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Assessing the combinatorial influence of climate, formulation and device on powder aerosolization using the Taguchi experimental design

Desmond Heng [a,*], Sie Huey Lee [a], Jin Wang Kwek [a], Wai Kiong Ng [a], Hak-Kim Chan [b], Reginald B.H. Tan [a,c,**]

[a] Institute of Chemical and Engineering Sciences, A*STAR (Agency for Science, Technology and Research), 1 Pesek Road, Jurong Island, Singapore 627833, Singapore
[b] Advanced Drug Delivery Group, Faculty of Pharmacy A15, The University of Sydney, Sydney, NSW 2006, Australia
[c] Department of Chemical and Biomolecular Engineering, National University of Singapore, 4 Engineering Drive 4, Singapore 117576, Singapore

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ABSTRACT

In dry powder inhaler therapy, it is often highly desirable to maximise the fine particle fraction (FPF) while reducing the throat and inhaler retention. While there are a number of factors affecting aerosolization, there is at present no combinatorial study comparing the relative importance of each variable on dispersion and retention. In this work, the Taguchi experimental design, suitable for analysing a large number of factors and interactions within a reasonable number of runs, was applied to study the combinatorial effects of climate, air flow, carrier type and inhaler type on the aerosolization of micronized salbutamol sulphate as a model powder. Taguchi analysis revealed that FPF and throat deposition were highly dependent on the airflow rate and inhaler type, while device and capsule retention could be minimised via judicious selection of carrier and inhaler type respectively. The impact of dispersion climate (temperature and humidity) on aerosol penetration and retention was found to be of secondary importance. Analysis via the Taguchi experimental design thus represents a novel and useful approach for dissecting and understanding the large number of confounding variables affecting aerosolization.

1. Introduction

The dry powder inhaler (DPI) is emerging as an important non-invasive delivery technology in the new decade and beyond. Despite its growing popularity, its delivery efficiency is not high and in some cases, only 10% of the inhaled dose reaches the lung [1]. Therefore, there is a need to study and understand the crucial factors affecting dry powder aerosolization in a DPI, as well as to identify the most feasible optimization pathways.

There are a number of factors affecting dry powder aerosol delivery, and they include air flow, inhaler resistance, climate (temperature and humidity), effect of carrier and particle surface nature [2]. While climate [3,4], air flow [2,5,6], carrier type [7] and inhaler device [2,8] have all been studied either individually or in pairs, a detailed combinatorial assessment involving all parameters has not been explored. This was further complicated by the possibility of potential or known interaction between certain variables [9].

As there are a significant number of factors affecting aerosol formulation and delivery, optimization and study via conventional optimization protocols (e.g. factorial designs) would have been deemed highly laborious and inefficient. The Taguchi Method, being highly applicable for the study of a large number of factors and interactions within a reasonable number of experiments [10,11], was therefore applied in this work to study and dissect the combinatorial effects of climate, formulation and device on aerosolization and to identify the key parameters controlling aerosol penetration and retention. This method is a combination of mathematical and statistical techniques incorporated into an empirical study [11] and has previously been applied to the spray drying of nano-pharmaceuticals [12,13] and in the development of tablet formulations [10,14,15]. It establishes a series of experiments aimed at determining the optimum combination of parameters that have the greatest influence on the performance and with the least variation from the design target [16].

This work aims to examine the feasibility of the Taguchi experimental design to innovatively study and dissect the combinatorial effects of climate, air flow and carrier type on the aerosolization of micronized salbutamol sulphate powders using two different inhalers: the Rotahaler® — low efficiency and low resistance (GlaxoSmithKline, UK) and the Aerolizer® — high efficiency and medium/low resistance (Novartis, Switzerland) [17]. Two representative administration climates (in addition to the base condition of 25 °C, 40% RH) are to be investigated in the Taguchi analysis: cool and moderately moist (15 °C, 60% RH) and hot and dry (40 °C, 20% RH) while the studied carriers are to be selected from the following classes: crystalline and non-hygroscopic sugar alcohols (e.g. mannitol), crystalline and non-hygroscopic sugars

* Corresponding author. Tel.: +65 67963861; fax: +65 63166183.
** Corresponding author. Tel.: +65 67963855; fax: +65 63166183.
E-mail addresses: desmond_heng@ices.a-star.edu.sg (D. Heng), reginald_tan@ices.a-star.edu.sg (R.BH. Tan).

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Table 1
Experimental parameters (factors) and levels.

Parameters		Levels		
		1	2	3
(A)	Climate	Cold and wet 15 °C, 60% RH[a]	Base condition 25 °C, 40% RH	Hot and dry 40 °C, 20% RH[b]
(B)	Flow rate (L/min)	60	100	150
(C)	Carrier type	Mannitol	Lactose	Sorbitol
(D)	Inhaler type	Rotahaler	Aerolizer	

RH: relative humidity.
[a] Cool and moderately moist.
[b] Hot and dry.

(e.g. lactose monohydrate), and crystalline and hygroscopic sugar alcohols (e.g. sorbitol).

2. Materials and methods

2.1. Materials

Mannitol (Pearlitol 160C, Roquette, France), lactose monohydrate (DMV-Fonterra Pharmatose 110M, New Zealand) and D-sorbitol (Aldrich, USA) were sieved to a 63–90 μm size fraction using a stainless steel mechanical shaker (Retsch AS 200, Germany). Salbutamol sulphate (Junda Pharma, China) was micronized to the inhalable range (1–5 μm) via a spiral jet mill (Hosokawa Alpine 50AS, Augsburg, Germany) operating at an injection pressure of 6 bar and grinding pressure of 2.8 bar.

2.2. Blend preparation and uniformity testing

Micronized salbutamol sulphate and excipient blends (i.e., 1:67.5 w/w) were initially pre-mixed via geometric blending (5 g batch size), then subjected to final mixing for 15 min in a shaker–mixer (Turbula T2F, Switzerland) at 46 rpm. In accordance with pharmacopoeia methodology, ten doses (40 ± 1 mg) of the drug-excipient blend were individually assayed for their drug content via UV-spectrophotometry at 276 nm (Agilent Technologies Cary 50 Conc, California, USA). Batches were accepted when the amount of drug in each dose fell within 85 to 115% of the average content.

2.3. Experimental design

The Taguchi design method was applied in this study to identify the dominant factors affecting the fine particle fraction, throat deposition, inhaler retention and capsule retention. A total of four factors (climate, flow rate, carrier type and inhaler type) were considered. Climate, flow rate and carrier type were evaluated at three levels while inhaler type involved two levels (Table 1) — L_9 orthogonal array. Optimum conditions were indicated by high signal to noise (S/N) ratios. To optimise the fine particle fraction, Taguchi's 'larger-is-better' criterion (Eq. (1)) was adopted, while the 'smaller-is-better' criterion (Eq. (2)) was utilised for the throat deposition, device retention and capsule retention [18,19].

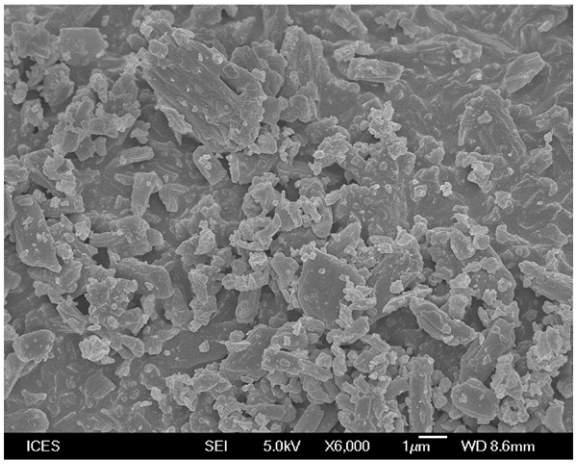

Fig. 1. FESEM image of micronized salbutamol sulphate.

Maximise performance characteristic ('larger-is-better'):

$$(S/N)_i = -10 \cdot \log_{10}\left[\frac{1}{n} \cdot \sum_{i=1}^{n} \frac{1}{y_i^2}\right] \quad (1)$$

Minimise performance characteristic ('smaller-is-better'):

$$(S/N)_i = -10 \cdot \log_{10}\left[\sum_{i=1}^{n} \frac{y_i^2}{n}\right] \quad (2)$$

where y_i is the characteristic property and n is the number of experimental replicates.

2.4. Scanning electron microscope (SEM) imaging

Powder samples were mounted onto metal sample stubs and coated with gold. The samples were then examined under a high resolution field emission scanning electron microscope (Jeol JSM 6700, Japan) at 5 kV.

2.5. Powder crystallinity

Powder crystallinity of the micronized drug and sieved carriers was assessed by X-ray powder diffraction (XRD). Samples were

Table 2
Experimentally measured values and their corresponding S/N ratios for the response variables.

Expt. no.	Parameter				Fine particle fraction (%)		Throat deposition (%)		Device retention (%)		Capsule retention (%)	
	A	B	C	D	y (n = 3)	S/N ratio (dB)	y (n = 3)	S/N ratio (dB)	y (n = 3)	S/N ratio (dB)	y (n = 3)	S/N ratio (dB)
1	1	1	1	1	2.5	7.8	0.8	1.3	9.6	−19.7	4.1	−12.4
2	1	2	2	2	27.3	28.7	1.8	−5.3	5.0	−14.1	10.0	−20.1
3	1	3	3	2	36.6	31.3	2.1	−6.4	5.9	−15.5	3.2	−10.8
4	2	1	2	1	4.9	13.7	1.0	0.0	9.3	−19.4	3.2	−10.1
5	2	2	3	1	3.8	11.4	0.7	3.2	4.8	−13.6	1.6	−4.9
6	2	3	1	2	39.1	31.8	2.8	−8.9	5.6	−15.0	7.3	−17.8
7	3	1	3	2	9.1	18.7	1.0	−0.5	3.7	−11.3	12.4	−21.9
8	3	2	1	1	5.3	14.4	0.7	2.7	6.3	−16.0	2.1	−7.1
9	3	3	2	1	14.1	23.0	1.5	−3.3	6.1	−15.7	2.3	−8.1

y: raw data (response variable).