List of Publications


Summary

Pulmonary Arterial Hypertension (PAH) is WHO Group I class of pulmonary hypertension (PH) defined by the blood pressure higher than 25 mmHg at rest or 30 mmHg during physical activity, in the pulmonary arteries. Pulmonary hypertension is a severe pathophysiological condition in which the right heart needs to work harder to force the blood to the lungs through constricted small pulmonary arteries eventually leading to right heart failure. New treatment guidelines and increasing awareness of PAH is now attracting R&D investment to enter this compact but lucrative market due to the high unmet needs and high treatment values per patient. Commercially available treatments like Flolan® (Epoprostenol sodium) and Remodulin® (Treprostinil) as a continuous intravenous infusion; Tracleer® (Bosentan, twice a day), Revatio® (Sildenafil, thrice a day) as tablet dosage form are associated with limitations of frequent dosing and patient compliance. Further, once a day available treatments like Thelin® (Sitaxsentan), Letairis® (Ambrisentan) and Adcirca® (Tadalafil) are associated with non-specific vasodilation and other toxic effects in whole vasculature instead of reducing pulmonary vascular resistance.

For respiratory conditions, non-invasive pulmonary route of delivery is preferred to deliver the drug for instant and enhanced local (pulmonary arteries) action while reducing the exposure of drug to the systemic circulation and hence potentially minimizing adverse effects. Ventavis® (Iloprost sterile solution) and Tyvaso® (Treprostinil sterile solution) are the only commercially available inhalations, but with a drawback of high inconvenience to patient due to very frequent dosing of 6-9 times and four times (3 inhalations per treatment) per day respectively.

Several lipid and biodegradable polymer based sustained-release systems have been explored as potential carriers for pulmonary delivery. Components of the delivery system must be non-toxic, non-immunogenic, biodegradable and without inflammatory and alloreactive reactions. Using lipid based dry powder inhaler formulations like liposomes and lipid particles, these limitations can be largely circumvented due to its ability to act as pulmonary sustained release reservoir. Furthermore, the key challenge with the pulmonary delivery of dry powders is the high dispersibility of the powder for reproducible and higher deposition at the required site. Large porous particle technology has been shown to improve the dispersibility of the powders and hence reproducible delivery of the drugs to the patients via lungs. Use of spray
drying technique can further perk up the lung deposition by enhanced dispersibility of the particles with required aerodynamic diameter and narrow particle size distribution.

Further, in pulmonary circulation, cGMP plays a major role on pulmonary vascular resistance. PDE5, the enzyme that specifically hydrolyzes cGMP, is abundantly expressed in the whole lung and predominates in pulmonary artery smooth muscle cells and both the activity and the expression of PDE5 are increased in pulmonary arteries with PAH. Recently, sildenafil citrate, a potent and selective PDE5 inhibitor successfully used for the treatment of erectile dysfunction has now been approved to treat PAH. It is available as tablet and injection dosage forms and is associated with non-specific vasodilation and other toxic effects.

This study was planned to overcome the problem of frequent administration and systemic side effects associated with the currently available therapy of pulmonary arterial hypertension. This issue was addressed by:

1. Formulation of various dry powder formulations of sildenafil citrate for pulmonary delivery to achieve practically feasible, scalable and stable formulations with desired formulation characteristics for better lung deposition and sustained release effect.
2. Characterization and comparison of these formulations with respect to desired parameters of dry powder formulations for inhalation like geometric and aerodynamic particle size, solid state characteristics, moisture content, aerosolization behaviour and storage stability.
3. In-vitro evaluation of the optimized formulations with respect to release pattern or kinetics to compare sustained release potential of the prepared formulations. Comparison of macrophage uptake of lipid based formulations with standard 2μ fluorescent latex beads to intimate the existence time of formulation in lungs.
4. Pulmonary delivery of sustained release dry powder formulations of sildenafil citrate to evaluate its prolonged local efficacy in monocrotaline-induced pulmonary hypertensive rats.

Aforementioned extensive experimentation disclosed following outcomes and inferences:

- Inhalation formulations of Sildenafil citrate were formulated by conventional mixing of micronized drug with lactose carrier i.e. conventional DPI method and by spray drying technique with mannitol as carrier or/as well as with lipid based carriers.
• Formulations prepared by spray drying technique presented better particle size distribution and aerosolization behaviour as compared to conventional DPI formulations. Spray drying parameters like feed rate, air pressure, inlet temperature and vacuum have individual as well as combined impact on formulation characteristics.

• Drug-sugar composites with mannitol showed better lung deposition than drug-lipid composites with Trehalose, determined by Andersen Cascade Impaction technique.

• Liposomal dry powder for inhalation and large porous lipospheres displayed better lung deposition and dispersibility as compared to conventional DPI, drug-sugar and drug-lipid composites with large porous lipospheres having the best aerosolization characteristics.

• The pulmonary administration of sildenafil citrate dry powder formulations could significantly prevent and reverse PAH without affecting systemic arterial pressure in monocrotaline treated rats.

• Lipid based formulations showed better prevention and reversal of PAH in monocrotaline injected rats. This connotes the better deposition and longer stay in lungs for lipid based formulations linking the improved hemodynamic and biochemical parameters for better prevention and treatment of PAH in MCT model. This assessment was also supported by the histological demonstration of significant reduction of fully muscularized peripheral pulmonary arteries and reduced inflammatory reaction and medial thickening of the peribronchial arteries after treatment with inhalation formulations.

• Out of all different formulations studied, inhalation of spray dried drug-sugar composites showed the fastest drug action and large porous lipospheres demonstrated the most prolonged localization in the lungs of male Wistar rats.

• Thus, lipid based inhalation formulations have revealed the potential to increase the $t_{1/2}$ of the drug in the lungs that can be further explored to reduce the patient inconvenience of frequent administration of currently available therapies while exerting the minimum systemic side effects.

The present results propose the promising innocuous potential of lipid based dry powders as pulmonary delivery system for prolonged localized drug effect to treat pulmonary arterial hypertension.