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TRENDS

Mask device as a new wearable sampler for breath analysis: what can we expect in the future?

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Abstract

Human exhaled breath is becoming an attractive clinical source as it is foreseen to enable noninvasive diagnosis of many diseases. Because mask devices can be used for efficiently filtering exhaled substances, mask-wearing has been required in the past few years in daily life since the unprecedented COVID-19 pandemic. In recent years, there is a new development of mask devices as new wearable breath samplers for collecting exhaled substances for disease diagnosis and biomarker discovery. This paper attempts to identify new trends in mask samplers for breath analysis. The couplings of mask samplers with different (bio)analytical approaches, including mass spectrometry (MS), polymerase chain reaction (PCR), sensor, and others for breath analysis, are summarized. The developments and applications of mask samplers in disease diagnosis and human health are reviewed. The limitations and future trends of mask samplers are also discussed.

Keywords Mask · Breath analysis · Breath sampling · Exhaled breath · Face mask

Abbreviations

AMR	Antimicrobial resistance
CA	Cellulose acetate
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
DART	Direct analysis in real time
DMS	Differential mobility spectrometer
DNA	Deoxyribonucleic acid
EBA	Exhaled breath aerosols
FFP	Filtering facepiece
FP	Flame photometer
FPSM	Fabric-phase sorptive membrane
GC	Gas chromatography
HA	Henderson apparatus
ICA	Immunochemistry analysis
IM	Ion mobility
LC	Liquid chromatography
MALDI	Matrix-assisted laser desorption/ionization
MS	Mass spectrometry
Mtb	*Mycobacterium tuberculosis*
PCR	Polymerase chain reaction
PSI	Paper spray ionization
PVA	Polyvinyl alcohol
RNA	Ribonucleic acid
RT	Real-time
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SFP	Sodium flame photometry
SPME	Solid-phase microextraction
TB	Tuberculosis
TD	Thermal desorption
TEA	Triethylamine
TOF	Time of flight
VOCs	Volatile organic compounds

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Introduction

Human exhaled breath is a typical bioaerosol that contains a vast variety of metabolites and bioparticles such as proteins, cytokines, bacteria, and viruses. Much evidence has proven that mask devices can be efficiently used for filtering exhaled infectious viruses and bacteria from patients, and thus the spread of respiratory diseases can be effectively prevented by

wearing masks [1–3]. In the past few years, mask devices have been widely used in daily life and unprecedented research efforts have been focused on the developments and applications of mask devices since the outbreak of the coronavirus disease 2019 (COVID-19) [2–4]. Many studies have been focused on the development history, manufacture, utilization, and impact on the environment of mask devices [1, 5–7]. New masks are also increasingly developed for better performances and new functions [7]. In general, the mask is a safe, noninvasive, and cost-effective wearable device to protect wearers.

There are commercially available various types of mask devices, which offer different levels for filtering exhaled and inhaled substances for different purposes, ranging from sneezing droplets to gaseous molecules [7, 8]. Therefore, mask devices can serve as wearable samplers for breath sampling. After sampling, mask samplers can be coupled with various (bio)analytical methods for different applications. By wearing a mask sampler, various exhaled substances such as metabolites, proteins, and microorganisms are allowed to filter onto the mask. In general, the sampling of mask samplers is mainly dependent on permeability and filtration efficiency of mask devices [6, 7]. Compared to traditional breath sampling devices such as gas bag, gas canister, breath condenser, and adsorbent tube [9–13], the mask sampler has many advantages including safe, convenient, simple, wearable, and low-cost, and enables new possibilities to gain insights into human biology [13, 14]. For example, the mask device is a safe breath sampler under highly infectious environments such as COVID-19 and tuberculosis.

In recent years, there is a new trend to develop mask devices as new versatile wearable breath samplers for breath analysis [8, 15]. This paper aims at describing the current developments of mask devices as breath samplers for wearable sampling of exhaled substances, emphasizing the mask types and their versatile couplings with different (bio)analytical methods, and trying to indicate the trends, prospects, and challenges on further developments and applications of mask samplers.

Mask samplers for breath sampling

As shown in Fig. 1, exhaled bioparticles such as microdroplets, bacteria, proteins, and viruses can be directly filtered onto a common mask [16]. Although small volatile molecules such as breath metabolites can pass through the pore of mask,

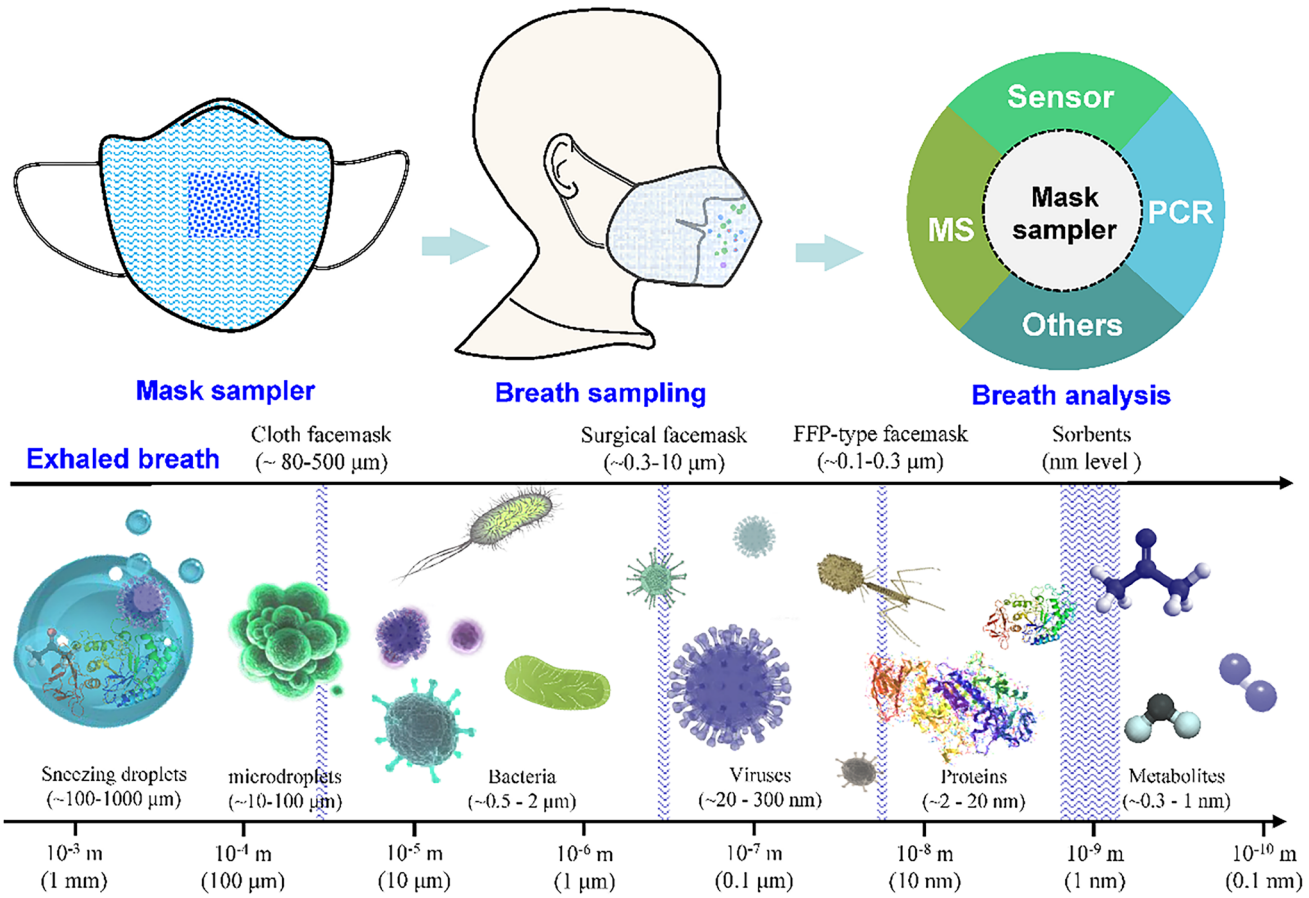

Fig. 1 Mask devices for sampling different sizes of exhaled substances and couplings with analytical approaches, adapted from ref [8] and ref [36] with permission

many exhaled volatile metabolites can be selectively collected onto modified masks using different sorbents [17, 18].

Original masks

Direct mask sampling of exhaled microorganisms including bacteria and viruses has attracted intensive attention, because exhaled microorganisms usually relate to infectious diseases. For example, various masks including surgical masks [19], N95 masks [20], three-layer disposable masks [21], woven masks [22], medical disposable anesthetic masks [23], IIR surgical masks [24], and CPAP-type masks [25] have been demonstrated for collecting exhaled severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from COVID-19 patients. Various exhaled bacteria, e.g., *Bacillus*, *Staphylococcus*, and *Acinetobacter* spp. from patients, were also successfully achieved by mask sampling [26–28]. These studies show the convenience of wearable breath sampling and the unique feature that could prevent airborne transmission of exhaled virus/bacteria. However, the low exhaled virus/bacteria load on mask could cause false negative results in clinical practices.

Moreover, it should be noted that the outer layer of masks is exposed to ambient air, and many environmental exposures such as volatile chemicals, (bio)aerosols, and (bio)particles can also be adsorbed onto the mask [29–32]. In addition, mask devices are mainly manufactured by petrochemical materials, which might cause many residues of mask contaminants (chemical residues and plastic particles) [8, 33–35]. Therefore, mask contaminants and air exposures could be confused with exhaled metabolites and bioparticles. It is an important task to identify the exhaled substances rather than the contaminants.

Modified masks

Modifying masks is an attractive strategy for enhanced sampling of target analytes from exhaled breath. The molecular

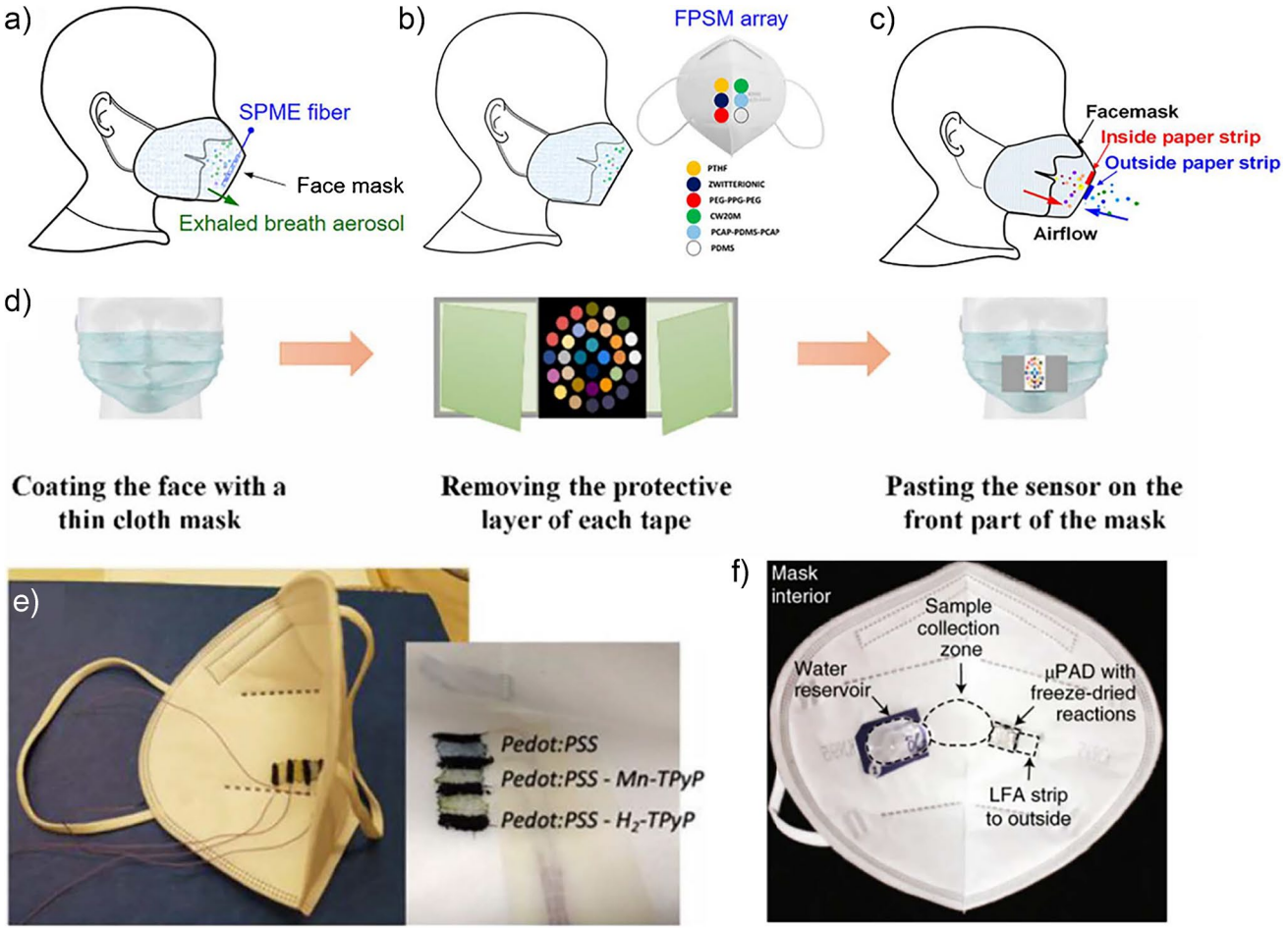

Fig. 2 Typical modified mask samplers for breath sampling: (**a**) SPME-in-mask, reproduced from ref [36] with permission; (**b**) FPSM-in-mask, reproduced from ref [37] with CC-BY 4.0 license; (**c**) strip-in-mask, reproduced from ref [32] with permission; (**d**) sniffer sensor-in-mask, reproduced from ref [77] with permission; (**e**) porphyrin sensor-in-mask, reproduced from ref [78] with permission; (**f**) CRISPR sensor-in-mask, reproduced from ref [80] with permission

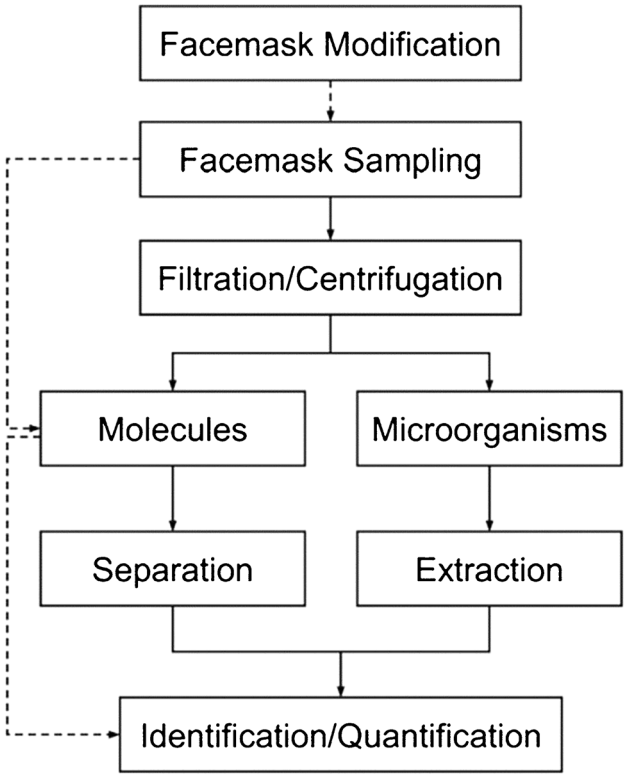

Fig. 3 Workflow of (bio)analytical procedures of human breath with mask sampling. Solid lines show the conventional processes, while dotted lines show optional processes, reproduced from ref [8] with permission

sizes of breath metabolites (~1 nm) are much smaller than the pore size of mask fibers (>100 nm) and thus exhaled breath VOCs can pass through the mask [8]. Therefore, breath metabolites are usually collected by modified masks. Figure 2 shows various typical modified mask devices by fixing sensors or sorbent materials onto the inner surface of the mask surface. For example, solid-phase microextraction (SPME) fibers (Fig. 2a) [36], fabric-phase sorptive membranes (FPSM) (Fig. 2b) [37], porous paper strips (Fig. 2c) [32], adsorbent trap [38, 39], thermal desorption (TD) tubes [40–42], carbon-filled sorbent tubes [43], and other devices [44–46] can be fixed in masks to extract targeted breath metabolites.

Furthermore, adsorption materials have been developed to modify masks for enhanced sampling of exhaled microorganisms. For example, gelatin filters [47], cellulose acetate membranes [48], and 3D-PVA matrix [49] were fixed into masks for enhanced adsorption of exhaled bacteria. Huynh et al. [50] developed a breath sampling method for placing electret filter material into homemade PVC masks to collect exhaled viruses (i.e., influenza virus, parainfluenza 3 virus, and human rhinovirus). Particularly, much effort has been devoted for developing modified masks for enhanced sampling of exhaled SARS-CoV-2 from patients with COVID-19., e.g., electrostatic filters [25, 51], PVA strips [52–54], gelatin membrane filters [55], gelatin membrane [56], cold trap [57], Steri-Strips™ [58], and copper-coated materials [59].

A modified mask sampler is a simple yet efficient method for enhanced breath sampling of exhaled substances including metabolites and bioparticles. The unique feature of the modified mask is that sorbents in the mask can be designed to extract target analytes. The main limitation of modified masks is that not only exhaled substrates but also contaminates from the mask and ambient air can be collected, especially for small molecules. Designing new materials to selectively and efficiently extract exhaled biomarkers is a new trend in breath sampling.

Mask sampling coupled with (bio)analytical approaches

Analyzing exhaled substances could provide insights into biomarker research and disease diagnosis. Mask samplers can couple with various (bio)analytical techniques

Fig. 4 Mask sampling coupled with portable GC-MS for onsite investigation: **a**) werable mask sampler, **b**) portable GC-MS analysis, reproduced from ref [15] with CC-BY 4.0 license

for versatile analysis, including mass spectrometry (MS) approaches, polymerase chain reaction (PCR) approaches, sensors, and others. A typical analytical procedure [60], including mask preparation, sample collection, and identification, was proposed (Fig. 3).

MS approaches

Mass spectrometry is a powerful analytical technique used to analyze different complex samples with unique advantages in specificity, sensitivity, and speed, and has been widely used for breath analysis [61]. The LC-MS approach is usually used to analyze nonvolatile metabolites [37], while the GC–MS approach is mainly used for analyzing semi-volatile and volatile metabolites [38–42, 62–67]. Particularly, mask samplers (Fig. 4a) coupled with portable GC-MS can be used for onsite analysis of breath VOCs (Fig. 4b) [15, 66]. GC-MS and LC-MS are usually combined with multivariate data analysis methods for breath analysis [15, 68, 69]. MALDI-MS approaches are mainly used for analyzing biomacromolecules (e.g., exhaled proteins collected onto mask [70]) and microorganisms (e.g., exhaled bacterial load on mask [28]). Using such microbial MALDI-MS, the microbial cultivation and sample preparation of exhaled microorganisms are necessary processes. Without chromatographic separation and sample pretreatment, some modified masks can be coupled with ambient MS approaches for rapid analysis of breath metabolites via ambient ionization techniques such as direct analysis in real-time (DART) [36] and paper spray ionization (PSI) [32].

Mask samplers coupled with MS-based approaches can be viewed as a powerful analytical technique to analyze different exhaled substances, as summarized in Table 1. Breath MS analysis can be divided into two methods: targeted analysis and nontargeted analysis. Targeted analysis mainly focuses on the identification and quantification of specific substances, while the goal of the nontargeted analysis is mostly used to classify samples and to identify or tentatively identify as many substances as possible in breath metabolites using data analysis methods. Targeted and nontargeted MS methods are complementary approaches for evaluating the composition of exhaled substances. The major problem of breath MS analysis is that conventional MS approaches (e.g., LC-MS, GC-MS, MALDI-MS) require large-volume sample consumption and a tedious analytical procedure involving sample storage, transportation, preparation, and separation, while ambient MS approaches usually suffer low sensitivity and matrix effect [71]. Other drawbacks of MS-based approaches in high-cost equipment and low on-site for breath analysis [71].

PCR approaches

PCR is a very sensitive molecular biology technique that allows amplification of a specific segment of DNA and RNA sequences, and has been widely used to identify bacteria and viruses [26, 51]. It is true that there are a variety of viruses and bacteria in exhaled breath bioaerosol, which are larger than most of pore sizes of mask fibers and thus can be directly collected by wearing a mask [8]. For example, Williams and coworkers for the first time developed a mask sampler to offer a highly efficient breath method for sampling exhaled *Mycobacterium tuberculosis* (Mtb), and then DNA of Mtb was extracted and detected by the PCR approach (Fig. 5) [72–74]. These findings showed the presence of active infection both with

Table 1 Typical couplings of mask samplers with MS approaches for breath analysis

Breath samples	Masks	Modifications	MS approaches	Ref
Healthy VOCs	Nonvented pin full mask	Adsorbent trap	GC-MS	[38]
Asthma childhood–related VOCs	Full-face air-tight mask	Hydrophobic adsorbent trap	GC-MS	[39]
Chronic kidney disease–related VOCs	ReCIVA breath sampler	Stainless steel sorbent tube	GC-MS	[67]
Colorectal cancer–related VOCs	ReCIVA breath sampler	TD tube	GC-MS	[40]
Asthma childhood–related VOCs	ReCIVA breath sampler	TD tube	GC-MS	[41]
Food/drug-related VOCs	KN95 mask	SPME probe	GC-MS	[66]
Obesity diabetic-related VOCs	ReCIVA breath sampler	TD tube	GC×GC-MS	[42]
COPD-related VOCs	Medical breath mask	Adsorbent trap	GC-MS	[62]
Intake-related aerosols	FFP2 mask	FPSM	LC-MS	[37]
Food/drug/smoke-related aerosols	KN95 mask, surgical mask	SPME fibers	DART-MS	[36]
Food/drug/smoke-related aerosols	KN95 mask	Paper strips	PSI-MS	[32]
Bacteria	Surgical masks	Without modification	MALDI-MS	[28]
β-Casein	KN95 mask	Gold foil sheets	MALDI-MS	[70]
Oral flora	Surgical mask	Without modification	MALDI-MS	[28]

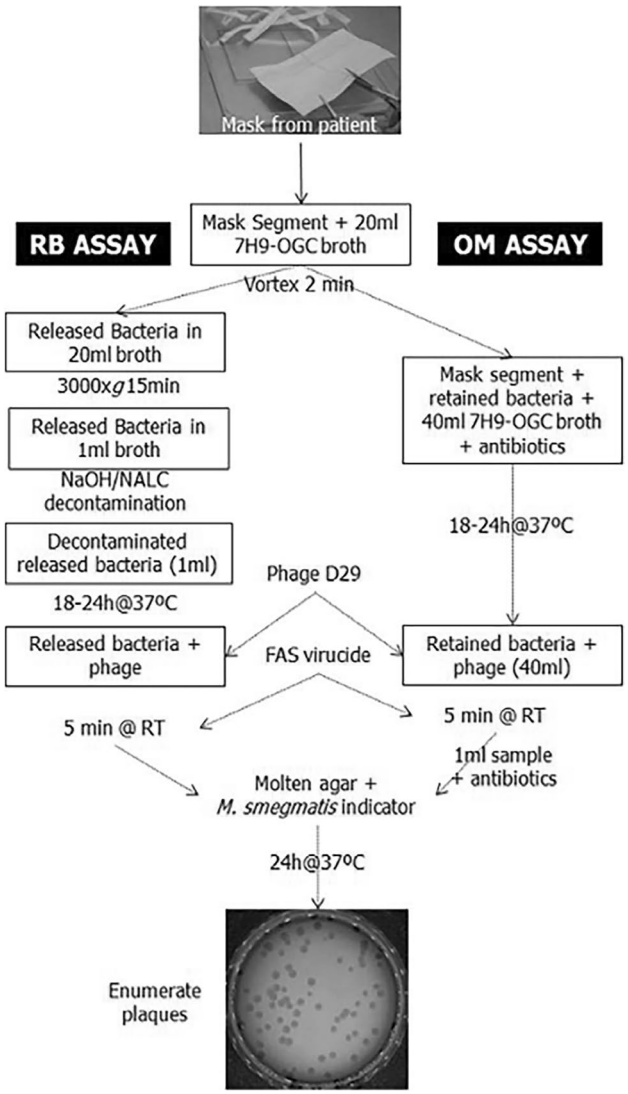

Fig. 5 Schematic of mask processing and biological analysis of exhaled Mtb, reproduced from ref [72] with permission

greater consistency and at an earlier disease stage than with sputum samples. Recent advances in mask samplers coupled with PCR approaches have been demonstrated for a useful bioanalytical tool for identifying various exhaled bacteria [26] and viruses such as SARS-CoV-2, influenza virus, parainfluenza 3 virus, and human rhinovirus [50, 57], as listed in Table 2.

The high resolution of whole-genome sequencing allows precision microbial identification and characterization for accurate microbial investigations, facilitating new insight into respiratory disease and a better understanding of infectious pathogens. Rapid detection and identification of exhaled microorganisms from mask samplers are important tasks for onsite investigation and large-scale medical examination. Although PCR is a sensitive method, the ultra-trace load of exhaled microorganisms is usually far reach to the load limit of PCR detection, which poses a serious risk for false-negative diagnosis [20, 58]. A long time wearing could collect more exhaled microorganisms. Another drawback of PCR test is the labor-intensive sample preparation and time-consuming analytical procedures [75].

Sensor approaches

The chemical and biological sensor is a type of green analytical device that detects and responds to target analytes from complex matrices such as exhaled substances [76]. Two of the most important features of the sensor are selectivity and sensitivity. Modified mask by inserting small sensors into the mask is a novel wearable device for monitoring breath changes (Table 3). Breath metabolites, biomacromolecules, and microorganisms can be detected by sensor-in-mask. Bordbar et al. [77] demonstrated that a strip of colorimetric sensor array was taped in the inner surface of the mask to display the changes of exhaled breath metabolites from patients, healthy and cured participants. Using such sensor array, special breath metabolites could show color changes by interacting with volatile metabolites through colorimetric responses (Fig. 2d). Zazzo et al. [78] embedded porphyrin-based chemical sensor array onto the inner surface of FFP masks to identify breath VOCs (Fig. 2e), showing the monitoring of various special breath VOCs, e.g., ethanol, hexane, toluene, acetone, triethylamine, and acetic acid, which are mainly generated due to the ingestion of beverages (e.g., coffee and wine) and solid food (banana and mint-flavored candies). Jin et al. [79] placed sensing strips into masks to detect α-amylase from exhaled aerosols and its distribution in masks. Nguyen et al. [80] invented a modified mask device that puts a lyophilized CRISPR sensor into an N95 mask to detect SARS-CoV-2 (Fig. 2f).

The unique feature of the sensor-in-mask technique is that sampling and detection are integrated into a mask sampler, giving a noninvasive, in vivo, wearable, and real-time monitoring of exhaled substances. The relatively low cost is another advantage of sensor technology. The major limitation of the sensor-in-mask technique is that sensors can be only used for detecting some special analytes [81], which need to be pre-identified by other (bio)analytical methods such as MS, PCR, or others. Other obvious drawbacks of the sensor-in-mask technique include low accuracy, low precision, as well as low sensitivity.

Other approaches

Coupling mask sampling with other (bio)analytical methods further promotes and prospers the use of mask samplers in

Table 2 Typical couplings of mask samplers with PCR approaches for breath analysis

Breath samples/analytes	Masks	Modifications	PCR approaches	Ref
Bacterial DNA	Surgical mask and cotton mask	Without modification	PCR	[26]
SARS-CoV-2	N95 mask	Gelatin membrane filter	RT-PCR	[55]
SARS-CoV-2	N95 mask	Gelatin membrane	RT-PCR	[56]
SARS-CoV-2	Three-layer disposable mask	Without modification	RT-PCR	[21]
SARS-CoV-2	Copper-coated KF94 mask	Without modification	RT-PCR	[59]
SARS-CoV-2	KF94 mask	Electrostatic filter	PCR	[51]
SARS-CoV-2	KN95 mask	PVA strip	qRT-PCR	[53]
SARS-CoV-2	Woven mask	Without modification	qRT-PCR	[22]
SARS-CoV-2	CPAP-type mask	The electrostatic filter	qRT-PCR	[25]
SARS-CoV-2	Anesthetic mask	Bioaerosol sampler	RT-qPCR	[23]
SARS-CoV-2	IIR surgical face mask	Household vacuum cleaner	RT-qPCR	[24]
SARS-CoV-2	Duckbilled surgical mask	PVA sampling matrix strips	RT-qPCR	[52]
SARS-CoV-2	Duckbilled mask	3D-PVA strip	RT-qPCR	[54]
SARS-CoV-2	Surgical mask	Without modification	RT-qPCR	[19]
SARS-CoV-2	Surgical masks	Three Steri-Strips	RT-qPCR	[58]
SARS-CoV-2	Unspecified mask	EBC collector	RT-PCR	[57]
SARS-CoV-2	N95 mask	Gelatin matrix	RT-PCR	[20]
Mtb	FFP1 mask	Gelatin filter	qPCR	[74]
Mtb	N95 mask	CA membrane	qPCR	[48]
AMR genes	FFP1 mask	Gelatin filter	qPCR	[47]
Rhinovirus, influenza A virus, parainfluenza virus	PVC mask	Electret filter material	PCR	[50]

breath analysis (Table 3). For example, a flame photometer (FP) was used to determine the concentration of certain sodium ions that were collected by a miniature and low-weight respirable sampler designed for FFP masks [82]. A mask sampler coupled with immunochemistry analysis (ICA) was applied to analyze the exhaled cytokines [18]. Schorer et al. [16] investigated the microdroplets, proteins, and virus-like particles sprayed onto surgical masks via infrared (IR) spectroscopy, showing that the IR optical technique is a promising tool for direct virus detection at the surface of masks. Davies et al. [27] applied Henderson apparatus (HA) to test the effectiveness of homemade cotton T-shirt fabric surgical masks using *Bacillus atrophaeus*, bacteriophage MS2 produced during coughing. A flame photometer (FP) was used to determine the concentration of certain sodium ions that were collected by a modified mask [82].

The key performance indicators of (bio)analytical methods include sensitivity, specificity, and speed of signal response, which are mainly determined by the sample pretreatment and analytical mechanism. These (bio)analytical methods including FP, ICA, IR, and HA show their main advantages of relatively low-cost, easy operation, and versatile couplings with mask samplers, and show their potential abilities for new applications. However, there

Table 3 Typical couplings of mask samplers with sensor and other approaches for breath analysis

Breath samples	Masks	Modifications	Sensors and others	Ref
COVID-19-related VOCs	Three-layer medical mask	Breath sniffer device	Sensor	[77]
Food-related VOCs	FFP2 mask	Porphyrins sensor	Sensor	[78]
SARS-CoV-2	N95 mask	CRISPR sensor	Biosensor	[80]
α-Amylase	Cloth mask, surgical mask, N95 mask	Sensing strip	Biosensor	[79]
Cytokines	Hard-surface plastic mask, paper mask	Without modification	ICA	[18]
Bacillus atrophaeus, Bacteriophage MS2	Cotton t-shirt fabric and surgical mask	Without modification	HA	[27]
Proteins and virus-like particles	Surgical masks	Without modification	IR	[16]
Sodium chloride aerosol	FFP3 masks and one-half mask	Miniature sampler	SFP	[82]

are several drawbacks of mentioned techniques consisting in limited detectable analytes and relatively low analytical performances.

Outlook

A mask sampler is a new sampling technique that fulfils the criteria of simple, low-cost, in vivo, noninvasive, easy-to-operate, wearable, and higher acceptability among patients by comparing with other clinical samples such as urine, blood, and sputum. Because exhaled metabolites, proteins and microorganisms can be collected by mask devices, mask sampling coupled with multi-omics approaches (e.g., metabolomics, proteomics, and microbiomics) is a new trend which allow a better elucidation of the relation between the breath compositions and human biology studies such as diseases, behaviors, and exposures. Furthermore, coupling mask–based breath analyses with new data analysis methods such as big data, artificial intelligence, and machine learning are also highly expected to be a trend for elucidating exhaled substances. Onsite screening rather than a laboratory examination will be more beneficial for patients, and the coupling of mask samplers with portable analytical instruments for on-site investigation is a new trend in breath analysis. Therefore, it can be expected that mask samplers will become a new clinical tool in the future.

Mask device as a new type of breath samplers for breath analysis, many limitations and potential pitfalls must be considered. Current main limitations of mask sampler techniques are the relatively low efficiency of breath sampling and the need of sample extraction for further analysis. It is expected to design new mask samplers for enhanced collection of exhaled substances, and to couple with more sensitive and specific detection methods. Another problem is chemical and biological contamination, which could come from mask materials and ambient air. It is expected that the design and manufacture of mask samplers can be significantly improved. A potential pitfall is that quantitative analysis of continuous exhaled breath using mask samplers is unclear; it is of paramount importance to elucidate the quantitative evaluation of human health state and disease development, and the quantitative relationship between breath and other clinical specimens in the future.

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Declarations

Conflict of interest The authors declare no competing interests.

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