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Mapping the evolution of inhaled drug delivery research: Trends, collaborations, and emerging frontiers

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Inhaled drug delivery is a unique administration route known for its ability to directly target pulmonary or brain regions, facilitating rapid onset and circumventing the hepatic first-pass effect. To characterize current global trends and provide a visual overview of the latest trends in inhaled drug delivery research, bibliometric analysis of data acquired from the Web of Science Core Collection database was performed via VOSviewer and CiteSpace. Inhaled drug delivery can not only be utilized in respiratory diseases but also has potential in other types of diseases for both fundamental and clinical applications. Overall, we provide an overview of present trends, collaborations, and newly discovered frontiers of inhaled drug delivery.

Keywords: inhaled drug delivery; bibliometrics; visualization; nanoparticles; inhalers; diseases

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Introduction

To date, attention has been focused on inhaled drug delivery (IDD) because of its ability to direct delivery to the lung or central nervous system (CNS) for local and systematic treatment.[p1] The historical origins of IDD may be traced back to the anecdotal use of inhaled natural ingredients in ancient India and China.[p2] Inhalers, pivotal carriers of inhaled drugs in modern therapy, have a direct impact on the efficacy of IDD. They serve as the primary dosage forms for the prevention and treatment of acute and chronic respiratory diseases, playing a crucial role in managing conditions such as asthma and chronic obstructive pulmonary disease (COPD).[p3] While inhalers have undergone significant advancements, the emergence of inhaled insulin and vaccines has expanded the clinical possibilities of IDD. Notably, diseases such as diabetes, lung cancer, and Parkinson's disease are garnering significant interest, suggesting the potential of IDD beyond respiratory disorders.

IDD is achieved by depositing aerosols throughout the lungs in both conducting and peripheral airways. Benefitting from its direct entry into the lungs, ample surface area for absorption, rich capillary network, and thin alveolar epithelial cell layer, IDD offers several advantages: (1) rapid entry into pulmonary capillaries, making it suitable for delivering biologically active macromolecules such as proteins and nucleic acids; (2) circumventing the first-pass effect in the liver, allowing for reduced dosages and minimizing adverse reactions; and (3) concentrating drugs in the lungs initially, thereby enhancing the prevention and treatment of lung and respiratory diseases. To achieve therapeutic goals, the drug particles must have an appropriate size. Inhaled particles with a diameter greater than 10 μm will stay at the level of the mouth and pharynx and be swallowed into the stomach for absorption. Particles with a diameter between 5 and 10 μm will precipitate in the trachea and main bronchus. Only particles with a diameter between 2 and 5 μm can truly reach the peripheral bronchioles.[p4],[p5] Therefore, the most important characteristics of an ideal inhalation treatment device are: (1) It can transport a large number of small particles (diameter < 5 μm) to ensure high deposition of bronchus; (2) It can provide a constant and accurate drug dose, maintaining consistent performance even when patient inspiratory volume decreases; (3) It can protect the drug from temperature and humidity changes; (4) It is easy to use; the inhalation device must make it easy for most patients to use, which helps patients to adhere to long-term use; (5) It is low cost and environmentally friendly; these are also important research targets to reduce the generation of nonrecyclable plastic devices.

Furthermore, the potential of IDD extends to the nasal cavity's respiratory and olfactory areas. The well-vascularized nasal epithelium and exposed olfactory neurons provide a direct route for drug transport into the brain.[p6] The formidable blood–brain barrier (BBB) impedes the majority of substances from crossing from the blood to the brain. In this context, IDD emerges as an alternative method, demonstrated in both preclinical and clinical studies to effectively bypass the BBB.[p7]

Bibliometric analysis offers a systematic approach to investigating research progress in a specific field, identifying trends, hotspots, and contributors through quantitative data analysis.[p8] Visualization tools such as VOSviewer and CiteSpace assist in this endeavor.[p9] Despite numerous previous bibliometric studies exploring various fields, a comprehensive graphical examination of IDD evolution and trends is absent.[p10],[p11] In our work, we aim to bridge this gap by analyzing IDD articles from 2001 to 2022 in the Web of Science Core Collection (WoSCC), encompassing annual publication patterns, affiliations, authors, and keywords. Utilizing a bibliometric approach, we not only outline the current state of IDD disciplines but also delve into its breadth, offering both newcomers and experts unique visual insight into the latest trends in this dynamic field.

Methodology

The data of articles from 2001 to 2022 were gathered based on the search strategy shown in Figure 1a for this cross-sectional study and obtained as 'Plain text' from WoSCC. Bibliometric analysis could assist in tracking the evolution and trends of notable productions. Lately, knowledge maps have been created using bibliometric visualization software such as VOSviewer (version 1.6.18) and CiteSpace (version 6.1. R6), which are frequently used to collect, evaluate, and visualize publication data.[p9],[p12] Co-authorship, co-occurrence, and co-citation analysis are the most common algorithms used in bibliometric analysis. Trends of author, institution, and country collaboration are shown via co-authorship analysis. The frequency of keywords in a single article is used in co-occurrence analysis to determine how closely related the keywords are, revealing hot themes and trends. Co-citation analysis could help scholars find and understand the knowledge base in a field. These visualizations enable scientists to pinpoint current collaborations of authors, institutions, and countries/regions, as well as key concepts, research patterns, frontiers of researches, and other bibliometric data for a specific topic. In this work, we collected the following basic data: authors, institutions, countries/regions, keywords, and co-cited references. Each node in the VOSviewer and CiteSpace visualization maps is shown as a circle with a label. Greater frequency is indicated by larger circles in the co-occurrence analysis. Each circle's hue corresponds to the cluster to which it belongs. The strength of the connection and importance of related sites are represented by the thickness and length of the linkages between them. The presentation of the 1000 strongest linkages between nodes was limited to a maximum of 1000 lines.

Basic information about inhaled drug delivery

In total, 19 332 articles related to IDD research from 2001 to 2022 were retrieved from WoSCC. As shown in Figure 1b, the output of publications on IDD increased steadily year by year, indicating that IDD has attracted significant attention in the last few years. From 525 publications in 2001 to 1512 publications in 2022, the number of annual global publications increased by 288%. In addition, IDD research has flourished, especially in the last 8 years, accounting for approximately half of the total publications. As shown in Figure 1c, IDD is a topic arousing interest all over the world, with 88/126 countries/regions contributing to this field. The USA had the most research output (6313 publications), followed by China (2085 publications) and Japan

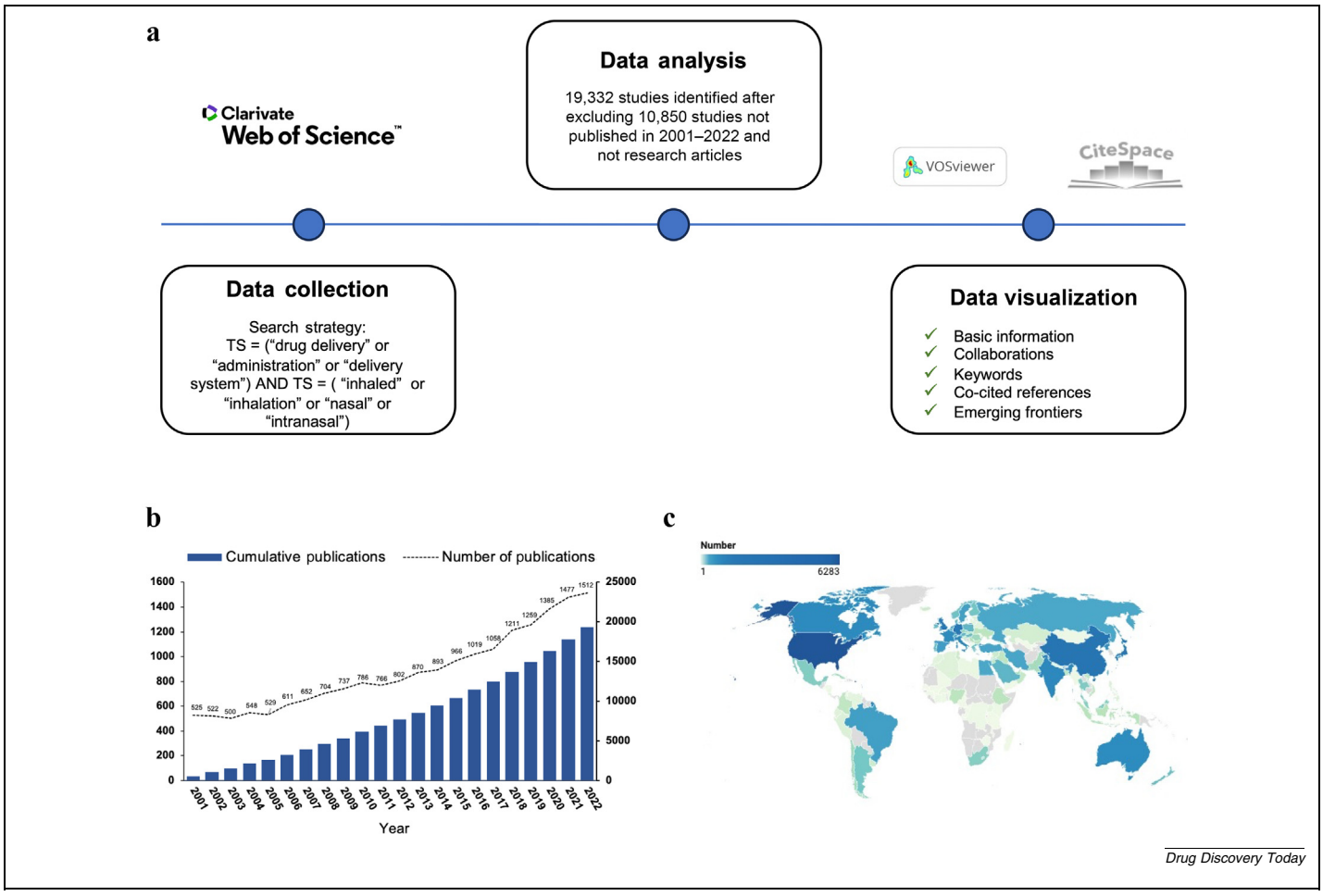


FIGURE 1

(a) Schematic diagram of the data collection and analysis process. **(b)** Annual global output of publications on IDD from 2001 to 2022. **(c)** Geographical distribution map of countries/regions' output from 2001 to 2022.

(1625 publications). Overall, these findings demonstrated that IDD has high potential for further research.

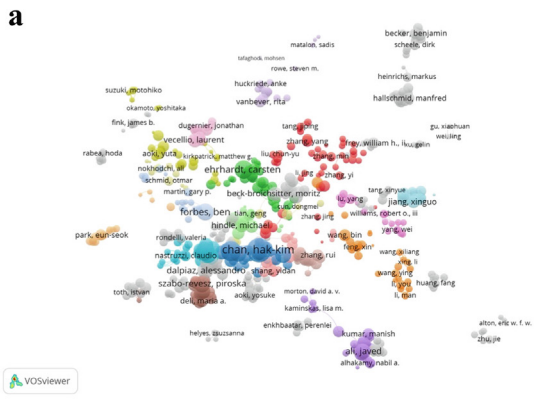
Collaborations of authors, countries/regions, and institutions

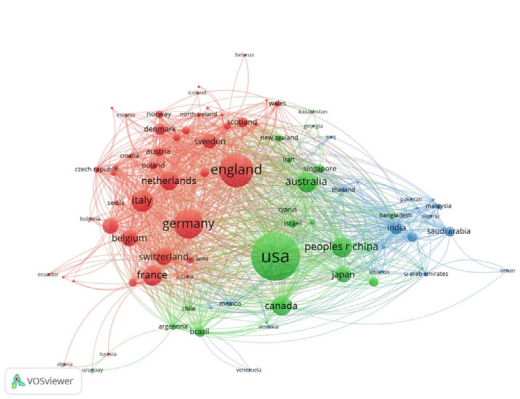
VOSviewer was used to analyze co-authorship across authors, countries/regions, and institutions to uncover global collaborations in this area. The 19 332 retrieved articles were written by 77 114 authors in total. The 601-author co-authorship network was separated into 39 clusters indicated by different colors (Figure 2a). The largest cluster was a red cluster of 48 writers mainly focused on Warren Finlay, and the collaborations between authors are continual. The co-authorship network, including 88 countries/regions, was divided into 10 clusters represented by different colors (Figure 2b). The cluster in red was made up of 21 Asian countries, with China, Japan, and India representing the core. A total of 12 062 institutions contributed to IDD research. The 999-institution co-authorship network was divided into 15 clusters represented by different colors (Figure 2c). The largest cluster was the red cluster, which included 198 institutions, mainly from America, centered on Harvard University and the University of California.

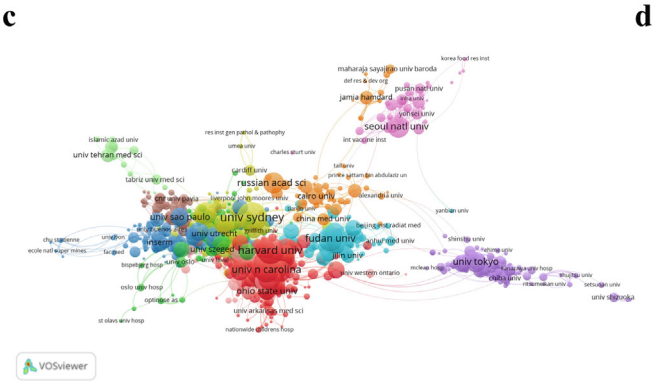
Approximately 77 113 writers from 12 063 research institutions in 126 countries/regions have contributed to the scientific research on this subject, demonstrating that IDD has piqued interest all over the world. There was substantial collaboration across countries/regions with no geographical boundaries. However, the collaborations between institutions from the same continent are closer. More than 90% of institutions contributing to IDD research were in the cooperation network, even though the cooperation between institutions in the same country was 'closed', i.e. the red cluster was dominated by American institutions, and Japanese institutions dominated the green cluster. The USA was the most productive nation and the hub of international collaboration. Thus, the USA is at the forefront of scientific and intellectual study, and their organizations are the leading institutions in IDD research in terms of quantity.

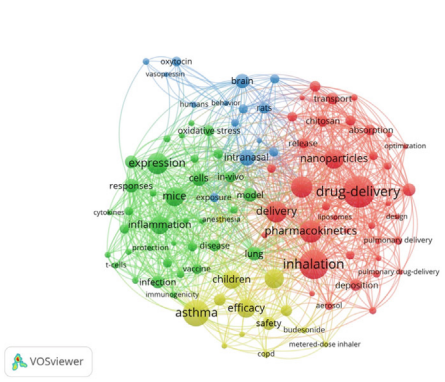
Co-occurrence analysis of keywords

Keywords cover the main topics of articles; therefore high-frequency keywords are suitable for co-occurrence analysis. The keywords from recent research were gathered from WoSCC and co-occurrence was analyzed via VOSviewer (Figure 2d). Table 1 displays the top 20 most frequent co-occurrence keywords about









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Top 25 keywords with the strongest citation bursts

Keywords	Year	Strength	Begin	End	2001 - 2022
Cholera toxin	2001	31.61	2001	2011	
Nitric oxide	2001	30.28	2001	2007	
Halothane	2001	24.61	2001	2007	
Guinea pig	2001	24.5	2001	2009	
Salbutamol	2001	22.98	2001	2009	
Heat labile enterotoxin	2001	22.81	2001	2006	
Nasal absorption	2001	22.58	2001	2010	
Beclomethasone dipropionate	2001	22	2001	2006	
Intranasal immunization	2001	21.35	2001	2011	
Mucosa	2001	21.02	2001	2011	
Isoflurane	2001	20.96	2001	2011	
Insulin	2001	20.46	2001	2009	
Airway hyperresponsiveness	2001	20.15	2001	2012	
Antibody response	2001	18.36	2001	2005	
Absorption enhancer	2001	18.21	2001	2007	
Fluticasone propionate	2001	17.32	2001	2006	
Absorption	2001	19.53	2002	2010	
Bronchial asthma	2002	17.51	2002	2009	
Inhaled insulin	2004	23.67	2004	2010	
Nose	2015	18.49	2016	2022	
Optimization	2016	34.23	2018	2022	
Intranasal delivery	2003	23.14	2018	2022	
Nanostructured lipid carrier	2016	18.89	2018	2022	
Impact	2010	17.3	2019	2022	
Nose-to-brain delivery	2020	21.35	2020	2022	

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TABLE 1

The top 20 keywords related to inhaled drug delivery.

Rank	Keyword	Count	Rank	Keyword	Count
1	Drug delivery	2018	11	Asthma	737
2	Expression	1092	12	Formulation	730
3	Inhalation	1087	13	Pharmacokinetics	713
4	*In vitro*	1084	14	Model	699
5	Delivery	1072	15	Nanoparticles	684
6	Therapy	926	16	Infections	683
7	Efficacy	870	17	Response	651
8	Mice	819	18	System	648
9	Children	769	19	Inflammation	608
10	Cell	747	20	Rat	580

IDD derived from the analysis of keywords from all 19 332 articles retrieved via VOSviewer and ranked based on their counts. Drug delivery (n = 2018), expression (n = 1092), inhalation (n = 1087), and *in vitro* (n = 1084) were the highest-frequency keywords appearing in the articles. Moreover the strength of the keyword bursts was investigated to explore research frontiers, hotspots, and emerging trends over time. As shown in Figure 2e, the top 25 keywords with the strongest citation burst were divided into two parts based on the timeline. Part 1 was mainly about the application of IDD in respiratory disease through traditional means, while part 2 was mainly about novel nose-to-brain delivery to treat neurological diseases, such as Parkinson's disease and Alzheimer's disease (AD). Moreover, the citation bursts in part 2 mainly occurred in recent years, indicating that IDD to the brain is the latest trend in this area and has huge potential.

Co-citation analysis of references

In our work, the 19 332 retrieved publications cited 328 216 references. After clustering these keywords, CiteSpace automatically divided all keywords into nine groups based on their similarity (Figure 3a, b). According to the results, 'nose-to-brain delivery' (#0) was the largest cluster, followed by 'trimethyl chitosan' (#1), 'inhalation' (#2), 'chitosan' (#3), 'oxytocin' (#4), 'microdialysis' (#5), 'stress' (#6), 'inhaled insulin' (#7), and 'Parkinson's disease' (#8). Then, a timeline of these clusters was formed via CiteSpace to represent how the research and hotpots have changed over time (Figure 3c). 'Nose-to-brain delivery' (#0), and 'Parkinson's disease' (#8) were the newest topics in recent years according to the timeline, indicating that an emerging trend in IDD is the utilization of IDD to the brain. Meanwhile, the 'trimethyl chitosan' (#1) and 'chitosan' (#3) clusters represented the utilization of micro/nanoparticle systems for IDD.

Emerging frontiers in inhaled drug delivery research

The emerging frontiers of IDD research can be conveniently disclosed by co-occurrence analysis of keywords and co-citation analysis of references. As indicated in Figures 2e and 3c, the citation burst visualization map of the top 25 keywords and timeline visualization map of co-cited references mostly relate to emerging frontiers in the application of IDD for drug delivery to the brain according to the keywords from part 2 and clusters #0, #7, and #8. The citation bursts of keywords and timeline visualization map of co-cited references helped us elucidate the development and future direction of this field and improved our understanding of subtopics of IDD. Based on the above analysis, as shown in Figure 4, four IDD subtopics can be distinguished.

Micro/nano inhaled drug delivery system

Microparticles and nanoparticles (M/NPs) are microscopic particles with micro (1–1000 μm), submicron (100–1000 nm), or nanometer (1–100 nm) scales that are frequently surface modified to increase stability and introduce functional or multifunctional features.[p13] Currently, researchers are increasingly interested in M/NPs that increase bioavailability to target locations and have achieved continuous release at a lower internal dose with minimal toxicity, exceeding the limitations of traditional delivery techniques.[p14] In designing M/NPs drug delivery systems, M/NPs features such as particle size, composition, shape, surface charge, and surface functioning all play significant roles.[p15] The physicochemical stability, biological stability in bronchioles, drug loading, drug entrapment effectiveness, sustained release, and *in vivo* performance of the nanoparticles can all be impacted by these characteristics. While the inhalation of M/NPs has primarily been explored in terms of toxicology, it is important to note that the unusual properties of particular nanosized materials may also be advantageous in the creation

FIGURE 2

(a–c) Co-authorship visualization map of authors, countries/regions, and institutions from 2001 to 2022 generated via VOSviewer. **(d)** Co-occurrence visualization map of keywords from 2001 to 2022 generated via VOSviewer. **(e)** Citation burst visualization map of the top 25 keywords generated via CiteSpace.

of pulmonary drug carriers.[p16] Such pharmacological nanocarriers must obviously be made from biocompatible and biodegradable materials, and as with any novel medication, proper preclinical and clinical trials are required to verify their quality, safety, and efficacy. Currently, the design of inhalers and improvements in particle engineering have helped researchers construct highly accurate IDD systems.[p13] The application of micro/nanotechnology in particle engineering has led to some of the most promising developments.[p17] These have produced several novel systemic administration formulations and fresh perspectives for therapy. Various M/NP-based formulations are widely used in IDD systems to treat different types of diseases. Here, we divide them into three categories: polymer-, surfactant-, and inorganic-based M/NPs.

Polymeric M/NPs are excellent candidates for drug delivery that provide several advantages, as they are biodegradable and biocompatible.[p18] Most importantly, natural polymers, synthetic polymers, and a mix of natural and synthetic polymers can all be used to synthesize polymeric M/NPs.[p19],[p20],[p21] Three well-known polymer-based transport carriers are poly (lactide-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and poly(lactic acid).[p22] PLGA M/NPs exhibit the benefits of low toxicity, good biocompatibility, and strictly controlled drug release.[p23] Moreover, the problems of low-efficiency delivery of the particles to the lung and phagocytosis by alveolar macrophages can be solved by PLGA M/NPs. For instance, Yang et al. demonstrated that afatinib-loaded PLGA M/NPs may be a prospective delivery strategy for lung cancer treatment, in which they achieved highly efficient delivery to the tumor site but had low concentrations in other tissues.[p24] Furthermore, M/NPs are commonly coated with biodegradable PEG and PLA as a gatekeeping layer, which might lessen particle clearance by macrophages and enhance aerosolization. Fiegel et al. combined PEG with IDD to evade phagocytic clearance and provide controlled release for efficacious and prolonged delivery to the lung.[p25] To improve polymeric particles' lung retention and accomplish effective penetration and high lung accumulation, the PEGylation approach is employed to alter the particles.

One essential component of drug delivery that targets the lung is pulmonary surfactant.[p26] It is vital to consider the role of pulmonary surfactant, a thin film with lipid and protein covering the respiratory surface of the lungs.[p27] Moreover, pulmonary surfactant could maintain the pulmonary fluid balance and create a natural barrier against xenobiotics, transferring inhaled particles to prevent adherence in the upper airways; this modulates the ability of drugs to reach alveoli, thus affecting the drug delivery efficiency.[p28] Against this background, the idea of utilizing pulmonary surfactant as a transporter over the respiratory air–liquid interface was developed, increasing the delivery efficiency of hydrophobic drugs; experiments have proven its potential.[p29] These studies have mostly specialized in drug delivery with limited water solubility. However, surfactant-based M/NPs could also optimize the interaction and association of pulmonary surfactant with hydrophilic molecules and hydrophobic chemicals in their membranes for transportation. For instance, Kotta et al. designed an endogenous surfactant-based liposomal naringin delivery platform, a noninvasive formulation that supports efficient treatment of pulmonary fibrosis.[p30] Moreover, surfactant-based M/NPs could increase drug uptake with better therapeutic effects, establishing a novel delivery strategy for IDD.

Inorganic M/NPs offer benefits over polymer- and surfactant-based M/NPs for IDD because of their great stability and distinctive material- and size-dependent physicochemical characteristics.[p31] Currently, a variety of inorganic-based M/NPs with various structures have attracted extensive attention. Silica (Si) NPs have been widely applied in a variety of industries owing to their relatively affordable price, excellent biocompatibility, and controllable manufacturing.[p32] Napierska et al. examined the effect of monodisperse amorphous Si NPs of different diameters on endothelial cell function. They found that Si NPs enhanced cell-adhesive properties.[p33] In addition, dry powder aggregates of biocompatible Si NPs have been manufactured for potential development as IDD vehicles, producing NPs with both the desired morphology and excellent aqueous redispersibility.[p34] Nowadays, metal nanoparticles have a wide range of applications and play a crucial role in drug delivery as well as IDD. Aurum (Au) NPs are inorganic materials that offer high potential in drug delivery due to their application in magnetic resonance imaging and triggering of hyperthermia for photothermal therapy. They are stable, biocompatible, and could be easily functionalized.[p35] Silva et al. proved that strawberry-like Au NPs could be potential drug vehicles for IDD with high pulmonary-targeting efficacy.[p36] Other types of inorganic NPs, such as TiO_2 NPs,[p37] CaP NPs,[p38] ZnO NPs,[p39] CeO_2 NPs,[p40] and $MnFe_2O_4$ NPs,[p41] all have broad application prospects in IDD.

In conclusion, different M/NPs offer various benefits and drawbacks. For instance, the synthesis of inorganic M/NPs still necessitates the use of costly organic solvents or inorganic chemicals. Furthermore, there is still great concern about the toxicity and *in vivo* clearance of inorganic M/NPs. In contrast, polymer- and surfactant-based M/NPs show superior biocompatibility, biodegradability, and surface modification, but their subsequent application in the IDD is still constrained by larger M/NP size, limited target efficacy, and manufacturing challenges.

Manifestations of inhaled drug delivery

The dosage form of IDD in clinical use is inhalers. Inhalers can be divided into three types, nebulizers,[p42] dry powder inhalers (DPIs),[p43] and metered-dose inhalers (MDIs),[p44] as shown in Figure 5. In practical applications, it is necessary to select suitable inhalers according to the effectiveness of drug inhalation and patient factors, taking into account the advantages and disadvantages of different inhalers.

Although the inhaler's design has not changed much over time, some elements have led to advancements that provide new prospects for the treatment of diseases. The invention of vibrating mesh systems was the most important advancement in nebulizer technology.[p45] The eFlow (Pari) and iNeb (Philips) are the two most notable vibrating mesh systems.[p46],[p47] Even though the technology has been around for a while, the applications seem to be expanding the range of drug delivery sizes from extremely small (single micrograms: treprostinil and iloprost) to enormous (dozens of milligrams: tobramycin).[p48] Additionally,

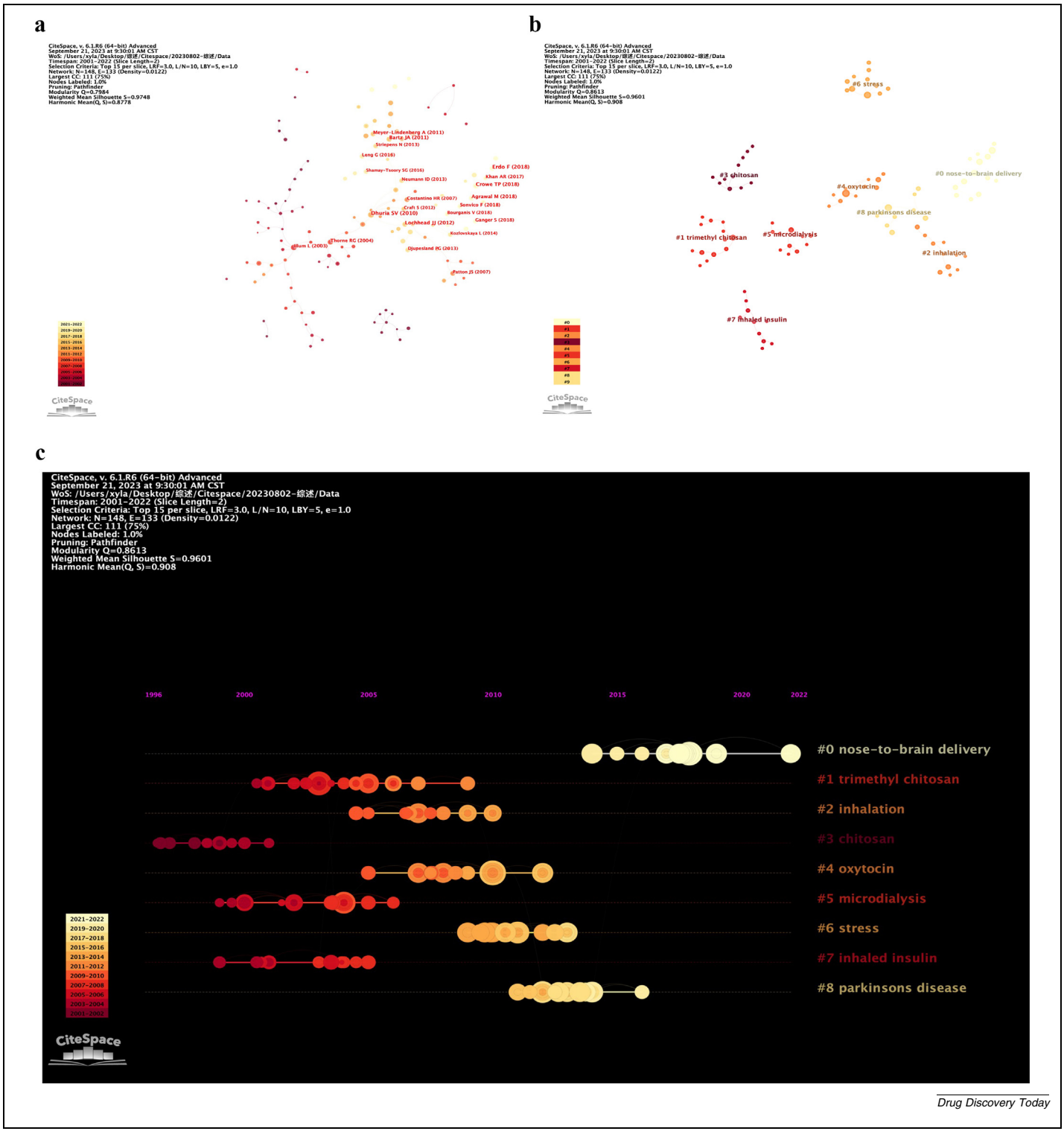

FIGURE 3

(a, b) Co-cited visualization map of references and reference clusters from 2001 to 2022 generated via CiteSpace. **(c)** Time line visualization map of co-cited references from 2001 to 2022 generated via CiteSpace.

the novel possibility of vaporizing vibrating mesh nebulizer output to produce an aerosol that may be inhaled using a nasal cannula has been investigated. The addition of hygroscopically growing excipients in this aerosol causes an increase in peripheral lung deposition.[(p49)]

MDI technology has gradually advanced in terms of improved actuator orifice inserts and diameters, as well as elastomers, O-rings, and seals that are compatible with the switch from chlorofluorocarbons (CFCs) to hydrofluoroalkanes (HFAs) as the propellant, where the loss of stratospheric ozone was related to CFC-

induced environmental damage.[p50] These are crucial to the goods they support, although they have no impact on the device's fundamental principles of operation. The introduction of counters and the investigation of electronic patient data recording systems, which may potentially result in significant advancements in customized treatment, are possibly the most significant recent breakthroughs in MDI technology.[p51]

Three main elements make up DPI technology: the formulation, the metering equipment, and the aerosol dispersion properties.[p52] Every inhaler on the market today is passively activated in response to the patient's inspiratory flow. One of the most important breakthroughs at the start of the new century was the regulatory approval and marketing of Advair/Seretide (GlaxoSmithKline).[p53] The salmeterol xinafoate/fluticasone dipropionate combination, the first dry powder product for asthma maintenance medication, notably includes a long-acting β2-agonist, unlike previous combination formulations. The approval of Ellipta devices, which can deliver two drugs independently from two different blister strips, was one of the most important developments of the past 10 years in this regard, avoiding the difficult task of ensuring combination drug stability and optimizing the performance of two drugs from a single formulation.[p54]

However, drug delivery via IDD is not as simple as oral medications. One of the reasons for this is the poor inhaler technology.[p55] Although most nebulizers can be operated with relaxed breathing, patients still misuse them via coughing, not properly installing the nebulizer equipment, or taking the facemask away. The main issues in inhaler technique for MDIs are not activating the inhaler while inhaling (poor compliance) and failing to reach the alveolated airways. As for DPIs, insufficient inhalation force and device-specific handling and preparation errors, such as incorrect device orientation, are the main concerns. These difficulties constitute significant hurdles to both the pharmaceutical industry and medical workers. In the current period, it is generally accepted that because of the benefits provided by the pulmonary route, the obstacles that the route brings are worth overcoming. If these issues were to be successfully solved, it would have enormous potential to fulfill unmet clinical requirements.

Barriers to inhaled drug delivery

In IDD, the lung defense systems that a drug particle may come into contact with can act as barriers, such as mechanical and immunological barriers.[p56] The conducting (tracheobronchial) airways of the lungs, the alveolated airways, and the upper (extrathoracic) airways make up the human respiratory system. The upper airways (nasal and oropharyngeal), which are small, angled channels with a range of sizes, are ideal locations for inertial impaction, which prohibits particles from entering the lungs.[p57] Inhalation through the mouth is preferred for distribution into the lungs since the nasal passages serve as a particularly effective aerosol 'filter'. The lungs are composed of an intricate web of branching airways known as the 'bronchial tree'. A particle must cross several airway bifurcations where it may be deposited to reach the alveolated area and reach the large epithelial target location.

Although there are several definitions of what constitutes a 'fine particle', an aerosol with an aerodynamic diameter of less than 5 μm is needed to deliver to the whole lung.[p58] Particles of an even smaller size, such as an aerodynamic diameter of 3 μm, are needed for delivery to the alveolar epithelium.[p59] Deposition, however, is also highly dependent on inhalation factors, including the inhaled flow velocity, inhaled volume, and breathhold pause. The inhaled flow rate for drugs delivered by MDI should be slow, but for drugs delivered by DPI, a 'quick', 'fast', or 'forceful' inhalation is typically advised in patient instruction leaflets because the shear forces produced by such inhalations are used to disperse the drug powder and ensure a sufficiently high respirable dose.[p60] Less than 20% of the dosage is typically deposited in the lungs by most inhalers,[p61] with the

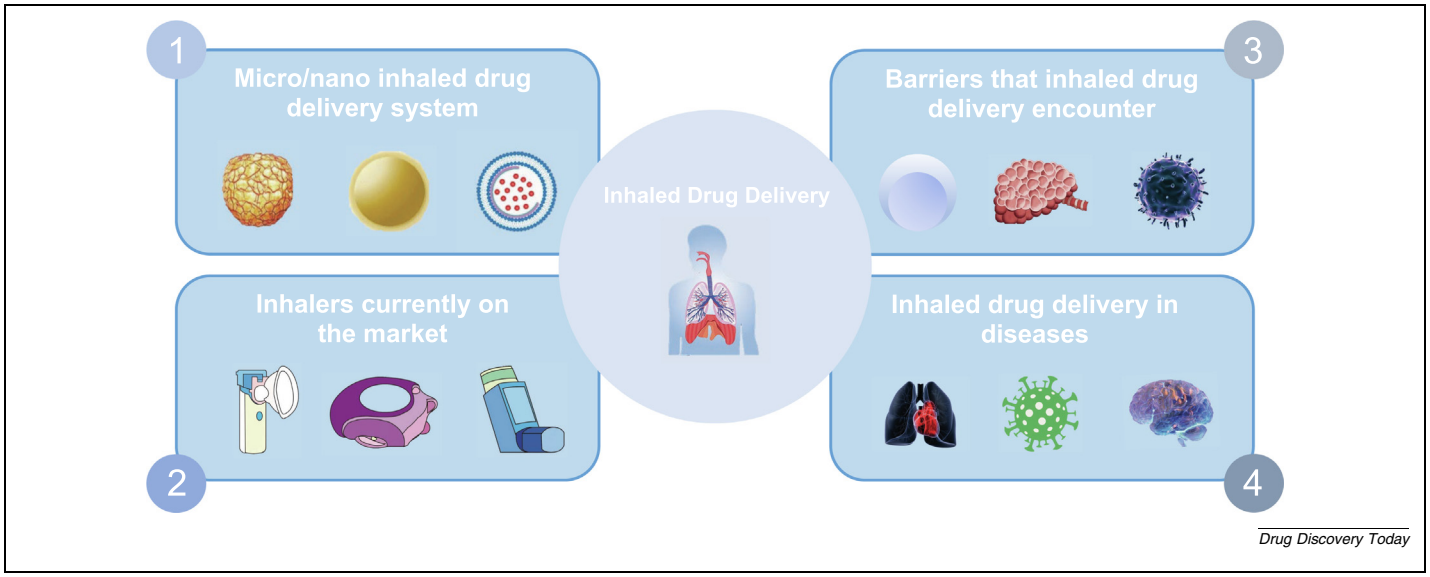

FIGURE 4
Schematic diagram of IDD subtopics.

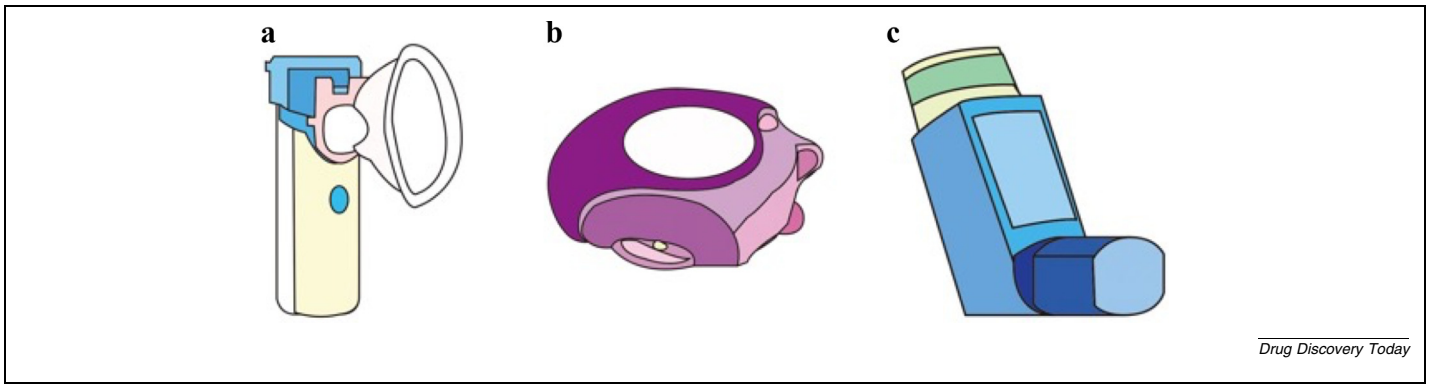

FIGURE 5
Schematic diagram of **(a)** nebulizer, **(b)** DPI, and **(c)** meter-dose inhaler.

bulk typically being retained in the device (for nebulizers) or the oropharynx (for MDIs and DPIs).

A gel layer sits on top of a liquid layer that contains cilia in lung mucus. A natural lung defense system called lung mucociliary clearance works to remove deposited items from conducting airways and transport them to the oropharynx, where they can be swallowed or expectorated.[p62] Within 24 hours, the tracheobronchial airways of a healthy lung are free of any deposition. Mucociliary clearance may be advantageous if it directs deposited medication toward target sites from less desirable locations, but it may be harmful if it directs drugs away from target sites. In addition, the immunological barrier made up of alveolar macrophages cannot distinguish between possibly hazardous and potentially advantageous compounds.[p10] Particles of the drug might be taken up by macrophages and removed from the lungs, perhaps through the lymphatic system or by moving them to the foot of the mucociliary escalator.

The wide application of inhaled drug delivery in diseases

According to the 19 332 articles we retrieved, IDD can be applied not only in respiratory diseases but also in other fields. At present, many innovative IDD products are marketed or are under research worldwide, such as antibiotics for infectious diseases [cystic fibrosis (CF)], vaccines against viruses (influenza and COVID-19), and systemic drugs with poor efficacy through oral administration (insulin for diabetes and levodopa for Parkinson's disease patients in the intermittent period). The first inhaled insulin, developed by Pfizer under the trade name Exubera, was approved by the US FDA on January 26, 2006. However, due to the product's poor patient compliance and many safety concerns in clinical practice, it was withdrawn from the market in 2007. Afrezza was developed by MannKind and was the second inhaled insulin product to be launched globally after Exubera. MannKind did not abandon the development of inhaled insulin due to the failure of Exubera and continued to invest billions of dollars in the Afrezza project. Afrezza finally debuted in 2014 and obtained FDA approval for marketing. In Table 2, we summarize the innovative IDD products that have been approved. Moreover, we also rereview basic research on IDD in various diseases, indicating the broad application of IDD.

Lung cancer

Lung cancer is the main cause of mortality globally.[p63] The currently available therapeutic methods (intravenous or oral drug administration) are typically accompanied by several systemic and dose-related side effects and are ineffective at accumulating the given medicine into the target tumor cells.[p64] In comparison to intravenous and oral delivery, the pulmonary drug delivery approach would permit the preferential accumulation of medicine within the cancer cell, hence being superior in lowering cancer cell growth and minimizing systemic side effects. Lung cancer therapy with inhaled site-specific medication delivery is both practical and effective. The IDD method bypasses first-pass metabolism, gives great bioavailability at a low dosage, and is noninvasive.[p65] Inhalation therapy has been explored in combination with different anticancer drugs, such as chemotherapeutics, proteins, and gene therapy, with significant outcomes.[p66] For instance, afatinib-loaded inhalable PLGA nanoparticles solve the problem that clinical application of afa-

TABLE 2
Innovative inhaled drug delivery products.

Trade Name	Drug	Manufacturer	Indication	Released to market
Exubera	Insulin	Nektar, Pfizer	Diabetes	2006[a]
Adasuve	Loxapine	Alexa Pharm	Schizophrenia	2012
Tobi	Tobramycin	Novartis	Cystic Fibrosis	2013
Afrezza	Insulin	MannKind/Sanofi	Diabetes	2014
Inbrija	Levodopa	Acorda Therapeutics	Parkinson's Disease	2018
Valtoco	Diazepam	Neurelis	Epilepsy	2020
Tyvaso	Treprostinil	MannKind/United Therapeutics	Pulmonary Hypertension	2022

[a] Withdrawn in 2007.

tinib alone is highly limited by its poor solubility and consequently low bioavailability.[p67] In addition, researchers designed human ferritin heavy-chain nanocages that are capable of rapidly penetrating both lung tumor tissue and the mucus layer to protect the airway.[p68] Thus, the application of IDD provides benefits as adjuvant therapy for lung cancer patients.

COVID-19

Recently, the COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) occurred, characterized by rapid spread and a high incidence rate of clinical sequela worldwide.[p69] Significant efforts have been made to prevent the deterioration of lung function, including the use of ventilators to promote gas exchange in extreme cases.[p70] However, as the pathogenesis of the disease becomes better understood, the ability to maintain lung patency is key to survival. Remdesivir is one of the most promising anti-SARS-CoV-2 drugs. Its therapeutic value is debatable due to its limited clinical effects, which may be attributed to the low lung accumulation and activation of remdesivir. As a result, scientists created lyophilized remdesivir liposomes that can be reconstituted as pulmonary liposomal aerosol. Liposome encapsulation endowed remdesivir with much higher solubility and better biocompatibility.[p71] Additionally, IDD has been utilized in other types of anti-SARS-CoV-2 drugs, such as inhaled edoxaban dry powders and triazavirin.[p72],[p73] In conclusion, the combination of anti-SARS-CoV-2 drugs and pulmonary delivery will be a potent formulation to improve drug efficacy and exert better therapeutic effects in COVID-19 treatment.

Cystic fibrosis

CF is an autosomal recessive disease that affects several organs, with the lungs being the most severely affected, ultimately resulting in death in 90% of sufferers[p74] due to a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[p75] A faulty CFTR gene causes thick, sticky mucus to misbalance waterflow, leading to a hyperdense mucus and persistent biofilm-mediated infections in the airways.[p76] Since oral antibiotics are inadequate for treating *Pseudomonas* infections in the lungs, injections have always been necessary. However, it was shown that inhalation can achieve high sputum concentrations of antibiotics while reducing systemic administration.[p77] Early in the 1980s, CF patients received inhaled antibiotics by inserting injectable formulations in nebulizers.[p78] These medications, such as gentamicin, carbenicillin, and colistin, need dosages of several hundred milligrams, which can be easily provided by nebulizers but are too big to be administered by MDI or by most forms of DPI.[p10] To improve patient acceptance, a tobramycin formulation made specifically for inhalation was created in the 1990s. This medication (TOBI; Novartis, Basel, Switzerland) had a 300-mg nominal dosage that was to be taken twice daily on a 4-week-on, 4-week-off schedule. It was shown to be both reliable and secure when used over an extended period of time.[p78] Another inhaled antibiotic that is prepared as a solution and permitted for administration by a vibrating mesh nebulizer is aztreonam (Cayston; Gilead, Foster City, CA, USA),[p79] indicating that IDD may be a better choice for treatment than injections for local pulmonary delivery.

Mycobacterium tuberculosis

Mycobacterium tuberculosis, the bacterium that causes tuberculosis, is one of the top 10 causes of mortality in the world, ranking above HIV/AIDS.[p80] When treating drug-susceptible tuberculosis, the typical four-drug regimen administered daily for 6 months has been shown to be highly successful, with cure rates of between 90% and 95% both in clinical trials and in the therapy of tuberculosis control programs.[p81] However, the present medication regimen has several drawbacks: patients must be given high doses of pharmaceuticals, there is a significant pill load, there are severe drug side effects, and individuals stop the therapy sooner.[p82] IDD for the treatment of tuberculosis has numerous benefits, including improved targeting to the infected alveolar macrophages and quick action on the target.[p17] Singh et al. found that DPI was an excellent adjuvant to the first-line therapy of isoniazid and rifabutin, with preclinical efficacy and safety/tolerability.[p83] Additionally, the inhalable formulation, mucus-penetrating microparticles (NAC/PLGA-MPP), had a good therapeutic effect on tuberculosis.[p84] Thus, inhalable antituberculosis medications may be a viable therapeutic strategy that might help to effectively eradicate tuberculosis while also enhancing patient adherence to the regimen.

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a type of disease caused by a cardiopulmonary arterial pressure disturbance that sets off a chain of fatal events at the intersection of capillaries and alveoli.[p85] The main therapeutic targets for PAH are soluble guanylate cyclase modulators.[p86] Due to its better delivery capabilities, including delivering certain relatively low-dose molecules to the deep lungs, targeted delivery to the pulmonary alveolus has been the predominant strategy. As systemic side effects must be reduced and a speedier onset of action is needed, this approach offers advantages.[p4] The pulmonary route also has several drawbacks related to respiratory barriers that might interfere with medication retention and, consequently, drug availability in the lungs.[p10] According to research, inhalable PLGA particles of sildenafil may be utilized as an alternative to oral sildenafil in the treatment of PAH since they prolong the medication's release, cause pulmonary-specific vasodilation, and minimize systemic exposure to the drug.[p87] Although the inhalation route may be useful to some extent, the limited half-life and off-target adverse effects of drugs necessitate the development of effective new carriers to target pulmonary sites in PAH.

Cerebral diseases

Oral and parenteral administration are the most common drug administration routes to treat cerebral diseases. Such an effort lessens the effectiveness and potency of pharmacological therapy. However, the efficacy of this administration route is limited because of the low passing rate of active compounds to the brain from the blood.[p88] The existence of the BBB prevents nearly all substances from entering the brain to protect it from injury. Additionally, systemic clearance (in the oral and parenteral modes) and first-pass metabolism (oral delivery) also considerably lower drug bioavailability.[p89] The IDD route evolved as a practical method that avoids the BBB and delivers the medication directly to the brain via the nasal cavity, obviating the com-

plications of brain drug delivery.[p90] Based on various studies, the IDD route of drug delivery to the brain circumvents the drawbacks of systemic drug administration and speeds up the drug delivery process,[p91] offering a noninvasive and effective way to treat CNS disorders.[p92],[p93] Thus, the IDD route has become a preferred method of drug delivery to the systemic circulation along with topical application.[p94] William H. Frey II introduced the concept of using the intranasal route to directly delivery therapeutically active compounds to the CNS in 1989.[p95] Subsequently, investigations focused on the IDD of insulin to the brain for the treatment of AD. It was soon discovered that in addition to insulin, a number of other proteins and peptides are effectively transported to the brain via the IDD pathway.[p96]

AD is a disease of aging defined by cognitive deterioration.[p97] Additionally, insulin dysregulation is linked to this disease, and AD patients have lower cerebrospinal fluid (CSF) insulin levels, higher plasma insulin levels, and a lower CSF-to-plasma insulin ratio than healthy people.[p98] The intranasal administration of 20 IU insulin daily resulted in increased CSF insulin and improved delayed story recall (recalling a story 20 minutes after it was read to participants) in AD patients.[p99] Recently, researchers found that proresolving lipid mediators can rescue memory and gamma oscillation impairment in animals.[p100] A study from the University of Navarra in Spain found that repeated short-term inhalation of menthol can regulate the immune system and prevent the cognitive decline typical of this neurodegenerative disease.[p101] However, most of the novel platforms for the treatment of AD via IDD remain in the animal experiment phase. Nevertheless, the appearance of IDD brings hope to AD patients.

Concluding remarks: perspectives in inhaled drug delivery research

This groundbreaking study performed a thorough bibliometric analysis of IDD research. It examined publication trends, global collaborations, and dominant research themes from 2001 to 2022, offering a comprehensive overview that could guide future research in this area. The citation burst visualization map of the top 25 keywords and the timeline visualization of co-cited references reveal that the IDD field is rapidly evolving, driven by various innovative trends. A significant area of focus is the application of nanotechnology in IDD systems, where nanoparticles are being explored for their potential to enhance drug solubility, bioavailability, and targeted delivery, especially to specific lung lesions or cells. Concurrently, there is a growing emphasis on personalized medicine and precision drug delivery, tailoring treatments based on individual genetic profiles, disease states, and biomarkers to optimize efficacy and reduce adverse effects. The development of smart inhalation devices, equipped with sensors and remote monitoring, is another frontier promising improved disease management through accurate tracking of medication usage. Another promising area is the direct inhalation of drugs for delivery to the brain for treating cerebral diseases, a method that could bypass the BBB and offer more effective treatments. Environmental and safety considerations are also paramount, with a push toward developing ecofriendly and safe IDD systems. Finally, enhancing patient compliance and adherence through user-friendly inhalation devices is a critical area of focus. Overall, the future of IDD research is oriented toward creating more efficient, safer, and personalized delivery systems, leveraging technological advancements to overcome existing challenges in the field.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Xinyuan Li: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Zhengxing Su:** Data curation, Resources. **Chunyou Wang:** Data curation, Resources. **Wen Wu:** Supervision, Writing – review & editing, Funding acquisition. **Yan Zhang:** Supervision, Writing – review & editing, Project administration. **Chenhui Wang:** Funding acquisition, Supervision, Writing – review & editing.

Data availability

No data was used for the research described in the article.

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