MiniReview Article

Transfiguring Healthcare: Three-Dimensional Printing in Pharmaceutical Sciences; Trends During Covid-19: A Review

Three-dimensional(3D) printing is a unique technique that allows for a high degree of customisation in pharmacy, dentistry and in designing of medical devices. 3D printing satiates the increasing exigency for consumer personalisation in these fields as custom-made medicines catering to the patients' requirements are novel advancements in drug therapy. Current research in 3D printing indicates towards reproducing an organ in the form of a chip; paving the way for more studies and opportunities to perfecting the existing technique. In addition, we will also attempt to shed light on the impact of 3D printing in the COVID-19 pandemic.

ABSTRACT:

Key words: 3D Printing, Additive manufacturing, 3D Printing in Pharmaceutical sciences, 3D Printed Drugs, Personalised medicine, COVID-19 impact on 3D printing.

INTRODUCTION:

Three-dimensional printing or 3D printing is a technique of additive manufacturing, where a three-dimensional structure can be obtained by deposition or solidification of many layers successively[1,2][3]. The material extruded in many layers can be a polymer, hydrogel, photosensitive resin and many more. This technology finds applications in a wide variety of fields such as aerospace research[4,5], automotive industry, consumer goods industry[6][7]. The extraordinary features of this method are accuracy, repeatability and reliability. [8][9]

Recent studies have led to the introduction of a novel application of this technique in the fields of regenerative medicine[10][11–18] which utilizes cell-based materials[19] and stem cells[20][21], medical device development[22–28], dentistry and especially 3D printing of drugs in pharmaceutical sciences and printing of organs. [29]

Some of the most recent achievements using 3DP in the field of pharmacy are drug delivery systems with multifunctionality, personalised medicines, adjustable dosage forms, accelerated drug release delivery systems, personalised implants suitable for a specific patient body anatomy.

3D printing technique has garnered a substantial attention from all over the world for being a helpful tool in precision placement of biologics such as live cells, nucleic acids, growth factors and proteins to imitate natural anatomy, biology and physiology of tissues. The researches on the same have showed potential of precision placement of drug particles, kindling interest in personalised medicine. [30]

As the medicine field is pressing forward, it is inevitable to accept the fact that tailor-made formulas won't work because of the overwhelming differences in the physiological action of a drug from an individual to other. Personalised medicine is the future in order to upsurge the efficiency of drug delivery systems as well as to decrease the toxicity[31], and this is where 3D printing finds its

applications. With the help of this technique, manufacturing of complex pharmaceuticals, the on-demand manufacture of drugs becomes easier[6]. The ability to fabricate pharmaceutical products during pandemics, in emergency operations, in military and in health care units where time and resources are limited poses an interesting pharmaceutical application of 3D printing.[8] [32]

As of dentistry, 3DBP has emerged as an exciting technique in regenerative aspect. Printing of cellularised scaffolds has allowed the precise positioning on demand [33]. In order to obtain functional tissues, the scaffolds play an important role, as the support they give helps stimulating the attachment, proliferation and differentiation. 3DBP is a prospective helpful tool to help investigate the application of scaffolds in dentistry to enhance the regeneration tissue and alveolar bone.[34]

After the coronavirus disease 2019 (COVID-19) started as an outbreak in Wuhan, China, the demand for N95 respirator masks, face shields, ventilator valves, testing kits, and other personal protective equipment (PPE) are on the rise but the supply has been limited world-wide. To address this issue, 3DP is an interesting approach, which poses the question of effect of this pandemic on the design innovation and prototyping during a pandemic.[35]

2. 3D PRINTING IN PHARMACEUTICAL SCIENCES- CURRENT ADVANCES [36]

In line with the advances, there are also certain challenges in using traditional methodologies in drug discovery. Figure 1 and 1A below is a schematic representation of challenges and the application of 3D printing as an effort to overcome the challenges.

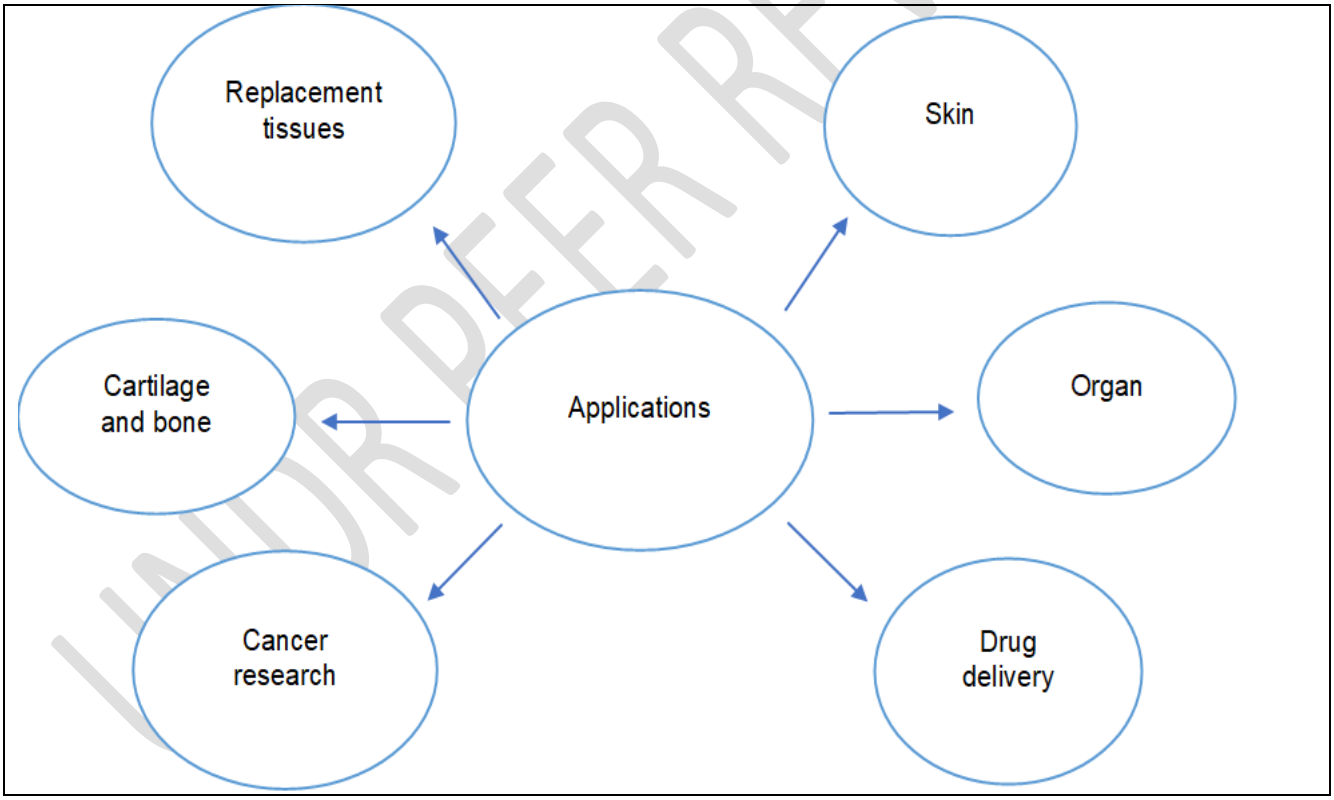

Figure 1: Applications of 3D printing

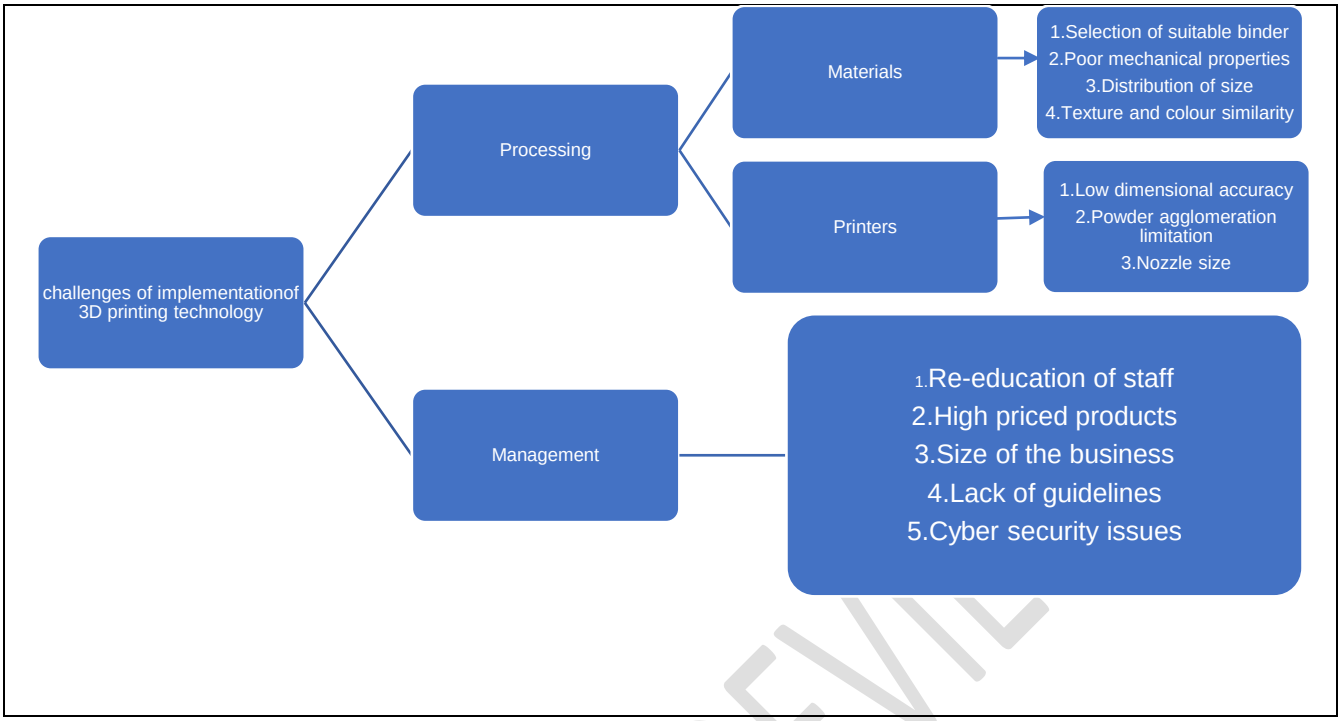

Figure 1A:Challenges of implementation of 3D printing technology

As the applicaations of 3D printing are being discovered, the possible use of various techniques in 3D printing of pharmaceuticals are being looked into. Table 1 below shows the various 3D printing techniques used in pharmaceutical sciences and their principles.

Table 1: Various 3D Printing techniques used in Pharmaceutical Sciences.

Sl no	Name of the technique	Principle	Dosage form prepared using the technique	Ref
1	Binder jetting	• Powder solidification • Selective deposition of binder onto powder bed, causing the adherence of that part, building layer-by-layer.	Levetiracetam tablets for oral suspension, Chlorpheniramine maleate and fluorescein tablets.	[48] [49] [50]
2	Drop on solid deposition	• Powder solidification • Liquid binding of powdered material	Isoniazid sustained release implant, Captopril rapidly dispersing tablets.	[19]
3	Drop on drop disposition	• Solidification of liquid • Solidification of droplets.	Ropinirole HCL tablets, Fenofibrate tablets.	[19]
4	Stereolithography	• Liquid solidification. • Solidification of photosensitive resin	Paracetamol tablets	[19]
5	Inkjet printers	• Droplet based printing, drop-	Folic acid	[49]

		on-demand printing • Thermal, piezo or acoustic forcefully expels the droplets onto the supportive substrate, later solidified by mechanisms like crosslinking agents, pH and ultraviolet (UV) radiation.	nanosuspension, Rifampicin nanoparticle, Salbutamol sulphate solution, Levofloxacin implant.	
6	Fused deposition modelling	• Extrusion based • Solidification of melted material.	Aripiprazole orodispersible films, Theophylline tablets, Budesonide caplet, Prednisolone tablet.	[19] [51] [52]
7	Pressure assisted Syringe	• Layer-by-layer disposition • A multi-syringe system with a single nozzle and a mixing chamber to mix bio-inks before deposition with the assistance of pressure.	Guaifenesin bilayered tablet, Tablet 'polypill' with captopril, glipizide and nifedipine.	[53] [51]
8	Laser assisted printing/ Laser direct write	• Laser based • laser is centred on the substrates that absorb (example: gold or titanium) to create a bubble, later creating shock waves that push the cell-containing resources from the donor slide to the collector slide.	4-aminosalicylic acid, paracetamol tablet.	[54]
9	Selective laser sintering	• Laser based, powder solidification. • Hardening of powdered material by a potent beam of laser.	Paracetamol orodispersible tablets.	[19]
10	Acoustic ink printing	• Drop-on-demand • Droplets of ink are created and expelled underneath the effect of an acoustic field. The acoustic beam targeted on a free liquid surface to expel distinct ink droplets of measured diameter.	Engineering of microenvironments with stem cells	[55] [56] [52]
11	Microvalve based systems.	• drop-on-demand. • Microvalves are attached to separate gas regulators which give pneumatic pressure and valve opening time is managed through solenoid coil and plunger. The bio-ink is placed after the pneumatic pressure overpowers the fluid viscosity	gastro-floating tablets with hydroxypropyl methylcellulose-based dipyridamole paste.	[57] [56] [58]

		and surface tension at the opened orifice.		
12	Pneumatic/ Mechanical (piston or screw based)	• Extrusion based. • An extensive variety of drive forces allows deposition of an array of biological substances with dissimilar rheological properties.	Tissue printing substitutes or scaffolds of soft tissues, as well as the manufacture of complex drug delivery systems	[59]

Advantages of exploiting 3d printing in pharmaceutical sciences:

- Drug discovery is a very time consuming, costly process that adjure a huge investment as well as human resources. Some recent efforts in 3D *in vitro* assay systems have shown potential in becoming ideal solution of improving the prediction of efficacy and toxicity of drug candidates, thus speeding up the process of conversion on novel drugs to clinics. Researches done by many researchers shed a positive light on 3D printing being an effective tool in drug discovery.[30]
- 3D printing can be considered as the future of personalised medicine. With the current technologies of commercial methods of drug manufacture, it is impossible to cater to the need of customising the medicines.
- Because tissue models are fabricated in microarrays using 3D printing, they resemble and closely mimic the native tissues, thus can be used in high-throughput assays and toxicology studies[37].
- Printing is superior in terms of micro architecture, decreased risk of cross-contamination and size controllability[38].
- Generation of co-culture as well as single cell array with a precision in control of cell density is an added advantage for 3D printing. [30]
- 3D printing helps fabricating geometrically complex structures and enables architectural intricacy, simplistic construction of multi-layer drug delivery systems, and assists numerous controlled release mechanisms. [29][19]
- It enables the printing of custom-made multi-dose and multi-drug containing dosage forms, designed based on the weight, lifestyle of the patient and help adjust dose and dosage form as essential for individual patients which would prevent the risk of over or under dosing. [19][29][8]
- The shear ability of scalability and relative low cost of production of drugs, especially for orphan drugs which have a small demographic of patients is what makes 3D printing more attractive approach.[19]
- The bioavailability of drugs can be tweaked by fabrication of multiple separate chambers that can be loaded with different substances.
- 3D Pharming (the direct printing of pharmaceutical dosage forms) signifies an innovative process for engineering of controlled release drug delivery systems. [8]
- An effective drug metabolism was demonstrated with the help of micro-liver chamber fabricated with the help of elastomer soft lithography united with micro-moulding technique designed by the by the investigators of Sun's group, the drug used being a pro drug named 7-ethoxy-4-trifluoromethyl coumarin (EFC).[30]
- Tumour models that are widely used in cancer research are usually two dimensional, however they are not the accurate representation of cell-cell and cell-matrix interactions found in the internal environment. 3D printing offers accurate representation of cancer microenvironment to pinpoint the locations of various cell types and microcapillaries which could be of great help in the study of pathogenesis and metastasis.[30]

Limitations of 3d printing in pharmaceutical sciences:

- To be able to personally use the 3D printer at home, the patient needs to be given a special training. Even so, he/she might not be able to identify and correct the deformities in the design itself which could highly likely alter the bioavailability and other aspects of drug.[30]

- Polymers, which are crucial in printing a clinically significant tissue pose a challenge as the polymers that are widely used in various traditional tissue engineering processes might not be most appropriate biologically, as many of them are biologically too active, potentially causing unwanted effects on the 3D printed tissues. [39]
- The shortcomings associated with the usage of conventional polymers has led to the invention of more biologically appropriate polymers and hydrogels, but these are not compatible with currently available 3D printing technologies as they lack structural integrity. [39]
- The mechanical forces used by the printer can cause an alteration in the geometry of the cell and signal pathways, even could potentially cause cell death.
- Current technologies of 3D printing are generally inefficient and takes a lot of time for completion of the whole process. There is a need to improve the efficiency so that the number of cells needed to print the various tissues can be delivered consistently and death due to mechanical forces are avoided. [39]

The limitations of applying 3D printing in the pharmaceutical sciences is schematically represented in Fig 2 below

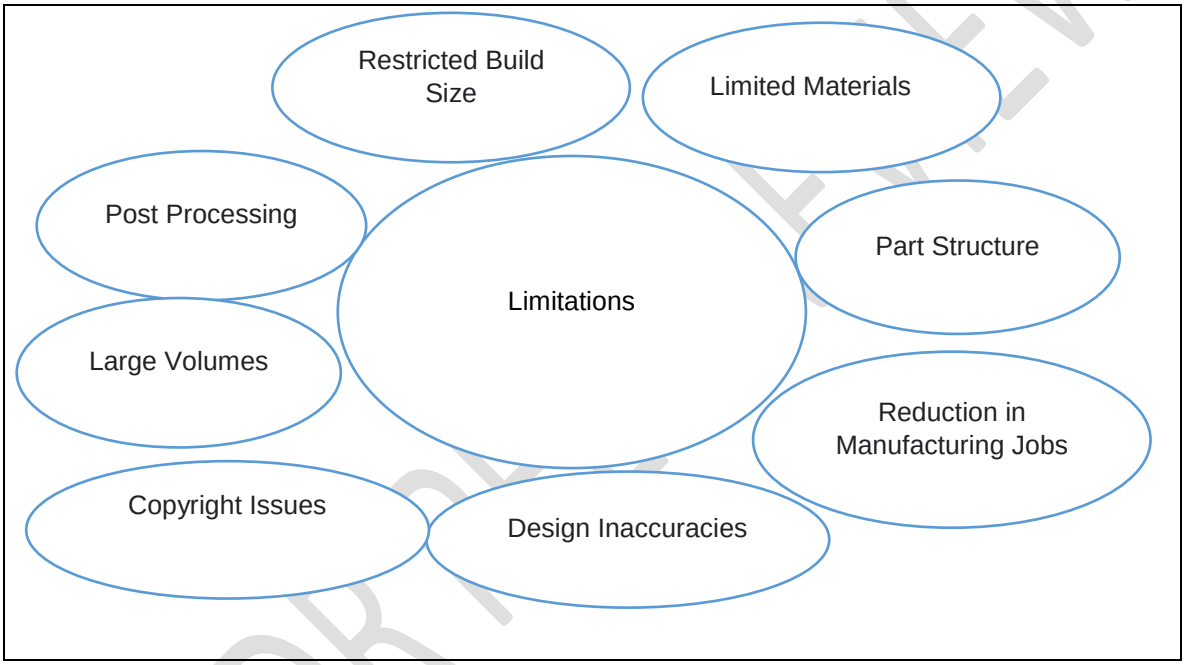

Figure 2. Limitations of applying 3D printing in the pharmaceutical sciences

4. COVID-19: EFFECTS ON 3D PRINTING DESIGN INNOVATIONS AND PROTOTYPING:

The official records regarding the outburst of coronavirus disease 2019 (COVID-19), identifies Wuhan, China as the point of initiation; where the first case was identified on December 8, 2019[35][40]. With this being a virulent and highly contagious disease, the epidemic soon considered to have become a global pandemic when a definitive information about this disease being spread across all continents was made available to world. The death toll is rising exponentially all over the world with 79,232,555 confirmed cases as of on 27 December, 2020 according to WHO.

The patients affected with the novel corona virus have known to show a spectrum of symptoms such as fever, cough, myalgia or fatigue. Some patients have shown headache and haemoptysis. Comorbid patients are likely to experience respiratory failure. Some experience organ failure which would sometimes lead to death, many are known to show no known symptoms (asymptomatic). In short, a person showing the symptoms such as fever, upper respiratory tract symptoms with lymphopenia or leukopenia is more likely to have contracted the novel coronavirus.[41]

This pandemic has caused a worldwide shortage of personal protective equipment (PPE) such as N95 masks, face shields, respirator masks, testing kits and so on. 3D printing, among numerous other applications is being researched on to find its potential use to overcome the said shortage and to fill in the critical gap in supply chains[35][42]. Many efforts are being made to look for alternative, cheaper ways to mitigate this void caused by the pandemic and 3D printing is an interesting and potential approach.

3D printing-innovations due to the drive that is; the pandemic:

- In a research article by Cavallo and others, they talk about expanding the use of CAD/CAM technology and 3D printing technologies used in dentistry to print plastic valves with the help of dentists in the hopes of helping mitigate the shortage of respiratory devices.[43]
- Due to the pandemic, many companies are experiencing delay in shipping, forced turndown of an order or delay taking a new order. The ability to virtually be able to print anything at anywhere has governments, universities, 3D printing enthusiasts, professionals readily volunteer to look for innovative ways to overcome this problem. [42]
- The European Association for Additive Manufacturing has urged their member states to help aid in manufacturing medical equipment and other personal protection kits by lending the equipment in their AM industries.
- The colleges under the university of Idaho have teamed up and have successfully 3D printed the components of PPE kits for the usage of healthcare workers.
- Researchers of RMIT university, Australia have produced a “clip-on” filter which can turn normal cameras of smartphones into a dominant microscope, with the help of 3D printing technology.
- 3D printing firms have been volunteering in producing ventilator components, facemasks, test kits. An innovation of a 3D printed add-on has been made which allows the user to open the modern doors without coming in contact with the door handles by ‘Materialize’.
- A company in China, has mass produced 3D printed safety goggles for the healthcare workers in China. Another company of architectural basis Winsun, has produced around 15 3D printed quarantine booths.[42]
- As the efforts are going on to come up with a vaccine for the virus, new efforts to make a novel drug delivery system is being researched on too. It has been identified that with the help of 3D printing it is possible to dispense low volumes of drugs with precise special control and very high accuracy.[40]

Figure 3 below is a schematic representation of effects of covid-19 on 3d printing.

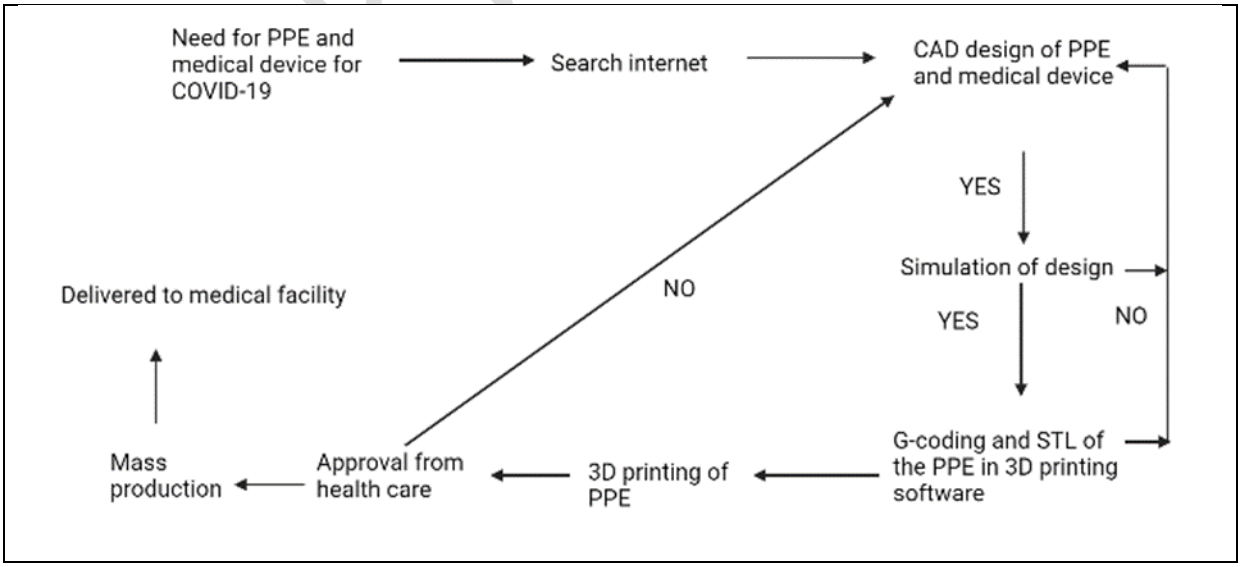

Figure 3: schematic representation of effects of COVID-19 on 3D printing.

Table 2 below shows the compilation the US patents which indicate the use of 3D printing in either the whole process or at least one process or step relevant to the fields of pharmaceutical sciences and dentistry.

Table 2: Some patents regarding the usage of 3D printing in Pharmaceutical Sciences and Dentistry.

SL no	Patent heading	Inventors	US Patent no	Year of filing	Field of application
1	Medical devices including medicaments and methods of making and using same including enhancing comfort, enhancing drug penetration, and treatment of myopia	Doshi; Praful	10,632,068	July 27, 2019	Pharmaceutical sciences, Medical devices.
2	Expandable gastroretentive dosage form	Menachem, et al.	10,485,758	June 2, 2015	Pharmaceutical sciences
3	3-D printed packaging	Divine, et al.	10,435,185	February 2, 2016	Pharmaceutical sciences, dentistry.
4	Dental implant system	Hertz; Paul	10,779,912	December 19, 2015	dentistry
5	Robotic ophthalmology	Gerrans; Lawrence J.	10,194,799	March 9, 2015	Prosthetics

5. REGULATORY ASPECT OF 3D PRINTING IN PHARMACEUTICAL SCIENCES AND DENTISTRY:

Legal aspect:

The increasing use of additive manufacturing in pharmaceutical, dentistry and medicinal sectors have pointed towards the need for various legal considerations. According to Kririkos[44], they can be grouped as:

- The aspect of data protection;
- Intellectual property rights (IPRs);
- Legal classification of 3D printing;
- Liability;
- Issues regarding safety;
- Security difficulties; and
- Socio-ethical planning.

Concerns and gaps in the current regulatory aspects regarding the use of 3d printing in pharmaceutical sciences:

Till today, there are no clear regulatory guidelines in any country that defines the clear differences between bulk manufactured medicine and personalised medicine. According to the regulatory and

cGMP guidelines available currently, it is possible to use 3D printing technology on an industrial scale based on the “one size fits all” ideology. The real problem arises when the idea of fabricating the products in a doctor’s office, hospital, pharmacy or even for personal use [45].

Currently, the regulatory structure that controls the manufacture, distribution and compounding of pharmaceuticals using 3D printing differs from country to country, which adds to the issue.[46][45]

In the US, drugs compounded with 3D printing technology doesn’t come under the compounding regulations of bulk manufactured drugs; it is highly necessary to include this under the existing compounding regulations.

The main concerns with printing at clinical study sites, hospitals and pharmacies are health threats and safety features which arises as a result of usage of raw materials, organic solvents and possible toxic degraded products which might be unknown. 3D printing involves the portability aspect, from where the concerns about robustness during shipping, changes in environmental conditions arises.

Protecting a CAD file is challenging as the final product under claim is basically a physical object. CAD file is just a set of instruction on basis of which a physical product can be reproduced with the assistance of a 3D printer.[47]

As of printing in a doctor’s workplace or home, there are no guidelines for that yet.[45]

Intellectual property rights- For most IPRs, it is a given that they give the ability to prevent any third party from doing or undertaking certain actions. The IPRs are territory based, meaning they are governed by national basis which implies that they slightly differ from jurisdiction-to-jurisdiction.[46]

3D printing products- European union (EU) regulations: [44]

The new regulations i.e., ‘The new Medical Devices Regulation (2017/745/European Union (EU)) (MDR) and the *in vitro Diagnostic* Medical Devises regulation (2017/746/EU) (IVDR) help in creating a strong, transparent and workable regulatory framework thus helping to lessen the risk of inconsistencies in explanation across the EU market.
Figure 4 below is the schematic representation of key points of EU regulatory framework.

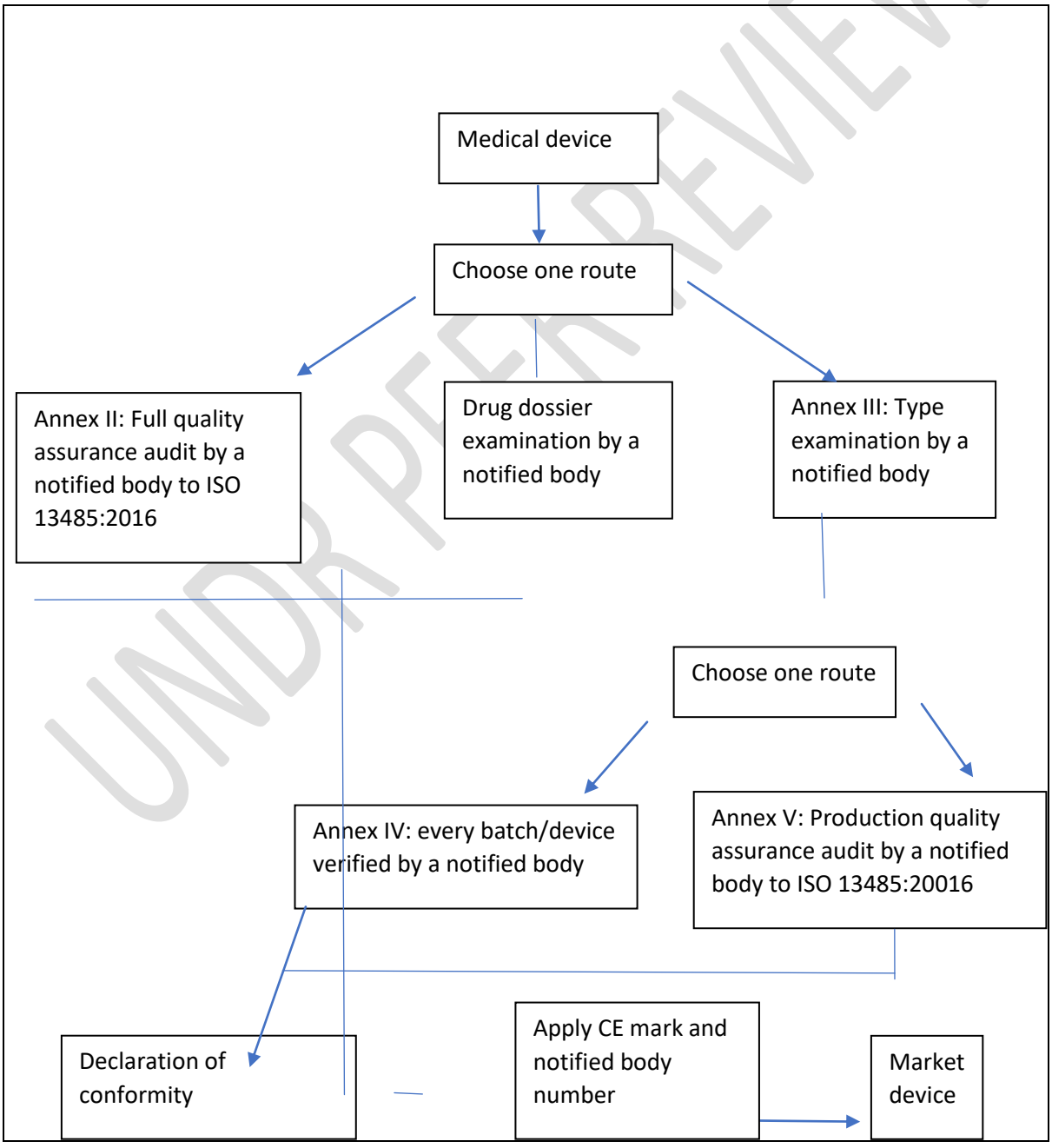

Figure 4: schematic representation of key points of EU regulatory framework

6. CONCLUSION:

3D printing is an attractive tool for the customised production of medical devices, pharmaceuticals with personalised bioavailability. Dentistry has a fair share when it comes to the use of 3D printing techniques for various purposes such as 3D printing on surgical tools with accurate grooves, dentures, crowns, implants and many more. The COVID-19 pandemic, though has affected thousands of lives, has provided the 3D printing enthusiasts with opportunities to innovate and prototype newer techniques to help the lack of availability of personal protection equipment. This articles briefly summarises the above-mentioned aspects, based on the data obtained from recently published works in the relevant areas.

7. CONFLICT OF INTEREST:

Authors reported no conflict of interest in the current work.

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