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Integration of Nanotechnology and 3D Printing for Next-Generation Drug Delivery Systems

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Abstract: Incorporating nanotechnology and three-dimensional (3D) printing have recently emerged as a strategy for creating next-generation drug delivery systems that offer a better level of control of drug loading, release, spatial distribution, and dosage-form design. Nanotechnology offers the advantage of nanoscale platforms such as nanoparticles, liposomes, nanogels, nanocrystals and nanocomposites that can assist in improving the protection and controlled delivery of drugs and 3D printing provides the advantage of customised structures that have controlled geometry and internal architecture. The combination of their two components allows for multiscale control, linking nanoscale properties of drug carrier functions with digitally designed 3D structures. This review covers the basics of nanotechnology and pharmaceutical 3D printing, integration strategies, fabrication methods, drug loading/release mechanisms, and drug delivery applications such as oral, localized, implantable, transdermal, tissue related, and personalized drug delivery. Recent developments, major advantages and challenges are also discussed. There are several challenges, such as material compatibility, dispersion and printability of nanoparticles, drug stability, reproducibility, scale-up, biological safety, quality control, and regulatory demands. Key to successful translation will be optimized materials, manufacturing processes, standardized characterization, and quality assurance in order to overcome these challenges. Overall, a flexible platform for the controlled, personalized and multifunctional drug delivery system is provided by nano-enabled 3D printing.

Keywords: *Nanotechnology; 3D Printing; Drug Delivery Systems; Nanocarriers; Personalized Drug Delivery; Controlled Drug Release; Pharmaceutical 3D Printing; Nano-Enabled Drug Delivery; Additive Manufacturing; Nanocomposites.*

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I. INTRODUCTION

The clinical efficacy of a drug is determined not only by the pharmacological activity but also by the delivery of the drug to the right site, concentration and time. Conventional dosage forms like tablets, capsules, injections and topicals are in wide use due to their well-known manufacturing and clinical use. They can, however, have poor drug solubility, low bioavailability, early drug degradation, not controlling the release of the drug, frequent dosing, and inadequate site-specific delivery [1]. This has given rise to a growing interest in the development of more sophisticated delivery systems that could enhance drug stability, prolong the drug's duration of activity, target drug delivery, and enable personalised therapy.

Recently nanotechnology has been identified as one of the key solutions to overcome a number of these drawbacks. Nanoparticles, liposomes, lipid nanoparticles, nanogels, nanocrystals, and other nanoscale systems can enhance the dispersion of the drug, protect therapeutic agents, and control the release of these drugs [2]. Nano based systems may however have problems with aggregation, stability, drug loading capacity, reproducibility and control of the final geometry and spatial arrangement of the dosage form [3].

Three dimensional (3D) printing offers an extra degree of control as it enables the creation of pharmaceutical products layer-wise from a digital design. It could be utilized to alter the shape, dimension, internal architecture, porosity and spatial distribution of drugs. Fused Deposition Modelling, semi-solid extrusion, stereolithography, selective laser sintering and inkjet printing are some techniques that have been explored for pharmaceutical applications [4]. One of the great benefits of 3D printing is the ability to customize dosage forms to achieve specific drug content, geometry and release, based on the therapeutic needs.

Nanotechnology is being integrated with 3D printing and is taking advantage of these complementary benefits. Nanotechnology can control the drug encapsulation, protection, transport and release at the nanoscale and 3D printing can control the larger geometry, porosity and spatial organization of the delivery system [5]. Therefore, 3D-printed systems based on this technology will be able to

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deliver multiscale control of drug delivery, offering a pathway to controlled, localized, personalized, and multifunctional drug delivery systems. This holistic approach is a promising route for the development of new-generation pharmaceutical delivery systems.

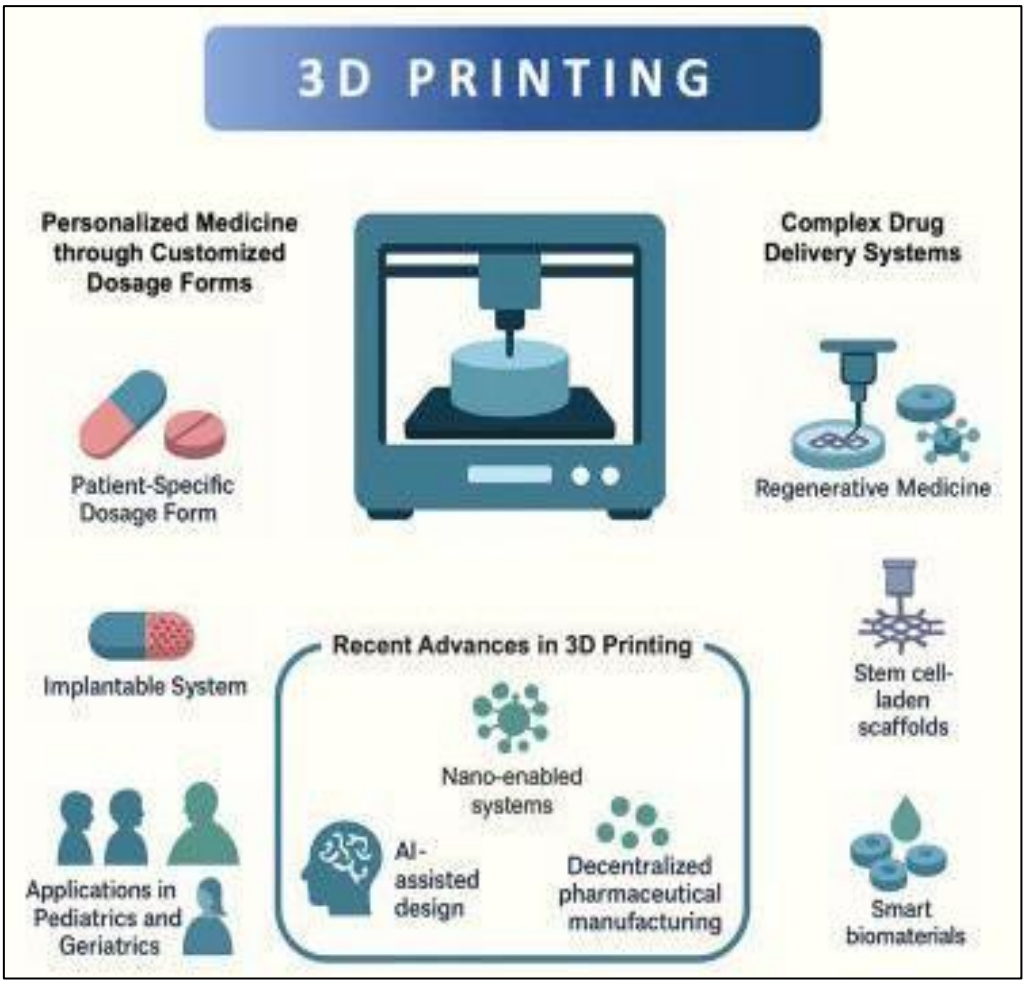

Fig 1 Evolution of Drug Delivery Systems from Conventional Approaches to Integrated Nano 3D-Printed Drug Delivery Systems.

Incorporation of nanotechnology and 3D printing also presents formulation and manufacturing challenges. Nanoparticles can affect the viscosity, flow behaviour, mechanical properties and printability of formulations and aggregation can lead to non-uniform distribution and release of drugs [6]. The stability of drugs and nanocarriers can also be influenced by printing conditions (e.g., heat or light). Thus, it is important to ensure that there is compatibility between the drug, nanomaterial, printable matrix and the printing process. For practical applications in pharmaceuticals, reproducibility, stability, scale-up, quality control, safety and regulatory requirements are also crucial.

The research interests have been up to date devoted to the nanocomposite matrices, to a system loaded with nanoparticles printed, to a personalized dosage form, and to a spatially controlled drug delivery. The design and optimization of these technologies can be further enhanced by emerging technologies including but not limited to artificial intelligence, smart materials, and cutting-edge printing technologies [7]. This review highlights the basics of nanotechnology, the basics of pharmaceutical 3D printing, the integration of the two, the fabrication process, the drug-release mechanisms, key applications, recent advances, benefits and challenges of the combination, regulatory issues and future prospects with a focus on the use of nanotechnology and 3D printing for controlled, targeted, personalized, and multifunctional drug delivery.

- *Fundamentals of Nanotechnology in Drug Delivery*

Nanotechnology is a significant way to create new drug delivery systems due to the physicochemical and biological properties that are not easy to obtain with traditional formulations. Nanocarriers can carry, protect and deliver therapeutic agents and their properties can be manipulated to match the drug and its application [8].

One of the key challenges in nanotechnology is to resolve issues like poor solubility, instability and low absorption. Nanomaterials with a high surface area can have a significant effect on drug dissolution, dispersion and release and can be used to facilitate controlled and targeted drug delivery [9].

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There are a number of nanomaterials that have been studied for pharmaceutical applications. Different compositions and degradation properties of the polymeric particles can be designed for controlled drug release. Incorporation of different therapeutic agents using lipid-based nanocarriers, which can provide protection and controlled delivery of the therapeutic agents, is possible. Nanogels are cross-linked polymeric networks which may swell in response to environmental conditions, and nanocrystals may be used to enhance the dissolution of poorly water-soluble drugs [10]. Safety and biocompatibility of inorganic nanomaterials such as silica-based nanoparticles, which are also under investigation for loading drugs and functional applications, should be carefully evaluated.

Drug release can be controlled by diffusion, dissolution, swelling and degradation using nanotechnology. Some of the other factors which can affect their performance and biological behaviour include particle size, surface properties, composition, aggregation, stability and drug loading. Thus, such properties need to be optimized carefully [11].

These factors are especially relevant when using nanotechnology with 3D printing. Nanomaterials should be stable and evenly dispersed in the printable formulation without negatively influencing the viscosity, flow behaviour or any other printing attributes. Therefore, knowledge of the interaction between nanomaterials and printable matrices is crucial for the successful development of a reliable nano-enabled 3D-printed drug delivery system [12].

Table 1 Major Nanomaterials Used in Drug Delivery

Nanomaterial	Main characteristics	Role in drug delivery	Relevance to 3D-printed systems
Polymeric nanoparticles	Biodegradable and structurally tunable	Drug encapsulation and controlled release	Can be incorporated into polymeric matrices
Liposomes	Lipid-based vesicular structure	Drug protection and delivery	Can be incorporated into suitable hydrophilic matrices
Lipid nanoparticles	Lipid-based nanoscale carriers	Delivery and protection of therapeutic agents	Potential incorporation into printable formulations
Nanogels	Cross-linked and water-responsive networks	Controlled or stimuli-responsive release	Suitable for hydrogel-based printed systems
Nanocrystals	Nanosized drug particles	Improved dissolution of poorly soluble drugs	Can be incorporated into appropriate printable matrices
Silica-based nanoparticles	High surface area and modifiable surface	Drug loading and controlled delivery	Potential use in nanocomposite printing
Nanocellulose	Biocompatible nanoscale structural material	Matrix modification and functional delivery	Useful in printable hydrogel and polymer systems
Nanocomposites	Combination of nanoscale and bulk materials	Multifunctional drug-delivery properties	Directly relevant to nano-enabled 3D printing

Thus, Nanotechnology can supply the functional part of the advanced drug delivery system at the nanoscopic level. Its capability of modulating drug encapsulation, protection, transport and release gives an important base for its integration with 3D printing. The benefits of these systems can only be realised, however, if suitable nanomaterials are used in conjunction with the printing technology, which enables the system to retain the properties of the nanomaterials and allow for precise control of the structure of the final dosage form [13].

- *Fundamentals of 3D Printing in Pharmaceutical Formulations*

The three dimensional (3D) printing is an additive manufacturing process where the material is deposited, solidified, or fused layer-by-layer in accordance with a digitally designed model. While the typical pharmaceutical industry approach to drug manufacturing is based on geometry and fixed manufacturing processes, 3D printing offers flexibility in the design and control of the shape, size, internal structure, formulation and distribution of a dosage form [14]. The technology can be easily customized, and the digitality of the technology also enables changes in the dose, geometry, porosity, and internal structure as required by a particular therapeutic need. Thus, the 3D printing technology has received significant attention in the area of drug delivery systems with special features and individualization [15].

It is a simple process of taking a digital 3-D design and creating a real-life pharmaceutical product. The thickness of layers, the speed of printing, the infill pattern, the porosity and the distribution of the material can be varied to affect the properties of the dosage form. It can be very helpful in personalized medicine, which uses customized doses, release rates, or drug mixtures in patients [16]. The potential of pharmaceutical 3D printing is further enhanced by the capability to create such complex structures, which are hard to develop in a conventional manner.

A number of printing techniques have been explored in order to use them in a pharmaceutical setting. Fused deposition modelling (FDM) is an extrusion-based process where a thermoplastic filament is melted and extruded, layer by layer, through a nozzle. Drugs could be embedded in the filament before it is printed, resulting in the drug being dispersed across the entire structure [17]. The processing temperature for FDM is somewhat high, which can constrain its applications for thermolabile drugs, biological molecules, and sensitive nanomaterials, while providing good control of

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geometry and internal architecture. Semi-solid extrusion (SSE) process is utilizing a formulation of semi-solid such as hydrogel, paste, polymer material. Usually uses gentler conditions and is able to be used for temperature-sensitive drugs. However, print quality is greatly affected by the viscosity, the rheological behavior, the extrusion pressure and the shape holding capability of the deposited layers [18].

Inkjet printing is a method that introduces small drops of liquid formulations to a specific site, thus offering very accurate spatial control over the drug deposition. It is an advantage for accurate distribution of small quantities of drug, but care must be taken with the viscosity, surface properties and with nozzle clogging. Stereolithography (SLA) is an optical method that uses a photosensitive material to selectively polymerize it to create a high-resolution structure. It can create complex shapes, but care needs to be taken with drug compatibility, conditions of photopolymerization, and remaining photoreactive materials. Selective Laser Sintering (SLS) is a technology that utilises a laser to melt powdered materials and can be used to create complex and porous structures free of conventional support materials. But, during the processing, there is a possibility of adverse effect on the stability of the drug due to thermal exposure [19]. The process of binder jetting selectively deposits a liquid binder onto a powder bed and can generate porous dosage forms, but the key parameters of the powder, the binder distribution and mechanical strength need to be carefully controlled [20].

The appropriateness of the selected printing technique is thus dependent on the properties of the drug, the nanomaterial, the formulation that can be printed, the desired architecture, and the desired release profile [21]. If the nanocarriers are used for drug delivery, this choice is especially significant due to the possibility of affecting the stability and the functionality of nanocarriers by heat, light, mechanical forces or other processing conditions. In conclusion, the optimization of formulation composition, printing parameters, digital design, and post-processing conditions are essential to achieve reproducible dosage forms with the desired structural and drug-release characteristics, which defines successful pharmaceutical 3D Printing [22].

The 3D-printed system's pharmaceutical performance is not only related to the 3D printing technique used, but also to the compatibility of the drug with the excipients and printing material. The final structure and drug-release behaviour can depend on several parameters like printing temperature, layer thickness, deposition rate, infill pattern, nozzle conditions and formulation rheology. Thus, it is essential to optimize formulation and printing parameters to achieve reproducible products [23].

For systems that are nano-enabled, extra factors must be taken into account. The printing process should ensure the uniform dispersion of nanoparticles, and ensure that there is no aggregation or degradation. Processing by heat can impact sensitive nanocarriers, and viscosity changes in the formulation due to nanoparticles can impact extrusion and deposition. As a result, the adoption of a suitable 3D-printing method is a key factor on the road to a successful integration of nanotechnology for pharmaceutical production [24].

Table 2 Comparison of Major 3D-Printing Technologies Used in Pharmaceutical Drug Delivery

Technology	Printing principle	Typical materials/formulations	Major advantage	Key limitation
FDM	Thermal extrusion of filament	Thermoplastic polymers	Complex geometry and controlled architecture	High temperature
SSE	Extrusion of semi-solid material	Hydrogels, pastes, polymeric formulations	Mild processing conditions	Strong dependence on rheology
Inkjet printing	Controlled droplet deposition	Solutions and low-viscosity formulations	High spatial precision	Nozzle clogging and viscosity limitations
SLA	Light-induced polymerization	Photosensitive polymers/resins	High resolution and complex structures	Photochemical compatibility concerns
SLS	Laser-induced powder fusion/sintering	Polymeric or pharmaceutical powders	Complex and support-free structures	Thermal exposure
Binder jetting	Selective binder deposition onto powder	Pharmaceutical powders and binders	Porous structures and rapid disintegration potential	Powder and mechanical-strength control

3D printing offers structural and manufacturing flexibility in addit ion to the nanoscale functionality offered by nanotechnology as a whole. The architecture and spatial organization of the final dosage form can be controlled with 3D printing, but the behaviour of the drug can be controlled at the nanoscale, using nanotechnology. This complementary relationship will serve as the basis for the interconnection of both technologies in the future for next-generation drug delivery systems [25].

- *Integration of Nanotechnology and 3D Printing for Drug Delivery*

The combination of nanotechnology and 3D printing could be a great way to create new drug delivery systems that work at the nanolevel and on a larger scale. Drug loading, protection, targeting and controlled release can be enhanced by nanotechnology and the shape, geometry, porosity and spatial distribution of the dosage form can be controlled by 3D printing [26].

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The direct incorporation of drug loaded nanocarriers in printable formulations like polymers, hydrogels and pastes is one of the approaches. In this case, the nanocarrier is used to manipulate the behaviour of the drug and the printed matrix provides structural support and an extra barrier to drug diffusion. Here, a nano-composite 3D-printed system has been proposed where nanomaterials are embedded in polymeric or biomaterial matrices to impart functional and drug delivery properties [27].

It is also possible to include nanomaterials in particular parts of a dosage form by 3D printing. Different drug concentrations or nanocarriers can then be delivered in a spatial manner to enable sequential drug delivery or combination drug delivery. This enables multiscale control of drug release of particle size and composition of nanoscale properties, and geometry, porosity and layer arrangement of macroscale properties [28].

The technology is also capable of personalized and localized drug delivery. The dose, shape, dimensions, and internal structure of the printed formulation can be tailored to meet therapeutic needs and nanocarriers offer further control over drug release and biological interactions.

But for a successful integration, there are factors of material compatibility as well as printability to be considered. Changes in viscosity and flow behaviour due to nanoparticles, and non-uniform drug distribution due to aggregation can occur. Sensitive drugs or nanocarriers can also be compromised with heat, light or mechanical stress during printing. Thus, the drug, nanomaterial, nanogrid or printable matrix and printing process must be chosen simultaneously. Reproducibility, stability and scale-up are also significant hurdles in the development of a reliable nano-enabled 3D-printed drug delivery system [29].

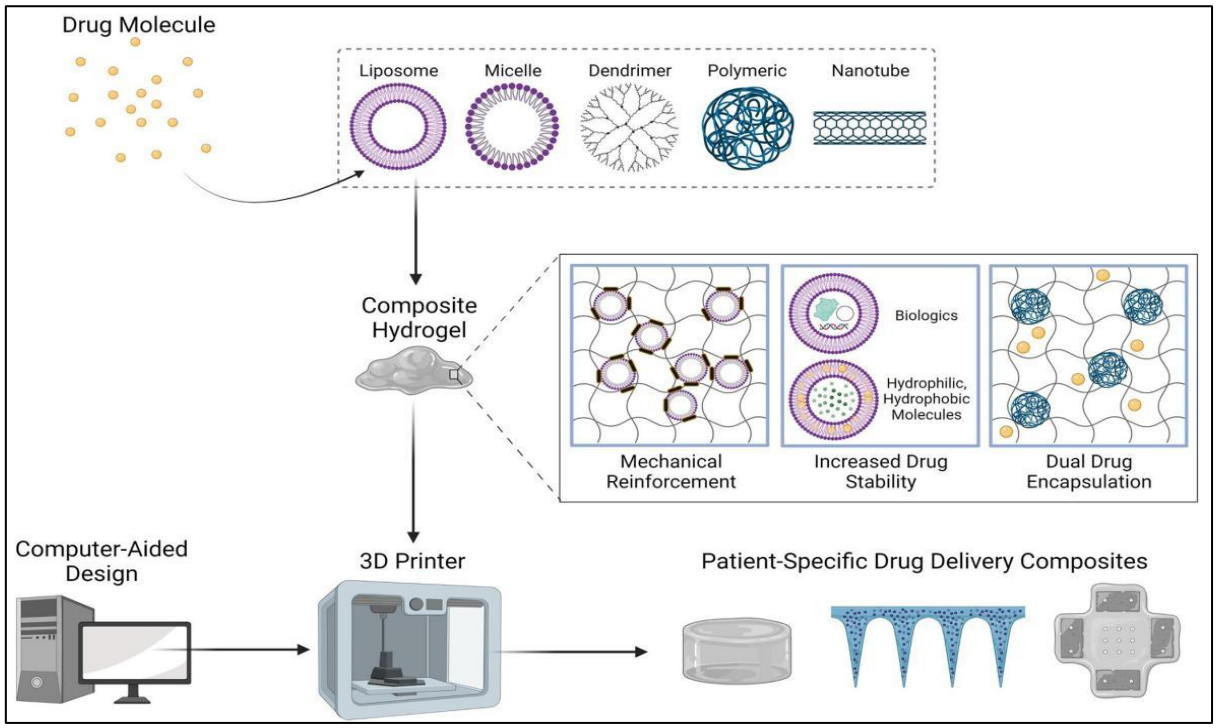

Fig 2 Integration of Nanotechnology and 3D Printing for Advanced Drug Delivery

An essential part of the integrated approach is that it does not need to be thought of as the mere inclusion of nanoparticles in a 3D printed formulation. The goal is to design a system where the characteristics of the nanomaterial and the structure of the printed structure match. The functional control of the drug can be achieved by nanotechnology and the structural and spatial control of the delivery platform can be achieved by 3D printing. Drug delivery mechanisms can then be chosen depending on the therapeutic need and not just a single mechanism [30].

In conclusion, the combination of nanotechnology and 3D printing offers a promising platform for the creation of next-generation drug delivery systems. The unique pairing lends opportunities for controlled release, targeted and localized delivery, personalized dosage forms, and complex multi-component systems [31]. However, the optimization of selection of nanomaterials, the loading of the drug onto the nanomaterials, formulation for printing, printing conditions and product characteristics are key factors in ensuring successful development.

- *Fabrication Strategies for Nano-Enabled 3D Drug Delivery Systems*

Manufacturing of nano-enabled 3D drug delivery systems requires a careful selection of drug, nanomaterial, printable matrix, and printing technique. It must ensure the stability of the nanomaterial and achieve reproducible production of the structure that has the desired drug content and drug release properties [32].

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The first step is to select the drug and nanomaterial, depending on the solubility, stability, required release profile and intended application. Examples of nanocarriers that can be used are polymeric nanoparticles, lipid-based carriers, nanogels, or nanocrystals. The drug is then incorporated into the system by various techniques, like encapsulation, entrapment or adsorption. The resulting nanocarrier should be stable, be capable of loading drugs and be compatible with the chosen printing process [33].

The drug loaded nanocarrier is then added to a printable formulation, e.g., polymer or hydrogel. The formulation should deliver the following: even distribution of nanoparticles and proper flow characteristics. In the case of extrusion-based printing, flowability must be high enough for smooth nozzle movement and structural recovery must be sufficient to ensure the shape of layers that are deposited [34]. The concentration of the nanoparticles thus has to be optimized to prevent significant changes in the viscosity and printability.

A digital 3D model is then created to establish the desirable shape, dimensions, internal structure, infill, porosity and drug distribution. Production parameters such as printing speed, layer thickness and processing conditions are precisely regulated to fabricate the structure using the selected printing technique. If they can influence the stability of the drug or nanocarriers in the system, they should be avoided during the processing and should be minimized when heating or light exposure is involved.

The strategic distribution of drugs and nanocarriers in various parts of the dosage form can also be accomplished by 3D printing. This can be used to achieve either localized, sequential or multi-drug release. Depending on the formulation and printing process, subsequent drying, curing, cooling or crosslinking processes might be necessary after printing.

Lastly, the printed system is tested for structural accuracy, drug content, stability of the nanomaterials, mechanical properties, and drug-release behaviour. The aggregation and non-uniform distribution of nanoparticles should be monitored carefully as this may impact on product consistency and release performance [35]. Therefore, the optimization of nanocarriers preparation, printable formulation, digital design, printing, post-processing and characterization is an intertwined process in order to obtain a successful fabrication.

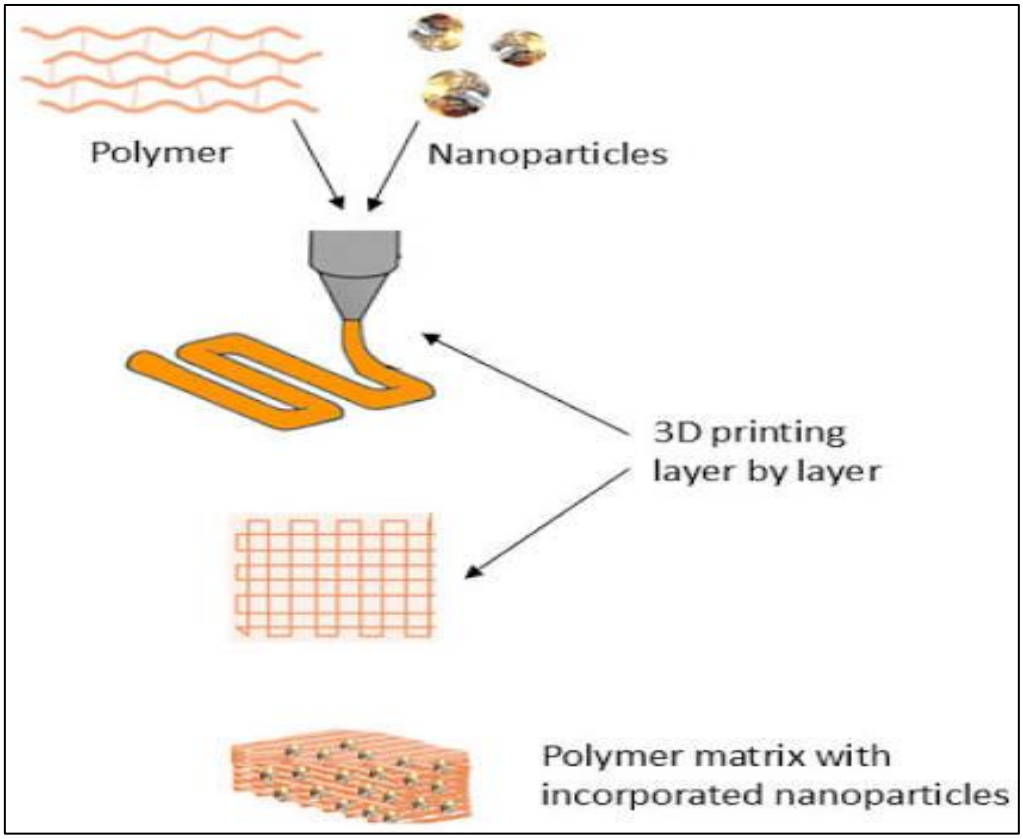

Fig 3 Fabrication Workflow of a Nano-Enabled 3D-Printed Drug Delivery System

The quality of an actual system that has been 3D-printed with nanotechnology is a function of the success of integration of all these stages. Optimization of the nanocarrier may not be enough as optimization of the printing process may affect the next stage(s). For instance, more nanoparticles can be encapsulated, but it can also make the prints less printable. Likewise, optimising the printing parameters for a more accurate structure may impact on the stability of the drug or nanocarriers [36]. Thus a systematical formulation and process-development approach is needed.

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In general, there is a need for a careful coordination between pharmaceutical formulation and the process of additive manufacturing for fabrication of nanotechnology-enabled 3D drug delivery systems. The nanoscale drug delivery is achieved by the nanomaterial, and the structural and spatial control is given by the printable matrix and 3D printing technology, respectively. The ultimate goal of a successful fabrication should be to generate a uniform drug delivery, stable nanomaterials, repeatable geometry and predictable drug delivery profile. Drug loading and release from these integrated systems [37].

- *Drug Loading and Release Mechanisms*

For the performance of nano-enabled 3D-printed drug delivery systems, drug loading and controlled release are critical. Incorporation of the drug can be controlled with nanotechnology and 3D printing imparts control in the architecture and spatial arrangement of the dosage form.

Drugs may be encapsulated, entrapped, adsorbed or incorporated in a matrix. Depending on the property of the drug and nanocarrier, encapsulation or entrapment can be used to protect the drug and/or to create other options. The drug loaded nanocarriers and the printed matrix have an effect on the overall release profile [38].

One of the common mechanisms is diffusion-controlled release. The drug transport relies on the characteristics of the nanocarrier, the porosity of the matrix and the architecture of the printing. Structures with high porosity and internal waterways can help water to flow through them, while structures that are dense can hinder water flow. Swelling controlled release is a release of a drug that happens when the hydrophilic polymers or hydrogels absorb water and the drug moves through the swollen matrix. Degradation-controlled release involves the progressive degradation of the biodegradable nanocarriers or printed matrices and can be used to achieve sustained release.

Nanotechnology and 3D printing can also give multiple-release and stimuli-responsive release. The printed structure can be used to regulate the movement and distribution of the drug, and the nanocarriers or matrices can be pH sensitive, temperature sensitive, or even enzyme sensitive. The location of the drug within the printed structure is also significant: surface located drug may release faster while the deep located drug may release longer [39].

The final release profile will depend on the interplay of the drug with nanocarrier, printable matrix and printed architecture. Hence, drug-release studies should thus consider the quantity and rate of release as well as the structural and formulation properties. In general, the integrated approach could be applied to the development of controllable, sustained, localized, and personalized drug-release systems [40].

Table 3 Major Drug-Loading and Release Mechanisms in Nano-Enabled 3D-Printed Systems

Mechanism	Basic principle	Role of nanotechnology	Role of 3D printing
Encapsulation	Drug is enclosed within a nanocarrier	Protects and carries the drug	Provides the surrounding structural matrix
Adsorption	Drug associates with nanomaterial surface	Provides drug-loading sites	Controls spatial placement of the loaded material
Diffusion	Drug moves through the carrier or matrix	Controls nanoscale drug transport	Porosity and geometry influence diffusion pathways
Swelling	Matrix absorbs fluid and expands	Nanomaterial can modify matrix–drug interactions	Printed architecture influences fluid penetration
Degradation/erosion	Carrier or matrix gradually breaks down	Nanocarrier degradation can control release	Printed structure provides additional structural control
Stimuli-responsive release	Drug release changes in response to environmental conditions	Provides responsive nanoscale functionality	Enables spatial placement of responsive materials
Multi-stage release	Drug is released through more than one mechanism or region	Provides nanoscale control	Enables structural and spatial control

The combination of these capabilities illustrates how the use of nano-enabled printing of 3D objects can offer more flexibility than traditional drug delivery methods. The therapeutic agent is controlled in a 'nanoscale environment' through nanotechnology, and the distribution of that environment is controlled in a 'larger 3D structure' through 3D printing. It can be possible to create a delivery system with varying release rates in different parts of the dosage form [41].

But, the desired release profile must be optimized carefully. Drug release can change with increasing concentration of the nanoparticles, changing polymer composition, modifying the porosity, or altering the printing pattern. Thus, formulation and printing parameters should be taken together and optimized simultaneously. Reproducibility is also crucial because small variations in the distribution of the nanoparticles or in the printed architecture can result in variations in the release behaviour.

In all, the mechanisms of drug loading and release in nano-enabled 3D-printed systems are intricately linked at both nano and macro scales. On one hand, the nanocarrier can afford protection, encapsulation, targeting, or controlled release of the drug, and on the other, the 3D-printed structure can ensure control of the drug distribution, drug diffusion pathways and the spatial release [42]. It is very important to understand these mechanisms in order to

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develop systems for predictable and application-specific drug delivery. The same abilities could be the foundation for integrated nanotechnology and 3D printing in other pharmaceutical and biomedical applications.

II. APPLICATIONS IN NEXT-GENERATION DRUG DELIVERY

The combination of nanotechnology and 3D printing offers the potential to create drug delivery solutions that offer greater control over drug distribution, release, dose and administration. Nanotechnology offers the ability to deliver drug-carrying particles of nanoscale size and a variety of functional materials, whereas 3D printing allows the shape, internal structure, composition, and location of the drug to be controlled. These are important applications in the fields of oral, targeted, implantable, transdermal, tissue and personalised drug delivery [43].

- *Oral Drug Delivery:*

Drugs that are poorly soluble, unstable and/or poorly absorbed can be enhanced by nanotechnology, as these drugs may be formulated into nanotechnology-based drug carriers. The incorporation of these carriers into dosage forms that are 3D printed can offer additional control over the distribution of the drug and release. Based on the drug needs, different shapes, inner structures and concentrations of drugs can be developed. This could facilitate controlled or sustained release and multiple drugs. But, it is important to take into account the stability of the nanocarriers in the print, storage and gastrointestinal environment [44].

- *Targeted and Localized Drug Delivery:*

The size, composition and surface properties of nanocarriers can alter drug distribution, and 3D printing can create 3D shapes of structures, featuring regions with drugs. This is very beneficial for localised delivery, as a printed system could be placed in close proximity to the treatment area. The nanocarrier can modulate the behaviour of the drug and the printed structure determines the release location and pattern. The actual targeting, however, would depend on the type of nanomaterial and the biological environment [45].

- *Cancer Drug Delivery:*

Advanced drug delivery is an important application in cancer therapy, as it is possible to localize therapeutic agents in a controlled manner and thereby minimize unnecessary exposure of healthy tissues. Drug loaded nanoparticles can be either embedded in the 3D-printed matrices or targeted to specific areas of a 3D-printed structure. These systems can offer persistent local delivery of the drug and may be capable of delivering multiple therapeutic agents [46]. However, their effectiveness and safety depends on the appropriate biological evaluation.

- *Implantable Drug Delivery Systems:*

Combining 3D printing with controlled drug loading and release (obtained using nanotechnology) with controlled geometry and internal structure (obtained using 3D printing) allows the production of implantable systems. The nanoparticles containing the drug may be mixed into biodegradable polymers, hydrogels or other materials used in implants. The printed architecture can control over the presence of the drug containing regions and the nanocarrier can control over the release of the drug. Biocompatibility, mechanical stability, degradation, sterilization and the release of the drug over extended periods are important factors to consider [47].

- *Transdermal and Microneedle-Based Delivery:*

Skin is a very important barrier for drug delivery. Nanotechnology can be used to facilitate delivery of selected therapeutic agents, and 3D printing can be used to achieve precise fabrication of transdermal systems and microneedle structures. Digital design allows for control of dimensions and arrangement of the microneedles and the use of nanomaterials can also incorporate further drug loading and release. Material safety and mechanical strength are important considerations for these applications [48].

- *Tissue Engineering and Regenerative Applications:*

3D printing allows for the creation of drug delivery systems in conjunction with tissue engineering scaffolds, using a technology called nano-enabled 3D printing. The combination of 3D printing and nanoparticles offers controlled scaffold geometry and architecture and targeted drug delivery. Drug loaded nanomaterials can, therefore, be used to achieve sustained release over time within the scaffold, and the printed structure can be used to support the desired tissue related application. The assessment of biocompatibility, degradation and drug-release properties should be done as a whole [49].

- *Personalized Drug Delivery:*

Combining these two technologies nanotechnology and 3D printing offers a huge potential opportunity in personalized drug delivery. Dose, shape, size, internal structure and distribution of the drug can be customized based on individual needs. The drug release behaviour can be further controlled by the type and concentration of the nanocarriers. Multiple drugs or nanocarriers can also be combined in various parts of a single dosage form. But personalized manufacturing relies on digital design, an ability to reproduce designs, ensure quality control and have the correct regulatory systems [50].

III. CRITICAL ANALYSIS OF RECENT RESEARCH

The new wave of research for integration of nanotechnology and 3D printing has been about the merging of nanoscale drug delivery capabilities with the structural flexibility of Additive Manufacturing. Nanotechnology offers the potential for the drug to be encapsulated, protected, released at a controlled rate, and functionalized; 3D printing offers control over the geometry, internal architecture, spatial distribution, and composition. This has thus paved the way for multifunctional and structurally controlled drug delivery systems from conventional nanoparticle formulations [51].

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One of the key research strategies is to formulate drug loaded nanoparticles into printable polymeric and hydrogel matrices. Here, the main role of the nanocarrier is to deliver the drug and the matrix is used only for its structure and to exert further control on the drug transport. A hierarchical system can be achieved, with a drug released at the nanoscale, and a matrix- and architecture-controlled release. Incorporation into the formulation, however, may affect the viscosity, flow behaviour and printing properties, and therefore optimization of the formulation is necessary [52].

Another promising way is nanocomposite 3D-printed systems. Drug loading, mechanical properties, surface properties and drug release behaviour of polymeric matrices can be modified by incorporation of nanoscale materials. These systems may be able to offer several functions in a single print. The concentration and dispersion of the nanoparticles, however, should be carefully monitored to prevent the nanoparticles from clumping together and becoming unprintable [53].

There is also research into different 3D-printing technologies for nano-enabled formulations. Extrusion-based and light-based techniques can be employed for polymeric and hydrogel formulations, respectively, with higher resolution in structure. But the environment in which the printing is done should be consistent with the drug and the nanomaterial. Sensitive therapeutic agents or nanocarriers can be impacted by thermal or photochemical exposure.

Another important advancement in drug delivery is the spatially controlled drug delivery. Compared to conventional formulations, 3D printing offers the possibility to distribute different drugs or nanocarriers in targeted areas of a dosage form. This can facilitate local, sequential or simultaneous drug delivery [54]. Different regions of the structure or nanocarrier systems can be used to incorporate multiple therapeutic agents. But there is a need to carefully consider interactions between the drugs, nanomaterials and printing matrix.

The technology is also very promising for personalized drug delivery. The digital design enables changes in dose, dimensions, internal architectures and drug distribution. Further, nanotechnology can be used to control the nanoscale drug delivery properties. But, in order to meet the requirements of personalized manufacturing, the printing process must be reproducible, the digital workflow must be reliable, the materials must be consistent and quality control procedures must be in place [55].

Although these advances have been made, there are still some research gaps that need to be addressed . It is difficult to compare different studies because they vary in the type of nanomaterials used, the type of polymers, the printing technologies, the formulation compositions and the methods used to test for release. Therefore, standardized methods for printability assessment, distribution of nanoparticles, amount of drug, and the release behaviour need to be developed [56].

Long-term stability and reproducibility also needs to be emphasized. The performance may vary due to aggregation of nanoparticles, migration of the drug and changes in the structure of the polymers during storage. There is also a lack of information on scale-up and industrial manufacturing in many studies, plus those at the laboratory or proof-of-concept stage [57].

Lastly, there is a need for improved biological evaluation. The in vitro release profile may not guarantee suitable bioperformance. Finally, further studies are needed to establish more robust links between material properties, printing condition, drug release, biological response and long term safety [58].

In summary, these recent studies showcase promising potential for the development of nano-enabled 3D drug delivery systems, yet further standardization, reproducibility, biological validation, and scale up studies are needed to enable the systems to be successfully translated to the pharmaceutical and clinical levels.

Comparing the two suggests that the field has moved from studying a single nanocarrier and a single printing method to multiple levels of control, that is, integrated systems. However, the research conducted to date is varied and there is no universal solution for the selection of the nanomaterial, printable matrix and the printing technology. The proper system should be used based on the characteristics of the drug and the treatment use [59].

A key potential area of future study is the establishment of systematic design approaches that integrate material selection, nanocarrier feature design, printing parameters, structural design, and drug release properties. These structures may contribute to minimizing formulation development through trial and error, and to the reproducibility of the process. Presence of computational modelling and data driven approaches could also help in predicting printability and release characteristics before experimental fabrication [60].

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Table 4 Critical Comparison of Research Approaches in Nano-Enabled 3D Drug Delivery

Research approach	Major contribution	Key limitation	Research need
Nanoparticle-loaded printed matrices	Combines nanoscale drug delivery with structural control	Nanoparticle dispersion can be difficult	Improved formulation stability
Nanocomposite printing	Provides multifunctional printed systems	Nanomaterials may alter printability	Better material optimization
Extrusion-based nano-printing	Suitable for polymers and hydrogels	Process parameters affect structure	Standardized printing conditions
High-resolution printing	Enables complex architectures	Material and drug compatibility issues	More pharmaceutical-compatible materials
Spatial drug distribution	Allows localized or sequential release	Requires precise material deposition	Improved multi-material printing
Multi-drug systems	Supports combination therapy	Drug–drug and material interactions	Independent control of drug release
Personalized systems	Enables customized dose and geometry	Quality control and regulatory challenges	Reliable personalized manufacturing

Overall, the studies conducted in recent times have shown that the combination of nanotechnology and 3D printing has great potential for creating advanced drug delivery systems. The field is still in its early stages, however, and several hurdles remain to be overcome for its potential translation to the pharmaceutical and clinical arena. To translate these systems from laboratory-stage demonstrations to actual therapeutic applications, greater standardization, complete characterization, long-term stability testing, biological validation, scalable manufacturing and appropriate regulatory approaches will be required .

IV. ADVANTAGES OF THE INTEGRATED NANOTECHNOLOGY–3D PRINTING APPROACH

Nanotechnology combined with three-dimensional (3D) printing offers a combination of nanoscale drug-delivery functionality and macroscale structural control. Nanotechnology can alter the physicochemical and biological properties of therapeutic agents and 3D printing has the ability to control the geometry, internal architecture, spatial distribution and composition of the final dosage form. There could be a number of advantages to this complementary relationship, compared to traditional drug delivery and to the independent use of either technology [61].

- *Controlled Drug Release*

By combining nanotechnology and 3D printing, there are several ways to control the release of the drug. The drug release can be controlled by the diffusion, degradation, dissolution of nanocarriers and 3D printed matrix, and the drug transport can be further controlled by the porosity, infill pattern, layer arrangement and material composition of 3D printed matrix. This combination provides the opportunity to create release profiles which may be hard to obtain through traditional dosage forms [62].

The nanocarrier may also offer prolonged or controlled drug delivery of the drug entrapped within it and the printed structure around it may constitute an additional barrier to drug delivery. Depending on therapeutic needs, Adjusting the properties of the nanocarriers and printed architecture can potentially allow drug release to be adjusted.

- *Improved Drug Protection and Stability*

Therapeutic agents can be protected from degradation and undesirable interactions with the surrounding environment via the use of nanocarriers. Some sensitive drugs can be encapsulated in nanoparticles, liposomes, nanogels, or other nanotechnology-based carriers, which can enhance the stability of the drug. The 3D-printed matrix can also serve as an extra physical barrier for the nanocarrier and can also help to control drug exposure to the external environment [63].

This hierarchical structure is capable of enhancing the stability of the drug during delivery, but of course this would be contingent on the drug, nanomaterial, matrix, and printing conditions. So, experimental testing of the complete system must be performed to assess the stability of the system under study.

- *Personalized Drug Delivery*

3D printing offers a high level of flexibility in producing patient-specific dosage forms. The digital design can be changed to tailor the dose, size, shape, internal architecture and drug distribution to the needs of the individual. The addition of nanotechnology provides additional flexibility, as the type and amount of nanocarriers can be chosen depending on the desired release behavior [64].

These types of systems can be beneficial for patients who need varying doses, release rates or a combination of therapeutic agents. In the real world, however, a reliable digital design, repeatable production, quality control and suitable regulatory processes must be followed.

- *Spatial Control of Drug Distribution*

The ability to place drugs or drug loaded nanocarriers within specific areas of a printed structure is unique for 3D printing when compared with traditional dosage forms. Drug-available materials near the surface might have a relatively rapid drug availability, while deeper situated materials might have a longer duration of drug release.

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Each region of the same dosage form may also contain different nanocarriers or drugs. This spatial control offers possibilities for localized delivery, sequential release and combination therapy [65].

- *Complex Dosage-Form Design*

The 3D printing method can be used to create complex geometries, such as porous structures, internal channels, cavities, and multilayer systems. Nanomaterials can be integrated into these structures to enable custom-tailored three-dimensional structure and provide the added benefit of nanoscale drug delivery [66].

The shape of the dosage form may then be a significant aspect of the drug delivery system design [67]. In addition to the conventional formulation composition, changes in internal structure and porosity might affect drug transport and release.

- *Combination and Multi-Drug Delivery*

The integrated approach can help to make delivery of multiple therapeutic agents possible within a single delivery vehicle. Nanocarriers can be filled with different drugs or located in various parts of a 3D-printed entity. This provides an opportunity to control the release of individual drugs according to their therapeutic requirements.

These systems could be beneficial for combination therapy and may allow for the possibility of simplifying complex dosing regimens. But it's important to consider the interactions between the various drugs, nanocarriers and printing materials to maintain stability and performance.

- *Targeted and Localized Delivery*

Nanotechnology can modify drug distribution and biological interactions due to the characteristics of the particles (such as size, composition and surface properties). These can be combined with 3D printing's ability to create delivery structures of specific shapes and sizes that can be administered at a specific location [68].

The pairing can be helpful where the delivery system must stay in a specific treatment facility. The printed structure can define where and how the drug is administered and the overall architecture, whereas the nanocarrier can shape the behaviour of the drug once it has been administered.

- *Multifunctional Delivery Platforms*

Nano-enabled 3D printing can create multifunctional delivery systems that deliver drugs, control release, organize the structure, and deliver it locally in a single system. In addition to these, depending on their composition and design, nanomaterials can make available other functional properties [69].

This multifunctionality may help to decrease the requirement for separate delivery elements and can facilitate the creation of more complicated therapeutic programs. As one adds more features, however, it becomes more important to take care that this does not compromise the material, and that the material is evaluated properly.

V. CHALLENGES AND LIMITATIONS

The combination of nanotechnology and 3D printing offers many possibilities for the development of new, advanced drug delivery systems, however, a number of challenges remain that need to be overcome. Two complex technologies are combined, and these pose extra formulation, manufacturing, characterization, safety and regulatory challenges. The promise of nano-enabled 3D printing must be considered in conjunction with the challenges of material selection, processing, repeatability, and translation [70].

- *Material Compatibility and Nanoparticle Dispersion*

The compatibility of the drug, nanomaterial, printable matrix and selected 3D-printing technique is one of the key challenges. Properties suitable for printing are not necessarily those possessed by a nanomaterial that is effective at carrying a drug. Also, the printability of polymers or hydrogels can alter the stability of nanoparticles, their loading or release properties of drugs. So, both pharmaceutical and printing requirements must be taken into account when selecting materials [71].

Ensuring even distribution of the nanoparticles is also crucial. Formulation, printing, and storage conditions can lead to aggregation of the nanoparticles, which may lead to a non-uniform drug distribution and to changes in the drug release behaviour. Hence, it is essential to have appropriate formulation design and process control to ensure uniform and stable distribution of nanomaterials in the printed structure.

- *Printability and Processing Stability*

Nanomaterials could change the rheological properties (viscosity, flow behaviour and others) of the printable formulations. For extrusion based systems, the formulation needs to flow easily through the nozzle, and also maintain its shape after extrusion. If the viscosity is too high, the nozzle may become blocked; if it is too low, the nozzle may be malformed and the structural accuracy may be compromised [72].

The stability of the drug and the nanocarriers can also be influenced by printing conditions. Thermal printing can subject formulations to high temperatures and light printing can subject formulations to photochemical conditions. Mechanical forces also can be created during the extrusion process. So, the printing parameter needs to be optimized to ensure the stability and functionality of both the drug and the nanomaterial.

- *Drug Distribution and Reproducibility*

A key challenge is achieving uniform distribution of the drug, as the drug can be added to the nanocarrier, and the nanocarrier is distributed in the printed matrix. The drug concentration and release profile can be affected by any variation at either level. It is more complicated in systems

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with different drugs or nanocarriers in different parts of the system [73].

For applications in the pharmaceutical sciences, repeatability is crucial. The final product may vary due to variations in properties of the nanomaterials, variations in formulation, parameters of printing the nanomaterials, environmental parameters, or post processing. The drug content, the distribution of nanoparticles, the dimensions, the porosity, mechanical properties and the release behaviour should therefore be taken into consideration for quality evaluation [74].

- *Scale-Up and Manufacturing Challenges*

Most 3D drug delivery systems so far have been only laboratory and small experimental size. Scaling up to larger-scale production may pose challenges in terms of printing speed, handling materials, distribution of the nanoparticles, control of process and reproducibility. A successful formulation in the lab may not work well in a different manufacturing process [75].

Personalized drug delivery is of special concern with scale-up. While 3D printing offers flexibility in making customised dosage forms, efficient use of digital workflows, standardisation of materials, process control and quality assurance are all crucial for successful manufacturing. Keeping uniformity at the nanoscale scale in the larger production scale is still an important research need [76].

- *Storage Stability and Shelf Life*

Another big restriction is long-term stability. During storage, the nanoparticles can cluster together and/or change in structure, and the polymeric matrix can also undergo physical or chemical changes. The changes may impact on drug loading, properties of the nanomaterials and the release profile.

Thus, it is necessary to assess the whole system (nano-enabled printed system) in stability studies and not just the drug itself [77]. Under suitable storage conditions, changes in physical structure, drug content, characteristics of the nanoparticles, and release should be monitored to determine the expected shelf life.

- *Biological Safety*

Biological safety aspects of nanomaterials need to be carefully evaluated since the biological behavior of nanomaterials may differ from that of the bulk material. The interactions with cells and biological tissues may be affected by properties like particle size, composition, surface characteristics and degradation behaviour.

Therefore, the full printed formulation, including the drug, nanocarrier, printable matrix, and potential degradation products should be assessed for safety. Biological evaluation is the appropriate evaluation needed to ascertain that the system can perform the therapeutic function without undesirable biological effects [78].

- *Regulatory and Standardization Challenges*

Because 3D-printed systems with nanotechnology and pharmaceutical formulations are a blend of materials, regulatory evaluation can be complex. The evaluation could thus require the inclusion of nanomaterial-specific properties and characteristics as well as properties linked to the 3D-printed dosage form. Clear and consistent regulatory approaches will be important for future clinical translation.

The implementation of standardised methods for the evaluation of printability, nanoparticle distribution, structural properties, drug release, stability and biological safety is also needed. Reliable standards in these systems could be developed and research findings compared if there was consistent testing and reporting [79].

- *Cost and Technical Requirements*

The development of nano-enabled 3D-printed drug delivery systems could necessitate the use of specialized printers, formulation equipment, characterization facilities, digital design tools and personnel. Development may also become more complex and costly due to further requirements on characterizing and testing nanomaterials for quality [80].

To realize a wider pharmaceutical application, more efficient, reproducible and economically feasible manufacturing processes are required. These limitations can be mitigated with advances in automated printing, process monitoring, standardized materials, and formulation strategies to ensure the appropriate pharmaceutical quality and performance.

- *Regulatory Considerations and Quality Assurance*

When combining 3D printing with nanotechnology, regulatory and quality control concerns arise, as they are related to the drug delivery system that will be a combination of drugs, nanomaterials and a digitally controlled manufacturing procedure. There is a strong need to ensure safety, uniformity and repeatability of these systems for pharmaceutical and clinical translation [81].

It's essential to take into account the quality of raw materials. Consistent and well characterized properties of the drug, polymer, excipients, and nanomaterials should be present. However, for nanomaterials, their physical parameters (particle size, distribution, surface properties, composition, and stability) may affect their drug loading, release, and biological behaviour.

The printable formulation should also have proper characteristics for the printing process of choice. These characteristics - viscosity, flow behaviour, stability and compatibility of the nanomaterial and printing matrix - can have an impact on the quality of the final product. Poor formulation properties could lead to sub-optimal printing accuracy or drug/nanomaterial non-uniformity [82].

The control of 3D-printing parameters is quite essential as well. Printing temperature, speed, layer thickness, extrusion condition and infill pattern may impact

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the geometry, internal structure, drug distribution and release profile of the printed dosage form. These parameters must thus be optimised and monitored accordingly [83].

Final product must be sufficiently characterised in terms of quality. Parameters that are important can be dimensions, drug content, drug distribution, mechanical properties, structural characteristics, drug-release behaviour, and nanomaterial stability. In the case of nano-enabled systems, it is especially significant to achieve uniform distribution of nanoparticles as the aggregation or non-uniform distribution can impact the release of the drug and the performance of the product [84].

Stability testing is also required to see if the drug, nanomaterial and printed matrix retain its desired properties when stored. The performance of the delivery system could be altered due to changes like nanoparticle aggregation, degradation of the drug or alteration of the polymeric matrix.

A framework for linking material properties and printing conditions with the critical quality attributes for the final product can be helpful using the principles of quality-by-design. This systematic approach can help in enhancing the product reproducibility and help identify the factors which have the maximum impact on the product.

The regulatory assessment may be more complicated due to the overlap of these systems with other drug product, nanomedicine and AM systems. Requirements may differ based on the composition, intended use, route(s) of administration and regulatory jurisdiction. Hence, it is necessary to have standardized characterization and quality-control methods to facilitate consistent evaluation [85].

In summary, the translation of a 3D-printed drug delivery system for nanotechnology will depend on control of materials, nanomaterial properties, formulation properties, printing parameters, product quality and stability. It will be key to develop reproducible manufacturing and standardized evaluation processes to bring these systems from the laboratory to the market for pharmaceutical applications [86].

VI. FUTURE PERSPECTIVES

Nanotechnology, in conjunction with 3-D printing, holds great promise for creating new generations of drug delivery systems. Researchers are likely to work on digitizing 3D structures coupled with nanoscale drug carriers to achieve a more precise drug loading, drug spatial distribution, and controlled release in the future. More focus needs to be given to patient-specific dosage forms, multifunctional systems, and localized drug delivery. Other developments in printable biomaterials and nanocomposites can further enhance the bio-compatibility, stability, and function of these systems. Moreover, understanding the relationship between the characteristics of these nanomaterials, printing parameters and drug-release behaviour will be useful in creating more predictable delivery platforms.

To ensure the scale-up and long-term stability of these materials, their reproducibility and safety, and the standardisation required for their standardisation by regulatory authorities, the following limitations need to be addressed for future development. Automated manufacturing and digital design can be integrated, which can facilitate more accurate and personalized drug delivery system production. The development of these, however, should be accompanied by a systematic characterization and evaluation of their biological and stability properties. In summary, ongoing advancements in nanomaterials, 3D printing, and customisable drug production may lead to more precise, flexible, and personalized drug delivery systems.

VII. CONCLUSION

Nanotechnology and 3D Printing can be utilized to create innovative medical products for drug delivery. Nanotechnology allows for nanoscale control over these four elements of drug encapsulation, protection, targeting, and release, and 3D printing allows for precise control over the geometry, internal architecture, drug distribution, and personalized design of dosage forms. The co-assembly of these two components can thus enable multi-scale control over drug delivery and the advancement of patient-specific, localized and controlled therapeutic systems.

However, there are a number of constraints on material compatibility, nanoparticle stability, printability, reproducibility, scale-up, biological safety, quality control, and regulatory issues. These limitations will need to be overcome with better materials, better fabrication methods, better standardized characterization, and appropriate quality assurance to ensure successful translation. Overall, the ongoing advancement of 3D printing with nanotechnology could be a transformative step forward in next-generation drug delivery, given the ability of 3D printing to integrate nanotechnology's functionalities with the precision of digitally controlled 3D printing.

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