International Journal of Pharmaceutics 514 (2016) 282–289

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Laser irradiation to produce amorphous pharmaceuticals

Varin Titapiwatanakun, Junlathip Tankul, Abdul W. Basit, Simon Gaisford*

UCL School of Pharmacy, University College London, 29-39 Brunswick Square, London, WC1N 1AX, UK

ARTICLE INFO

Article history:
Received 29 April 2016
Received in revised form 14 June 2016
Accepted 16 June 2016

Keywords:
CO_2 laser
Phase-transformation
Indomethacin
Paracetamol
PVP K30
Amorphous
Solid amorphous dispersion

ABSTRACT

Using a high-power CO_2 laser to irradiate powder beds, it was possible to induce phase transformation to the amorphous state. Irradiation of a model drug, indometacin, resulted in formation of a glass. Varying the settings of the laser (power and raster speed) was shown to change the physicochemical properties of the glasses produced and all irradiated glasses were found to be more stable than a reference glass produced by melt-quenching. Irradiation of a powder blend of paracetamol and polyvinylpyrrolidone K30 was found to produce a solid amorphous dispersion. The results suggest that laser-irradiation might be a useful method for making amorphous pharmaceuticals.

1. Introduction

The limiting factor controlling bioavailability of many actives delivered via the oral route is solubility. When an active is formulated in the stable crystalline form, solubility and dissolution rate are minimised. Poor bioavailability might be overcome by formulating the active in a metastable crystal form, although care must be taken when using this formulation strategy to ensure there is no conversion to the stable polymorph during storage. If the metastable form also does not have acceptable solubility then formulation in the amorphous state may be necessary. In cases where the drug itself is a good glass former, no excipients are necessary to stabilise the amorphous form, but for other drugs incorporation into a polymeric matrix to form a solid amorphous dispersion may be necessary.

It follows that methods that may result in phase transformation to an amorphous state will always be important, either for evaluation purposes during preformulation or for large-scale manufacture. Several methods are well known to produce amorphous materials; for instance, spray-drying, freeze-drying, melt-extrusion or melt quenching. Spray-drying requires the compound to have appreciable solubility in a suitable solvent (which is typically organic, because of the low aqueous solubility) while melt quenching requires the compound to be stable upon melting and also requires handling of cryogenic liquids, typically liquid nitrogen. Neither freeze-drying or quench-cooling are particularly suited to large-scale manufacture, although freeze-frying is used to prepare thermally-labile compounds, such as proteins, commercially. Melt-extrusion is widely use to prepare drug-polymer blends but cannot general be used to prepare amorphous samples of pure, low molecular weight compounds.

In principle, any method that can rapidly heat a material above its melt and then quench cool has the potential to cause transformation to an amorphous matrix. Since a laser is a high-energy power source, we wondered whether irradiating a sample with a laser, in this case a carbon dioxide (CO_2) laser, might be an effective approach. CO_2 lasers have many applications in the medical (tissue ablation) (Landthaler et al., 2004) and chemical (fabrication of microfluidic arrays, Prakash and Kumar, 2015) fields and we have recently shown that they can cause phase transformations in binary powder blends to produce co-crystals (Titapiwatanakun et al., 2016). In that work we posited that the laser supplied sufficient energy to the powder blend to raise the temperature above the melting point and the compounds mixed and recrystallised in a co-crystal lattice. However, the technique appeared to require that the compounds sublimed to an appreciable extent for molecular rearrangement to occur, suggesting molecular mixing occurred primarily in the vapour phase. The possibility, explored in this work, is that for other compounds molecular rearrangement cannot occur sufficiently rapidly, either during the heat-cool cycle or because they do not vapourise, and so amorphous states may be produced. The hypothesis is tested with

* Corresponding author.
E-mail address: s.gaisford@ucl.ac.uk (S. Gaisford).

http://dx.doi.org/10.1016/j.ijpharm.2016.06.040
0378-5173/

two model systems; a pure drug substance, indomethacin, and a binary blend of drug substance and excipient, paracetamol and polyvinylpyrrolidone K30. Indomethacin was selected as it has low aqueous solubility and exists in the solid state in three monotropically-related polymorphs (the stable γ form and the metastable α, and δ forms) as well as the amorphous state and is known to be a good glass former (Andronis and Zografi, 2000; Fukuoka et al., 1986; Otsuka et al., 2001; Crowley and Zografi, 2002). In addition, indometacin is well-known to appear yellow in colour when amorphous (Tanabe et al., 2012), providing a simple visual reference that phase-conversion has occurred, and it is stable in the liquid form. Paracetamol/PVP K30 was selected because PVP is known to increase the solubility of paracetamol (Afrasiabi Garekani et al., 2003) and because PVP has been shown to inhibit crystallization of paracetamol on storage (Miyazaki et al., 2004; Wen et al., 2008).

2. Materials and methods

Indometacin (γ form, IDM) and paracetamol (monoclinic form I, PARA) were purchased from Sigma-Aldrich Ltd. Polyvinylpyrrolidone (PVP K30), was purchased from Fluka Analytical (UK). All materials were used as received.

2.1. Laser irradiation

A 40 W CO_2 laser (Full Spectrum Laser LLC, Las Vegas, US) was used for this study. For IDM experiments, an image of a square (3 cm × 3 cm, 300 dpi) was used as a template. IDM powder was spread in a thin layer in sample holders for the respective characterisation experiments (DSC and XRPD, see below) so that no additional mechanical stress needed to be applied to the sample to move it once irradiated (all samples were placed with the 3 cm × 3 cm area so as to be irradiated by the laser). The focal length of the laser was 7.4 cm. The laser allows user selection of power (P) and raster speed (S); various combinations were used (P75, P50, P25, S100, S75, S50; the numbers reflect the percentage of the maximum speed or power that the laser could achieve). Irradiated samples were stored in a desiccator over phosphorous pentoxide at ambient temperature until further analysis.

For PARA experiments, an image of a square (5 cm × 5 cm, 300 dpi) was used as a template. Physical mixtures of PARA and PVP K30 at ratios of 30:70, 50:50 and 70:30 were mixed in a sample bottle. The powder blend (100 mg) was spread on aluminium foil as a thin layer and placed in the working field of the laser at a focal length of 6.8 cm. A range of laser scanning speeds (100 and 75%) and powers (20, 30, 40 and 50%) were used. Irradiated samples were transferred from the aluminium foil to a small vial and stored in a desiccator over P_2O_5 until use.

2.2. Melt quenching

Crystalline IDM was melted on aluminium foil at 165 °C for 3 min and then quench-cooled by dropping into liquid nitrogen. The resulting amorphous solid was warmed to room temperature before being stored in a desiccator over P_2O_5.

2.3. X-ray powder diffraction (XRPD)

Data were collected on a Miniflex 600 diffractometer (Rigaku, Tokyo, Japan) with Cu Kα radiation at 40 kV and 15 mA. Samples were contained within a zero background holder. Scanning was performed from 5° to 35° 2θ at 0.01° 2θ step size and speed 5° 2θ/min.

2.4. Differential scanning calorimetry (DSC)

DSC measurements were made with a Q2000 (TA Instruments, LLC, USA). Samples (3–5 mg) were encapsulated in Tzero aluminium pans and lids. Samples were heated from −50 to 175 °C at a heating rate of 10 °C/min. Modulated Differential Scanning Calorimetry (MDSC) experiments were performed using the modulated mode with an underlying heating rate of 3 °C/min, a modulation amplitude of ±1 °C and a modulation period of 60 s. The instrument was calibrated using a standard reference material (indium, T_m = 156.6, ΔH = 28.71 J/g) in accordance with the manufacturer's instructions. Data were analysed with Universal Analysis 2000 (TA Instruments, LLC, USA). Experiments were performed in triplicate. Crystallization and melting values are reported as extrapolated onset (T_{onset}) while glass transition temperatures (T_g), are calculated as the mid-point (T_m).

2.5. Fourier-transform infrared (FT-IR)

Data were obtained with a 100 FT-IR spectrophotometer (PerkinElmer). The spectrum of an empty cell was used as the background. The scan was performed in the range of 4000–650 cm^{-1} for each sample at ambient conditions. Spectrum Express software (version 2008) was used to process the data.

2.6. Scanning electron microscopy (SEM)

Samples were mounted on an aluminium stage using adhesive tape and sputter-coated with gold (Quorum model Q150, Quorum Technology, UK) at 40 mA. Images were collected using an SEM (SEM, Quanta 200 FEG, FEI, Netherlands).

2.7. Stability testing

IDM samples were evaluated for stability under three conditions: at room temperature over P_2O_5, at 40 °C/0% RH and 40 °C/75% RH. The physical form of the samples was monitored at various time intervals with XRPD as described above.

3. Results and discussion

3.1. Irradiation of indometacin

Immediately following laser irradiation, a change in colour of the IDM powder from white to yellow was observed and the powder bed transformed to a contiguous glass (Fig. 1). The yellow

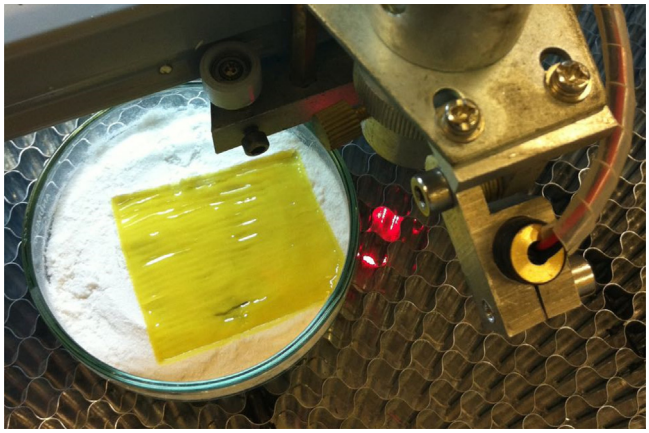

Fig. 1. IDM sample during irradiation with the CO_2 laser, showing crystalline powder around the edge and a glass in the 3 × 3 cm square exposed to the laser beam.