Production of pH-Responsive Microparticles by Spray Drying: Investigation of Experimental Parameter Effects on Morphological and Release Properties

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ABSTRACT: During spray drying, emphasis is placed on process optimisation to generate favourable particle morphological and flow properties. The effect of the initial feed solution composition on the drug release from the prepared microparticles (MPs) is rarely considered. We investigated the effects of solvent composition, feed solution concentration and drug-loading on sodium salicylate, hydrocortisone and triamcinolone release from spray-dried Eudragit L100 MPs. Eudragit L100 is a pH-responsive polymer whose dissolution threshold is pH 6 so dissolution testing of the prepared MPs at pH 5 and 1.2 illustrated non-polymer controlled burst release. Increasing the water content of the initial ethanolic feed solution significantly reduced hydrocortisone burst release at pH 5, as did reducing the feed solution concentration. These findings caution that changes in feed solution concentration or solvent composition not only affect particles' morphological characteristics but can also negatively alter their drug release properties. This work also illustrate that drug-free MPs can have different morphological properties to drug-loaded MPs. Therefore, process optimisation needs to be carried out using drug-loaded systems. Depending on the physicochemical properties of the encapsulated active pharmaceutical ingredient (API), drug-loading can affect the polymer solubility in the initial feed solution with consequent impact on MPs morphological and release properties. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:566–579, 2011

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INTRODUCTION

Spray drying transforms a feed solution, suspension or emulsion from a fluid state into a dried particulate form by spraying into a hot drying medium.[1] This technique has found wide applications in the food, pharmaceutical and chemical industries. In the pharmaceutical industry, spray drying is an attractive microencapsulation method for oral, pulmonary and topical drug delivery. Unlike solvent-based microencapsulation methods, such as oil in water and oil in oil emulsification processes, spray drying offers a number of advantages. It is a one step, continuous process that does not involve secondary drying of the produced particles. The method is highly reproducible, relatively, easy to scale up and offers a narrow particle size distribution.[1–3]

However, despite a large number of experimental investigations[4–6] and mathematical modelling,[1,7–9] the mechanisms of droplet drying and drug incorporation are not fully understood and remain difficult to predict. In simple terms, as the evaporating droplet shrinks, its receding droplet surface leads to increased solute concentration at the surface with consequent diffusional flux to the centre.[10] It is therefore expected that variables which affect the evaporation rate and the diffusional flux within the drying droplet, such as solvent composition and concentration of the feed solution, will ultimately affect morphological and drug release characteristics of the spray-dried microparticles (MPs). During process development, emphasis is often placed on the operating parameters of the spray drying process, such as

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the pump rate, drying temperature and aspirator rate, and their effects on the flow and morphological properties of the prepared powders.[5,6,11,12] Although these factors are important, investigation of solvent and concentration effects on the release properties of drug-loaded MPs is rarely undertaken.

Enteric polymers such as Eudragit have been used to produce spray-dried MPs.[2,3,5,13,14] Encapsulation of both hydrophilic and hydrophobic model drugs has been explored using both aqueous suspensions and polymeric solutions,[2,15,16] although the reported release studies are often performed under non-sink conditions[6,17]; deviations between drug release under sink versus non-sink conditions are significant, especially for slowly releasing formulations.[18] In the case of sodium diclofenac, a model hydrophobic drug which has been spray dried from an aqueous dispersion of Eudragit RS 30D, release was extremely low at acidic pH (less than 10% of the drug released after 2 h at pH 1.2) and was attributed to the low solubility of sodium diclofenac in acidic media (<2.0 mg/L).[6] In fact, due to the low solubility of the sodium diclofenac in the acid medium, sink conditions were not maintained. It is therefore unclear whether the reported controlled release properties were obtained as a result of efficient drug encapsulation or simply due to non-sink conditions.

In this work, Eudragit L100, a pH responsive polymer with a dissolution threshold of pH 6, was used to investigate the effect of solvent composition and concentration of the initial feed solution on morphological and release properties of hydrocortisone-loaded spray-dried MPs. Physical parameters such as the hydrodynamic diameter of the polymer in the initial feed solution and tap density measurements of the collected powders were used to explain the differences observed between the produced MPs. The transferability of the optimised spray drying method to model lipophilic and hydrophilic drugs was also assessed using triamcinolone and sodium salicylate, respectively.

MATERIALS AND METHODS

Materials

Sodium salicylate, hydrocortisone and triamcinolone were purchased from Sigma-Aldrich (Poole, Dorset, UK). Eudragit L100 was kindly provided by Röhm (Darmstadt, Germany). Ethanol (laboratory grade) was obtained from Sigma-Aldrich (UK). Sodium phosphate dibasic heptahydrate and sodium phosphate monobasic dehydrate (Sigma-Aldrich, UK) were used in the preparation of the dissolution media.

Drug Solubility

Three model drugs, hydrocortisone, triamcinolone and sodium salicylate, with variable aqueous solubilities were chosen to study the possible effect of the API's physicochemical properties on MPs production. Drug solubility was determined in 50:50 w/w ethanol/water, pH 5 and pH 7 phosphate buffer using the shake-flask method. Excess drug in 10 mL of solvent was placed in a water bath (Grant OLS 200) at 25 ± 0.1°C and shaken at 40 rpm for 72 h. Samples of the supernatant were filtered using a Millipore syringe filter (0.45 μm pore size) and diluted appropriately with the same solvent. Drug concentrations were determined by ultraviolet (UV) spectroscopy against a calibration curve of the drug (Jasco V-530 UV–visible (VIS) spectrophotometer). For each reported solubility result, three independent experiments were performed.

Polymer Solubility

The amount of water required to precipitate the polymer and produce sustained turbidity was used as an indicator of polymer solubility in the ethanol/water co-solvent system. The solubility of Eudragit L100 with or without model drug was determined at three different concentrations by dissolving 0.2, 0.5 or 1 g of the polymer in 10 g ethanol. Upon the addition of 10 g of water, the concentration of the polymer in the resulting 50:50 w/w ethanol/water co-solvent system is 1%, 2.5% and 5% w/w, respectively; similar to the concentrations used in the spray drying process. The amount of water required to precipitate the polymer provides information on how far the polymer is from its solubility limit in the different spray-dried feed solutions.

Compatibility of Drugs and Enteric Polymers

The solubility of the model hydrophobic drugs hydrocortisone and triamcinolone, within the polymer matrix was determined through microscopic examination of polymeric films.[19] Drug-free and drug-loaded Eudragit films were prepared by casting 2% w/v ethanolic solutions into glass Petri dishes. The percentage drug loading varied from 0% to 25% w/w with respect to the polymer. Films were dried for 72 h at room temperature. The prepared films were then examined under a polarised light microscope (Zeiss Axioskop, Welwyn Garden City, UK; 40 digital microscope) for the presence of drug crystals.

Dynamic Light Scattering

Dynamic light scattering was used to determine the hydrodynamic diameter (d_H) of polymer particles in the initial feed solutions. Hydrodynamic diameter measurements were used to estimate the diffusional flux, D, of the polymer in the different feed solutions, calculated from the Stokes-Einstein equation.[20]

$$D = \frac{k_B T}{6\pi \eta d_H} \quad (1)$$