Water elimination by CO_2 cryospraying technology to obtain dry microparticles from biphasic, lipid dispersed systems

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Introduction

Variosol® cryospraying technology exploits the physical properties of rapidly expanding liquid or dense CO_2 [1] to perform as cryogenic agent (Joule-Thomson effect), while providing mechanical energy through a rapid pressure drop. This rapid expansion can induce phase change, solidification and atomization in a sprayed fluid, forming a dynamic mixture with the expanding CO_2 and transforming the liquid product into a micronized, dried powder. The main advantage of this technology is that it operates at relatively low temperatures and pressures, and does not require supercritical CO_2, thus reducing the use of energy-consuming elements, and making the process simple and efficient.

One peculiar feature of the expanding CO_2 cryospraying is the capability to eliminate significant amounts of water from biphasic disperse systems, during the fluid atomization at low temperatures. This "dewatering" effect occurs when the product is sprayed under certain conditions of CO_2 pressure and temperature [2]. Presumably, the water contained in the atomized fluid product is rapidly cooled down and micronized with very high specific surface, and subsequently eliminated in the surrounding atmosphere (phase equilibria) leaving the spray tower with the exhaust gas. Therefore, it is possible to obtain solid, dry microparticles with a residual moisture of about 0.5 to 3%, and diameters below 100 µm, after atomization under dense CO_2 expansion [2,3]. This feature offers the possibility to formulate and produce lipophilic or amphiphilic micromatrices containing hydrophilic, water soluble molecules. The technology can also directly encapsulate natural extracts containing significant amounts of water, transforming them in formulated, micronized powders [4], without the need to reach supercritical CO_2 conditions, as it occurs in PGSS-drying technology [5].

The main objective of this study is to evaluate the impact of different process parameters on particles size, morphology and residual water content. Parameters such as pressure applied to sprayed fluid, nozzles type, diameters and geometry were investigated using aqueous disperse systems of lipidic excipients with amphiphilic properties. The results obtained could be used to explain and understand the key features of particles formation and dewatering phenomenon by CO_2 cryospraying technology. This will help us investigate and optimize the physical properties of the microparticles and process water elimination capability.

Materials and methods

Mono, di- and triglycerides with medium to long chain fatty acids, and their amphiphilic derivatives (e.g. poly-hydroxylated fatty esters) were used for these studies. These materials were selected because of their known function in pharmaceutical preparations as solubilization or absorption enhancers, and as controlled release excipients. In addition, their relatively low melting point (typically ranging from 35 ºC to 75 ºC), combined with the rapid solidification properties at low temperatures, makes them suitable to formulate thermolabile molecules, and processable with the CO_2 cryospraying technology. Different operating conditions were applied in these studies. Gas pressure applied to sprayed material ranged between 1 to 4 bar, and fluid product temperatures were maintained between 55 ºC and 85 ºC, depending on the formulations. Nozzles producing capillary flow, with diameters between 0.36 to 0.85 mm were used to spray the fluid product. Two different types of dense CO_2 nozzles - full cone flow geometry or swirling flow pattern, were tested and compared. Dense CO_2 pressure was maintained between 48 and 55 bar. Microparticles were characterized by particles size analysis, Optical Microscopy, SEM and residual moisture content by Karl-Fisher Analysis or TGA.

Results and discussion

Spherical or spheroidal microparticles, with a matrix-type morphology were obtained at all the conditions studied. Depending on applied process conditions, the average diameters varied between 20 to 100 µm approximately, with narrow particle size distribution and good powders flowability. Optical Microscopy and SEM observation indicated that different surface features could be obtained, depending on excipients combinations and on applied processing conditions. Microparticles with different surface morphology and porosity could be obtained. The porosity and water residual areas observed by SEM suggest that the "dewatering" phenomenon is likely generated from water rapid freezing and subsequent evaporation during the spraying in the presence of CO_2.

Applying different conditions of pressure, temperature, nozzles diameter and geometry, we observed that effective water elimination to obtain dry microparticles can be achieved when the formulations to be sprayed contain up to about 35% of water. This makes it possible to obtain dry microparticles by spraying, for instance, drug – containing emulsions, microemulsions, and more complex systems such as natural extracts fractions. The water elimination capacity and the residual moisture in the particles also depend on the nature of the sprayed materials, being affected by their affinity to bind and retain water molecules or moisture. In fact, we observed how microparticles containing more hydrophilic excipients (e.g. polyhydroxylated – lipid derivatives) tend to retain more moisture. The dewatering effect may be enhanced by generating higher surface area within the sprayed material, during the liquid CO_2 expansion. This can be obtained by introducing modifications in the equipment design, while formulating disperse systems with smaller inner-phase droplets.

Conclusions

Cryospraying technology exploits the physical properties of rapidly expanding liquid-dense CO_2 to perform as cryogenic agent while providing mechanical energy through a rapid pressure drop. Such features allow to produce dry microparticles from biphasic dispersed systems, facilitating the elimination of water directly during the atomization at low temperatures.
Formulations including up to about 35% of water can be sprayed using the existing equipment design. It is thus possible to manufacture amphiphilic, composites microspheres containing combinations of different drugs or moieties, in a simple, one step process.

References

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Figures

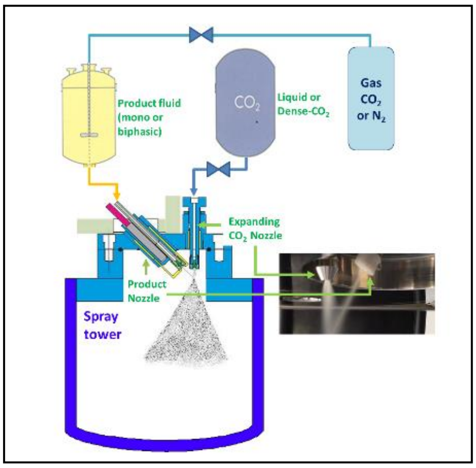

Figure 1. Scheme of dense CO_2 Cryospraying technology

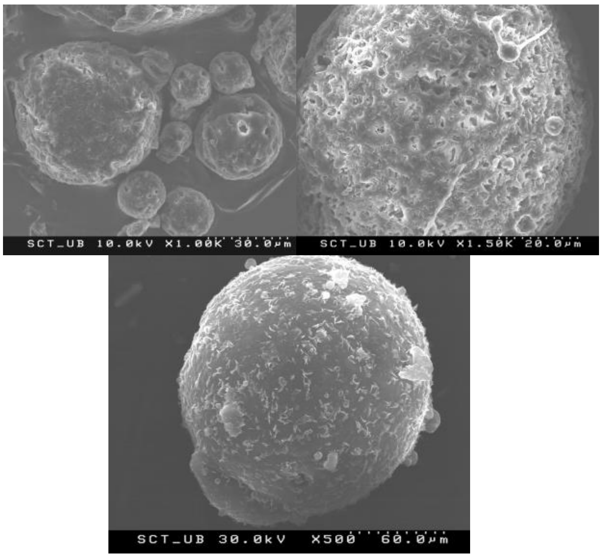

Figure 2. SEM Images of formulated microparticles with porous and not porous morphology

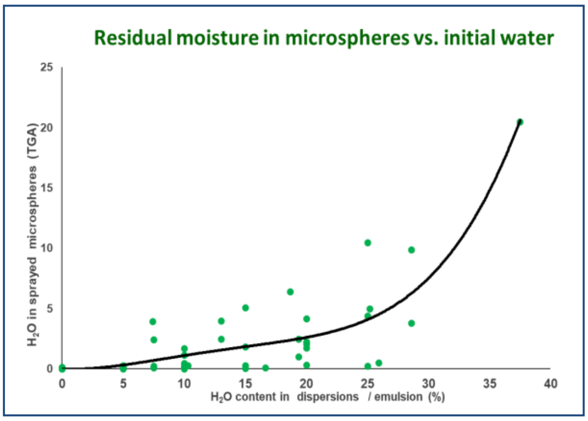

Figure 3. Residual moisture (%w) in microspheres (TGA) vs. water content in formulated emulsions before spraying