pa s), leading to development of the free volume theory which essentially states that the glass transition occurs when a material has a specific fractional free volume (Aharoni, 1998). On addition of a plasticizer, not only is a material with a lower T_g being introduced but also the presence of the smaller molecule increases the free volume of the system, thereby both lowering the temperature at which that free volume equates to the critical value while also increasing the flexibility of the material as a result of the increased volume available for movement of the substrate molecules. It should be noted that alternative approaches to the interpretation of the glass transition (and hence by implication mechanism of plasticization) are available, particularly relating to the molecular interactions measured via cohesive energy density calculations which allow molecular flexibility to be assessed. More details of the theoretical background of plasticization may be found in Kern Sears and Darby (1982) and Marcilla and Beltran (2004).

As crystallization is greatly accelerated above T_g, this lowering may transform a stable product to one that is highly susceptible to physical (and quite possibly chemical) instability. From a pharmaceutical development perspective, therefore, water sorption from prolonged exposure to atmospheric water vapour poses a major formulation challenge (Ahlneck and Alderborn, 1989). As amorphous drugs and excipients are increasingly being considered as principal components of pharmaceutical formulations it follows that strategies to anticipate and understand the molecular events underlying their physical and chemical stability need to be developed.

Numerous studies have examined the relationship between water content and T_g, with the majority utilising the well known Gordon–Taylor equation as a means of modelling the relationship (Gordon and Taylor, 1952). The common assumption is that when the T_g is lowered to the temperature of study, the increased molecular mobility afforded by the transition allows recrystallization to occur. This has been supported by numerous studies, although the relationship between T_g lowering and the subsequent crystallization process do not appear to be a simple one. There may, for

---

* Corresponding author. Tel.: +44 1603 592023; fax: +44 1603 592015.
E-mail address: d.craig@uea.ac.uk (D.Q.M. Craig).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.10.055

example, be significant delays between the T_g being lowered to that of the experiment and the crystallization process commencing, or indeed, crystallization may commence prior to T_g being reached (i.e. crystallization may commence below T_g) (Yoshioka et al., 1994; Surana et al., 2004). A further, associated complication lies in the use of recrystallization processes as a means of assessing the degree of crystallinity. Techniques such as gravimetric vapour sorption, microcalorimetry and some DSC-based approaches all rely on the plasticization/crystallization process for quantification of amorphous material, usually in comparison to a 100% amorphous standard. There is a significant question as to whether such crystallization, either for the sample or the standard, runs to completion or not, with several studies showing compelling evidence that it may not (Lefort et al., 2004; Qi et al., 2010; Grisedale et al., 2011). Overall, therefore, there is a common and well supported consensus that the lowering of T_g may well lead to stability issues and hence should be avoided in most cases. However the precise nature of the relationship between water uptake, T_g lowering and sample crystallization remains less well understood than may be ideally desirable.

In a previous study (Grisedale et al., 2011) we examined the effects of milling on the structure and behaviour of salbutamol sulphate, with particular emphasis on ascertaining the most appropriate means of quantifying the amorphous content and examining the use of spray dried material as a standard by which to compare the milled systems. In the current investigation, we examine the long term storage uptake of water into milled and spray dried material in terms of the lowering of T_g and associated recrystallization behaviour. In particular we examine how the long term stability may be predicted from rudimentary short term experiments via the development of the model based on earlier work by Royall et al. (1999). As a supplementary issue, we also discuss the observation of a double glass transition for the spray dried material.

2. Materials and methods

2.1. Materials

Crystalline salbutamol sulphate was used as received (GSK; Stevenage, UK). The spray dried sample was prepared from a 10% aqueous crystalline salbutamol sulphate solution spray dried in a Büchi 290 Mini-Spray Dryer as described by Grisedale et al. (2011). The milled samples were prepared using a Planetary Micro Mill “Pulverisette 7” at a rotational speed of 800 rpm for 60 min. Previous studies (Grisedale et al., 2011) indicated that these samples had an amorphous content of circa 65–70%, although this communication compared numerous methods of making that assessment and found considerable variations in outcome between approaches.

2.2. Storage and water uptake studies

The storage studies were conducted at 20 °C. Airtight Kilner jars with enclosed drying agent (phosphorus pentoxide) and saturated salt solutions (magnesium chloride and sodium dichromate) were prepared as humidity chambers. Separate chambers were prepared for each testing point to prevent the disruption of equilibrium within the chamber owing to the continual opening and closing. All chambers were allowed 48 h to equilibrate before the samples were added. The relative humidity was measured using a hygrometer placed in the chamber, and the temperature checked daily. The nominal RH values were 0% (phosphorous pentoxide), 33% (magnesium chloride) and 54% (sodium dichromate); hygrometer readings were slightly higher than these values, possibly because of the slight temperature difference between the storage temperature (20 °C) and the temperature associated with the predicted RH environments (25 °C); the nominal values are used for simplicity. The samples were tested from 1 to 28 days; testing was ceased if a sample recrystallized before the end of the storage period. For studies whereby the water content and T_g were modelled, the spray drying conditions were varied to allow production of material with varying initial water contents. More specifically, a range of combinations of inlet temperatures from 100 to 160 °C was used to generate material with water contents between 1 and 4% w/w.

2.3. Analytical methods

Thermogravimetric analysis (TGA; TA Instruments Hi-Res TGA2950, Delaware, US) was used to determine the changes in the water content of the samples during the storage study. Immediately on removal from the humidity chambers, approximately 3–4 mg of the sample was placed in open pan and heated at 10 °C min^{-1} from 30 °C to 200 °C. The plateau region reached prior to decomposition (typically between 100 and 120 °C) was taken as the water loss. Towards the end of the study, Karl Fischer analysis became available and comparisons between the two methods indicated that the KF method yielded slightly higher results. However the TGA method used here was utilised in a consistent manner and hence the data used in the study is considered to be reliable.

Modulated temperature DSC (Q1000, TA Instruments, Delaware, US) experiments were used during the study to determine the temperature and the change in heat capacity of the glass transition of the samples. Hermetically sealed DSC pans and lids were used to encapsulate the samples as the water content of the samples was of interest. The samples were heated from 0 to 200 °C with an underlying heating rate of 2 °C min^{-1} and modulation amplitude of ±0.212 °C every 40 s. Temperature calibration was performed using indium, benzoic acid and n-octadecane, while heat capacity calibration was performed using dried aluminium oxide.

ATR-FTIR spectrometry (Bruker Optics IFS66/S spectrometer (Coventry, UK) with a Golden Gate MkII Accessory from Specac Ltd. (Orpington, UK)) was used as a qualitative technique to confirm the recrystallization of the samples during the storage study. Spectra were collected from the region 4000 to 400 cm^{-1} with 200 scans at a resolution of 8 cm^{-1}. Scanning electron microscopy (SEM; Jeol JSM5900LV SEM and a Quorum carbon coater) was also used at selected testing points during the study to observe changes in morphology of the samples on recrystallization.

3. Results

3.1. Storage studies

3.1.1. Storage study at 0% relative humidity

Tables 1a and 1b summarise the data for the spray dried and milled samples respectively, including the water contents, the glass transition values determined from the MTDSC reversing heat flow signal and the baseline change in heat capacity (ΔC_p) determined from the reversing heat capacity signal, while Fig. 1a and b shows the reversing heat flow for the fresh and stored spray dried and milled samples respectively. In both cases, an increase in T_g is seen, indicating a loss of water on storage. It is also noted that, as previously reported (Grisedale et al., 2011), the spray dried samples showed clear separation of the T_g and the non-isothermal recrystallization event (seen as a sharp discontinuity in the reversing heat flow profile) while the milled samples recrystallized immediately following the T_g. For the spray dried sample, two glass transitions were visible in the reversing heat flow signal throughout the storage study. The observation of double glass transitions in this sample has been previously reported (Grisedale et al., 2011) and is discussed in more detail in Appendix A; for simplicity, discussion of