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The influence of lung surfactant liquid crystalline nanostructures on respiratory drug delivery

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ABSTRACT

The respiratory route increasingly has been used for both local and systemic drug delivery. Although drug is absorbed rapidly after respiratory delivery, the role of lung surfactant in drug delivery is not well understood. The human lung contains only around 15 mL of surface lining fluid spread over ~100 m^2 surface. The fluid contains lung surfactant at a concentration of 8–24 mg/kg/body weight; the lung surfactant which is lipo-protein in nature can form different liquid crystalline nanostructures. After a brief overview of the anatomy of respiratory system, the review has focused on the current understanding of lung surface lining fluid, lung surfactants and their composition and possible self-assembled nanostructures. The role of lung surfactant in drug delivery and drug dissolution has been briefly considered.

Lung surfactant may form different liquid crystalline phases which can have an active role in drug delivery. The hypotheses developed in this review focuses on the potential roles of surface epithelial fluid containing liquid crystalline nanostructures in defining the dissolution mechanism and rate. The hypotheses also focus an understanding how liquid crystalline nanostructures can be used to control dissolution rate and how the nanostructures might be changed to influence delivery and induce toxicity.

1. Introduction

The respiratory drug delivery route has enormous potential to be an attractive drug delivery route for both local and systemic action (Patton and Byron, 2007), especially because of the route's advantages of non-invasiveness, lack of enzymatic degradation and large surface area of absorption. New chemical entities that are under investigation for delivering via this route include antibiotics, proteins, peptides and vaccines.

The absorption of drugs from the lung is very rapid. However, the systemic absorption, bioavailability and therapeutic action rely on the dissolution of the drug in the lung (Riley et al., 2012). Drug particles that are delivered to the tracheo-bronchial regions undergo dissolution but can be removed by mucociliary clearance. Drug particles that are delivered to the peripheral region undergo dissolution and can be engulfed by alveolar macrophages. Although the dissolution of orally administered drugs has been well researched and documented in the literature, the mechanism of drug dissolution in the lung is not known and no acceptable method for measuring dissolution in the lung has been proposed despite the fact that many dissolution methods for measuring dissolution have been attempted (Gray et al., 2008; Riley et al., 2012). The surface area of absorption in the lung is extremely high, but the lung contains only a small amount of fluid with relatively large amounts of surfactants in the peripheral region. It is, therefore, important to understand how dissolution takes place in this low fluid-high surfactant environment of peripheral (alveolar) region.

Dissolution is defined as a physical process by which a solid substance interacts with a solvent to form a solution. The understanding of the mechanism of dissolution of aerosol particles

Abbreviations: API, active pharmaceutical ingredient; C_I, cubic phase; C_{II}, inverse bi-continuous cubic phase; DPPC, 1, 2 dipalmitoyl phosphatidylcholine; H_I, hexagonal phase; H_{II}, inverse hexagonal phase; IPAC – RS, International Pharmaceutical Aerosol Consortium on Regulation and Science; Lα, lamellar liquid crystalline phase; L_I, micelles; L_{II}, inverse micelles; LS, lung surfactant; ^{99}mTc-DTPA, ^{99}mTc-diethylene triamine penta acetate; PC, phosphatidylcholines; PE, phosphatidyl ethanolamine; PG, phosphatidylglycerols; PI, phosphatidylinositol; PL, phospholipids; PMPC, 1-palmitoyl-2-myristoyl phosphatidylcholine; POPC, 1-palmitoyl-2-oleyl-phosphatidylcholine; SAXS, Small Angle X-ray Scattering; SP-A, surfactant protein A; SP-B, surfactant protein B; SP-C, surfactant protein C; SP-D, surfactant protein D.

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is not as fully developed as it is for oral delivery of drugs. The lung environment is considerably different to that of the gastrointestinal tract. In particular, since the lung contains very low amount of aqueous fluid and high amount of surfactants in the alveolar region, the formation of liquid crystalline phases such as cubic, lamellar, inverse cubic, inverse hexagonal and inverse micellar is possible. In fact, the early literature indicates that lung surfactants, after production in the type II cells, are secreted as lamellar bodies which are then transformed into tubular myelin (Wauthoz and Amighi, 2014). Although the mechanism of dissolution was speculated to be solubilisation by lung surfactants followed by diffusion, the liquid crystalline phases might also have a role in the dissolution process.

Understanding the dissolution of drugs in the lungs will help to establish its relation with pharmacokinetic, pharmacodynamic and clinical data which may vary with both products and patients, e.g. the inspiratory flow, the anatomy of the lung, disease conditions, etc. (Riley et al., 2012). For a better understanding of this complexity, the anatomy of lung, composition of fluid and the phase behaviour of surfactant components have been considered.

2. Understanding of respiratory environment

2.1. Respiratory system

The respiratory system is divided into two anatomical parts, namely (a) the upper respiratory tract that consists of nose, pharynx and larynx, and (b) the lower respiratory tract that includes trachea, bronchi and lungs (i.e., bronchioles, alveolar ducts and alveoli) (Weibel, 1973). Functionally, the bifurcations to the terminal bronchioles are referred to as the conducting zones or airways and the bifurcations from the terminal bronchioles to the alveolar sacs are referred to as the transitional and respiratory zones or alveolar regions (Weibel, 1973). Each lung has approximately 130,000 lobules and each lobule contains many alveolar sacs or alveoli (the smallest unit of respiratory functional system) (Weibel, 1973). Progression from the trachea to the alveolar ducts is characterised by decreasing component tube length, an increasing number of tubes and decreasing cross-sectional tube area (Bastacky et al., 1995). While the trachea is about 2.5 cm wide in the lumen, the alveolar ducts are only 0.2–0.5 mm in diameter. The surface area of airways is ≈2.5 m^2 (Mercer et al., 1994), while that of alveoli is 102 ± 21 m^2 (Stone et al., 1992). Lung epithelium also gradually becomes thinner while advancing from trachea to bronchiole to alveoli (Fig. 1).

The lung consists of a multitude of cell types. Ciliated cells are located in the conducting airway along with goblet cells. It is unlikely that these cell types exist in the alveolar region.

2.2. Surface lining fluid

A thin fluid sheet lies on the surfaces of airways and alveolar region which is known as surface lining fluid. Lucas and Douglas proposed this layer is made up of two layers (Lucas and Douglas, 1934): sol layer or periciliary sol, the liquid that surrounds cilia, and gel layer, the mucus blanket that lies on top of the cilia (Bhaskar et al., 1985; Widdicombe, 2002). Mucus is produced by the submucosal glands and goblet cells in the epithelium when trachea and bronchi are irritated. In contrast, mucus-secreting cells are absent from respiratory bronchioles. Thus, the airway fluid contains mucus that constantly moves towards the trachea with ciliary activity whereas the thin alveolar fluid does not contain mucus and is not transported by cilia. Mucus volume in airways can vary dramatically. There have been various reports about the thickness of this lining fluid. For example, Yoneda (1976) mentions that the thickness of the surface lining fluid is about 5–10 μm in the airways, which gradually decreases to only 0.05–0.08 μm in the alveolar region (Fig. 1). The surface lining fluid may be several microns thick in pooled areas of the alveolar region and as thin as 15–20 nm (Weibel, 1973). Widdicombe, in a review paper (Widdicombe, 2002), also mentions that the average thickness of the airway lining fluid is 10 μm which is spread in two layers (sol and gel). The direct measurement of the volume of epithelial surface lining fluid is difficult, so several indirect approaches have been adopted. Considering surface area of the airways for men of ≈2.5 m^2 (Mercer et al., 1994) and thickness of airways surface fluid (5–10 μm) (Yoneda, 1976), the volume of airways surface lining fluid was estimated to be ≈12.5–25 mL (Zuo et al., 2008). The total volume extracellular fluid in the first 17 generations was estimated to be about 4–9 mL (Anderson, 1992). When Weibel's average thickness of 0.068 μm of alveolar lining fluid was multiplied by an average human alveolar surface area of 102 m^2, the average

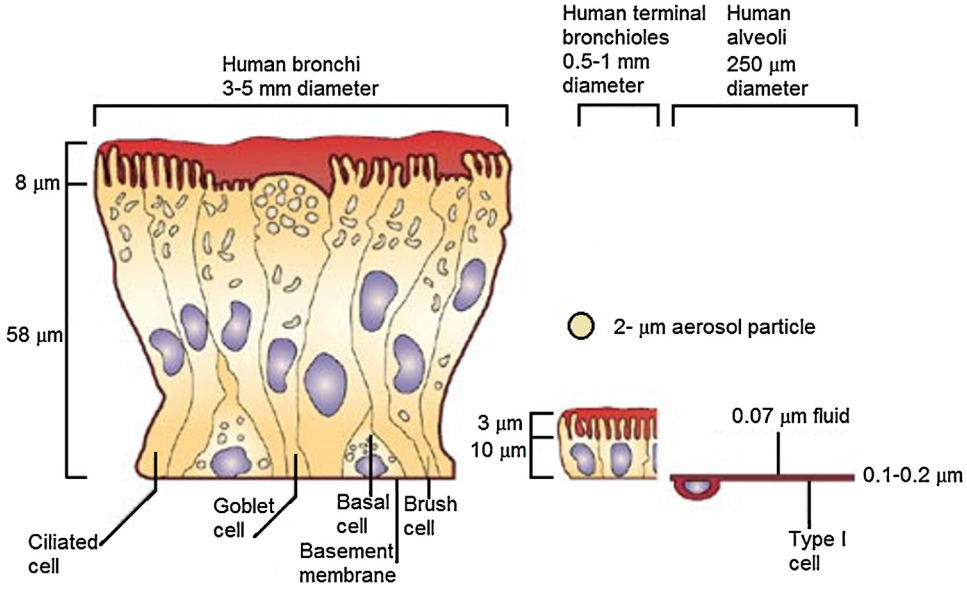

Fig. 1. The lung epithelium at different parts within the lungs.
(Patton and Byron, 2007, Reprinted with permission from Nature Publishing Group).