CHAPTER 1

INTRODUCTION

Improving drug delivery to the pulmonary system has been an area of increasing interest among several disciplines. There has been extensive effort to define the factors that influence the deposition of aerosolized drug in deep lungs within the respiratory tract, clearance mechanisms from the lung, circulation in the airways, and absorption and metabolism of compounds by the lung (Chediak et al, 1990; Byron et al, 1990). With this information, strategies to improve drug delivery to the respiratory system have developed. Particulate carriers such as liposomes have many attractive features as pulmonary drug delivery systems particularly with respect to controlled delivery. Aerosolized route of administration can deliver therapeutic agents to the diseased regions while reducing their distribution to the other organs; it provides an excellent example of targeted drug therapy. Hence, a more favorable therapeutic index can be obtained for the treatment of lung diseases when drugs are administered by inhalation rather than by the oral or parenteral route. Bronchodilators, anti-inflammatory agents, mucolytics, antiviral agents, anticancer agents and phospholipid protein mixtures for surfactant replacement therapy are all routinely given as aerosolized formulation.

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 (Marriott, 1990; Taylor 1990). This often leads to poor patient compliance with the therapeutic regime and increases the possibility of associated side effects. Deposition of drugs in the desired site of lung will be particularly beneficial since drug can be delivered to and retained at the targeted site for prolonged period of time and thus can maximize therapeutic index of the drug.

Liposomes are useful tools for pulmonary delivery of drugs due to their solubilization capacity for poorly water-soluble drugs, rendering them more practical to be aerosolized. Their biodegradability allows for prolonged pulmonary residence times without danger of allergic or other deleterious side effects. The targeting capacity of infected or immunologically impaired alveolar macrophages is a unique feature of liposomes.

Opportunistic fungal infections are significant threat to immuno-compromised individuals such as individuals receiving chemotherapeutic agents, transplant recipients and AIDS patients. Amphotericin B is a mainstay treatment for many fungal infections, including disseminated cryptococosis. Major limitations to its use are severe renal toxicity, anemia and hypokalemia (Byron, 1986; Schmitt, 1993). Cystic Fibrosis, an autosomal recessive disease, affects many organs including the lungs, pancreas, male genital tract, sweat glands, liver and intestine. The major cause of morbidity is lung disease, which is responsible for more than 95% of mortality in humans (Franz et al, 1994). The popularity of aerosol administration is increasing. This would offer several advantages over the intravenous route (Trembley et al, 1985). 1. The direct application of antibiotics to the site of action in the lung is very efficient as 50% less drug is used compared to the intravenous injection. 2. Systemic adverse reactions of aminoglycosides are avoided. Liposomal encapsulation of amikacin will further help in enhancing therapeutic index of the drug and reduce the side effects.

Liposomal encapsulation of amphotericin B is expected to decrease the drug toxicity due to selective transfer of drug to the ergosterol part of the fungal cell without interfering with the cholesterol of human cell membranes (Janknegt et al, 1992;

Welsh, 1994). This fungicidal polyene has high affinity with ergosterol and causes fungal cell death by disrupting the fungal plasma.

The use of liposome in pulmonary delivery was first investigated as a potential treatment for respiratory distress syndrome. One of the perceived benefits of liposomes as a drug carrier is based on their ability to alter favorably the pharmacokinetic profile of the encapsulated species and thus provide selective and prolonged pharmacological effects at these sites of administration. Liposomal encapsulation will provide control and selective drug release which intern will reduce number of asthma exacerbation. The resulting decrease in the frequency of drug dosing will significantly improve the quality of life for such patients and at the same time reduce healthcare cost. The selective and controlled release of the drug is also expected top reduce or eliminate hypersensitivity and systemic toxicities. The challenging aspect still remains unanswered are the mode of delivery for liposomally encapsulated drug. Metered dose inhalers (MDI) are currently being reformulated as a result of the band being implemented throughout the world by the United nations on the use of chlorofluorocarbons (CFCs) (Juliano et al, 1986) to meet this challenge, one such alternative is the development of new and improved "Dry Powder Inhaler (DPI) system that will allow inhalants administration of all drugs presently delivered with MDIs. With constrain of propellant phase out and short-term stability of liposomal aqueous dispersion the most viable alternative would be to deliver the liposomal drug in dry form.

RESEARCH ENVISAGED

The project focuses on the pharmaceutical development of liposomal drug formulations for various parameters influencing DPI of selected drugs will be

evaluated, optimized such as control of flow and dispersion (deaggregation) characteristics of the formulations under development and the evaluation of the selected formulations in animals.

The proposed plan of work include

I. Literature reviews covering various aspects of liposomes in pulmonary drug delivery, dry powder inhalation formulation development and drug profiles of selected drugs like Amikacin and Amphotericin B.

II. To find an ideal liposomal form as far as encapsulation efficiency is concern. Liposomes containing drugs will be prepared by reverse phase evaporation and lipid film hydration method. The prepared liposomes will be characterized with respect to: Encapsulation efficiency, size and size distribution, lamellarity and trapped volume.

III. To incorporate the liposomal drug into an appropriate cryoprotectant to lyophilize and stabilize the formulation and developing formulations using different lactose grades or size to achieve desired fine particle fraction.

IV. Evaluation of the prepared Liposomal DPI will be carried out in terms of flow and dispersion properties using appropriate derived properties including, angle of repose, bulk density, compressibility and dispersibility. Physical changes like caking and discoloration in stability studies.

V. Various parameters influencing DPI of selected drugs will be evaluated and optimized to establish control parameters at the end of studies.

VI. Comparative evaluation of the optimized formulations will be conducted for *In vitro* and *In vivo* drug release.

References

Byron P R (1986) Prediction of drug residence times in regions of the human respiratory tract following aerosol inhalation. J. Pharm. Sci. 75: 433-438.

Byron P R (1990) Aerosol formulation, generation and delivery using metered systems In: Byron P R Eds. Respiratory Drug Delivery, CRC Press, Boca Raton, FL, 167-205.

Chediak AD and Wanner A (1990) The circulation of the airways: anatomy, physiology and potential role in drug delivery to the respiratory tract Adv. Drug Deliv. Rev. 5 11-18.

Franz M N, Cohn R C, Wachonowsky-Diakiw D M (1994) Hosp. Formul. 29: 364.

Janknegt R, De Marie S, Bakker-Woudenberg I A J M, Cromellin D J A (1992) Liposomal and lipid formulations of amphotericin B. Clinical Pharmacokinetics 23: 279-291.

Juliano R L, Grant C W M, Barber K R, Kalp M A (1986) Mechanism of the selective toxicity of amphotericin B incorporated into liposomes. Mol. Pharmacol. 31: 1-11.

Marriott, C (1990) Mucus and mucociliary clearance in the respiratory tract Adv. Drug Deliv. Rev. 5: 19-35.

Schmitt H J (1993) New methods of delivery of amphotericin B Clin. Inf. Dis. 17: S501-506.

Taylor G (1990) The absorption and metabolism of xenobiotics in the lung Adv. Drug Deliv. Rev. 5: 37-61.

Trembley C, Barza M, Szoka F, Lahav M, Baum (1985) Reduced toxicity of liposome-associated amphotericin B injected intravitreally in rabbits Invest. Ophthalmol. Vis. Sci. 26: 711-718.

Welsh M J (1994) The path of discovery in understanding the biology of cystic fibrosis and approaches to therapy Am. J. Gastroentrol. 89: S97-105.