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Microarray Patches: Poking a Hole in the Challenges Faced When Delivering Poorly Soluble Drugs

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Poorly soluble drugs constitute more than 60% of currently marketed pharmaceuticals with over two-thirds of promising new chemical entities failing to enter a clinical setting due to solubility issues. Although oral formulations have made some impact, alternative enhancement strategies for administration of such molecules are actively sought. Over the last decade, innovation on a global scale has enabled the expansion of the frontiers of microarray patches (MAPs) further than ever before. Initially designed to load low doses of hydrophilic and potent therapeutic agents, MAPs are now becoming a viable strategy for the immediate and long-acting delivery of poorly soluble drugs through the skin. This together with the advantages of transdermal administration over the oral and parenteral routes, make of MAPs an appealing platform for the development of products with increased patient compliance. Undoubtedly, MAPs will soon become a readily available therapeutic alternative, and experts from academia, industry and regulatory bodies are working together aiming to facilitate the progression of MAPs toward safe and effective clinical use. This review aims to highlight the ability of MAPs to deliver poorly soluble actives, discuss the mechanisms behind in-skin drug absorption, and evaluate the future direction of the field.

1. Introduction

Poor aqueous solubility of preexisting and emerging drug molecules is a common issue faced in the field of pharmaceutics.

With more than 60% of new chemical entities being poorly soluble in water and 40% of drug candidates in the main pipeline failing development due to the same reason, the magnitude of this obstacle is considerable.[1] The term “hydrophobic drug” is typically used by those in the field of drug delivery to describe a diverse group of molecules that display poor solubility in an aqueous solvent, but are typically soluble in organic solvents.[2] Such substances are then further subdivide into descriptive categories based on the extent of their aqueous solubility, that is, slightly soluble (1–10 mg mL$^{-1}$), very slightly soluble (0.1–1 mg mL$^{-1}$), and practically insoluble (<0.1 mg mL$^{-1}$).[3]

One of the main challenges that researchers in the field of pharmaceutics face nowadays is that, even though newly emerging drug candidates might be highly active, their bioavailability is impaired due to their low solubility in physiological fluids and, additionally, their low permeability to their site of action.[4] In the past, the research focus lay mainly on conventional drug delivery systems such as oral formulations or injectables. However, over recent years, this focus has slowly shifted to more advanced systems that seek to not only improve the bioavailability of poorly soluble therapeutic agents but also increase patient adherence by overcoming common issues such as frequent dosing, swallowing difficulties, or needle phobia. Moreover, these novel systems can control, target, or modulate the delivery of drugs to increase the effect at their site of action and reduce the occurrence of unspecific and unwanted side effects.[5] Oral drug delivery systems such as tablets and capsules are still the most popular route of application. They are cost-effective, can be self-administered by the patient, and provide precise dosage. Nevertheless, the swallowing of solid dosage forms can prove problematic for many patient types, especially geriatric and paediatric patients and the high pill burden associated with polypharmacy grows increasingly undesirable. Furthermore, the observed bioavailability of a poorly soluble drug post oral administration can be highly dependent on external and concomitant factors such as intake of water or food.[6] For injectables on the other hand poorly soluble drugs must be processed specifically to allow for injection, and such formulations often require specific storage conditions.[6] They usually have to

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be administered by trained personnel in a healthcare setting, and as they are associated with the induction of pain, instances of poor patient adherence due to needle phobia is commonplace. Therefore, it is important to focus on alternative drug delivery systems, for example, via the transdermal route.

Transdermal drug delivery traditionally occurs via three main routes: transappendageal, transcellular, and intercellular routes. Passive permeation in this manner typically favors drug molecules with specific physicochemical characteristics, that is, a log $p$-value between 1 and 3, relatively low molecular weight (500–600 Da) and low doses (<10 mg per day).\(^7\) Unfortunately, although valued at over $32$ billion most recently, the transdermal drug delivery market is currently based on just 19 marketed products. This surprisingly low market translation strike-rate is due to the relatively small proportion of drug molecules that meet the previously stated requirements; resulting in a limited number of therapeutic applications having been realized.\(^8,9\) Frustrated by the perceived inefficiency of traditional transdermal drug delivery, innovative individuals working in the field were compelled to investigate previously unexplored ideas to discover ways of enhancing the permeation of topically applied therapeutics. One such approach is to circumvent the outermost layer of the skin, which is arguably the body’s most effective barrier, known as the *stratum corneum*. The role of the *stratum corneum* is to provide protection to the rest of the body by preventing the entry of external entities via the skin. Methods of bypassing this natural gateway can be characterized as chemical, biochemical, or physical in nature. However, regardless of the type used, each approach is intended to temporarily disrupt the nanostructure of the *stratum corneum* thereby enhancing therapeutic permeation into and across the skin. Important to note, while effective permeation enhancement is of paramount value, high levels of permeation into deeper layers of the skin can result in the unfavorable occurrence of tissue irritation.\(^10\) Physical permeation enhancing techniques such as iontophoresis, cavitational ultrasound, and electroporation have been explored extensively as complimentary strategies for the increased permeation of drugs that are already suited to transdermal delivery. However, those that are not suited to such permeation, that is, hydrophobic drugs, often necessitate further assistance, usually in the form of a combination of permeation enhancing techniques to achieve sufficient delivery across the skin.\(^11\) Until recently, such limitations, in addition to the need for specialized devices, that is, iontophoresis machines, have ultimately rationalized the small number of viable clinical applications for the transdermal delivery of hydrophobic drugs realized to date.\(^12\) Increased research into the development of alternative methods of physical permeation enhancement has undeniably and irreversibly broadened the range of suitable clinical applications of transdermal drug delivery. As a result, the potential for the development of an effective, reliable, and convenient transdermal delivery system for poorly soluble drugs is no longer an aspiration, rather it is a reality.

Microarray patches (MAPs) are considered to be one of the most innovative and exciting developments born out of the evolution of this field. MAPs, also known as microneedle (MN) arrays or MN patches, are minimally invasive intradermal drug delivery platforms comprised of micron-sized projections that protrude outward from, and perpendicular to, a flat base plate. Upon application to the skin these MNs painlessly penetrate the *stratum corneum*, creating microscopic conduits through which drugs can be delivered to the dermal microcirculation.\(^13\) Crucially, this technology combines the distinct advantages of transdermal drug delivery with the highly targeted nature of parenteral delivery via hypodermic needles. These advantages include, but are not limited to: 1) a reduced level of invasiveness leading to increased patient acceptance especially in those with needle phobia, 2) potential for self-application without the assistance of trained healthcare personnel, 3) absence of sharps waste generation and therefore minimal risk of infectious disease transmission via needle-stick injuries, 4) avoidance of first pass metabolism, and 5) rate controlled delivery of therapeutics with rapid treatment cessation upon MAP removal leading to increased patient compliance and treatment adherence.\(^14\) All these characteristics together make of MAPs a unique platform for the design of novel drug delivery systems, which is consequently reflected in a sharp increase in the number of reports on the field, as shown in Figure 1.

Regarding MAP morphology, MN height can range from 50 to 900 $\mu$m, that is, within the micron range, with MN densities of up to 2000 cm$^{-2}$ previously reported.\(^15\) Through the application of microfabrication techniques, MNs can be produced in numerous geometries and from various materials, including silicon, metals, ceramics, and polymers.\(^16\) Some examples of different MAPs are shown in Figure 2. MAP technology was first conceptualized and subsequently patented in the 1970s.\(^17\) However, the drive toward commercialization only truly surfaced approximately 20 years later, when advances in microfabrication techniques allowed for the first practical realization of consistent and reproducible MAP fabrication.\(^18,19\) Calcein, a low-molecular weight compound, was the first substance to be delivered using MAPs,\(^20\) with numerous investigations into the capabilities of MAPs for the purpose of drug delivery rapidly following. Although they were initially introduced as a technique intended for the delivery of small quantities of highly potent therapeutic agents, subsequent ground-breaking research has widened the range of viable applications. MAPs have also been successfully utilized in the delivery of peptides, including desmopressin,\(^21\) insulin,\(^22\) genetic materials,\(^23\) oligonucleotides,\(^24\) DNA,\(^25\) vaccines,\(^26\) and human growth hormone.\(^27\) Encouragingly, successful delivery of these compounds has already been demonstrated in vivo using animal models and in clinical trials with humans.\(^28\)
There are five types of MAPs, namely solid, coated, dissolving, hollow and hydrogel-forming, which are illustrated in Figure 3. Solid MAPs were the earliest form of this physical permeation enhancing technology and are applied as part of a two-step “poke and patch” strategy to facilitate transdermal drug delivery. The first step of this process, that is, the “poke,” comprises pretreatment of the skin with a solid MAP in order to create temporary microchannels in the outermost layers of the skin. Following MAP removal, topical application of a conventional drug formulation, that is, the “patch,” results in enhanced permeation of the therapeutic agent into and across the skin. Although this now conventional methodology has been utilized with great success in a multitude of research, its two-step nature is widely considered to be a limitation in terms of clinical application.

With the aim of establishing a one-step application process, MAPs with MNs coated in a drug-containing formulation were developed. Following application, this coating dissolves and the incorporated active ingredient is released intradermally. Due to the limited quantity of formulation that can be coated onto the MNs of such MAPs, much of the research in this is focused on the delivery of highly potent therapeutic agents. Furthermore, small molecules namely metronidazole, caffeine, lidocaine, and theophylline have also been delivered using this strategy. Dissolvable MAPs also possess great potential for the delivery of therapeutically relevant doses of hydrophobic compounds. Instances of their success for this novel application have been previously reported in the literature; as such, dissolvable MAPs will be discussed in great detail within.

Hollow MAPs are typically used for the delivery of liquid formulations transdermally through bores within the MN structure. In a similar manner to common intradermal injections, the formulation is administered via the MAP device with the aid of positively applied pressure or an electrically driven flow. Modulation of this external driving force through the combination of hollow MAPs with purpose-built injection devices enables both rate controlled and continuous drug delivery, which is a desirable attribute of this system. The main drawbacks associated with this approach include concerns surrounding the physical and chemical instability of liquid drug formulations in addition to the potential occurrence of MN bore closure by compressed dermal tissue after the application. Materials including silicon, metal, glass, and polymer have been used to fabricate hollow MAPs. Successful applications include the delivery of vaccines, insulin and sol-gel formulations in addition to the extraction of interstitial fluid or blood for diagnostic purposes. Considering the use of hollow MAPs for the delivery of hydrophobic drugs, the requirement of drug solubilization prior to delivery represents a considerable challenge due to the frequent presence of organic solvents in liquid formulations. Hollow MAPs coupled with biosensors have been extensively used with monitoring purposes because of their ability to absorb the interstitial fluids by capillarity, with special interest being placed in the biosensing of glucose and drugs. The sensing mechanisms and the different strategies comprising the use of MAPs for transdermal
biosensing exceed the scope of this article, however, excellent reviews on the topic can be found in the literature.[65-67]

Hydrogel-forming MAP systems consist of a highly swellable MAP made from cross-linked polymers atop which is fixed a separately formulated drug reservoir.[28,33] Upon application to the skin these MAPs rapidly imbibe interstitial fluid and swell to form an aqueous hydrogel matrix in situ.[68] When the inserted MAP reaches a sufficiently swollen state, the affixed drug reservoir begins to dissolve, resulting in drug diffusion into and through the hydrogel matrix before subsequent delivery into the viable epidermis.[68] This emerging and innovative technology possesses distinct advantages over other types of MAP such as increased drug-loading due to the separately formulated drug-containing layer and rate controlled drug delivery which can be modified through variation in polymer cross-linking. Moreover, upon MAP removal from the skin, MNs remain in their swollen state and therefore incapable of reinserter and without polymer deposition.[68] Hydrogel-forming MAPs have proven to be highly efficient in the delivery of several small molecules.[35] However, their application in the delivery of poorly soluble drugs is met with increased difficulty due to the reduced tendency of such molecules to diffuse through the aqueous hydrogel matrix of the swollen MAP.

To date, the aforementioned types of MAPs have most commonly been used to explore the delivery of hydrophilic, potent and low-molecular-weight drugs. By comparing the advantages
and disadvantages of each type, dissolving MAPs appear the most suitable for the delivery of hydrophobic compounds to the skin. This is due to their relatively greater payload, ease of formulation and rapid in-skin dissolution. Hence, a considerable portion, although not the entirety of this review will be dedicated to the combination of this MAPs with various nanotechnologies such as nanocrystals (NCs) or nanoparticles (NPs).

The aim of this review is to highlight the ability of MAP technology to deliver hydrophobic drugs intradermally. Specifically, this review will focus on how the combination of different types of MAPs with NP-based systems, solid dispersions, microparticles (MPs), cosolvency or cyclodextrin (CD) complexation can enhance the transdermal delivery of such compounds. Moreover, we aim to discuss the mechanisms behind in-skin drug absorption with particular emphasis on targeting of the lymphatic system (LS); before finally providing an evaluation of future perspectives in the field.

2. Intradermal Administration of Hydrophobic Drugs

Over recent years, an increasingly wide range of studies has explored the challenging field of delivering poorly soluble drugs intradermally via MAPs. Some researchers chose model drugs such as Nile Red (NR) for formulation purposes only; without specifying explicit therapeutic targets. Others investigated the localized delivery of therapeutics, for example, lidocaine for improving local anaesthesia or minoxidil for advanced treatment of hair loss. Additionally, many researchers have studied the delivery of drugs to the systemic circulation via MAPs for the treatment of diseases such as lymphyatic filariasis and human immunodeficiency virus (HIV); or they investigated similar delivery of hormonal contraceptives in a rate-controlled manner.

2.1. Nanocrystals

NCs are crystalline drug particles with sizes in the nanometer range. Nanocrystallization techniques, first reported in the early 1990s, are typically reserved for poorly soluble drugs as they aim to enhance drug solubility by increasing the ratio of total drug surface area to drug mass. An advantageous characteristic of NCs when compared to other nanoparticle-based drug delivery systems, is the fact that they are derived from the therapeutic agent itself which results in their drug content consistently approaching 100%. Additionally, NCs are inherently stable with minimal stability inferring surface active agents required for successful formulation.[114] Furthermore, rate controlled drug release from such formulations can be achieved by variation in particle size.[114] NCs can be delivered in powdered form, however, they are more commonly formulated as a dispersion in liquid, termed a nanosuspension.[115,116]

When compared to other types of nanoparticle-based drug delivery systems, NCs can be obtained using techniques that are relatively easier to scale-up and can be described as bottom-up or top-down. The first approach implies building up the particles by precipitation of dissolved molecules and the latter, involves the application of disintegration forces to a coarse drug suspension.[117] Although the bottom-up techniques hold promising potential regarding the possible preparation of NCs with mean diameters lower than 100 nm, they require the use of organic solvents in which the drug must dissolve at suitable concentrations, which is not always a possible scenario. This together with the need for further solvent removal, make of bottom-up techniques a less attractive alternative for pharmaceutical industries, which is reflected in the fact that most NCs-based products commercially available are produced by semi-top-down techniques such as media milling or high-pressure homogenization (HPH).[118-121] Both processes are simple and fast to perform, highly reproducible, easily scalable and free of organic solvents. In media mills, an aqueous suspension of the drug and stabilizers is agitated together with milling beads made of hard and dense materials (diameters of 0.1 mm to 2 cm), that is, yttrium-stabilized zirconium oxide, alumina, stainless steel, glass, and highly cross-linked polystyrene and methacrylate.[122]

As schematized in Figure 4, this section will address the potential for successful transdermal and intradermal delivery of hydrophobic drugs when combined with various nanotechnology approaches, namely NCs, solid lipid NPs (SLNs), liposomes, NLCs, and polymeric NPs, via MAP technology.

2.1.1. Nanocrystals

NCs were also explored. Some studies investigated the intradermal delivery of hydrophobic drugs using dissolving MAPs as aforementioned, the possibility of using other types of MAPs such as coated or hydrogel-forming MAPs was also investigated. For enhanced intradermal delivery, many researchers have focused on nanoparticulate systems, namely NCs, liposomes, nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLNs), or polymeric NPs, by but other formulation approaches such as polymeric or lipidic MPs, solid dispersions, drug solutions, and cosolvency and complexation with CDs were also explored. Some studies investigated the intradermal delivery of the coarse drug only without processing prior to delivery. All these strategies share the same aim of increasing the in-skin absorption of poorly soluble drugs. The implementation of the mentioned techniques, their advantages, as well as their disadvantages will be discussed in great detail in the following sections. Table 1 presents an overview of the different technical approaches found in the literature and the correspondent therapeutic targets of the hydrophobic therapeutic agents delivered transdermally and intradermally via different types of MAPs.

2.1. Nanoparticle-Based Microarray Patches

NPs have been widely used in the delivery of many conventional drugs, proteins, vaccines, and nucleotides.[109] They can be formulated from a broad variety of materials including lipids, sugars, metals, degradable or non-degradable polymers, and organic or inorganic compounds.[110] NPs possess numerous advantages over conventional drug delivery platforms as they can be tailored in terms of particle size, matrix materials or surface properties to regulate the drug release rate, or to achieve site-specific delivery (targeting).[110-113] Moreover, NPs can shield encapsulated active substances delivered into the body from chemical or proteolytic degradation.[110-113] As illustrated in Figure 4, this section will address the potential for successful transdermal and intradermal delivery of hydrophobic drugs when combined with various nanotechnology approaches, namely NCs, solid lipid NPs (SLN), liposomes, NLCs, and polymeric NPs, via MAP technology.
Table 1. Multiple formulation approaches used to deliver hydrophobic drugs into the skin.

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Therapeutic target</th>
<th>Formulation approach</th>
<th>Type of MAP</th>
<th>MAP material</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D3</td>
<td>Model drug</td>
<td>Nanocrystals</td>
<td>Dissolving</td>
<td>PVP, PVPA</td>
<td>[69]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Model drug</td>
<td>Nanocrystals</td>
<td>Dissolving</td>
<td>PVA</td>
<td>[70]</td>
</tr>
<tr>
<td>Doxycycline/ricobendazole</td>
<td>Lymphatic filariasis</td>
<td>Nanocrystals</td>
<td>Dissolving</td>
<td>PVP, PVPA</td>
<td>[71]</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Intradermal delivery for HIV/AIDS</td>
<td>Nanocrystals</td>
<td>Dissolving</td>
<td>PVA</td>
<td>[72]</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Intradivaginal delivery for HIV/AIDS</td>
<td>Nanocrystals</td>
<td>Dissolving</td>
<td>PVA</td>
<td>[73]</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>Benign prostatic hyperplasia</td>
<td>Nanocrystals</td>
<td>Dissolving</td>
<td>CMC, trehalose, polysorbate 80</td>
<td>[74]</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Skin candidiasis</td>
<td>Nanocrystals</td>
<td>Dissolving</td>
<td>PVP, PVPA</td>
<td>[75]</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Cancer treatment</td>
<td>Liposomes</td>
<td>Solid</td>
<td>Not reported</td>
<td>[76]</td>
</tr>
<tr>
<td>Triptolide</td>
<td>Rheumatoid arthritis</td>
<td>Liposomes</td>
<td>Dissolving</td>
<td>Gelatine, PVP and Viscomat™ NP-700</td>
<td>[77]</td>
</tr>
<tr>
<td>Nile Red</td>
<td>Model drug</td>
<td>Nanostructured lipid carriers</td>
<td>Dissolving</td>
<td>Hyaluronic acid</td>
<td>[78]</td>
</tr>
<tr>
<td>Accontine</td>
<td>Arthritis</td>
<td>Nanostructured lipid carriers</td>
<td>Dissolving</td>
<td>N-vinyl pyrolidone</td>
<td>[79]</td>
</tr>
<tr>
<td>Doxycycline/ricobendazole</td>
<td>Lymphatic filariasis</td>
<td>Solid lipid nanoparticles</td>
<td>Dissolving</td>
<td>PVA-PVP</td>
<td>[80]</td>
</tr>
<tr>
<td>Nile Red</td>
<td>Model drug</td>
<td>Polymeric nanoparticles</td>
<td>Dissolving</td>
<td>PMVE/MA</td>
<td>[81]</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Analgesia</td>
<td>Polymeric nanoparticles</td>
<td>Solid</td>
<td>Silicon</td>
<td>[82]</td>
</tr>
<tr>
<td>Nile Red/capsaicin</td>
<td>Model drug/rheumatic arthritis</td>
<td>Polymeric nanoparticles</td>
<td>Dissolving</td>
<td>Hyaluronic acid/PVP</td>
<td>[83]</td>
</tr>
<tr>
<td>Nile Red</td>
<td>Model drug</td>
<td>Polymeric nanoparticles</td>
<td>Solid</td>
<td>Titanium</td>
<td>[84]</td>
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<tr>
<td>Vitamin D3</td>
<td>Vitamin deficit</td>
<td>Polymeric nano- and microcarriers</td>
<td>Dissolving</td>
<td>PVP, PVPA</td>
<td>[85]</td>
</tr>
<tr>
<td>Quercetine</td>
<td>Model drug</td>
<td>Lipidic microcarriers</td>
<td>Solid</td>
<td>Silicon</td>
<td>[86]</td>
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<td>Lidocaine</td>
<td>Local anaesthesia</td>
<td>Hydrogel microparticles</td>
<td>Solid</td>
<td>Stainless steel</td>
<td>[87]</td>
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<tr>
<td>Lidocaine</td>
<td>Local anaesthesia</td>
<td>Solid dispersion</td>
<td>Coated</td>
<td>Stainless steel</td>
<td>[88]</td>
</tr>
<tr>
<td>Leuprolide acetate</td>
<td>Prostatic cancer and endometriosis</td>
<td>Solid dispersion</td>
<td>Dissolving</td>
<td>Sodium chondroitin sulfate</td>
<td>[89]</td>
</tr>
<tr>
<td>Aspirin/lisinopril/atorvastatin</td>
<td>Cardiovascular disease</td>
<td>Solid dispersion</td>
<td>Dissolving</td>
<td>PVP, methyl vinyl ether and maleic acid</td>
<td>[90]</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Insomnia treatment</td>
<td>Solid dispersion</td>
<td>Dissolving</td>
<td>Bioceramics</td>
<td>[91]</td>
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<tr>
<td>Voriconazole/itraconazole</td>
<td>Candida spp. infections</td>
<td>Drug solution for MN coating</td>
<td>Coated</td>
<td>Polyglycolic acid</td>
<td>[92]</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Candida spp. infections</td>
<td>Drug solution for MN coating</td>
<td>Coated</td>
<td>Polyglycolic acid</td>
<td>[93]</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Candida spp. infections</td>
<td>Drug solution for MN coating</td>
<td>Coated</td>
<td>Gantrez 169 BF</td>
<td>[94]</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Candida spp. infections</td>
<td>Drug solution for MN coating</td>
<td>Coated</td>
<td>Gantrez 169 BF</td>
<td>[95]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Model drug</td>
<td>Drug solution for MN coating</td>
<td>Coated</td>
<td>Stainless steel</td>
<td>[96]</td>
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<td>Minoxidil</td>
<td>Hair loss</td>
<td>Drug solution for MN coating</td>
<td>Coated</td>
<td>Stainless steel</td>
<td>[97]</td>
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<td>Autoantigen peptides</td>
<td>Type 1 diabetes</td>
<td>Drug solution for MN coating</td>
<td>Coated</td>
<td>Stainless steel</td>
<td>[98]</td>
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<td>Cyclosporin A</td>
<td>Immunomodulation</td>
<td>Coarse drug</td>
<td>Dissolving</td>
<td>HPC</td>
<td>[99]</td>
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<td>Coarse drug</td>
<td>Dissolving</td>
<td>CMCT</td>
<td>[100]</td>
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<td>Coarse drug</td>
<td>Dissolving</td>
<td>PVA/sucrose + PLA/PLGA</td>
<td>[101]</td>
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<td>Coarse drug</td>
<td>Dissolving</td>
<td>PLGA</td>
<td>[102]</td>
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<td>Etonogestrel</td>
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<td>Coarse drug</td>
<td>Dissolving</td>
<td>HPMC and PVA</td>
<td>[103]</td>
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<td>Coarse drug</td>
<td>Dissolving</td>
<td>PLGA</td>
<td>[104]</td>
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<td>Hydrogel forming</td>
<td>Gantrez S-9/PEG</td>
<td>[105]</td>
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<td>Analgesia</td>
<td>Cosolvency</td>
<td>Solid</td>
<td>Not reported</td>
<td>[106]</td>
</tr>
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<td>Contraception</td>
<td>Cycloextrin complex</td>
<td>Dissolving</td>
<td>Chitosan/beta-sodium glycerophosphate/Dextran</td>
<td>[107]</td>
</tr>
<tr>
<td>Triamcinolone acetoneide</td>
<td>Treatment of hypertrophic scars</td>
<td>Cycloextrin complex</td>
<td>Dissolving</td>
<td>HP-β-CD/Hyaluronic acid</td>
<td>[108]</td>
</tr>
</tbody>
</table>

*Poly(vinyl alcohol); **Poly(vinyl pyrolidone); †Human immunodeficiency virus/acquired immune deficiency syndrome; ‡Carboxymethyl cellulose; §Poly(methylvinylether/male anhydride; ‡Hydroxypropyl cellulose; ©Carboxymethyl cellulose; ¶Poly-O,l-lactide-co-glycolic acid; ¤Hydroxypropyl methylcellulose; ‹Poly-O,l-lactide-co-glycolic acid; ‼Poly(ethylene glycol); ‡Hydroxypropyl-β-cyclodextrin; ‡Polyactic acid (PLA).
a number of factors lead to a reduction in drug particle size, namely shearing forces, pressure, bead collisions and mechanical attrition.\[124–127\] In high-pressure homogenizers, on the other hand, the suspension is forced to pass through a very thin gap at extremely high velocity, which produces a cavitation phenomenon and the subsequent disintegration of drug particles as illustrated in Figure 5.\[128\] Due to the high process flexibility and availability of industrial-scale equipment, media milling is the most commonly used production technique for drug nanocrystals at mass-scale.\[129\] Nevertheless, a large number of research works are based on the use of precipitation (or combinational) approaches that can be performed at the laboratory scale using inexpensive experimental set up.

In 2018, Vora et al. reported for the first time the successful incorporation of a hydrophobic drug as NCs into dissolving MAPs.\[69\] The authors prepared a nanosuspension of the lipophilic vitamin D3 by a bottom-up sonoprecipitation methodology (solvent evaporation antisolvent precipitation method). To achieve the desired particle size, they used poly (vinyl alcohols) (PVAs) and poly (vinyl pyrrolidones) (PVPs) of different molecular weights for stabilization and two different solvents, namely acetone and ethanol. The smallest particles with a mean diameter of 302.5 nm were obtained by using low molecular weight PVA (10 kDa) and acetone. These were taken forward for MAP fabrication as smaller particles are less likely to disrupt the structure of MAPs upon casting. The optimized nanosuspension was mixed with a polymer solution composed of high molecular weight PVP (360 kDa) and the resultant gel was cast into laser-engineered MAP molds. Obtained MAPs were mechanically strong and scanning electron microscopy confirmed that NC particle size was not influenced during MAP fabrication. In an in vitro study employing Franz diffusion cells it was found that dissolving MAPs released a significantly higher (6.8-fold) amount of cholecalciferol into the acceptor compartments compared to MN-free cholecalciferol patches confirming that incorporation of NCs into dissolving MAPs is a promising strategy for the intradermal delivery of hydrophobic drugs.\[69\]

A similar approach was used by Abdelghany et al. to enhance the intradermal permeation of curcumin for treatment of a range of localized and systemic conditions.\[70\] A curcumin nanosuspension with a particle size of approximately 520 nm was prepared by nanoprecipitation with probe sonication to achieve a faster dissolution of curcumin compared to the unmodified powder (34% release compared to 16% release after 48 h in 10% w/v Tween 80). In this study, sodium lauryl sulfate functioned as a stabilizer for the nanosuspension. Two layered dissolving MAPs with NCs incorporated in the MNs only were prepared from PVA (9–10 kDa). MAPs (total MN height 900 \(\mu\)m) could successfully be inserted into excised neonatal porcine skin to a depth of 500 \(\mu\)m. Complete dissolution of MNs occurred within 60 min and the released curcumin diffused from the application site down as far as 2300 \(\mu\)m in deeper skin layers. This was significantly deeper compared to topical application of a curcumin nanosuspension.\[70\]

Permana et al. focused on passive targeting of the lymphatic system via dissolving MAPs.\[71\] Contrarily to the previously described studies, the authors focused not only on one but three different therapeutic agents, namely doxycycline, albendazole, and ivermectin. These drugs are commonly administered in combination to treat the human parasitic disease lymphatic filariasis which damages the lymphatic system and can, thus, lead to elephantiasis, hydrocele, and kidney damage. To realize high lymphatic uptake the drugs were formulated as nanosuspensions with mean particle sizes below 100 nm. Two different bottom-up techniques under probe sonication were employed. While the authors formulated doxycycline and ivermectin using solvent–antisolvent precipitation method, albendazole nanosuspension was prepared using acid-base neutralization precipitation. A wide range of polymers and surfactants was investigated for stabilization. Prior to MAP fabrication, the nanosuspensions were lyophilized. MAPs were then prepared in two steps. Lyophilized nanosuspensions were added.
to an aqueous polymer blend and cast into silicone micro-molds, manufactured by injection molding. A precast baseplate made from PVP (360 kDa) and glycerol was then placed onto the cast formulation for support. MAPs were mechanically strong and upon insertion into excised neonatal porcine skin a significantly higher amount of doxycycline, albenzazole, and ivermectin was delivered into the skin within 24 h compared to needle-free patches. However, even though the results presented in the described study are highly promising, the authors did not carry the work forward to an in vivo study to investigate the lymphatic pharmacokinetic profile of the drugs described.\(^{[71]}\)

McCrudden et al. developed dissolving polymeric MAPs for the sustained delivery of the antiretroviral agent rilpivirine to improve the adherence to prevention and treatment regimens of HIV, particularly in the development. MAPs consisted of MNs composed of low molecular weight PVA (9000–10 000 Da) and an industrially manufactured long-acting rilpivirine nanosuspension that is currently under clinical development as an injectable, attached to a preformed bioadhesive baseplate. This proof of concept study reported the fabrication of mechanically strong MAPs and an in vivo investigation conducted in rats showed comparable distribution of rilpivirine in plasma, localized tissue, and lymphoid tissue between nanosuspension delivery via MAPs and intramuscular injections. Based on the results obtained from this study, a cautious extrapolation estimated that a patch size of approximately 28 cm² could be sufficient to maintain therapeutic plasma levels of rilpivirine in humans over 7 days.\(^{[74]}\) Subsequent work from the same research group has led to the development of similar MAPs for the intravaginal delivery of rilpivirine in a discrete manner. Encouragingly, positive results comparable to intramuscular injection were once again achieved.\(^{[73]}\)

**Figure 6.** Schematic representation of a commonly used method of preparing dissolving MAPs loaded with NCs.

The previously described studies have demonstrated the successful intradermal delivery of hydrophobic drugs as NCs via dissolving MAPs. While bottom-up techniques of nanocrystallization often use volatile organic solvents, top-down approaches merely require the use of shear force and occasionally surfactants. Such methodologies can be easily scaled upward and consistently facilitate the production of mechanically strong MAPs. Although this utilization of NCs infers a limited degree of control over the rate of drug release, this issue is considered negligible as such control can be achieved easily by MAP formulation modification. Low drug loading is a perceived limitation of dissolving MAPs. However, the previously described high drug content of NC formulations maximizes the drug payload of such MAPs and therefore the amount of drug delivered intradermally. The utilization of in silico modeling has provided an indication of the suitability of this technique for the delivery of therapeutically relevant doses of hydrophobic drugs to humans.\(^{[74]}\) While such predictions provide immense encouragement for the field, ultimately, further research is required to confirm their validity.
2.1.2. Lipid-Based Nanoparticles

The first cases of incorporating hydrophobic drugs into lipid droplets were in the 1960s when fat emulsions were developed for parenteral delivery; the principles of which are still used today in formulations including those used for total parenteral nutrition.[130–132] It was in 1991 that an alternative carrier to traditional colloidal systems was first introduced; the SLN.[132] SLNs are generally between 50 and 1000 nm in diameter, and use a solid matrix of encapsulated lipid stabilized by surfactants, polymers or a combination of both as the vehicle for molecule transfer.[131–133] The use of SLNs results in a final product that is physically stable, and one where the encapsulated drug is protected from degradation, as well as having the potential for a controlled release preparation and the added bonus of low cytotoxicity if appropriate excipients are used.[133] When compared to polymeric nanoparticles, SLNs have the distinct advantage of being able to be produced by HPH, an already well accepted technique in the pharmaceutical industry that can be easily scaled-up.[132] Following the success of SLNs a second generation was developed, which are described as NLCs. The lipid component of an NLC is formed of both solid lipid and liquid oil when at body temperature, resulting in a formulation with increased drug loading and reduced drug leakage, and are thus generally considered an upgrade over SLNs.[78,79,131,134]

The manufacturing method for both SLNs and NLCs are vastly similar. The most common method of production is via HPH. HPH is the most common formulation method due to its acceptability within industry, and offers the major advantage of the use of no organic solvents, resulting in a more straightforward scale-up and less issues with toxicity.[131,133] HPH can be divided into two subcategories: hot homogenization and cold homogenization. In hot homogenization the drug is dispersed in molten lipid when regarding SLNs, and with respect to NLCs the active is dispersed in either liquid lipid or a combination of liquid lipid and molten lipid. This is then mixed with a hot solution of surfactant or stabilizer and magnetically stirred to form a premulsion. The temperature this occurs at is usually 5–10 °C above the melting point of the lipid components. The premulsion is then passed through a HPH machine at the same temperature, usually for three cycles at 500 bar, to create the nanoparticles. With cold homogenization the drug is dispersed as above, although it is then cooled to a solid. This solid is then ground up to form lipid microparticles which are then mixed with cold surfactant solution and passed through a HPH machine for 5–10 cycles at 1500 bar.[131,134,135] Of the many HPH machines available, piston gap homogenizers are preferred over jet-stream homogenizers due to ease of control over temperature.[135] Hot homogenization is more suited to lipophilic drugs, and as the exposure to increased temperatures is relatively short, the technique can be used with heat sensitive drugs too.[136]

Another formulation method commonly used is emulsification–evaporation. In this method, the chosen lipid and drug are dissolved in an organic solvent. This is then transferred to an aqueous phase containing surfactant and homogenized. This coarse emulsion is sonicated to reduce particle size to form a nanoemulsion, which is then stirred until the organic phase is removed. Once the organic component has completely evaporated, the SLNs are formed and can be collected.[133,135,137,138]

Lesser-used methods of production include the solvent–anti-solvent technique, where the active is dissolved in a water miscible solvent. This solution is then dissolved into an aqueous solution of surfactant, causing instant precipitation of drug loaded nanoparticles.[80,139] Other reviews offer more detailed descriptions of manufacturing methods including microemulsion technique, emulsification–solvent diffusion, solvent injection (or solvent displacement), phase inversion, multiple emulsion technique, ultrasonication, and membrane contractor techniques.[111,112,115]

Liposomes are another encapsulation method, first described in England in 1961.[140] They are commonly formed from amphiphilic phospholipids and it is the hydrophilic and hydrophobic interactions between lipid–water and lipid–lipid which are the principle behind the system.[141,142] All manufacturing methods involve the combination of an aqueous phase and a lipid, which usually occurs in the following four steps; removal of organic solvent from lipid solution, dispersion this lipid film in aqueous media, concentration and purification of the resulting liposome and finally analysis of the final formulation.[142] Unfortunately, most methods of liposome production involve the use of organic solvents, which have the potential to cause toxicity and cause problems during the scale-up of the process. The most common formulation method is known as the “Bangham method,” or film method.[76,77,140,141]

In this method, the drug and lipid(s) of choice are dissolved in an organic medium and placed in a round bottomed flask. The organic phase is evaporated, resulting in a lipid film in the flask which can be removed and dispersed in aqueous media with agitation or sonication, to produce self-assembled and self-sealing liposomes.

The liposomes, NLCs and SLNs above are all methods of encapsulating lipophilic drugs. These formulations can then be combined with other drug delivery technology, such as MAPs, to enhance their delivery.

The first instance of these systems being used in conjunction with MAPs was with Qiu et al. in 2008. They demonstrated the use of a modified liposome with high deformability, an elastic liposome, to deliver docetaxel across the skin. In this case, solid MAPs with 484 needles per patch, which were created via a combination of wet and dry etching, were applied to the skin as a pretreatment. Individual needles were 150 μm in height and had a midpoint–midpoint spacing of 400 μm, while docetaxel elastic liposomes were formulated using the Bangham film method. In an in vitro study, an applicator was used to apply the MN array into 600 μm thick dermatomed porcine skin. The MNs were then removed, and once the microconduits were formed from this pretreatment the docetaxel loaded elastic liposomes were applied to the skin. It was found that the elastic liposomes increased transdermal delivery of docetaxel in untreated skin when compared to unformulated docetaxel, and when combined with MAP technology the transdermal flux was increased by 1.3–1.4 μg cm−2 h−1. Additionally, it was seen that the lag time for transdermal delivery of docetaxel loaded elastic liposomes was decreased by around 70% following the use of MAPs, indicating that this approach has potential for increased transdermal delivery of hydrophobic drugs.[76]
investigated the use of triptolide for the treatment of rheumatoid arthritis. Triptolide liposomes were produced via the Bangham film method and had an average size of $201.52 \pm 18.43$ nm with an encapsulation efficiency of $83.62 \pm 1.97\%$. These liposomes were then formulated into a hydrogel composed of gelatine, PVP and Viscomate NP-700 which was then coated onto woven fabrics to produce a hydrogel patch. In a pharmacokinetic in vivo study, Sprague Dawley rats with induced arthritis were pretreated with a dermal application of $200 \mu m$ solid MNs, followed by the application of the hydrogel patch corresponding to $1.6 \text{mg kg}^{-1}$ of triptolide. Using oral administration as the control, the MAP hydrogel patch combination greatly decreased the time for the triptolide to reach $C_{\text{max}}$ and significantly increased the AUC, showing an increase in bioavailability by avoiding first-pass metabolism. A pharmacodynamic study showed that both joint swelling and immune markers were suppressed following the MAP hydrogel patch application, while toxicity was also greatly reduced. This study clearly demonstrated the potential of this MAP hydrogel patch system for the treatment of rheumatoid arthritis with triptolide.\[77\]

NLCs have also been combined with MNs for transdermal delivery. In 2015, NR was formulated into NLCs by the process of hot HPH, resulting in particles with a mean diameter of $268$ nm and a PDI of $0.273$. These NLCs were subsequently developed into HA-based dissolving MAPs and fully characterized. Figure 7A,B and 7B shows the microscopic appearance of the MNs, whereas the release profile of NR from a micellar solution (control) and the NLC is shown in Figure 7C. HA is a hydrophilic polymer and through use of a drawing lithography method the resultant array had a $7 \times 7$ MN arrangement with $350 \mu m$ MN height, and was supported on a $1 \text{cm}^2$ CMC baseplate. Using $600–700 \mu m$ thick dermatomed minipig dorsal skin, an in vitro Franz diffusion cell study showed, that $24$ h post-application of the NLC-loaded MAPs, $70\%$ of the drug was localized in the skin. Interestingly, the results indicated that the drug diffused outward in a radial fashion from the insertion site over time, showing the potential of this system in a controlled release formulation.\[78\]

Studies with aconitine and dissolving MAPs were used to show the potential of the system in treating arthritis. Aconitine NLCs were produced via emulsification–evaporation followed by lyophilization to produce a particle with a mean diameter of $152.1 \pm 5.6$ nm.\[79\] The lyophilized powder was then mixed with $N$-vinyl pyrrolidone and cast into a $2 \times 2 \text{cm}$ mold. This mold was placed under a pressure of 3 bar for 30 s to drive

![Figure 7. A) Optical microscopy image of a microneedle loaded with NLC. B) Fluorescence photomicrograph of a microneedle loaded Nile Red NLC. C) Release profile of Nile Red (NR) from a micellar solution (control) and from the NLC. Reproduced with permission.\[78\] Copyright 2013, Dove Medical Press, Ltd.](image-url)
the formulation into the cavities of the mold, followed by crosslinking of the polymer chains by exposure to UV light for 4 h. The resulting MAP had MNs which were 350 μm in height and capable of dissolving rapidly, that is, within 3 min.[79] An in vivo study was performed in a rat model, using rats which had adjuvant-induced arthritis. Tape stripping and microdialysis showed the NLC-MAP system was capable of greatly enhancing the delivery of aconitine transdermally, which led to a significant increase in the efficacy of the drug in the model, exhibited by greatly reduced paw swelling and inflammation alongside decreased toxicity. The delivery system also appeared to form a drug reservoir in the model, which suggests the system has potential to form localized, controlled release preparations.[79]

A proof-of-concept study was conducted by Permana et al., which centered on lymphatic targeting via the use of SLN-loaded MAPs for the treatment of lymphatic filariasis.[80] In this work, doxycycline and albendazole sulfoxide were encapsulated into lipid-based NPs by hot emulsification-ultrasonication, and double emulsification, respectively, and were less than 100 nm in diameter. PVA and PVP blends were used to load the SLNs into dissolving MNs as well as for the preformed baseplate. An in vivo study, using rats, demonstrated that these SLN-loaded MAPs were able to significantly increase delivery to the lymphatic system (between four- and sevenfold) when compared to oral administration. This was done without increasing plasma concentrations of the drugs used. Relative bioavailabilities of the drugs were increased when compared to oral administration, however, further studies are needed to optimize this system by fully clarifying the dose of drug needed to kill adult filarial parasites in the lymph nodes.[80]

These studies highlight the versatility of lipid-based NPs to deliver hydrophobic drugs via MAPs. Enhanced skin permeation was extensively demonstrated with the potential for lymphatic-targeting displayed by particles with diameters below 100 nm. While the production techniques of lipid-based NPs are highly scalable, these NPs are predominantly composed of matrix materials which reduces their overall drug loading capacity.

2.1.3. Polymeric Nanoparticles

Polymeric NPs are particles of less than 1 μm in diameter that are prepared from natural or synthetic polymers. Natural polymers (i.e., proteins or polysaccharides) have not been widely used for this application as they vary in purity and often require crosslinking that presents the risk of drug degradation. Consequently, synthetic polymers have received more attention in this area.[145] As a result of the progress of polymer chemistry and polymer colloid physicochemistry, it is possible now to synthesize polymers with controlled composition and structure, and therefore, formulate polymeric NPs with a wide range of advantageous properties.[144] However, there is a limited number of available polymers that can be used to formulate NPs due to the following requirements: 1) to minimize the risk of adverse effects caused by polymer accumulation, the polymer should be biodegradable or at least eliminated from the body in a short period of time, 2) polymers and their degradation products should be non-immunogenic and non-toxic, and 3) polymers should be amenable to the processes involved in the formulation of NPs intended for drug delivery.[144] Biodegradable polymeric NPs are widely used to improve the bioavailability, solubility, and retention time of insoluble drugs. The most commonly used polymers for this purpose include poly-d,l-lactide-co-glycolide (PLGA), polyactic acid (PLA), poly-caprolactone (PCL), poly-alkyl-cyanoacrylates, chitosan, and gelatine.[144] Biodegradable polymeric NPs formed from these polymers are highly preferred due to their ability to release drug in a rate controlled manner, subcellular size, and inherent biocompatibility.[144] PLGA is one of the most successfully used biodegradable polymers for the development of nanomedicines because it undergoes hydrolysis in the body to produce the biodegradable metabolite monomers, lactic acid and glycolic acid.[145] With a high level of interest associated with the use of polymeric NPs for the purpose of drug delivery, instances of success when such NPs are used in combination with MAPs are numerous.

One of the first studies that combined the use of polymeric NPs and MAPs was to improve the delivery of the model hydrophobic drug NR by Donelly et al.[81] PLGA polymeric NPs encapsulating NR, with a diameter of 150 nm and a low polydispersity index of 0.087, were prepared by a salting out method before being loaded into dissolving MAPs made of PMVE/PMA. In order to study the penetration depth of NR in full-thickness porcine skin, in vitro studies were carried out using the widely reported Franz cell apparatus set up. As expected, the concentration of NR was lowest in the deeper skin layers, with a mean tissue concentration of 383.63 ng cm⁻² detected at a depth of 1.125 mm. No dye was detected in the receiver compartments of the Franz cells.[81] Although this study demonstrated the ability of MAPs to load and deliver PLGA NPs in the skin, the use of dichloromethane as solvent, may limit the clinical applications of this systems.

In an alternative study, polymeric NPs were combined with solid silicon MAPs to improve the percutaneous delivery of ketoprofen.[82] Ketoprofen is a potent antiinflammatory drug with low aqueous solubility and a short elimination half-life. Ketoprofen-loaded NPs were prepared from PLA using a modified solvent displacement method.[82] The encapsulation efficiency of the obtained ketoprofen-loaded NPs was 75.3 ± 0.96%. To investigate the effect of silicon MAPs on the permeation of ketoprofen an in vitro permeation study across porcine skin was performed using Franz cells. Ketoprofen NPs were either applied to skin in the absence of skin pretreatment or skin was pretreated using 1 cm² solid MAPs that had a total of 36 MNs (needle height 200 μm). After 24 h, 48.6 ± 3.2 μg cm⁻² of ketoprofen had been delivered to MAP-treated skin, whereas, only 20.6 ± 1.6 μg cm⁻² had permeated through untreated skin, demonstrating the significant effect of silicon MAPs on the percutaneous delivery of ketoprofen-loaded NPs.[82]

Another novel approach for the delivery of hydrophobic drugs via dissolving MAPs was carried out by Dangol et al.[83] In this work, novel MAPs containing the model hydrophobic drug NR and the therapeutic agent capsaiacin (CAP) were formulated using a solvent-free methodology. The authors reported that chemical interactions between the drugs and the MAP polymers (HA and PVP) permitted the formation of nanosized colloidal structures. Investigation of these MAPs in an in vivo setting demonstrated enhanced delivery of CAP, in comparison to control cohorts, for the treatment of rheumatic arthritis. The
microscopic appearance of the MAPs tested, the appearance of skin post-insertion, MAP drug release profiles and in vivo effect are presented in Figure 8.

Chiu et al. carried out a study that aimed to investigate the novel use of solid MAPs in combination with polymeric NPs for the treatment of conditions that affect nails.[84] Currently available topical formulations for nail conditions display poor diffusion into and through nails due the highly compacted structure of nails, and therefore, reduced efficacy. NPs, containing NR as a model hydrophobic drug, were prepared from PCL using a solvent-displacement method, a single step formulation procedure that brings about spontaneous NP formation. To evaluate the effect of MAPs on delivery of NR in an in vitro setting, nails were treated with a Dermaroller comprising 250 µm long titanium MNs prior to NP application. The authors used several fluorescence techniques to demonstrate that model drug loaded into polymeric NPs was able to penetrate the nails more efficiently after a pretreatment with MNs Figure 9. They also proved that the NPs remained as immobile reservoirs, sequestered on the nail surface and in the MN-generated pores, from which NR was released and diffused laterally into the nail over an extended period of time.[84]

The studies discussed within this section demonstrate that the combination of polymeric NPs with MAPs is technically feasible. Nevertheless, the incorporation of the hydrophobic drugs into the NPs often required the use of organic solvents, which is an undesirable characteristic when considering the translation of a process to an industrial setting and indeed patient delivery. Additionally, in a similar manner to other carrier-based systems, polymeric NPs have reduced drug-loading capacity which ultimately restricts their use to potent, low dose drugs. Finally, there is a need for enhanced understanding of the in vivo behavior of polymeric NP-based MAPs. To this end, the completion of a greater number of in vivo pharmacokinetic studies as well as increased in silico modeling could improve the future perspective of this combinational strategy.

2.2. Microparticle-Based Formulations

Microparticles (MPs), as their name suggests, are micron-sized particles, that is, larger in size than NPs, that are used as drug delivery systems through the process of drug encapsulation.[146]
This microencapsulation technology, which is similar in nature to the nanoencapsulation techniques discussed previously, facilitates an improvement in drug bioavailability which in turn reduces required drug dosing and therefore side effect incidence. Additional benefits associated with the use of this technique are the achievement of site-specific delivery, stabilization and protection of reactive substances, elimination of incompatibilities, and masking of unpleasant taste for oral administration. \cite{69,85,146–149} To be successfully applied as a homogeneous drug delivery system, the particle size should range from 1 to 5 \(\mu m\). \cite{150} Due to the ability of MPs to extend the release of hydrophilic therapeutics, the literature includes a range of work that combines the use of MPs and MAPs to deliver vaccines,\cite{151,152} calcein,\cite{153} enzymes,\cite{154} and proteins \cite{155} in a rate-controlled manner. In this section, the MAP-mediated delivery of hydrophobic drugs using different types MPs will be discussed.

Quercetin is a naturally occurring antioxidant that has poor water solubility and as a result displays low permeation through the skin.\cite{156} As a strategy to improve the intradermal delivery of this compound, Paleco et al. developed lipid MPs, using phosphatidylcholine and tristearin, that contained quercetin at a concentration of 11.7% w/w.\cite{86} Adopting a “poke and patch” methodology, the authors treated skin with solid silicon MAPs followed by the topical application of a formulation containing quercetin MPs. Using this two-step application process, a five-fold increase in the epidermal deposition of quercetin compared to a formulation that did not contain MPs was observed in vitro.\cite{86}

In a similar manner, Nayak et al. formulated a hydrogel containing MPs to improve the delivery of lidocaine, a commonly used local anaesthetic.\cite{87} In this work, MPs were formed through electrostatic interactions between a hydrogel composed of sodium CMC and gelatine, and a water/oil emulsion in paraffin oil. Again a “poke and patch” application methodology was adopted and a two-fold improvement in the delivery of lidocaine was observed, in comparison to MP topical application in the absence of skin pretreatment with MAPs.\cite{87} Additionally, this approach demonstrated extended release of lidocaine, due to the presence of the formulated MPs.

An innovative approach which utilized dissolving MAPs loaded with NPs and MPs containing vitamin D3 (or cholecalciferol) was described by Vora et al.\cite{85} This delivery system displayed a triphasic release phenomenon that included initial burst release of vitamin D3 from NPs and coarse drug on the surfaces of MPs as well as sustained-release dependent on MP polymer degradation. For the preparation of both NPs and MPs, an emulsion solvent evaporation technique was applied using poly(lactide-co-glycolide). MAPs were composed of two separate layers, with drug-containing NPs and MPs incorporated in the MNs only, thus avoiding drug wastage and improving delivery efficiency. Briefly, this methodology involved casting of the first layer (MN) which was composed of the drug-containing PVP/PVA hydrogel formulation followed by casting of a drug-free hydrogel to form the secondary backing layer.\cite{85} As mentioned previously, a distinct advantage of this delivery system was its ability to display drug delivery in both an immediate and sustained manner due to the presence of NPs and MPs, respectively. In an ex vivo setting, these MAPs demonstrated a 4.9-fold (196 \(\mu g cm^{-2}\)) enhancement in vitamin D3 delivery when compared to a patch without needles (40 \(\mu g cm^{-2}\)).\cite{85} However, the formulation process applied in this work required the use of organic solvents (dichloromethane) and/or elevated temperatures which is undesirable as it can damage biomolecules and volatile species.\cite{157}

Figure 10 presents scanning electronic micrographs of the bilayered MAPs used in this study. Upon inspection it is possible to...
see the porous structure of the MNs and the drug containing NPs and MPs which are distinguishable.

The formulation of MPs is a well-documented strategy for the delivery of hydrophobic drugs; the proof-of-concept studies reviewed here prove that MP-based platforms can be successfully combined with MAPs. This approach possesses the distinct advantage of providing a significant degree of control over the release rate of drugs through the modification of particle sizes. However, as outlined previously, the frequent use of organic solvents in MP formulation is a drawback of this approach.

2.3. Solid Dispersions

In a solid dispersion a hydrophobic therapeutic agent is dispersed in a solid hydrophilic matrix. This system increases
the surface area of the drug; providing enhanced drug dissolution and, therefore, drug absorption which culminates as improved overall drug bioavailability.\[159\] Solid dispersions are most commonly prepared by a process of melting or solvent evaporation; techniques that can be easily up-scaled and commercialized. Crucially, the possibility of drug–carrier interactions has to be considered during solid dispersion formulation.\[158\]

In 2014, Ma and Gill demonstrated, for the first time, the use of MAPs coated with a solid dispersion for the delivery of a hydrophobic drug.\[88\] Lidocaine base, a hydrophobic model drug, was dispersed in poly (ethylene glycol) (PEG) (3350 Da) as a hydrophilic matrix by melting and ultrasonication. Stainless steel MAPs, fabricated by wet etching, were then coated with the molten mixture by microprecision dip coating. The coating dissolved in in vitro studies within 3 min and lidocaine diffused to a depth of 4.8 mm in excised porcine skin. Compared to topical application of a commercially available lidocaine cream, a significantly higher amount of drug was delivered.\[88\]

An alternative study, carried out by Ito et al. reported the fabrication of dissolving MAPs for the intradermal delivery of a solid dispersion containing a hydrophobic drug.\[89\] In this work, leuprolide acetate was directly dispersed within a hydrophilic matrix composed of sodium chondroitin sulfate and this blend was then micromolded to form MAPs. The fully formed MAPs contained approximately 14.3 \(\mu\)g leuprolide acetate which was localized in the MNs only. The entirety of this drug cargo was deposited intradermally within 3 min in in vitro studies. In vivo investigations indicated that, compared to subcutaneous administration, the relative bioavailability of solid dispersion containing MAPs was 99.2% for one full MAP and 105.6% for half a MAP, respectively.\[89\]

Quinn et al. formulated MAPs using a similar approach for intradermal delivery of a fixed-dose combination of the cardiovascular drugs aspirin, lisinopril dihydrate, and atorvastatin calcium trihydrate.\[89\] While lisinopril was readily soluble within the formulation, the amounts of aspirin and the hydrophobic atorvastatin added exceeded their solubility, therefore forming a solid dispersion with the polymers used to form dissolving MAPs, that is, PVA or Gantrez S-97, a copolymer of poly (methylvinylether/maleic anhydride) (PMVE/MA). All three compounds were successfully delivered in in vitro studies across neonatal porcine skin as shown in Figure 11; with MAPs demonstrating enhanced delivery up to 100-fold compared to application of a needle free patch.\[89\] Due to the hydrophobicity of atorvastatin a significantly lower amount was delivered compared to the other compounds. A theoretical extrapolation estimated a necessary patch size of approximately 50 cm\(^2\) for delivery of a dose comparable to existing oral dosage forms.\[89\] The authors noted that a MAP of this size would increase the difficulty associated with the reproducibility of successful application, however, they went on to state that the patch size may be reduced if an increased drug bioavailability, which is expected, was observed upon in vivo intradermal delivery.\[89\]

The intradermal delivery of the model drug zolpidem tartrate via ceramic MAPs was investigated by Cai et al. In this study, MAPs made from multiple self-setting biceramics (gypsum

![Figure 11](image1.png)

Figure 11. A) Release profiles aspirin (i), lisinopril (ii), and atorvastatin calcium (iii) from MAPs. B) Release profiles aspirin (i), lisinopril (ii), and atorvastatin calcium (iii) from MN-free patches. Reproduced with permission.\[90\] Copyright 2015, Elsevier.
and brushite) were developed and subsequently fabricated by a micromolding technique. Zolpidem tartrate was dispersed in the wetted ceramic pastes before casting of MAPs. In vitro release was tested over 48 h using a moisturized cellulose material and demonstrated that the drug release rate could be controlled by the surface area of MAPs, MN porosity, and the extent of resorption displayed by the biodegradable matrix.\cite{91} The formulation of therapeutic agents as solid dispersions is a promising approach for intradermal delivery of hydrophobic drugs via MAPs. Importantly, manufacturing processes are simple with few steps and facilitate high levels of drug loading. Moreover, the ability to cast a solid dispersion directly into a MAP micromold highlights the ease of MAP fabrication using this methodology. While some approaches necessitate heat or the use of organic solvents, instances of solid dispersion formation without such conditions have been demonstrated. As outlined previously, drug–carrier interactions need to be taken into consideration to ensure the production of an amenable formulation. Although all studies reported the successful transdermal delivery of hydrophobic drugs, in some cases the total quantity of drug delivered was relatively low. This may be due to the absence of processes such as melting or dissolution that increase total drug surface area prior to dispersion in the hydrophilic matrix.

2.4. Drug Solutions for Microneedle Coating

Coated MAPs are characterized as arrays coated with a solid, drug-containing film on the MN surface.\cite{160} After insertion into the skin, this coating dissolves, releasing the active compound intradermally. The advantages of this methodology include the avoidance of polymer deposition in skin which is a negating factor associated with dissolving MAPs.\cite{160} Coated MAPs have been used to deliver a wide range of compounds including both those with small molecular weights, and those with high molecular weights such as vaccines, proteins, and DNA. Unfortunately, a common criticism of coated MAPs is the fact that they are limited in terms of drug loading when compared to other types of MAPs.\cite{151,160} A number of varying coating techniques have been reported to modify the surface of MNs,\cite{19,98,150–162} such as immersion coating, drop coating, inkjet printing, spray coating, and layer-by-layer coating.\cite{160} Each technique utilizes variations in excipients used, viscosity and tension to adequately coat the surface of MNs.\cite{160} Coated MAPs have been used to deliver hydrophobic drugs including the antifungal agents voriconazole\cite{92} itraconazole,\cite{93} micazolone,\cite{94} and amphotericin B, as well as other compounds including curcumin,\cite{96} minoxidil,\cite{97} and hydrophobic peptides.\cite{98}

As a strategy to improve the delivery through the skin of the antifungal drugs itraconazole and voriconazole, coated MAPs were utilized by Boehm et al.\cite{92,93} The authors used piezoelectric inkjet printing to coat MNs with polyglycolic acid (PGA) containing both drugs to act against Candida albicans.\cite{92,93} Specifically, both types of MAP were manufactured based on injection molding in combination with drawing lithography. To prepare an antifungal voriconazole coating, a vehicle solution was produced by dissolving a copolymer PMVE/MA in dimethyl sulfoxide (DMSO). Following this, the vehicle solution was loaded with voriconazole to form a drug solution. During the coating process, 1 μg of voriconazole was evenly deposited on the surface of the MNs of each MAP. A similar vehicle solution which had benzyl alcohol and coconut oil added was prepared to solubilise itraconazole. In this case, a total dose 25 μg of itraconazole was coated onto the MNs of each MAP. Insertion into excised porcine skin indicated that the MAPs were able to penetrate the stratum corneum layer and release both therapeutic agents from the surface of MNs; with no residue detected on the surface of the skin. Both MAPs containing antifungal agents exhibited the ability to inhibit the growth of C. albicans as confirmed by in vitro microbiology studies.

In addition, Boehm and colleagues loaded micazolone\cite{94} and amphotericin B\cite{95} on the surfaces of Gantrez 169 BF MNs using piezoelectric inkjet printing. The MAPs were fabricated using an approach that involved a combination of visible light dynamic mask micro-stereolithography and indirect rapid prototyping. The drug solution with both drugs was prepared using DMSO, due to their poor solubility in aqueous solutions. Unlike the uncoated MAPs, the MNs modified with micazolone and amphotericin B exhibited antifungal activity against C. albicans and C. parapsilosis, respectively.

Using an alternative approach, stainless steel MAPs were dip-coated with the hydrophobic model drug curcumin dissolved in an organic solvent-based solution by Gill et al.\cite{96} In this study, the coating solution consisted of ethanol, curcumin, and PVP, which served as a viscosity enhancer. Upon submersion in an aqueous medium, effective release of this drug solution from the surface of MNs was observed after 15 min. In an in vivo setting, the same MAPs achieved a similar level of drug release after just 1 min post-insertion.\cite{96} Minoxidil is commonly applied as a topical solution to treat hair loss.\cite{97} However, the slow penetration of minoxidil and the increased thickness of the stratum corneum located on the frontal area of the head often lead to subtherapeutic levels of minoxidil observed in the plasma. In their work, Namrata et al. modified the surface of solid MNs with a formulation containing minoxidil, Eudragit E 100, propylene glycol and ethanol. Compared with a marketed minoxidil solution, an in vitro release study profile of the coated MAPs revealed that there was no significant difference in drug permeation through the abdominal skin of albino mice.\cite{97} Zhao et al. developed a coating formulation that contained hydrophobic autoantigen peptides that were under investigation for the treatment of type 1 diabetes.\cite{98} The formulation comprised the cosolvents: water, 2-methyl-2-butano, acetic acid, and PVA 2000 as coating excipients. The hydrophobic peptides were coated onto electropolished stainless steel MAPs using a drop coating approach with pipette tips and the appearance of the MNs was observed by electronic microscopy as displayed in Figure 12A. Importantly, no loss in the bioactivity of the peptide recovered from the surface of MNs was observed. The delivery efficiency of the hydrophobic peptides from the modified MNs in human and mouse skin was confirmed using fluorescence microscopy (Figure 12B). The results indicated that the delivery efficiency in human skin model (58.9 ± 3.2%) is significantly higher than that in murine skin (19.5 ± 34.7%).

The studies outlined in this section underpin the potential associated with the delivery of hydrophobic drugs using MAPs
coated by piezoelectric inkjet printing, dip coating, and drop coating. This technique offers the delivery of highly consistent quantities of drugs in a manner that is both convenient and discrete. As with other approaches discussed previously, the use of organic solvents is unfavored, however, the low level of organic solvent content present in final coating formulations provides reduced risk of patient harm. Furthermore, debate surrounding the requirement of complete drug dissolution prior to MN coating may prove that the use of organic solvents in many applications is unnecessary. Undoubtedly, the limited drug loading capacity of this approach is its largest drawback. As a consequence, regardless of species solubility, delivery of drugs via coated MNs continues to be solely applicable for those that are highly potent.

2.5. MAPs Loaded with Coarse Drug Particles

MAP-mediated delivery of hydrophobic drugs in their coarse state, that is, without an additional solubility enhancing system or process, is associated with a high level of difficulty. Upon MN application and subsequent drug deposition in the hydrophilic viable epidermis, these poorly soluble drug molecules demonstrate reduced diffusion within this skin layer compared to their hydrophilic counterparts. Crucially, this reduced level of drug diffusion within the epidermis often results in a reduction in the amount of drug successfully delivered to the dermal microcirculation. In many instances, this drawback may trump the numerous benefits that are associated with MAP mediated drug delivery. However, there are multiple examples in the literature where delivery of hydrophobic compounds via these minimally invasive devices has been shown to be both viable and indeed successful.

Delivery of the poorly soluble immunosuppressant cyclosporin A was enhanced by the incorporation of the drug into dissolving MAPs composed of hydroxypropyl cellulose by Jeong et al. The authors reported a $C_{\text{max}}$ value (15.9 ng mL$^{-1}$) that was not statistically different from that of orally administered cyclosporin A using an in vivo rat model. Additionally, MAP-mediated delivery of cyclosporin A displayed an AUC that was 2.7 times larger than that of oral cyclosporin A and plasma levels of the drug were maintained above 5 ng mL$^{-1}$ for up to 72 h as opposed to just 24 h with oral administration. While a long application time (60 min) and the use of the organic solvent methanol in MAP casting are limiting factors of this delivery system, it is an example of localized and sustained delivery of a poorly soluble therapeutic.

The synthetic drug finasteride is approved for the oral treatment of androgenic alopecia. Dissolving MAPs composed of CMC that had internal cavities filled with powdered finasteride demonstrated enhanced transdermal permeation at 24 h (7.57 ± 1.39 µg) when compared to a topically applied gel (3.79 ± 0.69 µg) in an in vitro setting using Franz cells. Importantly, a diffusion enhancing solution composed of ethanol and propylene glycol was added to MAP application sites post-application to aid drug diffusion through the hydrophilic viable epidermis. Low levels of finasteride were detected in the receiver compartments of the replicates where this diffusion enhancing solution was not applied (0.02 ± 0.02 µg) and visible finasteride plugs could be observed on the periphery of the skin. Furthermore, qualitative analysis of an in vivo study with a similar set up showed visibly better hair regrowth in shaved mice treated with finasteride-containing MAPs when used in combination with the diffusion-enhancing solution. This work highlighted the potential of MAP-mediated delivery of coarse finasteride in the treatment of androgenic alopecia.

Important aspects to note are that this delivery system used a complex, two-step MAP fabrication process and required the additional application of a diffusion enhancer, both of which are sure to reduce patient acceptance and therefore hinder translation into a marketed product.

**Figure 12.** A) Electronic microscopy photomicrographs of MNs coated with increasing amounts of hydrophobic peptides. B) Distribution of the hydrophobic peptides in human skin explant after MAP application. Reproduced with permission. Copyright 2017, Elsevier.
Levonorgestrel is a poorly soluble progestogen commonly prescribed as a method of hormonal contraception. Levonorgestrel is an ovulation inhibitor and is available in multiple different medicinal forms such as a long-acting implantable device, a low-dose contraceptive tablet, and as a high-dose emergency contraceptive tablet. Alternatively formulated levonorgestrel-containing MAPs intended for sustained release of the hormonal contraceptive were actualized by Li et al. The two-step manufacturing process adopted here produced MAPs with two separate phases; rapidly dissolving bases composed of PVA and sucrose, and slowly biodegrading, drug-containing MNs composed of PLA and PLGA as shown in Figure 13. Crucially, the casting methodology used facilitated the formation of an air bubble between each of these layers, that is, between each MNs base and tip, which ensured rapid MN tip detachment from the baseplate within 5 s of patch application to the skin and >95% of total tip deposition in the skin upon patch removal. In vitro and in vivo investigations of these MAPs displayed sustained-release of levonorgestrel over 46 and 60 days, respectively. Rats treated with these MAPs displayed a $C_{\text{max}}$ value of $1.05 \pm 0.14$ ng mL$^{-1}$ after $144 \pm 45.6$ h ($T_{\text{max}}$) with plasma concentrations maintained above human therapeutic levels (0.2 ng mL$^{-1}$) for slightly over 30 days post applica-
tion. While, the use of organic solvents in MAP fabrication and reduced mechanical strength of MAPs may be considered negligible characteristics of this delivery system, the high level of innovation demonstrated in this work cannot be refuted.

Subsequent work completed by Li et al. resulted in modifications to MAP formulation and, therefore, alteration in their mechanism of action. MNs that provided sustained-release of levonorgestrel were composed of PLGA only, while the base of MAPs was reformulated to contain PVP, citric acid and sodium bicarbonate making it effervescent upon contact with interstitial fluid. Importantly, this reformulation eliminated the need for an internal air bubble to ensure swift and extensive MN deposition. The newly formulated MAPs successfully deposited $91.7 \pm 2.4\%$ of their tips in an in vivo rat model after an application time of 50 s. A peak plasma concentration ($C_{\text{max}}$) of $0.83 \pm 0.03$ ng mL$^{-1}$ was reached after $98 \pm 84$ h ($T_{\text{max}}$) and plasma concentration of levonorgestrel was maintained above human therapeutic levels for slightly under 40 days. Sustained release of levonorgestrel followed roughly first-order kinetics and no burst release of levonorgestrel was observed in vivo. A successive human study investigating patient acceptance of a similarly formulated placebo device found that 100% of participants preferred the device to monthly injections and 90% to daily oral pills, respectively. Issues associated with this type of MAP include the use of organic solvents in MAP fabrication which is not only undesirable in an industrial setting but can lead to the formation of brittle MAPs. Additionally, the hygroscopic nature of these MAPs can lead to premature effervescence caused by moisture present in the atmosphere. Despite these issues, this cost-effective, discreet, and long-acting method of hormonal contraception possesses great promise as a feasible substitute for both implantable contraceptive devices and daily contraceptive tablets.

An alternative study that aimed to investigate the delivery of another contraceptive drug, etonogestrel, was carried out by He et al. In this work, the authors prepared dissolving MAPs with two distinct layers; the MN layer was composed of drug particles with diameters of 10–30 µm and aqueous solutions of PVA and hydroxypropyl methylcellulose (HPMC), whereas, the free-drug baseplate layer was prepared using a PVA solution (35% w/w). The in vivo pharmacokinetic studies
carried out in rats demonstrated the ability of these MAPs to deliver etonogestrel in a sustained manner for up to 1 week, with no significant differences when compared to the cohort treated with an intradermal injection of the drug. In a recent report from the same group, etonogestrel was loaded into implantable PLGA MNs with pyramidal and conical geometries (Figure 14A) with the aim to achieve a sustained release. As shown in Figure 14B, the pharmacokinetic trial showed that etonogestrel was detectable in plasma for up to 336 h. Interestingly, where the control cohort intradermal injection) demonstrated an AUC$_{0-48h}$ that accounted for 90.5% of AUC$_{0-\infty}$, the implantable PLGA MNs displayed an AUC$_{0-48h}$ of 37.8%.

The work reviewed in this section proves that loading coarse drugs into dissolving MAPs is an appealing strategy for the delivery of hydrophobic drugs. In particular, research on the delivery of hormone-like molecules and more specifically, of contraceptives is of particular note. From a formulation perspective, an intradermal contraceptive delivery alternative, such as the MAPs discussed within, is considered viable due to the ability to load weekly or monthly treatments in relatively small patches as a result of the highly potent nature of such drugs. Furthermore, the release of drug from effectively implanted MNs in a rate-controlled manner is a considerable advantage of this transdermal system. Additionally, the acceptance of a discrete transdermal device by those receiving contraceptive treatment is sure to be high due to the associated ease of application, extended drug release profile, and lack of sharp waste generation. Truly, this area of MAP-mediated sustained drug delivery is one that provides encouragement to others working in the field as well as anticipation of translation to a marketable product.

### 2.6. Delivery of Drugs Using Cosolvency

Cosolvency involves dissolving a hydrophobic drug in a suitable solvent before delivery into an aqueous environment. This process enhances the dissolution of the poorly soluble drug in this aqueous environment and increases the likelihood of successful systemic absorption. Most commonly, the organic solvents ethanol, propylene glycol and PEG are used as cosolvents for parenterally administered therapeutics.

Cosolvency was utilized in combination with novel hydrogel-forming MAPs by Kearney et al. As detailed above, upon application to the skin, these MAPs imbibe interstitial fluid and swell to form a hydrogel in situ. These swollen hydrogel...
projections acted as aqueous conduits through which olanzapine and atorvastatin were delivered across a suitable in vitro skin model from their respective cosolvent reservoirs. After 24 h, 49.07 ± 8.35% of olanzapine was delivered from a PEG 400 reservoir and 48.13 ± 4.70% atorvastatin was delivered from a similarly formulated reservoir. Propylene glycol reservoirs demonstrated 48.70 ± 11.13% and 41.16 ± 5.1% delivery of olanzapine and atorvastatin, respectively. The high levels of drug permeation observed indicated that the use of cosolvent reservoirs was complimentary to the mechanism of action of these innovative hydrogel-forming MAPs. However, due to the presence of a liquid reservoir, there is a greater perceived difficulty associated with the scalability of this delivery system. Further investigative work is required to address this issue and fully realise the potential of this delivery system.

So et al. used solid MAPs for the intradermal delivery of ketoprofen from a carbomer 940 gel containing the drug at a concentration of 3% w/v and 40% v/v of ethanol. In a pharmacokinetic experiment in rats they compared the effect of a pretreatment of the skin with MAPs and subsequent application of the gel, with a cohort treated with the same amount of gel loaded upon the MAPs as coating. Results showed that with the latter approach values achieved for the AUC and Cmax of ketoprofen were 186% and 286% higher than for the control group (skin pretreatment).

Cosolvency is a technique that is highly logical when working with hydrophobic drugs. Unfortunately, due to issues with drug stability and the use of organic solvents the combination of this methodology with MAPs appears to have reduced suitability for translation to a marketable product.

### 2.7. Cyclodextrin Inclusion Complexes

CDs are cyclic oligosaccharides that can act as carriers for hydrophobic drug molecules in an aqueous environment due to their lipophilic inner cores and hydrophilic external surfaces. Complexes are formed spontaneously in solution through a combination of hydrogen bonding and weak intermolecular associations between a drug and the inner cavity of a CD. CD complexes have been widely used to increase the aqueous solubility of poorly soluble drugs resulting in CDs being named on the patents of over 50 marketed drug products.

Yao et al. formulated chitosan-based dissolving MAPs containing micronized levonorgestrel that was complexed with the solubility enhancing oligosaccharide hydroxypropyl-β-cyclodextrin (HP-β-CD). The authors demonstrated superior in vitro transdermal drug permeation from these MAPs (75.62 ± 22.79% permeated after 10 h) using Franz cells when compared to a topically applied gel (no drug detected in receiver compartment after 10 h). Furthermore, in an in vivo study MAPs demonstrated a levonorgestrel delivery similar to that of an oral gavage with the same maximum drug concentration observed (Cmax 189.27 ± 57.46 ng mL⁻¹, Tmax 0.5 h). It was apparent that this formulation overcame the previously mentioned difficulties associated with the transdermal delivery of a poorly soluble drug and illustrated its potential as an alternative to oral emergency hormonal contraception.

### 3. In Vivo Fate of Hydrophobic Compounds When Administered Intradermally

#### 3.1. In-Skin Dissolution and Absorption of Drug Micro- and Nanocrystals

After a NC-based dissolving MAP is inserted into the skin, the extracellular fluids of the epidermis dissolve the polymers of the inserted MNs; exposing the enclosed drug depot to the aqueous environment of the viable layers of the skin. Under these conditions the unique physicochemical properties of NCs, that is, increased specific surface and therefore improved drug dissolution play a fundamental role in the in vivo performance of the formulation. Figure 15 represents the in-skin administration of MAPs loaded with micro- and nanosized drug particles. As explained by Maludin et al., drug particles with diameters in the nanometre range present an exponentially increased specific surface. In addition, they have a greater particle curvature which leads to an increased dissolution pressure and consequently to a greater number of dissolved molecules available for absorption. Furthermore, according to the Noyes–Whitney equation, the augmented specific surface and decreased diffusional distance around drug particles leads to an enhancement in the dissolution rate. With this in mind,
the redispersion of the nanosized drug particles upon contact with the aqueous physiological fluids is a critical step to be considered when aiming to achieve effective drug absorption.[172–174] An innovative approach that aims to control the plasmatic levels of a drug using MAPs is the combination of drug particles with a range of diameters. Such delivery would enable the rapid attainment of therapeutic plasma levels through the dissolution of NCs, and subsequently provide maintenance of these levels through sustained drug release by means of the slow dissolution of larger MPs. Several studies have demonstrated the validity of this concept and consequently NCs are widely considered to be an attractive approach for the delivery of therapeutically relevant doses hydrophobic drugs via MAPs.[70–73] Furthermore, the potential of the combination of long-acting nanosuspensions and MAPs has been discussed extensively by Larrañeta and Donnelly in a previous review.[14]

### 3.2. Targeting the Lymphatic System with Nanoparticle-Based MAPs

As a secondary vascular system in the body, the LS plays a key role in tissue homeostasis, immune response and clearance of the interstitial space.[175] Nevertheless, these essential functions are often hampered by diseases that adversely affect their functionality.[176] Owing to the inherent suitability of NP-based drug delivery systems for targeting of the LS, the reported instances where such systems have been developed for this purpose have increased substantially in recent years.[177] In a similar manner, due to the extensive and readily available body of work based on the application of NP-based methodologies for the delivery of hydrophobic drugs, a natural progression toward the delivery of hydrophobic drugs to the LS in a targeted manner has occurred. The mechanisms behind NP absorption to the LS can be divided into two main categories; active and passive targeting.[178] Moreover, the nature of the NP in terms of excipients, mean diameter and surface properties determines the absorption pathway of such NPs.[178–180] MAPs have been used as an effective approach to deliver drugs to the LS as recently reviewed by Sabri et al.[181]

PLGA NPs (69.3 ± 4.6 nm in diameter) containing the model compound Rhodamine B were formulated into dissolving MAPs and tested in vivo using mice by Kennedy et al.[180] The localized accumulation of Rhodamine B (RhB) in mice lymph nodes as observed in Figure 16, confirmed that successful targeting of the LS was achieved most likely due to the small size of the NPs used in this study. Additionally, owing to the greatly reduced level of flow present in the LS compared to the circulatory system, RhB remained detectable up to 168 h post MAP application.

The treatment of relevant infectious diseases like lymphatic filariasis can potentially be improved by the combination of tailored NPs and MAPs as described in a recent work from the Donnelly group, where SLN of <100 nm were loaded with antifilarial drugs (doxycycline, diethylcarbamazine, and ricobendazole) and delivered intradermally by means dissolving MAPs.[80] Encouragingly, in comparison with oral treatments, the novel formulations were able to deliver the drugs to the LS in a targeted manner, that is, with reduced biodistribution observed in other organs such as the liver, kidney, and spleen. Another infectious disease where the LS plays a vital role is HIV/AIDS, owing to the fact that the virus may form reservoirs that are not reached by common antiretroviral treatment approaches.[182] In alternative work from the same group, a nanosuspension of the hydrophobic drug rilpivirine was loaded into dissolving MAPs and, after administration to rats, the authors were able to quantify the drug in the lymph nodes up to 56 days post-administration.[72] Work completed by Yang et al., reported the in vivo behavior of hyaluronic MAPs loaded with doxorubicin transferomes.[183] The results of these studies demonstrated that statistically greater amounts of the drug had accumulated in the lymph nodes of rats when compared to the control cohorts treated with an intravenous injection of the drugs and an epidermal diffusion. Statistically superior accumulation of doxorubicin was observed in the lymph nodes of rats after administration of doxorubicin-loaded transferomes using the formulated MAPs when compared to the control.
The control cohort in this case was treated with a similar doxorubicin transferome formulation via intravenous injection followed by epidermal diffusion.

Each of the studies outlined above demonstrate that targeting the lymphatic system using NP-based MAPs is a feasible strategy for the delivery of drugs in a targeted and extended manner. The optimization of this approach holds exciting potential for the treatment of other diseases affecting the LS. Accordingly, lymphatic targeting through the combination of NPs with MAPs presents an interesting area with much to be explored.

4. Conclusion and Future Outlook

From their invention to present, MAPs were primarily viewed as viable platforms for the delivery of hydrophilic and potent...
drugs and vaccines. However, there is a clearly increasing trend toward the delivery of hydrophobic compounds at larger dose levels utilizing MAPs. As reviewed here, dissolving MAPs are the most promising strategy to deliver hydrophobic drugs into the skin. The combination of this approach with NP-based drug delivery platforms has been proven to be technically viable. Particularly, in vivo experiments showed that NC-based MAPs were able to deliver therapeutically relevant doses of different hydrophobic actives to the plasma. Both NCs and dissolving MAPs can be produced at the industrial scale using solvent-free manufacturing techniques. Therefore, the combination of these two strategies holds a substantial potential for the development of products with applications in human medicine.

Independently of the formulation approach used, there is a solid body of evidence that MAPs can deliver drugs systemically, which implies the potential of this technology to replace oral and injectable treatments. Furthermore, the literature shows the capability of MAPs to produce drug accumulation in the lymphatic system by means of using different types of nanoparticles.

The systemic delivery of drugs in a sustained manner seems to be one of the key aspects addressed by researchers in the field. Such long-acting formulations have the potential to increase patient compliance by substantially reducing the pill burden, permitting self-administration of formerly intramuscularly injectable formulations, and avoiding the typical peak-and-valley effect produced in drug plasma exposure after repeated oral administration. In this regard, the treatment and prevention of HIV is one of the most relevant targets to be addressed by the use of long-acting formulations. HIV still remains an important health concern globally, with an estimate of 37.9 million people living with the infection in 2018, and around 24.5 million people are currently accessing antiretroviral drugs. In this scenario, the development of long-acting MAP formulations for treatment and prevention of HIV is a singularly attractive goal since these systems can combine more than one antiretroviral, they can be self-applied and do not generate sharp waste that could spread the infection by accidental needlestick injuries. All these advantages are particularly relevant in sub-Saharan Africa, where AIDS still remains a leading cause of mortality in adults from 15 to 59 years old and proper healthcare facilities are not always available.

Even though MAPs have immensely evolved from the first reports and patents presented in the 1970s, industrial developments are still in their infancy and patients still do not have full access to the benefits of this technology. In this sense, it is necessary to strengthen the collaboration among academy, industry, and regulatory authorities to boost not only the development of the new products but also to direct the efforts toward the exploration of new good manufacturing practices and scalable methods for MAP production. In an effort to strengthen this collaboration, PATH, an international, non-profit, global health organization, has created the MAP Centre of Excellence and Regulatory Working Group. The overarching aim of this initiative is to facilitate the progression of MAP technology toward safe and effective clinical use. This previously unprecedented level of focus, provided by PATH, has already initiated the process of identifying an appropriate regulatory pathway for MAPs; for example, target product profiles that outline the key characteristics for rabies and human papillomavirus MAP vaccines have recently been published. Through continued collaboration in this manner, the regulatory questions surrounding MAP technology can be effectively investigated and addressed. Although frustrating for those in the field, this high level of scrutiny is vital to successful commercialization; it will only serve to enhance the level of confidence placed in the safety profile and industrial scalability of this technology.

It is likely that MAPs will be considered as a new dosage form rather than a variation of conventional transdermal patches. Consequently, it is crucial that extensive characterization of their mechanism of action and the risks associated with their use is carried out. Much debate has arisen concerning the risk of infection posed by the temporary disruption of the skin’s barrier function through MAP use. To date, in the vast plethora of research available concerning MAPs, there have been no reports of an increased risk of infection due to their use and original fears over the regulatory requirement of a sterile product have dissipated. Instead, it is now widely accepted that, due to the low propensity of microbes to penetrate the MN-induced holes in the skin, such a device need only possess a low bioburden to be considered safe for use. Deposition of material into the skin is another concern surrounding the use of MAPs, particularly in the long term. Local skin effects such as erythema or granuloma are potential side effects that may be caused by such deposition. Despite the fact that these reactions can be minimized by application site rotation and that the polymers used are biocompatible, there is still a need for further studies with repeat application in humans in order to fully understand the potential effects of MAPs use over prolonged periods. Furthermore, MAP devices intended for the delivery of drugs in a long-acting manner, such as those described within, are associated with a reduced dose frequency. Accordingly, concerns surrounding intra- skin deposition with such devices are justifiably negligible. Previous investigations into the ability of patients to successfully apply MAPs have demonstrated that this can be achieved with relative ease and in a consistent manner. It is believed that the provision of guidance from a Pharmacist, if required, regarding MAP application can only improve upon the levels of success previously demonstrated. Nevertheless, a visual confirmation of dose delivery or successful MN insertion would be wholly beneficial. Not only would this enhance the degree of confidence placed in the use of MAPs for drug delivery, but this confirmation would also facilitate the advancement of other applications, namely MAPs for diagnostic purposes. Considering the industrial scalability of MAP production, the PATH Centre for Excellence has recently brought together experts from industry, academia, regulators, and the Pharmacopeia to identify shared manufacturing challenges and risks. Among the challenges identified was the need to ensure the uniformity of MAP drug content either as a whole, or in respect of individual MNs. Packaging considerations, namely packaging security and device protection, were also highlighted as important considerations for the provision of consistently formed and effective MAPs. To this end, impressive advances in this area by both Lohmann Therapie-Systeme AG (Germany/USA) and Fujifilm (Japan) have resulted in each company now possessing fully scalable, high volume MAP manufacturing processes. In March of 2020, after a series of successful clinical trials, Zosano Pharma
Corporation (USA) announced the acceptance of their New Drug Application (NDA) by the U.S. Food and Drug Administration (FDA) for their product Qtrypta, a zolmitriptan-loaded MAP for the treatment of migraine headaches. This is the first successful NDA based on MAP technology to be accepted by the FDA and, if approved in 2021 as expected, represents a key milestone for the field as MAPs continue to advance toward commercialization.

Conflict of Interest
Ryan F. Donnelly is an inventor of patents that have been licensed to companies developing microneedle-based products and is a paid advisor to companies developing microneedle-based products. The resulting potential conflict of interest has been disclosed and is managed by Queen’s University Belfast. The companies had no role in the design of the review, in the collection, analyses, or interpretation of the literature, in the writing of the manuscript or in the decision to publish the review.

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