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Modification of the morphology and particle size of pharmaceutical excipients by spray drying technique

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ABSTRACT

This study investigates the effect of pneumatic spray drying using a two fluid nozzle on pharmaceutical excipients used in compression analyzing, modifications in the morphology, particle size and particle size distribution. The pharmaceutical excipients selected were classified into three groups according to their solubility in water: excipients that are soluble in water, partially soluble in water, and practically insoluble in water. Both spray drying conditions and properties of the liquid to be atomized were established for each of the excipients studied. The results obtained, in terms of the characterization of particles, were different depending on the excipient and the group to which they belonged. Properties such as flowability and compressibility that pertain to bulk level of solid state are strongly influenced by changes in characteristics at the particle level, such as size, size distribution and morphology of particles, which is the subject of study in this investigation.

1. Introduction

The rationale of the spray drying technique is based on the transformation of solutions or suspensions into a solid product via a process consisting of four stages. Generally, the medium of preparation to be spray dried is aqueous, although in some cases organic solvents are used. The prepared liquid is fed from its container to the spray nozzle of the spray dryer where it is spray dried forming small droplets. They rapidly come into contact with a stream of heated air or other drying gas capable of removing the solvent from these droplets, finally obtaining the spray dried product. Several types of spray dryers exist according to the energy involved (centrifugal, kinetic, pressure and vibrational). One of the most common types is the pneumatic spray drying using a two fluid nozzle, where the liquid stream is broken into droplets upon contact with a second fluid which is generally compressed air [1,2].

The conditions used during spray drying, and characteristics of the product in solution or suspension, are important for obtaining the final product as they affect a number of critical parameters such as particle size and morphology. The fact that the liquid to be spray dried is a solution or suspension also influences the results, since one of the conditions considered as essential in the spray drying process is the selection of a solvent or a common solvent system [1]. This work includes the study of the spray drying process of a series of excipients that are soluble, partially soluble and insoluble in water (the medium chosen for testing) to conduct a study of their behaviour. The properties of the liquid to be spray dried, as well as the concentration, viscosity, surface tension, solubility, etc. along with spray drying parameters set (inlet and outlet temperature, feed flow rate, heated air flow, etc.) and the fundamental variables (evaporation rate, vapour pressure, droplet size, etc.), directly affect particle properties (particle size and distribution, morphology, surface area, etc.) and consequently those of the obtained powder (bulk density, compressibility, flow rate, etc.) [3].

In common practice, the spray drying process is usually carried out empirically and experimentally despite the fact that traditional methods employ repetitive experimental designs or statistical treatments with intention of establishing relationships between process parameters and properties of the starting material with respect to the spray dried product [4].

Both the spray drying process and formulation are dependent parts in the process of obtaining the spray dried product, since they determine its characteristics.

The spray drying process is a widespread technique and is used in various fields with different applications, as it is a method in which particle size and particle morphology can be controlled. Currently, spray drying has become established in industries such as the chemical industry, in which, amongst others, applications in fertilizer and products used in agriculture, dyes and pigments, detergents and surfactants and products used in ceramics are noteworthy. The presence of products obtained by spray drying is also notable in the food industry which

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includes dairy products, egg derivatives, plant extracts and carbohydrates, amongst others. In addition to these applications, spray drying is also used in other industries such as cellulose and tannins, environmental control products, the electronics industry, catalysts, and magnetic and optical materials. The use of this technique in the pharmaceutical industry is also very important, due to the control of particle morphology and size is considered critical for obtaining the final product. Spray drying is commonly used in the preparation of microcapsules, for drying thermolabile products and for the production of amorphous solid dispersions. Two other applications in which researchers have dedicated their efforts are, obtaining excipients for pulmonary delivery formulations and obtaining and optimizing functional excipients via co-spray drying [3,5].

The available literature is remarkable when trying to study formulations for pulmonary administration, in which the spray dried mannitol and lactose show a constant presence as carriers in the preparation of dry powders for inhalation (DPI) [6–16], although other studies have also been carried out for the same purpose to deliver different alternatives, as is the case of trehalose and raffinose [17,18]. All these studies show a special interest in the size and morphology of the particles obtained, since they are of vital importance in this type of route of administration [19].

Currently, the spray drying technique is becoming increasingly relevant as a method of obtaining co-processed excipients in the pharmaceutical industry, where the fundamental and innovative principle is based on the ability to alter the functionality of a particular excipient retaining the favourable properties it could present and complementing them with those of another excipient, by processing the principal and majority excipient with other excipient(s) [20]. So far, spray drying has been used to obtain combinations of excipients with superior properties (flow, hygroscopicity and compactability) to those of the original or starting products and to those of these excipients' own physical mixtures.

Some examples of products in the market obtained by co-spray drying are Cellactose® (α-lactose monohydrate and powdered cellulose), Microcelac® (α-lactose monohydrate and microcrystalline cellulose) and Prosolv® (microcrystalline cellulose and silicon dioxide). However until now, co-spray drying has been seldom used in the processing of APIs with excipient(s) in order to improve physical properties of the active substance [21].

All these applications have in common the great interest in knowing and controlling particle size and morphology. Any change to the fundamental properties of the materials, such as size, morphology, surface area, porosity and density, can directly affect such derived properties as flowability, compressibility, compactability, dilution potential, disintegration and lubricity [22]. This is because properties of chemical solids are presented according to three levels: molecular, particle and bulk. Molecular level involves individual binding between molecules including the polymorphic, pseudo-polymorphic and amorphous forms. Particle level includes individual particle properties such as particle size and distribution, morphology, roughness and surface area and porosity. Bulk level represents properties such as cohesiveness, flowability, compressibility and bulk density. Therefore, any change in any of these levels directly affects the other levels [20]. Some properties such as flowability, compressibility, reproducibility of dosage and aerodynamic characteristics are strongly influenced by size, shape and surface of particles [6]. For example, larger and spherical particles usually flow much better than those of smaller size, and the latter tend to dissolve more easily and they are capable of obtaining suspensions with a higher viscosity than those that are larger.

Although there is a wide range of particle properties we can study, the objective of this work is the characterization of the particles in terms of size (particle size and particle size distribution) and morphology, before and after spray drying of a series of excipients belonging to different families according to their nature (disaccharides, polyols and inorganic salts, amongst others). These excipients are frequently used in the pharmaceutical industry, since amongst their properties they present an aptitude for compressibility and/or cohesiveness. According to the results obtained those excipients which present more interesting features for direct compression by co-spray drying with other excipients will be selected, since this work is part of a much larger study whose main purpose is to obtain a new co-processed excipient for direct compression.

2. Materials and methods

2.1. Materials

Advantose® 100, SPI Pharma (Septemes-Les Vallons, France). Maltose PH, Hayashibara Co. Ltd. (Okayama, Japan). Starch 1500®, Colorcon Iberica S.L. (Sant Cugat, Spain). Arbocel® P290, Vivapur® 101 and Vivapur® 102, JRS Pharma GMBH & Co. KG (Rosenberg, Germany). Avicel® 101 and Avicel® 102, FMC Biopolymer (Philadelphia, USA). Comprecel® M101 and Comprecel® M102, MingTai Chemical Co. Ltd. (Taoyuan Hsien, Taiwan). Microcel® MC101 and Microcel® MC102, Blanver Farmoquímica Ltda. (São Paulo, Brasil). Calcium lactate pentahydrate, calcium carbonate, maize starch and mannitol, Fagron Iberica S.A.U. (Terrassa, Spain). Magnesium trisilicate hydrate and dibasic calcium phosphate dihydrate, Sigma-Aldrich Química S.L. (Tres Cantos, Spain). Tribasic calcium phosphate, Panreac Química S.L.U. (Castellar del Vallès, Spain).

2.2. Spray drying

2.2.1. Preparation of solutions and suspensions

Given the advantages of working with a solvent such as water, all suspensions and solutions were prepared with this medium, by stirring until complete solubilization or until presenting proper homogenization by visual observation according to the nature of the excipient in terms of its solubility in water [23,24]. These excipients were classified into three groups: soluble in water (mannitol, Advantose® 100, maltose PH, and calcium lactate pentahydrate), partially soluble in water (Starch 1500® and maize starch), and practically insoluble in water (magnesium trisilicate hydrate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, calcium carbonate, group of microcrystalline cellulose, which comprises Vivapur® 101, Vivapur® 102, Avicel® 101, Avicel® 102, Comprecel® M101, Comprecel® M102, Microcel® MC101 and Microcel MC102® and powdered cellulose, Arbocel® P290). The concentration (w/w) of excipient for each suspension (practically insoluble and partially water soluble excipients) was established after carrying out a series of previous experimental tests. These tests were based on achieving maximum feed solids content in a known amount of water without high viscosity of the suspension, precipitating or observation of agglomerations, with the objective of obtaining the greatest possible yield and the lowest moisture content in spray dried products. Viscosities were measured in a laboratory viscosimeter (Brookfield CAP-2000 +, Middleborough, MA, US). For both partially soluble excipients, maize starch and Starch 1500® were set at 25% and 10% respectively; for practically insoluble excipients a concentration of 20% magnesium trisilicate hydrate and tribasic calcium phosphate, and 30% for calcium phosphate dibasic dihydrate and calcium carbonate were set. Initially, various concentrations from between 3% and 20% were established for the group of microcrystalline celluloses and cellulose powder. All excipients dispersed in water were constantly stirred during the entire process of spray drying. In the case of excipients soluble in water, previous tests were tried experimentally to reach the stage immediately prior to solution saturation point. Thus a 10% solid percentage (w/w) was established in mannitol solution, 20% in Advantose® 100 and maltose PH solutions, and 5% in calcium lactate pentahydrate solution.