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Note

Caffeine microparticles for nasal administration obtained by spray drying

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Abstract

This study investigated the possibility to use spray drying technique to prepare powders formulations containing caffeine intended for nasal delivery. Spray dried powders containing caffeine and excipients, as filler and shaper agents, were prepared. Powders were investigated for particle size, morphology and delivery properties from Monopowder P® nasal insufflator, assessing the influence of each excipient on microparticles characteristics. The results showed that the excipients strongly affected microparticle properties. Size, shape and agglomeration tendency are relevant characteristics of spray dried nasal powder.

Keywords: Nasal powders; Caffeine; Spray drying; Nasal insufflator

Caffeine is a methylxanthine that stimulates the central nervous system, creating a condition of wakefulness and increased mental activity. Recently, there has been evidence of the role of caffeine as antagonist of adenosine A_{2A} receptors in preventing neurodegenerative disorders, such as Parkinson's disease (Chen et al., 2001).

The nasal administered caffeine can target the brain taking advantage of olfactory pathways. Microparticles are a suitable dosage form for insufflation into nasal cavity.

Spray drying is one step process transforming liquid into a dried particulate form.

The application of spray drying to pharmaceuticals includes dry powders for aerosol formulation and processing of heat sensitive materials (Broadhead et al., 1992). Qualitative and quantitative composition of liquid feed and drying conditions strongly affects properties of the spray dried particles such as size, morphology, density, shape, porosity and flowability (Arshady, 1993; Maa et al., 1997; Billon et al., 2000; Esposito et al., 2000). Usually, spray dried powders are made of almost spherical and amorphous microparticles (Vidgrén et al., 1987), with a range of median diameter between 2 and 20 μm and a narrow size distribution (Broadhead et al., 1992). Nasal delivery requires microparticles that allow a reproducible dose reservoir filling and aerosolization for appropiate nasal deposition.

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The objective of this work was the preparation of caffeine spray dried microparticles useful for nasal powder preparation. This work was focused on the study of the influence of different excipients on microparticle properties.

The liquid preparations to be spray dried were solutions prepared by dissolving the components in distilled water to give a final concentration of caffeine of 15 mg/ml. The typical batch size was 10–20 g of powder. The spray drying of the solutions was carried out using a model B-191 Buchi Mini Spray Dryer (Buchi Laboratoriums-

Table 1
Composition (%) and particle size distribution of spray dried powders

Powder (#)	Caffeine	Mannitol	HPMC	PEG 6000	$d_{0.5}$ ($d_{0.1}$–$d_{0.9}$) (μm)
1	100	–	–	–	24.5 (10.1–39.6)
2	10	90	–	–	11.5 (3.9–23.2)
3	10	89	1	–	8.5 (3.6–15.3)
4	10	89.5	0.5	–	6.8 (2.8–11.7)
5	10	89	–	1	10.5 (4.6–21.1)
6	70	29.5	0.5	–	8.2 (4.1–13.6)
7	70	30	–	–	24.4 (9.3–42.3)
8	68.6	29.4	2	–	4.7 (2.6–7.1)
9	65.1	27.9	2	5	5.0 (2.5–7.6)
10	66.5	28.5	–	5	37.6 (13.2–62.9)

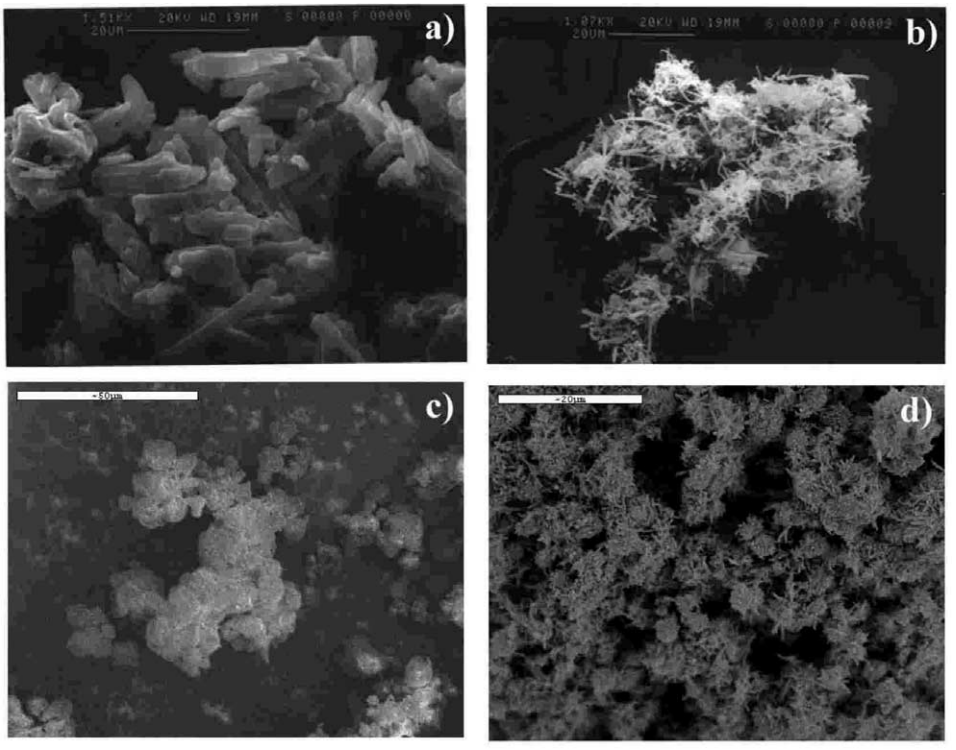

Fig. 1. SEM images of powders: (a) caffeine raw material, (b) spray dried caffeine powder, (c) caffeine:mannitol 10:90, (d) caffeine:mannitol 70:30.

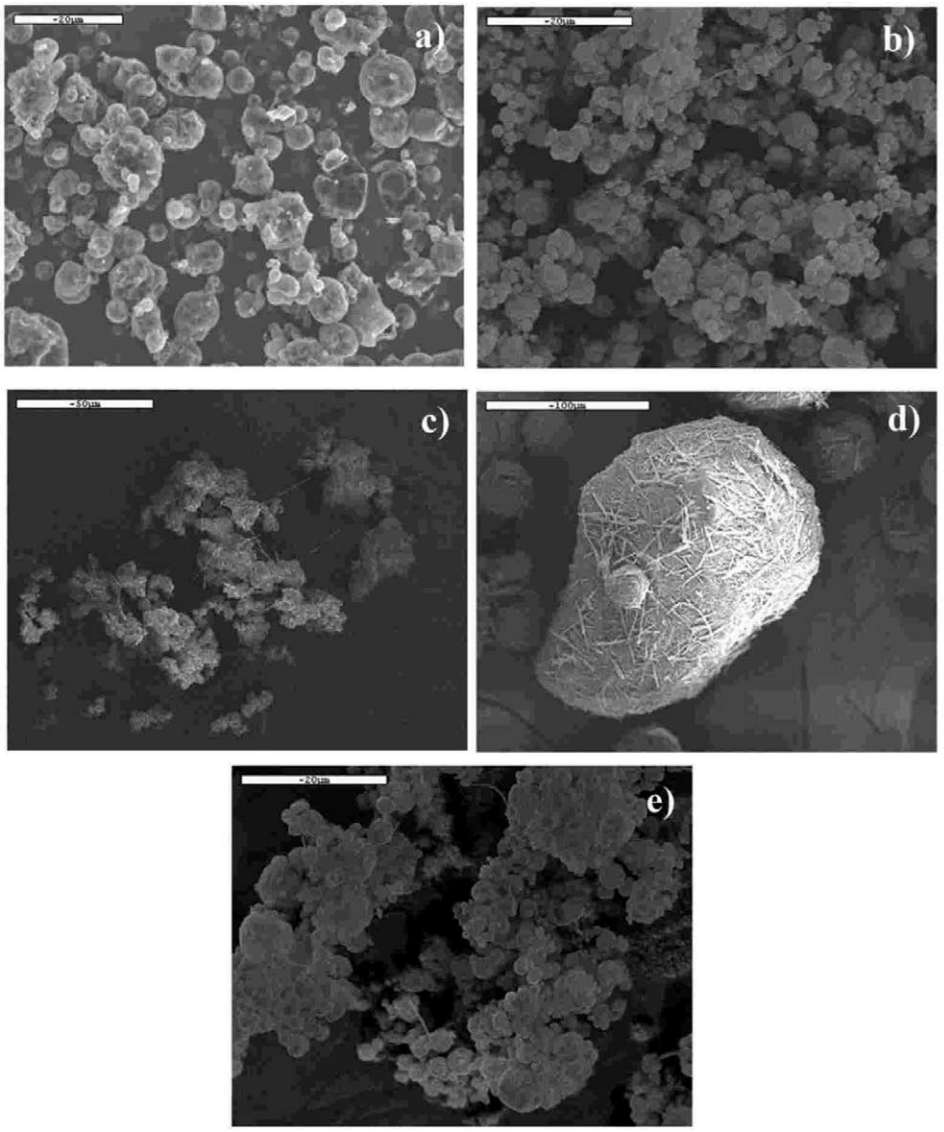

Fig. 2. SEM images of powders: (a) caffeine:mannitol:HPMC, 10:89:1, (b) caffeine:mannitol:HPMC, 68.6:29.4:2, (c) caffeine:mannitol:PEG 6000, 10:89:1, (d) caffeine:mannitol:PEG 6000, 66.5:28.5:5, (e) caffeine:mannitol:HPMC:PEG 6000, 65.1:27.9:2:5.

Technik, Flawil, CH) in the following experimental conditions: inlet temperature: 130 °C; outlet temperature: 45–50 °C; feed rate: 6.5 ml/min; nozzle diameter: 1.0 mm; drying airflow: 600 l/h. The microparticles obtained were characterized for size distribution using a laser light diffraction apparatus (Malvern Instruments Ltd., Spring Lane South Malvern, Worcestershire, UK).

Table 1 reports the composition and particle size distribution of the powders prepared.

The spray drying process modified the particle size of the caffeine powder raw material. Spray dried caffeine (powder # 1) showed a smaller diameter ($d_{0.5}$: 24.6 μm) and a narrower size distribution ($d_{0.1}$: 10.1, $d_{0.9}$: 39.6 μm), when compared with raw caffeine ($d_{0.5}$: 41.5, $d_{0.1}$: 15.5, $d_{0.9}$: 165.3 μm).

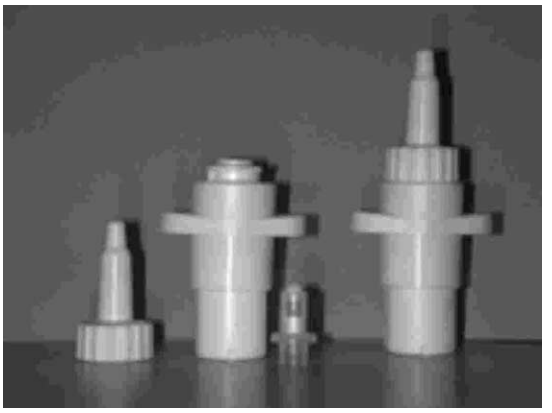

Fig. 3. Monopowder P® nasal insufflator. From left to right: nasal adapter, pump, solid formulation reservoir and assembled insufflator.

The mean volume diameter of the powders containing caffeine and excipients was in the range 4–37 μm, characterized by a narrow size distribution (Table 1).

Scanning electron microscopy (Scanning Microscope JSM 6400 Jeol) of raw material and spray dried caffeine (Fig. 1a and b) showed the morphology modification due to the spray drying processing. Spray dried caffeine particles appeared as small needles aggregated in 'clusters'.

Because of the unfavorable shape and entangled agglomeration, spray dried caffeine showed poor flow properties for reservoir loading of nasal insufflator. Therefore, in order to modify particle morphology and flowability, excipients were used. Excipients selected were mannitol, hydroxypropylmethycellulose (HPMC, Methocel E3) and PEG 6000, used as particle filler and shaper, respectively. Firstly, the influence of mannitol was evaluated, by preparing two powders containing caffeine:mannitol 10:90 and 70:30. As shown in Fig. 1c and d, the presence of mannitol changed the morphology of microparticles in comparison with spray dried caffeine (Fig. 1b).

In fact, increasing the amount of mannitol, the needle shaped particles became more roundish. Also, microparticles seemed to have a less tendency to agglomerate with respect to spray dried caffeine microparticles.

The use of HPMC, in a range 0.5–2% as third component in mannitol/caffeine mixtures, gave rise to almost spherical particles (Fig. 2a and b).

The use of PEG 6000, in a range 0.5–5% as alternative component in mannitol/caffeine mixtures, produced aggregation of individual microparticles giving rise to an irregular shape (Fig. 2c). When the amount of PEG 6000 was increased to 5% (Fig. 2d), microparticles aggregated in the powder collector of drying apparatus in almost spherical agglomerates. In this case an extensive sticking of dried material on the apparatus glass walls reduced the yield of this preparation (1%).

Microparticles containing caffeine, mannitol, HPMC and PEG 6000 (an example is powder #9, Fig. 2e), showed an almost rounded shape, like microparticles containing caffeine mannitol and HPMC, but they appeared more aggregated.

Because these microparticles containing caffeine were intended for nasal delivery, the characteristics of erogation from a nasal insufflator were investigated. The insufflator used was the single dose Monopowder P® (Valois Dispray, France, Fig. 3) that is constituted of a pump, a nasal adapter and a solid formulation reservoir typically containing 20 mg of formulation. When the insufflator piston is actuated, the airflow ejects the powder through the nose adapter.

The delivery of powders from the insufflator, determined by weighing the reservoir before and after each actuation, was almost quantitative (more than 98%).

In order to study the aerodynamic behavior of powders, the images of the delivery sequences of microparticles were recorded by means of a videocamera. For example, in Fig. 4 the sequence of powder #8 during the actuation is reproduced. The images of powder clouds demonstrated that microparticles were delivered forming an elongated puff. The core of clouds was homogeneous, showing a uniform density, likely due to narrow size distribution of microparticles. The results obtained in this work showed that spray dried powders containing caffeine and excipients were suitable for nasal delivery and were efficiently delivered from a nasal insufflator.

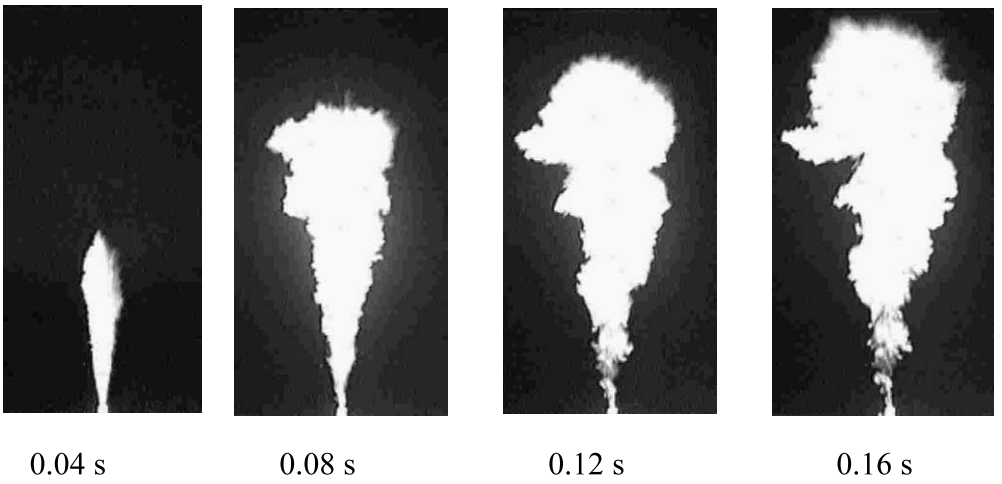

Fig. 4. Microparticles delivery sequence from Monopowder P® insufflator (Powder # 8).

Differently from pulmonary particles, nasal microparticles must be in non-respiratory size range in order to avoid lung deposition. This requirement can be achieved by affecting size of individual microparticles. The cohesion between these microparticles producing agglomerates can be considered beneficial for nasal deposition.

The use of a filler like mannitol, in conjunction with shaper like HPMC, allowed the modification of the typical needle shape of spray dried caffeine to a more useful roundish morphology. In addition the use of a shaper like PEG increased the cohesiveness between particles, opening the possibility to prepare more handable soft agglomerates of primary microparticles.

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