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Advances in Microneedle Patches for Long-acting Contraception

Xue Jiang[1], Yongnian Zeng[1], Wen Zhang[1], Chenyuan Wang[1], Wei Li[1,2,3]*

1 Department of Thyroid and Breast Surgery, Zhongnan Hospital of Wuhan University, School of Pharmaceutical Sciences, Wuhan University, Wuhan, 430071, China

2 TaiKang Center for Life and Medical Sciences, Wuhan University, Wuhan, China

3 Key Laboratory of Combinatorial Biosynthesis and Drug Discovery (Ministry of Education), School of Pharmaceutical Sciences, Wuhan University, Wuhan, China

* Corresponding author: weili.mn@whu.edu.cn

ABSTRACT

Despite the progress in contraceptives, there is still a high rate of unintended pregnancy all over the world, due largely to the lack of effective, convenient and safe birth control methods. Compared with short-acting contraceptives, approaches that can offer long-term pregnancy protection attract more interest because of the reduced dosing frequency and improved patient compliance. As a novel transdermal drug delivery system, MN patch has been widely used for a variety of biomedical applications, including long-acting contraception, owning to the unique properties, such as enabling self-administration, avoiding pain and eliminating 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

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1. INTRODUCTION

Birth control still faces a huge challenge. It has been reported that 85 million pregnancies were unintended in 2012, accounting for 40% of all pregnancies worldwide [1]. Also, approximately 121 million unplanned pregnancies occurred between 2015 and 2019 [2], and this figure is likely to grow in the next 5 years [3]. Unplanned pregnancy usually results in unhealthy children gestation or accident abortion [4], which can cause a variety of complications in utero [5], leading to harmful effect to women's physical and mental health and bringing financial burden to families [6, 7]. Such a magnitude of unintended pregnancy is associated with economic burden and history of unplanned pregnancy [8, 9], due largely to the lack of effective and convenient contraceptive approaches [10], thereby desperately requiring the innovation of new contraceptives. Current birth control methods mainly include short-acting and long-acting contraceptives [11]. Compared to contraceptives that are only short-acting, such as condom and daily oral pills, long-acting contraceptives that can achieve sustained release of hormones, provide long-term protection from pregnancy and reduce medication frequency, 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) or vaginal rings [13]. Transdermal patches are generally applied on skin surface, and enable the release of hormones across the skin for one week, thereby achieving pregnancy protection for 7 days [14]. However, they suffer from long wearing time (i.e., 7 days) and very limited drug permeation efficiency (< 1%) through the skin due to the physical barrier of stratum corneum [15]. Subcutaneous implants or injectables are effective for contraception for a couple of years [16, 17], but they either require surgical implantation or need hypodermic injection which always involves operations from healthcare providers and causes much pain to women [18], thus significantly reducing patient compliance. IUDs or vaginal rings can also provide contraceptive effect for years [19], but they are invasive to uterus and usually need to be operated by trained medical personnel, which is not eligible to women with irregular menstruation, hypermenorrhea or hysteromyoma [20].

Microneedles (MNs) are micro-scale needles with the length ranging from tens to hundreds of micrometers [21]. MNs can puncture the outermost skin barrier and reach

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the epidermis with negligible pain, achieving improved drug delivery efficiency through skin [22, 23]. There are six types of MNs that have been widely used for transdermal drug delivery, including coated MNs [24], hollow MNs [25], dissolvable MNs [26], polymeric biodegradable MNs [27], hydrogel MNs [28] and silk fibroin-based biodegradable MNs [29]. In recent years, researchers have dedicated to the exploration of MNs application in contraception given the unique properties of MNs [30-32], such as enabling self-administration [33], supporting long-acting efficacy [34], facilitating delivery efficiency [35] and eliminating pain [36]. Among the six types of MNs, three of them have been reported for long-acting contraception. In this review, we summarize the developed contraceptive MN patches in literatures (**Table. 1**), discuss acceptability and safety of long-acting MN patches for contraception and provide future perspectives on clinical translation of MN patches for long-acting contraception.

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	[41]
	PLGA and HPMC	Over 12 days	[42]
Silk fibroin-based biodegradable MN patches	Protein extracted from silk fibroin	Not applicable	[29]

2. TYPES OF MN PATCHES FOR LONG-ACTING CONTRACEPTION

2.1 Dissolvable MN patches for sustained release of contraceptives

Dissolvable MN patches are generally made of water-soluble polymers, and can get rapid dissolution within a short time after skin insertion, avoiding biohazardous waste and drug remain in the residual patch [43]. Dissolvable MN patches are generally

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made of natural polysaccharides, like hyaluronic acid (HA) [44], dextran [45] and chitosan [46], or water-soluble polymers like PVA and PVP [47]. They have good solubility and can dissolve rapidly after contact interstitial fluid (ISF) in the skin [48, 49], thereby achieving transdermal delivery of different kinds of drugs including contraceptives (**Figure. 1**). For example, Yao et al added chitosan and beta-sodium glycerophosphate (β-GP) in the formulation of MNs, which significantly speeded the dissolution of MNs after skin insertion. In addition, hydroxypropyl beta cyclodextrin (HP-β-CD) was used to incorporate contraceptive hormone levonorgestrel (LNG) to improve the solubility of LNG. In vitro experiments exhibited that the MN patch dissolved 40% within 10 min, and about 70% MNs penetrated and dissolved in skin within 2 h, which was almost 2-fold higher than that of conventional MN patches. In vitro cumulative LNG release profile showed that the MN patch delivered 75.62 ± 22.79 % 10 h after application. In vivo pharmacokinetic studies showed that C_{max} of the patch was slightly lower than that of oral administration of LNG suspension (equal drug amount), but there was not any difference in T_{max} between two groups, manifesting that the dissolvable MN patch could serve as an alternative to the oral contraceptive [50].

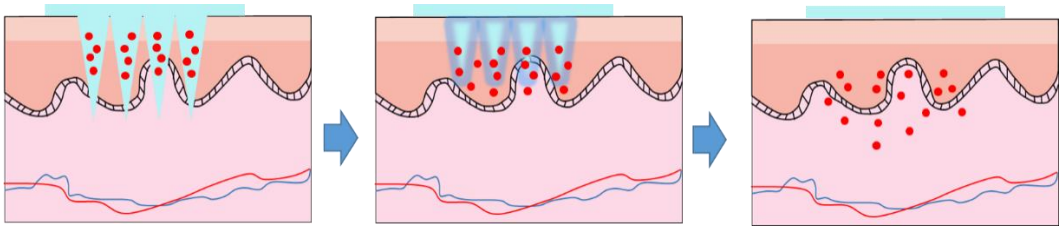

Figure. 1 the schematic of dissolving MN patches for sustained release of contraceptive hormones.

To achieve long-term contraception by using dissolvable MN patches, Donnelly group utilized the strategy of combing water-soluble MNs with nano-formulation to incorporate nanosuspension of nestorone (NES) in a dissolvable MN patch made of PVA and PVP, which extended the duration of the drug's active concentration in vivo for up to 2 days [38]. In this research, MNs were fabricated by a two-step casting method, including the first casting of the mixture of nanosuspension of NES and PVA aqueous solution in the mold as the MN tips and the second casting of the mixture of PVA 50K and PVP as the substrate. This fabricated MN patch can achieve a long-acting contraception for up to 2 days owing to the sustained release of nanoparticles. To obtain continuous release of contraceptives for longer time by

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applying water-soluble MN patches, Gao group further designed a fast dissolvable MN patch loaded with etonogestrel (ENG) microcrystals, which enabled sustained release of the contraceptive (i.e., ENG) for over 1 week [51]. Specifically, the MN tips were constituted by hydroxypropyl methylcellulose (HPMC), and the back layer was made of polyvinyl acetate, which allowed the HPMC to be dissolved completely after insertion, leaving separated PVA layer on the skin. Dissolution performance on rat's abdominal skin showed that the ENG-loaded MNs (ENG-MNs) could dissolve completely after skin insertion for 1 h with a drug delivery efficiency of over 60%. In vivo pharmacokinetic studies also showed that ENG-MNs exhibited 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 release of contraceptive

Polymeric biodegradable MN patches can also be applied for long-acting contraception, in view of biodegradable polymers have been used in the subcutaneous implants [52] or injectable in situ forming depots of hormones [53]. Not similar to dissolvable MN patches, biodegradable MN patches that are usually made of biodegradable polymers, such as PLGA [54], PLA [55] or polycaprolactone (PCL) [56], can continuously release drug from embedded MNs in the skin due to their slow degradation [57]. Dedicated to this strategy, several researches have designed different formulations of biodegradable MN patches for sustained release of contraceptives. For example, Li et al designed a bubble MN patch for continuous release of LNG which contained an air bubble structure between the LNG-loaded MN tip that were made of PLGA and PLA, and the back layer that were fabricated with water soluble materials, PVA and sucrose [41]. The bubble size could be controlled by adjusting the casting volume of backing layer during MN patch fabrication. Mechanical strength demonstrated that the bubble MN patch could tolerate more than 0.15 N/needle compression, but easily break when using a shear force above 0.05 N/needle, which facilitated rapid separation of MNs from patch backing. Ex vivo experiments on the porcine skin showed that more than 95% MNs detached from the patch backing and subsequently underwent slow degradation, achieving sustained release of LNG for over 1 month.

Based on the above research, Li et al further developed another MN patch formulation

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for long-acting contraception which had simpler structure and easier fabrication process by creating an effervescent formulation (sodium bicarbonate and citric acid) in the patch backing, promoting rapid separation of LNG-load MN tips from patch backing after skin insertion and contact with ISF in the skin [58]. Benefiting from the effervescence property, the MN patch only took 10.7 ± 1.2 s to finish MNs separation in phosphate buffered solution (PBS), which was significantly faster than that of conventional MN patches without effervescence formulation. After application of the effervescent MN patch in a female rat, the LNG concentration in rat plasma last over 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 were well tolerated by rat skin and received higher preference from women for the use of long-acting formulation than conventional approaches, such as hypodermic injection.

To facilitate the storage and use of long-acting contraceptional PLGA MNs containing LNG in hot seasons and regions, Wang et al designed a thermally stable MN patch by including 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 last for more than 21 days [59].

Apart from the long-acting contraception via sustained release of LNG, He et al developed an implantable MN patch that could be implanted into the skin in situ quickly for sustained release of ENG. They chose N-methyl pyrrolidinone as a solvent for needle tip matrix to improve stability and biocompatibility, avoiding the possible impact of high temperature on drug. Through optimization of MNs formulation, the patch contained about 153.0 μg ENG and displayed over 92% drug delivery rate. ENG level can be detected until 14 days after application of such implantable PLGA MNs in rats [54].

2.3 MN patches made of silk protein for sustained release of contraceptive

Silk fibroin, a natural polymer extracted from silk, accounts for about 70% to 80% of the content of silk, and contains 18 kinds of amino acids, among which glycine, alanine and serine occupied more than 80% of the total composition, thus possessing good biocompatibility [60]. 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

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different treatments, such as fiber, solution, film or gel, which have been widely used in biomedical applications [61, 62]. MNs that were 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**).

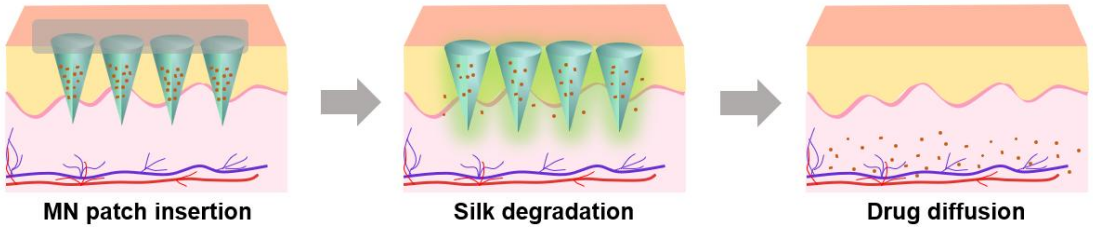

Figure 2. the schematic diagram of silk fibroin-based MNs for sustained transdermal drug delivery.

Yavuz et al have demonstrated the use of silk fibroin-based MN patches for sustained release of contraceptives up to 1 year [29]. They made two kinds of MN patches: one involved direct incorporation of LNG in MNs, and the other contained LNG pre-encapsulated microparticles (LNG-MP) in MNs. 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 more than one year when the drug was loaded inside microparticles prior to casting inside the MN patches. Apart from that, the authors examined the effect of different silk parameters (e.g., concentrations, molecular weights) 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 contraceptional transdermal patches were introduced in 2002, they failed to catch popularity of women due to the long wearing time (i.e., wearing the patch for 1 week) and low drug permeation efficiency [63, 64]. Not like the transdermal patches, MN patches have attracted increasing attention for long-acting contraception owning to the fact that they can directly penetrate the skin and deliver the payloads to the skin with significantly improved transdermal delivery efficiency [65]. Moreover, the MN patches currently developed for long-acting contraception can achieve either rapid separation of drug loaded MNs from patch backings or fast dissolution of MNs in skin,

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and only take a few seconds or minutes to complete the insertion and removal process [66], and therefore don't need to be worn as long as traditional transdermal patches [67], which provides much convenience to users. Some researches have been conducted to demonstrate the preference of MN patches for contraception by women.

Brunie et al conducted 16 focus group discussions and 20 in-depth interviews with women about preference for contraceptive MN patches in India and Nigeria [68]. Women thought that MN patches mainly had three advantages, including ease of use, not requiring daily intake and avoiding private part exposure, which made MN patches have higher preference than oral pills or IUDs. Most women showed great interest in self-application after learning correct use. 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 smaller patch size, less wearing time, more than 3 months contraception protection and affordable price were preferred in most people, which provided very important information for the future design of MN patch-based medical products.

To investigate the preference of MN patches among women after they received the application of MN patches, Li et al applied the forementioned effervescent MN patches to 10 human subjects [58]. In the patch, MNs were made of PVA and sucrose, and the backing layer was composed of effervescent formulation. The MN patch was 10×10 array, and each MN was conical with 600 μm in length and 150 μm in base radius. The authors performed placebo effervescent MN patches in dorsal skin of 10 women’s hands to test whether the patches were painless and acceptable. After administration of MN patches, all the participants said the pain was nearly ignored and much less than the pain induced by hypodermic injection. When being asked about the preference between MN patches and hypodermic injection or daily oral pills, over 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 fabricated 18 kinds of MN patches with different MN length (800-1500 μm), MN number (225 to 900 MNs per patch) and base diameters of MN (200-250 μm) and applied these MN patches to recruited human subjects of reproductive age. The authors firstly evaluated

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skin tolerability by scoring the pain and erythema intensity. 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 noninvasive or minimally invasive property and considerable acceptability of MN patches.

3.2 Biosafety of MN patches

In many research, skin irritation after MNs insertion has been evaluated to study the biosafety of MN patches. For example, Zhou et al carefully recorded the skin change over time after MN patch insertion [69]. 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 weren't any erythema or infection symptom occurred among the 72h after MN patch employment. Consistent with the result of experiments on animals, after the use of MN patches on human skin, the skin of most participants' hand occurred faint erythema at the administrated site, but faded away after 1 h and completely recovered to normal skin after 24 h, indicating excellent biosafety of MN patches. 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 skin, further suggesting satisfactory biosafety and biocompatibility to skin.

4. CONCLUSION AND PERSPECTIVES

MN patches have promising potentials as a long-acting contraceptional method due to the admirable properties, such as self-administration, minimal invasiveness, negligible pain and long-term protection, thus attracting a lot of interest. Three kinds of MN patches, including dissolvable MN patches, polymeric biodegradable MN patches and silk fibroin-based biodegradable MN patches, have been utilized for sustained release of contraceptives for long-term contraception. Compared with traditional long-acting formulations (e.g., hypodermic injections, subcutaneous implants), long-acting MN patches receive more preference and show higher acceptability owning to the above merits. Also, MN patches are well tolerated by animal or human skin, showing great biosafety and biocompatibility for pregnancy protection.

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Future clinical translation of these MN patches for long-term contraception requires that the patches are able to encapsulate more drug dose that are suitable for human long-term use. Current designs of long-acting MN patches can load ~1 mg drug per patch, which is enough for animal one-month use, but not sufficient for such a long time use in human. Therefore, the scaling-up of MN patches is very necessary, either by enhancing MN length or by increasing the number of MNs in a patch. Although researches about MN-based drug delivery systems already demonstrated there were 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 transepidermal water loss or staining [70, 71]. Hence, skin recovery time can be added in the safety test of contraceptive MN patches. In addition, current safety evaluation generally examines the skin immediate or a short time after MN patch use, long-term investigation of their 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 very important to make sure that the fabrication process of MN patches is under a safe and clean manufacturing condition. 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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DECLARATION OF COMPETING INTERESTS

The authors declare no conflicts of interest.

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