

# CHIMERAL AGGLOMERATES OF MICROPARTICLES FOR NASAL ADMINISTRATION OF ANALGESIC DRUG POWDERS

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## INTRODUCTION

Recently, nasal route has received a great deal of attention as a method for systemic administration of drugs, especially those that have to be administered by injection. The nasal route is advantageous because of the rapid absorption of drug molecules across the nasal mucosa and the relative ease of administration (1). 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. Nasal powders face similar technological paradox as inhalation powders: the particles must be small for aerosol delivery and drug dissolution, but large enough for handling during manufacturing of dosage form. This technological drawback could be solved by particle agglomeration, which is a process used to increase the powder particle size giving rise to microparticle clusters (2). These agglomerates are defined “chimeral” since their size is reversed by insufflation. Agglomerates have big size for easier dosage form manufacturing; the “chimeral” definition means that their size is temporary, since insufflation produces small fragments suitable for deposition and drug release. This concept of chimeral nasal powder was applied to an analgesic drug in view of its nasal administration for the management of postoperative pain and for moderate-to-severe pain in cancer patients. Hence, this paper describes the pharmaceutical development of a nasal powder of morphine.

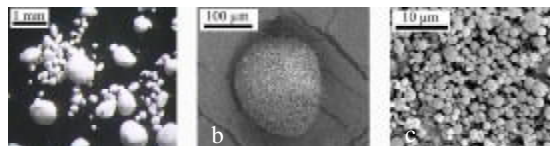
## EXPERIMENTAL METHODS

Morphine microparticle agglomerates were prepared from microparticles (mean diameter: 4  $\mu\text{m}$ ) obtained by spray drying a 4% w/v solution of morphine HCl:lactose:lecithin (90:6:4) in a water:ethanol mixture (10:1). Agglomeration was performed by tumbling 10g of this powder in a 1L glass pan rotating at 50 rpm for 5 min. Free flowing agglomerates between 106 and 850  $\mu\text{m}$  were recovered by sieving. Agglomerate and particle morphology was analyzed by scanning electron microscopy. The insufflation of the agglomerates was performed by means of the Monopowder<sup>®</sup> device (Valois S.A., France) loaded with 11.4 mg of the agglomerates. Plume formation was recorded with a high speed video camera with appropriate lighting

conditions. Transport across rabbit nasal mucosa (Franz cell 0.196  $\text{cm}^2$ ) was also studied. Pictures of agglomerate insufflation in a human nasal cast, which constituted of two parts corresponding to the nasal cavities and separated by a transparent PVC sheet simulating the septum, were taken (silicon cast of human cadaver, gift of Teijin Lim., Tokyo).

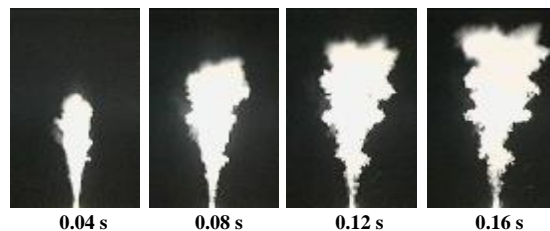
## RESULTS AND DISCUSSION

The SEM analysis showed that the spray dried microparticles constituting the agglomerates were spherical in shape. The microparticle agglomerates appeared round and compact with a smooth surface.



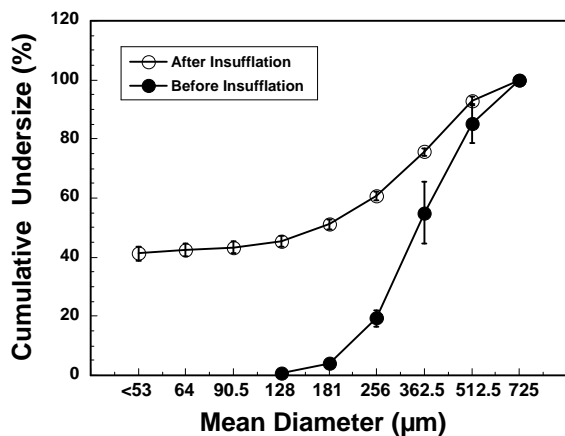
**Figure 1:** Morphine microparticle agglomerates (a); SEM image (b); spray dried microparticles (c).

Chimeral agglomerates were efficiently delivered in form of fragments after insufflation from the Monopowder<sup>®</sup> nasal device, since the insufflator emitted  $95.9\% \pm 0.4$  of the loaded dose in one shot. Visual assessment of the pictures of the delivery sequence showed that the agglomerates were extensively broken by insufflator actuation, as the fluffy aspect of the cloud evidenced.



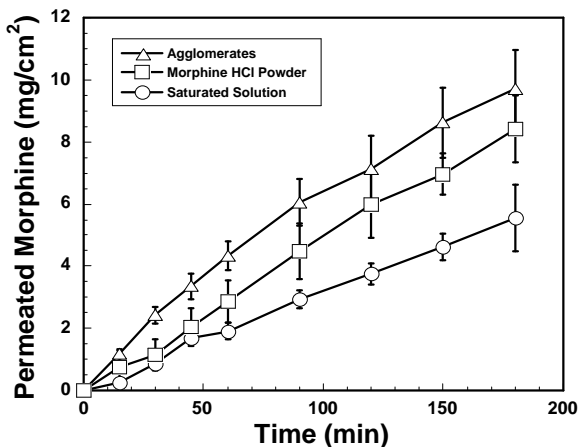
**Figure 2:** Delivery sequences of morphine microparticle agglomerates from nasal insufflator Monopowder<sup>®</sup> Valois.

The fragment size distribution after insufflation was dependent on the mechanical resistance of the agglomerates and on the type of insufflator. Figure 3 shows the size distribution of agglomerates before and after insufflation through Monopowder<sup>®</sup> Valois.



**Figure 3:** Size distribution before and after insufflation by Monopowder® Valois of morphine microparticle agglomerates.

Permeation profiles across rabbit nasal mucosa showed that the transport rate of morphine from crystals was significantly higher than from a morphine saturated solution. However, the profile obtained from morphine microparticle agglomerates showed the highest permeation rate, likely due to the amorphous structure of spray dried morphine as evidenced by DSC.



**Figure 4:** Permeation profiles through rabbit nasal mucosa.



**Figure 5:** Deposition into human nasal cast of agglomerates insufflated with Monopowder® Valois.

Figure 5 shows the insufflation of morphine microparticle agglomerates in the human nasal silicon cast. By washing out the deposited morphine particles

from nasal cavity, more than 50% of powder was found in the cast nasal cavity after insufflation. From the picture taken during insufflation, it was shown that part of the dose reached the nasal pharynx portion of the human nasal cast.

## CONCLUSIONS

We can conclude that microparticles of morphine obtained by spray-drying micronization can be successfully transformed into spherical and flowable agglomerates. Moreover, they can be efficiently delivered and morphine is quickly released and transported in vitro across rabbit nasal mucosa.

## ACKNOWLEDGMENTS

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