Open Access Full Text Article   Check for updates   Review Article

Development of Novel Drug Delivery Systems: Nanoparticles, Microneedles, and 3D Printed Personalised Medicine

Shreyash S. Virutkar *(ID), Swati Kale(ID), Alpana Asnani (ID)

Priyadarshini J. L. College of Pharmacy, Nagpur – 441110, India

Article Info:

Abstract

___

The continuous evolution of pharmaceutical sciences has led to the emergence of novel drug delivery systems (NDDS) aimed at enhancing therapeutic efficacy, reducing side effects, and improving patient compliance. Conventional dosage forms often face challenges, including poor bioavailability, limited targeting, and variable pharmacokinetics. To overcome these limitations, advanced platforms such as nanoparticles, microneedles, and three-dimensional (3D) printed personalized medicines have gained significant attention. Nanoparticle-based systems enable precise delivery through controlled release and site-specific targeting, thereby optimizing therapeutic outcomes in oncology, neurology, and infectious diseases. Microneedles offer a minimally invasive alternative for transdermal delivery, enhancing patient acceptability while bypassing gastrointestinal degradation and first-pass metabolism. Meanwhile, 3D printing technology has revolutionized personalized pharmacotherapy by allowing on-demand fabrication of dosage forms tailored to individual patient needs, drug combinations, and release profiles. Together, these innovative strategies represent a paradigm shift from conventional formulations toward intelligent, patient-centred therapeutics. This review discusses the principles, fabrication methods, therapeutic applications, and translational challenges of these emerging drug delivery technologies. Additionally, it highlights the integration of digital health and artificial intelligence to optimize formulation design, address regulatory considerations, and chart future perspectives for precision medicine.

Keywords: Novel drug delivery systems; Nanoparticles; Microneedles; 3D printing; Personalized medicine; Controlled release; Targeted therapy; Pharmaceutical innovation.

1. INTRODUCTION:

1.1 Background and Rationale

Drug delivery science has undergone a profound transformation over the past few decades, driven by the continuous pursuit of improving therapeutic efficacy, safety, and patient adherence. Traditional drug delivery methods such as oral tablets, injections, and topical formulations have been the foundation of pharmaceutical therapy for centuries. However, these approaches often fall short in achieving optimal pharmacokinetic and pharmacodynamic profiles. Many therapeutic agents exhibit poor solubility, rapid metabolism, or inadequate permeability, which limits their bioavailability and therapeutic potential. Moreover, systemic administration of drugs frequently results in off-target effects and toxicities that compromise treatment outcomes.[1] In recent years, the development of novel drug delivery systems (NDDS) has emerged as a central focus in pharmaceutical innovation. These advanced systems are designed to precisely control the release, distribution, and targeting of drugs within the body. By integrating principles of material science, nanotechnology, biomedical engineering, and computational modeling, researchers aim to overcome the biological barriers that limit traditional formulations.

NDDS platforms such as nanoparticles, microneedles, and three-dimensional (3D) printed dosage forms exemplify this technological evolution. Each system offers unique advantages in improving drug stability, site-specific delivery, and personalized therapy.[2] The global rise in chronic diseases, coupled with the demand for precision medicine, further underscores the importance of innovative drug delivery technologies. As therapeutic agents become more complex ranging from small molecules to peptides, proteins, and nucleic acids new strategies are required to ensure their effective and safe administration.[3] Consequently, the convergence of nanotechnology, additive manufacturing, and biomedical design has reshaped the future of drug delivery science.[4]

1.2 Limitations of Conventional Drug Delivery Systems

Conventional drug delivery systems, though widely utilized, face significant limitations that hinder therapeutic efficacy. Oral administration—the most common route—is often compromised by poor absorption of drugs unstable in the gastrointestinal tract and extensive first-pass metabolism. Many active pharmaceutical ingredients exhibit low solubility, leading to inconsistent plasma levels and variable clinical outcomes. Frequent dosing requirements further reduce

patient adherence, especially in chronic treatments.[1,4] Parenteral routes provide rapid action but introduce discomfort, infection risk, and the need for medical supervision. Moreover, systemic exposure often results in non-selective distribution, damaging healthy tissues and causing dose-limiting toxicities, as commonly observed in chemotherapy. Topical and transdermal methods, while painless and convenient, are restricted by the skin's impermeability to large or hydrophilic molecules. Likewise, pulmonary and ocular routes face physiological barriers that impede optimal deposition and sustained retention of therapeutic agents. These drawbacks highlight the inadequacy of traditional systems in achieving controlled, targeted, and sustained delivery. Conventional formulations are largely uniform, disregarding patient-specific factors such as metabolic rate, genetic profile, and disease variability. This "one-size-fits-all" approach conflicts with the growing emphasis on personalized medicine. As drug development expands to include complex biologics, nucleic acid therapies, and individualized regimens, traditional delivery routes struggle to provide the required precision.[2,5] Consequently, there is a pressing need for innovative drug delivery platforms capable of overcoming biological barriers, maintaining controlled release, and achieving site-specific targeting. Emerging technologies such as nanoparticles, microneedles, and 3D-printed systems are being developed to integrate adaptability, selectivity, and precision into therapeutic design. These systems represent a paradigm shift from passive administration toward intelligent, patient-centric drug delivery, offering the potential to enhance efficacy, minimize side effects, and align treatment strategies with the principles of precision medicine.[6,7]

1.3 Need for Innovation in Drug Delivery

Conventional drug delivery systems face major limitations that compromise therapeutic efficiency and patient outcomes. Oral administration, though preferred for convenience, often results in poor absorption of drugs that are unstable in the gastrointestinal tract or subject to extensive first-pass metabolism. Many active pharmaceutical ingredients exhibit low solubility, causing inconsistent plasma concentrations and unpredictable efficacy. Frequent dosing further reduces patient adherence, particularly in chronic therapy.[1,2] Parenteral administration enables rapid drug action but involves pain, infection risk, and the need for skilled personnel. Systemic exposure frequently leads to non-specific distribution, causing toxicity in healthy tissues as seen in chemotherapy. Topical and transdermal routes, while non-invasive, are limited by the skin's barrier to large or hydrophilic molecules, and pulmonary or ocular delivery faces similar physiological obstacles that restrict bioavailability and sustained retention.[6] Traditional dosage forms also fail to address patient-specific factors such as metabolic rate, genetic variability, and disease heterogeneity. This "one-size-fits-all" approach contrasts with the growing focus on personalized medicine, which demands adaptable and precise therapeutic systems.[1,5]Hence, there is an urgent need for advanced delivery technologies capable of controlled release, targeted action, and improved safety. Innovative systems such as nanoparticles, microneedles, and 3D-printed personalized medicines are emerging as transformative solutions. These modern platforms integrate adaptability, selectivity, and precision into drug delivery design, offering a pathway toward patient-centered, efficient, and responsive treatment strategies aligned with the goals of precision pharmacotherapy.[2,4]

1.4 Scope and Objectives of the Review

This review aims to provide a comprehensive examination of the emerging drug delivery technologies that are redefining pharmaceutical research and clinical therapeutics. It focuses on three major platforms—nanoparticles, microneedles, and 3D-printed personalized medicines—each representing a distinct dimension of modern drug-delivery innovation.[8]

The objectives of this review are fourfold:

1. To outline the scientific principles, mechanisms, and fabrication strategies underlying these novel systems.[9]

2. To critically analyze their therapeutic applications, advantages, and limitations across various disease domains.[10]

3. To discuss translational and regulatory challenges associated with their development and commercialization.[11]

4. To explore future directions, including the integration of artificial intelligence, smart materials, and digital health in advancing personalized drug delivery.[12]

2. OVERVIEW OF MODERN DRUG DELIVERY TECHNOLOGIES

2.1 Evolution of Drug Delivery Approaches

A steady shift from traditional dosage forms to increasingly complex, patient-centered platforms has been a defining feature of drug delivery system innovation. At first, the main goal of pharmaceutical formulations was to ensure that the active components were sufficiently stable and bioavailable. The market was dominated by injectables, tablets, and capsules because they were easy to make and administer. These forms, however, frequently provided little control over the location and rate of drug release, which resulted in variations in plasma drug levels and uneven therapeutic effects.[13] Thanks to developments in materials science and polymer chemistry, drug delivery saw its first significant change in the 1970s and 1980s. In order to decrease the frequency of dosage and preserve steady-state medication concentrations, controlled-release formulations were devised. During this time, biodegradable polymeric implants, transdermal patches, and osmotic pumps were developed. The objective changed from just administering a medication to adjusting the duration and kinetics of its release.[14] The field of drug delivery study was broadened by the following integration of molecular biology, nanotechnology, and bioengineering in the late 20th and early 21st centuries. Researchers started creating systems that could target particular tissues or cells, react to physiological cues, and change to meet the demands of

different patients. These contemporary systems, which include microneedle arrays, nanoparticle carriers, and 3D-printed formulations, constitute a new generation of "intelligent" drug delivery methods that combine biocompatibility, precision, and customization.[15,16]

2.2 Principles of Controlled and Targeted Drug Delivery

Therapeutic agents' temporal and geographical distribution throughout the body is regulated by controlled and targeted drug delivery systems. The fundamental idea behind controlled delivery is to minimize adverse effects and dosage frequency by maintaining an ideal drug concentration at the target site for an extended amount of time. Diffusion, degradation, or environmental cues like pH, temperature, or enzymatic activity can all be used to control drug release.[16]Conversely, targeted medication delivery aims to minimize systemic exposure while delivering the therapeutic substance precisely to sick tissues. Passive methods, like the increased permeability and retention (EPR) effect in tumors, or active targeting, in which ligands, antibodies, or peptides on the carrier surface identify and attach to particular cellular receptors, can be used to achieve this. The combination of targeted and controlled release guarantees that the medication acts where it is most required, lowering toxicity and enhancing therapeutic effectiveness.[14,15] Additionally, stimuli-responsive elements that can change their behavior in reaction to external inputs are incorporated into modern systems. In reaction to variations in pH, redox potential, or external stimuli like magnetic fields and ultrasound, these "smart" devices can release medications. The development of tailored therapy and precision medicine depends on this level of control and targeted accuracy.[16]

2.3 Classification of Novel Drug Delivery Systems

Novel drug delivery systems (NDDS) can be broadly categorized based on their physical structure, mechanism of release, or route of administration. The most prominent categories include:

1. Nanocarrier-based systems – encompassing nanoparticles, liposomes, dendrimers, micelles, and nanogels.[13]

2. Transdermal and intradermal systems – including microneedles, patches, and nanoemulsions.

3. Implantable and injectable systems – such as biodegradable depots, hydrogels, and microspheres.[14]

4. Mucosal delivery systems – nasal, buccal, and ocular formulations designed for localized or systemic delivery.

5. 3D-printed personalized medicines – dosage forms fabricated through additive manufacturing tailored to patient-specific needs.[15]

Each of these categories reflects the growing emphasis on improving drug targeting, release control, and patient-centric customization in modern pharmaceutics.

3. NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS

3.1 Introduction to Nanoparticles in Drug Delivery

Because nanotechnology provides nanoscale carriers that can control drug transport at the molecular and cellular level, it has completely changed the pharmaceutical development landscape. Therapeutic compounds can be encapsulated, adsorbed, or conjugated by nanoparticles, which are designed colloidal structures with a typical size range of 1 to 1000 nm. They have special physicochemical qualities due to their small size, including higher permeability through biological membranes, adjustable charge, and increased surface area. All of these characteristics work together to give prolonged or stimuli-responsive release, increase the solubility of hydrophobic medications, and extend systemic circulation. The capacity of nanoparticles to penetrate physiological barriers like the blood–brain barrier, the gastrointestinal epithelium, and tumor vasculature is one of its main advantages. Because of their design flexibility, they can be modified to provide desired pharmacokinetic behaviors using polymers, lipids, or inorganic matrices. Nanocarriers can be designed to take advantage of receptor-mediated transport processes in neuropharmacology, while in oncology, they promote passive accumulation at tumor locations through the increased permeability and retention (EPR) effect. Additionally, platforms for nanoparticles act as multipurpose vehicles for theranostics, or combined imaging and therapy, allowing for simultaneous diagnosis and treatment. Thus, the incorporation of nanotechnology into pharmaceutics offers a complex interface between medication, material, and biology in addition to a delivery system.[17]

3.2 Types of Nanoparticles

The diversity of nanoparticle systems stems from differences in their composition, structural organization, and preparation techniques. Each class offers distinct advantages for specific therapeutic applications.

3.2.1 Polymeric Nanoparticles

Biodegradable polymers like polylactic acid (PLA), polyglycolic acid (PGA), and their copolymer PLGA, as well as natural polymers like chitosan or alginate, are used to create polymeric nanoparticles. These systems can be either nanospheres (drug evenly distributed throughout the matrix) or nanocapsules (drug encased in a polymeric shell). Polymer erosion, diffusion, or degradation controls drug release, enabling sustained and regulated delivery. For the transport of peptides and proteins, where protection against enzymatic degradation is crucial, polymeric nanoparticles have been extensively studied. To enhance circulatory stability, their surface can be functionalized with polyethylene glycol (PEG) or ligands for targeted distribution. In order to improve site-specific therapy, recent research also investigates stimuli-responsive polymers that release medications in response to temperature or pH changes in the surrounding environment.[18]

3.2.2 Lipid-Based Nanoparticles (SLNs, NLCs, Liposomes)

Lipid-based carriers offer hydrophilic and hydrophobic medications a flexible and biocompatible platform. The medicine is trapped in the crystalline core of solid lipid nanoparticles (SLNs), which are made of solid lipids stabilized by surfactants. Second-generation systems called nanostructured lipid carriers (NLCs) combine liquid and solid lipids to increase drug loading capacity and avoid crystallization while being stored. High physical stability, regulated release patterns, and industrial scalability are characteristics of lipid nanoparticles.

The most therapeutically proven nanocarriers are liposomes, which are made up of phospholipid bilayers enclosing aqueous compartments. They ensure biocompatibility and lower immunogenicity by imitating biological membranes. Numerous medications can be encapsulated in small unilamellar or multilamellar vesicles, and surface modification with PEG or targeting ligands improves tissue selectivity and circulation time. When compared to free drug administration, Doxil®, a PEGylated liposomal version of doxorubicin, continues to be a seminal example that decreased cardiotoxicity and increased patient survival.[19]

3.2.3 Metallic and Inorganic Nanoparticles (Gold, Silica, Quantum Dots)

Different optical, magnetic, and mechanical properties are provided by metallic and inorganic nanoparticles. A unique property of gold nanoparticles (AuNPs) is their surface plasmon resonance, which enables photothermal therapy by converting light into heat. Drug delivery and dual imaging are made possible by the ease with which thiol-linked biomolecules can functionalize their surfaces. High drug loading and controlled release are made possible by the enormous surface areas and adjustable pore sizes of silica nanoparticles, particularly mesoporous silica nanoparticles (MSNs). To induce stimuli-responsive release in tumor microenvironments, their surfaces can be regulated using molecular valves or polymers. The foundation of nanotheranostics is the growing integration of quantum dots into multifunctional systems that combine medicinal administration and diagnostics, despite their primary usage in imaging due to their fluorescent features.

3.2.4 Dendrimers and Polymeric Micelles

Dendrimers are highly branched, tree-like macromolecules synthesized in successive generations around a central core. Their multivalent surface groups can be chemically modified to attach drugs, targeting ligands, or imaging agents. The internal cavities provide space for encapsulating small molecules, enabling the incorporation of both hydrophobic and hydrophilic drugs. Poly(amidoamine) (PAMAM) dendrimers are among the most studied, demonstrating efficacy in gene and anticancer drug delivery. Amphiphilic block copolymers in aquatic media create polymeric micelles, which are self-assembling structures. They are made up of a hydrophilic shell that stabilizes the system in biological fluids and a hydrophobic core that solubilizes

medications that are poorly soluble in water. They can be administered intravenously due to their modest size (10–100 nm) and dynamic stability. While stimuli-responsive micelles allow for regulated release under acidic or enzymatic conditions characteristic of diseased tissues, modifications like folate-decorated micelles improve receptor-mediated tumor targeting.[18,19]

3.3 Mechanisms of Drug Loading and Release

Drug incorporation within nanoparticles may occur through physical entrapment, adsorption onto the surface, or covalent conjugation. Physical entrapment protects the drug from degradation, whereas surface adsorption allows rapid release. Covalent bonding, typically through cleavable linkers, provides precise control over release triggered by enzymatic or chemical reactions. The release kinetics depend on matrix composition, particle size, and surrounding environment. For polymeric systems, degradation of the polymer backbone governs sustained release, while for lipid-based carriers, diffusion through lipid matrices dominates. pH-sensitive nanoparticles can exploit the acidic conditions of tumors or endosomes to release drugs selectively. Thermo- and magneto-responsive nanoparticles use external stimuli—heat or magnetic fields—to trigger localized drug liberation, offering spatiotemporal control unmatched by conventional formulations.

3.4 Surface Modification and Targeting Strategies

Surface functionalization transforms nanoparticles from passive carriers into intelligent, target-specific systems. PEGylation minimizes recognition by the mononuclear phagocyte system, prolonging circulation time. Active targeting involves conjugation of ligands such as antibodies, peptides, aptamers, or small molecules (e.g., folic acid) that bind to receptors overexpressed on diseased cells. Once bound, the nanoparticles enter cells via receptor-mediated endocytosis, ensuring precise intracellular delivery.Emerging strategies include dual-targeting nanoparticles, which employ two or more ligands for enhanced selectivity, and cell-membrane-coated nanoparticles, which camouflage carriers with natural membranes (e.g., red-blood-cell or cancer-cell membranes) to evade immune detection and exploit homotypic targeting. Such biomimetic designs exemplify how nanotechnology leverages biological principles to enhance delivery efficiency and safety.[17,18]
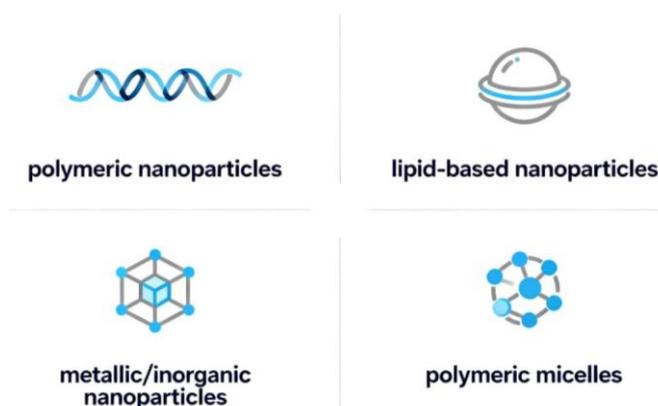

Figure 1: Types of Nanoparticles.

3.5 Applications in Cancer, CNS, and Infectious Diseases

In oncology, nanoparticle-based systems have significantly improved the therapeutic index of cytotoxic agents. By concentrating the drug within the tumor microenvironment and reducing exposure to healthy tissues, they alleviate systemic toxicity. Examples include liposomal doxorubicin, paclitaxel-loaded polymeric nanoparticles, and gold nanoparticles for hyperthermic ablation.For central nervous system (CNS) disorders, nanoparticles offer solutions to the challenge of crossing the blood–brain barrier. Surface modification with transferrin, lactoferrin, or apolipoprotein ligands facilitates receptor-mediated transport across endothelial cells. Nanocarriers have shown promise in delivering neuroprotective agents, siRNA, and anti-Alzheimer's drugs directly to the brain.In infectious diseases, nanoparticles enhance the solubility and stability of antibiotics, enabling sustained drug levels that help overcome microbial resistance. Lipid-based carriers are used for antifungal delivery (e.g., amphotericin B liposomes), while polymeric nanoparticles serve in vaccine delivery, acting as both antigen carriers and adjuvants to induce robust immune responses.[18]

3.6 Pharmacokinetics and Biodistribution

The pharmacokinetic profile of nanoparticles is governed by their physicochemical properties. Particle size below 200 nm promotes long circulation and tumor accumulation via the EPR effect. Surface charge also influences biodistribution—slightly negative or neutral nanoparticles exhibit reduced opsonization compared with highly charged ones. The route of administration determines systemic absorption; intravenous injection ensures immediate distribution, while oral or nasal delivery requires mucoadhesive or protective coatings to resist degradation. Biodistribution studies reveal that nanoparticles can be preferentially localized in the liver, spleen, or lungs depending on their composition and surface chemistry. Strategies such as PEGylation or zwitterionic coatings help reduce hepatic uptake and extend systemic availability, enabling improved drug exposure at the desired site.[19]

3.7 Toxicity and Biocompatibility Considerations

While nanoparticles offer substantial benefits, their safety profiles require meticulous evaluation. Toxicity may arise from particle accumulation, oxidative stress, or inflammatory responses. Metallic nanoparticles, if not adequately coated, can catalyze reactive oxygen species formation, damaging cellular components. Polymeric degradation products, though generally biocompatible, must be monitored for local acidity or cytotoxicity. The long-term fate of nanoparticles—especially their clearance routes and potential organ retention—remains a crucial research area. Regulatory authorities now emphasize comprehensive preclinical assessments covering physicochemical characterization, hemocompatibility, immunogenicity, and genotoxicity. Developing standardized testing protocols will be key to ensuring safe translation of nanomedicines into clinical practice.[18,19]

4. MICRONEEDLE-MEDIATED DRUG DELIVERY SYSTEMS

4.1 Concept and Design of Microneedles

Microneedle-mediated drug delivery represents one of the most innovative approaches in transdermal therapeutic systems. It is designed to overcome the principal barrier of the skin—the stratum corneum, a 10–20 μm thick outermost layer composed of keratinized cells and lipids that restrict the permeation of most drugs, particularly hydrophilic macromolecules and biopharmaceuticals. Conventional transdermal patches can only deliver small, lipophilic molecules, while invasive injections, though effective, often result in pain, needle phobia, and medical waste. Microneedles bridge this gap by enabling painless, minimally invasive, and patient-friendly transdermal delivery.Microneedles are miniature projections, typically ranging between 25 μm and 1000 μm in height, which can pierce the stratum corneum and reach the viable epidermis without stimulating dermal nerves or causing bleeding. They are usually fabricated into arrays (ranging from tens to hundreds per patch), capable of uniformly puncturing the skin surface. Once inserted, these microchannels facilitate the transport of therapeutic agents either by passive diffusion, dissolution, or active pumping mechanisms. The conceptual development of microneedles originated in the late 1990s with advances in microfabrication and materials science. Early prototypes were silicon-based and produced via photolithographic techniques derived from microelectromechanical systems (MEMS). Over time, the field evolved to incorporate biodegradable polymers, metals, ceramics, and composite materials, offering enhanced mechanical strength, safety, and drug compatibility. Current research focuses on smart microneedles that combine sensing, controlled release, and feedback mechanisms to enable closed-loop therapy.[20,21]

4.2 Types of Microneedles

Microneedles are broadly categorized based on their structural design and mechanism of drug administration. The four major types—solid, coated, dissolving, and hollow microneedles—represent distinct technological approaches within the same conceptual framework.

4.2.1 Solid Microneedles

Solid microneedles were the first generation to be explored for skin pre-treatment. They function by mechanically perforating the stratum corneum to create microchannels that increase skin permeability. Following this "poke and patch" method, a drug formulation—gel, cream, or patch—is applied over the treated site, where it diffuses into the microchannels. Fabrication materials include silicon, titanium, stainless steel, and certain rigid polymers. These systems are valued for their simplicity and mechanical robustness, but their two-step application (piercing followed by drug application) and lack of sustained delivery capability limit widespread

use. However, solid microneedles remain important in research and cosmetic applications (e.g., collagen induction therapy and topical drug enhancement).[21]

4.2.2 Coated Microneedles

Coated microneedles incorporate the drug directly on the needle surface via thin polymeric or sugar coatings. Techniques such as dip-coating, spray-coating, or layer-by-layer deposition are employed to achieve uniform coatings containing the desired drug load. Upon insertion, the coating dissolves quickly in the interstitial fluid, releasing the drug into the skin. This approach offers rapid drug release, precise dosing, and suitability for biomolecules, vaccines, and peptides. Studies have demonstrated effective transdermal delivery of influenza antigens, DNA plasmids, and desmopressin using coated microneedles. However, coating thickness, drug stability, and the potential for uneven distribution remain significant technical challenges. The integration of stabilizing excipients (e.g., trehalose, sucrose) has been shown to preserve protein conformation and bioactivity during coating and storage.[22]

4.2.3 Dissolving Microneedles

Dissolving microneedles are fabricated entirely from biocompatible, water-soluble polymers that encapsulate the drug within the matrix. When inserted, they dissolve or biodegrade, releasing the drug into the epidermis or dermis. Polymers such as polyvinylpyrrolidone (PVP), carboxymethyl cellulose (CMC), hyaluronic acid (HA), chitosan, and poly(lactic-co-glycolic acid) (PLGA) are frequently used. These microneedles eliminate the need for removal, leaving no sharp waste, thereby enhancing safety and patient compliance. The rate of dissolution—and consequently, the release kinetics—can be precisely tuned by modifying polymer concentration or cross-linking density. Such systems are ideal for delivering insulin, vaccines, analgesics, and growth factors. Notably, hyaluronic acid-based microneedles have demonstrated excellent biocompatibility and hydration-driven insertion, making them suitable for both therapeutic and cosmetic applications.[22,23]

4.2.4 Hollow Microneedles

Hollow microneedles contain an internal bore through which liquid formulations can be actively infused. They operate via a "poke and flow" mechanism, functioning as miniature hypodermic needles that deliver precise doses into the skin. Hollow microneedles are typically fabricated from metals, glass, or silicon and may be connected to micro-pumps or pressurized reservoirs to regulate infusion rates. They are particularly valuable for drugs requiring continuous infusion or large-volume

delivery, such as hormones, vaccines, or biologics. However, their complex fabrication, risk of blockage, and fragility present ongoing challenges. Advanced designs with side openings or multi-bore configurations have been developed to enhance flow and prevent clogging.[23]

4.3 Mechanism of Transdermal Drug Delivery

Microneedle-assisted transdermal delivery relies on the temporary disruption of the skin barrier. When microneedles penetrate the stratum corneum, they create aqueous microchannels that permit the diffusion of hydrophilic and macromolecular drugs, which otherwise cannot permeate the intact skin.

The delivery mechanism varies by microneedle type:

- Solid microneedles: Enhance permeability by creating channels for subsequent passive diffusion.

- Coated microneedles: Deliver drugs upon dissolution of the surface layer immediately after insertion.

- Dissolving microneedles: Gradually release the encapsulated drug as the matrix dissolves.

- Hollow microneedles: Permit active infusion or pressure-driven flow into deeper dermal layers.

After removal, the microchannels typically close within hours due to skin's natural repair mechanisms, minimizing infection risks. Studies using confocal microscopy and optical coherence tomography (OCT) confirm that microneedle-induced pores reseal rapidly, validating their safety for repeated use.[24]

4.4 Fabrication Techniques and Materials Used

Fabrication techniques are critical for ensuring structural precision, reproducibility, and scalability. The major fabrication processes include:

- Photolithography and Deep Reactive Ion Etching (DRIE) – Commonly used for silicon microneedles, providing excellent geometric precision but at high manufacturing costs.

- Laser Micromachining and Electroforming – Utilized for metallic microneedles, allowing high mechanical strength and sharpness.

- Micro-molding – The most widely used technique for polymeric microneedles. It involves pouring a polymer-drug mixture into molds, followed by drying or curing.

- 3D Printing (Additive Manufacturing) – An emerging approach that allows customization of microneedle geometry and integration of multiple drugs or sensors.

Microneedle Drug Delivery Types

Solid

Solid: Physical penetration for passive diffusion

Coated

Coated: Drug-coated surface for release during insertion

Dissolving

Dissolving: Biodegradable matrix dissolves to release drug

Hollow

Hollow: Fluid channel for active drug infusion

Hydrogel-Forming

Hydrogel-Forming: Swells in skin to form drug-releasing matrix

Epidermis	Epidermis	Epidermis	Dermis	Epidermis

Mechanism
Solid: Physical penetration for passive diffusion

Dissolving:
Biodegradable matrix dissolves to insertion

Dissolving:
Fluid channel for active drug dirar

Example Applications
• Vaccines   • Insulin
• Tip

Example Applications
• Vaccines   • Needle Shaft
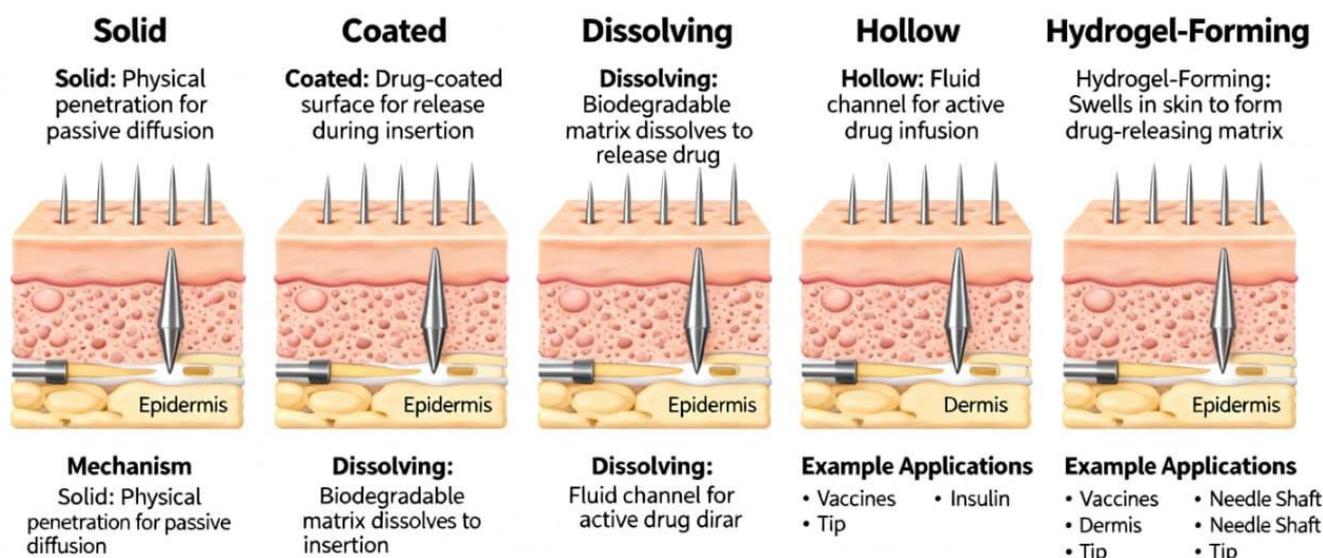• Dermis   • Needle Shaft
• Tip   • Tip

Figure 2: Microneedle Drug delivery and its types:

The choice of material depends on the intended use. Silicon and metals (e.g., titanium, stainless steel) provide strength for solid and hollow microneedles. Biopolymers (e.g., HA, CMC, PVP) are used for dissolving systems. Ceramic and composite materials are being explored for sustained-release and structural reinforcement. Surface modifications, such as hydrophilic coatings, drug reservoirs, or nanoparticle embedding, further enhance drug loading and diffusion control. Mechanical testing ensures that microneedles withstand insertion forces without bending or fracture.[25]

4.5 Applications in Vaccination, Diabetes, and Pain Management

The versatility of microneedle systems enables a wide range of clinical applications.

Vaccination:
Microneedle-based vaccination leverages the high density of antigen-presenting cells (Langerhans and dendritic cells) in the skin. Studies show that skin-targeted delivery can induce stronger immune responses than intramuscular routes while using smaller antigen doses. Influenza, polio, hepatitis B, and SARS-CoV-2 microneedle vaccines have all shown promising results. Moreover, dissolving microneedle patches eliminate cold-chain dependency by stabilizing vaccine components in solid form, facilitating global immunization campaigns.

Diabetes Management:

Microneedle patches for insulin delivery have emerged as a viable alternative to subcutaneous injections. Glucose-responsive microneedles that release insulin in proportion to interstitial glucose levels have been developed using pH-sensitive polymers and enzymatic glucose sensors. Continuous glucose monitoring (CGM) microneedles integrated with microelectrodes enable real-time metabolic feedback, paving the way for closed-loop insulin therapy.

Pain Management:

Microneedle patches containing local anesthetics (lidocaine, prilocaine) achieve rapid dermal anesthesia suitable for dermatological or cosmetic procedures. Controlled-release systems for opioids and NSAIDs are being investigated to improve chronic pain management while reducing systemic side effects. Other emerging applications include hormone replacement, cancer immunotherapy, and cosmetic delivery of bioactives such as hyaluronic acid and retinoids.[24,25]

4.6 Clinical Studies and Translational Aspects

Several microneedle systems have progressed to clinical evaluation. In a landmark Phase I study, influenza vaccines delivered via dissolving microneedles produced equivalent or superior immunogenicity compared to conventional injections, with over 90% of participants preferring patches for future vaccinations. Similarly, microneedle-based measles and rubella vaccines have demonstrated promising immune responses in pediatric populations. In diabetes, clinical testing of insulin-loaded dissolving microneedles has shown consistent plasma glucose control and minimal irritation. Patient feedback indicates significantly lower discomfort and higher satisfaction. For pain relief, lidocaine-coated microneedles have demonstrated faster onset and longer analgesia duration compared to topical creams. Despite these successes, regulatory translation faces hurdles related to scalability, cost, and sterility assurance. Commercial products such as the Soluvia® microinjection system and the MicronJet® platform have gained regulatory clearance, demonstrating feasible pathways for clinical integration. However, large-scale adoption will depend on robust manufacturing standards and long-term stability data.[25]

4.7 Safety, Patient Compliance, and Regulatory Considerations

The safety of microneedle systems has been validated through multiple preclinical and clinical investigations. Their shallow penetration avoids contact with blood vessels and nerves, minimizing bleeding and infection risk. Most formulations use biocompatible, non-toxic materials, and any transient erythema or edema typically resolves within hours. From a patient compliance standpoint, microneedle patches are painless, needle-free, and self-administrable, significantly improving adherence for chronic therapies and vaccinations. The elimination of sharps waste also enhances safety for healthcare workers and environmental sustainability. Regulatory agencies such as the U.S. FDA classify microneedles as combination products (drug + device), requiring compliance with both pharmaceutical and medical device regulations. Developers must provide detailed validation for dose uniformity, sterility, mechanical robustness, and in vivo performance consistency. The absence of specific regulatory guidelines for microneedles remains a challenge, but recent industry collaborations are moving toward standardized testing protocols.[23,24,25]

5. 3D-PRINTED PERSONALIZED MEDICINES

5.1 Introduction to 3D Printing in Pharmaceutics

Three-dimensional (3D) printing, also known as additive manufacturing, has emerged as a transformative technology in pharmaceutical sciences. It enables the precise fabrication of complex drug delivery systems through layer-by-layer deposition of materials guided by digital design. In contrast to conventional manufacturing processes such as compression or molding, 3D printing allows unprecedented control over dosage, geometry, release kinetics, and multi-drug integration within a single dosage form. The application of 3D printing in pharmaceutics aligns closely with the growing paradigm of personalized medicine, where therapies are tailored to the physiological, genetic, and pharmacokinetic profile of individual patients. This is particularly significant for drugs with narrow therapeutic indices, pediatric formulations requiring flexible dosing, and combination therapies targeting multifactorial diseases. The approval of Spritam® (levetiracetam) by the U.S. Food and Drug Administration (FDA) in 2015 marked a milestone, establishing 3D printing as a viable approach to pharmaceutical manufacturing. Since then, research has rapidly expanded to include controlled-release tablets, implants, transdermal systems, and even tissue-engineered scaffolds. By integrating computer-aided design (CAD), digital health data, and advanced polymers, 3D printing offers a pathway toward on-demand, patient-specific drug production within hospital or pharmacy settings. This shift from mass production to point-of-care manufacturing represents a paradigm change in pharmaceutical practice.[26]

5.2 Principles and Techniques of Pharmaceutical 3D Printing

3D printing operates on the fundamental principle of additive manufacturing, where a digital model is translated into a physical object through sequential layer deposition. Each layer is precisely constructed using thermoplastic, photopolymer, or powder-based materials embedded with active pharmaceutical ingredients (APIs) and excipients. Several 3D printing techniques have been adapted for pharmaceutical use, with variations in resolution, material compatibility, and drug stability. The most prominent among them include Fused Deposition Modeling (FDM), Stereolithography (SLA), and Inkjet/Binder Jet Printing.

5.2.1 Fused Deposition Modeling (FDM)

FDM is the most widely explored technique in pharmaceutics due to its simplicity and cost-effectiveness. In this method, a drug-loaded thermoplastic filament—typically composed of polymers such as polyvinyl alcohol (PVA), polylactic acid (PLA), or hydroxypropyl cellulose (HPC)—is fed into a heated nozzle. The polymer melts and is extruded in a layer-by-layer manner according to a computer-generated pattern. FDM allows precise control of drug loading, infill density, and release rate by adjusting printing parameters such as temperature, nozzle diameter, and layer height. However, the high processing temperatures (typically 150–250°C) may limit its use with thermolabile drugs. Researchers have addressed this limitation through hot-melt extrusion (HME) pre-processing and incorporation of plasticizers to lower melting points. FDM has been successfully used to produce multi-compartment tablets, osmotic-controlled release systems, and pediatric formulations with customized shapes and doses.

5.2.2 Stereolithography (SLA)

SLA is a photopolymerization-based printing technique that uses ultraviolet (UV) or visible light to solidify liquid resin in a pre-defined pattern. The printing platform moves incrementally to allow successive layers of polymerization, forming a solid 3D structure. In pharmaceutical contexts, SLA enables extremely high resolution and surface precision, making it suitable for microneedle fabrication, implantable devices, and microfluidic drug delivery systems. Photocurable polymers such as polyethylene glycol diacrylate (PEGDA) and methacrylate-based resins are commonly used. A critical challenge for SLA is ensuring biocompatibility and removal of residual photoinitiators, which could lead to toxicity. Nonetheless, SLA's capacity for intricate geometries and variable drug loading makes it a leading candidate for advanced dosage forms.[26]

5.2.3 Inkjet and Binder Jet Printing

Inkjet printing is a non-contact technique that deposits drug solutions or suspensions in picoliter-sized droplets onto a substrate, typically a polymeric film or powder bed. It operates via thermal or piezoelectric mechanisms that control droplet ejection. Binder jet printing, a variation of inkjet printing, involves depositing a binding solution onto a powder layer, which is subsequently fused through solvent evaporation or heating. The process is ideal for highly porous tablets that disintegrate rapidly upon contact with water. The most prominent example is Aprecia Pharmaceuticals' ZipDose® technology, which

underlies Spritam®. This platform can accommodate up to 1000 mg of API in a single, highly porous unit, ensuring rapid oral disintegration. Inkjet-based methods also allow for precise spatial placement of multiple drugs, enabling fixed-dose combination therapies and gradient release profiles. Limitations include the need for stable printable formulations and avoidance of nozzle clogging due to drug crystallization.[26,27]

5.3 Materials and Excipients Used in 3D Printing

The selection of appropriate materials—both active and inactive—is central to the success of pharmaceutical 3D printing. Materials must exhibit printability, mechanical integrity, drug compatibility, and biocompatibility. Polymers form the backbone of most formulations. Commonly used thermoplastic polymers include PLA, PVA, polycaprolactone (PCL), ethyl cellulose, and Eudragit® variants. For photopolymerization, PEGDA, poly(ethylene glycol) diacrylate, and methacrylate copolymers are preferred. Plasticizers such as glycerol, triethyl citrate, and polyethylene glycol are often added to enhance flexibility and reduce processing temperature. Fillers and porogens like mannitol or lactose are used to modulate disintegration and porosity. Drug-excipient compatibility is crucial to ensure chemical stability during high-temperature or photochemical processing. Excipients must comply with pharmacopeial standards and regulatory guidelines for pharmaceutical-grade safety.[28]

5.4 Personalized Dosage Forms and On-Demand Drug Manufacturing

One of the greatest advantages of 3D printing is its ability to fabricate personalized dosage forms tailored to individual patient needs. Using patient-specific parameters such as age, body weight, genetic profile, and disease state, healthcare professionals can design unique dosage geometries and strengths directly from digital prescriptions. This flexibility supports on-demand manufacturing, wherein medicines are produced at the point of care—such as hospitals or community pharmacies—without the need for large-scale factory production. Such a model significantly reduces storage and waste, especially for drugs with limited shelf life or specialized dosing requirements. 3D printing also allows combination therapy through multi-drug tablets that incorporate different APIs in separate compartments with distinct release kinetics. This is particularly valuable for polypharmacy patients, where medication adherence is a concern. Moreover, 3D-printed dosage forms can integrate controlled-release patterns, floating systems, and buccal films, making them adaptable across multiple therapeutic classes.[29]

5.5 Case Studies of 3D-Printed Medicines (e.g., *Spritam®*)

The first FDA-approved 3D-printed oral drug, *Spritam®* (levetiracetam), exemplifies the clinical feasibility of additive manufacturing. Developed by Apr Apr Pharmaceuticals using its proprietary ZipDose® technology, the product features a highly porous structure that allows rapid disintegration—within seconds—when taken with a sip of water. This innovation addresses the swallowing difficulties faced by epileptic patients requiring high-dose antiepileptic therapy. Beyond *Spritam®*, several investigational studies have explored 3D-printed polypills containing antihypertensive and statin combinations, pediatric chewable tablets, and implantable cancer therapeutics. Research in hospital compounding environments demonstrates that 3D printing could enable customized morphine doses or modified-release warfarin tablets based on individual pharmacogenomic data. The continuous expansion of such case studies underscores the transition from theoretical concept to clinically implementable technology.[29,30]

5.6 Quality Control, Scalability, and Reproducibility Challenges

Parameter	Challenge	Implications	Potential Solutions
Dosage Accuracy	Variability in layer deposition and extrusion rate	Inconsistent drug content and therapeutic response	Calibration of printers; in-process monitoring via spectroscopy[28]
Drug Stability	Exposure to heat, light, or solvents during printing	Degradation of thermolabile APIs	Use of heat-stable polymers and process optimization[29]
Mechanical Strength	Variations in infill pattern and porosity	Tablet fragility during handling	Optimization of printing parameters and post-curing processes[30]
Scalability	Limited throughput and long production time	Unsuitable for large-scale manufacturing	Development of multi-nozzle systems and automated workflows[29,30]
Reproducibility	Batch-to-batch variability in layer alignment	Quality assurance issues	Implementation of Process Analytical Technology (PAT) and AI-based quality control[30]
Storage and Shelf Life	Hygroscopic materials and poor moisture stability	Reduced product longevity	Incorporation of moisture barriers and controlled packaging systems[29]

5.7 Regulatory and Ethical Considerations

Aspect	Regulatory/Ethical Concern	Discussion and Implications
Regulatory Framework	Lack of specific guidelines for 3D-printed pharmaceuticals	FDA and EMA currently evaluate 3D-printed medicines under existing drug and device frameworks, but require new standards for digital design validation and on-demand manufacturing.
Quality Assurance	Validation of digital models and printer calibration	Regulatory authorities require evidence of consistency, sterility, and reproducibility across batches printed at different sites.
Intellectual Property (IP)	Risk of design duplication and unauthorized drug printing	The digital nature of 3D printing raises concerns about counterfeit medicines and IP protection for digital blueprints.
Data Integrity and Cybersecurity	Vulnerability of CAD files and prescription data	Secure data management and encryption are critical to prevent manipulation of dosage or patient-specific information.
Ethical Distribution	Accessibility of 3D-printing technologies across socioeconomic settings	Equitable access must be ensured to prevent healthcare disparities, particularly in low-resource regions.
Patient Safety and Oversight	Risk of errors in point-of-care manufacturing	Ethical responsibility falls on healthcare professionals to validate digital designs and ensure adherence to Good Manufacturing Practices (GMP).
Environmental Sustainability	Disposal of photopolymers and plastic waste	Sustainable material selection and recycling policies must accompany future large-scale adoption.[31,32]

6. COMPARATIVE ANALYSIS OF EMERGING DRUG DELIVERY PLATFORMS

6.1 Comparative Advantages and Limitations

Nanoparticles, microneedles, and 3D-printed personalized medicines represent three major innovations that are redefining modern drug delivery. Each platform exhibits distinct scientific and clinical advantages but also faces inherent limitations that influence its applicability. Through both passive and active methods, nanoparticles offer tremendous precision in targeting particular tissues or cells. They are appropriate for complicated ailments like cancer, neurological disorders, and infectious diseases because of their capacity to encapsulate a variety of medications and control release kinetics. However, its clinical translation is restricted by issues with toxicity, immunological response, stability, and large-scale reproducibility.[33] Microneedles, on the other hand, offer a minimally invasive, patient-friendly approach for transdermal and intradermal administration. They enable painless delivery and bypass first-pass metabolism, improving bioavailability of peptides, proteins, and vaccines. Nevertheless, their limited drug loading capacity, mechanical fragility, and variability in skin penetration remain technical challenges.[34] 3D-printed personalized medicines bring unparalleled flexibility by allowing tailored dosages, shapes, and release profiles. They can integrate multiple drugs within one dosage form and enable on-demand production close to the point of care. Despite this promise, high production costs, limited throughput, and lack of standardized regulatory frameworks constrain broader adoption.

Collectively, nanoparticles dominate in targeting precision, microneedles excel in patient compliance, and 3D printing leads in personalization—each addressing distinct gaps in drug delivery science.[35]

6.2 Selection Criteria Based on Therapeutic Applications

The selection of an appropriate delivery system depends on therapeutic objectives, drug properties, and patient factors. For systemic diseases such as cancer or autoimmune disorders, nanoparticles are preferred due to their controlled biodistribution and tissue targeting.[36] Microneedles are ideal for localized and transdermal therapies, particularly in vaccination, insulin administration, and pain management. 3D printing, conversely, is advantageous for oral and implantable formulations that require dose flexibility or multi-drug integration, making it highly suitable for pediatrics and geriatrics.[37,38] Thus, therapeutic application dictates platform selection: nanoparticles for precision delivery, microneedles for minimally invasive administration, and 3D printing for personalized pharmacotherapy.

6.3 Cost, Manufacturability, and Patient-Centric Aspects

From a manufacturing and economic standpoint, nanoparticles benefit from well-established synthesis methods but require stringent quality control, increasing production costs. Microneedles are comparatively cost-effective and scalable, enabling large-scale deployment for vaccines and chronic therapies. 3D printing, though currently expensive and time-intensive, holds future potential for on-demand manufacturing in hospitals or

pharmacies.[34,39] In terms of patient experience, microneedles and 3D-printed formulations enhance convenience, adherence, and comfort, while nanoparticles ensure improved clinical outcomes through effective targeting.[40,41] Overall, the integration of these technologies within a unified therapeutic framework could lead to a new era of precision, accessibility, and patient-centric medicine.[42]

7. INTEGRATION OF SMART TECHNOLOGIES IN NOVEL DRUG DELIVERY

7.1 Role of Artificial Intelligence and Machine Learning

The convergence of artificial intelligence (AI) and machine learning (ML) with pharmaceutical research has ushered in a new era of precision-driven drug delivery. These technologies play an increasingly critical role in designing, optimizing, and predicting the performance of novel drug delivery systems (DDS) such as nanoparticles, microneedles, and 3D-printed formulations.[43] AI algorithms can process complex datasets from pharmacokinetic, physicochemical, and patient-specific parameters to identify optimal drug-carrier combinations. For example, in nanoparticle design, ML models can predict parameters such as particle size, zeta potential, and encapsulation efficiency, which directly influence biodistribution and therapeutic efficacy. Similarly, deep learning models can simulate drug release kinetics and optimize formulations to achieve sustained or targeted release profiles with minimal experimental trials. In microneedle technology, AI-driven modeling assists in needle geometry optimization, insertion mechanics, and drug diffusion behavior, ensuring consistent transdermal delivery across variable skin types. For 3D-printed personalized medicines, AI supports dose prediction, digital blueprint validation, and process control, enabling accurate layer deposition and material selection.[44] Beyond formulation, AI integrates with predictive pharmacology to forecast individual patient responses, helping tailor drug release profiles to genetic or metabolic variability. This transition from empirical formulation to data-driven design significantly reduces development time, cost, and experimental burden, advancing the realization of truly personalized therapy.[45]

7.2 Biosensors, Wearables, and the Internet of Medical Things (IoMT)

The integration of biosensors, wearable devices, and the Internet of Medical Things (IoMT) is transforming drug delivery into a dynamic and responsive system. IoMT refers to interconnected medical devices capable of monitoring physiological parameters and transmitting real-time data for therapeutic adjustments.[46] In modern DDS, biosensors can be embedded into delivery platforms to monitor drug levels, tissue pH, glucose concentration, or inflammation markers. This feedback allows adaptive drug release depending on biological signals. For example, glucose-responsive microneedle patches release insulin when blood glucose levels rise, maintaining tight glycemic control without manual intervention.[47] Wearable systems, including smart patches and microfluidic devices, enable continuous monitoring and closed-loop drug delivery. Integration with smartphones or cloud-based systems allows clinicians to track adherence and modify dosing remotely. Such systems are especially valuable in chronic diseases like diabetes, cardiovascular disorders, and neurological conditions.[48] In addition, IoMT facilitates the collection of large-scale real-world data, which can be analyzed using AI to enhance understanding of patient responses and optimize treatment regimens. Collectively, the synergy between biosensors, wearables, and smart delivery systems is shifting drug administration from passive dosing toward interactive, feedback-regulated therapeutics.[49]
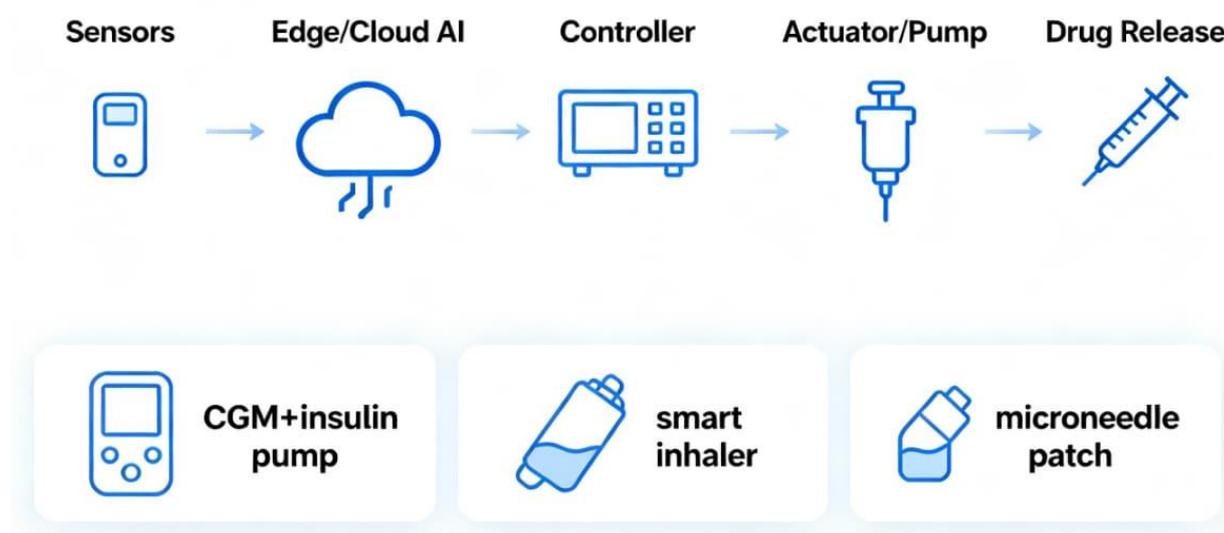

Figure 3: IoMT- Enabled Responsive Drug delivery system

7.3 Smart Polymers and Stimuli-Responsive Delivery Systems

Another remarkable development in advanced DDS is the use of smart polymers, which alter their physicochemical properties in response to external or internal stimuli. These materials provide controlled and localized drug release, improving therapeutic precision and minimizing systemic toxicity.[50] Smart polymers are categorized based on the type of stimulus they respond to—pH, temperature, redox potential, enzymes, light, or magnetic fields. For instance, pH-sensitive polymers such as Eudragit® are widely employed in colon-targeted delivery, where acidic and basic environments trigger specific release events. Thermo-responsive hydrogels made from poly(N-isopropylacrylamide) (PNIPAAm) release drugs when exposed to body heat or inflamed tissues.[51] In cancer therapy, enzyme-responsive nanoparticles degrade in tumor microenvironments, enabling targeted drug deposition. Similarly, magnetically guided nanoparticles and light-triggered nanocarriers allow remote-controlled release, combining diagnostics and therapeutics in one platform—an approach often termed theranostics.[52] The integration of these smart materials into microneedles and 3D-printed scaffolds enhances adaptability and precision. For example, dissolving microneedles composed of temperature-sensitive polymers can achieve controlled drug diffusion rates, while 3D-printed hydrogels embedded with stimuli-responsive networks enable site-specific release for implants or wound healing applications.[53] Thus, stimuli-responsive DDS exemplify the movement toward autonomous, self-regulating delivery systems, where drugs are released only when and where needed, significantly improving treatment efficacy and patient safety.

7.4 Personalized Medicine and Data-Driven Formulation Design

Personalized medicine seeks to tailor therapy to the unique characteristics of each patient—genetic, metabolic, and physiological. Smart technologies, when integrated with novel DDS, make this concept increasingly attainable.[54] Through AI-driven modeling, pharmacogenomic data can guide individualized dosage design, particularly for drugs with narrow therapeutic windows. For instance, 3D-printed tablets can be fabricated on demand, adjusting drug combinations and release patterns according to patient data derived from electronic health records (EHRs) and wearable sensors.[55] This data-driven formulation approach minimizes trial-and-error formulation, reduces adverse reactions, and enhances therapeutic outcomes. Integration of patient-specific data with digital manufacturing platforms allows precision pharmaceutics, aligning closely with the goals of predictive and preventive medicine.[56,57]

8. CHALLENGES IN THE DEVELOPMENT AND COMMERCIALIZATION OF NOVEL DDS

8.1 Manufacturing and Scale-Up Barriers

While laboratory-scale success is evident, scaling up novel DDS for commercial production remains a significant challenge. Nanoparticle synthesis often faces batch-to-batch variability, high solvent consumption, and complex purification processes. Similarly, microneedle fabrication requires stringent dimensional uniformity and sterile environments, raising production costs.[58] 3D printing, though customizable, currently lacks industrial throughput, making it suitable mainly for small-batch or hospital compounding. The need for process standardization, automation, and quality control frameworks remains a key barrier to commercialization.[59]

8.2 Stability and Shelf-Life Issues

Stability is another critical concern. Nanoparticles can undergo aggregation, oxidation, or drug leakage during storage. Microneedles, especially dissolving or coated types, are prone to moisture absorption and microbial contamination, while 3D-printed formulations may degrade under high humidity or temperature fluctuations.[60] Ensuring consistent physicochemical stability without compromising biocompatibility requires the development of novel stabilizers, lyophilization techniques, and protective packaging systems. Shelf-life validation must follow International Council for Harmonisation (ICH) guidelines to ensure long-term safety and efficacy.[61]

8.3 Safety, Toxicity, and Ethical Considerations

Safety evaluation is paramount for all advanced DDS. Nanoparticles, due to their small size, may cross biological barriers and accumulate in non-target organs, leading to cytotoxicity or immunogenicity. Microneedles, while minimally invasive, must ensure biomechanical integrity and sterility to prevent infections.[62,63] From an ethical perspective, personalized systems involving digital data and AI-driven decisions must safeguard patient privacy and prevent data misuse. Transparent reporting of algorithmic decisions, ethical approval in clinical studies, and patient-informed consent are essential for responsible innovation.[64]

8.4 Regulatory Framework and Approval Pathways

The regulatory landscape for novel DDS is still evolving. While traditional dosage forms follow well-defined approval procedures, nanocarriers, microneedles, and 3D-printed drugs require specialized assessment of material safety, device-drug combination status, and digital model validation.[65,66] The U.S. FDA and European Medicines Agency (EMA) currently evaluate these technologies under existing frameworks but acknowledge the need for new guidelines addressing digital manufacturing, adaptive release systems, and decentralized production models. Establishing harmonized international standards will be crucial for market authorization and global adoption.[67,68]

8.5 Cost-Effectiveness and Market Adoption

The economic feasibility of novel DDS remains a key determinant of their clinical success. Nanoparticle formulations involve high development and purification costs, while 3D printing demands expensive hardware and skilled operators. However, microneedles offer comparatively affordable production and higher patient acceptance, especially for self-administration.[69,70] As the

technology matures, the adoption of automation, continuous manufacturing, and AI-based optimization is expected to reduce costs. Collaboration between academia, industry, and regulatory agencies will play a pivotal role in achieving scalable and cost-effective production pathways.[71]

9. FUTURE PERSPECTIVES

9.1 Integration of Multimodal Drug Delivery Systems

Future drug delivery strategies are likely to converge multiple technologies to create hybrid systems with enhanced precision and functionality. Combining nanoparticles with microneedle arrays, for instance, can enable localized delivery of nanoformulations through minimally invasive routes. Similarly, 3D-printed scaffolds embedded with smart nanoparticles or biosensors could allow simultaneous drug release and real-time monitoring.[72]

Such multimodal DDS will unify therapeutic and diagnostic capabilities, leading to personalized theranostic platforms capable of sensing, responding, and adapting to physiological conditions dynamically.[73]

9.2 Role of 4D Printing and Bioprinting

Beyond 3D printing, 4D printing introduces the concept of time-dependent transformation, where printed materials can change shape, structure, or function in response to external stimuli such as temperature or pH. In pharmaceutics, this technology enables adaptive implants and responsive dosage forms that modify their behavior according to the body's environment.[74,75] Bioprinting, an extension of 3D printing, utilizes living cells and biomaterials to fabricate tissue-like constructs. Its potential extends to drug screening models, regenerative medicine, and localized therapeutic implants, representing a bridge between pharmacology and tissue engineering.[76,77]

10. CONCLUSION

The evolution of novel drug delivery systems—spanning nanoparticles, microneedles, and 3D-printed personalized medicines—marks a profound shift in pharmaceutical sciences from conventional formulations toward intelligent, adaptive, and patient-centered therapies. These technologies collectively enhance therapeutic precision, minimize systemic toxicity, and promote individualized treatment paradigms. While significant challenges persist in scalability, regulation, and cost, the integration of AI, IoMT, and smart polymers continues to expand the possibilities for next-generation drug delivery. The transition from static dosing to responsive, data-driven therapeutics reflects the broader transformation of healthcare toward precision medicine.In the coming decade, the fusion of material science, digital health, and computational intelligence will redefine the boundaries of pharmaceutics. The convergence of nanoparticles for targeted delivery, microneedles for painless administration, and 3D/4D printing for personalization holds the promise of therapeutics that are not only effective but also adaptive, affordable, and accessible. Ultimately, such innovations will bridge the gap between engineering, biology, and

medicine—ushering in a future where drug delivery is as dynamic and individualized as the patients it serves.

REFERENCES:

1. Ventola CL. Progress in nanomedicine: approved and investigational nanodrugs. P T. 2017;42(12):742-55.

2. Langer R. Drug delivery and targeting. Nature. 1998;392(6679 Suppl):5-10.

3. Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies. Nat Rev Drug Discov. 2014;13(9):655-72. https://doi.org/10.1038/nrd4363 PMid:25103255 PMCid:PMC4455970

4. Allen TM, Cullis PR. Drug delivery systems: entering the mainstream. Science. 2004;303(5665):1818-22. https://doi.org/10.1126/science.1095833 PMid:15031496

5. Langer R, Peppas NA. Advances in biomaterials, drug delivery, and bionanotechnology. AIChE J. 2003;49(12):2990-3006. https://doi.org/10.1002/aic.690491202

6. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261-8. https://doi.org/10.1038/nbt.1504 PMid:18997767 PMCid:PMC2700785

7. Ventola CL. Progress in nanomedicine: approved and investigational nanodrugs. P T. 2017;42(12):742-55.

8. Choudhury H, Pandey M, Lim YQ, Low CY, Lee CK, Marilyn TCY, et al. 3D-printed biodegradable microneedles for transdermal drug delivery: perspectives and challenges. Comput Struct Biotechnol J. 2021;19:1245-58.

9. Islam S, et al. Advances in nanoparticles in targeted drug delivery-A review. ScienceDirect. 2025. https://doi.org/10.1016/j.rsurfi.2025.100529

10. Tripathi D, et al. Advances in nanomaterials for precision drug delivery. PMC. 2024.

11. Khalid-Salako F, et al. The Nanocarrier Landscape: Evaluating Key Drug Delivery. ACS. 2025.

12. Saleh-Bey-Kinj Z, et al. 3D Printing in Oral Drug Delivery. PMC. 2025

13. Chenxi Z, et al. Review Nanoparticle-enhanced drug delivery systems. ScienceDirect. 2025 https://doi.org/10.1016/j.molliq.2025.126999

14. Li Y, et al. Advances in microneedle-based drug delivery system for... PMC. 2025

15. Meng F, et al. Recent progress of polymeric microneedle-assisted long... Frontiers Partnerships. 2024 https://doi.org/10.3389/jpps.2024.12434 PMid:38571937 PMCid:PMC10987780

16. Pharmacy Journal. Artificial intelligence and 3D printing in pharmaceuticals. Pharmacy Journal. 2025

17. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an Emerging Platform for Cancer Therapy. Nat Nanotechnol. 2007;2(12):751-760 https://doi.org/10.1038/nnano.2007.387 PMid:18654426

18. Panyam J, Labhasetwar V. Biodegradable Nanoparticles for Drug and Gene Delivery to Cells and Tissue. Adv Drug Deliv Rev. 2012;64:61-71 https://doi.org/10.1016/j.addr.2012.09.023

19. Parajapati S, Maurya S, Das M, Tilak VK, Verma KK, Dhakar RC. Potential Application of Dendrimers in Drug Delivery: A Concise Review and Update. Journal of Drug Delivery and Therapeutics. 2016;6(2):71-88 https://doi.org/10.22270/jddt.v6i2.1195

20. Donnelly RF, Moffatt K, Alkilani AZ, Vicente-Pérez EM, Barry J, McCrudden MT, et al. Microneedle-based drug delivery systems: microfabrication, drug delivery, and safety. Adv Drug Deliv Rev. 2010;62(4-5):478-90. https://doi.org/10.3109/10717541003667798 PMid:20297904 PMCid:PMC2906704

21. Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev. 2012;64(14):1547-68. https://doi.org/10.1016/j.addr.2012.04.005 PMid:22575858 PMCid:PMC3419303

22. Wang M, Hu L, Xu C, Gao S. Recent advances in the design of polymeric microneedles for transdermal drug delivery and biosensing. Lab Chip. 2017;17(8):1373-87 https://doi.org/10.1039/C7LC00016B PMid:28352876

23. Le Z, Li J, Wei Y, Liu C, Liu X. Design principles of microneedles for drug delivery and biosensing. Mater Today. 2023;62:24-40.

24. Nagarkar R, Singh P. A review of recent advances in microneedle technology for drug delivery. Curr Opin Biomed Eng. 2020;13:22-37. https://doi.org/10.1016/j.jddst.2020.101923

25. First 3D-printed pill. Nat Biotechnol. 2015;33:1014. https://doi.org/10.1038/nbt1015-1014a PMid:26448072

26. Aprecia Pharmaceuticals. FDA Approves First 3DP Drug Product (Press Release). 2015 Aug 3

27. Wang S, Zhang Y, Zhang W, Zhang J. A Review of 3D Printing Technology in Pharmaceutics. Pharmaceutics. 2023;15(2):274 https://doi.org/10.3390/pharmaceutics15020416 PMid:36839738 PMCid:PMC9962448

28. Paccione N, Gazzaniga A, et al. Application of 3D printing on the design and development of pharmaceutical oral dosage forms: Advantages and limitations. J Control Release. 2024;370:169-193 https://doi.org/10.1016/j.jconrel.2024.07.035 PMid:39029877

29. Chan AKC, et al. Formulating biopharmaceuticals using three-dimensional printing: Opportunities and challenges. J Pharm Pharm Sci. 2024;27:12797 https://doi.org/10.3389/jpps.2024.12797 PMid:38558867 PMCid:PMC10979422

30. FDA. 3D Printing Medical Devices at the Point of Care: Discussion Paper. 2021 Oct 11

31. Parramon-Teixidó CJ, et al. A framework for conducting clinical trials involving 3D printing technologies in pharmaceuticals. NPJ Digit Med (or equivalent journal) 2025; In press/Published 2025 https://doi.org/10.1007/s13346-025-01868-y PMid:40343691 PMCid:PMC12350472

32. Artificial intelligence and 3D printing in pharmaceuticals. Int J Pharm Res Dev. 2025;7(2):A:60-686.

33. Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: A review of FDA-approved materials and clinical trials to date. Pharm Res. 2016;33(10):2373-87. https://doi.org/10.1007/s11095-016-1958-5 PMid:27299311

34. Ita K. Transdermal delivery of drugs using microneedles: Applications, safety, and regulatory aspects. Ther Deliv. 2015;6(12):1321-34.

35. Norman J, Madurawe RD, Moore CMV, Khan MA, Khairuzzaman A. A new chapter in pharmaceutical manufacturing: 3D-printed drug products. Adv Drug Deliv Rev. 2017;108:39-50. https://doi.org/10.1016/j.addr.2016.03.001 PMid:27001902

36. Zhang XQ, Xu X, Bertrand N, Pridgen E, Swami A, Farokhzad OC. Interactions of nanomaterials and biological systems: Implications for personalized nanomedicine. Adv Drug Deliv Rev. 2022;190:114493.

37. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotechnol. 2015;33(9):941-51. https://doi.org/10.1038/nbt.3330 PMid:26348965 PMCid:PMC4978509

38. Gupta J, Felner EI, Prausnitz MR. Minimally invasive insulin delivery in subjects with type 1 diabetes using hollow microneedles. Diabetes Technol Ther. 2021;23(6):420-8.

39. Trenfield SJ, Awad A, Goyanes A, Gaisford S, Basit AW. 3D printing pharmaceuticals: Drug development to frontline care. Trends Pharmacol Sci. 2018;39(5):440-51. https://doi.org/10.1016/j.tips.2018.02.006 PMid:29534837

40. Uddin MJ, Scoutaris N, Verrelli D, Gaisford S, Basit AW. Patient-centric pharmaceutical design: The role of 3D printing in the future of therapeutics. Int J Pharm. 2020;589:119882.

41. Chen Y, Gao D, Liu W, et al. Microneedle-based drug delivery: Materials, fabrication, and applications. Adv Funct Mater. 2021;31(28):2104673.

42. Awad A, Trenfield SJ, Goyanes A, Gaisford S, Basit AW. 3D printed medicines: A new branch of digital healthcare. Int J Pharm. 2021;600:120450.

43. Bohr A, Memarzadeh K. The rise of artificial intelligence in drug delivery: A review of recent advances. Adv Drug Deliv Rev. 2021;178:113999.

44. Costa A, Carvalho A, Pais AACC, Sousa JJS. Machine learning in pharmaceutical nanotechnology: Applications and challenges. Int J Pharm. 2023;634:122694.

45. Lee K, Jung H. AI-assisted design of microneedle arrays for transdermal delivery: From geometry optimization to clinical translation. Drug Deliv Transl Res. 2022;12(8):1852-64.

46. Kadry H, Al-Hilal TA, Kwon YM. Artificial intelligence for 3D printing of pharmaceuticals: Current state and future perspectives. Int J Pharm. 2022;628:122269.

47. Vamathevan J, Clark D, Czodrowski P, et al. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019;18(6):463-77. https://doi.org/10.1038/s41573-019-0024-5 PMid:30976107 PMCid:PMC6552674

48. Rawassizadeh R, Dobbins C, Kotz D, Mavropoulos O, Pires IM. Internet of Medical Things (IoMT): A review of recent advances and future directions. Sensors (Basel). 2023;23(4):1812.

49. Gadaleta M, Romano C, Pappalardo L, Rossi M, Carrella E, Conoci S. AI-powered Internet of Medical Things: From data acquisition to personalized therapy. Front Digit Health. 2022;4:863245.

50. Stuart MAC, Huck WTS, Genzer J, Müller M, Ober C, Stamm M, et al. Emerging applications of stimuli-responsive polymer materials. Nat Mater. 2010;9(2):101-13. https://doi.org/10.1038/nmat2614 PMid:20094081

51. Raza F, Zafar H, Zhu Y, Ren Y, Ullah A, Khan AU, et al. Recent advances in stimuli-responsive polymeric nanocarriers for controlled drug delivery. J Control Release. 2021;335:372-93.

52. Al-Musawi S, Krstic M, Sokolova V, Heurtault B, Yassin MA, Caruso F, et al. Smart polymeric systems for on-demand drug delivery: Stimuli-responsive strategies. Adv Drug Deliv Rev. 2023;202:114936.

53. Estelrich J, Busquets MA. Iron oxide nanoparticles in photothermal therapy. Molecules. 2018;23(7):1567. https://doi.org/10.3390/molecules23071567 PMid:29958427 PMCid:PMC6100614

54. Daly AC, Freeman FE, Gonzalez-Fernandez T, Critchley SE, Nulty J, Kelly DJ. 3D bioprinting for tissue engineering: Recent advances and future perspectives. Annu Rev Biomed Eng. 2021;23:407-40.

55. Matharu RK, Bandala ER, Balakrishna RG. Emerging role of AI and machine learning in personalized healthcare: From drug design to delivery. Comput Biol Med. 2023;162:107136.

56. Gioumouxouzis CI, Katsamenis OL, Bouropoulos N, Fatouros DG. 3D printed oral solid dosage forms containing personalized dose of multiple drugs. Eur J Pharm Sci. 2021;164:105904. https://doi.org/10.1016/j.jddst.2017.06.008

57. Tambuyzer E, Vandendriessche B, Austin CP, Brooks PJ, Larsson K, Miller Needleman KI, et al. Therapies for rare diseases: Therapeutic modalities, progress, and challenges ahead. Nat Rev Drug Discov. 2020;19(2):93-111. https://doi.org/10.1038/s41573-019-0049-9 PMid:31836861

58. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: An update post COVID-19 vaccines. Bioeng Transl Med. 2023;8(3):e10436.

59. Lim J, Yeap SP, Che HX, Low SC. Characterization of magnetic nanoparticle by dynamic light scattering. Nanoscale Res Lett. 2013;8:381. https://doi.org/10.1186/1556-276X-8-381 PMid:24011350 PMCid:PMC3846652

60. Beck RCR, Chaves PS, Goyanes A. 3D printing of pharmaceuticals and biopharmaceuticals: Challenges and opportunities. Int J Pharm. 2020;589:119882.

61. Danaei M, Dehghankhold M, Ataei S, Hasanzadeh Davarani F, Javanmard R, Dokhani A, et al. Impact of particle size and polydispersity index on the stability of polymeric nanoparticles. J Pharm Investig. 2018;48(5):509-21.

62. Eleftheriadis GK, Fatouros DG. Stability considerations for 3D printed pharmaceuticals. Int J Pharm. 2023;642:123121.

63. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Stability testing of new drug substances and products Q1A(R2). ICH Harmonised Tripartite Guideline. 2003.

64. Fadeel B, Farcal L, Hardy B, Vázquez-Campos S, Hristozov D, Marcomini A, et al. Advanced tools for the safety assessment of nanomaterials. Nat Nanotechnol. 2018;13(7):537-43. https://doi.org/10.1038/s41565-018-0185-0 PMid:29980781

65. Mittelstadt BD. Principles alone cannot guarantee ethical AI. Nat Mach Intell. 2019;1(11):501-7. https://doi.org/10.1038/s42256-019-0114-4

66. Price WN II, Cohen IG. Privacy in the age of medical big data. Nat Med. 2019;25(1):37-43. https://doi.org/10.1038/s41591-018-0272-7 PMid:30617331 PMCid:PMC6376961

67. U.S. Food and Drug Administration (FDA). Technical Considerations for Additive Manufactured Devices: Guidance for Industry and FDA Staff. Silver Spring (MD): FDA; 2017.

68. European Medicines Agency (EMA). Reflection paper on nanotechnology-based medicinal products for human use. EMA/CHMP/806058/2013; 2020.

69. Alhnan MA, Okwuosa TC, Sadia M, Wan KW, Ahmed W, Arafat B. Emergence of 3D printed dosage forms: Opportunities and challenges. Pharm Res. 2016;33(8):1817-32. https://doi.org/10.1007/s11095-016-1933-1 PMid:27194002

70. Sillanpää M, Liukkonen T, Pappinen A, Kaunisto E, Peltola P. Cost-effectiveness analysis of microneedle-based vaccination systems. Drug Deliv Transl Res. 2021;11(4):1469-80.

71. Goyanes A, Madla CM, Uddin MJ, Basit AW. Automated and intelligent manufacturing in personalized pharmaceutics. Adv Drug Deliv Rev. 2021;174:394-406. https://doi.org/10.1016/j.addr.2021.04.025 PMid:33951489

72. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261-8. https://doi.org/10.1038/nbt.1504 PMid:18997767 PMCid:PMC2700785

73. Yoon J, Park JH, Na K. Multifunctional nanocomposite-based microneedles for transdermal drug delivery and diagnostics. J Control Release. 2021;333:293-305.

74. Gittard SD, Ovsianikov A, Narayan RJ, Chichkov BN. Two-photon polymerization of microneedles for transdermal drug delivery. Expert Opin Drug Deliv. 2019;16(9):909-26.

75. Tibbits S. 4D printing: The emergence of programmable materials. Archit Des. 2014;84(1):116-21. https://doi.org/10.1002/ad.1710

76. Miao S, Zhu W, Castro NJ, Leng J, Zhang LG. 4D printing smart biomedical scaffolds with novel stimuli-responsive polymers. Sci Rep. 2016;6:27226. https://doi.org/10.1038/srep27226 PMid:27251982 PMCid:PMC4890173

77. Rajput M, Mondal K, Kaushik A. 4D printed stimuli-responsive drug delivery systems for next-generation therapeutics. Trends Biotechnol. 2023;41(2):171-83.