P-017 **Mucoadhesive chitosan microspheres as a delivery system for nasal insufflation**

Patil S. [1#] and Sawant K. [1*]
[1] The M. S. University of Baroda, Vadodara, India
* Supervisor # sbpatil_99@rediffmail.com

INTRODUCTION AND OBJECTIVES

Nasal administration has attracted much attention of many researchers within the last few decades because of its great potential utility for drug delivery. The nasal cavity possesses many advantages as a site for drug delivery such as; a large surface area for absorption with a sub epithelial layer that is highly vascularised, ease of administration and applicability for long-term treatments. In addition, blood is drained directly from the nose into the systemic circulation, thereby avoiding first pass metabolism. Nasal powder formulations may improve chemical and microbiologic stability of the drug over liquid formulation, allowing larger amounts of drug to be administered. In any case, the effectiveness of nasal preparations depends on their appropriate deposition inside the nasal cavity (Illum 2003).

The aim of the present study was to develop and characterize mucoadhesive chitosan microspheres for nasal delivery. The microspheres were prepared by emulsification-cross linking method and evaluated for morphology, particle size and delivery properties from Miat® nasal insufflator.

MATERIALS AND METHODS

Chitosan was a gift sample from Ample Effect Sdn Bhd, Selangor (Malaysia) and used without any modification and purification (Molecular weight ~600,000 Daltons, Degree of deacetylation > 85%). Liquid paraffin, glutaraldehyde (25% aqueous solution) (GA), and hexane were purchased from S. D. Fine Chemicals, Mumbai, India. Dioctyl sodium sulfosuccinate (DOSS) was procured from Wilson Laboratories, Mumbai, India. All other chemicals and reagents used in the study were of analytical grade. The gift sample of Miat® nasal insufflator was provided by Miat, Milano, Italy.

Chitosan microspheres were prepared by simple w/o emulsification-cross linking process using liquid paraffin (heavy and light, 1:1) as external phase (Thanoo 1992). Briefly, chitosan was dissolved in 2% aqueous acetic acid solution by continuously stirring until a homogeneous solution was obtained. This solution was added slowly to liquid paraffin (heavy and light, 1:1) containing 0.2% w/v of DOSS as stabilizing agent under constant stirring at 1200 rpm speed for 15 min. using a Eurostar (IKA Labortechnik, Germany) high speed stirrer. To this w/o emulsion, GA was added slowly and stirring was continued for 2 h. The hardened microspheres were separated by vacuum filtration and washed several times with hexane to remove oil. Finally, microspheres were washed with distilled water to remove unreacted GA. The microspheres were air dried for 24 h and then stored in vacuum desiccator until further use.

Microsphere characterization

Morphology The microspheres were studied for shape and surface by optical microscopy (Olympus Microscope, Olympus Optical Co. Ltd., Japan). The samples were studied in the form of dispersion in paraffin oil.

Particle size analysis Particle size and size distribution was determined by the laser light scattering on a Malvern particle size analyzer (Malvern Mastersizer 2000, Malvern Instruments, UK). The dispersion of microspheres was added to the sample dispersion unit containing the stirrer and stirred in order to reduce the aggregation between the microspheres and the laser obscuration range was maintained between 3 and 15%. The average volume mean particle size was measured after performing the experiment in triplicate.

Characterization of microspheres delivered from a nasal device (Quantitative study) The Miat® nasal insufflator was tested for reproducibility of dose delivered by filling accurately weighed (10 mg) optimized microsphere formulation 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.

Analysis of spray pattern (Qualitative study) 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.

RESULTS AND DISCUSSION

The microspheres obtained were of good morphological characteristics, spherical shape, smooth surface without aggregation and free flowing powders (Fig. 1). However,

one noticeable characteristic of the cross linked chitosan microspheres was their yellow to brownish colour. The particle size of the microspheres was in the range of 22.36-41.85 µm which is favourable for intranasal administration.

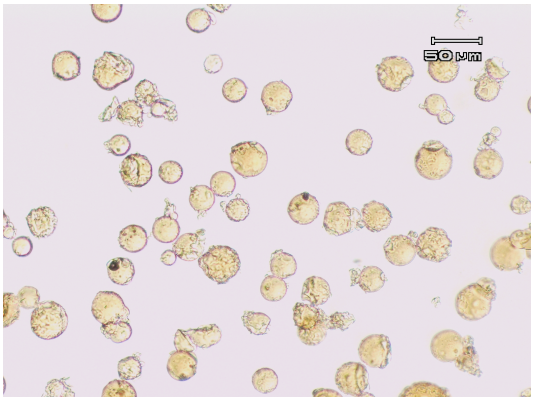

Figure 1: Photomicrograph of chitosan microspheres

Microspheres delivered from a nasal device (Quantitative study) In the present study, the characterization of powder insufflations 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. After three puffs, almost the entire amount of powder was delivered. (Table 1).

Table 1: Percent of formulations delivered from MIAT• nasal monodose insufflator

Formulation	Dose delivered* (%) after		
	1st Puff	2nd Puff	3rd Puff
Microspheres	90.4±0.6	95.8±0.5	98.9±0.6

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 1996).

Spray pattern of the microspheres (Qualitative study) 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. 2) 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. 2, 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.

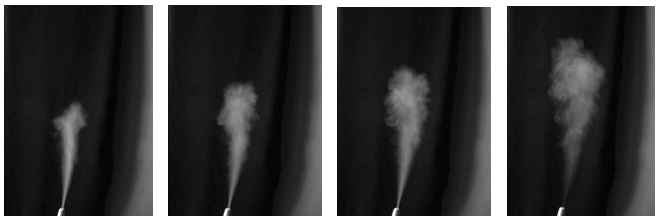

Figure 2: Delivery sequences of chitosan microspheres from Miat® nasal insufflator

CONCLUSIONS

Mucoadhesive chitosan microspheres prepared by emulsification cross linking method were spherical in shape and with smooth surface. The size of the microspheres was in the range of 22-41 µm which is favourable for intranasal absorption. The results obtained in the present work showed that the microspheres were suitable for nasal delivery and were efficiently delivered from a nasal insufflator.

REFERENCES

- De Ascentiis A. et al. (1996) *Delivery of nasal powders of β-cyclodextrin by insufflation*. Pharm. Research 13(5), 734-738.

- Illum L. et al. (2003) *Nasal drug delivery-possibilities, problems and solutions*. J. Controlled Rel. 87, 187–198.

- Thanoo B. C. et al. (1992) *Crosslinked chitosan microspheres: preparation and evaluation as a matrix for the controlled release of pharmaceuticals.* Journal of Pharmacy and Pharmacology 44, 283-286.