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CONTENTS

Generation of Budesonide Microparticles by Spray Drying Technology for Pulmonary Delivery

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Treating respiratory diseases with inhalers requires delivering sufficient drug to the lungs to bring about a therapeutic response. For optimal efficacy, drug administration must be reliable, reproducible and convenient. Enhanced powder dispersibility could be designed into microspheres and porous particles through a combination of novel formulation and process design[1]. The present work outlines the design of dry powder inhaler (DPI) formulations to achieve delivery goals. Formulation development, characterization strategies and processing methods have been discussed. Budesonide (BUD) has wide range of inhibitory activities against inflammatory mediators. Conventional BUD DPI formulations were developed and the effect of various grades of inhalable lactose on respirable fraction was studied. BUD microspheres and porous particles were developed using spray drying technology which resulted in improved respirable fraction of BUD.

MATERIALS AND METHODS

Budesonide was obtained from Lupin Ltd., Mumbai; gelatin and chitosan were procured from SD Fine Chemicals, Mumbai and different grades of inhalable lactose were obtained as gift sample from DMV Int., The Netherlands.

Development of conventional BUD DPI formulations:

Drug was mixed with fine lactose and this premix was dispersed over coarse lactose in geometric proportions and developed formulations were characterized (Table 1)[2]. Degree of deacetylation of chitosan was determined by IR spectroscopy[3].

Development of microspheres and porous particles by spray drying:

Polymers chitosan, gelatin and their combination were spray dried using a Labultima Mini Spray Dryer. Process parameters were optimized using 2^2 factorial design. Effect of different parameters was studied (fig. 1). Gelatin /BUD and chitosan/ BUD were spray dried in water: methanol (1:1) as 1.0% and 0.5% w/v, respectively[4]. Porous particles were generated by adding chloroform (5% v/v) as blowing agent[5]. *In vitro* deposition was determined using a Twin Stage Impinger apparatus[2]. Particles were also subjected to Anderson Cascade Impactor studies to determine mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). DSC studies were performed.

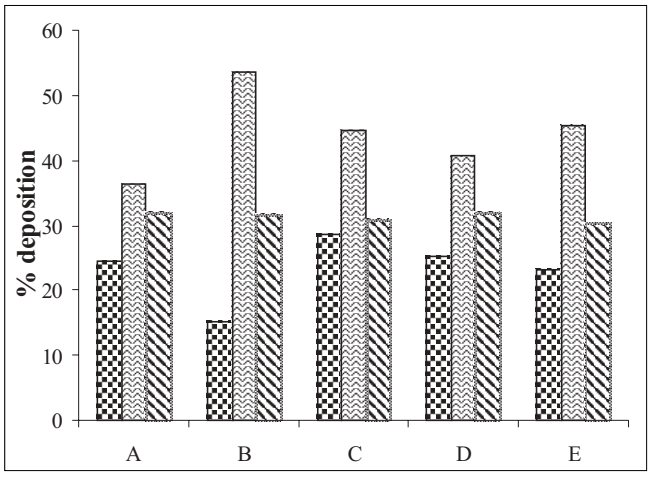

Fig. 1: Comparative in vitro pulmonary deposition pattern of BUD conventional formulations
-Device; - Stage I; and - Stage II

TABLE 1: QUALITY CONTROL TESTS PREFORMED ON CONVENTIONAL BUD DPI FORMULATIONS

Batch code	Assay (% w/w)	Bulk density (g/cc)	Moisture content (% w/w)	% deposition in stage ii
A	109.6011	0.3333	0.0327	32.0487
B	103.5188	0.68	0.0109	31.6768
C	112.5635	0.3222	0.0020	30.9298
D	106.0086	0.625	0.0040	31.8673
E	108.5848	0.5875	0.0015	30.4080

Batch A contains Lactohale 300 and Pharmatose 150M (60:40); batch B contains Inhalac and Lactohale 100M (60:40); batch C contains Lactohale 300 and Pharmatose 150M (70:30); batch D contains Inhalac and Pharmatose 150M (70:30); batch E contains Inhalac and Lactohale 100 (70:30)

In vitro release studies:

These studies were conducted using Flow Through Cell assembly (USP IV) at 37° with flow rate of 16 ml/min (in 100 ml of phosphate buffer pH 7.0)[6]. Five milliliter sample was analyzed by UV Spectrophotometry at 246 nm. Mechanism of drug release was determined using various kinetic models. Coefficient of correlation from plots of Q vs. t (cumulative % drug release vs. time), log Q vs. log t and Q vs. square root of t were calculated.

RESULTS AND DISCUSSION

BUD DPI formulations were developed using various grades of inhalable lactose like Pharmatose, Lactohale, Inhalac and mannitol in various combinations. The effect of particle size of excipients on respirable fraction of BUD was assessed (Table 1 and fig. 1). Degree of deacetylation of chitosan was found to be 45%. Optimum process parameters were inlet temperature (130°), aspirator rate (50%), feed

TABLE 2: RESULTS OF OPTIMIZED DPI FORMULATIONS PREPARED BY SPRAY DRYING TECHNOLOGY

Parameters	Observations	
	BUD microspheres	BUD porous particles
Appearance	Hollow, porous	Hollow, porous, free flowing microspheres
Particle size	1- 10 μm	1- 10 μm
% yield	20-30	20-30
% moisture content	0.3770	0.3280
% drug entrapment	86.00 (RSD= 0.4890)	96.00 (RSD= 0.2616)
% FPF	35.6785%	46.8199%
MMAD	4.60 μm	4.30 μm
GSD	1.75 μm	2.54 μm

FPF is fine particle fraction; MMAD is mass median aerodynamic diameter and GSD is geometric standard deviation

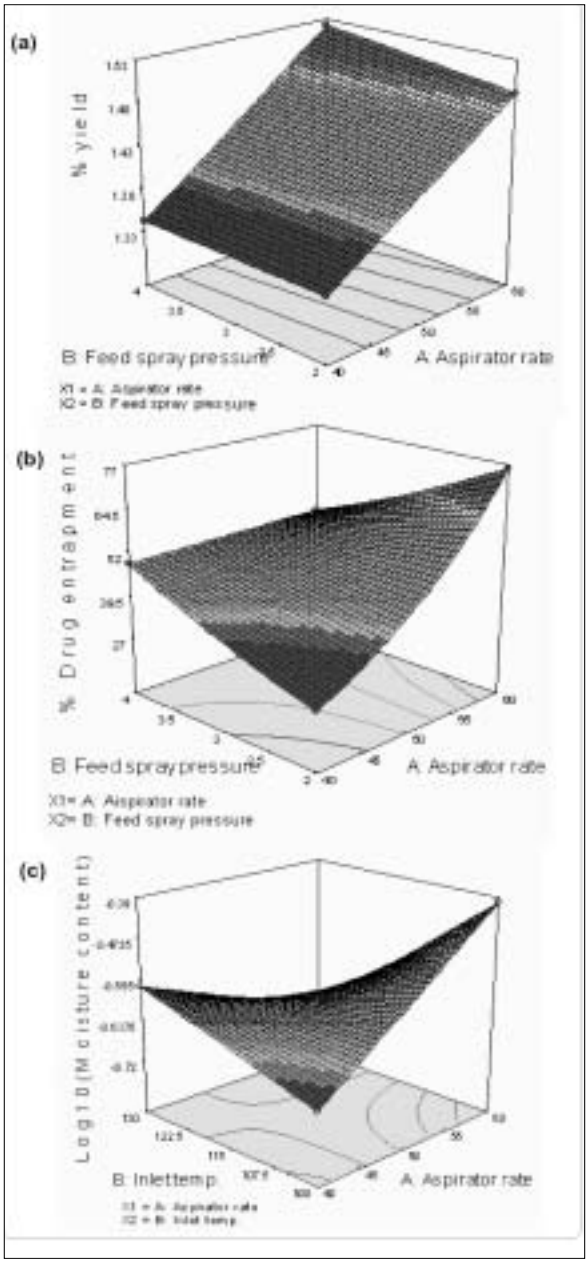

Fig. 2: Factorial design for optimization of process parameters. (a) Effect of aspirator and feed spray pressure on % yield; (b) Effect of aspirator rate and feed spray pressure on % drug entrapment; (c) Effect of aspirator rate and inlet temperature on moisture content of product

rate (30%) and outlet temperature (80°) (fig. 2). Microspheres and porous particles of BUD were prepared with chitosan (1:2, drug: polymer ratio) with 86% and 96% w/w entrapment efficiency, respectively. Developed chitosan microspheres and porous particles were characterized for particle size (SEM analysis

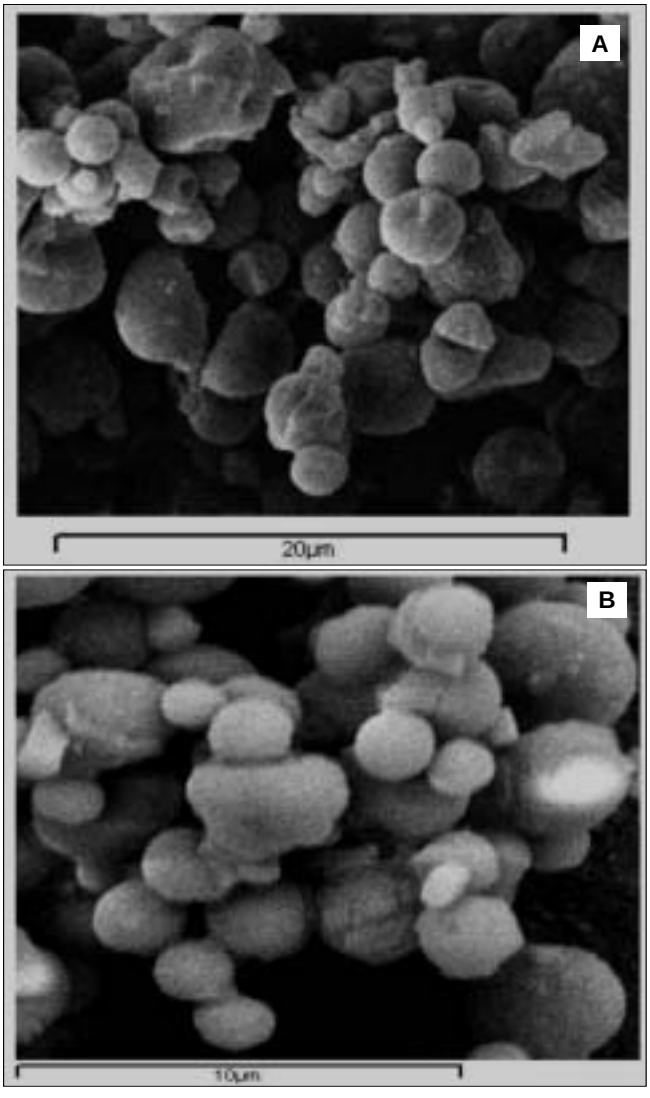

Fig. 3: SEM micrograph of developed formulations (a) Chitosan microspheres and (b) chitosan porous particles

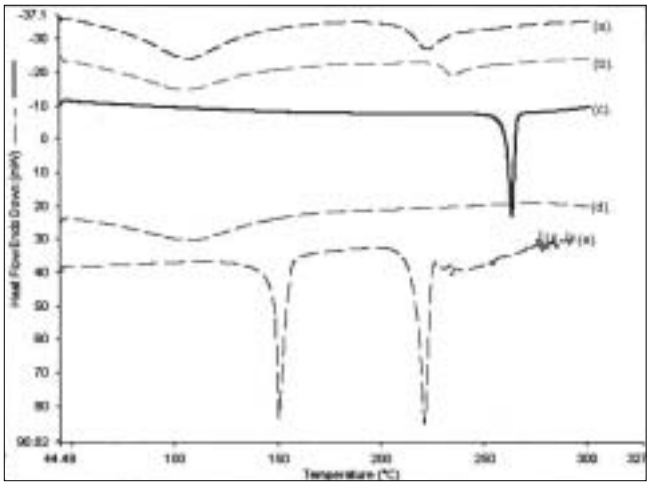

Fig. 4: DSC spectra of developed formulations
(a) BUD porous particles; (b) BUD microspheres; (c) BUD pure; (d) Chitosan pure; (e) BUD conventional formulation

TABLE 3: REGRESSION COEFFICIENTS FOR FORMULATIONS

Formulations	R2		
	Zero order	Korsmeyer-peppas	Matrix
Gelatin microspheres	0.4272	0.9920	0.9166
Chitosan micropsheres	0.8338	0.9722	0.9898
Gelatin porous particles	1.0000	1.0000	1.0000
Chitosan porous particles	0.8315	0.9877	0.9906

- JSM- 840A-/WDS/EDS Sys- JEOL instrument, fig. 3), % drug entrapment and % FPF (Table 2). DSC studies confirmed no interaction between drug and polymer (fig. 4). *In vitro* release profile is shown in fig. 5a. Regression coefficients (near to 1) for zero order, matrix and Korsmeyer-Peppas kinetic equations confirmed release by slow zero order kinetics through diffusion matrix (Table 3, fig. 5b and 5c). Korsmeyer-Peppas plot indicated good linearity ($r^2 = 0.9722$).

Microspheres and porous particles were engineered to be both hollow and porous and these exhibited excellent flow and dispersion from passive DPIs. *In vitro* characterization predicted highly efficient lung delivery. The results indicated that spray drying technology can be used to generate inhalable particles like microspheres and porous particles with improved pulmonary deposition as compared to conventional DPI formulations.

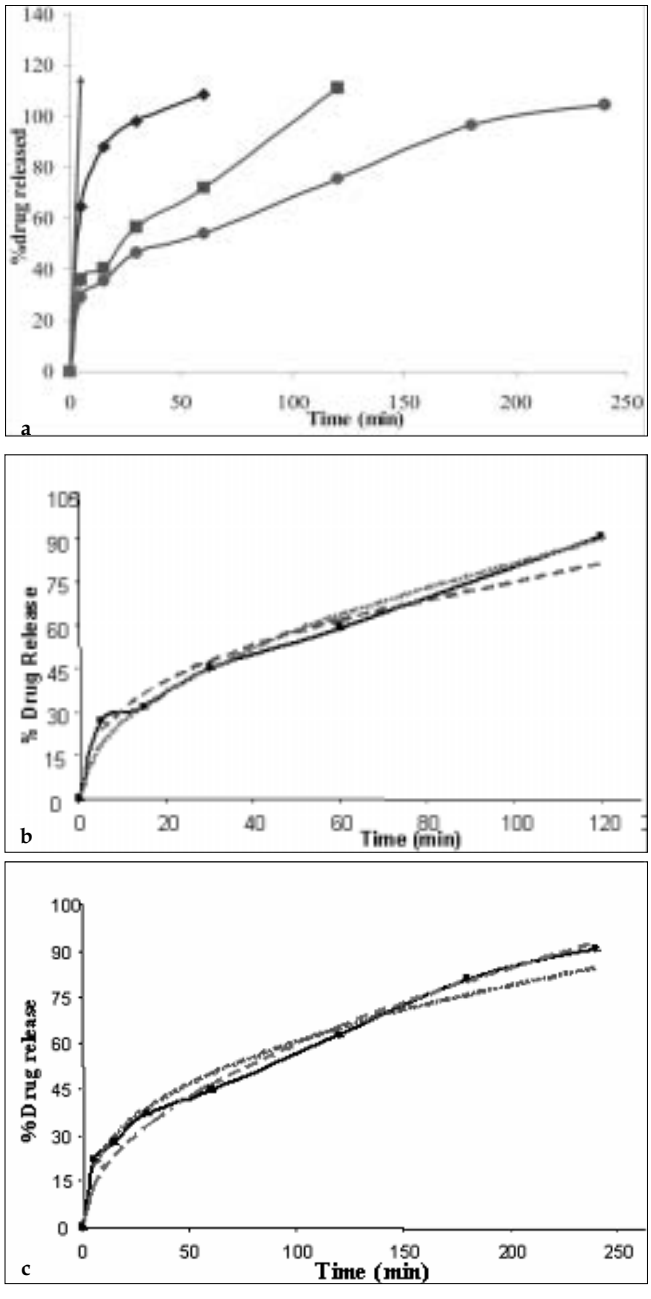

Fig. 5: *In vitro* release profile and release kinetics of formulations
a. *In vitro* release profile of microspheres and porous particles prepared by spray drying method; gelatin microspheres; - chitosan microspheres; - gelatin porous particles; chitosan porous particles; (b) Release kinetics of chitosan microspheres; actual; - matrix; Peppas model (c) Release kinetics of porous particles of chitosan; - actual; - matrix; - Peppas model

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