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Sensing and 3D printing technologies in personalized healthcare for the management of health crises including the COVID-19 outbreak



Ashish Kalkal^a, Prince Allawadhi^a, Pramod Kumar^c, Abhishek Sehgal^b, Ashmit Verma^d, Kaustubh Pawar^a, Rangadhar Pradhan^{e,**}, Biswaranjan Paital^{f,*}, Gopinath Packirisamy^{a,e,***}

^a Department of Biosciences and Bioengineering, Indian Institute of Technology Roorkee, Uttarakhand, 247667, India

^b Department of Chemical Engineering, Indian Institute of Technology Roorkee, Uttarakhand, 247667, India

^c Institute Instrumentation Center, Indian Institute of Technology Roorkee, Uttarakhand, 247667, India

^d Divyasampark iHUB Roorkee for Devices, Materials and Technology Foundation, Indian Institute of Technology Roorkee, Uttarakhand, 247667, India

^e Centre for Nanotechnology, Indian Institute of Technology Roorkee, Uttarakhand, 247667, India

^f Redox Regulation Laboratory, Department of Zoology, College of Basic Science and Humanities, Odisha University of Agriculture and Technology, Bhubaneswar, 751003, India

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ABSTRACT

A major threat that has surrounded human civilization since the beginning of the year 2020 is the outbreak of coronavirus disease 2019 (COVID-19). It has been declared a pandemic by the World Health Organization and significantly affected populations globally, causing medical and economic despair. Healthcare chains across the globe have been under grave stress owing to shortages of medical equipments necessary to address a pandemic. Furthermore, personal protective equipment supplies, mandatory for healthcare staff for treating severely ill patients, have been in short supply. To address the necessary requisites during the pandemic, several researchers, hospitals, and industries collaborated to meet the demand for these medical equipments in an economically viable manner. In this context, 3D printing technologies have provided enormous potential in creating personalized healthcare equipment, including face masks, face shields, rapid detection kits, testing swabs, biosensors, and various ventilator components. This has been made possible by capitalizing on centralized large-scale manufacturing using 3D printing and local distribution of verified and tested computer-aided design files. The primary focus of this study is, “How 3D printing is helpful in developing these equipments, and how it can be helpful in the development and deployment of various sensing and point-of-care-testing (POCTs) devices for the commercialization?” Further, the present study also takes care of patient safety by implementing novel 3D printed health equipment used for COVID-19 patients. Moreover, the study helps identify and highlight the efforts made by various organizations toward the usage of 3D printing technologies, which are helpful in combating the ongoing pandemic.

1. Introduction

According to the World Health organization, Coronavirus disease 2019 (COVID-19) has reached the necessary epidemiological criteria to

be declared a pandemic on March 11, 2020 [1]. It has affected most of the countries, territories, or areas, with more than 505 million (511,965,711) confirmed cases and 6.2 million (6,240,619) death as of May 3, 2022, according to the official number declared by WHO [2]. In this pandemic

* Corresponding author. Redox Regulation Laboratory, Department of Zoology, College of Basic Science and Humanities, Odisha University of Agriculture and Technology, Bhubaneswar, 751003, India.

** Corresponding author. Centre for Nanotechnology, Indian Institute of Technology Roorkee, Roorkee, Uttarakhand, 247667, India.

*** Corresponding author. Centre for Nanotechnology, Indian Institute of Technology Roorkee, Roorkee, Uttarakhand, 247667, India.

E-mail addresses: rangadhar@gmail.com (R. Pradhan), biswaranjanpaital@gmail.com (B. Paital), gopi@bt.iitr.ac.in, genegopi@gmail.com (G. Packirisamy).



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situation, there has been a continuous strain on the global health care system due to the shortage of medical equipments and accessories like PPE (personal protective equipment) kits for the medical staff and doctors who were on the frontline treating critically ill patients. It is well known that COVID-19 is an acute respiratory syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has been found to affect the patient's ability to breathe and respire, necessitating the urgent demand for ventilators and their supporting accessories [3]. A fraction of patients suffering from acute respiratory distress syndrome (ARDS) requires high-level respiratory support. Major disruption was observed in the supply chain of these medical supplies at the hospital level in several countries. To fight these crises, several researchers, hospitals, and industries joined hands and collaborated to meet the demand for these medical equipment economically viable [4].

To address the necessary requisites and pre-requisites during the pandemic, 3D printing technologies provided enormous potential in creating these personalized healthcare equipments [5]. Medical attention refocused on 3D printing of PPE like face masks, face shields, rapid detection kits, testing swabs, sensing platforms, and ventilator components for COVID-19 management, which was adopted by international medical communities by implementing the safety protocols developed by the appropriate regulatory body. Different 3D designs of the masks and head frames for face shields were detailed for 3D printing [6]. The primary advantages of 3D printing of PPEs is that the manufacturer can modify the design as per the manufacturing requirements. Rapid detection kits were found to be vital, particularly in developing countries that were at advanced risk because of limited access to high-quality diagnostic facilities. Similarly, biosensing platforms or biosensors were found to be very crucial for the rapid detection and analysis of multiple analytes including SARS-CoV-2 [7–10]. They proved to be very effective in high demand and crisis situations. Some of the readily available biosensing platforms have been addressed in this study which could be commercialized shortly [11,12]. Besides, the study discusses different 3D printing designs, which were helpful in creating hand-held rapid testing kits to assist the health care workers in the point of care diagnosis of COVID-19. Further, Nasopharyngeal swabs developed by 3D printing using biocompatible polymers have been detailed [5]. Finally, different 3D printed masks and ventilator components, for example, non-return valves, sensor mounting, pressure reducers, ball valves, and flow regulating valves (FRVs), CPAP (Continuous positive airway pressure) machine component have been described [13,14]. The acute plea has caused the 3D printing community of researchers and engineers to effectively

develop methods and materials to manufacture PPE to reinforce indigenous sources [15].

2. Sensors, POCTs, and 3D printing technology

The current pandemic caused by COVID-19 is still booming and spreading throughout the world, with new and mutated variants infecting the population. Therefore, testing and diagnosis of the virus play a crucial role in safeguarding a healthy population. General testing and diagnostic techniques such as RT-PCR were found crucial, precise, and specific. However, the requirement of trained personnel, limited sampling rate and lengthy procedure are the drawbacks of this technique. Therefore methods such as biosensors and POCTs (Point-Of-Care Testings) plays a crucial role in these situation of major crises.

Biosensors are analytical devices that are highly sensitive, reliable, and effective, easy to deploy and manufacture compared to other laboratory equipment. Biosensors are basically made-up of three parts: a bio-receptor (e.g., antibodies, aptamers, enzymes, etc.); a transducer (e.g. electrochemical, mechanical, optical, etc.); and an immobilization matrix (nanomaterials, quantum dots, polymeric materials, etc.) [16,17]. Biosensors are used to detect different analytes, including biomolecules, cancer biomarkers, nucleic acids, blood impedance, cellular cytotoxicity, bacteria, and viruses [18–21]. Some of the recently developed biosensing techniques used for COVID-19 detection have been mentioned in Table 1. For example, Qui et al. developed a dual-functional plasmonic biosensor combining the plasmonic photothermal (PPT) effect and localized surface plasmon resonance (LSPR) sensing [22]. The plasmonic biosensor based on gold nanoislands (AuNIs) is capable of sensing selected sequences from SARS-CoV-2 through *in situ* hybridization. It showed some promising results and was found to be highly sensitive and reliable. In addition, electrochemical biosensors are also playing a vital role in the diagnostic process of this disease since they are highly sensitive, reliable and cost-effective. Seo et al. developed a Field-effect transistor (FET)-based biosensor for the detection of SARS-CoV-2. The sensor was made with graphene-based FET sheets and specific antibody for SARS-CoV-2 spike protein [23,24]. Recent, RT-PCR-based biosensors has also been reported [25]. This technique is named as digital RT-PCR (dPCR). The basic analogy behind this system is that it distributes the single reaction mixture into multiple sub-reactions before amplification [26]. Therefore, these devices prove to be highly sensitive and inhibitor-resistant. CRISPR/Cas (Clustered regularly interspaced short palindromic repeats) based sensors can work as an alternative of dPCR which has shown

Table 1

List of recently developed detection methods for SARS-CoV-2.

Type of Biosensors	Target	Nanomaterials	Advantages	Reference
Lateral flow immunoassay	IgM/IgG antibody	Selenium nanoparticle	Sensitivity of the kit is 94.74% and the specificity is 95.12%, portable, fast	[86]
Lateral flow immunoassay	IgG antibody	Colloidal gold nanoparticles	Sensitivity of the kit is 69.1% and the specificity is 100%, portable, fast	[87]
Lateral flow immunoassay	IgM antibody	Colloidal gold nanoparticles	Sensitivity of the kit is 100% and the specificity is 93.3%, portable, fast	[88]
Lateral flow immunoassay	IgM/IgG antibody	Colloidal gold nanoparticles	The overall testing sensitivity is 88.66% and specificity is 90.63	[89]
Surface-enhanced Raman scattering (SERS)	Virus particles	Silver-nanorod array	Rapid and on-site diagnostic tool	[24]
Immunochromatographic assay	Nucleoprotein antigen	Colloidal gold nanoparticles	Sensitivity of the kit is 30.2% and the specificity is 100%, fast	[90]
Colorimetric assay	Nucleic acid	Gold nanoparticles	Naked-eye detection	[91]
chemiluminescent immunoassays	IgM/IgG antibody	Magnetic microbeads	100% sensitivity for IgG and 88% sensitivity for IgM	[92]
Microfluidic ELISA	Monoclonal anti-S1 antibodies	Glass capillary	Small testing volume, fast, point-of-care	[93]
Immunochromatography assay (GICA) and enzyme-linked immunosorbent assay (ELISA)	IgM antibody	Colloidal gold	Reducing false-positive results	[94]
Plasmonic biosensor	N protein	Gold nanoparticles	Label-free	[95]
Microfluidics	Nucleic acid	Complementary metal oxide semiconductor	Fast	[96]
Electrowetting-on-Dielectric	Nucleic acid	Indium tin oxide	Small testing volume, fast, safeguard against contamination	[97]

to be highly effective as a point-of-care (POC) devices. A rapid assay named CRISPR-COVID has been reported for detecting SARS-CoV-2 [27]. U.S. Food and Drug Administration (USFDA) has recently approved a biosensing diagnostic kit named GenMark ePlex[®] for detection of SARS-CoV-2 [28]. Similarly, another biosensing platform named Covid-Nudge is also been reported [29]. It is a POC device with a sensitivity of 94% and overall specificity of 100%.

Because of the massive surge for medical and testing equipment during the pandemic, scientific and industrial community took advantage of 3D-printing technology in the development of biosensors, POCTs, etc. With the current advanced and industrial level 3D printing technology it has been made possible to 3D print some parts or whole sensor and POCTs devices for rapid deployment and testing. This has reduced the time and cost of these devices which could ultimately result in high production rate. A 3D-printed COVID-19 immunosensor prototype has been developed by Pumera and co-workers harbouring COVID-19 recombinant protein on a 3D-printed graphene-based nanocomposite

electrode surface [11]. The developed immunosensor showed promising electroanalytical properties in both the buffer and human serum samples Fig. 1 (A). Similarly, Ali et al. developed a 3D nanoprinted electrodes specific to S1 protein of SARS-CoV-2. The 3D-printed electrode is coated with nanoflakes of reduced-graphene-oxide (rGO) and are immobilized with viral antigen such as receptor-binding-domain (RBD) using standard electrochemical cell method. The characteristic is defined with the help impedance spectroscopy Fig. 1 (B). The testing results showed that the biosensing platform can detect the SARS-CoV-2 virus in just a couple of seconds [12].

Point-of-care testing (POCTs) means detecting and diagnosing the disease at the nearest point of the patient. It is essential for the rapid detection of analytes near to the patient that enables better diagnosis, monitoring and management. This method facilitates early diagnosis of the spread hence ensures faster treatment in a controlled fashion [30]. Similarly, with the outbreak of this pandemic these POCTs devices and assays played a key role in controlling the spread of the virus in the

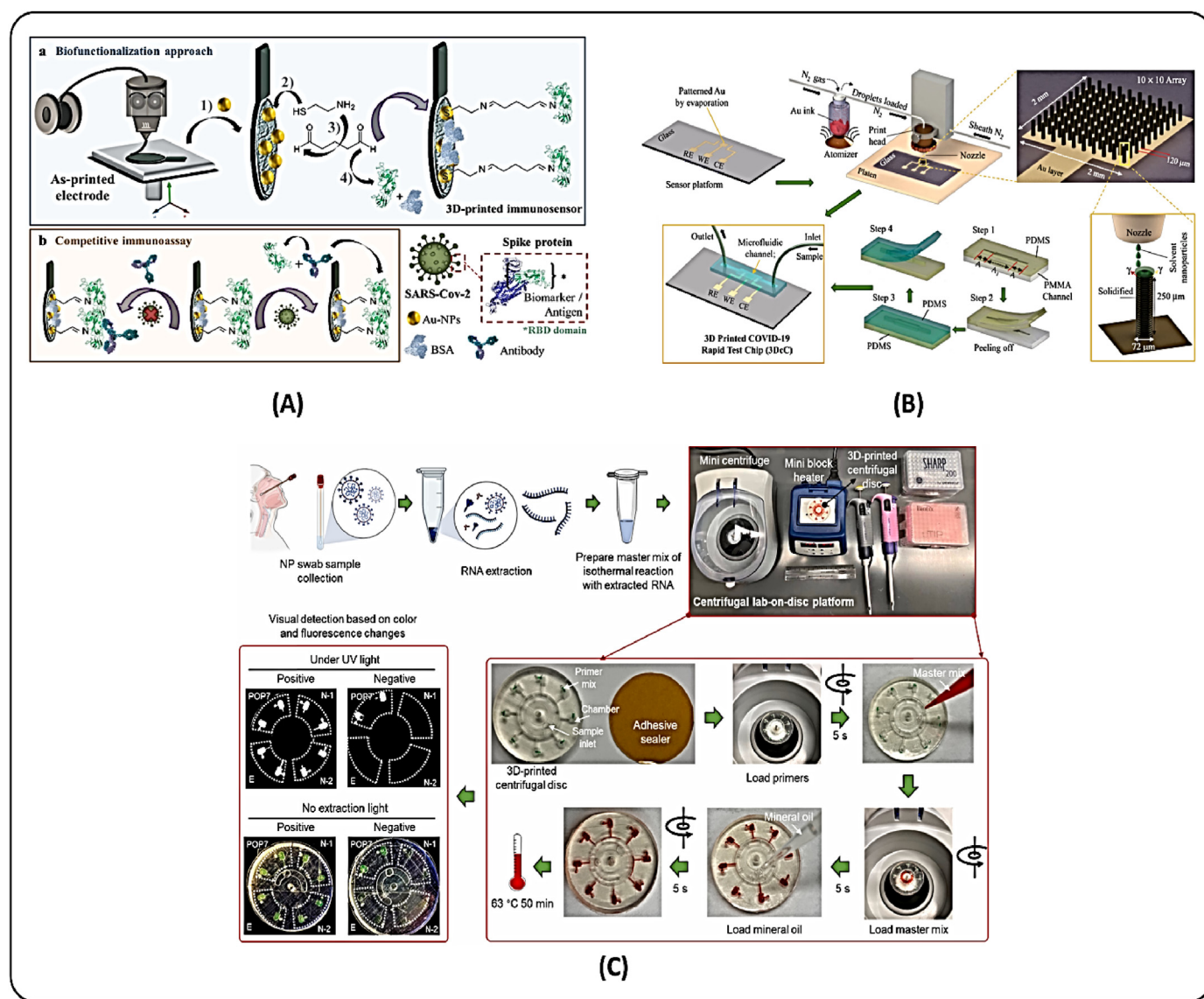


Fig. 1. 3D printing industry and their applications in biomedical sciences.

(A) a) Illustration of the 3D-printed electrochemical COVID-19 immunosensor fabrication steps. b) Indirect competitive assay carried out for detecting the COVID-19 recombinant protein (antigen), the one against the SARS-CoV-2 virus. Reprinted from Ref. [11], Copyright (2021), with permission from Elsevier; (B) Schematic of the manufacturing process of the 3D-printed COVID-19 test chip (3DcC) by Aerosol Jet nanoparticle 3D printing. Reprinted from Ref. [12], Copyright (2020), with permission from Wiley; (C) Procedures of the monolithic, 3D-printed lab-on-disc platform for rapid, multiplexed detection of SARS-CoV-2. The NP swab samples are collected first, followed by RNA extraction and master mix preparation. Reprinted from Ref. [32], Copyright (2022), with permission from Elsevier.

community. Currently, POCTs being used for COVID-19 testing are generally antigen-based assays which are found to be moderate in sensitivity but high in specificity [31]. 3D-printing technology has also played a key role in the development of these POCTs. For example, Xiaong et al. and his colleagues reported detection of SARS-CoV-2 virus using multiplexed targeting technique [32]. It is a monolithic, 3D-printed, lab-on-disc platform for multiplexed molecular detection of SARS-CoV-2 virus. The developed kit is capable of diagnosing not only envelope gene and found to be capable of detecting nucleoprotein, and internal components of the SARS-CoV-2 virus. It can detect upto a 100 copies of SARS-CoV-2 RNA within a period of 50 min. The resultant device reported an accuracy of 50% and sensitivity of 100% Fig. 1 (C).

3. Personal protective equipment (PPE)

The COVID-19 pandemic has posed many challenges to health care professionals globally. Personal protective equipments (PPE) are crucial for minimizing the virus's spread to and from the patients and health care professionals. However, their increasing demands have induced shortage of personal protective equipment (PPE). In this context, 3D printing technologies have provided several reusable, cost-effective, and improved PPEs to fill the PPE supply chain gap [33]. The following sections will explain the individual 3D printed PPE in detail.

3.1. Face masks

Face masks help in protecting the person from the spread of infectious diseases, including coronavirus. These impede the inhalation and exhalation of contagious droplets, thereby reducing aerosol transmission. Ideally, these should be reusable, biocompatible, and cost-effective. However, the majority of masks used are made from cloth, and hence they are quite less efficient in filtering viruses. Moreover, if the virus stays on cloth, it can lead to more harmful consequences. According to the Food and Drug Administration (FDA), widely used surgical masks don't provide complete protection against viruses due to their loose fit. Also, these masks can be used once and then need to be disposed of safely. Also, it has been reported that the higher viral loading in surgical masks could be a source of viral transmission. Therefore, the demand for improved masks was increasing due to the COVID-19 pandemic. In this context, 3D printing played a crucial role. Masks fabricated by 3D printing were sturdy, fit quite good on the face, provide high filtration of microorganisms, and also they were reusable and can be disinfected easily. Personalizing these masks can also be done to ensure the best fit, and for this 3D face scan software, printing in various sizes, experimenting with flexible materials, and carrying out additional CAD can fit masks on an individual basis [34]. Different 3D printed masks that are

Table 2
List of various 3D printed Masks and their characteristics.

S.No.	Description	Key Features	References
	World advanced Saving Project (WASP) masks	Biomaterial is used as a filament which melts at 100 degrees. There is a choice of filter such as Cylindrical, HEPA, WASP (N95 and DIY Fabrics), Montana (N95 surgical mask), circular.	[35]
	N95 respirator mask	Can filter airborne particles with a size range of 0.3 μm with an efficiency greater than 95%	[50]
	The copper 3D Nano hack mask	Biocompatible and recyclable polymer with embedded copper nanocomposite is used. PLA can also be used.	[34]
	Stopgap face Mask (SFM)	Comes in multiple sizes made from biocompatible nylon material.	[47]
	HEPA Masks (SPARC Industries)	Open-spurce free to use for anyone HEPA filter mask.	[40]
	Budmen V4	3D printable face shield made from biocompatible material.	[45]

addressed in this study are listed in Tables 2 and 3D design characteristics of different face shields in Table 3.

3.1.1. World advanced Saving Project (WASP) masks

WASP (Fig. 2-A) provided a 3D printing process to fabricate the personalized and reusable face mask using the Delta WASP 4070 3D printer. Polycaprolactone (PCL), a biocompatible polymer, was used as the printing material due to its inherent property of staying in contact with the skin. The correctly adhered personalized 3D mask can be printed in about 4 h of printing. These masks can also be disinfected quickly and reused by merely changing the central interchangeable filter [35].

3.1.2. N95 respirator mask

These masks have certain advantages over surgical masks. These masks can filter airborne particles with a size range of 0.3 μm with an efficiency greater than 95% [36]. N95 masks are also recommended for health care workers by the Centers for Disease Control and Prevention (CDC). For improving the fitting and comfort level of masks, 3D printing can be used to produce seal designs. Generally, N95 masks are made from polypropylene fibers, which are lightweight and semi-rigid, but also, at the same time, their semi-crystalline structure may produce difficulties in 3D printing due to their distortion upon cooling. To resolve this issue, a mixture of polypropylene (PP) and styrene-(ethylene-butylene)-styrene (SEBS), which forms 3D printable thermoplastic elastomeric material has shown to provide better printability and flexibility for N95 mask design [37,38]. Besides, PP is mostly used due to its low cost, printability, processability, and recyclability. SEBS is an elastomeric polymer that shows less distortion during extrusion and low processing temperature [37]. Other variants include N99, which has a filtering efficiency of 99% for airborne particles, N100, which has 99.97% efficiency, R95 having 95% efficiency, P95 having 99%, P99 has 99% efficiency, and P100 has 99.97% efficiency [36].

Due to the increasing demand of N95, it is necessary to search for alternatives with better efficiency in filtering airborne particles, and also, it should have low cost, reusability, and, at the same time should take less time in printing.

3.1.3. The copper 3D nano hack mask

NanoHack Mask protects against airborne particles and uses a biocompatible and recyclable polymer with embedded 3D copper, which shows antimicrobial properties. Modified PLA (Poly-lactic acid) filament can be used to print the mask, and it is heated to a temperature of 55–60 $^{\circ}\text{C}$ for its final assembly [34].

These masks (Fig. 2-B) use PLACTIVE® and MDflex® embedded with nano-copper, which possess antimicrobial properties. In addition to this, it also incorporates a Modular Filtration System in which three layers of non-woven Polypropylene embedded in nano-copper have been used as the active filter material, which provides the efficiency of 96.4% for microorganisms of size 1 μm and 89.5% for microorganisms of size 0.02 μm [39]. These are popular due to their ease of design and takes less time for printing [14].

3.1.4. Stopgap face mask (SFM)

3D Systems at the Veterans Health Administration developed an emergency Stopgap Face Mask (SFM) using selective laser sintering (SLS)

Table 3
Design Characteristics of different face shields.

Name	RC1	RC2	Budmen V3	Easy 3D face shield
Print volume requirements	135 × 120 × 20 mm	144 × 191 × 20 mm	141 × 187 × 20 mm	146 × 165 × 15 mm
Print time	2 h 30 min	3 h 17 min	2 h 06 min	1 h 40 min
Tools for assembling	DIN A4 perforator	DIN A4 perforator	DIN A4 perforator	No requirement.

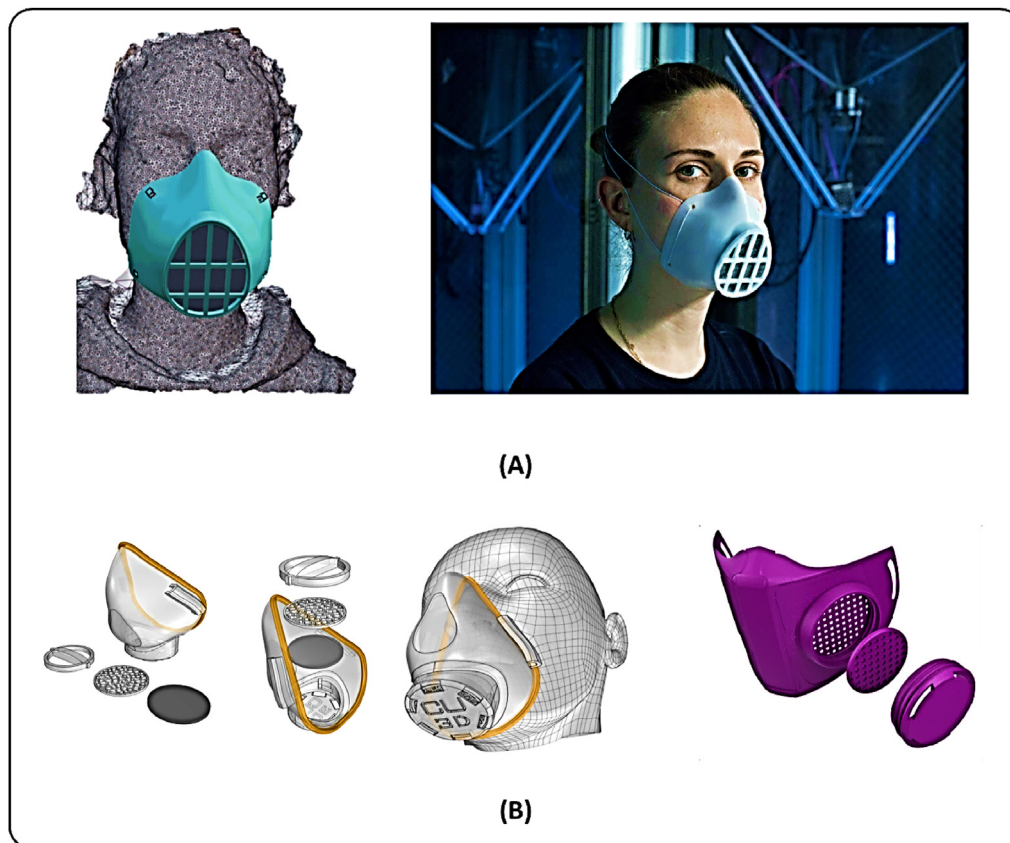


Fig. 2. Applications of 3D printing in the production of face mask.

(A) World advanced Saving Project (WASP) masks [35]; (B) 3D printed double filter NanoHack N95 mask by Thingiverse [34].

3D printing technology. The SFM has been fabricated with a biocompatible nylon material and is available in multiple sizes. The 3D SFM comprises of the mask body, four strap attachment points, two elastic straps, a filter box, and cover. It has been recommended that the adjustable straps and square filter patch need to be disposed off after single use. However, the remaining parts of the SFM can be reused by simply autoclaving or disinfection. Filter material to be used in SFM needs to be cut in a 2.25 in x 2.25 in size. Moreover, the 3D systems are also prototyping the 3D printed surgical masks and Surgical N95 Respirator [33].

3.1.5. HEPA masks

HEPA masks come with HEPA (High-Efficiency Particulate Air) filters, which provide an excellent filtration capacity of at least 99.97% for particles of diameter equal to 0.3 μm . The desktop printers can manufacture the HEPA mask described by the SPARC industries [40]. To maintain proper air seal conditions, PLA filament can be used after heat exposure to fit the mask according to individual users. Similarly, a Chinese company named Creality proposed a similar design. However, the filter holder's configuration has been changed to insert a layer of folded fabrics for filtration.

3.1.6. ViriMASK- protective oculo-respirator

TheViri mask covers nose, eyes, and mouth without outside air penetration. The mask provides 0.1- μm filters, thus offers protection against 99.99% particles. It has been reported that this mask can protect against environmental aerosols, exhaled aerosols, bacteria, and viruses, including COVID-19. The mask also prevents infection/contamination through the eye. It has a 5x larger breathing area and is more comfortable for breathing. It can be washed and its disinfected filter can be replaced (Fig. 3-A) [41].

3.2. Face shields

A face shield is a part of PPE kit used by the health care workers to provide the barrier protection from splashes and sprays of body fluids to the facial area (lips, nose, and eyes) and related mucous membranes. It majorly consists of two parts: (i) Visor, also called as lenses or windows and is usually made of polycarbonate, polyethylene terephthalate glycol (PETG), acetate, propionate and polyvinyl chloride (PVC). It also comes in reusable, recyclable, and biodegradable types. Polycarbonate is the most widely used material [42] while, PETG tends to be the most economical, whereas acetate provides the best clarity [43], but polycarbonate is the one that is mostly used. (ii) Head-frame the part which is 3D printed. It is generally made from lightweight plastic. Typically, 3D printing is used to produce headframe to which a transparent sheet mainly made from polyvinyl chloride (PVC) is attached, thus protecting the user's facial areas. Generally, materials used to print head frames like acrylonitrile butadiene styrene (ABS) has shown good strength, but they lack the property of biodegradability, and also they require higher printing temperatures of 240–250 $^{\circ}\text{C}$ in comparison to Polylactic Acid (PLA) which requires a temperature of 180–220 $^{\circ}\text{C}$. To resolve these issues, polyethylene terephthalate glycol (PETG) can be used, which provides high fracture strength of ABS and also overcomes drawbacks of PLA [44]. Lignin, a biodegradable polymer, is another suitable material that can be used for 3D printing of headframes [45].

According to the Centers for Disease Control and Prevention (CDC) guidelines, healthcare workers are required to wear eye protection, either goggles or a disposable face shield, while contacting COVID-19 patients. Class, I medical devices include Face shields, which are exempted by the Food and Drug Administration (FDA) in Pre-Market Notification [4]. A face shield, along with an N95 mask, is now considered a compelling choice. Face shields can be made reusable by using proper disinfection techniques.

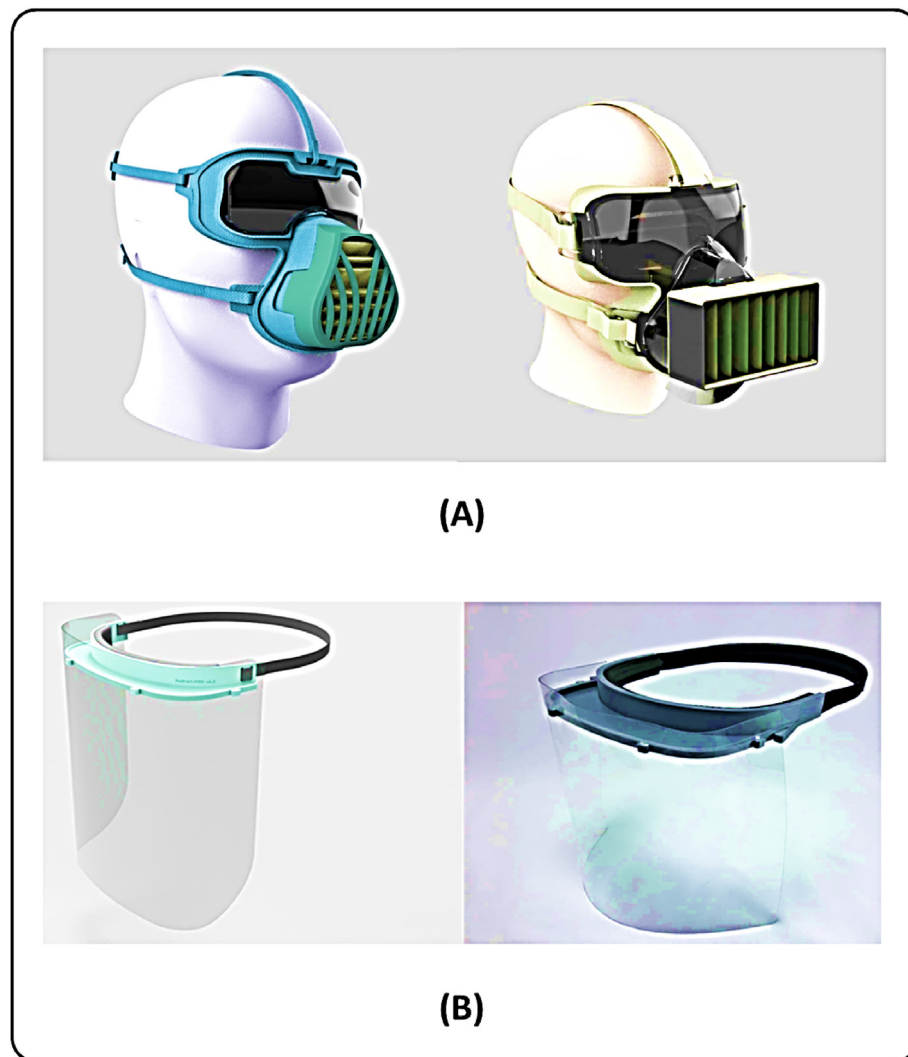


Fig. 3. Use of 3D printing in production of face shields.

(A) Protective Oculo-Respirator by ViriMASK [41]; (B) NIH certified Face shield V3 by Budmen, left one is with an elastic head strap while the right one is with Velcro head strap [47].

Prusa has developed prototypes of face shields, consisting of different versions like RC1, RC2, and RC3, and fully open-source STL files have been provided. Other models include Budmen V3 [46] and Easy 3D face shields (Table 3). Easy 3D has an additional benefit for assembly as they do not require DIN A4 perforator, and their mass production is easily possible as they need less time to print [44]. Suppose scalability of Face shields is taken into consideration. In that case, stacked RC3 frames become a better option in non-industrial environments and provide additional protection if sealing is taken into account. However, RC2 should be preferred for large scale production due to better fit and time needed for printing [44].

Similarly, the University of California San Francisco (UCFS) 3D printed the face shield following the Prusa RC2 model (Fig. 3-B). However, several iterations were performed in the shield frame design for having the optimal model. Also, a readily available 8.5"x11" transparency sheet was used to produce the UCSF face shield [47]. Moreover, 3D systems also provided a reusable face shield frame design, which can be printed using any Selective Laser Sintering (SLS) Printer. The design comprises a two-part flat-pack, which needs to be clipped into each other to have the required frame. The designed face shield is highly comfortable because of its form-fitting non-rigid and flexible design [48]. Similarly, Stratasys has also provided the open-source STL files to 3D print the visors [44].

3.3. 3D printed rapid detection kits

Rapid testing plays a significant role in the fight against COVID-19 by preventing its further spread. Rapid detection of the virus was essential, especially in developing countries that were at higher risk because of limited availability to specialist facilities. It enables immediate quarantine and access to care. Clinical diagnosis mostly includes CT scan, nucleic acid detection, Immunological detection kits, ELISA (enzyme-linked immune sorbent assay), and sequencing of the genome. However, the current need of the hour is the rapid detection of the virus with high accuracy, specificity, and low cost. 3D printing can provide the hand-held rapid testing kits that will help the health care workers to test for the COVID-19 virus without the need for specialist medical supplies. The designs of the rapid testing kits can be iterated in-house for making the rapid diagnostic kits. Different 3D printing technologies such as fused deposition modeling (FDM), stereolithography (SLA), etc. can be utilized to print the diagnostic devices. However, better surface quality has been obtained with SLA 3D printers. SLA provides a balance of dimensional accuracy, choice of materials, durability, surface finish, and feature resolution. Moreover, SLA is fast, easy to use, and provides a wide range of materials for printing. Therefore, Mologic, a leading developer of rapid diagnostic technologies and lateral flow assays, are using Formlabs 3D printers for producing the housing of all diagnostic devices related to COVID-19 crises [47].

3.4. 3D printing testing swabs

Nasopharyngeal (NP) swabs are typically used for collecting test samples for related respiratory infections, including COVID-19. NP swabs are around 6-inch long, flexible sticks with a bristled end that are inserted into the cavity between the nose and mouth and rotated to ensure enough material is collected. The swab is then placed into a container having a culture medium and transported to a laboratory for testing. The current COVID-19 pandemic has severely impacted the supply of nasal swabs needed for COVID-19 test kits. There has been a nationwide shortage of nasopharyngeal (NP) swabs required to collect samples for COVID-19 testing. Creating test swabs with 3D printing has helped in filling the gap in the swab supply and demand, thereby increasing COVID-19 testing efficiency. In this context, researchers have developed the prototypes of flexible NP swabs with secure polymeric material. Markforged provided two 3D printed testing swab described as Fiberflex Rayon and Fiberflex Flocked (Fig. 4-A). The design of Fiberflex Rayon combines a wrapped rayon tip to the 3D printed nylon swab base to collect the COVID-19 sample, whereas Markforged swabs include a Nylon shaft flocked with Nylon fibers [49]. Similarly, Forms labs also produced a 150 mm long 3D printed swab using Surgical Guide Resin as the printing material [50]. Callahan et al. clinically validated four 3D printed NP swabs prototypes through an institutional review board (IRB) approved clinical trial [51]. EnvisionTEC has also completed the IRB approved clinical trials of 3D printed collection tips [52]. Other 3D printing companies, such as 3D systems, are also working with clinicians to validate the print process and materials used [48].

3.5. Ventilator components

Ventilator shortage has been a crucial reality as the Covid-19 outbreak continues to worsen globally, as it is a respiratory syndrome, these ventilators are required to be certified under some FDA-approved standards and have to pass several human trials [14,53].

The government of different countries has turned to the manufacturer from various industries lie automotive and aerospace to produce ventilators. Companies like Jaguar, land Rover, Airbus, Ford, General Motors, and Tesla have come forward to make the devices alleviate the shortage after relaxation in regulation by the FDA.

As ventilators itself is made up of several parts, which can be 3D printed, for example, Non-return Valves, Sensor mounting, Pressure reducers, Ball valves, Flow regulating valves (FRVs), CPAPs (Continuous Positive Airway Pressure) Component, PEEP (Positive end-expiratory Pressure) valves. 3D printing company Isinnova based in northern Brescia, designed a component to connect Decathlon snorkeling mask to breathing machine [35]. The open-source CAD model of the PEEP valve is also available verified by inter surgical [54].

As most of the parts being used in a ventilator required precision in their manufacturing, so mostly SLS or SLA 3D printing technology is being used to build them, such as flow measuring sensor build by IIT Roorkee on Orifice-meter principle [53]. For parts where precision is not an issue, FDM works fine; it is also faster than other 3D printing technologies like for manufacturing airway connectors, pipeline fittings, Sensor mountings, etc. Companies like HP have come forward with how easily printable CPAP components and Field respirators are the first industrialized 3D printed emergency respiration device [35]. Three major categories of parts of ventilator where 3D Printing is involved are :-

I. Structural Supports and Sensor Mountings

Structural parts of the Ventilators like side panels, chassis parts, display mountings and sensor mountings like Orifice Meter for flow measuring, pressure sensor and hot-wire anemometer mountings. These mounting don't require that much precision and could be made using FDM 3D-printing technology with printers having accuracy of 500 nm or more. An orifice made for a ventilator is shown in Fig. 4-B. It's used for measuring the flow of air through the pipeline of a ventilator by measuring the pressure difference across an orifice of known diameter. An hot wire anemometer holder CAD model used to measure flow of air based on change in resistance of wire is also shown in Fig. 4-B.

II. Custom Pipeline connectors and Divisions

Pipelines divisions and interflow dividers for flow controlling and of custom sizes as per the requirements of the ventilator can be manufactured using 3D printing. These flow dividers can be made of custom diameters, lengths and even custom shapes for proper flow control. A Y connector made for Prana-Vayu Ventilator is shown in the Fig. 4-B. Similarly custom pipeline connectors and divisions can be made using FDM and SLA 3D-Printing Technology depending upon tolerance of friction that air flow can bear under given pressure and temperature conditions. These connectors can also work in ventilator sharing method. In which the ventilator can be split into two and which could be operated on two or more patients simultaneously [55].

III. Valves

Another major part of the Ventilator are Valves which helps us to convert the continuous flow of pressurised air into pulse as per the BPM (Breathe Per Minute) of the patient. There are many types of valves that are used in a ventilator like Ball Valves, Needle Valves, Butterfly Valves and Non-return Valves. Ball Valves and Butterfly Valves are used for real time flow control to switch over various modes of ventilator and also to



Fig. 4. 3D printed Nasal swabs [51]; (B) 3D printed ventilator parts [55].

During COVID-19 infection monitoring, nasal swab testing is considered as one of the important area of investigation. Nasal swab collectors are designed and produced with the help of 3 D prining. Similarly, the use of 3D printing technology in production of ventilator organs are very promient.

operate over a particular mode. While Non-Return Valves are used to prevent any backward flow inside the pipeline like while pumping air inside the lungs there must not be any kind of losses due to backward flow otherwise it will inflate the lungs with negative pressure. A Non-return valve design has been shown in Fig. 4-B below. These valves require high precision during operation as well as during their manufacturing so mostly SLA 3D-printing technology is preferred over FDM but they can be printed using FDMs technology having precision of 200 nm or more.

4. 3D printing based approaches in medicine

The fast proliferation of SARS-CoV-2 has put a massive strain on the healthcare sector globally with increasing demand for crucial supplies mounting, medical equipment, and manufacturing or repurposing of drugs. Emerging technologies like 3D printing have the ability to meet the challenges of drug delivery systems as they have the caliber to fight against the COVID-19 epidemic by giving preventive, personalized, and predictive medical approaches [1]. 3D printed drugs are flexible as they can revolutionize the field of medicine and open up novel opportunities and possibilities that are hard to overestimate (Fig. 5 and Fig. 6). The designed 3D printed medicines are becoming an increasingly appealing alternative to conventional drugs due to easy and decentralized processes, active pharmaceutical ingredient (API) deliver profile, tailored manufacturing, personalized therapy, or patient-centric cure of the disease [56]. The appealing advantages of 3D printed medicines include the potential to generate pill, tablets or capsule of any size, shape, and optimization of dose individually and specifically, control the number and amount of active ingredients in the composition of the drug, replace or remove specific components that will aid in taking medications even if there is allergy or hypersensitivity to a single substance [15].

3D printing technology has the prospective to transform the pharmaceutical industry as they substitute a large figure of drugs with one pill

that decreases the frequency of taking medication. The 3D printed drugs have the capability to regulate the task of the release of active ingredients that can decrease or increase the effect of the drug, that in turn enhance the effectiveness of the drug [57]. Moreover, the manufacturing of drugs on a 3D printer reduces the chances of mixing up of drugs or mistakenly takes another patients drug because manufacturing can be taken place in small batches [58]. Fig. 5 and 6 describe the detailed use of 3D printing technology in drug formulation technologies.

Due to wide potential of 3D printing in pharmaceutical, it can be exploited for the robust and dynamic drug supply to manage the current crisis of COVID-19. During an epidemic, the expenses and production time of supplies are crucial variables; the 3D printing technology can be constructed quickly with relatively less manufacturing cost. Due to affordable prices, small size and convenience of 3D printing technology, it can be consumed in any environment such as pharmacy stores and hospitals thus results in eliminating the issues related to delayed delivery of essential medicines due to disturbed supply chain during COVID-19 [59,60]. Furthermore, the structure of a drug can be conveyed to a 3D printer from any other place in the world for a fast and patient centric manufacturing of drug delivery systems. The first FDA approved 3D printed drug, spritam (Levetiracetum) in 2015 has opened wide area of opportunities in pharmaceutical manufacturing using 3D printing [61]. Several drug administration systems have been made such as microchips, pills, instant tablet release, implants, and oral regulated released and multiphase release doses. A variety of 3D printing methods have been developed with different features but among the established, the most commonly used techniques in pharmacy and drug formulations are ink-jet, fused filament, extrusion, fused deposition modeling and powder extrusion that allows the fabrication of 3D printed drugs. 3D printed technology in medicine mainly uses a small nozzle to set a thin disc fashioned films of powder and deposited microscopic liquid droplets to adhere the materials [62,63]. To print an active ingredient of pharmaceutical product a coaxial needle extrusion technology is used that can

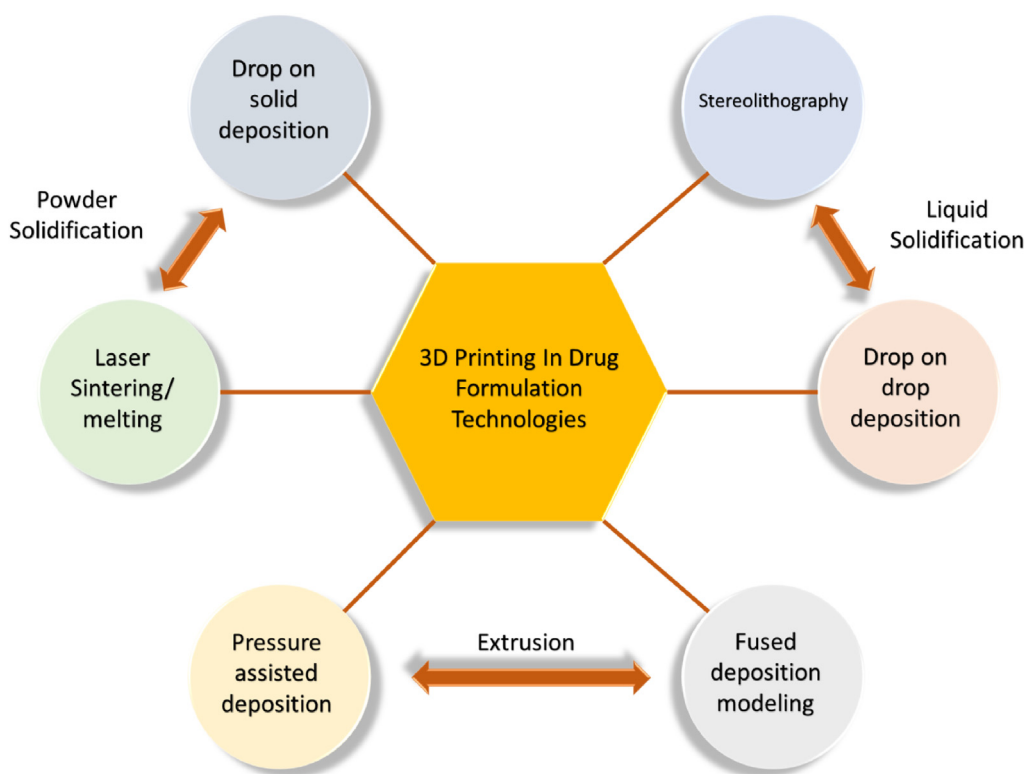


Fig. 5. Use of 3D Printing in drug formulation technologies.

3D printing has a lot of use in pharmaceutical sciences. In pharma sectors such as in drop on solid deposition, extrusion and laser sintering, 3D printing has definite applications.

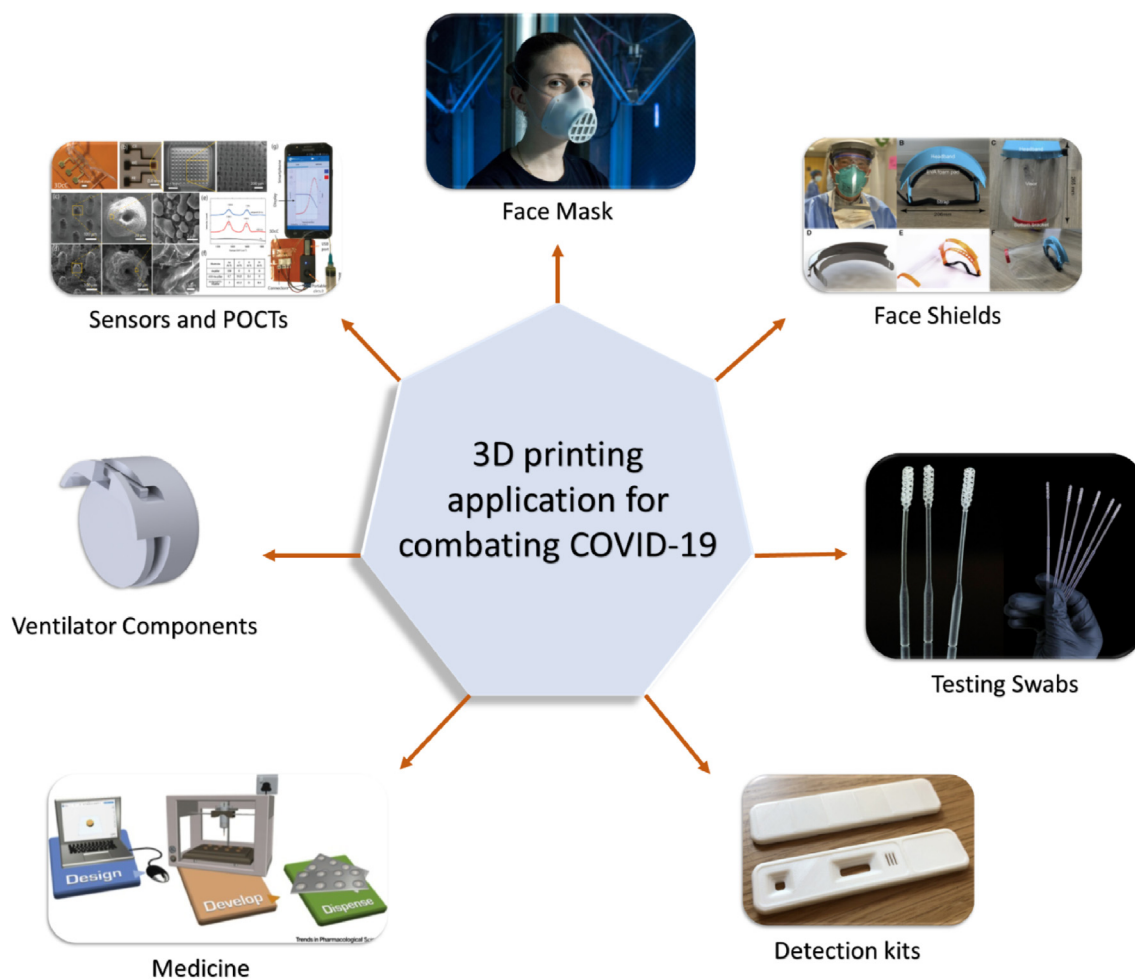


Fig. 6. 3D-printing applications in combating COVID-19.

3D printing can be useful in POCTS, for making face mask, face shields, for kits in testing swabs, in detection kits, in medicines and clinical sciences, for example in ventilator components etc.

generate combinations of regulated drug dosing. Even though currently no specific vaccine or antiviral candidates are there for COVID-19, so as therapy some distinctive antiviral drugs are considered [58,64]. It may be feasible to take advantage of 3D printing medication technology to functionally and swiftly print chloroquine, hydroxychloroquine, ritonavir and lopinavir dosage forms. Recently most of the drugs that are under investigation for the treatment of COVID-19 can be manufactured using FDM 3D printing as solid oral dose, for example an under investigation novel oral drug named as EIDD-2801 [65–67]. Additionally, oral drugs that are generally employed for the treatment of other viruses, malaria are also under the investigation phase with or without mixing with other drugs as a cure for COVID-19, such as the potency of an antacid namely famotidine in combination with HCQ, CQ diphosphate with azithromycin (an antibiotic) and oseltamivir (an antiviral) is tested; though scientists have presumed that these can cause abnormalities in some patients in a dose dependent manner [68]. 3D printing can be used for fast manufacturing of patient centric dose dependent drug delivery systems in hospitals as per the need of patient to avoid these complications. For the productive manufacturing of drug delivery systems by 3D printing, it is crucial to select the appropriate printing parameter and material by understanding the properties of drug molecules individually those are under investigation. In UK June 2020, a clinical study with a codename “RECOVERY” shows that dexamethasone, a steroid drug decreased the mortality rate of COVID-19 patients by one third. Dexamethasone filaments can be generated via hot melting extrusion and formulations can be printed by FDM 3D printing in accurate doses. The appropriateness of

different 3D printing technologies will be based on physicochemical properties, dosage strength, biopharmaceutics classification system (BCS) categorization of repurposed drug compounds which are recently being assessed for corona virus [69,70]. Most of the repurposed trialed drug candidates are facing low aqueous solubility and oral delivery of these drugs will need bioavailability possessing formulations like amorphous solid dispersion (ASD) for their favorable outcome. This is reasonable especially when they possess low antiviral potency and hence require heavy doses. In this situation fused deposition modeling (FDM) printed ASD by employing hydrophilic polymeric excipients can be appropriate. On the other hand, high dose requirement pose a different challenge such as chloroquine is a well-known antimalarial drug with characterized biopharmaceutics profile [71–73]. Though its therapeutic dose for COVID-19 is unknown, it is mainly delivered at a high dose (upto 1000 mg per delivery). Thus, managing such a high drug load into FDM considering dose specificity for swallowing in patient can be challenging. Therefore, the inkjet powder bed printing technique could be an alternative, as it is well known for producing high doses of drugs successfully and could be more suitable for this compound. Moreover, it is also crucial to eliminate the chances of saturation in case of one treatment approach as it may result in drug resistance mainly in case of antivirals [74]. In such cases, multi layered and multicompartimentalized 3D printing can be anchored for developing fixed or variable combination of doses using two or more than two antiviral therapeutics [75–77]. Thus 3D printing technologies can be used for the preparation of drug delivery systems for COVID-19 patients as they possess various economic and

medical benefits. Continuous refinement and innovations in 3D printing methods are in process to overcome the recent pandemic of COVID-19 and promote patient-specific treatment.

The COVID-19 outbreak has devastated the world starting for the human society to their immediate outsourcings and their work environment [78–81]. Under the status of limited or no knowledge on the quick spreading disease, clinicians tried their best for public health management. Bedside vaccination, using mask, PPE kits etc has been the prime source of adaption to prevent the disease [82–85]. Under the crisis having very limited knowledge on this disease management, needless panic buying of medical materials was observed during the COVID-19 outbreak with an understanding of uncertainty in production of such materials. Hence, waste of money, time and shortage of medical requirements for medical practitioners and front line COVID-19 workers was noticed. It was due to the plethora of designs for such reusable medical devices and medicines were the need of the day. However, the exact need based sensing and producing the required clinical materials was highly desired at all time. From the literature review, it is noteworthy to mention that various 3D sensing and printing system seems to decrease the supply demand ratio under such crisis at present and also in future.

5. Conclusions

Needless panic buying during the course of the pandemic resulted in a limited supply of PPE, which were extremely significant for health care staff to attend to critically ill subjects. It was observed that 3D printing community members all across the globe have premeditated a plethora of designs for reusable PPE devices, including insertable filters, which were produced utilizing inexpensive desktop filament extrusion printers. Different PPE such as splash-proof face shields, surgical face masks, N95 masks, N90 masks, copper 3D nano hack mask, stopgap face mask, HEPA masks, Viri mask protective oculo-respirator, powered air-purifying respirator (PAPR), 3D printed face shield, 3D printed rapid detection kits, 3D printed test swabs and components of ventilator were discussed. These PPEs are meant to be reused, and consequently, any efforts to manufacture them locally should be carefully considered along with compatible and accessible techniques for their sterilization. It is therefore recommended that 3D printing manufacturers and engineers might work in direct communication with the local supply chain of medical devices and possibly with national strategic policymakers. An integrated tactical local rejoinder to this crisis entails or necessitates open and organized interaction between policymakers and researchers. However, it is to be noted that even with the urgency of the increasing COVID-19 emergency, regularized safety and quality procedures of 3D printing labs must be carried out. The medical effectiveness of many of these accounted PPE devices described in this study has been tested, and they have not undergone the strict regulatory tests. Few of them may have not yet been approved for forefront clinical use by pertinent governing bodies. We, the authors, absolutely do not vouch for the medical efficacy of the listed PPE devices and would request usage of these devices only when the situation is dire, and there are no scientifically approved substitute's available. We hope that this pandemic will encourage creativity worldwide, including the collaboration of knowledge and innovation via the scientific interactions between health authorities and engineers. 3D printing may result as power for an optimistic impression on disease and impermanence in these difficult and developed by several central model repositories with novel original designs and figures, explanations of envisioned usage, directives for their assembly, and object material/printer elaborations. Also an appropriate association between researchers, investors, and regulatory body is required to implement safety to enhance the quality of life of COVID-19 patients by 3D printing.

Ethics approval and consent to participate

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Authors' contributions

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Consent for publication

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