Expert Opinion

1. Introduction
2. Evaluation of dispersions of drugs in perfluorocarbon compounds
3. Gene drug delivery
4. Novel perfluorocarbon compound-drug formulations for intrapulmonary administration
5. Conclusion
6. Expert opinion

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

For reprint orders, please contact:
Ben.Fisher@informa.com

informa
healthcare

Perfluorocarbon compounds as vehicles for pulmonary drug delivery

Hans-Joachim Lehmler
University of Iowa, Department of Occupational and Environmental Health, Iowa City, IA 52242, USA

Drug delivery to the diseased lung is hindered by the buildup of fluid and shunting of blood flow away from the site of injury. The use of perfluorocarbon compounds (PFCs) as drug delivery vehicles has been proposed to overcome these obstacles. This drug delivery approach is based on the unique properties of PFCs. For example, PFCs can homogeneously fill the lung and recruit airways by replacing edematous fluid. Analogously, drugs administered with a PFC vehicle are expected to be homogeneously distributed throughout the lung. At the same time, intrapulmonary administration of the drug will achieve higher drug concentrations in the lung than conventional approaches, while reducing systemic exposure. Unfortunately, PFCs are poor solvents for typical drug molecules. To overcome this obstacle, several approaches, such as dispersions, prodrugs, solubilizing agents and (micro)emulsions, are under investigation to develop homogeneous PFC–drug mixtures suitable for intrapulmonary administration.

Keywords: emulsions, gene therapy, intrapulmonary administration, liquid ventilation, lung disease, prodrugs

Expert Opin. Drug Deliv. (2007) 4(3):247-262

1. Introduction

1.1 Perfluorocarbon compounds for biomedical application

Perfluorocarbon compounds (PFCs) are a group of perfluorinated aliphatic compounds that are clinically used as contrast agents [1-3]. Due to their unique properties, PFCs are also of interest as blood substitutes [4-8] and oxygen carriers during liquid ventilation [9-14]. Unfortunately, the outcome of a recent clinical trial studying partial liquid ventilation in adult patients with acute respiratory distress syndrome [15] were not promising, and liquid ventilation is unlikely to be used clinically in the foreseeable future. PFCs are also under investigation for a wide range of biomedical applications, such as drug delivery, gene therapy, brain cooling, and organ and cell preservation [14,16]. Due to their use as an oxygen carrier during liquid ventilation, PFCs are of particular interest as vehicles for the direct administration of drugs to the diseased lung [14].

PFCs are a structurally diverse group of aliphatic compounds; the chemical structure of selected PFCs is shown in Table 1. Some PFCs, such as perfluorodecalin, are simple perfluorinated compounds, whereas other PFCs have functional groups or contain heteroatoms. Many PFCs are manufactured by an electrochemical fluorination process and are mixtures of several perfluorinated compounds [17]. Although some commercial grade PFCs have been used successfully in animal studies, most commercially available PFCs are not suitable for biomedical applications (e.g., liquid ventilation [18]) and need to be purified prior to use in animals and/or humans to remove toxic impurities [19]. Perfluorooctyl bromide is the most widely studied PFC in humans [10,15].

RIGHTSLINK

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

Overall, PFCs are of interest for the aforementioned biomedical applications, due to their unique properties. The fluorine-carbon bond is the most stable covalent bond known. As a result, PFCs are stable against chemical and biological degradation. PFCs also display weak inter-molecular interactions and are highly volatile, which results in rapid clearance from the lung or systemic circulation by exhalation [20,21]. They are lipophobic and hydrophobic at the same time, which limits their cellular and systemic uptake by passive diffusion. Instead, PFCs can be taken up by macrophages and other cells by phagocytosis [21]. Furthermore, PFCs have a significantly higher solubility for oxygen and carbon dioxide than water, and can be used as oxygen carriers, for example to the lung. PFCs also have a low surface tension, which allows them to flow through extremely narrow airways. In contrast, water would obstruct the airways because it cannot flow freely due to its high surface tension. Therefore, PFCs such as perfluorooctyl bromide have been used as a respiratory medium in animals and humans during liquid ventilation [9-13]. Overall, biomedical applications of PFCs utilize their physicochemical and biophysical properties. However, PFCs are known to have biological effects. For example, PFC can be cytoprotective by unknown mechanisms [10,22].

1.2 Perfluorocarbon compounds as drug delivery vehicles – advantages and problems

Intrapulmonary delivery of drugs is expected to achieve higher (i.e., therapeutically useful) local tissue concentrations compared with systemic drug delivery approaches. At the same time, local drug delivery reduces systemic uptake (which protects non-targeted organs from pharmaceutical side effects) and allows delivery of the entire dose of the drug (which is not the case with aerosols). The unique properties of PFCs make them attractive as vehicles for the intrapulmonary administration of drugs.

PFCs are evenly distributed throughout the lung due to physicochemical characteristics, such as low surface tension, low viscosity and high spreading coefficient. Intrapulmonary administration of drugs using a PFC as a vehicle is, therefore, expected to result in a homogeneous distribution of the drug throughout the lung. PFCs can displace the debris present in diseased lungs because of their high densities [23] and, thus, transport the drugs to the site of injury. In contrast, drug delivery using conventional approaches is less effective in the diseased lung. For example, drugs delivered as aerosols cannot reach debris-, or fluid-filled parts of the lung. Systemic treatment is typically less efficient because lung injury shunts blood flow away from the site of injury, thus preventing the effective delivery of the drug to the site of injury.

Although PFCs are promising vehicles for the administration of drugs directly to the lung, the poor solubility of typical drug molecules in PFCs [24-26] represents a major obstacle for their use as a drug delivery vehicle [14]. The ability to disperse or solubilize drug molecules in PFCs is, therefore, a critical step towards using PFCs as pulmonary drug delivery vehicles. A variety of methods, including dispersions of aqueous drug solutions or solid drug particles, prodrugs, solubilizing agents and reverse (water-in-PFC) emulsions, have been studied to disperse or solubilize drugs in PFCs. The following sections will review these different approaches, with an emphasis on the outcomes of *in vivo* studies.

2. Evaluation of dispersions of drugs in perfluorocarbon compounds

Initial investigations of PFCs as a vehicle for intrapulmonary drug administration employed dispersions of aqueous drug solutions. In these studies, the respective aqueous drug solution was administered with the PFC, either to animals undergoing some kind of liquid ventilation or to spontaneously breathing animals. One disadvantage of this approach is that the aqueous phase and the PFC phase are not miscible, and the aqueous phase will float on top of the PFC phase due to its lower density. These studies relied on bulk flow turbulent mixing in the lung for the homogeneous dispersion of the aqueous drug solution in the PFC. Alternatively, aerosol delivery of such formulations has been proposed, but this drug delivery approach has not been studied *in vivo* [27-29] and will not be discussed further in this review.

2.1 Intrapulmonary administration of vasoactive substances

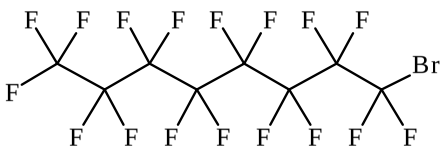
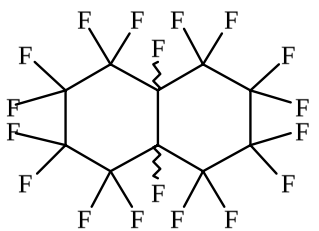
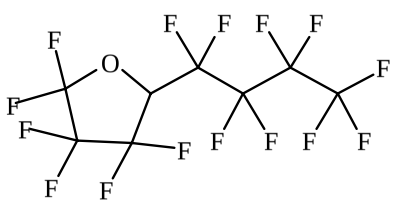
Several vasoactive drugs that are insoluble in PFCs were administered in a lamb animal model using perfluorodecalin (APF 140) as a drug delivery vehicle [30,31]. In these early studies, acetylcholine, adrenaline and priscoline were dispersed in perfluorodecalin and administered through the endotracheal tube in premature and full-term lambs undergoing liquid ventilation. Control groups, also undergoing liquid ventilation, received the drugs intravenously. Despite being insoluble in perfluorodecalin, acetylcholine and adrenaline caused dose-dependent and compound-specific responses after intravenous or pulmonary administration. The response in mean arterial pressure over time depended on the route of administration for both drugs. After intravenous administration, changes in mean arterial pressure occurred earlier and were more pronounced; whereas, intrapulmonary administration resulted in a more prolonged change.

In the same study, priscoline caused an earlier and more pronounced systemic response (i.e., decrease in mean arterial pressure) after intravenous administration [30]. The pulmonary and the systemic response to priscoline depended on the route of administration. This difference is illustrated in Figure 1, which shows the ratio of the response of the pulmonary artery to mean (systemic) arterial pressure. For up to concentrations of ≥ 2.00 mg/kg, this

RIGHTSLINK

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

Table 1. Physicochemical properties of perfluorocarbon compounds.

PFC	Chemical structure/composition	Density (g/ml)	Vapor pressure at 37°C (mmHg)	Surface tension (dyn/cm)	Oxygen solubility (ml/l)	Carbon dioxide solubility (ml/l)	CAS Number
Water		1.00	47	72	30	570	
Perfluorooctyl bromide		1.92	11	18	530	2100	423-55-2
Cis/*trans*-perfluorodecalin (APF-140)		1.95	14	15	490	1400	52623-00-4
FC-75		1.78	64	15	520	1600	335-36-4
Rimar-101 (RM-101)	A mixture of perfluoro(2-butyltetrahydrofuran), perfluoro(2-propyltetrahydro-furan) and unidentified PFCs	1.77	64	15	520	1600	58206-51-2

PFC: Perfluorocarbon compound. Data from [14,76,77,78].

RIGHTSLINK

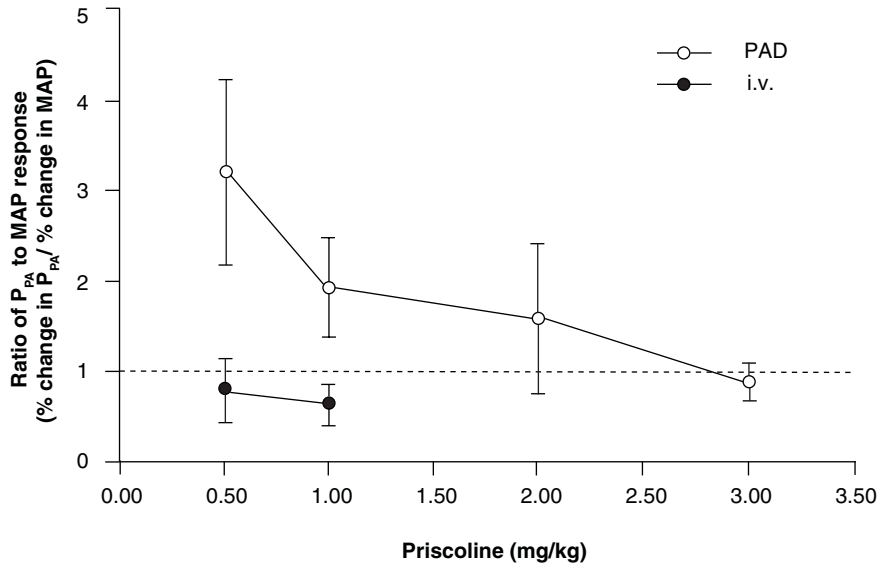


Figure 1. The change of the ratio of pulmonary artery pressure versus mean arterial pressure (expressed as percent change from baseline for pulmonary arterial pressure relative to percent change from baseline for mean arterial pressure) after pulmonary and intravenous administration of incremental doses of priscoline in lambs undergoing tidal liquid ventilation.
Reproduced with permission from Pediatrics 97(4):449-455, Copyright © 1996 by AAP.
i.v.: Intravenous administration; MAP: Mean arterial pressure; PAD: Pulmonary administration; P_{PA}: Pulmonary arterial pressure.

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

ratio is > 1 for intrapulmonary administration of priscoline; whereas, it is < 1 for intravenous administration. This suggests that direct administration of priscoline to the lung has a greater effect on pulmonary responses relative to systemic responses. The opposite is true for intravenously administered priscoline.

2.2 Intraplumonary administration of aqueous solutions of antibiotics

The administration of antibiotics during liquid ventilation is of particular interest for the treatment of pneumonia, particularly of hospital-acquired nosocomial pneumonia, and has been investigated in several animal studies [32-35]. As shown in Figure 2, a comparison of the pharmacokinetics of antibiotics (such as gentamicin) reveals distinct differences between routes of administration and treatment modalities.

The first study investigating the administration of an antibiotic using a PFC vehicle compared the intravenous and intrapulmonary administration of gentamicin in healthy newborn lambs undergoing liquid ventilation [32]. Serum levels of gentamicin showed a peak immediately after intravenous administration and subsequently decreased due to its excretion (Figure 2a). In contrast, serum levels of gentamicin increased with time, peaked after 1.5 h and remained relatively constant for several hours after intrapulmonary administration. Serum levels of gentamicin were below the clinical threshold for nephrotoxicity (~ 12 µg/ml serum) over the entire study period in both treatment groups. After 6 h, antibiotic levels in the lung of animals receiving gentamicin during liquid ventilation were higher than in animals receiving the drug intravenously. Furthermore, the tissue levels attained in the intratracheal treatment group were > 8 µg/ml – the minimum inhibitory concentration for many bacteria causing pneumonia [36]. The observed kinetics of serum and tissue gentamicin absorption is similar to the aerosol delivery of gentamicin and reflects gentamicin's initial uptake up by pulmonary tissue compartments prior to its release into the systemic circulation.

A recent study compared the intrapulmonary administration of perfluorodecalin–gentamicin or perfluorodecalin–vancomycin emulsions (as opposed to dispersions) with the intravenous administration in rabbits undergoing mechanical ventilation [37,38]. Natural bovine surfactant was employed as an emulsifier to minimize the phase separation of the aqueous drug solution and the PFC and, thus, to result in an improved distribution of the drug in the lung. The plasma concentration of both antibiotics after intravenous administration could be described with a two-compartment model, and peaked at the end of the infusion of the antibiotic solution (i.e., after 15 min). Similar to the earlier study in lambs [32], the pharmacokinetics after intrapulmonary administration of the antibiotic–perfluorodecalin emulsions was distinctively different from intravenous administration, and suggests that the lung (and not the PFC emulsion) functions as an additional compartment. Specifically, the plasma concentration of both antibiotics did not reach the peak levels seen with intravenous administration and, in the case of vancomycin, occurred later after administration (i.e., after 30 min). Plasma levels of both antibiotics were higher in

RIGHTSLINK

animals receiving the antibiotics by the pulmonary route, due to a slower rate of elimination at 1 – 5 h after administration. Tissue concentrations in these animals were not only similar throughout the lung, but also 23.5-(gentamicin) and 23.2-times (vancomycin) higher than after intravenous administration.

2.3 Solid-in-perfluorocarbon compounds dispersions

Hollow, porous nanoparticles such as PulmoSpheres® (Nektar Therapeutics) have been developed for pulmonary administration using metered dose inhalers [39] or a PFC vehicle [33,36]. These particles form stable solid-in-perfluorooctyl bromide dispersions. The intrapulmonary administration of gentamicin nanoparticles was investigated, with similar results in lambs [33] and rabbits [36].

The intrapulmonary administration of a gentamicin/PFC nanocrystal suspension either at the beginning ('slow-fill' treatment modality) or during liquid ventilation ('top-fill' treatment modality) was compared with intravenous administration during conventional mechanical ventilation in a lamb model [33]. As shown in Figure 2b, conventional intravenous injection resulted in gentamicin serum levels that were higher compared with serum levels after intrapulmonary administration of the gentamicin/PFC nanocrystal suspension. In the intrapulmonary treatment groups, serum levels were always below levels at which gentamicin causes systemic toxicity; whereas, these levels were exceeded for a few minutes after intravenous administration. However, the gentamicin tissue levels in the lungs from animals in the intravenous treatment group were significantly lower than levels in the intrapulmonary treatment groups.

There were also differences in serum levels over time and tissue levels, depending on the pulmonary administration modality. Gentamicin serum levels peaked 15 min after administration of a bolus dose of the gentamicin/PFC nanocrystal suspension during liquid ventilation (top-fill treatment modality). However, when drug treatment and liquid ventilation were initiated at the same time (slow-fill treatment modality), no peak in gentamicin levels in serum were noted. This mode of administration also resulted in overall lower plasma levels compared with the other two treatment modalities, but a higher retained dose of gentamicin in the lung. These differences between the two methods of pulmonary administration are thought to be due to the different extent to which lung volume and, thus, pulmonary surface area has been recruited for the drug exchange across the alveolar–capillary barrier.

Intrapulmonary administration of recombinant human CuZn superoxide dismutase (rhSOD) is under investigation as a possible supplemental treatment to improve the antioxidant defence in premature infants with acute lung injury [40,41]. As with small drug molecules, instillation of rhSOD in saline or inhalation of an aerosol did not result in a homogenous distribution of rhSOD in the lung [41]. However, administration of a bolus dose of a nanocrystal suspension of rhSOD with a PFC mixture (perfluoromethylcyclohexane:perfluoromethyldecalin ratio of 1:4) resulted in an enhanced delivery of rhSOD to the lung and a more homogenous distribution of the enzyme within the lung in a lung injury model of juvenile rabbits [40]. Furthermore, a decrease in oxidative lung damage (measured as protein carbonyl levels) was noted in the parts of the lung containing the highest rhSOD levels.

2.4 Intrapulmonary administration of dispersions in models of lung injury

The administration of antibiotics in an uninjured lung does not reflect the situation present during pulmonary infections or lung injury, where both ventilatory and perfusion abnormalities exist. From a clinical perspective, it is, therefore, more relevant to investigate the intrapulmonary administration of antibiotics in a model of lung injury. Similar to the studies discussed above [32,33], intrapulmonary administration of gentamicin to the acutely injured lung of lambs during liquid ventilation with perfluorooctyl bromide results in higher lung tissue levels compared with intravenous administration, and gentamicin serum levels have been shown to be comparable between both routes of administration (Figure 2c) [34]. Furthermore, liquid ventilation provided more effective respiratory support than conventional gas ventilation.

In a study employing a surfactant-depleted rabbit lung injury model, the intrapulmonary administration of perfluorodecalin–gentamicin or perfluorodecalin–vancomycin emulsions also resulted in higher pulmonary antibiotic levels compared to intravenous administration of the antibiotics [37]. However, due to the increased permeability of the alveolar capillary barrier in this lung injury model, the pharmacokinetics of both antibiotics at 1 – 5 h after intrapulmonary administration was similar to the intravenous pharmacokinetics. As a result, the pulmonary antibiotic tissue levels were not as high as in healthy animals receiving the same treatment, but still higher than in animals receiving the antibiotics intravenously.

Intrapulmonary or intramuscular administration of a single dose of ampicillin during liquid ventilation with perfluorooctyl bromide significantly reduced the mortality of rats with pneumococcal pneumonia [35]. Alternatively, ampicillin could be effectively administered in animals undergoing liquid ventilation using PulmoSpheres. Treatment with liquid ventilation or intramuscular ampicillin alone did not improve mortality. This suggests that administration of ampicillin, independent of its route of administration, in combination with liquid ventilation improved the survival in this animal study. This suggests that, contrary to the studies discussed earlier, intrapulmonary administration of ampicillin did not offer advantages over the conventional intramuscular route of administration. However, intramuscular administration of ampicillin and other antibiotics is also not a clinically recommended treatment modality for pneumococcal pneumonia.

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

RIGHTSLINK

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

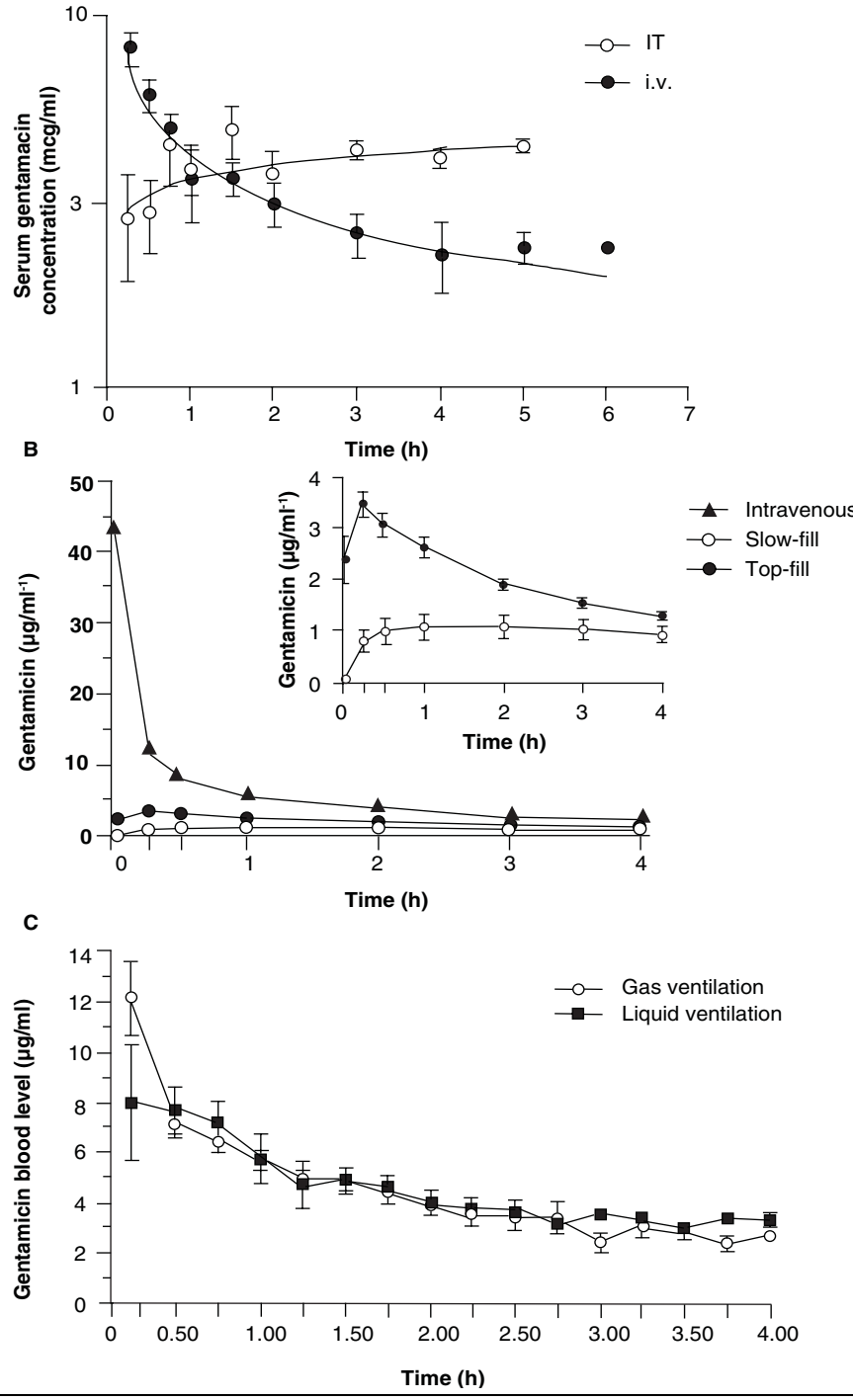


Figure 2. A comparison of serum gentamicin levels over time after pulmonary or intravenous administration in different animal models. A. Serum gentamicin levels over time for intravenous and intratracheal administered gentamicin in healthy lambs during tidal liquid ventilation. **B.** Serum gentamicin levels over time after intravenous administration of gentamicin compared with serum levels over time after slow-fill (the drug is administered with the PFC at the beginning of liquid ventilation) or top-fill (the drug is administered to animals undergoing liquid ventilation) pulmonary administration of a gentamicin/perfluorochemical nanocrystal suspension. The insert shows an expanded view of the gentamicin levels after slow-fill and top-fill administration. **C.** Serum gentamicin levels over time after intravenous and intratracheal administration of gentamicin in a newborn lamb lung injury model. Lambs receiving intravenous gentamicin underwent gas ventilation, whereas animal receiving intratracheal gentamicin underwent tidal liquid ventilation.

A. Reproduced from [32] with kind permission of Springer Science and Business Media.
B. Reprinted from [33], Copyright (1999), with permission from Elsevier.
C. Reproduced with permission from Pediatrics 100(5):e5, Copyright © 1997 by AAP.
i.v.: Intravenous administration; IT: Intratracheal administration.

RIGHTSLINK

2.5 Distribution of drugs within the lung

Several studies have shown that PFCs are evenly distributed within the lung of laboratory animals undergoing liquid ventilation [42] or receiving a single dose of a PFC [43]. One important question is if a drug administered with a PFC is also evenly distributed throughout the lung. The distribution of radiolabelled dipalmitoylphosphatidylcholine in the lung of preterm lambs has been investigated after administration of a suspension of the phospholipid in saline during liquid ventilation with perfluorodecaline [30]. The dipalmitoylphosphatidylcholine was homogeneously distributed throughout the lung, thus demonstrating that PFC-assisted drug delivery indeed results in the expected, even distribution of a drug throughout the lung.

Other studies have shown that gentamicin is evenly distributed between different lobes of the lung in lambs with healthy [32,33] or diseased lungs [34]. Figure 3 shows that gentamicin levels in different lobes of lamb lungs after injury are indeed comparable and within a therapeutically relevant range. Although gentamicin tissue levels in animals receiving gentamicin intravenously (and undergoing conventional mechanical gas ventilation) are also similar between lobes, they are below therapeutically useful gentamicin levels.

3. Gene drug delivery

Gene therapy is of great interest for the treatment of both congenital and acquired lung diseases. As with small drug molecules, the homogeneous introduction of the gene vector into the airways is one major problem associated with gene therapy. Several studies have shown that co-administration of PFC (e.g., perfluorooctyl bromide, FC-80 or FC-75; Table 1), can facilitate the distribution of a gene vector in mice [43-46], rats [43,45,47], rabbits [42] and non-human primates [48]. Although the vector was not delivered to the lung using the PFC in these studies, the PFC did facilitate its distribution within the lung. These studies consistently reported an increase of total lung gene expression and an improved distribution of *in situ* gene expression within and between lung lobes, independent of species and/or gene vector used. Most importantly, gene expression in the distal airway and alveolar epithelium was typically increased in these studies compared with animals receiving the vector alone. Furthermore, gene expression was also improved in rodent models of lung injury, including at sites of debris accumulation [44,47]. The improved gene drug delivery resulting from the co-administration of a PFC is thought to be the result of improved propulsion of the gene vector throughout the airways, possibly due to the recruitment of increased numbers of alveoli and small airways. Other mechanisms, such as a transient increase in lung epithelial tight junction permeability or inhibition of alveolar macrophages due to ingestion of the PFC, may also explain the increased gene expression in the alveolar epithelium [46].

4. Novel perfluorocarbon compound-drug formulations for intrapulmonary administration

Aqueous solutions of drugs and PFCs are not miscible. Although *in vivo* studies have clearly demonstrated that the PFC-assisted administration of aqueous solutions results in a homogeneous distribution of the drug within the lung, the phase separation of the drug solution and the PFC make this approach less useful, both from a pharmaceutical and a clinical point of view. Therefore, it is desirable to develop new approaches to disperse or solubilize drugs in a PFC. The following sections will provide an overview of the different methods presently under investigation.

4.1 Perfluorocarbon compound soluble drugs and prodrugs

The most straightforward approach to use PFCs as vehicles for drug delivery is to dissolve the drug in the PFC and administer this solution directly to the lung. Although PFCs are poor solvents for typical drug molecules, some fluorophilic drug molecules are an exception. For example, the anesthetic halothane is soluble in perfluorodecalin [49] and can be successfully delivered during liquid ventilation with RIMAR 101 (see Table 1) in adult female hamsters [50].

Perfluorooctyl bromide in not a typical PFC and has some unexpected solubilization properties [14,51,52] (i.e., some organic compounds are miscible with perfluorooctyl bromide). These observations suggested that a prodrug approach can be used to enhance the solubility of drug molecules in perfluorooctyl bromide. As part of a prodrug approach, a PFC-soluble prodrug would be synthesized by modifying the parent drug with a promoiety, with the goal to achieve solubility in the PFC. Similar to a conventional prodrug approach, the prodrug would be expected to partition into the lung tissue after administration with perfluorooctyl bromide, where the parent drug is released by chemical or biological degradation [14].

To further investigate this hypothesis, a series of hydrocarbon and fluorocarbon ester prodrugs of nicotinic acid were synthesized in one study [51]. Nicotinic acid, which itself is not soluble in perfluorooctyl bromide, is a precursor of NAD and has been proven beneficial against acute lung injury [53-55]. Solubility measurements supported the hypothesis that a prodrug can be used to solubilize drugs in perfluorooctyl bromide and other PFCs (Table 2). Even simple nicotinic acid alkyl esters were soluble in perfluorooctyl bromide in millimolar concentrations. Some highly fluorinated octyl nicotinates were even miscible with perfluorooctyl bromide. These nicotinate prodrugs have properties that make them potentially suitable for pulmonary administration. Both hydrocarbon and fluorocarbon nicotinates readily partitioned into model membranes [56,57] and had a low toxicity in cells in culture [58]. Furthermore, nicotinates were hydrolyzed by esterases [51] and are expected to release the parent drug, nicotinic acid, in cells in culture and *in vivo*. Indeed, preliminary studies have shown that nicotinates dissolved in

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

RIGHTSLINK

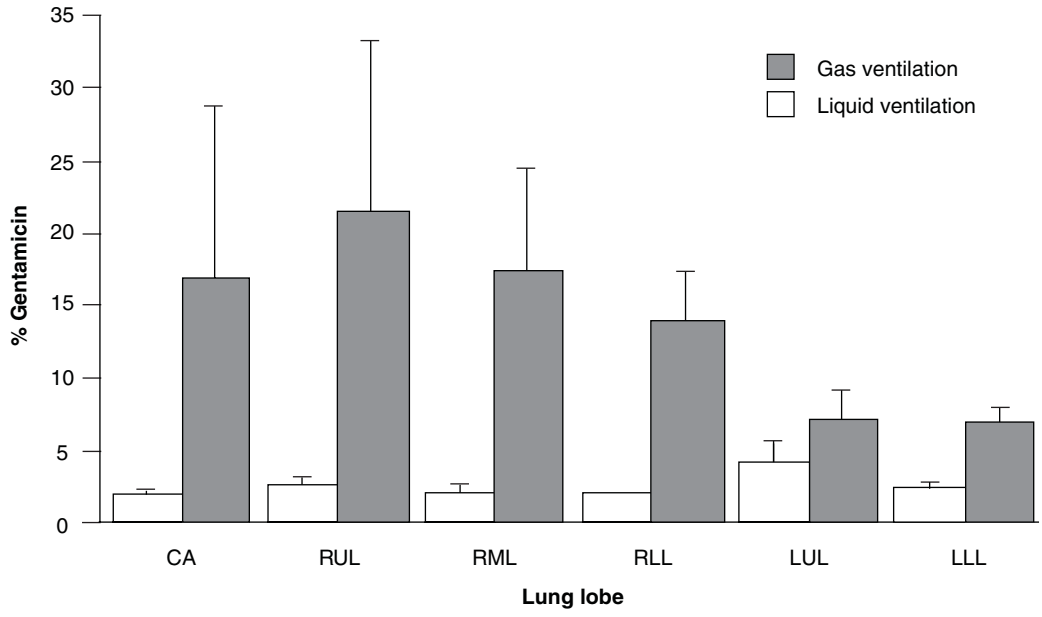


Figure 3. A comparison of lung tissue levels of gentamicin 4 h after administration in animals undergoing conventional gas or liquid ventilation. Gentamicin levels are expressed as the percent of the total dose.

Reproduced with permission from Pediatrics 100(5):e5, Copyright © 1997 by AAP.
CA: Cranial apical lobe; LLL: Left lower lobe; LUL: Left upper lobe; RLL: Right lower lobe; RML: Right middle lobe; RUL: Right upper lobe.

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

PFCs can increase NAD levels in cells in culture (Lehmler *et al*., unpublished results) and, possibly, *in vivo*.

4.2 Solubilizing agents

Solubilizing agents are another possibility to enhance the solubility of drugs in a PFC. Unlike prodrugs, where a promoiety is covalently attached to the drug molecule, solubilizing agents form a PFC-soluble complex by interacting noncovalently with the drug molecule of interest. This approach was studied *in vitro* using phenols as model drugs and a series of solubilizing agents [59]. Each solubilizing agent contained a saturated fluorocarbon chain, a feature necessary for sufficient solubility in the PFC, and a carbonyl group. All solubilizing agents investigated enhanced the solubility of phenols in perfluorooctyl bromide, due to hydrogen bonding between the phenolic OH group and the carbonyl group of the solubilizing agent. Although this study showed that phenolic drugs can be dissolved in perfluorooctyl bromide by adding a solubilizing agent, this approach has several limitations. Not only is it limited to drugs with phenolic hydroxyl groups, but several equivalents of the solubilizing agent must be added to dissolve one equivalent of the drug. Overall, these limitations make it unlikely that solubilizing agents will be useful for clinical applications.

4.3 Reverse water-in-perfluorocarbon compound emulsions

Reverse water-in-PFC emulsions or microemulsions are a promising approach to the use of PFCs, such as perfluorooctyl bromide, for the intrapulmonary administration of drugs. The goal is to dissolve typical, water-soluble (thus, PFC-insoluble) drugs in the aqueous phase of the reverse water-in-PFC emulsions or microemulsions. At the same time, these emulsions are expected to retain desired properties such as high fluidity and gas solubility. Although this is a straightforward and versatile approach, the phase behavior and structure of only a limited number of fluorinated microemulsions, including reverse water-in-PFC microemulsions, have been investigated [52,60-63]. These studies used a limited range of surfactants, such as fluorinated poly(oxyethylene) derivatives, carboxylic acids and dimorpholinophosphates. Unfortunately, with the exception of the dimorpholinophosphates, all other surfactants investigated in these systems are not biocompatible.

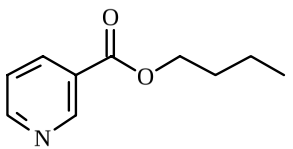
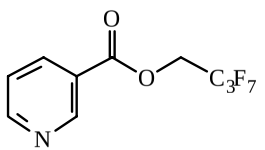
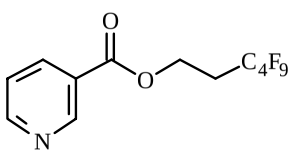
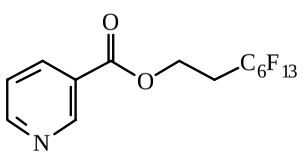
4.3.1 *Physicochemical characteristics of reverse water-in-perfluorooctyl bromide emulsions*

Partially fluorinated dimorpholinophosphates have been studied as surfactants for the preparation of reverse water-in-perfluorooctyl bromide emulsions for intrapulmonary administration [60,64]. These surfactants can be easily synthesized by reacting the corresponding alcohol with phosphoryl chloride and morpholine [65]. So far, dimorpholinophosphates with a long perfluorinated tail (i.e., $-C_6F_{13}$ and $-C_8F_{17}$) and a long hydrocarbon spacer (i.e., 5 or 11 methylene groups), for example F8C11DMP (Figure 4b), are the most promising surfactants for the formation of reverse water-in-perfluorooctyl bromide.

RIGHTSLINK

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

Table 2. Physicochemical properties of perfluorocarbon compound soluble hydrocarbon and fluorocarbon nicotinic acid ester prodrugs.

Chemical name	Chemical structure	Melting point (°C)	Aqueous solubility at pH 6 (µg/ml)	log P*	Solubility in perfluorooctyl bromide (M)	$t_{½}$ in buffer at pH 7.4‡ (h)	Enzymatic $t_{½}$§ (min)
Butyl nicotinate		< -30	1934	3.91	0.17	646	170
2,2,3,3,4,4,4-Heptafluorobutyl nicotinate		3.6	133	4.97	0.62	12	3
3,3,4,4,5,5,6,6,6-Nonafluorohexyl nicotinate		-2.8	11	5.43	0.84	178	163
3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl nicotinate		21.5	Nd	Nd	Miscible	316	> 24 h

*log P is an apparent partition coefficient between 1-octanol and phosphate buffer (pH 7.4). log P of nicotinic acid is -2.47.

‡ $t_{½}$ was calculated by the extrapolation of the Arrhenius plot at 37°C [51].

§ 100 U/l porcine liver esterase.

Nd: Not determined because of poor water solubility.

RIGHTSLINK

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

Emulsions with low concentrations of F8C11DMP were milky in appearance, but became more and more transparent, with pronounced Tyndall scattering with increasing surfactant concentrations [60]. These emulsions were highly fluid and their water content ranged from 1 – 30% (v/v) at a surfactant concentration of 2% (w/v) [64]. These reverse emulsions could be heat sterilized or filtered through a sterilizing membrane, without significant change in the average particle size. In comparison with other dimorpholinophosphates, emulsions obtained with F8C11DMP had a narrow size distribution and were more stable over time [60,64]. For example, in one study, the average particle diameter of an emulsion containing 2% (w/v) F8C11DMP immediately after preparation was 0.15 µm, whereas the average particle diameter increased to 0.27 µm after 4.5 months at 25°C [64].

Reverse water-in-perfluorooctyl bromide emulsions have been investigated at F8C11DMP concentrations ranging 1.5 – 30% (w/v) [60]. The mean droplet diameter of these emulsions changed with increasing F8C11DMP concentration (Figure 4). Samples prepared with < 1.5% (w/v) of surfactant formed unstable macroemulsions that phase-separated after ~ 80 days. Miniemulsions were obtained between 1.5 and 5.0% (w/v) of surfactant. The mean droplet diameter of these miniemulsions decreased from ~ 110 to ~ 23 nm with increasing surfactant concentration. The droplet size of these samples increased due to molecular diffusion (Ostwald ripening) and plateaued below 180 nm after 200 days.

At surfactant concentrations ≥ 6% (w/v), the mean droplet diameter plateaued at 12 nm and remained constant for at least 6 months. The small particle size, the long shelf life and the transparent appearance of the samples in this concentration range suggests the formation of micro-emulsions, which is an important observation from a drug delivery point of view. Microemulsions are thermo-dynamically stable and form spontaneously over a well-defined composition range by the addition of the surfactant to the otherwise immiscible water–PFC system. Therefore, water-in-PFC microemulsions are, in principle, very promising intrapulmonary drug delivery systems.

4.3.2 *Biocompatibility of reverse water-in-perfluorooctyl bromide emulsions*

Many PFCs, such as perfluorooctyl bromide are biocompatible (Section 1.1) and have been studied extensively, both in the laboratory and clinically. In contrast, the biocompatibility of partially fluorinated surfactants and their respective water-in-perfluorooctyl bromide emulsions is only poorly investigated, partly because partially fluorinated compounds with acceptable purities are not readily available.

Several studies showed that surfactants with a high degree of fluorination display low-to-moderate toxicity in cells in culture and, despite their high surface activity, have no hemolytic activity [66-72]. Similarly, partially fluorinated dimorpholinophosphates with a chain length > C12 have been shown to be less toxic than surfactants, with shorter, partially fluorinated chains in cells in culture [65,73]. One of the least toxic compounds in the cell culture experiments was F8C11DMP (Figure 4b). Furthermore, partially fluorinated dimorpholinophosphates have been shown to be non-hemolytic [65]. In contrast, analogous hydrocarbon surfactants were highly toxic [65,73] and strongly hemolytic [65]. *In vivo* studies in mice have also shown the low toxicity of fluorinated dimorpholinophosphates after intravenous administration. For example, the LD_{50} of F8C11DMP was ~ 4 g/kg bodyweight [64,65].

Some data about the toxicity of solutions and emulsions of partially fluorinated dimorpholinophosphates in perfluoro-octyl bromide have been reported for cells in culture and in mice [64,65,73,74]. From these studies, solutions of F8C11DMP in perfluorooctyl bromide were shown to be toxic at concentrations ≥ 1% (w/v) in cells in culture [73]. Surprisingly, emulsions stabilized with F8C11DMP were less toxic than the respective surfactant–perfluorooctyl bromide solutions [73]. It has also been demonstrated that intraperitoneal administration of perfluorooctyl bromide-based dispersions or solutions of F8C11DMP are well tolerated in mice [64,65]. Intranasal administration of a single dose or four consecutive doses of a water-in-perfluorooctyl bromide emulsion did not adversely affect tissue integrity or cause any airway inflammation in mice in one study. However, a reversible weight decrease was observed 3 – 4 days after the first administration of the emulsion [74]. Overall, these initial toxicity studies are promising, but further preclinical studies are needed before these emulsions can be investigated clinically.

4.3.3 *Evaluation of drug-containing reverse water-in-perfluorooctyl bromide emulsions*

A number of drugs have been incorporated into reverse emulsions (Table 3) [64]. Many of these emulsions were stable and contained pharmacologically relevant concentrations of the drugs. In one study, the average particle size of a reverse emulsion containing the vasoactive bronchodilator tolazoline was 0.15 µm after preparation, 0.17 µm after heat sterilization and 0.23 µm after storage at 25°C for one month [64].

In contrast, significant differences between insulin-loaded and unloaded reverse emulsions have been demonstrated [74]. Specifically, insulin-containing reverse emulsions had a milky appearance and did not cream. Their initial mean diameter was larger than the mean diameters of unloaded control emulsion (115 ± 8 nm versus 60 ± 5 nm). Furthermore, insulin-loaded emulsions were less stable compared with the unloaded control emulsions. These observations not only raise the question of how drugs alter properties of reverse emulsions, but also if the stability of the drugs is affected after formulation of the reverse emulsion.

The feasibility of administering insulin-loaded reverse emulsions has been investigated *in vivo* [74]. However, instead of using intrapulmonary administration, these emulsions were administered intranasally in mice. The effect of a plain emulsion, an insulin-loaded reverse emulsion or a solution of free insulin on

RIGHTSLINK

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

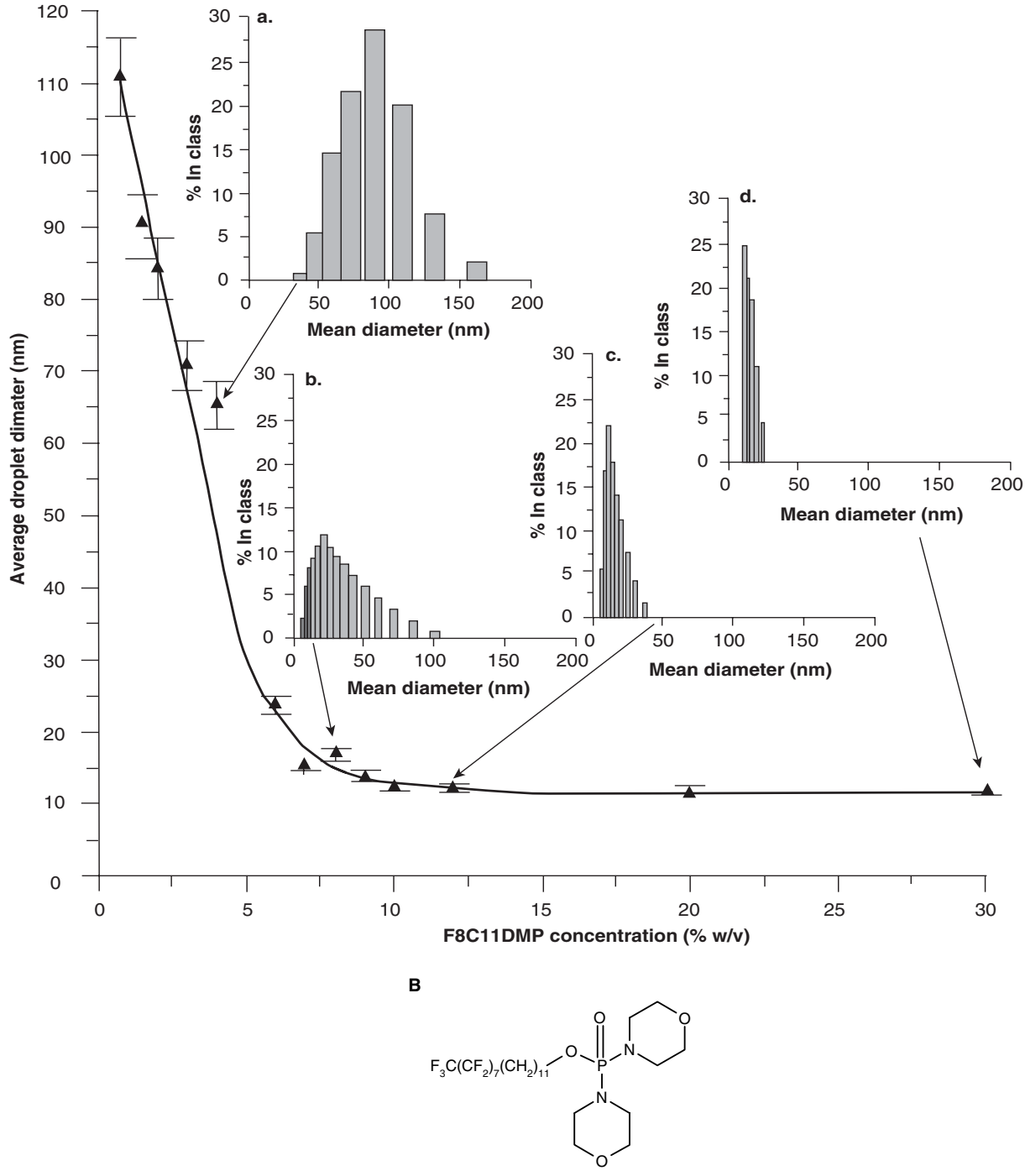


Figure 4. A line graph of the variation of the mean droplet diameter in water-in-perfluorooctyl bromide emulsions versus F8C11DMP concentration after a 20-day annealing period at 25°C. The histograms show the distribution of droplet size at F8C11DMP concentrations of **a.** 4% (w/v), **b.** 8% (w/v), **c.** 12% (w/v) and **d.** 30% (w/v) **B.** The chemical structure of F8C11DMP.
A. Reprinted from [60], Copyright 2004, with permission from Elsevier.

RIGHTSLINK

Table 3. Drugs incorporated into reverse water-in-perfluorooctyl bromide emulsions*.

Class	Drug	Ref.
Antibiotics	Doxycycline	[64]
	Gentamycin	[64]
	Erythromycin	[64]
Antidiabetic agent	Insulin	[74]
Antituberculosis agent	Ethambutol	[64]
	Pyrazinamide	[64]
Antitumor agent	Cyclophosphamide	[64]
Cholinergic	Acetylcholine chloride	[64]
Glucocorticoid	Prednisone	[64]
Mucolytic agent	Acetyl cysteine	[64]
Respiratory stimulant	Caffeine	[28]
Vasoactive bronchodilators	Adrenaline	[64]
	Tolazoline	[64]

*Reverse emulsions typically contained perfluorooctyl bromide (95% v/v), sodium chloride (2.5% solution in water; 5% v/v) and F8C11DMP (2% w/v).

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

blood glucose levels over time is shown in Figure 5. The plain emulsion caused a slight decrease in blood glucose levels immediately after administration. Over time, the blood glucose levels returned to the original levels. Intranasal administration of a solution of free insulin lowered blood glucose levels by 70% within 10 min and maintained this hypoglycemic effect over a period of 40 min. In contrast, administration of insulin with a reverse emulsion progressively lowered glucose levels over the same time period. The maximal hypoglycemic effect was achieved 40 min after administration, thus suggesting a sustained systemic release of insulin from the reverse emulsion. As shown in Figure 2, several animal studies reported a similar delay in the pulmonary and systemic release of gentamicin after PFC-assisted intrapulmonary administration. The mechanism(s) of release and absorption of insulin from the reverse emulsions is (are) unknown and additional studies are needed.

5. Conclusion

PFCs are biocompatible materials that have been studied for a range of biomedical applications, both in animals and in humans. Properties such as high solubility for oxygen and carbon dioxide, low viscosity, high spreading coefficients, high density and high volatility, make them promising ve-hicles for the intrapulmonary administration of drugs. The PFC-assisted intrapulmonary delivery of dispersions of drugs has been studied in several animal models. The results from these studies suggest several advantages of this novel drug delivery approach over conventional approaches, such as intravenous administration. Drugs administered with a PFC are evenly distributed throughout the lung. In the diseased lung, PFCs replace fluid and debris accumulated at the site of injury and, thus, allow delivery of drugs even to injured parts of the lung. Compared with intravenous administration, PFC-assisted, intrapulmonary drug delivery results in higher lung tissue levels, and at the same time reduces systemic uptake.

Many of these animal studies investigated the administration of aqueous dispersions, an approach of limited usefulness in a clinical setting, due to the immiscibility of the aqueous and the PFC phase. Novel approaches, such as nanoparticles, PFC-soluble prodrugs, solubilizing agents and reverse water-in-PFC emulsions, are being developed to achieve PFC–drug formulations for intrapulmonary administration. However, studies of these approaches are still in their infancy and further research is needed to demonstrate that these approaches live up to their promise *in vivo*.

6. Expert opinion

Based on their properties, PFCs are considered to be promising vehicles for the administration of drugs directly to the lung. Animal studies support the hypothesis that PFC-assisted drug delivery will result in an even distribution of the drug within the diseased lung, including at sites of debris accumulation. Furthermore, pharmacokinetic studies show that intrapulmonary drug administration achieves higher, therapeutically relevant local drug levels compared to conventional approaches and, at the same time, keeps systemic drug levels below threshold levels of systemic toxicity. However, many challenges need to be addressed before PFCs can be evaluated clinically as drug delivery vehicles.

The intrapulmonary administration of water-in-PFC dispersions during liquid ventilation represents a relatively crude approach with many potential pitfalls. For example, water-in-PFC dispersions are unlikely to be uniform and stable for extended periods of time, which poses a significant problem for clinical applications. Furthermore, no PFC is approved as a ventilatory medium in humans. Thus, intrapulmonary administration of drugs dispersed in PFCs as an adjunct to liquid ventilation is not a clinically promising approach. As an alternative to a liquid ventilation-based drug delivery approach, a PFC–drug formulation could be administered intratracheally to spontaneously breathing animals. Although PFCs can be administered to spontaneously breathing animals and be evenly distributed throughout the lung, this approach has not been studied for the intrapulmonary delivery of small drug molecules.

In addition to developing clinically useful approaches for the actual administration of drugs using PFCs as a drug delivery vehicle, it is necessary to further investigate promising approaches aimed at developing stable PFC-drug formulations (e.g., prodrugs and [micro]emulsions) and to answer some fundamental questions. For example, what is the ideal PFC for intrapulmonary administration of drugs? Although quantitative structure–activity relationships of PFCs as respiratory media have been investigated [75], systematic studies of many other

RIGHTSLINK

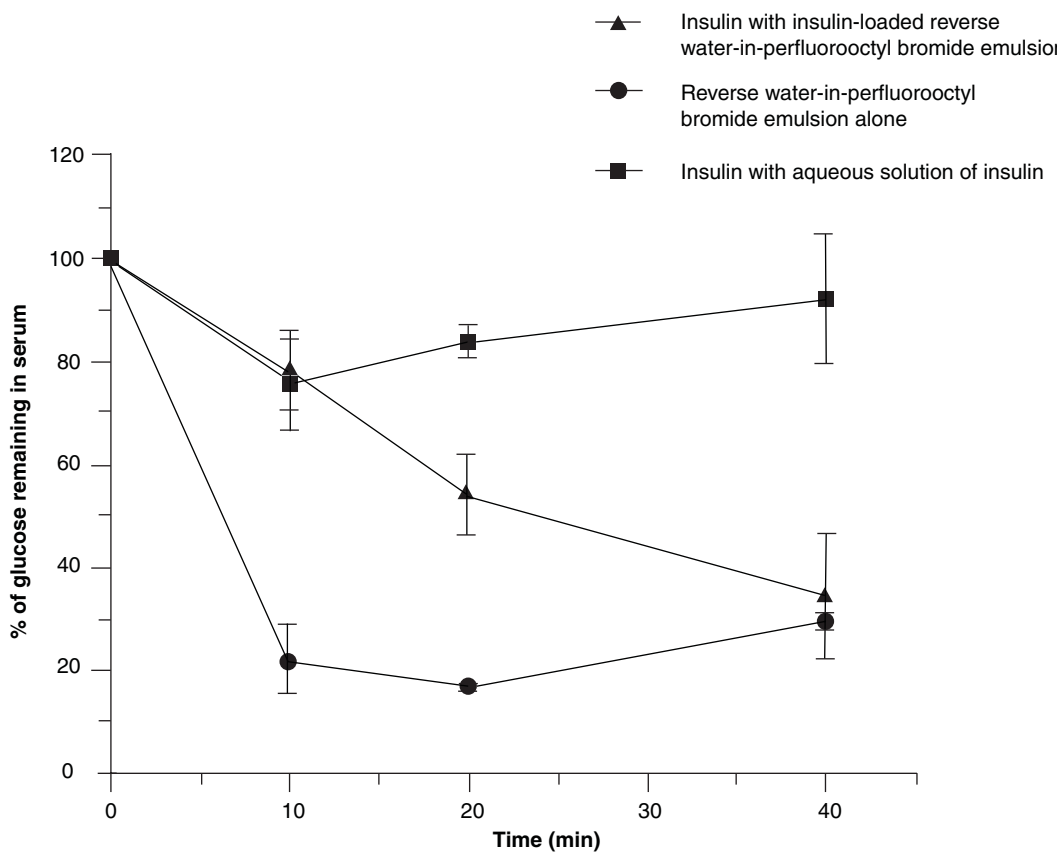


Figure 5. The time course of serum glucose levels in mice receiving insulin intranasally either with an insulin-loaded reverse water-in-perfluorooctyl bromide emulsion or with an aqueous solution of insulin. Serum glucose levels in animals receiving a reverse water-in-perfluorooctyl bromide emulsion alone are shown for comparison. Data points are expressed as a percent of serum glucose levels of untreated animals and are the means ± SEM for n = 4 animals.
Reproduced from reference [74], Copyright 2004, with permission from Elsevier.

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

desirable properties of PFCs are not available. These include studies of the solubility of small drugs in different PFCs, the phase behavior of water-in-PFC emulsions, and the structure–activity-type studies of the biological effects (e.g., cytoprotective effects) of PFCs. Other challenges that need to be addressed include the unavailability of suitable, fluorinated compounds, such as promoieties and surfactants, and a poor understanding of the toxicity of these fluorinated compounds.

Acknowledgements

The author would like to thank R Epp for helpful suggestions during the preparation of this manuscript. This publication was made possible by financial support from the National Institute for Biomedical Imaging and Bioengineering (EB002748) and the National Institute of Environmental Health Sciences (ES012475).

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. MAIN ML, GRAYBURN PA: Clinical applications of transpulmonary contrast echocardiography. *Am. Heart J.* (1999) 137(1):144-153.
2. BROWN JJ: Gastrointestinal contrast agents for MR imaging. *Magn. Reson. Imaging Clin. N. Am.* (1996) 4(1):25-35.
3. MATTREY RF: The potential role of perfluorochemicals (PFCs) in diagnostic imaging. *Artif. Cells Blood Substit. Immobil. Biotechnol.* (1994) 22:295-313.
4. SPAHN DR, VAN BREMPT R, THEILMEIER G *et al.*: Perflubron emulsion delays blood transfusions in orthopedic surgery. *Anesthesiology* (1999)91:1195-1208.
5. SPAHN DR: Current status of artificial oxygen carriers. *Adv. Drug Deliv. Rev.* (2000) 40(3):143-151.

RIGHTSLINK

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

6. COHN SM: Blood substitutes in surgery. *Surgery* (2000) 127(6):599-602.
7. LANE TA: Perfluorochemical-based artificial oxygen carrying red cell substitutes. *Transfus. Sci.* (1995) 16(1):19-31.
8. HABLER O, PAPE A, MEIER J, ZWISSLER B: Artificial oxygen carriers as an alternative to red blood cell transfusion. *Anaesthesist* (2005) 54(8):741-754.
9. WOLFSON MR, SHAFFER TH: Liquid ventilation: an adjunct for respiratory management. *Paediatr. Anaesth.* (2004) 14(1):15-23.
•• Excellent review of the present status of the clinical use of liquid ventilation by leaders in the field.
10. WOLFSON MR, SHAFFER TH: Pulmonary applications of perfluorochemical liquids: ventilation and beyond. *Paediatr. Respir. Rev.* (2005) 6:117-127.
•• Excellent review of the present status of the clinical use of liquid ventilation by leaders in the field.
11. NUMA AH: Acute lung injury: outcomes and new therapies. *Paediatr. Respir. Rev.* (2001) 2:22-32.
12. KACMAREK RM: Liquid ventilation. *Respir. Care Clin. N. Am.* (2002) 8(2):187-209.
13. FUHRMAN BP, HERMAN LJ, ROTTA AT: Partial liquid ventilation: a multifaceted approach to acute respiratory distress syndrome. *New Horiz.* (1999) 7:433-439.
14. LEHMLER H-J, BUMMER PM, JAY M: Liquid ventilation - a new way to deliver drugs to diseased lungs? *Chemtech* (1999) 29(10):7-12.
•• An older review of the use of PFCs, especially perfluorooctyl bromide, as a drug delivery vehicle.
15. KACMAREK RM, WIEDEMANN HP, LAVIN PT *et al.*: Partial liquid ventilation in adult patients with acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* (2006) 173(8):882-889.
• This clinical trial did not show any advantages of partial liquid ventilation for the treatment of acute respiratory distress syndrome compared to conventional ventilatory support techniques. As a result of the disappointing outcome of this trial, partial liquid ventilation is unlikely to be approved by the FDA as a treatment modality for acute respiratory distress syndrome in the near future.
16. COSTANTINO M-L, SHAFFER T, WAUER RR, RUDIGER M: The 5th European symposium on perfluorocarbon (PFC) application. *ASAIO J.* (2006) 52:483-484.
• Excellent symposium summary that discussed potential biomedical applications of PFCs.
17. LEHMLER H-J: Synthesis of environmentally relevant fluorinated surfactants-a review. *Chemosphere* (2005) 58(11):1471-1496.
18. PATEL MM, SZANTO P, YATES B, LONG DM: Survival and histopathologic changes in lungs of hamsters following synthetic liquid breathing. *Fed. Proc.* (1970) 29:1740-1745.
19. LE BLANC M, RIESS JG, POGGI D, FOLLANA R: Use of lymphoblastoid namalva cell cultures in a toxicity test. Application to the monitoring of detoxification procedures for fluorocarbons to be used as intravascular oxygen carriers. *Pharm. Res.* (1985) 5:246-248.
20. REICKERT C, PRANIKOFF T, OVERBECK M *et al.*: The pulmonary and systemic distribution and elimination of perflubron from adult patients treated with partial liquid ventilation. *Chest* (2001) 119(2):515-522.
21. FLAIM SF: Pharmacokinetics and side effects of perfluorocarbon-based blood substitutes. *Artif. Cells Blood Substit. Immobil. Biotechnol.* (1994) 22(4):1043-1054.
22. NAKSTAD B, WOLFSON MR, SHAFFER TH *et al.*: Perfluorochemical liquids modulate cell-mediated inflammatory responses. *Crit. Care Med.* (2001) 29(9):1731-1737.
23. HIRSCHL RB, OVERBECK MC, PARENT A *et al.*: Liquid ventilation provides uniform distribution of perfluorocarbons in the setting of respiratory failure. *Surgery* (1994) 116:159-168.
24. SCOTT RL: The anomalous behavior of fluorocarbon solutions. *J. Am. Chem. Soc.* (1958) 62:136-145.
25. PATRICK CR: Physicochemical properties of highly fluorinated organic compounds. *Chem. Brit.* (1971) 7(4):154-156.
26. MUKERJEE P, YANG AYS: Nonideality of mixing of micelles of fluorocarbon and hydrocarbon surfactants and evidence of partial miscibility from differential conductance data. *J. Phys. Chem.* (1976) 80:1388-1390.
27. KANDLER MA, VON DER HARDT K, SCHOOF E, DOTSCH J, RASCHER W: Persistent improvement of gas exchange and lung mechanics by aerosolized perfluorocarbon. *Am. J. Respir. Crit. Care Med.* (2001) 164(1):31-35.
28. BUTZ N, PORTE C, COURRIER H, KRAFFT MP, VANDAMME TF: Reverse water-in-fluorocarbon emulsions for use in pressurized metered-dose inhalers containing hydrofluoroalkane propellants. *Int. J. Pharm.* (2002) 238(1-2):257-269.
29. SCHOOF E, VON DER HARDT K, KANDLER MA *et al.*: Aerosolized perfluorocarbon reduces adhesion molecule gene expression and neutrophil sequestration in acute respiratory distress. *Eur. J. Pharmacol.* (2002) 457:195-200.
30. WOLFSON MR, GREENSPAN JS, SHAFFER TH: Pulmonary administration of vasoactive substances by perfluorochemical ventilation. *Pediatrics* (1996) 97(4):449-455.
31. SHAFFER TH, WOLFSON MR, GREENSPAN JS, RUBENSTEIN SD, STERN RG: Perfluorochemical liquid as a respiratory medium. *Artif. Cells Blood Substit. Immobil. Biotechnol.* (1994) 22(2):315-326.
32. ZELINKA MA, WOLFSON MR, CALLIGARO I *et al.*: A comparison of intratracheal and intravenous administration of gentamicin during liquid ventilation. *Eur. J. Pediatr.* (1997) 156:401-404.
33. CULLEN AB, COX CA, HIPP SJ, WOLFSON MR, SHAFFER TH: Intra-tracheal delivery strategy of gentamicin with partial liquid ventilation. *Respir. Med.* (1999) 93:770-778.
34. FOX WW, WEIS CM, COX C *et al.*: Pulmonary administration of gentamicin during liquid ventilation in a newborn lamb lung injury model. *Pediatrics* (1997) 100(5):e5.
35. DICKSON EW, HEARD SO, TARARA TE *et al.*: Liquid ventilation with perflubron in the treatment of rats with pneumococcal pneumonia. *Crit. Care Med.* (2002) 30(2):393-395.
36. SMITH DJ, GAMBONE LM, TARARA T *et al.*: Liquid dose pulmonary instillation of gentamicin PulmoSpheres® dormulations: Tissue distribution and pharmacokinetics in

RIGHTSLINK

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

rabbits. *Pharm. Res.* (2001) V18(11):1556-1561.

- The authors of this manuscript not only demonstrate that gentamicin nanoparticles dispersed in perfluorooctyl bromide can be delivered directly to the lung, but also provide an excellent discussion of the potential clinical advantages of the intrapulmonary administration of antibiotics.

37. FRANZ AR, ROHLKE W, FRANKE RP *et al.*: Pulmonary administration of perfluorodecaline-gentamicin and perfluorodecaline-vancomycin emulsions. *Am. J. Respir. Crit. Care Med.* (2001) 164(9):1595-1600.

38. BRUN-BUISSON C, LEMAIRE F: Administration of antibiotics for pneumonia during respiratory failure: reaching the target. *Am. J. Respir. Crit. Care Med.* (2001) 164(9):1554-1555.

39. DELLAMARY LA, TARARA TE, SMITH DJ *et al.*: Hollow porous particles in metered dose inhalers. *Pharm. Res.* (2000) 17(2):168-174.

40. BRUNELLI L, HAMILTON E, DAVIS JM *et al.*: Perfluorochemical liquids enhance delivery of superoxide dismutase to the lungs of juvenile rabbits. *Pediatr. Res.* (2006) 60(1):65-70.

41. LANGENBACK EG, DAVIS JM, ROBBINS C *et al.*: Improved pulmonary distribution of recombinant human Cu/Zn superoxide dismutase, using a modified ultrasonic nebulizer. *Pediatr. Pulmonol.* (1999) 27(2):124-129.

42. LISBY DA, BALLARD PL, FOX WW *et al.*: Enhanced distribution of adenovirus-mediated gene transfer to lung parenchyma by perfluorochemical liquid. *Hum. Gene Ther.* (1997) 8:919-928.

- This article describes for the first time the administration of a gene vector in animals undergoing liquid ventilation.

43. WEISS DJ, STRANDJORD TP, JACKSON JC, CLARK JG, LIGGITT D: Perfluorochemical liquid-enhanced adenoviral vector distribution and expression in lungs of spontaneously breathing rodents. *Exp. Lung Res.* (1999) 25(4):317-333.

- This excellent manuscript demonstrates that intratracheal instillation of perfluorooctyl bromide in spontaneous breathing animals results in a homogeneous distribution of the PFC in the lung. Furthermore, the authors demonstrate that the PFC enhances the distribution and expression of an adenoviral gene vector.

44. WEISS DJ, STRANDJORD TP, LIGGITT D, CLARK JG: Perflubron enhances adenovirus-mediated gene expression in lungs of transgenic mice with chronic alveolar filling. *Hum. Gene Ther.* (1999) 10(14):2287-2293.

45. WEISS DJ, BONNEAU L, ALLEN JM, MILLER AD, HALBERT CL: Perfluorochemical liquid enhances adeno-associated virus-mediated transgene expression in lungs. *Mol. Ther.* (2000) 2(6):624-630.

46. WEISS DJ, BECKETT T, BONNEAU L *et al.*: Transient increase in lung epithelial tight junction permeability: an additional mechanism for enhancement of lung transgene expression by perfluorochemical liquids. *Mol. Ther.* (2003) 8(6):927-935.

47. WEISS DJ, BONNEAU L, LIGGITT D: Use of perfluorochemical liquid allows earlier detection of gene expression and use of less vector in normal lung and enhances gene expression in acutely injured lung. *Mol. Ther.* (2001) 3(5):734-745.

48. WEISS DJ, BASKIN GB, SHEAN MK, BLANCHARD JL, KOLLS JK: Use of perfluorochemical liquid to enhance adenoviral-mediated gene expression in lungs of spontaneously breathing non-human primates: feasibility and initial studies. *Pediatr. Pulmonol. Suppl.* (2000) 20:235-236.

49. TREMPER KK, ZACCARI J, CULLEN BF, HUFSTEDLER SM: Liquid-gas partition coefficients of halothane and isoflurane in perfluorodecalin, fluosol-DA, and blood/fluosol-DA mixtures. *Anesth. Anal.* (1984) 63:690-692.

50. KIMLESS-GARBER DB, WOLFSON MR, CARLSSON C, SHAFFER TH: Halothane administration during liquid ventilation. *Respir. Med.* (1997) 91:255-262.

51. HSU C-H, JAY M, BUMMER PM, LEHMLER H-J: Chemical stability of esters of nicotinic acid intended for pulmonary administration by liquid ventilation. *Pharm. Res.* (2003) 20(2003):918-925.

- This paper demonstrates that a prodrug approach can be used to enhance the solubility of drug molecules, such as nicotinic acid, in perfluorooctyl bromide.

52. SCHUBERT K-V, KALER EW: Microemulsifying fluorinated oils with mixtures of fluorinated and hydrogenated surfactants. *Colloids Surf. A* (1994) 84:97-106.

53. GURUJEYALAKSHMI G, WANG Y, GIRI SN: Taurine and niacin block lung injury and fibrosis by down-regulating bleomycin-induced activation of transcription nuclear factor-kappaB in mice. *J. Pharmacol. Exp. Ther.* (2000) 293(1):82-90.

54. GURUJEYALAKSHMI G, WANG Y, GIRI SN: Suppression of bleomycin-induced nitric oxide production in mice by taurine and niacin. *Nitric Oxide* (2000) 4(4):399-411.

55. VENKATESAN N, CHANDRAKASAN G: *In vivo* administration of taurine and niacin modulate cyclophosphamide-induced lung injury. *Eur. J. Pharmacol.* (1994) 292(1):75-80.

56. LEHMLER H-J, FORTIS-SANTIAGO A, NAUDURI D, BUMMER PM: Interaction of long-chain nicotinates with dipalmitoylphosphatidylcholine (DPPC). *J. Lipid Res.* (2005) 46:535-546.

57. LEHMLER H-J, BUMMER PM: Interaction of a partially fluorinated long-chain nicotinate with dipalmitoylphosphatidylcholine. *J. Lipid Res.* (2005) 46(11):2415-2422.

58. XU L, VYAS SM, LEHMLER H-J, LUDEWIG G: Structure-activity relationships for cytotoxicity of nicotinic acid ester prodrugs for pulmonary delivery. *Abstracts of Papers, 229th ACS National Meeting.* San Diego, CA, USA (13-17 March 2005) MEDI-097.

59. WILLIAMS TD, JAY MJ, LEHMLER H-J, STALKER DJ, BUMMER PM: Solubility enhancement of phenol and phenol derivatives in perfluorooctyl bromide. *J. Pharm. Sci.* (1998) 87:1585-1589.

60. COURRIER HM, VANDAMME TF, KRAFFT MP: Reverse water-in-fluorocarbon emulsions and microemulsions obtained with a fluorinated surfactant. *Colloids Surf. A* (2004) 244(1-3):141-148.

- This manuscripts is an interesting, in-depth investigation of the formation of reverse water-in-perfluorooctyl bromide macro-, mini- and microemulsions intended for pulmonary administration.

61. LONOSTRO P, CHOI S-M, KU C-Y, CHEN S-H: Fluorinated microemulsions: a

RIGHTSLINK

study of the phase behavior and structure. *J. Phys. Chem. B* (1999) 103(25):5347-5352.

62. MATHIS G, LEEMPOEL P, RAVEY JC, SELVE C, DELPUECH JJ: A novel class of nonionic microemulsions: fluorocarbons in aqueous solutions of fluorinated poly(oxyethylene) surfactants. *J. Am. Chem. Soc.* (1984) 106(21):6162-6171.
63. CESCHIN C, ROQUES J, MALET-MARTINO MC, LATTES A: Fluorocarbon microemulsions. *J. Chem. Tech. Biotechnol.* (1985) 35A(2):73-82.
64. SADTLER VM, KRAFFT MP, RIESS JG: Achieving stable, reverse water-in-fluorocarbon emulsions. *Angew. Chem. Int. Ed. Engl.* (1996) 35(17):1976-1978.
65. SADTLER VM, JEANNEAUX F, KRAFFT MP, RABAL J, RIESS JG: Perfluoroalkylated amphiphiles with a morpholinophosphate or a dimorpholinophosphate polar head group. *New. J. Chem.* (1998) 22:609-613.
66. RIESS JG, PACE S, ZARIF L: Highly effective surfactants with low hemolytic activity. *Adv. Mat.* (1991) 3(5):249-251.
67. GUILLOD F, GREINER J, RIESS JG: New anionic glycophospholipids with two perfluorocarbon or two hydrocarbon or mixed hydrophobic chains. *Chem. Phys. Lipids* (1995) 78:149-162.
68. KRAFFT M-P, ROLLAND J-P, VIERLING P, RIESS JG: New perfluoroalkylated phosphocholines. Effect on particle size and stability of fluorocarbon emulsions. *New. J. Chem.* (1990) 14(11):869-875.
69. MILIUS A, GREINER J, RIESS JG: Synthesis of *F*-alkylated glycosides as surfactants for *in vivo* uses. Effects of the length of the hydrocarbonated spacer in the aglycone on Königs-Knorr reaction, surface activity and biological properties. *New J. Chem.* (1991) 15:337-344.
70. ZARIF L, GREINER J, PACE S, RIESS JG: Synthesis of perfluoroalkylated xylitol ethers and esters: new surfactants for biomedical uses. *J. Med. Chem.* (1990) 33(4):1262-1269.
71. KRAFFT MP, VIERLING P, RIESS JG: Synthesis and preliminary data on the biocompatibility and emulsifying properties of perfluoroalkylated phosphoramidates as injectable surfactants. *Eur. J. Med. Chem.* (1991) 26:545-550.
72. VYAS SM, TURANEK J, KNOETIGOVA P *et al.*: Synthesis and biocompatibility evaluation of partially fluorinated pyridinium bromides. *New J. Chem.* (2006) 30(6):944-951.
73. COURRIER HM, KRAFFT MP, BUTZ N *et al.*: Evaluation of cytotoxicity of new semi-fluorinated amphiphiles derived from dimorpholinophosphate. *Biomaterials* (2003) 24(4):689-696.
- This article is the first systematic investigation of the cytotoxicity of partially fluorinated surfactants used for the preparation of reverse water-in-perfluorooctyl bromide emulsions.
74. COURRIER HM, PONS F, LESSINGER JM *et al.*: *In vivo* evaluation of a reverse water-in-fluorocarbon emulsion stabilized with a semifluorinated amphiphile as a drug delivery system through the pulmonary route. *Int. J. Pharm.* (2004) 282(1-2):131-140.
- This manuscript is a logical continuation of the toxicity studies described in reference [73] and investigates the intranasal administration of reverse water-in-perfluorooctyl bromide emulsions in mice.
75. GABRIEL JL, MILLER TF, WOLFSON MR, SHAFFER TH: Quantitative structure-activity relationships of perfluorinated hetero-hydrocarbons as potential respiratory media. Application to oxygen solubility, partition coefficient, viscosity, vapor pressure, and density. *ASAIO J.* (1996) 42(6):968-973.
76. LEONARD RC: Liquid Ventilation. *Anaesth. Intens. Care* (1998) 26:11-21.
77. COX CA, WOLFSON MR, SHAFFER TH: Liquid ventilation: a comprehensive overview. *Neonatal Net.* (1996) 15(3):31-43.
78. SANCHEZ V, MANFREDI A, GREINER J, RIESS JG: (Perfluoroalkyl)- and 1,2-bis(perfluoroalkyl)-iodo- and polybromo ethenes: synthesis and preliminary evaluation as contrast agents for diagnosis. *Bull. Soc. Chim Fr.* (1994) 131:648-657.

Affiliation

Hans-Joachim Lehmler PhD
Research Scientist, University of Iowa, Department of Occupational and Environmental Health, Iowa City, IA 52242, USA
Tel: +1 319 335 4414;
Fax: +1 319 335 4290;
E-mail: hans-joachim-lehmler@uiowa.edu

Expert Opin. Drug Deliv. Downloaded from informahealthcare.com by Hacettepe Univ. on 12/02/12
For personal use only.

RIGHTSLINK