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Invited Review

The controlled delivery of drugs to the lung

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Abstract

Inhalation of aerosolised drugs has become a well established modality in the treatment of localised disease states within the lung. However, most medications in aerosol form require inhalation daily at least 3–4 times because of the relatively short duration of resultant clinical effects. Some studies have been conducted with a view to sustaining release of drugs in the lung so as to prolong drug action, reduce side effects and improve patient compliance. Liposomes have been shown to have the potential to produce controlled delivery to the lung, since they can be prepared with phospholipids endogenous to the lung as surfactants. Up to now, many drugs have been incorporated into liposomes and tested in both human subjects and animal models as pulmonary delivery systems. Other biodegradable microspheres (MS) such as albumin MS and poly(lactide and/or glycolide) copolymer MS are also being investigated. In contrast to liposomes, these MS may be more physico-chemically stable both in vitro and in vivo. Thus, drugs entrapped in biodegradable MS may have a slower release rate and a longer duration of action than those incorporated in liposomes. The prodrug approach has been successful in producing long-lasting bronchodilators whilst conjugation of drugs to macromolecules provides a possible mechanism for controlled release of drugs for either localised or systemic actions. Sustained release in the lung can also be achieved by reducing the aqueous solubility of the drug or co-precipitating relatively insoluble materials with aqueous soluble drugs. In contrast, inclusion of drugs in cyclodextrins is unable to sustain drug release in the lung, which may be due to the premature breakdown of drug-cyclodextrin conjugates in vivo. Many interdependent factors, involving the lung, carrier, drug and device have been shown to influence the overall disposition of drugs in the respiratory tract after inhalation. Current studies on pulmonary delivery systems have many limitations, mainly due to the lack of suitable animal models and the chronic side effects of drug carriers have yet to be established. Thus, more inter-disciplinary collaboration is essential for the development of effective controlled drug delivery systems intended for administration to the lung.

Keywords: Controlled release; Aerosol; Inhalation; Liposome; Microsphere; Drug macromolecular conjugate; Cyclodextrin

1. Introduction

Aerosolised administration of drugs to the lung has been employed for many years to treat primarily localised disease states within the bronchi. Since this route of administration can deliver therapeutic agents to the diseased regions whilst reducing their distribution to the other organs, it provides an excellent example of targeted drug therapy. Hence, a more favourable therapeutic

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index can be obtained for the treatment of lung diseases when drugs are administered by inhalation rather than by the oral route. Bronchodilators, anti-inflammatory agents, mucolytics, antiviral agents, anticancer agents and phospholipid-protein mixtures for surfactant replacement therapy are all routinely given as aerosolised formulations whilst more recently, there has been an increasing interest in the delivery of pentamidine via the lung to treat *Pneumocystis carinii* pneumonia associated with AIDS. Moreover, the development of potent protein drugs by biotechnology has also stimulated a growth of interest in inhalation aerosols because of the possibility of systemic delivery of these drugs via the airways (Thompson, 1992).

A significant disadvantage of many existing inhaled drugs is the relatively short duration of resultant clinical effects and most medications in aerosol form require inhalation at least 3–4 times daily (Byron, 1986). This often leads to poor patient compliance with the therapeutic regime and increases the possibility of associated side effects due to the risk of self-administration of the drug by the patients. A reduction in the frequency of dosing would be convenient, particularly for chronic treatments such as those for asthma. Most brochodilator β_2-agonists have the potential to induce significant cardiovascular side effects such as hypotension and tachycardia due to stimulation of the β_2-adrenoreceptors in the systemic circulation and cross-reactivity with cardiac β_1-adrenoreceptors. Sustained release of such drugs in the lung would be particularly beneficial since they could be delivered to and retained at the targeted receptors for a prolonged period of time and thus minimise the biodistribution throughout the systemic circulation. Furthermore, since asthma symptoms exhibit a diurnal rhythm in a large percentage of patients and pulmonary function is reduced from midnight to about 8 a.m. (Smolensky et al., 1987), the ideal treatment should be effective at preventing bronchospasm for the 6–8 h during which the patients are asleep. However, few of the current bronchodilators can produce this duration of action and therefore frequent inhalation is essential for anti-asthmatic therapy. The potential advantages of achieving sustained release to the lung has been shown by the improved therapeutic effects obtained with a corticosteroid inhaled four times a day compared to two times a day (Malo et al., 1989).

Controlled release of drugs within the pulmonary tree also offers many distinct advantages for agents which are administered for systemic actions. Many of these, in the future, are likely to be potent proteins and peptides designed to regulate important biological responses (Patton and Platz, 1992) and the pulmonary route provides many potential advantages compared to other portals of delivery. It is important that the drugs are released and absorbed into the systemic circulation at a controlled rate to maintain drug levels for the desired time for effective therapy to be elucidated.

Currently, a number of methods have been investigated as potential pulmonary sustained-release systems for short-acting drugs. These include the incorporation of drugs in liposomes and other biodegradable microspheres, the modification of chemical structure to produce either prodrugs or drug conjugates with macromolecules, the use of sparingly soluble forms of the drug and the preparation of magnesium hydroxide co-precipitates and complexes of the drug with cyclodextrins. In this article, we review the development and future prospects for these methods as well as considering the possible problems related to the use of pulmonary controlled release systems. However, the strategy of producing long-acting drug entities, which is also an active field, will not be discussed.

2. Liposomes

Liposomes are one of the most extensively investigated systems for controlled delivery of drug to the lung, since they can be prepared with phospholipids endogenous to the lung as surfactants. Liposomes can also be produced with a wide range of size and will incorporate both hydrophilic and lipophilic drugs. Many drugs have been incorporated into liposomes with a view to improving their pulmonary delivery and some

have been tested in animal and human subjects (Kellaway and Farr, 1990). These include, for example, cytotoxic agents, anti-asthma drugs, antimicrobial and antiviral compounds, antioxidant agents and drugs with systemic actions.

2.1. Cytotoxic agents

Free and liposome-encapsulated arabinoside ([^{3}H]Ara-C) was administered to rats by intratracheal instillation (McCullough and Juliano, 1979). Free Ara-C was rapidly cleared from the lung ($t_{1/2}$ = 40 min) and absorbed into systemic circulation while liposome-encapsulated drug was retained in the lung for a prolonged period ($t_{1/2}$ = 8 h) with little distribution to other tissues. As a result, free Ara-C inhibited [^{14}C]thymidine incorporation in the gastrointestinal tract, bone marrow and lung, while liposomal drug efficiently suppressed thymidine incorporation within the lung but had little effect on the other sites. A subsequent study reached similar conclusions (Juliano and McCullough, 1980), suggesting that liposomal encapsulation could not only target Ara-C to the lung but also prolong its anticancer activities by retaining the drug at the targeted sites.

2.2. Bronchodilators

Sympathomimetic amines, such as isoprenaline or orciprenaline, are particularly suitable candidates for pulmonary controlled release. The drugs can alleviate airway obstruction by stimulating β_2-adrenergic receptors but they can also cause tachycardia via β_1-adrenergic activities. Liposomal formulation has proved to be successful in reducing such cardiovascular side effects by minimising the distribution of the drugs to the circulation. Liposomal orciprenaline instilled intratracheally to the anaesthetised guinea pig was shown to prolong bronchodilatory effects when compared with the free drug administered at the same dose. Moreover, the former showed a sustained, low intensity tachycardia compared to the relatively large initial tachycardia peak induced by free drug (Kamarel et al., 1989). Another study also demonstrated that liposomal encapsulation can improve bronchodilatory effects and reduce cardiovascular side effects (Fielding, 1989).

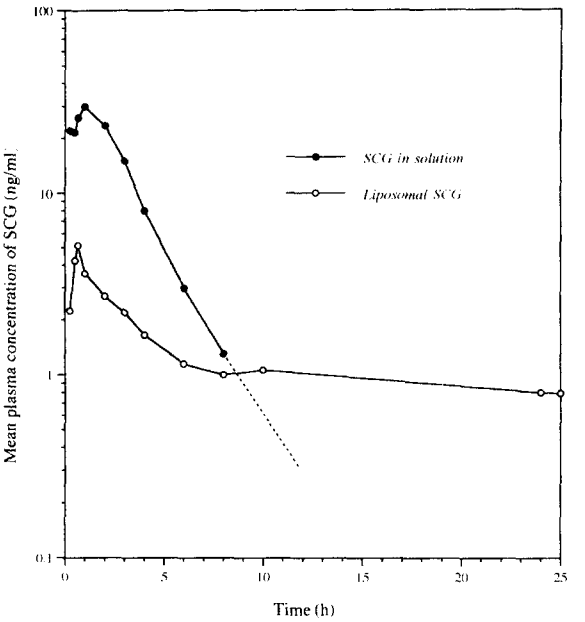

Fig. 1. Mean plasma concentrations following nebulization of 20 mg sodium cromoglycate (SCG) to volunteers (adapted from Taylor et al., 1989).

2.3. Anti-asthma drugs

Sodium cromoglycate (SCG), a prophylactic anti-asthma drug, is ineffective when taken orally because of its poor bioavailability. SCG pharmacokinetics have been investigated in healthy volunteers after administering SCG encapsulated in liposomes (Taylor et al., 1989). Liposomal SCG produced detectable plasma concentrations of drug up to 25 h after inhalation, whereas an equivalent dose of free drug produced peak plasma concentration 7-times greater than that of the liposomal drug and could not be detected in 25 h plasma samples (Fig. 1). It is apparent that liposomes can be employed to extend the duration of drug plasma levels in man following pulmonary administration.

2.4. Antimicrobial and antiviral agents

Incorporation of antibiotics within liposomes has been shown to enhance bactericidal activity

when compared to free drug, especially for the treatment of monocyte and macrophage infections (Couvreur et al., 1991). Inhalation of liposomal-entrapped antibiotics provides a possible means of targeting these drugs to infected alveolar macrophages since in vitro studies have demonstrated the rapid alveolar macrophage uptake of liposomes (Gonzalez-Rothi et al., 1991). Hence, liposomal amikacin has been used for the treatment of *Mycobacterium avium-intracellulare* infections, commonly associated with immunosuppressed patients, which are difficult to treat (Wichert et al., 1992). Liposomal formulation was shown to increase drug activity by approx. 100-fold compared to that of the free drug. When given intratracheally to sheep, amikacin in solution exhibited a half-life of about 2 h with a maximum plasma level (C_{max}) of 8.3 μg/ml, whilst the half-life of the drug encapsulated in soy phosphatidylcholine/phosphatidylglycerol/cholesterol (4:3:3) liposomes was found to be greater than 10 h with a C_{max} of 3.3 μg/ml (Schreier et al., 1992). Since the absorption of amikacin into the circulation after administration as liposomal suspensions was reduced, formulation in this way should reduce systemic side effects and enhance local pharmacodynamics. Benzylpenicillin and oxytocin have also been incorporated into liposomes and administered intratracheally to rats, with plasma analysis being undertaken for up to 3 h post-instillation (Mihalko et al., 1988). Liposomes did not affect the absorption rate constants of either of these drugs, although, areas under the plasma concentration time curves were three times smaller for the liposomal benzylpenicillin and almost eight times smaller for liposomal oxytocin compared with the respective free drugs. Thus, it was concluded that drug distribution to the systemic circulation was dependent upon the drug release from liposomes which could serve to retain drugs in the lung and minimise their distribution to other organs.

Liposomes containing the antiviral compound enviroxine have been prepared and tested for anti-rhinovirus activity and toxicity in cell culture (Wyde et al., 1988). Free and liposomal enviroxine was found to have similar efficacies but encapsulation was shown to reduce its side effects by 10–50-times to cultured cells. The enviroxine-entrapped liposomes were inhaled by five healthy volunteers after atomisation within a jet nebuliser (Gilbert et al., 1988). 1 h after inhalation, a large amount of enviroxine was found in the upper airways whereas little was absorbed systemically, the drug being detected in only one of the five blood samples. No side effects to the therapy were observed.

Liposomal pentamidine has also been evaluated and no significant difference between the uptake of free and liposome encapsulated drug was apparent in murine lungs (Debs et al., 1987). This was attributed to the high sequestration of the drug within the lung, both free and liposomal drug producing substantially higher deposition in the alveolar region when inhaled than when given intravenously. There was no evidence of drug clearance from the lung between 1 and 48 h after administration. These results suggest that liposomal pentamidine may be a suitable candidate for direct aerosolisation to the lung, although the administration of free drug is no longer advocated as a front-line therapy due to associated toxicity.

2.5. Antioxidant agents

Liposomes have been shown to enhance the antioxidant effects of oxygen radical scavengers, such as catalase and superoxide dismutase. Vesicular entrapment of these scavengers enables intracellular access and delivery of the enzymes within closer proximity of the production sites of the toxic oxygen radicals (Freeman et al., 1983). Thus, when instilled into rat lungs previously treated with toxic levels of oxygen, the liposomal antioxidant drugs exhibited greatly enhanced effects as shown by a dramatic improvement in the mortality rate of the animals as well as a distinct improvement in the histological appearance of excised lungs (Padmanabhan et al., 1985). Free glutathione has been shown to be ineffective in the treatment of oxidant-induced lung damage because of its rapid clearance from the lung. Liposomal encapsulation, however, can prolong its retention in the tissue and confer protection against oxygen-induced lung damage (Suntres and Shek, 1994).

2.6. Drugs for systemic action

Pulmonary delivery of insulin has been shown to induce a significant hypoglycaemic effect following both instillation and inhalation via the lungs (Clothorpe et al., 1992). The influence of insulin-encapsulation within liposomes on pulmonary absorption was studied using intratracheal instillation in rats (Liu et al., 1993). Liposomally entrapped insulin was absorbed systemically over a prolonged period as compared with free insulin. The encapsulation of insulin in liposomes could facilitate pulmonary uptake and enhance the hypoglycaemic activity (Fig. 2). However, no significant difference in the rate of absorption was observed between liposomally entrapped insulin and the physical mixture of empty liposomes with insulin solution. Thus, enhanced and prolonged absorption was attributable not only to the entrapment of drug in liposomes but also presumably, to the binding of insulin to the surface of liposomes.

2.7. Formulation factors influencing drug release from liposomes

The rate at which drug release from liposomes occurs may be critical in determining the duration of activity. A more rapid release may result in a higher absorption rate and a shorter duration of action whilst too slow a release may result in non-therapeutic drug concentrations. For a given dose and minimum effective concentration, there is an optimum rate of release for a maximum duration of action (Byron et al., 1978). Several factors have been shown to influence the drug release and absorption of liposome-encapsulated molecules within the lung. For example, the pulmonary absorption of liposomal carboxyfluorescein (CF) was demonstrated to be lipid dose dependent with higher doses of phospholipids inducing a higher rate of absorption (Woolfrey et al., 1988). This effect was attributed to the possible biological response initiated by the higher lipid doses. The encapsulated dye was also absorbed more than twice as quickly from negatively charged vesicles than from comparable neutral vesicles. The absorption of liposomal [^{3}H]terbutaline was found to be dependent on both the composition and size of the liposomes used (Abra et al., 1990). The presence of cholesterol and phospholipids with saturated hydrocarbon chains increased the drug residence time within the lung. Inclusion of cholesterol for example, extended pulmonary half-life of [^{3}H]terbutaline almost 10-fold. The presence of both of these components is known to decrease liposome membrane permeability to encapsulated drug and to protect liposomes from in vivo destabilization. In a more recent report, α-tocopherol, an amphipathic compound, was shown to improve the retention of liposomally entrapped glutathione in the rat lung after intratracheal instillation (Suntres and Shek, 1994). However, inclusion of phosphatidylglycerol was thought to increase spreading of liposomes at the alveolar surface, potentially decreasing vesicle stability and accelerating drug release (Oyarzun et al., 1980).

Any other factors which influence the deposition of liposomes in the respiratory tract, such as particle size, size distribution, the nature of the delivery device and patient breathing pattern, could have effects on subsequent drug release and absorption by modifying the overall clearance of liposomes from the lung. For example, after

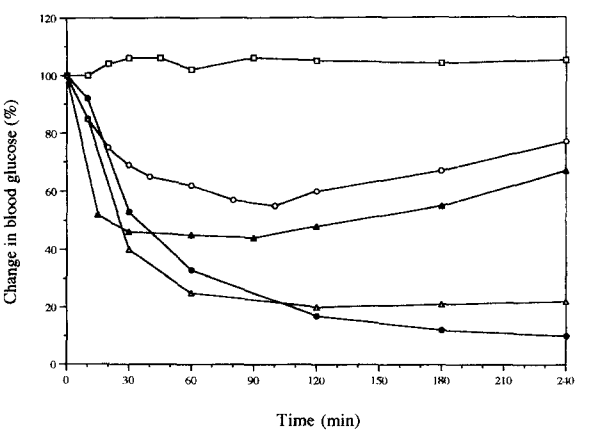

Fig. 2. Percentage change in blood glucose concentrations following the administration of insulin formulations (adapted from Liu et al., 1993). (△) Intracheal administration of liposomal insulin; (●) intracheal administration of blank liposome and insulin; (▲) intravenous administration of insulin; (□) blank liposomes; (○) intracheal administration of insulin.

intratracheal instillation, large liposomes (3.9 μm) were more effective at prolonging the residence time of [^{3}H]terbutaline in the lung than the small, extruded liposomes (0.27 μm) of the same lipid composition. However, this phenomenon was partly attributed to the increased membrane permeability of the membranes of the extruded liposomes (Fielding and Abra, 1992). However, it must be acknowledged that inhaled liposomes with different particle sizes will deposit at different sites in the respiratory tract, leading to complications in determining the factors which affect the net pharmacokinetics of drugs within the lung.

Although there have been a number of studies investigating the fate of liposomal drugs in the lung, most have been conducted in animal models by instilling liquid formulations so as to obtain accurate dosimetry. Such studies have a number of potential limitations. First, the distribution of inhaled aerosol can be different from that of instilled liquids, resulting in a different disposition of the drug in vivo. Despite similarities in the absorption profiles when drugs were given by intratracheal injection or as an aerosol, onset of action was doubled after aerosol administration (Schanker et al., 1986). It is possible that similar differences between dosage forms will become apparent when the drug is administered by these techniques after entrapment in liposomes. In addition, it is conceivable that a portion of the instilled liposomes could deposit in the upper airways where they would be subject to rapid mucociliary clearance (Farr et al., 1985). In such cases, a large part of the instilled liposomes could be cleared before an extended therapeutic effect is obtained. In contrast, well-formulated liposomes, inhaled in a controlled manner may be anticipated to distribute evenly throughout the lung and show a greater penetration into the alveolar region than if administered by intratracheal injection of a small volume of solution. Thus, the residence time and drug absorption from instilled liposomes can be expected to be lower than the corresponding parameters obtained from inhaled vesicles. Second, the difference in size and aerodynamic properties between human airways and those of the animal model are likely to result in significant differences in distribution profiles of the administered liposomes. Finally, certain diseases can influence the dimension and properties of the airways and hence, the disposition of any inhaled drug. Thus, great care must be taken when extrapolating the findings based on intratracheal administration to animals to predicted deposition profiles after inhalation of aerosol formulations by patients suffering from airway disease.

3. Biodegradable microspheres

Biodegradable microspheres (MS) produced from natural and synthetic polymers have been extensively investigated as drug carriers for administration via a number of different routes, since a number of these particles have many desirable characteristics for ensuring both targeted and sustained drug release. For example, biodegradable MS can be prepared over a wide range of particle sizes, which is a decisive factor in the in vivo disposition of particulate carriers. Accordingly, biodegradable MS can be used to deliver drugs to various organs, such as the liver, the kidney, the reticuloendothelial system and the lung. Many hydrophilic and lipophilic drugs can be entrapped or incorporated in biodegradable MS with relatively high efficiency and manipulation of the synthetic process produces MS with different drug release rates. In comparison to liposomes, biodegradable MS may be more physicochemically stable both in vitro and in vivo. Thus, drugs entrapped in biodegradable MS may have a slower release rate and a longer duration of action than those incorporated within liposomes. The higher stability may enable biodegradable MS to be more easily formulated in a suitable pulmonary delivery device than liposome formulations. A number of biodegradable MS have proved to be non-toxic, biodegradable and non-immunogenic following systemic injection. However, studies employing inhaled MS are few, even though there have been a number of investigations which considered the targeting of intravenously injected MS to the lung for diagnostic and therapeutic purposes. Only the poten-

tial of albumin and poly(lactide and/or glycolide) MS for sustained release of drugs to the lung has been so far considered.

3.1. Albumin microspheres

Albumin MS are biodegradable colloidal particles that can be prepared by either physical denaturation or chemical cross-linking of albumin droplets. The role of albumin MS as drug delivery systems for targeted and sustained release after intravenous administration has been the subject of extensive research. Some of these studies have been conducted with the intention of targeting drugs selectively to the lung (Gupta and Hung, 1989). However, the biodegradability, lack of toxicity and immunogenicity, ready availability and capability to undergo chemical modification could render them suitable as a carrier for inhalation of drugs. For example, albumin MS with a particle size range between 1.94 ± 1.47 and 3.42 ± 1.51 μm have been prepared using a high-speed homogenisation and heat denaturation process (Haghapanah et al., 1993). A twin-stage liquid impinger was used to assess the deposition pattern of the MS in vitro and the percentage deposition in the lower stage, considered to represent the respirable fraction was found to vary between 11.6 ± 3.65 and $23.4 \pm 3.85\%$. These results suggest that it may be possible to deliver a reasonable fraction of the albumin MS to the lower airways.

The possibility of using drug-containing albumin MS (Zeng et al., 1994) as an inhaled dry powder was also investigated, employing similar preparation and in vitro evaluation procedures (Zeng et al., 1995). Tetrandrine, an antisilicotic alkaloid, was entrapped in albumin MS and factorial design employed to optimise particle size and drug entrapment. Albumin MS with mean diameter of 4.41 ± 0.45 μm ($n = 6$) and drug entrapment of $12.02 \pm 2.62\%$ (w/w) ($n = 6$) were prepared. The tetrandrine recovered from the lower stage of a twin-stage liquid impinger operated under the pharmacopoeial conditions was $13.83 \pm 2.58\%$ ($n = 6$) and such levels were considered sufficient for therapeutic efficiency (Zeng et al., 1995). Thus, albumin MS have the potential to deliver tetrandrine to the alveolar region where they may be metabolised to incorporate the drug in alveolar macrophages, which are thought to be the main site of action of tetrandrine.

Human albumin MS have been shown to reach alveolar regions after inhalation although a proportion became embedded and partially digested in the mucus layers within the upper airways. The coating of albumin MS with surfactants could decrease the interaction with mucus layer and possibly increase the deposition in the lower airways (Todisco et al., 1990).

Gudapaty et al. (1985) covalently attached the succinyl peptide chloromethyl ketone (SPCK), an elastase inhibitor for the treatment of elastase-induced emphysema, to 2–4 μm albumin MS. After intratracheal instillation of the MS suspension to hamsters, pretreated with elastase, the albumin-bound SPCK exhibited a protective effect against emphysema which was prolonged up to 8 h as compared with 15 min for the free SPCK. Furthermore, the required therapeutic dose of bound SPCK was low and histopathologic examinations did not show any toxic effects. Microscopic examination of the lung tissues of animals killed at the end of the experiment (after 4 weeks) could not identify the presence of any remaining intact MS.

3.2. Poly(glycolide and/or lactide) (PGL) microspheres

PGL microspheres are prepared by the polymerisation of lactide and/or glycolide monomers via polyester linkages, the hydrolysis of which will result in the breakdown of the polymers to produce non-toxic substances. As a successful drug delivery system, PGL microspheres have been used for targeting and controlled release of a wide range of drugs, including peptides and proteins (Tice et al., 1989). Their potential use in pulmonary delivery has also been explored recently. Boyes et al. (1988) produced PGL microcapsules containing sulbutamol or terbutaline using spray drying techniques and showed release of the encapsulated drugs to occur very quickly. However, the release rate was shown to be reduced by more than 2-fold when surfactants, such

as sorbitan trioleate, were used as formulation excipients and it was concluded that such microcapsules might have potential use in CFC-propelled or dry powder formulations of bronchodilators.

Masinde and Hickey (1991) were able to prepare poly(lactic acid) (PLA) microspheres with particle sizes between 1 and 11 μm by a solvent evaporation technique. After suspending the MS in a non-surfactant solution this was subsequently atomised by a jet nebulizer, particles were generated which were suitable for drug delivery to the lower airways, having a median diameter of 2 μm and geometric standard deviation of 2.4 μm.

Gupta et al. (1990) have evaluated the effect of propellant blends, types and concentrations of surfactants on the in vitro performance of aerosol formulation of PLA microspheres. The respirable fraction (RF; identified as particles with a diameter < 4.8 μm) generated from a pressurised package ranged from 2.4 to 47.8% for different formulations. The surfactant nature did not discernibly affect the RF of the microspheres whereas increasing surfactant concentration was found to increase the RF. In a more recent report, although Kulkarni et al. (1991) confirmed that surfactant type had only a minor influence on the particle size of pressure-generated PLA microspheres, the RF, in contrast, was found to be decreased markedly by an increase in the surfactant concentration. An RF of 22.9% was obtained at a surfactant concentration of 0.1% (w/w) compared with only 3.9% for the 1.0% concentration. Microspheres with good suspension properties and minimal aggregation were developed with all the surfactants.

Sustained bronchodilation was reported by Lai et al. (1993) after PGL microspheres with a mean diameter of 4.5 μm containing entrapped isoproterenol (7% w/w) were intratracheally administered to Long-Evans rats. Even though 70% of the incorporated isoproterenol had been released from the MS into the instillation medium prior to administration, the drug still significantly ameliorated serotonin-induced bronchoconstriction for more than 12 h at a dose of 0.1 mg kg^{-1}. In contrast, free isoproterenol at the same dose induced a protection for less than 30 min. The free isoproterenol with the dose equivalent to that remaining in the microspheres at the time of administration did not provide any protection. Thus, the isoproterenol dose in the microspheres could be decreased by 50–100-fold in comparison to the required dose of free drug, without loss of activity.

4. Modification of chemical structures

4.1. Prodrug approach

A prodrug approach has long been used to improve the bioavailability, biocompatibility, targeting and sustained actions of the parent drugs. For such an approach to be effective, it is essential that an enzyme which can cleave the prodrug to release the parent compounds must be present. Up to now, several enzymes have been identified as being present in the lung. Esterase activity, for example, is higher in the lung than in the heart (Shargel and Dorrbecker, 1976). Thus, in order to reduce the cardiovascular side effects commonly associated with the use of brochodilators, some β_2 stimulants structurally related to isoproterenol and its analogues have been esterified to obtain prodrugs that have a higher uptake in the lung but a lower metabolic transformation to the parent drug in the heart. Moreover, in the lung, the prodrugs can be designed to be metabolised slowly to parent the drug so as to achieve a sustained bronchodilation. For example, bitolterol is the di-β-toluolyl ester of *N*-(*t*-butyl)arterenol (Fig. 3) and is an effective long-lasting bronchodilator when given by intravenous injection, inhalation or intraduodenal administration (Friedel and Brogden, 1988).

Ibuterol is the diisobutyryl ester of the resorcinol function of terbutaline (Fig. 3). After inhalation, ibuterol is 3-times as effective as terbutaline. In vivo studies showed that ibuterol is absorbed more rapidly than terbutaline, but that both lung and serum terbutaline concentrations were lower after ibuterol administration to the lung than those obtained after the administration of the free terbutaline, indicating that the prodrug acts as a reservoir and then releases parent drug over a prolonged period (Andersson, 1976).

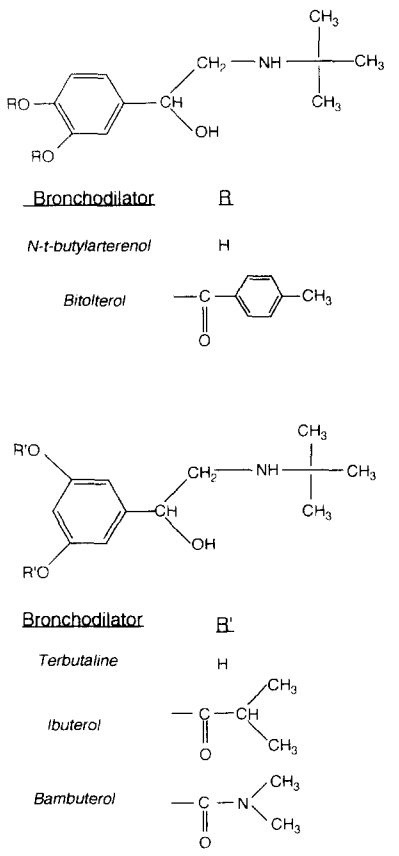

Fig. 3. The chemical structures of some β_2-agonist bronchodilators.

Bambuterol (Fig. 3) is another prodrug worthy of mention, being a biscarbamate ester of terbutaline. It is, however, only effective after oral administration since it is poorly metabolised within the lung. Preliminary clinical studies indicated a mean terbutaline half-life after bambuterol ingestion of about 21 h (Sitar et al., 1992) and hence, it is effective in treating asthma when given once or twice daily.

4.2. Conjugation with macromolecules

Since drug absorption through lung epithelium often occurs by passive diffusion, drugs with higher lipophilicity are usually absorbed more rapidly than those with lower lipophilicity. For hydrophilic drugs, molecular weight has proved to be a decisive factor in determining absorption through the airway epithelium, smaller molecules being absorbed more rapidly than larger molecules (Schanker et al., 1986). Given the esterase activity of the lung as discussed above, then conjugation of drugs to macromolecules by means of esterification provides a possible mechanism by which drugs can be retained in the lung. The subsequent metabolism of the conjugates over a prolonged period of time would release active drugs for either local actions, or alternatively systemic actions after their penetration through the lung membranes.

Dextran, a hydrophilic macromolecule, has been used to form a variety of complexes with drugs, owing to the high stability of the glucosidic bond and the presence of numerous reactive hydroxyl groups. Drugs containing carboxylic acid residues, such as cromoglycic acid (CGA), may be attached directly to the matrix by a simple esterification (Molteni, 1985). Williams and Taylor (1992) have prepared a CGA-dextran (Mol. Wt 10000) conjugate, which contained between 0.8 and 40% w/w CGA. The release rate of cromoglycate from the conjugate in vitro in pH 7.4 buffer at 37°C over 40–290 min was inversely related to the amount of the drug contained in the conjugates.

PEG is also a hydrophilic macromolecule containing many reactive hydroxyl groups and it can be synthesized with a range of molecular weights. PEG is a versatile drug carrier with one of its most prominent uses involving its conjugation with proteins to alter the latter's potency, reduce immunogenicity as well as increase the duration of action (Tomlinson, 1989). For example, the circulating half-life of PEG bound L-asparaginase in rabbits was increased to 125–160 h compared with about 20 h for the native enzyme. The clearance of the conjugated enzyme from the blood was reduced from about 100 to about 3 ml/kg per day and there was an almost 40-fold increase in the area under the plasma concentration-time curve. An asparaginase-PEG conjugate was well-tolerated by patients who had been pretreated with the native drug and developed neutralising anti-asparaginase antibodies (Ho et al., 1988). PEGs and related polymers may thus have poten-

tial for the binding of drugs for sustained pulmonary release, although the capacity to act as such a carrier has yet to be studied.

Poly(2-hydroxyethyl)aspartamide (PHEA) is another water-soluble polymer which may be used for delivery of drugs to the respiratory tract. PHEA after injection into the circulation is excreted as a function of the molecular weight and accumulation in the tissues during long-term use is unlikely to occur. Furthermore, it displays a lack of immunotoxicity, is non-immunogenic and exhibits a remarkable stability to enzymatic cleavage of the peptide and side chain bonds (Niven, 1992). Niven et al. (1990) have also covalently bound PHEAs of different molecular weight with fluorescein and administered the aqueous solutions of the conjugates to the isolated rat lung in order to investigate the absorption of PHEA across the pulmonary barrier. The polymer transfer rates were shown to be dependent upon molecular weight, larger molecules being absorbed more slowly. Therefore, the covalent linkage of a therapeutic agent with PHEA of suitable molecular weight could enable the drug to be released slowly into the lung or systemic circulation.

The science of linking small molecular weight drugs to macromolecules is well developed mainly because of the amount of interest in such systems for site-specific delivery via the intravenous route. To employ these conjugates as platforms for controlled drug release within the respiratory tract is clearly an attractive proposition. However, there may be several distinct disadvantages related to the use of macromolecules within the lung. For example, the lung has a lower enzymatic and macrophage activity than the general circulation and this is likely to result in a slower metabolism of the carriers. There is thus the potential for accumulation of macromolecular materials within the lung over a prolonged administration period which in turn may induce possible side effects.

5. Sparingly soluble forms and coprecipitates

It is commonly accepted that drugs in the solid state are absorbed more slowly than drugs in solution. In the former case, the absorption rate of drugs is often dependent upon the release and dissolution rate of drugs from the dosage form. Generally, the slower the dissolution rate, the slower the overall absorption of the drug will be. As the dissolution rate is proportional to the aqueous solubility of the drug, sustained release of drugs can be achieved by reducing the aqueous solubility of the drug. This simple principle can also be used for the delivery of drugs to the lung. Chowhan and Amaro (1976) have compared the absorption of two structurally related xanthone-2-carboxylic acids and their sodium salts. 7-methylsulphinylxanthone-2-carboxylic acid and 7-(methylthio)xanthone-2-carboxylic acid and their salts were administered intratracheally to anaesthetised rats as a 0.1 ml solution or suspension containing either the sodium salts or free forms of the drugs, respectively. The absorption from the solution was 3–4-times faster than that from the suspensions. It is apparent that drug dissolution from the suspensions was the rate-limiting step in determining the absorption of the drugs. This was also demonstrated in the case of pentamidine, which has a very low aqueous solubility and high affinity for the macrophages, though after inhalation it was retained in the lung for a period of 48 h (Debs et al., 1987). Another example is hexamethylamine (HMM), an anticancer agent, which also has a very low aqueous solubility at neutral pH. It was suggested that solid HMM delivered to the lung would provide a local concentration of dissolved drug for an extended period. Thus, Gonda et al. (1985) prepared HMM aerosols with a mass median diameter of about 4 μm and geometric standard deviation of about 1.3, although no further reports have apparently appeared reporting upon its biological activities.

A number of sparingly soluble metal hydroxides are known to absorb soluble material from solutions. Utilisation of this property during co-precipitation of relatively insoluble materials with aqueous soluble drugs has led to the preparation of controlled release forms. Fluorescein has been shown, for example, to form a stable co-precipitate with magnesium hydroxide, its dissolution rate in vitro being reduced by 10^4 in comparison to fluorescein sodium alone. When administered

as a bolus suspension to the isolated perfused rat lung, the absorption of fluorescein from the co-precipitate was greatly delayed as compared to fluorescein solutions (Hickey and Byron, 1986). However, the formulation of inhalation aerosols with a view to obtaining deposition within the lower airways requires that the particle size be less than 4 μm. This will increase the total surface area of the insoluble particles and hence the dissolution rate of the drug. Thus, the particle size of the co-precipitate would require careful control so as to obtain suitable controlled release and in vivo drug deposition. Furthermore, the utilisation of insoluble metal hydroxide of basic properties may induce many possible side effects within the lung, as can be seen in the case of silicosis which is caused by the inhalation of silica particles. However, this approach of achieving prolonged pulmonary release may be a useful strategy for carriers which prove to be non-toxic and biodegradable in the lung.

6. Complexes with cyclodextrins

Cyclodextrins (CYDs) are cyclic non-reducing oligosaccharides containing six, seven or eight glucopyranose units (α-, β-or τ-CYD, respectively). Many drugs are able to form non-covalently bonded complexes with CYDs by inclusion entirely or partially into the slightly apolar CYD cavity. Because of this property, CYDs have been used to sustain or prolong the release of drugs (Uekama and Otagiri, 1987). The possibility of using CYDs for pulmonary controlled release has been investigated in a series of studies using sulbutamol as a model drug. Carbral Marques et al. (1990a) were able to prepare sulbutamol-cyclodextrin complexes in both liquid and solid states. According to molecular modelling and ^{1}H-NMR evidence, the inclusion of salbutamol into β-CYD resulted from the penetration of salbutamol aromatic ring into β-CYD cavity with its aliphatic chain resting outside the cavity. The stoichiometric ratio of the complex was suggested to be 1:1 (salbutamol/β-CYD) (Carbral Marques et al., 1990b).

The in vivo disposition of β-CYD and its derivatives was investigated following intravenous injection and intratracheal instillation in rabbits (Carbral Marques et al., 1991a). Of the three CYDs investigated, namely, β-CYD, dimethyl-β-cyclodextrin (DM-β-CYD) and 2-hydroxypropyl-β-cyclodextrin (HP-β-CYD), HP-β-CYD was absorbed more slowly from the respiratory tract than the others. The mean absorption time of HP-β-CYD was 113 min compared to 26 and 21 min for β-and SM-β-CYDs, respectively. Thus, on the basis of this study, HP-β-CYD was considered to have potential as a drug carrier for pulmonary sustained release. The ability of HP-β-CYD to sustain sulbutamol release was studied in rabbits after intratracheal administration (Carbral Marques et al., 1991b). The pulmonary absorption of salbutamol as a complex was only slightly prolonged, as shown by the fact that approx. 23 min was needed to reach maximum plasma concentration after instillation for the complexed salbutamol compared with 14 min for the free drug. However, since complexation with cyclodextrin reduced the availability of sulbutamol it was concluded that complexation with cyclodextrin was not an appropriate strategy for formulating a sustained release pulmonary delivery system for salbutamol.

More recently, Wall et al. (1994) have confirmed that although HP-β-CYD was able to reduce the absorption rate of rolipram and salbutamol through the pulmonary epithelium in vitro, it did not show any effects on the absorption of either drug when given intratracheally into rat lungs. The inefficiency of cyclodextrin in sustaining drug release may be due to the possible premature breakdown of the drug-cyclodextrin complex in vivo. Such complexes, when administered to the peripheral lung, might encounter a surfactant layer which contains cholesterol, a molecule with a high affinity for HP-β-CYD (Frijlink et al., 1991a). Consequently, cholesterol may compete for the CYD binding site and displace drugs from the complex. This phenomenon has been observed when naproxen and flurbiprofen cyclodextrin complexes were added to rat plasma (Frijlink et al., 1991b). None of the previous reports have established the in vivo stability of drug-cyclodextrin complex and it is still hard to

rationalise the potential of cyclodextrin complexes as pulmonary controlled release systems.

7. Discussion and conclusions

As described above, the sustained release of drugs in the lung possesses many advantages in comparison to the ready availability of free drug. However, for a sustained release carrier to be effective, it must be retained in the lung for a prolonged period so that the therapeutic agent can be released and then be absorbed. Generally, when administered to the airways, carriers (or drugs) may be removed by mucociliary transport, phagocytosis or be absorbed systemically (Niven, 1992). Mucociliary transport decreases between the upper airways and the lower airways and particulate carriers will be rapidly removed if they deposit in a region with high mucociliary clearance. Therefore, for a controlled release delivery system to be retained in the lung for a longer period of time, it should be delivered to the lower airways or alveolar region where mucociliary transport is minimal. Metabolism in the lung is generally believed to be lower than that in the liver, although many metabolic enzymes have been identified in this organ (Crooks and Damani, 1989). Drugs deposited in the upper airways are less likely to be metabolised than those in the lower airways, where there is much more phagocytic activity due to the presence of alveolar macrophages. Absorption is another important means of drug clearance, although it is relatively slow in the upper airways, owing to the lower epithelial permeability, thicker mucus layer and smaller relative surface area of this region. Drugs are absorbed much more rapidly in the alveolar region as a result of high permeability and large surface area (Thompson, 1992).

Gonda (1988) has generated a mathematical model to predicate the fate of controlled release dosage forms in the lung. He suggested that if a drug is rapidly cleared from the airways, release of the active compounds from controlled release formulation might result in only very low local drug levels, in some instances even below the therapeutic concentration. In contrast, slowly cleared drugs may accumulate in the lung after multiple doses, leading to possible toxic reactions. Thus, the release rate of a drug from the formulation should be carefully controlled and matched to the overall clearance, considering both therapeutic and toxic concentrations of drugs, so as to ensure both pharmacological activity and safety.

The actual site of drug action is another important consideration. The drugs which have been most extensively investigated for pulmonary controlled release are anti-asthmatics. Local therapy with bronchodilator and anti-inflammatory steroids requires ideally that they should be deposited in the bronchi and bronchiolar regions (Ruffin et al., 1981) since the smooth muscle in this region is the primary target site of such drugs. However, particulate material deposited in this region is subject to rapid mucociliary transport, leading to a short duration of residence of both drugs and carriers. To overcome this problem, temporary reduction in the mucociliary transport is suggested, but this is not a realistic option since mucociliary clearance is an important protective mechanism in the lung. An alternative approach may be to deposit the carrier in the deeper unciliated regions where clearance is slower than further up the tract. As the carriers are swept up the respiratory tract, the slow release of drug will occur within the vicinity of its site of action (Niven, 1992). However, up to now, it has to be acknowledged that the controlled deposition of inhaled drugs to a precise site within the lung is not a feasible proposition.

Considering drugs which may be administered to the lung for systemic action, then ideally deposition in the alveolar region is desired. It is envisaged that, as a result of the relatively higher metabolic activity in this region, drug conjugates, microspheres and liposomes will be metabolised to release active drugs which will penetrate the alveolar epithelium and diffuse into the circulation to obtain predetermined systemic drug concentrations. However, should metabolic breakdown of carriers occur in this region, the selection and design of the conjugated or incorporated drug should be undertaken with care so as to ensure that the active component does not undergo similar degradation.

Another major concern relates to potential toxicity of the carriers. According to Gonda (1988), chronic administration of materials with slow elimination may result in their accumulation in the lung. As stated previously, it is essential that carriers be non-toxic, non-immunogenic and biodegradable. Even though liposomes, albumin MS and PLA microspheres have proved to be non-toxic carriers already used in human subjects, the toxicity of such microspheres after chronic pulmonary administration has yet to be established.

Finally, several pharmaceutical aspects need to be considered. There are at least five important factors to be evaluated in order to achieve a useful pulmonary controlled release delivery systems, namely, particle size, efficiency of drug incorporation, release rate, stability and nature of delivery devices. Particle size is critical in determining the site of deposition in the airways. In order to achieve deposition in the lower airway, the particle size should be between 1 and 6 μm. Polydispersity of particle size also affects in vivo deposition (Hickey, 1992), although the detailed influence of this factor remains to be fully investigated. However, it can be stated that for a delivery system to be retained in the lung for a prolonged period will require careful control of both the particle size and polydispersity of the particulate carrier. It is not unusual for an inert matrix to form a large portion of the controlled release system. It is essential that the highest proportion of drug possible is incorporated within the particulate system without adversely affecting other factors, such as particle size. Optimisation techniques need to be employed to identify the ideal preparative conditions (Zeng et al., 1994). Reducing the proportion of inert matrix within the system will also have the advantage of decreasing the possibility of side effects attributable to the accumulation of the carrier particles. Also, if a large dose of powder is required to be administered, because of low drug incorporation within the carrier, this is likely to result in poor patient compliance. Control of release rate is complicated, and many factors make an impact upon this process. Drug release from microspheres, for example, often follows a biphasic process, with an initial burst release followed by a more prolonged slow release phase. The rate of drug release from albumin and PGL microspheres is influenced by factors such as the carrier/drug ratio, the degree of stabilisation and/or polymerisation and the particle size (Kitchell and Wise, 1985; Gupta and Hung, 1989). Release of drug in the pulmonary environment is also determined by the overall clearance of carriers and drugs.

The pharmaceutical requirements of a delivery device are that it should provide chemical and physical stability before ensuring the optimal delivery to the site of drug action. Both nebulisers and metered-dose inhalers (MDIs) have been used for the delivery of liposomes and microspheres. Nebulisers were formerly restricted to the hospital setting, but although portable pocket nebulisers are now available, these are currently bulky and depend upon expensive technology. Some liposomal formulations have been shown to be unstable and a large portion of incorporated drugs can be lost during nebulization (Taylor et al., 1990). MDIs have been used to deliver liposomes, based on the principle of forming liposomes in situ from a phospholipids/CFC solution after aerosol deposition onto a moist surface (Farr et al., 1987). The amount of drug entrapped within the resultant liposomes has been shown to be dependent upon the physico-chemical properties of the drug molecule. However, this approach is not suitable for hydrophilic drugs, such as salbutamol sulphate, because of their poor incorporation into the liposomes (Farr et al., 1989). Stability is also an important factor in the formulation of particulate carriers within the propellent medium of an MDI since hydrophobic drugs may be released from suspended carriers into the propellant medium. The chlorofluorocarbons currently used are to be replaced before 1997 because of their detrimental effects to the Earth's ozone layer and hence there has been a resurgence of interest in the development of dry powder inhalers (DPIs) (Martin et al., 1994). Such devices may provide opportunities to overcome many of the stability problems associated with other devices since both drugs and carriers are kept in a solid state. Liposomes have been prepared as inhaled dry powders by spray-drying

(Taylor and Farr, 1993) and micronisation (Schreier et al., 1994) and the micronised liposome powders have been effectively aerosolized for pulmonary delivery. Albumin MS may also be delivered as dry powders (Haghapanah et al., 1993) and their in vitro deposition is primarily determined by particle size. Other factors, such as surface charge, deaggregation, flowability and hygroscopicity should also be evaluated before a suitable delivery system is developed.

In conclusion, prolonged drug delivery to the lung can be employed for either local or systemic effects, and can be achieved by both chemical and physical means. Relatively few scientific studies have been undertaken in this field and hence the commercially available products claiming sustained action in the lung are few, with the possible exception of long-lasting prodrugs of bronchodilators such as bambuterol. This is partly due to the lack of a thorough understanding of the disposition of drugs in the lung in general as well as the lack of studies considering chronic effects of carriers on the lung. Many interdependent factors, involving the lung, carrier, drug and device can influence the resultant drug disposition in the lung. Low lung burden of biodegradable carriers are required in order to reduce the side effects of chronic medication. Thus, potent drugs should be more suitable candidates for pulmonary controlled release. More and more potent protein and peptide drugs are being developed due to advances in recombinant DNA technology and pulmonary delivery has proved to represent a valuable potential route for the chronic delivery of these drugs. This in turn will undoubtedly accelerate further interest in the development of systems appropriate for controlled pulmonary delivery.

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