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Article

iBCS: 3. A Biopharmaceutics Classification System for Orally Inhaled Drug Products

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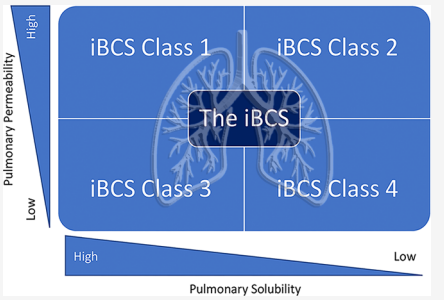
ABSTRACT: In this article, we specify for the first time a quantitative biopharmaceutics classification system for orally inhaled drugs. To date, orally inhaled drug product developers have lacked a biopharmaceutics classification system like the one developed to navigate the development of immediate release of oral medicines. Guideposts for respiratory drug discovery chemists and inhalation product formulators have been elusive and difficult to identify due to the complexity of pulmonary physiology, the intricacies of drug deposition and disposition in the lungs, and the influence of the inhalation delivery device used to deliver the drug as a respirable aerosol. The development of an inhalation biopharmaceutics classification system (iBCS) was an initiative supported by the Product Quality Research Institute (PQRI). The goal of the PQRI iBCS working group was to generate a qualitative biopharmaceutics classification system that can be utilized by inhalation scientists as a "rule of thumb" to identify desirable molecular properties and recognize and manage CMC product development risks based on physicochemical properties of the drug and the deposited lung dose. Herein, we define the iBCS classes quantitatively according to the dose number and permeability. The proposed iBCS was evaluated for its ability to categorize marketed inhaled drugs using data from the literature. The appropriateness of the classification of each drug was assessed based on published development, clinical and nonclinical data, and mechanistic physiologically based biopharmaceutics modeling. The inhaled drug product development challenges for each iBCS classification are discussed and illustrated for different classes of marketed inhaled drugs. Finally, it is recognized that discriminatory laboratory methods to characterize regional lung deposition, dissolution, and permeability will be key to fully realizing the benefits of an iBCS to streamline and derisk inhaled drug development.



KEYWORDS: *inhalation biopharmaceutics classification system (iBCS), inhalation, biopharmaceutics, lung permeability, lung dose, lung dissolution, lung solubility, inhaled medicines*

1. INTRODUCTION

The bioavailability of an inhaled drug is influenced by several interdependent factors including physicochemical properties of the drug, lung deposition, and drug disposition. Further factors influencing bioavailability include the formulation, the delivery device, and the physiology, anatomy, and pulmonary function of the patient. The concept of an inhalation-based biopharmaceutics classification system (iBCS) has progressed since the concept was discussed at an AAPS workshop in 2014.[1] The principles of the iBCS presented here are based on those used for oral immediate release drugs (giBCS) and are firmly rooted in biopharmaceutics.[2] However, the framework of the iBCS is modified from that used in the giBCS to produce a delivery-route-specific classification system taking account of pulmonary anatomy and physiology. The need for an iBCS is based on the premise that it is desirable from a drug discovery, development, and regulatory perspective to anticipate the performance of inhaled medicines. We propose that categorizing a drug based on a classification system constructed from critical drug attributes will aid in understanding how to reduce the risk and overall complexity of orally inhaled drug product development, scale-up, and postapproval changes.

The giBCS clearly illustrates the benefits of a classification system that provides a scientific framework for classifying drug substances based on their aqueous solubility and mucosal permeability. When combined with the dissolution of the drug product, the giBCS takes into account three major factors that

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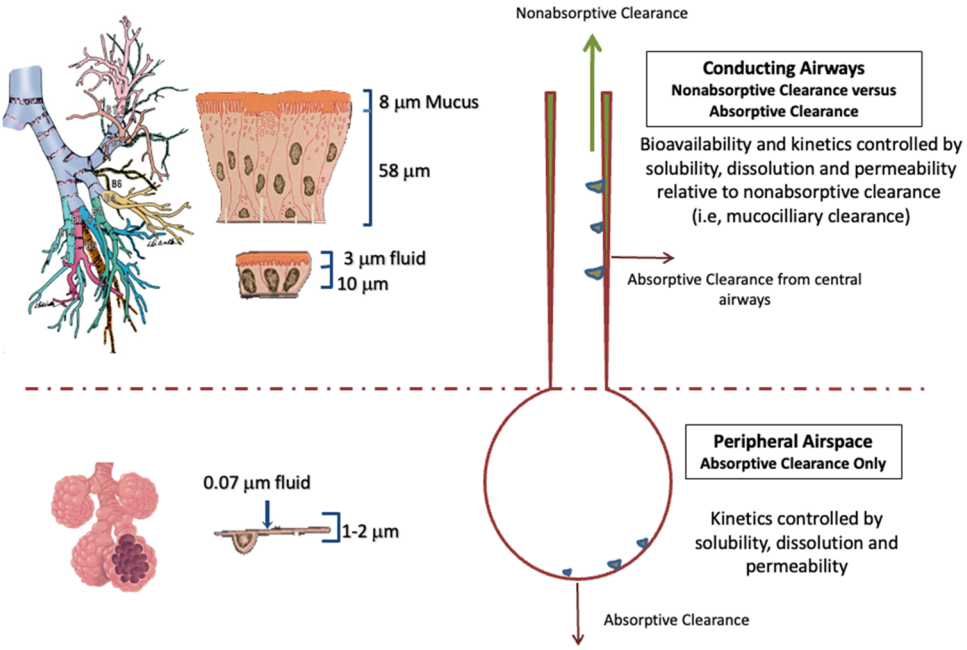

Figure 1. Simplified lung anatomy and clearance mechanisms used to develop the iBCS framework.[3] Adapted with permission from ref 3. Copyright 2022, American Chemical Society.

govern the rate and extent of drug absorption from immediate release solid oral dosage forms: (i) drug solubility, (ii) drug intestinal permeability, and (iii) product dissolution. Similarly, the iBCS presented herein classifies drug substance according to solubility and permeability (in the lungs), with dissolution of the inhaled drug product providing an additional, product-specific factor that determines the rate and extent of drug absorption.

Classification of an inhaled drug using the proposed iBCS will provide an understanding of development, clinical, and regulatory risks. This insight will inform mitigation strategies that can be used in drug discovery to design inhaled drug candidates with reduced product development risks. The underlying philosophy for establishing an iBCS and the model underpinning its application have been reported previously.[1,3,4] This publication provides a synopsis of the methodology used to generate a classification system for inhaled medicines, critiques the resulting approach to classification, and for the first time defines the iBCS classes quantitatively according to the dose number and permeability before evaluating the iBCS for its ability to categorize marketed inhaled drugs using data from the literature.

2. METHODS

2.1. iBCS Foundation: Principles and Framework.

Using the same scientific principles as the giBCS, we assumed that the rate and extent of absorption from the airway lumen into the lung tissue are controlled by the attributes of solubility, dose, dissolution rate, and permeability. However, the essential building blocks were modified for the iBCS to reflect the pulmonary route of administration.

Clearance of drug from the lung is location-dependent and can be defined by absorptive and nonabsorptive clearance mechanisms (Figure 1). Absorptive clearance is controlled by permeability, which determines transfer of drug from the epithelial lining fluid (ELF) in the lumen into the lung tissue. We assume that this mechanism of clearance follows Fick's first law and therefore the flux (J) is based on effective permeability (P_{eff}) and the concentration gradient (ΔC) across the membrane (eq 1).

$$J = \frac{dM}{A \cdot dt} = -D\frac{dC}{dx} = P_{eff}\Delta C \quad (1)$$

where M is the mass of the dissolved drug, A is the surface area available for transport, D is the diffusivity, x is the distance, and t is the time.

As with the giBCS, we have focused on permeability as a measure of drug transport from the lumen into the tissue and disregarded active transport which can impact the time course of drug loss from the lumen.[5]

We assume that only the dissolved drug can diffuse into the lung tissue. To account for dissolution of solids in lumen, dissolution of drug in the lung was modeled by the Nernst–Brunner equation, which is an adaptation of the Noyes–Whitney equation describing the dissolution rate based on the concentration gradient (solubility (C_s) − concentration (C_t)), diffusivity (D), particle surface area (S_i) and diffusion layer thickness (h_i), mass of the dissolved drug (M), and time (t) (eq 2).

$$\frac{dM}{dt} = \sum_{i=1}^{n} \frac{DS_i(t)}{h_i(t)}(C_s - C_t) \quad (2)$$

Mucociliary clearance is the nonabsorptive clearance mechanism in the ciliated airways of the lungs, and macrophage uptake is the nonabsorptive clearance mechanism in the peripheral, nonciliated regions. When the dissolution rate of the drug is slower than the rate of nonabsorptive clearance of a solid drug, incomplete absorption of the lung dose occurs, and therefore, the fraction of the dose available for absorption is less than 1. To simplify the iBCS model development, clearance in the peripheral airspace was assumed to be predominantly controlled by absorptive clearance, and macrophage clearance was omitted from the iBCS since this form of clearance is more relevant to modified release formulations,

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Mol. Pharmaceutics 2024, 21, 164−172

which are currently out of scope for the iBCS. Based on this simplification, whatever dose is deposited into the peripheral lung is absorbed (i.e., the fraction absorbed = 1).

Therefore, the rate and extent of drug loss from the luminal space of the lungs can be described by the basic principles that govern dissolution and permeability in combination with a pulmonary-specific nonabsorptive clearance mechanism that reflects mucociliary clearance.

Product attributes that factor into the fate of an inhaled drug are (i) the mass delivered to the lungs and the regional distribution of the lung dose and (ii) the rate of dissolution of an inhaled solid drug. As depicted in Table 1, when a drug is inhaled, the dose is instantly deposited throughout the entire lung by the breathing maneuver, and therefore, dissolution, clearance, and absorption processes occur simultaneously for inhaled drugs, whereas these processes for oral drugs occur sequentially in different regions as the drug moves through the GI tract. Because of this difference, the time-based unidirectional plug flow relationship used to estimate the residence time in the giBCS is not applicable to an iBCS. To estimate the residence time in the lungs for the iBCS, a mechanistic modeling approach was developed to determine loss of drug from the lumen into the lung tissue (see Section 2.2).

Table 1. Key Differences between Oral and Inhaled Routes of Administration

characteristic	oral drugs	inhaled drugs
therapeutic target	systemic	local
absorption site geometry	open (unidirectional tube)	closed (bidirectional tube and bucket)
therapeutic route and dose	ingestion (dose = nominal)	inhalation (dose = fraction of nominal)
temporal dose availability	plug flow (time-based transit)	bolus (instantaneous deposition)
nonabsorptive clearance mechanisms	unidirectional peristalsis and chemical degradation	primarily mucociliary transport

To describe the propensity for dissolution rate-limited uptake of the deposited dose in an iBCS, we use the same relationship for the dose number (D_o) as used by the giBCS (eq 3), but instead of the nominal dose, the dose is defined as the fraction of the nominal dose that is deposited in the lungs or in a specific lung region i (D_{o_i}). Therefore, knowledge of the lung (or regional) dose (M_i), the volume of solution available for dissolution (V_i), and the solubility of the drug (C_{s_i}) are parameters that are required in order to calculate the iBCS dose number.

$$D_{o_i} = \frac{(M_i/V_i)}{C_{s_i}} \quad (3)$$

In summary, the regional dose (D_{o_i}) and dissolution, effective epithelial permeability (P_{eff}), and mucociliary clearance from the central airways were presumed to govern the local concentration time profiles within the lung lumen. Since common scientific principles were used to develop the giBCS and iBCS, both systems classify drugs according to the permeability and dose number. The framework for the iBCS is based on pulmonary physiology and, therefore, includes estimates for the volume available for dissolution in the lung lumen and drug deposition. The retention time in the lumen is based on the dissolution rate of the regionally deposited dose, mucociliary clearance, and permeation of the dissolved drug from the luminal space into the lung tissue. Further details regarding the principles and framework used to develop the iBCS can be found in the iBCS 1 publication.[3]

2.2. Defining the Grid Boundaries. To create the iBCS grid classification boundaries, a physiologically based biopharmaceutics (PBB) mechanistic model (Mimetikos Preludium) was used to assess the impact of key iBCS drug and drug product attributes (solubility, P_{eff}, and dose) on the rate of drug loss from the luminal space into lung tissue (drug half-life in the lung luminal space, $t_{1/2}$) and the extent of drug absorbed from the luminal space (the fraction of the luminal dose absorbed into and across the airway epithelium, F_{abs}). Three hundred modeling simulations were generated using a range of values representative of those for inhaled drugs as input parameters for solubility, regional dose, and P_{eff}. The parameters used in the modeling are summarized in Table 2 with full details available in the iBCS 2 publication describing mechanistic modeling of pulmonary availability of inhaled drugs.[4]

Table 2. Physiological, Molecular, and Model Drug Properties Used to Identify the iBCS Grid Boundaries

properties	parameter	value or range
fixed physiological properties	BB ELF volume	0.3 mL
	bb ELF volume	1.7 mL
	AI ELF volume	8.0 mL
	BB area	0.031 m^2
	bb area	0.43 m^2
	AI area	54.7 m^2
	MCC rate constant for undissolved drug (K_{CBB})	0.69 h^{-1}, $t_{1/2}$ BB = 1 h
	MCC rate constant for undissolved drug (K_{Cbb})	0.078 h^{-1}, $t_{1/2}$ bb = 9 h
fixed molecular properties	molecular weight	500 g/mol
	diffusivity	3×10^{-4} cm^2/min
	VMD/GSD	2 μm/2.0
	lung tissue partitioning and free fraction in ELF	1
	oral bioavailability	0
	volume of distribution	10 L
	hepatic clearance	80 L/h
varied model drug properties	solubility in ELF	0.01−10,000 μg/mL
	deposited dose Bb	0.2 μg to 200 mg
	deposited dose AI	0.8 μg to 800 mg
	deposited dose, whole lung	1 μg to 1000 mg
	epithelial permeability (non scaled)	1×10^{-5}−1×10^{-7} cm/s
regional drug deposition	Bb:AI	40:60, 30:70, 20:80
	BB:bb	2:1
	fraction exhaled	0

Quantitative boundaries for the iBCS grid were assigned based on the modeling results.[4] The dividing line for the dose number (D_o) was set at D_o = 1. Above this value, a discontinuity in the half-life of drug in the luminal space as a function of the dose number was observed as the dose number increased. Below a dose number of 1, deposited drug can be fully dissolved in the available ELF volume, and above a dose number of 1, only a fraction of deposited drug mass can be dissolved in the available ELF volume. Hence, at dose numbers >1, the half-life of the drug in the luminal space is affected by the dissolution rate and nonabsorptive clearance mechanisms.

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Mol. Pharmaceutics 2024, 21, 164−172

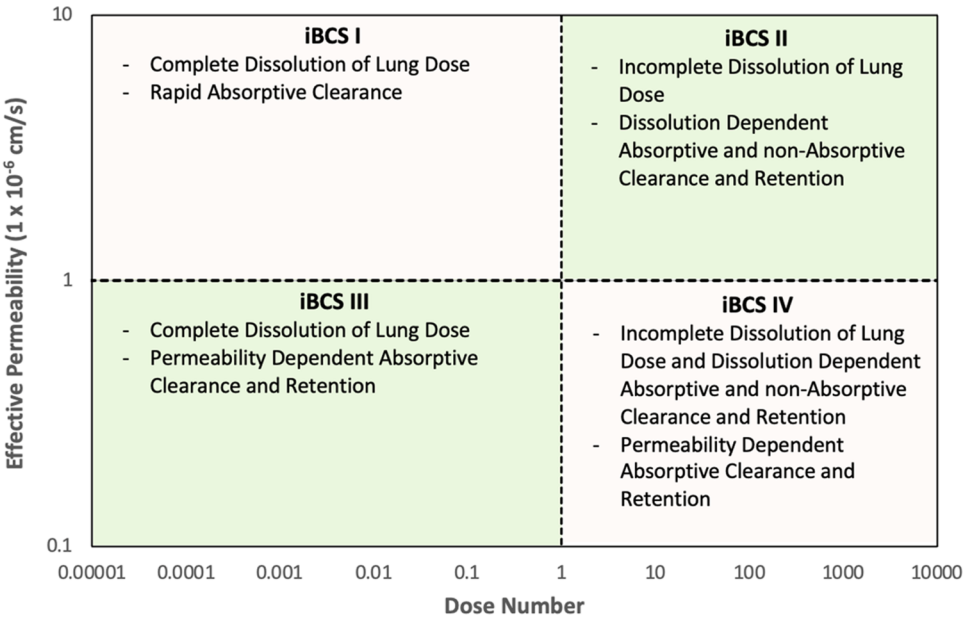

Figure 2. iBCS grid with boundaries delineating high/low permeability and dose number and descriptions of the dissolution and absorption characteristics of drugs falling within the iBCS classes I–IV.

Table 3. Lung Dose, Aqueous Solubility, Dose Numbers, and Permeability Data for Marketed Drug Products[d]

drug	drug class	drug product	lung dose[a] (μg)	aqueous solubility[b] (μg/mL)	dose number (D_o)	effective epithelial permeability (P_{eff})[12] (10^{-6} cm/s)	drug mean absorption time[c] (MAT) (h)
budesonide	ICS	Turbuhaler	400	26.3	1.52	5.2	0.3–1.8[6,7]
fluticasone propionate	ICS	Flovent Diskus	500	0.09	556	3.8	2.1–6.9[6,8,9]
fluticasone furoate	ICS	Arnuity Ellipta	100	0.02	500	3.5	6.5–13.0[8,10]
mometasone furoate	ICS	Asmanex HFA	200	0.26	76.9	3.8	4.1[11]
mometasone furoate-DPI	ICS	Asmanex Twisthaler	220	0.26	84.6	3.8	4.1[11]
terbutaline	SABA	Bricanyl Turbuhaler	250	666,000	0.000038	1.4	
vilanterol trifenetate	ULABA	Anoro Ellipta	12.5	33	0.04	1.1	0.3–1.5[10]
salbutamol sulfate	SABA	Albuterol Sulfate HFA	90	17,700	0.00051	0.82	
salmeterol xinafoate	LABA	Serevent Diskus	25	107	0.023	0.86	
tiotropium bromide	LAMA	Spiriva Handihaler	9	25,000	0.000036	0.55	
ipratropium bromide	SAMA	Atrovent HFA	84	90,000	0.000093	0.28	

[a]Lung dose = dose depositing in the lungs, assigned as 50% of the nominal dose (label claim) for the highest strength of the drug product. [b]Solubility in phosphate-buffered saline, pH 7.4 or similar simple aqueous media.[4] [c]Reported MAT results are from clinical trial data as reported in references for the drugs listed. See the references for product information details. [d]Abbreviations: ICS, inhaled corticosteroid; SABA, short-acting β-2 agonist; LABA, long-acting β-2 agonist; ULABA, ultra-long-acting β-2 agonist; MABA, muscarinic antagonist-β 2 agonist; SAMA, short-acting muscarinic antagonist; and LAMA, long-acting muscarinic antagonist.

The permeability dividing line was determined to be 1x 10^{-6} cm/s. Based on a plot of F_{abs} vs dose number for the conducting airways, permeabilities less than 1×10^{-6} cm/s resulted in F_{abs} values less than 85% and luminal half-lives of greater than 1 h in the conducting airways. Drugs in solution with P_{eff} values greater than or equal to 1×10^{-6} cm/s were rapidly and completely absorbed ($t_{1/2}$ < 17 min).

The iBCS grid with these boundaries is provided in Figure 2 along with the associated dissolution and absorption characteristics of drugs that fall within each iBCS class.

3. RESULTS AND DISCUSSION

The functionality of the iBCS was evaluated by mapping marketed orally inhaled drug products onto the iBCS grid defined in Figure 2. The dose depositing in the lungs (lung dose) was set as 50% of the nominal dose (label claim) of the highest strength for each product, and data for solubility and effective epithelial permeability of each drug are provided in Table 3 (adapted from Bäckman,[4] supplemental information). The inhaled products used in this exercise were selected based on the availability of solubility and permeability data needed to

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Mol. Pharmaceutics 2024, 21, 164–172

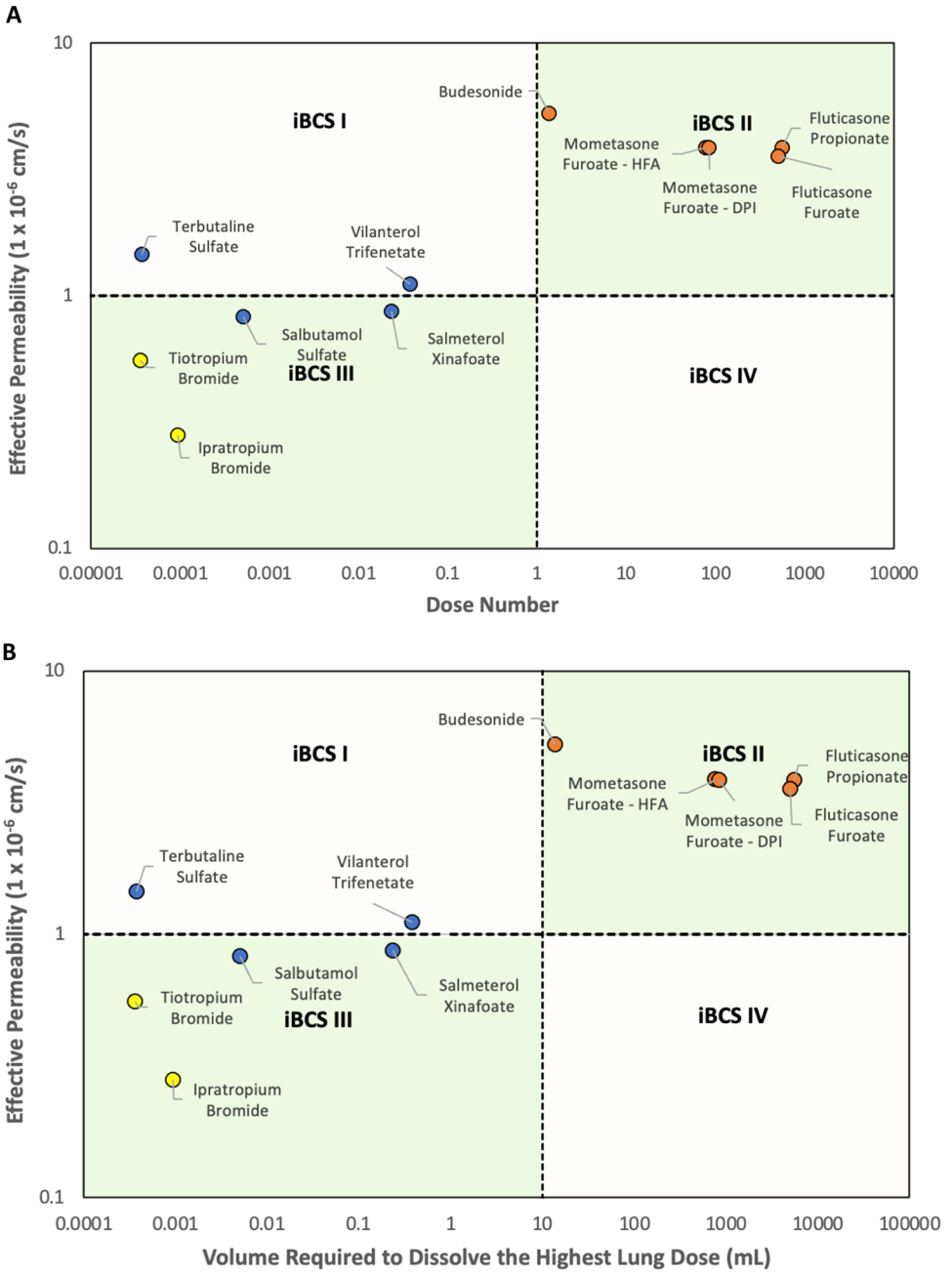

Figure 3. Inhalation biopharmaceutics classification grids, based on (A) the dose number and (B) the volume required to dissolve the highest lung dose, populated with existing drug products identified by therapeutic categories (orange: inhaled corticosteroids, blue: β_2 agonists, and yellow: muscarinic antagonists).

classify the products using the iBCS criteria. Although these are well established potent low-molecular-weight molecules, the dose number takes into consideration the dose and accommodates potency; as such, the system is equally applicable to higher-dose inhaled medicines such as antibiotics, e.g., Tobi Podhaler.

As the iBCS applies to all immediate release orally inhaled dosage forms, the 11 products used for the iBCS model assessment included dry powder inhalers (DPIs), pressurized metered dose inhalers (pMDIs), or soft mist inhalers. For these products, the dose numbers were calculated based on the assumption that the lung dose would be 50% of the nominal dose (label claim) of the highest dose strength. This is likely a conservative assumption. The marketed drug properties span a calculated lung dose number ($D_{o,lung}$) range from 4×10^{-5} to 560 and P_{eff} values from 0.3×10^{-6} to 5×10^{-6} cm/s. The P_{eff} values are estimations of effective pulmonary permeability using an *ex vivo* rat model and computational analysis,[12] which is a complex methodology for widespread adoption but has the advantage for this analysis of being a coherent data set. Populating the proposed iBCS grid results in a distribution and classification of the marketed drugs, as depicted in Figure 3A,B.

3.1. Implications of iBCS Classification Category for Inhaled Drug Product Development. Based on the proposed classification system, an iBCS class I drug will have a short retention time in the luminal space of the lung and, thus, may require more frequent dosing. An iBCS class I drug also has a risk of a limited time to produce a therapeutic effect

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Mol. Pharmaceutics 2024, 21, 164−172

unless other lung retention mechanisms (such as high tissue affinity) are present. For this class of drugs, a formulator may need to identify a way to extend the half-life in the lumen, for example, by using solid-state properties or other formulation strategies to slow the dissolution/release rate. This may be of particular importance when repurposing oral drugs that will frequently have inhaled class I drug characteristics. Retention of an iBCS class II drug will be controlled by the dissolution rate, and pulmonary bioavailability may be reduced due to nonabsorptive mucociliary clearance from the central airways. Therefore, material and formulation related properties that impact dissolution are critical product attributes for iBCS II drugs. Permeability is a critical attribute for an iBCS class III drug, and therefore, lung retention of drugs in this class will depend on molecular properties associated with low membrane permeability and possibly by the presence of excipients or disease states with potential to affect the permeability barrier function. As permeability is drug loss from the lumen rather than appearance in the systemic circulation, tissue binding provides an additional lung retention mechanism for both highly membrane permeable molecules, e.g., class I and poorly permeable molecules in class III. Most marketed inhaled drugs were classified as either class II or class III which suggests that for locally acting drugs, a longer retention time may be advantageous to efficacy. However, based on the grid verification exercise, none of the selected drugs were classified as iBCS class IV compounds. This suggests that there may be an upper limit to the luminal retention time, rendering drugs expected to be both permeability- and solubility-limited suboptimal due to either safety or efficacy concerns (the latter due to low free drug fractions).

A summary of the assigned iBCS classification of the 11 marketed inhaled drugs is provided in Table 4.

Table 4. Classification of Marketed Inhaled Drugs Based on the iBCS[a]

inhaled drug	drug class	iBCS classification
budesonide	ICS	I/II
fluticasone propionate	ICS	II
fluticasone furoate	ICS	II
mometasone furoate	ICS	II
terbutaline	SABA	I/III
vilanterol trifenetate	ULABA	I/III
salbutamol sulfate	SABA	I/III
salmeterol xinafoate	LABA	I/III
tiotropium bromide	LAMA	III
ipratropium bromide	SAMA	III

[a]Abbreviations: ICS, inhaled corticosteroid; SABA, short-acting β-2 agonist; LABA, long-acting β-2 agonist; ULABA, ultra-long-acting β-2 agonist; MABA, muscarinic antagonist-β 2 agonist; SAMA, short-acting muscarinic antagonist; and LAMA, long-acting muscarinic antagonist.

The appropriateness of the iBCS classification for the drugs in each pharmacological class was considered by using published development, clinical and nonclinical data, and PBB modeling results.

3.2. Classification of Inhaled Corticosteroids. All five inhaled corticosteroids (ICS) budesonide, mometasone, beclomethasone, fluticasone propionate (FP), and fluticasone furoate were classified as iBCS class II drugs. Budesonide, the most water-soluble ICS in the group, sits on the border between iBCS classes I and II, and thus, this inhaled drug may be a potential reference compound for the dividing line between these classes based on the dose number. The iBCS class II categorization for ICS drugs was expected since their solubility, with the exception of budesonide, is less than 1 μg/mL, and even though they are potent low dose drugs, their calculated dose numbers are greater than 1. Drugs in this class will undergo slow and/or incomplete dissolution and will therefore be impacted by nonabsorptive clearance in the luminal space of the lungs. Drugs in iBCS II are not permeability-limited. An analysis by Bäckman and Olsson[13] has demonstrated the impact of dose on the dissolution rate of FP in the combination product Advair Diskus. As the strength of FP increased, the dissolution rate decreased, and the shape of the dose-normalized plasma concentration/time profiles changed from sharp to blunt as the dose-normalized C_{max} decreased with increasing dose. All strengths of Advair had low t_{max} values, but these shifted to longer times as the strength of FP increased from 100 to 500 μg. On this basis, the influence of drug particle size distribution on temporal dissolution profiles was inferred to be critical to product performance for FP. The impact of slow dissolution rate on bioavailability has also been observed for FP in a study which showed a pronounced decrease in bioavailability as a result of a more central deposition pattern leading to a higher nonabsorptive mucociliary clearance.[14]

3.3. Classification of β_2-Agonists. The four marketed β-2 agonist drugs are highly soluble with dose numbers much less than 1 and permeabilities ranging from 0.8×10^{-6} to 1.4×10^{-6} cm/s. Therefore, these drugs fall close to the border between iBCS I and iBCS III. Terbutaline is a highly soluble, short-acting β-2 agonist, with a P_{eff} value of 1.4×10^{-6} cm/s in the isolated perfused rat lung (IPL),[12] which classifies terbutaline as an iBCS class I drug. However, this absorption rate in the IPL was more similar to the elevated absorption rate seen in clinical studies when terbutaline was administered to smokers or during exercise compared to control subjects.[15,16] This indicates that the IPL model may overestimate the permeability of this drug.[17]

Salmeterol and vilanterol are long-acting β-2 agonists, salbutamol and terbutaline are short-acting β-2 agonists, and they all straddle the line between iBCS classes I and III. In clinical trials, vilanterol was shown to have a t_{max} of ~10 min and a mean absorption time (MAT) ranging from 0.3−1.5 h.[10]

3.4. Classification of Muscarinic Antagonists. Both tiotropium and ipratropium are classified as iBCS class III drugs. They are both highly soluble drugs with permeability <1 $\times 10^{-6}$ cm/s. From a clinical perspective, tiotropium is believed to have an absorption profile with fast and slow absorption phases.[18] The initial rapid systemic absorption of tiotropium was also documented by Algorta and colleagues and was used to demonstrate PK BE.[19]

4. CONCLUSIONS

This paper is the third in a series that explores the development of an iBCS. The previous papers on this topic proposed a foundational framework and used PBB modeling to identify the effect of the dose number and P_{eff} on the rate of drug loss from the luminal space of the lungs. In this publication, we have introduced a quantitative iBCS classification grid based on the scientific principles used by the giBCS and the pulmonary-specific framework described in the previous papers. The iBCS classifies inhaled drugs

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Mol. Pharmaceutics 2024, 21, 164−172

according to factors that impact their predicted rate of depletion from the airway lumen. For drugs that do not have a great deal of interaction within the lung tissue (extended receptor occupancy, lysosomal trapping, drug degradation), such as those mapped to the iBCS class II in Figure 3, the rate and extent of uptake from the lung lumen is expected to be reflected by the plasma concentration−time profiles. The classification of orally inhaled drugs using the iBCS can provide insight into both technical and clinical development risks. The development of iBCS class III drugs will require the consideration of epithelial barrier integrity and any effects of species, disease, or excipients on permeability. For iBCS class II drugs, consideration should be applied to the effect of species, disease, and formulation/material properties that may affect dose numbers, nonabsorptive clearance, and dissolution rate. We also propose that the iBCS grid boundaries (D_o = 1, and P_{eff} = 1 × 10^{-6} cm/s) can be used by discovery chemists to design inhaled drugs with desirable pharmacokinetic properties or to inform drug repurposing strategies involving lung administration. These applications of the iBCS will currently be limited by challenges in estimating P_{eff}, and efforts toward *in vitro*−*in vivo* correlation and/or quantitative structure−property relationships are needed. Further, drug design aimed at modulating tissue affinity can override the impact of the iBCS classification as the latter only considers absorption from lumen.

The iBCS features discriminating boundary values to classify the dose number and permeability as high or low. The dose boundary is defined as a dose number of 1, which for the iBCS means that the highest anticipated lung dose must be able to dissolve in a volume of 10 mL of the aqueous phase of the epithelial lining fluid (solubility in phosphate-buffered saline pH 7.4, or similar, was used to classify the drugs in Table 3 and Figure 3). The classification dividing line for the permeability boundary is set at 1 × 10^{-6} cm/s which was based on the permeability below which F_{abs} falls below 85% in the Bb region due to mucociliary clearance in the central airways. Given that the majority of the pulmonary dose generally deposits in the AI region, the resulting pulmonary F_{abs} for a drug with permeability greater than 1 × 10^{-6} cm/s is >90%.[4] These values are different from the 250 mL of volume required to dissolve the highest oral dose and a permeability boundary on the order of 10^{-5} cm/s for oral drugs set by the giBCS because of fundamental differences between the orally ingested and inhaled routes of drug delivery. These differences in how dose number and permeability are defined mean that a drug can be classed differently by the iBCS than by the giBCS. Doses delivered to the lungs are smaller than delivered orally, and the amount of fluid that is available to dissolve the dose is also less. If dose sparing dominates, then this will shift a drug substance from low solubility (giBCS) to high solubility (iBCS). Permeability classification thresholds are different for the inhaled and oral route, e.g., salbutamol is clearly class III for giBCS and on the class I/class III boundary for iBCS. In this manuscript, the iBCS grid boundaries were assessed by populating the grid with marketed inhaled drugs, and the resulting classification of the 11 marketed drugs was in accordance with the biopharmaceutics and clinical data available in the literature.

Inhaled products are typically more complex than orally ingested medicines because of the interactions among the formulation, the device, and the patient's inhalation maneuver such that the rate at which the drug is delivered to the site of absorption is not entirely controlled by the formulation. An attractive application of the iBCS would be to alleviate or replace the resource heavy clinical end point/pharmacodynamic clinical studies in the US FDA weight of evidence paradigm for establishing inhaled drug product bioequivalence.[20] However, there are currently gaps that require consideration if this objective is to be attained. These include experimental tools to better predict regional deposition and well-characterized *in vitro* test methods for dissolution and permeability, which can be combined using PBB modeling and validated using pharmacokinetic studies.

Once the scientific and technical progress to address the gaps in our understanding has been made, it may be possible to link an iBCS class to an understanding of bioequivalence (BE) for inhaled drugs, but this is not the focus for developing an iBCS at this time. The current goal is to enable the application of the iBCS to facilitate the identification of inhaled drug candidates based on pulmonary biopharmaceutics and to use the classification system to facilitate formulation development, manufacturing scale-up, and postapproval changes.

A fourth paper in this series will explore the gaps that exist pertaining to predictive methods for regional lung dose, dissolution technology, media composition, solubility determination, and the characterization of pulmonary permeability and tissue interactions. These test methods include characterization techniques for reliably, conveniently, and appropriately determining drug permeability *in vitro*, estimating lung-deposited dose using germane inhalation conditions, and making biorelevant solubility determinations and will need to be developed in order to fully utilize an iBCS to facilitate the development and regulation of orally inhaled medicines.

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■ ABBREVIATIONS

Al	alveoli and alveolar ducts, generations 17−23
APSD	aerodynamic particle size distribution
Bb	central airways, generations 0−16
BB	tracheobronchial region, generations 0−8
bb	bronchiolar region, generations 9−16
BE	bioequivalence
CMC	chemistry, manufacturing, and control
CF	coarse fraction, fraction deposited in the mouth-throat
C/P	central to peripheral deposition pattern
D_o	dose number
D_{o_i}	dose number for a specific lung region "i"
DPI	dry powder inhaler
ELF	epithelial lining fluid
F_{abs}	fraction of the dose absorbed from the lungs
FP	fluticasone propionate
giBCS	gastrointestinal biopharmaceutics classification system
GI	gastrointestinal
GSD	geometric standard deviation
iBCS	inhalation biopharmaceutics classification system
IPL	isolated perfused lung
IR	immediate release
MAT	mean absorption time
MCC	mucociliary clearance
MMAD	mass median aerodynamic diameter
PBB	physiologically based biopharmaceutics
PBBM	physiologically based biopharmaceutics modeling
PBPK	physiologically based pharmacokinetics
P_{eff}	effective epithelial permeability
PQRI	Product Quality Research Institute
$t_{1/2}$	half life
VMD	volume median diameter

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Mol. Pharmaceutics 2024, 21, 164−172