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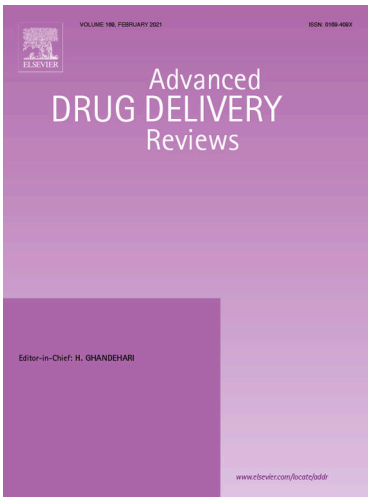

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Additive Manufacturing in respiratory sciences - current applications and future prospects

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Abbreviations

3D	Three-dimensional
4D	Four-dimensional
AM	Additive Manufacturing
API	Active pharmaceutical ingredient
CFD	Computational fluid dynamics
DEM	Discrete element methods
DPI	Dry powder inhaler
FDM	Fused Deposition Modelling
OINDP	Orally inhaled and nasal drug products
OIP	Orally inhaled drug products
SLA	Stereolithography
SLS	Selective Laser Sintering
TPP	Two-Photon-Polymerisation

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Abstract

Additive Manufacturing (AM) comprises a variety of techniques that enable fabrication of customised objects with specific attributes. The versatility of AM procedures and constant technological improvements allow for their application in the development of medicinal products and medical devices. This review provides an overview of AM applications related to respiratory sciences. For this purpose, both fields of research are briefly introduced and the potential benefits of integrating AM to respiratory sciences at different levels of pharmaceutical development are highlighted. Tailored manufacturing of microstructures as a particle design approach in respiratory drug delivery will be discussed. At the dosage form level, we exemplify AM as an important link in the iterative loop of data driven inhaler design, rapid prototyping and *in vitro* testing. This review also presents the application of bioprinting in the respiratory field for design of biorelevant *in vitro* cellular models, followed by an overview of AM-related processes in preventive and therapeutic care. Finally, this review discusses future prospects of AM as a component in a digital health environment.

Keywords

3D printing, Bioprinting, Rapid Prototyping, Inhalation, Particle design, Airways, Drug delivery to the lungs

1. Introduction

Additive manufacturing (AM) allows the fabricating of tailor-made objects that the existing manufacturing technologies are not capable of achieving. The current refinements and improvements in AM technologies constantly introduce novel approaches for application in pharmaceutical research. Such advances particularly apply to respiratory sciences, where numerous developments have taken place recently. This review provides an overview of AM processes that relate to respiratory sciences. This includes the development of particulate formulations for pulmonary administration, rapid prototyping of inhaler devices, fabrication of accessories for *in vitro* testing, preventive and therapeutic applications of AM as well as bioprinting approaches. Moreover, this work aims at identifying gaps in respiratory sciences that could potentially be bridged with the help of AM technologies, highlighting future prospects in this research area to develop novel medical devices, pharmaceutical products and testing equipment.

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2. Additive Manufacturing

2.1. Basic principles of additive manufacturing technologies

In the last four decades, AM technologies have been developing fast impacting various fields of engineering and manufacturing. In contrast to conventional fabrication methods, AM technologies allow the production and replication of an almost unlimited variety of object geometries, even with complex internal structures. This unprecedented design space is due to the digitalised process chain, which includes the construction of tailor-made objects on the computer.

As a starting point, a digital three-dimensional (3D) model is created either by geometric modelling from scratch or by reverse engineering based on an existing physical object. The structure of this 3D model can also be optimised with computer simulations of the performance of this object in its intended physical environment. From this digital model, a computer-aided design (CAD) file, construction patterns for the fabrication are compiled to an AM file format (e.g. STL, AMF, PLY). Then, this file is converted into the respective process parameters, defining for example the location of the energy focus (e.g. by means of a laser or electron beam) or the material or binder application (e.g. by means of an extruder nozzle) depending on the physical principle of the utilized AM technology. By solidifying the applied material, the digitally generated object is finally physically created. Fine finishing is the final step in the process chain. The entire workflow can thus be classified into three phases: pre-processing, fabrication, and post-processing (Figure 1).

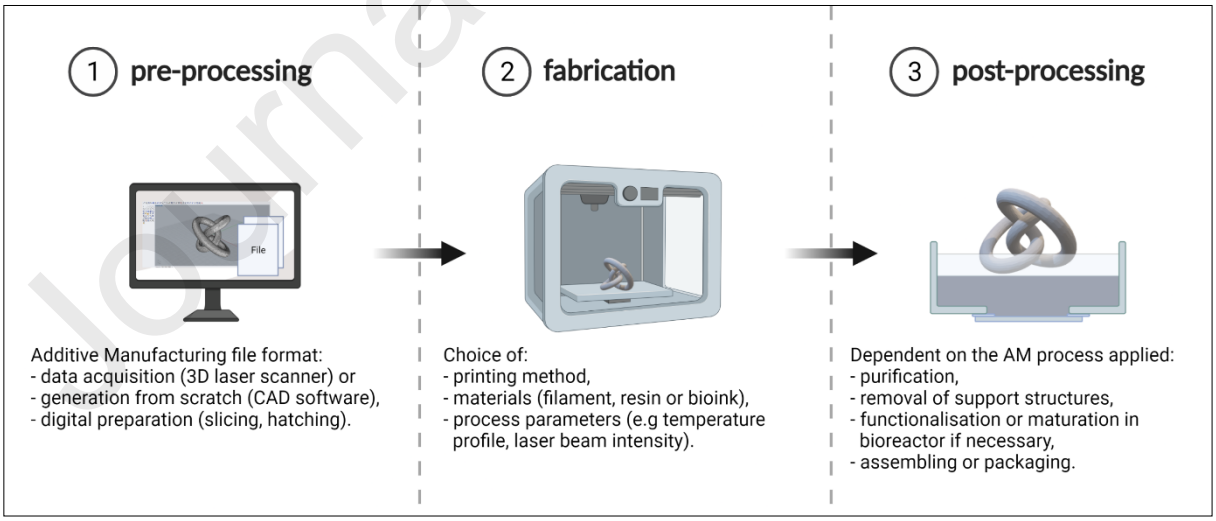

Figure 1: The process chain of AM comprises pre-processing, fabrication, and post-processing. From digital design to preparation of materials to a validated printing process including post-processing, such workflows are very diverse. Created with BioRender.com.

2.2. Additive Manufacturing of pharmaceuticals

AM technologies ultimately yield a tailor-made object, where function and purpose are defined by its morphological design and structural composition. Each AM method has specific technical limitations and distinct requirements on the materials to be used. The respective methods can be divided into three main groups, namely extrusion, powder solidification and liquid solidification, and the general challenges related to each group of methods has been discussed [1,2]. Many of the methods are still at their infancy considering their direct use for respiratory sciences, and more basic engineering research is needed to make the full potential available. From a pharmaceutical perspective, the properties of the processable components eventually determine the applicability of the resulting product. Several AM techniques have been used in pharmaceutical and medical research, covering examples from printed drug delivery systems to tissue engineering, surgery training, implants or prostheses [2–5].

Seoane-Viaño et al. provided an overview on AM technologies in pharmaceutic applications and recent pre-clinical as well as clinical applications [2]. Most of these examples demonstrate the design of drug product prototypes, which are analogous in appearance to conventional drug delivery systems such as tablets. Conventional mass production of pharmaceuticals involves several powder-based unit operations in which excipients and active ingredients are processed together. However, this approach does not allow for straightforward customisation of the drug product. In contrast to mass production methods, the integration of AM processes envisages the preparation of personalised doses or multicompartmental drug filling with modulated release profiles [6]. In this context, mass customisation due to product modularisation has recently been proposed as a pharmaceutical concept to provide dosage form individuality [7]. Continuously operating manufacturing solutions have been identified as important for the transition from mass production towards mass customised products. Some of these technologies, such as pellets, are already well-established as technological platforms [8]. However, remaining challenges include the holistic integration into the healthcare ecosystem and the implementation within regulatory boundaries.

A medicinal product basically passes through various phases of research and development, production, quality assurance, distribution and therapeutic application. The same requirements that are imposed on classical dosage forms must principally also be met by AM-based products. In turn, this requires a highly controlled and validated workflow, which is not yet fully existing for AM based products.

In 2017, the U.S. Food and Drug Administration (FDA) published a guidance providing a regulatory framework for the additive manufacturing of medical devices [9]. Key questions concerning assurance of quality, safety and efficacy of printed pharmaceuticals on the other

hand remain less clear. However, the approval of the ZipDose™ manufacturing process (Aprecia Pharmaceuticals), in which a binding fluid (ink) is iteratively applied to powdered drug-excipient layers, is considered the initial spark for AM-based mass production. Such AM application has so far been limited to a single FDA-approved product called Spiritam™ [3,10]. A further example is an extrusion-based process offered by the company Triastek, with which solid oral dosage forms with customisable release kinetics can be produced in an automated and real-time monitored process [11]. In part because the diversity of printing technologies continuously grows, this FDA guidance does not yet include either dosage forms or biological, cellular and tissue-based products. Generally described as bioprinting, the manufacturing of the latter products using AM technology demands additional production process and product life cycle monitoring considerations, as well as novel regulatory pathways [4,5].

Rapid advances in the development and fabrication of novel solid dosage forms haven taken place in the recent past. Although encouraging and promising, considerable scientific work is still needed to extend such advances to the manufacturing of highly functional, biomedical tools or even artificial organs. As an intermediate step, additively manufactured replicas, stents and functionalised cell cultures serve as precursors for 3D-printed organs. Furthermore, the criteria for customised objects for surgical or implantological purposes (such as durability or biodegradability) differ fundamentally from the criteria for prints that are utilised in *in vitro* studies or merely serve as prototypes of medical devices.

3. Current needs in respiratory sciences

For the treatment and control of both respiratory and systemic diseases via the lung a variety of active pharmaceutical ingredients (API) combined with suitable inhaler devices are available. To meet the patient needs, public authorities, pharmaceutical industries, healthcare providers as well as researchers all over the world are constantly and comprehensively challenged. The challenges arise from the complexity in developing pharmaceuticals and medical device. To develop dosage forms and devices comprehensive knowledge of physiology, pathology, diagnosis, pharmacology, clinical practice and data science is as crucial as pharmaceutical and technological expertise.

Regulatory criteria for quality, safety and efficacy set high standards on the production of such products. For orally inhaled and nasal drug products (OINDP), the criteria apply to formulation excipients, the design and manufacture of the device, as well as the composition of the final drug product [12]. The development of both low-cost and highly efficient as well as easy-to-use devices is in the focus of current efforts [13], since socio-economic aspects determine therapeutic success to a considerable extent [14]. Likewise, the development and global launch of new medicines entail high financial, labour, infrastructural and time expenditure.

These prevailing circumstances suggest that an emerging technology such as AM has the potential to accelerate research and development (R&D). Such an acceleration is attributed to AM, because it enables fast prototyping, product personalisation and the possibility to demonstrate and validate computer simulations. Such technological capabilities ultimately culminate in improved devices and formulations, which in turn may lead to better healthcare at lower costs.

4. Additive Manufacturing in respiratory sciences

Although a steadily growing role of AM in various areas is acknowledged, apparently it has not yet been widely applied in the field of respiratory science. In contrast to the multitude of publications dealing with the manufacture of oral dosage forms, there are only a few references on the use of AM in the respiratory field. In respiratory sciences, AM can be applied not only at the level of the dosage form, but in principle also at other aspects related to the broader pharmaceutical development process. From the authors' perspective, each application is associated with different technological needs and practical factors to consider:

- At the formulation level, control of particle characteristics is the aim for the development of customised drug delivery systems utilising AM. The efficiency of respiratory drug delivery is determined by physical dispersion and deposition mechanisms during inhalation, which in turn depend on particle properties such as size, shape, density and surface microstructure. Manufacturing inhalable particles would therefore imply accurate processing of biocompatible materials in the micrometre range. Besides this technical challenge to fabricate tailor-made particles, their use in clinical settings would require efficient production in sufficient quantities.
- To develop medical devices that meet patient- and disease-specific needs, the use of AM would allow for rapid prototyping, testing and manufacture of customised device designs. These need to take the 3D tomography of the patient and physiological conditions into account ensuring individual safety and efficacy. Optimally, design development and optimisation go hand in hand with *in silico* based computer modeling to facilitate perfect patient-device interfaces utilising AM. However, customisation of pharmaceutical products is not always in line with the current regulatory framework.
- The lung as the target organ with its sensitive, fine microstructure and unique gas-liquid interface poses additional challenges to any product intended for respiratory application. Such a product needs to account for the physiological dynamics of breathing and mucociliary clearance requiring biocompatible, highly dynamic and adaptable materials that are also durable. Overall, the complexity of such approaches

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is compounded by the specific legal framework for the use of artificial, cell-based products.

The following sections will provide an overview on current and envisioned future applications of AM related to respiratory sciences including latest advances in particle design, rapid prototyping of inhaler devices, fabrication of *in vitro* testing accessories, manufacturing of equipment for preventive and therapeutic use as well as bioprinting applications.

Particle design

The application range of AM is determined by the different fundamental operating principles and corresponding print resolution as well as the composition of the material used. In contrast to the production of tablets or implants, the size distribution of individual particles needs to be typically lower in dosage forms for pulmonary administration. This is because in orally inhaled drug products (OIP) an aerodynamic particle size below five microns is associated with physiological effects of the API contained in the particle. To date, the production of comparably small objects with intricate details in the micron range remains a considerable challenge. With classical oral solid products, there are examples of AM based particle design, however, typically in the millimetre scale for proof-of-concept [15,16]. As recently reviewed by Hahn et al., only very few approaches, such as Two-Photon Polymerisation (TPP), Electron Beam Induced Deposition (EBID) and Direct Ink Writing (DIW), meet the criteria of submicron-size and resolution [17].

In respiratory sciences, TPP has been used as a method to fabricate well-defined morphologies for the investigation of particulate interactions. Particularly, utilisation of various printed ridges down to 1 µm in size provided general insights into the interplay of surface morphology on the one hand and adhesion, deposition and detachment of particles on the other [18]. In contrast to this high-resolution technique appears the methodological complexity, the printing speed as well as the non-pharmaceutical composition of the substrates or photoresins needed [17]. Therefore, it appears to be more feasible to engineer particles with lower level of detail but on the scale of carriers in dry powder inhaler (DPI) formulations.

On a formulation level with particle sizes in the single-digit micrometre range, López-Iglesias et al. introduced the production of porous particles via thermal inkjet printing followed by supercritical drying. In the latter process the printed polysaccharide-based aerogel yields microspheres with a relatively narrow particle size distribution but a strikingly rough topology. These particles loaded with a model substrate have already been tested in aerodynamic assessments, indicating a general suitability as DPI carriers (Figure 2, A) [19].

At present, direct manufacturing of tailor-made particles in the sense of AM lacks methodological capabilities. Instead, particle design and production are currently based on

moulding processes. As an example, the encapsulation of API in microdevices offers precise control over topology and size. As shown by McHugh et al., the underlying SEAL® technology features the assembly of pre-moulded, biodegradable lactid-glycolide copolymers in a layer-by-layer manner to form 3D structures. The authors demonstrated, that such container microparticles could potentially be useful for parenteral applications [20]. Such a micro drug delivery system can in principle be sensitised to certain environmental conditions such as pH value or enzymatic activity allowing specific drug release. From our point of view, the production of similar biodegradable DPI carrier particles would also be conceivable.

Torge et al. reported the fabrication and comparison of cylindrical and spherical shapes in the size range of API particles using a template-assisted and a spray-drying process, respectively. This enabled the investigation of nanoparticle-embedded drug delivery systems amendable for pulmonal administration. According to the authors, further progress in this technology allows fine-tuning of drug loading and disintegration behaviour, depending on particle size and morphology [21]. Another approach that provides precise control over the latter properties is the particle replication in non-wetting templates (PRINT®) technique [22]. Garcia et al. introduced this methodology in the fabrication of dry powder particles, that are principally suitable for aerosol generation [23]. Using this manufacturing process, it was further shown how the particle morphology and the shape factor, respectively, influence the aerodynamic diameter [24]. However, the morphology of the resulting objects with at least one flat surface suggests a high tendency to form agglomerates, which will be detrimental for particle dispersion in inhalation (Figure 2, B) [23,24].

The abovementioned studies are mainly limited to inhalable API particles with sizes in the single-digit micrometre range. As complex geometries in this range become in principle accessible, Fromen et al. pointed out that new characteristic parameters for describing the aerodynamic behaviour need to be identified [24]. A simple transfer of the characteristics of such API particles to much larger DPI carrier particles seems implausible. Flat surfaces would potentially counteract the suitability of microstructures as DPI carriers because “flat-on-flat” arrangements cause strong adhesive strength [25]. The resultant tendency to adhere and form aggregates could in turn hamper particle dispersion while inhalation.

Despite current methodological limitations, an implementation of AM on a DPI formulation level might just be a matter of technical progress and process acceleration (Figure 2, C). In a different size category, the insertion of additively manufactured geometries into DPI devices as free-levitating accessories for dispersion enhancement was presented. In the relevant proof of principle, a shift in mass median aerodynamic diameter (MMAD) was derived from the use of relatively large dispersing aids [26]. This principle derives from the finding by Buttini et al., that an add-on accessory, which contains an axial oscillating bead, improves the aerosol

dispersion of a commercial DPI inhaler. Such an add-on device influences the airflow patterns within the unit and thus affects the device flow resistance [27]. Replacing the oscillating bead with complex, dispersion-promoting geometries has not yet been investigated. Therefore, considering the multitude of variations in accessory geometry and size, a novel strategy for enhanced particle deagglomeration behaviour was recently anticipated by us [26]. In this context, AM offers a wide design space for the oscillating object and allows fine-tuning of the entire internal structure of a device.

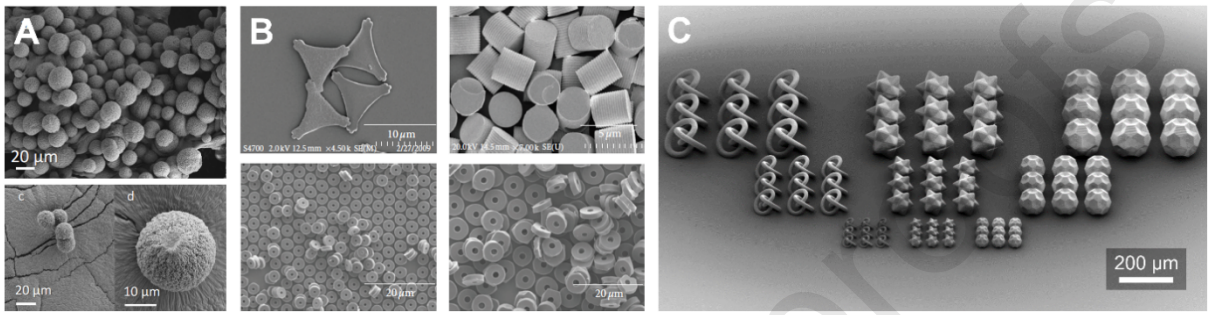

Figure 2: Particle design. (A) Integrating AM methodologies in particle engineering processes emerged as a novel approach to prepare porous microspheres (based on Inkjet printing, with permission from López-Iglesias et al. [19]). (B) Micromolding offered accurate control on geometric features providing geometric and aerodynamic size consistency (based on PRINT® moulding, with permission from Garcia et al. [23]). (C) Nanoscale precision of advanced AM technologies will allow intricate details for next-generation particle engineering in the future (based on TPP, with kind permission from M. Wegener and P. Kiefer from KIT, Karlsruhe).

4.1. Rapid prototyping of inhaler devices

Established examples of AM are especially evident in the development and rapid prototyping of inhaler devices and enables the realisation of device concepts in small quantities for rapid *in vitro* evaluation. The variables include technical design features of an inhaler such as the arrangement of air inlets, mouthpiece, or grid characteristics [28–32] (Figure 3, A). Integrating *in silico* simulation models in the development process provides valuable information about fluid and particulate flow. In turn, numerical data allow refinements to be made on the device design (Figure 3, B) [30–34].

To study the flow patterns within inhalers, computational fluid dynamics (CFD) has been used by Versteeg et al. for metered dose inhaler (MDI) [35] and by Coates et al. for DPIs (Figure 3, C) [36]. Due to the enormous complexity of predicting how a multicomponent solid/gas/liquid system with complex inhalable particles behaves, simulations without assumptions and simplifications are currently not feasible [31–34,37]. This is especially challenging for DPI formulations with different size/shape distributions and bulk properties, inhomogeneous surface energy distributions as wells as potential deformations of the individual particles. Recently, Longest and Farkas demonstrated the applicability of CFD in combination with rapid prototyping to design high-performance DPI aerosolisation units. The presented approach provides a blueprint for the development of future inhaler generations, even if this experimental

setup is based on a principally well-dispersible powder [37]. A formulation with other properties in terms of aerosolisability may require a different dispersion mechanism.

Since CFD analysis simulates only the patterns of a fluid and does not account for particle-particle interactions, coupling with methods that can in turn incorporate such interplay is of relevance. By coupling CFD models with discrete element methods (DEM), thus including both air flow and particle interactions, a more comprehensive representation of the underlying effects is achieved [33,34,38,39].

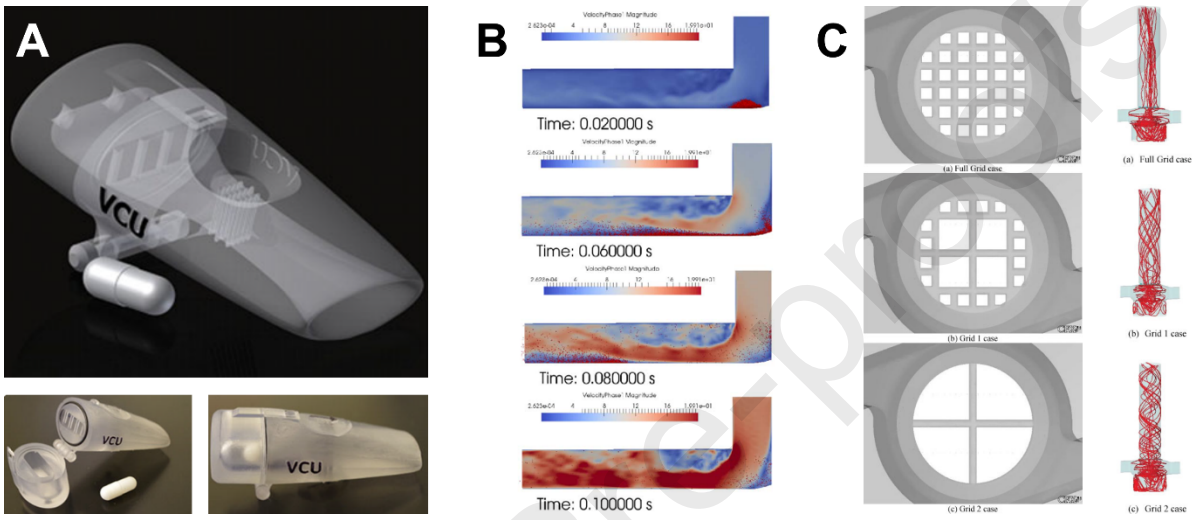

Figure 3: Rapid prototyping of inhaler devices. (A) Combining computational modelling and rapid prototyping with in vitro evaluation enabled the development of a high-performance DPI device (based on SLA printing, with permission from Behara et al. [29]) (B) To mimic the complexity of physical mechanisms involved in aerosolisation, multi-scale modelling provided valuable information on powder dispersibility (with permission from van Wachem et al. [33]). (C) Numerical modelling of particle trajectories in the flow field of an inhaler reveals potential for design optimisation (with permission from Coates et al. [36]).

Overall, the linkage of computational analysis and design with AM closes the loop of iterative testing procedures for the optimisation of inhalers (Figure 4) [32,34,37]. The intention of such design thinking processes is usually related to the development of both generic and innovative devices [34]. Corresponding detailed records are mostly undisclosed because such practices generally entail the preservation of intellectual property.

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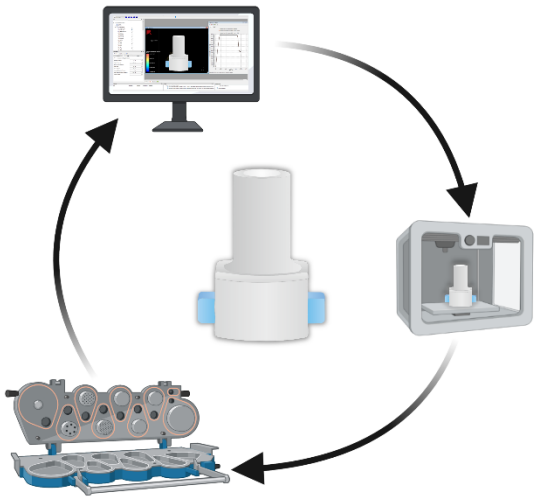

Figure 4: Iterative loop of device design, rapid prototyping and in vitro evaluation. Device designs derived from numerical data are rapidly fabricated using AM. The prototypes are then evaluated using standardised procedures (e.g., impaction analysis). Resulting in vitro data, in turn, facilitates optimisation of the product. Created with BioRender.com.

4.2. Accessories for *in vitro* testing

In the development of a pulmonary drug delivery system, both device and formulation are inextricably intertwined. An appropriate verification of inhaler properties must take the formulation it shall disperse into account. From the regulatory and scientific point of view, *in vitro* studies provide important evidence for approval and batch release of OIP. Pharmacopoeias specify a number of laboratory procedures for testing critical quality attributes [40]. Logically, such standardised methods fail to reflect e.g. patient-to-patient variability [41]. A proof of correlation of *in vitro* to *in vivo* studies however, is of high interest, providing a way to predict product performance with less laborious and costly clinical trials [41,42].

To investigate the fate of OIP formulations in the human respiratory tract, reality-mimicking test systems are continuously under development. For instance, idealised replica models of the upper airways combined with realistic inhalation profiles [41,43–47] provide deeper insights into drug delivery compared to standard set-ups. Initially, replicas of the respiratory tract were produced by moulding cadaver specimens with silicone components and by wax casting [48]. Comprehensively demonstrated by Burnell et al., magnetic resonance imaging (MRI) data of the respiratory tract can serve as a template for more accurate replication of the airways. In this study, effects of the anatomy on the drug deposition in the respiratory tract for various inhalers were demonstrated with models manufactured out of polyurethane in an AM process (Figure 5, A) [49]. With regards to the anatomical complexity, it should be noted here that the models represented a population of 20 individual, healthy adults. Nevertheless, the idealised dimensions shown and the corresponding *in vitro* results are in good agreement with data provided by other authors [43,45,50].

In a series of publications, Delvadia et al. demonstrated the application of mouth-throat models on the development of test methods with improved *in vitro-in vivo* correlation (IVIVC) [43–45]. In these studies, AM processes facilitated the investigation of how morphological features influence drug deposition in the upper airways (Figure 5, B). To incorporate the findings into assessment of OIPs, modified induction ports for standard test procedures were developed and additively fabricated [51]. In addition to efforts to accurately represent the anatomy, idealised models can alternatively mimic the prevailing flow patterns in the upper airways. Commercially available examples are anatomical throat models offered by Emmace and the Alberta Idealised Throat (AIT, Copley Scientific), which have been used in several studies for aerodynamic evaluation (Figure 5, C) [52,53].

As AM facilitates the rapid construction of new accessories, it provides a toolkit for the development of novel test methods. This particularly includes the investigation of fundamental aerosol behaviour and is illustrated in studies by Golshahi et al. on condensational growth. Components of the experimental setup originated from an AM process, with which aerosolised particles were generated. Based on fluid dynamic simulations and *in vitro* data obtained using an additively manufactured airway replica, a scenario for pulmonary aerosol delivery via the nose was evaluated [54]. In a simplified setting, Kolewe et al. showcased lobe-specific particle targeting. This study comprised an *in vitro* model in which the inlet flow rate and the location of particle administration in the mouth could be optimised. The results derived from numerical simulations and additively manufactured test equipment including a tracheobronchial replica that was based on tomographic data [55].

Physically simplified models of the distal airway segments provided inferences on delivery and distribution of therapeutics. Copploe et al. reconstructed a human tracheobronchial airway tree to study the delivery of surfactant in analogy to the treatment of respiratory distress syndrome (Figure 5, D) [56]. This approach generally enables *in vitro* parametric studies on the formulation level. It is therefore anticipated that the deployment of such tools made by AM contributes to optimisation of therapies and refinement of clinical guidelines [57]. It is imperative to consider that the characteristics of each model type are substantially defined by the material properties from which it is fabricated. A realistic representation of the airways is currently not feasible, because the materials do not comply with the physiological conditions of the airways. In particular, this applies to the lower airways due to a considerable increase in both anatomical and histological complexity [58]. The materials used are hitherto incapable of emulating the dynamics of the soft tissue in the airways. This explains, why it is still out of reach to imitate the mechanisms and mechanics of the lungs on a realistic scale, resulting in a lack of comparability to *in vivo* conditions [41,42,46,59].

It appears to be most patient-related to conduct deposition profile measurements with reconstructed models mimicking both the airway structure and cyclic respiration patterns [43]. Considering the complex individuality of anatomical and physiological determinants, the question arises as to whether a realistic description of the processes during aerosolisation and deposition can actually be depicted with the aforementioned add-ons. It is further questionable whether the apparently realistic models rather represent an idealised and optimised set-up whose clinical utility ultimately remains ambiguous [42]. However, Soares et al. complementarily demonstrated that the use of additively manufactured airway models generally promises substantial benefits for evaluation of diagnostic equipment. In their study, a comparison of commercially available devices to assess impedance in obstructive diseases based on such an airway replica has been presented [46].

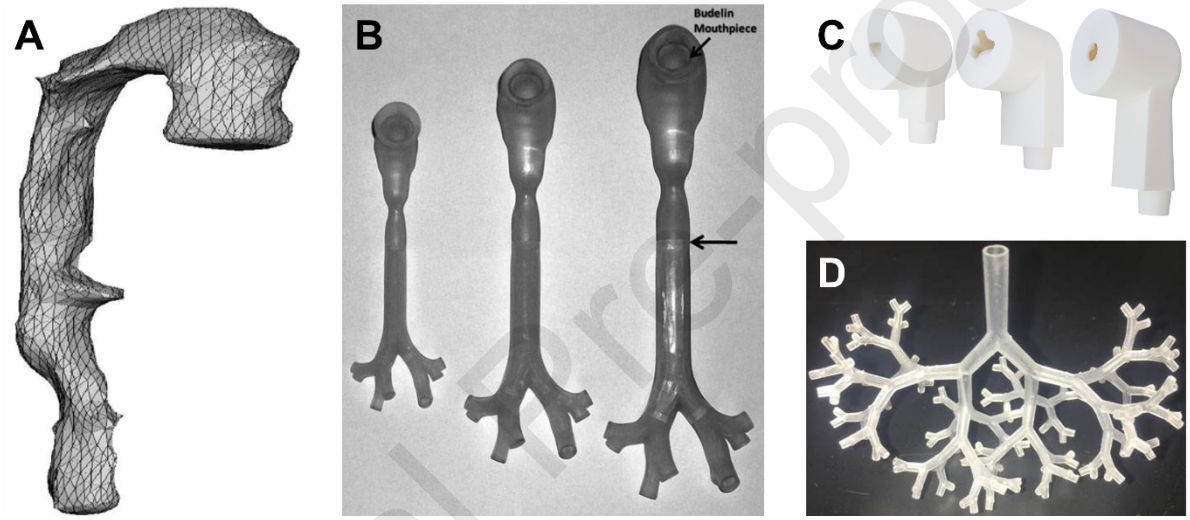

Figure 5: Accessories for in vitro testing. (A) Integration of 3D throat models into experimental studies on particle retention in the upper airways (from Burnell et al. [49]). (B) Technical capabilities of AM facilitated accurate replication of the morphometry of the tracheobronchial tract for IVIVC studies (based on SLA printing, with permission from Delvadia et al. [43]). (C) Anatomical throat models with idealised interior geometry for evaluation of IVIVC (based on SLS printing, with kind permission from Emmace [51]). (D) Fabricating a physical airway tree provided insights into the pulmonary distribution of instilled surfactant for therapeutic applications (based on SLA printing, with permission from Copploe et al. [56]).

4.3. Biomedical tools

From an overall pharmaceutical perspective, large knowledge gaps are apparent between *in vitro* investigations, tissue studies, animal experiments and finally clinical trials. Corresponding trials require numerous financial, logistic, infrastructural, and human resources. A major bottleneck is the availability of living test objects, either tissues, animals, or humans for clinical trials in the late phase of a regulatory approval. Moreover, animal models are reported to poorly imitate the conditions in the human respiratory tract. Inter-species differences regarding anatomy and physiology including inspiration mechanism, cellular composition, airway branching and immune system function hinder clinical translation [60]. Therefore, a strong endeavour in research is to reduce, refine and replace (3R) the use of these natural test systems. At the same time, the urge to improve and accelerate studies on disease

mechanisms, drug screening as well as pharmacokinetics is omnipresent. To bridge the gaps, biomedical tools with equivalent properties to human tissues such as alveoli are under development. Even though the use of two-dimensional lung tissue, i.e. epithelial monolayers, to study cellular processes and interactions is well established, literature reveals that 3D co-cultures are crucial for congruent adaptation of native cell functions [58,61–63].

Technologies that involve the 3D-printing of living cells to cultivate heterogeneous tissues or fabricate entire organs with associated biological functionalities are referred to as bioprinting. Introduced by Robert J. Klebe in 1988 [64], micro-positioning of cells ultimately evolved to the scientific ambition to create a personalised, fully functional human organ [58,65]. Bioprinting includes similar techniques as in classical AM, based on extrusion, photocuring or droplet processing [5,58,65]. Recently, new approaches such as acoustic wave bioprinting [66] and sacrificial writing into functional tissue (SWIFT) [67] were introduced. In most cases, an established technique is adapted with additional accessories, depending on the properties of the specialised material to be handled. These so-called bioinks are generally described as composite materials consisting of cells, growth factors and matrix forming agents [5,58,68]. As with any manufacturing process, a balance between method-specific printability, biocompatibility and final mechanical properties must be considered when selecting the relevant bioink [5].

In contrast to classical AM, the process of bioprinting in many cases comprises the implementation of scaffolds, which serve as temporal mechanical support promoting the reorganisation of added cells into a functional tissue. The requirements for the scaffold must match the respective biological specification, particularly, when the cellular components shall form a structured tissue with simultaneous degradation of the support skeleton. Although in some publications synthetic and inorganic materials were utilised [5,68], the scaffolds are mostly made of biological polymers such as fibrinogen, collagen, alginate or gelatin [58,68–70]. Conversely, tissue composites usually consist of multiple cell types in an organ-specific arrangement. Those components can be embedded in an extracellular matrix, which ideally mimics the physiological environment [68,69,71].

Despite the showcase of an artificial, cellularised heart with nature-mimicking microarchitecture gives rise to the capabilities of bioprinting in the future, such approaches are still at an early stage of development [72]. After all, to produce biomedical parts that have the same properties as natural tissue, a replica of the biochemical microenvironment is also required. Consequently, the production of whole organs for transplantation purposes remains a quite distant prospect. This is particularly true for the application to the respiratory tract [58]. Besides such rather visionary research activities, other efforts are already yielding more concrete results. A growing number of articles describing a variety of applications and

emphasising the usefulness of *in vitro* 3D models of different tissues have been published [73,74]. As an example, bioprinting processes were applied to generate perfusable vessel models with biofunctional layering, which hold potential for pre-screening of drugs. Schöneberg et al. indicated that 3D-printed, cell-based bioreactors can occasionally mimic the conditions in natural tissues and organ parts very well [69].

4.4. Bioprinting in respiratory sciences

The application of bioprinting does not yet play a considerable role in the field of respiratory science. A substantial difficulty with 3D-bioprinting of the respiratory architecture is the heterogeneity of the distinct regions such as respiratory epithelium, vasculature, lymphatics, interstitium, muscles or cartilage [58].

To the best of our knowledge, there are only a few substantial publications on this matter. As elaborated by Galliger et al., most studies focused on the fabrication of tracheal grafts, mainly relying on polycaprolactone scaffolds [75]. Overall, *in vivo* studies indicated an unfavourable ratio between scaffold degradation and cell proliferation in the grafts. The formation of tracheal cartilage, however, is considered a precursor to alveolar bioprinting, as it also involves the development of epithelialised hollow and tubular organs [75]. Recently, Dhasmana et al. reviewed the principles and current challenges in tracheal tissue engineering [76].

Further scientific interest lies in the development of histological models that represent the various interfaces between air, fluids and cells. Horváth et al. demonstrated a reproducible and automatised fabrication of a human alveolar air-blood barrier analogue (Figure 6, A) [77]. This method comprises the addition of several respiratory-related cell types on a porous membrane covered with extracellular matrix in a layer-by-layer fashion. In their study, homogeneity, viability, proliferation, barrier quality, and reproducibility of bioprinted cultures were evaluated. Therefore, the application of such *in vivo* human-alveolar barrier structures promises a viable option for high-throughput screening in safety assessment and drug research related to the respiratory tract [77].

In addition, a stereolithographic approach was recently described in which the fabricated object was inspired by the entangled vascular architecture of the alveolar region. Although this work lacks alveolar cell studies, it indicated a pathway for the bioproduction of mechanically stable, ventilatable structures that could mimic vascular perfusion of artificial tissues in the future (Figure 6, B) [78]. The native architecture of the alveoli, characterised by hollow, spherical epithelial cysts, can in principle be reproduced by photodegradable microspheres, which serve as sacrificial templates [62]. By equipping this modifiable substructure with suitable cells and using the resulting composite material as bioink, it is postulated that bioprinting enables the construction of an *in vitro* lung-like model [79].

As the knowledge of tissue engineering is growing, the integration of microfluidics promises the development of functional tissue platforms for screening pathogens or drugs on a chip [79,80]. Recently, the current development of models based on such lung-on-a-chip approaches and 3D bioprinting techniques have been summarised by Barros et al. (Figure 6, C) [70]. Despite the general leeway with regards to design and material combined with accuracy and reproducibility of AM procedures, the application of bioprinting to issues in respiratory science is still in its infancy. The capabilities of this approach cannot be foreseen at the current stage of research due to the complexity of lung histology and structure - both in terms of spatial arrangement and biochemical interplay [58]. Instead, the existing results reveal that bioprinting has emerged as a promising platform with numerous potential applications for fundamental medical research and the pharmaceutical industry.

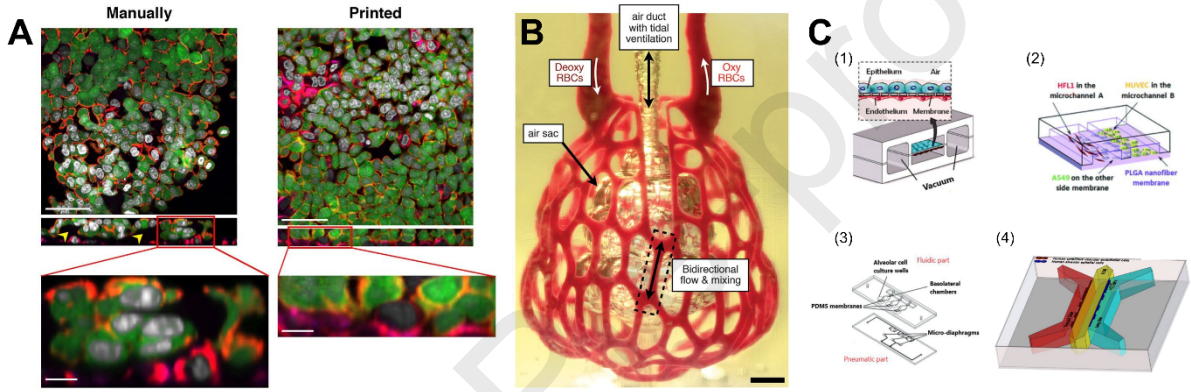

Figure 6: Bioprinting. (A) In comparison to manually seeded cell layers, bioprinted co-cultures possessed improved structural and functional resemblance to complex cellular networks (with permission from Horváth et al. [77]). (B) 3D-Printed alveolar models based on hydrogels served as artificial ventilation systems capable of oxygenating red blood cells (with permission from Grigoryan et al. [78]). (C) Recent developments in bioprinting techniques applied in lung-on-a-chip approaches were collected by Barros et al. [70].

4.5. Preventive and therapeutic applications

During the global COVID-19 pandemic global supply chains were disrupted. Applying AM allowed for fabricating a variety of medical tools closer to the point of need [81]. This included personal protective equipment (PPE) such as face shields and masks that were used supportively to prevent individuals from airborne infections [82,83]. Manero et al. furthermore enumerated ventilator components, which were produced in close proximity to the point-of-care providing sufficient capacity for critical patient ventilation [81,84]. It should be noted, however, that not all prototypes used during the pandemic meet the strict specifications for PPE.

Besides the capability of AM to overcome occasional shortages in material supply, its application in treating airway diseases has previously been demonstrated. Some diseases or injuries that particularly involve the respiratory tract require surgical intervention, which includes careful operational preparation. In such pulmonological settings, the use of 3D

models holds substantial clinical advantages [85]. The models typically derive from a virtual image obtained by computer tomography (CT) scans of the patient. Such scans, in turn, enable the printing of personalised airway replicas that allow pre-surgical planning [85–89]. The planning comprises practice and optimisation of a surgical strategy based on the replicated anatomical environment. AM assists in deciding on bronchial intubation techniques to facilitate lung lavage [86] or in guiding lobectomies [88].

In some pathophysiological cases, it is necessary to implant stents maintaining proper ventilation of the lungs and normal passage of secretions [89–91]. It has been shown that the assistance of 3D models facilitates airway stenting [87,89]. Ideally, implants are adapted to the patient considering individual anatomical and motional peculiarities of inspiration, expiration and coughing. According to Alraiyes et al, commercial implants carry the risk of not fitting properly and thus causing harm. Mismatching between stent structure, anatomy and physiology may lead to tissue injury or hazardous stent migration [91]. Personalised stent modifications based on patient-specific replicas were reported by Xu et al. In this study, a 3D-printed airway cast served as a true-to-scale template for modifying a standard stent and to ensure its correct positioning (Figure 7, A) [87]. Casting processes, in which the mould is customised using 3D modelling, enable the manufacture of precision-fit stents [90,92–94]. The final step of stent fabrication is mostly conducted with silicone casting, whereas AM functions as an intermediate step in the development of the respective mould. This step comprises appropriate mechanical or chemical surface finishing of the 3D-printed mould [94].

In principle, AM procedures allow accurate adaptation to individual characteristics making this technology preferable for direct fabrication. Königshofer et al. concluded that 3D-printing of stents as such has failed in the past due to a lack of materials comparable to the standard made of silicone [93]. In addition to biocompatibility and sterilisability, silicone also possesses mechanical durability while being elastic. Since other materials that fulfil these criteria are now available, AM is deemed to hold further potential for the manufacturing of stents [87,93,95]. This potential is further demonstrated by Zurita-Gabasa et al. who recently manufactured customisable tracheobronchial stents out of medical grade silicone. In this study, the stents were custom-designed using computational modelling and manufactured using ACEO® printing technology (Figure 7, B) [96].

As a landmark for the potential of AM in pulmonology, Morrison et al. demonstrated the use of additively manufactured scaffolds that served as supportive structures for the bronchial airways. To prevent internal collapse or excessive, external compression due to trachea-bronchomalacia, bioresorbable airway splints were implanted into critically ill paediatric patients. In addition to providing immediate pulmonary ventilation support, the splints expanded with airway growth due to their four-dimensional (4D) design. Such a design

approach considers self-evolving structures able to change their properties upon environmental conditions. According to the authors, the 4D splints caused no device-related adverse effects over the period of time until bioresorption (Figure 7, C) [97,98]. Notwithstanding these sophisticated case studies, as mentioned previously, the legal basis for the use of such additively manufactured products remains vaguely delineated [9]. On one hand, an implant is intended to support life and prevent harm. On the other hand, the risk of causing injuries or impairments is high. Therefore, such devices have to pass premarket approval pathways reviewing safety and effectiveness. Additive manufacturing of a single individualised stent, splint or other device is diametrically opposed to the established procedures of regulatory guidelines, which demand detailed standardisation. To date, surgical interventions utilising 3D-printed devices are therefore generally subject to an emergency exemption or compassionate use.

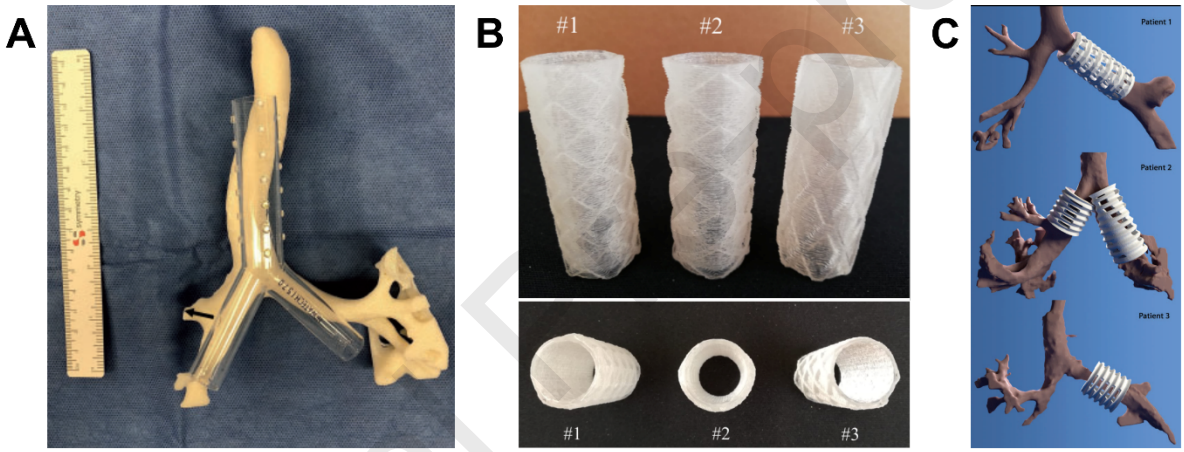

Figure 7: Preventive and therapeutic applications. (A) Customising commercial stents with the help of additively manufactured airway models allowed for optimised cross-ventilation of the branching airways (based on FDM printing, with permission from Xu et al. [87]). (B) Combining computer-aided parametric design with AM exemplified practical feasibility in fabricating tailor-made stents (based on Polyjet printing, with permission from Zurita-Gabasa et al. [96]). (C) To treat tracheobronchomalacia, individual airway models enabled a virtual assessment of fit prior to 3D printing of suitable tracheobronchial splints (based on SLS printing, with permission from Morrison et al. [98]).

5. Future prospects

Optimal medication entails personalised drug selection and dosing, as well as targeted administration to specific areas of the human body. These requirements apply to all dosage forms, including OINDPs for the treatment of local airway and systemic diseases. Technical, pharmaceutical, and patient-specific factors determine the efficiency of drug delivery and absorption of such pharmaceuticals. In the best-case scenario, this complexity can be considered at every stage of the development and production of respective products. To address this complexity, the application of AM offers novel solutions. An optimised therapeutic approach is generally based on a thorough understanding of the underlying disease. Ideally, the application of artificial, 3D lung tissues enable a functional and realistic representation of the corresponding mechanisms. To realistically represent the mechanisms, however, further

scientific efforts are required with current bioprinting technologies. For this reason, we expect that future work will increasingly emphasise on the *in vivo* imitation of histological and physiological conditions. The replication of elastic and mucus-mimicking segments is of special relevance to overcome the limitations of current models. This particularly involves the research on novel materials, capable of mimicking the physiological nature of the respiratory tract. Still, the fabrication of artificial lungs for transplantation purposes is not within a scientific reach.

The anatomy of the airways is an important individual factor. Patient-specific replicas could principally be produced with the help of AM technology in a short period of time. The lack of clinical data examining safety, efficacy and practicality of personalised implants indicates an ample scope for further research and development. Need for innovation also applies to materials for manufacturing such implants. In the absence of suitable materials, AM is apparently still just one of many process elements involved. Nevertheless, we perceive high potential in AM technologies for mass customisation of such medical devices in the future.

In contrast, the integration of (idealised) airway replicas in development and pre-clinical assessment of OIP is gradually increasing. But the translational potential of such *in vitro* models to clinical outcomes still reveals considerable gaps that require additional efforts to be fulfilled. Evidently, combinatorial use of numerical simulations with laboratory and clinical data holds promising scientific prospects. The latter are the common basis for research and development approaches in the respiratory field. In this discipline, computing is considered to simplify the search for optimal medical treatments including appropriate devices for inhalation. Fundamental effects of device design on the mechanisms of aerosol dispersion are currently fragmentarily understood. Coupling with computational modelling bears the risk of misinterpretation unless the material and particulate properties are fully considered. An accurate depiction of the particulate attributes in numerical simulations is practically unobtainable at this point. In this respect, solid dosage forms for inhalation pose a particular challenge. AM offers the capability of rapid prototyping and thus quick, practical testing of inhalers. Hence, an iterative cycle of simulation, fabrication, testing, and refinement ensues. Considering highly patient-centred care, this approach could even enable individualisation of the devices in the future.

Micronised drug particles as the most important component of such formulations are associated with both operational and computational difficulties [33]. For DPI products, the influence of morphology and size of micronised particles on aerosol performance is of key scientific interest. Unfortunately, current bulk production processes result in particle-to-particle and thus in batch-to-batch variability. In this regard, technical potential is identified in microscale AM processes, which are capable of manufacturing in a very precise manner and

in high detail [17]. Current AM methods allow the fabrication of particles that are three-dimensionally identical but predominantly feature at least one flat surface. Once complex structures in the micron range are accessible in 3D form, we expect a whole new field of research to emerge in respiratory science. Controlled fabrication of such structures would allow customisation on the particle level, including particle design and surface tailoring. Prospectively, it would be ideal to manufacture chemically and morphologically identical DPI carrier particles that match the properties of a certain API (Table 1).

Table 1: Prerequisites for particle design of new carrier generations.

Process capabilities	**Material properties**	**Design characteristics**
- Wide morphological design space - Replication of uniform particles in high resolution (nano roughness) - Rapid production at low costs	- Biodegradability, non-toxicity, safety - Chemical consistency - Durability - API matching adhesion properties	- Adjustable drug loading capacity - Intrinsic flowability and processability - Easy to fluidise and aerosolise - Turbulent particle trajectories in air flow

In the long term, DPI carrier particles that change their characteristics due to external stimuli, namely four-dimensional (4D) carriers, would provide further benefits. 4D bioprinting in tissue engineering and drug delivery has previously been reported by Gao et al [99]. Creating DPI carriers whose tendency to form agglomerates with API particles changes according to the inhalation phase could be highly valuable. This would be the case, if the corresponding decrease of adhesion leads to higher detachment rates and thus enhanced API deposition in the lungs. This approach implies particles that transform shape and thus aerosol behaviour in response to an external stimulus during inhalation such as acceleration, moisture, sound, or heat. To implement AM in the production workflow of such carrier particles, there is currently a lack of technological capabilities in terms of process speed, capacity and accuracy. In this context, research on novel materials applicable in current AM processes with outstanding resolution is inevitable. A more tangible concept in the medium term would be the insertion of numerically evaluated and additively manufactured dispersing aids into an inhaler. The impact of such auxiliaries on the fluid dynamics and deagglomeration forces in DPI devices remains unclear. It is postulated that both dispersing aid design and size affect the dispersion and potentially reveal an increased drug delivery to the lungs [26]. In addition to the use in DPIs, structurally complex packing disruptors in pressurised metered dose inhaler (pMDI) suspensions could facilitate resuspension.

In the course of AM, pharmaceuticals can be created that - just like conventionally manufactured dosage forms – need to comply with legal regulations and industrial standard specifications in terms of their quality, safety and efficacy. However, current guidelines do not have a directly applicable regulatory framework for additively manufactured pharmaceuticals. This regulatory uncertainty prevents the integration of innovative AM approaches in both the pharmaceutical and clinical sector. In addition, complying with regulatory and manufacturing standards entails a variety of technical challenges for the deployed AM equipment. To produce pharmaceutical products, applying AM processes in an industrial scale requires the development of hardware that meets the relevant standards.

To meet the expectations of all stakeholders involved in an efficient drug development process, computer-based methods such as physiologically-based pharmacokinetic (PBPK) models [100], numerical simulations [101], and AM [2,70,102] are increasingly implemented. Such methods allow the generation and analysis of data in a structured and objective way. Growing capabilities of these technologies allow advanced predictability of processes and product performance. At best, such data provide insights into aspects that were previously unconsidered. An implementation of computational methods into a pharmaceutical environment addresses the whole drug development process starting from R&D, as well as commercial production, monitoring and quality assurance. Through a digitally controlled process using scanning, imaging, modelling, simulation technologies and ultimately AM, medical devices and dosage forms can be much more custom-fit, but also more cost effective. With regards to personalised medicine in pulmonology and respiratory drug delivery, this ideally implies data driven matching of patients' health status (clinical and paraclinical data), anatomy (tomographic imaging) and medical evidence with appropriate drug formulation and a choice of device. Integration of complex data into operational healthcare principally requires appropriate software and connecting the drug product into digital health environment. Currently, machine learning algorithms allow for automatic interpretation of diagnostic data, providing clinical decision support and facilitating disease management [103,104]. To match the individual characteristics of a patient with a comprehensive therapy regime, application of such algorithms promises high potential. This potential is already evident in the use of so-called smart inhalers, which contain electronic sensors for data collection [105]. At the dosage form level, coupling machine learning and numerical simulation with AM could further assist the design and manufacture of carrier particles, dispersion aids and devices for respiratory drug delivery.

6. Conclusion

This review presents the extensive array of AM applicability on different levels in respiratory sciences (Table 2). On the particle level, manufacturing of simple, flat structures in a size range that can in principle be inhaled is already technically feasible. Manufacturing of far more complex geometries is within reach because of technological improvements, even if limitations in material choice, printing speed and quantity still hamper practical application. Vast research and development opportunities for drug delivery to the respiratory tract will emerge, once thorough control over morphology and size of inhalable particles or carriers becomes feasible at a larger scale. On the therapeutic level, linking data driven inhaler design with rapid prototyping in an iterative process allows to optimise drug delivery performance. General refinements in AM technology will further enable the development of highly detailed airway replicas and accessories for *in vitro* studies. With such tools, in turn, researchers will further fathom out fundamental mechanisms of respiratory drug delivery. In a similar optimisation loop, AM enables to fabricate customised airway implants for critical care. The use of 3D-printed implants has so far been limited to only a few applications, mainly because such devices are generally subject to an emergency exemption or compassionate use. An expansion of such procedures in therapeutic care requires a comprehensive legal framework and validated mass customisation processes. Replicating the histological environment of the airways still demands substantial research activities. For respiratory scientists, to manufacture an artificial lung in its holistic complexity still remains an inscrutable endeavour. Based on the facets of AM mentioned in this review, we believe that this technology will be of tremendous benefit to the research and development of medical products and devices in the future, especially in addressing the manifold challenges in respiratory sciences.

Table 2: Recent applications of Additive Manufacturing in respiratory sciences.

Application	**Investigated issues**	**References**
Particle design	Tailor-made fabrication and replication of solid particles in the micrometre range	[19–24]
	Investigation of morphology and size of dispersing aids and DPI carrier particles	[26]
Rapid prototyping of inhaler devices	Modification of device features and development of novel inhaler designs accompanied by numerical simulation data, involving performance testing of the fabricated device in *in vitro* settings	[28–32,34,37]
Accessories for *in vitro* testing	Manufacturing of micron-scale geometries for studies on particle interactions	[18]

	Fabrication of airway replicas for *in vitro* drug deposition and distribution studies of OIPs	[43–47,49,55,56]
	Development of devices for the generation of novel aerosol formulations	[47]
Bioprinting in respiratory sciences	Tracheal implants	[75]
	Analogue of the human alveolar air-blood barrier	[77]
Preventive and therapeutic applications	Fabrication of customised stents and implants	[87,93,94,96]
	Airway splints	[97,98]

7. Declaration of interest

SB and RS are inventors of a patent application on “Powdered formulations for inhalation” (WO2021115877).

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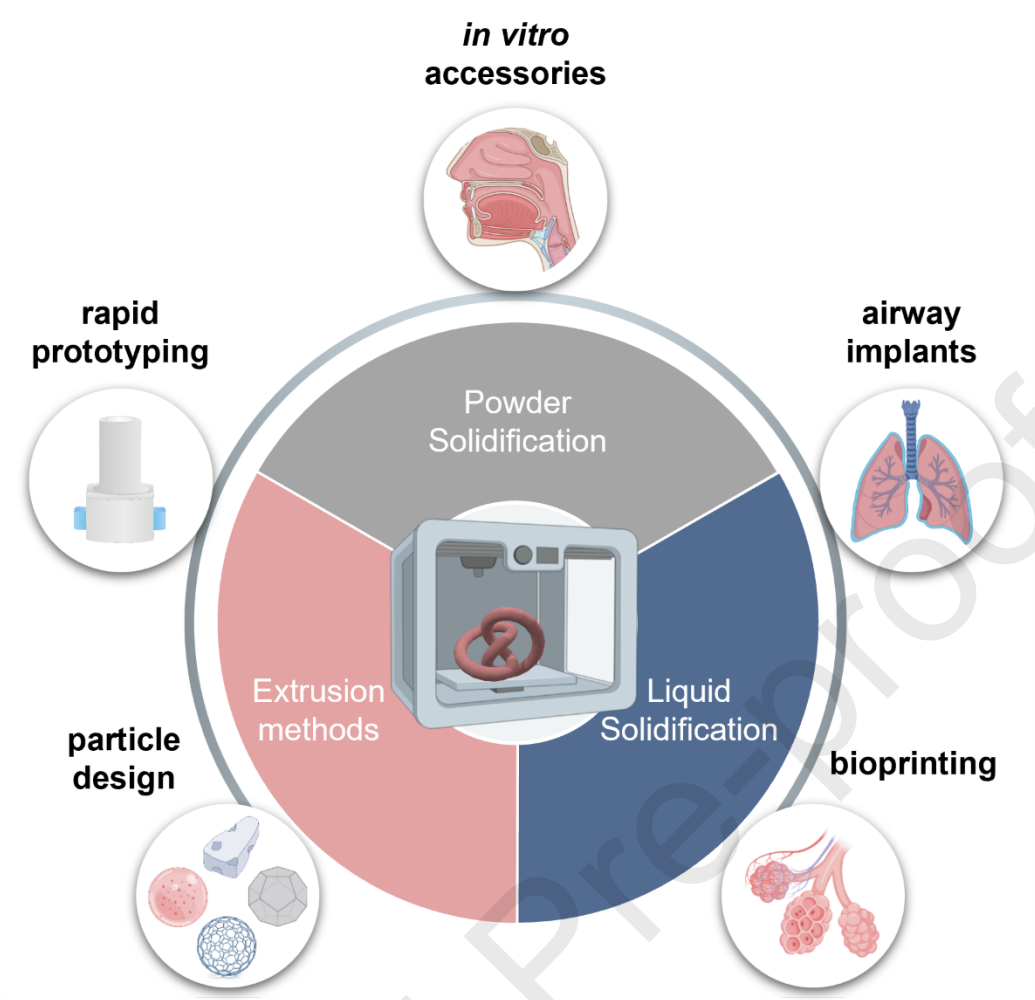

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