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Development of a supercritical fluid CO_2 granulator: Effect of mixing and composition

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ABSTRACT

Conventional wet granulation is commonly used in the pharmaceutical industry for size enlargement, where small primary particles are binded together using agitation and a liquid binder. However, after the wet mass is produced, it needs to dry the granules for long periods of time causing high-energy inputs. This report presents a novel supercritical fluid CO_2 granulator (SFG) to produce granule batches with low particle size distribution (PSD), while using less drying time and minimizing the additional drying steps. This study focused on understanding the effect of mixing (*e.g.*, flow rate, location of inlet flow, agitation) and composition (*e.g.*, binder and solvent type water vs. ethanol) in the SFG process. Sieves were used to measure the PSD, and scanning electron microscopy (SEM) was performed to observe the granules' shape. The PSD and the shape of the granules were used to evaluate the efficiency of the SFG process. The excipients used included anhydrous lactose and monohydrate lactose, while acetaminophen was used as the active pharmaceutical ingredient (API). The results show that the SFG process could effectively be used as an alternative to the conventional wet granulation process (Patent Pending # 62/398,645). The study also discusses how changes in the mixing and composition conditions affect the resulting granule size, distribution, and shape.

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1. Introduction

Wet granulation is the most commonly used method for size enlargement of granulation [1,2]. It is primarily used to improve the properties of the excipients used in products such as pharmaceuticals, ceramics, detergents, and fertilizers [1]. Granulation is generally used in the pharmaceutical industry during the tablet manufacturing process to reduce segregation and improve the content uniformity of the final product [1,3,4]. The wet granulation process often causes agglomeration via the addition of solvent or binder solution to powder [2]. The most common types of granulators used in pharmaceutical manufacturing are: tumbling, fluidized-bed and mixer granulators [1,3]. Granulation guarantees homogeneity of resulting granules [5]. These are expected to contain the active pharmaceutical ingredient (API) and the excipient in the same proportion as the original bulk mixture [5].

Although conventional wet granulation processes are the granulation method of choice in the pharmaceutical industry, they have several disadvantages. The process is sensitive to raw materials and operating conditions [1,3]. Other relevant issues include cost and product quality [2]. In some cases, aqueous systems are inappropriate and organic solvents may be necessary for the binder solution. Finally the additional drying process to remove residual solvent requires a substantial amount of energy to dry the granules [6] and can be incompatible with thermally labile substances.

In an effort to overcome some of the limitations of the conventional wet granulation process, a novel supercritical fluid CO_2 granulator (SFG) was developed. A supercritical fluid (SCF) is defined as a substance whose pressure and temperature are above the critical point [7]. Close to the critical point a SCF has both liquid-like densities and gas-like mass transport properties (e.g., viscosity and diffusivity) [8]. SCF's are widely used in: nanomedicine [9], food [10], material [11], environmentally benign separations [8], energy [12], reaction engineering [13], polymers, nanomaterials and chromatography [8]. CO_2 is the most commonly SCF used [7]. It is non-toxic, non-flammable, chemically inert and inexpensive [7]. Its critical point (31 °C and 73.8 bar) is easily accessible and it can be removed from the system by depressurization and then recycled after compression [7]. The advantages of a SFG granulator over conventional wet granulator processes include but are not limited to: 1. Use of an environmentally benign, non-combustive, inert and inexpensive CO_2 to granulate pharmaceutical formulations. 2. The process is fast and effective as it eliminates or reduces the need for additional solvents. 3. The uniform nature of the SCF process should produce uniform particle size distribution (PSD) of the granules. 4. The process is suitable for heat-sensitive products. 5. The process could be operated in batch or in a continuous mode. 6. The process can be applicable to water-sensitive formulations. 7. The process can reduce dust hazards

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Table 1
Formulations of the conventional wet granulation experiments.

Formulation	Excipient		API	Binder		
	Lactose monohydrate (g)	Lactose anhydride (g)		Liquid (wt.%)	Povidone (wt.%)	Binder solution (vol%)
Water	21.5768	79.0010	0	92.45	7.55	12.5
Ethanol 1	21.0784	79.1011	0	92.51	7.49	12.5
Ethanol 2	20.9689	79.2456	0	92.49	7.51	21.1
Ethanol 3	21.0045	78.9995	0	92.51	10.01	21.0

for the operator. Although the technique is novel, some of the disadvantages of a SFC granulator are: 1. Requires special high-pressure equipment for the SCF and 2. Additional safety measures (*e.g.*, pressure relief valve), might be required.

This investigation describes the development of a SFG as an alternative for wet granulation processes. Mixing and composition variables such as: SCF inlet flow rate, location of SCF entering the SFG process, mechanical agitation speed, binder solvent, binder concentration and binder solution composition were critically investigated. The performance of the SFG process was evaluated measuring the particle size distribution (PSD) and visual observation of the granule's shape using scanning electron microscopy (SEM). The granule PSD and shape were also investigated upon the incorporation of the API acetaminophen.

2. Materials and methods

2.1. Materials

Anhydrous lactose (99.0%) was obtained from Kery Bio-Science. Monohydrate lactose (99.0%) was purchased from Neggle Granulation 140. Ultra-high purity CO_2 (99.998%) was purchased from Linde Gas Puerto Rico. Povidone (99.0%) was obtained from ISP Technologies Inc. Ethanol anhydrous (95%, pure) was purchased from Fisher-Scientific, while acetaminophen (99.0% purity) was purchased from Sigma-Aldrich. All chemicals were used without any further purification.

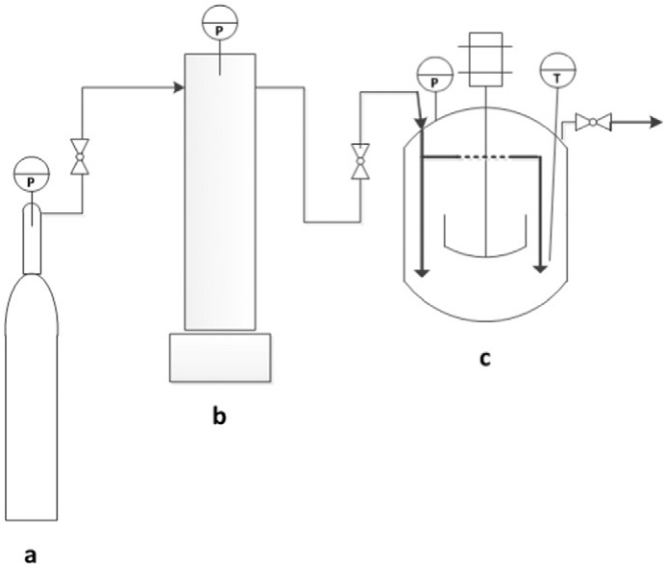

Fig. 1. Supercritical fluid equipment used for the supercritical CO_2 granulator. Consist of three mains parts. Part (a) is the CO_2 cylinder. Part (b) is the CO_2 260 mL high-pressure syringe pump. Part (c) is a 300 mL reactor where the entire process takes place.

2.2. Conventional wet granulation

In order to make the proper comparison between the SFG and the conventional wet granulation process, the conventional wet granulation process was performed first using the suggested procedure and equipment described elsewhere [14]. For all the experiments conducted, a 1.0:3.8 mass ratio of lactose monohydrate (110 μm) to lactose anhydride (60 μm) was used. The particle size values stated for the two lactose species were provided by the manufacturer. We used US Standard Tyler's sieve trays to verify this information. The resulting size and PSD of the granulated product were used as the basis of comparison for the variables studied ahead in the SCF granulation (SFG) process.

Aqueous granulation liquid binder was added to the lactose mixture using a peristaltic pump through a top nozzle and the powder mixture was granulated. In addition, since the solubility of water in SCF CO_2 is extremely low, a more CO_2-phillic solvent (ethanol) was studied in the SFG process. For comparison purposes, the conventional granulation process was also performed using an ethanol granulation binder liquid solution. The formulations used in the conventional wet granulation experiments are listed in Table 1.

2.3. Experimental design

In order to achieve a rationale design for the SFG process, variables pertaining to the mixing and phase equilibria inside the SFG were systematically investigated. The specific variables studied in the SFG process include: 1. SCF inlet flow rate (35, 45, and 60 mL/min). 2. Location of SCF entering the SFG process (top vs. bottom, and single entry vs. multiple entries). 3. Mechanical agitation speed (0, 110, 144, and 200 rpm). 4. Binder solvent (water vs. ethanol). 5. Binder concentration (7.5% and 14%). 6. Solution concentration (86% ethanol vs. 67% ethanol). After the effect of the previous variables was investigated, acetaminophen was added to evaluate the

Table 2
Formulations of the supercritical CO_2 granulation experiments.

Formulation	Granulation composition		API (g)	Binder	
	Excipient (wt.%)	Solution (wt.%)		Ethanol (wt.%)	Povidone (wt.%)
Water	69.0	31.0	0.00	92.5	7.5
Ethanol	69.0	31.0	0.00	92.5	7.5
3	69.0	31.0	0.00	92.5	7.5
4	69.0	31.0	0.00	86.0	14.0
5	69.0	31.0	0.00	86.0	14.0
6	69.0	31.0	0.00	86.0	14.0
7	69.0	31.0	0.00	86.0	14.0
8	69.0	31.0	0.00	86.0	14.0
9	69.0	31.0	0.00	86.0	14.0
10	69.0	31.0	0.00	86.0	17.0
11	69.0	31.0	0.00	86.0	14.0
12	69.0	31.0	5.02	86.0	14.0
13	69.0	31.0	0.00	86.0	14.0
14	69.0	31.0	5.01	86.0	14.0
15	69.0	31.0	5.00	86.0	14.0
16	69.0	31.0	5.01	86.0	14.0
17	69.0	31.0	0.00	86.0	14.0
18	69.0	31.0	4.78	86.0	14.0
19	69.0	31.0	0.00	86.0	14.0
20	69.0	31.0	0.00	86.0	14.0
21	69.0	31.0	5.01	86.0	14.0
22	69.0	31.0	5.02	86.0	14.0
23	69.0	31.0	5.00	86.0	14.0
24	69.0	31.0	0.00	86.0	14.0
25	100.0	0.0	0.00	0.0	3.5 g
26	100.0	0.0	0.00	0.0	9.9 g
27	85.0	15.0	0.00	67.0	33.0
28	85.0	15.0	5.02	67.0	33.0