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Long-acting transdermal drug delivery formulations: Current developments and innovative pharmaceutical approaches

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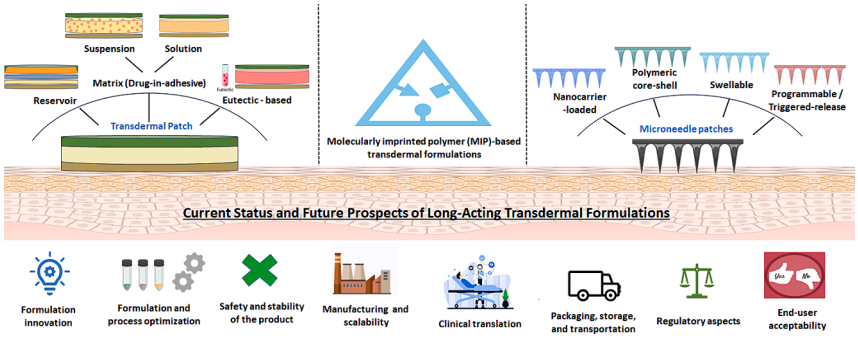
GRAPHICAL ABSTRACT



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ABSTRACT

Transdermal administration remains an active research and development area as an alternative route for long-acting drug delivery. It avoids major drawbacks of conventional oral (gastrointestinal side effects, low drug bioavailability, and need for multiple dosing) or parenteral routes (invasiveness, pain, and psychological stress and bio-hazardous waste generated from needles), thereby increasing patient appeal and compliance. This review focuses on the current state of long-acting transdermal drug delivery, including adhesive patches, microneedles, and molecularly imprinted polymeric systems. Each subsection describes an approach including key considerations in formulation development, design, and process parameters with schematics. An overview of commercially available conventional (adhesive) patches for long-acting drug delivery (longer than 24 h), the reservoir- and matrix-type systems under preclinical evaluation, as well as the advanced transdermal formulations, such as the core-shell, nanoformulations-incorporated and stimuli-responsive microneedles, and 3D-printed and molecularly imprinted polymers that are in development, is also provided. Finally, we elaborated

Abbreviations: TDS, transdermal delivery systems; MNs, microneedles; GI, gastrointestinal; HIV, Human Immunodeficiency Virus; HPMC, Hydroxypropylmethyl cellulose; MIP, molecularly imprinted polymer; DIA, drug-in-adhesive; SIS, styrene–isoprene-styrene; SEBs, Styrene-block-(ethylene-co-butylene)-block-styrene; NPs, nanoparticles; PSA, pressure-sensitive adhesive; PIB, polyisobutylene; Tg, glass transition temperature; PVA, poly-vinyl-alcohol; PLGA, poly-lactic-cogycolic-acid; PVP, polyvinylpyrrolidone; DDS, drug delivery system; PLA, poly (dl- lactic acid); PLLA, poly(l-lactide); FDA, Food and Drug Administration; Abs, antibodies.

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on translational aspects, challenges in patch formulation development, and future directions for the clinical advancement of new long-acting transdermal products.

1. Introduction

Treatment and prevention of diseases may necessitate frequent dosing over long periods, depending on the drug and formulation characteristics [1,2]. Currently, the main routes of drug administration are enteral (oral pills) and parenteral (intramuscular, subcutaneous, or intravenous injections) [3,4]. Oral dosing is the most common route due to simple administration, patient convenience, cost-effectiveness, and ease of large-scale manufacturing; however, the first-pass metabolism and low bioavailability of most drugs necessitate high or multiple daily oral doses to maintain systemic therapeutic levels [5,6]. Thus, this route is typically accompanied by gastrointestinal (GI) side effects and poor adherence due to high pill burden, which reduces the effectiveness of treatment regimens [7–9]. Moreover, oral routes are not suitable for patients suffering from GI diseases or with difficulty in swallowing pills [10]. A parenteral long-acting sustained drug delivery system, providing continuous and controlled release of drugs, reduces administration frequency and GI side effects, while improving PK and patient compliance [1,11]. Parenteral dosing via hypodermic injections, however, is invasive, painful, requires trained medical personnel or patient training (in case of self-injectable systems), and may also result in poor patient compliance [12]. Additionally, injections generate sharp bio-hazardous waste, and pose the risk of disease transmission via needle reuse, especially in low-resource countries [13]. Therefore, there is considerable interest in developing long-acting delivery systems that are minimally-/non-invasive, provide higher drug bioavailability with fewer or no GI side effects, are affordable, and offer better treatment adherence.

Transdermal delivery systems (TDS) can provide a convenient and effective means of long-term systemic and/or local drug delivery for a variety of indications that cannot be achieved with oral or parenteral administration. The transdermal route of drug administration refers to the permeation of drug molecules across the layers of the skin, absorption into the bloodstream from the dermis, and subsequent distribution throughout the body [14]. TDS has the benefit of bypassing the first-pass metabolism and GI side effects from oral dosing to provide continuous delivery of drugs over an extended period [15]. Perhaps the most important advantage of TDS over injectables is that it is a near-painless drug delivery approach and the formulations can be administered by health care providers (HCPs) or potentially self-administered by the end-users with minimal training. Moreover, TDS promotes minimizing fluctuations in drug systemic exposure, leading to improved treatment. These features make TDS particularly advantageous to improve medication adherence, especially in low- and middle-income countries with limited health system resources. Owing to these advantages, and the increasing emphasis on patient convenience and compliance, the market potential for TDS is substantial, and expected to grow greatly in the coming years. Long-acting TDS have the potential to fulfill needs that are unmet by currently approved therapies using oral and injectable formulations. This is especially true for chronic illnesses, which have been on the rise in recent decades and often require adherence to daily medication regimens for a long time. Long-acting TDS, including wearable skin devices offer promising approaches for better management of these diseases with improved adherence and health outcomes [16]. According to the Polaris Market Research report [17], the global TDS market in general is valued at $27.42 billion in 2023 and it is anticipated to generate a revenue of $40.01 billion by 2032. For transdermal microneedles (MNs), a recent analysis by Persistence Market Research shows that the market is expected to reach $10.9 billion by 2033 [18]. Recent regulatory support [19] and significant advancements in the design, development, and safety of long-acting TDS [20–22] further fuel the market potential for such products.

Due to the above drug delivery advantages and market potential, the development of TDS through the skin has gained significant attention in recent years [20–22]. In general, an ideal long-acting TDS should be easy to administer and able to deliver the required therapeutic dose while maintaining a steady flux of drug permeation across the skin for an extended period. The uppermost layer of the skin, the stratum corneum, is a lipidic layer comprising dead skin cells, predominantly keratinocytes, in a tightly packed brick–mortar structure [23]. This layer provides the primary barrier to the passive diffusion of drug molecules and is thereby limited to unionized molecules having a molecular weight (MW) of < 500 Da, a log P of 1–3, and a low melting point [14,24]. Such drugs with an 'ideal' physicochemical profile for passive transdermal delivery can be loaded into traditional adhesive dosage forms. Standard adhesive transdermal patches, which include matrix- and reservoir-types, allow high drug loading and continuous drug delivery over long periods. This is achieved via the steady release of the drug from the TDS layers, direct contact with the stratum corneum (owing to their adhesive properties), and gradual diffusion across the skin layers into dermal microcirculation [25]. However, the poor permeability of certain therapeutic molecules, which do not meet the physicochemical properties described above, hampers the widespread use of adhesive TDS.

To broaden the spectrum of drugs that can be administered transdermally and to overcome the diffusional barrier of the skin, modifications to a drug's physicochemical properties, development of novel transdermal formulations, and physical enhancement technologies have been explored [26]. Microneedles (MNs) are a minimally invasive technique that use micron-sized needles to disrupt the stratum corneum by creating micro-channels in the skin [27,28]. The needle length is designed to avoid reaching nerve endings, thereby providing painless drug delivery. The hydrophilic micro-channels created by MNs not only allow for an enhanced delivery of hydrophilic drugs (small molecules, peptides, proteins, vaccines) [14], but also for hydrophobic molecules by diminishing the physiological skin barriers faced by these compounds. In the last few years, there has been an exponential increase in research related to MNs, especially for long-acting drug delivery applications for indications such as HIV (Human Immunodeficiency Virus), neurological disorders, diabetes, cardiovascular diseases, contraception, and cancer, among others [29,30]. Several types of MNs such as dissolvable, core–shell, stimuli-responsive, and delayed/pulsatile-release formulations have been explored for controlled/extended drug delivery. To widen the applicability of the transdermal route in sustained drug delivery, molecularly imprinted polymers (MIPs) are also being explored. These are new drug delivery materials that are gaining importance for their ability to modulate drug release profiles in a feedback-regulated way and are being investigated for designing TDS [32]. Three-dimensional (3D)-printing technologies such as stereolithography, digital light processing, two-photon polymerization, selective light sintering, fused deposition modeling, and continuous liquid interface production are also being used in transdermal application. The application is primarily for MNs-based patches to generate customized patches tailored to the individual needs of each patient and/or with precise control on drug loading and delivery [33–37], but a few studies also used this technology to generate conventional patches [38,39].

Several reviews have been published in recent years focused on transdermal formulations for long-term drug delivery [40–44]. However, these articles primarily covered the polymeric or hydrogel MNs-based approaches providing little, if any, information on other types of transdermal technologies that have advanced in the field, including reservoir- or matrix-type adhesive patches, nanocarrier-based TDS, eutectic-mixture patches, MIP-based transdermal systems, and novel core–shell type or stimuli-responsive MNs under development for

controlled, programmable long-term drug delivery applications. As the transdermal delivery landscape for controlled/extended drug delivery is evolving rapidly, this review aims to provide a comprehensive overview of advancing technologies for long-acting TDS, including their design, fabrication approaches, and formulation-development strategies. In addition, this paper also summarizes currently marketed and traditional adhesive patches, and the evolution of those over time for controlled drug delivery. As the focus of this review is long-acting transdermal formulation strategies, we have concentrated on the studies with a drug delivery duration of > 24 h from adhesive patches and > 3 days from MN patches. The current progress, clinical development, and potential future application of new long-acting TDS, including the formulation types, along with their advantages and drawbacks, are also discussed. Though transdermal technology provides many advantages compared to oral or injectable formulations, it does not come without challenges. Hence, obstacles associated with the transdermal formulation development, characterization, and clinical translation, are also covered in this review.

2. Adhesive transdermal patches for controlled drug delivery

Adhesive patches provide a prescribed dose of therapeutics that is absorbed through the skin and into systemic circulation over an extended period [20]. These are considered drug-device combination products, and have been historically divided into two types – reservoir and matrix, based on their design. Currently, 13 patches on the US market (all of which are matrix-type) are for sustained drug delivery from 24 h to a week as summarized in Table 1. As mentioned earlier, drugs with ideal physicochemical properties (e.g., MW of < 500 Da, log P of 1–3) are most suitable for conventional adhesive transdermal patches [14,24], but chemical penetration enhancers can be incorporated to increase the permeation flux of drug molecules that have low skin permeability. In addition, to facilitate sustained drug release, researchers have explored various types of adhesive polymers (such as acrylates, polyisobutylene, and silicones), and the effect of their functional groups on the drug release kinetics. They have also investigated the use of ion-ion pairs/eutectic mixtures in patch formulations. These eutectics mixtures are especially beneficial when the drug molecules have low solubility in the polymer adhesives. The following sections review the formulation strategies under preclinical development that are reported thus far (summary in Table 2 **and** Table 3 for reservoir and matrix patches, respectively) for sustained transdermal delivery (>24 h). Fig. 1 provides a schematic for the design of different types of transdermal patches that are discussed in detail in the following sections.

2.1. Reservoir patches

A reservoir-type TDS consists of a gel-based drug reservoir heat-sealed between a backing membrane and a semipermeable, rate-controlling membrane [20]. The rate-controlling membrane is followed by an adhesive layer and a release liner (Fig. 1). The adhesive layer ensures intimate contact of the patch with the skin's surface, whereas the rate-controlling membrane maintains the desired flux profile across the skin. The drug reservoir gel consists of viscosity-enhancing agents (hydrophilic polymers such as Eudragit®, Carbopol, etc.), in a hydro-alcoholic solvent system. A drug reservoir of hydroxypropyl methylcellulose (HPMC: 2 % w/w), with a synergistic combination of permeation enhancers (2.5 % w/v each of menthol and oleic acid) was used to deliver imipramine hydrochloride [46]. *In vivo* permeation studies showed that the steady state plasma concentration was reached at 8 h, followed by sustained release up to 30 h. Histopathological studies were conducted to evaluate inflammation from the transdermal patch application with or without the drug. There was no significant change in microscopic findings observed, except slight inflammatory responses (cell infiltration) after the application of drug-loaded patches. Another such study compared a reservoir (Eudragit®S100 and colloidal silicon dioxide) system and matrix-type (acrylate, silicone, and polyisobutylene) patches of raloxifene. Here, the gel-based drug reservoir demonstrated sustained drug delivery over 7 days, using oleic acid (10 % w/v) as the penetration enhancer [47].

To achieve sustained drug delivery, researchers have also incorporated nano/micro or lipidic carriers within the reservoir matrix. Incorporation of novel biphasic lipidic vesicles containing insulin has been described using a reservoir patch. A comparison in diabetes-induced rats showed depot formation of insulin that facilitated sustained delivery to

Table 1
Commercially available transdermal patches for sustained drug release for longer than 24 h.

Drug (product name)	Indication	Frequency of application	Type of adhesive	Company	Approval year
Estradiol and Norethindrone Acetate [167] (Combipatch)	Management of symptoms of menopause	Twice weekly	Mixture of acrylate and silicone	Noven Therapeutics, LLC.	1998
Estradiol[168] (Climara)	Management of symptoms of menopause	Once weekly	Acrylate	Bayer Healthcare Pharma., Inc.	1999
Estradiol[169] (Vivelle Dot)	Moderate-severe menopausal changes	Twice weekly	Mixture of acrylate and silicone	Novartis Pharma., Corp.	1999
Estradiol and Levonorgestrel[170] (Climara Pro)	Management of symptoms of menopause	Once weekly	Acrylate	Bayer Healthcare Pharma., Inc.	2003
Oxybutynin[171,172] (Oxytrol)	Overactive bladder treatment	Twice weekly	Acrylate	Allergan, Inc.	2003
Estradiol[173] (Menostar)	Prevention of osteoporosis	Once weekly	Acrylate	Bayer Healthcare Pharma., Inc.	2004
Granisetron[174] (Sancuso)	Chemotherapy-induced nausea and vomiting	Once weekly	Acrylate- vinylacetate copolymer	Kyowa Kirin Inc.	2008
Buprenorphine[175] (Butrans)	Management of chronic pain	Once weekly	Polyacrylate cross-linked with aluminum	Purdue Pharma	2011
Estradiol[176] (Minivelle)	Management of symptoms of menopause	Twice weekly	Mixture of acrylate and silicone	Noven Therapeutics, LLC.	2012
Scopalamine[177] (Transderm-Scop)	Motion sickness and postoperative nausea and vomiting	Once every 3 days	Polyisobutylene (PIB)	Baxter Healthcare Corp.	2016
Ethinyl Estradiol; Levonorgestrel [178] (Twirla)	Contraception	Once weekly	Mixture of acrylate and PIB	Agile Therapeutics, Inc.	2020
Clonidine[179] (Catapres-TTS)	Hypertension	Once weekly	PIB	Boehringer Ingelheim/ Technomed Inc.	2022
Donepezil hydrochloride[180] (Adlarity)	Alzheimer's Disease	Once weekly	Acrylate	Corium, Inc.	2022

Table 2
Summary of current literature on long-acting reservoir-type transdermal patches.

Type of patch	Drug	Indication	Duration of action (model)	Reservoir	Patch specifics	Permeation enhancer
Gel-based	Imipramine hydrochloride [46]	Depression	*In vivo* delivery up to 30 h (Sprague – Dawley rats)	HPMC (Methocel K4 M)	Release liner (Scotchpak™1022); Porous membrane (CoTran™ 9711); Backing membrane (Scotchpak™ 1009)	2.5 % (w/v) menthol and 2.5 % (w/v) oleic acid
	Raloxifene[47]	Breast cancer prevention	*In vitro* delivery up to 7 days (dermatomed human and porcine skin)	Eudragit®S100 and colloidal silicone dioxide	Release liner (Scotchpak™ 1022) and backing membrane (CoTran™ 9707)	8.63 % (w/w) and 9.1 % (w/w) oleic acid
Drug powder-based	Zidovudine[52]	HIV/AIDS	*In vivo* delivery up to 7 days (BALB/c mice)	Lyophilized powder of drug + mannitol	Sterile cylindrical containers (diameter 8 mm and depth 5 mm)	–
Lipidic vesicles-loaded	Insulin[48,49]	Diabetes	*In vivo* delivery up to 73 h (Sprague – Dawley rats)	Biphasic vesicles in a reservoir	Biphasic vesicles Phase I: soya phosphatidylcholine, cholesterol, propylene glycol and N¬-capryloyl-Ne-lauroyl L-lysine ethyl ester Phase II: linoleamidopropyl-PG-d imonium chloride phosphate and olive oil	–
	Paroxetine[50]	Depression	*In vivo* delivery up to 48 h (New Zealand rabbits)	Liposomes of drug in HPMC-E4M reservoir	Liposomes: lecithin phosphatidylcholine and cholesterol	
Nanoparticle-loaded	Repaglinide[51]	Type-2 diabetes	*In vivo* delivery up to 60 h (Wister rats)	Polymeric nanoparticles of drug in Methocel	Nanoparticles: poly-lactic acid, polycaprolactone, and poloxamer 407	10 % (w/w) polyethylene glycol and 1 % dimethyl siloxane

the lymph nodes [48,49]. In a similar study, paroxetine-loaded lipid vesicles were formulated and loaded in HPMC gel to make the reservoir patch for controlled drug release over 2 days in rabbits [50]. The *in vivo* drug bioavailability from the patch was also compared with the oral administration of the marketed paroxetine tablet. The skin irritation study confirmed no noticeable irritation or inflammation during the period of study or after the removal of the patch. Similarly, repaglinide-loaded polymeric nanoparticles (NPs) using poly(D,L-lactide) (PLA), polycaprolactone, poloxamer 407, and chitosan, were loaded in a hydrophilic Methocel K100M reservoir. This study showed steady delivery of repaglinide over 5 days and a sustained hypoglycemic effect *in vivo* in diabetic rats [51].

Traditionally, the reservoir is present in a semi-solid form and most commonly as a gel formulation. In the study by Kakar et al., an ablative fractional laser (AFL) method was introduced to enable week-long sustained transdermal delivery of powder hydrophilic drugs, namely sulforhodamine b, zidovudine, and bovine serum albumin [52] They described a mechanism where the evaporation of water from these micro-channels slowly dissolves the drug cargo to achieve sustained delivery. The cylindrical reservoir patches were able to hold up to 70 mg of drug per 0.5 cm^2 of reservoir patch. Hence, 3-day to a week-long sustained delivery was obtained by this design of a laser-assisted powder reservoir patch [52].

The transdermal formulations specific to the above studies of reservoir patches have been included in Table 2.

2.2. Matrix patches

A matrix-type TDS, commonly known as a drug-in-adhesive (DIA) system, consists of an adhesive matrix sandwiched between a backing membrane and a release liner formulation [20]. Apart from these three fundamental layers, additional layers may be added to aid with the desired drug release profile and the overall performance of the formulation [20]. The adhesive-matrix layer comprises a pressure-sensitive adhesive (PSA), along with the drug, chemical enhancers, viscosity-building agents, plasticizers, and preservatives. The constituents of the adhesive layer can be dissolved or suspended in the PSA to form a homogeneous or heterogeneous adhesive layer, respectively [45]. Thus, the matrix system has a drug layer of a semisolid polymer matrix containing a drug solution or suspension. The matrix-type patch is layered using the solvent casting method. The polymers/PSAs explored for the preparation of matrix-type patches include polyacrylate copolymers (acrylates), polysiloxanes (silicones), polyisobutylene (PIB), styrene–isoprene-styrene (SIS), Styrene-block-(ethylene-co-butylene)-block-styrene (SEBs), and others [53–55]. Acrylate polymers are further classified based on their functionality into carboxyl (–COOH), hydroxyl (–OH), ester (−COOR), and so on. The choice of polymer and its functionality can significantly affect the patch characteristics and overall performance of the patch [56]. Similarly, the choice of excipients and their interaction with the drug influence the drug release and permeation profile. Accordingly, matrix-based TDS and their types that are explored for > 24 h of drug delivery have been reviewed in the following section and summarized in Table 3.

2.2.1. Solution and suspension patches

In the case of a homogeneous matrix patch, the entire drug cargo is soluble in the PSA matrix (solution patch), whereas, for a heterogeneous matrix patch, the drug is partially suspended in the PSA (suspension patch). It is known that only the solubilized form of the drug is capable of permeating into and across the skin [57]. Hence, in the solution-type matrix patch, the amount of solubilized drug is maximum at the point of application and decreases as the drug permeates through the skin. In a suspension-type matrix patch, the majority of the drug is uniformly suspended throughout the adhesive layer. As the solubilized portion of the drug permeates through the skin, part of the suspended drug continually gets solubilized in the adhesive matrix, thereby maintaining a state of saturation in the adhesive layer [57]. This approach is adopted to achieve a high drug loading of poorly soluble drugs in the PSA.

2.2.1.1. Acrylate PSAs-based patches. Various types of acrylate PSAs differ in functional groups, viscosity, performance properties (sheer, tack, peel resistance), and presence/absence of vinyl acetate and cross-linkers [58]. The type of acrylate polymer and its compatibility with the drug can have a distinct effect on the release and permeation of the drug through the skin. Many researchers have compared the performance of TDS fabricated from a variety of acrylate polymers. A DIA patch of s-amlodipine besylate (hydrophilic salt) was compared with the s-amlodipine free base in 87–2677, 87–4098, and 87–9301 acrylates for the sustained drug delivery over 3 days [59]. Acrylate 87–9301 had superior transdermal permeation in combination with free base, owing to its

Table 3
Summary of current literature on long-acting matrix-type transdermal patches.

Type of patch	Drug	Indication	Duration of action (model)	Polymer/Adhesive/Formulation specifics
Matrix-based patch	Olanzapine[31]	Schizophrenia and bipolar disorder	*In vitro* delivery up to 3 days (human cadaver skin and porcine ear skin)	Acrylate PSA (DURO-TAK® 87–2516), Silicone, and PIB
	Azasetron[56]	Chemotherapy-induced nausea and vomiting	*In vivo* delivery up to 9 days (Bama miniature pigs)	Acrylate PSA (DURO-TAK® 87–9301, 87–2852, and 87–2677)
	Tranylcypromine[57]	Depression	*In vitro* delivery up to 48 h (porcine ear skin)	Acrylate PSA (DURO-TAK® 87–2516), and PIB
	S-Amlodipine[59]	Hypertension	*In vivo* delivery up to 3 days (Wister rats)	Acrylate PSA (DURO-TAK® 87–2677, 87–4098, and 87–9301)
	Letrozole[60]	Breast cancer	*In vivo* delivery up to 7 days (Wister rats)	Acrylate PSA (DURO-TAK® 87–4098, 87–2852, and 87–2677)
	Fluoxetine[61]	Depression	*In vivo* delivery up to 36 h (Sprague – Dawley rats)	Acrylate PSA (DURO-TAK® 87–2852, 87-900A, 87–2510, and 87-502B) and PIB
	Ibuprofen, Ketoprofen, Loxoprofen, Naproxen, Diflunisal, Suprofen, Flurbiprofen, Etodolac, Zaltoprofen, and Diclofenac[62]	Pain management	*In vivo* delivery up to 48 h (Wistar rats)	–COOH polyacrylate polymer (synthesized by the authors)
	Palonosetron[63]	Chemotherapy-induced nausea and vomiting	*In vivo* delivery up to 3 days (rabbits)	Acrylate PSA (DURO-TAK® 87–4098, 87–2677, and 87–2516)
	Oxybutynin[64]	Overactive bladder	*In vivo* delivery up to 3 days (Wistar rats)	Acrylate with $CONH_2$ group (synthesized by the authors), Acrylate PSA (DURO-TAK® 87–2287, 87–2852, and 87–4098)
	Levonorgestrel[69]	Contraception	*In vitro* delivery up to 7 days (full-thickness porcine skin)	Acrylate PSA (Duro-TAK® 2516) and silicone PSA (Bio-PSA)
	Captopril[69]	Hypertension	*In vitro* delivery up to 7 days (hairless rat skin)	Acrylate PSA (Duro-TAK® 2516) and silicone PSA (Bio-PSA)
	Physostigmine[70]	Antimuscarinic toxicity and glaucoma	*In vitro* delivery up to 48 h (hairless mice skin)	Silicone, PIB, Styrene–Isoprene–Styrene (SIS), Acrylic, and Styrene–Butadiene–Styrene (SBS) adhesives
	4-Benzylpiperidine[71]	Cocaine dependence	*In vitro* delivery up to 48 h (human cadaver skin)	Acrylate PSA (DURO-TAK® 87–2287 and 87–2516), Silicone, and PIB
	Tenofovir alafenamide[72]	HIV and Hepatitis B	*In vitro* delivery up to 7 days (human cadaver skin)	Acrylate PSA (DURO-TAK® 87–2516), Silicone, and PIB
	Tenofovir alafenamide[73]	HIV and Hepatitis B	*In vivo* delivery up to 7 days (hairless rats)	Silicone Bio-PSA 7–4301
	Lidocaine[74]	Pain management	*In vitro* delivery up to 3 days (porcine ear skin)	Acrylate PSA (DURO-TAK® 87–2287), Silicone, and PIB
	Escitalopram[80]	Depression and Anxiety	*In vivo* delivery up to 3 days (Wistar rats)	Acrylate PSA (DURO-TAK® (87–4098, 87–2677, 87–2852, and 87–2287)
	Rotigotine[81]	Parkinson's Disease	*In vivo* delivery up to 48 h (Wistar rats)	Acrylate PSA (DURO-TAK® 87–2287, 87–2852, and 87–2677)
	Rivastigmine[82]	Alzheimer's Disease	*In vivo* delivery up to 3 days (rabbits)	Acrylate PSA (DURO-TAK® 87–4098)
	Tizanidine[83]	Muscle spasticity	*In vivo* delivery up to 48 h (Wistar rats)	Acrylate with $CONH_2$ group (synthesized by the authors), Acrylate PSA (DURO-TAK® 87–2287, 87–2510, and 87–4098)
Ion-ion pair-based matrix patches	Gliclazide[84]	Type-2 diabetes	*In vivo* delivery up to 3 days (Goto-Kakizaki rats)	Acrylate PSA (DURO-TAK® 87–4098)

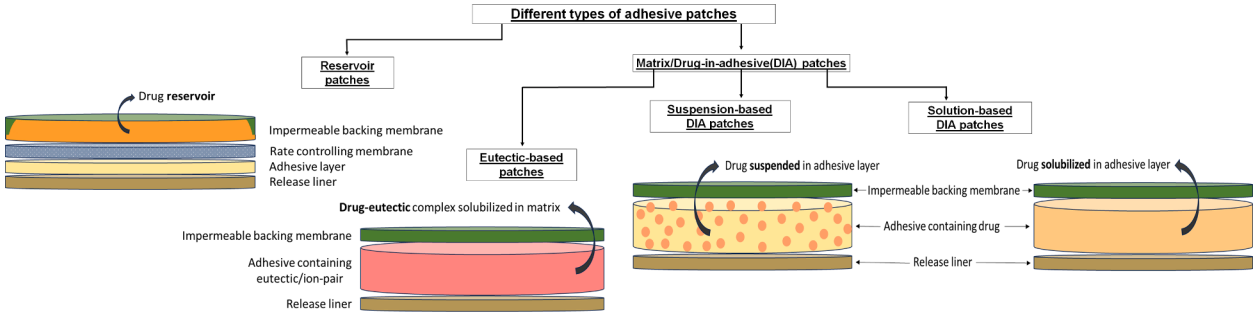

Fig. 1. Schematic for the design of different types of adhesive-based transdermal patches.

higher lipophilicity and lower melting point. Authors found that 87–4098 showed sustained release of letrozole over 7 days with an absolute bioavailability of 53.5 % [60]. Similarly, comparing three polymers (87–9301, 87–2852, and 87–2677), the –COOH-based acrylate polymers (87–2852 and 87–2677) showed significant interaction with the six hydrogen bond acceptors of drug molecule – azasetron, thereby retarding permeation [56]. The 87–9301 polymer had the highest permeation up to 9 days with an absolute bioavailability of 60.8 %. Along similar lines, four acrylates (87–2852, 87-900A, 87–2510, and 87-502B) and PIB were compared to design a sustained delivery DIA patch of fluoxetine [61]. The 87-502B –OH group PSA had the highest skin flux, whereas the carboxyl PSA 87–2852 had the lowest skin flux owing

to its interactions with the amine group of fluoxetine. In contrast to this, a study discussed the synthesis of a carboxyl acrylate polymer that showed better release than acrylates with no functional group for permeation of ten non-steroidal anti-inflammatory drugs over 2 days [62]. Together, these studies show that a 'one size fits all' approach cannot be adopted when choosing a PSA adhesive.

Consideration of the interaction of polymer's moieties with the drug is crucial in modulating the drug release and developing a long-acting TDS. In line with this, a few recent studies have delved deeper into the factors governing polymer behavior related to drug release. Upon testing different acrylates, the two main factors affecting drug release were found to be drug-PSA interaction and the thermodynamic activity of the PSA itself [63]. The high delivery from 87 to 2516 (having –OH group) was attributed to lower glass transition temperature (Tg) – hence higher free volume flow within the polymer, as compared to 87–4098 (no functional group), 87–2677 (–COOH group). The effect of molecular mobility through the comparison of three acrylates with amino/–OH/–COOH groups was further explained [56,64]. Molecular dynamic simulation and thermal analysis revealed interactions between Span® 80 (used as a chemical enhancer) and the AA-$CONH_2$ PSA, which led to reduced cohesive forces (lower Tg) among the PSA chains and an improved release of oxybutynin [64]. This confirmed that a low Tg of PSA polymer is desirable because it aids molecular mobility, thermodynamic activity, and drug release from the PSA.

The interaction between the drug and PSA shows a double-edged effect where a higher interaction can significantly improve drug loading and hence aid permeation but can also retard drug release below the desired level. Hence, a thorough consideration of these aspects is necessary while developing a TDS for sustained release. Techniques such as Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FT-IR), X-ray Photoelectron Spectroscopy (XPS), and molecular dynamic simulation have been fundamental in studying the interaction of adhesives, penetration enhancers, excipients, and drug molecules with one another [62,65–68].

In solution patches, the drug loading is limited by the drug's solubility in the polymer adhesive. Moreover, metamorphosis makes solution patches prone to long-term stability issues such as drug crystallization. Crystallization inhibitors can be incorporated to prevent such instability as well as improve the drug loading. The potential of copovidone, polyvinylpyrrolidone (PVP), and poloxamer as crystallization inhibitors has been explored for model drugs captopril (logP 1.9) and levonorgestrel (logP 3.8) in acrylate and silicone-based PSAs [69]. PVP was able to increase the saturation solubility of captopril in acrylate PSA, whereas no appreciable improvement in solubility or permeation was observed for levonorgestrel, signifying that a drug's physicochemical properties greatly influence the effectiveness of crystallization inhibitors and solubility in the PSA.

2.2.1.2. Silicone and PIB-based patches in comparison with acrylates. Along with considerable attention given to acrylate polymers, researchers have examined and compared PIB and silicone adhesives with acrylates. Recently, a suspension-based TDS of tranylcypromine was developed using acrylate DURO-TAK® 87–2516 and PIB polymers, to obtain sustained delivery over 2 days [57]. The permeation of physostigmine was compared from matrix patches of silicone, PIB, SIS, acrylic, and SEBs [70]. Upon formulation of 10 % physostigmine patches, silicone and PIB formed suspension patches, whereas the rest formed solution patches. Sustained transdermal delivery over 2 days was highest from silicone, followed by PIB, and was attributed to the higher thermodynamic activity offered by the suspension patch, similar to the results reported in earlier studies [69]. In another study, a 4-benzyl piperidine PIB patch demonstrated higher and sustained delivery for 2 days as compared to other polymers [71]. In related studies, a week-long sustained delivery of tenofovir alafenamide was achieved from a silicone matrix patch [72,73]. Among the three adhesive types (acrylate, silicone, and PIB), acrylate had the highest solubility (2 % w/w), but the resultant solution patch demonstrated insufficient flux across the skin. Optimized suspension patches were developed using silicone and PIB, where the silicone patch gave the best performance *in vitro*; the patch was successfully tested *in vivo* in rats [73]. In a comparison of three solution patches, a much higher solubility of lidocaine in acrylate (25 %) led to higher permeation as compared to PIB (3.5 %) and silicone (2.5 %) [74]. Interestingly, the silicone-based patch showed the lowest lag time (hence the fastest permeation across the skin) despite having the least drug loading. This corroborated the importance of drug release from the PSA matrix, which proved to be higher in silicone as compared to PIB and acrylate. Another study reported the development of a 3-day TDS of olanzapine while comparing solution and suspension patches, where only the PIB suspension patch was able to cross the desired target permeation [31].

The above studies indicated that acrylate adhesives often exhibit higher solubility of drugs but do not necessarily provide efficient drug release, owing to low drug activity and poor distribution within the matrix. This may be attributed to the ester functional groups involved as well as high lipophilicity. As seen in the EXELON® patch, which is composed of four layers, the addition of a silicone adhesive layer to the drug-incorporated acrylate matrix supported the patch adhesion to the skin and increased the drug activity in the acrylate layer [75]. Although PIB and silicone are less explored for designing long-acting TDS, the aforementioned experiments provide encouraging results, confirming that further studies are required to understand the mechanism behind efficient drug release from PIB and silicone polymers.

2.2.2. Eutectic-based patches

In the literature, certain excipients have been reported to interact with the drug via strong electrostatic or hydrogen bonding to form an eutectic, also known as a 'deep eutectic' or an 'ion-pair' [76]. These novel entities are predominantly utilized in separation and extraction technology [77,78], but in recent years, substantial research has been conducted involving the use of eutectics in topical and transdermal drug delivery. The concept involves mixing two components in a fixed ratio such that the mixture is a homogenous liquid at room temperature with a melting point lower than either of its constituents. The formation of eutectics/ion-pairs allows for modification to the apparent physicochemical properties of the drug, such as the melting point and partition coefficient, which can significantly improve transdermal permeation. The incorporation of ion-pairs in TDS has been reported to aid in the modulation of drug release profiles to facilitate sustained delivery [79].

Organic acids are the most common compounds investigated for the formulation of drug-based eutectics. Escitalopram was paired with five different organic acids and *in vitro* permeation studies revealed that escitalopram-benzoic acid ion-pair had the highest flux across the skin over 3 days [80]. Escitalopram-benzoic acid was further incorporated into PSAs with different functionalities to observe the effect on the patch performance. Acrylate PSA with –OH functionality showed the highest *in vivo* delivery. Another study also reported that –OH-functionalized acrylate PSA showed the highest delivery of an eutectic ion-pair consisting of rotigotine and lactic acid [81]. The incorporation of rotigotine-lactic acid led to an enhanced drug loading from 13 % (free base) to 25 %, increasing drug-polymer miscibility and reducing the required patch size. *In vivo*, the optimized patch (6 cm^2) had an area under the curve comparable to the commercial patch product (8 cm^2) of rotigotine – Neupro™ over a 2-day study duration. The authors reported increased hydrophilicity of rotigotine-eutectic, leading to better stratum corneum-epidermis partitioning. DSC and rheology studies demonstrated an increased thermodynamic activity of rotigotine-eutectic in the PSA, leading to a lower risk of crystallization, higher molecular mobility, and enhanced skin permeation. In another study, salicylic acid was used as a counter ion for rivastigmine to formulate a –OH-based acrylate PSA patch [82]. The *in vivo* permeation studies showed that control patches (marketed Exelon® patch and other rivastigmine free base patches)

exhibited dose exhaustion followed by a decline in flux, whereas the formulated rivastigmine-salicylic acid patch showed sustained release up to 3 days. In all these studies, the –OH-functionalized PSAs showed the optimum drug release characteristics, which can be attributed to their ability to form hydrogen bonds with the drug and chemical enhancer, resulting in increased drug loading and sustained drug release.

Instead of using organic acids, various fatty acids were explored to form an ion-pair with tizanidine [83]. They observed that caproic acid showed the highest transdermal delivery as well as the best enhancement in tizanidine solubility in the PSA (5 %) – 16-fold of tizanidine-free base. The FTIR and thermal analysis showed that the hydrogen bonding within tizanidine-caproic acid and the ester-functionalized PSA led to better drug miscibility and matrix mobility. A controlled and sustained drug release of tizanidine was observed from *in vivo* studies over 2 days. These ion-pairs are predominantly based on hydrogen bonding interactions. Similarly, electrostatic interactions between charged species can also be designed into ion-pairs for incorporation in TDS. A gliclazide-based ionic liquid TDS has been reported, where the gliclazide sodium salt was first prepared and then paired with tributyl (tetradecyl)phosphonium chloride[84]. The gliclazide ionic liquid possessed higher lipophilicity than gliclazide, facilitating the drug's passage across the stratum corneum. The *in vivo* studies in rats demonstrated a sustained release of gliclazide over 3 days with a relative bioavailability of 92 % as compared to oral suspension. Histopathology confirmed no irritation at the site of patch application.

Overall, the adhesive (reservoir- and matrix-types) patches are simple formulations and can be designed for extended drug release from several hours to days. However, for longer-term drug release applications, the challenges with these adhesive patches are limited drug delivery duration and several design factors, such as excipient type and interactions amongst the drug, excipients, and skin that can potentially affect drug delivery. The invention of microneedle (MN)-based transdermal patches has solved some of these issues, with the potential for controlled/extended drug delivery for months. These benefits have resulted in significant research efforts into the development of MN patches for long-acting drug delivery applications as discussed below.

3. Transdermal MNs for controlled/extended drug delivery

MNs-based formulations have emerged as an attractive platform to provide long-acting drug delivery of small or macromolecules through transdermal administration. Various review articles have provided a detailed description of MNs fabrication, their types and use for transdermal drug delivery [40,85]. The MN patches are applied in a minimally invasive manner, typically removed within a few minutes, penetrating the skin's upper layers or mucosal tissues to provide systemic drug delivery for a longer duration. Since these formulations deliver drugs to the epidermis or upper dermis, they avoid the pain receptors found in the lower dermis and allow minimally invasive drug delivery. The types of MNs (Fig. 2) primarily investigated so far include solid, hollow, coated, dissolving, core–shell, swelling, and bio-inspired [27,41,85,86].

Briefly, solid MNs are usually made of metal or water-insoluble materials; these are primarily used to create micro-channels in the skin, followed by the application of a suitable formulation (solution/semi-solid or patch) to facilitate and enhance drug delivery preferably for hydrophilic drugs [27]. Hollow MNs are designed with holes at their tips and have empty space inside, which is filled with the drug solution or dispersion. Hollow MNs are mostly used to deliver large quantities of a drug (non-potent) and the delivery is modulated based on drug flow rate and release pressure [85]. Coated MNs, as the name suggests, traditionally use solid MNs with a coating made of a potent drug molecule/vaccine, which is released upon insertion of the MNs into the skin and is useful when the drug is potent [87]. Dissolving MNs comprise biodegradable, biocompatible water-soluble polymers, which dissolve within minutes upon insertion into the skin and release the drug cargo [27]. Swelling MNs are usually composed of swellable polymers, which, upon insertion into the skin, take up the interstitial fluid and swell, leading to sustained release of the drug from the MNs array [41]. Nanocarrier-loaded MNs are the type where the drug is incorporated in them and these nanocarriers are then loaded in the MNs polymeric matrix. With nanocarriers, there is the possibility of incorporating even hydrophobic drugs with low passive permeation. The MNs can also be used for microporating the skin to create micro-channels where the desired drug formulation is then applied on top of the microporated skin. This way of administration is thus referred to as "poke and formulation" or "poke and patch" (Fig. 3).

As shown in Fig. 3, the "poke and formulation" or "poke and patch" approaches use a 2-step administration where a) first, MNs (solid or polymeric) without any drug are used to microporate the skin, and then b) the desired drug formulation (drug solution/dispersion/semi-solid formulation) or drug patch is applied on the microporated skin. In contrast, if a drug is incorporated within the MNs, those are typically referred to as drug-loaded MNs. As the drug is present within the MNs, the drug-loaded MNs follow one-step process where once the MNs are

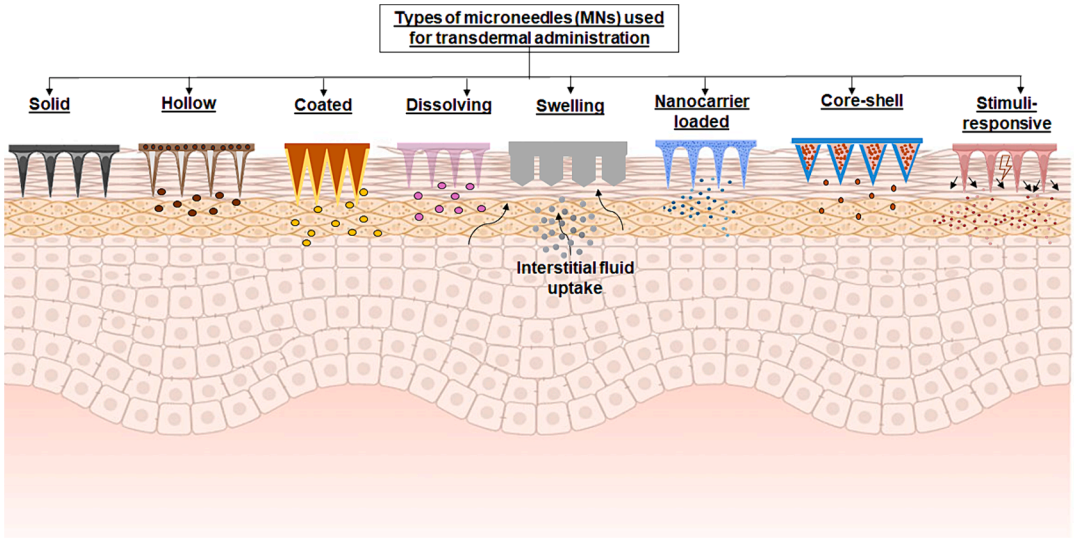

Fig. 2. Schematic for the design of different types of microneedles (MNs) for transdermal controlled drug delivery.

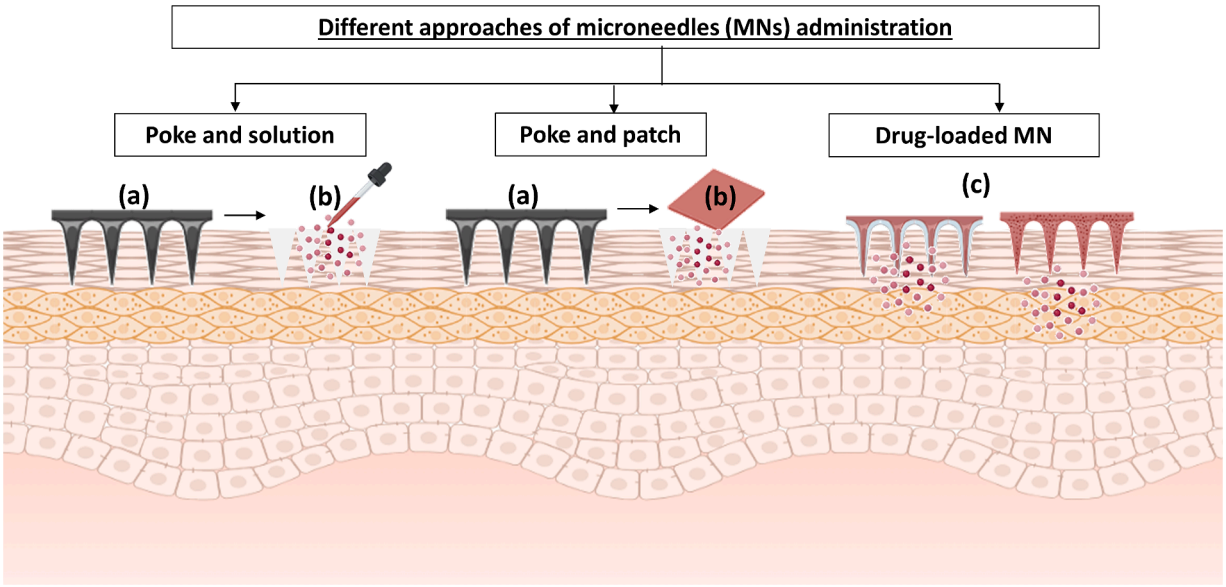

Fig. 3. Different approaches for transdermal microneedles (MNs) administration. (a)"poke and formulation approach where first MNs (solid or polymeric) without any drug is used to microporate skin and then b) the desired drug formulation (drug solution/dispersion/semi-solid formulation) or drug patch is applied on the microporated skin. The approach (c) is with the regular drug-loaded MNs formulation for direct administration on the skin.

inserted in the skin, the drug is released as the MNs dissolve [88]. Drug loading can be achieved in various ways including dissolving the drug in the polymer matrix, incorporating drug-loaded particles in the MNs, or coating the polymer with the drug. Based on the type of drug loading, the methods of drug administration via MNs include "poke and formulation", "poke and patch", and drug-loaded MNs as seen in Fig. 3, which are selected on a case-by-case basis [89–91].

The methods of fabrication of drug-loaded MNs include micromolding and casting, vacuum compression molding, photolithography, hot embossing, and 3D-printing [92,93]. Selection of the appropriate polymer, the geometry of MNs, optimizing the formulation for maximum strength, and high drug loading are key considerations in these approaches. Recent reviews have covered MNs, in general, for drug delivery applications. Herein, we have focused our discussion on MN types for long-term (>3 days) drug delivery, primarily emphasizing newer approaches such as polymeric core–shell, nanocarrier-loaded, swellable, and other advanced technologies. Table 4 summarizes the studies conducted for long-acting MNs formulations.

3.1. *Polymeric MNs for controlled drug delivery*

Polyvinyl alcohol (PVA), poly-lactic-co-glycolic acid (PLGA), and PVP are some of the most used polymers for MNs [94,95]. The fabrication of etonogestrel-loaded PLGA MNs has been reported for sustained transdermal delivery [96]. *In vitro* release profile for two types of MNs with polymer: drug ratio of 75:25 and 60:40 showed sustained release till 23 days, whereas *in vivo* study showed delivery till 14 days. The authors predicted the possibility of achieving a therapeutic dose of the drug for 14 days with a 3.6 cm^2 patch, showing the feasibility of transdermal delivery for contraception. In another study, the fabrication of dissolving and implantable MNs loaded with finasteride was investigated [97]. For dissolving MNs, the researchers used PVA and PVP polymers, whereas PLGA was used for implantable MNs. Both these MNs showed sustained release of finasteride for 14 days *in vitro*. Extrapolation of this *in vitro* data predicted that the dissolving and implantable MNs could deliver the drug up to 7 and 67 days, respectively. A more recent study reported the fabrication of a two-layered MNs patch containing cabotegravir [98]. Here, the drug was incorporated in a powder form as both salt and free acid form. In addition, the concentrated form of commercially available nanosuspension of cabotegravir was also tested. The drug dissolution was dependent on particle size, where the salt form and concentrated suspension showed faster dissolution (<60 min) from MNs as compared to the free acid form, which had a comparably larger particle size. *In vivo* studies in rats showed successful delivery via all three MNs patches, maintaining high plasma levels of the drug for 28 days, and no signs of irritation for inspected application sites. It was predicted that a MN patch of suitable size (50 cm^2) could help maintain drug levels in humans after an initial intramuscular loading injection.

Besides these commonly used polymers and methods, other materials and processes have also been explored to fabricate MNs. Sodium hyaluronate MNs loaded with huperzine A have been reported for treating Alzheimer's disease [99]. The MNs were fabricated by a unique sandwich method where a concentrated polymeric solution of sodium hyaluronate (15 %) was first added with the help of centrifugation and dried, followed by the addition of drug in the form of powder, and finally, one more layer of sodium hyaluronate (10 %) as backing layer. These MNs demonstrated a sustained delivery over 3 days with a burst release in the first 12 h *in vitro* across rat skin. They showed slow and sustained delivery of the drug via MNs as compared to the oral route at the same dose with a similar pharmacodynamic effect *in vivo* in rats. Blank MN patches were tested for acute irritation up to 24 h post-application with no signs of erythema or edema observed. Furthermore, a unique formulation approach of an effervescent MNs patch containing levonorgestrel for contraception was also investigated, demonstrating sustained delivery of more than one month in rats in the absence of any signs of irritation or inflammation histologically [29]. The authors proposed a concept of an effervescent MNs patch where the backing layer gets separated within a minute due to the effervescent interaction of citric acid and sodium bicarbonate (incorporated in the backing layer) with skin's interstitial fluid. The MNs stay in the skin and release the drug over time. The *in vivo* studies in rats demonstrated that a single dose of MNs showed peak plasma concentrations around 1 ng/mL and sustained delivery of levonorgestrel for more than 30 days. Further, the authors have fabricated a MNs patch using the same drug but with a different technique where the MNs were made strong enough to insert in the skin. The backing can be detached immediately due to fracture at the MNs and backing surface, achieved by making the backing layer (PVA-PVP) more porous using lyophilization [100].

Table 4
Summary of long-acting transdermal microneedle (MN) formulations currently in development.

Type	Drug	Target indication	Formulation details	MNs geometry	Observed drug release duration
Polymeric MNs	Levonorgestrel[29]	Contraception	MNs composed of PLGA while backing layer of PVP, citric acid, and sodium bicarbonate	Conical MNs (10 x 10 array) 600 μm long	30 days (*In vivo*)
	Rilpivirine[30]	HIV treatment	MNs composed of marketed NS with PVA; backing layer of PVP and glycerol	MNs (14 × 14 array) 600 μm long	7 days (*In vivo*)
	Etonogestrel[96]	Contraception	MNs composed of PLGA with a combination of PVA, PVP as backing layer	Conical MNs (11 x 11 array) 700 μm long	14 days (*In vivo*)
	Finasteride[97]	Androgenic Alopecia	Implantable MNs composed of PLGA; dissolving MNs composed of PVA and PVP.	Pyramidal MNs (16 x 16 array) 850 μm long	14 days *(In vitro)*
	Cabotegravir[98]	HIV prevention	Combination of PVA and PVP with concentrated suspension of drug as MNs	Pedestal MNs (16 x 16 array) 600 μm long	28 days (*In vivo*)
	Huperzine A[99]	Alzheimer	MNs composed of sodium hyaluronate gel with drug	Conical MNs (6 x 6 array) 500 μm long	3 days (*In vitro*)
	Dutasteride[109]	Symptomatic benign prostatic hyperplasia	MNs composed of NS of drug with CMC, trehalose, and Tween 80	Conical MNs (11 x 11 array) 600 μm long	4 days (*In vivo*)
	Fluorescein Sodium[121]	Diagnostic stain used as model drug	MNs composed of Gantrez and PEG 10000	Conical MNs (19 × 19 array) 600 μm long, bas	4 days (*In vitro*)
	Rhodamine B[181]	Model hydrophilic dye	MNs composed of hydrogel of novel synthesized polysaccharide	Conical MNs (7 x 7 array) 800 μm long	4 days (*In vitro*)
	Bovine Serum Albumin [182]	Model protein in vaccine formulations	MNs composed of chitosan hydrogel	Pyramidal MNs (15 x 15 array) 600 μm long	8 days (*In vitro*)
Polymeric core–shell MNs	IgG and other model antibodies[37]	HIV therapy and prevention	Shell and cap using PLGA; core of lyophilized powder of drug and excipients	MNs (15 x 15 array) 600 μm long	25 days *(In vivo)*
	Prevnar-13 vaccine[101]	Immunization	PLGA core and shell with varying degradation kinetics	MNs (15 x 15 array) 600 μm long	~1 month *(In vitro)*
	Levonorgestrel[102]	Contraception	PLGA core and PLA cap and shell	Conical MNs (1 1 2) 600 μm long arranged in circle	6 months *(In vitro)*
Nanocarrier loaded MNs	Ivermectin[105]	Parasitic disease	Hyaluronic acid-based MNs containing drug loaded PLGA microparticles	Tiny needles of 3 mm height long	9 days (*In vivo*)
	Minoxidil[106]	Androgenetic Alopecia	PVA sucrose MNs loaded with drug loaded PLGA particles	Conical MNs (10 x 10 array) 850 μm long	2 weeks (*In vivo*)
	Levonorgestrel[107]	Contraception	MNs composed of silk solution along with cyclodexterin, Tween 80, and drug loaded microparticles	Conical MNs (20 x 20 array) 700 μm long	30 days (*In vitro*)
	Etonogestrel[108]	Contraception	MNs composed of drug microparticles in HPMC with backing layer of PVA	Pyramidal MNs (20 x 20 array) 0.55 mm long	7 days (*In vivo*)
	Artemether and Lumefantrine[110]	Malaria	Freeze dried nanosuspension of drug loaded with polymeric backing	Conical MNs (19 x 19 array) 600 μm long	3 days (*In vivo*)
	Bictegravir[111]	HIV therapy and prevention	Freeze dried nanosuspension of drug loaded with polymeric backing	Conical MNs (19 x 19 array) 600 μm long	4 weeks (*In vivo*)
	Etravirine[112]	HIV therapy	MNs of freeze dried nanosuspension with polymer backing	Pyramidal MNs (16 x 16 array)	30 days (*In vivo*)
	Olanzapine and Simvastatin [183]	Combination tested as model drugs; Olanzapine: Psychotic Disorders Simvastatin: High Cholesterol	Marketed dermaroller device with needle length of 500 μm	Not mentioned	2 days (*In vivo*)
	Vaccine antigen (Ovalalbumin and other relevant antigen)[184]	Immunization	PVA-sucrose MNs loaded with PLGA microparticles	Both conical and pedestal designed MNs ~ 600 to 800 μm long	2–4 weeks *(In vitro)*
Swellable MNs	Cabotegravir sodium[115]	HIV prevention	Optimized swelling MNs composed of hydroxypropyl-β-cyclodextrin (HP-β-CD), PVA, PVP, and/or citric acid	MNs (11 × 11 array) of 900 μm long	28 days (*In vivo*)
	FITC-dextran[113]	Model drug	Modified silk solution treated with urea for swellability	MNs (15 x 15 array) 500 μm long	4 days (*In vitro*)
Stimuli-responsive MNs	Ibuprofen[120]	Inflammation	MNs composed of 2-hydroxyethyl methacrylate, ethylene glycol dimethacrylate	Conical MNs (11 x 11 array) 600 μm long	160 h (*In vitro*)
	Methotrexate[118]	Solid tumors	Poloxamer solution forming in situ MNs	A total of 81 maltose MNs	3 days *(In vitro)*
	Model Mg particles[119]	Pain management	Fast acting MNs with CMC; sustained release MNs by Eudragit	48 MNs arranged in in circular pattern in two compartments	90 days *(In vitro)*
	Exendin-4[185]	Type 2 diabetes	Glucose oxidase and drug particles loaded in alginate MNs	Conical MNs (11 x 11 array) 500 μm long	9 days *(In vivo)*

3.2. Core-shell polymeric MNs for programmable controlled drug release

Recently, core–shell MNs designs have been explored to provide a programmed or delayed drug release. In these patches, the core acts as the drug/excipient carrier whereas the biodegradable shell acts as a rate-controlling membrane to control the release of drug from the core (**Fig. 4**). Drug encapsulation in the core–shell MNs minimizes initial burst and provides a more controlled release rate depending on its polymeric composition for an extended duration. The ability to load high amounts of antibodies (Abs) or vaccine immunogens in core–shell MNs as well as delay their release by controlling the degradation of the shell polymer is also explored [37,101]. They have fabricated the MNs by a high-throughput, scalable 3D-manufacturing approach and alignment of vaccine cores and PLGA shells with varying PLGA degradation kinetics for the pre-programmed release of vaccine over a few days to more than a month from a single administration [101]. Except for mild irritation immediately after insertion of the MNs, the patch did not cause any noticeable skin irritation even after long-term implantation. Using a similar manufacturing design, they have also developed a new powder loading method to achieve a significantly high loading of Abs that are thermally stabilized for a longer duration using a specific combination of excipients in the core of MNs [37]. Via a single application in rats, the MNs co-delivered multiple Abs at various programmed time points, thus potentially sustaining their systemic concentrations for months. Based on the rat skin testing, only minimal and transient skin irritation was observed following MNs administration.

The core–shell MNs design was also tested to achieve long-term contraception by developing a patch where the drug (levonorgestrel) was encapsulated in a PLGA core surrounded by a poly(l-lactide) (PLLA) shell and a poly (dl- lactic acid) (PLA) cap, fabricated by sequential casting into a MNs mold [102]. This design provided a controlled *in vitro* release of drugs by avoiding the initial burst observed in the case of conventional polymeric MNs. Upon application to skin, the MNs utilized an effervescent interface to separate from the patch backing within a minute and provide an extended drug release. In another work, a novel powder-based core–shell chitosan MNs patch for high-dose and controllable delivery of various drugs was developed [103]. *In vitro* testing suggested that the drug release kinetics could be tuned by adjusting the crosslink density of the MN's shell.

3.3. Nano/micro-carrier or drug-nanosuspension loaded MNs

MNs with the drug loaded in the form of a nanocarrier or nanosuspension is another approach being investigated to achieve sustained delivery of drugs [104]. This differs from polymeric MNs in that instead of dissolving the drug directly in the polymeric MNs solution, the drug is encapsulated in a different polymeric matrix and dried to get microparticles/NPs, or prepared in the form of nanosuspension. These drug-loaded carriers are then loaded in the MNs. As the release of the drug is now dependent on its release from its carrier along with from the MN matrix, the studies are focused on optimizing the microparticles/NPs, drug loading, drug-nanosuspension form, and polymer ratio to achieve the desired skin permeation and drug release profile.

Self-implantable MNs fabricated with anti-malarial drug ivermectin showed delivery for up to 9 days both in the *in vitro* and *in vivo* studies in rats [105]. The drug is loaded in MNs in the form of PLGA microparticles. The rats were monitored for signs of irritation and no reactions or adverse effects were observed at the site of the MN application. A similar approach was used for the delivery of minoxidil-PLGA microspheres loaded in PVA based MNs, which showed *in vivo* delivery for more than 2 weeks [106]. Researchers have also compared the drug loaded in the nano/microcarriers versus the drug incorporated in the polymeric MNs. In a study, silk was the material of fabrication for MN patches and modulated release of the drug levonorgestrel was observed [107]. The authors tested different molecular weights of silk as well as different drug loading along with solubility enhancers such as Tween 20 and cyclodextrin. In addition, silk microparticles containing the drug were also prepared using PVA and then incorporated into MNs. The drug directly loaded in MNs showed *in vitro* sustained delivery for up to 3 months. In contrast, the microparticulate form showed slower release, as long as 1 year *in vitro*, demonstrating the impact of drug nano or microcarriers on its controlled release. The development of a bilayer MN patch of etonogestrel is also reported by incorporating drug crystals of various sizes and comparing its delivery to when the drug is not loaded in the form of microcrystals using different polymeric solutions [108]. The *in vitro* release with microcrystal drug form showed sustained delivery for 10 days, whereas the non-crystal form showed rapid release. *In vivo*, the release resulted in drug delivery for up to 7 days with a projected delivery of therapeutic dose in humans for 10 days with a 1 cm^2 patch size. Thus, the particle size of the drug and polymer resulted in a significant difference in the drug delivery from MNs.

Another innovative formulation approach to provide controlled drug delivery involves using a nanosuspension of the drug to be incorporated in the MNs. The fabrication of MNs composed of a nano-milled suspension of dutasteride was reported [109]. The *in vivo* studies showed sustained drug delivery for more than 4 days, and plasma concentration

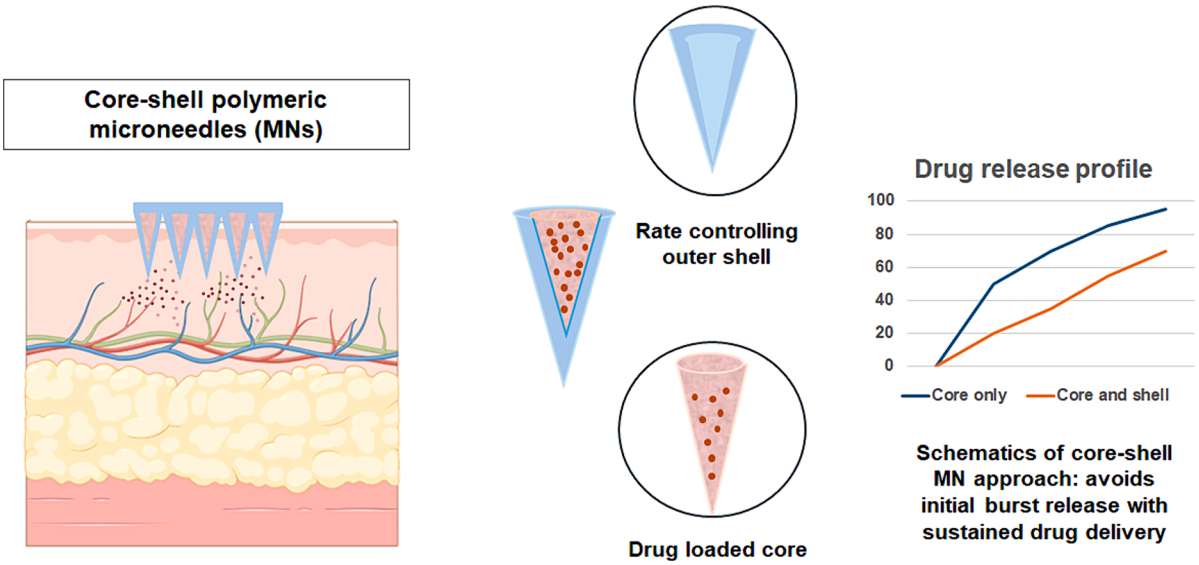

Fig. 4. Schematic of the design of core–shell polymeric microneedles (MNs) for controlled-/extended-release transdermal drug delivery.

was detectable for up to 1 week. *In silico* modeling predicted a weekly administration of a 2 mg drug MNs patch to maintain therapeutic levels, describing a novel way for the fabrication of long-acting transdermal delivery. A similar approach was tested for the fabricating dissolving MNs array patch using commercial rilpivirine nanosuspension and PVA polymer that can show sustained delivery of the drug and can be used to maintain a therapeutic maintenance dose for 7 days in humans [30]. Upon testing these MNs *in vivo* in rats, a single application resulted in delivery for up to 56 days with maximum plasma drug concentration one-day post-application. Although a therapeutic dose of the drug was not achievable using a practical patch size (maximum 50 cm^2), a MNs array patch of 28 cm^2 was predicted to maintain a maintenance dose for 7 days in humans.

One of the newer approaches to making nanocarriers is freeze-drying the drug nanosuspension, and then loading the carriers into the MNs. A recent paper discussed this approach to fabricate dissolving MNs loaded with anti-malarial drugs, namely artemether and lumefantrine [110]. The respective drugs were dissolved in an appropriate solvent along with polymer P108 and PEG to make the nanosuspension, which was then freeze-dried at optimized parameters. For the artemether-loaded MNs, the freeze-dried particles were incorporated into PVP K-90 hydrogel, whereas lumefantrine used a sodium hyaluronate gel. The *in vivo* results demonstrated that the MNs approach delivered a comparable or higher amount of drug as compared to oral administration, and a therapeutic human dose can be achieved with a 1 and 13 cm^2 patch for artemether and lumefantrine, respectively. A similar approach was studied for etravirine delivery up to 30 days and bictegravir delivery up to 4 weeks in rats using the method of incorporating freeze-dried nanosuspension in a polymeric matrix of MNs [111,112]. In addition, no signs of rat skin irritation were observed from etravirine MNs [112].

3.4. Swellable MNs

These are the more recent type of MNs investigated for long-acting transdermal delivery, employing swelling polymers to make MNs. These MNs, once inserted, can take up the interstitial fluid and swell, which results in slower and sustained release of the drug. The fabrication of swellable silk MNs and delivery of model molecule FITC-dextran is reported [113]. *In vitro* tests of optimized MNs showed sustained drug delivery over 4 days, where the authors demonstrated the possibility of controlling release by varying the swelling capacity according to the molecular weight of the intended drug. The conversion of silk fibroin into swellable material and controlled release of different molecular weights of drugs from it are key points established in this study. An acryl resin-based swellable MNs formulation was developed for controlled delivery of poorly water-soluble drugs [114]. In-vitro release of swellable MNs-loaded drug (granisetron) showed that 7 days long controlled drug release was obtained when the MNs contained pore-foaming agents (PVP and dicalcium phosphate). *In vivo* testing in rats indicated a dose-dependent plasma profile and controlled drug release for 6 days.

Another study demonstrated the use of hydrogel-forming swellable MNs for long-acting delivery of the hydrophobic drug cabotegravir sodium [115]. The authors reported the use of a complex of the drug with hydroxypropyl-β-cyclodextrin to enhance the solubility of the drug and then to lyophilize the complex, followed by direct compression to get a drug reservoir in the form of a tablet. This reservoir was then coupled with hydrogel forming MNs. The *in vivo* studies conducted with these MNs coupled with a tablet reservoir showed similar plasma concentration as that of an intramuscular injection over 28 days. Thus, this research demonstrated for the first time the use of complexation with cyclodextrin to enhance the solubility of a lipophilic drug, followed by the use of hydrogel-forming MNs for long-acting transdermal delivery. As seen, optimizing the polymeric material for the balance of appropriate swelling capacity and mechanical strength for sufficient penetrability in the skin is a key consideration for obtaining sustained delivery from swelling MNs.

3.5. Stimuli-responsive MNs

Stimuli-responsive MNs patch approach offers an innovative and promising avenue for controlled, on-demand, or triggered release drug delivery [116,117]. The major components of such systems are the materials and the chemistry involved in achieving stimuli-responsive drug release triggered by external (light, electric, magnetic, heat, and mechanical force) or internal (pH, enzyme, glucose, temperature, and reactive oxygen species) biomarkers **(**Fig. 5**)**. Although the stimuli-responsive MNs approaches are mostly designed for on-demand and/or immediate (burst) drug release, a few studies have explored the concept for controlled long-term drug delivery.

A glucose oxidase-based glucose-responsive MNs patch was reported for exendin-4 delivery [185]. The alginate-based MNs patch was integrated with dual mineralized particles separately containing exendin-4 and glucose oxidase. This design can specifically release exendin-4 while the glucose oxidase particles remain intact. In a hyperglycemic state followed by low pH, the particles degrade and release the exendin-4. The resulting patch design separately encapsulated a bio-sensing component and a bio-sensitive drug-releasing mineralized particle to support the long-term drug release. Another study used the sol–gel property of poloxamer polymer for *in vitro* delivery of methotrexate for about 3 days [118]. Here, the solution (liquid) at room temperature turned into a gel on the skin due to the skin temperature, leading to formation of in situ forming hydrogel MNs. A novel dual-action patch system, which could provide tunable fast-acting and sustained drug release, depending on the dissolution rate of the polymeric materials, was recently explored [119]. Using this approach, a tunable release of Mg particles where the design allowed initial rapid release (within ~ 5 min) using active particles in dissolvable carboxymethylcellulose polymer, whereas a controlled/sustained payload release was achieved using pH-dependent Eudragit polymer [119]. Another study reported the fabrication of swelling MNs composed of 2-hydroxyethyl methacrylate and ethylene glycol dimethacrylate [120]. Here, they incorporated a drug conjugated to a light-sensitive molecule loaded in the MNs, which can deliver the drug ibuprofen upon triggering by light, thereby providing "on-demand" delivery. This trigger could release the drug *in vitro* for up to 160 h. More importantly, the light-triggered system could turn on and off the release of the drug when tested, providing a proof-of-concept for on-demand and controlled drug delivery via MNs.

Thermo-responsive polymers are also being investigated for their in-situ gelling properties via the "poke and solution" approach. The delivery of a model drug – fluorescein sodium from a thermo-responsive in-situ forming poloxamer gel was studied using skin treated with MNs for 4 days [121]. They screened various polymers, such as Gantrez S-97/polyethylene glycol combination and PVP K32/K90, for the fabrication of MNs. Among the polymers tested, MNs composed of Gantrez S-97 with polyethylene glycol 10,000 in the ratio of 10:7.5 % showed good penetration properties and were used for creating microchannels. Further, the delivery of the model drug was tested from MNs-treated versus untreated skin using thermo-responsive gels. The MNs-treated skin showed increased and sustained delivery for 4 days. This approach thus used a unique property of polymers combined with microporation for long-term transdermal delivery as one of the recently investigated formulation approaches.

4. Molecularly imprinted polymer (MIP) delivery systems

MIP-based delivery systems are a new area of research also explored in long-acting TDS. The MIPs are advanced materials that can selectively interact with a target compound and have been used in many other areas besides pharmaceutics [32]. MIP systems are formed by synthesizing a polymer having specific recognition sites in them via the use of a template followed by polymerization and removal of the template **(**Fig. 6**)** [32]. The resultant polymeric network retains those specific binding sites and cavities to recognize the target. Thus, these systems when used

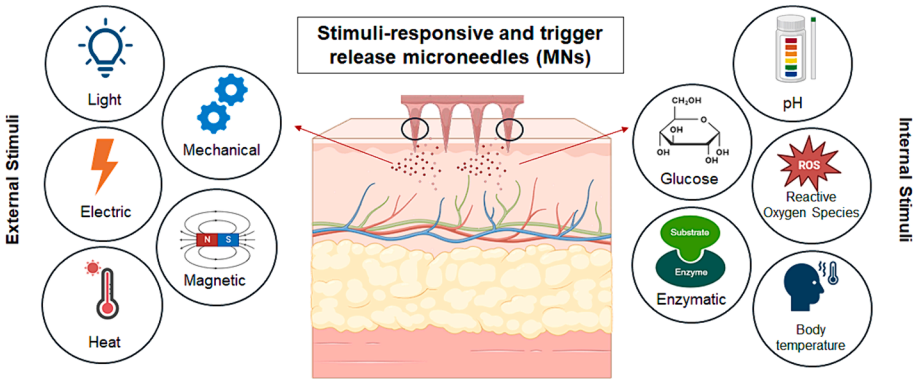

Fig. 5. Schematics of the design of stimuli-responsive microneedles (MNs).

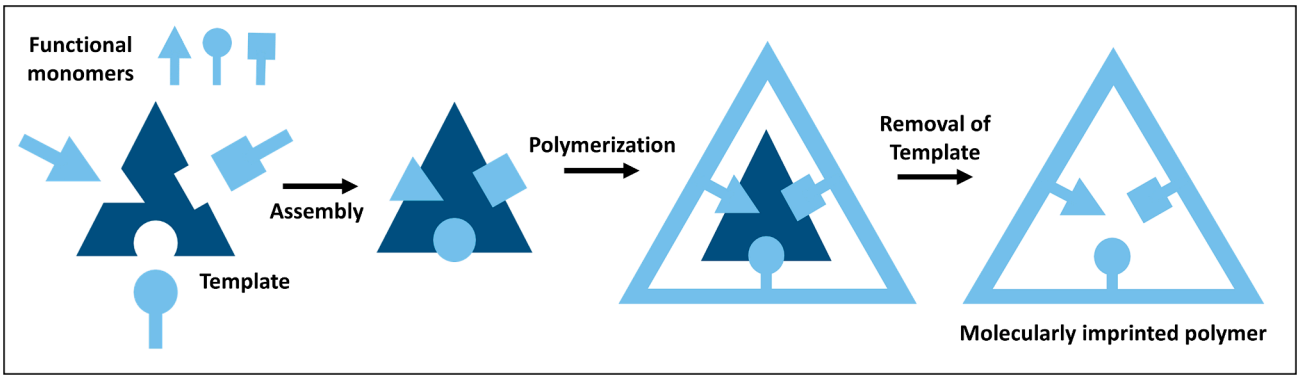

Fig. 6. Molecularly imprinted polymers (MIPs) in the design of transdermal delivery systems.

in formulation can interact with those specific targets and help in drug delivery with the advantages of improved delivery profile, long-term release, and increased residency of drug [122,123]. In pharmaceutical applications, these MIPs are synthesized to interact with the target molecule, which in most cases is the drug or a particular biological marker. Compared to Abs-based drug delivery systems (DDS), MIPs are thermally stable with a heterogeneous binding site [124]. Reviews about MIPs provide more details about their preparation and characterization [32]. These can be potentially used for sustained or controlled release and drug release rate from such polymer matrix can be altered based on desired target delivery.

The MIPs are being explored as functional excipients or as a DDS in long-acting transdermal delivery. However, only a couple of drugs (nicotine and propranolol) have been tested so far via this approach for the long-acting TDS [125,126]. The authors demonstrated controlled administration of nicotine over 2 days using molecularly imprinted particles of the nicotine using bulk polymerization of methacrylic acid and ethylene glycol dimethacrylate using nicotine as a template [125]. The possibility of skin hypersensitivity due to the use of organic components and the initial uncontrolled burst release of the drug were some of the identified problems in this system. The same research group later used the precipitation polymerization technique selecting the MIPs for their improved adsorption capacity and selectivity [127]. The MIP particles dispersed in mineral oil (a non-polar vehicle) were used to prepare a transdermal formulation that showed a faster release than the formulation prepared using non-imprinted polymers. Ex-vivo studies using ear porcine skin indicated that MIP-based formulations were able to control the skin permeation flux for prolonged times (2 days). Although both polymers could bind the templates in their matrixes, MIPs due to the presence of selective recognition sites in their structure showed better performance for transdermal delivery, and overall, MIP formulation exhibited a longer duration of action than the commercial nicotine patches. MIP's can also be used for selective isomer delivery due to their selectiveness. Such studies focused on exploring the MIP of propranolol to show the controlled release of only one of the enantiomers (S-propranolol) using cellulose and other co-polymers [126,128]. These used stereo-selective delivery of the S-enantiomer of the drug to resolve a biocompatibility issue. The concept of having MIPs as a drug reservoir was also proven *in vivo*, which confirmed their ability to selectively regulate the release of S-propranolol [128].

5. Technical challenges, design considerations, and translational features of long-term drug delivery from transdermal patches

As discussed in the above sections, unique formulation and design approaches have been used in the TDS, including but not limited to higher drug loading, improved drug and excipient compatibility and stability, enhanced skin penetration and insertion efficiency, and programmable drug release for immediate and/or sustained delivery. Using these novel approaches, researchers have provided new avenues in the fabrication of adhesive patches, MN patches, or other systems for long-acting transdermal delivery. Although there have been significant advances made in controlling and extending the drug release from transdermal patches, there are still several challenges to overcome.

Adhesive (reservoir- and matrix-type) patches have been successfully designed for controlled drug release from several hours to days, however, for long-acting delivery, the primary concern with adhesive patches is the limited drug delivery duration. The MN-based patches offer controlled/extended drug delivery for several months. These benefits have resulted in significant research efforts into the development of MNs for long-acting drug delivery applications. Despite good progress, so far, no transdermal MN products for drug delivery applications have made it to market, though several are in the clinical trials

[129–133]. The novelty in design of MNs also carries challenges, creating hurdles in their widespread clinical development. These challenges range from complications in reproducible manufacturing, limited drug loading, fabrication issues, end-user acceptability, safety of the materials, and a reliable delivery of complete dose of therapeutics [87,134].

The formulation development challenges related to the design considerations for long-acting drug delivery and clinical development of adhesive- and MN-based transdermal patches are summarized in Figs. 7 and 8, respectively. Some of the key obstacles related to R&D development, design considerations, scale-up manufacturing and successful clinical translation are briefly discussed below.

5.1. Ideal drug and excipients for appropriate adhesiveness, skin permeation, and preservation of drug stability

Excipients play a vital role in transdermal delivery. Since sustained drug delivery for a longer duration from adhesive patches relies on prolonged skin contact, maintaining compatibility between the drug and the adhesive is critical so that they do not alter each other's physical properties. The formulation design as well as interactions among the drug, excipients, and skin membrane can affect patch adhesion and drug delivery. The adhesive/excipients may be combined with the drug or kept in different layers. If mixed together, the strength of the adhesive may be weakened because of incompatibilities, but if separated, compatibility issues are less pronounced as in the case of zolmitriptan delivery [135]. In addition, poor skin permeability of therapeutics not meeting the ideal physicochemical characteristics (molecular weight, hydrophobicity, and melting point) limits adhesive patch application to only a few adequate molecules. For the rest, achieving target systemic/local drug concentrations requires high drug loading in the patch or increased number of patches or frequency of administration.

For MNs, selection of polymer and excipients, and the fabrication process plays a critical role in their design (e.g., solid, hollow, coated, core–shell, dissolvable, swellable) as discussed earlier in this manuscript. It is also important whether materials are used in liquid or powder form for supporting the long-term delivery and stability of active molecules. For example, by using a powder loading method, Abs combined with excipients were successfully loaded into a long-acting MNs patch platform [37]. In powder form, the Abs were thermally stabilized for at least 3 months under physiological temperature conditions. Further evaluation of these kinds of approaches are required for developing patch formulations with enhanced stability and eliminating cold-chain storage requirements.

5.2. Biocompatibility and safety of the materials

Biocompatibility of the materials is important for the performance of transdermal products because of long-term interaction between skin and the patch components. If there are any physicochemical properties that lead to unstable compounds or residues left on the site of administration that are not biocompatible, this may lead to skin irritation or safety concerns. Hence, the selection of excipients is critical to assuring the safety, stability, and efficacy of transdermal products. PIBs are known to have lower allergenicity as compared to acrylates and silicones [136]. Researchers examine the patch for residue post-removal by visual observation [31,71,72], and skin irritation potential by assessing skin edema/erythema [81,84]. MNs can cause mild or moderate skin irritation to sensitive skin leading to redness and swelling. Bal et al. conducted *in vivo* assessment of MNs in human skin and showed that needle length, shape and design were factors affecting skin irritation. The irritation, however, was minimal [137]. The created micropores can also be susceptible to infections depending on their duration or resealing time [138]. Safety concerns might also arise in case of MNs break inside skin [85]. Hence the material and type of MNs along with patient compatibility studies are essential while developing MN-based products. Arya et al. evaluated the skin tolerability, usability and acceptability of dissolving MN patches in human subjects [139]. The patches were well tolerated primarily due to the use of biocompatible materials in the formulation and the minimally invasive nature of the MNs. Each one of the patch types described previously comes with the potential for irritation and/or sensitization that requires assessment before advancing to clinical trials. It is therefore essential to establish preclinical safety of the patches. The US Food and Drug Administration (FDA) guidance provides recommendations for TDS regarding use of an appropriate scientific approach during product design, development, and manufacturing to ensure that the amount of residual drug is minimized at the end of the labeled use period [140]. Guidance documents are also available for the

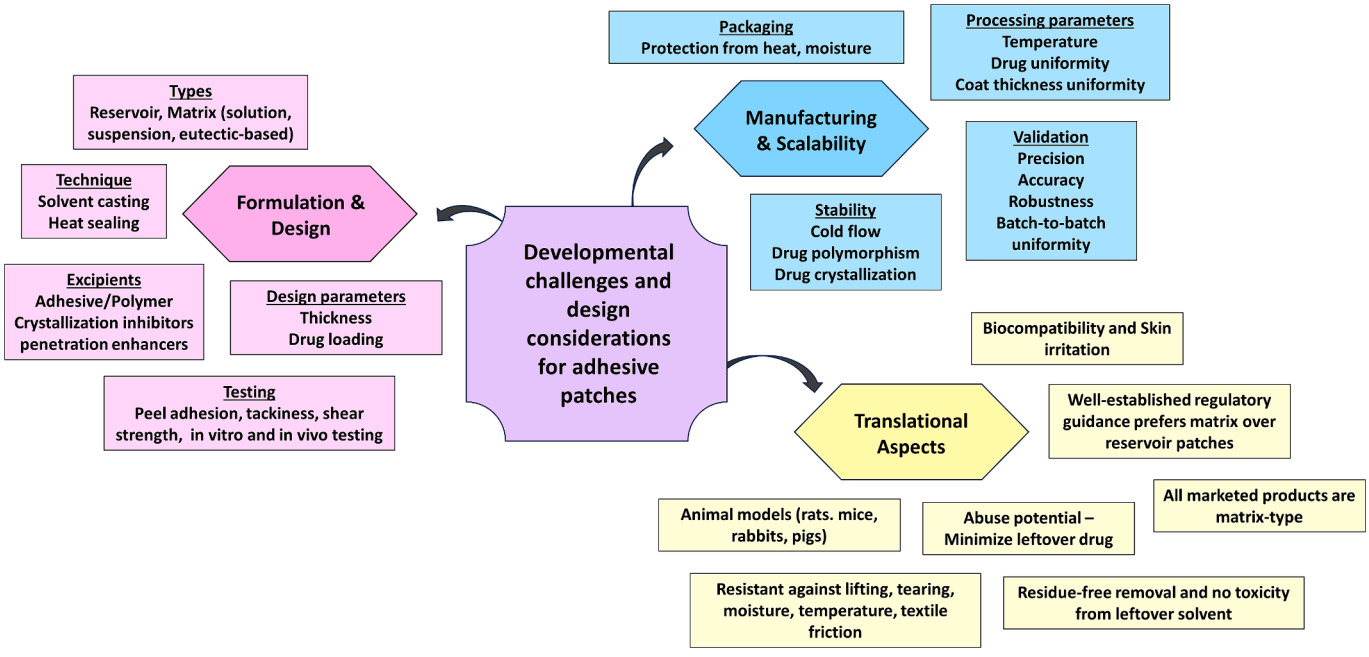

Fig. 7. Developmental challenges and design considerations for adhesive transdermal patches.

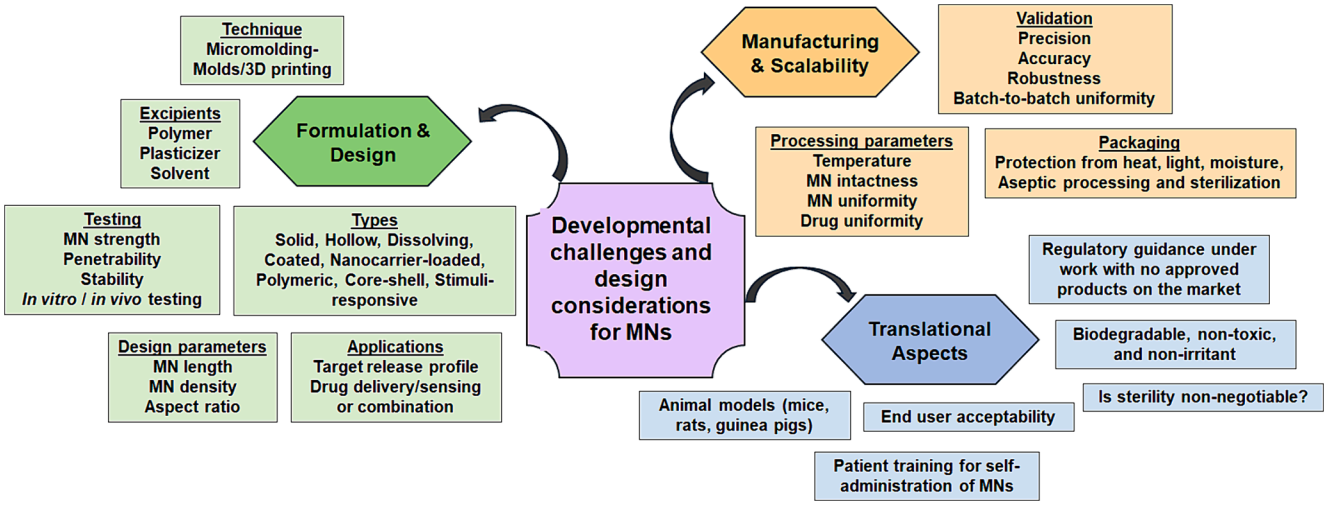

Fig. 8. Developmental challenges and design considerations for microneedles (MNs)-based transdermal patches.

design and conduct of studies to evaluate the local safety of transdermal products [141]. The International Organization for Standardization (ISO) developed a standard for biological evaluation of medical devices (ISO 10993) that is applicable to TDS [142], and the FDA has recently issued an accompanying document to these standards for thoroughly assessing the safety of TDS prior to clinical testing [143]. These guidelines include study design and methodology recommendations for stepwise tests of assessing the potential for sensitization and irritation following single or repeated administration, preferred *in vivo* animal models, and alternative *in vitro* models for consideration.

5.3. Drug loading limitations

High drug loading is a major advantage of reservoir-type patches, but it leads to concerns regarding dose dumping and drug content left over in used patches, especially in the case of controlled substances such as fentanyl [140]. In cases of solution-based matrix patches, the drug loading is limited by its solubility in the polymeric adhesive and dose depletion over time that leads to lower permeation flux [144]. The design of a suspension-type matrix patch inherently leads to a higher amount of leftover drugs in a used patch, which can be a cause of concern for prescription drugs and controlled substances [57]. Moreover, having unnecessarily high drug loading leads to increased costs of production and retail, reducing the availability of the product to the general population. Furthermore, if the drug is insoluble in the PSA matrix, a drug suspension is unable to create the necessary flux across the skin to facilitate delivery [47].

For the eutectic-based patches, although there is not much research done yet, what is known is promising. Eutectic drug loading offers a solution for typical problems including insufficient solubility and poor drug permeation flux. This approach also enables a better understanding of the molecular mobility of the adhesive and the impact of various polymer functionalities on the permeation flux. Using a eutectic mixing approach can also help enhance drug loading in patches but may not be feasible for all types of drugs. These points must be considered while choosing between a solution, suspension, or eutectic-mixture patch. Accordingly, the drug loading and choice of polymer and other excipients can be optimized to obtain the target release pattern for sustained transdermal delivery.

For MN patches, one of the major factors behind their limited success in clinical development is limited drug loading capacity (generally ≤ 1 mg in a one cm^2 size patch) [37,87], which requires repeated or multiple applications or use of a large size patch to ensure sustained therapeutic levels of drugs are maintained over a prolonged period. The limited drug loading of MNs presents an obstacle, especially for biomolecules such as Abs, given the relatively large dose requirement for Ab-based therapies. Hence, formulation approaches are needed to enhance the drug loading in MNs to support prolonging their drug delivery duration. Promising recent studies with enhanced drug loading achieved with powdered materials, pure drug form, or modifications to the fabrication processes provide tools to increase the delivery duration while minimizing the number or size of the patches [37,52,81,145].

5.4 Manufacturing process robustness, characterization, and dosing consistency

For both adhesive- or MNs-based patches, having a manufacturing process that can consistently produce quality products is critical for reproducible dosing and therapeutic effects. There were incidents where manufacturing defects caused issues, for example, defects in seal and membrane that produced drug leakage during use led to the recall of the Duragesic® (fentanyl) patch [146,147]. The design of reservoir-type patches is prone to leakage, dose dumping, and subsequent systemic toxicity, which has led the FDA to recommend the development of matrix-type patches over reservoir patches [148]. Hence, the research on reservoir-type patches for sustained release has been sparse in recent years.

The drug delivery efficacy and dosing consistency of the transdermal systems also largely rely on the condition of the patient's skin, affected by factors such as age, location of patch application, and temperature of the site of administration. There are regulatory concerns about some of these parameters that may lead to variations in drug release rate and dosing [45]. For MNs, their successful development is highly dependent on the assurance of reliable and repeatable insertion into the skin. If not inserted correctly, it may result in the drug not being delivered consistently, leading to reduced efficacy of the treatment. The importance of effective application was recently observed in the clinical results of Qtrypta, a titanium-based MNs patch to deliver zolmitriptan in blood at a faster absorption rate than oral pills. FDA highlighted inconsistent drug levels across clinical studies with different lots of Qtrypta, flagging the robustness in the insertion and/or the manufacturing processes [149].

Manufacturing MN patches must be precise and robust. These types of patches have micron-sized needles loaded with small amounts of drug relying on accurate drug loading and adequate skin penetration to be effective. The robustness of their fabrication process can be improved via automated manufacturing approaches that are fast and use minimal numbers of processing steps. Recently, an automated process for printing COVID-19 mRNA vaccine MNs patches has been developed [150]. The process was vacuum-based, compatible with a wide range of MN

designs, and optimized to minimize vaccine waste. The vaccine ink includes RNA vaccine molecules encapsulated in lipid NPs, which help them to remain stable for long periods, and a dissolvable polymer blend that can be easily molded into the right shape. Such systems and a new way of creating MNs patches where the vaccines or other drugs can be stabilized easily will further increase the utility of MNs-based transdermal delivery approaches globally.

For the newer approaches such as the nanoformulations or MIP-based systems, though promising, compared to simple polymeric MNs, the manufacturing of nanocarrier or nanosuspension drug-loaded MNs is a more complex system since it involves two steps – preparing the nanocarriers and optimizing their loading in MNs. The use of appropriate excipients to prepare nano or microparticles for optimum particle size, drug loading, and optimizing compatible material to incorporate these in MNs are some of the critical parameters that need further exploration. For MIPs, these are synthesizing a new material for drug delivery, their preparation or fabrication classifies as part of polymer synthesis and needs a case-by-case approach to identify and design a material targeting a particular compound. Moreover, the lack of *in vivo* release profiles, cytotoxicity assays, and other compatibility tests to ensure the safety of such newly synthesized material is a major hurdle in implementing this technology for drug delivery. Further, future improvements to ensure the reproducibility and scalability of such systems are necessary to apply this technology for commercial production [124].

5.5 Terminal sterilization or aseptic manufacturing

Sterilization methods and maintaining the sterility of the final formulation is a key requirement for MN-based transdermal patches since they breach the outermost layer of the skin [151]. Since, MNs technology falls between transdermal patches (can be manufactured in low-bioburden settings) and intradermal injection (must be produced aseptically and/or terminally sterilized), it is unclear what level of sterility assurance will be required for clinical use of MN products. Terminal sterilization may release toxic residues and/or affect the product characteristics, which demands in-depth understanding of the sterilization process on the critical quality attributes of the product. McCrudden et al., explored the sterile manufacturing of MNs and discovered that terminal methods such as autoclaving and dry heat sterilization damaged the MNs but gamma sterilization did not [152]. The effects of gamma sterilization on the properties of MNs patches made from different polymers have been explored [153]. This study found that some of the polymers were not compatible with gamma sterilization and made MNs deformed. Since molecules such as vaccines and biologics may not withstand terminal sterilization, it needs to be confirmed whether it is essential to devote significant resources to terminal sterilization or pursuing aseptic production or any other lower-cost, low-bioburden manufacturing process is adequate if an acceptable level of safety risk to the end-users is demonstrated.

5.6 End-user acceptability with ease of administration and painlessness

One of the most prominent advantages of transdermal formulations is the ease of application on the skin. For adhesive patches, a number of factors can influence adhesive performance and end-user acceptability, for example, the design must ensure that the patch comfortably adheres and conforms to application sites and while wearing, the product maintains proper adhesion during normal exposure to moisture, temperature, etc. A good example is the evaluation of new fentanyl matrix systems that were characterized by a high level of patient acceptance, ease of use, improved skin compatibility, and adhesive properties, compared to the standard marketed drug reservoir-based patch[154]. The matrix patches had a similar bioavailability and PK as the reservoir patch; however, further studies exploring long-term use of the new system are required.

In case of MNs, this also includes the painless insertion compared to conventional hypodermic needles-based products, which has a significant impact on patients' acceptance of this technology. Administration of MNs presents a lower risk of infection or skin irritation, including added convenience of a self-administered drug delivery option compared to standard hypodermic needle-based injections [155,156]. Earlier, the MNs design factors have been investigated that affect the pain scores in human volunteers [157]. They discovered MNs length has a major influence relative to the MNs numbers per array on the participants' pain score and confirmed that MNs cause less pain than a hypodermic needle. Another *in vitro* study proved that the chances of infection while applying MNs is much less than that of a conventional hypodermic needle [158]. Since then, there have been substantial studies to demonstrate the painlessness and tolerability of MNs application in humans, including in the pediatric population [139,159–161]. Although the risk of infection associated with MNs is low, because of their small size and fragile nature, their incorrect application may break off the MNs and remain in the skin. If the materials used to fabricate the MNs are not bioabsorbed, any residual fragments would cause irritation.

5.7 Packaging, storage, and transportation

Transdermal patches, like any other pharmaceutical product, must be adequately packaged to assure their claimed shelf life, quality parameters, and drug content is maintained under recommended storage/transportation conditions, patient handling, and administration. Therefore, the assessment of appropriate packaging for transdermal patches is critical for their successful development and translation. Traditionally, adhesive transdermal patches are enclosed within sealed packaging material, i.e. pouches. The moisture permeability of packaging material is also considered while selecting them [162]. For this, especially to provide the moisture barrier over long periods of storage, packaging materials made of multiple layers are typically required. Such packaging specification may result in a higher product cost. Because of their potentially diverse applications, different packaging options in single- or multi-dose designs are being proposed for MNs [163]. The designs may affect the overall supply chain volume, cost, and the packaging waste after the product use. Various methods such as vacuum packaging, dry room packaging, storing the product in desiccating atmosphere have also been employed for moisture sensitive drug or final product. For example, in case of dissolving MNs, these are typically fabricated from water-soluble polymers and/or sugars and since these materials are hygroscopic, the exposure to the moisture/temperature may result in drug degradation or weakening of the overall mechanical properties of MNs [164,165]. This would result in poor insertion into the skin and/or sub-therapeutic drug doses being delivered upon administration. Recently, the effects of primary packaging for the storage, transport, and distribution of MNs patches was investigated according to the International Council for Harmonisation (ICH) and World Health Organization (WHO) guidelines over 168 days [165]. The study demonstrated that Protect™ 470 foil was more effective than poly(ester) foil in creating moisture barrier and temperature resistance for MNs patches containing amoxicillin sodium. Additional such studies are needed to identify the suitable primary packaging options for patches for their usability, especially in hot and humid countries. The 3D-printed MAP-box packaging has been explored as a novel and suitable system for packaging and transportation of MNs patches [166]. Nevertheless, future work will be needed to explore further options and their evaluation on storage, transport, and patient's usability of transdermal patches for long-term drug delivery applications.

6 Conclusion and future prospects

The field of long-acting TDS has continued to grow over the last few years with the development of innovative technologies. The feasibility and proof-of-concept of patches designed for extended drug release from several hours to days (adhesive and MNs patches) and months with MNs-

based formulations have been demonstrated in preclinical studies and some in clinical trials. With more than ten long-acting formulations on the market, the transdermal patch is a growing and well-established DDS in spite of challenges. Physicochemical properties of drugs required for use in adhesive patches narrows drug candidates for consideration. Other limitations include loading capacity, long-term integrity and delivery, manufacturing and scalability, and regulatory standards. Several factors can affect adhesive performance and hence designing a reservoir- or matrix-type patch for long-term drug delivery is complicated. Maintaining proper adhesion on the skin can also be difficult with exposure to outside conditions such as external moisture and high temperatures. Because of that, patient usability of the matrix- and reservoir-patches presents challenges since these need to have appropriate adhesiveness to prevent detachment from the skin, which is particularly challenging for once a week or biweekly systems. Among recent advances, eutectics/ion-pairs offer benefits such as improved drug stability, better drug loading, and enhanced permeation, but need further studies to establish the safety and effectiveness of such systems. Apart from that, MIP systems are still in the nascent stage but hold promise due to enormous progress made in material science approaches. The primary advantage of MIPs is their high stability that makes them a suitable candidate for long-term drug delivery application.

MNs have gained significant attraction in recent years for their capacity to be able to deliver hydrophilic and hydrophobic molecules, including macromolecules such as proteins and even vaccines. However, there are development challenges associated with MNs. These include appropriate selection of the type of MNs-based system, limited drug loading, complex manufacturing process, issues with MNs skin penetrability, and uncertain regulatory standards. The irritation, sensation from the application, variability associated with application pressure, and inability to stop drug delivery in case of adverse events are some other points under consideration and of concern with regulatory approval of MNs. Solid MNs, while being robust and providing enough penetrability, require a two-step application approach, which can lead to reduced patient compliance. Dissolving and coated MNs can provide one-step application but have issues with low drug loading capacity and insertion capabilities, whereas hollow MNs have drug leakage issues. Apart from these obstacles, biocompatibility and appropriate geometry remain parameters for optimization in any type of MNs. The large-scale production of MNs and concerns with their reproducibility and robustness are also major limiting factors that require resolution. With progress in regulatory guidance and the industry investing more in such technologies, this area will likely see a large expansion once one MN-based patch is approved and launched. The FDA recently released guidance on microneedling devices and products, considering them a drug-device combination and not just a drug product [19]. Perhaps due to all these challenges, there is not yet an FDA-approved MNs-based transdermal system, although considerable efforts have been made, including a recent submission of Qtrypa (MN patch for migraine) by Zosano Pharma in 2020.

Newer techniques such as 3D-printing and additive manufacturing processes have been explored as novel techniques for developing long-acting and programmable/tunable drug release transdermal systems. The advanced forms of MNs, including stimuli-responsive, core–shell, MNs have made use of controlled drug release using various available 3D-printing options (e.g., stereolithography, continuous liquid interface). These can make the future of continuous manufacturing and personalized medicine a possibility, provided the same challenges of robustness and reproducibility can be tackled. Core-shell design MNs represent a strong candidate for addressing the challenges in long-acting controlled/programmable transdermal drug delivery, which may further benefit therapy for the diseases that require administration of multiple doses for treatment. A combinatorial MNs patch with dual and tunable release kinetics is also developed targeting variable dissolution timeframes in a single application. This novel manufacturing approach provides the ability of the MNs patch to load several types of drugs within the same patch, but spatially resolved, for burst or controlled release kinetics.

The newer TDS concepts in development are fascinating and are nurtured by the exchange of knowledge and collaborative efforts among different fields, including material science, engineering, and pharmaceutical formulations, helping bridge gaps and enabling the use of these technologies for next-generation long-acting and low-cost transdermal delivery products. Although these development approaches face unique challenges, significant efforts are underway to overcome them ensuring the full potential of long-acting transdermal drug delivery will be realized soon.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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