Microarray patches: breaking down the barriers to contraceptive care and HIV prevention for women across the globe

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HIV prevention for women across the globe

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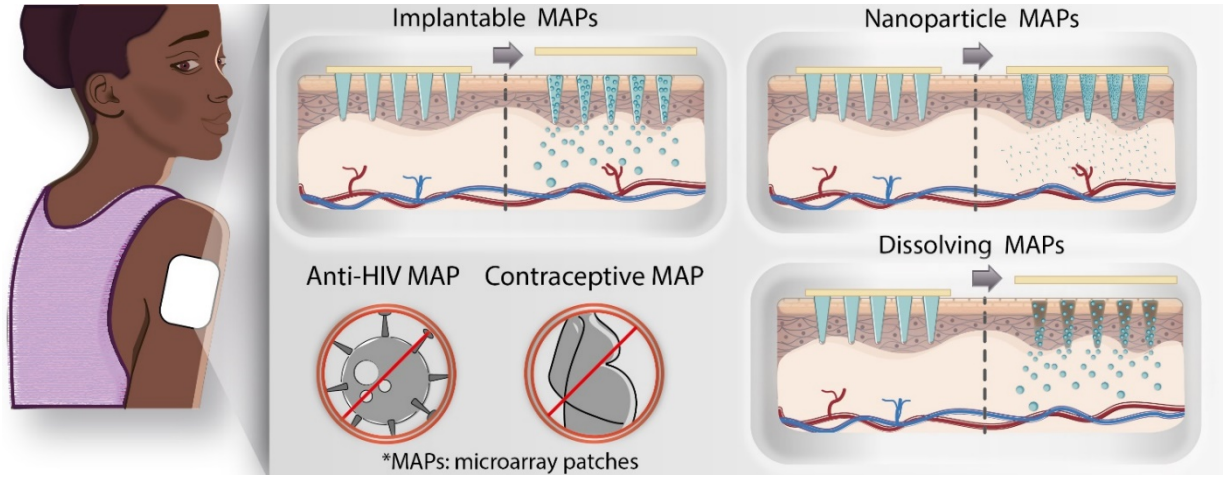
- There is a need for new products to protect women's sexual and reproductive health
- MAPs are capable of delivering contraceptives and antiretroviral drugs to the body
- MAPs have the potential for long-acting release, thus increasing users' compliance
- Nanocrystals are a promising approach for loading high doses of drugs into MAPs
- Issues surrounding both user needs and regulatory issues will need to be addressed

Despite the existence of a variety of contraceptive products for women, as well as decades of research into the prevention and treatment of human immunodeficiency virus (HIV), there is still a globally unmet need for easily accessible, acceptable, and affordable products to protect women's sexual and reproductive health. Microarray patches (MAPs) are a novel platform being developed for the delivery of hormonal contraception and antiretroviral drugs. MAPs provide enhanced drug delivery to the systemic circulation *via* the transdermal route when compared to transdermal patches, oral and injectable formulations. These minimally invasive patches can be self-administered by the user, reducing the burden on health care personnel. Since MAPs represent needle-free drug delivery, no sharps waste is generated after application, thereby eliminating possible MAP reuse and risk of needle-stick injuries. This review discusses the administration of contraceptive and antiretroviral drugs using MAPs, their acceptability by end-users, and the future perspective of the field.

Keywords: transdermal, microneedles, HIV, contraception, women's health, long-acting.


Implantable MAPs
Nanoparticle MAPs
Dissolving MAPs
Anti-HIV MAP
Contraceptive MAP
*MAPs: microarray patches

Despite the existence of various contraceptive products, as well as decades of research into the prevention and treatment of human immunodeficiency virus (HIV), there is still an unmet need for easily accessible biomedical products that allow women to protect their sexual and reproductive health. A significant portion of women in low- and middle-income countries experience insufficient access to contraception, which has negative effects on their health and well-being as well as negative impacts on families and communities. For women aged 15–44 years, HIV is the leading cause of death globally, with unsafe sex being the main risk factor [1]. Sub-Saharan Africa is the region that has been hardest hit by HIV, with women experiencing a greater risk of infection then men [1]. Lack of access to available, affordable, and acceptable products and confidential sexual and reproductive health services impacts women's ability to prevent unintended pregnancies and protect from sexually transmitted infections, including HIV [2]. By addressing these issues through the introduction of a women-centred approach for health services, leading to increased empowerment of women regarding their sexual autonomy and decision-making, the overall health of women in sub-Saharan Africa could be greatly improved [3]. Novel drug delivery systems, such as microarray patches (MAPs), which are being developed for the delivery of contraceptives and antiretroviral (ARV) drugs, could help to meet this need, significantly impacting women's health, not only in low- and middle-income countries but globally. This review discusses the development of MAPs for the delivery of contraceptive and ARV drugs, the hypothetical acceptability of these microneedle (MN)-based systems by end-users, and the future perspective of the field.

1.1. Contraception

Since oral contraceptive pills first became available in the 1960s [4], significant advances have been made in the field of contraception resulting in a variety of short- and long-term contraceptive methods. While approximately 60% of women globally use contraception [5], rates vary widely across countries and regions. In low- and middle-income countries, it is estimated that 218 million women have an unmet need for contraception [6], resulting in approximately 111 million unintended births and 73.3 million abortions annually [7].

Contraceptive methods are classified as hormonal or nonhormonal and can be either short-term, long-term, or permanent. Short-term methods include a range of delivery systems for hormonal contraceptives (oral pills, injectables, transdermal patches, vaginal rings) and barrier methods such as male and female condoms and diaphragms [5]. Long-term reversible contraception consists of intrauterine devices (hormonal and nonhormonal) and implants. Male and female sterilisation are permanent methods of contraception. [5]. However, not all these methods are available in every country. In some countries, traditional and less-effective methods, such as withdrawal and the calendar rhythm method, account for a high portion of method use [5]. **Figure 1** shows the contraceptive prevalence by

[5].

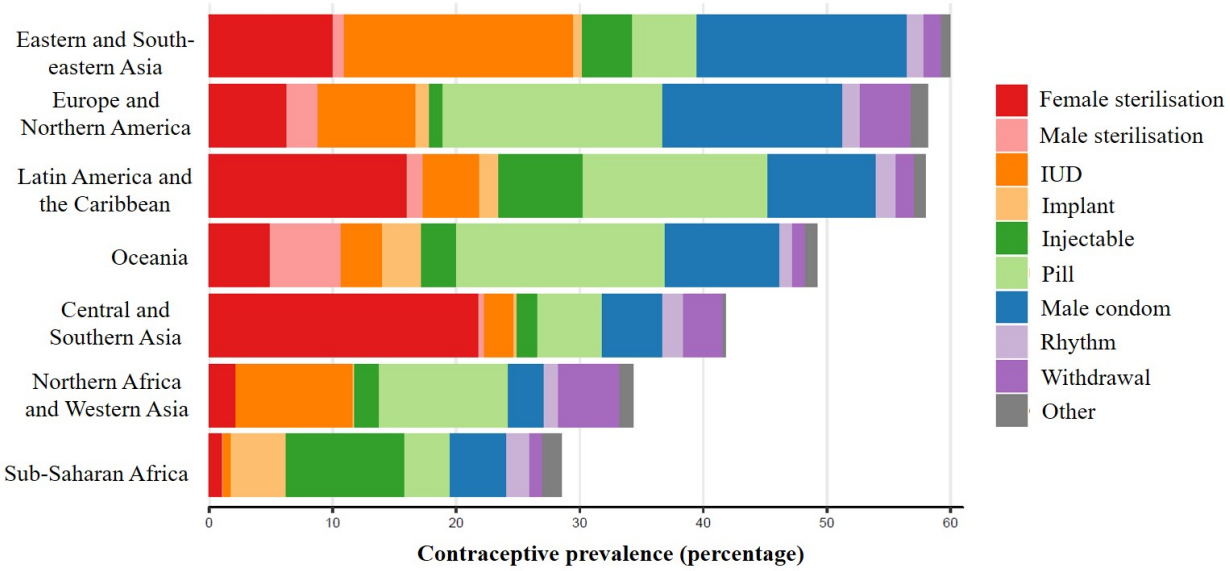


Figure 1. Prevalence of contraceptive methods among women of reproductive age (15–49 years) per region in 2019. Adapted and reprinted from reference [5] Copyright© 2019 United Nations, made available under the CC BY license http://creativecommons.org/licenses/by/3.0/igo/.

Female sterilisation and the male condom are the two most widely used methods worldwide, representing 24% (219 million) and 21% (189 million) of users, respectively [5]. However, female sterilisation is appropriate only when a woman has achieved her desired family size and—similar to most contraceptive methods—offers no protection from sexually transmitted infections. Additionally, this clinical procedure requires a highly trained provider and an appropriate facility [8–10]. Male condoms (and also the less widely available female condom) currently are the only methods that protect from both unintended pregnancy and sexually transmitted infections [11]. Condoms are highly effective but require consistent and correct use. Intrauterine devices are the next most widely used method globally [5]. They provide highly effective protection for 5 to 10 years depending on the type but require a trained provider for insertion and removal of the device. About 151 million women (16% of contraceptive users globally) use oral contraceptive pills [5]. Although access to contraceptive pills has dramatically changed women's freedom and autonomy regarding reproductive and sexual health since they were first introduced in the 1960s, some women have difficulty complying with the daily pill regimen. Inconsistent pill-taking is common, which leads to reduced use effectiveness [12]. Although sub-Saharan African countries report some of the lowest levels of contraceptive use [5], injectable contraception is the most widely used method among women in this region (Figure 1). Injectables

with the discreetness of the method (*i.e.* after delivery there is no obvious indication of method use) and method familiarity contribute to the method acceptance. Intradermal contraceptive implants recently have become more widely available in sub-Saharan African countries and represent one of the next most widely used methods. Subdermal implants provide contraceptive protection for up to 5 years depending on the brand but are—like other long-acting, highly effective methods—provider dependent [5] in that they require a trained health care provider to ensure correct insertion and removal [14].

Challenges with the above-described methods are that they either need to be taken daily (*e.g.* oral pills), require consistent and correct use (condoms), or require access to trained providers and clinic facilities (intrauterine devices and implants). Although transdermal contraceptive patches address some of these challenges, they are not readily available in low- and middle income countries [15] . Also, they need to be worn constantly, so they are not highly discreet, and a new patch must be applied weekly. Nonetheless, the uptake of transdermal patches in countries where they are available suggests the potential acceptability of the transdermal route for contraceptive care and brings focus to MAPs. These novel devices share the advantages of conventional transdermal patches while facilitating shorter wear times paired with the delivery of higher doses to potentially provide protection over a longer period of time. Later in this review, the advantages of MAPs for the delivery of contraceptives will be discussed in detail.

1.2. Human immunodeficiency virus

The first reports of a new fatal disease that later became known as acquired immune deficiency syndrome (AIDS) emerged in 1981 [16]. HIV, the retrovirus that causes AIDS, was identified two years later in 1983 [17]. While HIV spreads by sexual, percutaneous, and perinatal routes, the most common route of transmission is heterosexual contact [18]. In 2019, women accounted for more than half the number of people living with HIV worldwide, with 5,500 young women aged 15 to 24 years becoming infected every week [19,20]. So far, HIV has claimed almost 33 million lives, and at the end of 2019, approximately 38 million people across the world were living with HIV [20]. The AIDS epidemic disproportionately affects sub-Saharan Africa, especially the eastern and southern regions [20]. These areas are home to only 6.2% of the world's population but in 2019 they recorded almost half of the world's new HIV infections and AIDS-related deaths [20].

The highest risk factors for HIV transmission are unprotected sex or contact with contaminated blood; for example, through reuse of syringes, or accidental needlestick injuries. Developments in highly active ARV therapy over the past 20 years have dramatically increased the life expectancy of HIV-infected individuals [21]. With access to appropriate medication and care, HIV can be managed as a chronic condition with a life expectancy comparable to someone who is HIV-negative. However, access to HIV testing and viral suppression is still insufficient and varies by country/region, with only 67% of HIV-

the leading cause of death among girls and women of reproductive age in sub-Saharan Africa [23], and among adolescent girls and young women (aged 10–24 years) the number of new infections is double the rate that is observed in males of the same age group, as shown in **Figure 2** [23]. Various factors influence this high incidence, including behavioural, biological, and social issues [2]. For example, not only are adolescent girls and young women biologically at greater risk of infection, they often have sexual relationships with older men for economic support for their families or to pay for school fees [2]. The same behaviours and social norms that put women at risk of HIV also contribute to their risk for unintended pregnancies [2].

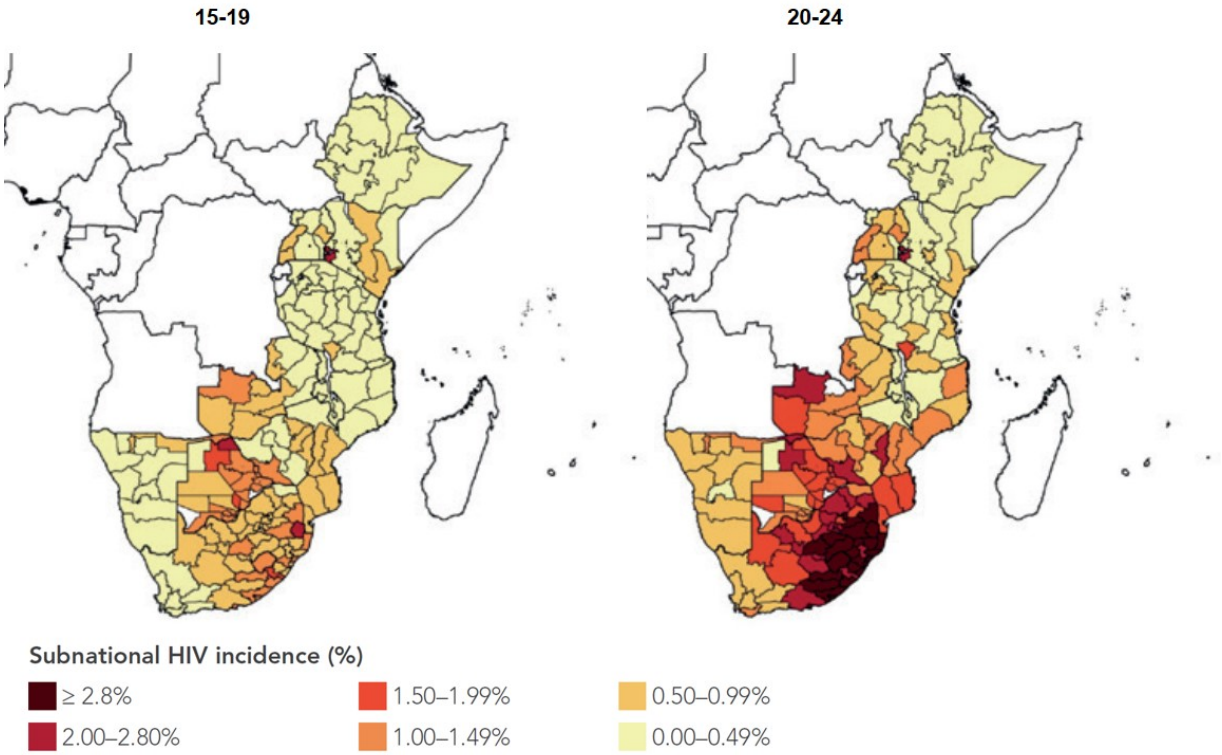


Figure 2. Map of HIV incidence (percent) among young women in selected countries in eastern and southern Africa. Reprinted and adapted from reference [2], Copyright© (2016), with permission from UNAIDS.

By promoting human rights and gender equality and introducing a women-centred approach for health services, the situation of women could be vastly improved [3]. Next to providing necessary information around sexual and reproductive health and rights, easily accessible medication for preventing and treating HIV is of the highest importance. Although the use of male and female condoms is the most common method for preventing the spread of sexually transmitted infections, including HIV (as well as the incidence of unintended pregnancies), pre-exposure prophylaxis for an HIV-negative individual and effective suppression of HIV through ARV therapy for an infected sexual partner greatly reduces the risk of transmission of the virus during sexual intercourse [24].

be offered to persons at high risk of HIV [25]. Currently, the only regimen available is oral tablets taken daily. Some user groups find daily pill-taking challenging, resulting in poor adherence [26]. Researchers are developing alternative options for delivery of long-acting ARV therapy and pre-exposure prophylaxis. One of these is the dapivirine vaginal ring, which recently received positive review by the European Medicines Agency [27]. Another investigational product involves the intramuscular injection of the long-acting ARV drug cabotegravir for pre-exposure prophylaxis [28]. The potential of these new systems is high, as the treatment intervals are greatly reduced compared to the daily oral regimen. Nevertheless, injections come with many drawbacks. Important to note is that next to causing pain, their deliverability is resource-intensive. The application requires trained personel and users frequently need to visit health care facilities [26].

Both unintended pregnancy and HIV have significant impacts on women's sexual and reproductive health, education, and social, emotional, and economic well-being. Additional development is needed to advance contraceptive and HIV prevention methods that are user-initiated and easy to use. New delivery methods—designed with users, providers, and other stakeholders in mind—could improve women's protection options, remedying the user, provider, and health care constraints that curently affect treatment provision, accessibility, acceptance, and overall success.

1.3. Microarray patches

One such delivery system, which could fulfil the previously mentioned requirements, is MAPs. MAPs are composed of micron-sized projections (microneedles, MNs) that are regularly arranged on, and protrude outwards from, a flat base plate. Upon MAP application, these MNs painlessly penetrate the outer layer of the skin, known as the *stratum corneum*, creating temporary microchannels in this highly effective barrier to diffusion, through which enhanced transdermal drug delivery can be achieved [29–31]. Many researchers are developing MAPs for different health indications. With upwards of 1,600 peer-reviewed articles based on drug delivery *via* MAP technology published since 2010, this innovative method of drug delivery has garnered sizeable attention across many research areas in recent years [32]**.**

MN-based devices can be classified into five categories, namely those that possess solid, coated, hollow, dissolving/biodegradable, and hydrogel-forming MNs as illustrated in **Figure 3**. MAPs with solid MNs, the first type to be invented, are used following a 'poke and patch' methodology, wherein the MAP is applied to the skin and then removed before a conventional drug formulation (*i.e.* a cream or liquid) is topically applied, resulting in increased drug permeation into and through the skin [33,34]. MAPs with coated MNs, as their name suggests, possess solid MNs that are coated with a drug-containing formulation. Following a one-step, 'coat and poke' methodology, these MAPs deliver drug intradermally upon dissolution of the MN coating post-application [35–37]. Devices that have hollow

the delivery of liquid drug reservoirs, which can be easily administered *via* inserted MNs with the aid of positively applied pressure [38–40]. MAPs comprising dissolving or biodegradable MNs ('poke and dissolve') are typically composed of a biocompatible and soluble or biodegradable matrix, in which drug is dispersed. Upon application, the inserted MNs absorb interstitial fluid and dissolve or biodegrade, depositing the therapeutic agent intradermally [41–43]. The final MN-based device type, hydrogel-forming, or 'poke and swell' MAPs, is a recent innovation in the field. These MAPs consist of an array which is formed from a highly swellable polymer, atop which is fixed a separately formulated drug reservoir [44–46]. In a similar manner to dissolving MNs, hydrogel-forming MNs imbibe interstitial fluid upon application to the skin; however, rather than dissolve, these MNs swell to form an aqueous hydrogel matrix *in situ.* At this point, drug diffuses from the separately fabricated reservoir, through the swollen matrix and into the skin [47–49].

Importantly, the two latter types of MAP (*i.e.* dissolving/biodegradable and hydrogel-forming) are removed from the skin with their MNs in the dissolved or swollen state, respectively. This means that they are incapable of re-insertion and therefore pose no risk of infectious disease transmission; a desirable characteristic, particularly in high-risk areas such as sub-Saharan Africa [50]. Furthermore, depending on the stability of the delivered drug or vaccine, these devices may not require cold chain storage at any point before administration, again highlighting their suitability for effective provision in resource-constrained areas [51]. MAPs are minimally invasive devices that can be successfully self-administered without assistance once the client has been initially trained by a provider. This could reduce the burden of clinic visits both for the provider and the client. Not only does this technology eliminate the fear typically associated with hypodermic needle use, but it also provides an ideal platform for administering contraceptive and/or HIV treatment in a discreet manner. Additional advantages of this technology, such as avoidance of first-pass metabolism and drug delivery in a rate-controlled or long-acting manner, can serve to reduce side-effect incidence and dosing frequency, which in turn may lead to increased treatment adherence [52–54].

Figure 3. A schematic representation of the five different microneedle-based device types used to facilitate transdermal and intradermal drug delivery. **A-** solid, **B**- coated, **C-** hollow, **D-** dissolvable/biodegradable and **E**- hydrogel-forming.

The skin is the largest organ in the human body and carries out a wide range of functions such as keeping the temperature and electrolyte balance, and providing protection from harmful physical, chemical and

dermis and hypodermis, which vary in terms of thickness with age, anatomical site and level of hydration, among other factors. In the forearm dorsal of healthy humans, for instance, the average thickness of the epidermis is approximately of 75 μm [56], with the dermis ranging from 2 to 4 mm in different parts of the body. As a rule of thumb, the length of the MNs must be of less than 1 mm in order to avoid bleeding and stimulation of the nociceptive sensory neurons that innervate the skin [29]. As schematized in Figure 3A, MNs can easily pierce the epidermis, depositing their drug cargo in the viable epidermis. The extracellular fluids present in this layer dissolve the actives and allow their diffusion to deeper layers of the skin, reaching the microcirculation, and ultimately the systemic circulation. Several factors come into play when considering a local or systemic effect, and are related to the physicochemical nature of the drug, formulation strategy in place (i.e. particle size reduction, encapsulation, use of surfactants, etc.) and MAP geometry and composition. Some examples of works dealing with these variables will be discussed in the following sections of this review.

2. MAPs for contraception

Globally, women encounter high rates of unintended pregnancies [57], and between 2015 and 2019, these unintended pregnancies led, on average, to 73.3 million induced abortions each year [58]. Annually, 111 million pregnancies in low- and middle-income countries are unintended, which accounts for approximately half of all pregnancies (49%)[6]. This high incidence of unintended pregnancies poses a heavy emotional and economic burden, not only on women, but on society at large.

Nonhormonal contraceptive methods, such as condoms and diaphragms, provide physical barriers for pregnancy protection but are susceptible to failure if used incorrectly [59]. Hormonal contraceptives like oral pills require frequent dosing which might lead to compliance problems, while the use of long-term methods such as implants or intrauterine devices requires access to trained health personnel. Moreover, women's concerns about side effects, misperceptions about the risk of pregnancy, and opposition from family members or other individuals in society can reduce the likelihood of contraceptive use [15,60,61]. Therefore, to improve the utility of contraception, there is an urgent need to develop new contraceptive methods with high accessibility and acceptability. MAPs are currently attracting great interest in the field of trans- or intradermal drug and vaccine delivery as well as therapeutic drug monitoring [62]. All the advantages that MAPs possess in comparison to hormonal contraception *via* conventional drug delivery systems, such as pills, patches, and injectables, make MAPs a unique alternative for the development of novel and user-friendly contraceptive products. Furthermore, there is a need for long-acting formulations that women can use conveniently, easily, and discreetly. To this end, a number of contraceptive MAP formulations have been studied, representing substantial preclinical progress over the past five years in the field of long-acting, contraceptive MAPs (**Table 1)**.

Drug	Type of microarray patch	Microneedle material	Backing layer material	Release of therapeutic dosages	Ref.
Levonorgestrel	Biodegradable	Silk fibroin	Silk fibroin	Up to 100 days	[63]
Levonorgestrel	Biodegradable + air bubble	PLGA + PLA	PVA + sucrose	Over 30 days	[64]
Levonorgestrel	Biodegradable + effervescence	PLGA	PVP + citric acid + sodium bicarbonate; adhesive paper	Over 30 days	[57]
Levonorgestrel	Biodegradable	PLGA + trehalose	PVA + PVP	Up to 13 days	[65]
Etonogestrel	Biodegradable	PLGA	PVA + PVP	Up to 14 days	[66]
Etonogestrel	Dissolving	HPMC	PVA	Up to 9 days	[67]
Levonorgestrel	Dissolving	Dextran + chitosan + beta-sodium glycerophosphate + HP-β-CD	PVP	Up to 4 hours	[68]

Abbreviations: HPMC, hydroxypropyl methylcellulose; HP-β-CD, hydroxypropyl-β-cyclodextrin; PLA, poly(lactic acid); PLGA, poly(lactic-co-glycolic) acid; PVA, poly(vinyl alcohol); PVP, polyvinyl pyrrolidone.

Yavuz *et al* studied the sustained release of levonorgestrel from biodegradable MAPs made from natural polymer silk fibroin [63]. For this purpose, they isolated silk fibroin of different molecular weights from *Bombyx mori* cocoons. MAPs were cast from aqueous blends of levonorgestrel, silk fibroin, and other excipients using polydimethylsiloxane moulds. Each MAP consisted of 400 conical MNs (20 x 20 arrangement, height 700 μm, base diameter 360 μm) in an area of 1.5 cm x 1.5 cm (2.25 cm^2). Air bubbles were removed using a vacuum oven. Different formulations were tested regarding their *in vitro* release of levonorgestrel. All formulations delivered this contraceptive above the required daily dose of 30 μg/d, but the release profiles differed significantly. Loading the drug powder only into the MAPs (5 mg/mL levonorgestrel, 7% w/v silk fibroin) resulted in a release of 73.3 ± 5.9% over 43 days. The incorporation of levonorgestrel into silk microparticles prior to loading the MAPs led to a reduced total drug load and no improvement regarding the release. Adding dimethyl sulfoxide to the blend resulted in higher drug loading (20 mg/mL in the formulation, 10 mg levonorgestrel/MAP) and a slower release over the course of 93 days (51.4 ± 1.1%). While the molecular weight of the silk fibroin did not have an impact on the release rate, the rate slowed down when the silk concentration was increased. The addition of solubility enhancers improved the total release of levonorgestrel (61.2 ± 1.1% for 1% Tween-20 and 62.1 ± 1.7% for 5% β-cyclodextrin). All MAPs were stable under accelerated conditions

term storage [63]. This study demonstrated successfully that the natural, fully biodegradable polymer silk fibroin is a feasible option for the fabrication of contraceptive MAPs, as the authors achieved a sustained release of levonorgestrel over a period of up to 100 days. However, MAPs were not tested regarding their insertion efficiency and, importantly, extensive *ex vivo* skin and *in vivo* pharmacokinetic studies are needed to show if this promising concept could be translated into a marketable product.

Li *et al* developed two different types of MAPs for the sustained delivery of levonorgestrel, with a special focus on the rapid separation of MNs from their backing layer to achieve short application times [57,64]. In both studies, MAPs were cast from polymeric solutions using polydimethylsiloxane moulds to obtain MAPs that had 100 conical MNs (10 x 10 arrangement) in an area of 7 mm x 7 mm (0.49 cm^2). Individual MNs had a height of 600 µm with a base radius of 150 µm and were attached to wider conical pedestals with a height of 350 µm. One study focused on the design of MAPs made from the biodegradable polymers poly(lactic acid) and poly(lactic-co-glycolic) acid [64]. To achieve rapid separation from the backing layer upon application, an air bubble was trapped at the base of each MN as described in **Figure 4A**. Under application of a shear force, MNs could, thus, easily be snapped off and the backing layer removed. MNs were cast from a solution of 5% (w/v) poly(lactic acid), poly(lactic-co-glycolic) acid, and levonorgestrel (72:8:20) dissolved in a mixture of dioxane, tetrahydrofuran, and water (70:25:5). The fabrication process for filling the MN cavities involved application of the casting solution to the mould and centrifugation, followed by application of dioxane only and centrifugation, and was repeated three times. After a drying period of 12 hours, the backing layer was cast from an aqueous solution of 18% (w/v) poly(vinyl alcohol) 6,000 Da, and 18% (w/v) sucrose. This was gently applied to trap an air bubble between the two layers. The bubble size ranged between 310 to 105 µm in depth, depending on the amount of solution used for the backing layer. MAPs tolerated compression forces expected for successful skin insertion and the MNs snapped off easily under a shear force. In comparison, the MNs on MAPs without air bubbles merely bent under shear force rather than detaching fully. *Ex vivo* skin insertion into porcine skin demonstrated that after an application time of 5 seconds (thumb pressure) followed immediately by a gentle sliding movement, 95% of MNs were detached from the backing layer, and 90% of an incorporated fluorescent model dye (Nile red) was delivered. In an *in vitro* release study, a relatively constant release of 0.3% to 2.2% per day for up to 45 days, depending on the release medium used, without initial burst release was observed. The authors confirmed these results in an *in vivo* study in Sprague-Dawley rats. Upon application for 5 seconds and removal of MAP backing layers, the MNs were fully embedded under the skin. The peak plasma concentration of levonorgestrel of 1.05 ± 0.14 $ng \cdot mL^{-1}$ was reached 6.0 ± 1.9 days post-application and an overall bioavailability of 70% was achieved (AUC 598 ± 141 $ng \cdot h \cdot mL^{-1}$). Plasma levels remained above the therapeutic concentration of 200 $pg \cdot mL^{-1}$ for 30 days, and then hovered around this level until 45 days, before dropping to insignificant levels by 60 days. These data and the

MAPs would be sufficient for contraception for at least one month [64]. The results achieved by Li *et al* are highly promising due to the short application time and the constant release of therapeutic concentrations of levonorgestrel for 30 days. Whilst this MAP design shows great promise, it is not without certain drawbacks. For example, the process of up-scaling, with particular reference to the preservation of the mechanical integrity of MAPs during storage and transportation, may prove difficult due to the presence of delicate air bubbles inside the MNs, and therefore will need to be evaluated further. Additionally, the biodegradation of poly(lactic acid) occurs over a time period of approximately 24 months. This may be problematic as repeated MAP application may lead to polymer build-up in the skin over time. Future research may allay some, if not all, of the issues highlighted here.

Leading on from the work detailed above, similar results were achieved by the same research group in a follow-up study that explored the delivery of levonorgestrel using effervescent MAPs [57]. In this study, MNs were made from poly(lactic-co-glycolic) acid and levonorgestrel only, without addition of poly(lactic acid). The first casting solution contained levonorgestrel microcrystals (17.1 ± 7.6 μm) suspended in a solution of poly(lactic-co-glycolic) acid in diglyme/water (95%/5% v/v). After application of the casting solution and centrifugation, the moulds were washed once with the solvent solution only, before a drying period of 12 hours. The effervescent layer was cast from a solution of 13% (w/v) poly(vinyl pyrrolidone) (360/55 kDa, 50/50% w/w), 4% (w/v) citric acid, and 5% (w/v) sodium bicarbonate in pure ethanol. After complete drying, MAPs were removed from their moulds with a layer of adhesive paper. The idea behind this was that upon insertion, citric acid and sodium bicarbonate present in the base of each MN would be exposed to the skin's interstitial fluid and react, producing bubbles of carbon dioxide which would mechanically weaken the interface between the backing layer and the MN tips, leading to rapid separation as indicated in **Figure 4B**. Indeed, upon contact with fluid *in vitro*, the MNs separated within 10.7 ± 1.2 seconds, and an application time of 50 seconds in *ex vivo* porcine skin was sufficient to ensure the separation of 96 ± 4% of all MNs from the backing layer. Release of levonorgestrel *in vitro* and results of a pharmacokinetic study *in vivo* in Sprague-Dawley rats showed similar results compared to the study of the same research group as detailed above [64]. The peak plasma concentration of 0.83 ± 0.03 $ng \cdot mL^{-1}$ was reached after 98 ± 84 hours and concentrations stayed above therapeutic levels of 200 $pg \cdot mL^{-1}$ for more than 30 days (AUC was 482 ± 79 $ng \cdot h \cdot mL^{-1}$). The release over 30 days was constant, following roughly first-order release kinetics. After 60 days, drug plasma levels dropped to essentially zero [57]. This study by Li *et al* highlighted clearly the advantages of MAPs for the intradermal delivery of contraceptives, especially in low- and middle-income countries. The straightforward MAP fabrication process developed here is substantially more amenable to up-scaling than that of the precursor, bubble-containing MAPs. It should be noted, however, that in order to prevent premature MN effervescence during storage, package humidity must be controlled through the use of a suitable desiccant.

Figure 4. Rapidly separable MAPs for long-acting delivery of levonorgestrel developed by Li *et al* [57,64]. **A-** The rapid separation of the microneedles is achieved by the incorporation of an air bubble between each microneedle and the baseplate [64]. In **B- T**he rapid separation of the microneedles is achieved by the incorporation of effervescent excipients on the microneedle bases [57]. Abbreviations: MN, microneedle; PLA, poly(lactic acid); PLGA, poly(lactic-co-glycolic) acid; PVA, poly(vinyl alcohol).

Zhao *et al* proposed MAPs with implantable MNs that consisted of drug-containing poly(lactide-co-glycolic) acid arrowheads regularly arranged on a water-soluble supporting array [65]. Trehalose was introduced as a porogen to modulate the release of the hydrophobic drug levonorgestrel from the poly(lactide-co-glycolic) acid-based MNs. Upon skin insertion and contact with interstitial fluid, trehalose dissolved to create pores in the biodegradable poly(lactide-co-glycolic) acid matrix, through which levonorgestrel diffused intradermally. The MAPs were fabricated utilising polydimethylsiloxane moulds with a 700 μm MN height, 320 μm base width, and 600 μm interspacing. To manufacture the MNs, a solution of poly(lactide-co-glycolic) acid, levonorgestrel, and trehalose in N-methyl-2-

excess formulation and evaporation of the solvent, the moulds were placed on a heating plate at 75°C to melt the MNs. Preformed water-soluble supporting MAPs of the same dimensions made from an aqueous blend of poly(vinyl alcohol) (30 kDa) and poly(vinyl pyrrolidone) (3,000 kDa) were aligned with the cavities of each mould and inserted into the molten MNs. Finally, MAPs were separated from the moulds after rapid cooling. To visualise skin penetration and the separability of the MNs from their supporting, dissolvable MAPs, levonorgestrel was replaced by a hydrophobic red fluorescent dye. Confocal laser scanning microscopy analysis illustrated that MAPs exhibited a favourable insertion depth of approximately 300 μm. At 20 minutes post-application, the MNs were fully separated from the dissolving MAPs and implanted in the skin to form drug depots. The incorporation of trehalose into the MNs significantly improved the *in vitro* drug release because the pores created allowed for a quick diffusion of levonorgestrel. After 21 days, 76.2 ± 3.9% of levonorgestrel was released from the MNs with 33% (w/w) trehalose. An *in vivo* pharmacokinetic study (Sprague-Dawley rats) demonstrated that the release of levonorgestrel from trehalose-containing MNs (13 days) was 3 days shorter than for those without a pore-forming agent. Meanwhile, achieved levonorgestrel plasma concentrations were clearly higher. Drug delivery was additionally enhanced by faster erosion of porous MNs due to their increased surface area [65]. In this study, it was demonstrated that MAPs with implantable porous poly(lactide-co-glycolic) acid-based arrowheads are a promising way to modulate the intradermal release of hydrophobic drugs. However, whether the *in vivo* release performance of levonorgestrel over a duration of only 13 days meets stakeholder needs for a new contraceptive product is uncertain and will have to be investigated further.

In a different study, He *et al* developed MAPs with poly(lactide-co-glycolic) acid MNs that can be implanted into the skin for sustained contraceptive release [66]. These MAPs were composed of separable poly(lactide-co-glycolic) acid MNs containing encapsulated etonogestrel, and a water-soluble backing layer. Specifically, poly(lactide-co-glycolic) acid and etonogestrel were dissolved in N-methyl pyrrolidinone and the solution was injected into polydimethylsiloxane moulds. For rapid precipitation of etonogestrel into fine crystals evenly distributed throughout the MNs, the optimal evaporation conditions for the solvent were 70°C for 4 hours. An aqueous blend containing poly(vinyl pyrrolidone) (360 kDa) and poly(vinyl alcohol) was used for casting the backing layer. After drying for 6 hours, MAPs were removed, fully intact, from the moulds. It was found that a maximum drug loading of 153.0 ± 13.5 μg and an effective drug utilisation rate of 92.6 ± 8.1% were obtained for a polymer-to-drug ratio of 60:40 (% w/w). For MAPs with an MN interspacing of 500 μm, the implantation rate into porcine ear skin was only approximately 30%, whereas an MN implantation rate of 100% was achieved for interspacings of 600 μm and 700 μm. Furthermore, the smooth surface of conical MNs facilitated their intradermal implantation as observed in **Figure 5A** and **B**. No burst release was observed during *in vitro* release studies in skin, and the release remained relatively constant over a duration of 9 days, reaching

MAPs (600 µg etonogestrel, administration area 2.56 cm^2) were applied to each rat for 6 hours. Maximum plasma concentrations in the control group (subcutaneous injection of the same dose) were reached after 1 hour (41.0 ± 11.6 ng/mL) and the drug was able to be detected for up to 72 hours. Encouragingly, MAPs provided a more gradual release profile, with peak plasma levels of 6.6 ± 0.9 ng/mL reached after 8 hours and etonogestrel detectable up to 336 hours after application, as illustrated in **Figure 5C**. Theoretical calculations revealed that an administration area of 3.6 cm^2 would be sufficient for reaching therapeutic plasma levels of etonogestrel in humans for a duration of 14 days [66]. These results clearly suggest that MAPs with implantable MNs could provide a convenient method to deliver long-acting contraceptives for women by self-administration.

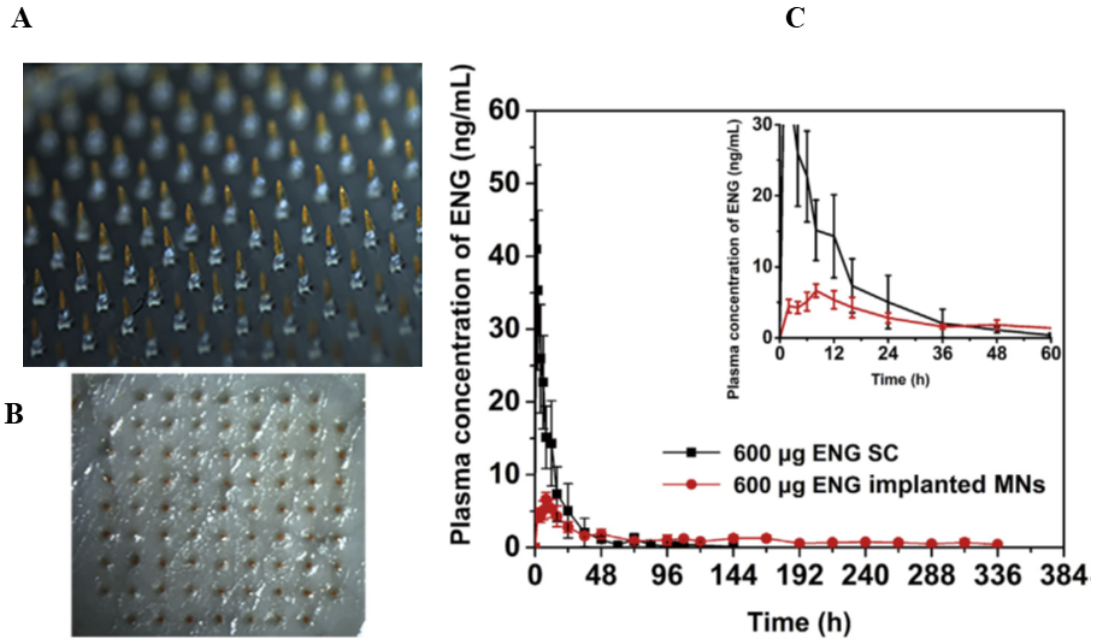


Figure 5. Systemic long-acting delivery of etonogestrel from implantable MAPs. **A-** Optical microscopy images of poly(lactic-co-glycolic) acid implantable microneedles prepared with conical moulds. **B-** Optical microscopy images of in-skin microneedle insertion. **C-** Plasma exposure of after subcutaneous injection (-■-) and implantable microarray patches (-●-). Abbreviations: ENG, etonogestrel; MN, microneedle; SC, subcutaneous. Reprinted from reference [66], Copyright© (2020), with permission from Elsevier.

In contrast to the studies described above that utilised biodegradable polymers for the sustained delivery of contraceptives, He *et al* explored the possibility of loading etonogestrel microcrystals into dissolving MAPs [67]. Each MAP consisted of 400 pyramidal MNs with a height of 550 µm and a base width of 300 µm. Etonogestrel microcrystals of two different size distributions (10–30 µm and < 10 µm) were obtained by filtration. For fabrication of MNs, they were mixed with an aqueous hydroxypropyl methyl

aqueous poly(vinyl alcohol) solution. Not only did this bilayer MAP design avoid unnecessary drug wastage, but it also facilitated easy separation of MNs from their backing layer upon skin insertion due to the different dissolution rates of the polymers that made up each component. Each MAP contained 550 µg etonogestrel and was strong enough to be inserted into porcine ear skin, exhibiting an insertion depth of approximately 280 µm. An *in vivo* in-skin dissolution test (abdominal skin of rats) demonstrated that the MNs rapidly dissolved within 60 minutes, producing a drug delivery efficiency of 63.8 ± 2.0%. The *in vitro* release rate across porcine skin of MAPs loaded with etonogestrel microparticles sized 10–30 µm was almost 7-fold higher than for those loaded with particles sized less than 10 µm over a period of 15 days. An *in vivo* pharmacokinetic study in Sprague-Dawley rats (application of one, two, or four MAPs per rat for 1 hour) showed that the plasma concentrations of etonogestrel were dose-dependent. Maximum plasma concentrations (4.2–16.5 ng/mL) were reached after 2 hours. Although the relative bioavailability of etonogestrel encapsulated in MAPs was almost the same as that of intradermal injections, the plasma level of etonogestrel after the application of MAPs was steadier and detectable up to 216 hours post-application (etonogestrel was only detected up to 144 hours post intradermal injections). Comparison with the contraceptive implant Nexplanon® and theoretical calculations revealed that the application of two MAPs would be sufficient to release therapeutic plasma levels of etonogestrel for 10 days [67]. Thus, this study successfully demonstrated the potential of yet another MAP-based alternative for the delivery of contraceptives in a sustained manner.

Using an alternative method, Yao and colleagues presented levonorgestrel-loaded dissolving MAPs as a form of emergency contraception, rather than regular birth control [68]. Their focus lay on improving the dissolution capability of this hydrophobic drug as well as enhancing MAP drug loading. MAPs were cast using polydimethylsiloxane moulds consisting of 100 conical MNs, with a base width of 300 µm, height of 800 µm, and tip-to-tip interspacing of 900 µm. A thermosensitive gel of chitosan and beta-sodium glycerophosphate was incorporated into the dextran matrix to enhance the dissolution process. Fastest dissolution times were achieved by a material with a phase transition temperature of 37°C. Levonorgestrel was encapsulated into hydroxypropyl-β-cyclodextrin to increase its aqueous properties, thus the total drug load could be increased from 1.73 µg to 66.94 µg per array. The MAP backing layer was cast from an aqueous poly(vinyl pyrrolidone) (360 kDa) blend. The mechanical strength of fabricated MAPs was high enough for successful penetration into porcine skin, and upon application, 69.32 ± 4.23% of all MNs dissolved within 2 hours. Moreover, MAPs showed higher *in vitro* transdermal drug delivery efficiency (75.62 ± 22.79% of the total drug load was delivered 10 hours post-application) than MAPs prepared only from dextran (30%) as a result of the accelerated dissolution rate of the novel MN matrix. Levonorgestrel plasma concentrations (AUC) achieved in an *in vivo* study in Sprague-Dawley rats after application of MAPs or an oral suspension were comparable. Peak plasma

were achieved after 0.5 hours. No drug was detectable 4 hours after application [68]. In this study, Yao *et al* successfully fabricated MAPs that were able to deliver a high dose of levonorgestrel within a very short period of time, exhibiting similar drug plasma levels as an oral formulation. Before taking an oral emergency contraceptive, women are warned that gastrointestinal side effects, such as nausea and vomiting, commonly occur, and that repeated doses are sometime required. Not only do these side effects amplify the unpleasantness of what is often a highly stressful situation for many women, but they can adversely affect the extent of drug absorption, and therefore the overall efficacy of emergency oral contraceptive treatments. This work has illustrated that intradermal delivery of an emergency contraceptive in a minimally invasive manner using MAPs represents a viable alternative to conventional oral formulations by potentially avoiding gastrointestinal side effect incidence and therefore providing an improved standard of emergency contraceptive care.

In comparison to other contraceptive methods, the potential benefits of future MAP-based delivery of long-acting contraceptives could include ease of use (by eliminating the daily obligation of oral contraceptives); avoidance of the invasive placement of implants, injections, or intrauterine devices; expansion of access to women in low- and middle-income countries; and provision of sustained contraceptive protection that can be self-administered in a highly discreet manner. Additionally, by avoiding first-pass metabolism, the delivery of contraceptive drugs *via* MAPs could potentially provide birth control that simultaneously demonstrates increased overall efficacy and reduced side effect incidence compared to oral contraceptives. The studies discussed here clearly indicate that MAPs hold a great deal of promise as an alternative method of contraception for women, especially those who live in low-resource settings. The high level of acceptability potentially associated with this novel technology, as briefly mentioned before, will be discussed further below. However, MAPs are still at an early stage of preclinical translation and there is still a great deal of work to be completed in order to fully evaluate and maximise their potential in the field of contraceptive care. Many questions still remain around the safety of MAPs, particularly regarding their use over time. Only through clinical investigations—facilitated by collaboration between academia, industry, researchers, users, and regulatory bodies—can the answers to these questions, and indeed future questions, be found.

3. MAPs for the prevention and treatment of HIV

ARV therapy emerged in the mid-1990s and revolutionised both HIV treatment and more recently HIV prevention (*via* pre-exposure prophylaxis), where there has been great success in controlling and reducing the rate of new HIV infections [69]. While oral dosing is convenient and non-invasive, it can lead to poor treatment adherence due to a significant pill burden [24,70]. An alternative delivery method in the form of intramuscular injections, such as the combination of rilpivirine and cabotegravir long-acting injections recently approved by the US Food and Drug Administration (FDA) [71], are not

administration. This may again negatively affect user compliance and adherence to the therapy [70,72–74]. Furthermore, the creation of sharps waste and the associated risk of needle-stick injuries, together with the need for suitable disposal infrastructure, might pose other challenges for the use of these injectable formulations.

The ARV delivery system closest to licensure is the one-month dapivirine vaginal ring developed by the International Partnership for Microbicides (IPM). Similar to a contraceptive vaginal ring, the woman inserts the ring into her vagina where it delivers dapivirine to reduce the transmission of HIV. The ring is intended to be worn continuously and is replaced monthly. Two phase III clinical trials have been completed showing that the ring is safe, easy to use, provides partial protection, and is acceptable to some user groups. The European Medicines Agency gave the dapivirine ring a positive scientific opinion, and it also achieved World Health Organization prequalification, which could facilitate introduction in low- and middle-income countries. IPM plans to soon submit applications to individual countries in sub-Saharan Africa [75–77]. Some women find the ring highly acceptable, but in the phase III studies, younger women had difficulty using the ring consistently, which limited the reported effectiveness. While the dapivirine ring brings a new protection option for women, and IPM is developing a 3-month version of the ring and a 3-month ring that offers both HIV prevention and contraception, additional research is needed since no one method will meet the needs of all users [78].

Implants are another class of technologies in early-stage development for sustained release of ARV agents for HIV pre-exposure prophylaxis, with several designs in development for delivery of drugs such as tenofovir alafenamide, cabotegravir, and islatravir [79–82]. Such devices could provide 6 months or more of protection and be administered subcutaneously with a trocar device similar to contraceptive implants. Another implantable subcutaneous delivery device, known as a nanochannel delivery system, was developed by Chua *et al* to deliver both tenofovir diphosphate and emtricitabine for the prevention of HIV infection. This system is refillable and showed delivery of both drugs over the course of 83 days in rhesus macaques at levels consistent with those needed to successfully provide pre-exposure prophylaxis. Additionally, the levels of tenofovir diphosphate needed to provide pre-exposure prophylaxis were detected as soon as 3 days post-implantation. While the refillable nature of this device is promising due to a possible reduced need for clinic access, it does still have several disadvantages. This system must be initially implanted by trained medical personnel and can only be removed by invasive surgery; there is also an increased cost associated with medical grade titanium, such as is used in this implant, while silicon is prone to biofouling [83]. In contrast to implants, MAPs offer the potential for a woman-administered method of long-acting HIV pre-exposure prophylaxis (**Table 2**).

Drug / Vaccine	Type of microarray patch	Microneedle material	Backing layer material	Release of therapeutic dosages	Ref.
Lamivudine	'Poke and Patch'	Stainless steel	Stainless steel	Not reported	[84]
Rilpivirine	Dissolving	Polyvinyl alcohol 9–10 kDa	Polyvinyl pyrrolidone 360 kDa and glycerol	56 days	[85]
Rilpivirine	Dissolving	Polyvinyl alcohol 9–10 kDa	Polyvinyl pyrrolidone 360 kDa and glycerol	28 days	[74]
Cabotegravir	Dissolving	Polyvinyl alcohol 9–10 kDa and polyvinyl pyrrolidone 58 kDa	Polyvinyl alcohol 31–50 kDa and polyvinyl pyrrolidone 58 kDa	28 days	[86]
Plasmid DNA and nucleic acid toll-like receptor agonists	Coated	Biocompatible polymers	Biocompatible polymers	N/A	[87]
Adenovirus 5 vectors encoding model HIV antigens	Coated	Polylactic acid	Polylactic acid	N/A	[88]
Recombinant HIV CN54 clade C gp140 envelope protein and the TLR4 agonist adjuvant MPLA	Dissolving	Gantrez® AN-139	Gantrez® AN-139	N/A	[89]
Recombinant human adenovirus type 5 vector (AdHu5) encoding HIV-1 gag	Dissolving	Sodium Carboxymethyl cellulose/lactose	Sodium Carboxymethyl cellulose/lactose	N/A	[90]
HIV envelope trimer (BG505 SOSIP variants) with adjuvants	Dissolving	Silk protein	Polyacrylic acid	N/A	[91]

Abbreviations: kDa, kilodalton; MPLA, monophosphoryl lipid A; N/A, not applicable.

The first reported use of MAPs for ARVs was in 2016, when lamivudine was delivered across excised dorsal skin from male albino rabbits with the aid of solid MAPs in a 'poke and patch' method [84]. Lamivudine is a nucleoside reverse transcriptase inhibitor, used for the treatment of HIV and hepatitis B. First, lamivudine was formulated into nanoparticles *via* the double emulsion-solvent evaporation preparation method using poly(lactic-co-glycolic) acid as the polymer and bovine serum albumin as the main stabiliser. These nanoparticles ranged from 152.87 ± 1.27 nm to 196.67 ± 1.74 nm, with a polydispersity index ranging from 0.089 ± 0.01 to 0.145 ± 0.03 and a zeta potential range from –42.2 ± 7.35 mV to –47.5 ± 6.55 mV. Solid MAPs (56 individual MNs, height 750 μm) made from stainless steel were applied to the skin using a simplified applicator designed from an inverted syringe. Using a Franz cell apparatus, lamivudine-loaded nanoparticles (100 mg/2 ml) were applied to each donor compartment, and the drug release across MAP pre-treated skin and untreated skin was compared. In both cases, lamivudine was seen to cross the skin in a biphasic pattern, suggesting the system could provide a sustained delivery of the drug and, promisingly, cumulative release was significantly greater in MAP pre-treated skin than in untreated skin (15.77 ± 1.5 μg cm^{-2} h^{-1} and 7.49 ± 1.46 μg cm^{-2} h^{-1}, respectively). This increase in delivery was due to the channels created by the MNs, which provided a pathway for drug molecules to transfer through the skin with less resistance [84]. This study demonstrated that transdermal delivery of lamivudine can be significantly enhanced by using MAPs.

Furthermore, this study demonstrated the potential of combining ARVs, nanoparticles, and MAPs for increased delivery of these drugs across the skin. The combination of nanoparticles and MAPs is not a new concept, with numerous examples shown in the literature, many of which were summarised in a recent review by Paredes *et al* [32]. MAPs have been shown to be capable of delivering nanoparticles to viable skin layers both *in vivo* and *in vitro,* as well as having the capability to incorporate and deliver high doses of undissolved drug [41,92]. With regard to nanoparticles, there are several different types of particles and a wide range of production methods that can be employed in their fabrication. Poly(lactic-co-glycolic) acid–based nanoparticles, solid lipid nanoparticles, and nanostructured lipid carriers are some of the most commonly seen nanoparticles delivered *via* MAPs, but all bring some significant disadvantages [32,93]. These disadvantages are mainly related to the encapsulation efficiency of the drug during the manufacturing process and the final percentage drug loading of the formulation, as well as the use of organic solvents in their preparation [32]. In general, these factors can contribute to a low yield and, therefore, a low drug content in a MAP.

One way to circumvent the drawbacks with nanoparticles is by using nanocrystals. Nanocrystals are essentially pure drug crystals within a nanometre size range, stabilised by polymers or surfactants, or indeed a combination of both, to provide ionic and steric stability [94,95]. As nanocrystals are essentially pure drug, there are no issues with encapsulation efficiency, and drug loading is significantly

as acid-base neutralisation and solvent evaporation, or 'top-down' approaches, such as wet bead milling or high-pressure homogenisation [98–100]. In particular, wet bead milling is an attractive method due to it being a flexible and industrially accepted process with low inter-batch variability, which also avoids the use of organic solvents [101–103].

Nanocrystal formulations have also been shown to perform well when utilised for long-acting indications, for example in the form of injectable nanosuspensions, in which the release rate can be influenced by the particle size. One example is the long-acting nanosuspension of the non-nucleoside reverse transcriptase inhibitor rilpivirine, which is produced by Janssen Pharmaceutica (The Pharmaceutical Companies of Johnson & Johnson) [32,104,105]. This long-acting formulation has the potential to revolutionise HIV prevention and treatment, improving adherence without a reduction in product efficacy. However, the administration with hypodermic needles and syringes is not ideal due to the aforementioned reasons. In this scenario, the use of dissolving MAPs for the delivery of long-acting nanosuspensions is a particularly appealing strategy, as highlighted in recent publications [32,106,107].

In a study in 2018, McCrudden *et al* pioneered the delivery of a long-acting ARV nanosuspension with the use of dissolving MAPs [85]. A two-step formulation was used to formulate these dissolving MAPs, with the first layer in the MN tips being made up of Janssen's rilpivirine nanosuspension mixed with an aqueous blend of polyvinyl alcohol 9–10 kDa. A preformed and dried polymer baseplate made of polyvinyl pyrrolidone and glycerol was then added to provide both structure and support to the formulation. This two-layered system reduced drug wastage, and with the individual MNs being made of polyvinyl alcohol, this ensured a rapid dissolution time, ultimately leading to a decreased 'wear' time for the end user. In this case, the geometry of the MAP involved a 14 x 14 layout of pyramidal MNs, with heights of 600 µm, a 300 µm base width, and 300 µm interspacing at the base (**Figure 6A** and **B**). The delivery of rilpivirine from these MAPs, and from conventional intramuscular injection, was compared in female Sprague-Dawley rats. After 24 hours, delivery from the MAP exceeded that from the intramuscular injection, and after 56 days there was no significant difference in plasma levels between each method of delivery (**Figure 6C** and **D**). This showed that delivery of a long-acting ARV nanosuspension is possible with a rapidly dissolving MAP. Additionally, rilpivirine was detected in lymph nodes following delivery *via* MAPs, indicating that this method can be used to deliver ARVs to the lymph over an extended duration, which is useful as this is one of HIV's main sites of replication. The study also cautiously predicted by extrapolation that a patch of 28 cm^2 could be used to deliver clinically efficacious doses of rilpivirine to adult humans over a 7-day period [85].

Figure 6. Systemic delivery of rilpivirine using dissolving MAPs. **A** and **B-** Photomicrographs of exemplar rilpivirine long-acting microarray patch. **C-** Plasma levels of the drug at 1, 4, 7, 28, and 56 days post-intramuscular injection. **D-** Plasma levels of the drug at 1, 4, 7, 28, and 56 days post-microarray patch application. Abbreviations: IM, intramuscular; MAP, microarray patch; RPV, rilpivirine. Adapted and reprinted from reference [85],

A subsequent follow-on study by the same research group then looked at the application of similar MAPs into vaginal tissue [74]. Mechanical testing of the MAPs was carried out in synthetic model vaginal tissue, which included a novel 'drag test' to mimic shear forces in the vagina. During these *in vitro* studies, MNs were arranged in a 14 x 14 design and were 600 μm in height. For *in vivo* studies, an MN 'rod' was custom designed to 2 mm width x 5 mm length × 2 mm depth, and shorter MNs were used with a height of 300 μm. These MAPs were prepared again using the two-step process with a preformed baseplate, and were then cut to the desired MN density of 3 x 9. Two of these MAPs were then joined back-to-back. Each MAP 'rod' contained 4 mg of rilpivirine. On insertion into the vaginal cavity of rats *in vivo*, rilpivirine content was found to be 925.6 ± 569.4 ng g^{-1} after 7 days, and 1039.7 ± 436.5 ng g^{-1} after 28 days. Interestingly, this localised delivery of rilpivirine into vaginal tissue resulted in plasma levels comparable to those achieved by conventional intramuscular injection of the

prophylaxis, with localised delivery to one of the main sites of HIV infection [74].

Tekko *et al* developed a novel MAP design with 16 x 16 pedestal MNs measuring 900 μm in length and 300 μm base width. Each individual MN consisted of a cuboidal base with a pyramidal tip measuring 300 μm and 600 μm in height, respectively, and were employed to deliver the integrase inhibitor cabotegravir for pre-exposure prophylaxis of HIV [86]. The new MAP design allowed for manufacture of a bilayered MAP with an increased drug load localised in the pyramidal tips, approximately 3 mg/0.5 cm^2 per MAP, and improved insertion capability. Using a two-step formulation method, a long-acting cabotegravir nanosuspension produced by ViiV Healthcare was combined with an aqueous blend of polyvinyl alcohol 9–10 kDa and polyvinyl pyrrolidone 58 kDa to form the pyramidal MN tips in the MAPs, with the baseplate and cuboidal bases of the MNs made of a drug-free blend of polyvinyl alcohol 31–50 kDa and polyvinyl pyrrolidone 58 kDa. During *in vitro* testing, these MAPs were shown to be mechanically strong enough to insert into a previously validated model skin substitute [108]. Approximately 90% of the drug-loaded pyramidal MNs dissolved in less than 30 minutes upon insertion into excised neonatal porcine skin (*ex vivo*), which indicates a decreased 'wear' time for the end user. The *in vivo* studies in rats showed that the MAPs were able to deliver cabotegravir with plasma levels several-fold higher than the effective human concentration for HIV pre-exposure prophylaxis, which is 664 ng/ml, and that these levels were maintained over the course of 28 days [86].

With respect to HIV treatment and prevention, and in particular the use of ARVs with MAPs, further *in vivo* studies will be needed to assess the complex pharmacokinetic profiles of ARV nanosuspensions, perhaps in larger mammals with a physiology more closely resembling that of humans, and in particular looking at repeated dosing using MAPs. Detailed biodistribution evaluation of the ARVs must now also be conducted, as this could provide better insight as to where the drug may accumulate in the body and if MAPs can be used to selectively target the lymphatic system and associated organs, a known site for latent HIV reservoirs and replication [85,109,110]. In the past, small animal models have been used in the form of mice and rats before moving to larger, non-human primates, but it is thought that an HIV infection challenge model could provide greater understanding of the MAP-assisted pharmacokinetic profile of these ARV drugs prior to advancing into human models [111–113].

3.2. MAPs for HIV vaccination

Over the past three decades, great efforts have been directed towards the development of an effective vaccine for HIV prevention, with limited success [114]. Although hundreds of vaccine candidates have been clinically tested, to date only six HIV vaccine efficacy trials have been completed [114]. Most of these vaccines work through elicitation of protective antibody responses [114]. Several studies have demonstrated that MAP technology represents a promising approach for HIV vaccine delivery (**Table 2**), not only because they are minimally invasive and can be self-applied, but also because they can

delivery systems [115].

DeMuth *et al* and Pattani *et al* were first to employ MAP technology for HIV vaccine delivery [87–89]. In one study from 2012, DeMuth *et al* developed a MAP prepared from biocompatible polymers which was then coated with a biodegradable polymeric blend containing plasmid DNA and nucleic acid toll-like receptor agonists, to create thin coatings with tuneable dosages of vaccine cargo and thus variable vaccine release rates [87]. The authors demonstrated that following application of these coated MAPs to mice for approximately 5 minutes, the intact film coatings were rapidly implanted in the skin for sustained release of vaccine components over time. MAP delivery of DNA vaccines encoding SIV-gag proteins induced a 5-fold increase in antigen-specific T cell expansion, and generated serum IgG titres 5-fold in excess of those observed for traditional intramuscular or intradermal immunisations. Not only this, but MAP-assisted DNA vaccine delivery also induced enhanced generation of long-lived memory T cells [87].

In another study from the same group, a novel biodegradable MAP was formulated from poly(lactic acid) with a base pedestal of 1 cm in diameter, bearing 78 conical MNs, each 650 μm in height and 250 μm in diameter at the base [88]. These MAPs were coated with a sucrose sugar-glass matrix entrapping adenovirus 5 vectors encoding model HIV antigens, which were confirmed to be stable at room temperature for several months after coating. These formulations demonstrated their capability to effectively deliver their cargo into the skin of mice without loss of bioactivity, as evidenced by the fact that the adenovirus 5-HIV MAP elicited systemic and even mucosal immune responses largely equivalent to traditional injections using needle and syringe. Compared to intramuscular vaccines, adenovirus 5-HIV MAP vaccines induced mice to generate modestly increased frequencies of peripheral antigen-specific central memory T cells but markedly elevated levels of vaginal wash IgG titres. Going further, the researchers assessed vector delivery and immunogenicity of the novel formulation in rhesus macaques and observed reliable MAP insertion in the epidermis of the non-human primates. Rhesus macaques were immunised with an adenovirus 5-HIV MAP encoding the model HIV antigens, SIV Gag or SIV Env, by applying four MAPs for each vector to the shaved deltoid skin, followed by a boost with the same MAP administration regimen at 12 weeks. The researchers demonstrated that MAP delivery of adenovirus-vectored vaccines could induce systemic cellular responses equivalent to traditional intramuscular injection of an adenoviral vaccine, while also eliciting strong humoral and cellular immunity, as well as mucosal immunity, in macaques [88]. This contrasts with the general conception that intradermal immunisation can rarely elicit mucosal immunity in mammals by showing that MAP vaccines can induce a wide mucosal immune response [115].

Pattani *et al* then developed Gantrez® AN-139-based dissolving MAPs, which contained trimeric recombinant HIV CN54 clade C gp140 envelope protein, and assessed them for their ability to elicit

subcutaneous injection [89]. The authors demonstrated that MAP-assisted vaccine delivery generated similar serum and mucosal gp140-specific IgG levels to the systemic and adjuvanted subcutaneous inoculations [89].

Becker *et al* explored the capacity of dissolving sodium carboxymethyl cellulose and lactose-based MAPs coated with recombinant human adenovirus type 5 vector (AdHu5) encoding HIV gag to program antigen-experienced T cells into providing long-term memory, and to respond rapidly to antigen re-encounter, which is the hallmark of an effective vaccine [90]. The authors showed that despite a slightly lower frequency of dividing T cell receptor transgenic CD8(+) T cells in secondary lymphoid tissue at an early time point, the absolute number of CD8(+) T cells expressing an effector memory (CD62L(–)CD127(+)) and central memory (CD62L(+)CD127(+)) phenotype during peak expansion were comparable after MAP and intradermal vaccination in a C57BL/6 (H-2b) mouse model. Similarly, both vaccination routes resulted in CD8(+) memory T cell subsets capable of responding to secondary antigens being detected in draining lymph nodes for at least two years post-vaccination. These data suggest that CD8(+) T cell effector memory generation and long-term memory are largely unaffected by physical differences in vaccine delivery to the skin *via* MAP or intradermal suspension [90].

Recently, Boopathy *et al* engineered dissolving MAPs with solid pyramidal MNs and implantable silk fibroin protein tips. These tips encapsulated a stabilised HIV envelope trimer immunogen and an adjuvant for sustained-release delivery [91]. During *in vitro* release studies, the authors demonstrated that the structural integrity of the antigen was preserved and exhibited a molecular weight-dependent release over time from the MAPs. Within 5 minutes of MAP application to the skin, the vaccine-loaded silk tips were implanted in the deep intradermal space, where they then released the vaccine over a period of time which was controlled by the crystallinity of the silk matrix. *In vivo* studies in mice demonstrated that when in the skin, the subunit vaccine was released over 2 weeks, correlating with increased germinal centre B cell responses, an approximate 1300-fold increase in serum IgG titres, and a 16-fold increase in bone marrow plasma cells when compared with bolus immunisation. This early study proved that implantable MAPs have the practical potential to substantially enhance humoral immunity to subunit vaccines [91].

MAPs have shown great potential in both the delivery of ARV drugs and HIV vaccines. With respect to delivery of ARVs, MAPs could be used to treat an active HIV infection or could be utilised in a pre-exposure prophylaxis regimen. When coupled with HIV vaccines, the use of MAPs can greatly increase the initial immune response and successfully raise an immune response on rechallenge. The data from these studies show that there is great potential for further growth in this area. The opinions of individuals at risk of and living with HIV about the potential use of MAPs will be discussed below.

The path to market for MN-based devices, as with all new delivery systems, is not without hurdles that need to be overcome before they are widely accepted. As the variety of devices and delivery systems continues to increase, it is becoming increasingly important and, in accordance with regulatory guidance and product development standards, there is an expectation that consideration of the opinions of the end-users and other key stakeholders are taken into account at an early stage. Engagement with these individuals can, in turn, shape the development and marketing of a product and, consequently, determine the success or lack thereof of a new device. Moreover, it is now generally acknowledged that a thorough consideration of the views of the end-user early on and throughout the process is critical for successful user uptake upon market implementation [116]. This is particularly relevant for MAPs, wherein commercial success will depend not only on the efficacy and performance of the product but also on the acceptability of and confidence in this new delivery system to both users and health care providers as well as program staff and policy/regulatory stakeholders who will be involved in the administration and authorisation of the product.

To understand the acceptability of long-acting contraceptive MAPs, Brunie *et al* conducted a user preference study [61]. This involved 16 focus group discussions and 20 in-depth interviews with female end-users, as well as 20 in-depth interviews with public- and private-sector providers in New Delhi (India) and Ibadan (Nigeria). They used an exploratory study design to investigate the qualitative aspects of selected MAP features and to quantify the relative importance of MAP-assisted contraceptives compared to other contraceptive options. The qualitative research objectives were to explore the initial acceptability of MAPs, identify the preferred product features for end-users, and to provide context on user preferences. Most of the participants considered MAPs as straightforward to apply by hand after learning about the correct use and were excited by the potential for easy self-administration. Most women favoured MAP formulations providing protection from pregnancy for 3 or 6 months, while some women also backed 1-month MAPs. Many women and providers were initially concerned about localised skin erythema or possible pain caused by MAPs, but further conversations about these concerns found that a feeling similar to an insect bite or injection would generally be acceptable considering a single application for a long-term contraceptive effect. Survey inputs clearly indicated that women were less concerned about issues regarding the site of MAP application, MAP size, and possible short-term skin erythema than they were about hiding skin redness to conceal contraceptive use [61].

Another MAP acceptability study was conducted by Li *et al* in 10 healthy, nonpregnant female adults (21–36 years old) with normal skin [57]. Each volunteer applied one MAP with a rapidly separable effervescent feature to the dorsal surface of their left hand. Out of 10 participants, 3 applied an additional MAP to their right hand. Pressure was applied to insert each MAP for 3 seconds, then left in place on

successful MAP insertion and to visualise any possible redness, the skin on the left hand was imaged by a camera 0, 1, and 24 hours after patch application (**Figure 7B**). The application sites on the participants' right hands were stained with Gentian violet solution and imaged 5 minutes after staining (**Figure 7C**). The penetration and separation of the microneedles was close to 100% in both cases as observed in **Figure 7D**. Finally, using a standard set of questions, all volunteers were investigated to seek information about the acceptability of MAPs for delivery of long-acting contraceptives, as well as any possible pain of the MAP administration, which was scored from 0 (no pain) to 10 (pain of a hypodermic injection). All participants reported either no pain or slight pain that was much less than that caused by a conventional hypodermic injection. No participant reported pain 1 hour or 24 hours after application. After MAP application, faint erythema was evident at the site of patch administration, which largely faded within 1 hour and almost completely vanished after 1 day, as shown in **Figure 7B** and **7E**. There was no tenderness, swelling, or other notable effect seen at the patch application site at any time. In this case, all participants manifested that they would prefer contraceptive administration by a monthly MAP compared to monthly hypodermic injection (**Figure 7F**), and 90% of participants said they would choose a monthly MAP compared to oral administration of daily pills (**Figure 7G**) [57]. Both user preference case studies imply that long-acting MAP contraception was well accepted and preferred over daily pills or a monthly injection.

Figure 7. Application of effervescent microarray patch (MAP) to human participants. **A-** Representative bright-field microscopy images of a section of an effervescent MAP before (top) and after (bottom) application to human skin. Scale bar, 500 μm. **B-** Representative images of the site of effervescent MAP application (yellow arrows) to the skin of a human participant over time. Inset shows magnified images of the skin application site. These images are all from the same participant. **C-** Representative photographic image of skin on a human participant stained to show where a 10 × 10 array of MAP punctured into skin. Scale bar, 2 mm. **D-** The efficiency of penetration and detachment of effervescent MAPs in skin of human participants. Each point represents mean ± SD (n = 3). **E-** Normalized erythema intensity of human skin over time at the site of effervescent MAP application. Each point represents mean ± SD (n = 10). **F-** Preference of human participants for monthly application of effervescent MAP compared to monthly hypodermic injection for delivery of contraceptive (n = 10). **G-** Preference of human participants for monthly application of effervescent MAP compared to daily oral administration by pill for delivery of contraceptive (n = 10). Reprinted from reference [57]

MAPs with interviews and focus group discussions with women and health care providers in South Africa [74]. Participants were asked what their thoughts were on the use of vaginally administered MAPs for pre-exposure prophylaxis, which was viewed positively as a discreet and self-enabling way to protect against HIV. The women in the focus group also stated that this delivery method inspired confidence in the product, due to their familiarity with it [74].

A recent study in 2020 by Moffatt *et al* involved investigating both health care professionals' and members of the lay public views on MAPs, and in particular their potential use with ARV therapy [117]. The findings demonstrated that both demographic groups displayed positive perceptions of MAPs, with further support highlighted for their postulated use within HIV treatment and prevention. The study also utilised smaller qualitative focus groups, consisting of 12 patients with HIV, in which they were asked about their thoughts on the use of MAPs within HIV therapy. The consensus from the patients with HIV was positive, with benefits such as the discreet self-application and the potential for long-acting delivery resulting in the avoidance of daily oral therapy, associated pill burden, and side effects highlighted as particularly relevant for future MAP-mediated HIV therapy. However, as expected, the study did highlight some hesitation to adopting MAPs as a primary source of ARV therapy, with the need for varied dosing schedules and an unfamiliarity when compared to oral dosing proving to be the greatest concerns [117]. Overall, this study showed that MAPs are thought of positively by end-users in respect to HIV, but further translational research will be important to overcome some of these issues.

As mentioned previously, many of the MN-based systems currently being investigated are based upon the use of biocompatible polymers. From a user-safety standpoint, such polymers have the potential to accumulate within the user's skin, particularly when considering dissolving MAPs, and while these are manufactured with FDA-approved and biocompatible polymers, they have not been specifically approved for intradermal administration. Consequently, regulatory bodies may require more information about the deposition of such polymers in the skin and may demand data analysing their accumulation and subsequent clearance. These factors may not present an issue when considering a single, one-off dose, such as with MN-based vaccine products. However, for conditions that require repeated dosing (*e.g.* delivery of ARVs or hormonal contraceptives), repeated MAP applications may become a more pressing regulatory issue to governing bodies. One recent study aimed to investigate this, where repeated applications of polymeric MAPs were performed in immunocompetent mice [118]. MAPs were applied to approximately the same site over the course of a number of weeks, and throughout the full study duration there was no detected deterioration in skin barrier or function [118]. This study provided the necessary preliminary data that repeated application could be conducted with increased confidence that the skin barrier remains unchanged. This concept was then further examined in more detail in humans in a study conducted by Al-Kasasbeh *et al* [119]. This study involved repeated application of hydrogel-forming MAPs over a period of 5 days in volunteers aged 24 to 39 years. The

transepidermal water loss, while screening for the presence of systemic inflammatory biomarkers *via* blood sampling. The results demonstrated that repeated MAP application did not lead to prolonged changes in skin barrier function, and all inflammatory markers measured were within the normal range [119]. Again, this study increased confidence in repeat application of MAPs.

One study has shown that users can correctly self-apply a prototype MAP following appropriate counselling from a pharmacist, further assisted with a user information leaflet [120]. However, in line with this work and based upon similar, previous studies, it may be reasonable to assume that both the FDA in the United States and the Medicines and Healthcare products Regulatory Agency in the United Kingdom may require a method of confirmation that correct MAP application has been achieved in order to gain their full acceptance [121]. It has been theorised that a visual feedback mechanism could be used to provide this confirmation and, as such, a study conducted by Vicente-Perez *et al* employed a pressure-sensitive film to signal to volunteers when they had applied sufficient pressure to insert a MAP into their own skin [62]. The packaging of any MAP system will also require careful consideration, not only for marketing and information purposes for the end-user, but it should also be user friendly in that it is easy to open and easy to dispose of. Additional factors to consider include the potential need for the packaging to protect the system from damage, including exposure to light and moisture.

The various studies mentioned above highlight the importance of engaging with end-users at the development stage and further promote the need for translational research and full involvement of those in the MN field. These studies also give pharmaceutical companies an indication that marketing as well as detailed labelling and information leaflets, used in combination with appropriate user counselling, could be key to ensuring the success of MN-based systems.

5. Future perspective of MAP technology

Despite the barrier properties imposed by the *stratum corneum*, limiting the number of drugs that can be successfully delivered across the skin, the global transdermal market is still expected to rise to upwards of $80 billion by 2024 [122]. One of the main reasons for this anticipated market growth is the technological advancements involved in transdermal delivery devices, such as MAPs. In line with this, MAPs were included amongst the top 10 emerging technologies of 2020 in a recent report from the World Economic Forum [123].

Industrial bodies and associated pharmaceutical companies have heavily invested in MAP technology in recent years. The most prominent current example is Zosano Pharma, which presented to the FDA a new drug application for their Qtrypta™ (M207) product. Qtrypta™ is used to deliver zolmitriptan for the treatment of migraine using its Adhesive Dermally-Applied Microarray (ADAM™) intracutaneous

the company noting differences in zolmitriptan exposures between subjects receiving different lots of Qtrypta™ and inadequate pharmacokinetic bridging between the lots that made interpretation of some safety data unclear [125]. The FDA has requested new bioequivalence studies using three different batches of the product, together with the product quality validation data and an inspection of the manufacturing facilities where the MAPs are produced [125]. Provided that the company manages to successfully revert the points raised by the FDA, it will represent the first true MN-based drug delivery system to obtain market approval.

Due to the nature of a MAP, it alters the skin's barrier function in the short-term by disrupting the *stratum corneum*. Subsequently, it was hypothesised that this disruption could lead to an increased risk of infection due to microbial infiltration. However, studies have shown the risk of infection due to MAP application is negligible [126]. The channels created by MAP application tend to be hydrophilic, and so microorganisms may tend to remain in the lipophilic *stratum corneum*. The skin also contains numerous antigen presenting cells and is an immunocompetent organ, possibly dealing with any potential microbes before they have a chance to cause problems [127]. To support these findings, to date there are no reported cases of systemic infection following MAP application. Current best practice of a hypodermic injection involves preparation of the skin prior to injection; however, this is known to not always be performed [128]. It is possible that this guidance could be extended to MAPs, yet this may in turn increase the complexity of the process. While microbial infiltration through channels created by MAPs may be negligible, there is still concern over whether MAPs will need to be a sterile product. The issue for many of the currently available sterilisation methods is that while they are suitable for solid MAPs, they are destructive in their nature and so they may have a marked effect on both the active pharmaceutical ingredient and MAP performance and mechanical properties. Promisingly, low-dose gamma irradiation has been shown in one study to sterilise a polymeric MAP without having a negative effect upon the physical characteristics of the system [129]. In early, encouraging stakeholder discussions involving academia, industry, and regulatory bodies, it has been suggested that if low-bioburden manufacturing processes which adhere to good manufacturing practice (GMP) standards can be followed, it may remove the need for continuous-line, sterile manufacturing [129,130].

Currently, one of the main barriers to successful translation of MAP products to market is the scale-up of the manufacturing process to industrial level. This scale-up will require extensive planning, as many of the production methods that presently exist in the literature are small-scale microfabrication methods [131]. Several studies have explored possible larger-scale novel production methods for MAPs, including a study by Lutton *et al* in which the methods investigated could potentially be applied to the manufacture of nanosuspension-loaded MAPs [132,133]. The issue with many of the microfabrication processes is that they involve many complex stages. This provides a significant challenge to transfer into a continuous-line process, which may not only increase production costs but also pose difficulties

step. Pharmaceutical companies may not see the economic viability in obtaining these new facilities, and so may look at both alternative active pharmaceutical ingredients and indeed specific MAPs that can be coupled with terminal sterilisation methods as a more attractive option. The first, and currently only, company to gain a GMP license in Europe for large-scale MN manufacture was LTS Lohmann, while other institutions with the potential capacity for large-scale production include Kindeva and Fujifilm.

For regulatory purposes, it is forecasted that MAPs will be classified as a 'combination product with a drug primary mode of action' in the United States and likely as a 'drug and device' system in Europe, rather than a medical device. Once confirmed, this will enable current GMP and quality control processes to be more directed to their classification, as current methods for transdermal patches and hypodermic needles are entirely different. Another distinction should be made as to whether the product is intradermal or transdermal, which could change what GMP standards will need to be met, and possibly shape production methods and marketing decisions. Many of these barriers, issues, and questions may only be answered with extensive post-marketing surveillance. Consequently, it is likely that the first true MAP product to reach market implementation and achieve successful commercial uptake will shape the direction of future MN-based products. If all necessary components involved in manufacture can be aligned—namely, engineering, product design, GMP, sterility requirements, and packaging—then progress through regulatory channels should be a more streamlined and more rapid process.

6. Conclusions

It is clear that MAPs have great potential for drug delivery, and in particular, long-acting delivery for uses such as contraception and HIV treatment. However, issues surrounding both user needs and regulatory issues will need to be addressed, and efficacy in clinical studies needs to be shown before MAPs can take the next step and become a commercial success. In order to achieve this, dedicated collaboration between academia and industry, supplemented by a significant injection of funding from investing bodies, must continue so that market implementation becomes a reality and, ultimately, MAPs can finally deliver their intended user benefit. This review has sought to shine a light on the potential of MAPs for contraceptive care and ARV treatment. If MAP systems make it to market, they will improve patient/user care worldwide, particularly for end-users requiring both contraception and ARV therapy, whether for treatment or prevention of HIV infection. Undoubtedly, there are few user groups that would gain more from such devices than women who live in low- and middle-income countries, such as those in sub-Saharan Africa.

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