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PRECLINICAL EVALUATION OF EAR DOSAGE FORMS

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INTRODUCTION

The World Health Organization estimates that by 2050, over 700 million people, or one in every ten people, globally will experience disabling hearing loss. Hearing loss negatively impacts personal well-being. Studies have shown that children and adults with hearing loss have a poorer quality of life due to reduced social interactions, isolation, a sense of exclusion, and depression, and in older people, this can lead to accelerated cognitive decline. Hearing loss can result from many different types of inner ear disorders, including presbycusis (age-related hearing loss [ARHL]), genetic polymorphisms, trauma, exposure to noise, and ototoxic medications, to name a few. There are several therapeutic strategies to treat inner ear disorders, including systemic or local delivery of therapeutic agents, surgical intervention, and acoustic (e.g., hearing aids) and electric (cochlear implants) amplification (Fig. 1).

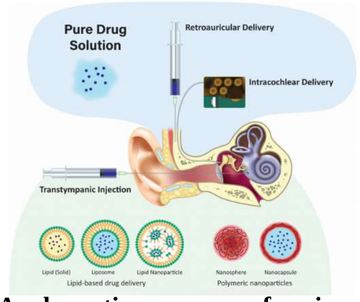

Fig. 1 A schematic summary of various drug delivery routes to the inner ear

Preclinical evaluation is an integral part of the development of any drug, including ear dosage forms. The availability of specific animal disease models and technical developments in the imaging of small animals provide valuable information for the evaluation of new drugs prior to clinical trials.

AIM AND OBJECTIVES

This research aims to give information covering all aspects of preclinical testing and aspects related to in vitro and in vivo preclinical evaluation of ear dosage forms.

MATERIALS AND METHODS

Electronic databases: Medline, Cochrane, Embase and Springer were accessed using "preclinical research", "ear dosage forms". Also, the search was conducted by using printed pharmaceutical and chemical journals and the 21 CFR Part 58.1: Good Laboratory Practice for Nonclinical Laboratory Studies.

RESULT

The vast majority of preclinical studies are carried out with well established radiopharmaceuticals and can be used to:
(a) validate an animal disease model;
(b) evaluate the effect of a drug;
(c) determine a drug's receptor occupancy as part of drug development programmes.

All animal experiments need to follow applicable laws in the country where the experiment is conducted. It is recommended to have a well defined national structure to assure judicious use of animals in experimentation, as well as for licensing facilities for animal handling.

A model recreated in mice is ideal given their anatomical and physiological similarity to the human middle ear, the natural occurrence of otitis media, the large background research defining their genome and immune system, and the ability to generate large and efficient in vivo throughput screens for therapeutics in a consistent, efficient, and reproducible way. Larger animals are difficult to study given the tortuosity of their external ear canals, preventing direct middle ear access (Fig. 2).

Any animal experiment has to take into account the following ethical principles of laboratory animal science, known as the 3R principles: replacement, reduction and refinement. Animal models can be divided into five groups: spontaneous, experimentally induced, genetically modified, negative and orphan models. It is important to carefully choose the right number of animals. The most common method to determine the necessary number of animals is to perform a power analysis. This analysis establishes a mathematical relation.

RESULT

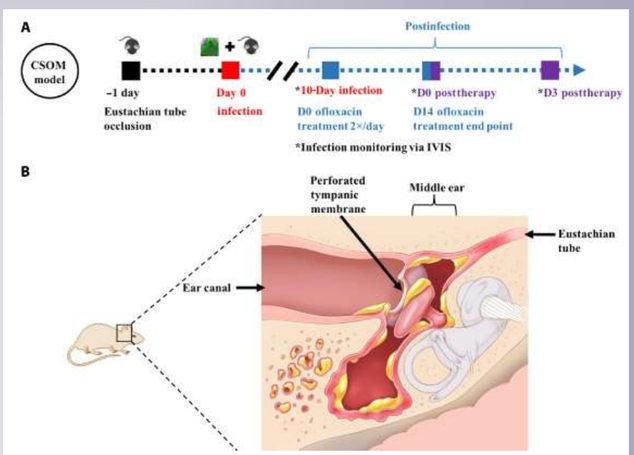

Fig. 2 An exemple of mouse model of preclinical study of an ear dosage form

(A)Timeline for bacteria inoculation and antibiotic administration. Mice underwent procedures of Eustachian tube occlusion and acute tympanic membrane perforation 1 day before bacteria inoculation.

(**B**) Axial view of middle ear anatomy relevant to the generation of a mouse model of chronic

CONCLUSIONS

Preclinical or non-clinical evaluation is an integral part of the development of any drug. The process of developing a new drug includes rigorous testing before it can be cleared for use in humans. In-depth characterization of its behaviour is necessary to assess its safety and suitability for the intended clinical application.

KEYWORDS

preclinical evaluation, animal models, ear dosage forms.