Nanoparticles of 5-FU for Inhalation Precipitated by Supercritical Carbon Dioxide

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INTRODUCTION

The mortality rate associated with primary and metastatic lung cancer is very high (1). Although airway administration might be a hypothetically attractive, noninvasive way to reach the systemic circulation or increase the local concentration of drug in the lungs while reducing whole-body toxicity, the fact remains that it is not often exploited for lung cancer treatment (2, 3).

We assert that this mode of administration would be more attractive if inhaled particles had a smaller and narrower particle size distribution which offered more site-specific targeting. Recently, micro- and nano-particle formation processes based on the use of supercritical fluids as solvents or antisolvents for active pharmaceutical ingredients (APIs) have been introduced, and are a promising means of controlling particle formation to improve solid state physicochemical properties (4). This approach may allow particle size, shape, surface, crystal structure, morphology, crystallinity and polymorphism to be manipulated to control dissolution rate and bioavailability (5, 6).

This study describes supercritical antisolvent processing of 5-fluorouracil (5-FU), a drug that is commonly used as both a palliative and therapeutic treatment for a variety of carcinomas (7).

METHODS

The apparatus used in this study is presented elsewhere (8). Briefly, each experiment began by delivering CO_2 into a thermostatted (room temperature to 50°C) precipitation vessel using a syringe pump until the pressure reached 100 bar. For particle production, 5-FU (5mg/ml) was dissolved in methanol/dichloromethane 50%v/v and delivered at flow rate of 1ml/min through a two fluid nozzle with CO_2 at a flow rate of 20ml/min. Particles were precipitated on a filter located at the bottom of the chamber and on the walls of the chamber. Precipitated 5-FU particles were

analyzed via photon correlation spectroscopy (PCS), scanning electron microscopy (SEM), and differential scanning calorimetery (DSC).

Precipitated particles of 5-FU were mixed with coarse (63-90μm) and fine (5μm) lactose (Pharmatose® 80, DMV International, The Netherlands) carrier particles. Fine lactose was pre-blended with coarse lactose for 15mins before addition of 5-FU (220μg). All formulations were blended in a Turbula mixer (DorsaBehsaz, Iran) at 90rpm for 90mins.

The resulting 5-FU: lactose carrier ratio was 1:67.5 (w/w). Approximately 15mg of this blend was filled in size #3 gelatin capsules (Capsugel, France) for testing in a Cyclohaler® dry powder inhaler (DPI).

Following aerosolization in-vitro deposition of formulation within a Twin Stage Liquid Impinger (TSLI) was evaluated. Four capsules were successively placed inside the Cyclohaler® and pierced. A vacuum pump established an air flow rate through the DPI of 60 l/mins for 4secs for a total simulated inhalation volume of 4L. After all simulated inspirations, the TSLI apparatus was dismantled and each stage was washed with appropriate volumes of distilled water. The amount of drug was determined by HPLC based on the USP 29 monograph for 5-FU during both powder blend content uniformity testing and following TSLI stage recovery. The fine particle dose (FPD) was defined as the amount of drug deposited in the lower stages of the TSLI.

RESULTS AND DISCUSSION

The precipitation of 5-FU resulted in the formation of crystalline nanoparticulates that SEM revealed were comprised of loose aggregations of approximately spherical particles with smooth surfaces. The particles showed a narrow size distribution with a mean particle size of 247nm.

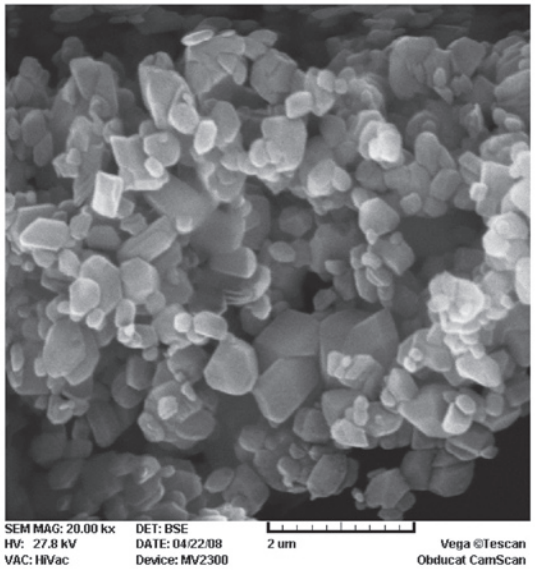

Figure 1. SEM images of nanoparticles of 5-FU.

Differential scanning calorimetry (DSC) revealed that supercritical antisolvent processed and unprocessed 5FU particles exhibited no significant change in melting point which suggests that crystal form was unaffected by this type of process.

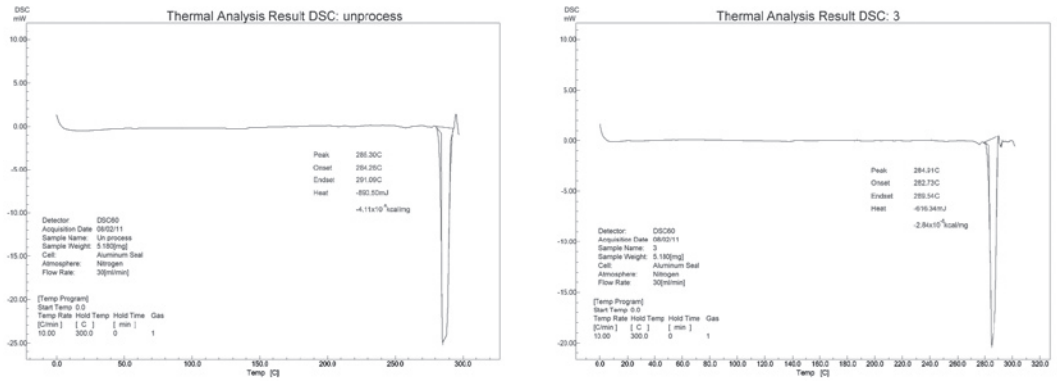

Figure 2. DSC thermograms of unprocessed (Left) and processed (Right) 5-FU particles.

After blending with carriers, content uniformity of 5-FU was between 95.5% and 104.5% of target with coefficients of variation less than 2%.

Formulation delivered into the TSLI resulted in a fine particle fraction (define as the percentage of encapsulated 5-FU that was emitted a particles smaller than 6.4μm) of 19.6%. Figure 3 shows the percentage of 5-FU recovered from stage 1, stage 2, the device (capsule and Cyclohaler) and the throat of the TSLI as a percentage of initial 5-FU loading in each capsule.

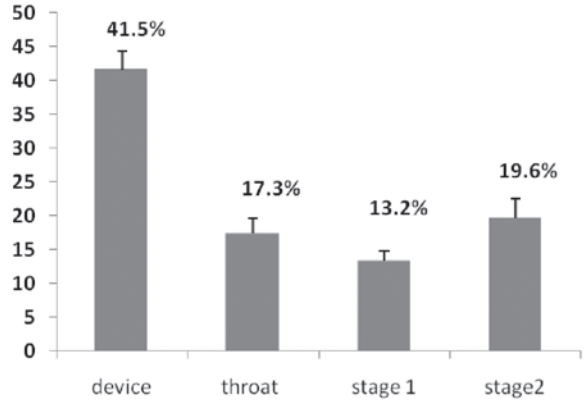

Figure 3. Percentage of 5-FU recovered from each location in the TSLI and DPI.

CONCLUSION

We have demonstrated the viability of preparing 5-FU nanoparticles using supercritical carbon dioxide, and showed they can be aerosolized with a DPI following blending with lactose.

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