



Review

Engineering Advances in Modern Drug Delivery Devices: Current Technologies, Challenges, and Future Directions

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Abstract

Background: The expansion of biologics, Gene therapies and personalized medicine has been significant ever since it was initiated in the late 20th century which created an immediate need for advanced drug delivery platforms that could enhance therapeutic output, improve patient compliance and precision-in-treatment. So far, traditional routes of oral and parenteral administration are commonly hampered by limited bioavailability, systemic adverse effects, and poor patient compliance; thus, driving next-generation delivery technologies. **Key Technologies Reviewed:** The aim of this review is to critically evaluate state-of-the-art developments in drug delivery devices and systems-including prefilled syringes (PFSs) and autoinjectors; inhalation-based delivery platforms; microneedle (MN) patches; nanoparticle-enabled delivery systems; tissue-engineered scaffolds; and advanced transdermal technologies. These platforms are engineered to address biological limitations, improve site-specific drug targeting, and facilitate minimally invasive or self-administered therapies. **Engineering and Clinical Aspects:** Great strides have been made with respect to advances in device engineering, biomaterials, particle design, microfabrication and digital health integration. However, autoinjectors and very recently prefilled syringes have emerged as the devices of choice for improving dosing accuracy and patient convenience; inhalation systems and MN technologies have offered new options for non-invasive delivery. Nanoparticle-based platforms have shown improved targeting and controllable delivery of therapeutics, especially for complex therapies. The drug delivery device market worldwide is anticipated to exceed USD 450 billion by the year 2030, a reflection of how clinically relevant these technologies have become. **Future Outlook:** Among current innovations, the most transformative advances in minimally invasive delivery uses MN systems and nanoparticle-enabled precision delivery to overcome significant barriers of bioavailability, therapeutic targeting and patient acceptability. Nonetheless, large-scale manufacturing, long-term safety assessment, regulatory harmonization and cost-effective commercialization still represent some of the main hurdles towards broader clinical translation. Future technologies will be dependent on the incorporation of artificial intelligence, smart sensors and customized manufacturing strategies to progress towards precision medicine and patient-centered health care.

Keywords

Prefilled syringes, Autoinjectors, Microneedle patches, Nanoparticle delivery systems, Bioprinting, Biosimilars

Article History

Received: 05 January 2026

Revised: 13 July 2026

Accepted: 24 August 2026

Available Online: 28 August 2026

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1. Introduction

The science of drug delivery has been radically transformed over the last 20 years, due to the growth of complex therapeutic molecules, increasing incidence of chronic diseases and a global trend to patient-centered and precision medicine [1]. Although clinically proven, conventional drug delivery routes especially oral and intravenous delivery methods, are commonly characterized by significant constraints including low bioavailability, system toxicity and poor patient compliance, errors in dosing and poor site specificity [2]. Such deficiencies have spurred the creation of novel drug delivery systems with the objective of enhancing drug potential, safety, and patient well-being, and reducing invasiveness and reliance on medical professionals [3].

The global drug delivery device market has witnessed tremendous growth in the past 10 years, mainly due to increase in prevalence of chronic diseases, expansion of biologic therapeutics and requirement for patient-centric healthcare solutions. Market research reports indicate that the global drug delivery systems market will surpass USD 80 billion by early 2030s, with injectable devices, inhalation systems, and transdermal technologies as the fastest-growing sectors. Chronic diseases, such as diabetes mellitus, autoimmune disorders, respiratory illnesses, cancer, and chronic cardiovascular diseases, represent a large proportion of global healthcare spending and often present challenging complexities to therapy that require prolonged drug delivery. At the same time, a considerable number of biologics, monoclonal antibodies, nucleic acid therapeutics and gene-based medicines are now coming into the forefront as high potential drug candidates that pose serious challenges to traditional oral delivery approaches commonly used for low molecular weight compounds due to their extremely poor stability. Their inherently limited permeability and likelihood of undergoing enzymatic degradation in gastrointestinal tract during passage also prompted innumerable attempts to devise novel transport routes for these new classes of drugs [3]. Therefore, the design of advanced drug delivery devices is an important enabling technology for targeted delivery with improved pharmacokinetic performance, reduced dosing frequency, and enhanced patient adherence.

It can be stated that modern drug delivery systems are no longer regarded as passive agents of active pharmaceutical agents but rather as combined and multifunctional systems that integrate materials science, mechanical engineering, digital technologies and regulatory science [4]. The autoinjectors and pre-filled syringes have reached a high clinical maturity level and allow to perform the accurate dose, decreased administration errors, and self-administration reliability, especially when it comes to biologics and chronic disease therapies [5]. Architecture of the devices, main packaging materials, injection mechanics, and wearable injectors on the body have also contributed to an improvement in usability, pharmacokinetics (PK), and patient compliance and have also raised new possibilities of engineering and regulation [6]. Simultaneously, inhalation drug delivery has become one of the most advanced techniques of local and systemic delivery [7]. Advances in aerosol science, particle engineering, inhaler design, and digital health have greatly enhanced the pulmonary drug deposition and have greatly increased therapeutic uses out of respiratory diseases [8].

The convergence of the formulation science and device optimization can be seen in the development of the dry powder inhalers (DPIs), electrosprays technologies, smart inhalers, and disease-specific strategies of particle engineering [9]. However, inconsistency in patient inhalation, scalability in production and the future viability of the device are some of the major concerns with successful clinical translation [10]. Microneedle (MN) patch technology has also been found to have an impressive advancement in transdermal drug delivery [11]. With a minimally invasive and mostly pain-free process of overcoming stratum corneum barrier, MN systems promise to be an important alternative to traditional injections of vaccines, insulin, biologics, and small-molecule drugs [12]. The recent innovations in the design of MN, choice of materials, methods of fabrication, and intelligent functional integration have made it possible to control and maintain drug delivery, real-time monitoring, and closed-loop therapy [13]. Despite being at an early clinical development stage, MN patches are a disruptive platform with considerable opportunities to disrupt self-administration and the management of chronic diseases.

In addition to the use of devices to provide delivery methods, nanoparticle-mediated drug delivery has become one of the pillars of precision medicine [14]. Nanoparticles based on lipids and polymers and inorganic, extracellular vesicles (EVs) and cell mediated delivery systems offer the most remarkable control of drug targeting, biodistribution and release kinetics that have never been realized before [15]. Nanoparticle systems have shown disruptive possibilities in oncology, gene therapy, immunotherapy and regenerative medicine. With the use of artificial intelligence, machine learning, and computer-aided design (CAD), optimization of nanoparticles and predictive formulation modeling has been further expedited to allow bench-to-clinic translation to be done more quickly [16]. Moreover, localized and patient-specific drug delivery has received new opportunities through tissue engineering technologies and three-dimensional (3D) printing [17].

Additive manufacturing allows accurate architecture, porosity, and drug loading of a scaffold, which is useful in designing customized implants, hydrogel, and bioactive matrices [18]. In addition, notable non-invasive drug delivery methods have expanded to include topical and transdermal delivery strategies, such as hydrogels, flexible liposomal systems, iontophoresis-assisted delivery, marine polysaccharide-based delivery systems and stimuli-responsive materials [19]. Such systems tackle issues associated with skin permeability, stability of drugs and controlled release that enhance patient compliance and adherence [20].

With such massive improvements, some challenges have been left such as manufacturing scalability, and harmonization of regulations, long-term safety testing, compatibility between devices and drugs, and cost-effectiveness. The future of drug delivery needs to be in the combination of novel materials, the growth of smart devices, the evolution of digital health, and optimization using data [21]. This review gives a global scope of the latest drug delivery technology with special attention given to the engineering design, material development, PK, patient compliance, manufacturing factors, regulatory approaches, and future opportunities indicating how new generation of delivery technology can transform clinical practice to patient-centred, minimally invasive, and personalized healthcare.

Polysaccharides originated from marine organisms, like alginate, fucoidan, carrageenan and chitosan (all of them commercially available), including ulvan from algae or seaweeds represent potential new biomaterials and also are known as multifunctional drug delivery excipients. These features allow for excellent biocompatibility, biodegradability and mucoadhesion as well as a large matrix-forming potential [22]. Recent studies have shown improvement of stability and tuning the release profile using these systems in the drug delivery field [21,24,25]; they are also promising candidates to improve therapeutic efficacy by optimizing their use stages while enlarging the scope of applications from transdermal [23], oral drug delivery systems [24].

This review was conducted using a structured literature-search approach to ensure comprehensive coverage of recent advances in drug delivery technologies. Scientific databases including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar were systematically searched for articles published between January 2015 and March 2025. Keywords included “drug delivery devices”, “autoinjectors”, “prefilled syringes (PFSs)”, “MN patches”, “nanoparticle drug delivery”, “inhalation systems”, “3D printed drug delivery”, and “transdermal delivery systems”. The initial search identified approximately 1,250 records. After removal of duplicate publications, conference abstracts without full text, non-English articles, editorials, and studies lacking sufficient technical or clinical relevance, approximately 285 articles remained for full-text assessment. Following detailed screening, 112 highly relevant publications were included in the final review. The study selection process followed PRISMA principles to improve transparency and reproducibility. A PRISMA flow diagram summarizing identification, screening, eligibility, and inclusion stages should be added as Supplementary Figure S1.

Records identified through database searching (n = 1,250)

• PubMed (n = 320) • Scopus (n = 285) • Web of Science (n = 240) • ScienceDirect (n = 225) • Google Scholar (n = 180)

↓

Duplicate records removed (n = 315)

↓

Records screened by title and abstract (n = 935)

↓

Records excluded (n = 650)

Reasons: • Irrelevant topic • non-drug delivery focus • Insufficient engineering content • non-pharmaceutical applications

↓

Eligibility

Full-text articles assessed for eligibility (n = 285)

↓

Full-text articles excluded (n = 173)

Reasons:

• Conference abstracts only (n = 38) • Non-English publications (n = 24) • Insufficient technical depth (n = 46) • Lack of clinical relevance (n = 31) • Duplicate datasets/redundant studies (n = 18) • Inaccessible full text (n = 16)

↓

Included

Studies included in qualitative synthesis (n = 112)

↓

Technology Categories Included

• PFSs & Autoinjectors (n = 18) • Inhalation Drug Delivery Systems (n = 22) • MN Technologies (n = 21) • Nanoparticle Drug Delivery Systems (n = 28) • Tissue Engineering & 3D Printing (n = 11) • Advanced Transdermal Systems (n = 12)

Total Included Studies (n = 112)

2. Prefilled Syringes and Autoinjectors: Innovation and Engineering Development

2.1 Prefilled Syringes: Basics and Market Development

The use of pre-filled syringes, valued for their convenience and precise delivery, is a recent application in parenteral drug delivery. A particular area that has led to self-administered injection treatment as a desirable means of patient-centred care is the fast-emerging biopharmaceutical sector, particularly in chronic disease treatment and immunotherapies. PFSs-based autoinjectors (AIs) have quickly gained popularity as the most utilised AI device, thanks to their ease of use and disposability, and have become commonplace among patients, caregivers, and Healthcare Professionals, with critiques of

United States Food and Drug Administration (FDA)-approved products systematically reviewed since 1980 [1]. More recent developments in PFS as a preferred primary container system, both in clinical and business terms, have been fostered by growing attention to ready-to-use presentations, minimised wastage of expensive biologic drugs, and lifecycle management approaches, making PFSs more likely to be adopted commercially than other system types. The development of primary packaging, autoinjector architecture, on-body injection systems, injection mechanics, and patient-centred regulatory considerations is schematically represented in Figure 1. The predominant packaging materials (PPMs) for PFSs are silica glass barrels and silicone-oiled plungers, which control the so-called break-loose and gliding forces (BLGFs) during injection. Dimensional variability in these packaging materials can, however, have a significant influence on drug delivery performance. The latest technological advances in optical shaft and tactile measurements have demonstrated that dimensional changes in contact primary packaging parts (PPMs) can negatively impact BLGF, even when the parts meet specifications, suggesting there may be further room to improve primary packaging quality in critical drug products like ophthalmics [2]. This has established product-specific standards for primary packaging systems, founded on a broad range of knowledge that has emerged with the packaging of drug products. Figure 1 illustrates the effect of primary packaging materials, silicone lubrication, and break-loose/gliding forces on delivery performance.



Figure 1. Clinical implications of on-body drug delivery systems design architecture, injection mechanics and clinical implications of on-body drug delivery systems.

2.2 Autoinjectors Design Innovations and Clinical Performance

Another development in self-injection device technology involves the use of autoinjectors, which have been developed to overcome patient discomfort with injections, especially needle phobia and injection anxiety [1]. Single-use AI have been a significant advantage across various therapeutic disciplines, as clinical investigations have shown they are readily adopted for various diseases. A multicentre trial of Avonex Pen, a single-use autoinjector for intramuscular injection of interferon beta-1a in multiple sclerosis patients, indicated that 96 percent of patients attended the study, and the overall rate of appropriate dosing with the prefilled pen was 89 percent. In the current research, 94 percent of patients believed the prefilled pen was superior to the PFS, and both devices had similar safety profiles and triggered the interferon action biomarkers [3]. AI using springs to combine injectable formulations were experimentally tested and analysed in detail, leading to the development of safe and effective autoinjector platforms [1]. Bioequivalence trials and administration trials are important pieces of evidence for regulatory approval. Pulmonary fibrosis (PF)-autoinjector vs. PF-syringe. According to the comparative results, all data for pegfilgrastim-cbqv (UDENYCA), a pegfilgrastim biosimilar, lie within the 80-125% bioequivalence limit range. Approximately 75 percent of patients reported treatment-emerging Adverse Events (AEs) in both groups, which were musculoskeletal (mostly myalgia and bone pain) and headache, and were associated with device-related AEs that were limited to injection-site pain and injection-site bruising [4]. The main elements of spring-based autoinjector design and how they help to minimise variation in use and anxiety about injections are illustrated in Figure 1.

2.3 On-Body Injectors: New Platform Technology

Another advancement in autoinjector technology is on-body injectors, which allow alternative injection paths to be added, making them more versatile for drug administration. Pilot bioequivalence studies of on-body infusors and PFSs, along with pharmacodynamic and pharmacokinetic studies, have demonstrated a similar bioequivalence profile. In a cross-over, randomised trial on the PK and PKD parameters of healthy male subjects, the geometric mean ratios of on-body injector-delivered pegfilgrastim-cbqv to prefilled arm injector-delivered syringes fell within the prespecified bioequivalence limits for the Pharmacokinetic-Pharmacodynamic Relationship parameters. AEs during treatment were reported by subjects treated with on-body injectors and PFSs (87.8% and 75.8%, respectively). The most prevalent was injection site erythema (31.7%), which was mild, self-limiting, and transient [5]. Wearable on-body injection systems that allow infusion and delayed dosing are described in Figure 1.

2.4 Compliance of Patients and Preference of the Devices

It has received a couple of harsh comparisons regarding the usability of equipment and patient preference, underscoring the great benefits of advanced delivery systems. The researchers conducted a 2-armed crossover trial in which methotrexate was administered to patients with juvenile idiopathic arthritis to compare the prefilled pen with Subcutaneous Administration (SC) delivery of methotrexate, assessing which was the preferred method of delivery. 82.6 percent of patients and caregivers preferred the prefilled pen for methotrexate administration over the SC method. In addition, prefilled pen administration was much less painful than SC administration ($p < 0.01$), and most of the drug's side effects were also less severe with prefilled pen administration, particularly gastrointestinal AEs ($p < 0.01$) [6]. The results of the study underscore the importance of designing devices based on patient acceptance and treatment effectiveness.

2.5 Pharmacokinetic Implications and Dynamics of Injection

The mechanical properties of injection delivery systems strongly influence injectate dispersion and uptake, which may in turn affect PK and drug efficiency. Comparative experiments on the porcine model suggested that the injected volume (and therefore the degree of dispersion) was much greater with autoinjectors than with manual syringes. The EpiPen autoinjector exhibited larger dispersion volumes and an initial dispersion ratio, suggesting a higher rate of injectate uptake into porcine tissue compared with any other autoinjector tested [7].

2.6 Regulatory Environment and Market Growth

The combination of drugs and the medical device market, namely autoinjectors, has grown tremendously. Autoinjector pharmaceuticals that combine drugs are being approved in Japan and are currently under review, as the number of drug-carrying items whose injection device (pen-type drug injector) has already been registered will increase. Specifically, the number of total drug products approved in AI was 53 percent, with the approval authorization of the first product in Japan, and over 50 percent of those approved had a different formulation within five years of the first approval [8].

While autoinjectors and PFSs have transformed parenteral administration, increasing interest in non-invasive therapies has accelerated the development of pulmonary drug delivery systems. These technologies provide opportunities for localized and systemic treatment while improving patient convenience and adherence.

3. Inhalation Devices: Engineering Solution and Therapy Prospects

3.1 The pulmonary Drug Delivery Systems are Described in the Following Manner

It has been demonstrated that pulmonary drug delivery is a route for local and systemic administration of various drugs and biopharmaceuticals to treat diseases of both pulmonary and non-pulmonary origin. Figure 2 schematically represents engineering approaches, types of inhaler devices, particle engineering methods, digital integration of inhalation drug delivery, and their therapeutic applications. Inhaler device and patient. The development of pulmonary drug delivery systems requires close collaboration between drug formulation and inhaler device design [9]. Non-invasive systemic and local effects of medicines are delivered through pulmonary drug delivery systems (metered-dose inhalers (MDIs), DPIs, and nebulisers). Inhalation therapy has been improved over the years through various advances, with a focus on patient compliance and maximisation of drug delivery efficiency [10].

3.2 Optimization and Design of the Device

The valved holding chambers and the aerodynamic filtering concept are device-level optimisation strategies, as visually presented in Figure 2. Also important in recent engineering optimisation are valved holding chambers (VHCs), which are crucial aerosol drug delivery devices. New valve designs, developed based on particle impaction theory, have shown better performance in both simulation and experimentation. A later comparative study examined the optimal filter separation of particles, enabling more than 95 percent to be less than 7 μm and achieving high removal of particles larger than 8 μm using an optimised filter, compared with the valve design [11]. The summary of these device optimisation strategies and performance characteristics is shown in Table 1.

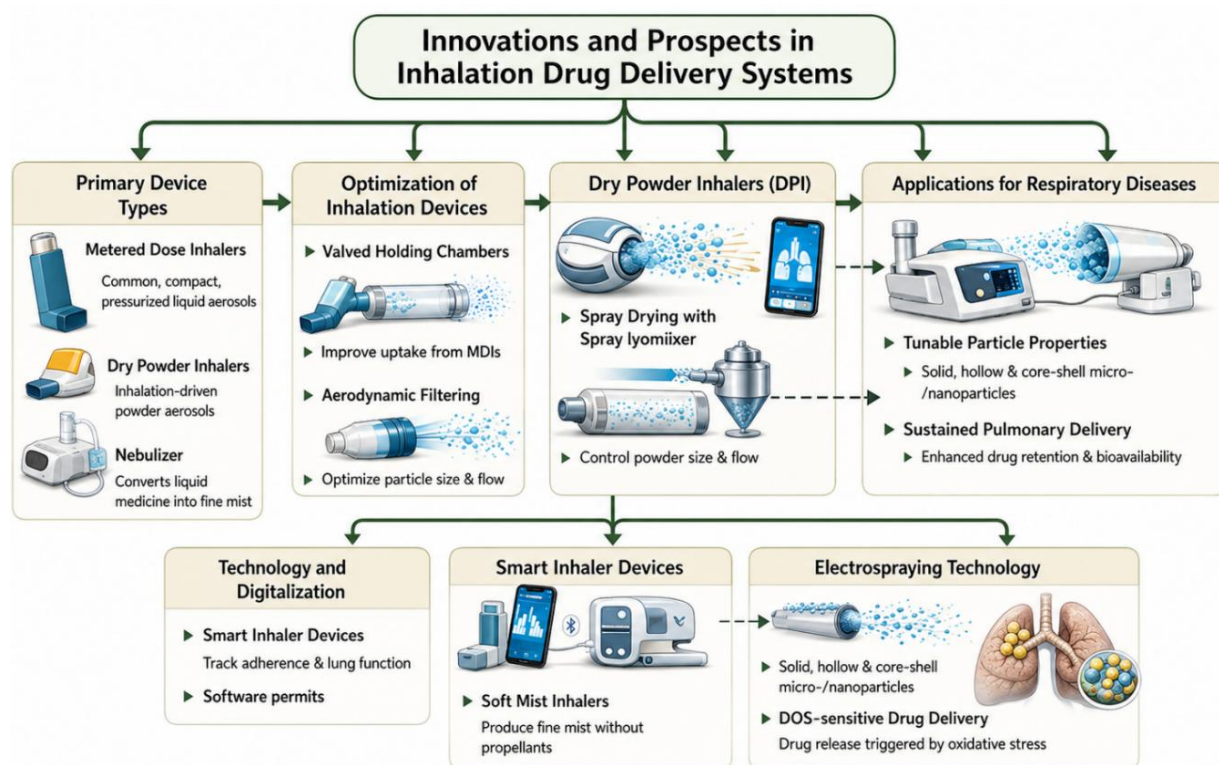


Figure 2. Review of developed inhalation delivery devices and inventive technologies.

3.3 DPIs: Clinical Uses and Particle Engineering

DPIs are highly advanced delivery systems, and a complete understanding of the intricate relationship among formulation, device, and patient is essential [12]. Advanced particle engineering techniques, such as spray drying of inhaled dry powders under varying parameters, have been used to design particles. A recent investigation into simvastatin DPI formulations as a treatment/PAH agent revealed that nanostructured microparticles could be produced, and that all powders could be easily aerosolised using the three FDA-approved DPI devices. Simvastatin aerosol delivery was also useful in improving endothelial function in a shunt lamb model of pulmonary hypertension [13]. Table 1 provides an overview of DPI technologies, particle-engineering strategies, and typical clinical applications. Figure 2 demonstrates the inhaler design and dry powder and particle engineering strategies involving spray-drying.

3.4 Technology and Digitalization

Following the Coronavirus Disease 2019 (COVID-19) pandemic, aerosol delivery of pulmonary drugs is booming, though the underlying research in particle engineering and inhaler device development spans decades [14]. The technology of pulmonary drug delivery devices has been addressed in terms of pMDIs development, DPIs, nebulisers, and soft mist inhalers. This means that inhalers will be more closely monitored using digital health solutions [15]. Table 1 provides a summary of key technological and digital advances in the pulmonary drug delivery systems.

3.5 Electro-Spraying and Advanced Manufacturing

Electrospray technology has been widely investigated for its application as a new and flexible drug delivery platform, as it enables precise control of particle size, morphology, surface features, and drug-release dynamics. Compared with less efficient particle-engineering methods, the electrospray process enables the formation of uniform micro- and nanoparticles by applying a high electric field, making it feasible to construct core-shell structures, hollow spheres, and even nanofibrous matrices. The tunable architecture offers the potential to optimise drug encapsulation, dispersibility characteristics, and particle stability, especially for sensitive or insoluble drugs [16]. Figure 2 schematically presents the electrospray-based advanced manufacturing strategies for inhalation delivery. Table 1 lists the benefits and uses of electrospray-based particle engineering for inhalation delivery.

Another highly promising solution in this context is ES-derived particles, whose physicochemical properties can be controlled. As a result, they can deposit more in the distal lung, penetrate more into small airways, and interact more with pulmonary mucus or epithelium, owing to their optimal aerodynamic diameter, surface charge, and morphology. The synergistic effect of these attributes results in enhanced bioavailability and the opportunity to control or sustain drug delivery over an extended duration, making Electro sprayed formulations a desirable system for inhalation therapy and targeted drug delivery to the lungs [16].

Table 1. Inhalation devices: engineering solutions and therapy prospects - elaborate, comprehensive.

S. No.	Technology/System	Key Mechanism	Clinical Applications	Advantages	Limitations	Current Clinical Status	Ref.
1	Pulmonary Route Drug Delivery	Local and systemic absorption through the pulmonary epithelium	Asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, Pulmonary arterial hypertension (PAH), PF, Insulin delivery	Non-invasive, rapid onset, avoids first-pass metabolism	Limited by lung physiology, mucociliary clearance, patient inhalation variability	Widely established clinical route; several approved products	[9]
2	MDIs, DPIs, Nebulizers	Aerosolized drug delivery to the respiratory tract	Asthma, COPD, antibiotics, antivirals	Improved compliance, multiple device options, targeted delivery	Technique-dependent administration, device maintenance requirements	Numerous FDA/EMA-approved commercial products	[10]
3	Valved Holding Chambers (VHCs)	Physics-optimized aerosol deposition and reduced particle velocity	Pediatric and elderly populations	Enhanced lung deposition and reduced oropharyngeal deposition	Additional device cost, cleaning requirements, portability concerns	Clinically established adjunct device for inhalation therapy	[11]
4	Optimized Filter Technology	Precision particle separation (>95% particles <7 µm)	Precision pulmonary drug targeting	Maximizes lung bioavailability and deposition efficiency	Increased manufacturing complexity and device optimization requirements	Experimental to early translational stage	[11]
5	DPIs	Formulation-device-patient integration for powder aerosolization	Chronic respiratory diseases	Stable formulations, propellant-free, reproducible dosing	Performance dependent on inspiratory flow rate and patient technique	Widely approved and commercially available	[12]
6	Spray Drying & Particle Engineering	Tunable particle size, morphology, and aerodynamic properties	Disease-specific inhalation formulations	Enables customized pulmonary targeting	Scale-up challenges, formulation stability concerns	Advanced development and industrial application	[13]
7	Simvastatin DPI for PAH	Nanostructured spray-dried particles for pulmonary delivery	PAH	Reduced systemic toxicity, enhanced local therapeutic effect	Limited long-term clinical data and regulatory validation	Preclinical and early translational research stage	[13]
8	Smart Inhalers (Digital Health)	Real-time adherence monitoring and connectivity	Medication adherence improvement	Data-driven interventions, improved disease management	Cost, privacy concerns, dependence on digital infrastructure	Several commercial products and ongoing clinical adoption	[15]
9	Electrospray Technology	Precise control of particle size, morphology, and release characteristics	Sustained-release and difficult-to-deliver drugs	Superior bioavailability, tunable release profiles	Manufacturing scalability and regulatory challenges	Primarily preclinical and developmental stage	[16]
10	Reactive Oxygen Species (ROS)-Sensitive Liposomes	ROS-triggered targeted drug release	Idiopathic PF	Multi-mechanism antifibrotic activity, targeted delivery	Potential formulation instability and limited long-term safety data	Preclinical research and translational development stage	[17]

3.6 Inhalation Delivery of Respiratory Diseases

Inhalation delivery of medication has been found particularly useful for treating pulmonary hypertension and other chronic lung diseases. In a high-ROS environment, a ROS-sensitive liposome construct was observed to rapidly release a therapeutic drug, delivering it to fibrotic lungs using the ROS agonist dimethyl fumarate. The nanoparticles strongly induced Nrf2-dependent heme oxygenase-1 (HO-1) and inhibited excessive production of transforming growth factor-beta (TGF-β) and ROS [17]. Table 1 is a summary of representative advanced inhalation-based therapeutic approaches to respiratory disease.

Despite the advantages of inhalation-based delivery, transdermal administration remains attractive because of its simplicity and avoidance of pulmonary variability. Consequently, MN technologies have emerged as a promising alternative for minimally invasive therapeutic delivery.

4. MN Patch: High-End Transdermal Engineering

Figure 3 presents a schematic overview of the materials, fabrication, functional integration, and therapeutic applications of MN patch technology.

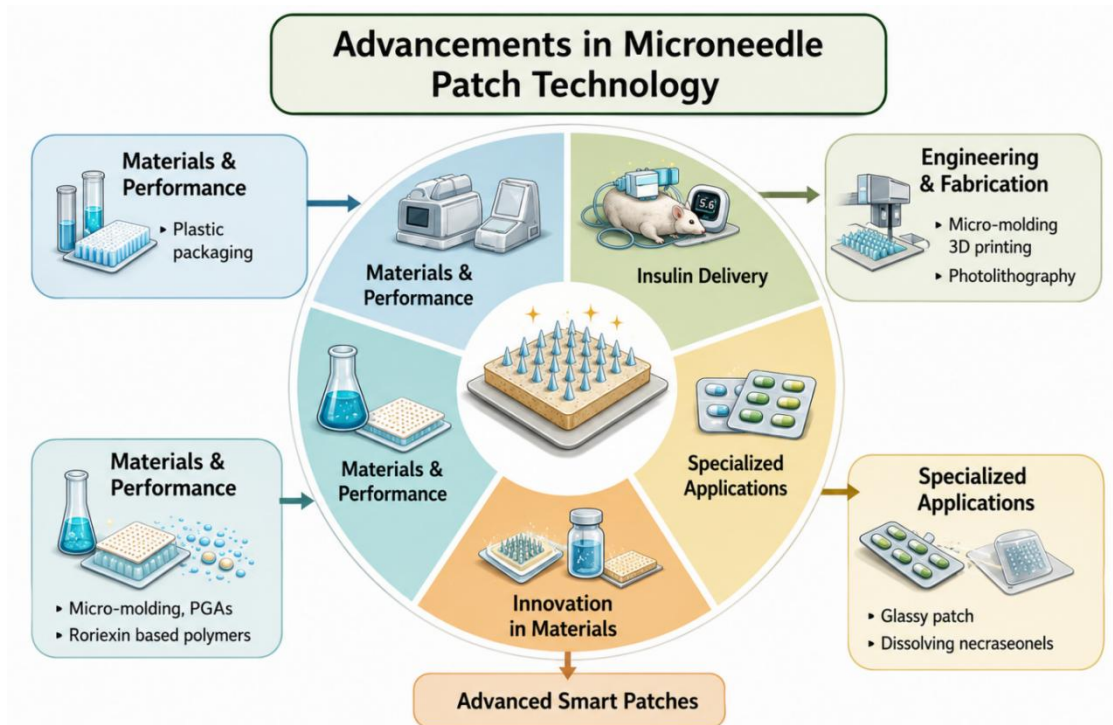


Figure 3. The innovations in MN patch systems in the dissemination of drugs through a transdermal route.

4.1 Fundamentals of MN Technology

Among existing technologies that would have a positive effect on the transdermal drug-delivery system is MN technology, which offers a less invasive method of delivering drugs into the skin. This is because such MN penetrate through the stratum corneum, the outermost layer of the epidermis, to administer therapeutics such as vaccines, insulin, and biologics. There are four main types of MN, namely solid, coated, dissolvable, and hollow, each with various uses to increase the efficiency of drug delivery and convenience for the patient [18].

4.2 Development of Engineering Design and Fabrication

Recent advances in MN production methods, particularly micro-moulding, photolithography, and 3D printing, have enabled precise manipulation of needle patterns and scalable production at large quantities [18]. The direct ink drawing technique has also enabled a low-cost, scalable process for manufacturing drug-loaded MN, with freestanding MN produced by pneumatic extrusion and drawing [19]. Finite element method analysis of MN has shown that reduced insertion force is generated during insertion, thereby improving penetration. In this regard, the 60 0m diameter three-section MN exhibited lower maximum insertion force than conical MN, or a reduced effective penetration length [20]. Figure 3 is the conclusion regarding the need to choose the material and performance of MN patches.

4.3 MN Patches: Materials and Performance

Dissolving MN are made from biodegradable polymers, including Poly(lactic acid) (PLA) and Poly(glycolic acid) (PGA), which degrade in skin tissue and deliver drugs [18]. Drug permeability was generally enhanced with hyaluronic acid (HA) MN patches featuring 80 μm -tall needles, and low-molecular-weight HA provided ex vivo human skin drug permeability 12.5 times higher than that of needleless patches [21]. Figure 3 summarises the material choices and performance of MN patches.

4.4 Clinical Implementations and Therapeutic Effect: Insulin Administration Case Study Diabetes Insulin Administration Application

A particular instance of technological progress and the use of MN patches in medicine is their application in the management of diabetes mellitus, particularly in insulin administration. The painless, rapid delivery of insulin via transdermal delivery is enabled by an intelligent MN patch, offering a fresh outlook for the management of diabetes. In this new technique, insulin/poly-L-glutamic acid (PGA) multilayer films at pH 3.0 are coated on MN. At pH 3.0 and above, insulin is deprotonated, making the net charge directly proportional to negative charge. When insulin is in solution

at pH 7.4, it results in immediate release from the skin. It requires only two applications of 30 seconds to the epidermis to attain complete epidermal separation, and the covered MN patch exhibits the same pharmacodynamics and PK as insulin administered by subcutaneous injection [25]. This is a significant engineering solution that offers a clue to a major clinical issue; insulin injections are available, but many patients still use insulin as first-line therapy because of fear of injection, pain, and issues with patient compliance. Subcutaneous injection is therapeutically identical to transdermal insulin injected with a MN, and it is painless and self-injectable [26]. *In vivo* experiments in rodent diabetes models showed that insulin-impregnated skin-contacting MN array patches kept diabetic rats normoglycemic for the longest duration of diabetes therapy reported to date using MN as a transdermal delivery system [27]. In addition, a mechanistic model has been used to design MN-based dissolvable patches for drug delivery, identifying critical parameters for controlling drug PK, including the drug loading fraction, the MN base radius, and the MN height [28]. Figure 3 presents the application of MN patches for insulin administration and diabetes control.

4.5 Advanced Functional Integration and Smart Patches

The array of Wearable patches is MN-based, designed to enable continuous electrochemical monitoring and drug delivery and to support closed-loop therapeutic systems. Patches made from hollow microarray needles have been demonstrated to be varied with conductive pastes and cross-linked chitosan for voltametric analysis for continuous monitoring of methotrexate and have been shown to be highly proficient at 25-400 μM [29]. Future systems for functional integration and smart MN patching systems that enable sensing and closed-loop therapy are shown in Figure 3.

4.6 Specialized Applications

MN patches have been shown to be effective for delivering therapeutically active molecules and treating certain disease conditions. In transdermal delivery, a hydrogel-based system using two MN methods that can form hydrogels was adapted to create polymeric MN-capable systems that act as dissolving MNs and as direct-compressed tablets. Both dissolving and hydrogel-forming MNs with a slow plasma release profile (5 days) have successfully delivered pramipexole *in vivo* [30].

Another application of 3D-printed bioresorbable MN arrays is the use of dexamethasone to manage pain. Dexamethasone-loaded bioresorbable drug MN array patches manufactured by continuous liquid interface production 3D printing demonstrated controlled drug release in cell culture and a pronounced analgesic effect on postoperative pain in animal experiments [31].

4.7 Innovation in Materials and Mechanical Properties

Recent advances in MN materials and mechanical characteristics (such as glassy and supramolecular systems of MNs) are summarised in Figure 3. Newer materials have enabled the use of MNs for plasticising glassy patches by supramolecular engineering methods. Tobramycin Sulfate monolithic glass MNs have a 100 percent drug payload, are exceedingly potent, and enable instantaneous transdermal drug delivery [32].

Although MNs improve transdermal transport, nanoparticle-based systems offer additional capabilities including targeted delivery, intracellular transport, and controlled release, making them central to precision medicine applications.

5. Sophisticated Nanoparticle Systems of Drug Delivery

5.1 Nanoparticle Engineering to Precision Medicine

Nanoparticle drug delivery systems have ushered in a breakthrough in drug development, delivering immense gains in drug bioavailability, therapeutic efficacy, and patient compliance [33]. The resolution has been to engineer nanoparticles to overcome the weaknesses of free therapeutics and to avoid the biological barriers that are not homogeneous across patient populations and diseases [34,35]. Advancements in nanoparticle-based systems have enabled the development of smart drug delivery systems that can cross complex biological barriers, reach their targets, and enable the regulated release of therapeutics [34].

5.2 Lipid-Based Nanocarriers

Lipid nanoparticles (LNPs), solid LNPs, and liposomes are lipid nanocarriers that can restore treatment efficacy. In recent developments, the most significant innovation in LNPs has been achieved, demonstrating its effectiveness in mRNA vaccine technologies [34]. Proper regulation of particle diameter, surface modification, and encapsulation efficiency in lipid-based nanoparticle synthesis has also been addressed by microfluidic technology [36].

5.3 Nano Systems Polymeric and Inorganic

One method of delivering complex drugs is through polymeric, dendrimer, and albumin-based nanosystem, which provide biocompatible drug-delivery platforms. Nanoparticles of gold, silica, and magnetic materials are inorganic nanomaterials with stimuli-responsive and multifunctional properties [34]. The design and optimisation of nanoparticle-based drug

delivery systems have been assisted by computers and have promised significant improvements [37]. The nanoparticle delivery system consists of a cell-mediated process.

Recent advances in nanomedicine have pointed out the role of biological transport phenomena and fluid-dynamic interactions directing nanoparticle bio-distribution within living systems. Factors allowing nanoparticles to marginate, penetrate cells, and extravasate into tissues include physical and chemical parameters (particle size, shape, charge), blood rheology or microfluidics of blood flow (streamlines), vascular architecture; physics of electrokinetic transport mechanisms. More recently, computational fluid dynamics and modeling of bioconvection transport have also been used to simulate NP behavior in much more complex vascular environments and optimize design and targeting of carriers [37,38]. Although the manner for carriers to control their properties is the electroosmosis flow, entropy generation and heat transport characteristics; emerging experiments based on zinc oxide and graphene oxide nanoparticles expose that these effects can greatly influence the dispersion of nanoparticles as well as drug delivery efficiency of diseased vascular tissues. Training in these engineering principles is anticipated to enhance the rational design of future precision nanomedicine platforms.

5.4 Cell-Mediated Nanoparticle Delivery Systems

Cell-mediated nanoparticle delivery systems build upon the cell-based features of nanoparticle drug delivery, in which cells are used to deliver drug-loaded nanoparticles. They offer the added benefit of leveraging cell properties, such as stem cells' homing capacity and neutrophils' inflammatory chemotaxis. Such systems can easily traverse biological barriers, such as the blood-brain barrier, and reach damaged areas at a very high rate [38].

5.5 Targeted Drug Delivery for Cancer Therapy

The concept of a targeted drug delivery system is another significant development in modern pharmacology [39]. Nanoparticle-based drug delivery systems for cancer treatment are highly accurate, effective, and less harmful to healthy tissues during tumour cell targeting. Liposomes, polymeric nanoparticles, and metallic nanoparticles are among the types of nanoparticles that can be used to target tumours, as they possess distinguishing features that enable their application in tumour targeting [40].

5.6 Extracellular Vesicles as Drug Delivery Systems

Another current trend in drug delivery is the use of EVs. EVs are less immunogenic and more engineerable than synthetic vectors such as liposomes [41]. Characteristics of red blood cell-based delivery systems include biocompatibility, biodegradability and long circulation time [42].

6. Tissue Engineering and 3D Printing of Drugs

6.1 Drug Delivery with 3D printing Technologies

Two important innovations enabled by 3D (three-dimensional) additive manufacturing have redefined opportunities in drug delivery and tissue engineering [43]. 3D printing technologies have enabled the production of scaffolds capable of controlling pore size, porosity, and interconnectivity. A few of the 3D-printing techniques include powder bed fusion, fused deposition modelling, binder deposition, inkjet printing, photopolymerization and many more [44].

Figure 4 shows the key 3D printing methods used in drug delivery and tissue engineering.

6.2 Scaffold Design and Fabrication

Restoring the complexity of the native extracellular matrix has been identified as a challenge in tissue engineering. The recent emergence of additive manufacturing, specifically 3D printing, creates unprecedented possibilities for individually tailoring scaffolds to an absolute degree. This is supplemented by CAD, which enables designs to be based on patient-specific data [45]. The designs of scaffolds created through CAD-based 3D printing to accommodate patients with specific needs will be described in Figure 4.

6.3 Drug Delivery Scaffolds Made of Polymers

Polymeric scaffolds are under extensive research for use in drug delivery and tissue engineering. Polymer-based drug delivery systems aid in the slow release of medicine, which can help in tissue healing and minimize swelling. Polymers that respond to physiological cues can also be used to deliver medicine to the areas where it is needed [46]. Figure 4 summarises polymer-based scaffolds that enable controlled, responsive drug delivery.

6.4 Hydrogel-Based Systems and Bioprinting

Even hydrogel-based drug delivery systems have emerged as significant platforms for therapeutic delivery. Hydrogels are mixtures of hydrophilic polymers with unusual three-dimensional structures that have attracted development for a

number of biomedical applications. The new trends in hydrogel-based drug delivery systems include oral, injectable, topical and ocular therapy [47] as shown in Figure 4.

6.5 Metal-Based Nanomaterials in 3D-Printed Scaffolds

Illustrates hydrogel-based drug delivery platforms produced using 3D printing and bioprinting techniques. Nanomaterials, metal-based, in 3D Californian scaffolds. Nanoparticles made of metal can now be important constituents of targeted drug delivery. Recent advances in the engineering of metal nanoparticles have highlighted their unique properties and novel applications in drug delivery systems. Nanoproducts of gold, silver, iron and zinc oxide have better physicochemical properties and higher drug-loading capacities [48].

Nanomaterials are used to decorate 3D-printed scaffolds that can deliver drugs to the target site, as shown in Figure 4.

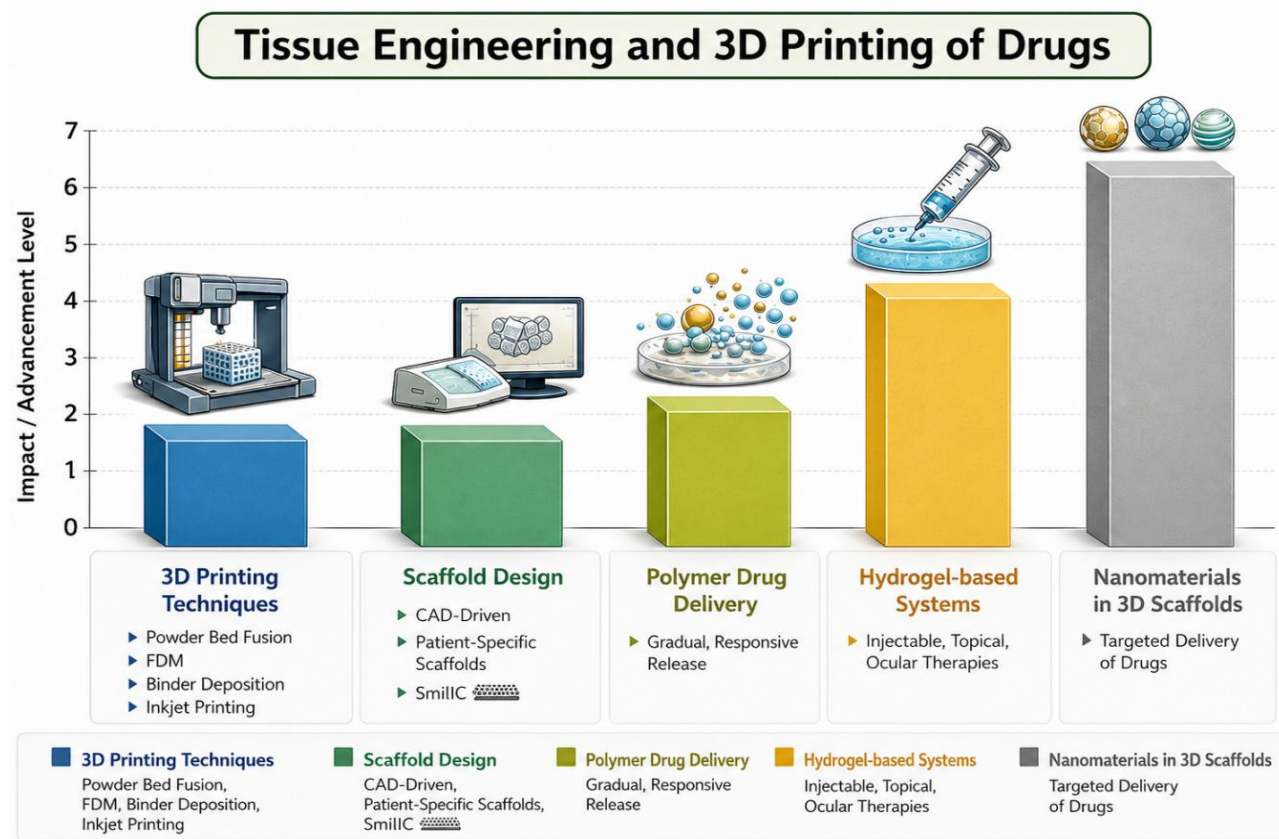


Figure 4. New progress in 3D-printed scaffolds, polymers, and hydrogels to deliver drugs.

7. Topical and Transdermal Drug Delivery Systems

7.1 Hydrogel-Based Transdermal Systems

With regulated delivery of transdermal cannabidiol, standardized silk fibroin hydrogel patches were prepared. Ethanol was used to create drug microencapsulation of optimal size [49]. Cross-linked hydrogel patches impregnated with natural plant extracts, which are in turn cross-linked by electron beam irradiation, have been demonstrated for use in transdermal drug delivery [50].

7.2 Liposomal Formulations that are Flexible

It has developed the alpha-tocopherol-impregnated liposomal nanocomposite pressure-sensitive adhesive, which is used to enhance the penetration of retinaldehyde through the skin. In this step, the liposomal stability and the chemical stability of the loaded drug were improved by adding alpha-tocopherol succinate [51].

7.3 Transdermal Delivery Iontophoresis-Enhanced

The application of transdermal delivery is enhanced using iontophoresis. A hydrochloride hydrogel patch has been developed that facilitates iontophoresis-assisted release of terbinafine for use as a transdermal delivery system. The concentration of terbinafine in the hydrogel was found to be 2.9 and 7.9 times higher, respectively, compared with iontophoresis-assisted delivery over an 8-hour drug test [52].

7.4 Systems Based on Marine Polysaccharides

Marine polysaccharides are said to possess biological properties and are applied in the drug delivery sector. Calcein and other substances have been tested for skin permeation using an Alginate/fucoidan hydrogel [53].

7.5 Ginger Extract-Loaded Transethosomes

Essential oils are claimed to enhance skin penetration when hydrogels containing essential oils are used in the marine environment [54]. Transethosomes: Ginger Extract-loaded Transethosomes. Ginger extract-loaded transethosomes, as a prospective nanovehicle, have been developed to improve transdermal delivery [55].

7.6 Stimuli-Responsive Hydrogel Systems

Hydrogel made of Transethosomal hydroxypropyl methylcellulose showed higher flux and apparent skin permeability compared with free ginger extract hydrogel [55]. A thermo-responsive ionic liquid microemulsion-based hydrogel for transdermal delivery of methotrexate has been prepared. A thermally sensitive hydrogel of isopropylacrylamide and silk fibroin serves as a drug reservoir, enabling temperature-dependent drug release [56].

8. Comparative Analysis and Engineering

8.1 Patient Compliance and Device Usability

Patient compliance and the usability of the device are the most important design considerations across all four of the most developed delivery platforms. Autoinjectors and MN patches offer painless or less painful injections, unlike traditional needles, which are a major barrier to patient compliance [30]. The application of MN patches is user-friendly and does not require any training or coordination of actuation and inhalation [9]. To create and replicate products, a company must allocate sufficient resources to physical production and logistics.

8.2 Manufacturing and Scalability

Manufacturing technologies have been developed to enable bulk production. The application of three-dimensional printing technologies has significantly changed the manufacture of reservoir-based oral delivery devices and MN patches [19]. High precision in particle size and morphology can be achieved with electrospray technology, and it can be applied to high-throughput production [16].

8.3 Loading and Bioavailability Drug

MN patches have excellent capability of enhancing bioavailability of insoluble drugs through direct skin penetration. Transdermal delivery was enhanced using highly lipophilic cannabidiol nanosuspension loaded into dissolving MN patches [57]. Fast onset of effect is achieved through inhalation devices, which deliver the drug directly to the lungs [9].

8.4 Regulatory Pathways and Clinical Translation

Regulatory requirements vary across platforms. Combination drug-device products must provide evidence of bioequivalence between novel and prevailing delivery systems [4]. This is because the FDA has already approved a number of autoinjector products, indicating that this platform has already cleared the regulatory hurdle [1].

8.5 Current Limitations and Translational Challenges

Although important advances have been made, numerous challenges remain to their widespread clinical translation. There are still significant issues with nanoparticle formulations, including difficulties in scaling manufacture, batch-to-batch variability and complex requirements for quality-control. They are on the more expensive side compared to traditional dosage forms and device-based platforms like autoinjectors and MN patches, which may limit their application in resource-limited healthcare systems. Because both pharmaceutical and medical-device requirements must be satisfied, regulatory approval pathways for combination products can be complicated. In addition, the long-term biocompatibility and immunogenicity, biodistribution and toxicity profiles of novel nanomaterials need targeted investigation. To overcome these barriers, the future commercialization of diffractive surgical devices will require standardized manufacturing processes, strong regulatory frameworks, and affordable production technologies.

9. Difficulties and Future Projections

9.1 Technical Challenges

Technical Challenges. Even in the example of PFSSs, maintaining the appropriate quantities of silicone oil is difficult without a drop in BLGF [2]. A trade-off is required between the mechanical stability and ease-of-use of autoinjectors [1].

Patient breathing patterns vary, posing a challenge for inhalation machines [12]. MN patches must address stability, dosing, skin irritation, and manufacturing cost [58].

9.2 Customization and Digital Cohesion

The trend of further development points towards the directions of individual medicine. The integration of digital health enables the refinement of tool operations through real-time surveillance and adaptive delivery systems [15]. Electrically powered MN patches have the potential to deliver drugs on demand and in controlled doses, providing the opportunity for closed-loop therapeutic control [59].

9.3 Nanoparticle Integration

The future of nanoparticles and delivery system sophistication is marked by an increasing trend. The synergistic effect is achieved by nanoparticles using MN array patches [60]. Recent research has indicated that similar use of analogous incorporation of nanostructured particles using inhalation apparatuses has been found to have a high therapeutic outcome in the management of respiratory ailments [17].

9.4 Artificial Intelligence and Machine Learning

Artificial intelligence has provided innovative ways for designing and rationalizing nanoparticle-based drug delivery systems. AI techniques, namely machine learning, neural networks, and optimization algorithms, have facilitated the efficient production of nanoparticles with desired properties. By using AI in predictive modelling, a large number of parameters can be filtered quickly, accelerating the identification of favourable nanoparticle structures [37].

10. Conclusion

The evolution of drug delivery systems has fundamentally transformed modern pharmaceutical engineering, enabling the transition from conventional administration approaches toward intelligent, patient-centric therapeutic platforms. Technologies including autoinjectors, inhalation systems, MN patches, nanoparticle-based carriers, tissue-engineered scaffolds, and advanced transdermal formulations have demonstrated substantial potential to improve bioavailability, therapeutic precision, patient adherence, and clinical outcomes. Among these technologies, nanoparticle-enabled targeted delivery and smart self-administration platforms represent the most transformative advances in contemporary medicine. Nevertheless, manufacturing scalability, regulatory complexity, long-term safety assessment, and economic feasibility remain significant barriers to widespread implementation. Future innovations driven by artificial intelligence, advanced biomaterials, biosensors, and digital healthcare integration are expected to establish adaptive, personalized, and autonomous drug delivery ecosystems. The convergence of these technologies will ultimately accelerate the realization of precision medicine and redefine therapeutic intervention across diverse disease states.

Acknowledgements

The authors acknowledge the support and scientific environment provided by the Formulation Analytical Research and Development Division, Extrovis Private Limited, Hyderabad, Telangana, India. The authors also thank colleagues and reviewers whose constructive comments helped improve the quality and clarity of this review article.

Funding

No funding agency supports this work.

Ethics Statement

This article does not contain any studies with human or animal subjects.

Data Availability Statement

No data was used for the research described in the article.

Author Contributions

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Lakshmi Prasanna Nalluri: Corresponding author, conceptualization, supervision, manuscript review, editing, and final approval of the submitted version.

Conflict of Interest

The authors declare no conflicts of interest.

Generative AI Statement

No Generative Artificial Intelligence (Gen AI) tools were used in the creation or writing of this manuscript.

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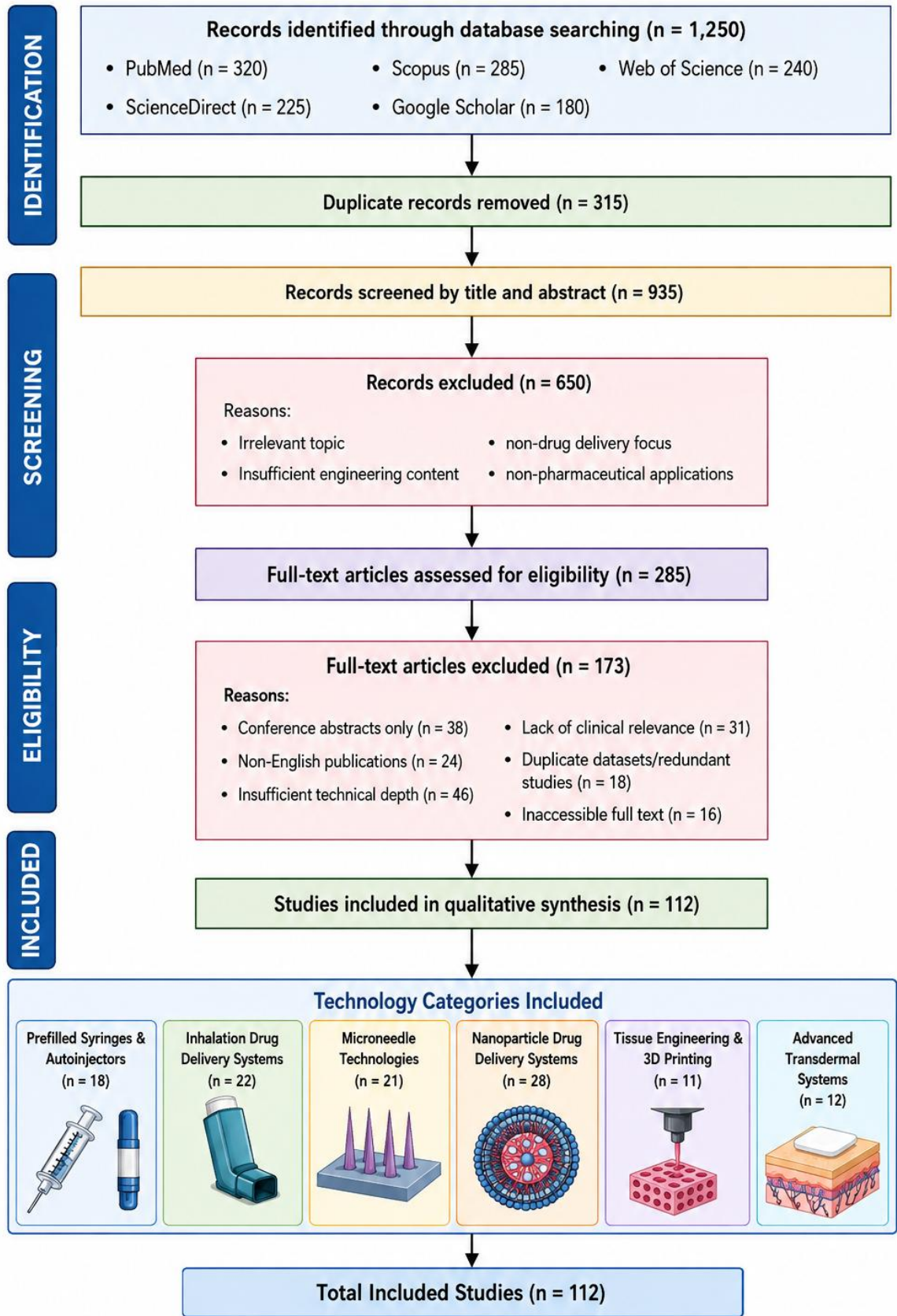


Figure S1. PRISMA flow diagram illustrating literature search and study selection process.