Liposomes for controlled delivery of drugs to the lung

Liposomes are one of several drug delivery systems known pharmaceutically as vesicles. They can be prepared from phospholipids with or without cholesterol in a wide range of sizes, from 20 nm to 10 µm, and structurally have one or more lipid bilayers, separated by aqueous compartments, surrounding an aqueous core. Liposomes are capable of entrapping a wide range of materials; hydrophilic drugs are dissolved in the aqueous regions and hydrophobic drugs associated with the lipid bilayers. Liposomes have been administered to the lung both as a means of delivering phospholipids to the alveolar surface and to modulate the duration of activity or pulmonary absorption of pharmacologically active agents.

Liposomes seem particularly appropriate for delivery of drugs to the lungs as they can be prepared from materials endogenous to the lung as components of lung surfactant. Lung surfactant is a complex mixture, of which about 85% is phospholipid, mostly dipalmitoylphosphatidylcholine, with phosphatidylglycerol as the next most prevalent phospholipid. Surfactant also contains cholesterol and two groups of non-serum proteins that are considered important in the spreading, adsorption, and reutilisation of surfactant. The mechanisms for the clearance and reutilisation of lung surfactant are likely to be of major importance in determining the fate of liposomes deposited in the alveoli. Administration of radiolabelled liposomes to the respiratory tract of rodents has shown that liposomal phospholipid rapidly becomes associated with the lung parenchyma. Exogenous phospholipids enter the process for reutilising lung surfactant, being taken up by type II epithelial cells, and become incorporated into lamellar bodies.

The rate and extent of pulmonary uptake of liposomes are a function of their composition, significantly faster rates occurring when liposomes contain phosphatidylglycerol.

A recent study of the acute effects of liposome inhalation by healthy volunteers indicated that small soya phosphatidylcholine liposomes were well tolerated, with no apparent changes in pulmonary function. Chronic administration of liposomes, however, may result in cumulative doses of phospholipid greater than the size of the lung surfactant pool. In clinical cases of phospholipidosis, occurring as an adverse reaction to amiodarone, concentrations of phospholipids in cell free bronchoalveolar lavage fluid remain normal but there is a large increase in the lavage cell population, predominantly of alveolar macrophages, and their phospholipid content. This suggests that macrophage activity may be an important clearance mechanism in response to chronic administration of liposomes.

Gamma scintigraphy has been used to study the deposition and clearance of radiolabelled liposomes in the human respiratory tract. These investigations have indicated that liposomes can be efficiently deposited in the lung, where they remain intact for prolonged periods. Whether they are deposited in the central or peripheral airways depends on the size of the droplets in the aerosols produced by nebulisers used for their delivery, rather than on properties of the vesicles themselves. The desired site of deposition within the lung will clearly be governed by the site of drug action. Rapid removal of particulates, including liposomes, by the mucociliary clearance process suggests that peripheral lung deposition will be required to achieve much longer drug action.

Multilamellar and small unilamellar liposomes with bilayers of dipalmitoylphosphatidylcholine, with a mean size of 2.9 µm and 70 nm respectively, had their outer surface labelled with 99mTc before inhalation by healthy volunteers from a Hudson jet nebuliser. The distribution of activity within the lung depended on the size of droplets in the nebulised aerosol cloud (mass median aerodynamic diameter (MMAD) 3.2–3.7 µm) rather than vesicle size or type. The rate of clearance of the two vesicle types was similar, with about 40% of deposited activity cleared within 20 hours by the mucociliary clearance process. The activity remaining in the lung after 20 hours probably represented vesicles that had been deposited in the alveoli.

Dipalmitoylphosphatidylcholine-cholesterol multilamellar liposomes (mean size 0.9 µm) with their aqueous phase labelled with 99mTc DTPA were atomised by a Respirigid jet nebuliser (MMAD 1.2 µm) and inhaled by healthy volunteers. Such a small droplet size ensured peripheral lung deposition. Single photon emission computed tomography images one hour after inhalation showed that activity was widely distributed throughout the lungs. After 24 hours 45% of the initially deposited activity persisted within the lungs, representing the fraction of radiolabel remaining in intact liposomes in the alveolar regions, as free radiolabel was rapidly absorbed and cleared from the airways. When an equivalent dose of free 99mTc DTPA was inhaled as a solution, activity could not be detected in the pulmonary regions after six hours.

In the earliest studies of pulmonary administration of liposomes for therapeutic purposes liposomes were given as an exogenous lung surfactant in the treatment of the neonatal respiratory distress syndrome. Subsequently a range of liposome associated drugs have been administered to the lungs of humans and animals. These include cytotoxic drugs, antiasthma drugs, antimicrobial compounds, and drugs delivered for a systemic action.

When cytarabine was administered to the lungs of rabbits in free and liposomal form, the free drug was rapidly absorbed whereas the liposomal drug remained in the airways for prolonged periods, with little distribution to other tissues. Free cytarabine inhibited [14C]thymidine incorporation in the gastrointestinal tract, bone marrow, and lung, whereas liposomal drug effectively inhibited [14C]thymidine incorporation within lung tissue but with little effect in the gastrointestinal tract and bone marrow.

Pulmonary administration of orciprenaline sulphate to guinea pigs produced bronchodilatation of short duration accompanied by considerable tachycardia. Liposome for-
mulations of that drug produced immediate bronchodila-
tion after histamine induced bronchoconstriction, but with
an appreciably prolonged duration of activity. Additional-
ly, the cardiovascular side effects of orciprenaline were
significantly reduced by liposomal incorporation.

cytarabine and one per cent sulphate are hydrophilic
drugs entrapped within the aqueous compartments of
liposomes. Similar findings have been reported for hy-
drophobic drugs, such as atropine, associated with lipid
bilayers. These studies show the potential of liposomes
for prolonging the time that drugs associated with them are
retained in the lung, resulting in localised high drug
concentrations within the respiratory tract and decreased
adverse effects at sites distant from the lung.

Studies of inhaled liposomal drug formulations in man
are scarce. Liposomes containing the antiviral compound
enviroxime have been inhaled by healthy volunteers after
atomisation from a Puritan-Bennett jet nebuliser produc-
ing aerosols with mass median diameters of 2-4-3 1 m. From
7 to 10 mg of drug was deposited in the respiratory
tract over one hour. Large amounts of drug were found in
nasal washes one hour after inhalation. Enviroxime could
not be detected in urine samples, and was detectable in only
one of five blood samples. No side effects were observed
and the authors concluded that such a liposome formula-
tion had potential for delivering hydrophobic drugs for the
treatment of respiratory disease. Nebulisation of free
enviroxime is problematic owing to its poor solubility in
water.

A Hudson jet nebuliser was used to produce aerosols
(MMA D 2-6 mm) from a dipalmitylophosphatidylcholine-
cholesterol liposome formulation of sodium cromoglycate.
This preparation when inhaled by healthy volunteers
produced detectable plasma concentrations of drug up to
25 hours after inhalation. An equivalent 20 mg dose of
sodium cromoglycate inhaled as a nebulised solution
produced peak plasma concentrations seven times greater
than liposomal sodium cromoglycate, but the drug was not
detectable in 25 hour plasma samples. Maximum, mean,
and minimum steady state plasma concentrations likely to
result from repeated administration of the liposomal for-
mulation were calculated. These indicated that one dose a
day would result in plasma concentrations of the drug that
have been shown to be associated with a protective action in
bronchial asthma.

The absorption half life of inhaled liposomal sodium
cromoglycate was 57 hours, about three times faster than
predicted from in vitro experiments. This suggests that
diffusion of drug across liposome bilayers may not be the
major determinant of drug release and subsequent plasma
concentrations. Drug release may be enhanced by vesicle
degradation at the alveolar surface or within alveolar
macrophages, fusion of liposomes with epithelial cells, or
fusion or phospholipid exchange (or both) with constitu-
tuents of lung surfactant.

Currently liposome delivery to the lung in man is
achieved through the use of nebulisers.8 12 14 Formulation
of liposomes for delivery from nebulisers is relatively
simple. They can be prepared by conventional techniques
and, except for removal of material not associated with the
vesicles, usually require no further processing.

The effect of jet nebulisation on a range of liposome
preparations of sodium cromoglycate has been investigated
with a modified liquid impinger.8 The size and size
distribution of the droplets in the aerosols produced
depended on the design of the nebuliser rather than any
property of the liposomes themselves. The results suggest
that the appropriate liposome formulation for delivery
from such devices will be governed by the oil:water
partition coefficient of the drug and its therapeutic dose.

Larger liposomes encapsulate more hydrophilic materials,
but these vesicles are the least stable during atomisation.
Reducing the size of liposomes by extrusion or sonication
makes them more stable. Disruption of vesicles on atomi-
sation is likely to be less critical for hydrophobic drugs,
associated as they are with lipid bilayers.

The use of ultrasonic nebulisers for liposome delivery
has been investigated.10 Small liposomes were stable during
nebulisation, though dipalmitylophosphatidylcholine ves-
icles of 500 nm or more increased in size within the
nebuliser, suggesting fusion of vesicles, with the likely loss
of entrapped hydrophilic materials.

In the future alternative devices may become available
for delivery of liposomes to the lung. For instance, a recent
United States patent11 described the use of a dry powder
inhalation device for delivering vesicles loaded with spray
dried drug. This approach to pulmonary delivery will rely
on rehydration of vesicles in situ. The potential of metered
dose inhalers has also been investigated. A solution phase
system has been developed in which phospholipid and drug
are dissolved in a chlorofluorocarbon based propellant
blend.12 After atomisation of the emitted droplets it is
postulated that rapid phospholipid hydration will result in
spontaneous formation of vesicles. This approach has
proved applicable for delivering systems containing small
doses of salbutamol12 and would seem suitable for delivery
of corticosteroids. Other approaches for metered dose
inhaler systems include a two compartment system, in
which a chlorofluorocarbon based solution containing
phospholipid and drug is mixed with an aqueous phase on
actuation,14 and a system in which preformed dehydrated
liposomes are suspended in a chlorofluorocarbon blend
with poor solubilising capacity for phospholipids.15 These
alternative approaches are limited by the fact that smaller
amounts of phospholipid or liposomes can be delivered
than with nebulisers.

From a toxicological viewpoint, then, liposomes seem
particularly appropriate for drug delivery to the lung. The
limited data pertaining to their use in man and the results of
animal studies indicate that encapsulation in liposomes can
modulate the fate of inhaled drugs, increasing the residence
time of drug in the lung. This may allow prolonged drug
action within the respiratory tract or a prolonged presence
in the circulation. By providing a controlled delivery of
drug at the surface of the lung such systems may allow a
decreased frequency of dosing, with a reduction in systemic
side effects. How controllable drug release from a liposome
system deposited in the lung will be has yet to be
established, in healthy or diseased lungs. Generally, in-
clusion of cholesterol in liposomes increases in vivo
stability, decreasing the rate of drug release.16 Studies of
the fate of exogenous surfactant in the lung suggest that
inclusion of phosphatidylglycerol aids spreading at the
alveolar surface.17 Thus inclusion of phosphatidylglycerol
in liposomes may potentially enhance drug release. If
fusion of vesicles with the alveolar surface or lipid exchange
between vesicles and surfactant (or both) is an important
release mechanism, liposomes with more than one bilayer
may be more appropriate than unilamellar liposomes for
producing sustained drug release.

The ability of liposomes to encapsulate hydrophilic and
hydrophobic drugs makes them potential carriers for many
compounds. Drugs having small therapeutic doses will be
obvious candidates, as concomitantly administered phos-
pholipids can be minimised. Obvious drug candidates for
future investigation are the β2 agonists and corticosteroids
such as beclomethasone. The sustained release of materials
within the lung, together with the large absorptive alveolar
surface, indicates that pulmonary delivery of liposomal
drugs has potential not only for locally acting drugs but also
for systemically active compounds, including peptides.

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