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Mini Review

Advances in microneedle patches for long-acting contraception

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ABSTRACT

Despite the advances in contraceptives, there is still a high rate of unintended pregnancies worldwide, due in large part to the lack of effective, convenient, and safe birth control methods. Compared with short-acting contraceptives, approaches that offer long-term pregnancy protection have attracted greater interest because of the reduced dosing frequency and improved patient compliance. As a novel transdermal drug delivery system, the microneedle (MN) patch has been widely used for a variety of biomedical applications, including long-acting contraception, due to unique properties, such as painless self-administration and elimination of biohazardous waste. In this review we provide a systemic review of MN patches that have been utilized for long-term contraception, including dissolvable MN patches, polymeric biodegradable MN patches, and silk fibroin-based biodegradable MN patches. The acceptability and biosafety of these contraceptive MN patches are also discussed. Finally, we give our perspectives on the future clinical translation of MN patches for long-acting contraception.

Keywords: Contraception, microneedle patch, long-acting, sustained release

1. INTRODUCTION

Birth control still faces huge challenges. It has been reported that 85 million pregnancies were unintended in 2012, accounting for 40% of all pregnancies worldwide [1]. Moreover, approximately 121 million unplanned pregnancies occurred between 2015 and 2019 [2], and this number is likely to increase in the next 5 years [3]. An unplanned pregnancy often results in an unhealthy gestation or unintentional abortion [4], which can cause a variety of complications *in utero* [5], leading to harmful effects on maternal physical and mental health and imparting a financial burden on families [6, 7]. Such an enormous magnitude of unintended pregnancies is associated with an economic burden and a history of unplanned pregnancies [8, 9] due largely to the lack of effective and convenient contraceptive methods [10], thereby highlighting the need for the development of new contraceptives. The current birth control methods mainly include short- and long-acting contraceptives [11]. Compared to contraceptives that are only short-acting, such as condoms and daily oral pills, long-acting contraceptives achieve sustained release of hormones, provide long-term protection from pregnancy and reduce the administration frequency of medications, and have more admirable advantages and receive greater interest from women [12].

A variety of approaches can achieve long-term contraception, such as transdermal patches, subcutaneous implants, injectables, intrauterine devices (IUDs), and vaginal rings [13]. Transdermal patches are generally applied on the skin surface, and enable the release of hormones across the skin for 1 week, thereby achieving pregnancy protection for 7 days [14]. Transdermal patches, however, must be worn for a time (i.e., 7 days) and have a limited drug permeation efficiency (<1%) through the skin due to the physical barrier of the stratum corneum [15]. Subcutaneous implants or injectables are effective for contraception for several years [16, 17], but require surgical implantation or need hypodermic injection, which always involve surgical procedures from healthcare providers and causes

pain [18], thus significantly reducing patient compliance. IUDs and vaginal rings also provide a contraceptive effect for years [19], but IUDs and vaginal rings are invasive to the uterus and usually require a procedure by trained medical personnel [20]. In addition, women with irregular menstruation, hypermenorrhea, or hysteromyoma are not eligible for IUDs and vaginal rings [20].

Microneedles (MNs) are micro-scale needles with lengths ranging from 10-100 μm [21]. MNs puncture the outermost skin barrier and reach the epidermis with negligible pain, achieving improved drug delivery efficiency through the skin [22, 23]. There are six types of MNs that have been widely used for transdermal drug delivery, including coated [24], hollow [25], dissolvable [26], polymeric biodegradable [27], hydrogel [28], and silk fibroin-based biodegradable MNs [29]. In recent years, researchers have focused on the application of MNs in contraception given the unique properties of MNs [30-32], such as self-administration [33], long-acting efficacy [34], delivery efficiency [35], and eliminating pain [36]. Among the six types of MNs, three have been reported for long-acting contraception. In this review we have summarized the development of contraceptive MN patches in the literature (**Table 1**), discussed the acceptability and safety of long-acting MN patches for contraception, and provided future perspectives on the clinical translation of MN patches for long-acting contraception.

2. TYPES OF MN PATCHES FOR LONG-ACTING CONTRACEPTION

2.1 Dissolvable MN patches for sustained release of hormones

Dissolvable MN patches are generally made of water-soluble polymers and can achieve rapid dissolution within a short time after skin insertion, thus avoiding biohazardous waste and residual drugs [42]. Dissolvable MN patches are generally made of natural polysaccharides, such as hyaluronic acid (HA) [43], dextran [44], and chitosan [45], or water-soluble polymers, such as polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) [46]. Dissolvable MN patches have good solubility and can dissolve rapidly after contacting interstitial fluid (ISF) in the skin [47, 48], thereby achieving transdermal delivery of different types of drugs, including contraceptives (**Figure 1**). For example, Yao et al. [37] added chitosan and beta-sodium glycerophosphate (β-GP) in the formulation of MNs, which significantly accelerated the dissolution of MNs after skin insertion. In addition, hydroxypropyl beta cyclodextrin (HP-β-CD) was used to incorporate the contraceptive hormone, levonorgestrel (LNG), to improve the solubility of LNG. *In vitro* experiments showed that 40% of MN patches dissolve within 10 min and approximately 70% of MNs penetrate and dissolve in the skin within 2 h, which is nearly 2-fold higher than conventional MN patches. An *in vitro* LNG cumulative release profile showed that the MN patch

Table 1 | Types of MN patches for long-acting contraception.

Types of MN patches	Materials	Acting time *in vivo*	Reference
Dissolvable MN patches	Dextran	10 hour	[37]
	Poly(vinyl alcohol) (PVA) and poly(vinyl pyrrolidone) (PVP)	2 days	[38]
	Hydroxypropyl methylcellulose (HPMC), and PVA	Over 1 week	[39]
Polymeric biodegradable MN patches	Poly(lactic-co-glycolic acid) (PLGA) and polylactic acid (PLA)	Over 45 days	[40]
	PLGA	Over 1 month	[40]
	PLGA and HPMC	Over 12 days	[41]
Silk fibroin-based biodegradable MN patches	Protein extracted from silk fibroin	Not applicable	[29]

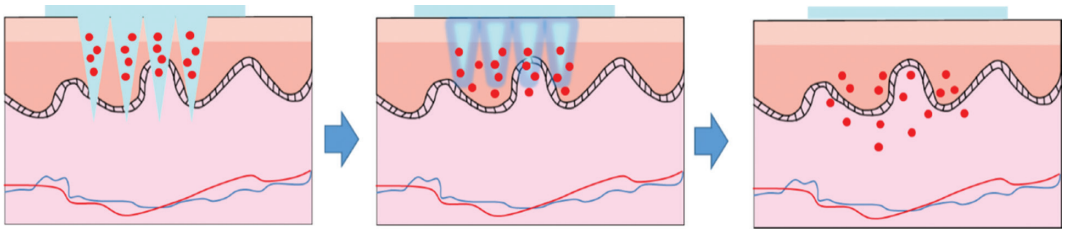

Figure 1 | The schematic of dissolving MN patches for sustained release of contraceptive hormones.

delivers 75.62 ± 22.79% 10 h after application. *In vivo* pharmacokinetic studies showed that the patch maximum serum concentration (C_{max}) was slightly lower than oral administration of an LNG suspension (equal drug amount), but there was not any difference in the time for LNG to reach C_{max} (T_{max}) between the two groups, indicating that the dissolvable MN patch could serve as an alternative to oral contraceptives [37].

To achieve long-term contraception using dissolvable MN patches, the Donnelly group [38] combined water-soluble MNs with a nano-formulation to incorporate a nanosuspension of nestorone (NES) in a dissolvable MN patch made of PVA and PVP. In so doing, the *in vivo* duration of the drug active concentration *in vivo* for up to 2 days [38]. MNs were fabricated by a two-step casting method, as follows: first casting, the NES and PVA nanosuspension is an aqueous solution in the mold as the MN tips; and second casting, the PVA 50K and PVP mixture as the substrate. This fabricated MN patch achieves a long-acting contraception for up to 2 days owing to the sustained release of nanoparticles. To obtain continuous release of contraceptives for a longer time by applying water-soluble MN patches, the Gao group [49] designed a rapidly-dissolvable MN patch loaded with etonogestrel (ENG) microcrystals, which had sustained release of the contraceptive (i.e., ENG) for > 1 week. Specifically, the MN tips were constituted by hydroxypropyl methylcellulose (HPMC), and the back layer was made of polyvinyl acetate, thus the HPMC dissolved completely after insertion, leaving a separated PVA layer on the skin [49]. ENG-loaded MNs (ENG-MNs) dissolve completely 1 hour after abdominal skin insertion in rats with a drug delivery efficiency > 60% [49]. *In vivo* pharmacokinetic studies also showed that ENG-MNs follow a more stable curve than intradermal injections with the same delivered drug amount, demonstrating a great potential of dissolvable MN patches for weekly contraception in a minimally invasive manner.

2.2 Polymeric biodegradable MN patches for sustained hormone release

Polymeric biodegradable MN patches are also suitable for long-acting contraception because biodegradable polymers have been used in subcutaneous implants [50] or in *in situ* injections, thus forming a hormone depot [51]. Unlike dissolvable MN patches, biodegradable MN patches are usually made of biodegradable polymers, such as poly[lactide-co-glycolide] (PLGA) [52], poly-lactic acid (PLA) [53], or polycaprolactone (PCL) [54], that continuously release drug from embedded MNs in the skin due to their slow degradation [55]. Further pursuing this strategy led to different formulations of biodegradable MN patches for sustained release of contraceptives. For example, Li et al. [40] designed a bubble MN patch for continuous release of LNG, which contains an air bubble structure between the LNG-loaded MN tip made of PLGA and PLA. The back layer is fabricated with water soluble materials, PVA, and sucrose [40]. The bubble size is controlled by adjusting the casting volume of the back layer during MN patch fabrication. Mechanical strength experiments demonstrated that the bubble MN patch tolerates > 0.15 N/needle compression, but easily breaks when using a shear force > 0.05 N/needle, which facilitates rapid separation of MNs from the patch backing. *Ex vivo* experiments on the porcine skin showed that > 95% of MNs detach from the patch backing and subsequently underwent slow degradation, achieving sustained release of LNG for > 1 month.

Based on the above research, Li et al. [56] developed another MN patch formulation for long-acting contraception that had a simpler structure and easier fabrication process by creating an effervescent formulation (sodium bicarbonate and citric acid) in the patch backing, thus promoting the rapid separation of LNG-load MN tips from the patch backing after skin insertion and contact with ISF in the skin [56]. Because of the effervescent property, only 10.7 ± 1.2 s was required to complete MN separation in phosphate-buffered solution (PBS), which was significantly faster than conventional MN patches without an effervescent formulation. After application of the effervescent MN patch in female rats, the LNG concentration in rat plasma persisted > 30 days above the human therapeutic level (i.e., 0.2 ng/mL), suggesting the great potential for long-term contraception. Moreover, the MN patches did not irritate rat skin and were preferred by women as a long-acting formulation over conventional approaches, such as hypodermic injection.

To facilitate the storage and use of long-acting contraceptive PLGA MNs containing LNG in hot seasons and regions, Wang et al. [41] designed a thermally-stable MN patch by including hydroxypropyl methylcellulose (HPMC) in PLGA MN tips due to its good biocompatibility and high glass transition temperature. After implantation of MN tips in rat skin, the release of LNG from embedded MNs in skin can persist > 21 days [41].

Apart from the long-acting contraception via sustained release of LNG, He et al. [52] developed an implantable MN patch that could be implanted into the skin *in situ* quickly for sustained release of ENG. He et al. [52] chose N-methyl pyrrolidinone as a solvent for the needle tip matrix to improve stability and biocompatibility, thus avoiding the possible impact of high temperature on the drug. By optimizing the MN formulation, the patch contained approximately 153.0 μg of ENG and had a > 92% drug delivery rate. The ENG level was detected until 14 days after application of such implantable PLGA MNs in rats [52].

2.3 MN patches made of silk protein for sustained hormone release

Silk fibroin, a natural polymer extracted from silk, accounts for 70%–80% of the silk content, and contains 18 kinds of amino acids, among which glycine, alanine,

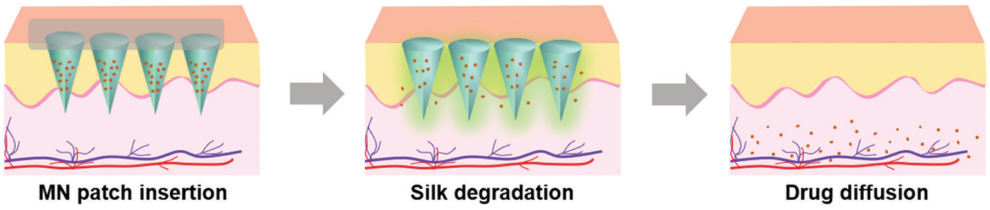

Figure 2 | The schematic diagram of silk fibroin-based MNs for sustained transdermal drug delivery.

and serine occupied > 80% of the total composition, thus possessing good biocompatibility [57]. Silk fibroin has satisfactory mechanical and physicochemical properties, such as good flexibility, strong tensile strength, great permeability, and slow degradation, and can be obtained in a variety of forms after different treatments, such as fiber, solution, film or gel, which have been widely used in biomedical applications [58, 59]. MNs made of silk fibroin have good skin insertion and slow degradation in the skin, thereby achieving sustained release of drugs in the skin (**Figure 2**).

Yavuz et al. [29] have demonstrated the use of silk fibroin-based MN patches for sustained hormone release up to 1 year. Yavuz et al. [29] made two kinds of MN patches: one MN patch involved direct incorporation of LNG in MNs; and the other MN patch contained LNG pre-encapsulated microparticles (LNG-MP) in MNs. An *in vitro* release test showed that sustained drug release reached up to 100 days when the drug was loaded directly inside the MNs, while release continued for > 1 year when the drug was loaded inside microparticles prior to casting inside the MN patches. In addition, Yavuz et al. [29] examined the effect of different silk parameters (e.g., concentration and molecular weight) in the MNs for drug release. The MNs with the highest concentration of 10% silk released the drug at the slowest rate, indicating the feasibility of silk protein-based MN patches for long-acting contraception.

3. ACCEPTABILITY AND BIOSAFETY OF MN PATCHES FOR LONG-ACTING CONTRACEPTION

3.1 Acceptability of MN patches for long-acting contraception

Although contraceptive transdermal patches were introduced in 2002, the transdermal patches failed to gain popularity by women due to the long wearing time (i.e., 1 week) and low drug permeation efficiency [60, 61]. Unlike transdermal patches, MN patches have attracted increasing attention for long-acting contraception owing to the fact that MN patches can directly penetrate the skin and deliver the payload to the skin with significantly improved transdermal delivery efficiency [62]. Moreover, the MN patches currently developed for long-acting contraception achieve rapid separation of drug-loaded MNs from patch backings or fast dissolution of MNs in skin, and only take a few seconds or minutes to complete the insertion and removal process [63]. Therefore, MNs do not need to be worn as long as traditional transdermal patches [64], which is more convenient for users. Indeed, some studies have been conducted to demonstrate the preference of MN patches for contraception by women.

Brunie et al. [65] conducted 16 focus group discussions and 20 in-depth interviews with women involving contraceptive MN patch preferences in India and Nigeria [65]. The study participants were of the opinion that MN patches had three advantages, including ease of use, not requiring daily intake, and avoiding private part exposure, which made MN patches more highly preferred than oral pills or IUDs [65]. Most women showed interest in self-application after learning correct use. The participants favored formulations affording protection from pregnancy for 3 or 6 months, and interest in short-acting MN patches for contraception was quite low. MN patches with a smaller patch size, less wearing time, >3 months of contraception protection, and affordable price were preferred bu most participants, which provided very important information for the future design of MN patch-based medical products.

To determine the preference of MN patches among women after using MN patches, Li et al. [56] applied the aforementioned effervescent MN patches to 10 human subjects. MNs were composed of PVA and sucrose, and the backing layer had an effervescent formulation. The MN patch had a 10×10 array, and each MN was conical (600 μm in length and a 150-μm base radius). The authors placed placebo effervescent MN patches on the dorsal skin of 10 women's hands to determine whether the patches were painless and acceptable. All the participants said the pain was negligible and much less than the pain induced by hypodermic injection. When asked about the preference between MN patches and hypodermic injection or daily oral pills, >90% participants were inclined to use monthly MN patches for long-acting contraception.

To further investigate the biosafety of long-acting MN patches by women and identify the optimal design of MN patches suitable for human use, Li et al. [66] fabricated 18 kinds of MN patches with different MN lengths (800–1500 μm), MN number (225–900 MNs per patch), and base diameters of MN (200–250 μm), and

applied these MN patches to recruit human subjects of reproductive age. Li et al. [66] first evaluated skin tolerability by scoring the pain and erythema intensity. The results showed that the pain scores induced by all the MN patches with different parameters were lower than shallow hypodermic needles and all MN patches were generally considered acceptable by the study participants. Some participants even reported that they felt no pain during the skin insertion of MN patches. These results demonstrated the non-invasive or minimally invasive property and considerable acceptability of MN patches.

3.2 Biosafety of MN patches

Skin irritation after MN insertion was evaluated to determine the biosafety of MN patches. Specifically, Zhou et al. [67] carefully recorded the skin changes over time after MN patch insertion. After MN patch insertion and removal, skin indentation appeared first and gradually recovered after 10 min. Slight swelling was observed after 1 h, but slowly disappeared within 24 h. There was no erythema or infectious symptoms 72 h after MN patch application. Consistent with the results of experiments involving animals, after applying MN patches to human skin, the skin of most participants' hands had faint erythema at the administration site, but faded after 1 h and completely recovered to normal skin after 24 h, indicating excellent biosafety. Even after application of the forementioned 18 big MN patches to human skin, the big MN patches only induced mild, or sometimes moderate, transient erythema on the skin, further suggesting satisfactory biosafety and biocompatibility to skin.

4. CONCLUSION AND PERSPECTIVES

MN patches have a promising potential as a long-acting contraceptive method due to highly-desireable properties, including self-administration, minimal invasiveness, negligible pain, and long-term protection. Indeed, these properties have attracted considerable interest. Three kinds of MN patches, including dissolvable, polymeric biodegradable, and silk fibroin-based biodegradable MN patches, have been utilized for sustained hormone release for long-term contraception. Compared with traditional long-acting formulations (e.g., hypodermic injections and subcutaneous implants), long-acting MN patches are preferred and have higher acceptability. In addition, MN patches are well-tolerated on animal or human skin, showing great biosafety and biocompatibility for pregnancy protection.

Future clinical translation of these MN patches for long-term contraception requires that the patches encapsulate an increased drug dose suitable for long-term use by humans. Current designs of long-acting MN patches can load ~1 mg drug per patch, which is sufficient for 1 month use in animals, but not sufficient for long-term use in human. Therefore, scaling-up of MN patches is necessary, either by enhancing MN length or by increasing the number of MNs in a patch. Although studies focusing on MN-based drug delivery systems have already demonstrated there is no severe erythema or inflammation caused by the application of MN patches, there is still a possible risk of infection considering the open microchannels caused by MNs after skin insertion. The time that it takes for skin resealing after MN patch application is important, which can be detected visually by trans-epidermal water loss or staining [68, 69]. Hence, skin recovery time can be added in the safety test of contraceptive MN patches. In addition, current safety evaluation generally examines the skin immediately or after a short time after MN patch use; long-term investigation of MN patch biocompatibility will be helpful to better evaluate the safety of MN patches. Moreover, the MN patches should have acceptable sterility and enough safety before they are applied to human subjects. Therefore, it is essential to make sure that the fabrication process of MN patches is under safe and clean manufacturing conditions. Finally, how to achieve reproducible insertion and application of the MN patches by patients for long-acting contraception is also a challenge, which requires the MN patches to possess a special design that can provide "feedback" to patients when the MNs successfully penetrated in the skin. Nevertheless, MN patches is a very promising alternative to traditional contraceptives and can enable women to better control their fertility by providing a self-administered, painless, and long-acting contraceptive.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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