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Triggered-release nanocapsules for drug delivery to the lungs

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Abstract

This study demonstrated the feasibility of trigger-responsive inhaled delivery of medicines using soft solid shelled nanocapsules. The delivery system was a 50 nm sized lipid rich capsule carrier that distended rapidly when mixed with an exogenous non-ionic surfactant trigger, Pluronic® L62D. Capsule distension was accompanied by solid shell permeabilisation which resulted in payload release from the carrier; 63.9 ± 16.3% within 1 h. In electrolyte rich aqueous fluids Pluronic® L62D was loosely aggregated, which we suggest to be the cause of its potency in lipid nanocapsule permeabilisation compared to other structurally similar molecules. The specificity of the interaction between L62D and the nanocapsule resulted in carrier payload delivery into human epithelial cells without any adverse effects on metabolic activity or barrier function. This effective, biocompatible, trigger-responsive delivery system provides a versatile platform technology for inhaled medicines.

From the Clinical Editor: This study demonstrates the feasibility, efficiency and biocompatibility of trigger-responsive inhaled delivery of 50nm lipid-rich capsule carrier that distends rapidly when mixed with an exogenous non-ionic surfactant trigger, Pluronic L62D.

Key words: Nanomedicines; Lipid nanocapsules; Permeabilisation; Pluronic® surfactant; Pulmonary drug delivery

The rapid clearance of therapeutic agents from the lungs following inhalation presents a major challenge to treating pulmonary disorders such as asthma and chronic obstructive pulmonary disease using conventional respiratory medicines.[1] Nanocarriers provide a potential solution to this problem as their small size enhances their ability to moderate active molecule presentation to the tissue whilst limiting rapid clearance from the lung that occurs for larger particulate carriers.[2-5] However, nanosized drug carrier systems can suffer premature payload leakage upon storage and this renders these systems unsuitable for inhaled delivery and therefore new approaches are required for this route of administration.[6]

Trigger-responsive delivery systems have the capability of switching between two states; one in which the drug is held within a carrier without significant release, termed 'off', and a second where drug is released, termed 'on'.[7] They are typically used for 'site-specific' drug delivery once an active pharmaceutical compound has entered the body, but the concept has not as yet been adapted to meet the specific demands of inhaled medicines. In the lung, endogenous triggering, which in other areas of the body has been shown to be an effective way of targeting therapeutic agents,[8] is restricted by the need to exploit a physiological environment capable of inducing a unique chemical or physical change in the nanocarrier to initiate the delivery process.[9] However, the characteristics of some reported exogenously triggered systems appear well matched to inhaled drug administration.[10,11]

Portability and ease of use are important considerations for patients who inhale medicines, thus exogenous triggered delivery systems that do not use specialist equipment for administration, e.g. systems requiring co-administration of chemical triggers, offer the most convenient approach.[12-18] Pulmonary administration devices are available that allow two liquids to be combined at the point of administration,[19] providing a system where the trigger and the nanomedicine mix at the mucosal surface of the lung where the aerosol deposits. For such a system to be effective however, the carrier must possess sufficient responsiveness to the trigger to enable control of drug release.[20-23] This aspect of chemically-triggered nanomedicines appears to be more problematic than co-delivery to the mucosal surface because many highly reactive nano-sized carriers with the ability to release payloads have a

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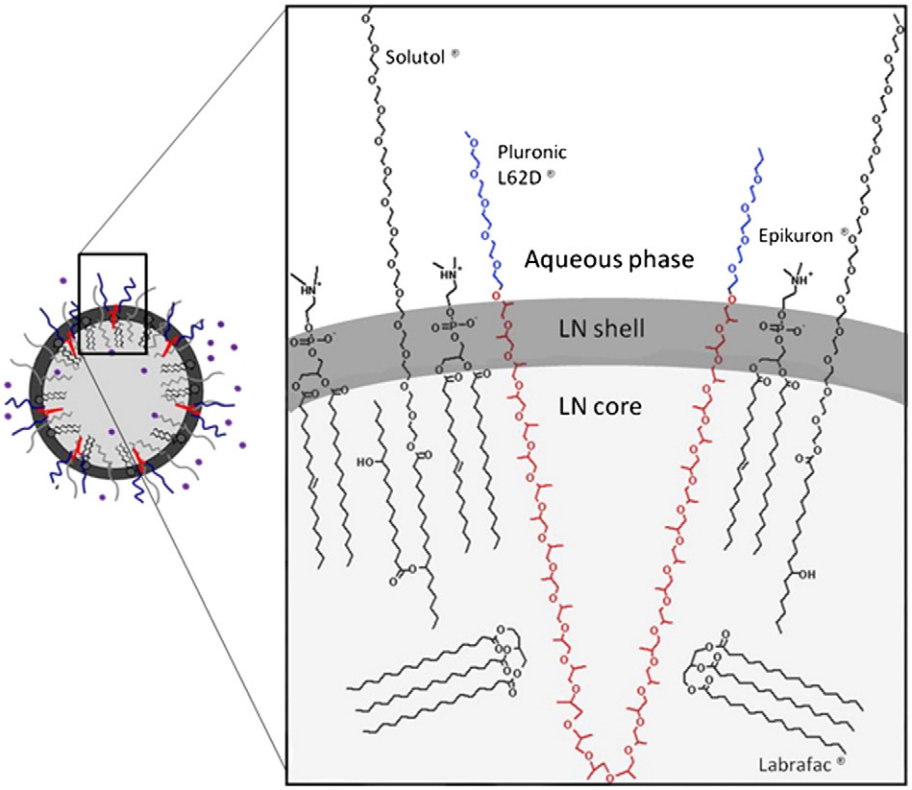

Figure 1. Schematic of engineered lipid nanocapsules (LN) formed via emulsion phase inversion precipitation showing the shell structure and the proposed means by which the Pluronic® L62D trigger could insert and permeabilise the nanocapsule shell to provide trigger responsive delivery (nanocapsule structure adapted from Heurtault et al[30]).

tendency to induce potentially detrimental biological effects, e.g., disruption of cell homeostasis,[24] induction of inflammatory responses,[5] damage to cell membranes[25] or protein adsorption.[26]

One trigger-responsive carrier system that appears distinct in its biocompatibility profile is the liposome.[27] Liposomal carriers have been reported to show limited immunogenic potential[28] and have the ability to respond to surfactant triggers,[10] but they are prone to drug leakage upon storage.[25,29] Nanocapsules formed by an emulsion phase inversion-precipitation technique exhibit similar properties to liposomes, but possess a solid outer shell that is less permeable.[30] The aim of this study was to investigate whether solid shelled lipid nanocapsules, fabricated using an Epikuron® Solutol® mixture (Figure 1), could be formed into a trigger-responsive nanomedicine suitable for inhaled delivery. These charge neutral nanocapsules are physically stable in protein-containing physiological salt solutions and they do not induce an inflammatory response in the lungs of mice.[31] Therefore, this study focused on the ability of a Pluronic® triggering system to induce structural changes in the nanocapsules at an airway epithelial surface, the transfer of the released agent across the epithelial barrier and the response of the epithelial cells to the delivery system. The particles were characterised using photon correlation spectroscopy, Fourier transform infrared spectroscopy, transmission electron microscopy, x-ray spectroscopy and the delivery of rhodamine, used as a model drug, was determined using Calu-3 bronchial epithelial cell layers and the MucilAir™ system (constructed from primary human airway epithelial cells). The specificity of Pluronic® L62D to induce payload release was characterised by comparison with three structurally similar molecules.

Methods

Materials

Medium chain triglycerides (Labrafac® lipophile 1349), hydrogenated soybean lecithin (Epikuron® 200) and macrogol 15 hydroxystearate (Solutol® HS15) were kindly supplied by Gattefossé S.A. (Saint-Preist, France), Cargill GmbH (Germany) and BASF (Ludwigshafen, Germany), respectively. Rhodamine 6G was purchased from Sigma Aldrich, (UK). High performance liquid chromatography (HPLC) grade water was obtained from Fisher Scientific (Leicestershire, UK) and ethanol absolute from VWR (Leicestershire, UK). Pluronic® surfactants L62D, L44NF, L64 and L81 were sourced from BASF (New Jersey, USA). Cell culture reagents were sourced through Sigma Aldrich (Dorset, UK). Cell culture flasks (75 cm^2 with ventilated caps) and Transwell cell culture systems (0.33 cm^2 polyester, 0.4 μm pore size) were from Costar (through Fisher Scientific, Leicestershire, UK).

Nanocapsule manufacture and purification

Nanocapsules were manufactured via precipitation from a stable emulsion following repeated phase inversion, as described