3D PRINTING TECHNOLOGY & SHORT INTRODUCTION IN 3D BIO-PRINTED MATRICES FOR IN VITRO TUMOR MODEL

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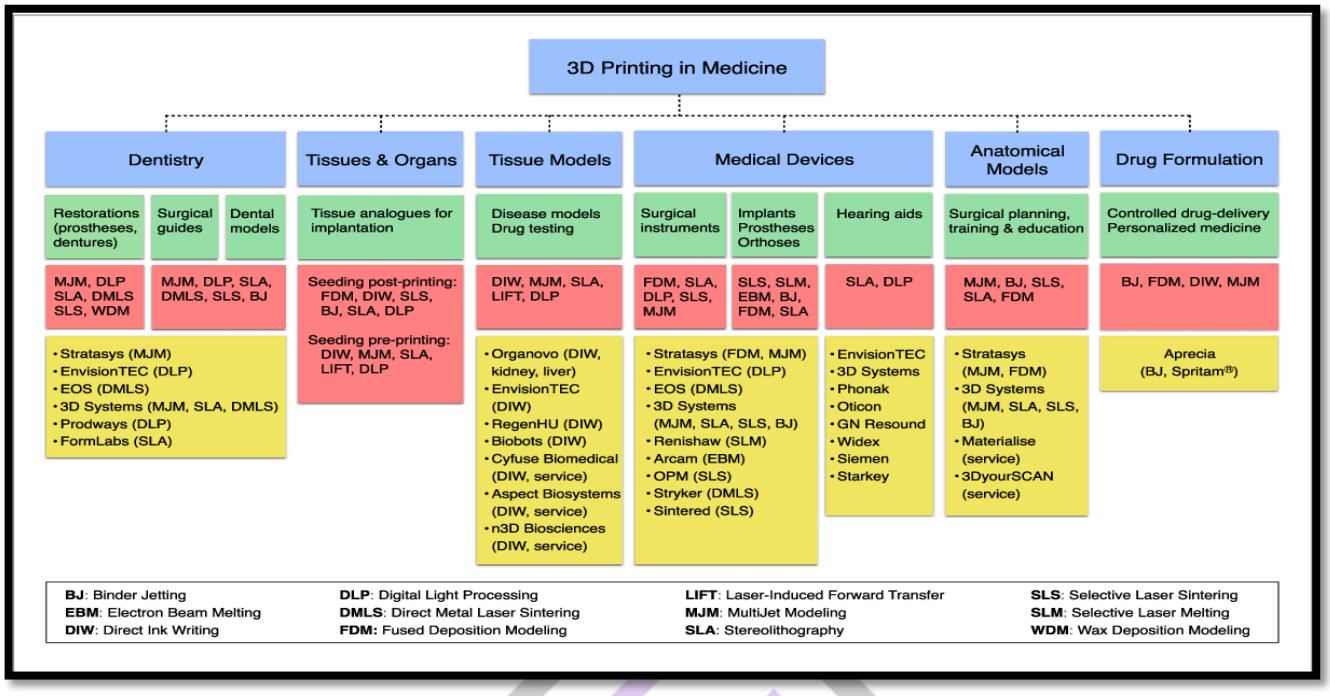
***Abstract*: Food and Drug Administration (FDA) has approved a drug product (Spritam®) and lots of medical devices factory-made by three-dimensional printing (3DP) processes for human use. There's Brobdingnagian potential to print customized medicines victimization 3DP. Several 3DP strategies are reportable within the literature for pharmaceutical applications. However, selective optical device sintering (SLS) printing has remained least explored for pharmaceutical applications. There square measure several blessings and challenges in adopting a SLS methodology for fabrication of customized medicines. Solvent-free nature, convenience of authority approved thermoplastic polymer/excipients (currently utilized in hot heat-extrusion process), lower/no post-processing step, etc. square measure a number of the benefits of the SLS printing. Major challenges of the technology square measure apparatus of a minimum of one thermoplastic element within the formulation and thermal stability of drug and excipients. This review provides a summary of the SLS printing methodology, excipient necessities, method watching, quality defects, restrictive aspects, and potential pharmaceutical applications.**

***Keywords:* 3D Printing, Material Jetting, Binder Jetting, Material Extrusion, Powder Bed Fusion, Fused Deposition Modeling, Extrusion 3D Printing, Tumor spheroid formation in 3D printed matrices, Organotypic cancer models, 3D Bioprinting in Medicine**

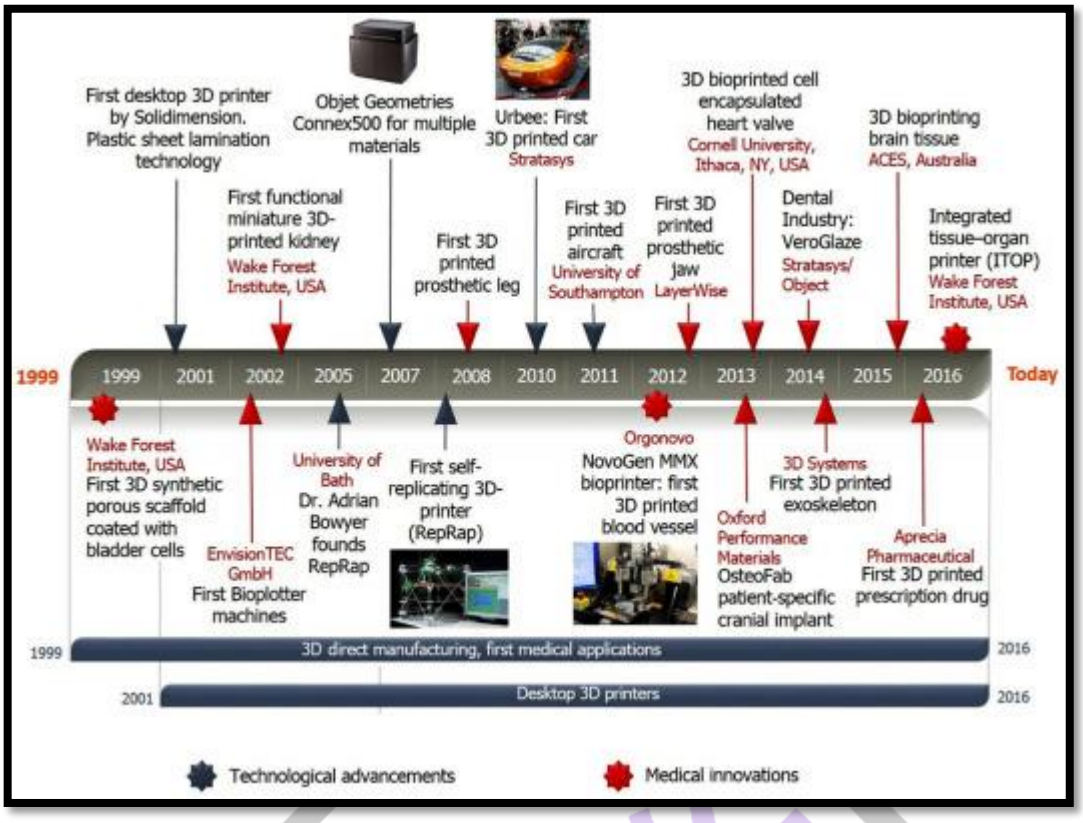
I. INTRODUCTION

There is a relentless motivation towards new ideas in drug style, higher understanding of fabric properties, producing technology and processes that assures prime quality of dose forms. The diversity of chemistry and biopharmaceutical characteristics of active pharmaceutical ingredients (APIs) ought to be thought- about and studied through every stage of development. Auxiliary substances have to be compelled to be examined similarly so as to manufacture of the required dose type. It was targeted on novel dose forms and technological processes. Growing them innovation associate degreed for tailor-made devices combined with an enlargement of technological drives the most important progress in personalized drugs expressed e.g. by the assembly of tiny series of individually-selected doses and bespoken prostheses meet the anatomical desires of patients. Nowadays, three-dimensional printing is one in all the quickest developing branch of technology, art and science, and still broadens the applications. The term three- dimensional printing was outlined by International Customary Organization (ISO) as: "fabrication of objects through the deposition of a fabric employing a print head, nozzle, or another printer technology". In distinction to unremarkably used subtractive and formative producing methodologies, this system is one in all the ways of additive producing (AM) within which the components area unit ready from 3D model knowledge within the method of connation materials layer by layer. the sensible approach of AM is named fast prototyping (RP) [1]. and its benefits embrace the reduction of prototyping time and prices, straightforward modifications of a product at a designed level, the likelihood of producing of tiny objects, personalized product series or structures not possible to be fashioned with subtractive techniques [2].



II. HISTORY

- 3D Printing is a platform for personalized drugs from the start of 1990.
- There are a unit major successes in 3D written medical device, FDA's Center for Device and tomography Health (CDRH) has revised and cleared 3DP medical devices.
- The initial 3D printing methodology utilized in pharmacy was earned by inkjet printing, a binder answer onto a powder bed, so the particles bind along.
- The technique was continual till the ultimate desired structure was obtained. This initial happened within the early 90's at the Massachusetts Institute Technology developed and proprietary by Sachs etal [3].
- In 1989 Scott Crump filed a patent on another 3D printing technology, amalgamate deposition modeling, to harden the surface wherever extruded chemical compound filaments heated into a semi-liquid state and extruded through a heated nozzle and deposited onto a build platform as layer bilayer [4,5].
- Inkjet printing was the technique wont to manufacture Spritam tablets (levetiracetam) for oral use, the primary 3D written drug approved by the Food and Drug Administration (FDA) in 2016 by Aprecia prescribed drugs
- 3D printing is most advanced technique within the fields such as automobiles, aerospace, biomedical, tissue engineering and currently within the pharmaceutical trade (initial phase).
- FDA motivates the event of advanced producing technologies like 3D-printing and by means that risk base approach.
- The plan of 3DP has evolved from early 70′ of the 20 the century when state capital A. L. Ciraud delineated the strategy of application of fine material and consequent hardening of every layer through the action of high energy beam.
- In this case soluble materials like plastics or metals is on paper used for object preparation. In early 80′ during a patent entitles: "A molding method for forming a three- dimensional article in layers", Ross Housholder delineated a concept of sand binding by totally different materials and Carl Deckard developed a technique of hardening of fine bed by shaft of light referred to as selective optical device sintering(SLS).
- The 1st commercially on the market technology created by Chuck Hull was stereolithography (SLA). This methodology was supported photo polymerization of liquid rosin by ultraviolet light.
- At the tip of 80's Scott Crump filed a patent for coalesced deposition modelling (FDM) – a way that used thermoplastic material for object preparation.
- In the 90's Emanuel Sachs - Massachusetts Institute of Technology soul with co-workers proprietary "Three-dimensional printing techniques" supported connation the chosen regions of powder by binding material [6].

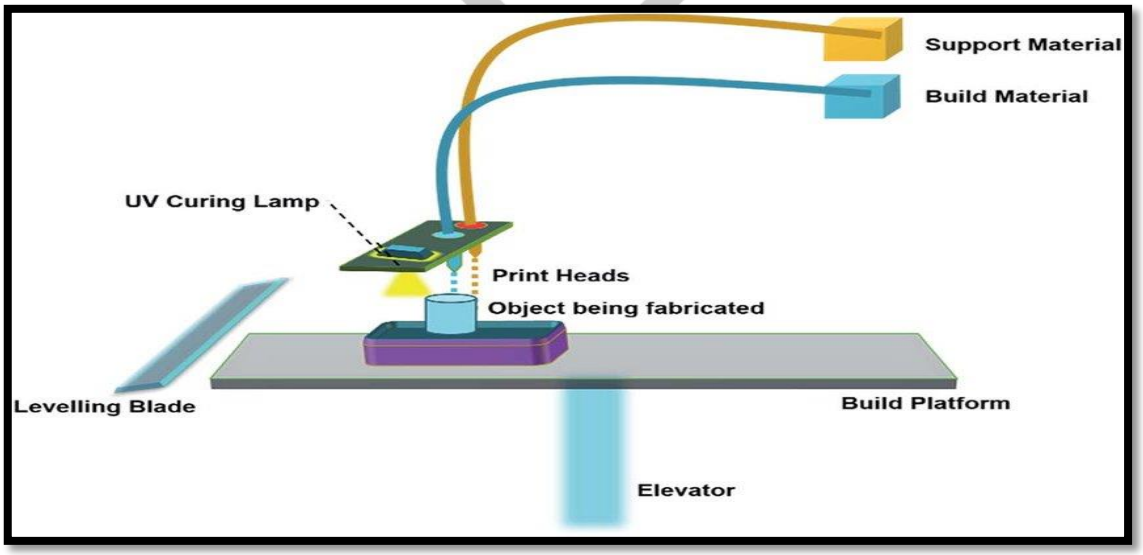


II. WORK ON 3D PRINTING TECHNOLOGY

It starts with creating a virtual style of the item to be created. This virtual style is formed in a very CAD (Computer power-assisted Design) file employing a 3D modeling program or with the utilization of a 3D scanner. 3D styles are generally born-again to the STL file format, that describes the external surface of a 3D model. 3Dprinting programs —slice these surfaces into distinct printable layers and transfers layer by-layer directions digitally to the printer. When printing, product could need drying, sintering, sprucing or different post-processing steps [7]. To be additional precise: since 2010, the yankee Society for Testing and Materials(ASTM) cluster cluster F42 – Additive Manufacturing, developed a group of standards that classify the Additive producing processes into seven classes per customary nomenclature for Additive producing Technologies. These are as follows:

1. Material Jetting

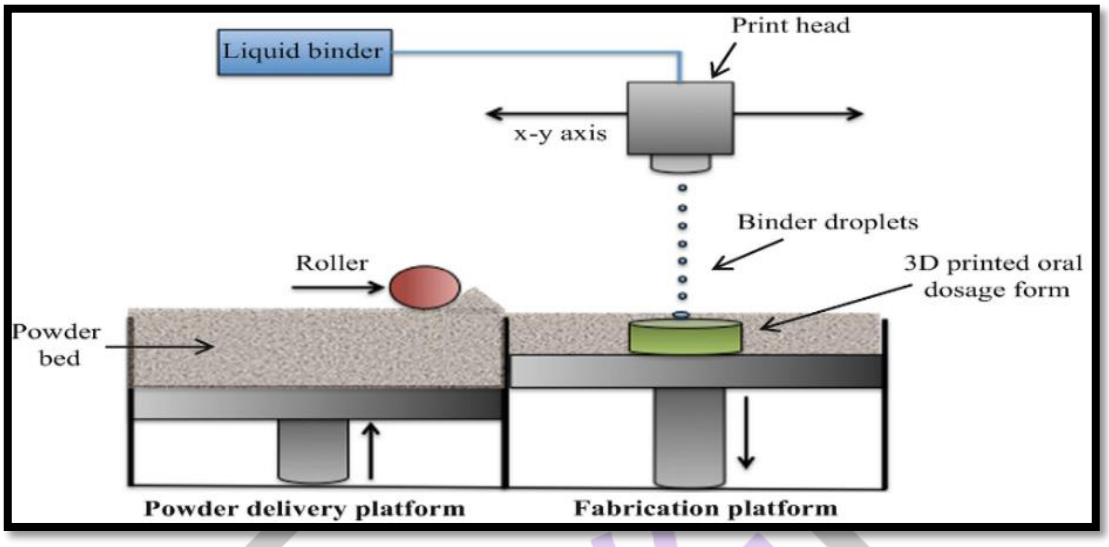
It differs well from binder spouting, and may be difficult to implement. Advantage of fabric spouting over binder spouting and different strategies is spouting are smaller than the drop diameter. usually jetted materials embrace melted polymers and waxes, UV-curable resins, solutions, suspensions, and sophisticated multi part fluids [8].



"Figure. 1 Material Jetting"

2. Binder Jetting

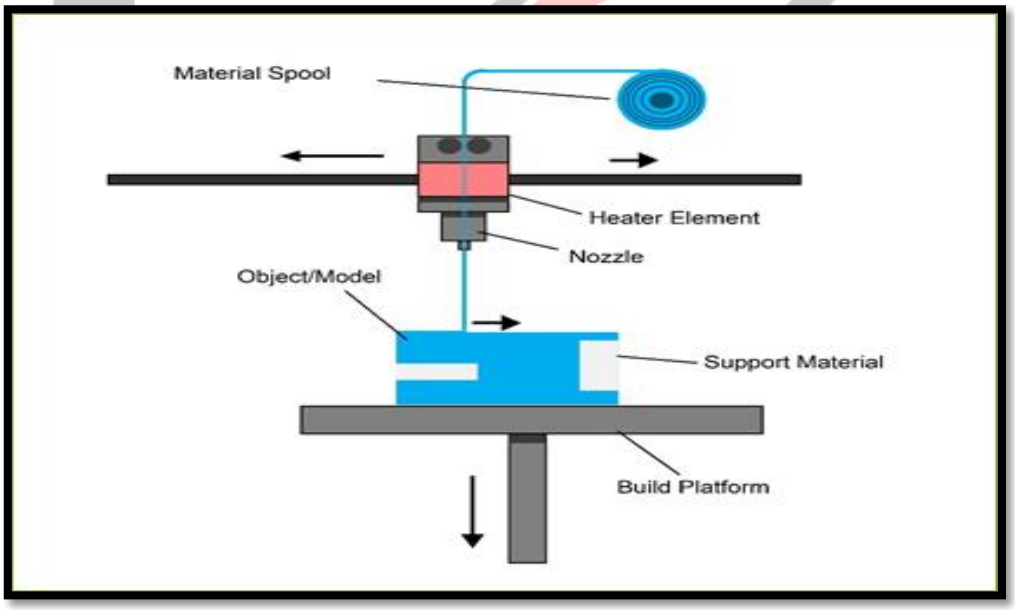
The first 3D printing technology used for pharmaceutical production is inkjet deposition on powder beds. Inkjet printers spray formulations of medicine or binders in tiny droplets at precise speeds, motions, and sizes onto a powder bed. The liquid the active ingredient (API) with extra excipients or else arthropod genus may be jetted onto powder beds as solutions or Nano particulate suspensions [9].



"Figure. 2 Binder Jetting"

3. Material Extrusion

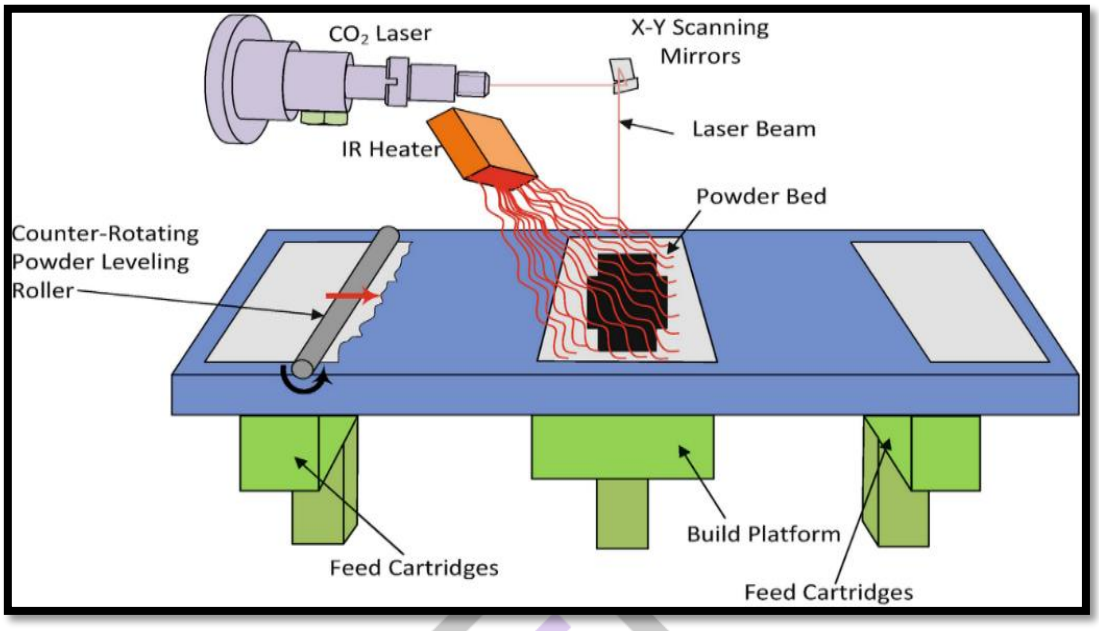
The material is extruded from robotically-actuated nozzles. in contrast to binder spouting, which needs a powder bed, extrusion strategies will print on any substrate. Common form of extrusion printing is amalgamating filament fabrication (FFF), conjointly celebrated by the proprietary name: amalgamate deposition [10]. Thermoplastic polymers like polylactic acid (PLA), polyvinyl alcohol (PVA), and cyanide hydrocarbon vinylbenzene (ABS) are used with the FDM method.



"Figure. 3 Material Extrusion"

4. Powder Bed Fusion

It involves sintering (partial surface melting and congealing) or binding of high- melting-point particles with a low-melting-point binder [11]. It's an additional speedy, complex, various to extrusion for warmth process able materials like poly (lactic acid) [12].



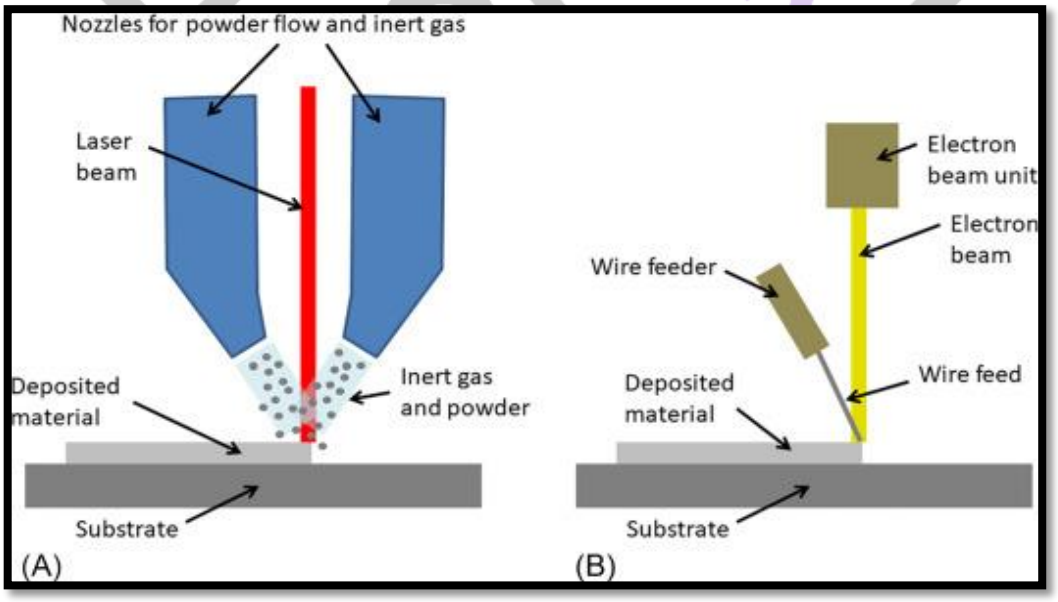
"Figure. 4 Powder Bed Fusion"

5. Photopolymerisation

Photopolymerisation also referred to as stereolithography [13]. involves exposing liquid resins to ultraviolet or different high-energy source of illumination to induce chemical action reactions. In 1689 technique uses photopolymerizable material. Associate in Nursing example drug delivery application is 3D printing of photopolymerizable hydrogels.

6. Directed Energy Deposition

Directed Energy Deposition may be a method wherever raw materials are fusible by a targeted energy supply (ex: optical maser or negatron beam) as they're being deposited the tactic permits the utilization of powders or different raw materials that can't be extruded [13].



"Figure. 5 Directed Energy Deposition"

7. Sheet Lamination

Sheet Lamination is machine-driven laser-cutting and sheet-by-sheet assembly of product. This method is fast and cheap however conjointly low-resolution and additional wasteful than most printing strategies [13]. There are various types of producing practices in tricate in 3D printing, that are grounded on digitally organized depositing of materials (layer-by-layer) to form morpheme geometries.

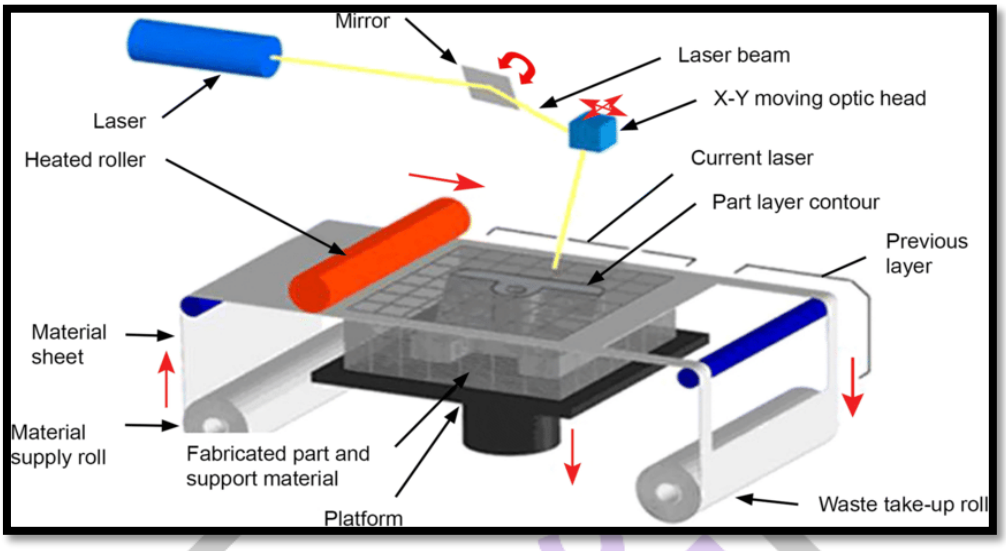
Thermal dot matrix printer Printing:

In thermal inkjet printing, the binary compound ink fluid is reworked to vapors state through heat, expands to push the ink drop out

of a nozzle [14]. it's utilized in the preparation of drug- loaded perishable microspheres, drug-loaded liposomes, patterning microelectrode arrays coating, loading drug eluting stents. [15,16]. It is additionally associate degree effectual and applied methodology of generating films of biologics while not interacting protein activity [17].

Inkjet Printing:

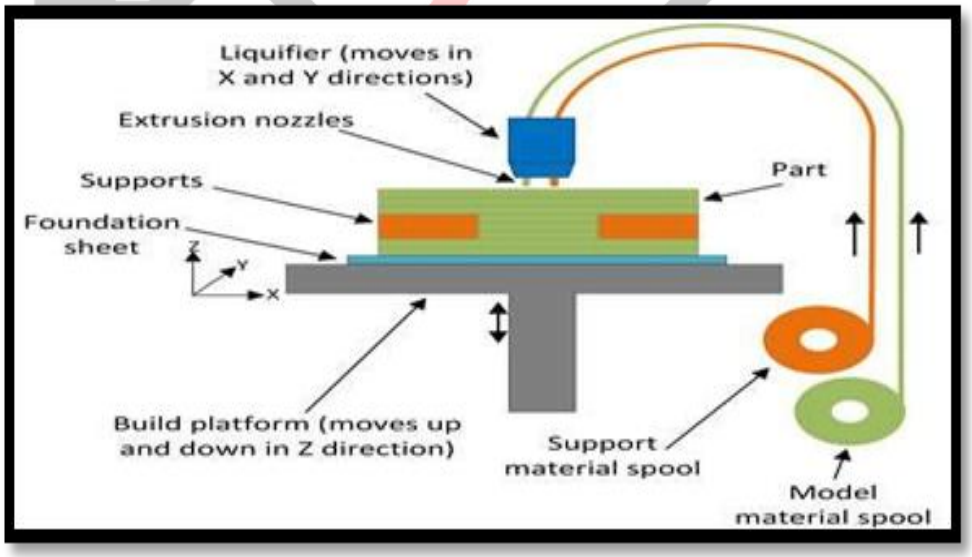
Inkjet printing called 'mask-less' or 'tool-less' approach for its desired structure formation primarily depends upon the inkjet nozzle movement or substrate movement for associate degree correct and reproducible formation. • In this system, the Ink is deposited onto a substrate either within the sort of Continuous Inkjet printing / Drop on demand printing. thus it provides a capability of high-resolution printing. It incorporates a low value, rate of process in printing and generation of low level of wastes. It gives CAD information in a 'direct write' manner and process material over large areas with minimal contamination [18,19].



"Figure. 6 Sheet Lamination"

10. FUSED DEPOSITION MODELING

Fused deposition modelling (FDM) is commonly used methodin 3D printing, the materials are softer or melt by heat to create objects during printing [20]. Fused deposition modeling 3D printing helps in manufacturing delayed release print lets without an outer enteric coating and also provides personalized medicines doses. This 3D Printing indicates some limitations for system like lack of suitable polymers [21] slow and often incomplete drug release, because of the drug remain trapped in the polymers, miscibility of drug and additives with the polymers used was not valued.

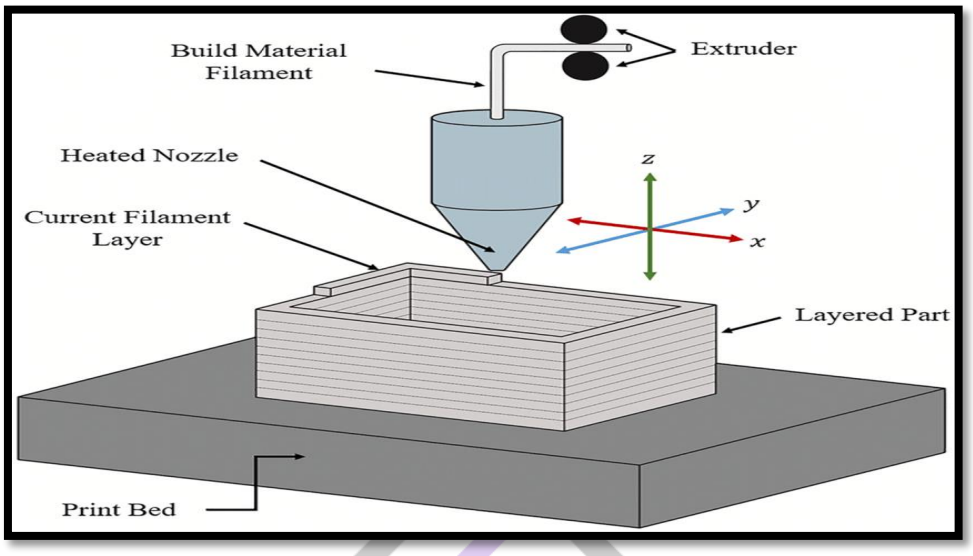


"Figure. 7 Fused deposition modeling"

11. EXTRUSION 3D PRINTING

In this method the material is extruded from the auto mated nozzle onto the substrate without any higher support material. It is only

utilized to fabricate tablet containing Guaifenes in act as expectorating. The components that can be extruded are molten polymers, suspensions, semisolids, paste [22,23].



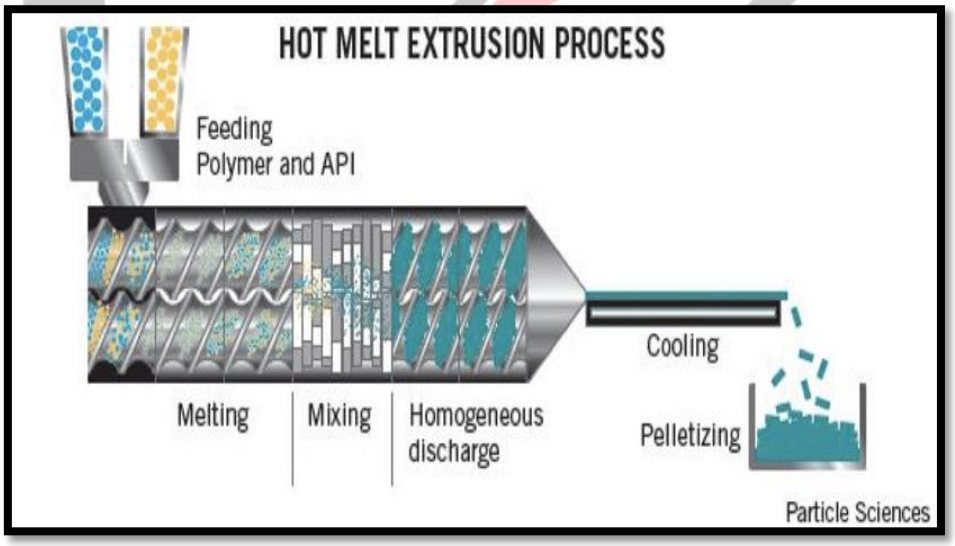
"Figure. 8 Extrusion 3D Printing"

12. ZIP DOSE

Zip dose is the world's initial and only FDA-approved, commercial-scale 3DP in current therapeutic areas for pharmaceutical manufacturing areas. It has a distinctive digitally coded layering and zero compression practices, used for tablet formulation with large dosage and prompt disintegration. Hence, it helps in overwhelming a difficulty in swallowing [24] Spritam-R (Anti-epilepsy drug) is an oral dispersible tablet, marketed by Aprecia Pharmaceuticals based on powder bed fusion by layer-by- layer production system. In which it consists of the active ingredient, excipients and a binder liquid to produce a matrix tablet [25].

13. HOT MELT EXTRUSION (HME)

Hot melt extrusion (HME) is the method of melting polymer and drug at elevated temperature and the pressure is employed in the instrument sequentially for blending [26]. It is a continuous manufacturing technique that involves feeding, heating, mixing and shaping [27]. In recent years, it has proved that Hot melt extrusion capable to optimize the solubility and bioavailability of moderately soluble drugs [28].



"Figure. 9 Hot melt extrusion (HME)"

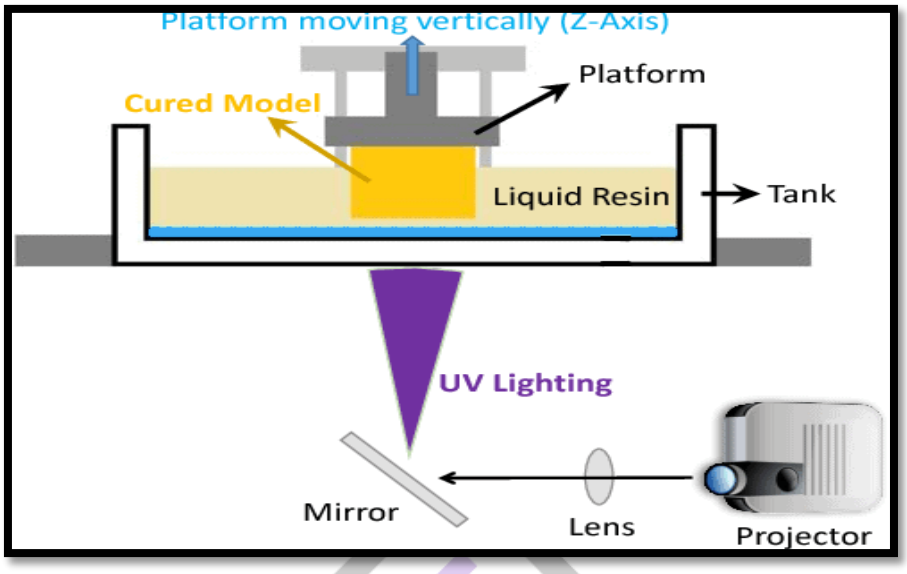
III. 3D PRINTER

The 3D printer was an exclusive tool is used to create optimized medications with tailored release profiles and for patients 'comfort.

1. **Stereolithography**

   Stereo lithography is the method of computer regulated laser beam is used to make liquid polymer/resin as solid, by this means creating a 3Dstructure [29] Stereolithography has several advantages over former types of other 3DP, predominantly

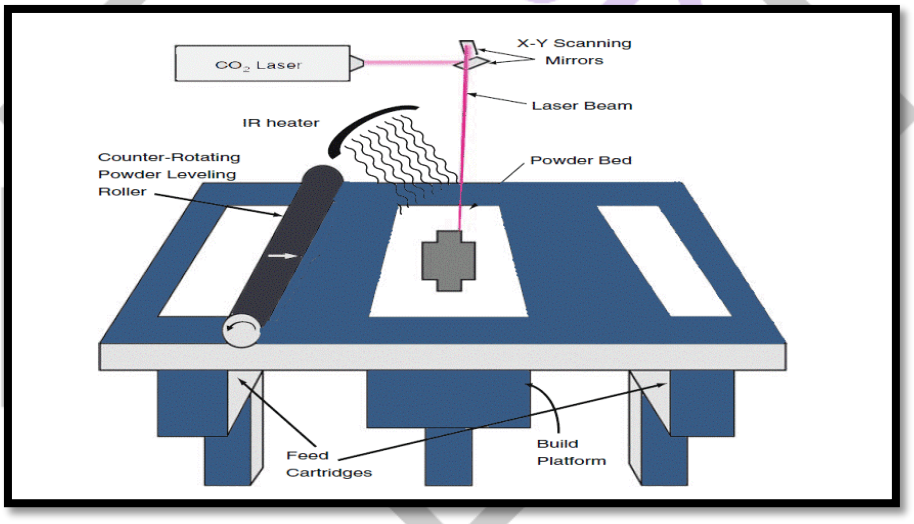
it's astonishing resolution and dodging of thermal practices can be harmful for specific drug molecules [30].



"Figure. 10 Stereolithography"

2. **Selective laser sintering**

Selective laser sintering (SLS) act as a way in the powder bed to bind. The laser is designed to draw a specific pattern on the surface of the powdered bed during the printing process, thus creating a3D structure. For example, Paracetamol is an or dispersible tablet prepared by this manner. It is currently used for industrial manufacturing of plastic, metallic and ceramic objects [31].



"Figure. 11 Selective laser sintering"

3. **Laser-Based Writing System**

On grounded to the photo polymerization principle, the free radicals which can contribute to the numerous diseases are released then to the interactions in among the photo originator and Ultra Violet light.

4. **Continuous Layer Interface Production**

It is associate advancement within the technology in relation of speed of printing. But the strategy negotiates within the 3D structure manufacture through non-layer fashion. The speed is amplified by the gas introduction zone which assists rapid solidification.

5. **Powder based mostly 3D Printing**

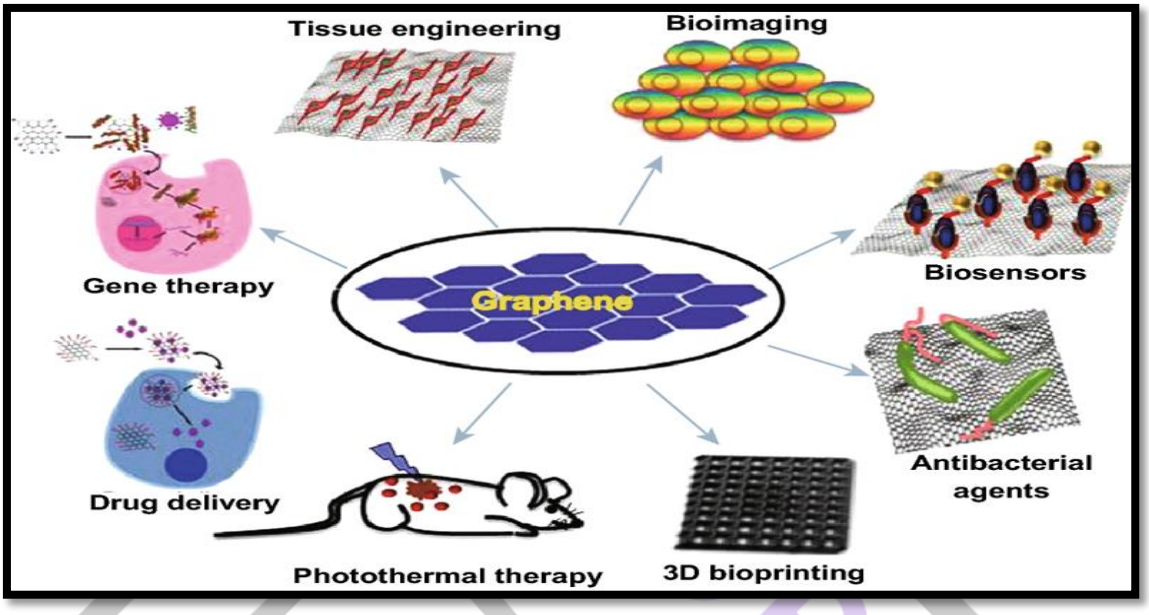
This methodology customs powder jetting/powder bed to feast skinny layers of powder and in a flash applying liquid binder drops with inkjet printers. The ink (binders and genus Apis or binder solutions) is besprent over a powder bed in two-dimensional (2D) approach to form the decisive product in a very layer by layer fashion. The adaption of this approach into pharmaceutical producing is comfy than alternative approaches as powder and binder solutions are broadly speaking utilized in the pharmaceutical trade. The own disadvantages of this approach are; to get rid of solvent residues extra drying is needed, throughout printing excess powder accumulates and contributes to wastage and because of the porous style of

the powder the drug delivery system's mechanical strength may poor activity [32].

IV. APPLICATIONS OF 3D PRINTING:

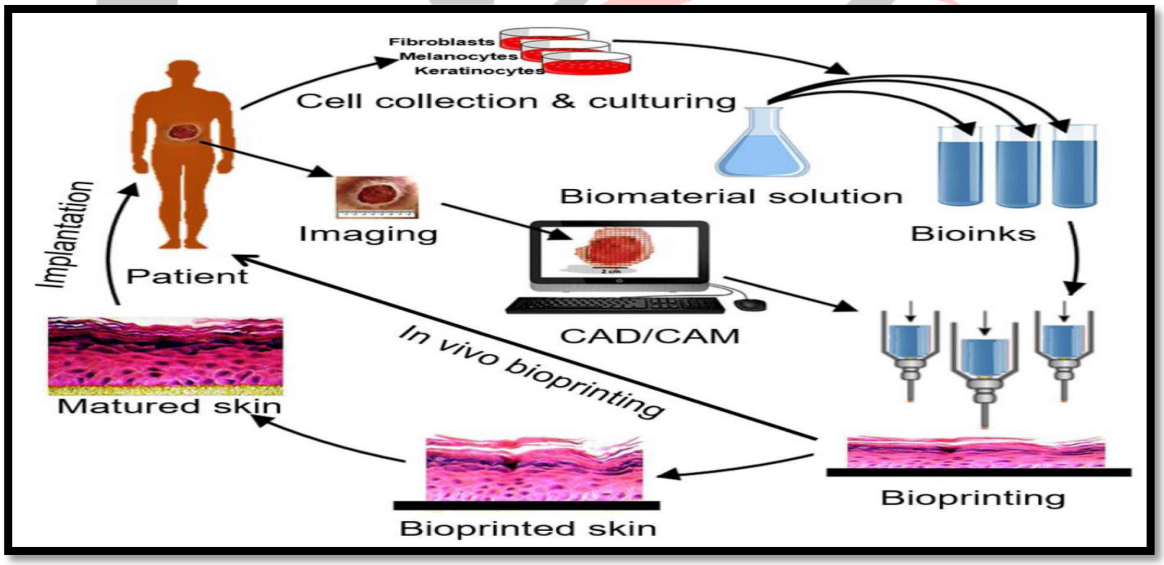
- Potential use in up method, modifying performance for industrial style, aerospace, medical engineering, tissue engineering, design, pharmaceuticals.
- It largely targets on the 2 potential sites to rise pharmaceutical development to undiscovered areas, producing subtle structures for the delivery and personalized medicine.
- In health care trade to form dental implants. On fabricating associate organized unharness multi- drug implant for bone infectious disease is keep in mind Helps in organ printing, biomaterials and cell- laden materials.

BIOMEDICAL APPLICATION



"Figure. 12 Biomedical Application"

3D BIOPRINTING IN MEDICINE



"Figure. 13 3D Bioprinting in Medicine"

V. 3D PRINTED MATRICES FOR IN VITRO TUMOR MODELING

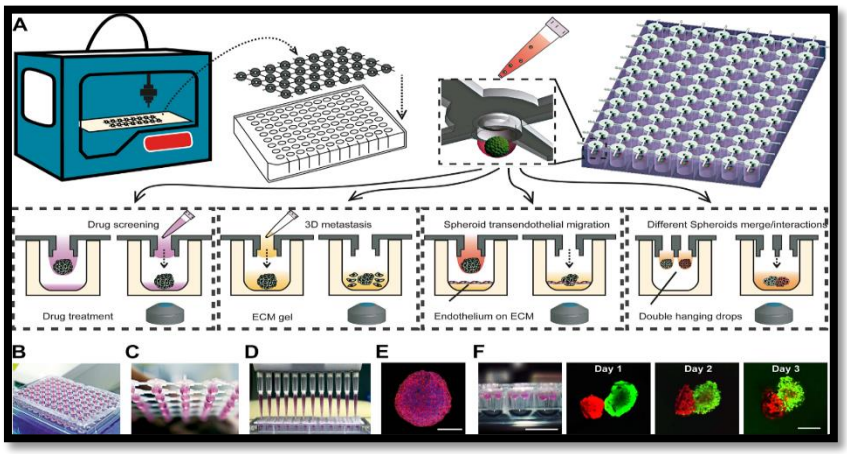
Various methods are discovered in Cancer model evaluation this are as follow

- Mono-culture models to investigate cancer cell proliferation and migration
- Co-culture models to study the interactions of tumor cells with auxiliary cell types
- Modeling cancer cell metastasis to bone tissue
- Tumor spheroid formation in 3D printed matrices

- Organotypic cancer models

1. Tumor spheroid formation in 3D printed matrices

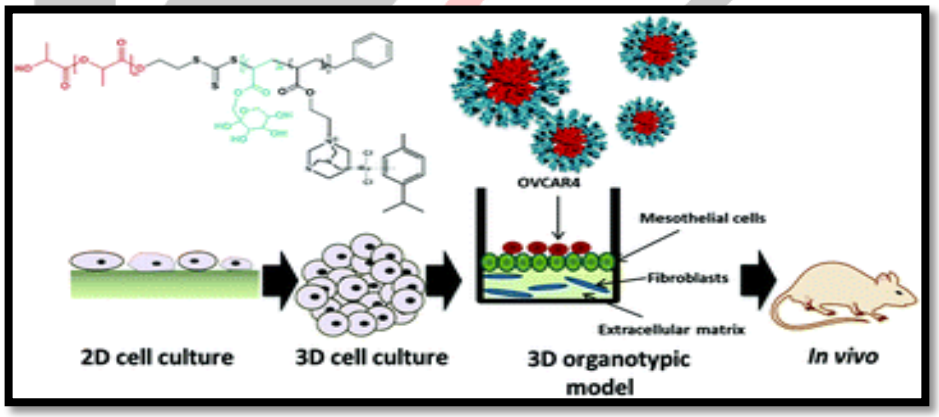
The cellular spheroid formation is one of the most accurate methods to recreate *in vivo* like cell culture-based assay for therapeutically orientated biomedical study. Many Conventional methods are developing limitation like variation in spheroids size , cell no , labor-intensive, high-shear force, and difficulties on massive production by considering all mentioned limitation some microfabrication based methods, such as microcell , microfluidics and micro fabricated hanging drop, have developed with much more attention due to formation of large amount of well controlled aggregate with uniform size less laborious, and amenable to high throughput screening[31].



"Figure. 14 Tumor spheroid formation in 3D printed matrices"

2. Organotypic cancer models [32]

3D-bioprinted tissue models has found large application in toxicology, drug discovery, regenerative medicine, cancer research and basic research. This technique major gives advantages such as the ability to design specific, consistent and reproducible tissue and/or cell models for HTS and precise spatiotemporal positioning of biomaterials to achieve layer-by-layer printing. This technology involves printing of cells with a biomaterial, ECM components and certain biochemical factors to mimic the native and diseased tissue. It works mainly on three different principles for extrusion from the printing head: a micro extrusion system, inkjet printing system and laser-assisted system. Micro extrusion-based printing is used for both biological and no biological application deposits of biocompatible printing material such as polymers, cells and hydrogels as a continuous bead based on the computer-aided design and computer-aided manufacturing (CAD-CAM) software.



"Figure. 15 Organotypic cancer models"

"Table no.1 3D bioprinted models of various cancers for drug screening and toxicity evaluation" [32]

Sr No	Organotypic cancer tissue model	Biomaterials	Cells
1	Head and neck cancer	Collagen matrix Patient-sourced	fibroblast and squamous carcinoma cells of hypopharynx (FaDu) were cocultured
2	Breast cancer	Rat tail collagen I	Dual cell having co-unit of MCF-7
3	Breast cancer and prostate cancer cells	Silk fibroin from Antherae mylitta MDA MB-231 breast cancer cells and LnCaP prostate cancer	Effect of growth factors and signaling peptides on matrices
4	Ovarian cancer	Biomaterial-free spheroid Cell	spheroids cultured in 384- microwell plate from single cells derived from patient biopsy
5	Hepatocellular carcinoma	(HCC) cells	Hydroxypropyl cellulose HCC-patient-derived xenograft (PDX)

CONCLUSION

3D printing technology represents a good potential in drug development, formulation, and administration because of its nice flexibility and effectiveness in innovation and creation of novel medical products. In addition, the quality of the technology as a tool for drug secernment is huge given its ability to manipulate high degrees of drug deposition pattern to assess different unharness profiles. The new technique permits for reformulating and remanufacturing a medical formulation to differentiate it from generics competition within the market, which may give supplementary patient edges and ultimately leads to diminished cost of product. In producing oral pharmaceutical dosage forms. The selected studies showed success in the use of the current development for manufacturing oral drug products. In most cases, poorly water-soluble drugs were included, which are the main challenges in the pharmaceutical industry. The studies indicated that using a suitable 3D printing method and well- formulated pharmaceutical ink for printing, higher solubility and bioavailability of poorly soluble drugs can be achieving.

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