Delivery of Nasal Powders of β-Cyclodextrin by Insufflation

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Purpose. Delivery of nasal powders of granulated β-cyclodextrin by insufflation was studied in order to find the relationship between powder properties and delivery behavior.

Methods. Three nasal powder formulations, prepared by granulating β-cyclodextrin with different binders, were delivered from a powder insufflation device, in which the dose to be emitted was loaded in a gelatin capsule. The delivery sequence of powder was recorded and characterized using an image analysis program.

Results. Particle size was the main parameter affecting nasal powder delivery, both as to the amount of dose sprayed and the aspect of cloud produced. Between 50–150 μm of particle size a substantial change in delivery behavior of powders was observed. Powder of around 100 μm in size showed useful insufflation characteristics for nasal delivery. Bioavailability of nasal formulations of progesterone/β-cyclodextrin powders was discussed in term of delivery behavior.

Conclusions. The formulation approaches for improving nasal delivery of powders require the use of size optimized carriers. Insufflation of powders over 50 μm can favour the particle deposition by impaction, whereas for powders below 50 μm, deposition by sedimentation is moved. β-cyclodextrin is a suitable carrier for achieving high systemic availability following nasal administration of powder formulations.

KEY WORDS: nasal powder; powder properties; nasal powder delivery; insufflation.

INTRODUCTION

Nasal administration of systemic drugs is presently under investigation due to the favourable anatomical and physiological characteristics of nasal mucosa (1–4). This route appears very promising for non-chronic therapy where a rapid effect is desirable; this explains nasal administration in drug abuse and in tobacco consumption (5). Some attempts, however, at prolonged drug release in the nose have also been carried out (6).

Liquid preparations are common dosage forms for nasal administration. They present technological problems linked to formulation stability, low drug concentration at absorption site and short residence time in the nasal cavity (7–8). Nasal powders are an alternative dosage form with improved chemico-physical and microbiological stability (9–11). Administration of powders with a nasal insufflator requires dose delivery facilitating local deposition of particles in the nose. It has been assessed that the site and pattern of inhalatory powder deposition in the respiratory tract are affected by the aerodynamic properties of the powder. Moreover the modality of dose delivery controls the deposition mechanisms i.e. inertial impaction, sedimentation and diffusion (12–13). It could be postulated that efficient nasal delivery of powder from a spraying device requires impaction with adhesion and/or sedimentation of the particles on nasal mucosa; therefore powder properties such as particle size, shape, density and flow must be optimized in order to activate the proper mechanism for the therapeutical treatment.

However the number of drugs directly administrable to the nose in powder form is limited by unsuitability as to particle size, low solubility, poor absorption and irritability. These limits can be overcome through the use of a suitable excipient as carrier. Such a carrier must be compatible, hydrophilic, swellable and soluble, and with an aerodynamic size favourable to nasal deposition. β-cyclodextrin is a substance able to enhance dissolution and to promote transport through mucosa (14).

In this work delivery of nasal powders of granulated β-cyclodextrin from an insufflation device was studied in order to find the relationship between powder properties and delivery behavior. The fraction of the dose emitted from the insufflator (*quantitative aspect*), and the aerodynamic characteristics of the powder cloud produced (i.e. dimension, shape, density) (*qualitative aspect*), were determined. Both these aspects, linked to the fundamental and derived properties of the powder and to the type of insufflation device, affect the deposition of the powder on nasal mucosa.

Finally, the use of β-cyclodextrin as carrier in nasal powder formulation was discussed examining progesterone bioavailability in rabbits.

MATERIALS AND METHODS

Materials

β-cyclodextrin (β-CD), batch 416502 (Roquette Fréres, F); mannitol (B.P. 1993); polyvinylpyrrolidone (B.P. 1993); progesterone (B.P. 1993); progesterone/β-cyclodextrin high energy co-ground (Vector Pharma Int., Trieste-I); spray-dried lactose (B.P. 1993).

Preparation of β-cyclodextrin Granulations

Three granulations were prepared according to the following procedure: 100 g of β-CD powder were kneaded in a mortar, respectively, with 20 ml of 4% w/v mannitol solution in water, or with 6 ml of 10% w/v polyvinylpyrrolidone solution in ethanol, or with 13.5 ml of purified water. The wet mass was forced through a ASTM n° 25 sieve and oven dried at 30°C until constant weight was reached.

Progesterone Nasal Powder Preparation

Using β-CD as carrier, two nasal powders of progesterone having the same composition and containing 12 μg/mg of progesterone were prepared according to (15).

Fundamental and Derived Properties of Granulations

Granulations were sieved collecting the 0–45, 45–63, 63–88, 88–125, 125–180, 180–250, 250–355 μm dimensional fractions. Mean particle size of the fraction was calculated as the sieve diameter obtained averaging the two sieve range limits.

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Poured and tapped densities were measured using 100 g of powder and a 250 ml glass cylinder. Improvement in packing (%) of granulations was calculated according to the following expression:

$$\text{Improvement in Packing} = \frac{\rho_t - \rho_o}{\rho_t} \times 100$$

where ρ_t is the tapped density and ρ_o is the poured density.

Delivery of Powders from the Nasal Insufflation Device

Delivery of powders was performed at 20°C and 60% RH, using a nasal insufflation device (MIAT S.p.A. Milan, I) designed for delivering powders loaded in #3 hard gelatine capsules. Powders in the dose of 20 mg were loaded into the capsule. The filled capsule was inserted in the proper seat of the insufflation device. After having made a hole of approximately 2 mm in the cap and in the body of the capsule, the capsule content was sprayed out with the nasal insufflation device. This operation was performed in an insulated cabinet in order to record the sequences of the delivery process by video camera (WV-F15E Panasonic, Matsushita Electric Industrial Co., Ltd., Osaka, Japan) and video recorder (S-VHS AG-7350 E, Panasonic). The powders were emitted in controlled conditions by substituting the rubbery pump of the insufflator with a spraying system, consisting of a pressurized air reservoir connected to the insufflator nasal adapter through a circuit including pressure reducers and valves (air pressure 0.3 bar; impulsion time 0.2 s). The images of delivery sequences were analyzed by means of an image analysis program (NIH Image 1.49). Height and area of the clouds were measured, together with the time required for the complete ejection of the dose from the capsule inserted in the insufflation device. Completion of emission was considered as corresponding to the moment when the powder flow from the tip of the nose adapter finished. After that time, the height and the area of the cloud continued to grow. Each powder was tested ten times.

RESULTS AND DISCUSSION

Drug insufflation in the nose can be used for various therapeutical activities, the most common of which is local treatment in seasonal rhinitis. Vaccine administration into the nose is done to obtain both local and systemic immunity. Peptidic drugs, such as calcitonin and LHRH, are administered for absorption from nasal mucosa, giving rise to a systemic effect. However the possibility exists to target the brain compartment through the olfactive area situated at the roof of the nose. According to the therapeutic activity, different deposition mechanisms of the insufflated dose must be obtained. Brain targeting would require powder impaction in correspondence with the olfactory area, whereas seasonal affections and peptide absorption would benefit from a more wide-spread deposition. Thus, during powder insufflation, the deposition mechanism suitable for the desired therapy has to be activated, working on powder properties and insufflator characteristics. In this study the characterization of powder insufflation was carried out by measuring the amount sprayed and observing the aspect of cloud produced. The insufflation device used was designed to work with gelatine capsules as reservoirs. The capsule loaded with the powder in poured packing conditions was inserted in the insufflator for a single delivery.

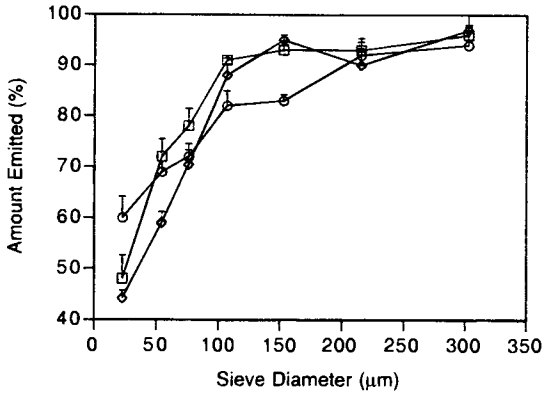

Fig. 1. Influence of particle size of the three β-cyclodextrin granulations on the amount of dose emitted (○ water; □ mannitol; ◇ PVP). The bars represent the standard error of the mean (n = 10).

Quantitative Aspect of Insufflation

The fundamental and derived properties of the three nasal carriers, prepared by granulating β-cyclodextrin, were measured and subsequently related to the quantitative aspect of delivery. For all three carriers, particle size, below a certain limit, strongly affected the amount of powder ejected from the insufflator. Figure 1 shows that the percentage of dose emitted increased with particle size, becoming practically complete and constant over 100 μm.

The packing conditions of the powder inside the capsule are dependent on the interactions between particles and could affect emission from the insufflator. As index of powder packing in the capsule, the improvement in packing was used. Different amounts of delivered dose, as a function of the improvement in packing, for the three granulations, are shown in Figure 2. For the PVP and mannitol granulations, a limiting value of improvement in packing existed and determined a sudden drop in the amount of powder delivered. For the granulation prepared with water, the amount emitted continuously decreased with the increase of the improvement in packing value. However, it has to be observed that powder packing is a derived property

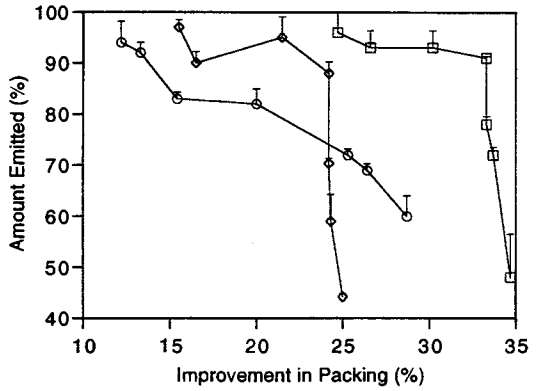

Fig. 2. Influence of the improvement in packing of the three β-cyclodextrin granulations on the amount of dose emitted (○ water; ◇ PVP; □ mannitol). The bars represent the standard error of the mean (n = 10).

of particle size and the different packing conditions reported in Figure 2 were obtained by using different particle sizes, as reported in Figure 1. Therefore, it is hard to distinguish between the powders' individual contribution of particle size and improvement in packing.

An empty space determined by the difference between the apparent volume of powder and the volume of the capsule remains inside the capsule when it is filled with powder. Such a void can affect the movement of the powder inside the capsule during spraying, since a turbulence is generated by the air forced through for dose emission. Therefore the relationship between the loaded dose and the percentage emitted was checked in capsules containing increasing amounts of powder (up to 100 mg). Surprisingly, the percentage of powder delivered was quite insensitive to the level of loading, even when the capsule was completely filled with powder in poured density conditions. However, the dependence of the amount emitted on the particle size, shown in Figure 1 for capsules filled with 20 mg of powder, was maintained in these experiments.

Qualitative Aspect of Insufflation

The aerodynamic behavior of the cloud was evaluated from the pictures recorded during delivery of the powder from the insufflation device. The powder cloud, looking like a plume of pollutant emerging from a chimney, grows in dimensions during emission, with the max height and width achievable depending on the characteristics of the powder sprayed. The powder delivery was fast and complete in less than one second (Figure 3).

The cloud aspect depended on powder particle size, as illustrated comparatively in Figure 4, where clouds recorded at the same time of emission for each examined particle dimension, are reproduced. The clouds originating from small particle size powders were fluffy and homogeneous in density, whereas the clouds obtained from large particle size powders were characterized by visible individual particle trajectories. Variable powder deposition patterns on nasal mucosa could be expected because of differences in cloud behavior determined by size. Therefore area, height and ejection time of powder clouds delivered were measured and compared with powder properties. The height reached by the cloud during the ejection of different size fractions of β-cyclodextrin granulated with PVP is reported in Figure 5, as a function of time. In the first 0.2 s of delivery (corresponding to the time of impulsion of the insufflation device), the particles of the different fractions moved fast, reaching approximately the same height, but then they slowed down more evidently for the smaller particles. Therefore, the rate of particle delivery decreased with decreasing size, whereas the time needed for completely emitting the dose through the nose adapter of the insufflator increased with decreasing size in the range 150–50 μm (Figure 6).

For nasal impaction, the cloud should remain as compact as possible in order to achieve an efficient shot of powder to the nasal mucosa, whereas for sedimentation a larger cloud would be preferred. The packing of the cloud was evaluated by measuring the expansion in area of the axial section of the cloud delivered. The area measured at the maximum expansion was related to particle size: as the particle size decreased below 100 μm, the area of the puff increased (data not shown).

Finally, although the correlation between in vitro behavior and in vivo performance of nasal powder was not the aim of the present work, preliminary evaluation of the links between these aspects has been obtained re-examining previously published data on nasal delivery of progesterone using β-cyclodextrin as carrier (15). Serum progesterone levels, following nasal administration in the rabbit of two powder mixtures containing

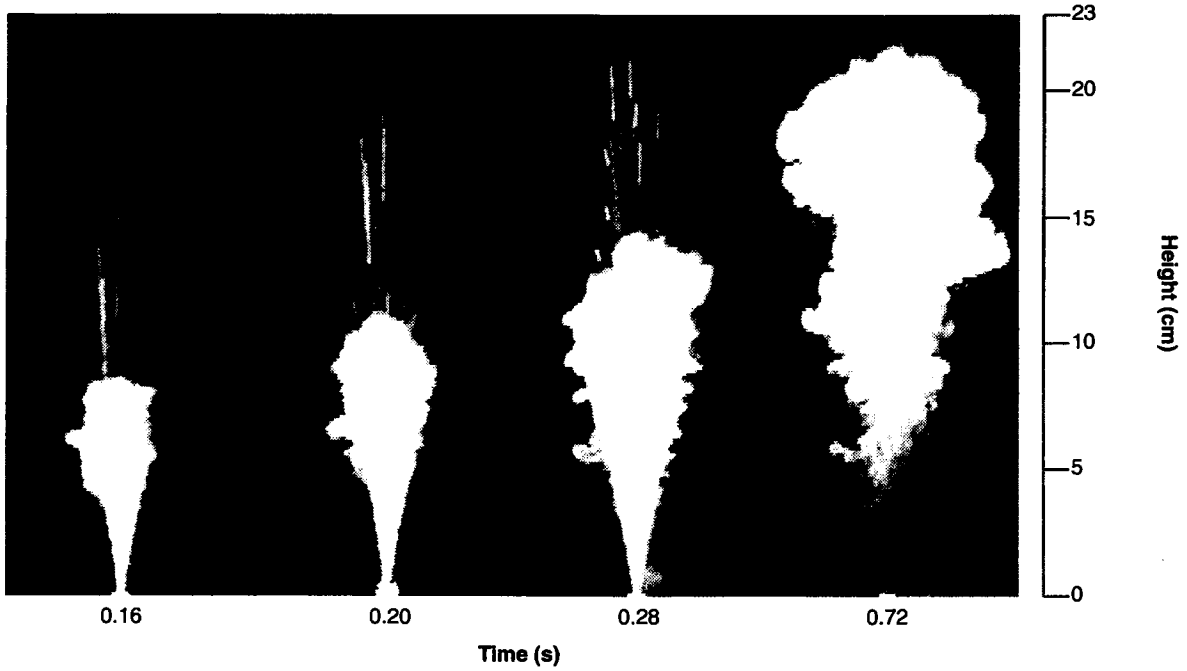

Fig. 3. Delivery sequence recorded for β-cyclodextrin powder (volume-surface diameter, d_{vs} = 8 μm).

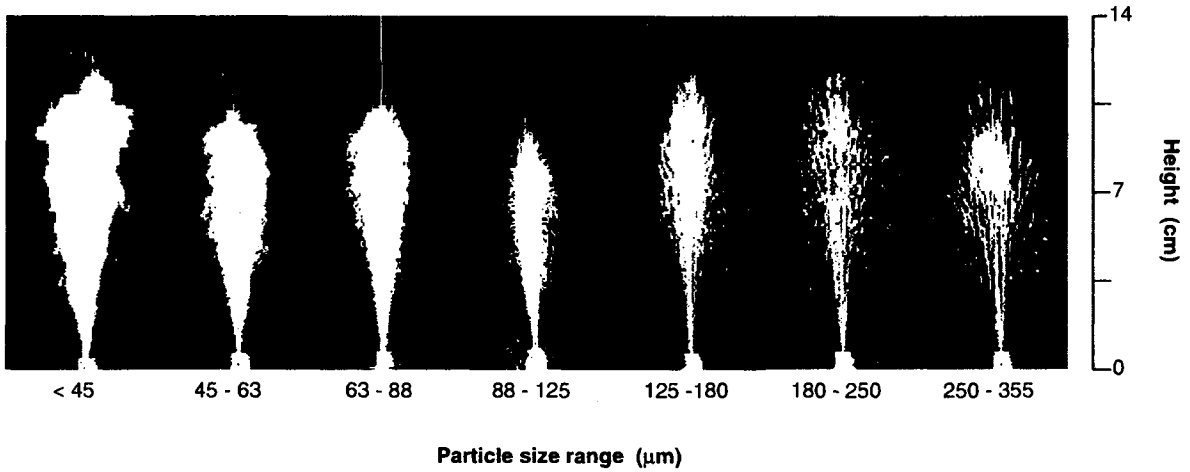

Fig. 4. Influence of particle size of β-cyclodextrin PVP granulation on the cloud appearance (recorded at 0.28 seconds insufflation time).

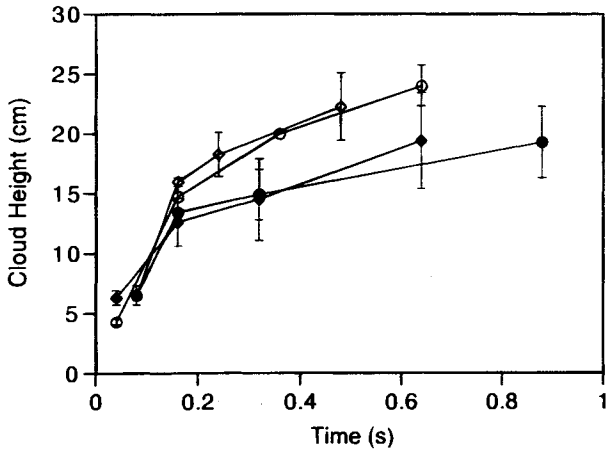

Fig. 5. The height of cloud of PVP β-cyclodextrin granulation as a function of time (particle size range: ● <45 μm;. ♦ 63–88 μm; ○ 125–180 μm; ◇ 250–355 μm). The bars represent the standard error of the mean (n = 10).

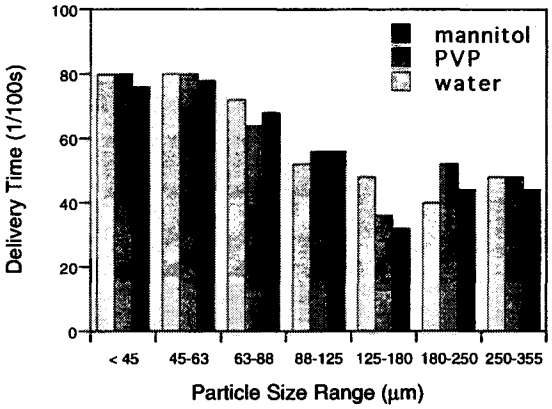

Fig. 6. Delivery time of the three β-cyclodextrin granulations as a function of particle size.

co-ground progesterone-β-cyclodextrin or co-lyophilized progesterone and β-cyclodextrin, showed a rapid response (see Figure 2 of Ref. 15). The powder obtained by co-lyophilization gave the highest progesterone serum peak, although the level was quite transient, whereas the mixture prepared by co-ground progesterone-β-cyclodextrin showed a more prolonged drug level. Progesterone-β-CD co-grounded powder exhibited a significantly higher extent of bioavailability, without a significant difference in rate compared to the co-lyophilized powder. The progesterone-β-CD co-grounded powder was ejected from the insufflator at higher speed and as a compact cloud. Furthermore, its dissolution gave rise to a supersaturated solution of progesterone, whereas dissolution from freeze-dried powder was significantly slower. In the absence of a direct estimate of in vivo deposition patterns and nasal mucociliary removal of powder, the combined effect of delivery, deposition and dissolution of progesterone powder on residence time in the nasal cavity can be deduced from these bioavailability data. More specific experiments need to be performed in order to establish the existing relationship between in vitro and in vivo aspects of nasal powder delivery.

CONCLUSIONS

Powders for nasal administration need careful technological studies because of the special delivery required. According to this work, the formulative approaches for improving nasal deposition of powders consist in the use of size optimized carriers. Particle size greatly affects both the quantitative and qualitative aspects of delivery. It was found that powders around 100 μm in size are efficiently delivered in terms of amount and type of delivery when an insufflation device is employed. In the size range between 150–50 μm there was an evident change in insufflation behavior: over 50 μm size the delivery pattern becomes favorable to impaction of nasal powder formulations, below 50 μm a more uniform deposition by sedimentation is expected, but the risk of particle respirability can increase as well. The device designed for a gelatine capsule can be advantageously loaded with different amounts of powder without adversely affecting its behavior. Nasal powders may provide elevated drug concentration at the absorption site, giving rise to a high flux of substance.

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