Transdermal Delivery via Medical Device Technologies

Shubhangi Shukla[1], Ryan H. Huston[2], Blake D. Cox[3], Abhay R. Satoskar[4], Roger J. Narayan[1]

[1] Joint Department of Biomedical Engineering, University of North Carolina at Chapel Hill and North Carolina State University

[2] Department of Microbiology, The Ohio State University, 484 W. 12 Ave, Columbus, OH 43210

[3] Division of Anatomy, The Ohio State University, 370 W. 9th Avenue, Columbus, OH 43210

[4] Departments of Pathology and Microbiology, Wexner Medical Center, The Ohio State University

Corresponding authors:

Abhay R Satoskar

Departments of Pathology and Microbiology

The Ohio State University

Columbus, Ohio 43210

Abhay.Satoskar@osumc.edu

Roger Narayan

Joint Department of Biomedical Engineering

at UNC-CH and NC State University

1840 Entrepreneur Drive, Raleigh, NC 27695-7115

roger_narayan@ncsu.edu

Abstract

Introduction: Despite their effectiveness and indispensability, many drugs are poorly solvated in aqueous solutions. Over recent decades, the need for targeted drug delivery has led to the development of pharmaceutical formulations with enhanced lipid solubility to improve their delivery properties. Therefore, a dependable approach for administering lipid-soluble drugs needs to be developed.

Areas covered: The advent of 3D printing or additive manufacturing (AM) has revolutionized the development of medical devices, which can effectively enable the delivery of lipophilic drugs to the targeted tissues. This review focuses on the use of microneedles and iontophoresis for transdermal drug delivery. Microneedle arrays, inkjet printing, and fused deposition modeling have emerged as valuable approaches for delivering several classes of drugs. In addition, iontophoresis has been successfully employed for the effective delivery of macromolecular drugs.

Expert opinion: Microneedle arrays, inkjet printing, and fused deposition are potentially useful for many drug delivery applications; however, the clinical and commercial adoption rates of these technologies are relatively low. Additional efforts is needed to enable the pharmaceutical community to fully realize the benefits of these technologies.

Keywords: Additive manufacturing, drug delivery, hollow microneedles, inkjet printing, iontophoresis, 3D printing, water-insoluble drugs.

Article highlights:

- Different kinds of 3D printed microneedle arrays have been used for transdermal drug delivery
- Additive manufacturing techniques were used to prepare microneedles for transdermal drug delivery
- Piezoelectric printing has been considered for the controlled release of lipophilic drugs
- Fused deposition modeling can be used for drug encapsulation applications
- The iontophoresis process drives drugs to the target body site under electrical influence

1. Introduction

Numerous drugs with hydrophobic characteristics, low bioavailability, or narrow therapeutic windows require the use of drug delivery systems to achieve their full therapeutic potential. [1-2] However, conventional delivery methods of some drugs are associated with undesirable side effects. To eliminate the challenges linked with prevalent drug administration schemes, additive manufacturing (AM) has gained popularity as an approach for processing drug-containing medical devices. [2-3] Three-dimensional (3D) printing technology is perceived to be an efficient route to design 3D structured materials [4-8] according to software-created design. Its potential has been materialized to develop hollow and dissolvable microneedle arrays [3] and other medical devices by fused deposition modeling (FDM) [9]. FDM involves the melting and extrusion of molten material in the layer-by-layer format to create a 3D item. Another technique known as inkjet printing [7] has been introduced recently as a promising method for precise drug processing. This approach often involves the coating of microneedle arrays [10-15] with drug binder and drug–polymer solutions at various ratios. The controlled release of a variety of drug compounds is facilitated by 3D printed drug delivery systems [4-7]. In addition to these approaches for transdermal drug delivery of lipophilic drugs, iontophoresis is another form of relatively unintrusive drug delivery that involves the application of a weak electric current (0.3–0.5 mA/cm^2) [16-20]. Iontophoresis is often utilized for the delivery of charged, low molecular weight drugs; however, studies involving a variety of larger-molecular weight or hydrophobic molecules have also taken place [21-25]. This review provides an overview of the latest achievements made in AM devices for personalized drug delivery via 3D printing, microneedles, and iontophoresis for drugs with poor water solubility.

2. Microneedle array-based transdermal delivery

The skin contains a layer rich in capillaries in the dermis that would be ideal for systematic drug administration if the top layer of the epidermis, the stratum corneum can be bypassed [1]. Lipophilic drugs are more prone to being metabolized and often must be delivered in high doses to overcome the poor dissolution rates [2]. One technique suggested to combat the obstacles of water-insoluble drugs is microneedles, small-scale needle-shaped medical devices that can administer drugs into the dermal circulation. The first microneedle arrays for practical use were developed in the 1990s; as such, there are over three decades of research on microneedles [3]. There is currently a trend towards innovation in microneedle technologies since 90% of the candidate drugs in the drug discovery pipeline have been noted to be poorly water soluble or water insoluble [4]. Administration in the dermis allows the medication to travel throughout the body without first encountering the liver, which breaks down many pharmaceuticals [10]. Microneedles come with the added benefit of causing little to no pain; since sensory neurons are in the dermis of the skin, an injection in the upper layers of the dermis or epidermis prevents the sensation of pain [11]. Thus, microneedles could make healthcare encounters faster and less challenging [12]. Although injections are commonly administered by healthcare providers, hypodermic injections at home can be challenging [13, 14]. With the increase in home care for chronic conditions, patients and home aides are using hypodermic needles more often; the use of these devices

is associated with potential injury and the generation of sharps waste [13]. As shown in Figure 1, four distinct groups of microneedles are being developed. The advantages and disadvantages of various microneedle materials, including silicon, glass, biodegradable polymers, nonbiodegradable polymers, natural materials, and composite materials, is discussed in detail elsewhere [25-41].

2.1 Solid microneedle arrays

Solid microneedles are small-scale needles that enter the skin, allowing medication to then be applied. These can be made of any material capable of piercing the skin, including but not limited to silicon, metals, or polymers [15]. Solid microneedles assist in the transport of topically applied drugs across the skin [25]. For example, Nguyen et al. used solid microneedles alongside a topical solution of amphotericin B, the most common antileishmanial drug, for treatment of leishmaniasis in a murine model; they showed a reduction in a lesion size and parasitic burden for *Leishmania mexicana* (but not *Leishmania major*) [40].

2.2 Hollow microneedle arrays

Another way to design microneedles is to make them hollow, so drugs can be injected into the circulation of the skin. Although most like hypodermic needles, they are much more accepted [15]. Using hollow needles, drugs are actively transported into the skin circulation with force instead of via passive diffusion as with solid or coated needles [30]. This approach allows for more efficient drug delivery, with few limitations on the medications that can be injected [31]. One potential drawback comes from the increased drug volume capable of being injected by hollow microneedles. The most common solvents used with water-insoluble drugs, dimethyl sulfoxide (DMSO) and toluene, are noted to cause acute irritation and dizziness as well as neurotoxicity [32].

2.3 Dissolvable microneedle arrays

Microneedles also can be made of a biodegradable material that contains medication such that as the needle undergoes degradation, the contents are released into the skin. There is a relatively narrow selection for materials for dissolvable microneedle design since the microneedle material must be degraded by the skin. This technology allows for the medication to be released over time [33-34]. There are also no sharps to take care of after administration, making this option appealing for at home administration. As noted by Dangol et al., dissolving microneedles can be implemented with an innovative polymeric system (IPS) for transdermal delivery without a solvent [34]. They showed that microneedles are effective for delivering capsaicin to treat rheumatoid arthritis and may also prove beneficial for other drugs with poor water solubility [35].

2.4 Coated microneedles

Coated needles are used in a similar manner as solid needles; in this case, the needles are coated with the medication of interest. Another benefit of this technology is a more stable drug, since the drug is in direct contact with the circulation of the dermis [28]. The main drawback of this type of needle is the small amount of drug that can be applied due to the small amount that can fit on microneedles [28]. Ma and Gill showed that microneedles coated with a solid dispersion are an effective solution to delivering water insoluble drugs such as lidocaine into the skin [29].

2.5 Additive manufacturing of microneedles and other medical devices

Additive manufacturing has attracted attention in recent years for creating structures that can be used for targeted delivery and for developing other interventions in response to the challenges associated with drug delivery [5-6]. It is anticipated that polymer-based drug delivery devices made by additive manufacturing can improve patient compliance and drug efficacy parameters [5-7, 9]. The following sections consider the use of additive manufacturing to create drug-loaded microneedles and other medical devices.

2.5.1 Drug loaded 3D printed medical devices

Economidou et al. coated stereolithography-manufactured microneedles with insulin and sugar alcohol or disaccharide carrier layers using a piezoelectric inkjet printing process [6]. The excipients used here were 5-7 membered sugars and their derivatives like mannitol, xylitol, and trehalose, which help in binding the poorly soluble insulin to the microneedle surfaces. The release behavior of insulin from these microneedle arrays was studied in an *in vivo* animal study [6]. The hollow microneedle array was shown to be able to deliver insulin transdermally with a minimum applied force of 2-5 N. The strong adhesion forces between the coated films and the polymeric microneedle array surface after skin penetration were demonstrated via micro–CT analysis. Microneedle array-based delivery led to rapid insulin delivery lowering the blood glucose levels in around one hour of application, which is much faster than conventional subcutaneous injections [6].

In another study, 3D printed semi-solid tablets were prepared via a layer-by-layer extrusion-based deposition process with three drug dosages, 75, 100, and 125 mg, under ambient temperature and pressure conditions (as shown in Figure 2). The water insoluble drug theophylline with a concentration of 10 – 12% w/w was loaded on semi-solid hydroxypropyl methylcellulose) tablets [42]. This study demonstrated the possibility of loading a variable theophylline dosage with shape retention using an extrusion-based approach [42]. Almeida et al. developed tailor-made three-dimensional systems made from chitosan-based polymers for effective delivery of the drug model drug camptothecin. 3D printed structures called print fills were incorporated with camptothecin [43]. The print fills assembly were further coated with an enteric layer to prevent the premature dissolution of the drug in the gastrointestinal tract [43]. This approach

enabled the structure to remain intact in the simulated gastric pH of the stomach; the micelles released the drug at the colonic pH. The camptothecin-loaded chitosan micelles provided a much higher apparent permeability coefficient than the camptothecin-free drug [43].

In another study, 3D printed semi-solid tablets were prepared in a layer-by-layer manner with a semisolid extrusion-type 3D bioprinter, under ambient conditions [44]. Tagami et al. loaded water insoluble drug, naftopidil on hydroxypropyl methylcellulose tablets; various amounts of hydroxypropyl methylcellulose (30%, 40%, and 50%) were included in the ink. Changing the concentration of hydroxypropyl methylcellulose was shown to alter the viscosity. Release behavior showed that naftopidil was diffusion as well as erosion controlled [44, 45]. An increase in the hydroxypropyl methylcellulose concentration was associated with decreased hardness, decreased weight, and slower drug dissolution. This study showed that semisolid extrusion-type 3D printers may be used for creating tablets for targeted drug delivery [44].

Seoane-Viano et al. investigated the 3D printing of suppositories containing tacrolimus with a semi-solid extrusion 3D printer; these suppositories may be useful for local treatment of ulcerative colitis [46]. The suppositories contained the lipophilic active pharmaceutical ingredient tacrolimusalon with lipid pharmaceutical excipients (e.g., Gelucire 44/14 or Gelucire 48/16) and coconut oil. The suppositories containing Gel 44 were shown to release tacrolimus more slowly than those containing Gel 48 [46, 47]. The drug release profiles showed over 80% of the tacrolimus was efficiently released within 120 minutes. This study suggested that drug-loaded suppositories could be manufactured via 3D printing for personalized drug delivery.

Chang et al. investigated the use of a binder jet 3D approach to create tablet-like dosages from pharmaceutical-grade feedstock materials [48]. They used inkjet printing of a liquid binder to selectively bind pharmaceutical-grade powders. The disintegration time was affected by the porosity of the printed structures. Indomethacin was used as an active pharmaceutical ingredient in the study. The breaking force and degradation time of the as processed and post-processed structures (Figure 3) demonstrated the release properties of indomethacin in the 3D printed structures [48].

Liu et al. demonstrated the use of a semi-solid extrusion-type 3D bioprinter, a hydrogel-based printer ink [49], and exposure to an ultraviolet LED source [50-51] to create hydrogel patches with fish gelatin methacryloyl; the viscosity of the gelatin methacryloyl was increased by adding carboxymethyl cellulose sodium [49]. PEGylated liposomal doxorubicin, an antineoplastic agent, was added to the hydrogel. Structures with cylinder, torus, and gridline morphologies were manufactured; the drug release rate was shown to depend on the shape of the structure and the ultraviolet light exposure time. Ambrus et al. investigated the use of polyvinylpyrrolidone

nanofibers for delivering loratadine, a drug with poor water solubility [52]. An inexpensive 3D-printed electrospinning instrument with a counter-flow air attachment was used to create the loratadine-loaded nanofibers with a mean diameter of 372 nm [52]. Vibrational spectroscopy results confirmed the conversion of the initial crystalline phase of loratadine to an amorphous phase [52]. X-ray diffraction analysis and differential scanning calorimetry demonstrated the amorphous morphology of the nanofibers. A dissolution experiment showed that the nanofiber structure released 66% of the drug within 10 minutes [52]. The nanofiber structure exhibits suitable drug delivery properties for further consideration.

2.5.2 Deposition of drugs using inkjet patterning

Personalized medicine may be transformed by inkjet printing-based manufacturing technology. The term "printable medicines" was coined by Voura et al. to describe a microdrop printing approach for creating drug models. Inkjet printing has been successfully utilized to incorporate active pharmaceutical ingredients (APIs) into drug delivery devices such as transdermal microneedle systems, [52-54], thin films, and tablets for oral consumption. One type of inkjet printing approach, known as continuous inkjet printing, utilizes a continuous jet stream; in this approach, the degree of drop deflection is modulated by an electrical field [55]. Drop-on-demand (DoD), piezoelectric, and thermal mechanisms for inkjet printing have also been demonstrated. Piezoelectric inkjet printing involves the application of an electric driving voltage pulse which results in the mechanical deformation of a piezoelectric component [56-57]. Depending on the orientation of applied electric field with respect to the polarization direction and the ink channel construction, the piezoelectric operation is categorized into bend mode, squeeze mode, bump mode, and shear mode [58-59].

Kiefer and Breitkreutz compared piezoelectric print heads made by Spectra (SE-128 AA) and Konica Minolta (KM512SHX); thin films containing 15% (w/w) hypromellose casting solution were used in this study [60]. The print head with the larger nozzle, SE-128 AA, was more efficient in printing and showed lower scattering rates. Processing parameters such as ink composition, process pattern, and drop size of the nozzle were the primary parameters for inkjet printing; geometry selection had a secondary role [60].

Edinger et al. investigated the usage of inkjet printing for processing quick response (QR) code patterns, which contain both the drug and encoded information, on edible dosage forms. [57] The neuroleptic water insoluble drug haloperidol was used as model; the drug was printed on an orodispersible substrate. The QR pattern was processed on a porous and malleable substrate; the mechanical properties of the substrate remained intact. The actual drug content in the printed dosage was shown to match the encoded drug amount. These QR encoded dosage forms did not show a large amount of edge bleeding [57]. After storage under harsh conditions, the QR encoded dosage form was read by a smartphone. This technology can enable the development of more patient-friendly and safer drug products.

Machekposhti et al. used piezoelectric inkjet printing to deposit an antifungal drug, amphotericin B, and an antibacterial drug, azithromycin, to the surfaces of silicon, aluminum, and gauze [61]. An in vitro disk diffusion assay showed that the azithromycin-coated surfaces provided antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*; the amphotericin B-coated surfaces provided antifungal activity against *Candida albicans*. The results of this study showed that piezoelectric inkjet printing may be used to load gauze with antimicrobial drugs with poor water solubility.

Clark et al. demonstrated the feasibility of three-dimensional (3D) inkjet printing in combination with an ultraviolet light photocuring process to fabricate solid dosage forms that incorporate a common water insoluble drug called carvedilol [62]. The mixture prepared to generate an effective printing ink consisted of of 10 wt% carvedilol, a photocurable N-vinyl-2-pyrrolidone (NVP), the photoinitiator Irgacure 2959, and a poly (ethylene glycol) diacrylate matrix. X-ray analysis revealed that the printed materials possessed an amorphous structure [62]. Cylinder, ring, mesh, and thin film structures were prepared; the fastest release was observed for the thin films and the slowest release was observed for the cylinders. Accelerated release depended on the surface area to volume ratio of the printed [62]. As noted in Figure 4, the tablets with the tested geometries showed an 80% drug release rate within 10 hours. This study showed that inkjet printing is suitable for creating solid dispersion tablets containing poorly soluble drugs; moreover, tablet geometry was shown to play an important role in determining the release rate.

Eleftheriadis et al. used a two-dimensional printing to create edible films for the oral cavity containing diclofenac sodium; ethanol and propylene glycol were used as solvents in this study [63]. A variation in the dose was obtained by increasing the number of printed drug-loaded ink layers on the substrates. An *in vitro* release study using simulated saliva showed that the drug was released in 10 minutes. An in vitro permeation study showed that the number of printed layers was correlated with the apparent permeability coefficient.

In another study, oral cavity films made from sugar loaded with the vitamins thiamine hydrochloride and nicotinic acid were printed using a piezoelectric inkjet printing. [64] Eleftheriadis et al. evaluated the parameters required for the fabrication of vitamin loaded system [64]. In this study ethylene glycol used as principal solvent. Several types of doses were created by increasing the number of printing steps [64]. The *in vitro* drug release profile showed release in a burst manner over ten minutes [64]. The *in vitro* studies revealed that a higher concentration of the vitamins was associated with enhanced *in vitro* permeation properties.

Amphotericin B is one of the most promising drugs for the treatment of broad-spectrum fungal infections; however, the drug exhibits poor water poor solubility [65]. Boehm et al. discussed the deposition of amphotericin B coatings on methyl vinyl ether-maleic anhydride copolymer microneedles through piezoelectric inkjet printing; the microneedles were manufactured via a combination of microstereolithography and micromolding prior to the drug coating process [65]. Dimethylsulfoxide was used to create an amphotericin B solution, which was used in the inkjet printing process. An *in vitro* a radial diffusion assay showed that the amphotericin B-loaded microneedles provided activity against the yeast *Candida parapsilosis*. This study indicates that inkjet printing may be used to load microneedles with amphotericin B for the transdermal delivery of antifungal pharmacologic agents.

Palo et al. investigated the fabrication of inkjet printed dosage structures on electrospun fibrous gelatin substrates for oromucosal delivery [66]. Lidocaine hydrochloride was inkjet printed on the electrospun and cross-linked gelatin substrates by inkjet printing. piroxicam was encapsulated into the substrate fibers using the electrospinning process [66]. In addition, to lidocaine single-drug structures, a combination drug system containing lidocaine and piroxicam were manufactured. The amount of printed lidocaine, 2-3 mg, was in good agreement with the expected dose. Degradation of the inkjet printed lidocaine was observed within a few months. Release of over 85% release of the two drugs after 8 minutes was demonstrated. The electrospun gelatin was shown to be useful as substrates for inkjet printing of drugs for oromucosal delivery.

2.5.3 Manufacturing of drug delivery devices via extrusion-based additive manufacturing

Among the various AM techniques, fused deposition modeling (FDM) has attracted significant attention owing to its low cost and flexibility [9]. FDM relies on various parameters such as the adhesive forces between the successive layers. This approach may be used for the targeted administration of drugs with poor water solubility [9].

Chai et al. explored the development of tablets for floating sustained release within the stomach using FDM; this drug delivery approach may provide a reduction in administration frequency and an increase in oral bioavailability [67]. In this study, an insoluble weak base, domperidone was incorporated in a layer-by-layer manner onto hydroxypropyl cellulose filaments via a hot melt extrusion process; filaments were printed into hollow structured tablets via alterations to the infill amounts and shell numbers. A structure containing 10% domperidone and two shells provided sustained release and floated for approximately 10 h in an *in vitro* study. Moreover, radiographic imaging revealed that the $BaSO_4$-labeled tablets were retained in a rabbit stomach for over 8 hours [67]. This study showed the value of hollow tablet technology for intragastric floating drug delivery.

Another study demonstrated the processing of tablets loaded with bicalutamide via a two-material co-extrusion-based fused deposition modeling process. The DualPro printhead in the ZMorph® 3D printer was used to co-extrude two filaments via a single nozzle. This setup can be used to prepare tablets for immediate release as well as controlled release. Jamroz et al. studied the dissolution profile of tablets with one material, two components, and three compartments [67]. Tablets with immediate, controlled, and combined release mechanisms were demonstrated.

Wei et al. studied the use of fused deposition modeling to prepare water-soluble polymer called polyvinyl alcohol into melt-extruded filaments and subsequently into 3D printed tablets. The incorporation of two drugs with pH-dependent solubility, carvedilol and haloperidol, and a plasticizer, sorbitol, was demonstrated [69]. By adding 10% sorbitol, the temperature for extrusion of filaments containing 10% and 20% drug reduced from 180°C-190°C to ~150°C (shown in Figure 5). Drug release from tablets containing 10% and 20% carvedilol and 60% infill occurred within ~45 min at pH values of 2 and 6.8. Limited drug-polymer miscibility and high processing temperatures were noted to be challenges associated with the use of polyvinyl alcohol.

Jamroz et al. investigated fused deposition modeling-based melt extrusion 3D printing of dispersible films loaded with the drug aripiprazole [70]. The gradual conversion of aripiprazole to an amorphous form was demonstrated. The films were observed to exhibit high dissolution rates [70-71]. Tiboni et al. demonstrated fused deposition modeling processing of clotrimazole-loaded polyurethane rings for the intravaginal treatment of vulvovaginal candidiasis [72]. Rings containing two different drug concentrations, 2% and 10% w/w, were demonstrated. The 10% loaded ring showed complete *C. albicans* growth inhibition in simulated vaginal fluid after 5 days. Drug release in 50% ethanol and vaginal fluid simulant was shown to be sustained over seven days. The 3D printed intravaginal rings showed potential for treatment of vulvovaginal candidiasis.

Shi et al. studied the manufacturing of 3D printed sustained release tablets via hot melt extrusion in combination with fused deposition modeling, in particular the use of several release modifying excipients. Ibuprofen was utilized as the model drug and ethyl cellulose was utilized as the polymeric matrix in this study; Eudragit® RL PO/RS PO, hydroxypropyl methylcellulose K4M/E10M/K100M, polyethylene glycol 6000, poly (vinyl alcohol), Soluplus®, and Kollidon® vinyl acetate 64 (VA 64)/17PF/30 were studied for use in modulating the drug release profile. [73] The release of the drug over 24 h was modulated by altering the type of modifiers; for example, PEG enabled the release of the drug as a zero-order reaction. This study showed that tablets with tunable drug release profiles could be made by hot melt extrusion in combination with fused deposition modeling.

In another study, caplets containing perforated channels for accelerated release of the drug hydrochlorothiazide were created by fused deposition modeling. Channels with widths of 0.2, 0.4, 0.6, 0.8, or 1.0 mm with parallel or perpendicular alignments to the tablet long axis were created (as shown in Figure 6) [74]. A channel width exceeding 0.6 mm was shown to be associated with immediate release of the drug; at similar surface area/mass ratio values, shorter multiple channels were shown to be better at drug release than longer channels [74-75]. The use of short channels was shown to accelerate the rate of drug release.

Guluzar et al. considered the use of a twin-screw extruder to create filaments containing hydroxypropyl cellulose and up to 30 wt% griseofulvin [76]. They showed that tablets containing these filaments with a higher surface area to volume showed a higher release rate. In addition, a near zero-order release was obtained. This study indicated that many parameters may be optimized to control drug release from fused deposition modeling-manufactured tablets.

Lim et al. manufactured complex geometries using fused deposition modeling for zero-order release of the anti-epileptic drug carbamazepine. They created scaffolds with a variety of parameters, with variation in the number of holes, hole positions, and hole diameters [77]. Linear release profiles were demonstrated with carbamazepine-containing scaffolds that contained side holes [77]. Moreover, enlarging the hole diameter (1, 1.5, and 2 mm) resulted in an increased rate in drug release from the scaffolds. Dumpa et al. used a hot-melt extrusion-paired fused deposition modeling and direct compression to create core-shell tablets for floating pulsatile drug delivery in the gastrointestinal tract [78]. A hot-melt extrusion approach was used to prepare hydroxypropyl cellulose and ethyl cellulose containing filaments; a theophylline tablet served as the core of the tablet. The core-shell tablets exhibited good floating properties as well as pulsatile release of theophylline from 30 min to 6 h. This approach was demonstrated to be suitable for manufacturing customized drug delivery systems.

In another study, solid dosage forms were designed by coupling hot melt extrusion with fused deposition modeling to create floating tablets out of cinnarizine, a drug with a narrow absorption window drug, as well as hydroxypropyl cellulose and vinylpyrrolidone vinyl acetate copolymer [79]. As shown in Figure 7, the floating force, unit dose, and release profile were altered by changing the printing parameters and design. A constant floating force up to 12 h was demonstrated using this approach. A zero-order kinetics of over 12 h was shown. This approach can be used to rapidly manufacture tablets for many drugs and delivery profiles.

3. Drug delivery via iontophoresis

Another approach to improve the delivery of insoluble drugs through medical devices involves iontophoresis. Iontophoretic devices must have two points of contact on the target site for current to exit the device, enter the body, repel/attract buffer and bioactive solutes,

and then return current into the device [16]. Thousands of peer-reviewed papers involving the use of iontophoresis with various drugs and for various diseases have been published; iontophoresis has been used on the skin [19-24, 80-82], eyes [83-88], nails [89,90], ears [91], as well as less common sites on the body such as bone allografts [92,93]. Furthermore, iontophoresis has been reviewed in the context of delivering peptides [94-95], nucleotides [87,96,97], chemotherapeutic agents [98], and analgesic agents. However, little attention has been given to the use of iontophoresis in the context of nonpolar, lipophilic, or large molecules, which tend to be more water insoluble. Here, we focus on insoluble drugs to better highlight potential utility of iontophoresis and possibilities for further research.

3.1 Mechanism of Iontophoresis

Any current is composed of flowing electrons; therefore, it was long thought that iontophoresis worked only on ionic compounds due to electrostatic repulsion or attraction of the current inducing the ions of interest deeper into the target tissue [100]. It has now also been shown that other forces aside from electrostatic action can aid delivery of different insoluble drugs. For example, the action of electric current enhances the permeability of skin via a "damage factor" that adds to drug permeation even after current application ends [95,101-103]. Other tissues may show a similar effect. In addition, the bulk movement of the water/buffer solution into the target site contributes to penetration of uncharged solutes by electroosmosis (originally coined "iontohydrokinesis") [101]. This effect was first studied in non-electrolytes such as thymidine and 9-β-D-arabinofuranosyladenine, which exhibited an improvement of penetration *in vivo* into mouse skin (up to 488% for 9-beta-D-arabinofuranosyladenine) under iontophoresis relative passive diffusion, despite their uncharged nature; the electrical current was noted to not change the skin permeability [104].

Later studies expanded on these findings by observing alkanol chains of varying lengths under ionized and unionized conditions with excised mouse skin [105]. Del Terzo et al. showed *in vitro* that pores mediate iontophoretic-facilitated transport. Furthermore, in the un-ionized state, iontophoresis of smaller carbon chains outperformed passive diffusion; larger alcohol chains saw the opposite trend and favored passive diffusion [105]. However, when the same alkanol chains were tested under ionizing conditions, iontophoresis outperformed passive diffusion in all of the carbon chain lengths tested; this data demonstrates the potential utility of iontophoresis with a charged drug and the ability to enhance delivery of certain uncharged drugs [105].

Iontophoresis is especially promising in medicine because it transmits a relatively high dose of drug to a localized target site of disease, as directed by the current from the electrodes. However, iontophoresis can have some side effects at the target site such as irritation from drug permeation or electrical burns, which are associated with excessive current duration or poorly controlled frequency of use [106-109]. Studies have also looked at iontophoresis with the aim of delivering drugs systemically through subcutaneous breast papillae

or blood vessels [18,110]. As already mentioned regarding systemic delivery via microneedles, these uses have an additional benefit compared to oral ingestion as the drug escapes first-pass metabolism (degradation or modification of the active drug at a site other than the target site) by the stomach and liver [111].

3.2 Iontophoresis of Water-Insoluble Drugs

While drugs come in innumerable structural combinations, one way to classify them easily is using two main characteristics which provide unique advantages or challenges to their use, specifically drug permeability and drug solubility; hence these two traits define the Biopharmaceutics Classification System taxonomy [112]. Iontophoresis has been shown to benefit many drugs with varying combinations of these traits; however, the most challenging drugs to deliver are those with low permeability and low solubility. Compared to water-soluble drugs, iontophoresis has not been thoroughly researched for use with lipophilic/hydrophobic or otherwise water-insoluble drugs. The current research has been largely focused on delivery of drugs via iontophoresis using water-based buffers and water-soluble ions; however, the principle of electroosmosis clearly supports the penetration of nonpolar or uncharged molecules as well [101]. In addition, creative drug formulations can enhance iontophoretic delivery by (a) placing drugs in liposomes or micelles; (b) mixing solutes with surfactants, cosolvents, or complexion solutes; or (c) substituting the solvent altogether [113].

3.2.1 Iontophoresis of Liposomes

Liposomes are formed from a bilayer of amphipathic molecules [113]. The bilayer of hydrophobic tails, combined with hydrophilic heads, makes the structure very similar to cellular vesicles and a unique carrier to enhance drug solubility in iontophoresis. This structure creates two regions for the transport of drugs. Water-insoluble, lipophilic drugs can be transported inside the membrane region, while water-soluble drugs can be transported inside the inner vesicle region (bordered by hydrophilic heads).

One way that liposomal formulations have been applied to iontophoresis is with small RNA products that must be shielded from degradation while in transit to their target site [114-117]. One study combined transcutaneous delivery of siRNA against the overexpressed oncogene STAT3 with the delivery of the anti-cancer drug curcumin in a dual-function liposome [114]. Jose et al. first showed that the *in vitro* liposomal curcumin release profile into media was greatly elongated; *in vitro* cell cultures enhanced uptake of both curcumin and siRNA when they were present in the liposomal formulation rather than free siRNA or curcumin due to endocytosis [114]. Furthermore, significant synergistic effects were seen with the liposomal co-delivery of STAT3 siRNA and curcumin, with an ~80% inhibition of *in vitro* tumor cell growth and similar encouraging results in an apoptosis assay [114]. It was also observed that passive diffusion of free and liposomal curcumin both had a meager ability to penetrate *ex vivo* porcine ear skin; liposomal formulations

were not able to penetrate the uppermost layer of the skin [114]. However, iontophoresis of liposomal siRNA/curcumin had significantly higher penetration into the skin [114].

Furthermore, recent developments around related deformable, charged liposomes may also prove uniquely beneficial for the iontophoresis of those drugs which are insoluble or poor penetrators [118]. These "iontosomes" containing 2-dioleoyl-3-trimethylammonium-propane and Lipoid-S75 were tested *ex vivo* in porcine esophageal mucosa for their ability to deliver two chemotherapeutic drugs, cisplatin and docetaxel, with potential use for oral cancer drug delivery. The hydrophobic drug docetaxel residing in the liposome membrane saw enhanced permeation by approximately 57-fold while the hydrophilic cisplatin residing in the interior of the liposome benefited from iontophoresis by approximately 68-fold relative to passive diffusion in the buccal mucosa [118]. Taken together, this data demonstrates the potentially utility of liposomal transport in iontophoresis.

3.2.2 Iontophoresis of Micelles

Micelles are similar structures to liposomes as they are made from individual amphipathic molecules; however, they form a lipid monolayer instead of a bilayer [113]. Unlike liposomes, only nonpolar drugs can be dissolved in the center of the micelle as this area is now surrounded by hydrophobic tails while the hydrophilic heads remain exposed at the exterior of the structure.

One study investigated drug release from simple or mixed micelles made from either taurocholate alone or taurocholate with egg lecithin for their ability to carry dexamethasone, an anti-inflammatory corticosteroid used in many eye diseases, in *ex vivo* cadaveric human sclera [119]. The authors established *in vitro* that dexamethasone solubility had a positive linear correlation with lipid concentration [119]. Despite this correlation, in *ex vivo* sclera, permeability was highest under iontophoresis conditions with free dexamethasone rather than with micelle formulations; however, micelles exhibited a slow release profile and ultimately were found to deliver significantly more drug [119]. The mixed and simple micelle formulations used in the study were found to slow the release of dexamethasone but at different rates [119]. Additionally, micelle formulations differed based on the chemistry of their components with respect to their suitability for anodal versus cathodal iontophoresis [119].

The same authors later conducted another study to characterize mixed micelles for their ability to carry and release several other model lipophilic drugs, specifically triamcinolone acetonide, dexamethasone, and β-estradiol, for transscleral iontophoresis of *ex vivo* human eyes [120]. Chopra et al. found that more lipophilic drugs have slower release profiles from the micelles in the sclera, but this can be

advantageous where a controlled release of drug over time is desired [120]. These studies on iontophoresis reveal a variety of customizable attributes for lipophilic drug delivery, which warrant further investigation.

3.2.3 Drug Complexation & Iontophoresis

Complexation is yet another method that can be suitable to improve water solubility of certain drugs. For example, propofol is an anesthetic that is highly lipophilic; this characteristic has led to two main formulations being developed in the clinic, including surfactant-based and oil-emulsion based delivery; however, both of these can result in distinct side effects for patients, hence a new delivery mechanism is required [121,122]. The hydrophobic nature of propofol renders it ineffective at delivery via iontophoresis when it is delivered alone. A novel ionized version of propofol was shown to be effective in iontophoresis; however, this ionized version has altered bioavailability, possibly impacting its accumulation in the brain and throughout the body [123]. These challenges led to an investigation of the complexation of propofol and the common solubilizing agent, cyclodextrin, for use in iontophoresis [123]. Complexation of propofol with cyclodextrin was shown via NMR as well as UV absorption spectra and resulted in a linear increase of soluble propofol correlated 1:1 with the concentration of cyclodextrin [123]. These large (2 kDa) complexes were tested under iontophoresis as well as passive transport. The complex enhanced propofol passive transport; the enhancement of propofol delivery in *ex vivo* porcine skin was attributed to increased thermodynamic activity and the delayed recovery of the skin barrier (due to disruption by iontophoresis) [123].

Larger nanocarriers such as complexed polyamidoamine (PAMPAM) dendrimers have been used with iontophoresis. PAMPAM dendrimers are semi-rigid nanoparticles with customizable surface groups that can tailor the solubility and interactions of the dendrimers, resulting in their use for transport across small epithelial barriers [124]. The hydrophobic nature of dexamethasone results in its short half-life within the eye as it is easily cleared by normal eye homeostasis mechanisms [124]. Dexamethasone-PAMPAM complexes were found to not alter the particle size of the PAMPAM dendrimers, which points to the inclusion of dexamethasone in the hydrophobic cavities of PAMPAM [124]. Iontophoresis of these PAMPAM nanocarrier complexes revealed improved transcorneal penetration of PAMPAM *ex vivo* as indicated by detection of fluorescently tagged PAMPAM at greater depths in the eye [124]. PAMPAM also improved the solubility of dexanethasone by tenfold, leading to a sixfold increase in dexamethasone availability both in *ex vivo* and *in vivo* eye samples when combined with iontophoresis. In contrast, the penetration of dexamethasone alone was enhanced via iontophoresis by only two-three fold in both experiments [124].

3.2.4 Iontophoresis with Surfactants

Surfactants are another avenue to improve the water solubility of a drug before performing iontophoresis. Surfactants disrupt the molecular arrangement of water with their large nonpolar or amphipathic structures. This mechanism creates more space for sparingly soluble substrates to improve their solubility in water [113]. Surfactants have been studied with iontophoresis both in drug formulations and as a pretreatment approach for patient skin.

While including surfactants in drug solutions can impact drug solubility, a separated surfactant pretreatment step has also been investigated as another strategy to enhance drug permeability. A surfactant formulation containing laureth-7 ethyloxylene ether, laureth-3 ethyloxylene ether, and sodium sulfosuccinate in a 0.3:0.7:0.05 molar ratio was evaluated for use as an iontophoretic skin pretreatment in a study involving sixteen patients [125, 126]. In this study, R-apomorphine, which is used in the treatment of Parkinson's disease, was delivered via iontophoresis [125,126]. A pharmacokinetic model indicated that 1.9% of the dose was released from the iontophoresis patch. The patients who were treated with surfactant formulations showed a statistically significant increase in bioavailability compared to those treated with iontophoresis without absorption enhancers [125]. Clinical improvement was noted in five of eight patients in the pretreatment group and in three of eight patients in the control (i.e., no absorption enhancer) group. This surfactant pretreatment may work similarly to other chemical enhancers, which have been shown to improve drug uptake by changing the structure of the skin to improve permeability [81].

Evidence of the successful use of surfactants in solution with a drug to enhance iontophoretic delivery has also been described. In a model of onychomycosis nail infection treatment, *ex vivo* bovine hoof slices were used to study the iontophoretic delivery of the high molecular weight and water insoluble drug nystatin. The delivery of nystatin benefited from formulations with either cetylpyridinium chloride or Tween™ 80, which provided fivefold and twofold improvement, respectively, over passive diffusion [127].

Another surfactant, sodium dodecyl sulfate (SDS), has also been shown to improve solubility and penetration during iontophoresis of hydrocortisone, an uncharged solute, in *ex vivo* mouse skin [128]. Some surfactants like cetylpyridinium chloride and SDS can form micelles when used in sufficient amounts; however, the release profile for the drug must be tailored to the target site and drug type [127,128]. Regarding SDS interactions with hydrocortisone, the permeability was noted to reach a peak level when the SDS concentration reached the critical micelle concentration [128].

An cationic surfactant that has shown synergistic effects with iontophoretic drug delivery is benzalkonium chloride in the context of keratoconus [129]. Gore et al. revealed that in the presence of the surfactant benzalkonium chloride, the iontophoresis of riboflavin across an intact corneal epithelium produced riboflavin penetration similar to that from the clinical standard practice of debridement of

this epithelium without iontophoresis [129]. Thus, the use of iontophoresis with a surfactant offers a significant improvement to the procedure by avoiding the need for invasive debridement to achieve effective drug delivery to the cornea. However, iontophoresis protocols performed without the surfactant benzalkonium chloride were only 60% as effective at drug delivery [129]. This data further reveals the potential for the use of iontophoresis alongside surfactants to enhance the delivery profile.

3.2.5 Iontophoresis of Alternative Solvents

Researchers have chosen to avoid the water solubility issue by using other nontoxic organic solvents for their iontophoresis buffer mixture. One study dissolved triamcinolone acetonide in a solution of N-N,-dimethylacetamide (as the organic solvent) and water at a ratio of 7/3 v/v [130]. Triamcinolone acetonide is an uncharged drug that is used to inhibit collagen synthesis for keloid and hypertrophic scar treatment. This drug was typically administered via pressure jet injection; however, this approach caused discomfort to patients, necessitating the development of alternative delivery methods [130]. Rats that were treated with iontophoresis for 30 minutes were found to retain triamcinolone acetonide in their skin 24 hours after treatment, indicating the success of N-N,-dimethylacetamide as an alternative solvent for drugs that may not otherwise be suitable for delivery using iontophoresis [130].

4. Conclusions

This report summarizes advancements related to the targeted delivery of lipophilic drugs. Recently developed technologies to administer drugs with poor water solubility and enhance the bioavailability of drug with poor water solubility were considered. Microneedle arrays, 3D printed products (e.g., tablets), inkjet patterned surfaces, melt extrusion combined with polymeric filaments, and electrostatic pathways are some of the technologies that have been utilized for the delivery of water insoluble drugs.

5. Expert Opinion

Medical devices such as microneedle arrays, 3D printed products (e.g., tablets), and iontophoretic devices have tremendous potential for the delivery of drugs with poor water solubility and the enhancement of bioavailability of such drugs. In particular, their administration to targeted regions may be achieved using these medical device technologies. For example, transdermal delivery devices such as microneedle arrays have demonstrated their ability to deliver many types of drugs. The global transdermal industry is growing, and is expected to exceed one billion US dollars in size [131]. The potential of microneedle array-based devices has been recognized by the World Economic Forum as a promising research advancement [131]. Transdermal delivery systems may enable the effective pharmacologic management of many chronic diseases. The use of additive manufacturing for the preparation of drug delivery devices

has garnered significant interest by scientific community. [132] Additive manufacturing techniques have enabled the development of many types of targeted drug release systems. For example, additive manufacturing enables the preparation of devices with complex geometries for the improved delivery of drugs to many regions of the body, which advances efforts to personalize medical care. Additive manufacturing can also enable the development of multifunctional devices and multimaterial devices in which the material type and composition can be optimized. The use of a type of additive manufacturing known as 4D printing (i.e., additive manufacturing of stimulus responsive materials, which are also known as "smart" materials) may facilitate the preparation of smart drug delivery devices that respond to an external or physiological stimulus. These devices may be used for the stimulus-driven release of drugs [133].

Unlike hypodermic needles, microneedles exhibit many structural variations. This variety opens the potential for different microneedles that best suit patient treatment plans. As the number of water-insoluble medications on the market increases, the translation of microneedles and other medical devices may become more impactful. These technologies may enable the delivery of new types of water insoluble drugs; moreover, the technologies may allow drugs to be delivered to a greater variety of target tissues and organs than before. These medical devices must be tailored based on the target body sites, drug, and solvent. In particular, special care will have to be taken to choose a solvent with minimal or no toxicity. It should be noted that user handling issues such as the appropriate application of the microneedle to the skin surface and safe microneedle disposal present challenges to the commercial translation of microneedle technology. In addition, manufacturing (e.g., low-cost mass production of devices) and quality control (e.g., manufacturing of identical devices at low cost) limitations may need to be overcome for clinical translation of these technologies. It is anticipated that, as in other industries, manufacturing and quality control will be overcome to enable clinical translation of these technologies.

Additional human clinical studies are needed to facilitate clinical translation of microneedles and other medical devices for transdermal drug delivery. It should be noted that medical devices can meet the needs of patients belonging to several age groups; modifying the dosage for different patient groups via on demand production approaches is a current technical challenge. Low-cost solutions to manufacturing and quality control challenges associated with device uniformity must also be developed. In AM, multimaterial printing can include multiple drugs in a single system and can be incorporated with timely and regulated release. Another important consideration for the translation of microneedles and other medical devices is the regulatory pathway for approval and distribution of the devices. Medical devices such as microneedle arrays and iontophoretic devices may be considered by regulatory agencies such as the U.S. Food & Drug Administration and its Japanese counterpart as a combination product; this term includes therapeutic devices that exhibit attributes of drugs, devices, and/or biological components [134]. Many combination products have been developed for the delivery of drugs that cannot be orally administered. Nearly twenty years ago, the U.S. Food & Drug Administration created the Office of Combination Products to enable appropriate review and oversight of combination products. The approval of a combination product is largely governed by the regulatory status of the drugs or devices that are incorporated in the combination product. In contrast, combination products are regulated by the European Union as medical devices or pharmaceutical products based on the attribute of the

product that is determined to possess the primary function. International bodies such as the International Coalition of Medicines Regulatory Authorities (ICMRA) and the International Medical Devices Regulators Forum (IMDRF) may play a role in harmonizing the regulation of combination products over the coming years [135].

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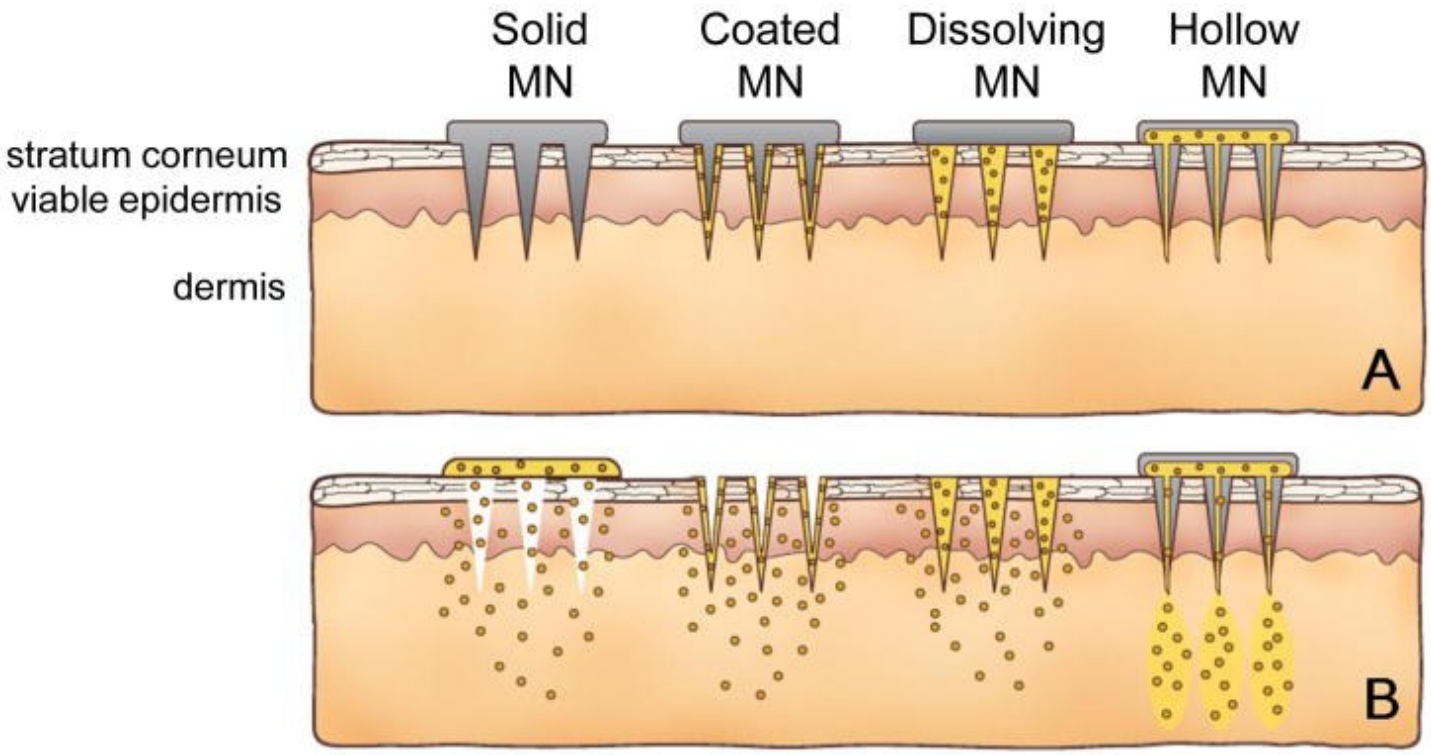

Figure 1. The four different types of microneedles as discussed in this paper. A. Solid microneedles puncture the skin for topical drug delivery. B. Coated needles are also solid needles; however, are covered in a drug such that topical medication does not have to be applied later. C. Dissolvable microneedles are made of biodegradable material such that they release drug as they are dissolved. This method does not involve the generation of sharps waste. C. Hollow needles are like hypodermic needles in that the drug is injected, allowing for a greater amount of drug to be applied. Reproduced from [1] with permission.

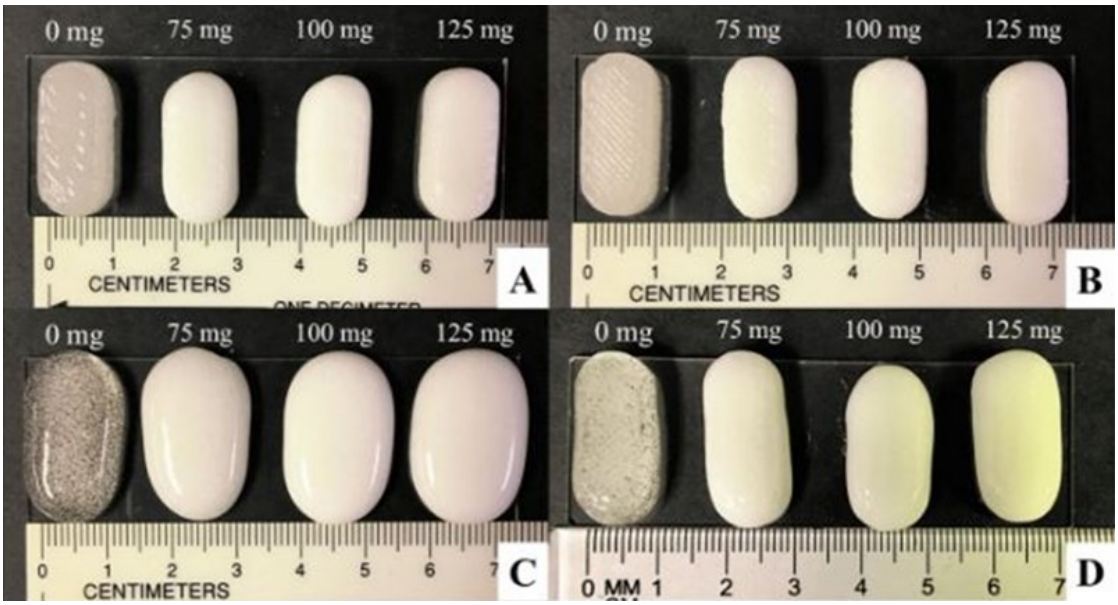

Figure 2. The appearance of printed tablets with different formulas: A) K4M10%, B) K4M12%, C) E4M 10%, and D) E4M 12% (w/w). Reproduced from [41] with permission.

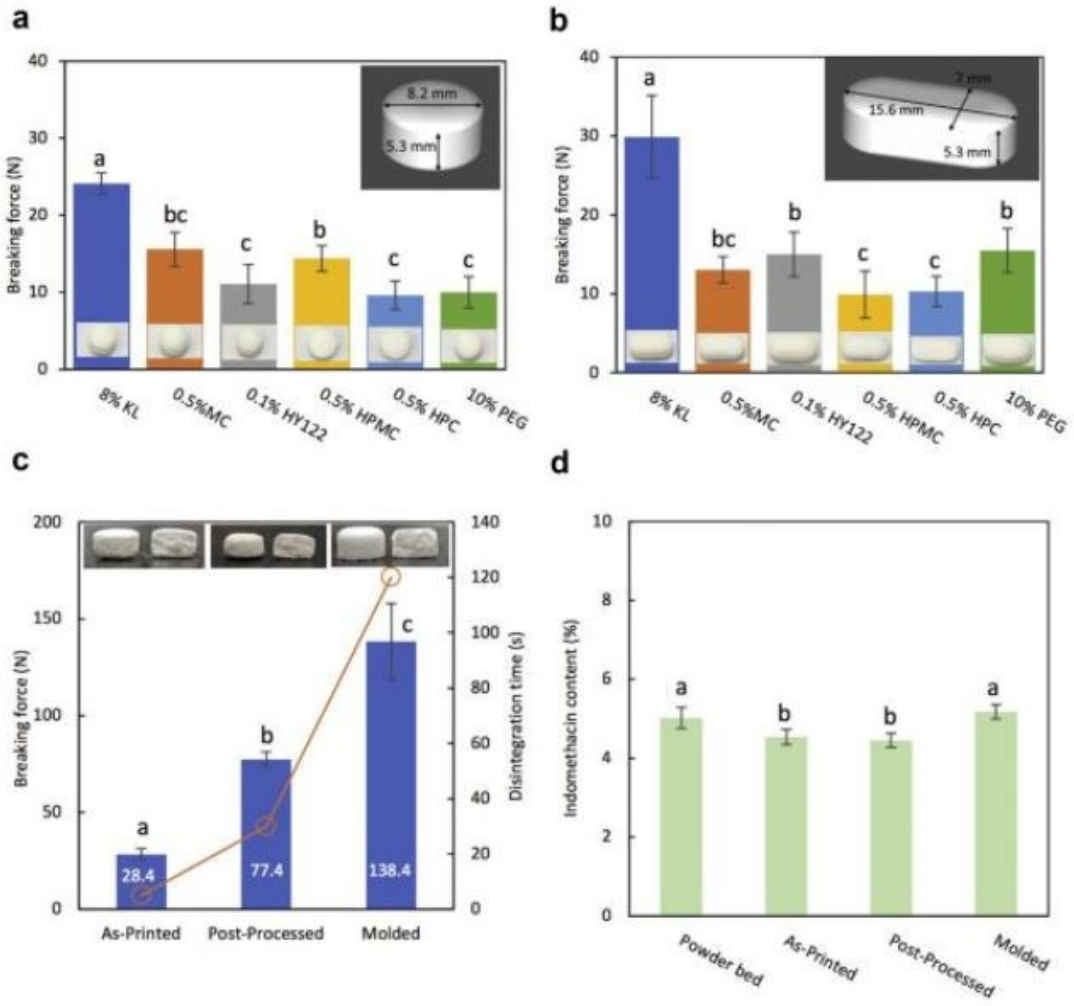

Figure 3. Breaking forces of (a) round and (b) oblong samples printed with 100% LM and different binders. Inset figures (in the top right corner) show the input CAD design models and dimensions. (c) Breaking forces (bars) and disintegration times (circles) of as-printed, post-processed and molded samples containing 85% LM, 10% KL, and 5% Indo. (d) Indomethacin contents in the powder bed, as-printed, post-processed and molded samples. Same letter denotes the data are insignificantly different at $p < 0.05$ according to the oneway ANOVA and LSD test. Reproduced from [45] with permission.

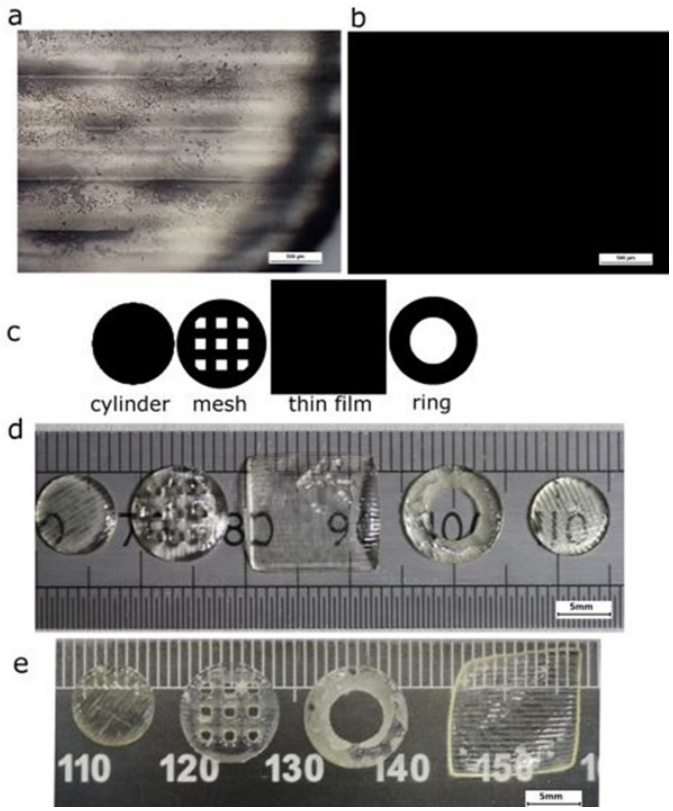

Figure 4. Images of the printed geometries. (a) Optical microscopy (reflection) and (b) cross polarized optical microscopy (transmission) of a cylindrical tablet (c) BMP 2D images used to build the 3D geometries (d) images of dosages printed (top scale in mm) (e) images of the tablets after leaching and drying. The scale is in mm. Reproduced from [56] with permission.

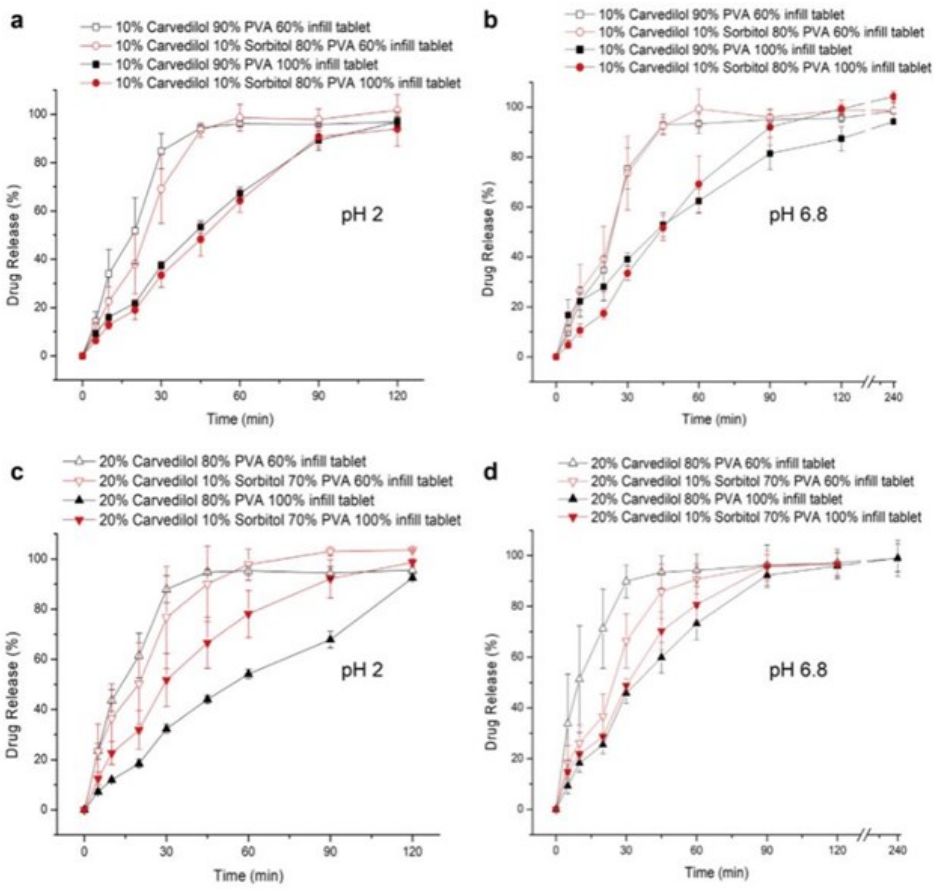

Figure 5. In vitrodrug release profiles of (a) tablets containing carvedilol-PVA and carvedilol-sorbitol-PVA mixtures with 10% carvedilol and both 60% and 100% infills, (b) the sametablets at pH 6.8, (c) tablets containing carvedilol-PVA and carvedilol-sorbitol-PVA mixtures with 20% carvedilol and both 60% and 100% infills at pH 2, and (d) the same tablets atpH 6.8. Each point represents mean±SD of 3 determinations. Reproduced from [63] with permission.

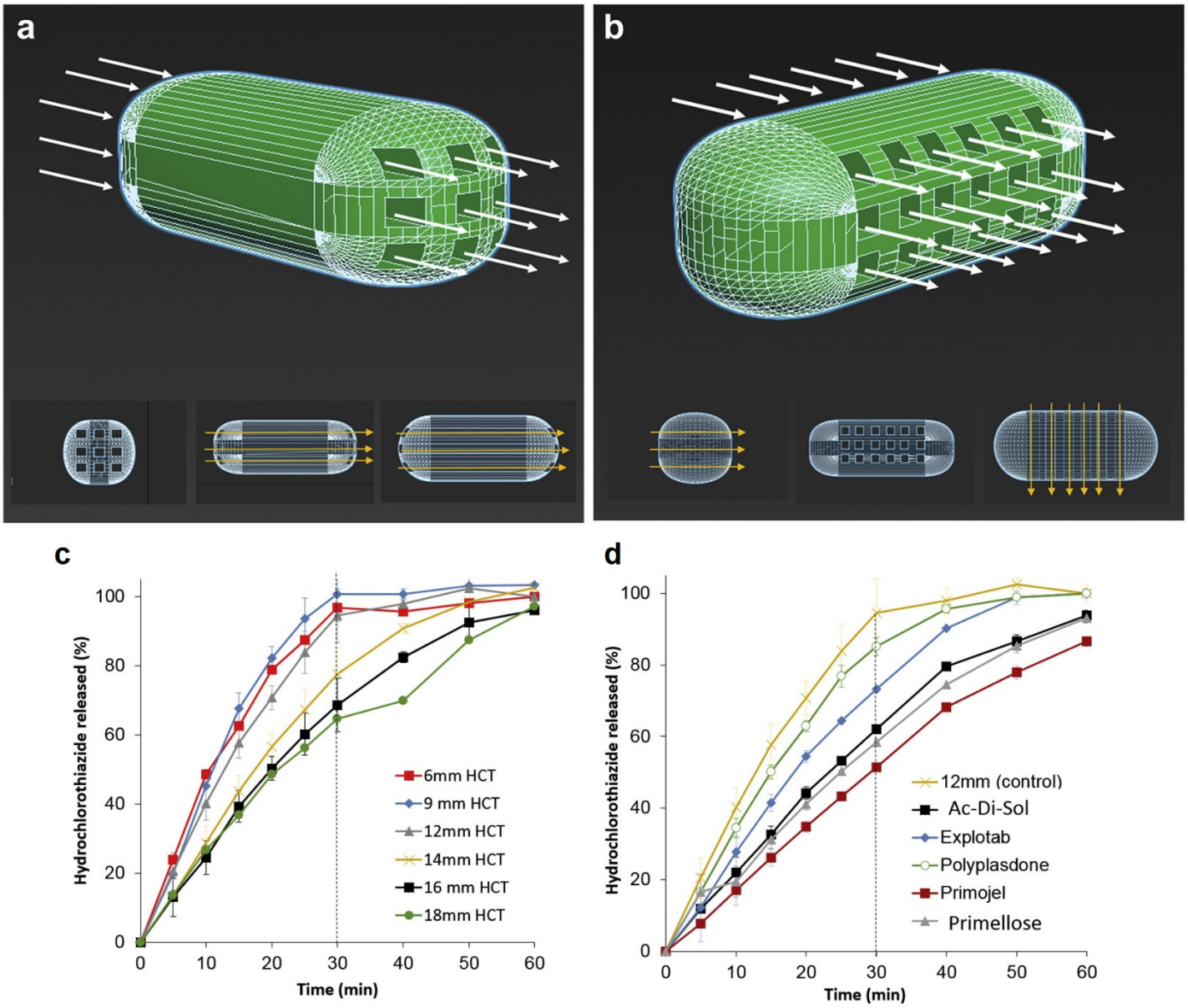

Figure 6. (A) Schematic illustration concept of perforating square sectioned channels in caplet design. The dissolution medium will perforate through the channels and accelerate tablet disintegration and dissolution. The perforating channels were a1) parallel to long axis (9 long channels) or b1) at right angle with the long axis with 3D max rendered images of frontal, side and top view of channelled tablet designs. (B) Impact of caplet dimensions and inclusion of disintegrant on *in vitro* drug release from 3D printed tablets (solid design). C) *In vitro* release of hydrochlorothiazide from different sizes of Eudragit E tablets, the percentages of drug release at $T = 30$ min were considered as functionality outcome, one way ANOVA, $P < 0.05$ (mean ± SD, n = 3), D) *in vitro* release of hydrochlorothiazide from Eudragit E caplets with/without commercially available disintegrants (mean ± SD, n = 3). Reproduced from [67] with permission.

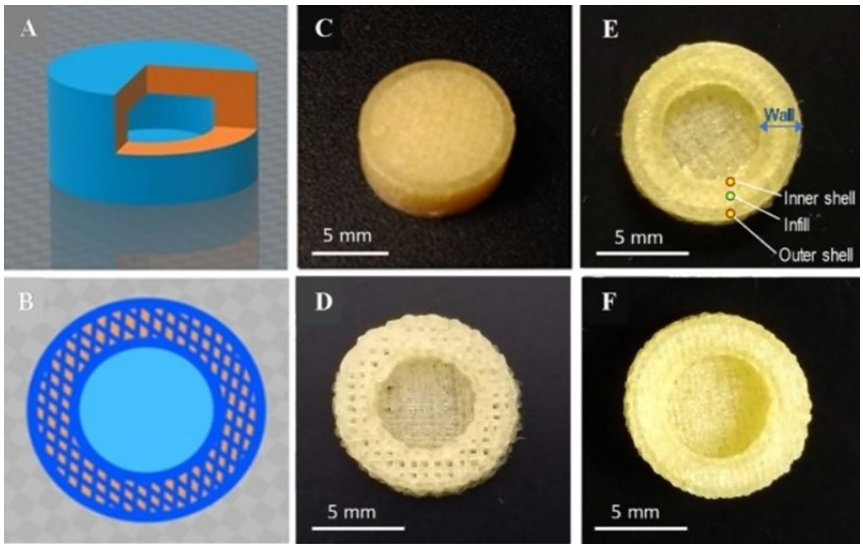

Figure 7. Image of model tablet and printed tablets. A) The hollow tablet model; B) Design of tablet wall structure; C) representative 3D printed tablet (diameter 10.0 mm, height 6.5 mm, wall thickness 2.5 mm); D) horizontal cross section of the tablet with 50 % infill, 0.4 mm shell; E) cross section of the tablet with 80 % infill, 0.8 mm shell; F) cross section of the tablet with 80 % infill, 0.4 mm shell. Reproduced from [71] with permission.