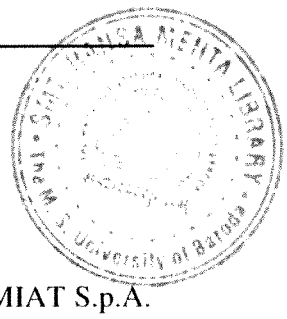
Chapter 8
Performance Evaluation of Nasal Insufflator



8.1 MATERIALS AND METHODS

8.1.1 Materials

- MIAT® nasal monodose insufflator device was gift sample from MIAT S.p.A. Milan, Italy.
- Hard gelatin capsules No. 3 were received as the gift sample from Associated Capsules Pvt. Ltd. (A member of ACG Worldwide), Mumbai, India.
- Electronic weighing balance (Mettler AE 163)
- Yashica digital video camera (EZ Digital F524, Yashica, Japan)
- Microsoft Windows® Movie Maker Version 5.1 software (Microsoft Corporation, USA).
- Adobe® Photoshop CS2 computer software (Adobe Systems Incorporated, California, USA)

8.2 Introduction

The nasal cavity can be used for the delivery of several compounds and offers rapid absorption into the systemic circulation, providing rapid onset of desired therapeutic effect, lower required dosages, fewer side effects, and improved patient compliance. Moreover, this route may also permit the delivery of challenging molecules such as proteins and peptides.

In the past, drops were instilled in the nose, but with the advent of insufflator technology, drops are seldomly used now. Nasal dosage forms consist mainly of preparations containing dispersed or dissolved drugs placed in a container that is squeeze- or spray-activated. Alternatively, liquid solutions can be delivered using metered atomizing pumps or metered-dose pressurized nasal inhalers. Butorphanol (Stadol NS Nasal Spray, Bristol Myers Squibb Co., USA), calcitonin (Miacalcin Nasal Spray, Novartis), dihydroergotamine (Migranal Nasal Spray, Novartis, Inc.), sumatriptan (Imitrex Nasal Spray, Glaxo-SmithKline), and desmopressin (DDAVP Nasal Spray, Aventis Pharma, USA) are some of the drugs marketed in the form of a nasal spray. Cromolyn sodium (Nasalcrom Nasal Solution, Fisons Pharmaceuticals) is available in a solution form. Budesonide (Rhinocort Nasal Inhaler, Astra) and beclomethasone diproprionate (Rino Clenil, Chiesi Farmaceutici) are marketed in the

form of metered-dose pressurized aerosols. Beclomethasone diproprionate is also available in the form of a metered-dose manual spray unit (Beconase AQ, Glaxo-SmithKline, and Vancenase AQ, Schering Plough Corporation).

Nasal powders are an alternative dosage form and may show improved stability. Administration of powders requires nasal insufflators that are either mechanically or respiration actuated. In mechanical devices, a rubber bulb is connected through the dose reservoir to a nasal adapter. Squeezing the rubber bulb provides a stream of air that is capable of emitting the loaded powder in the insufflator. Rinoflatore (Fisons, Italy), Miat Nasal Insufflator (Miat, Italy), and Puvlizer (Teijin, Japan) are some of the marketed insufflators for nasal administration of powders. Respiration-actuated devices are a nose-adapted version of dry powder inhalers (DPIs).With both types of devices, the drug is loaded in a gelatin capsule that is pierced just before activation. The capsule is located between the air jet producer and the nose adapter, and the flowing air stream creates turbulence inside the capsule, which aerolizes and releases the powder from the capsule (Verma and Garg, 2001). Nasal delivery requires microparticles that allow a reproducible dose reservoir filling and aerosolization for appropriate nasal deposition. Ridley et al. (Ridley et al., 1995) and Illum et al. (Illum et al., 1987) reported different clearance half-lifes in humans after administration of starch microspheres using different delivery devices. The Rhinyle catheter used by Ridley et al. (Ridley et al., 1995) resulted in a shorter half-life of clearance as the powder was deposited in the anterior part of the nose as well as in the turbinates, while the Lomudal nasal insufflator used by Illum et al. (Illum et al., 1987) deposited the powder mainly in the anterior part of the nose leading to a slower clearance. It can be concluded that the delivery device is important in the development of a nasal powder formulation as it has an impact on the deposition pattern and hence the nasal clearance.

Nasal powder delivery requires that the dose may be quantitatively released and distributed in the nasal cavity. The deposition pattern may certainly affect drug bioavailability (Vidgren et al., 1988), and thus it is important to investigate the behaviour of the microspheres during their delivery from a commercial device (Provasi et al., 1993a; Provasi et al., 1993b; Provasi et al., 1994).

8.3 MIAT® Nasal Monodose Insufflator

8.3.1 General information

This device was patented by Miat in 1987, and the patent was extended world-wide in 1988. It can be used with hard gelatin capsules no. 3, filled with either the active alone or with a carrier, as a free flowing powder. Sealed capsules are recommended.

The insufflator is presently marketed in some European countries, for the administration of nasal powdered vaccines and steroids, but it has been tested as suitable for the insufflation of typical anti asthma drugs.

The insufflator (Fig.8.1) is made of:

a – A body
b – A protective cap (1)
c – A nozzle (2)
d – A revolving chamber (3) with grip tab (4)
e – Two red push-buttons (5)
f – A white push-button (6)
g – A pump (7)

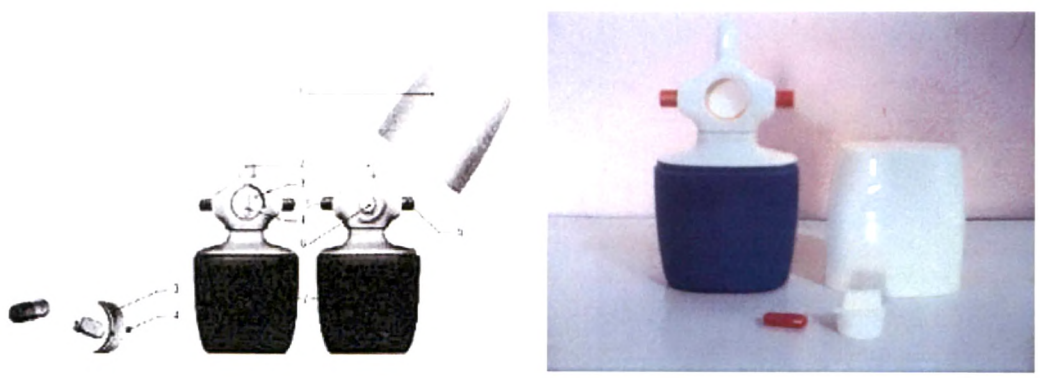
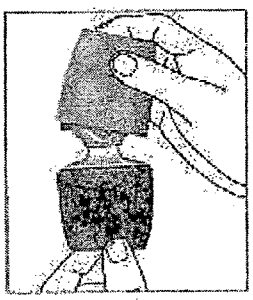


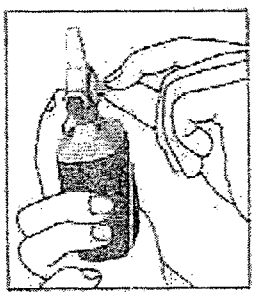
Fig. 8.1 Miat® monodose nasal insufflator

8.3.2 Instructions for use

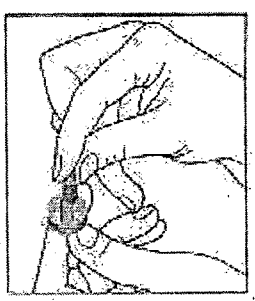
1. Remove the protective cap (1)



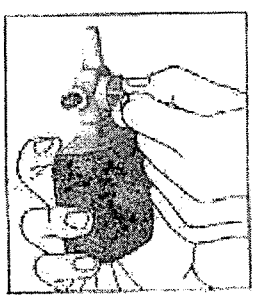
2. Push the white button (6) to eject the revolving chamber (3)



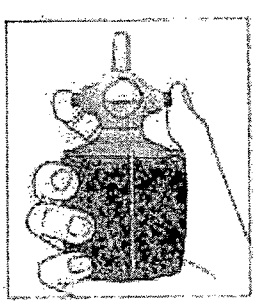
3. Position the capsule in its proper seat. the Make care not to deform it.



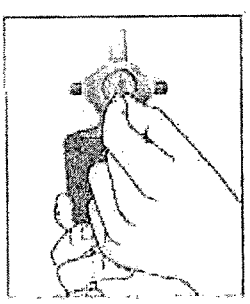
4. Introduce the revolving chamber (3) in body and turn it clockwise until the grip tab is horizontal (position 1)



5. Thoroughly press the red buttons (5) to pierce the capsule



6. Turn the revolving chamber 90^0 anti-clock wise, till the grip tab is vertical (position 2)

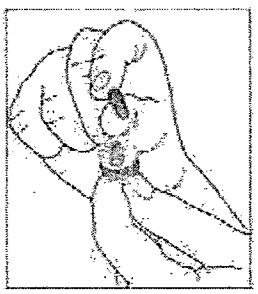


7. Introduce the nozzle (2) into a nostril

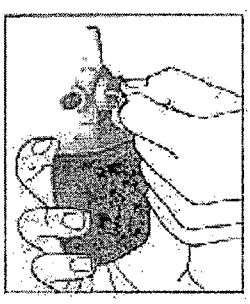
8. Push the white button (6) to extract

and vigorously press the pump two-three times (better with two hands). Keep the mouth open during the insufflation.

the revolving chamber (3) and control the capsule is empty, if it isn't, repeat the insufflation in the same nostril.
Press the grip tab to discard the empty capsule.



9. Put the revolving chamber (3) in the body and close the system with the protective cap (1).



8.3.3 Cleaning Suggestions

Clean the nozzle with the moistened tissue paper or a cotton flock. Both the out-let and revolving chamber can be cleaned with a pipe-brush, to avoid powder lodging.

8.3.4 Warnings

It is suggested to properly follow the above instructions to avoid any incorrect use of the insufflator.

8.4 Methods

8.4.1 Characterization of microspheres delivered from a nasal device (Quantitative aspect)

The Miat® nasal insufflator was tested for reproducibility of dose delivered by filling accurately weighed optimized microsphere formulations (CHCR, ALCR, CHNT and ALNT) into a No. 3 capsule. The capsule was placed in the insufflator and pierced with a needle. Then the powder was sprayed by squeezing the rubber bulb (puffing). The amount of powder delivered after each puff was measured using weight difference in the capsule. The measurements were taken after each puff for a total of three puffs. The insufflator was characterized for different doses of microsphere powders (5, 10, and 20 mg). The same device was used throughout the entire study for all the formulations.

8.4.2 Analysis of spray pattern (Qualitative aspect)

The appearance of the puffs during the delivery of microsphere powder formulations from the Miat nasal insufflator were recorded by means of a video camera (Yashika, Japan) and Microsoft® Windows Movie Maker Version 5.1 software (Microsoft Corporation, USA). The image analysis was carried out by means of Adobe® Photoshop CS2 computer software (Adobe Systems Incorporated, California, USA) and characterized in terms of the area and shape of the powder clouds (Provasi et al., 1993b; Provasi et al., 1994).

8.5 Results and Discussion

In the present 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 gelatin capsules as reservoirs. The fraction of the dose actually delivered by the device is important quantitative information. We determined that after the second puffing more than 95% of the content was delivered for all the formulations with 5, 10 and 20 mg loading. After three puffs, almost the entire amount of powder was delivered for all the microsphere formulations (Table 8.1 to Table 8.3).

Table 8.1 Percent of formulation delivered from MIAT® nasal monodose insufflator with 5 mg loading

Formulation (5 mg)	Dose delivered* (%) after		
	1st Puff	2nd Puff	3rd Puff
CHCR	88.6±0.6	95.2±0.7	98.6±0.8
CHNT	90.3±0.4	96.4±0.2	99.1±0.5
ALCR	91.2±0.9	95.1±0.4	98.8±0.7
ALNT	89.7±0.7	96.5±0.3	98.3±0.5

* Mean ± SD, n = 3

Table 8.2 Percent of formulations delivered from MIAT® nasal monodose insufflator with 10 mg loading

Formulation (10mg)	Dose delivered* (%) after			Puff area (cm^2)
	1st Puff	2nd Puff	3rd Puff	
CHCR	90.4±0.6	95.8±0.5	98.9±0.6	52.96
CHNT	88.9±0.4	96.1±0.8	98.4±0.6	47.52
ALCR	91.2±0.8	97.3±0.5	99.2±0.4	50.49
ALNT	92.2±0.8	96.8±0.7	98.8±0.5	51.90

* Mean ± SD, n = 3

Table 8.3 Percent of formulation delivered from MIAT® nasal monodose insufflator with 20 mg loading

Formulation (20 mg)	Dose delivered* (%) after		
	1st Puff	2nd Puff	3rd Puff
CHCR	91.5±0.7	96.1±0.8	98.2±0.3
CHNT	90.4±0.9	95.8±0.5	99.6±0.7
ALCR	92.6±0.4	96.2±0.4	98.3±0.6
ALNT	90.7±0.9	95.9±0.5	98.1±0.4

* Mean ± SD, n = 3

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 turbulence is generated by the air forced through for dose emission (De Ascentiis et al., 1996). Therefore the relationship between the loaded dose and the percentage emitted was checked in capsules containing increasing amounts of powder (5, 10, 20 mg). There was no significant difference in percentage of formulation delivered after each puffing for different loadings of 5, 10 and 20 mg (Table 8.1 to Table 8.3).

Beside the delivery device, the spray pattern of the powder formulation may also influence the deposition, and consequently contribute to the nasal bioavailability. Therefore, the spray pattern (shape) of the microsphere formulations was investigated using Miat nasal monodose insufflator.

The images of microsphere powder clouds (Fig. 8.2 – Fig. 8.5) demonstrated that microspheres were delivered forming an elongated puff. The core of the clouds was homogeneous which can be expected to provide effective distribution pattern. As shown in Fig. 8.2 to Fig. 8.5., the homogeneous clouds showed a uniform density of the microspheres, likely due to narrow size distribution of the microparticles. The shape and area of the clouds give qualitative information about the delivery ability of the microsphere formulations. The values for puff area for all the four formulations

with 10 mg loading are shown in Table 8.2. It is interesting to note that there was no significant difference in cloud delivery between different formulations. The results obtained in this work showed that all the microsphere formulations were suitable for nasal delivery and were efficiently delivered from the nasal insufflator.

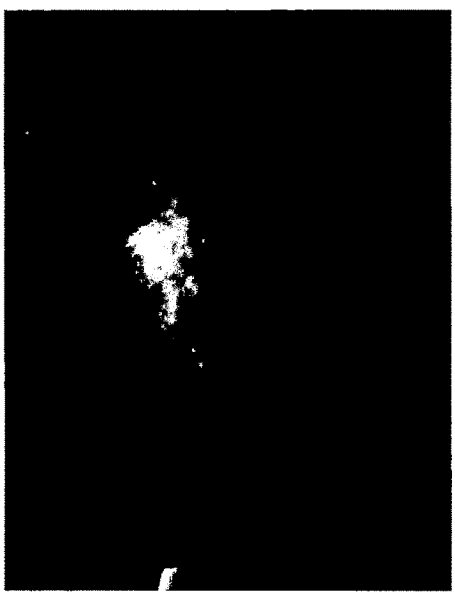


Fig. 8.2 The spray pattern (shape) of CRV loaded chitosan microspheres from MIAT® nasal monodose insufflator.

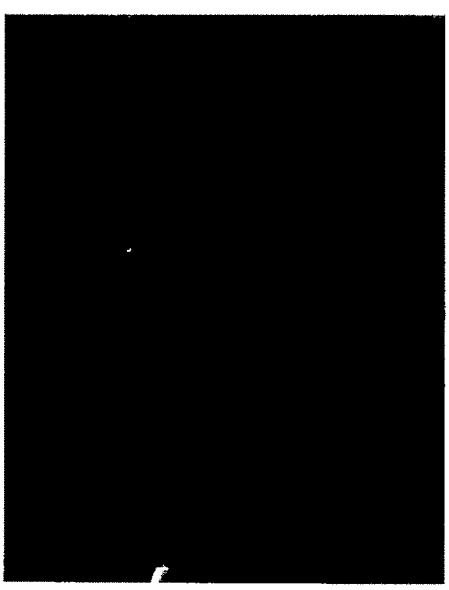


Fig. 8.3 The spray pattern (shape) of NTD loaded chitosan microspheres from MIAT® nasal monodose insufflator.

Fig. 8.4 The spray pattern (shape) of CRV loaded alginate microspheres from MIAT® nasal monodose insufflator.

Fig. 8.5 The spray pattern (shape) of NTD loaded alginate microspheres from MIAT® nasal monodose insufflator.

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