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REVIEW ARTICLE

Advances in the pulmonary delivery of poorly water-soluble drugs: influence of solubilization on pharmacokinetic properties

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Abstract

Background: Pulmonary drug delivery is an accepted route of drug administration for the management of lung conditions and diseases as well as an evolving route of administration for the systemic delivery of agents. Many inhaled drugs pose formulation and delivery challenges in part because of poor aqueous solubility. The influence of poor aqueous solubility and formulation-based solubility enhancements on the pharmacokinetic profile of inhaled agents was reviewed. *Method*: A systematic review was performed to identify literature that reported pharmacokinetic findings following the pulmonary delivery of a poorly water-soluble agent. *Results*: The influence of solubility and formulation-based solubility enhancements on pharmacokinetic parameters following inhalation of corticosteroids, antifungals, oligopeptides, and opioids, was compiled. *Conclusion*: Poor aqueous solubility did not uniformly affect the pharmacokinetic profile for inhaled agents. Physicochemical and formulation-based solubility enhancement did affect drug absorption from the lungs. Numerous drug- and formulation-dependant pharmacokinetic effects were identified.

Key words: *Absorption; antifungals; fentanyl; inhalation; peptide; pharmacokinetics; solubility; steroids*

Introduction

Therapeutic administration of active pharmaceutical ingredients (APIs) to the lungs has long historical significance[1]. Despite the long-term use of therapeutic aerosols, the scientific principles governing the in vivo performance of inhaled drugs have only recently been probed. In the modern age of drug research and development focused on pulmonary drug delivery, the fate of inspired aerosols has been correlated to patient-specific as well as formulation/device factors. The in vivo action of inhaled aerosols can be affected by patients through the control and the regulation of the physiologic parameters of breathing including respiration rate, tidal volume, inhalation air flow, and breath holding[2]. Additionally, the formulation scientist can influence in vivo aerosol performance through the manipulation of the interrelationships between the formulation and the inhalation device, for example, pressurized metered dose inhaler (pMDI), nebulizer, and dry powder inhaler (DPI). These modifiable relationships govern the aerodynamic particle size distribution, pH, tonicity, and physiologic compatibility of the inspired aerosol.

Traditionally, these APIs have been intended for local drug action in the lungs for treatment of topical conditions in the airways; examples include the treatment of airway inflammation, lung diseases, and lung infections. However, drug delivery to the lungs has recently received increased scientific attention and expansion. This renewed interest coincides with advances in particle engineering technologies[3,4], advances in biotechnology-derived therapeutic macromolecules[5], and new APIs with low and/or erratic bioavailability[6–8]. Much of the expanded interest in pulmonary drug delivery focuses on systemic drug delivery via the lungs because of the rapid bioavailability and the avoidance of the pH, food effects, enzymatic, and first-pass metabolic barriers following oral drug administration. Despite these potential advantages, inhaled drugs must overcome numerous barriers for adequate deposition in the lung.

Several excellent reviews have explained in detail the physiologic barriers to inhaled drug delivery[7,9–11]. Briefly,

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the lungs are a natural particle filter because of a ciliated and mucous-producing epithelium that lines the airways. Additionally, the airways in the lung subdivide through a tortuous pathway of bifurcations throughout the lung, which allow air communication with the gas-exchange specializing lung structures, the alveoli, also referred to as the deep lung. An inspired particle must, therefore, avoid contact with the ciliated and mucus-covered epithelium to avoid ingestion, via the mucociliary escalator, as well as traverse numerous potential impaction sites for deposition along the airways or in the deep lung. The aerodynamic properties and particle behavior of the inhaled particle are therefore crucial for drug delivery to the lungs, typically 1–5 μm in size[9]. The inhaled particle must also be physiologically compatible with the lung membranes (i.e., isotonic, iso-pH, and nonimmunogenic) to avoid airway hyper-responsiveness, cough, or airway spasticity, or inflammation[12]. The deposition of particles can also be affected by the increasing relative humidity in the lungs as a particle is inhaled into the deep lung[13].

Once a particle has bypassed these pulmonary barriers and been deposited in the alveolar region, the API must be absorbed for systemic drug action. The ability for APIs to be absorbed across the alveolar membrane has not been investigated to the degree of gastrointestinal (GI) drug absorption. Mechanistic explanations of GI absorption have recently been re-reviewed and form a foundation for explaining pulmonary drug absorption[14,15]. The primary differences between modeling GI and pulmonary drug absorption focus on the fact that the lungs have different physiologic and cellular structures at absorption sites, have a dramatically decreased metabolic capacity, lack the degree of active transport sites, and have a much higher surface area and corresponding blood flow than the GI tract.

An excellent review from Sakagami was published in 2006 and numerous methodological approaches to investigating the mechanisms underlying pulmonary drug absorption and disposition were summarized[16]. As with any model, control and evaluation of the numerous variables associated with pharmacokinetic profile and properties of a drug following inhalation is very difficult. As a result, researchers have employed ex vivo, cellular, in silico and in vitro models to isolate and quantify the different variables present in whole animals when investigating the factors affecting drug absorption in the lungs. However, these isolated or simplified models do not adequately simulate the numerous factors involved with pulmonary drug delivery in a living system.

To further complicate the literature describing the pharmacokinetics of inhaled drug delivery, researchers have used whole animal models with varying methods of pulmonary drug administration, that is, intratracheal instillation of a liquid, orotracheal intubation and administration of a liquid spray or powder insufflator, and natural whole-body or nose-only exposure. The method of pulmonary drug administration can affect the reported results because of species-specific differences in the respiratory system between animals. For example, the majority of mammal species are obligate nose breathers with the inability to breathe through the mouth, causing airflow differences and resultant differences in deposition from humans[17]. Although these whole animal-modeling systems have difficulty isolating the specific contributing factors involved in drug absorption, they are applicable as screening mechanisms for different formulations and can represent a more realistic approach to understanding drug absorption in the lungs. Of the numerous factors that can influence drug absorption from the lungs, the effect of drug solubility, solubility-enhancing excipient, and drug solution or solid state for poorly water-soluble APIs has not been explained in whole animal or in isolated component systems for pulmonary drug administration.

Poorly water-soluble APIs are becoming increasingly common for new chemical entities[18–21]. A compound with poor aqueous solubility presents challenges and limitations for formulation development and the clinical utility of a dosage form, particularly in the lungs. The absorption would be limited by the number of dissolved molecules for diffusion through biological membranes. Although there is no unified definition for poorly water-soluble drugs, the United States Pharmacopeia uses descriptive terms related to quantifiable solubility ranges, that is, very soluble (>1 g/mL) to insoluble (<0.1 mg/mL)[22]. Instead, the Center for Drug Evaluation and Research describes solubility as 'high' or 'low' based on the ability of 250 mL of dissolution medium to dissolve the dose of drug by in vitro methods[23]. This categorical classification is intended to describe the impact of solubility on drug absorption and bioavailability[24]. However, the definition of low solubility has little physiologic significance on absorption when applied to pulmonary drug delivery because of low masses in inhaled drug doses and a small and dispersed fluid volume within the lungs[7,25,26]. Therefore, the relationship between low solubility and observed pharmacokinetic properties of drugs when administered to the lungs does not fall into the definitions and testing parameters that are applicable for other routes of drug administration.

Several therapeutic agents with low aqueous solubilities have been investigated for pulmonary drug delivery. These agents include corticosteroids in the management of asthma and inflammation; anti-infective agents to treat and prevent bacterial, fungal, and viral pneumonias; chemotherapeutic agents for lung cancers and tumors; and numerous other APIs. The low solubility of these APIs can influence the absorption and the retention of the drug in the lung tissue and can directly affect drug activity, side effects, and dosing regimens.

Accordingly, this article will review the literature available describing the pulmonary drug administration of poorly soluble APIs where some pharmacokinetic data are available. Although drug absorption across membranes in the lungs is the parameter of interest, few researchers directly measure absorption rates across the pulmonary epithelium, for example, mean absorption times or absorption rate constants (k_{abs}). Instead, proxy markers of drug absorption could include other observed pharmacokinetic parameters such as maximal drug concentration in the blood and in the lung tissue if available (C_{max}), the time to reach maximal concentrations (T_{max}), elimination half-life ($t_{1/2}$), and drug exposure (AUC). These proxy markers will allow comparative relationships to be established to evaluate the influence of formulation and solubility enhancements on drug absorption. Therefore, the influence of solubility and formulation-based solubility enhancements on pharmacokinetic parameters following inhalation of various classes of poorly water-soluble drugs, including corticosteroids, antifungals, oligopeptides, and opioids, will be reviewed.

Inhaled corticosteroids

Inhaled corticosteroids are the most commonly inhaled class of poorly water-soluble API. They are therapeutically used to inhibit inflammatory processes in the lungs, primarily in the management of asthma. These structurally related agents have a steroid backbone, some with modifications to the steroid ring, and appended functional groups[27]. These modifications primarily affect ligand–receptor interactions and lead to varied binding affinities with the glucocorticoid receptor. Because all corticosteroids affect the same receptor, competitive binding assays have allowed the relative potencies of these agents to be stratified as fluticasone propionate > beclomethasone-17-monopropionate > budesonide > beclomethasone dipropionate > triamcinolone acetonide[28]. These relative potencies affect drug efficacy as well as the side-effect profile and propensity for long-term adverse events. However, many adverse events associated with inhaled corticosteroids result from systemic exposure following absorption. In addition to these structure-based pharmacodynamic properties, most corticosteroids remain poorly water-soluble compounds with aqueous solubilities of 21 μg/mL for triamcinolone acetonide, 16 μg/mL for budesonide, 0.14 μg/mL for fluticasone propionate, and 0.13 μg/mL for beclomethasone dipropionate (15.5 μg/mL for the beclomethasone-17-monopropionate active metabolite)[29]. Reported log $P_{o/w}$ values also indicate that these agents are very lipophilic with values of 3.4 for triamcinolone acetonide, 3.6 for budesonide, 4.5 for fluticasone propionate, and 4.9 for beclomethasone dipropionate (4.3 for beclomethasone-17-monopropionate). The molecular weights for these compounds are 430.5 g/mol for budesonide, 434.5 g/mol for triamcinolone acetonide, 500.6 g/mol for fluticasone propionate, and 521.1 g/mol for beclomethasone dipropionate. These high log *P* values and small molecular weights indicate the potential for good passive membrane permeability, leading to dissolution-limited drug absorption following inhalation.

Ideally, an inhaled corticosteroid would have high potency, would be retained in the airways and lung tissue for prolonged anti-inflammatory action, and would then have low drug absorption leading to low systemic drug exposure with consequently low incidence of adverse events. Accordingly, several researchers have investigated the pharmacokinetic properties of inhaled corticosteroids to understand the mechanisms of drug deposition and absorption from the lungs to the systemic circulation[30–35]. Some pharmacokinetic profiles of these agents are also influenced by the structural differences between the APIs, specifically the avenues of clearance and metabolic pathways between the various agents[36]. The other pharmacokinetic properties of inhaled corticosteroids, including the C_{max}, t_{max}, AUC, and $t_{1/2}$, vary between the agents based, in part, on the physicochemical properties of the API. The interrelationship of pharmacokinetic and pharmacodynamic properties of this drug class defines their clinical utility. For that reason, many researchers have investigated adverse events of these agents through the biomarker of endogenous cortisol secretion suppression and corresponding bioavailabilities between inhaled and other routes of administration[37]. However, the utility of a biomarker in this investigation is limited when correlating the influence of drug solubility and solubilization properties of the formulation on drug absorption following inhalation. Through independent evaluation of corticosteroids with reported pharmacokinetic parameters, categorical relationships can describe the influence of solution state and formulation on pulmonary absorption of these inhaled agents.

Fluticasone propionate

The majority of systemic pharmacokinetic data on inhaled fluticasone propionate are with the DPI formulation branded as the Flutide®, Flovent® or Flixotide® administered with the Diskhaler®, Diskus®, or Accuhaler® devices[30,38–42]. These formulations use micronized fluticasone propionate blended with a lactose carrier particle and de-aggregate from the carrier via turbulent airflow through the device. Some pharmacokinetic data are also available with the pMDI branded as Flovent®. The pMDI formulation contained a

microcrystalline suspension of fluticasone propionate in a propellant mixture of CFC-11 and CFC-12 with soya lecithin as a surfactant and a lubricant for the metering valve. Both the DPI and the pMDI formulations deliver solid fluticasone propionate particles to the lung and rely on particle size reduction of the API to improve the rate of dissolution for this poorly water-soluble drug. Therefore, fluticasone propionate has little data to describe the influence of drug solubilization and solubility enhancement through the formulation on drug absorption from the lungs. However, it does serve as a reference and comparator for the remainder of the inhaled corticosteroids with a moderate aqueous solubility (0.14 μg/mL), log *P* value (4.5), and molecular weight (500.6 g/mol) for this class of poorly water-soluble compounds (Table 1).

Following a single inhalation, maximal concentrations were observed after an average of 0.9–1.88 hours (54–118 minutes). Dose-normalized maximal concentrations ranged from 0.1 up to 0.3 pg/mL/μg whereas dose-normalized AUC values ranged from 0.3 to 3.0 pg h/mL/μg with no real difference between the DPI and the pMDI forms. Concentrations and AUC values were not controlled for the influence of oral ingestion of the drug through oral administration of activated charcoal and must be assumed to have been affected by minor, but nontrivial, oral ingestion of fluticasone propionate. However, despite possible oral ingestion of the inhaled product and 3- to 10-fold difference in maximal drug concentrations and drug exposure, plasma fluticasone concentrations remained very low, in the pg to ng range, following large inhaled doses. The very low systemic fluticasone propionate concentrations indicate very little drug absorption from the inhaled particulate systems.

Several researchers reported the mean residence time (MRT), the average time a molecule resides within the system from absorption to elimination, for fluticasone following inhalation. The reported MRT values were 7.1–12 hours for DPIs and 5.3 hours for the pMDI, indicating a prolonged but variable time for the drug to be retained in the studied population. Additionally, Brindley et al.[30] specifically investigated the absorption kinetics of fluticasone propionate following inhalation using both the DPI and the pMDI devices. Following inhalation from both DPI and pMDI devices, 50% of the bioavailable dose was absorbed within 1.6–2.4 hours (95–145 minutes) whereas 90% of the dose was absorbed by 11.4–12.3 hours. The average time it takes for a drug molecule to be absorbed, the mean absorption time, was 4.3–4.4 hours. The authors identified that fluticasone propionate is retained in the lungs for an extended period of time with an initial rapid phase of drug absorption followed by a period of prolonged drug absorption.

Budesonide

Inhaled formulations of budesonide were more diverse than those for fluticasone propionate and included DPI, pMDI, and nebulizer formulations. The branded DPI products included the Pulmicort Turbohaler®, with only micronized budesonide in the formulation, and the Giona® Easyhaler® containing budesonide blended with a lactose carrier particle[34,38,39,41,43]. The pMDI formulation, Pulmicort® (no longer available in the United States), contained a micronized suspension of budesonide with sorbitan trioleate as a metering valve lubricant, and a propellant mixture of CFC-11, CFC-12, and CFC-114[44]. Budesonide suspensions for nebulization were also tested and included the marketed Pulmicort Respules® and two different novel nanoscale suspensions[44–46]. The Pulmicort Respules® contained a micronized suspension of budesonide with disodium edetate, sodium chloride, sodium citrate, citric acid, and polysorbate 80 in water for injection. The first nano-suspension from Kraft et al. did not contain information on the formulation. However, the second nano-suspension from Shrewsbury et al. contained submicron budesonide in a sterile aqueous formulation containing surface modifiers, possibly including a cyclodextrin[47], and sodium chloride, citric acid, sodium citrate, and disodium edentate dehydrate in water. Despite the differences, the DPI, pMDI, and suspension for nebulization formulations all deliver solid budesonide particles to the lung following inhalation and utilize particle size reduction to improve the dissolution rate of the drug. The low aqueous solubility (16 μg/mL), high log *P* (3.6), and low molecular weight (430.5 g/mol) promote a model of solubility-limiting drug absorption following inhalation of budesonide particles. However, the novel nano-suspension formulations contain excipients that could improve or augment drug solubility in the lung and subsequent drug absorption following inhalation (Table 2).

Following inhalation of budesonide, t_{max} values were achieved within 0.13–0.58 hours (8–35 minutes) for the DPI devices, 0.15–0.24 hours (9–14 minutes) for micronized suspensions, and 0.051–0.19 hours (3–11 minutes) for nano-sized suspensions with no values reported for the pMDI. Dose-normalized C_{max} values for DPI devices, the pMDI, micronized suspensions, and nano-sized suspensions ranged from 0.9 to 1.8 pg/mL/μg, 0.6 pg/mL/μg (assuming a 2 hours t_{max} because of limited reported data), 0.7 to 1.3 pg/mL/μg, and 1.8 to 2.5 pg/mL/μg, respectively. These C_{max} ranges indicate approximate equivalence for reported maximal concentrations for all methods of budesonide administrations except a twofold increase in reported concentrations for nanoscale suspensions. However, no difference was observed for dose-normalized AUC

Table 1. Properties of inhaled fluticasone propionate.

Delivery device and formulation	Dose (μg)	Pertinent pharmacokinetic findings			Studied population	References
DPI	1000	t_{max}	1.4 ± 1	hours	Healthy human volunteers (plasma samples)	40
Administered as Flutide Diskhaler®, Glaxo Ltd.		C_{max}	0.24 ± 0.1	ng/mL		
Contained microfine fluticasone propionate blended with lactose		AUC	2.44 ± 0.69[a]	ng h/mL		
DPI	1000	t_{max}	1.88 (1.4, 2.38)	hours	Healthy and asthmatic human volunteers (plasma samples)	41
Administered as Flovent®, Diskus®, GlaxoSmithKline		C_{max}	0.35 (0.3, 0.45)	ng/mL		
Contained microfine fluticasone propionate blended with lactose		AUC	2.75 (2.25, 3.45)	ng h/mL		
		MRT	7.1 (5.6–8.5)	hours		
pMDI	1000	t_{max}	1.67 (1.1, 2.25)	hours		
Administered as Flovent®, GlaxoSmithKline		C_{max}	0.25 (0.2, 0.3)	ng/mL		
Contained microcrystalline suspension of fluticasone propionate in a mixture of CFC-11 and CFC-12 with soya lecithin		AUC	1.75 (1.45, 2.15)	ng h/mL		
		MRT	5.3 (4.0–6.6)	hours		
DPI	200	t_{max}	1.5	hours	Healthy human volunteers (plasma samples)	38
Administered as Flovent®, Diskus®, GlaxoSmithKline		C_{max}	0.037	ng /mL		
Contained microfine fluticasone propionate blended with lactose		AUC	0.22	ng h/mL		
		MRT	7.2	hours		
	500	t_{max}	1.5	hours		
		C_{max}	0.094	ng/mL		
		AUC	0.79	ng h/mL		
		MRT	12	hours		
DPI	1000	t_{max}	0.9 (0.68, 1.20)	hours	Stable human asthma patients (plasma samples)	39
Administered as Flixotide®, Accuhaler®, GlaxoSmithKline (Marketed as Flovent®, Diskus® in the United States)		C_{max}	0.09 (0.07, 0.10)	ng/mL		
Contained microfine fluticasone propionate blended with lactose		AUC	0.38[b] (0.30, 0.47)	ng h/mL		
		MRT	8.46 (6.70, 10.7)	hours		

(*Continued*)

Table 1. (*Continued*).

Delivery device and formulation	Dose (μg)	Pertinent pharmacokinetic findings			Studied population	References
DPI	800	AUC	0.256	ng h/mL	Human asthma patients (plasma samples)	42
Administered as Flovent®, Diskus®, GlaxoSmithKline						
Contained microfine fluticasone propionate blended with lactose						
pMDI	704	AUC	0.919	ng h/mL		
Administered as Flovent®, GlaxoSmithKline						
Contained microcrystalline suspension of fluticasone propionate in a mixture of CFC-11 and CFC-12 with soya lecithin						
DPI	1000	$T_{10\%}$	0.19 (0.14, 0.26)[c]	hour	Healthy human volunteers (plasma samples)	30
Administered as Flixotide®, Diskhaler®, GlaxoWellcome		$T_{50\%}$	1.58 (1.14, 2.20)[c]	hours		
Contained microfine fluticasone propionate blended with lactose		$T_{90\%}$	12.3 (7.99, 18.9)[c]	hours		
		MAT	4.29 (2.90, 6.34)[c]	hours		
DPI	1000	$T_{10\%}$	0.26 (0.22, 0.30)[c]	hour		
Administered as Flovent®, Diskus®, GlaxoSmithKline		$T_{50\%}$	2.42 (2.01, 2.91)[c]	hours		
Contained microfine fluticasone propionate blended with lactose		$T_{90\%}$	12.1 (8.76, 16.8)[c]	hours		
		MAT	4.4 (3.26, 5.95)[c]	hours		
pMDI	1000	$T_{10\%}$	0.28 (0.20, 0.38)[c]	hour		
Administered as Flovent®, GlaxoSmithKline		$T_{50\%}$	2.18 (1.77, 2.67)[c]	hours		
Contained microcrystalline suspension of fluticasone propionate in a mixture of CFC-11 and CFC-12 with soya lecithin		$T_{90\%}$	11.4 (8.15, 16.0)[c]	hours		
		MAT	4.31 (3.17, 5.86)[c]	hours		

Values are geometric mean (95% confidence interval, mean ± SD, or median. unless otherwise specified, the units are as follows: t_{max} (hours); C_{max} (ng/mL); AUC (ng h/mL); $t_{1/2}$ (hours); and MRT (hours). MRT, mean residence time; MAT, mean absorption time. [a] AUC_{0-12}; [b] AUC_{0-8}; [c] 90% CI.

Table 2. Properties of inhaled budesonide.

Delivery device and formulation	Dose (μg)	Pertinent pharmacokinetic findings			Studied population	References
DPI	400	t_{max}	0.17	hour	Healthy human volunteers (plasma samples)	38
Administered as Pulmicort Turbohaler®, AstraZeneca		C_{max}	0.45	ng/mL		
Contained micronized budesonide		AUC	0.99	ng h/mL		
		MRT	3	hours		
		$t_{1/2}$	2.1	hours		
	1000	t_{max}	0.17	hour		
		C_{max}	0.9	ng/mL		
		AUC	2.53	ng h/mL		
		MRT	3.9	hours		
		$t_{1/2}$	3.5	hours		
DPI with oral charcoal	1000	t_{max}	0.5 ± 0.18	hour	Healthy human volunteers (plasma samples)	34
Administered as Giona®, Easyhaler®, Orion Pharma		C_{max}	1.22 ± 0.41	ng/mL		
Contained micronized budesonide blended with lactose		AUC	3.48 ± 0.93	ng h/mL		
		MRT	3.05 ± 0.48	hours		
DPI with oral charcoal	1000	t_{max}	0.38 ± .017	hour		
Administered as Pulmicort Turbohaler®, AstraZeneca		C_{max}	1.29 ± 0.44	ng/mL		
Contained micronized budesonide		AUC	3.46 ± 1.13	ng h/mL		
		MRT	2.85 ± 0.38	hours		
DPI	1000	t_{max}	0.28 (0.17, 0.4)	hour	Human asthma patients (plasma samples)	41
Administered as Pulmicort Turbohaler®, AstraZeneca		C_{max}	1.64 (1.46, 1.98)	ng/mL		
Contained micronized budesonide		AUC	4.52 (3.66, 5.68)	ng h/mL		
		MRT	0.6 (0.3 – 0.9)	hour		
DPI	800	t_{max}	0.13 (0.10, 0.16)	hour	Stable human asthmatic patients (plasma samples)	39
Administered as Pulmicort Turbohaler®, AstraZeneca		C_{max}	1.46 (1.18, 1.79)	ng/mL		
Contained micronized budesonide		AUC	3.28 (2.82, 3.81)	ng h/mL		
		MRT	3.47 (3.21, 3.76)	hours		
		$t_{1/2}$	2.63 (2.46, 2.82)	hours		
DPI	600	t_{max}	0.58 (28.9)[a]	hour	Healthy human volunteers (plasma samples)	43
Administered as Pulmicort Turbohaler®, AstraZeneca		C_{max}	0.66 (69.8)[a]	ng/mL		
Contained micronized budesonide		AUC	1.9[b] (57.1)[a]	ng h/mL		
			2.32[c] (47.4)[a]	ng h/mL		
		$t_{1/2}$	2.19	hours		
pMDI	800	C_{2h}	0.47[d]	ng/mL	Human asthma patients (plasma samples)	44
Administered as Pulmicort®, AstraZeneca						
Contained micronized suspension of budesonide with sorbitan trioleate, CFC-11, CFC-12, and CFC-114.						
Nebulized suspension	1000	C_{2h}	0.73[e]	ng/mL		
Administered as Pulmicort Respules®, AstraZeneca						

(*Continued*)

Table 2. (*Continued*).

Delivery device and formulation	Dose (μg)	Pertinent pharmacokinetic findings			Studied population	References
Contained micronized suspension of budesonide with disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80, and water for injection	4000	C_{2h}	2.15[e]	ng/mL		
Nebulized suspension	500	t_{max}	0.24 (0.19–0.3)	hour	Healthy human volunteers (Plasma samples)	45
Administered as Pulmicort Respules®, AstraZeneca		C_{max}	0.66 (0.42–0.91)	ng/mL		
Contained micronized suspension of budesonide with disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80, and water for injection		AUC	1.63 (1.13-2.14)	ng h/mL		
		$t_{1/2}$	5.42	hours		
Nebulized suspension	500	t_{max}	0.14 (0.09–0.18)	hour		
Administered as Nanobudesonide (smaller particle size distribution than Pulmicort Respules®)		C_{max}	1.21 (0.75–1.67)	ng/mL		
Formulation composition not reported		AUC	1.66 (1.28-2.03)	ng h/mL		
		$t_{1/2}$	6.62	hours		
	1000	t_{max}	0.19 (0.1-0.27)	hour		
		C_{max}	2.48 (1.24-3.73)	ng/mL		
		AUC	2.89 (2.12-3.67)	ng h/mL		
		$t_{1/2}$	5.46	hours		
Nebulized suspension	250	t_{max}	0.15 ± 0.12	hour	Healthy adult volunteers (Plasma samples)	46
Administered as Pulmicort Respules®, AstraZeneca		C_{max}	0.30 ± 0.18	ng/mL		
Contained micronized suspension of budesonide with disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80, and water for injection		AUC	048 ± 0.16[d]	ng h/mL		
			0.53 ± 0.18[c]	ng h/mL		
		$t_{1/2}$	2.42 ± 0.68	hours		
Nebulized suspension	60	t_{max}	0.075 ± 0.055	hour		
Administered as nano-scale budesonide suspension		C_{max}	0.11 ± 0.06	ng/mL		
Contained submicron budesonide in a sterile aqueous formulation containing surface modifiers sodium chloride, citric acid, sodium citrate, and disodium edentate dehydrate		AUC	0.066 ± 0.033[d]	ng h/mL		
Incomplete report of formulation composition			0.073 ± 0.024[c]	ng h/mL		
		$t_{1/2}$	1.17 ± 0.56	hours		
	120	t_{max}	0.051 ± 0.025	hour		
		C_{max}	0.24 ± 0.14	ng/mL		
		AUC	0.143 ± 0.070[d]	ng h/mL		
			0.131 ± 0.061[c]	ng h/mL		
		$t_{1/2}$	1.31 ± 0.45	hours		
	240	t_{max}	0.062 ± 0.025	hour		
		C_{max}	0.43 ± 0.25	ng/mL		
		AUC	0.369 ± 0.161[d]	ng h/mL		
			0.422 ± 0.196[c]	ng h/mL		
		$t_{1/2}$	2.33 ± 0.90	hours		

Values are the geometric mean (95% confidence interval), mean ± SD, or median. MRT, mean residence time. Unless otherwise specified, the units are as follows: t_{max} (hours), C_{max} (ng/mL), AUC (ng h/mL), $t_{1/2}$ (hours), MRT (hours). [a]Values are mean (coefficient of variation %); [b]AUC_{0-12}; [c]$AUC_{0-\infty}$; [d]AUC_{0-8}; [e]Not expressly reported by the authors. Values inferred from figures, tables, and methodological descriptions.

values between delivery methods with ranges of 2.5–4.5 pg h/mL/μg for DPI devices, 2.1–3.3 pg h/mL/μg for micronized suspensions, and 1.1–3.3 pg h/mL/μg for nano-sized suspensions with no reported value for the pMDI. As mentioned for inhaled fluticasone propionate, no report was made to control for possible oral ingestion of budesonide following inhalation. In a similar manner, the reported C_{max} and AUC values could have a minor, but nontrivial, contribution of orally absorbed budesonide. The elimination half-life, $t_{1/2}$, for inhaled budesonide also varied by the method of inhalation with DPIs ranging from 2.1 to 3.5 hours, the micronized suspension reporting 2.43 hours, and the nanoscale suspension reporting 1.17–2.33 hours. Of note, Kraft et al. reported much higher $t_{1/2}$ values, from 5.42 to 6.62 hours for inhaled micro- and nano-sized suspensions without corroboration from the other sources, possibly indicating a sampling outlier. Some researchers reported MRT values for DPI devices that ranged from 0.6 to 3.9 hours, indicating varied but relatively rapid drug transit through and low drug retention by the patient.

Beclomethasone dipropionate (beclomethasone 17-monopropionate)

Beclomethasone dipropionate is converted in the lungs via epithelial esterases from a functional prodrug into the active and more potent beclomethasone-17-monopropionate. Therefore, pharmacokinetic studies involving beclomethasone specify the molecule of interest and involve a metabolic process if results are reported for the mono-propionate metabolite. The di- and monopropionate forms have different solubilities (0.13 μg/mL for the dipropionate and 15.5 μg/mL forthe monopropionate) but similar log *P* values (4.9 for dipropionate and 4.3 for monopropionate) and molecular weights (521.1 g/mol for dipropionate and 465.0 g/mol for monopropionate). Although the active metabolite has a 100-fold improvement in aqueous solubility over the dipropionate form, absorption must take place with the prodrug dipropionate before metabolic conversion. Despite these metabolic complications in assessing systemic pharmacokinetics following inhalation of beclomethasone dipropionate, investigators have administered beclomethasone dipropionate as a nebulized solution in addition to the typical DPI and pMDI devices reported by other researchers (Table 3).

Specifically, Esposito-Festen et al. generated very low-dose monodisperse particle-sized aerosols from an alcoholic solution containing budesonide dipropionate and administered them to healthy volunteers[49]. This formulation delivered aerosolized droplets to the lung that contained beclomethasone in solution as a molecular dispersion. In contrast, particle size reduction of the API was utilized for pMDI and DPI formulations. A pMDI formulation containing a suspension of micronized beclomethasone dipropionate in CFC-11 and CFC-12 with oleic acid as a valve lubricant, marketed as Beclovent®, was tested in human patients with and without concomitant oral administration of activated charcoal to eliminate oral ingestion and absorption of the API following inhalation[48]. Pharmacokinetic values were also evaluated for a DPI device used to administer micronized beclomethasone dipropionate on lactose carrier particles, branded as Becodisks®, to stable human asthma patients[39].

Marked differences were observed for inhaled beclomethasone dipropionate, and the active metabolite beclomethasone-17-monopropionate, based on the formulation. T_{max} values for inhaled particulate formulations of beclomethasone dipropionate from DPI and pMDI devices were 0.8–2.5 hours (48–150 minutes). In contrast, t_{max} values were much more rapid for inhaled alcoholic solutions with values of 0.17–0.33 hours (10–20 minutes). Additionally, the dose-normalized C_{max} values for DPI and pMDI devices were 0.41 and 0.94 pg/mL/μg, respectively, whereas normalized AUC values with the same devices were 2.13 and 3.85 pg h/mL/μg. However, when patients received oral charcoal to negate GI absorption of the drug when administered with the pMDI dose, normalized C_{max} and AUC values were 0.71 and 2.40 pg h/mL/μg, indicating substantial increases in plasma concentrations of beclomethasone-17-monopropionate because of oral ingestion and absorption after normal inhalation with the pMDI. These findings are in stark contrast with pharmacokinetic results reported following inhalation of a solubilized form of beclomethasone dipropionate. When administered as a nebulized alcoholic solution, dose-normalized C_{max} values ranged from 3.9 to 9.1 pg/mL/μg. These values resulted in a 4- to 20-fold increase in maximal concentrations compared with inhaled particulate drug via DPI or pMDI devices. Additionally, dose-normalized AUC values for the inhaled alcoholic solution ranged from 6.0 to 16.0 pg h/mL/μg, representing a 2.5- to 22.5-fold increase in drug exposure. The administration of an alcoholic solution of beclomethasone dipropionate promoted much more rapid maximal concentrations of the active metabolite as well as markedly elevated drug concentrations and drug exposure compared with inhalation of solid particulate forms of the API.

Triamcinolone acetonide

Inhaled triamcinolone acetonide was administered to human subjects by both DPI and pMDI devices. The DPI device used was a breath-actuated inhaler, the Ultrahaler®, to optimize lung deposition of the inhaled

Table 3. Properties of inhaled beclomethasone dipropionate (and beclomethasone 17-monopropionate).

Delivery device and formulation	Dose (μg)	Pertinent pharmacokinetic findings			Studied population	References
pMDI	1000	BDP			Healthy human volunteers (plasma samples)	48
Administered as Beclovent®, GlaxoWellcome		t_{max}	0.3 (0.2, 0.5)[a]	hour		
Contained suspension of micronized beclomethasone dipropionate in a mixture of CFC-11 and CFC-12 with oleic acid		C_{max}	0.32[b] (0.18, 0.55)	ng/mL		
		AUC	0.15[b] (0.09, 0.27)	ng h/mL		
		17-BMP				
		t_{max}	1.0 (0.8, 6)[a]	hour		
		C_{max}	0.94[b] (0.67, 1.3)	ng/mL		
		AUC	3.85[b] (2.8, 5.2)	ng h/mL		
		MRT	4.1 (3.5, 4.6)	hours		
		$t_{1/2}$	2.7 (2.1, 3.6)[a]	hours		
pMDI with oral charcoal	1000	BDP			Healthy human volunteers (plasma samples)	
Administered as Beclovent®, GlaxoWellcome		t_{max}	0.5 (0.2, 0.5)[a]	hour		
Contained suspension of micronized beclomethasone dipropionate in a mixture of CFC-11 and CFC-12 with oleic acid		C_{max}	0.46[b] (0.25, 0.72)	ng/mL		
		AUC	0.22[b] (0.13, 0.35)	ng h/mL		
		17-BMP				
		t_{max}	0.8 (0.8, 1)[a]	hour		
		C_{max}	0.71[b] (0.44, 1.1)	ng/mL		
		AUC	2.4[b] (1.5, 3.7)	ng h/mL		
		MRT	3.5 (3, 4)	hours		
		$t_{1/2}$	2.3 (1.7, 5.8)[a]	hours		
DPI	800	17-BMP			Stable human asthma patients (plasma samples)	39
Administered as Becodisks®, Allen & Hanburys		t_{max}	2.5 (1.9, 3.3)	hours		
Contained micronized beclomethasone dipropionate blended with lactose		C_{max}	0.33 (0.28, 0.39)	ng/mL		
		AUC	1.7[c] (1.5, 2.0)	ng h/mL		
		MRT	9.1 (7.1, 11.5)	hours		
		$t_{1/2}$	5.3 (4.1, 7.0)	hours		
Nebulized solution	100	17-BMP: 1.5 μm MMAD			Human patients with stable mild asthma (plasma samples)	49
Administered as a monodisperse aerosal generated by the electrohydrodynamic technique		t_{max}	0.17[b]	hour		
Contained 4% beclomethasone dipropionate solubilized in 97% ethanol		C_{max}	0.39	ng/mL		
		AUC	0.60	ng h/mL		
		17-BMP: 2.5 μm MMAD				
		t_{max}	0.33[b]	hour		
		C_{max}	0.91	ng/mL		
		AUC	1.6	ng h/mL		
		17-BMP: 4.5 μm MMAD				
		t_{max}	0.33[b]	hour		
		C_{max}	0.74	ng/mL		
		AUC	1.2	ng h/mL		

MRT, mean residence time; DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler. [a]Values are median (range); [b]Not expressly reported by the authors. Values inferred from figure, tables, and methodological descriptions; [c]AUC_{0-8}.

powder containing micronized triamcinolone acetonide blended with lactose as a carrier particle[50]. The pMDI formulations included CFC and HFA formulations of triamcinolone acetonide, marketed as Azmacort® and developed as Azmacort® HFA[43,51]. The CFC-based formulation contained a microcrystalline suspension of triamcinolone acetonide in CFC-12 and 1% (w/w) dehydrated alcohol to improve drug loading of the API in the propellant. The Azmacort® HFA inhaler contained a microcrystalline suspension of triamcinolone acetonide in HFA 143-a, but insufficient detail was provided to identify other excipients if present. Both DPI and pMDI formulations utilized particle size reduction to improve the dissolution rate of the API with an insignificant contribution of the alcohol in the CFC-pMDI formulation to alter solubility of triamcinolone acetonide after dose administration. Additionally, Lim et al.[50] administered oral-activated charcoal to some patients to assess the influence of oral ingestion and gut absorption following pMDI and DPI use[50]. Triamcinolone acetonide has the highest aqueous solubility (21 μg/mL) and lowest log *P* value (3.4) for these poorly water-soluble inhaled corticosteroids. However, a log *P* of 3.4 is still very high and suggests good membrane permeability, particularly with a mid-range molecular weight (434.5 g/mol) (Table 4).

Following inhalation, t_{max} values for the DPI device was 0.25 hours (15 minutes) whereas pMDI formulations peaked at 0.66–1.74 hours (40–104 minutes). Despite these differences in the speed to achieve maximal concentrations, dose-normalized C_{max} values were very similar for both DPI and pMDI devices. C_{max} values for the DPI inhaler ranged from 1.77 to 2.25 pg/mL/μg whereas pMDI values ranged from 0.69 to 2.52 pg/mL/μg. In contrast, AUC values were more varied with a range of 6.88–8.10 pg h/mL/μg for the DPI formulation and 2.69–12.90 pg h/mL/μg for the pMDI formulation. This variability could be due to oral ingestion of triamcinolone acetonide as demonstrated by C_{max} ratios between DPI and pMDI formulations of 2.44 under typical usage and 1.56 with oral ingestion of charcoal. A similar pattern was reported for AUC ratios between DPI and pMDI formulations without and with charcoal of 1.99 and 1.44, respectively. No change was reported in the elimination half-life based on device and formulation with values ranging from 2.2 to 2.5 hours.

Comparison of Inhaled corticosteroids

The reduction in inhaled corticosteroid absorption from the lungs is clinically relevant to minimize adverse events associated with systemic drug exposure for all inhaled corticosteroids. All included studies employed a method to enhance drug solubility or improve the rate of drug dissolution including particle size reduction of the API (i.e., micronization or nanoscale particle production) or drug solubilization in a nonaqueous solvent. The methods of solubility enhancement demonstrated that following doses in the μg range, normalized plasma drug concentrations, in the pg mL^{-1} range, and as well as total drug exposure, as indicated by normalized AUC values, remained low for all the formulations and drug delivery devices included. However, the differences in pharmacokinetic parameters within and in-between formulations were illustrative for solubilization effects on pulmonary drug absorption. Specifically, systemic t_{max} values were within 2 hours, with the majority of reported values within 1 hour, for all reported drug-formulation combinations. The fastest relative t_{max} values, when compared between different formulations of the same API, were obtained for nano-budesonide suspensions (≥3 times faster than other formulations) and alcoholic solutions of beclomethasone dipropionate (≥4 times faster than other formulations). These values suggest that increasing the velocity of particle dissolution, through administration of a pre-solubilized drug or through extreme particle size reduction into the nanoscale range, promoted the most rapid drug absorption following inhalation of a poorly water-soluble API[52–54]. However, no consistent differences were observed in dose-normalized C_{max} and AUC values for DPI, pMDI, or nebulized suspensions when the formulation contained micro- to nano-meter range particles, suggesting that total drug absorption was eventually achieved from the lungs. A striking elevation in drug concentrations and drug exposure was observed for nebulized alcohol solutions, suggesting that pre-solubilized drug actually can improve the extent of drug absorbed from the lungs[55].

Inhaled antifungals

Most typical fungal infections are found on the skin, genitorurinary, or GI tract and involve superficial infiltration of the fungi into the epithelium or mucosal membranes and are readily treated with topical or oral antifungal therapy[56]. However, systemic fungal infections can involve numerous organs and systems and are much more difficult to treat with some causative organisms and infections associated with very high rates of mortality[57–59]. Many systemic fungal infections begin with the inhalation of fungal spores, or conidia, into the deep lung followed by the establishment of an infection and potential dissemination to the distal organs via the systemic circulation[60]. However, systemically administered antifungal agents are limited by poor tissue penetration into lung tissue and associated with high rates of adverse events and the potential for serious drug

Table 4. Properties of inhaled triamcinolone acetonide.

Delivery device and formulation	Dose (μg)	Pertinent pharmacokinetic findings			Studied population	References
DPI	200	t_{max}	0.25 (0.25–1.00)[a]	hour	Healthy human volunteers (plasma samples)	50
Administered using the breath-actuated Ultrahaler®, Aventis Pharma		C_{max}	0.45 (30.50)[a]	ng/mL		
Contains micronized triamcinolone acetonide blended with lactose		AUC	1.62 (20.80)[a]	ng h/mL		
		$t_{1/2}$	2.30 (12.61)[a]	hours		
	450	t_{max}	0.25 (0.25–0.50)[a]	hour		
		C_{max}	0.88 (26.08)[a]	ng/mL		
		AUC	3.13 (15.04)[a]	ng h/mL		
		$t_{1/2}$	2.24 (10.12)[a]	hours		
	900	t_{max}	0.25 (0.25–1.00)[a]	hour		
		C_{max}	1.59 (33.39)[a]	ng/mL		
		AUC	6.19 (27.29)[a]	ng h/mL		
		$t_{1/2}$	2.52 (18.55)[a]	hours		
pMDI	800	t_{max}	1.74 (44.1)[a]	hour	Healthy human volunteers (plasma samples)	51
Administered as Azmacort®, Aventis Pharma		C_{max}	0.92 (33.4)[a]	ng/mL		
Contained microcrystalline suspension of triamcinolone acetonide in CFC-12 and 1% (w/w) dehydrated alcohol		AUC	4.96 (40.7)[a]	ng h/mL		
			5.12[b] (39.8)[a]	ng h/mL		
		$t_{1/2}$	2.52	hours		
pMDI with oral charcoal	800	t_{max}	0.66 (31.4)[a]	hour		
Administered as Azmacort®, Aventis Pharma		C_{max}	0.55 (57.0)	ng/mL		
Contained microcrystalline suspension of triamcinolone acetonide in CFC-12 and 1% (w/w) dehydrated alcohol		AUC	1.95 (62.2)[a]	ng h/mL		
			2.15[b] (56.5)[a]	ng h/mL		
		$t_{1/2}$	2.47	hours		

pMDI Administered as Azmacort® HFA 225, Aventis Pharma Contained microcrystalline suspension of triamcinolone acetonide in HFA 143-a (*uncertain formulation due to acquisitions*)	675	t_{max} C_{max} AUC $t_{1/2}$	1.59 (57.6)[a] 1.70 (53.2)[a] 8.32[c] (53.7)[a] 8.71[b] (52.1)[a] 2.26	hours ng/mL ng h/mL ng h/mL hours	Healthy human volunteers (plasma samples)	43
DPI Administered using Ultrahaler®, Aventis Pharma Contains micronized triamcinolone acetonide blended with lactose pMDI Administered as Azmacort®, HFA 225, Aventis Pharma Contained microcrystalline suspension of triamcinolone acetonide in HFA 143-a	720 for DPI 450 for pMDI	Ratio of DPI to pMDI C_{max} 2.44 (75)[a] Ratio of DPI to pMDI AUC 1.96 (77)[a]			Healthy human volunteers (plasma samples)	50
DPI Administered using Ultrahaler®, Aventis Pharma with oral charcoal Contains micronized triamcinolone acetonide blended with lactose pMDI Administered as Azmacort®, Aventis Pharma with oral charcoal Contained microcrystalline suspension of triamcinolone acetonide in HFA 143-a	720 for DPI 450 for pMDI	Ratio of DPI to pMDI C_{max} 1.56 (35)[a] Ratio of DPI to pMDI AUC 1.44 (42)[a]				

Values are the geometric mean (95% confidence interval), mean ± SD, or median. DPI, dry powder inhaler; pMDI, a pressurized metered-dose inhaler. Unless otherwise specified, the units are as follows: t_{max} (hours), C_{max} (ng/mL), AUC (ng/mL), $t_{1/2}$ (hour), MRT (hours). [a] Values are mean (coefficient of variation %); [b] $AUC_{0-\infty}$; [c] AUC_{0-12}.

interactions[61,62]. Therefore, targeted antifungal delivery to the lung could elevate and retain drug concentrations in the lung for improved efficacy and reduce systemic drug exposure to reduce adverse events and drug interactions. Theoretically, an ideal inhaled antifungal would have minimal drug absorption following inhalation for optimum efficacy and minimal adverse events and drug interactions.

Antifungal pharmacology, like that for all anti-infective agents, focuses on selective targeting of microbiological or biochemical differences between the pathogen and the host. For fungal infections, the available targets have been difficult to identify and optimize because of the similarities in eukaryotic cellular physiology and biochemical pathways between fungal and animal cells. However, the most commonly used antifungals in systemic fungal infections target ergosterol, a cellular membrane stabilizer and a fungal equivalent to animal cholesterol. Polyene antifungals, including amphotericin B, form drug–ergosterol complexes to create nonselective transmembrane channels that disrupt cellular integrity. The low aqueous solubility, log *P* value, and relatively large molecular weight (0.25 μg/mL, 1.6, and 924 g/mol, respectively, for amphotericin B) allow the polyene to partition into fungal cell membranes for pharmacologic activity[63]. Triazole antifungals, including itraconazole, inhibit ergosterol biosynthesis through reversible antagonism of fungal cell cytochrome P450 isomers[64]. Triazoles are also very poorly water soluble but with much higher log *P* values indicative of better lipophilicity (~0.001 μg/mL and 5.7 for itraconazole, respectively)[65,66]. The low solubility and high lipophilicity of triazole antifungals as well as relatively large molecular weight (705.6 g/mol for itraconazole) allow them to be absorbed into fungal cells and be metabolized by fungal cytochrome P450s responsible for normal ergosterol biosynthesis. Accordingly, the evaluation of antifungal pharmacokinetic parameters following inhalation will elucidate additional influences of drug solubilization and solubility enhancement on drug absorption.

Amphotericin B

The medical management of fungal infections was limited by poor pharmacologic selectivity between eukaryotic cellular physiology in both fungal and animal cells until the identification and development of amphotericin B in the mid-twentieth century[67]. Amphotericin B preferentially forms nonselective pore or channel complexes with fungal cell membrane ergosterol, a membrane stabilizer analogous to cholesterol in animal cell membranes, to cause a loss of osmotic integrity and ultimately fungal cell death[68,69]. These ergosterol–amphotericin B complexes form through nonspecific Van Der Waals forces between the hydrophobic region of the amphiphilic amphotericin B molecule and the lipophilic ergosterol molecule[70]. Amphotericin B is a 38-membered cyclic lactone ring composed of a distinct lipophilic region, with seven conjugated ester bonds, and a separate hydrophilic region with ester and ether bonds, a carboxylic acid group, a primary amino group in an attached sugar moiety, and several hydroxyl groups. Amphotericin B has a low aqueous solubility (0.25 μg/mL), a large molecular weight (924 g/mol), and lower than expected log *P* value (1.6) that allow the API to distribute into the membrane to be pharmacologically active (Table 5).

Accordingly, four commercially available amphotericin B formulations use stabilizers and/or solubilizers to produce pharmaceutically acceptable products. Although all have been administered in an off-label manner via inhalation for analysis of efficacy and tolerability, only reports with the amphotericin B deoxycholate (Fungizone®, hereafter referred to as AmB-d) and liposomal amphotericin B (AmBisome®, hereafter referred to as L-AmB) formulations have associated systemic pharmacokinetic parameters[73,74]. Some investigators have also reported lung tissue or fluid drug concentrations to demonstrate high drug concentrations in the lung following inhalation[72,74–76]. Additionally, Diot et al.[71] reported serum amphotericin B concentrations following nebulization of pure amphotericin B powder and water dispersions without additional excipients. AmB-d is a suspension for reconstitution containing deoxycholate as a solubilizer and stabilizer and sodium phosphates as a buffer that forms a colloidal dispersion when reconstituted. L-AmB is suspension for reconstitution containing a bilayered liposome of amphotericin B in lipid membranes of hydrogenated soy phosphatidylcholine, cholesterol, and distearoylphosphatidylglycerol (2:0.5:0.8 ratio) in a 1:10 ratio. Aerosols of both products have been inhaled using various nebulizers, and systemic pharmacokinetic properties have varied widely.

Following inhalation of all formulations, lung t_{max} values were approximately 1 hour whereas t_{max} values in bronchoalveolar lavage (BAL) fluid following inhalation of AmB-d ranging from 0.5 to 4 hours (30–240 minutes). Similarly, serum t_{max} values following inhalation of pure amphotericin B ranged from 0.5 to 3.5 hours (30–210 minutes). However, there was great variability in dose-normalized C_{max} and AUC values for lung tissue, BAL, and plasma/serum values based on the formulation. An inhaled dose in the mg range, concentration values in serum, lung tissue, and BAL fluid ranged spanned over three orders of magnitude across the μg/mL to ng/mL range. Specifically, dose-normalized C_{max} values in serum following inhalation of pure amphotericin B ranged

Table 5. Properties of inhaled amphotericin B.

Delivery device and formulation	Dose (mg)	Pertinent pharmacokinetic findings			Studied population	References
Nebulized suspension	5	Fisoneb® (Ultrasonic Nebulizer)			Human patients with posttuberculosis lung aspergilloma (serum samples)	71
Administered as a nebulized suspension of pure amphotericin B in sterile water (5 mg in 5 mL)		t_{max}	0.5	hour		
		C_{max}	21.0 ± 1.4	ng/mL		
		DP100® (Ultrasonic Nebulizer)				
		t_{max}	3.5	hours		
		C_{max}	16.8 ± 6.9	ng/mL		
		Respirgard II® (Air-jet Nebulizer)				
		t_{max}	1.5	hours		
		C_{max}	5.7	ng/mL		
Nebulized suspension	5	t_{max}	0.5	hour	Healthy adult sheep (bronchial wash fluid samples)	72
Administered as a colloidal dispersion of AmB-d, Fungizone®, diluted with 5% glucose		C_{max}	233.8 ± 138.3	ng/mL		
Contained amphotericin B, sodium deoxycholate, and sodium phosphates	30	AUC	481.8 ± 204.1	ng h/mL		
		t_{max}	0.5	hour		
		C_{max}	217.7 ± 53.8	ng/mL		
		AUC	11990 ± 163.8	ng h/mL		
Nebulized suspension	10 twice daily (usual dose)	$C_{1\,h}$	> 200 to 900 ($n = 5$) Only 2 patients had detectible levels	ng/mL	Long-term prophylaxis in human lung transplant patients (plasma samples)	73
Administered as a colloidal dispersion of AmB-d, Fungizone®						
Contained amphotericin B, sodium deoxycholate, and sodium phosphates						
Nebulized suspension	20 twice daily (usual dose)	$C_{1\,h}$	> 200	ng/mL		
Administered as a nebulized suspension of L-AmB, AmBisome®			$n = 4$			
Contains amphotericin B intercalated into a liposomal membrane (hydrogenated soy phosphatidylcholine, cholesterol, distearoylphosphatidylglycerol, α-tocopherol) with sucrose and disodium succinate hexahydrate.						

(*Continued*)

Table 5. (*Continued*).

Delivery device and formulation	Dose (mg)	Pertinent pharmacokinetic findings			Studied population	References
	30	t_{sample}	0.53 ± 0.17	hour	Human lung transplant patients (plasma, BAL, and lung tissue samples taken sequentially)	74
Administered as a colloidal dispersion of AmB-d, Fungizone®		C_{plasma}	23 ± 67[a]	ng/g		
		t_{sample}	0.67 ± 0.14	hour		
Contained amphotericin B, sodium deoxycholate, and sodium phosphates		C_{uBAL}	680 ± 360	ng/g		
		t_{sample}	0.73 ± 0.13	hour		
		C_{IBAL}	500 ± 0.13	ng/g		
		t_{sample}	0.83 ± 0.10	hour		
		C_{lung}	29,600[b]	ng/g		
Nebulized suspension	6	t_{max}	4	hours	Human lung transplant patients (BAL fluid sample)	75
Administered as a colloidal dispersion of AmB-d, Fungizone®		C_{max}	15,750 (10,930–20,580)	ng/mL		
Contained amphotericin B, sodium deoxycholate, and sodium phosphates						
Nebulized suspension	35.4 ± 6.2	C_{max}	22,050 ± 5581	ng/g	Healthy rats (lung tissue samples)	76
Administered as a colloidal dispersion of AmB-d, Fungizone®						
Contained amphotericin B, sodium deoxycholate, and sodium phosphates						
Nebulized suspension	57.2 ± 10.2	C_{max}	21,650 ± 1741	ng/g		
Administered as a nebulized suspension of L-AmB, AmBisome®						
Contains amphotericin B intercalated into a liposomal membrane (hydrogenated soy phosphatidylcholine, cholesterol, distearoylphosphatidylglycerol, α-tocopherol) with sucrose and disodium succinate hexahydrate.						

Values are the median or mean ± SD. AmB-d, amphotericin B deoxycholate; L-AmB, liposomal amphotericin B; t_{sample}, time after completion of dose until sample was taken (hours) $C_{plasma, uBAL, IBAL, lung}$: concentration in the plasma, upper lung bronchoalveolar lavage fluid, lower lung bronchoalveolar lavage fluid, and lung tissue respectively. [a]Only 1/8 samples had a detectible amphotericin B concentration (value for $n = 1$); [b]Only 2/6 samples had detectible amphotericin B concentrations (value for $n = 2$).

from 1.1 to 4.2 ng/mL/mg whereas plasma C_{max} values ranged from 0.8 to 45 ng/mL/mg following inhalation of AmB-d and was 5 ng/mL/mg for L-AmB. In stark contrast, C_{max} values ranged from 7.3 to 2625 ng/mL/mg for BAL fluid and from 623 to 987 ng g/mg for lung tissue following inhalation of AmB-d. The dose-normalized lung tissue C_{max} value was also 379 ng/g/mg following inhalation of L-AmB. The dose-normalized AUC following inhalation of AmB-d in BAL fluid ranged from 40 to 96 ng h/mL/mg. The wide range of observed differences in these pharmacokinetic parameters based on the formulation obfuscated the trends for absorption of inhaled amphotericin B. However, the ratio of lung to plasma concentrations for inhaled AmB-d was over 1000:1, indicating negligible drug absorption following inhalation.

Itraconazole

Itraconazole must distribute in fungal cells to inhibit the cytochrome P450 enzymes responsible for ergosterol biosynthesis. However, itraconazole has dissolution-limited absorption because of the extremely low aqueous solubility (1 ng/mL). Several particle engineering technologies, including spray-freeze into cryogenic liquid (SFL)[77], ultra-rapid freezing (URF)[78], and evaporative precipitation into aqueous solution (EPAS)[79] have been investigated with itraconazole as a model API[80]. These processes have been reviewed elsewhere, but briefly produce amorphous (SFL and URF) or crystalline (EPAS) nano-structured powder agglomerates with enhanced dissolution properties[81]. These engineered powders have been nebulized as dispersions to rodents to evaluate the pharmacokinetic parameters following inhalation[80,82–84]. Most of these manuscripts reported lung tissue and plasma drug concentrations allowing more-direct evaluation of drug absorption from the lungs. Additionally, these researchers have provided detailed formulation information allowing a more thorough comparative analysis of the contributing factors involved in solubility and solubilization on pulmonary drug absorption. Specifically, EPAS formulations contained itraconazole and surfactant(s) including polysorbate 20 or polysorbate 80 and poloxamer 407. SFL formulations contained polysorbate 80 with or without poloxamer 407. In contrast, the reported URF formulation contained mannitol and lecithin (Table 6).

Following inhalation, lung t_{max} values ranged from 0.5 to 1.0 hour (30–60 minutes) for all itraconazole formulations whereas plasma t_{max} were delayed with values of 5.4 hours (342 minutes) for SFL itraconazole and 2.0 hours (120 minutes) for URF itraconazole. Dose-normalized lung C_{max} values were 1.7 μg/g/mg for the crystalline EPAS formulation with polysorbate 20. However, normalized maximal lung concentrations increased approximately threefold, to 5.4 μg/g/mg, when containing polysorbate 80 and poloxamer 407. This elevated lung concentration was associated with a low normalized plasma C_{max} value of 0.44 μg/mL/mg. In comparison, the dose-normalized lung C_{max} value for amorphous SFL formulations containing only polysorbate 80 was 0.48 μg/g/mg. The SFL formulation maximal lung concentrations also increased to 1.1–2.4 μg/g/mg when poloxamer 407 was added. The corresponding SFL itraconazole, containing polysorbate 80 and poloxamer 407, produced plasma C_{max} values from 0.1 to 0.2 μg/mL/mg and were much lower than those reported for the comparable EPAS formulation. In contrast, the amorphous URF formulation contained only mannitol and lecithin but had a high dose-normalized lung C_{max} value of 3.0 μg/g/mg but low plasma C_{max} value of 0.2 μg/mL/mg. Similar trends were observed for dose-normalized AUC values. Namely, the addition of poloxamer 407 to EPAS formulations increased normalized lung AUC values from 8.7 up to 14.8 μg h/g/mg and SFL formulations from 1.6 μg h/g/mg to a range of 5.8–15.1 μg h/g/mg. The normalized lung AUC values for URF itraconazole of 21.1 μg h/g/mg were also the highest reported. Dose-normalized plasma AUC values also followed lung AUC trends with a range of 0.1–0.3 μg h/g/mg for SFL itraconazole that contained polysorbate and poloxamer achieving whereas the URF formulation produced a normalized plasma AUC of 0.8 μg h/g/mg. Despite these consistent trends in concentration and AUC values for EPAS, SFL, and URF itraconazole formulations, the lung elimination half-life was variable. The $t_{1/2}$ ranges for itraconazole were 6.7–7.2 hours for EPAS, 2.3–5.5 hours for SFL, and 7.4 for URF and indicate variability independent of formulation, crystallization state, and other pharmacokinetic parameters.

In addition to comparison of observable and dose-normalized pharmacokinetic properties, reported itraconazole concentrations and AUC values in lung tissue and plasma from the same study population allow calculation of drug ratio values and distribution coefficients. Specifically, mice with a lung fungal infection had a lung to plasma C_{max} ratio of 59:1 for crystalline EPAS itraconazole whereas mice administered amorphous SFL itraconazole had a ratio of 12:1. In comparison, healthy mice administered SFL itraconazole had C_{max} lung to plasma ratios of 112:1 whereas mice that received amorphous URF drug had a ratio of 13:1. A lung to blood partition coefficient can also be calculated using a ratio of lung AUC and plasma AUC values. The calculated partition coefficients were 57 for SFL and 21 for URF.

Table 6. Properties of inhaled itraconazole.

Delivery device and formulation	Dose (mg)	Pertinent pharmacokinetic findings				Studied population	References
Nebulized suspension	10	t_{max}	0.5		hour	Healthy mice (lung tissue samples)	83
Administered as a nebulized suspension of EPAS itraconazole		C_{max}	16.8		µg/g		
		AUC	86.8		µg h/g		
Contains nanoparticulate itraconazole with polysorbate 20		$t_{1/2}$	6.7		hours		
Nebulized suspension		t_{max}	1.0		hour		
Administered as a nebulized suspension of SFL		C_{max}	4.8		µg/g		
		AUC	15.8		µg h/g		
Contains nanoparticulate itraconazole with polysorbate 80		$t_{1/2}$	2.3		hours		
Nebulized suspension		t_{max}	1.0		hour		
Administered as a nebulized suspension of SFL itraconazole		C_{max}	13.4		µg/g		
		AUC	79.8		µg h/g		
Contains nanoparticulate itraconazole with polysorbate 80 and poloxamer 407		$t_{1/2}$	5.5		hours		
Nebulized suspension	4.8		Lung	Plasma		Aspergillus infected mice (lung and plasma samples)	82
Administered as a nebulized suspension of EPAS itraconazole		t_{max}	0.5		hour		
		C_{max}	25.9	0.44	µg/g		
Contains nanoparticulate itraconazole with polysorbate 80 and poloxamer 407		AUG	70.9		µg h/g		
		$t_{1/2}$	7.2		hours		
Nebulized suspension	4.8	t_{max}	0.5		hour		
Administered as a nebulized suspension of SFL itraconazole		C_{max}	5.3	0.44	µg/g		
Contains nanoparticulate itraconazole with polysorbate 80 and poloxamer 407		AUC	28.0		µg h/g		
		$t_{1/2}$	2.9		hours		
Nebulized suspension	5.7		Lung	Plasma		Healthy mice (lung and plasma samples)	84
Administered as a nebulized suspension of SFL itraconazole		t_{max}	1.0	5.4	hour		
		C_{max}	13.4	0.12	µg/g		
Contains nanoparticulate itraconazole with polysorbate 80 and poloxamer 407		AUC	85.8	1.69	µg/g		
		$t_{1/2}$	5.5	3.7	hours		
Nebulized suspension	7.1		Lung	Plasma		Healthy mice (lung and plasma samples)	80
Administered as a nebulized suspension of URF itraconazole		t_{max}	0.5	2.0	hours		
		C_{max}	21.1	1.64	µg/g		
Contains nanoparticulate itraconazole with mannitol and lecithin		AUC	149.9	5.6	µg/g		
		$t_{1/2}$	7.4	3.6	hours		

Values are the geometric mean. EPAS, evaporative precipitation into aqueous solution (crystalline nanoparticles); SFL, spray freeze into liquid (amorphous nanoparticles); URF, ultra-rapid freezing (amorphous nanoparticles).

Comparison of Inhaled Antifungals

Inhaled amphotericin B and itraconazole demonstrated more variable pharmacokinetic parameters compared with inhaled corticosteroids due, in part, to dose differences. These differences can be attributed, in part, to the physicochemical differences between inhaled corticosteroids and inhaled antifungals. Inhaled antifungal doses were also very large, in the milligram range, and produced plasma concentrations in the μg/mL to ng/mL range for amphotericin B and μg/mL for itraconazole whereas inhaled corticosteroid doses were much smaller, in the microgram range, and produced plasma concentrations in the ng/mL to pg/mL range. Although the scale of dose to affect concentrations was conserved between the agents, the deposition mass of inhaled antifungals was potentially several orders of magnitude larger than for inhaled corticosteroids and could affect the absorption kinetics of the inhaled API[85].

The incorporation of surface-active excipients in the nebulized formulation of amphotericin B elevated the dose-normalized plasma C_{max} range from 1.1 to 4.2 μg/mL for AmB dispersion to 0.8–45 μg/mL for AmB-d. Inhaled AmB-d also produced very high normalized lung tissue C_{max} values from 627 to 987 μg kg/mL/mg. The relative ratio of lung to plasma concentrations for inhaled AmB-d of 1000:1 suggests very low drug absorption despite the presence of a surface-active agent, deoxycholate. Although insufficient data were available for evaluation, L-AmB only elevated plasma concentrations by a factor of 10 and would not significantly improve drug absorption from the lung.

Inhaled itraconazole allows a more thorough analysis of formulation effects and drug solubilization on pulmonary drug absorption. For example, the addition of a second surface-active agent, poloxamer 407, increased dose-normalized lung concentrations by 2–5 times and normalized lung AUC values by 2–9 times for both crystalline EPAS and amorphous SFL itraconazole formulations compared with only a polysorbate surfactant. These increases suggest that itraconazole improved inhaled particle deposition in the lung or aided in drug wetting and solubilization in lung fluid as has been suggested for other routes of administration[86,87]. Inhaled URF itraconazole contained lecithin instead of poloxamer 407 but produced the highest dose-normalized lung AUC values despite consistent lung C_{max} values, suggesting that drug wetting by a surface-active agent could be a probable mechanism of improved lung drug exposure and lung concentrations. However, elevated lung concentrations and drug exposure did not correlate to improved drug absorption in the lungs. Specifically, lung to plasma concentration ratios suggested marked drug retention in the lungs with high AUC-based partition coefficients between lung tissue and plasma. In addition, comparison of dose-normalized C_{max} and AUC values for formulation-matched crystalline EPAS and amorphous SFL formulations suggest that inhalation of crystalline itraconazole dispersions led to higher drug concentrations and AUC values in the lung and plasma. The authors suggest that physiologic factors of mucociliary clearance of amorphous particles or other biopharmaceutical process resulted in lower tissue concentrations of amorphous SFL itraconazole.

Inhaled oligopeptides

Recent trends in biotechnology have led to a surge of protein and peptide candidate drug molecules[88]. However, formulation and effective noninvasive delivery of these APIs have been very challenging[89–91]. The pulmonary delivery of proteins and peptides as a route for systemic drug delivery is intended to improve systemic bioavailability and reduce the pharmacokinetic variability compared with oral administration. Therefore, goal for most pulmonary peptide administration is typically systemic drug absorption instead of local action in the lungs. However, some therapeutic peptides could exert local action in the lung and targeted delivery could minimize systemic drug exposure. Although several manuscripts have been published that review inhalation of proteins and peptides[5,6,8,92], examples of small molecular weight cyclic peptides with low aqueous solubility are pertinent to an examination of the influence of solubility and solubilization on pulmonary absorption. These agents include the immunosuppressant cyclosporine and an investigational substance P and neurokinin antagonist, FK224. Cyclosporine, a relatively small (1203 g/mol) cyclic undecapeptide, is very poorly water soluble (0.03 μg/mL) with a high log *P* value (2.9). FK224 is also a small cyclic hexapeptide (1041 g/mol) and also has low aqueous solubility (21 μg/mL) and a lower log *P* value (1.3).

Cyclosporine

Cyclosporine is a polypeptide immunosuppressant used primarily to prevent tissue rejection after organ and tissue transplants through inhibition of signaling pathways involved in normal T-cell activation. Although effective following lung transplantation, acute rejection can occur because of delays in drug distribution into lung tissue following systemic drug administration. Additionally, targeting immunosuppressant delivery to the lung can reduce adverse events associated with systemic immunosuppression. Initial pharmacokinetic experiments with inhaled cyclosporine used nebulized alcoholic solutions, associated with

poor patient tolerability and high rates of adverse events[93–95], or nebulized propylene glycol solutions[96–98]. A nebulized suspension of cyclosporine in multi-lamellar dilauroylphosphatidylcholine liposomes was also investigated in dogs[99,100]. Recently, a nanoscale amorphous dispersion of cyclosporine was produced by controlled precipitation (CP), a stabilized anti-solvent precipitation, and nebulized to mice[101]. The use of provided or estimated dose masses for pharmacokinetic parameter normalization produced study-dependent variability in calculated values. Therefore, dose normalization of C_{max} and AUC values was generally performed with the reported mass-based dosing (mg/kg) rather than the dose mass comparisons used for earlier poorly water-soluble APIs (Table 7).

Following inhalation of an alcoholic solution of cyclosporine, lung and whole blood t_{max} values ranged from 0.5 to 1.0 hours (30–60 minutes) whereas propylene glycol solutions achieved more variable t_{max} values of 0.1–4.6 hours (6–276 minutes) in the lung and 0.1–2.0 hours (6–120 minutes) in the blood. Aerosolization of the liposomal cyclosporine had a t_{max} of 0.5 hours (30 minutes) in lung tissue but was faster in the blood with a value of 0.25 hours (15 minutes), indicating very rapid absorption following inhalation. The nebulized CP nanoscale dispersion also produced a similar lung t_{max} value, 1.0 hour (60 minutes) but with a delayed blood t_{max} value, 3.7 hours (222 minutes). The nebulized alcoholic cyclosporine solution produced dose-normalized C_{max} values from 33 to 35 μg kg/g/mg in the lung and 0.7 to 0.8 μg kg/mL/mg in the blood that then decreased to trough concentration ranges from 2.2 to 4.1 μg kg/g/mg in the lung and 0.1 to 0.2 μg kg/mL/mg in the blood. In contrast, nebulized propylene glycol solutions produced markedly lower normalized C_{max} values from 1.3 to 6.8 μg kg/g/mg in the lung and 0.04 to 0.2 μg kg/mL/mg in the blood. Comparable values were observed for dose-normalized C_{max} values for the amorphous CP dispersion in the lung, 3.0 μg kg/g/mg, and blood, 0.1 μg kg/mL/mg. Even lower normalized C_{max} values were observed following inhalation of liposomal cyclosporine in lung tissue, 0.2–0.3 μg kg/g/mg, and blood, 0.002–0.01 μg kg/mL/mg. Inconsistency in dose-normalized AUC values was observed for inhaled alcoholic solutions with values of 96–138 μg h/kg/g/mg in the lung and 5.1–5.5 μg h/kg/mL/mg in the blood when the dose was 3–5 mg/kg but 20–24 μg h/kg/g/mg in the lung and 25–27 μg h/kg/mL/mg in the blood when the dose was increased to 10–25 mg/kg. Similar inconsistencies were observed following inhalation of the propylene glycol solution with normalized AUC values of 0.05–0.1 μg h/kg/mL/mg in the blood at doses of 4.4–9.7 mg/kg (no lung tissue values reported for that dose range) and increasing to 11–46 μg h/kg/g/mg in the lung and 0.8–1.7 μg h/kg/mL/mg in the blood when the dose was increased to 8.4–112.6 mg/kg. Comparable normalized values were calculated for inhaled CP cyclosporine with a lung value of 41 μg h/kg/g/mg and blood value of 2.8 μg h/kg/mL/mg. The reported pharmacokinetic parameters for both lung and plasma also allow calculation of concentration ratios and partition coefficients for inhaled cyclosporine formulations. Calculated drug concentration ratios were 40:1 up to 50:1 for alcoholic solutions, 30:1 up to 42:1 for propylene glycol solutions, 25:1 up to 100:1 for liposomal suspensions, and 28:1 for amorphous CP dispersions. The corresponding partition coefficients were 1–27 for inhaled alcoholic solutions, 14–27 for propylene glycol solutions, and 15 for the CP dispersion.

FK224

FK224 is an investigational cyclic hexapeptide (L-Ser-L-Thr-L-Leu-D-Phe-L-allo-Thr-L-Asp-NH_2) used as a substance P and neurokinin antagonist with potential utilization in the management of conditions associated with neurotransmitter release, such as depression, analgesia, nociception, inflammation, and nausea and emesis[102–104]. However, very low bioavailability was observed following oral administration because of GI proteolytic degradation as well as formulation difficulty prompting dose limitations because of the physicochemical properties of the drug[105]. Two publications have investigated systemic pharmacokinetic parameters following pulmonary delivery of FK224 with different mechanisms of solubility enhancement[105,106]. Specifically, a micronized coprecipitate of β-cyclodextrin and FK224 was incorporated into a CFC-based pMDI as well as with lactose carrier particles for a DPI formulation (Table 8).

The addition of β-cyclodextrin decreased plasma t_{max} values in rats to 0.25 hour (15 minutes) compared with a value of 1.0 hour (60 minutes) when no cyclodextrin was present. This value was clearly different for pMDI- and DPI-administered formulations in humans with values of 2.7–3.0 hours (162–180 minutes) and 0.7–2.2 hours (42–132 minutes), respectively. Increasing concentrations of β-cyclodextrin also affected pharmacokinetic parameters in rats when administered drug via a pMDI device with dose-normalized plasma C_{max} values increasing from 0.01 to 0.03 μg kg/mL/mg, to 0.09 μg/kg/mL/mg for API to cyclodextrin ratios of 1:0, 1:1, and 1:7, respectively, with corresponding dose-normalized AUC values of 0.06, 0.43, and 1.35 μg h/kg/mL/mg. The marked increase in both maximal plasma concentrations and drug exposure from FK224 without cyclodextrin up to a 1:7 mixture of API and cyclodextrin corresponded to an increase in drug solubility from 21 to 1 mg/mL. When a 1:1 FK224 : β-cyclodextrin pMDI was administered to humans, dose-normalized C_{max} values

Table 7. Properties of inhaled cyclosporine.

Delivery method and formulation	Dose	Pertinent pharmacokinetic findings				Studied population	References
Nebulized solution	1 mg/kg	$C_{lung,\ trough}$	2.56 ± 1.33		µg/g	Rats having received a lung transplant (whole blood samples)	94
Administered as a solution of cyclosporine in 100% alcohol (40 mg/mL)		$C_{blood,\ trough}$	0.16 ± 0.08		µg/mL		
No other excipients were used		L/B Ratio[a]	16.0				
	2 mg/kg	$C_{lung,\ trough}$	4.41 ± 1.50		µg/g		
		$C_{blood,\ trough}$	0.27 ± 0.10		µg/mL		
		L/B Ratio[a]	16.6				
	3 mg/kg	$C_{lung,\ trough}$	12.35 ± 8.83		µg/g		
		$C_{blood,\ trough}$	0.73 ± 0.22		µg/mL		
		L/B Ratio[a]	17.0				
Nebulized solution			Lung	Blood		Healthy rats (lung and blood samples)	95
Administered as a solution of cyclosporine in 100% alcohol (40 mg/mL)	3 mg/kg	t_{max}[b]	0.5	0.5	hour		
		C_{max}[b]	>100	>2.5	µg/g		
No other excipients were used		AUC	413.32	15.16	µg h/g		
		L/B Ration[c]	27.3				
	5 mg/kg	t_{max}[b]	1.0	1.0	hour		
		C_{max}[b]	>175	>3.5	µg/mL		
		AUC	477.96	27.45	µg h/mL		
		L/B Ration[c]	17.4				
Nebulized solution			Lung	Blood		Healthy rats (lung and blood samples)	93
Administered as a solution of cyclosporine in 95% alcohol (33.3–3.3 mg/mL)	10 mg/kg	AUC	200	253	µg h/g		
No other excipients were used	25 mg/kg	AUC	588	684	µg h/g		
Nebulized solution	300 mg	t_{max}	1.0		hour	Human lung transplant recipients with persistent acute rejection (whole blood samples)	97
Administered as a solution of cyclosporine in propylene glycol (62.5 mg/mL)		C_{max}	0.23 ± 0.13		µg/mL		
No other excipients were used		C_{trough}	0.02 ± 0.02		µg/mL		
Nebulized solution	300 mg	t_{max}	0.68 ± 0.30		hour	Human lung transplant recipients (whole blood samples)	96
Administered as a solution of cyclosporine in propylene glycol (62.5 mg/mL)		C_{max}	0.21 ± 0.09		µg/mL		
No other excipients were used		AUC	1.03 ± 0.43		µg h/mL		
		$t_{1/2}$	40.7 ± 17.7		hours		
Nebulized solution			Lung	Blood		Healthy rats (lung and blood samples)	98
Administered as a solution of cyclosporine in propylene glycol (62.5 mg/mL)	8.4 mg/kg	t_{max}	4.6	0.1	hour		
		C_{max}	57	1.9	µg/g		
No other excipients were used		AUC	386	14.2	µg h/g		
		$t_{1/2}$	2.2	10.0	hour		

(*Continued*)

Table 7. (*Continued*).

Delivery method and formulation	Dose		Pertinent pharmacokinetic findings			Studied population	References
	56.2 mg/kg	t_{max}	0.1	0.3	hour		
		C_{max}	121	2.9	µg/g		
		AUC	771	48.2	µg h/g		
		$t_{1/2}$	5.2	18.5	hours		
	112.6 mg/kg	t_{max}	0.1	0.6	hour		
		C_{max}	150	5.0	µg/g		
		AUC	1248	90.3	µg h/g		
		$t_{1/2}$	5.8	20.1	hours		
	4.4 mg/kg	t_{max}	0.1		hour	Healthy beagle dogs (whole blood samples)	
		C_{max}	0.28		µg/g		
		AUC	59.2		µg h/g		
		$t_{1/2}$	3.6		hours		
	7.7 mg/kg	t_{max}	0.6		hour		
		C_{max}	0.36		µg/mL		
		AUC	109.4		µg h/mL		
		$t_{1/2}$	4.0		hours		
	9.7 mg/kg	t_{max}	2.0		hours		
		C_{max}	0.45		µg/mL		
		AUC	174.0		µg h/mL		
		$t_{1/2}$	3.9		hours		
Nebulized liposomal suspension	25 mg		Lung	Blood		Healthy Balb/c mice (lung and blood samples)	100
Administered as a dilauroylphosphatidylcholine (DLPC) cyclosporine multi-lamellar liposome		C_{max}	5.0 ± 1.5	0.05 ± 0.05	µg/g		
Contained cyclosporine in a DLPC multi-lamellar liposome of dissolved in ultrapure water							
Nebulized liposomal suspension	25 mg		Lung	Blood		Healthy mongrel dogs (lung and blood samples)	99
Administered as a dilauroylphosphatidylcholine (DLPC) cyclosporine multi-lamellar liposome		t_{max}	0.5	0.25	hour		
Contained cyclosporine in a DLPC multi-lamellar liposome of dissolved in ultrapure water		C_{max}	7.5[c]	<0.3	µg/g		
Nebulized suspension	3.5 mg/kg		Lung	Blood		Healthy mice (lung and blood samples)	101
Administered as a nebulized suspension of CP cyclosporine		t_{max}	1.0	3.7	hours		
Contained nano scale cyclosporine with polysorbate 80		C_{max}	10.5	0.37	µg/g		
		AUC	144.4	9.7	µg h/g		
		$t_{1/2}$	9.6	18.2	hours		

Values are the geometric mean or the mean ± SD. [a]L/B Ratio = ratio of lung C_{max} to blood C_{max} [b]L/B Ratio = ratio of lung AUC to blood AUC [c]Values not expressly reported by the authors. Values inferred from figures, tables, and methodological descriptions.

Table 8. Properties of inhaled FK224.

Delivery device and formulation	Dose	Pertinent pharmacokinetic findings			Studied population	Reference
pMDI	5 mg/kg	FK224 : β-CD :: 1 : 0			Healthy rats (plasma samples)	105
Administered as a suspension of FK224 and β-cyclodextrin		t_{max}	1.0 ± 0.3	hour		
		C_{max}	0.05 ± 0.03	μg/mL		
		AUC	0.32 ± 0.13	μg h/mL		
		FK224 : β-CD :: 1 : 1				
Contains micronized FK224/β-cyclodextrin in various ratios with soybean lecithin in a mixture of CFC-11, CFC-12, and CFC-14		t_{max}	0.25 ± 0.1	hour		
		C_{max}	0.17 ± 0.09	μg/mL		
		AUC	2.15 ± 0.25	μg h/mL		
		FK224 : β-CD :: 1 : 7				
		t_{max}	0.25 ± 0.2	hour		
		C_{max}	0.43 ± 0.22	μg/mL		
		AUC	6.76 ± 0.92	μg h/mL		
pMDI	1 mg	t_{max}	2.7 ± 1.3	hours	Healthy human volunteers (plasma samples)	106
Administered as a suspension of FK224 and β-cyclodextrin in propellant		C_{max}	0.07 ± 0.02	ng/mL		
		AUC	0.13 ± 0.05	ng h/mL		
Contains micronized FK224/β-cyclodextrin in a 1:1 ratio with soybean lecithin in a mixture of CFC-11, CFC-12, and CFC-114	4 mg	t_{max}	3.0 ± 0.8	hours		
		C_{max}	0.36 ± 0.07	ng/mL		
		AUC	3.16 ± 0.80	ng h/mL		
	8 mg	t_{max}	2.7 ± 0.6	hours		
		C_{max}	0.55 ± 0.09	ng/mL		
		AUC	5.88 ± 1.57	ng h/mL		
DPI	4 mg	t_{max}	2.2 ± 1.2	hours		
Administered using filled capsules and with a Spinhaler®		C_{max}	1.36 ± 0.17	ng/mL		
		AUC	14.44 ± 2.69	ng h/mL		
Contained micronized FK224/β-cyclodextrin in a 1:1 ratio blended with lactose	10 mg	t_{max}	0.7 ± 0.1	hour		
		C_{max}	3.66 ± 0.56	ng/mL		
		AUC	30.51 ± 2.86	ng h/mL		

Values are the mean ± standard deviation.

ranged from 0.07 to 0.09 μg kg/mL/mg but considerably increased to 0.34–0.37 μg kg/mL/mg for the DPI-delivered formulation. A similar pattern was observed for normalized AUC values when the same formulation when administered with a pMDI device, 0.13–0.79and 3.05–3.61 μg h kg/mL/mg with a DPI device.

Comparison of inhaled oligopeptides

Numerous formulation and delivery devises have been investigated for inhaled poorly water-soluble oligopeptides including solutions, suspensions, particle size reduction, solubilizing excipients, nebulizers, DPIs, and pMDIs. Inhalation of solubilized cyclosporine in alcohol and propylene glycol solutions produced similar t_{max} values in lung tissue and plasma but with very different dose-normalized C_{max} and AUC ranges, suggesting alcoholic solutions enhanced pulmonary drug absorption compared with propylene glycol solutions, possibly through alterations in hydrodynamics across alveolar membranes[107]. In addition, tissue and blood concentration ratios and partition coefficients for pulmonary absorption suggest that alcohol solutions promote increased retention of cyclosporine in the lungs following inhalation compared with propylene glycol solutions. Therefore, although alcohol solutions promote improved relative absorption of the oligopeptide, propylene glycol solutions do not promote retention of drug in lung tissue, possibly through nonabsorptive lung clearance mechanisms. Further studies are needed to elucidate possible causes of this behavior. Inhalation of a nanoscale dispersion of CP cyclosporine retained drug in the lungs in a similar manner to solutions but had slightly improved drug absorption as evidenced by concentration ratios compared with solutions and could be due to enhanced absorption of nanoparticles[4]. Inhalation of liposomal cyclosporine seemed to inhibit systemic drug absorption and could be due to tissue retention of the liposome[108].

The incorporation of β-cyclodextrin into FK224 formulations markedly enhanced the aqueous solubility of the oligopeptide resulting in better pulmonary absorption of the API[109]. However, incorporation of solid-state micronized FK224–cyclodextrin powders into pMDI and DPI devices prompted divergent pharmacokinetic parameters as evidenced by a three- to fourfold increase in dose-normalized plasma C_{max} values and 4- to 28-fold increase in normalized plasma AUC values following inhalation of the DPI-delivered powder. The authors suggested the DPI produced higher C_{max} and AUC values because of device-dependent differences in the delivered dose[106]. Ideally, a pMDI and a DPI would produce similar systemic pharmacokinetic parameters for equivalent inhaled doses.

Inhaled fentanyl

Opioid analgesics are based on the prototypical opioid, morphine, but structurally diverse through various ring structures and functional groups to provide consistent binding sites to opioid receptors. As a result of this inconsistency in chemical structures, opioids have varied aqueous solubilities, molecular weights, and log *P* values. For this review, fentanyl is a poorly water-soluble compound and has been administered via inhalation for the treatment of breakthrough pain. Fentanyl is a small-molecule compound (336.5 g/mol) with low aqueous solubility (200 μg/mL) and high log *P* value (3.9) suggesting dissolution-limited absorption and good propensity for diffusion-controlled absorption. The inhalation of fentanyl gained popular interest when fentanyl derivative was pumped into the ventilation system of a building in Moscow that held terrorists and more than 800 hostages[110]. Following the exposure to the inhaled fentanyl derivative and neutralization of the terrorists, a military operation brought the standoff to a close. However, after that incident, over 80% of the hostages required hospitalization with a total of 16% who died as a result of the inhaled fentanyl derivative. Despite these negative results, the controlled and therapeutic use of inhaled fentanyl was investigated as a route of administration for rapid and potentially prolonged systemic drug action using a nebulized suspension of a 50/50 mixture of free and liposome-encapsulated (phospholipon 90-G and cholesterol) fentanyl (FLEF) and as a pMDI-containing micronized fentanyl base in a mixture of CFC-11 and CFC-12 propellants with sorbitan trioleate as a metering valve lubricant[111–113]. A DPI formulation of engineered micronized fentanyl on lactose carrier particles was also administered to humans via the Taifun® device[114,115] (Table 9).

The plasma pharmacokinetic profile following inhalation of the FLEF formulation could be considered the summation of the inhaled encapsulated fentanyl pharmacokinetic profile with the pharmacokinetic profile of the inhaled free fentanyl. However, those two profiles are impossible to isolate based on the available pharmacokinetic data from FLEF. In addition, the pMDI formulation and the DPI fentanyl-lactose system provided different pharmacokinetic profiles, suggesting none of the inhaled fentanyl systems provided a unmodified free liposomal comparator. Specifically, the pMDI formulation used a solution of fentanyl in CFC propellants that volatilized on actuation to deliver particulate fentanyl to the lungs. Administration of the pMDI formulation achieved very rapid plasma t_{max} values of 0.1–0.12 hour (6–7 minutes) with corresponding dose-normalized plasma C_{max} values of 9.5–15.0 μg kg/mL/mg and a normalized AUC range of 91–154 μg h kg/mL/mg. The DPI

Table 9. Properties of inhaled fentanyl.

Delivery device and formulation	Dose	Pertinent pharmacokinetic findings			Studied population	References
Nebulized suspension	2 mg	t_{max}	0.38 ± 0.11	hour	Healthy human volunteers (plasma samples)	111, 112
Administered as a mixture of free (50%) and liposome-encapsulated (50%) fentanyl (FLEF)		C_{max}	1.2 ± 0.4	ng/mL		
Contained free fentanyl and liposome-encapsulated (phospholipon 90-G and cholesterol) fentanyl in sterile water	≤ mg	t_{max}	0.25	hour		
		C_{max}	2.53	ng/mL		
pMDI	100 µg	t_{max}	0.12 ± 0.08	hour	Healthy human volunteers (plasma samples)	113
Administered as a fentanyl solution in propellant using a pMDI fitted with SmartMist™ (breath-actuated adapter)		C_{max}	1.5 ± 1.5	ng/mL		
		AUC	15.4 ± 5.57	ng h/mL		
Contained fentanyl base solution in a mixture of CFC-11 and CFC-12 with sorbitan trioleate	200 µg	t_{max}	0.12 ± 0.12	hour		
		C_{max}	1.9 ± 0.9	ng/mL		
		AUC	19.0 ± 7.90	ng h/mL		
	300 µg	t_{max}	0.10 ± 0.07	hour		
		C_{max}	4.2 ± 2.7	ng/mL		
		AUC	27.4 ± 24.0	ng h/mL		
DPI	200 µg	t_{max}	0.017	hour	Healthy human volunteers (plasma samples)	114, 115
Adminsitered as fentanyl-lactose blend in Taifun® device Contained fentanyl blended with lactose carrier particle		C_{max}	0.94	ng/mL		

Values are the mean or mean±SD.

formulation provided an even quicker t_{max} value, 0.017 hour (1 minute), but with a lower dose-normalized C_{max} of 4.7 μg kg/mL/mg. However, when compared with the FLEF formulation, plasma t_{max} values were slightly slower and ranged from 0.25 to 0.38 hour (15–23 minutes) but with much lower dose-normalized C_{max} values of 0.6–2.5 μg kg/mL/mg. Therefore, a component of both the pMDI and the DPI formulations enhanced pulmonary absorption from the lung, or the nebulized liposomal fentanyl suspension behaved in a substantially different manner than suggested by the pMDI formulation. A more thorough analysis was not possible because of incomplete reporting of AUC values for the DPI fentanyl and FLEF. However, fentanyl particle size reduction was the likely mechanism of rapid and high maximal drug concentrations for both the DPI and the pMDI formulations, which occurred either in the particle-manufacturing process (DPI) or following volatilization of the CFC propellant from the fentanyl solution, which caused precipitation of discrete micro- to nano-sized particles (pMDI). Further studies are needed to better elucidate this possible mechanism of improved drug solubilization for fentanyl.

Summary

Pulmonary drug delivery is an accepted route of drug administration for lung condition and disease management including asthma and other inflammatory processes, lung infections, immunosuppression following lung transplantation, and others. The lungs were also investigated as a route of systemic drug administration to bypass oral barriers to absorption and avoid parenteral administration and the pain and inconvenience associated with injections for other APIs. These biopharmaceutical advantages for interest in pulmonary drug delivery have led researchers to administer an increasingly wide variety of APIs to the lungs. Although poorly water-soluble drugs pose formulation and drug delivery limitations for typical delivery methods, an evaluation of their impact on pulmonary drug delivery with emphasis on in vivo pharmacokinetic effects has not been performed. A sample of poorly water-soluble APIs were selected from the literature and included for analysis where a formulation was provided or suggested, the drug was inhaled by an in vivo system, and some form of pharmacokinetic evaluation was performed such that drug concentration values were reported. Studies that evaluated a biomarker or physiologic response were not included in the current evaluation. Studies with noncompartmental pharmacokinetic parameters of t_{max}, C_{max}, and AUC were preferentially included and normalized for the drug dose, as an exposure dose instead of a calculated or estimated delivered or inhaled dose, to facilitate inter-API comparison.

Application of particle size reduction to inhaled poorly water-soluble agents provided inconsistent effects on pulmonary absorption. Micronized drug formulations had plasma t_{max} values generally less than 2 hours (120 minutes) with some decreases to less than 0.5 hour (30 minutes) and were influenced by the API. Although blood collection procedures limit the earliest reported values, micronized drugs can be rank ordered with the earliest reported value as budesonide (0.13–0.58 hour) < beclomethasone-17-monopropionate (0.17–2.5 hours) < triamcinolone acetonide (0.25–1.75 hours) < amphotericin B (0.5–3.5 hours) < fluticasone propionate (0.9–1.88 hours). The minimal t_{max} values correlate with aqueous solubilities of the APIs (R^2 = 0.70), suggesting the rate of drug absorption from the lungs, as suggested by t_{max} values, is limited by the intrinsic solubility of the API when micronized. However, when the particle size is reduced into the nanometer range, plasma t_{max} values decreased to 0.051–0.19 hour for nano-budesonide but were 2.0 hours for URF itraconazole and 5.4 hours for SFL itraconazole. Although insufficient data were available to draw conclusions for t_{max} values for nano-sized poorly water-soluble APIs, inhalation of nanoparticles could introduce additional and more variable mechanisms of absorption than affecting micron-sized inhaled drugs[4,16]. The pulmonary administration of alcohol and propylene glycol-based beclomethasone-17-monopropionate and cyclosporine solutions generally achieved rapid plasma t_{max} values. Dissolved fentanyl in a propellant mixture also demonstrated very rapid drug absorption with low t_{max} values following inhalation. Incorporation of solubilizing excipients also reduced the t_{max} value as evidenced in the inclusion of cyclodextrin with FK224, surfactants with amphotericin B and itraconazole, and encapsulation of fentanyl, cyclosporine, and amphotericin B into liposomes. The formulation-based inclusion of solubility-enhancing excipients did appear to improve the rate of drug absorption following inhalation as has been demonstrated for poorly water-soluble APIs in other routes of drug delivery[15,87,116,117].

The relationships between drug solubility and solubilization were more complex for dose-normalized tissue and systemic drug C_{max} and AUC values than for t_{max} values. This could be because pharmacokinetic parameters were adjusted based on the total inhalation exposure dose and not actual deposited doses. The inter-study and intra-study differences in pulmonary deposition based on utilization of different delivery systems, formulations, study populations and species, and physiologic properties following inhalation could not be corrected in the dose normalization because of insufficient and methodologically varied deposition

and aerosol aerodynamic information provided by the many authors[16,118,119]. Additionally, systemic effects were inappropriate to consider parameter normalization precisely because of the objective of the study to investigate the influence of solubility and solubilization parameters on pulmonary absorption of poorly water-soluble APIs. However, normalizing noncompartmental pharmacokinetic parameters based on exposure doses did provide a uniform adjustment for all APIs across varied methodologies and allow for inter-API evaluation.

The most noticeable relationship is the scope of drug concentrations in the systemic circulation following pulmonary absorption, that is, inhaled corticosteroids and inhaled amphotericin B had dose-normalized concentrations in the ng/mL/mg range (equivalent to pg/mL/μg) whereas the other APIs had a 1000-fold increase in concentration in the μg/mL/mg range. Although this could be an artifact from dose normalization of pharmacokinetic parameters, inhaled corticosteroids and amphotericin B have very low drug distribution to the plasma from the lungs and suggest mechanistic differences in pulmonary absorption between different APIs. Additional studies are required to control for possible differences in pulmonary deposition and investigate mechanisms of absorption for these agents from the lung.

The differences in tissue and systemic drug concentration scales did not affect trends in drug concentration and drug exposure based on formulation-based solubilization adjustments. Alcoholic solutions prompted higher normalized C_{max} and AUC values, suggesting enhanced drug absorption following inhalation, than propylene glycol solutions. Therefore, the pulmonary administration of predissolved poorly water-soluble API does not equate to equivalent rates or extents of drug absorption. Studies have suggested that ethanol could function as a permeation enhancer or disrupt the hydrodynamic balance in tissues to promote drug absorption[107,120].

Inhalation of nanoscale formulations caused divergent pharmacokinetic findings for nano-budesonide compared with nano-structured compositions of itraconazole and cyclosporine. Inhaled suspensions of nano-budesonide promoted rapid and markedly elevated systemic drug concentrations but with an equivalent dose-normalized AUC, suggesting an improved rate of drug absorption without altering the extent of drug absorption. However, for inhaled nano-structured itraconazole and cyclosporine, rapid and extensive tissue concentrations were observed but with very little systemic drug absorption. For those APIs, the rate and the extent of systemic drug absorption from the lungs was decreased. The inhaled itraconazole and cyclosporine particles could experience nonabsorptive clearance mechanism from the lung tissue, the possible alveolar macrophages, or the lymphatic system, that could segregate drug from the systemic circulation[17,121].

Cyclodextrin also promoted high normalized C_{max} and AUC values following inhalation, suggesting similar mechanisms of improved drug absorption as other routes of delivery[109,122,123]. However, nebulized liposomal formulations promoted relatively low systemic drug concentrations for cyclosporine and fentanyl but elevated concentrations for amphotericin B. Although amphotericin B has been shown to bind to systemically circulating liposomes and cause a high but pharmacologically inactive systemic concentration following IV administration[124], the pulmonary administration of liposomes was suggested to cause enhanced drug retention in the lung and act as a form of drug depot for prolonged action[111,112]. Supplemental AUC values for inhaled liposomal poorly water-soluble APIs could resolve this effect.

Although the pharmacokinetic evaluation of select inhaled poorly water-soluble APIs demonstrated many drug-dependent and as yet unexplored effects, drug physicochemical and formulation-based solubility enhancement did affect drug absorption from the lungs. Additional insights will be gained as researchers continue to investigate the delivery of drugs to the lungs and explore the factors that relate drug solubility, formulation-based enhancements to solubility, and local and systemic pharmacokinetics.

Declaration of interest

The authors report no conflicts of interest.

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