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Achievements and challenges of targeted drug delivery to a human respiratory tract: Bridging traditional and novel approaches to modelling and clinical needs

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ABSTRACT

Achievements and challenges of targeted drug delivery to a human respiratory tract are summarised. These include an analysis of the means of targeted drug delivery, which were used in the past, are currently available, and are expected to be used in the future. Particular attention is paid to the prioritisation of drugs and means of their targeted delivery. This analysis is followed by a description of pharmacological, experimental and theoretical advances in targeted drug delivery to a human respiratory tract. A description of the theoretical advances focuses on the theoretical tools currently available and used for the analysis of drug delivery processes, and those which were developed for different applications, mainly in engineering, but could potentially be applicable to the analysis of drug delivery processes in human airways. The latter include the full Lagrangian approach, and recently developed models of mono- and multi-component, and spherical and non-spherical droplet/aerosol heating and evaporation. Particular attention is given to molecular dynamics approaches to modelling aerosols, including their dynamics, heating and evaporation.

Contents

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1. Introduction

Targeted drug delivery is a rapidly advancing field, driven by the need for safe, effective, and patient-friendly therapies. In respiratory diseases, localised drug action via inhalation enhances treatment precision and minimises side effects. The growing prevalence of chronic bronchopulmonary diseases has prompted the development of new therapeutic molecules, advanced targeting strategies, and safer delivery methods, including targeted vaccines (Topol & Iwasaki, 2022; Wu, Huang, Zhang, Wu, et al., 2021; Ye, Jiao, Li, He, et al., 2023).

Chronic respiratory diseases, such as bronchial asthma (BA), chronic obstructive pulmonary disease (COPD), and occupational lung diseases, are among the leading global causes of morbidity and mortality (GBD, 2018). According to the 2017 Global Burden of Disease Study, over 500 million people (7.13% worldwide) suffer from chronic respiratory conditions, with COPD (3.92%), BA (3.57%), interstitial lung diseases and sarcoidosis (0.08%), and pneumoconiosis (0.007%) being most common (Soriano, Kendrick, Paulson, Gupta, et al., 2020). Prevalence is the highest (10.6%) in high-income countries (e.g. the USA, Germany, Japan), and lowest in sub-Saharan Africa (5.1%) and South Asia (5.5%).

Inhalation therapy remains the cornerstone of treatment, especially for obstructive pathologies.

Over four years have passed since the beginning of the SARS-CoV-2 pandemic, and it remains a global challenge, with official deaths nearing 7 million, though WHO estimates the true toll to be over 14.9 million (Hassan, Aljabali, Panda, Ghosh, et al., 2021; World Health Organisation, 2022). Vaccination efforts, including mRNA and vector vaccines, have shifted the focus to prevention, reducing severe cases and saving lives (Ao, He, Liu, & Xu, 2023; Labouta, Langer, Cullis, Merkel, et al., 2022). mRNA vaccines, like those from Moderna and Pfizer, use the body's machinery to produce antigens, marking a breakthrough in vaccine technology (Labouta et al., 2022).

Lipid nanoparticles (LNPs) are the leading drug delivery technology due to their high efficacy and safety (Ao et al., 2023; Chaudhary, Weissman, & Whitehead, 2021; Hou, Zaks, Langer, & Dong, 2021; Labouta et al., 2022). The rapid FDA approval of LNP-based mRNA COVID-19 vaccines highlights the growing demand for advanced delivery strategies. The first clinical trial of an inhaled COVID-19 vaccine demonstrated the safety and immunogenicity of an Ad5-nCoV-based vector, showing similar immune responses to intramuscular administration (Li, Wu, Guo, et al., 2022; Wu et al., 2021). Studies have also confirmed the effectiveness of aerosol vaccines as booster doses and explored new delivery technologies, such as PACE-mRNA polyplex complexes and microfluidic microsphere-based aerosols (Loo, Lee, & Zhou, 2023; Ye et al., 2023).

Inhalation is a key route for treating bronchopulmonary diseases, as particles under 5 μm reach the respiratory tract's terminal areas, ensuring targeted effects with some systemic absorption (Laube, Janssens, de Jongh, & Devadason, 2011). This method offers advantages over oral or injectable drugs, though its efficiency depends on particle size, inspiration effort, and disease-related changes in lung structure, ventilation/perfusion ratio and airflow (Avdeev, 2013).

Despite advances in inhaler technology and pharmacology, targeted drug delivery remains challenging due to factors such as device design, drug properties, and anatomical and physiological barriers (Liang, Pan, Vllasaliu, & Lam, 2020). Critical errors in using an inhaler further limit its effectiveness, with studies showing high error rates, especially for pMDIs and DPIs (Usmani, Lavorini, Marshall, Dunlop, et al., 2018). Successful inhalation therapy relies not only on selecting the right drug but also on effective delivery to the respiratory tract. The optimisation of drug deposition requires synergy between the drug, dosage form, and delivery device. For all ages and disease stages, an ideal inhaler should maximise lung deposition and be easy to use, reliable and affordable (Avdeev, 2013). Patient breathing patterns also impact drug delivery.

The diameters of the respiratory tracts control the average flow velocity of the aerosol-containing air in the lung and the total number of particulates to which the lung is exposed. Respiratory frequency affects the residence time of aerosols in the lungs and, hence, the probability of deposition by gravitational and diffusional forces. Lower ventilation rates increase deposition in the bronchiolar region, while higher rates shift deposition to the bronchial region. Breathing patterns affect where aerosols of different sizes settle: breathing frequency mainly impacts smaller aerosols (with diameters of the order of 10^{-7} m), while ventilation rate, which is a product of breathing frequency and tidal volume, controls the deposition of larger aerosols (Pilou, 2020). With increased physical activity, the modelled alveolar deposition fraction of ultrafine aerosols (with diameters in the range 0.005–0.1 μm) rises

Abbreviations

AMR	Adaptive mesh refinement
BA	Bronchial asthma
CFC	Chlorofluorocarbon
CFD	Computational Fluid Dynamics
CFF	Consistent Force Field
COMPASS	Condensed-phase Optimised Molecular Potential for Atomistic Simulation Study
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CVFF	Consistent Valence Force Field
DDS	Drug delivery systems
DPI	Dry powder inhaler
DPM	Discrete phase model
FDA	Food and Drug Administration of the USA
FLA	Full Lagrangian Approach
FV	Finite volume
GBD	The global burden of diseases, injuries, and risk factors study
gFLA	generalised FLA
HFA	Hydrofluoroalkane
HRT	Human respiratory tract
ICS	Inhaled corticosteroids
LABA	Long-acting β2-agonists
LAMA	Long-acting muscarinic antagonist
LBM	Lattice Boltzmann Method
LDA	Laser Doppler Anemometry
LES	Large Eddy Simulation
LNPs	Lipid nanoparticles
MABA	Drugs with both mAChR antagonism and β2-AR agonism in the same molecule
mAChR	M-cholinergic receptor
MCBC	Mucociliary clearance boundary condition
MD	Molecular dynamics
MMAD	Mass median aerodynamic diameter
mRNA	messenger Ribonucleic acid
OPLS	Optimised Potentials for Liquid Simulations
PEG	Polyethylene glycol
PIV	Particle image velocimetry
PLGA	Polylactic-co-glycolic acid
pMDI	Pressurised metered-dose inhaler
QMOM	Quadrature Method of Moments
SMI	Soft mist inhaler
VOF	Volume of Fluid
WHO	World Health Organization

by 70% in adults and 40% in children. In contrast, bigger aerosols (with diameters greater than 0.1 μm) deposit less in the alveolar region and more in the extra-thoracic (from nose/mouth to larynx) region (Linell, Isaxon, Olsson, et al., 2024).

Common delivery systems include pMDIs, DPIs, soft mist inhalers, and nebulisers (Dongare & Narkhede, 2023; Martin & Finlay, 2015; Roche & Dekhuijzen, 2016; Ye, Ma, & Zhu, 2022). Developing integrated drug-device systems may be key to enhancing inhaler effectiveness and patient outcomes (Hoppentocht, Hagedoorn, & Frijlink, 2014). Smart inhalers providing treatment monitoring and feedback help address improper inhalation techniques, though patient education remains crucial (Cataldo, Hanon, Peché, Schuermans, et al., 2022; Newman, 2017). There is a need for pMDIs that function independently of air flow rate (Ari & Fink, 2020). The optimisation of drug formulation, delivery methods, and physicochemical properties is key to safe and effective therapy. Research has explored new nebuliser technologies, including jet, ultrasonic, and mesh systems, with aeration improving droplet distribution (Naidu, Kahraman, & Feng, 2022; Ochowiak & Matuszak, 2017; Xie, Zeng, Gui, Ma, et al., 2023). Studies confirm that airflow rate, surface tension, and viscosity impact aerosol delivery efficiency, influencing targeted drug delivery (Broniarz-Press,

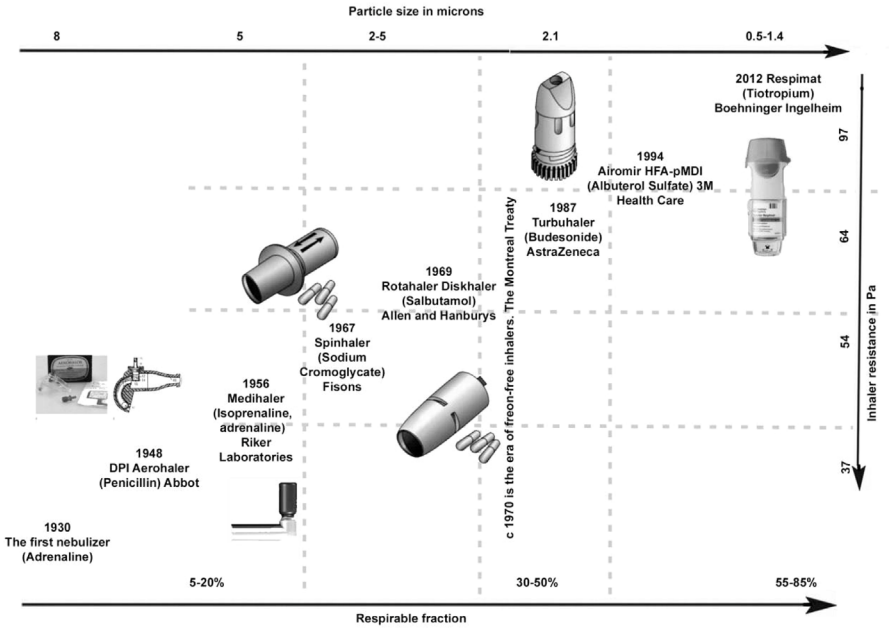

Fig. 1. The evolution of aerosol devices for the treatment of pulmonary diseases.

Ochowiak, Matuszak, & Wlodarczak, 2014a; Broniarz-Press, Sosnowski, Matuszak, Ochowiak, & Jabłczyńska, 2015a; Kole, Jadhav, Shirsath, Dudhe, et al., 2023; Matuszak, Ochowiak, Wlodarczak, Krupińska, & Doligalski, 2022; Ochowiak & Matuszak, 2017).

This review summarises the main achievements and unsolved problems in the field of targeted (topical) delivery of drugs to the human respiratory tract. It concentrates on determining the role of drugs and the means of targeted delivery, and takes into account the relevant thermophysical, hydrodynamic features, as well as the molecular composition of droplets and particles when they move in the forms of aerosol or powder along complex human respiratory tracts.

2. Targeted drug delivery

In the 20th century, a number of scientific discoveries and events had a noticeable effect on the development of inhalation therapy. Among them were: (1) the development of theoretical models; (2) the use of indirect methods for measuring pulmonary deposition; (3) development of methods for estimating particle size and measuring them *in vitro*; (4) application of scintigraphic methods for measuring pulmonary deposition; (5) use of pharmacokinetic and pharmacodynamic methods; (6) the adoption of the Montreal Protocol in 1987, which bans the application of freon (CFC-containing) propellants (Anderson, 2005; Avdeev & Arkhipov, 2022; Stein & Thiel, 2017).

The targeted delivery is focused on a wide range of drugs in the form of aerosols which are used in medical practice (Anderson, Atkins, Bäckman, Cipolla, et al., 2022; Stein & Thiel, 2017). The main clinical and pharmacological groups among these drugs are: bronchodilators and their combinations (Table 1[1]), glucocorticosteroids and glucocorticosteroids in combination with bronchodilators (Table 2), mucoactive therapy drugs (Table 3), antibacterial and other drugs (Tables 4 and 5). A detailed analysis of the groups of drugs mentioned above and their main representatives is beyond the scope of this review.

The first portable nebuliser (a device for passing pressurised water through a fine mesh) was invented in 1858, and served as a powerful impetus for the development of inhalation therapy (Nikander & Sanders, 2010). In 1955, Riker Laboratories (USA) developed a metered-dose aerosol inhaler, as well as a metring valve, and propellants for the production of alcohol-containing pMDI solutions (Grossman, 1994). However, in 1987, at the initiative of the United Nations, the Montreal Protocol was adopted, according to which solutions containing freon were to be discontinued by 1996. Hydrofluoroalkane (HFA) was chosen as an alternative propellant (Partridge, Woodcock, Sheffer, Wanner, & Rubinfeld, 1998).

These developments became the basis for further improvements in inhalation therapy: the size of aerosol particles was reduced, the solubility of drugs was enhanced, deposition in the lungs was minimised, and deposition in the oropharynx was reduced (Leach, Davidson, & Boudreau, 1998). New types of inhalation-activated PMDI have been developed, as well as new types of DPI (Nikander & Sanders, 2010; Stein & Thiel, 2017) (see Fig. 1).

[1] All tables are presented in Supplementary Material

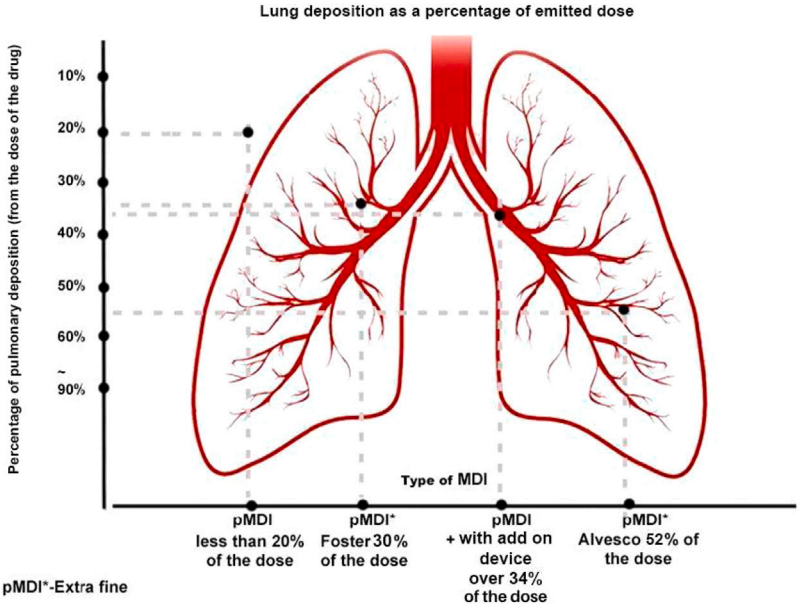

Fig. 2. Optimal lung deposition of some pMDI and of pMDI with an add-on device.

There are currently four main types in use: pMDI, DPI, soft mist inhalers (Respimat/SMI), and nebulisers. In addition to the delivery device, drug molecules, aerosol properties (in particular, deposition in the respiratory tract), and the state of the human respiratory system are of great importance in targeted delivery (Newman, 1995) (see Fig. 2).

One of the most widely used and affordable inhalers is the Turbuhaler® (Anderson et al., 2022). Studies comparing Turbuhaler® and Spiromax® showed that patients mastered Spiromax faster than Turbuhaler, made fewer mistakes when using it, and were more likely to prefer it in the future at the outpatient stage (Giner, Cerrillo, Sierra, Herrero, et al., 2020). The probability of errors when using pMDI is higher than when using DPI, due to the need to coordinate the activation of inhalers and inhalation (Cakmakli, Özdemir, Firat, & Aypak, 2023). The Liquid Soft Mist Inhaler (Respimat®) ensures high inhalation efficiency by creating a slow-moving fine-dispersed cloud. With proper inhalation technique, it allows the active substance to penetrate into the lower respiratory tract (Ciciliani, Langguth, & Wachtel, 2017) (see Table 6 in Supplementary Material).

Despite the evolution in inhalation delivery devices and the development of new molecules of active substances, inhalation remains one of the most complex drug therapies for patients, a complexity often underestimated by both patients and doctors. A wide range of factors contribute to challenges in inhaler use, including proper inhalation technique and pulmonary function variability (Newman, 1995). Ensuring correct use of inhalation devices and adherence to prescribed therapy are critical factors if patients are to achieve improved clinical management, enhanced quality of life, and reduced incidence of adverse effects (Newman, 1995; Pleasants & Hess, 2018).

Anderson et al. (2022) emphasised several issues that determine the innovation in targeted drug delivery. Among them: the electronic enhancement of inhalers; lung targeting and dose consistency; particle engineering technologies; aqueous aerosol delivery; sustained release in the lungs; and high dose delivery. These innovations primarily focused on pharmacological, experimental and theoretical developments, which are considered in the following sections.

2.1. Pharmacological advances

The field of pulmonary drug delivery has witnessed significant advancements over the past several years, particularly in the development of targeted inhaled therapies aimed at enhancing therapeutic efficacy and minimising systemic side effects. In what follows, recent innovations in inhalation technology, formulation strategies, and their implications for treating respiratory diseases are reviewed.

2.1.1. Progress in device technologies

Since the beginning of the 21st century, fully digital inhalers have been introduced to the market that use a variety of sensor technologies, mainly the Bluetooth Low Energy module, system-on-a-chip, and various mechanical switches (Henry, Raphaele, Manfred, Benjamin, et al., 2019; Morrison, Weitzel, Oliveras, & Buck, 2017). SmartMist (Aradigm Corporation, USA) was the first to develop such technologies more than 20 years ago, but the cost limited its market share. Among further developments are i-Neb-Mesh nebuliser, Respiro Sense, INCA, and Inspair. Currently e-modules are used mainly in external add-on devices, and in internal ones integrated inside the inhaler (Henry et al., 2019). Micro- or nano-electromechanical pressure sensor systems have been

developed specifically for more advanced inhaler devices to monitor the operational process (Mehta, 2021). ProAir Digihaler™ (Teva Pharmaceutical Industries Ltd) and Enerzair® Breezhaler® (Novartis) devices have a noticeable impact on medication adherence and inhaler technique, which provides important assistance for healthcare professionals and patients. Smart devices are connected with patients' smart phones and provide information about inhalation both to patients and physicians. Their main purpose is to control the inhalation technique, inhalation strength and other indicators and to transmit data through a mobile application to medical personnel for further assessment of the effectiveness of the therapy (Breezhaler, 2020; Kikidis, Konstantinos, Tzovaras, & Usmani, 2016; Proair Digihaler TM, 2018). Despite all the benefits of therapy and the generation of huge amounts of data, however, smart devices are associated with high cost which limits their application. Further studies in this area are needed (Henry et al., 2019; Sorino, Negri, Spanevello, Visca, & Scichilone, 2020).

2.1.2. Progress in formulations

Recent research has focused on optimising drug formulations and inhaler devices to improve lung deposition. For instance, studies have explored the use of 'bifunctional drugs' the new substances for targeted lung delivery, in which molecules simultaneously act as mAChR antagonists and β2-agonists. They are called MABA drugs (Cazzola & Matera, 2017). Conjugating a β2-agonist fragment with an M3 mAChR antagonist fragment is an example of this. These are expected to be large molecules with high lipophilicity, high metabolism and low oral absorption to minimise potential systemic side effects from the ingested portion of the dose after inhalation (Jones, Baldock, Bunnage, Burrows, et al., 2011). This approach may offer several advantages over combining two separate drugs in a single therapy. These include delivery of a fixed ratio of ingredients to the required area of the lungs, and reducing the complexity of combining inhalers (Cazzola & Calzetta, 2011; Cazzola & Matera, 2009). Additionally, the approach ensures a unified pharmacokinetic profile and a uniform ratio of activity at the cellular level (Steinfeld, Hughes, Klein, Smith, & Mammen, 2011). Unfortunately, the pharmacological half-lives of these components are mostly different. This influences pharmacological activity *in vivo*. Most MABA have either a predominant LABA or LAMA activity and it is not easy to correct their ratio. This limits dosing flexibility (Cazzola, Lopez-Campos, & Puente-Maestu, 2013). MABA compounds have clear advantages over LABA/LAMA combinations and are suitable for co-administration in 'triple therapy' combinations. This is justified by the fact that they are able to induce three complementary therapeutic effects in patients with COPD or asthma (Cazzola & Matera, 2017).

Moreover, novel approaches such as interactive physical blends have been developed to improve the delivery of nonsteroidal anti-inflammatory drugs (NSAIDs) like meloxicam potassium. These formulations aim to provide localised anti-inflammatory effects in conditions such as cystic fibrosis and chronic obstructive pulmonary disease (COPD) (Yildiz-Peköz & Ehrhardt, 2020).

2.1.3. Progress in drug delivery systems

Another aspect of pharmacology's advances is the advent of nanotechnology, which has introduced innovative drug delivery solutions that go beyond traditional methods. Numerous nanoscale carriers for drug delivery have opened up new perspectives and opportunities to deal with the limitations of traditional delivery systems. At the same time, many innovative variations of the designs of these carriers have appeared, expanding their initial capabilities. Targeted effects have found applications in various types of drug carrier systems, including but not limited to liposomes, polymer nanoparticles, dendrimers, and inorganic nanoparticles.

New drug delivery systems (DDS) have many benefits and advantages compared with traditional delivery methods. These advantages are mainly related to the small size of the systems, large contact areas, high physical and chemical stability and predictability *in vivo*. Hye, Moinuddin, Sarkar, and Nguyen (2023) defined the benefits as follows: effective drug deposition in the target location of the respiratory system, prolonged residence time in the lungs with minimal systemic exposure, and reduced dosing frequency with improved patient compliance.

DDS are particularly important when treating chronic obstructive lung diseases (including COPD and asthma), respiratory tract infections, lung cancers, and pulmonary hypertension. Combining several active ingredients into a single drug with a fixed dosage and simplified delivery device operation is very important for successful asthma and COPD therapy. The technology of porous particles has facilitated new combined formulations for treatment with pMDI. Sustained pulmonary delivery could be achieved through the use of polyethylene glycol-distearoyl glycerol-phosphate ethanolamine (PEG-DSPE)-modified polypropylene glycol-co-glycolide (PLGA) microspheres. Their combination with PLGA effectively penetrates the mucosal barrier and macrophage defence, thereby reducing systemic absorption.

The common therapy for lung cancer is systemic chemotherapy, that usually has numerous side effects and no target delivery. Nowadays, the benefits of delivering molecularly targeted medications and chemotherapeutic agents to the lungs via the respiratory route are commonly recognised. New DDS such as porous PLGA microspheres and LNPs in targeted therapy provide better efficacy and fewer side effects (Kim, Byeon, Kim, & Lee, 2012; Taratula, Kuzmov, Shah, & Garbuzenko, 2013). In the treatment of respiratory infectious diseases, new delivery systems provide reduced toxicity, better drug solubility, synergism and targeting of effects (Sheng, Tian, Duan, Sun, & Chu, 2022). Antibiotic carriers that are commonly used are: liposomes, microemulsions, and lipid nanoparticles (LNPs) (Drulis-Kawa & Dorotkiewicz-Jach, 2010; Ramos, Da Silva, Spósito, De Toledo, Bonifáio, et al., 2018; Thorn, Carvalho-Wodarz, Horstmann, Lehr, et al., 2021). These systems are also being actively investigated in inhalation vaccination targeting the respiratory system. Several studies (on measles and influenza vaccines) have demonstrated the efficacy of such vaccination compared to traditional methods (Audouy, van der Schaaf, Hinrichs, Frijlink, et al., 2011; Bennett, Fernandez de Castro, Valdespino-Gomez, Garcia-Garcia, et al., 2002; Hickey & Garmise, 2009).

Inhalation vaccines have become an effective tool in the prevention of COVID-19 (Quadros & Gupta, 2023). Several COVID-19 intranasal and inhalation vaccines went through clinical trials (Topol & Iwasaki, 2022).

Inhaled vaccines, in particular COVID-19 vaccines, combine a number of advantages due to the use of nanoparticle-based delivery systems and/or nanoadjuvants. First of all, they present the potential for direct access to the respiratory tract, i.e. providing a more targeted immune response to viruses that cause respiratory diseases, such as COVID-19. Also, such vaccines have a more convenient method of administration compared to injections, and a low number of systemic side effects (Miao, Huang, Li, Li, et al., 2023). Their nanostructure is able to facilitate absorption by target cells, even modulating the immune response (Zhang, Li, Hou, Ma, et al., 2022).

In addition, nanotechnology plays a pivotal role in the use of inhaled medicine for COVID-19 because it enhances drug delivery and targeting. Nanoparticles (NPs) facilitate effective treatment by improving drug solubility and bioavailability, and targeting specific lung receptors, such as ACE2, which the virus exploits for entry (Abdellatif, Tawfeek, Abdelfattah, El-Saber Batiha, & Hetta, 2021; Dash, Sahoo, Pattnaik, Sarangi, et al., 2024).

In clinical studies, it has been shown that a number of inhaled drugs without NPs have demonstrated anti-inflammatory effects and antiviral activity against SARS-CoV-2. For example, cyclesonide interacts with the viral protein NSP 15 and helps the body's defence systems to detect the virus (Matsuyama, Kawase, Nao, Shirato, et al., 2020). Budesonide reduces the expression of receptors (proteins of angiotensin converting enzyme-2 (ACE-2) and transmembrane serine protease 2 (TMPRSS2)) that promote the entry of the virus into the cell (Yu, Bafadhel, Dorward, et al., 2021). Inhalation therapies using NPs can minimise systemic side effects while delivering antivirals and vaccines directly to the lungs (Cojocaru, Petris, & Cojocaru, 2024; Quadros & Gupta, 2023).

Nanosystems are also used in the development of novel carriers for mRNA vaccines, ensuring their stability and efficacy in combatting SARS-CoV-2 variants (Dash et al., 2024).

Xu, Liu, and Song (2020) performed detailed analysis of novel DDS studying oxidative stress in patients with COPD. It was concluded that the most promising carriers for achieving effective lung deposition of inhaled drugs and controlled drug release are coarse-pored microparticles and porous microparticles with nanoparticles. In this case, delivery systems are capable of targeted deposition, controlling sizes of aerosol particles, controlling biodegradation, and slow release.

Thus, the use of nanocarriers can solve several key problems associated with traditional delivery methods, including:

1. Providing targeted action. Nanocarriers can be modified to recognise specific cells or tissues, allowing drugs to be delivered directly to the affected areas.

2. Resistance to degradation. Nanocarriers are able to protect active substances from destruction in the body, increasing their active lifetime.

3. Controlled delivery. Drug release can be controlled by various stimuli (such as ultrasound or light), allowing therapy to be tailored to the individual needs of the patient. Prospects for the use of inhaled nanopreparations in respiratory diseases are highly promising. However, when using these new drugs, it is necessary to take into account the toxic side effects of biological nanomaterials (Feng, Shi, Zhang, Lei, et al., 2024).

Key characteristics of novel drug delivery systems are shown in Table 7.

2.1.4. Targeting specific lung regions

Targeted drug delivery to specific lung regions has become a focal point in recent studies. For example, researchers have utilised computational fluid dynamics (CFD) simulations to tailor aerosol characteristics, enhancing deposition efficiency in distal lung areas. Studies indicate that adjusting particle size and shape can significantly influence where aerosols deposit within the respiratory tract (Andrew, 2022; Yildiz-Peköz & Ehrhardt, 2020).

The ongoing research and technological innovations in targeted inhaled drug delivery systems are reshaping the landscape of respiratory disease management. By improving drug formulations and optimising delivery devices, there is potential for enhanced therapeutic outcomes with reduced systemic side effects. Continued exploration in this area will likely lead to more effective treatments tailored to individual patient needs. Modelling of the processes leading to drug delivery to specific lung regions is discussed in Section 2.3.

2.2. Experimental advances

Targeted drug delivery is being actively studied both experimentally and theoretically. It is vital that we measure the key aerosol characteristics, including their velocities, sizes and shapes, in order to validate the models of the process. Aerosolization techniques directly affect regional deposition in the respiratory tract, thereby influencing the effectiveness of targeted delivery. In what follows, we provide an overview of how various experimental and simulation-based aerosolization methods contribute to targeting efficiency in respiratory drug delivery. The flow field in the trachea was measured using Laser Doppler Anemometry (LDA) and *in vitro* deposition using fluorometry (Prinz, Pokorný, Elcner, Lízal, et al., 2024a). A replica of a 5-year-old child's airway was prepared by altering the geometry of an adult airway and using a 3D printer. This replica included a face mask, oral and nasal cavities, pharynx, larynx, and tracheobronchial tree up to the second generation of branching (Prinz, Pokorný, Elcner, Lízal, et al., 2024b). The distribution of the flow in the replica was determined from the data produced by dynamic computed tomography of the respiratory cycle. The experiments were performed for a constant inhalation regime in a sitting position (Prinz et al., 2024a). A simplified realistic 3D replica of male and female airways, obtained using medical imaging, was used in the experiments described in Wedel, Steinmann, Štrakl, Hriberšek, et al. (2022a). These experiments focused on quantification of the deposition, distribution, and visualisation of trajectories of particles with a diameter of 6 μm. Such particles are of clinical relevance because their aerodynamic behaviour allows them to penetrate the lower bronchi, supporting targeted deposition in distal regions

of the lungs. It was found that the distribution of these particles in both lungs and five individual lobes of the lungs at a flow rate of up to 60 l/min corresponds to the distribution of the gas stream (Verbanck, Ghorbaniasl, Biddiscombe, Dragojlovic, et al., 2016a).

Such experiments were used to measure *in vitro* and *in silico* regional particle deposition coefficients (Wedel, Steinmann, Štrakl, Hriberšek, & Ravnik, 2021a, 2021b). The stationary flow field of the dilute suspension aerosol was considered. The hydrodynamic resistance of the replica airways was estimated (and found to be half the hydrodynamic resistance in the actual human airways) alongside the lung deposition of particles at a moderate flow rate (151 l/min) (Wedel, Steinmann, Štrakl, Hriberšek, et al., 2022b). As follows from experimental data, the rate of change in flow velocity is the same in most areas of the respiratory tract and there is a more pronounced localised accumulation of particles in the larynx (Wedel et al., 2022a). This effect reflects a common limitation in aerosol targeting, where inertial impaction dominates in high-curvature regions.

The characteristics of spraying aqueous solutions of glycerol and aqueous solutions of glycerol-polyacrylamide, using an ultrasonic inhaler, were investigated by Broniarz-Press, Sosnowski, Matuszak, Ochowiak, and Jabłczyńska (2015b) using laser diffraction. For aqueous solutions of glycerol and glycerol-polyacrylamide, different atomisation patterns were observed, which led to different distributions of aerosols. It was shown that the performance of the spraying process is highly dependent on shear viscosity and tensile viscosity (Broniarz-Press et al., 2015a). For Newtonian fluids, an increase in shear viscosity led to an increase in the share of large aerosols and a decrease in the share of smaller aerosols. For aqueous solutions of glycerol (a non-Newtonian fluid), this led to an increase in the number of smaller aerosols and the absence of larger ones. A correlation has been proposed for the Sauter mean diameter (volume-surface mean diameter) as a function of shear and tensile viscosities (Broniarz-Press, Ochowiak, Matuszak, & Wlodarczak, 2014b). The effect of capillary waves and physicochemical properties (surface tension and shear viscosity) of a liquid on aerosol distribution during ultrasonic spraying was investigated (Zhang, Yuan, & Wang, 2021). It was demonstrated that homogeneous capillary waves and low cavitation intensity led to a narrow distribution of aerosol sizes.

Based on the experimental data presented in Broniarz-Press et al. (2014a) the following correlation was obtained (Broniarz-Press et al., 2014b):

$$D_{32} = k\nu_s^{0.4}\mathrm{Tr}^{0.28}, \tag{1}$$

where D_{32} is the Sauter Mean Diameter (in m), ν_s is the kinematic shear viscosity of an aqueous solution of glycerol (in m^2/s), $k = 0.000075\ m^{0.2}s^{0.4}$, Tr is the Trouton number (ratio of shear and tensile viscosities). Approximation (1) predicts the initial average droplet size delivered to the oropharynx from the inhaler. The discrepancy between its predictions and experimental data was less than 13%. This correlation is of particular importance for the design of the device and the personalisation of treatment targeted at specific regions of the airways.

Pharmaceutical and medical applications of ultrasonic atomisation including the separation of organic molecules, especially bioethanol, from their aqueous solutions are reviewed in Naidu et al. (2022). Experiments on the spraying of deionised water in ultrasonic and vibrating mesh nebulisers demonstrated that ultrasonic nebulisers produced highly inhomogeneous distribution of aerosol/droplet sizes: aerosol/droplet diameters were either less than 1 μm or larger than 100 μm. It is possible to generate a stream of aerosol/droplets of certain sizes in vibrating mesh nebulisers (Sharma, Quazi, Vazquez, & Jackson, 2022). The outcomes of a randomised clinical trial (in patients with COPD) of spraying drugs in the form of a combination of ipratropium bromide and salbutamol using a mesh nebuliser (traditional and microdosing) are described by Qu, Gong, Li, Song, et al. (2023). When measuring the ventilation function of the lungs in each experimental group before and 30 min after nebulisation, no significant differences between the results produced by these two nebulisers were found. In particular, the microdosing mesh nebuliser used only 1/4 of the drug dose (Qu et al., 2023), illustrating enhanced delivery efficiency and the potential for precise targeting with reduced systemic exposure.

In medicine, shock spraying (soft mist inhalers) is often used. The experimental study of this process is not easy due to the complex geometry of the nozzle and the space–time evolution of the jets and droplets. The results of the relatively few investigations undertaken are described by Jin, Xiao, Ren, Li, et al. (2022). It was shown that with an increase in the angle of incidence and pressure at the nozzle inlet, the oscillation of the liquid layer became stronger, which directly affected the nature of its break-up and led to a significant decrease in aerosol/droplet sizes. Such changes in the aerosol/droplet size affect the selectivity of the deposition site, enabling the potential targeting of different lung regions based on nozzle design and actuation parameters. To date, there are many experimental investigations of the characteristics of respiratory particles and air flow in humans during breathing, coughing, and sneezing (Hu, Yuan, Gram, Yao, & Sadrizadeh, 2024). Typically, the factors that determine the location and size of aerosol/droplets in the respiratory tract are MMAD, morphology of the surface, anatomy of the airways, and ventilation parameters (breathing patterns) (Yang, Peters, & Williams, 2008).

The aerodynamic characteristics of inhaled microparticles (for pressurised metered-dose inhalers) were determined using low-dose water-soluble formoterol fumarate as a marker (Xi, Miao, Cao, & Wang, 2023). Using an indicator in the form of mometasone furoate (insoluble in water and in high doses), the effect of drug morphology and drug loading mode on the efficiency of drug delivery by microparticles was investigated (Xi et al., 2023). The behaviour of the flow during respiratory activity was studied using a thermal dummy (Jiang, Yao, Feng, Sun, & Liu, 2017). The particle flow rate was determined using the PIV method, and the temporal and spatial distribution of breathing air fluxes were assumed to be the same as in the convective boundary layer (CBL). The respiratory flow at different stages showed different flow behaviour during the process of breathing (Jiang et al., 2017).

Since this review is focused on liquid formulations, results referring to powder formulations are not discussed (see (Mueannoom, Srisongphan, Taylor, Hauschild, & Gaisford, 2012; Sharma, Mueannoom, Buanz, Taylor, & Gaisford, 2013)). The most important approaches to experimental studies of targeted drug delivery to the lungs are summarised in Table 8.

2.3. Theoretical advances (conventional approaches)

The first mathematical model of particle deposition in the respiratory tract was proposed by Findeisen (1935). In his studies, he used a simple model involving 9 generations of airways, excluding the upper airways, and 7 different particle diameters (from 0.03 to 30 μm). He proposed that the main mechanisms of aerosol particle deposition in the respiratory tract are impaction, sedimentation, and Brownian diffusion. He discovered that as the particle sizes increase, their deposition occurs closer to the trachea (Findeisen, 1935).

Landahl further developed the latter model by adding the upper airways (oral cavity and pharynx) and the alveolar region, and took into account different respiratory conditions (Landahl, 1950). More recent adjustments have been made to these models, but the model suggested by the Task Group on Lung Dynamics to the International Commission on Radiation Protection has been the most widely accepted (Dal Negro, 2015; Newman & Busse, 2002).

Geometric models of the respiratory tract were first proposed by Weibel (1963). This geometric model described the general one-dimensional structure of the human respiratory tract, and is divided into 23 generations of bifurcations and built on the principle of symmetrical division of the incoming bronchus into two outgoing bronchus. The Weibel model is considered to be the basis upon which subsequent computational models are built.

Two dimensionless numbers are most commonly used to describe the mechanisms of impaction, sedimentation, and Brownian diffusion in the respiratory tract: the Reynolds number (to quantify the gas flow) and the Stokes number (to quantify aerosol deposition). The Reynolds number is the ratio of inertial force to viscous friction force during the movement of the air flow along the respiratory tracts, which is usually calculated as $\mathrm{Re}_n = 2\rho U_n R_n/\mu$, where ρ is the density of the air, U_n is the velocity of the air flow in the nth bifurcation (branch of the respiratory tract), R_n is the radius of the nth bifurcation, μ is the dynamic viscosity of the air. In the approximation of the symmetric dichotomy (equality of the integral parameters of the air flow (average flow velocity and volume flow rate flow ($Q = \pi U_n R_n^2$)), the Reynolds number can be presented as $\mathrm{Re}_n = 2\rho Q/(2^{n-1}\pi\mu R_n)$ (Medvedev & Golysheva, 2022a). n shows the number of bifurcations at each of which the flow is assumed to be divided between two bronchi ($n = 1$ refers to the trachea). The laminar/turbulent transition of the flow is expected to take place at $\mathrm{Re}_n \approx 2300$. Typical air flow rates in the respiratory tract during human breathing are expected to be in the range of around 5 l/min (at rest) to 140 l/min (when running medium distances) in the absence of pathologies. In this range, the flow in the respiratory tract is expected to be laminar ($\mathrm{Re}_n < 2300$) (Medvedev & Golysheva, 2022a).

The Stokes number is the ratio of the kinetic energy of the suspended aerosol to the energy of its interaction with the gas flow. It is calculated as $\mathrm{Stk} = \rho_{ae} d_{ae}^2 |U_{ae} - U_n|/(18\mu R_n)$, where ρ_{ae} is the density of aerosols, d_{ae} is the mean aerosol diameter, U_{ae} is the average aerosol velocity. Characteristic Stokes numbers for aerosols in the respiratory tract range from 0.001 to 1 (Cheng, Zhou, & Chen, 1999). Less often the Froude number, the ratio of the inertial force to the gravitational force, is used to characterise the process (Jing et al., 2025; Xi, Kim, Xiuhua, Corley, & Zhou, 2016).

Theoretical analysis of aerosol dynamics in the respiratory tract commonly uses the Lagrangian-Eulerian approach in which the carrier phase (gas) dynamic is described by the conservation equations (energy, mass, and momentum) in the stationary frame of reference (Eulerian approach), while the dynamics of aerosols are described by following the trajectories of individual particles (Lagrangian approach). The effect of turbulence was in most cases described using the Reynolds averaging approach when the flow velocity was presented as the sum of its locally averaged value and turbulent perturbation. The equations describing these processes were solved numerically in most cases. The results of numerical analysis of these equations allowed the researchers to gain new insights into aerosol dynamics in the respiratory tract, including their local deposition, which often cannot be inferred from experimental observations.

Perhaps the most convenient way to perform this numerical analysis is to use one of the Computational Fluid Dynamics (CFD) packages, the majority of which use the Finite Volume (FV) approach. The concept of CFD and its application in medicine are described by Sazhin (2025) and Masic, Parojčic, and Durić (2013). The effect of appropriate boundary conditions was investigated through transient modelling of the complete respiratory cycle in the upper lungs (Wedel et al., 2022b). Apart from CFD, a number of other approaches to stimulation of the flow of aerosols in the respiratory tract, including the Lattice Boltzmann Method (LBM), have been considered (Prinz et al., 2024b). The authors of the latter focused their attention on the respiratory tracts of children, the study of which is particularly challenging due to limited *in vivo* data. Good agreement was found between the results obtained using the LBM and FV approaches and experimental data for average velocities and turbulence intensity in the range of particle sizes of 0.1–20 μm (Prinz et al., 2024a). Deviations of the numerical results from the results of experimental measurements were found in the upper respiratory tract. This was attributed to small deposition fractions in these areas.

The details of the flow in the human airway system, in the presence of glomus tumour with particle deposition, were investigated numerically by Singh (2021). The three-dimensional geometry was developed using computed tomography techniques. The nature of the flow velocity and the probable zone of inflammation were established by analysing the deposition of suspended particles (Singh, 2021). Similarly to Singh (2021), a three-dimensional geometry of a human respiratory tract (HRT) was used by Kumar and Singh (2023) with particular focus on the airflow from the oral cavity to the bronchi of the sixth generation.

Similarly to Singh (2021), Kumar and Singh (2023) used a three-dimensional (3D) computational HRT model, but their study focused on the behaviour of airflow from the oral cavity to the bronchi of the sixth generation. Particles with diameters in the range 1.5 to 10 μm were considered in that study. The FV approach and the analysis of turbulence based on Reynolds averaging were used. It was demonstrated that the overall deposition efficiency increases with increasing respiratory rate of flow and particle sizes. Particles with diameters of 10 μm in a flow of 60 l/min had the highest overall deposition efficiency. It was also found that the local efficiency of deposition in the right bronchus was higher than in the left. For particles with diameters of 1 μm the

right bronchus deposition efficiency increased with increasing flow velocity, whereas for particles with diameters of 5 μm, the right bronchus deposition efficiency decreased with increasing flow velocity. For particles with diameters of 10 μm, the maximum deposition efficiency was predicted in the oral cavity, and it increased with increasing flow velocity (Kumar & Singh, 2023).

In Luo and Liu (2008), the flow of inspiration was simulated using results from a CT scanner (chest of a 60-year-old male). The three-dimensional geometry of the airway surface of the lungs was reconstructed using Mimics image processing software. In this geometry of the lung, the airways were highly irregular and the flow pattern very complex. There was an imbalance in the distribution of discharges across the branches (Liu, So, & Zhang, 2003). With an increase in the Reynolds number (flow velocity), there was a displacement of most of the inspiratory flow to the left main bronchus and a weakening of the secondary flow when the effects of turbulence were considered (Liu et al., 2003). This effect was not observed for laminar flows. A similar individual approach (airway geometry, boundary conditions) was used by De Backer, Vos, Gorlé, Germonpré, et al. (2008), where imaging techniques using computed tomography were applied and the distribution of internal blood flow in a 73-year-old woman suffering from chronic obstructive pulmonary disease (COPD). Validation of the numerical results was performed by comparing them with gamma scintigraphy. The non-invasive test (CT) was shown to be sufficient to obtain the required input parameters for CFD analysis (De Backer et al., 2008).

Inspiratory flow rate in the range 50 to 500 cm^3/s (with deposition of spherical aerosols with diameter 1-7 μm, and density 1 g/cm^3) was modelled by Ertbruggen, Hirsch, and Paiva (2005). An increase in particle deposition with increasing aerosol diameters was predicted. Minimal particle deposition was predicted at an inspiratory volume flow rate of about 200 cm^3/s, but was markedly heterogeneous for branches of the same generation (Ertbruggen et al., 2005). The importance of considering turbulence during modelling of this process was demonstrated. A change in the turbulent flow structure and an increase in the maximum localised near-wall shear stress caused by the laryngeal jet was investigated (Lin, Tawhai, McLennan, & Hoffman, 2007; Luo & Liu, 2009). Using CFD modelling, the trajectories of inhaled and deposited monodisperse, radiolabelled aerosol particles, with diameters of 6 μm in the human lungs were visualised (Verbanck, Ghorbaniasl, Biddiscombe, Dragojlovic, et al., 2016b). A difference was predicted between the distributions of the aerosol and the air even in healthy human lungs (Verbanck et al., 2016a).

A new method for modelling mucociliary clearance (MCBC) near an airflow, without additional cells, applicable to any respiration geometry, was developed (Modaresi & Shirani, 2024). This method was based on the Lagrangian-Eulerian approach, mentioned earlier, and tested for the nasal cavity. The MCBC methodology is not geometry dependent and can be used for various computational domains. The simulations were performed using computed tomography images based on available radiological data from an 18-year-old woman suffering from airway obstruction in the right nasal cavity. To simulate the particle flow inside the nasal cavity the Delaunay method was used. A tetrahedral mesh was prepared using ICEM-CFD software. Also, a four-layer prismatic mesh was generated and attached to the tetrahedral mesh to calculate the deposition flux and velocity gradient near the nasal wall.

Mathematical modelling is also important in the study and improvement of existing spray devices. Modelling the nebulisation of soft mist inhalers is particularly challenging due to their complex nozzle geometry and the complex space–time evolution of the jets and droplets, the sizes of which can differ by several orders of magnitude (Jin et al., 2022). The results of using CFD to model the spraying process, using the Volume of Fluid (VOF) approach (tracing the droplet interface), the discrete phase model (DPM), and adaptive mesh refinement (AMR) were presented by Jin et al. (2022). It was found that the angle of incidence and the distribution of jet velocities, which depend on the flow conditions inside the nozzle, have a decisive impact on the size distribution of droplets leaving a nebuliser (Jin et al., 2022).

In recent years, a number of multi-scale three-dimensional geometric models of the respiratory tract have been developed (Heistracher & Hofmann, 1995; Kitaoka, Takaki, & Suki, 1999; Medvedev, Fomin, & Gafurova, 2020; Trusov, Zaitseva, & Tsinker, 2016). Currently, the arsenal of these models is quite extensive and includes both extrathoracic models at the level of the oropharynx and nose (Cheng, Cheng, Yeh, Guilmette, et al., 1996; Subramaniam, Richardson, Morgan, Kimbell, & Guilmete, 1998; Wang, Cai, Chen, Sun, & Tao, 2024; Xi & Longest, 2008; Zhang, Kleinstreuer, & Kim, 2002), and complete models from the point of view of respiratory tract architecture from the oropharynx to the alveoli (Jin, Fan, Zeng, & Cen, 2007; Martonen, Zhang, Yue, & Musante, 2002; Xu, Sasmito, Li, & Qiu, 2016). In one study by Kitaoka et al. the one-dimensional model of respiratory tract geometry was extended to a three-dimensional one (Kitaoka et al., 1999). Also, analytical models of asymmetrical respiratory tract structures are being developed (Heistracher & Hofmann, 1995; Trusov et al., 2016), including 'star-shaped' bronchial constriction in pathologies (Medvedev et al., 2020; Medvedev & Gafurova, 2019; Medvedev & Golysheva, 2022b), and for prosthetics (Malvé, Barreras, López-Villalobos, Ginel, & Doblaré, 2012; Malvé et al., 2011, 2011).

The geometric models described by Medvedev et al. (2020), Medvedev and Golysheva (2022b) and Medvedev and Gafurova (2019) have many limitations and their practical applicability is expected to be limited. A number of physical and chemical processes occur in the respiratory tract during the transportation of medicinal aerosols to a target located on the respiratory tract mucosa, and various mechanisms of heat and mass transfer need to be considered. These include heating, evaporation, fragmentation, sedimentation, and collisions of drug droplets/aerosols.

In their approach to the three-dimensional modelling of the upper human respiratory tract (from the mouth to the triple bifurcation), Jin et al. (2007) considered only drag and gravity forces, and the Large Eddy Simulation (LES) model of turbulence was used. In their simulation, the conditions of both a stable breathing mode and an unstable breathing mode with different intensity were tested. It was found that the deposition of particles strongly depends on their diameter and density, as well as the intensity and mode of respiration. Increasing the diameter of the particles, the density of particles and the intensity of respiration improved their deposition in the upper human respiratory tract. Also, the deposition of particles in the transient mode of respiration was predicted to be higher than in the steady-state mode. It was found that the greatest deposition of particles occurs in the larynx.

Zhang et al. (2002) described a laminar-turbulent transition in the extrathorocular region of the respiratory tract. The results of numerical estimates of polydisperse aerosol deposition in the human mouth-throat region, using a $k-\epsilon$ turbulence model, were

presented by Stapleton, Guentsch, Hoskinson, and Finlay (2000). A good match was obtained between the results of experiments and simulations for inspiratory velocity of 2 l/min but not for a highly turbulent flow with an inspiratory velocity of 28.3 l/min (Stapleton et al., 2000). Results of calculations for extreme high-temperature exposure (50-200 °C) and low relative humidity (5%–10%) of the inhaled flux through the upper human respiratory tract to the mucus layers, using a three-dimensional model, were presented by Kulkarni and Kleinstreuer (2020). Sera, Yokota, Himeno, and Tanaka (2013) and Tanaka, Ohgawara, Inagaki, Hishida, and Sera (2012) studied drug deposition taking into account the expansion and contraction of the human respiratory tract, using conventional computational fluid dynamics tools. The geometry was taken from tomographic images.

Oxygen distribution during inspiration along the human respiratory tracts was studied by Sera et al. (2013). An improvement in drug deposition for steady flows was demonstrated by Tanaka et al. (2012). Kleinstreuer, Zhang, Li, et al. (2008b) proposed the concept of controlled flow for targeted delivery of drugs to the respiratory tract based on the choice of the optimal diameter and density of aerosols/droplets, as well as the inspiratory waveform and the location of the delivery device. A more fundamental approach to controlling the flow of air and aerosols in the respiratory tract was described by Fresconi, Wexler, and Prasad (2008). Zhang and Kleinstreuer (2003) found correlations between the Nusselt and Sherwood numbers to describe the processes of heating and evaporation of drugs in the respiratory tract. Chen, Ma, Zhong, Sun, and Zhou (2019) studied the dynamics and deposition of G3-G6 aerosols in the lung airways at different body temperatures and bronchial humidities.

The most important approaches to modelling the processes related to targeted drug delivery to the respiratory system are summarised in Table 8.

2.4. Theoretical advances (prospective approaches)

In the theoretical advances described in the previous sections we focused mainly on the application of conventional in-house and commercial CFD codes to the analysis of aerosols in complex respiratory tracts. The effects of aerosol heating and evaporation, and most recent developments in this field, were ignored.

This section presents an overview of the most recent developments in droplet/aerosol fluid dynamics and heat/mass transfer modelling which could be potentially applicable to investigation of the behaviour of aerosol medicines in the respiratory tracts of humans. These will include a recently developed approach to studying the evolution of aerosol/droplet clouds, known as the Full Lagrangian Approach (FLA). It is sometimes referred to as the Osiptsov method (Osiptsov, 2000). In contrast to the traditional Lagrangian approach, FLA enables direct calculation of the evolution of particle number densities along particle trajectories, which makes it possible to increase the speed of calculations by several orders of magnitude. This overview will also include recent developments in the modelling of droplet/aerosol evaporation and heating (Sazhin, 2022). These processes always take place during aerosol/droplet movement in the respiratory tract and it is not at first evident why they can be ignored.

The modelling of aerosol dynamics in the papers discussed in the previous section was based on the assumption that the interaction of aerosols with ambient air can be considered in terms of conventional fluid dynamics. This assumption can be highly questionable for aerosols with diameters of about 1 μm or less. An approach that concentrates on modelling such small aerosols needs to consider the dynamics of individual molecules (the molecular dynamics (MD) approach). The most recent developments in this approach, that are potentially applicable to the analysis of aerosols in the respiratory tract, will also be summarised in this section.

2.4.1. Full Lagrangian approach to the analysis of aerosol clouds

The modelling of gas-droplet/particle flows entails modelling of the gas, or the carrier phase, the admixture (droplets or particles), also referred to as the dispersed phase, and interaction between the phases. Such two-phase flows are characterised by volume fractions of admixtures. For example, there are flows with high volume fractions of admixture, like granular flows. In the applications considered in the review, however, the two-phase flows are predominantly dilute meaning that the volume fraction of admixture is small. This leads to a series of simplifications in the model formulation. For example, the effect of admixture on the carrier flow as well as collisions between the particles can be neglected (Marble, 1970).

There are two large families of Eulerian and Lagrangian methods, which are used for calculations of the admixture properties. The most common approach to modelling particles or droplets in dilute two phase flows is Lagrangian tracking (Crowe, Schwarzkopf, Sommerfeld, & Tsuji, 2011). In this approach, each individual particle/droplet is tracked using the classic law of motion, and, if modelling droplets, it is complemented by the energy balance equation to correctly model their heating and evaporation. Note that there is an interest in modelling not just droplet dynamics, but also their size distributions, especially when modelling polydisperse and evaporating droplets. Calculation of droplet/particle concentration is essential for accurate estimation of the efficiency of targeted drug delivery to the site of action. In this case, the conventional Lagrangian tracking falls short of expectations as it requires a high number of seed particles to collect reliable statistical data on droplet distributions. To address this issue, both Eulerian and Lagrangian models based on continuous description of the dispersed phase have been developed. This approach is often referred to as a two-fluid approach, where the admixture is considered to be a continuous cloud and its parameters are treated as continuous fields. These include, for example, the droplet/particle velocity field and the droplet/particle number density field. This makes it possible to calculate the droplet/particle distributions using the mass balance equation, analogous to the mass balance equation used for the carrier phase.

While Lagrangian approaches are based on tracking seed droplets or particles, Eulerian approaches are based on the calculation of flow properties at fixed points in the flow domain. For a long time it has been considered that only the Eulerian approaches support continuous description of the dispersed phase. Probably, the most prominent family of the Eulerian methods for particle/droplet

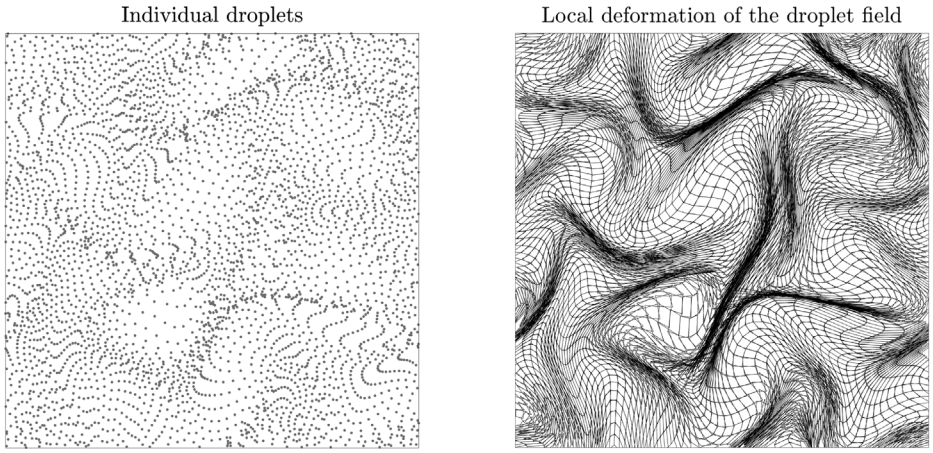

Fig. 3. Illustration of droplet field deformation on a test case of a synthetic turbulent flow. Left, instantaneous picture of droplet locations at a selected time instance. Right, visualisation of local deformation of the droplet field using quadrilaterals.

flows are the quadrature-based moment methods, which fall within the category of kinetic-based approaches. Originating from the Quadrature Method of Moments (QMOM) (McGraw, 1997), they have received strong support and are now considered to be accurate means of modelling dispersed flows. They have been developed to model complex physics, including polydisperse droplet flows, flows with droplet growth, coalescence and break up (see Fox (2024) for an analysis of the most recent advances in this area).

An alternative approach to quadrature-based moment methods, is a small group of the full Lagrangian approaches, which are so-called because they give more information than just the particle position. While conventional Lagrangian tracking is implemented in all widely-used computational fluid dynamics software, the full Lagrangian approaches are less well known. There are two types of full Lagrangian approach, where the number density is calculated using the conservation of mass for the admixture (Healy & Young, 2023). In the first, the method devised by Fernandez de la Mora and Rosner, it is suggested that the mass balance equation in the Eulerian form should be used, while the second, Osiptsov's method, is based on the mass balance equation in the Lagrangian form. Healy and Young (2023) compared the two approaches and concluded that Osiptsov's method is preferable as it has the potential to significantly reduce computational times. Osiptsov's method was also compared with the conditional quadrature method of moments (Gilfanov, Zaripov, Sazhin, & Rybdylova, 2023), where it was demonstrated that Osiptsov's method is more efficient for number density calculations in the benchmark cases considered. The remainder of the review will focus on Osiptsov's full Lagrangian approach (FLA).

The FLA was originally proposed by Osiptsov (1984), and became better acknowledged in the mathematical modelling community after the publication of paper (Osiptsov, 2000), which covered its theoretical foundations, along with several applications. A comprehensive review of the developments of the FLA is presented by Osiptsov (2024). In this section we will provide a high-level description of the approach with selected publications contributing to the development of the FLA without going into the details of the mathematical formulation.

The core of the FLA is the formulation and solution of the continuity equation along selected droplet/particle trajectories. This is achieved by calculating differential characteristics of the droplet/particle fields, which also carry information about local droplet/particle number density field deformation, which is illustrated in Fig. 3. This illustration is based on a test case of droplet dynamics in a synthetic turbulent field. In this study, the droplets were distributed uniformly at the start of the simulation, and then as the flow developed, the droplets redistributed creating spatial structures corresponding to accumulation regions as well as areas with lower droplet number density concentrations. Fig. 3 (left) presents an instantaneous picture of droplets at a selected time instance. The local deformation of the droplet field is visualised using quadrilaterals (Lagrangian elements), Fig. 3 (right), which were identical squares at the start of the simulation. The information about the local deformation of the droplet field is obtained from the partial derivatives of the droplet Lagrangian field. The latter are used for the number density calculations using the components of the so-called Jacobi matrix. The absolute value of the determinant of the Jacobi matrix (Jacobian determinant) has a straightforward geometrical interpretation, it is the volume of the Lagrangian element. A volume increase means that droplets are further from each other and the number density decreases, and vice versa. Due to the high compressibility of dilute admixtures, there may be cases of trajectory crossings. This leads to the collapse of a Lagrangian element from a 3D volume to a 2D surface. This structure is also referred to as caustic where droplets/particles accumulate. This might present a challenge in some modelling approaches. In the case of the FLA, however, this corresponds to a zero value of the Jacobian determinant and afterwards the Jacobian determinant might change its sign. This makes it simple to identify the caustics using the FLA. Further investigation of deformation of the droplet/particle number density field on a caustic is possible if one calculates second-order derivatives of the droplet number density fields (Hessian) (Papoutsakis, Danaila, Luddens, & Gavaises, 2022; Papoutsakis & Gavaises, 2020; Papoutsakis, Rybdylova, Zaripov, Danaila, Osiptsov, & Sazhin, 2018).

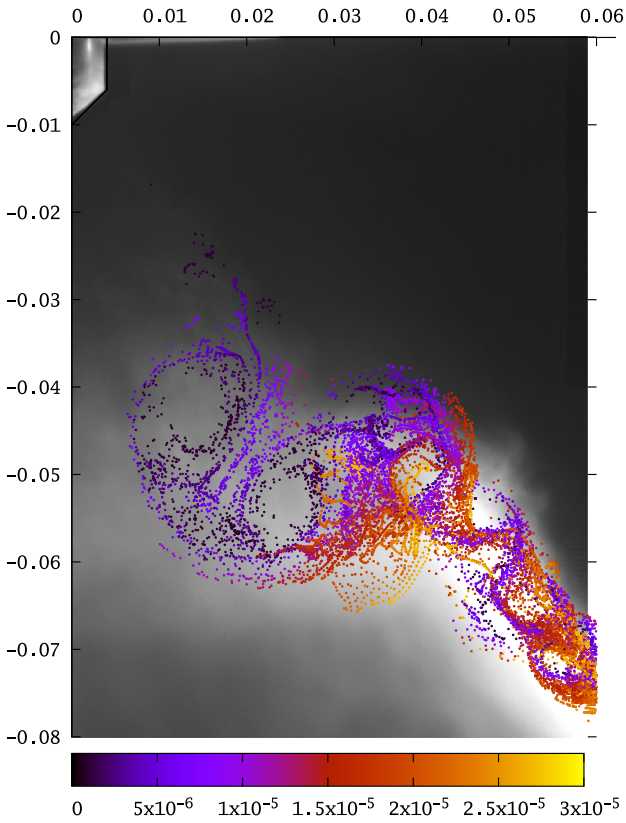

Fig. 4. Location of droplets with diameters 1–30 μm (see the colour legend) as predicted by ANSYS Fluent overlayed on an image of a spray (Zaripov et al., 2017). Reproduced from Fig. 10 (d) of (Zaripov et al., 2017) with the permission of Begell House.

As the Osiptsov approach is particularly advantageous in the simulation of flows with local accumulation regions, it has been extensively developed and applied to gas-particle flows, where, due to high inertia of solid particles, a region, or multiple regions, of high particle number density might be formed. Examples include colliding disperse viscous flows, vortical flows, shear flows and flows with shock waves (see for example Ahuja, Belonoshko, Johansson, & Osiptsov, 2004; Egorova, Osiptsov, & Sakharov, 2001; Lebedeva & Osiptsov, 2007, 2009; Osiptsov & Shapiro, 1992; Rybdylova, Sazhin, Osiptsov, Kaplanski, et al., 2018; Wang, Veselyi, Kulikovskii, & Osiptsov, 1991). These cases, however, were limited to 2D steady-state or transient flows, or 3D flows with axial symmetry, mostly with analytical solutions for the carrier phase, and where the admixture was assumed to be composed of identical solid spheres.

Meshless approaches to model fluid flow have attracted much interest in recent years. The most well-known are the smoothed particle hydrodynamics (SPH) and viscous vortex methods. The combined viscous vortex and full Lagrangian approach (Lebedeva, 2013; Lebedeva & Osiptsov, 2016; Lebedeva, Osiptsov, & Sazhin, 2013; Rybdylova, Osiptsov, Sazhin, Begg, & Heikal, 2016) is a meshless method for modelling gas-droplet flows. Apart from independence from the mesh, another advantage of this combined method is a more convenient calculation of exchange terms (interaction) between the carrier and the dispersed phase as both are calculated using the Lagrangian approaches.

As mentioned earlier, the FLA demonstrated potential to dramatically reduce calculation times (Healy & Young, 2023), which led to an initiative to develop it for engineering applications. The first works in this direction focused on coupling the FLA with computational fluid dynamics software ANSYS Fluent and Open-FOAM, which are well-known in the academic and industrial spray community (Li & Rybdylova, 2021; Zaripov, Gilfanov, Begg, Rybdylova, Sazhin, & Heikal, 2017; Zaripov, Rybdylova, & Sazhin, 2018). This made it possible to consider a wider range of flows, which can be modelled by ANSYS Fluent or OpenFOAM. An example of this is shown in Fig. 4, where the authors modelled gasoline injection in non-evaporative conditions (Zaripov et al., 2017).

When modelling sprays, it is essential to capture the polydispersity and evaporation of droplets. The theoretical foundation for this with regard to the FLA was described back in 2000 (Osiptsov, 2000). It was first applied to the modelling of evaporating droplets by Li and Rybdylova (2021). To account for evaporating droplets, the original FLA was generalised (gFLA) to include the distribution of droplet sizes. The dimensionality of the problem increased by 1 and the number density was generalised to a droplet distribution function, which describes droplet distributions in space and in size. It was demonstrated that operating with the droplet distribution function is a powerful tool, which has potential to bring useful statistics to the description of droplets. However, there

was a challenge in interpolating Lagrangian droplet data onto the Eulerian mesh used in OpenFOAM calculations. To overcome this barrier, a robust interpolation based on kernel regression was introduced to gFLA (Stafford & Rybdylova, 2023c). This combination of the FLA and gFLA with kernel regression was demonstrated to retain computational efficiency (the calculations were up to 100 times quicker when compared with the conventional Cloud-in-Cell method) and enabled calculations of statistical moments of the droplet fields. These included average droplet diameters or variations in droplet sizes, which is useful when analysing segregation of droplets by sizes. This combined gFLA and kernel regression was applied to the modelling of respiratory aerosol dispersion (coughing) (Stafford & Rybdylova, 2022). Finally, the implementation of kernel regression made it possible to accurately calculate source terms in interphase mass and momentum exchange, thus enabling simulations where the effect of droplets on the carrier phase is accounted for (Stafford & Rybdylova, 2023a).

So far the focus of this part of the review has been on laminar two-phase flows. In engineering applications, however, turbulent flows are more common than laminar flows, which motivated the development of the FLA for turbulent flows. Turbulent flows of the carrier phase can be described using averaging (Reynolds-Averaged Navier–Stokes equations, RANS), filtered velocity fields (Large Eddy Simulations, LES), or direct numerical simulations (DNS). IJzermans, Meneguz, and Reeks (2010), IJzermans, Reeks, Meneguz, Picciotto, and Soldati (2009), Meneguz and Reeks (2011) and Picciotto, Marchioli, Reeks, and Soldati (2005), used the FLA with direct numerical simulations of homogeneous and isotropic turbulent flow to study particle segregation and formation of caustics. Direct numerical simulations are the most accurate but also the most computationally expensive approach making them impractical for wider use. The first FLA model developed for the LES simulation was presented by Papoutsakis et al. (2018). In this model, the droplet parameters were calculated using spatially filtered carrier phase velocity, and the subgrid fluctuations were accounted for by the introduction of turbulent diffusion and neglecting turbulent stresses in the droplet continuum. An alternative model for LES simulations with a model for subgrid velocity fluctuations was proposed by Stafford and Rybdylova (2023b), where it was demonstrated that the contribution of subgrid scale velocity fluctuations might be as large as that of filtered velocities. Accounting for the carrier phase subgrid scale velocities led to particularly pronounced clusters and voids in the admixture.

To summarise this section, the full Lagrangian approach has demonstrated its potential for making faster calculations of droplet distributions, which is important for assessing the efficiency of respiratory drug delivery. It has been developed for polydisperse and evaporating droplet flows and can be used with powerful computational fluid dynamics software, which makes it more practical in use. There is a need, however, for further development of the FLA for turbulent flows (both isotropic and anisotropic), spray atomisation, droplet break-up and coalescence, and heating and evaporation of sprays based on complex multi-component mixtures, including nanofluids.

2.4.2. Hydrodynamics models of aerosol heating and evaporation

The most general analysis of droplet and aerosol heating and evaporation is expected to be based on the solution to equations of conservation of mass, momentum and energy in the liquid (or solid) and gas phases with the boundary condition at the droplet surface describing phase transition (Sazhin, 2022). This approach, however, is not commonly used in practical analysis of the phenomena in biological or engineering applications. This is primarily because the number of droplets/aerosols to be modelled in these applications can easily exceed thousands and even millions. The application of this approach to these arrays of droplets would require excessive computer resources, while the many details it can predict are not directly comparable with observed results. This stimulated the development of simplified approaches to modelling these phenomena which are summarised below.

Ignoring the effect of evaporation and temperature gradient inside the droplets/aerosols, and assuming that droplets/aerosols can be approximated by perfect spheres heated by convection by the ambient gas, the energy balance equation for those spheres can be presented as:

$$\frac{4}{3}\pi R_d^3 \rho_l c_l \frac{\mathrm{d}T_d}{\mathrm{d}t} = 4\pi R_d^2 h(T_g - T_d), \tag{2}$$

where R_d is the droplet/aerosol radius, ρ_l and c_l are liquid or solid density and specific heat capacity, respectively, T_d and T_g are droplet and ambient gas temperatures, respectively, h is the convective heat transfer coefficient, t is time.

The meaning of this equation is that all heat supplied from gas is spent on raising the temperature of droplets/aerosols. Assuming that T_g is constant, its solution can be presented as:

$$T_d = (T_{d0} - T_g)\exp\left(-\frac{3ht}{c_l \rho_l R_d}\right) + T_g, \tag{3}$$

where $T_d(t=0) = T_{d0}$.

Solution (3) is widely used in biological and engineering modelling. It is implemented in most in-house and commercial Computational Fluid Dynamics (CFD) codes, including ANSYS Fluent. It is justified by the fact that liquid thermal conductivity k_l is much larger than that of the ambient gas k_g. This criterion, however, can be misleading for the analysis of transient processes for which this justification depends on the value of the liquid diffusivity $\kappa_l = k_l/(\rho_l c_l)$, which is typically much smaller than that of gas (Sazhin, 2022).

The applicability of Solution (3) depends not on the value of liquid thermal conductivity, as is almost universally believed, but on the values of the heat diffusion time in a droplet/aerosol, $t_T = R_d^2/\kappa_l$, and the characteristic time of the process t_p. If

$$t_p \gg t_T \tag{4}$$

then Solution (3) can be used. If this condition is not satisfied then the effects of finite thermal conductivity inside droplets need to be considered, following, for example, an analytical/numerical approach such as that described by Sazhin (2022).

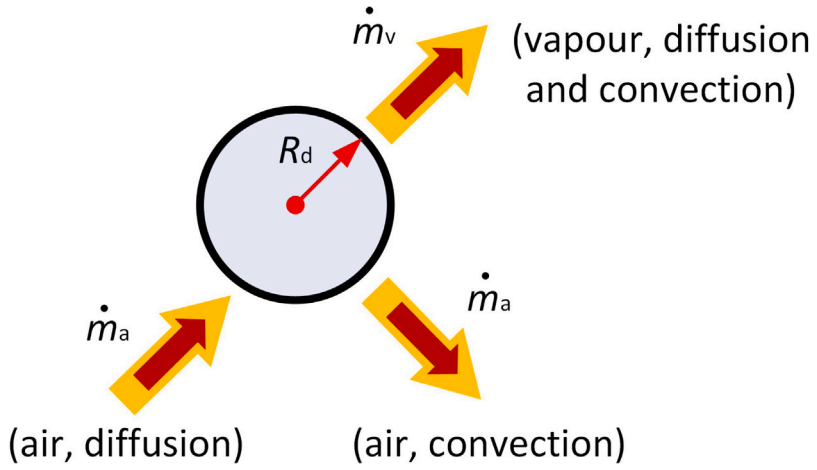

Fig. 5. Schematic presentation of the processes of mass diffusion of air from the surrounding gas towards the droplet surface, air convection from the droplet surface to the surrounding gas, and transfer of vapour, produced during the evaporation process, from the droplet surface to the surrounding gas due to diffusion and convection.

There are two ways to model the radiative heating of droplets/aerosols. Firstly, they can be considered as opaque grey spheres, in which case the radiative heating is modelled as a surface phenomenon. Secondly, the semi-transparency of droplets/aerosols can be considered, in which case their volumetric radiative heating needs to be modelled. The first approach is commonly used in in-house and commercial CFD codes, including ANSYS Fluent. Simplified methods using the second approach are described by Sazhin (2022). Radiative heating is not expected to play an important role in the heating of droplets/aerosols in human airways where ambient gas temperatures are not expected to exceed about 40°C.

When considering droplet/aerosol evaporation, two processes need to be considered in the general case. These are the detachment of the molecules from the droplet surface and the transfer of vapour from the droplet surface to the ambient gas. The description of the first process can be rather tricky (Sazhin, Gun'ko, & Nasiri, 2016) but it can be avoided altogether if we assume that the process is quasi-steady-state, and the vapour at the droplet surface is saturated. The latter assumption allows us to reduce the problem of droplet/aerosol evaporation to the problem of vapour transfer from the surface of the droplet to the surrounding gas.

The first and simplest approach to the latter problem was described by Maxwell in 1877 (Sazhin, 2022). His approach assumed that vapour transfer is controlled only by its diffusion and led to the following formula for droplet evaporation rate $\dot{m}$:

$$\dot{m}_v = -4\pi R_d D_v \left(\rho_{vs} - \rho_{v\infty}\right), \tag{5}$$

where D_v is the diffusion coefficient of the vapour in surrounding gas (air), ρ_{vs} and $\rho_{v\infty}$ are vapour densities at the droplet surface and in ambient gas.

Spalding (1953) and Fuchs (1959) were perhaps the first to draw attention to the fact that vapour can be transferred to ambient gas not only by diffusion but also by convection (together with ambient air; the so-called Stefan flow). Considering this effect and making a simplifying assumption that the density of a mixture of vapour and ambient air (ρ_{total}) is constant (it is not a function of the distance from the droplet/aerosol surface), they derived the following expression for $\dot{m}_v$:

$$\dot{m}_v = -4\pi D_v \rho_{\text{total}} R_d \ln\left(1 + B_M\right), \tag{6}$$

where

$$B_M = \frac{\rho_{vs} - \rho_{v\infty}}{\rho_{\text{total}} - \rho_{vs}} \tag{7}$$

is known as the Spalding mass transfer number.

Remembering our assumption that ρ_{total} does not depend on the distance from the droplet/aerosol surface, we can expect that the evaporation process results in a reduction in air density near the droplet surface, which leads to a diffusion of air from the surrounding gas to the droplet surface. Assuming that the process is steady-state, this diffusion of air is expected to be compensated for by air and vapour convection from the droplet surface to the surrounding gas. Vapour is removed from the droplet surface via its diffusion relative to the ambient air and its convection together with the ambient air. These processes are schematically presented in Fig. 5.

Tonini and Cossali (2012) relaxed the assumption that ρ_{total} is constant and developed a model that did not use it. Using a number of simplifying assumptions (which were later justified by Tonini, Cossali, Shchepakina, Sobolev, and Sazhin (2022)) they managed to find an implicit expression for $\dot{m}_v$ which predicted the experimental results more accurately than those predicted by (6). The original model, developed in Tonini and Cossali (2012), was based on the assumption that liquid thermal conductivity is infinitely large (Eq. (2) is valid). The results of the further development of this approach to the case when the gradients of temperature inside

droplets need to be considered are presented by Antonov, Tonini, Cossali, Dolgikh, et al. (2023). The results of recent developments of a model of spheroidal droplet/aerosol evaporation are presented by Antonov, Tonini, Cossali, Strizhak, and Sazhin (2024).

The models of droplet/aerosol evaporation presented so far in this section have assumed that droplets/aerosols are mono-component. For multi-component droplets/aerosols the effect of preferential evaporation of some components should be taken into account. This effect leads to the development of gradients of mass fractions for the components in the droplets and their diffusion in the radial direction (assuming that droplets/aerosols are spherical). The liquid phase model considering this diffusion, based on the analytical solution to the component diffusion equation, is described by Sazhin (2022). This solution was incorporated in the numerical code and used at each time step of the calculations. The predictions of this solution at the end of the time step were used as the initial conditions for the next time step together with updated values of other input parameters. In the limiting case, when one of the components was no longer evaporating, this model described droplet/aerosol drying.

The original version of the multi-component evaporation model described by Sazhin (2022) assumed that all components are transferred from the droplet/aerosol surface to the surrounding gas at the same speed. The effects of the differential transfer of the components in the gaseous phase was considered in several papers, including (Tonini & Cossali, 2015, 2022).

2.4.3. Molecular dynamics approaches to modelling aerosols

As follows from the above brief review of currently used approaches to modelling dynamics and heat/mass transfer processes in aerosols/droplets/particles in human airways, in most cases they are based on the assumption that these processes can be studied using the methods of continuum mechanics. This could be justified for relatively large droplets/particles with radii more than 5–10 μm (Sazhin, 2022). This approach, however, is expected to lead to considerable errors for aerosols with radii less than about 0.1–1 μm, for which the values of the Knudsen number ($\mathrm{Kn} = \lambda_c/R_a$, where λ_c is the mean free path of gas molecules, R_a is the radius of aerosol particles), are comparable to or greater than one.

It is commonly recognised that the most rigorous approach to modelling the dynamics and heat/mass transfer processes in these aerosols should be based on the molecular dynamics (MD) method. This method, derived from statistical physics, is a computational technique used to describe the processes at the micro and nanoscale. In MD, empirical potential functions or force fields are used to characterise all possible interactions between atoms and the motion of all atoms and molecules in the system is simulated using the numerical solutions to Newton's equations. It is commonly accepted that quantum mechanical effects can be ignored in modelling these processes in most cases, which considerably simplifies the analysis (Sazhin et al., 2016). This method has been widely applied across various areas, including chemistry, medicine, biology, and materials science (Elfiky, 2021; Jewett, Stelter, Lambert, Saladi, et al., 2021; Tian, Lin, Yan, & Zhao, 2022; Xue, Fu, Deng, Yang, et al., 2022). This section reviews the MD approaches which are used or can potentially be used to study aerosols in human airways.

The MD simulation starts with the construction of a molecular model and specification of the initial conditions, such as temperature, pressure, and molecular positions. The following step focuses on the intermolecular forces which are calculated based on the molecular model and empirical potential fields. Based on the principles of mechanics, the force acting on an atom within the model corresponds to the gradient (in the case of Cartesian coordinates this is a vector with components equal to partial derivatives of a scalar function with respect to x, y and z) of the system's potential energy (U) at the atom's specific location. It is important to mention that molecular dynamics (MD) disregards the motion of electrons, operating under the assumption that the system's potential energy is solely determined by the position of the atomic nucleus. Typically, the system's potential energy comprises various components, including bond length energy (U_b), bond angle energy (U_θ), dihedral angle energy (U_φ) (θ and φ are coordinates in the spherical coordinate system), and non-bonding energies (e.g. U_{VdW} and U_{Coul} produced by van der Waals and Coulombic forces, respectively). Then the positions $\overrightarrow{s_i}$ and velocities $\overrightarrow{v_i}$ of the molecules are updated at the end of the time step Δt when the forces produced by the gradients of these energies $\nabla U_{\mathrm{total}}$ are applied, as shown in Fig. 6 (m_i and $\overrightarrow{a_i}$ are masses and accelerations of the ith atoms). The simulation process continues until the predetermined simulation time is reached, which commonly leads to sufficiently accurate results (Frenkel & Smit, 2001). Based on this foundation, thermodynamic quantities and other macroscopic properties of the system are subsequently computed by employing statistical methods and additional techniques.

The specification of the potential function or force field is the most important part of the process leading to accurate MD simulations. The choice of the force field should be made appropriately, considering the properties of the simulated system and types of molecules. Various force fields and potentials are commonly used for studying organic small molecules, including those described in COMPASS, CFF, OPLS, and CVFF. COMPASS (Condensed-phase Optimised Molecular Potential for Atomistic Simulation Study), developed by Huai Sun (Sun, 1998; Sun & Rigby, 1997), is one of the most popular. It uses the *ab initio* force field, parameterised and validated using data referring to condensed-phase properties, various *ab initio* calculations of isolated molecules, and empirical data. Its areas of application include a wide range of organic and inorganic materials. CFF (Consistent Force Field) is a family of force fields that includes CFF91 (Maple, Dinur, & Hagler, 1988), CFF95 (Maple, Hwang, Stockfisch, Dinur, et al., 1994) and PCFF (Sun, Mumby, Maple, & Hagler, 1994). It can be used to perform calculations for many systems, from small organic molecules and large biomolecules to molecular sieves. OPLS (Optimized Potentials for Liquid Simulations) was developed by Jorgensen, Maxwell, and Tirado-Rives (1996) and is commonly used for liquid systems such as peptides, proteins, nucleic acids, and organic solvents. CVFF (Consistent Valence Force Field) has been applied to calculating the molecular structure of organic molecules, including amino acids, various peptides, and proteins (Dauber-Osguthorpe, Roberts, Osguthorpe, Wolff, et al., 1988).

The COMPASS force field is expected to be the most useful in the modelling of aerosols in the lungs due to its ability to accurately predict the structure, conformation, vibration, and thermophysical properties of various molecules and their condensed states over a wide range of temperatures and pressures.

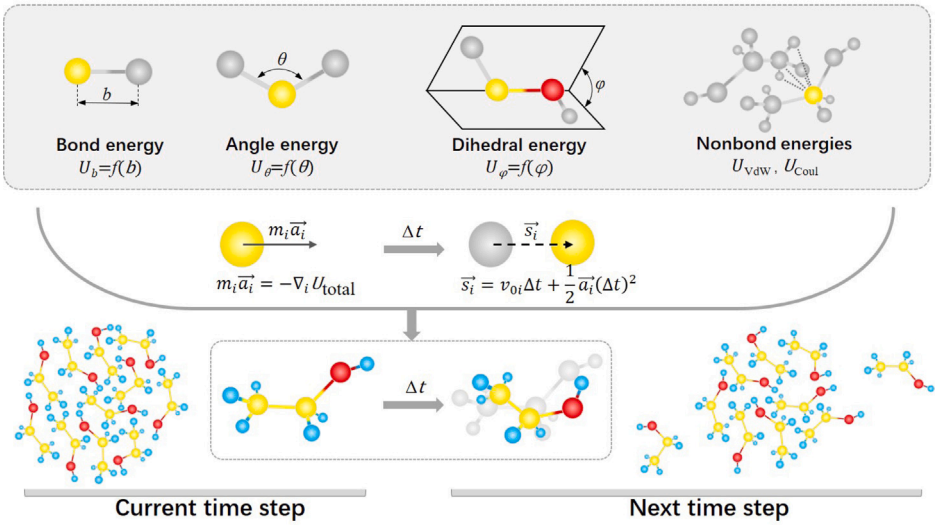

Fig. 6. Schematic presentation of MD simulation demonstrating interatomic interactions and molecular motion, using an ethanol molecule as an example.

MD has been used in the study of the microstructure, interfacial properties, and deposition mechanisms of aerosols (Amelyushkin & Stasenko, 2018; Darvas, Picaud, & Jedlovszky, 2013; Ji, Shi, Zhao, Wu, et al., 2024; Zhang, Yu, Ma, & Wang, 2024). For inhalable aerosol drugs, the reliability of using the MD method to investigate drug molecule diffusion, binding characteristics, and the mechanisms of formation of drug molecule groups has been validated based on comparisons between simulation predictions and experimental results (Estrada, Perdomo-Lápez, & Torres-Labandeira, 2000; Fatouros, Douroumis, Nikolakis, Ntais, et al., 2011). MD was used to study the compatibility of salbutamol sulfate with polyethylene glycol (PEG400) and isopropyl myristate. It was concluded that PEG400 can be used to replace ethanol as an environmentally friendly base liquid (Aldabet, Miller, Soltani, Golgoun, et al., 2022). The glycosylation of glucocorticoids by glycosyltransferase was investigated using the MD approach (Subedi, Kim, Lee, Park, & Oh, 2022). It was found that stable complexes formed between the protein, glucose donor, and substrate, were stabilised by hydrogen bonds. Qi, Xu, Wang, Cai, et al. (2023) used MD to demonstrate the synergistic mechanism of glycyrrhizin and salbutamol in helping asthma patients. Salbutamol adhered to the surfaces of the glycyrrhizin nano-drug delivery systems through hydrogen bonding and hydrophobic interactions. The targeting effect of the hydrophilic domains of glycyrrhizin was used to reach pathological sites and exert a synergistic anti-asthmatic effect (Qi et al., 2023). The impact of alcohol molecules (methanol and ethanol) as solvents, as well as three anti-asthmatic drugs (beclomethasone dipropionate, fluticasone propionate, and prednisone), on phospholipid bilayers was studied using MD methods (Famili, 2014). Similar studies have focused on aerosol inhalation drugs such as dextromethorphan (Oláh, Mulholland, & Harvey, 2011) and budesonide (Meng, Cui, Lin, Wang, et al., 2018).

As follows from this brief analysis, MD simulations could be a valuable tool in the development of aerosolized drugs, reducing the time and cost associated with the manufacture and testing of prototypes. The types of drugs contained in aerosol particles, the types of solvents, and the proportions of each component directly influence the dynamics and heat/mass transfer characteristics of aerosols, which in turn affect their transport and deposition in the respiratory tract. Regrettably, having conducted an extensive literature search, we have failed to identify any MD research on the heat and mass transfer properties of inhalable drug particles.

Note that the MD approaches have been widely used to study processes similar to those which take place in human airways (Guo, Yang, Qin, Zhu, et al., 2024; Quoika & Zacharias, 2024; Wang, Wang, Wang, & Lee, 2015; Xie, Sazhin, & Cao, 2011). The application of the methods described in these papers to the investigation of the dynamics and heat/mass transfer characteristics of aerosols in human airways would appear to be feasible, although we are unaware of any studies in this area.

The MD approach certainly cannot be directly applied to the analysis of the dynamics and heat/mass transfer characteristics of aerosols in human airways, taking into account their complex geometry. The results of the analysis based on this approach, however, could be used to introduce corrections to the drag force, and heat/mass transfer coefficients used in the conventional Computational Fluid Dynamics approach. Our vision of this role of MD in the investigation of drug aerosols in human airways is schematically presented in Fig. 7.

3. Discussion

The analysis presented in the previous sections shows that the efficacy of inhalation therapy depends on the characteristics of the drug and the delivery device, and on patient-related factors.

Recent advances have been made in several areas of targeted drug delivery, including nanomedicine, delivery mechanisms and mathematical modelling. Developments in nanomedicines have led to enhanced drug accumulation in lung tissues while

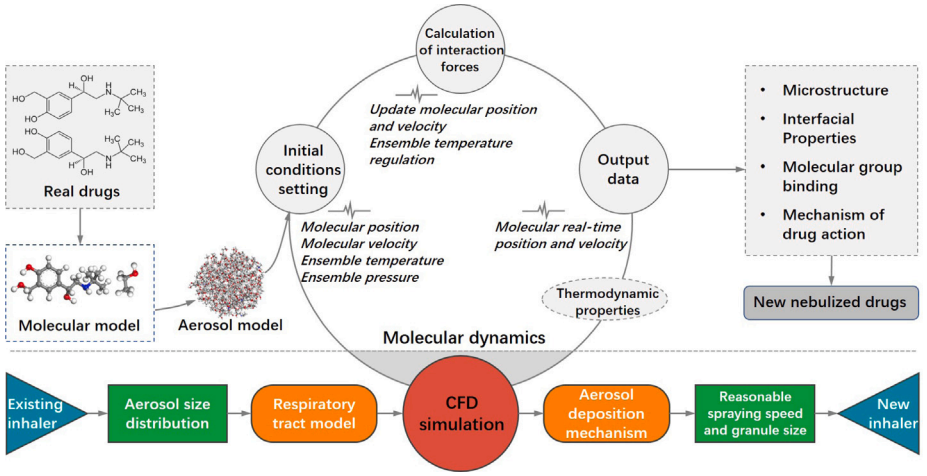

Fig. 7. Schematic diagram of the molecular dynamics simulation process and its links with other modelling tools for aerosol drugs.

minimising systemic side effects. Various pulmonary delivery targeting nanomedicines (PDTNs) have been developed to improve receptor-mediated strategies tailored for specific lung diseases such as lung cancer and infections (Wenhao, Ziqiao, & Zhengwei, 2024).

Innovations in aerosol therapy have established inhalation as a highly effective method for delivering drugs directly to the bronchopulmonary system. This method is not only beneficial for treating chronic conditions like asthma and COPD but is also being applied in vaccine administration and antiviral therapies. The development of advanced aerosol delivery systems has further facilitated targeted drug delivery, allowing for lower doses with improved therapeutic outcomes (Kleinstreuer, Zhang, & Donohue, 2008). The use of predictive mathematical models has emerged as a crucial tool in optimising aerosol drug delivery. These models help us to understand particle behaviour within the respiratory tract, thereby enhancing the precision of targeted therapies. Such advancements are essential for overcoming the variability in drug deposition caused by individual anatomical differences and inhalation techniques. Despite these advancements, achieving high specificity in drug delivery remains a challenge. Many existing aerosol devices lack directional capabilities, leading to ineffective deposition of particles at the intended sites within the respiratory system (Kleinstreuer, Zhang, & Donohue, 2008).

This inefficiency necessitates ongoing research into the optimisation of particle characteristics and inhalation techniques. The unique anatomy of the respiratory tract complicates targeted delivery efforts. Variability in airflow patterns, particle size, and patient-specific factors can significantly affect drug deposition and absorption (Wenhao et al., 2024).

It is vital to address these complexities in order to improve the efficacy of inhaled therapies. As new technologies emerge, ensuring regulatory compliance and safety remains a critical issue. The need for standardised evaluation systems to assess the efficacy and safety of aerosolized drugs is increasingly recognised within the scientific community.

While there have been notable achievements in targeted drug delivery systems for the human respiratory tract, significant challenges persist that require further investigation and innovation. The integration of advanced technologies, coupled with a comprehensive understanding of respiratory physiology, is essential to overcoming these hurdles and improving therapeutic outcomes for patients with respiratory diseases. Continuous collaboration among researchers, clinicians, and regulatory bodies is crucial in navigating this complex landscape effectively.

What follows is a summary of the main unsolved problems which we identified during the preparation of this review.

3.1. Current and new means of targeted drug delivery

We have identified the following knowledge gaps in current targeted drug delivery efforts and the development of new approaches.

- It is not clear how to deal with the strong dependence of the effectiveness of treatment by targeted delivery methods on the technique of inspiration.
- It is not clear how to improve cooperation between the patient and the delivery device.
- It would be helpful if the number of steps when performing the inhalation could be minimised.
- Universal inhalers with preset pulmonary deposition and the ability to control/correct this parameter are yet to be developed.

3.2. Pharmacological issues in targeted drug delivery

Additionally, the following pharmacological considerations are relevant to targeted drug delivery.

- Optimisation of dosing (frequency and number of doses per day) for patients of different ages.

• Methods of cortisol production/suppression during ICS therapy are yet to be developed.

• The pharmacopoeia prescription of aerosols needs to be improved, in order to exclude the unsafe effect of certain components on some groups of patients (e.g. ethanol).

• Instability of co-suspensions and the variability of the administered dose by a physician lead to difficulties in finding the optimal dose for long-acting $\beta 2$ agonists (LABA) and long-acting anticholinergics (LAMA) in fixed combination inhalers.

3.3. Model developments and data needed for model validation in targeted drug delivery

We have identified the following knowledge gaps in model development and data required for model validation.

• Simulation of the processes of targeted delivery of medical drugs using recently developed advanced models of droplet dynamics (Full Lagrangian Approach, Molecular Dynamic technique) has not been performed.

• Investigation of the role of aerosol heating and evaporation in the targeted delivery of drugs using recently developed advanced models of droplet evaporation and heating (hydrodynamic and Molecular Dynamic models) has not been performed.

• Modelling of the control of the processes of targeted drug delivery depending on the pathology and the current functional state of the human respiratory tract has not been performed.

• Identification of conditions where the supplied aerosols are not subject to heating/evaporation. This would allow us to obtain experimental data not affected by these processes, which could be used for model validation.

4. Conclusions

Achievements and challenges of targeted drug delivery to the human respiratory tract were summarised. These include an analysis of the means of targeted drug delivery, which were used in the past, are currently available, or are expected to be used in the future. Particular attention was paid to the prioritisation of drugs and means of their targeted delivery.

This analysis was followed by a description of pharmacological, experimental and theoretical advances in targeted medicine delivery to the human respiratory tract. The description of theoretical advances focused on the theoretical tools currently available and used for the analysis of drug delivery processes, and those which were developed for different applications, mainly in engineering, but could potentially be applicable to the analysis of drug delivery processes in human airways. The latter include the full Lagrangian approach, used for the study of the evolution of droplet/aerosol clouds in space and time, and recently developed models of mono- and multi-components spherical and non-spherical droplet/aerosol heating and evaporation. Particular attention was given to molecular dynamic approaches to modelling aerosols, including their dynamics, heating and evaporation.

Special attention was paid to the analysis of unsolved problems. These included current and new means of targeted drug delivery to the respiratory tract, and pharmacological, experimental and theoretical issues with advances in this process.

CRediT authorship contribution statement

R.M. Ainetdinov: Writing – review & editing, Resources, Methodology, Investigation, Formal analysis. **D.V. Antonov:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **S.N. Avdeev:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis. **B.-Y. Cao:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **S.A. Kerimbekova:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Formal analysis. **N. Liu:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis. **Z.M. Merzhoeva:** Writing – review & editing, Methodology, Investigation, Formal analysis. **O.V. Nagatkina:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualiation. **L.Yu. Nikitina:** Writing – review & editing, Methodology, Investigation, Formal analysis. **O. Rybdylova:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **S.S. Sazhin:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **E.S. Sokolova:** Writing – review & editing, Methodology, Investigation, Formal analysis. **P.A. Strizhak:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **O.A. Suvorova:** Writing – review & editing, Methodology, Investigation, Formal analysis.

Declaration of competing interest

The work described has not been published previously and it is not under consideration for publication elsewhere. Its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out. If accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.jaerosci.2025.106706.

Data availability

Data will be made available on request.

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