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Inkjet Printing of Pharmaceuticals

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Inkjet printing (IJP) is an additive manufacturing process that selectively deposits ink materials, layer-by-layer, to create 3D objects or 2D patterns with precise control over their structure and composition. This technology has emerged as an attractive and versatile approach to address the ever-evolving demands of personalized medicine in the healthcare industry. Although originally developed for nonhealthcare applications, IJP harnesses the potential of pharma-inks, which are meticulously formulated inks containing drugs and pharmaceutical excipients. Delving into the formulation and components of pharma-inks, the key to precise and adaptable material deposition enabled by IJP is unraveled. The review extends its focus to substrate materials, including paper, films, foams, lenses, and 3D-printed materials, showcasing their diverse advantages, while exploring a wide spectrum of therapeutic applications. Additionally, the potential benefits of hardware and software improvements, along with artificial intelligence integration, are discussed to enhance IJP's precision and efficiency. Embracing these advancements, IJP holds immense potential to reshape traditional medicine manufacturing processes, ushering in an era of medical precision. However, further exploration and optimization are needed to fully utilize IJP's healthcare capabilities. As researchers push the boundaries of IJP, the vision of patient-specific treatment is on the horizon of becoming a tangible reality.

1. Introduction

The current manufacturing model of medicines relies on mass production of large batches with a limited number of doses. However, this approach overlooks interindividual factors between patients, resulting in variations in the therapeutic response and potential inefficacy or toxicity reactions. Reports suggest that 40–70% of prescribed medications are ineffective and 1 in 15 hospital admissions are in relation to adverse drug effects resulting from inadequate doses.[1] Consequently, there is a growing trend in healthcare to move toward a more personalized medicine approach, taking into account individual needs and developing new pharmaceutical forms.[2]

The complexity of diseases and the heterogeneity of patients necessitate a more precise and bespoke approach to treatments. This requires technologies that offer accuracy and flexibility.[3] Additive manufacturing technologies are emerging as alternative methods in the healthcare field.

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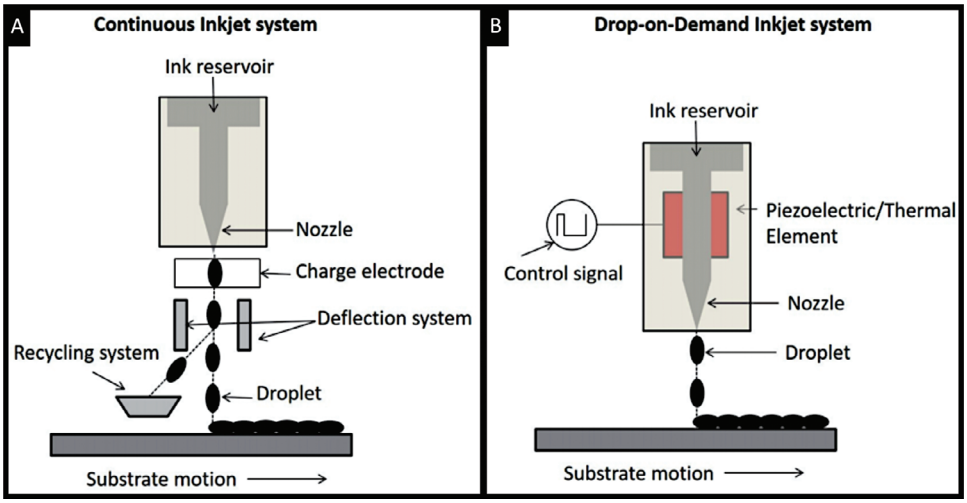

Figure 1. Graphical illustrations of the A) CIJP and B) DoD IJP systems. Reproduced with permission.[20] Copyright 2019, Books on Demand.

Specifically, inkjet printing (IJP) is gaining attention for various medical and pharmaceutical purposes, such as high throughput screening, drug development, and tissue engineering or regenerative medicine.[4,5]

The IJP technology is characterized by its high precision in ink deposition, avoiding contact with the substrate and allowing for accurate control of the printed dose based on the volume ejected through the nozzle.[6] Additionally, IJP offers great flexibility in terms of substrate, as formulated inks can be printed onto a wide variety of materials, including films, microneedles (MNs), clinical stents, contact lenses, and even nails.[7–11] This demonstrates the versatility of this technique in developing unique pharmaceutical forms and drug-loaded medical devices.

This comprehensive review provides an in-depth analysis of recent advances in the IJP technology, showcasing its potential in the pharmaceutical industry. It delves into the pivotal role of pharma-inks, which are meticulously formulated pharmaceutical compositions containing drugs, in enabling precise and flexible drug deposition using IJP. The extensive coverage includes an exploration of the diverse types of substrates used in IJP for pharmaceutical applications, offering a wide array of options for drug delivery platforms. The versatility and precision of IJP in producing various pharmaceutical forms and drug-loaded medical devices are showcased. Additionally, the potential for hardware and software improvements and the integration of Artificial Intelligence (AI) to expedite the adoption of IJP in the pharmaceutical manufacturing is discussed. Notably, the significant advantages of IJP, such as precise dosage delivery and formulation design flexibility leading to personalized medicines and improved patient outcomes, are summarized. Also, challenges associated with compatible pharmaceutical inks and the need for pharmaceutical hardware solutions for optimal printing performance are addressed. By thoroughly examining these aspects, this review aims to foster widespread IJP adoption in healthcare, revolutionizing drug formulation and delivery to advance personalized medicine on a broader scale.

2. IJP Technology

IJP is a material jetting technology that involves the deposition of small liquid drops of ink through a nozzle.[12] It can be classified into two techniques based on how the ink drops are generated: Continuous inkjet printing (CIJP) and drop-on-demand (DoD) IJP (**Figure 1**).

CIJP works by using a high-pressure pump to direct the ink through a nozzle, creating a continuous stream. This stream is then broken into droplets due to surface tension forces. The frequency can be adjusted to control the formation of drops.[12,13] To create a printed pattern, droplets are selectively charged by charging electrodes and pass through deflector plates that produce an electrostatic field. Charged drops are ejected onto the substrate, while uncharged droplets return to the system to be recycled back (Figure 1A).[14] The droplet formation mechanism[15,16] and the use of deflectors[17,18] in CIJP have been previously extensively studied and will not be discussed further in this review.

On the other hand, DoD techniques respond to an electrical stimulus to eject small volumes of liquid (Figure 1B). There are two types of DoD printheads: thermal and piezoelectric. In thermal IJP, an electrical signal is applied to a thermal element in the printhead, increasing the temperature of the liquid (i.e., up to 200–300 °C).[19] This temperature increase generates bubbles that expand and eject the fluid through the nozzle, creating a drop. In piezoelectric IJP (PIJP), the printhead has a piezoelectric element that deforms when subjected to an electric current, ejecting the drop.

DoD is commonly used in pharmaceutical applications due to its high precision and automation capacity, allowing for precise control of ink deposition. Both thermal and PIJP have distinctive advantages and drawbacks. Thermal printers are cheaper to manufacture but theoretically may have limitations with thermolabile materials. Nonetheless, this is yet to be proven as the contact between the micro resistor and the ink in thermal printheads is very short (i.e., ≈2 µs), which could minimize the impact on the active substances, even on biological molecules such as deoxyribonucleic acid (DNA).[21] In contrast, PIJP can be used with a wide

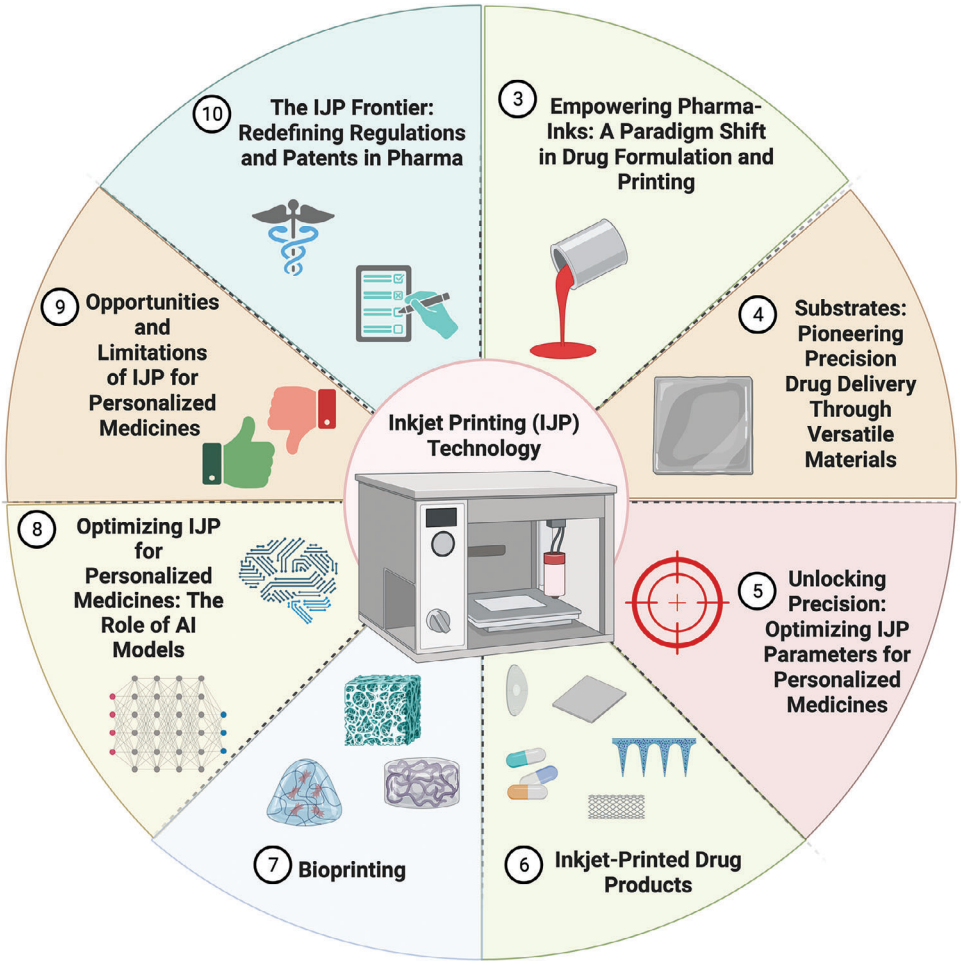

Figure 2. Summary of the scope of this review in the different sections.

range of pharma-inks and offers a more adaptable and scalable approach for pharmaceutical applications.

Regardless of the type of printhead used in the application of IJP in drug manufacturing, commercial ink cartridges are replaced with pharma-inks (i.e., formulations containing drugs). These pharma-inks can be deposited on a variety of substrates, allowing for the development of different pharmaceutical forms. **Table 1** provides examples of dosage forms and drug-loaded medical devices produced by DoD IJP. The scope of this review article is summarized in **Figure 2**. The literature searching criteria applied in this review can be found in File S1, Supporting Information.

3. Empowering Pharma-Inks: A Paradigm Shift in Drug Formulation and Printing

The IJP technology has expanded its applications beyond image transfer, with various innovations in fabricating polymeric electroluminescent materials, controlled-release drug delivery devices, and refractive microlenses.[80–82] To streamline the IJP process, commercial inks from leading companies like Fujifilm, Cabot, Heraeus, and Nano Dimension Ltd. are readily available, offering different colors for printing applications. However, these commercial inks are not suitable for pharmaceutical use as their contents are not Generally Recognized as Safe (GRAS) by the United States Food and Drug Administration (FDA).

Instead, specialized pharmaceutical-grade inks, termed pharma-inks, have emerged as a ground-breaking technology in the pharmaceutical industry, offering unparalleled opportunities for personalized medicine and precision drug delivery. These formulations play a pivotal role in fabricating patient-specific medicines, providing accurate dosing and targeted drug release tailored to individual therapeutic needs.

To effectively harness the potential of pharma-inks, a comprehensive understanding of ink formulation science is essential. This involves meticulously considering factors, such as drug compatibility, excipient selection, and the optimization of the IJP processes. By delving into the intricate details of ink preparation, pharmaceutical researchers can unlock the full potential of this revolutionary technology.

3.1. Crafting Pharma-Inks for Precision Medicine

Preparation of pharma-inks involves selecting the appropriate active pharmaceutical ingredient (API) or drug based on

Table 1. Examples of dosage forms and drug-loaded medical devices produced using DoD IJP. PET, Polyethylene terephthalate; TF, transparency film; PVA, polyvinyl alcohol; SCMC, sodium carboxymethyl cellulose; ODF, orodisperisble film; HMPC, hydroxypropyl methylcellulose; HPC, hydroxypropyl cellulose; PEG, poly(ethylene) glycol; NVP, *N*-vinyl-2-pyrrolidone; PEGDA, poly(ethylene glycol) diacrylate; PGA, polyglycolic acid; PDMS, Polydimethylsiloxane; FEP, fluorinated ethylene propylene; PLGA, poly(lactic-*co*-glycolic acid).

Dosage form	Drug(s)	Substrate(s)	Printer	Technology	Refs.
Oral film	Loperamide	Icing sheets	Dimatix DMP 2800	Piezoelectric	[22]
	Caffeine	PET films	Dimatix DMP 2800	Piezoelectric	[22]
	Indomethacin	Paper substrate Impermeable TF	PiXDRO LP 50	Piezoelectric	[23]
	Clonidine hydrochloride	Films 1:1 PVA:SCMC with 24% w/v glycerol	HP Deskjet 460	Thermal	[24]
	Salbutamol sulfate	Clear acetate films Commercial potato starch film	Deskjet D1660	Thermal	[25]
	Warfarin	ODF: 20% HPMC and 3% glycerol	HP 5940 Deskjet	Thermal	[26]
	Prednisolone	Poly(tetrafluoroethylene)-coated fiberglass	HP 970 Cxi DeskJet	Thermal	[27]
	Rasagiline mesylate	ODF: 14% HPMC, 4.7% crospovidone, 4.2% glycerol, and 77.1% water Copy paper Water impermeable TFs	Pixma MP495	Thermal	[28]
	Sodium picosulfate	HPMC Films HPMC + 2% TiO_2 Gelatin Gelatin + 2% TiO_2 Hydrophobic microcrystalline cellulose (pMCC) Hydrophilic microcrystalline cellulose (yMCC) Listerine films Rapidfilm	SciFLEXARRAYER S3	Piezoelectric	[29]
	Piroxicam	Edible paper substrate	Dimatix DMP 2800	Piezoelectric	[30]
	Sodium Picosulfate	Rapidfilm Hydrophobic nonporous film Hydrophilic porous film	SciDROP Pico	Piezoelectric	[31]
	Propranolol hydrochloride	Edible rice paper Edible icing sheet Coated edible rice paper	Pixma iP7250	Thermal	[32]
	Metoprolol tartrate	Films: 5% w/w HPMC and 3.5% w/w glycerol 85%	PiXDRO LP50	Piezoelectric	[33]
	Triiodothyronine (T3) Thyroxine (T4)	Films: 70% w/w HPMC and 30% w/w glycerol	HP 5940	Thermal	[34]
	Levothyroxine Prednisolone	Edible icing sheet Films: HPC:HPMC:glycerol:ethanol (7.5:7.5:5:80 w/w%)	PiXDRO LP 50	Piezoelectric	[35]
	Caffeine anhydrous	Single film-forming agents: HPC; PVA-PEG, Kollicoat instant release; maltodextrin, Glucidex IT6; sodium alginate Commercially available wafer edible sheets	Canon IP 1300	Thermal	[36]
	Haloperidol	Custom-made inorganic compacts HPMC dry foam and commercial paracetamol tablets	PiXDRO LP50	Piezoelectric	[37]
	Anhydrous theophylline	Uncoated copying paper	Pixma MP495	Thermal	[38]
	Warfarin	HPC films	PiXDRO LP50	Piezoelectric	[39]
	Theophylline	Seed gum from *Tamarindus indica* Linn	Epson L220	Piezoelectric	[40]
	Propranolol hydrochloride	Edible solid foams	PiXDRO LP50	Piezoelectric	[41]
	Enalapril maleate	HPC films 5.2% Hydrochlorothiazide films containing 15% HPC	PiXDRO JS 20	Piezoelectric	[42]
	Metformin hydrochloride	Wafer paper sheets Ethylene vinyl acetate Gelatin film strips Gelatin film strips with 2% titanium dioxide HPMC Edible icing sheets	sciFLEXARRAYER S3	Piezoelectric	[43]

(*Continued*)

Table 1. (Continued).

Dosage form	Drug(s)	Substrate(s)	Printer	Technology	Refs.
	Haloperidol	Films: HPMC, mesoporous fumed silica, glycerol	PiXDRO LP50	Piezoelectric	[44]
	Sativex Stenocare	Films: 2.5% w/v HPMC, 0.0825% w/v Lutrol, and 0.25% w/v PEG, Tween 20, and glycerol Porous foams Potato starch edible sheets	Epson XP-8500	Piezoelectric	[45]
Buccal film	Lidocaine hydrochloride	Fibrous gelatin substrates	PiXDRO LP50	Piezoelectric	[46]
	Lidocaine hydrochloride	HPMC films	Canon MG2950	Thermal	[47]
	Lysozyme Ribonuclease-A	PET sheets	HP Deskjet 1000	Thermal	[48]
	Ibuprofen	3D printed HPMC films	Canon MG2950	Thermal	[49]
	Diclofenac sodium	Sugar-sheet substrate	HP D4260	Thermal	[50]
	Lysozyme	HPMC films Chitosan films	HP Deskjet 1000	Thermal	[51]
	Thiamine hydrochloride Nicotinic acid	Sugar-sheet substrate	Canon MG2950	Thermal	[52]
	Rhodamine 123 Human insulin	HPMC films	HP Deskjet 1000	Thermal	[53]
Microdevice	Topotecan Insulin	Planar microdevices	sciFLEXARRAYER S3	Piezoelectric	[54]
	Insulin	Microdevice	sciFLEXARRAYER S3	Piezoelectric	[55]
Tablet	Thiamine hydrochloride	PET films	Dimatrix DMP 2850	Piezoelectric	[56]
	Minoxidil sulfate	3D printed PVA tablets	NanoPlotter II	Piezoelectric	[57]
	Carvedilol	3D printed NVP and PEGDA tablets and films	Dimatix DMP 2830	Piezoelectric	[58]
	Ropinirole hydrochloride	PET films	Dimatix DMP 2830	Piezoelectric	[59]
	Fenofibrate	PET films	PiXDRO LP50	Piezoelectric	[60,61]
Capsule	Vitamin B6 Vitamin B12F Folic acid	Edible paper carrier	Microdrop printing device	Piezoelectric	[62,63]
Microneedles	Amphotericin B	Gantrez 169 BF	Dimatix DMP 2831	Piezoelectric	[7]
	Miconazole	Gantrez AN 169 BF	Dimatix DMP 2831	Piezoelectric	[64]
	Itraconazole	PGA MN arrays	Dimatix DMP 2831	Piezoelectric	[65]
	Voriconazole	PGA MN arrays	Dimatix DMP 2831	Piezoelectric	[66]
	Cisplatin	Biocompatible Class I resin	NanoPlotter II	Piezoelectric	[67]
	Insulin	Biocompatible Class I resin	NanoPlotter II	Piezoelectric	[68–70]
	5-fluororacil Curcumin Cisplatin	Stainless steel sheets	NanoPlotter II	Piezoelectric	[71]
	Insulin	Stainless steel sheets	NanoPlotter II	Piezoelectric	[72]
	Seasonal trivalent inactivated Subunit influenza vaccine	PDMS, Sylgard molds	MicroFab JetDrive 3	Piezoelectric	[73]
	Thrombin, temozolomide, and bevacizumab	–	Dimatix DMP 2800	Piezoelectric	[74]
Patches	Fat- and water-soluble drugs	FEP/PLGA/HPC multi-layer membrane film	HP 5278	Thermal	[75]
	Indomethacin	Backing membrane	Epson stylus SX 400	Piezoelectric	[76]
Nail treatment	Terbinafine hydrochloride	Glass and polystyrene plastic	O2Nails V11 Printer	Thermal	[10]
Aerosols	Human growth hormone Insulin	–	Drive circuits by Defiant Pty. Ltd. and Vaptoronics Inc. Cartridges: HP 45 and HP 48	Thermal	[77]
	Glucono-delta-lactone (Additive)	–	HP Deskjet D1660 Printers	Thermal	[78]
Contact lenses	Itraconazole	Soft hydrogel contact lenses	PiXDRO LP50	Piezoelectric	[79]
	Timolol maleate	1-day Acuvue Moist disposable contact lenses	O2Nails V11 Printer	Thermal	[11]

therapeutic applications and solubility. The drug is then carefully dissolved, dispersed, or encapsulated in a suitable solvent (e.g., dimethyl sulfoxide (DMSO) for miconazole[64]) or carrier material to create a homogeneous and printable ink formulation.[83] Achieving uniform drug distribution within the ink is crucial to ensure precise drug deposition during printing. For instance, in the formulation of protein-containing pharma-inks, special consideration is given to the influence of shear rates or actuator displacement rates on proteins during the printing process. The addition of small sugar molecules like trehalose and glucose can minimize protein damage at low displacement rates.[84] The physicochemical constitution of the ink is also crucial for its jettability, with properties like surface tension and viscosity being essential factors.

pH is a key parameter in pharma-ink formulation, as it can control biomolecular conformation and intermolecular interactions, influencing processes such as protein/ribonucleic acid (RNA) stability, enzyme activity, and regulation through conformational switches.[85] The choice of solvents can also affect the pH of the ink formulation.

3.2. Types of Pharma-Inks

In the realm of pharma-inks, one form of classification that stands out is the division between aqueous and nonaqueous formulations. Pharma-inks can also be classified based on their content into polymer-, lipid-, and nanoparticle-based formulations. Each type of pharma-ink requires specific excipients to optimize ink properties and drug delivery characteristics.

3.2.1. Solvent-Based Classification

Aqueous Pharma-Inks: Water-based pharma-inks represent a powerful approach to ink formulation.[86] These formulations offer unique advantages, making them a popular choice for precision drug delivery applications. Aqueous pharma-inks typically employ water as the primary solvent, creating a stable and homogenous ink formulation that is compatible with a wide range of pharmaceutical compounds. This water-based approach ensures the safety and biocompatibility of the ink. By utilizing water as the solvent, the risk of introducing potentially harmful organic solvents into the ink formulation is minimized, ensuring the ink's compliance with strict regulatory standards.

Furthermore, aqueous pharma-inks enable precise control over drug release kinetics, offering tailored drug delivery profiles that match individual therapeutic needs. The water-based formulation allows for the incorporation of various excipients, such as hydrophilic polymers or stabilizers, to optimize drug release and enhance the stability of the ink during printing. This level of customization empowers pharmaceutical researchers to develop personalized medicines with optimal drug release profiles, ensuring effective treatment and minimal side effects.

Nonaqueous Pharma-Inks: In contrast, nonaqueous pharma-inks utilize organic solvents as the primary carriers for drug delivery. These formulations offer a different set of advantages and are particularly useful for drugs with limited solubility in water or when specific drug-carrier interactions are required. Nonaqueous pharma-inks often utilize organic solvents such as DMSO,[7] ethanol,[22] or acetone,[87] providing a versatile platform for dissolving a wide range of pharmaceutical compounds. These solvents effectively solubilize hydrophobic drugs, enabling their efficient incorporation into the ink formulation. The use of organic solvents expands the scope of drug candidates that can be incorporated into pharma-inks, broadening the potential applications of this technology. Moreover, nonaqueous pharma-inks offer unique opportunities for precise control over drug release kinetics. The choice of organic solvents can influence the rate of drug release, allowing researchers to tailor the ink formulation to achieve desired drug delivery profiles.

The classification of pharma-inks into aqueous and nonaqueous formulations underscores the diverse approaches available for precision drug delivery and personalized medicine. Both aqueous and nonaqueous pharma-inks offer distinct advantages, providing pharmaceutical researchers with a powerful arsenal of ink formulations to address complex therapeutic challenges.

3.2.2. Content-Based Classification

Polymer-Based Pharma-Inks: In polymer-based pharma-inks, a single or multiple polymers from synthetic or natural sources is used for the formulation of the ink. Synthetic polymers, such as polyvinylpyrrolidone (PVP),[6,87] polyethylene glycol (PEG),[88] polyvinyl alcohol (PVA),[89] poly(lactic-*co*-glycolic acid) (PLGA),[87] and semisynthetic polymers, such as methyl cellulose (MC), ethyl cellulose (EC) hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), microcrystalline cellulose (MCC), and hydroxypropyl methylcellulose (HPMC),[90] are instrumental in improving the viscosity and surface tension of the ink, preventing nozzle clogging, and ensuring the consistent formation of droplets during the printing process. These polymers also play a critical role in controlling drug release, enabling the development of dosage forms with precisely regulated drug release profiles.

Biopolymer-based pharma-inks epitomize the convergence of nature's ingenuity and advanced pharmaceutical technology, harnessing the potential of natural polymers, such as chitosan,[91] gelatin, or alginate. These biocompatible and biodegradable polymers serve as the cornerstone of innovative ink formulation, offering a sustainable approach to the development of personalized medications.

Lipid-Based Pharma-Inks: Lipid-based pharma-inks represent an innovative approach that harnesses the unique properties of lipids as the main component. These formulations often incorporate liposomes,[92,93] or solid lipid nanoparticles as carriers for the drugs. Examples of lipids commonly used in lipid-based pharma-inks include phosphatidylcholine[92] and cholesterol.[93] The choice of these specific lipids is driven by their biocompatibility and versatility.

Phospholipids, being key components of cell membranes, serve as a critical excipient in lipid-based pharma-inks, contributing to the stability and integrity of the formulation.[94,95] By emulating the natural cellular environment, phospholipids promote the successful incorporation and entrapment of drugs within the lipid carriers, maximizing drug encapsulation efficiency.

Nanoparticle-Based Pharma-Inks: Nanoparticle-based pharma-inks represent a cutting-edge formulation approach that incorporates drug-loaded nanoparticles into the ink

composition. These nanoparticles can be crafted from diverse materials, such as metals, metal oxides, or polymers,[96–98] imparting unique functionalities to the ink formulation. To ensure the stability and efficacy of nanoparticle-based pharma-inks, specific excipients play a crucial role in facilitating the successful integration of these nanoparticles into the ink formulation.

Excipients Used in Pharma-Inks: Excipients form an integral part of an ink's formulation and synergistically work in harmony to optimize its performance and functionality. For instance, cross-linking agents, such as glutaraldehyde, play a pivotal role in reinforcing the structural integrity of gelatin-based inks, transforming them into robust and versatile materials for tissue engineering and regenerative medicine applications.[99]

Surfactants (also known as wetting agents; e.g., dodecyl benzenesulfonic acid,[100] Poloxamer 188,[101] or Triton X-100[102]) play a multifaceted and indispensable role in the formulation of pharma-inks, serving two major purposes in the design of inkjet inks. First, they are critically important for stabilizing the dispersion of particles in the ink medium, making them a significant subset of all dispersants. Even in systems where covalently bound dispersants are utilized, the incorporation of surfactants further enhances dispersion stability, ensuring uniform distribution of drug particles within the ink. Second, surfactants play a pivotal role in controlling surface tension at the liquid–air interface, a parameter of utmost significance in the IJP process.[102] Proper control of surface tension is essential for several reasons. When the system's surface tension is too high, the ink may face difficulties moving through the nozzle, leading to sporadic printing because the ink beads in the nozzle.[103] Conversely, if the surface tension is too low, the opposite problem arises, resulting in ink leakage from the printhead. Once the ink reaches the substrate, surface tension becomes even more critical. To achieve a continuous track during printing, the deposited droplets should not bead, and it is equally important to prevent significant absorption of droplets into the substrate or lateral spreading to maximize the density of deposited drug particles.[104] Consequently, achieving optimal dispersion stability, printability, and as-deposited wettability must be considered. To address each of these essential aspects, the formulation of pharma-inks may employ intricately designed surfactant systems. However, it is crucial to be mindful of the potential consequences of using large amounts of surfactants. Excessive surfactant content can potentially decrease adhesion to the substrate. In fact, many surfactants are specifically designed to perform these functions.

Stabilizers are incorporated into pharma-inks to prevent drug precipitation and maintain the physicochemical properties of the formulation over time.[72] This crucial role in maintaining the integrity of the ink ensures that the drug remains uniformly dispersed within the formulation, even during prolonged storage, guaranteeing its efficacy and therapeutic potency. As an example, stabilizers such as Pluronic F68[105] and polyurethane[106] are utilized in metal nanoparticle inks, ensuring the stability of the nanoparticles and maintaining the desired properties of the ink. For specific applications, a binary solvent system, such as α-terpineol and toluene, is often chosen to prevent the coffee-ring effect (i.e., phenomenon observed when a liquid containing solids or 2D crystals evaporates, resulting in the formation of a distinctive ring-like pattern of the dissolved materials at the outer edges of the dried droplet) during the drying process of platinum nanoparticle inks, preserving the uniformity of the ink deposition.[107]

Plasticizers are employed to optimize ink rheology, ensuring smooth and consistent printing processes. Glycerol (or glycerin),[108-110] propylene glycol,[41,45,49] and PEG[111] are common plasticizers used in pharma-inks, known to improve ink flow characteristics. Furthermore, plasticizers influence the glass transition temperature of the ink, impacting its mechanical properties and drug release kinetics. Beyond flow improvement, these additives contribute to ink stability, adhesion, and controlled drug deposition during IJP, enhancing overall product quality and precision.

Humectants, such as glycerol[48,51] or mono propylene glycol,[89] also play a vital role in achieving the perfect balance of viscoelastic properties, while also serving as a safeguard against printhead blockages.[89] These essential components contribute to the overall formulation's stability and efficiency, ensuring precise and uninterrupted drug deposition during the IJP process.

3.3. From Commercial to Custom: Paving the Way for Pharmaceutical-Grade Inks

Typically, pharma-inks are loaded into commercial ink cartridges, which are opened, cleaned, and sterilized to prepare them for drug loading. However, this approach may not always be practical, as some cartridges are difficult or impossible to open while remaining usable. To address this challenge, Fujifilm Dimatix has introduced a cutting-edge MEMS-based cartridge-style printhead, known as the Samba cartridge. This innovation allows users to fill their own fluids and immediately print using the Dimatix Materials Printer.[112] With each cartridge reservoir boasting a capacity of 1.5 mL, waste of expensive fluids is minimized, enabling seamless printing of multiple fluids. The Samba cartridge's versatility extends beyond pharmaceutical applications, making it suitable for the deposition of biological fluids, including cell patterning, DNA arrays, and proteomics. This approach not only provides greater control and customization of ink formulation but also opens the gateway for the development of pharmaceutical-grade inks that strictly adhere to regulatory standards, such as being composed of GRAS materials.

By embracing the potential of pharma-inks, the pharmaceutical industry is driving drug development toward enhanced efficiency and the creation of bespoke medicines that cater to the unique healthcare needs of individual patients. Continued research and development in this field will undoubtedly optimize pharma-inks further, widening the horizons of digital healthcare and revolutionizing the future of drug delivery. As these advanced ink formulations continue to pave the way for personalized medicine, the pharmaceutical industry is poised to embark on a new era of patient-centric healthcare, redefining the very fabric of drug formulation, manufacturing, and administration.

4. Substrates: Pioneering Precision Drug Delivery Through Versatile Materials

In the realm of pharmaceutical IJP, substrates serve as the foundation for drug deposition, playing a pivotal role in determining

the properties and performance of printed pharmaceutical products. The selection of appropriate substrates is critical in achieving accurate drug delivery and tailored therapies, making it an indispensable aspect of IJP technology. Substrates control drug release by influencing various factors that impact the diffusion and dissolution of the drug within the substrate matrix. The properties of the substrate, such as porosity, surface area, and hydrophilicity, can significantly affect the rate at which the drug is released. For example, highly porous substrates with a large surface area can provide a larger area for drug diffusion, resulting in faster drug release.[113] Conversely, less porous substrates may hinder drug diffusion, leading to a slower release.

The interaction between the drug and the substrate's surface also plays a crucial role in drug release kinetics. Optimizing the surface energy of the substrate is crucial in IJP for pharmaceutical applications as it directly impacts the affinity of the API to the substrate's surface.[114] The surface energy of a substrate determines its hydrophilic or hydrophobic nature, influencing the wettability and adhesion of the ink containing the API. Hydrophobic substrates can interact more strongly with hydrophobic drugs, leading to slower drug release due to increased drug-substrate interactions. On the other hand, hydrophilic substrates can enhance the dissolution of hydrophilic drugs, resulting in faster drug release. Furthermore, the thickness and composition of the substrate can also impact drug release. Thicker substrates may delay drug release as the drug must travel a longer distance to diffuse out of the substrate.[115] Additionally, the addition of excipients or modifiers to the substrate formulation can influence drug release. For instance, the incorporation of polymer blends or additives can modify the porosity and hydrophilicity of the substrate, thereby altering the drug release profile.

4.1. Pharmaceutical Substrates

4.1.1. Edible Paper

Edible paper substrates, including rice paper, icing sheets, and wafer edible sheets, have emerged as innovative materials for producing orodispersible films (ODFs).[32,43,62,63] Embracing excellent biocompatibility and rapid dissolution in the mouth, these substrates deliver precise drug release, facilitating targeted drug delivery and patient compliance.

4.1.2. Gelatin

Gelatin film strips, enhanced with titanium dioxide, and fibrous gelatin substrates have garnered significant attention in IJP due to their biocompatibility and adaptability for tissue engineering applications.[43]

4.1.3. Cellulose

Cellulose-based substrates, such as HPC[39,42] and HPMC[51,53] films, offer excellent biocompatibility and drug compatibility. These substrates provide a conducive environment for drug encapsulation and controlled drug release, paving the way for regenerative medicine and advanced drug delivery systems. Furthermore, their hydrophilic nature facilitates rapid dissolution and disintegration upon contact with bodily fluids, ensuring efficient drug release and absorption.[26,32] The flexibility and thinness of cellulose films enable easy incorporation into various drug delivery systems, including oral, buccal, transdermal, and ocular routes.

4.1.4. Edible Foams

Edible foams have gained significant attention as substrates in pharmaceutical IJP due to their versatility and biocompatibility.[37,41] Their porous structure allows for the incorporation and encapsulation of a wide range of drug compounds, providing precise control over drug release kinetics.[41] This makes foams an attractive choice for formulating dosage forms with specific release profiles tailored to individual therapeutic needs. Additionally, foams possess high compressibility and rapid disintegration properties,[45] making them suitable for the development of orally disintegrating tablets (ODTs). ODTs are particularly advantageous for patients who have difficulty swallowing traditional tablets, offering a more convenient and patient-friendly mode of drug administration.[116] The biocompatibility of foams ensures their safety for use in drug delivery applications. Their ability to promote cell adhesion and proliferation also makes them a promising substrate for tissue engineering and regenerative medicine applications.[117,118] Furthermore, the foam structure of foams provides a large surface area for drug loading, maximizing drug payload capacity and enhancing drug dissolution rates.[45] This feature is crucial for improving drug bioavailability and efficacy.

4.1.5. Polyglycolic Acid (PGA)

PGA is a synthetic polymer widely utilized as a substrate in tissue engineering and drug delivery applications, making it an attractive choice for advanced pharmaceutical formulations for transdermal applications. PGA substrates offer excellent mechanical properties,[119] allowing for precise drug deposition and controlled drug release. Their biodegradability ensures that the substrate gradually breaks down over time, eliminating the need for additional removal procedures. This feature is especially advantageous for MN arrays, as the substrate eventually dissolves, leaving behind the therapeutic agents and promoting tissue regeneration.[65,66]

4.1.6. Polydimethylsiloxane

Polydimethylsiloxane (PDMS) is a silicone-based polymer widely used in various industries. PDMS substrates, such as Sylgard molds, showcase high flexibility, rendering them ideal for creating microdevices and drug-loaded microstructures.[73] PDMS substrates are characterized for their high elasticity and deformability,[120] which enable them to adapt to complex and intricate designs.[120] This distinctive flexibility is crucial in the precise fabrication of microdevices, ensuring that the final product accurately replicates the intended geometries. Beyond their flexibility, PDMS substrates also possess excellent

biocompatibility,[121,122] making them well-suited for applications involving interactions with biological tissues and fluids. This biocompatibility is a crucial factor when designing microdevices for targeted drug delivery, as it ensures minimal adverse reactions when the devices come into contact with the body. Furthermore, PDMS substrates can be easily functionalized and modified to incorporate various types of drug-loaded microstructures, such as channels and reservoirs, to precisely control the release of therapeutic agents.[123,124]

4.1.7. Contact Lenses

Contact lenses are suitable for IJP due to their flat and smooth surface, which provides an ideal substrate for precise drug deposition using the inkjet technology.[11,79] The microscale structure of contact lenses allows for accurate placement of pharmaceutical formulations and controlled release of drugs onto the ocular surface. Additionally, the biocompatibility and nontoxic nature of contact lens materials ensure minimal irritation or adverse effects on the eyes.

Various types of contact lenses can be suitable for IJP, including soft hydrogel contact lenses and silicone hydrogel contact lenses. Soft hydrogel lenses are made from hydrophilic polymers that are water-rich and offer high water content, making them comfortable for extended wear. Silicone hydrogel lenses combine the benefits of soft hydrogels with the oxygen permeability of silicone,[125,126] making them suitable for prolonged use and maintaining ocular health.[127]

4.1.8. 3D Printed Dosage Forms

3D printed tablets prepared using other technologies, such as fused deposition modeling (FDM), exemplify the cutting-edge approach in IJP, enabling the fabrication of customized drug-loaded tablets with precise dosing.[57,128] The addition of the API using IJP following FDM 3D printing ensures that thermolabile APIs remain intact and avoid thermal degradation.[129] Similarly, this could be beneficial in the case of light-sensitive APIs, preserving their integrity following powder bed fusion[130] and vat photopolymerization processes.[131] They also allow the tracking-and-tracing of medicines, preventing their falsification and ensuring their correct use.[128] In the same vein, IJP can be exploited for detailing patient and medicine information onto preformed dosage forms.[45,132]

4.1.9. Resins

Gantrez resins are a family of copolymers that are widely used in pharmaceutical and medical applications due to their unique properties and versatility. These resins are composed of various monomers, including methyl vinyl ether and maleic anhydride, which contribute to their distinctive characteristics. One of the key features that makes Gantrez resins unique is their ability to interact with both hydrophilic and hydrophobic substances,[133] making them suitable for a wide range of formulations. They have excellent adhesive properties[134–136] and can be used to enhance the solubility and stability of poorly soluble drugs, as well as to control drug release rates. Gantrez resins, such as Gantrez AN 169 BF[64] and Gantrez 169 BF,[7] have earned prominence in IJP for their biocompatibility and ability to enhance drug stability and release. Additionally, biocompatible Class I resins offer a versatile platform for custom-made inorganic compacts, broadening the horizons of drug delivery applications.[68–70]

4.1.10. Stainless Steel Sheets

Stainless steel sheets stand firm as substrates in IJP, boasting durability and mechanical strength.[71,72] These attributes make them suitable for producing medical devices and implants, empowering precision medicine in various therapeutic domains.

5. Unlocking Precision: Optimizing IJP Parameters for Personalized Medicines

The successful IJP of personalized medicines requires careful optimization of several critical processing and printing parameters (**Figure 3**).[56,100,137,138] These parameters play a crucial role in determining the quality, accuracy, and reliability of the printed dosage forms. The following key parameters need to be optimized to ensure the efficient and precise delivery of personalized medicines using the IJP technology.

First, the pharma-ink formulation must be optimized for IJP. The pharma-ink should be carefully designed to achieve the desired drug concentration, viscosity, surface tension, and other rheological properties.[11,56] These properties significantly impact the printing performance, including droplet formation, ejection, and deposition accuracy. Optimizing the pharma-ink involves selecting appropriate excipients, solvents, and drug carriers to ensure ink stability, compatibility, and suitability for the printing system.

Second, the printer settings and parameters need to be optimized.[88,100] This includes adjusting droplet volume, jetting velocity, nozzle diameter, and droplet spacing to achieve precise and consistent droplet deposition.[100] Optimizing these parameters ensures accurate dosing and uniform distribution of the printed medication on the substrate. Moreover, the refinement of the printing process extends to the adjustment of the "waveform." In the realm of IJP, the waveform denotes the specific electrical signal applied to the printhead, whether piezoelectric or thermal.[88] This tailored waveform is instrumental in achieving consistent drop formation, precise drop size, accurate placement, and controlled velocity. Notably, waveform optimization mitigates issues like ink satellites (i.e., small, unintended droplets or particles of ink dispersed around the main printing area) and overspray (i.e., the unintentional scattering or dispersion of ink droplets beyond the intended printing area), thereby enhancing print quality while preserving speed and precision.[88,139] Additionally, controlling the temperature, humidity, and environmental conditions during the printing process is crucial to maintain ink formulation stability and integrity.

Furthermore, substrate selection and preparation are critical factors in IJP of personalized medicines.[28,31,113] The substrate should possess suitable properties, such as porosity, surface roughness, and wettability to facilitate proper ink adhesion

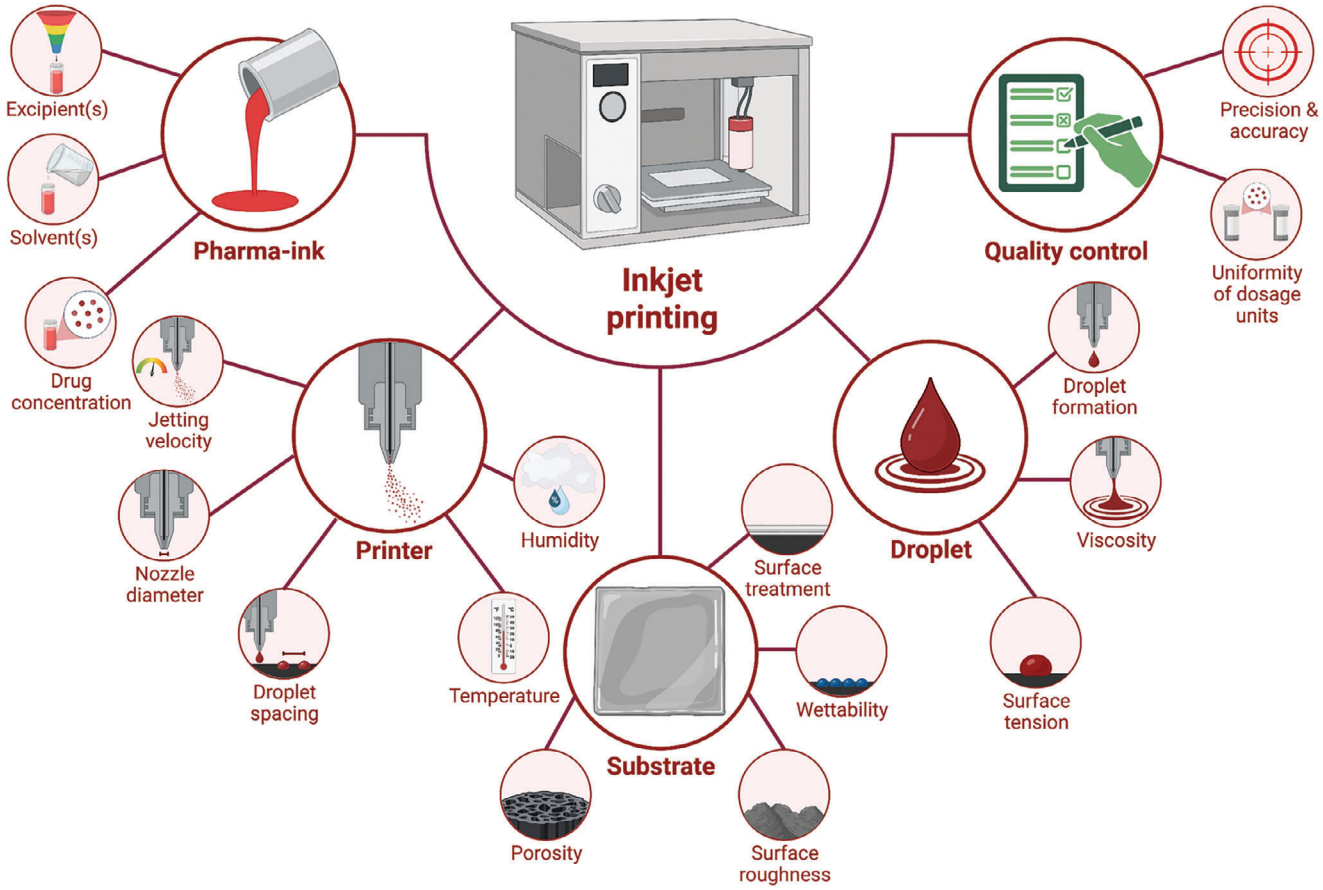

Figure 3. Summary of the critical processing parameters involved in the IJP process.

and penetration. Optimizing substrate surface treatment, such as precoating or modifying surface properties, can enhance printing quality and ink adhesion to the substrate.

Moreover, process validation and quality control (QC) are essential steps in ensuring the reproducibility and reliability of IJP for personalized medicines.[37,43,140,141] The printing process should be validated by verifying accuracy, precision, and uniformity of the printed dosage forms. QC measures, such as inspecting printed samples for defects, assessing drug content uniformity (e.g., using colorimetry,[141] Near-infrared spectroscopy (NIR),[43,140] and Raman spectroscopy[37,140]), and evaluating physical characteristics, are crucial for ensuring consistent and high-quality printed medicines.

6. Inkjet-Printed Drug Products

6.1. Oral and Buccal Delivery Systems

The oral route remains the preferred method for drug administration due to its comfort, safety, and cost-effectiveness for the pharmaceutical industry.[142] However, oral administration has limitations such as variable bioavailability due to the gastrointestinal (GI) tract's aggressive environment,[143,144] first-pass hepatic effect, and unpleasant taste and gastric irritation of conventional dosage forms.[145] To overcome these limitations and improve drug administration, new pharmaceutical forms for oral and buccal delivery are being explored. The IJP technology offers a precise and flexible technique for medication development in these areas.

6.1.1. Oromucosal Films

Oromucosal films are emerging as an alternative drug delivery system to conventional capsules and tablets. These films are easy to manipulate and administer, and are highly accepted by patients, improving adherence to treatment.[146] They do not require swallowing or co-administration with water, making them suitable for populations with swallowing difficulties (e.g., geriatrics and pediatrics, or patients with dysphagia, amyotrophic lateral sclerosis and Parkinson's disease).[8,147–150] Oromucosal films allow for the personalization of therapy by incorporating different APIs and/or excipients to achieve various characteristics, such as rapid dissolution or controlled release.[146,150]

Recently, the European Pharmacopoeia introduced a monograph for oromucosal preparations, differentiating between ODFs and mucoadhesive buccal films (MBFs).[149,150]

Orodispersible Films (ODFs): ODFs are novel pharmaceutical forms based on thin polymeric films formulated for practically instantaneous dispersion in the mouth.[151] Their main

advantages lie in their ability to be formulated to contain several types of APIs, such as drugs,[150] vaccines,[152] probiotics,[153] or vitamins.[154] Moreover, they provide a local drug release in the mouth, specifically on the tongue or buccal mucosa (i.e., the inner lining of the cheeks). ODFs quickly dissolve and release the drug directly into the saliva. This allows for efficient absorption of the drug through the oral mucosa, which is rich in blood vessels and capillaries. As a result, the drug bypasses the GI tract and the first-pass metabolism in the liver, leading to higher, and more consistent drug levels in the bloodstream.[155] This enhanced absorption and avoidance of the liver metabolism contribute to improved bioavailability, ensuring that a higher percentage of the administered dose reaches its intended target and produces the desired therapeutic effect. ODFs can also be used as carriers for other technologies such as micro-,[156] nanoparticles,[157] or nanocrystals.[158]

ODFs are conventionally produced using solvent casting,[159] wherein APIs are dissolved in a suitable solvent, cast onto intermediate liner, and subsequently dried and cut into films.[146,160] This product method has limitations such as content variability, air bubble formation, and the need for organic solvents.[146] An alternative approach to solvent casting is hot melt extrusion (HME). Herein, dry ingredients are mixed, melted and extruded through an orifice. This results in shorter processing times compared to solvent casting and avoids the use of solvents. However, despite these advantages, the high processing temperatures involved in HME can compromise the stability of some APIs and excipients.[161–163]

In contrast to solvent casting and HME, IJP offers advantages in terms of deposition without contact with the film, flexibility, and accuracy in dose control.[105,164] In a ground-breaking study, researchers compared solvent casting with IJP, utilizing a thermal printer for the manufacturing of films.[24] To assess the efficacy of this novel approach, clonidine, a model drug with a low therapeutic dose, was used. The results demonstrated significant differences between the films produced by the conventional and IJP methods in terms of mechanical properties and stability. While films produced using the IJP technology exhibited similar values of Young's moduli and tensile strength to solvent casting, those generated through solvent casting were found to be more brittle. The dissolution characteristics of printed and cast films displayed similarity, attributed to the swift disintegration of the cellulose polymer. During stress testing, it was observed that the drug crystallized from the casted films, whereas the printed films remained unaffected by this phenomenon. Additionally, films produced through casting exhibited a lower content of clonidine compared to those prepared via IJP. The dose variation was also more pronounced with the solvent casting method in contrast to IJP. The increased dose variability in casted films could stem from uneven blending or variations in film thickness. However, these findings highlight the potential of IJP in obtaining ODFs with superior characteristics compared to conventional methods, particularly in formulating precise doses of low-dose medicines with narrow therapeutic indices. This revolutionary advancement in film manufacturing opens up new possibilities for personalized medicine and enhanced patient care.

Studies have shown successful printing of different drugs on oromucosal films using the IJP technology. For example, inkjet printed ODFs containing propranolol hydrochloride for pediatric patients demonstrated precise and uniform doses with rapid disintegration.[32] Typically, doses must be adjusted to the weight and surface body of the child. However, suitable doses are not often available and conventional solid dosage forms for adults present several limitations for pediatric patients. As an alternative, thermal IJP can be used to directly prepare ODFs containing scaled doses of propanol for the treatment of hypertension, infantile hemangiomas, and arrhythmias (**Figure 4**).[32]

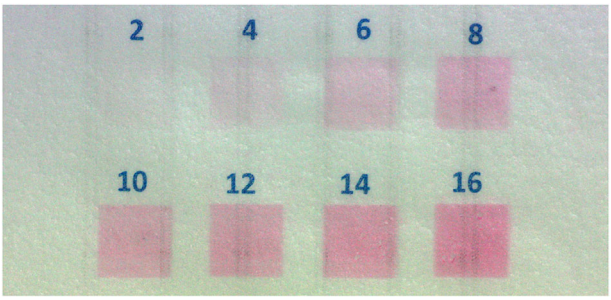

Figure 4. Inkjet-printed ODFs (2 cm^2 in size) containing escalating doses of propranolol hydrochloride printed onto edible rice paper. Reproduced with permission.[32] Copyright 2016, Elsevier.

Conventionally, children require a low therapeutic dose (e.g., 0.35 mg) of metoprolol tartrate compared to adult patients (e.g., 3.5 mg). Thus, inkjet-printed ODFs with scaled doses of metoprolol tartrate for pediatric patients have been developed. While the IJP approach resulted in uniform dosages, significant changes in the printed amount were observed with nozzle aging over a period of 5 months.[33] Thus, further improvement to the printheads is needed for future implementation. Inkjet-printed warfarin ODFs were also produced.[26] Warfarin is an anticoagulant agent with a narrow therapeutic index (i.e., the difference between the effective and toxic doses is minute) and large inter-individual variability. Due to this, its use often involves complex treatment regimens and continuous patient monitoring. Thus, IJP was explored for the preparation of ODFs containing different warfarin doses (e.g., 1.25 and 2.5 mg). Results have shown rapid disintegration of the films with high linearity being observed between the theoretical and the measured doses of warfarin.[26] Inkjet-printed ODFs with drugs like enalapril maleate,[42] rasagiline mesylate,[28] and sodium picosulfate[29] have also been developed. More details on the compositions of these ODFs films can found in Table 1.

Biologics are another class of drugs that are naturally derived by engineered biotechnological processes and are known for their complex and less stable structures.[165] They include hormones, cytokines, and peptides, and are used in the treatment of several human diseases such as cancer,[166] rheumatoid arthritis,[167,168] inflammatory bowel diseases,[169] and growth deficiencies. To allow higher control over the dose and release properties, IJP has been used to develop oromucosal films containing biologics. For instance, inkjet-printed oromucosal films with thyroid hormones T3 and T4 demonstrated adjustable doses and rapid disintegration.[34] Similarly, inkjet-printed oromucosal films with *Streptococcus salivarius* as a probiotic showed high printing efficiency and strong activity in managing dental caries.[170]

Mucoadhesive Buccal Films (MBFs): MBFs are another type of oromucosal films that provide controlled release and longer

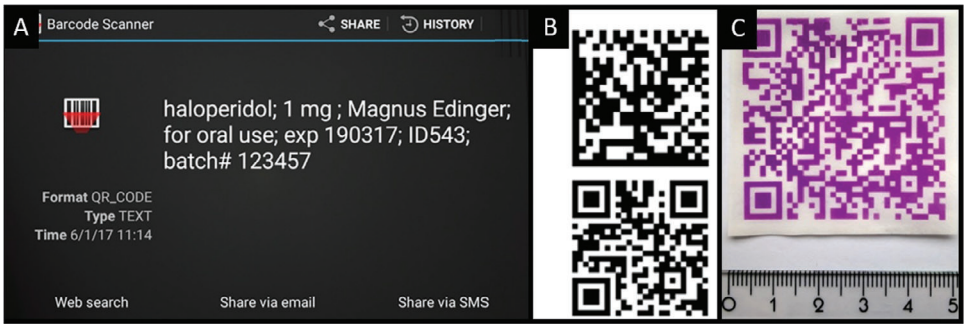

Figure 5. A) Example of data shown following the scanning of a QR code from a DEEP using a smartphone. B) Graphical illustration showing the difference between a (top) data matrix and (bottom) QR code. C) Image of a printed QR code pattern containing 2.5 mg haloperidol. Reproduced with permission.[44] Copyright 2018, Elsevier.

residence time in the oral cavity. Factors such as the mucoadhesion of the polymer matrix, the uni- or bidirectional drug release, and the permeability of the drug play a major role in the process.[171] To achieve correct functionality, the mechanical properties, composition, and structure of the films must be controlled.

MBFs offer an alternative to oral administration, preventing exposure to the GI tract and first hepatic pass.[172] The formulation of MBFs involves the incorporation of mucoadhesive agents, excipients for improved permeability, and layers or films for controlled drug release.[171] Similar to ODFs, conventional methods for manufacturing MBFs include solvent casting and HME, but as discussed above, these methods have limitations. IJP alone or combined with other printing technologies like FDM has been explored for MBF manufacturing. These approaches offer advantages such as avoiding thermal exposure to drugs and excipients and reducing the drying time of substrates.[49,173]

Inkjet-printed MBFs containing drugs like ketoprofen, lidocaine hydrochloride, and ibuprofen have demonstrated controlled release and drug loading capabilities.[47,49] Inkjet-printed MBFs with vitamins, thiamine hydrochloride, and nicotinic acid, have also been successfully developed, with adjustable doses and improved permeability with increased number of printed layers.[47]

The application of the IJP technology for the development of MBFs containing biologics has been explored as well. Inkjet-printed MBFs with ribonuclease-A and lysozyme showed high printing efficiency and preserved protein structure.[48] Lipid-core micelles containing rhodamine 123 and human insulin have also been successfully printed on MBFs, offering controlled and sustained release for over 24 h, reaching a cumulative release of 21.4 ± 1.8% and 64.6 ± 7.0%, respectively.[53]

6.1.2. Smart Pharmaceuticals

One of the great advantages of the IJP technology is its ability to easily tune the printed pattern. This unique feature has paved the way for the development of innovative pharmaceutical forms such as data-enriched edible pharmaceuticals (DEEPs).[44] DEEPs are designed to encode relevant information related to the patient and the prescribing instructions. The printed pattern, similar to a quick response (QR) code or data matrix,[45,132] not only contains the required dose but also encodes important information such as the patient's details, route of administration, batch number, and posology (**Figure 5**A).[44] These encoded patterns can be easily read using mobile devices, promoting digital healthcare and self-monitoring (**Figure 6**).[174,175]

The use of DEEPs has shown promising results in improving treatment adherence and reducing the number of visits to healthcare professionals.[177] Furthermore, DEEPs enhance drug traceability as each dose unit can be identified in real time, preventing falsification.[128] This approach is more reliable than including digital patterns on the packaging, where unit doses can be easily changed from one package to another.[178]

DEEPs are primarily intended for oral administration, with rapidly dissolving ODFs being the most common pharmaceutical form. The printed patterns on DEEPs can be in the form of QR codes or data matrix codes, with QR codes being larger in size (Figure 5B). Several studies have demonstrated the successful printing of DEEPs using IJP technology. For example, Edinger et al. demonstrated the applicability of IJP techniques in developing pharmaceutical forms in QR code format.[44] They printed the model drug haloperidol onto ODFs composed of HPMC, mesoporous fumed silica, and glycerol as a plasticizer. The piezoelectric printer successfully encoded data, which could be read using a mobile device (Figure 5C).

DEEPs have also been developed for controlled tracking and distribution of cannabinoids, such as cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC).[45] Although cannabinoids are an effective form of treatment, they are commonly associated with misuse, requiring a high level of monitoring. By using QR codes, strict tracking of each dispensed pharmaceutical form containing cannabinoids can be achieved. The DEEPs containing THC and CBD were successfully printed on porous substrates and remained readable even after 8 weeks of storage under cool, dry conditions.

6.1.3. Tablets

The IJP technology is not limited to loading dosage forms but also allows for the development of 3D structures such as tablets. Tablets are compressed solid dosage forms that contain drugs with or without excipients. Conventional tablet manufacturing involves powder compression, which has limitations in terms

of flexibility, complexity, and personalization. To address these limitations, IJP has emerged as a promising manufacturing method for tablets.[179] It enables the personalization of dosage forms, reduces the number of required steps, and offers a simple method involving ink formulation, jetting, and solidification.

Researchers have conducted studies to assess the viability of producing tablets using IJP. For example, tablets containing fenofibrate as the model drug and beeswax as the drug carrier were fabricated using hot melt 3D IJP.[61] The latter is a variation of traditional IJP that involves using hot melt inks, which are solid at room temperature but melt when heated, to create 3D structures. Unlike typical IJP, which deposits liquid inks onto a substrate, hot melt 3D IJP uses inks that are heated to make them liquid before IJP. Hot melt 3D IJP still requires substrates similar to traditional IJP, that serve as the base or foundation on which structures are built. The choice of substrate can impact the adhesion, stability, and overall quality of the printed structures. Herein, polyethylene terephthalate (PET) was used as the substrate, with printing set at 40 °C. This technique, which uses no solvent and employs a printer fitted with a hot melt chamber, allows for the development of adaptable geometries for controlled drug release. The tablets were fabricated with a honeycomb architecture, and by modifying the cell size, the rate of drug release could be regulated, enabling personalizing the medicine (**Figure 7**). A model was developed to predict dissolution trends based on cell diameter and wall thickness of the honeycomb. As the surface area-to-volume increased, the drug release rate increased.

IJP of 3D structures also involves the solidification of the material. One study combined IJP with ultraviolet (UV) curing, which enables rapid solidification.[180] This method requires the ink formulation to contain cross-linkable functional groups that can be activated by light using a photoinitiator. The study printed an ink containing ropinirole hydrochloride as the model drug using poly(ethylene glycol) diacrylate (PEGDA) as a monomer. The cross-linking and formation of an amorphous solid dispersion were successfully achieved. The flexibility of using different combinations of drugs and photoinitiators offers versatility in tablet design (**Figure 8A**).[59]

Furthermore, studies have demonstrated the feasibility of developing tablets containing poorly soluble drugs using IJP with UV.[58] An ink based on carvedilol, Irgacure 2959, and a photocurable *N*-vinyl-2-pyrrolidone (NVP) and PEGDA matrix was prepared. Tablets with different geometries (ring, mesh, cylinder, thin film) were printed, and over 80% of the carvedilol was released within 10 h. The results showed that high drug-loaded tablets with different release profiles can be manufactured using IJP and UV.

Another approach involves IJP onto PET films using an ink composed of PVP and thiamine hydrochloride.[56] The solidification mechanism relies on solvent evaporation, and the drug release from the tablets was achieved rapidly. The use of an edible substrate was not necessary (Figure 8B). Additionally, a 2D approach using IJP of minoxidil ethanolic solutions onto predeveloped PVA tablets by FDM was studied, resulting in tablets with sustained release profiles or initial bursts, depending on the solvent grade (e.g., 70% v/v or absolute ethanol) used in the formulation of the pharma-ink (Figure 8C).[57]

6.1.4. Capsules

Capsules, which are solid oral dosage forms enclosed in hard or soft soluble shells, have traditionally been manufactured in predefined doses. IJP offers the potential to bring capsules closer to personalized medicine by enabling the development of capsules with bespoke doses.[63] An example of such is the use of an IJP variant based on microdispensing.[62] In this production model, drugs are printed on a selected substrate, which is then rolled up and placed in a hard gelatin capsule.

Studies have demonstrated the feasibility of printing drugs such as vitamins B6 and B12 and folic acid onto paper substrates, which were then encapsulated in gelatin capsules. Dissolution tests showed the immediate release of the vitamins from the paper, indicating successful drug delivery. The use of barrier coatings between different drug deposits in the paper allowed for controlled drug release with the production of different layers (**Figure 9**). This approach simplifies treatments and enables the incorporation of different drugs with various release kinetics into a single pharmaceutical form.[62]

Similar methods have been used to print folic acid nanosuspensions onto paper substrates using microdispensing.[63] The folic acid nanosuspension exhibited an appropriately reduced particle size, facilitating uninterrupted microdrop formation. Remarkably, even after an hour of halted processing, no blockages in the drop ejector were encountered, indicative of the nanosuspension's suitability for IJP. The versatility of nanosuspensions for dispensing APIs using microdrop technology surpasses the application of drug solutions in IJP. Benefits include the potential to process poorly soluble drugs, enhance formulation stability, broaden the range of APIs applicable, and elevate both saturation solubility and dissolution velocity. Notably, the risk of

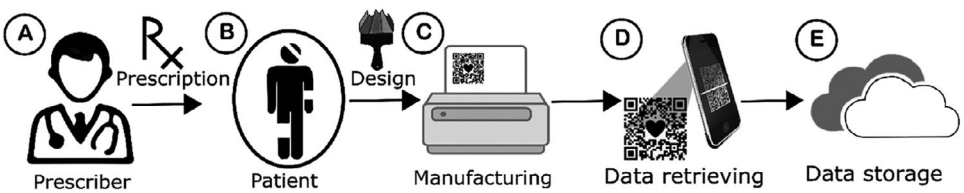

Figure 6. Graphical illustration of the process of data-enriched edible pharmaceuticals (DEEPs): A,B) Prescribing instructions by physician, C) designing and manufacturing process of DEEPs according to specific patient's needs, D) the QR or data matrix code is scanned and read using a smartphone device, and E) all data are stored. Reproduced with permission.[176] Copyright 2022, Elsevier.

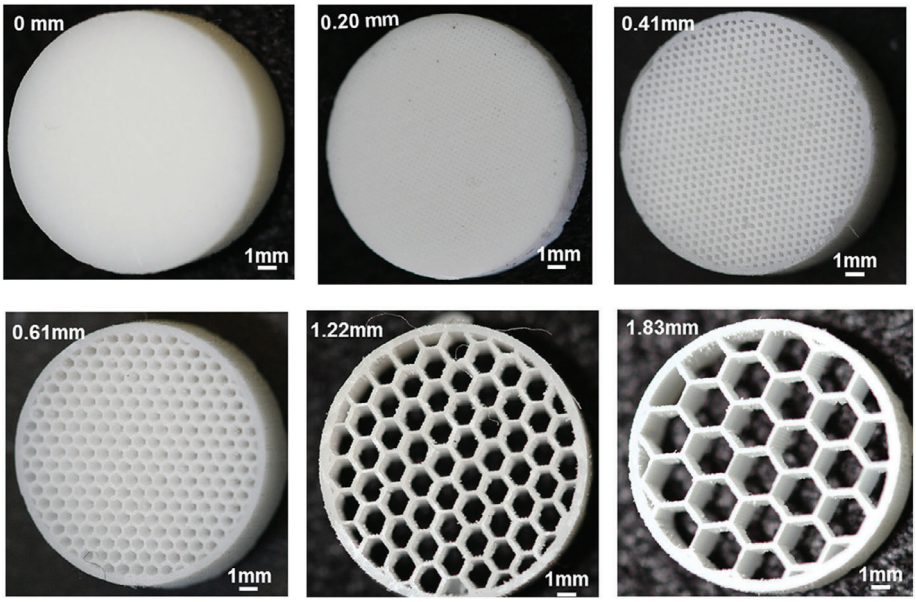

Figure 7. Images of the honeycomb-like tablets with varying cell sizes. Scale in mm. Reproduced with permission.[61] Copyright 2017, Elsevier.

API recrystallization inherent in dosing highly concentrated solutions, which often leads to nozzle clogs or uneven drug application, is eliminated when employing nanosuspensions. This advancement ensures accurate and reliable production of personalized dosage forms, particularly vital for high API concentration formulations.

6.1.5. Microdevices

Microdevices have been explored as a potential alternative to nanoparticles, hydrogels, microparticles, or patches, for successful oral drug delivery.[181,182] These planar and asymmetric shapes, made by microfabrication, offer advantages such as improved adhesion to the GI tract, minimized shear stress from the intestinal flow, enhanced bioavailability, and the ability to incorporate multiple reservoirs for the release of multiple drugs.[183]

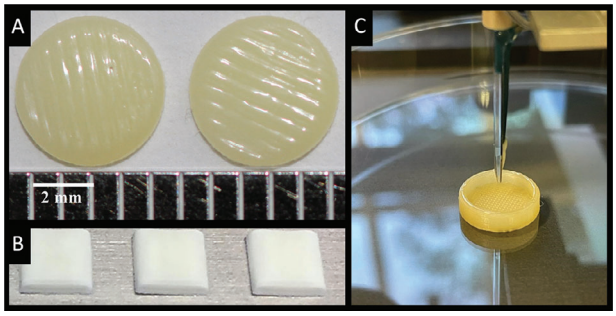

Figure 8. Images of: A) tablets with 115 layers +10 nonjetting post curing. Reproduced with permission.[59] Copyright 2017, Elsevier. B) Completely printed tablets. Reproduced with permission.[56] Copyright 2019, Elsevier. C) Minoxidil ethanolic solution inkjet printed on an FDM-printed PVA tablet. Reproduced with permission.[57] Copyright 2022, MDPI.

However, the efficient deposition of drugs into these microdevices remains a challenge.

IJP, particularly the DoD technology, has shown promise in the precise deposition of drugs into microdevices. A study demonstrated the feasibility of using a piezoelectric printer to deposit topotecan and insulin onto microdevices with an inner reservoir for unidirectional drug release (**Figure 10**).[54] This approach improved drug deposition precision, automated the process, and minimized drug waste. Multiple printing and drying cycles were possible without limitations on drug loading, allowing for the printing of biologics without degradation. Future studies may explore capping these microdevices to achieve tunable drug release.

6.2. Vaginal Drug Delivery

Bioadhesive films are emerging as an attractive alternative for vaginal drug administration, particularly for the treatment of local diseases. Cervical cancer, which has a significant impact on women in underdeveloped and developing areas, is one such disease that can benefit from localized treatment.[184] Traditional treatments for cervical cancer, such as chemotherapy and surgical interventions, often result in systemic side effects and low efficacy.[185,186] To overcome these limitations, bioadhesive films that can be easily applied to the tumor region for localized treatment have been proposed.

As an example, two low solubility drugs, paclitaxel and cidofovir, were formulated and printed onto bioadhesive films using the IJP technology (**Figure 11**).[187] Paclitaxel is an effective anticancer drug, while cidofovir is an effective nucleotide against herpes and human papillomavirus (HPV), both of which are major risk factors for cervical cancer. To improve its solubility, paclitaxel was formulated with cyclodextrins (e.g., hydroxypropyl-β-cyclodextrin; HpβCD). Cidofovir on the

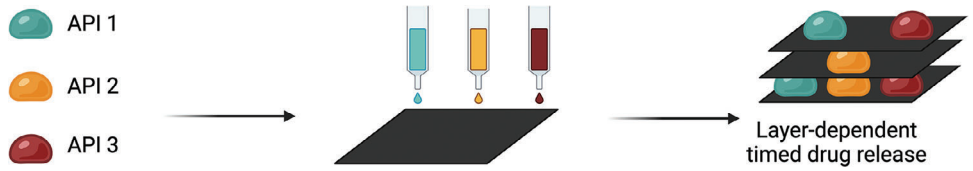

Figure 9. Graphical illustration of an IJP process involving multiple APIs and layers with different release kinetics.

other hand, was encapsulated in PEG nanoparticles. The mechanical and bioadhesive characteristics of the pre- and post-printed films were evaluated, and the results showed improved mechanical characteristics and bioadhesive capacity after printing. The drugs exhibited a controlled release, with rapid release from the surface and sustained release from the inner parts of the film, allowing for localized and prolonged drug delivery to the cervix tissue.

6.3. Transdermal Drug Delivery

6.3.1. Microneedles (MNs)

MNs have emerged as a novel approach for transdermal drug delivery, with dimensions smaller than 500 µm. These tiny needles are designed to penetrate the stratum corneum barrier, enabling the delivery of drugs without the need for hypodermic

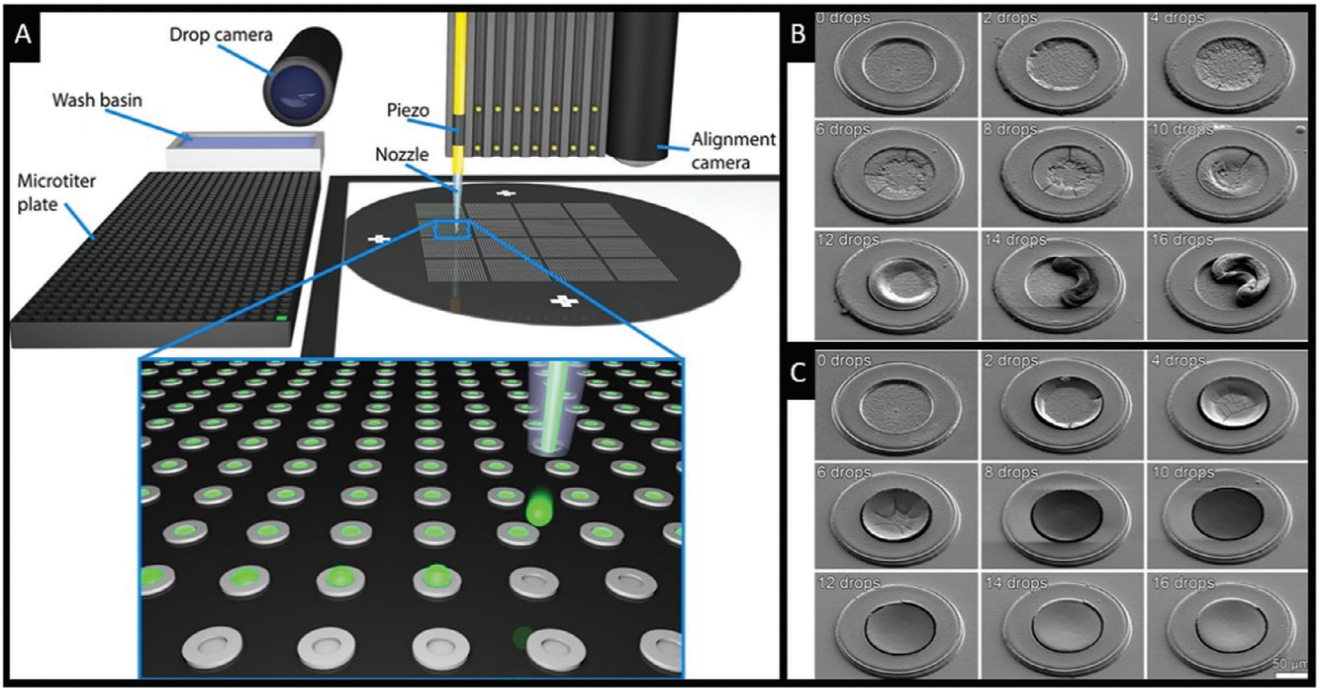

Figure 10. A) Graphical illustration of the printer configuration and printing process. SEM images of the topotecan and insulin microdevices. SEM images of representative microdevices loaded with increasing number of 400 pL drops of B) 10 mg mL^{-1} topotecan and C) 10 mg mL^{-1} insulin. Reproduced with permission.[54] Copyright 2017, Wiley.

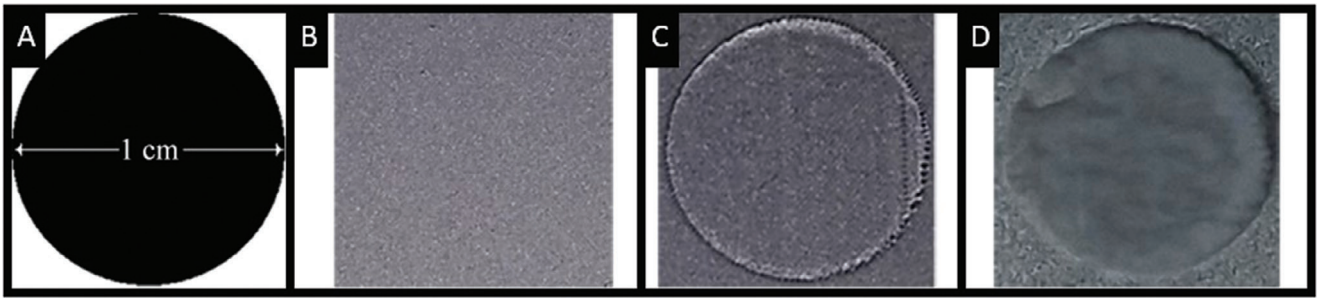

Figure 11. A) Template used for printing. Images of B) unprinted HPC film. C) paclitaxel:HPβCD complex printed film, and D) cidofovir PEG-polycaprolactone nanoparticle printed film. Reproduced with permission.[187] Copyright 2019, Elsevier.

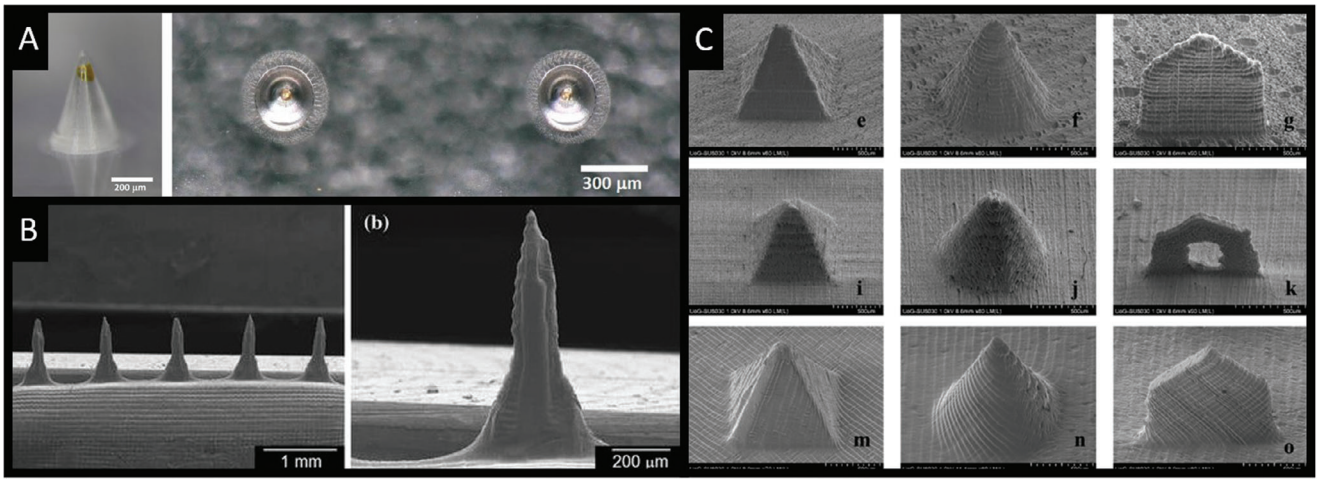

Figure 12. A) Images of reservoir-tipped MNs after the filling procedure. Reproduced with permission.[197] Copyright 2019, IOP Publishing. SEM images of B) inkjet-modified Gantrez AN 169 BF MNs. Reproduced with permission.[7] Copyright 2013, Springer, C) MNs with different geometries. Reproduced with permission.[69] Copyright 2021, MDPI.

needles.[188,189] Compared to the latter, MNs are easy to apply, do not require administration by medical personnel, and have lower pain indices due to the lower contact with corpuscles and nerve endings.[190]

There are various ways to load MNs with drugs, including preloading in the components prior to the fabrication process, as well as postprinting by coating or dipping them in drug concentrated solutions. This is particularly valuable when the fabrication process carries the potential to compromise the API's integrity during production. However, these approaches are dependent on the surface of the MNs, requiring different solvents and surfactants to improve their wettability and reduce surface tension.[191] Furthermore, these techniques are only suitable for a single API or drug dose. In contrast, the use of IJP offers an innovative alternative to address these limitations by preserving API integrity, mitigating cross-contamination in the presence of multiple APIs or doses, and improving precision.[192-194] Moreover, IJP is considered to be more efficient for creating coatings compared to dip-coating which is limited by the nonuniformity between coatings.[195]

Various studies have explored the use of IJP for drug deposition onto MNs. For example, three different anticancer agents, including 5-fluororacil, curcumin, and cisplatin, were printed onto metallic MNs using a Soluplus (i.e., a copolymer of polyvinyl caprolactame-polyvinyl acetate-polyethylene glycol) formulation.[71] The printed MNs exhibited high uniformity, and the drugs showed rapid release, making them suitable for personalized medicine applications. IJP has also been used to deposit insulin onto metallic MNs. The pharma-inks included different polymers, such as poly(2-ethyl-2-oxazoline), Soluplus, trehalose, and gelatin, in an aim to stabilize the insulin.[72] Stable insulin having intact α-helices and β-sheets were observed for trehalose and Soluplus, while potential structural configurations were detected for gelatin and poly(2-ethyl-2-oxazoline). Notably, rapid insulin release rates occurred within the initial 20 min for Soluplus and gelatin, indicating the feasibility of solid-state insulin delivery via MNs.

IJP has also found application in vaccine delivery. For instance, solutions of trehalose/PVA and trivalent inactivated subunit influenza vaccine were printed onto PDMS molds using PIJP.[73] The development of multilayered designs enabled the modification of drug and vaccine release profiles. Subsequently, a study demonstrated the high accuracy of droplet deposition on MNs using PIJP, with 95% of dispensed droplets depositing within 20 µm of the target pattern location (i.e., a lateral tolerance of 20 µm corresponds to an approximate vertical distance of 60 µm from the tip of the dispensing nozzle).[196] Preliminary *ex vivo* skin studies confirmed the successful transfer of materials from the needle to the skin. To enhance the loading capacity and facilitate ink injection without the need for MN inclination, a novel MN structure with a tip-reservoir was designed (**Figure 12A**). This study showcased the feasibility of IJP for the rapid and cost-effective preparation of coated MNs for medical applications.[197]

A series of studies were conducted to investigate the use of the IJP technology for modifying MNs in transdermal delivery, particularly for antifungal agents. Biodegradable Gantrez AN-139 MNs were manufactured containing quantum dots, fluorescent semiconductor nanocrystals, as a model drug.[198] In this study, visible light dynamic mask microstereolithography micromolding was combined with IJP using a piezoelectric printer, which allowed for the production of MNs with diverse geometries and pharmacological compositions. Subsequently, A similar approach was used to modify the surfaces of Gantrez 169 BF MNs for the delivery of amphotericin B, a poorly soluble drug with antifungal activity (Figure 12B).[7] The pharma-ink consisted of amphotericin B dissolved in DMSO. Results demonstrated that IJP did not significantly alter the MN geometry and effectively exhibited antifungal activity, highlighting the scalability of IJP for incorporating pharmacologic agents, even those with challenging solubility. Furthermore, the same technique was employed to modify MNs and deliver miconazole, another antifungal agent, which showed biodegradation and antifungal activity against *Candida albicans*.[64] Additionally, two more approaches were explored using PGA MNs, onto which antifungal coatings were deposited.[65,66] Herein, the pharma-inks developed

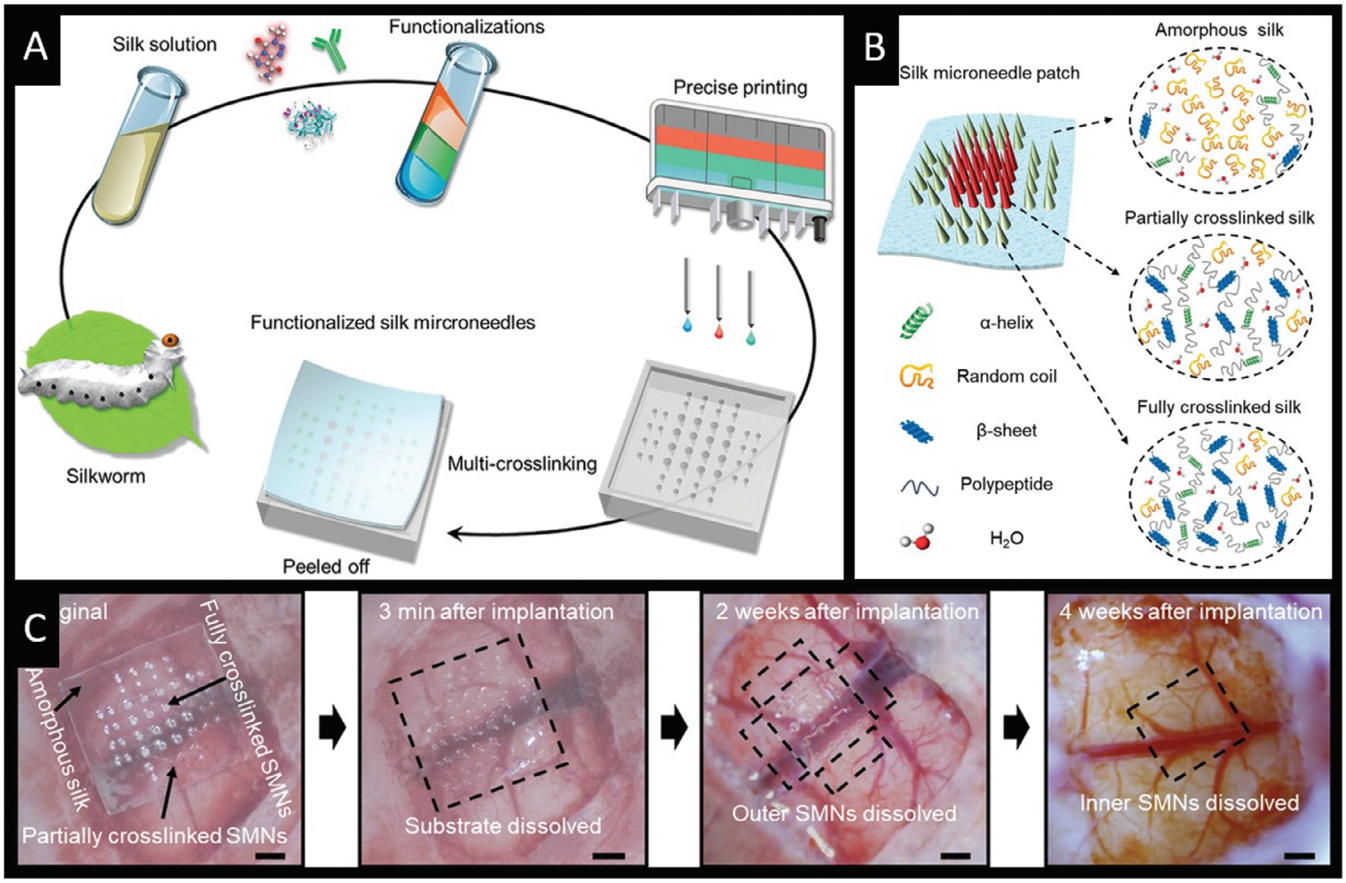

Figure 13. Graphical illustration of A) the multidrug MN patches manufacturing process and B) silk protein conformations corresponding to amorphous (substrate), partially crosslinked (inner MNs) and fully crosslinked (outer MNs) silks with varying dissolution behaviors. C) Optical images of the controllable dissolution of a MN patch being applied to a mouse brain. Scale bar: 1 mm. Reproduced with permission.[74] Copyright 2022, Wiley.

included (a) 180 mg mL^{-1} itraconazole with 10% v/v coconut oil in benzyl alcohol,[65] and (b) 5% w/w voriconazole in Gantrez AN 119 BF.[66]

In addition to conventional IJP, the combination of 3D printing techniques with IJP has been explored for MN fabrication. As an example, MNs composed of biocompatible photopolymer resins were fabricated using stereolithography (SLA), and cisplatin formulations were deposited on their surface using IJP.[67] Similarly, IJP was used to deposit thin layers of insulin and sugar alcohol or disaccharide carriers on the surface of MNs.[68] In a following study, insulin-polymer solutions were printed onto MNs with different geometries produced by 3D printing (Figure 12C).[69] The study showed that the geometry of the MN influenced the dissolution, skin insertion, and dimensional quality of the MNs, highlighting the potential of this combined approach for controlled drug delivery.

Another innovative approach involved the use of IJP and crosslinking polymerization to create MN patches for the treatment of glioblastoma. Silk fibroin MN patches were developed with different dissolution rates, allowing for the delivery of chemotherapeutic drugs and a drug with a specific target (**Figure 13**).[74] IJP enabled precise drug loading and control over the release profile of the MNs, demonstrating its potential for personalized medicine applications.

These studies collectively demonstrate the potential of IJP as a versatile method for enhancing the functionality of MNs in transdermal drug delivery.

6.3.2. Patches

In the realm of transdermal drug administration, IJP has also been introduced for the development of printed patches. An extensive study was conducted to explore patch printing as an alternative to traditional oral dosing for administering indomethacin, a drug renowned for its potent chemotherapeutic properties in treating various cancers.[76] As oral administration of indomethacin often leads to gastric irritation and ulcers, transdermal delivery was considered as a means to alleviate these side effects. Leveraging its high drug loading efficiency and capability to create personalized medications, IJP facilitated the easy and precise printing of indomethacin on patches. The drug release from the patches followed a first-order kinetics, indicative of immediate release dosage forms. This study not only showcased the viability of the IJP technology in transdermal drug delivery, but also highlighted its potential in advancing personalized medicine through its exceptional printing capabilities.

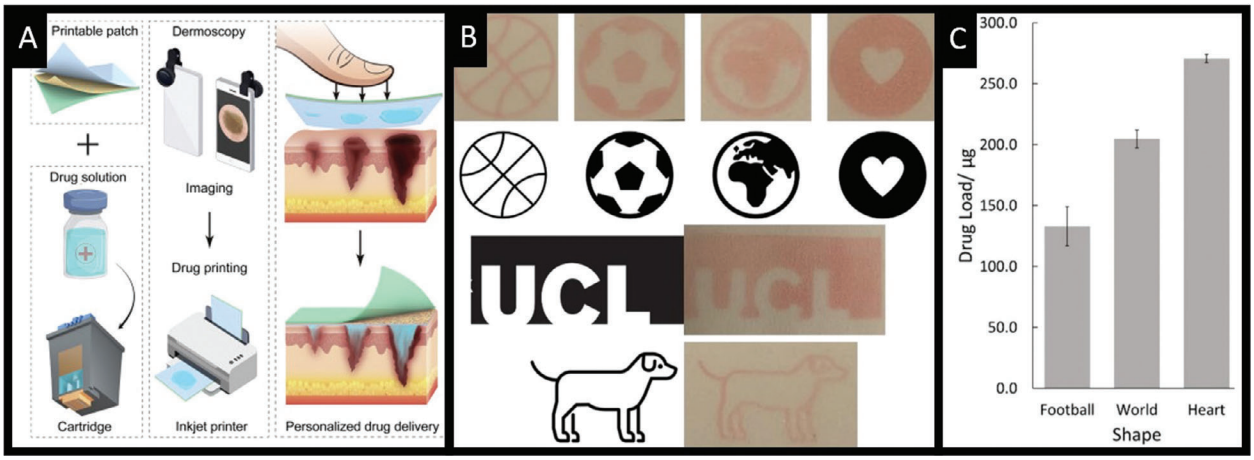

Figure 14. A) Graphical illustration demonstrating how IJP can be used to create personalized patches for topical drug delivery. Reproduced with permission.[75] Copyright 2023, Elsevier. B) Images and designs of inkjet-printed shapes, including a basketball, a football, an earth globe, a heart, the University College London logo, and a cartoon dog. C) The drug-load for the football, globe, and heart shapes. Reproduced with permission.[10] Copyright 2022, MDPI.

6.4. Topical Drug Delivery

6.4.1. Patches

IJP has also been explored for the development of printed patches for topical drug administration. A recent study used a modified inkjet printer to precisely print drug layers and protective layers onto patches, allowing for personalized treatment of various skin-related diseases (**Figure 14**A).[75] This approach demonstrated the efficient delivery of drugs with high resolution and adaptability to individual conditions, locations, and severity of lesions.

6.4.2. Nail Treatment

The IJP technology has extended its applications to the treatment of nail diseases, such as onychomycosis. One study utilized a commercial cosmetic nail printer to print antifungal drugs onto nails (Figure 14B,C).[10] The printer was modified to accommodate terbinafine hydrochloride formulations, and the efficacy of the treatment was tested using disc diffusion assays and human nail clippings. The results showed that the inkjet-printed drugs inhibited the growth of *T. rubrum* and penetrated the nail, demonstrating the potential of IJP for topical antifungal treatment.

6.5. Nasal Drug Delivery

6.5.1. Aerosols

Aerosols, which are solid or liquid particles suspended in a gas, have been used for the treatment of various diseases, particularly asthma and chronic obstructive pulmonary disease.[199] IJP has shown promise in the production of aerosols, offering advantages, such as precise control over droplet size and the ability to develop controlled-size aerosols for different applications.[78,200,201]

Studies have demonstrated the successful production of aerosols using the IJP technology. It was shown that thermal IJP can be used to produce aerosols containing proteins, such as human growth hormone and insulin, without damaging the proteins.[77] The process consists of a digital pump that relies on the geometry of a chamber to determine the volume of each droplet. Capillary action facilitates the flow of liquid into the chamber, where a heater heats the surface for a brief duration of 1–2 ms, up to 300–400 °C. This causes the liquid to superheat and form a vapor bubble, which pushes the liquid through the nozzle. Herein, firing was set at a duration of 1 s with a frequency of 10 kHz. After the bubble collapses and the chamber refills, the process repeats to create more aerosols. Several pharma-inks were studied, including a) 2 mg mL^{-1} of human growth factor in deionized water solution, b) 2 mg mL^{-1} of human growth factor in deionized water solution with 2% PEG 8000 and 0.1% Tween 20, c) 5 mg mL^{-1} of insulin in deionized water solution, and d) 10 mg mL^{-1} of insulin in deionized water solution. The use of humectants and surfactants helped prevent precipitation and maintain the bioactivity and structural integrity of the proteins.

IJP has also been utilized to produce aerosols from ink solutions, such as glucono-delta-lactone, using a thermal inkjet printer (**Figure 15**A).[78] The resulting microparticles were characterized for size distribution and demonstrated the cost-effective production of tunable aerosols with controlled particle size.

6.6. Ocular Delivery

6.6.1. Contact Lenses

Topical ocular administration poses unique challenges such as corneal and conjunctival barriers, blinking, tear turnover rates, and nasolacrimal drainage, which can hinder drug absorption and residence time, thereby affecting ocular bioavailability. An

innovative solution to overcome these challenges is the development of drug-loaded contact lenses, allowing for gradual drug release.[202]

The IJP technology has emerged as a promising method to load drugs onto contact lenses, offering high precision in droplet deposition. In a recent study, itraconazole nanocrystals were formulated and stabilized with Poloxamer 407, then printed onto hydrogel contact lenses using IJP (Figure 15B).[79] The use of nanocrystals improved solubility and residence time of the drug. In vitro drug release studies demonstrated a dual drug release profile, with ≈80% release achieved after 8 h. The printing process did not affect the structure of the nanocrystals. The study highlights the potential of IJP as an attractive technology for developing drug-loaded contact lenses for glaucoma treatment and other diseases.

In another study, IJP was used to successfully print timolol maleate, a glaucoma therapy drug, onto contact lenses using a modified commercial inkjet printer.[11] The pharma-ink was designed to match the properties of commercial ink while having maximum drug loading and avoiding ocular inflammation. The printing process demonstrated personalized drug dosing by printing multiple passes, and light transmittance was found to be unaffected by drug loading on the contact lens. A novel dissolution model was built, and in vitro dissolution studies showed drug release over at least 3 h, significantly longer than eye drops. NIR spectroscopy was used as an external validation method to accurately quantify the drug dose. Overall, the combination of IJP and NIR represents a novel method for point-of-care (PoC) personalization and quantification of drug-loaded contact lenses.

6.7. Implants

6.7.1. Stents

One intriguing application of IJP is the development of drug-coated intravascular stents, also known as drug-eluting stents (DES). DES have shown superior clinical outcomes compared to traditional bare metal stents by reducing late loss and target vessel revascularization. Conventionally, DES coatings are applied using spray coating or dip coating methods, which have limitations such as material loss and time consumption. IJP offers several advantages, including noncontact deposition, high accuracy, and minimal material waste. In a study, poly(D,L-lactide) with simvastatin and paclitaxel ink was printed onto stents, demonstrating the capability of IJP to deposit uniform and reproducible coatings.[9] Animal studies showed no inflammatory response to the printed coatings. This study showcased the potential of IJP for the deposition of a wide range of polymer/drug coatings on stents.

7. Bioprinting

Bioprinting enables the precise placement of cells, biomaterials, and biomolecules in predefined locations within complex structures. This technology has been extensively explored for tissue and organ engineering, as well as for studying cellular mechanisms. IJP has emerged as a valuable tool in bioprinting, particularly the DoD technology, which is crucial for minimizing the risk of ink contamination. Thermal IJP on the other hand has shown exceptional precision, with research indicating its capability to discharge individual cells in a single droplet.[203,204] This approach presents numerous benefits, encompassing elevated cell viability, rapid printing speeds, cost-effectiveness in manufacturing, and remarkable reproducibility across multiple prints.[204,205] Several studies have successfully utilized IJP for bioprinting, achieving high cell viability (>85%) and precise control over pore size using the piezoelectric technology.[206]

IJP has been utilized in the development of scaffolds for tissue engineering. Scaffolds provide a supporting framework for cell proliferation and tissue regeneration. Conventional techniques for scaffold fabrication, such as freeze-drying, electrospinning, and gas forming, often lack precise control over pore size and geometry.[207] In contrast, IJP allows for the precise patterning of scaffolds with accurate control over pore size and geometry. For example, an electroactive scaffold for tissue engineering was created by printing polypyrrole and collagen using IJP.[208] Another study explored the combination of human microvascular endothelial cells (HMVEC) and fibrin as bio-ink for printing microvasculature-like structures.[209] This study demonstrated the potential of IJP to promote cell proliferation and the construction of microvasculature. In another approach, a novel platform-assisted 3D inkjet bioprinting method has been introduced for the creation of intricate 3D constructs, including zigzag tubes.[210] This innovative bioprinting system has successfully

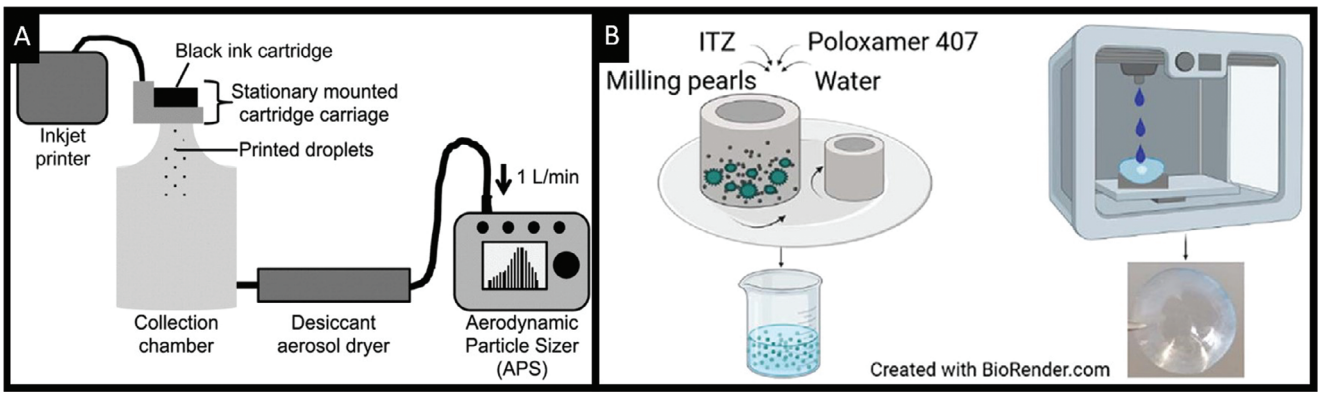

Figure 15. Graphical illustration of the A) IJP process involving the production of aerosols. Reproduced with permission.[78] Copyright 2013, Taylor & Francis. B) of the IJP of contact lenses. Reproduced with permission.[79] Copyright 2022, ACS Publications.

produced tubes featuring an overhang structure using fibroblast materials, also known as 3T3 cells. Notably, the viability of the 3T3 cells within the printed tubes remained at a commendable level of over 82% even after 3 days of incubation, indicating the robust potential of this bioprinting system. An intriguing aspect of this study is the demonstration that the tubular overhang structure can be achieved without the need for scaffolds through IJP, with the attainable height being contingent upon the inclination angle of the overhang structure.

Hydrogel-based structures can also be fabricated using IJP. Hydrogels, which are 3D networks of water-soluble polymers, have diverse applications in tissue engineering and regenerative medicine. However, loading drugs into hydrogels, particularly in a homogeneous and controlled manner, can be challenging. IJP offers advantages such as noncontact deposition and precise control over drug concentration and ejected volume, making it an attractive approach for drug loading in hydrogels. In a study, macromolecules were successfully printed onto a hydrogel matrix, demonstrating the preservation of biological activity and the controlled differentiation of neural stem cells.[211] IJP has also been employed for the rapid preparation of patterned hydrogel microarrays and the in situ polymerization of hydrogel microarrays, enabling the printing of thousands of individual polymer features.[212]

In an innovative approach, the utilization of bioprinted microvasculature has been suggested as a means to foster angiogenesis and enhance the diffusion of essential oxygen and nutrients throughout engineered tissue constructs.[213] An implant, created using thermal IJP, featured HMVECs and was strategically placed within both CB17severe combined immunodeficient (CB-17 SCID; i.e., strain bred mice that lack functional T and B cells) and NSG-SGM3 (i.e., non-obese diabetic SCID gamma mice with human stem cell factor, granulocyte macrophage colony stimulating factor and interleukin-3) animal models. This strategic positioning aimed to assess the kinetics of angiogenesis and the extent of cell viability. The fabrication of the implantable tissues hinged on a composite blend of alginate and gelatin, printed using a customized inkjet printer based on established protocols. The histopathological analysis yielded compelling findings, demonstrating a substantial surge in average microvasculature formation among mice receiving the printed constructs within the implant region, notably surpassing outcomes from manual and control implants. Evidently, this underscores the potential of inkjet bioprinting technology to proficiently serve the purpose of vascularization within the context of engineered tissue constructs.

Furthermore, DoD IJP has been used in biomedical tests such as real-time quantitative polymerase chain reaction (PCR), where precise droplet generation is crucial to minimize variation and contamination. A digital PCR system was developed using IJP, allowing for precise control over droplet size and achieving accurate quantification of an HPV sequence.[214] In another approach a piezoelectric inkjet bioprinter was designed, utilizing a disk membrane nozzle with a bending-type piezoelectric actuator.[215] This configuration minimizes shear stress and internal pressure, resulting in a gentle dispensing process. By adjusting ejection parameters for droplet size and speed, pressure and inertial forces upon landing are reduced. Importantly, no additional materials like hydrogels are needed for bioink preparation, eliminating chemical stress on cells. To assess the bioprinter's cell-friendliness, an RNA sequence and gene expression analysis was conducted on dispensed cells, alongside viability, proliferation, and pluripotency assessments. Results showed comparable cell-friendly capabilities to manual pipetting, with maintained cell viability, pluripotency, and gene expression. The stress-free design and chemical-free cell dispensing of this inkjet bioprinter offers potential applications in 3D organ development and drug discovery, particularly for stress-sensitive cells.

It is important to acknowledge that one study has demonstrated a significant alteration in cell phenotype as a result of thermal inkjet bioprinting.[216] These findings shed light on the substantial impact that this technology can have on the characteristics and properties of the cells being printed. This information underscores the need for a comprehensive understanding of the effects of IJP on cell behavior and function, particularly when considering its applications in tissue engineering and regenerative medicine. A recent study primarily focused on the comprehensive quantification of cell sedimentation-induced aggregation during and following inkjet-based bioprinting.[217] It was revealed that extending the printing time by 60 min results in a significant increase in the percentage of cells forming aggregates at the bottom of the bioink reservoir (i.e., from 3.6% to 54.5%). This escalation underscores the profound challenge posed by cell aggregation in the realm of 3D bioprinting. Remarkably, during the IJP process, a mere 15 min of printing time results in over 80% of cells aggregating within the nozzle. This intriguing behavior can be attributed to both individual cells and cell aggregates gravitating toward the proximity of the nozzle centerline, primarily attributed to the bioink's weak shear-thinning attributes. Subsequent to the bioprinting process, the average cell count per microsphere experiences a substantial elevation as the printing duration increases. The microspheres encapsulate a maximum of 10 cells within each, with approximately one-third of the microspheres containing encapsulated cells also harboring either small or large cell aggregates at the 15 min printing juncture.

8. Optimizing IJP for Personalized Medicines: The Role of AI Models

Despite the numerous advantages of IJP, developing a suitable pharma- or bio-ink with favorable printing outcomes can be challenging and time-consuming. Various parameters, both related to the ink and the printing technology, affect printability and can lead to undesirable printing performance, such as clogging or satellite droplets.[218,219] Traditional trial-and-error methods for ink development are costly in terms of material wastage and time.

To overcome these limitations, alternative approaches have been sought to anticipate printing results and optimize the process. For years, a dimensionless Onesorge (*Oh*) number has been used as a reference parameter to predict whether the developed inks are printable or not.[220] This *Oh* number is derived from an equation that takes into account three physical parameters of the ink (i.e., viscosity, surface tension, and density) and the diameter of the nozzle used (Equation (1)). Ranges have been established for the *Oh* number and for its inverse, the *Z* value, in which the ink would be printable. The *Z* value is commonly used in IJP applications, with ranges between 1 and 10 being often regarded as printable.[221,222] It should be noted however that

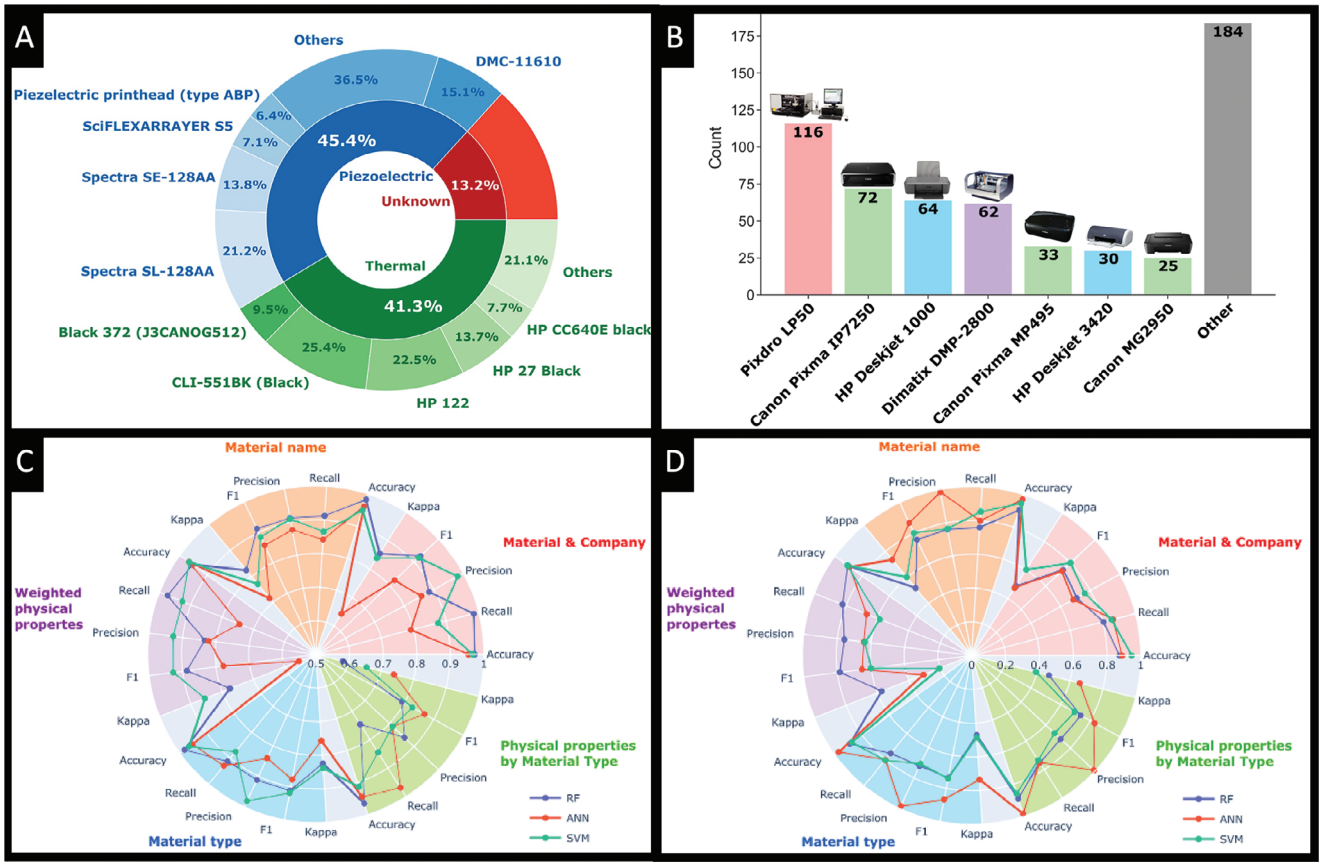

Figure 16. A) Nested pie-chart showing the distribution of piezoelectric, thermal, and unknown printing technologies used to fabricate formulations. The top 5 nozzles used for PIJP and thermal IJP are reflected in the outer pie-chart. B) Bar chart showing the 7 most frequently used printers, arranged in rank order from left to right. Colors correspond to the printer brands, and printers not in the top 7 were grouped as "others." Radar plot with metrics results of models predicting printability as C) (yes or no) and D) (good or satellite). Reproduced with permission.[232] Copyright 2023, Elsevier.

multiple studies reported that inks with Z values outside the accepted range were sometimes found to be printable.[223] These findings demonstrate the limited predictive capacity of these dimensionless numbers, which is mainly due to the multifactorial nature of this process. Thus, there is a need for another predictive tool that takes into account other variables that influence the process

$$Oh = \frac{\eta}{\sqrt{\gamma \rho \mathrm{d}}} \quad (1)$$

The use of AI models, particularly machine learning (ML) techniques, has shown great promise in various fields, including pharmacy and healthcare. ML uses algorithms and statistical models to analyze complex datasets and identify patterns. ML is part of Industry 4.0 and has the potential to transform industries.[224] In the pharmaceutical field, ML has been used to optimize and reduce the time and cost of personalized medicine.[225]

ML models have also been successfully employed in other printing processes, such as FDM,[226–228] to predict printing outcomes and dissolution behavior of dosage forms. For example, an open-source software called M3DISEEN was developed using ML techniques to predict critical manufacturing parameters and guide formulation development in FDM printing.[229] ML models have also been used to predict the design and fabrication performance of MNs[230] and the printing outcomes and dissolution rates of 3D printed tablets fabricated using digital light processing (DLP).[231]

Applying a similar approach to IJP would accelerate formulation development and bring this technology closer to the pharmaceutical market. ML models have already been developed to predict the printability of formulations, the quality of printing processes, and the total drug dose.[232] Leveraging a dataset of 687 formulations and a diverse array of parameters encompassing pharma-ink properties (e.g., composition, surface tension, density, Oh number, Z value, and viscosity), printer and print specifications (e.g., printer model, printed object, print area, print frequency, and number of printed layers), and process variables (e.g., nozzle, nozzle diameter, peak voltage, droplet volume, theoretical drug dose, and drop spacing), the ML models were meticulously developed with the most suitable combination of ML techniques, feature sets, and additional input parameters. Data collected showed that PIJP slightly surpassed thermal IJP in popularity, constituting 45.4% of the collected formulations compared to 41.3% for thermal IJP (**Figure 16A**). The Pixdro LP50 printer (from SUSS MicroTec, Germany) emerged as the most frequently utilized printer, chosen for 116 formulations (Figure 16B). The

optimized ML models exhibited remarkable predictive accuracy (Figure 16C,D), achieving 97.22% for printability formulations and 97.14% for print quality, surpassing the predictions based on *Z* values. Although the dataset imbalance posed a challenge to ML performance, the inclusion of new formulations holds the potential to substantially enhance machine learning accuracy.[227]

Notably, despite the dataset imbalance, the ML model for predicting printability outperformed the current guidance based on *Z* values. The conventional guidance yielded a false positive rate of 77.42%, a false negative rate of 28.16%, and an overall accuracy of 64.39%. In contrast, the optimized model demonstrated significant improvement, boasting an impressive accuracy of 97.22%, underscoring the criticality of considering a multifactorial approach that transcends a limited number of variables.[232]

In another approach, ML was harnessed to predict the number of printed cells in inkjet-based bioprinting.[233] This novel approach successfully detected the presence or absence of cells within single droplets and accurately predicted the total number of cells in multiple droplets. Five different ML algorithms were compared to identify the most suitable algorithm for each application. The random forest regressor algorithm exhibited an impressive 80% accuracy in predicting cell presence within single droplets, while the extra tree regressor demonstrated a remarkably low mean error of 12% in predicting the number of printed cells in multiple droplets, such as 20 droplets on the same spot. By integrating these advanced ML models into a droplet monitoring system, real-time assessment of the number of printed cells during inkjet-based bioprinting can now be achieved, revolutionizing the field of bioprinting and paving the way for more precise and efficient personalized medicine applications.

The integration of AI models, such as ML, in IJP would significantly enhance the formulation development process, reduce waste of time and resources, and provide better results than current prediction methods based on *Z* values.[234]

9. Opportunities and Limitations of IJP for Personalized Medicines

The IJP technology offers several opportunities for the preparation of personalized medicines. Its precision and accuracy allow for precise control over the deposition of pharmaceutical formulations, ensuring accurate dosage delivery tailored to individual patient needs. IJP is also highly flexible in formulation design, enabling the creation of various pharmaceutical dosage forms as aforementioned. It can deposit drug-loaded formulations on a wide range of substrates, facilitating the development of unique and patient-specific drug delivery systems. Additionally, IJP can enhance drug solubility and dissolution rates, particularly for poorly soluble compounds, by formulating drugs into nanosized particles or complex structures, improving drug absorption and bioavailability.

Furthermore, IJP offers cost and time efficiency benefits. By eliminating the need for traditional batch processing, it can potentially reduce manufacturing costs and time. The technology allows for rapid and scalable production of personalized medicines, enabling on-demand manufacturing and reducing the need for extensive stockpiling of medications.

However, there are certain limitations associated with IJP in the preparation of personalized medicines. Developing pharma-inks with suitable characteristics and printing outcomes can be challenging and time-consuming, as they need to be formulated to ensure compatibility with the IJP process. Unlike other printing technologies like semi-solid extrusion (SSE) or FDM, IJP is still in its early stages in terms of pharmaceutical hardware development. Current inkjet printers used in pharmaceutical research are often adapted from commercial desktop printers, resulting in limitations in printer specifications, nozzle size, and substrate compatibility.[232]

Customized hardware solutions tailored to pharmaceutical requirements are necessary for optimal IJP performance. In particular, the development of specific hardware systems adapted to pharmaceutical IJP, compliant with Good Manufacturing Practices (GMP), is crucial. Specialized pharmaceutical inkjet printers would improve process adaptability, scalability, and QC, bringing this technology closer to industrial production. The development of pharmaceutical inkjet printers would also enable the production of a wide variety of accurately dosed personalized medicines. Customized hardware systems would help the pharmaceutical industry meet GMP requirements and facilitate fault detection, process improvements, and implementation within clinical pratice.

QC and regulatory compliance are also important considerations. The current regulatory landscape surrounding IJP will be discussed in more details in the next section (Section 10). Ensuring consistent and reliable printing outcomes is crucial, requiring the establishment of process-specific QC measures to validate IJP processes and adhere to regulatory standards. Additionally, some drugs may not be compatible with IJP, as the technology is primarily suitable for liquid-based formulations. Certain therapeutic classes may require specific formulation techniques or technologies that are not well-suited for IJP, limiting its applicability.

10. The IJP Frontier: Redefining Regulations and Patents in Pharma

To address the evolving regulatory landscape for novel additive manufacturing techniques in healthcare, the FDA introduced a guidance in 2017.[235] This guidance focuses on technical considerations specific to devices utilizing additive manufacturing technologies, emphasizing recommendations for testing and characterizing devices, including the additive manufacturing steps.

As of now, the FDA has approved several printed medical devices, while only one pharmaceutical product, Spritam, intended for the treatment of epilepsy in both adults and children, is available on the market.[236] However, specific regulatory guidelines for the development of printed pharmaceutical dosage forms have yet to be established by any regulatory agency. This gap poses challenges, as additive manufacturing processes significantly differ from traditional manufacturing methods in terms of reduced production steps and the digitization of the design and production process.

The development of IJP standards and test methods is crucial for ensuring the safety, reliability, and quality of pharmaceutical products. However, it remains uncertain whether the regulation will exclusively apply to the final product or if it will extend to regulating various components and steps involved in the entire

process, given the unique characteristics and individualized approach of these new manufacturing methods.

Given the increasing production of innovative additive manufacturing products, especially at the point of patient care, governments are taking steps to introduce new regulatory frameworks. The Medicines and Healthcare products Regulatory Agency (MHRA) is particularly focusing on PoC and modular manufacturing, aiming to simplify the approval of medicines, conduct clinical trials, and evaluate regulatory compliance.[237] These efforts intend to enhance the safety, quality, and efficacy of medicinal products, while reducing unnecessary regulatory barriers. The FDA is also evaluating its risk-based regulatory framework for PoC manufacturing, with a focus on addressing the challenges and informing future policy development in this area. The fast-paced advances in this field demand the sculpting of new legislation tailored to accommodate evolving production models, driven by product personalization and flexibility. Although regulatory challenges persist, the implementation of good IJP practices promises to pave the way for streamlined pharmaceutical manufacturing and quality assurance.

In terms of patents, various applications of IJP have been protected, particularly in the modification of printers and the development of pharma-inks for printing. Notably, the University of Chile filed a patent (WO2017120689A1) for a pharmaceutical form comprising biomacromolecules, and a method for producing it using IJP.[238] Claims extend to polymeric film as a recording substrate and an injection ink printed on the polymer film comprising nanoparticles or suspensions of nanoparticles. The same institution presented another patent (US2022280440A1) that involves the manufacture of a highly controlled and stable dosage form with mucoadhesive properties for buccal administration of biologics, based on IJP of biologics included in polymeric nanoparticles.[239] Midatech Pharma Ltd. holds a patent (US2023077586A1) that involves an apparatus and method for producing microparticles and pharmaceutical compositions using CIJP, providing high-quality microparticles at an improved rate.[240] Wake Forest University has explored the use of IJP for cells and tissues, as reflected in its patent (US2014199276A1), which includes apparatus and methods for developing scaffolds and microparticles.[241] Claims encompass a method to produce a biodegradable scaffold with cells seeded in it, involving a biodegradable substrate produced by electrospinning and the printing of viable cells on the substrate using an IJP device.

Due to the growing significance of digital elements in the development of these technologies, intellectual property infringement prevention is essential. Designs, ideas, and software play a critical role in the development of different printing products.[242] This digital component, integral to the process, is often protected by copyright rather than patents. Additionally, ML software used may be considered as Software as a Medical Device (SaMD) by the International Medical Device Regulators Forum, as it serves medical purposes, either individually or in groups. To ensure user and patient safety, the FDA has established specific policies for this type of medical device. Manufacturers of SaMD are required to submit risk-based information before primary distribution. Many AI-based SaMDs have received FDA approval, and their adaptability over time through real-world experience improves their performance.[5] Regulations for SaMDs should follow a total product lifecycle approach to ensure reliability and safety. Good ML practices involve the management of data extraction training and evaluation.[243] Integrating ML into healthcare systems presents challenges but has the potential to transform drug manufacturing.

11. Conclusion

IJP is emerging as a versatile and innovative technology with tremendous potential in the pharmaceutical industry. Its precision, contactless deposition, and flexibility allow for the creation of diverse dosage forms, enabling immediate or controlled drug release tailored to individual patient needs. This personalized approach to drug delivery can greatly enhance therapeutic outcomes.

Moreover, IJP demonstrates its utility in the development of drug-loaded medical devices, such as stents and contact lenses. By incorporating drugs into these devices, targeted and localized drug delivery can be achieved, maximizing the therapeutic efficacy while minimizing systemic side effects. This opens up new possibilities for the treatment of various medical conditions.

However, the current hardware used in IJP falls short of meeting the specific requirements of the pharmaceutical industry. There is a pressing need for specialized pharmaceutical inkjet printers that can offer better process control, scalability, and compliance with GMP. These printers would ensure the production of high-quality, consistent drug formulations, streamlining the drug development and manufacturing process.

To further enhance the capabilities of IJP, the integration of AI models, particularly ML techniques, holds immense promise. ML models have already demonstrated their effectiveness in predicting printability, print quality, and total drug dose. By harnessing the power of AI, the formulation process can be expedited, reducing both time and material waste. This synergy between IJP and AI has the potential to revolutionize the field of pharmaceutical manufacturing, enabling faster and more efficient development of personalized medicines.

IJP presents a paradigm shift in the pharmaceutical industry, offering precise and customizable drug delivery systems. By addressing the limitations of current hardware through specialized printers and leveraging AI models, the full potential of IJP can be realized, leading to improved patient outcomes and a more efficient drug development process. The future of personalized medicine lies in the continued exploration and advancement of IJP technology.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

A.W.B. and A.G. are co-founders of the pharmaceutical companies FABRX and FABRX Artificial Intelligence.

Keywords

bioprinting, digital healthcare and industry 4.0, drop-on-demand and continuous ink-jet additive manufacturing, personalised medications, precision medicine, two- and three-dimensional printing of pharmaceuticals using pharma-inks, quick response (QR) codes and data matrix patterns

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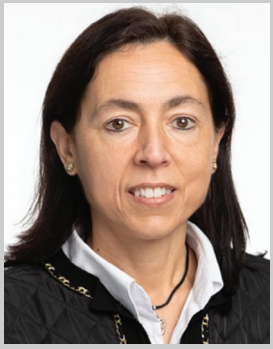

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