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Formulation of Apigenin-Loaded Liposomes for Pulmonary Delivery

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1. Introduction

Inhalation is one of the oldest drug delivery methods, whether the formulation is intended for a local or systemic effect. Several dosage forms are present on the market to deliver the active ingredient among which are dry powder inhalers (DPIs), which possess a safe, propellant-free formulation. Our aim was to develop apigenin loaded liposomes with adequate aerodynamic properties. Apigenin is a natural flavonoid with prominent antioxidant, anticancer and anti-inflammatory properties in the lungs. An interesting choice of carrier is liposomes, due to their ability to capture active pharmaceutical ingredients (APIs) and provide a controlled drug release in the lungs.

2. Review

Significance of the pulmonary drug delivery

The pulmonary route is an appropriate drug delivery method with a local effect for respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD). However, with the advances in pharmaceutical drug development, it became an interesting route for systemically acting treatments for conditions such as diabetes, certain types of cancer, and some autoimmune diseases [1].

The significance of this route is shown through the physiology of the lungs. They possess advantageous properties such as high permeability and a large surface area of 100 m², which is beneficial for absorption and allows a rapid onset of action of the drug. A high local concentration of the drug can be reached, which is then quickly absorbed through the alveoli. Moreover, there are no food effect, pH problems, and no first-pass metabolism issues. Therefore, a lower effective dose can be used, with minimized systemic adverse effects. Additionally, pulmonary drug delivery is a non-invasive route of administration, which is usually preferred by the patients.

The pulmonary drug delivery is a promising route of administration for both small molecules and macromolecules [1].

Drug deposition and absorption in the lungs

Particle deposition is the first step after inhalation and occurs by three main mechanisms: inertial impaction, sedimentation, and diffusion (as shown in Table I).

Large particles with an aerodynamic diameter above 5 μm have a tendency to collide on the wall of the upper airways and get swallowed. Thus, it is the particles with an aerodynamic diameter below 5 μm that have the highest chances of depositing in the lungs (see ***Figure 1***).

The absorption of a drug is also influenced by the physiological environment and the clearance mechanisms in the respiratory system: the mucociliary clearance (MCC), and the mechanical clearance.

Formulations in the pulmonary delivery

the lung deposition is highly influenced by the particle size of the drug. The drug needs to be delivered to its target site while concurrently avoiding the clearance mechanisms and still providing an effective therapy [1].

The drug particles should be micronized (to 1-5 μm), and blended with excipients of larger size (around 40 μm). In case of respirable nano-sized particles, they are embedded in microparticles in an aerodynamic size range [4]. Lactose is the most frequently used due to its advantageous properties.

Table 1 *Deposition mechanisms in the lungs [2]National Institute of Pharmaceutical Education and Research (NIPER-HYD*

Particle size	Mechanism	Parts of the respiratory tract
Above 5 μm	Inertial impaction	Oropharynx and conducting airways
0.5 – 5 μm	Sedimentation	Bronchi, Bronchioles and Alveoli
0.5 – 3 μm	Sedimentation and diffusion	
Below 0.5 μm	Diffusion and Brownian motion	Alveolar region

Therefore, we applied spray-dried lactose as a carrier for liposomes. The liposomes consist of phosphatidylcholine (PC) and dipalmitoylphosphatidylcholine (DSPC) 5%, 10% and 25%. We investigated the apigenin loading (%) and particle size (nm) after 3 and 6 high pressure homogenization cycles at 600 bar. The use of liposomes in the inhalation therapy is beneficial due to the advantages they possess, such as the solubilization of poorly soluble drugs, the modification of their release profiles, and protecting them from enzymatic or chemical degradation [5].

Inhalation devices – DPIs

Inhalation dosage forms can be divided into three main types: nebulizers, metered-dose inhalers (MDIs), and dry powder inhalers (DPIs). DPIs have a propellant-free formulation, which makes them the most advantageous ones. They can be classified according to the number of their doses or their powder dispersion mechanism. Their formulation requires the drug particles to be micronized. The particles exhibit cohesiveness and poor flow properties. Therefore, it is required for the API to be blended with coarse and fine carrier particles to enhance the flow properties and the particle aerodynamic behavior. The drug is present in a capsule, in an aggregated form of 100 -150 μm. A deep and strong inhalation through the inhaler is needed to de-aggregate the powder to an inhalable size of 1 – 5 μm that is able to deposit effectively in the lungs [1].

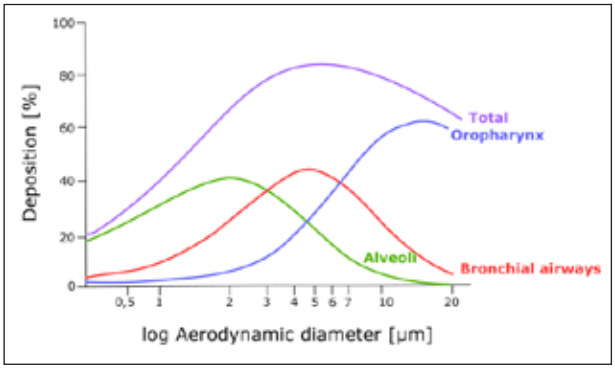

Figure 1 *Relationship between the particle aerodynamic diameter and the lung deposition (based on [3])*

3. Conclusion

The pulmonary route is significant for both local and systemic effects. However, the deposition in the lungs has a considerable importance in the absorption of the drug. Therefore, the particle size constitutes an essential requirement in the formulation. The liposomes have a high encapsulation efficiency and a small size (~100 nm), which indicates that a systemic effect can be achieved [6]. The investigation of the liposomes aerodynamic properties with a Next Generation Cascade Impactor (NGI) demonstrated an adequate distribution in the lungs.

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