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Review

Pulmonary drug delivery by powder aerosols

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ABSTRACT

The efficacy of pharmaceutical aerosols relates to its deposition in the clinically relevant regions of the lungs, which can be assessed by *in vivo* lung deposition studies. Dry powder formulations are popular as devices are portable and aerosolisation does not require a propellant. Over the years, key advancements in dry powder formulation, device design and our understanding on the mechanics of inhaled pharmaceutical aerosol have opened up new opportunities in treatment of diseases through pulmonary drug delivery. This review covers these advancements and future directions for inhaled dry powder aerosols.

Contents

Abbreviations: BSA, Bovine serum albumin; CF, Cystic fibrosis; CFD, Computational fluid dynamics; CIJ, Confined liquid impinging jets; COPD, Chronic obstructive pulmonary disorder; d_{ae}, Aerodynamic diameter; DEM, Discrete element method; DPI, Dry powder inhaler; FPF, Fine particle fraction; ICS, Inhaled corticosteroids; ISSR, Integral scale strain rate; MMAD, Mass median aerodynamic diameter; P/C, Peripheral lung to central lung deposition ratio; PET, Position emission tomography; PIFR, Peak inspiratory flow rate; pMDI, Pressurised metered dose inhaler; Q, Flow rate; SCF, Supercritical fluid; SPECT, Single photon emission computed tomography.

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1. Introduction

Drug delivery to the lungs is an attractive route for local treatment of pulmonary disease such as asthma, and chronic obstructive pulmonary disorder (COPD), and also delivering drugs systemically [1]. In particular, significant research and development efforts have been put into dry powder aerosols, which require no propellant, have superior chemical stability compared with solution, and are easy for patients to use. There are two types of dry powder inhalers (DPIs): passive or breath actuated devices, and active devices. With passive devices, the energy for dispersion is generated by the patient's inspiratory effort. In contrast, active devices minimise inspiratory effort by using an independent means (motor or compressed gas) to fluidize the powder. In the literature, the active devices have also been referred to the third generation DPIs (Table 2).

Clinical efficacy of inhaled therapeutics is governed by lung deposition, which depends on the aerosol properties. For DPIs, the aerosol properties are related to the dispersion of the powder, governed by the complex interaction between patient inspiratory flow rate, the device, and the formulation (Fig. 1). The effect of these variables on deposition in the lungs can be examined by *in vivo* lung deposition studies.

This review examines the intimate relationship between clinical efficacy of inhaled therapeutics and lung deposition, and how these are influenced by powder formulation and device factors.

Table 2
Examples of Current DPIs.

Device	DPI type	Company	Delivery system
Spinhaler	Single dose	Aventis	Capsule
Rotahaler	Single dose	GlaxoSmithKline	Capsule
Inhalator	Single dose	Boehringer-Ingelheim	Capsule
Cyclohaler	Single dose	Pharmachemie	Capsule
Handihaler	Single dose	Boehringer-Ingelheim	Capsule
Aerolizer	Single dose	Novartis	Capsule
FLowCaps	Single unit dose	Hovione	Capsule
TwinCaps	Single dose	Hovione	Capsule
Turbuhaler	Multi-dose	AstraZeneca	Reservoir
Easyhaler	Multi-dose	Orion Pharma	Reservoir
Ultrahaler	Multi-dose	Aventis	Reservoir
Pulvinal	Multi-dose	Chiesi	Reservoir
MAGhaler	Multi-dose	Boehringer-Ingelheim	Reservoir
Taifun	Multi-dose	LAB Pharma	Reservoir
Clickhaler	Multi-dose	Innovata Biomed	Reservoir
Asmanex Twisthaler	Multi-dose	Schering-Plough Corporation	Reservoir
Aerohaler	Multi-unit dose	Boehringer-Ingelheim	Capsule
Diskhaler	Multi-unit dose	GlaxoSmithKline	Blister package
Diskus/Accuhaler	Multi-unit dose	GlaxoSmithKline	Blister strip package
Exubera	Single-dose	Pfizer	Blister
Airmax	Multi-dose	Norton Healthcare	Reservoir

2. Clinical outcome and lung deposition

Clinical efficacy of inhaled drugs is primarily determined by the total and regional lung deposition of the drug [18]. Aerosol particles with a mass median aerodynamic diameter (MMAD) less than 5 μm are generally understood to deposit within the lungs [19]. Within this respirable range, the smaller particles have greater total lung deposition, peripheral airway deposition, and rate of systemic drug absorption and vice versa [18,20]. The desired particle size profile is dependent on the needs of the target disease state and can be controlled by particle properties, device choice, and patient factors. The importance of an optimised lung deposition for aerosol medications is discussed.

In general, increasing the lung to oropharyngeal deposition ratio reduces variability in lung dose. This in turn limits the incidence of unwanted side effects and cost to society, whilst reassuring the clinician and patient of therapeutic efficacy [21]. Borgstrom et al. [21] ascertained that throat deposition was a primary contributor to lung deposition variability. By reducing throat deposition, high deposition–low variability lung dosing can be achieved. However, variability in lung deposition determined *in vitro* is not necessarily an accurate predictor of *in vivo* variability. This was demonstrated in an earlier study comparing administration of terbutaline sulphate via a pressurised metered dose inhaler (pMDI) and DPI [22]. A similar disconnect between *in vitro* and *in vivo* findings by Daley-Yates et al. [23]. A salmeterol and fluticasone propionate combination administered via two different dry powder inhalers conferred similar *in vitro*

Table 1
Summary of lung deposition from different dry powder inhalers. The deposition values represent average range (%) from the referenced scintigraphic studies.

Inhaler & drug	Flow (L/min)	Oropharynx (%)	Central (%)	Intermediate (%)	Peripheral (%)	Lung (%)	Ref.
Turbuhaler® (budesonide)	58–66	49.3–57.9	8.5–9.6	7.4–10.1	5.9–11.2	25.1–29.8	[3–7]
Turbuhaler® (terbutaline)	55–60	53.3– 6.0	5.5–5.7	7.1–8.4	8.8–12.9	21.4–27.0	[4, 5, 8, 9]
Spinhaler® (sodium cromoglycate)	120	47.8	–[a]	–[a]	–[a]	17.1	[10]
Monodose® (budesonide)	47	57.3	7.5	7.4	6.4	21.4	[3]
Pulvinal® (salbutamol)	46	80.3	4.9	4.3	4.9	14.1	[11]
Easyhaler® (budesonide)	63	73.6– 4.1	5.8–7.3	6.1–6.4	5.1–6.7	18.5–24	[6, 12]
Clickhaler® (budesonide)	73	65.8	–[a]	–[a]	–[a]	26.8	[13]
Ultrahaler® (nedocromil Sodium)	75	84.7	4.5	4.5	4.3	13.3	[14]
Rotahaler® (disodium Cromoglycate)	55–70	–[a]	–[a]	–[a]	–[a]	6.2	[15]
Aerolizer® (mannitol)	38.9	42.4%	5	10	6.3	21.3	[16]
Aimax® (budesonide)	73.6	73.6	6.5	8.6	10.7	25.8	[7]
Taifun® (budesonide)	35.8	47.9	10.9	12.5	10.9	34.3	[17]

[a] The deposition data is not available.