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Cover story

Isolated lung model for assessing drug absorption from PLGA microparticles

Inhalation has been used widely over the years as a way of localizing drugs in the lungs. The direct aerosol delivery to the lungs ensures high local drug concentration, which favors a rapid onset of action with minimal systemic exposure, hence reducing undesired side effects. One major disadvantage of "conventional" inhalation therapy, however, is the relatively short duration of drug action at the target site. The maintenance of a therapeutic drug level requires frequent administrations which result in low patient compliance. Currently, however, no sustained release lung delivery system is available clinically. One of the reasons for the slow development of inhalable controlled release formulations is the absence of practical, preclinical lung models for testing different delivery systems. The isolated lung (IL) technique has a long tradition in the field of pharmacology for evaluation of mechanisms of drug action and drug absorption over the essential air/blood barrier. The IL models also enable an efficient administration of drug formulations and better control over relevant experimental parameters as compared with the *in vivo* setting.

The study performed by Beck-Broichsitter and his colleagues expands our understanding of the drug release and absorption processes of lung-delivered sustained release formulations [1]. A rabbit IL model was used to assess the performance of poly(lactide-co-glycolide) (PLGA) microparticles loaded with the drug sildenafil which is used for treating pulmonary hypertension. Administration of the free drug *via* inhalation, however, necessitates frequent daily inhalations, due to its short duration of action (<1–2 h following aerosol delivery). Sildenafil-loaded PLGA microparticles (particle size of ~5 μm) with distinct drug release profiles were prepared by vibrational spray-drying and administered to the airspace of the IL model using a dry powder insufflator. Drug delivery vehicles demonstrated an *in vitro* sildenafil release with a half-life of 15–200 min. The release kinetics of employed microparticles correlated well with the glass transition temperature and the molecular weight of the utilized polymers/polymer blends. The carriers composed of PLGA of lower molecular weight (and glass transition temperature) resulted in a faster *in vitro* drug release. The authors then followed the lung-specific absorption profiles, which differentiated the diverse sildenafil-loaded polymeric microparticles according to their *in vitro* release characteristics (half-life of 5–230 min).

The study by Beck-Broichsitter et al. has provided important information on sustained lung delivery of medications. The IL model enabled a precise analysis and discrimination of drug release from the distinct sildenafil-loaded polymeric microparticles, even though the differences in temporal delivery rate were comparably small (minute scale). The *ex vivo* sildenafil absorption also correlated well with the observed *in vitro* drug release kinetics. At the same time, however, the IL model discloses potential limitations of the technique in the analysis of long-acting medications. As compared with typical *in vivo* studies, IL preparations offer comparatively short duration of study time (~6 h) due to deterioration of the isolated organ. Furthermore, the IL model needs to be adapted to the specific properties of the utilized drug (*e.g.*, total recovery). In this respect, addition of albumin to the perfusion medium improves the analysis of absorption and distribution characteristics of hydrophobic drugs, such as sildenafil, simulating the expected plasma protein binding [2]. Most importantly, it still remains open whether the *ex vivo* findings are directly transferrable to the *in vivo* behavior of prolonged release formulations in the lungs. The drug release data for diverse PLGA vehicles in intact animals or humans often differ from what was observed during *in vitro* testing.

The study by the Beck-Broichsitter team presents valuable information for further development of inhalable controlled release formulations. The preclinical IL technique was able to differentiate diverse sildenafil-loaded PLGA microparticles with their own *in vitro* release characteristic. The IL model will continue to improve to expand its applicability to various drugs and delivery systems, which in turn will enhance our knowledge for accelerated development of inhalable sustained release formulations for clinical applications.

References

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