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CONTENTS

Sustained Release Budesonide Liposomes: Lung Deposition and Efficacy Evaluation

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Budesonide (BDS) is a corticosteroid used in the prophylactic management of asthma. However, frequent dosing and adverse effects (local and systemic) remain a major concern in the use of BDS[1]. A reduction in the frequency of dosing would be convenient, especially for chronic asthma. Liposomal systems for sustained pulmonary drug delivery have been particularly attractive because of their compatibility with lung surfactant components[2]. The present study aimed to evaluate the pulmonary deposition and *in vivo* efficacy of sustained release aerosolized budesonide liposomal systems for improved therapy of asthma.

MATERIALS AND METHODS

Liposomes were prepared by lipid film hydration method[3] and freeze dried using trehalose as cryoprotectant (Lebconco, England). The liposomes were characterized for entrapment efficiency, particle size, and surface topography by ESEM, *in vitro* drug release in simulated lung fluid at 37^0 at pH 7.4. The respirable or fine particle fraction (FPF) was determined by using twin stage impinger (TSI). The liposomes were radiolabeled with technetium (^{99m}Tc) using $SnCl_2$ as reducing agent. Rabbit, placed in a head only exposure chamber was allowed to inhale the nebulized spray of the labeled liposomes for 10 min. Scintigraphic images of rabbit lungs were recorded by a Gamma camera (Millenium MPS System) at periodic intervals and analyzed. *In vivo* acute toxicity of liposomes was evaluated in mice by intratracheal administration. *In vivo* efficacy of BDS liposomes was evaluated by histamine induced bronchoconstriction in guinea pigs.

RESULTS AND DISCUSSION

Liposomes were obtained as porous cake after freeze drying with narrow particle size distribution (3-7 μm). Freeze dried liposomes appeared as aggregated particles with lipids on the surface (fig. 1). Dynamic formation of liposomes was monitored by placing a drop of saline on the freeze dried liposomes; spherical structures were clearly seen and after two minutes liposomes were completely formed (figs. 2) The drug release was sustained for more than 70 h for all batches and FPF was found to be in the range of 19-26% based on emitted dose. In the *in vivo* deposition studies, only about 8-10% of delivered dose was found to be deposited in lungs. The major fraction was localized in peripheral region, due to fine particle nature of the nebulized droplets. The activity was

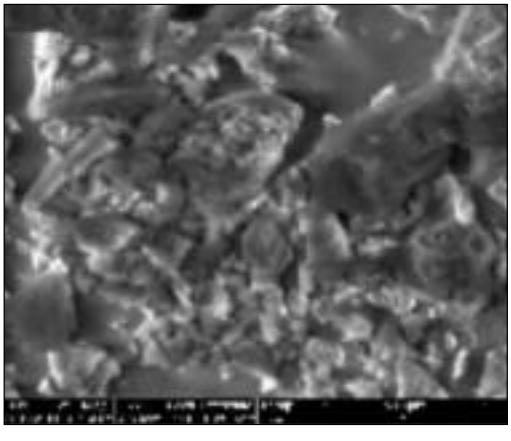

Fig. 1: ESEM photomicrograph of freeze dried liposomes

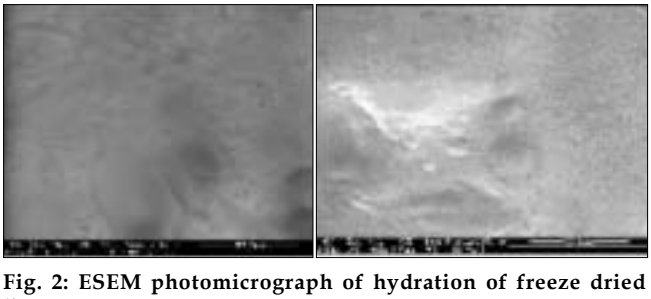

Fig. 2: ESEM photomicrograph of hydration of freeze dried liposomes
The photograph on the left shows liposomes at time zero and the photopraph on the right indicates complete hydration at two minutes

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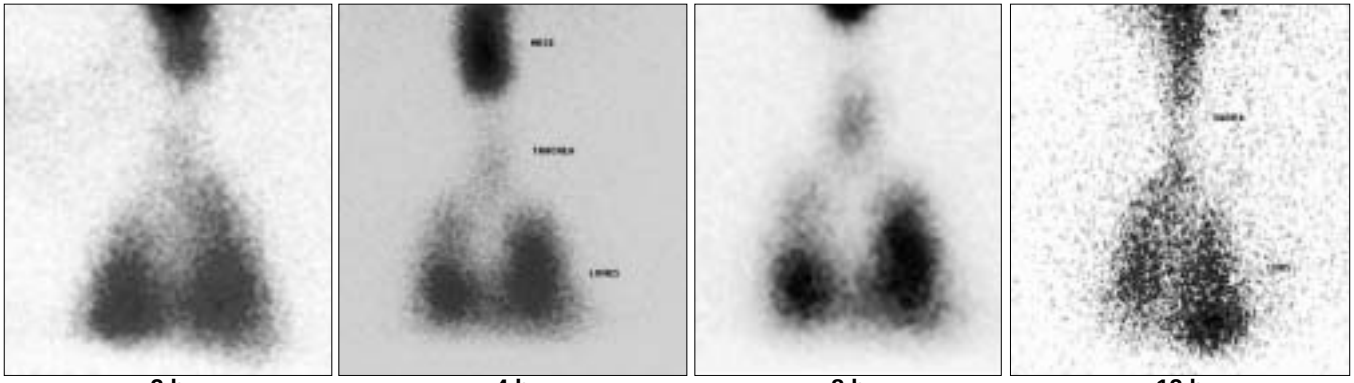

Fig. 3: Gamma scintigraphy images after administration of technetium labeled liposomes of BDS
Lung scans were taken at different time points after administration of technetium labeled liposomes of BDS to New Zealand White rabbits

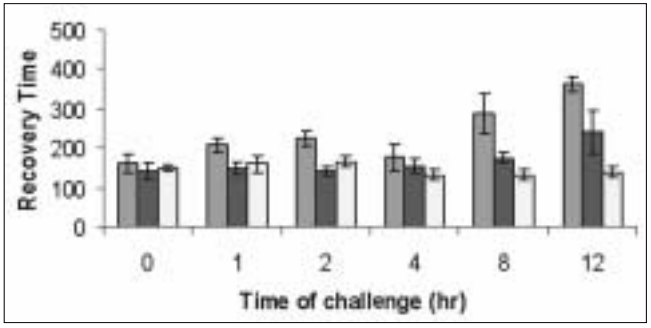

Fig. 4: ▫▪▫ represent control, free drug and liposome respectively

localized in the lungs for up to 12 h in comparison to 6 mins for free ^{99m}Tc, indicating prolonged retention of the BDS liposomes in lungs (fig. 3). *In vivo* acute toxicity study indicated the safety of budesonide loaded liposomes. In the *in vivo* efficacy studies, recovery time after histamine challenge significantly reduced in liposome treated guinea pigs at all time points confirming the sustained action of liposomal BDS (fig. 4). In conclusion, this investigation led to the development of stable freeze dried liposomal systems for pulmonary delivery of budesonide. With this system, it was possible to obtain localized sustained action of drugs in lungs with marked reduction in toxic effects associated with the drug.

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