INTRODUCTION

Inhalation administration is a highly effective delivery route allowing the bypass of first-pass metabolism and permitting local delivery to the lungs but the use of this route presents the pharmaceutical industry with some unique challenges. One such challenge is the acquisition and maintenance of suitable exposure and generation systems, and the expertise and ability to properly characterize atmospheres. Another challenge is the profligate use of candidate drug in inhalation which can lead on occasions to the test item costs exceeding the costs of the preclinical studies.

As a potential alternative to traditional inhalation exposure, we present experience with intratracheal powder aerosol delivery in rats using a delivery device. This technique permits the direct intratracheal delivery of small quantities of dry powder using a few milliliters of air.

METHODOLOGY

We performed a study with intratracheal insufflations of air, empty PLGA microspheres (50/50 DL-lactide/glycolide copolymer) (10 mg/day) and a pharmaceutical test item (10 mg/day) to female Sprague Dawley rats. Only the results of the air and PLGA control groups are presented. The study included a single administration arm and a 7-day repeat administration arm.

RESULTS

The rats were housed in stainless steel rodent cages with ad libitum access to food and water and were approximately 11 weeks of age and 250 grams of weight at onset of treatment. During the study, the rats were observed for adverse clinical signs, body weight measurements were taken at intervals and the food consumption was measured daily.

Prior to study initiation, trials were performed to optimize the powder loading in the delivery device and to determine the lowest volume of air needed to produce a reproducible delivery of the material. These trials confirmed that the device can block on occasions, and that loading 11 mg of PLGA improved chances of delivering the desired 10 mg/day. We also found that it is preferable to always keep the device in an upright position and <50% of the powder between actuations.

For administration, the rats were placed on an inclined platform, in a retro recumbent position. As a potential alternative to traditional inhalation exposure, we present experience with intratracheal powder aerosol delivery in rats using a delivery device. This technique permits the direct intratracheal delivery of small quantities of dry powder using a few milliliters of air.

DISCUSSION

Single or repeat intratracheal powder aerosol delivery to rats is a feasible and cost effective alternative approach to inhalation exposure during early discovery allowing for preliminary toxicological and pharmacokinematic evaluation. The results suggest that evaluation of the local effect on the respiratory tract can be informative but findings related to intratracheal administration may complicate distinguishing test item related effects from artifactual mechanical lung damage. Customization of the study design taking in account the nature of the test item under study and the specific targeted goals or objectives can limit or circumvent the influence of the inherent limitations to this technique when compared to traditional inhalation. Consideration should be given to the following points:

- Pretest trials with the test item are essential to improve the methodology used, delivery efficiency and technical expertise.
- Inclusion of a concurrent air control group is essential.
- The inclusion of a positive control group receiving inert and poorly soluble material (such as carbon black or titanium dioxide, see Reference 1) may improve chances to differentiate the chemical/pharmacological effect of the test item from non-specific macrophage response to poorly soluble material (such as PLGA) and the associated secondary inflammatory responses and/or tissue damage that may occur when large quantities of such material are deposited in the lungs.
- Values for individual achieved doses for each animal can assist in the evaluation of pharmacokinetics.
- It can be helpful to work with larger (aged) rats in order to minimize local effects on the respiratory tract.

CONCLUSION

We present here the findings following repeated intratracheal administration of air and dry powder aerosols (PLGA) to rats. At the dose-level of poorly soluble material employed here, the achieved dose variability and lung mechanical damage represented noteworthy limitations that may affect the toxicological evaluation, but careful study design can reduce their influence. The results suggest that this approach can offer a feasible and cost effective approach to pulmonary exposures during discovery stage studies, allowing preliminary toxicological and pharmacokinematic evaluation prior to commitment to traditional inhalation studies.

REFERENCE

1. KJ. nikula (2013) STP Position Paper: interpreting the Significance of increased bronchiolalveolar inflammation and associated findings

ACKNOWLEDGMENTS

Special thanks to for technical support (Anne Pozzi), Mireille Dagostini, Nathalie Leveque and Odile Facquet.