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Received: 26 November 2022 | Revised: 1 February 2023 | Accepted: 13 February 2023

DOI: 10.1002/wnan.1884

ADVANCED REVIEW

WIREs NANOMEDICINE AND NANOBIOTECHNOLOGY WILEY

Microneedle-assisted transdermal delivery of nanoparticles: Recent insights and prospects

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Funding information
Agencia Nacional de Investigación e Innovación, Grant/Award Number: PID2020-114530GA-I00

Edited by: Silvia Muro and Gregory Lanza, Co-Editors-in-Chief

Abstract

Transdermal delivery of drugs offers an interesting alternative for the administration of molecules that present certain troubles when delivered by the oral route. It can produce systemic effects or perform a local action when the formulation exerts an optimal controlled drug release or a targeted delivery to the specific cell type or site. It also avoids several inconveniences of the oral administration such as the hepatic first pass effect, gastric pH-induced hydrolysis, drug malabsorption because of certain diseases or surgeries, and unpleasant organoleptic properties. Nanomedicine and microneedle array patches (MAPs) are two of the trendiest delivery systems applied to transdermal research nowadays. However, the skin is a protective barrier and nanoparticles (NPs) cannot pass through the intact *stratum corneum*. The association of NPs and MAPs (NPs@MAPs) work synergistically, since MAPs assist NPs to bypass the outer skin layers, and NPs contribute to the system providing controlled drug release and targeted delivery. Vaccination and tailored therapies have been proposed as fields where both NPs and MAPs have great potential due to inherent characteristics. MAPs conception and easy use could allow self-administration and therefore facilitate mass vaccination campaigns in undeveloped areas with weak healthcare services. Additionally, nanomedicine is being explored as a platform to personalize therapies in such an important field as oncology. In this work we show recent insights that prove the benefits of NPs@MAPs association and analyze the prospects and the discrete interest of the industry in NPs@MAPs, evaluating different limiting steps that restricts NPs@MAPs translation to the clinical practice.

This article is categorized under:

Nanotechnology Approaches to Biology > NA

Therapeutic Approaches and Drug Discovery > NA

KEYWORDS

controlled drug release, microneedle, nanoparticle, transdermal drug delivery, vaccination

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1 | INTRODUCTION: NANOPARTICLES COMBINED WITH MICRONEEDLE ARRAYS PATCHES FOR SKIN DELIVERY OF DRUGS

"The molecular weight of a compound must be 500 Da to allow skin absorption" (Bos & Meinardi, 2000). This statement has been considered as an immovable dogma in pharmaceutical skin research (Brown et al., 2006; Chatterjee et al., 2022). However, more and more researchers question this idea since recent experimental evidence shows important exceptions (Billich et al., 2005; Lenn et al., 2018). Some larger molecules can passively overcome the skin barrier, because the absorption process also depends on other properties like the partition coefficient or ionization degree (N'Da, 2014). Specifically, non-ionized substances or molecules with an intermediate partition coefficient can easily dissolve in the lipophilic environment of the *stratum corneum* (SC) and diffuse along the intercellular route (Mitragotri et al., 2011; Singh & Singh, 1993). Nevertheless, these are rare exceptions, as the combination of all physicochemical properties must be optimal, and the axiom "the higher molecular weight of a drug, the more probability to fail in the

TABLE 1 Advantages and disadvantages of the different the transdermal drug delivery systems to enhance transdermal drug delivery

TDDS	Enhancement type	Advantages	Disadvantages	References
Chemical enhancers	-Passive -Chemical	High efficiency in the delivery of low sized compounds	-Skin reactions: irritation, inflammation, erythema and redness. -Discrete efficiency for macromolecules delivery.	Huang et al. (2002); Vasyuchenko et al. (2021)
Prodrugs	-Passive -Chemical	Good drug stability	Size increase reduces transdermal permeability	Ita (2016)
Thermal ablation, Iontophoresis, Sonophoresis, Microwaves	-Active -Physical	-Achieve faster effects -Control of transport magnitude	-More expensive devices -Logistic inconveniences for patients and need of specialized personnel -Intense skin reactions: irritation, inflammation, erythema and redness.	Dhote et al. (2012); Lin et al. (2014); Prausnitz et al. (1993)
Jet injectors	-Active -Physical	-Control of the skin depth where drug is deposited	-Risk of infections, -Pain or discomfort -Errors in drug dosage	Barolet and Benohanian (2018)
Microneedles	-Active -Physical	-Direct bypass the *stratum corneum* -Controlled release of drugs, low risk of infection, irritancy and humoral response	-Time that micropores remain open under in vivo conditions is short in poke and release approach. -Difficult location for local skin treatments without using an auxiliar TDDS. -Complex scalability and clinical translation.	Ali, Namjoshi, Benson, Mohammed, and Kumeria (2022); Guillot et al. (2020); Haridass et al. (2019)
Nanosystems	-Passive -Active -Physical -Chemical	-Applicable to local or systemic therapies -Possibility to combine physical and chemical methods -Controlled drug release and targeting -Coupling with other TDDS	-Large-sized systems cannot enhance the drug diffusion through the skin. -Instability of some nanosystems	Carreras et al. (2020); Guillot et al. (2021)

Abbreviation: TDDS, transdermal drug delivery system.

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passive skin absorption" is completely truthful. This fact could discourage the use of topical—local—and transdermal—systemic—strategies, but its potential benefits and advantages (Guillot et al., 2023), such as the good acceptance and compliance by patients (Alkilani et al., 2015), the large skin surface—around 20,000 cm^2 in adults—(Richardson, 2003), and the possibility to avoid the first pass effect, justify the efforts done to develop Transdermal Drug Delivery Systems (TDDS) (Prausnitz & Langer, 2008; Roberts et al., 2021) (Table 1). As a consequence, skin administration of many drugs has been possible thanks to this plethora of strategies, that modify the skin barrier function or change the physicochemical properties of molecules (Ramadon et al., 2022). Nanoparticles (NPs) and Microneedle Array Patches (MAPs) are two of the trendiest TDDS that highly attract the attention of the pharmaceutical industry (Alkilani et al., 2022; Box 1).

During the COVID-19 pandemic different companies relied in nanotechnology and made unprecedented economical investments to develop lipid NPs-based vaccines in a record time. The main reasons that pave the way for this technology are their ability to protect the active ingredients, produce personalized therapies and their targeting properties (Fang et al., 2022; Sahakyan et al., 2017). But can these NPs surpass the skin barrier? The answer to this question resides in an extra pathway that drugs can follow, the transfollicular or transappendageal route (Verma et al., 2016), where 210 nm-particles can accumulate in the hair follicles (Mathes et al., 2016), sebaceous glands or sweat glands (Figure 1). Additionally, some ultraflexible NPs like transfersomes and ethosomes can possibly pass through the external skin layers by a squeezing process, because of their deformability (Cevc & Blume, 1992).

The subsequent question to this topic could be if these routes are good enough to achieve significant results in the treatment of skin or systemic conditions when delivered to the skin. The answer to this question is not so clear. On one hand, the transfollicular route has often been ignored because hair follicles only occupy approximately 0.1% of the total skin surface (Barry, 2002), and on the other hand, the exact mechanism through which the lipid vesicles enhance the transdermal absorption has not been completely elucidated yet and it is still under discussion (Błaszczyk et al., 2022).

MAPs are one of the most promising resources to improve drug absorption via the skin. They are minimally invasive devices that contain micrometric needle-like projections which bypass the *stratum corneum* (SC), allowing the passage of large molecules and even proteins or NPs (Ali, Namjoshi, Benson, Kumeria, & Mohammed, 2022; Guillot et al., 2020). MAPs were initially developed as an attempt to overcome the usual drawbacks of hypodermic needles, but their applications are clearly a growing field in pharmaceutical research, as the number of scientific articles that include the keyword "microneedle" have been constantly rising after the appearance of dissolving or polymeric MAPs in the year 2000 (Chen et al., 2022). This trend has been previously predicted by several bibliometric studies that identified and extrapolated a growing trend in the short-medium term, which is currently being meet (Cheung & Das, 2016). Besides, the continuous growth of MAPs-patents registered points out in the same direction (Lhernould et al., 2015). The main reasons why MAPs devices have stand out over the rest of the TDDS are: MAPs bypass the SC barrier in a painless experience as needle tips length are enough to drill the SC but not to interact with the epidermal nerve endings; and they induce a significant less microbial penetration in comparison to a hypodermic puncture without the

BOX 1 Controlled release science timeline

Controlled release formulations include those with sustained release, timed release, extended release, etc. The different names have often become undistinguishable. Controlled drug delivery systems are classified in three generations: First, second and third. First-generation systems developed till the 80s were mostly related to oral and transdermal delivery, and were based on simple but effective mechanisms, such as controlled dissolution and diffusion, osmosis-based formulations and ion-exchange mechanism. Second generation systems (1980–2010) were zero-order release systems, self-regulated drug delivery systems (only in vitro), long-term depot formulations, and nanotechnology-based delivery systems. However, their success is limited, since they deal with important physicochemical and biological barriers and not all of them have been translated to the clinical practice. The third-generation drug delivery technologies developed nowadays, also known as modulated delivery systems, aim to overcome the biomedical demands much beyond the first- and second-generation systems. For that, they include special features that are designed to achieve less-invasive delivery, non/low-toxicity to non-target cells, high functionality over the system lifetime, better biodistribution control, in vivo self-regulating release and proper in vitro/in vivo correlations (Park, 2014; Park et al., 2022; Yun et al., 2015).

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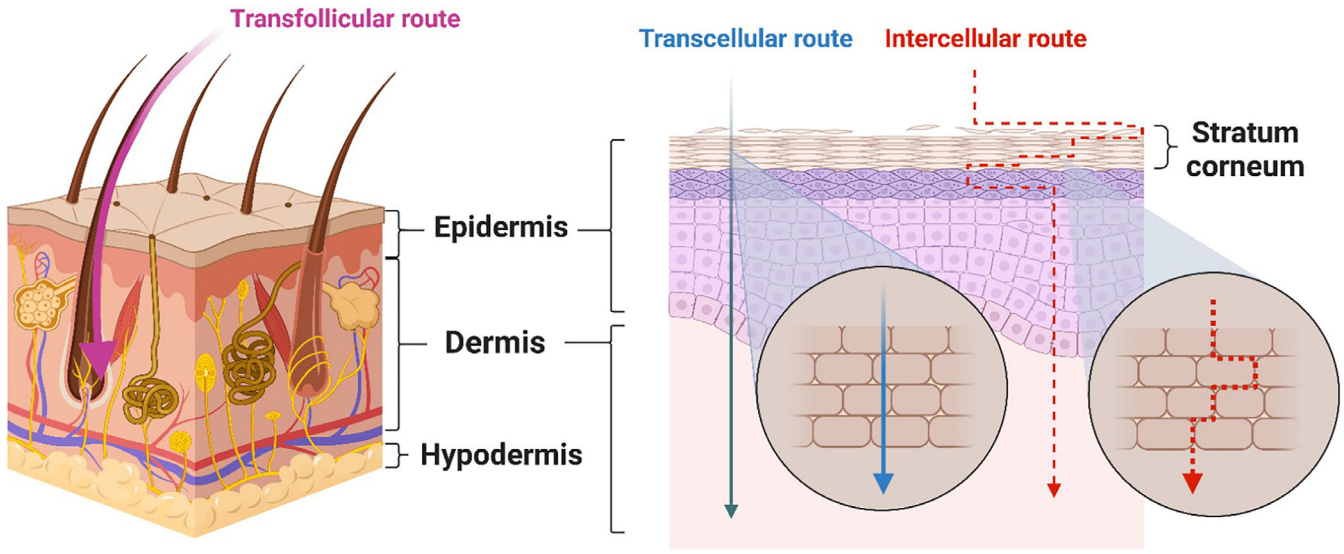

FIGURE 1 Schematic illustration of the skin structure (*stratum corneum*, epidermis, dermis and hypodermis) and the different drug diffusion routes through the skin. Among the three main routes of transepidermal administration, the transfollicular route represents the absorption via the hair follicle that emerges out of the *stratum corneum* to the outside and has its root at the dermis, from where the drug would be absorbed. The transcellular route is the one through which the drug penetrates through the corneocytes themselves, enabling the pass of very small hydrophilic or moderately lipophilic molecules. The intercellular route is a more tortuous and predominant one, it is made by ceramides, cholesterol, cholesterol esters, and fatty acids, thus it is preferred by molecules with higher lipophilic character.

stimulation of a humoral response from the immune system (Donnelly et al., 2009; Vicente-Perez et al., 2017). Once the SC is overcome, it is assumed that the drug can access the systemic circulation (Box 2).

The aim of this work is to offer a comprehensive review that shows the advantages of the synergistic NPs and MAPs association (NPs@MAPs) over the separate use of these two TDDS. For that, we show the insights of recent NPs@MAPs-based studies where the association produces a significant benefit or allows a specific milestone (Table 2).

BOX 2 A brief review of human skin structure

The skin is the interface which separates the body and the environment. In consequence, its main function is to offer a robust barrier against the penetration of external xenobiotics, substances, allergens, and microorganisms (Guillot et al., 2023). In addition, the skin plays other important roles, such as homeostasis maintenance—preventing the dehydration of the body, protection from the harmful effects of ultraviolet radiation, and interaction with the environment—since it presents different types of receptors sensitive to pressure changes, pain and temperature—(Brenner & Hearing, 2008; Kobayashi, 2015; Owens & Lumpkin, 2014; Sparr et al., 2013). It can be divided into three differentiated layers: Epidermis, Dermis and Hypodermis (Figure 1). The Epidermis is the external layer of the skin, and can be subdivided into four stratums: *basale*, *spinosum*, *granulosum* and *corneum*, being this last one the greatest barrier against drug diffusion. The Dermis is the vascularised and innerved layer located immediately below the Epidermis (Geyer et al., 2013; Kennedy & Wendelschafer-Crabb, 1993). The irrigation of this layer provides the nutrients to the dermal and epidermal cells and removes metabolites (Pérez-Sánchez et al., 2018). This process allows the systemic absorption of drugs, since every substance that reaches the dermis microcirculation is susceptible to absorption. The Hypodermis is the deepest skin structure and is often not considered part of the skin (Mittal, 2019). Finally, the skin appendages are dermal-associated structures, such as sweat and sebaceous glands, hair and hair follicles. It has been demonstrated that hair follicles can have an important impact on transdermal diffusion of drugs, because their structure offers a thinner barrier between the external environment and dermal microcirculation (Lademann et al., 2006).

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TABLE 2 Representative studies of different NPs@MAPs strategies for local and systemic drug administration summarized in this review

Carrier	Study (year)	Drug	BCS	Approach	Outcome
Microparticle material (MPs)	Peng et al. (2021)	Amphotericin B (AmB)	IV	Topical and systemic	The combination between MPs and MAPs for AmB topical and systemic delivery (AmB-MPs@MAP) was successful and could reach higher blood levels and deeper skin-levels penetration than IV injection of same drug. Drug bioavailability increased in 11%. No side-effects or other organ accumulation was notice.
	Permana, Anjani, et al. (2021); Permana, Paredes, et al. (2021)	Silver Nanoparticles (Ag NPs)	IV	Topical	The performance of the AgNPs/MPs@MAPs for treating bacterial-biofilm and infected wound using silver macroparticles was studied in vivo. The MAPs could deliver AgNPs efficiently to the wound, and the MP avoided migration Ag to non-infected tissues that would cause toxicity.
Micelles (MCs)	Wei et al. (2020)	NIR950	IV	Topical	In this study, photothermal therapy for melanoma eradication was compared between an intratumoral injection and a MAPs application, MAPs-assisted therapy reduced the tumor in 2 weeks without recidivism, while the injection eradicated the tumor in 8 days but started growing again.
	Chen et al. (2021)	IR780 Chloroquine (CQ)	IV IV	Topical	This time micelles were co-encapsulated with CQ and IR780 using MCs. The combination of micelles and MAPs technology improved the effectiveness of this treatment, that eliminated the melanoma in 40 days in half of the rats.
	Jung et al. (2022)	Paclitaxel (PTX) Resquimod (R848)	IV IV	Topical	MCs loaded into MAPs for co-transport of PTX and R848 were effective for skin cancer treatment and prevented metastasis They could also reduce side-effects.
	Jing et al. (2021)	Shikonin (SKN)	IV	Topical	Alternative treatment for psoriasis based on SKN-MCs@MAPs. The SKN encapsulated into a pH-sensible micelle to increase the skin permeability and "smartly" release the drug in the psoriasis tissues (they have lower pH).
	Tripathy et al. (2020)	Rhodamine B (RhodB)	III	Systemic	Transdermal drug delivery route used for the administration of kidney-targeted RhodB-MCs, assisted by MAPs. Kidney drug accumulation was 7.7 higher compared with non-targeted micelles.
Nanocrystal (NCs)	Xiang et al. (2022)	Curcumin (CU)	II	Systemic/ transfolicular	Different nanocrystal sizes of CU (model drug) NCs dispersion in the range of 50–480 nm were tested. The low size of the NCs greatly improved the pharmacodynamic and the pharmacokinetics of CU.
	Permana, Anjani, et al. (2021); Permana, Paredes, et al. (2021)	Albendazole (ABZ)	II	Topical	ABZ-NCs in transdermal application increased ABZ bioavailability in a 400% when applying free ABZ-NCs and in 500% when applying ABZ-NCs@MAPs, evidencing the efficacy on NCs for improving hydrophobic molecule solubility
	Permana et al. (2020)	Itraconazole (ITZ)	II	Topical	ITZ delivery was achieved by combining NCs with MAPs. The antifungal activity of the ITZ-NCs@MAPs was significantly higher than the same formulation without MAPs, proving the benefits in this combination.
	Wei et al. (2022)	Methotrexate (MTX)	III	Systemic	The NCs formulation of MTX could increase bioavailability of the drug and transdermal drug distribution. The MTX-NCs@MAPs was effective in reducing the rheumatoid arthritis symptoms in rats in less than a month of treatment.

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TABLE 2 (Continued)

Carrier	Study (year)	Drug	BCS	Approach	Outcome
Nanosuspensions (NSs) and Nanoemulsions (NEs)	Nagra et al. (2022)[a]	Acyclovir (AC)	III	Topical and systemic	The transferosome nanocarriers were more effective when a lyophilised wafer was applied onto the skin. AC rates were 4–16 times higher, than when the lyophilised formulation was not used
	(Vora et al., 2018)	Cholecalciferol (CL)	II	Topical and systemic	First time using nanosuspension loaded into MAPs as a strategy for hydrophobic drug delivery. The MAPs technology showed good compatibility and benefits for CL (model drug) delivery compared with a needle-free administration.
	Abdelghany et al. (2019)	Curcumin (CU)	II	Topical and systemic	In a further study on NSs@MAPs technology, a CU-NSs@MAPs evidenced a non-controlled, fast drug delivery into the skin, pointing out their synergistic effect for drug delivery to the skin.
	Altuntas et al. (2022)	Nestorone (NES)	II	Systemic	NES-NSs@MAPs were designed for "on demand" and self-applicable contraceptive. NES delivery was effective in a murine model, although presented some limitations such a rapid and non-controlled release all the drug loaded within the first hours. Increased amounts of drug were delivered when incorporated in NSs form, compared with the free-drug formulation.
	Pireddu et al. (2020)	Diclofenac (DC)	II	Systemic	A "patch and roll" MAPs was developed. This technology, combined with NSs, achieved good penetration parameters, but without the MAPs-assistance, DC-NSs was accumulated mainly only in the SC, not reaching the deeper skin layers.
	(Wu et al., 2022)	Triamcinolone acetonide (TA)	IV	Intravitreal	The fast deliver of high drug concentrations performed by NSs/NEs with MAPs was ideal for short-time administration for intravitreal treatments. The NSs was able to load high concentrations of TA to the back layers of the eye only 5 min after administrations.
	Albadr et al. (2022)	Amphotericin B (AmB)	IV	Intravitreal	The NSs@MAPs combination used a PVP matrix to enhance compatibility with the tissues and breaking the sclera barrier. The efficient permeation of the AmB-NSs delivered drug to 0.4 nm deep.
	Nasiri et al. (2022)	Amphotericin B (AmB)	IV	Topical	In this study, AmB-NEs showed good synergies with MAPs (rather than the needle-free formulation) and good skin permeation.
Metalic NPs	Dong et al. (2018)	Doxorubicin (DOX)	III	Topical	The combination between DOX and Au nanocages, both co-loaded into a MAPs (DOX-AuNCs@MAPs) were able to reduce the tumor, equally than the intratumoural injection of the same formulation.
	Cárcamo-Martínez et al. (2020)	Gold nanorods (GnRs)	IV	Topical	GnRs loaded into MAPs resulted in a more efficient delivery of the gold NPs. This combination achieved better skin heating, compared with single deeper needle-injections, and also achieved the lowest toxic rates
Polymeric NPs	Pu et al. (2022)	Doxorubicin (DOX)	III	Topical	The PNA/PDA NPs are pH-responsive and target the cancerogenic tissues selectively releasing the drug when NIR increases the tissue temperature, since PNA has temperature-responsive activity.

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TABLE 2 (Continued)

Carrier	Study (year)	Drug	BCS	Approach	Outcome
	(Vora et al., 2017)	Cholecalciferol (CHO)	II	Topical and systemic	PLGA nanogel showed good results for the transdermal delivery of poor soluble drugs (CHO) in MAPs-assisted approaches.
	Lin et al. (2022)	Rapamycin (RAPA) Epigallocatechin gallate (EG)	IV III	Systemic	MAPs and PLGA showed promising synergies when applied on transdermal drug delivery, since PLGA enhances the permeability and the bioavailability of the incorporated drugs.
	Mönkäre et al. (2018)	Ovalbumin (OVA) Poly(I:C)	IV III	Systemic	The MSs combined with MAPs showed an improved transdermal delivery since MS can reach high loadings and MAPs can administer them after piercing the SC.
	Zhou et al. (2022)	L-DOPA	I	Systemic	This L-DOPA-UCMR@MAPs provided good transdermic delivery for Parkinson treatments, since the azo-based nanomotor particles can start "in situ" the release when NIR irradiated.
Solid-Lipid Nanoparticles (SLNs) Cubosomes (CUBs)	Guo et al. (2022)	Alkaloids from *Aconitum sinomontanum* (AS)	–	Systemic	Alkaloids combined with MAPs (AS-SLNs@MAPs) improves their bioavailability and allowed a sustainable release. Rheumatoid arthritis treatment in rats was therefore improved (2–3 times more effective than those needle-free formulations, or IV injection).
	Lee et al. (2014)	Nile Red	II	Topical	Dissolving MAPs combined with a SLNs increased the long-term release of the lipophilic drugs.
	Prabhu et al. (2022)	Curcumin (CU)	II	Systemic	Using solid lipid CU-SLNs provides good release rates and improved the drug permeability through skin. CU-SNLs@MAPs showed good arthrosis symptoms amelioration and no toxicity.
	Permana et al. (2019)	Doxycyclin (DOX) Albendazole (ABZ) Diethylacarbamazine (DEC)	II II III	Systemic	Synergies between SLNs and MAPs increased the ABZ, DOX and DEC bioavailability and their skin permeability and accumulation in the deeper skin layers. This way the problems related to the drugs oral bioavailability were solved.
	Zhang (2020)	Insulin (IN)	III	Systemic	Nanocarriers based on carboxymethyl chitosan NPs loaded into MAPs achieved to maintain the normoglycemic levels for 6 h without hypoglycemic state. For enhancing IN penetration, NPs were derivatised with an Arg chain.
	Lan et al. (2018)	Cisplatin (CISPt)	III	Systemic	Lipid coated CISPt-NPs@MAPs increased the transdermic drug administration. Lipid coating avoided the toxic accumulation of CISPt in other organs, highly reducing its systemic toxicity
	Ramalheiro et al. (2020)	Rapamycin (RAPA)	III	Topical	CUB and MAPs presented synergies in the RAPA delivery for hair-loss treatment, not only in terms of permeability and penetration, but the RAPA@MAPs showed a better cell-inhibitor effect that those needle-free formulations.
Lipid vesicles[b]	Rajput et al. (2022)	Levonorgestrel (LNG)	I	Systemic	LNG-LPs assisted with MAPs were able to release the drug in a sustainable way for longer time (2–30 days) and showed promising results for long-acting contraceptives.

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TABLE 2 (Continued)

Carrier	Study (year)	Drug	BCS	Approach	Outcome
	Yu et al. (2022)	CD11 monoclonal antibodies	IV	Systemic	MAPs loaded with of CD11-Ts were able to increase the transdermal penetration and successfully reached the lymph system, where they trigger a cellular response.
	Yang et al. (2019)	Doxorubicin (DOX)	IV	Topical	Ts@MAPs were an effective transport method for response activation. Also, the bioavailability and DOX loading efficacy were increased.
	Ahad et al. (2017)	Eprosartan mesylate (EM)	II	Systemic	This study presented a "poke and patch" approach which offered higher transdermal fluxes (compared with other microneedle systems). Also, the transferosomes combined with the Dermaroller® achieved a controlled release for 24 h.
	Ahmed et al. (2019)	Doxorubicin (DOX) Celecoxib (CEL)	III II	Topical	Co-encapsulated lipid vesicles of DOX and CEL applied with Dermaroller® (poke and patch approach) were highly effective in tumor inhibition and increased drug accumulation in tumoral tissues.
Solid-lipid nanoparticles (SLNs)	Zhang (2020)	Insulin (IN)	III	Systemic	Nanocarriers based on carboxymethyl chitosan NPs loaded into MAPs achieved to maintain the normoglycemic levels for 6 h without hypoglycemic state. For enhancing IN penetration, NPs were derivatised with an Arg chain.
	Lan et al. (2018)	Cisplatin (CISPt)	III	Systemic	Lipid coated CISPt-NPs@MAPs increased the transdermic drug administration. Lipid coating avoided the toxic accumulation of CISPt in other organs, highly reducing its systemic toxicity
	Tu et al. (2017)	Ovalbumin (OVA)	IV	Systemic	A transdermic vaccination approach was designed with derivatised MSs and pH-sensitive (surface pyridine bounds).
	Lan et al. (2020)	anti-PD-1 (aPD-1) Cisplatin (CISPt)	IV III	Topical	a-PD-1 and CISPt were both able to give a better antitumoral combined response when co-encapsulated in a pH-responsive NPs and administered using MAPs. The "smart" NPs tumor-targeted the drug release to the cancer cells and avoided the side-effects of this drugs
Mesoporous silica (MSs)/ Nanomotor	Zhou et al. (2022)	L-DOPA	I	Systemic	This L-DOPA-UCMR@MAPs provided good transdermic delivery for Parkinson treatments, since the azo-based nanomotor particles can start "in situ" the release when NIR irradiated.

[a]Nagra et al. study was grouped into the Nes/NSs group, although it is a Freeze-dried wafer.
[b]Lipid Vesicles are included in the LB-NPs section, but correspond to an extended subcategory so that they are explained in other section on the table.

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The article search was performed on the Scopus Data Base in August 2022 using the following descriptors and Boolean operators: "ABS-TIT-KEY (microneedle AND lipid vesicle)", "ABS-TIT-KEY (microneedle AND nanoparticle)", "ABS--TIT-KEY (microneedle AND nanosuspension), "ABS-TIT-KEY (microneedle AND nanoemulsion)", ABS-TIT-KEY (microneedle AND nanocrystal)", ABS-TIT-KEY (microneedle AND micelle), and "ABS-TIT-KEY (microneedle AND nanocrystal)". The search was refined to articles published 5 years before the search date. Some of the articles found were excluded. The exclusion criteria were that they did not provide relevant or additional information to the rest of the considered articles, thus resulting redundant, or because their aim was not to treat any pathology. Finally, we analyze the prospects of this association and the aspects that should be improved to achieve a real translation from bench to bedside of these devices, that would result in their arrival to the market.

2 | MICRONEEDLE-ASSISTED APPROACHES APPLICABLE TO NANOPARTICLE DELIVERY: LIMITATIONS AND BENEFITS

Different prototypes of MAPs have been designed, namely: solid, coated, dissolvable, hydrogel-forming, rapidly separating, swelling and hollow. Each one follows an approach or administration strategy: "poke and patch"—solid MAPs, "coat and poke"—coated MAPs, "poke and release"—dissolvable, hydrogel-forming, rapidly separating and swelling MAPs, and "poke and flow"—hollow MAPs—(Guillot et al., 2020). On account of their design and characteristics, solid microneedles and dissolvable microneedles are the types of MAPs that have been associated with NPs. Specifically, the "poke and patch" approach consists in creating microchannels that reach the deeper layers by the insertion of solid MAPs that drill the SC. After removal, a drug-loaded formulation is applied as an external reservoir (Figure 2). These solid microneedles are commonly made of different metals (stainless steel, titanium, nickel or gold) using different techniques such as laser cutting and ablation, etching, electropolishing, and micro-stereolithography (Guillot et al., 2022).

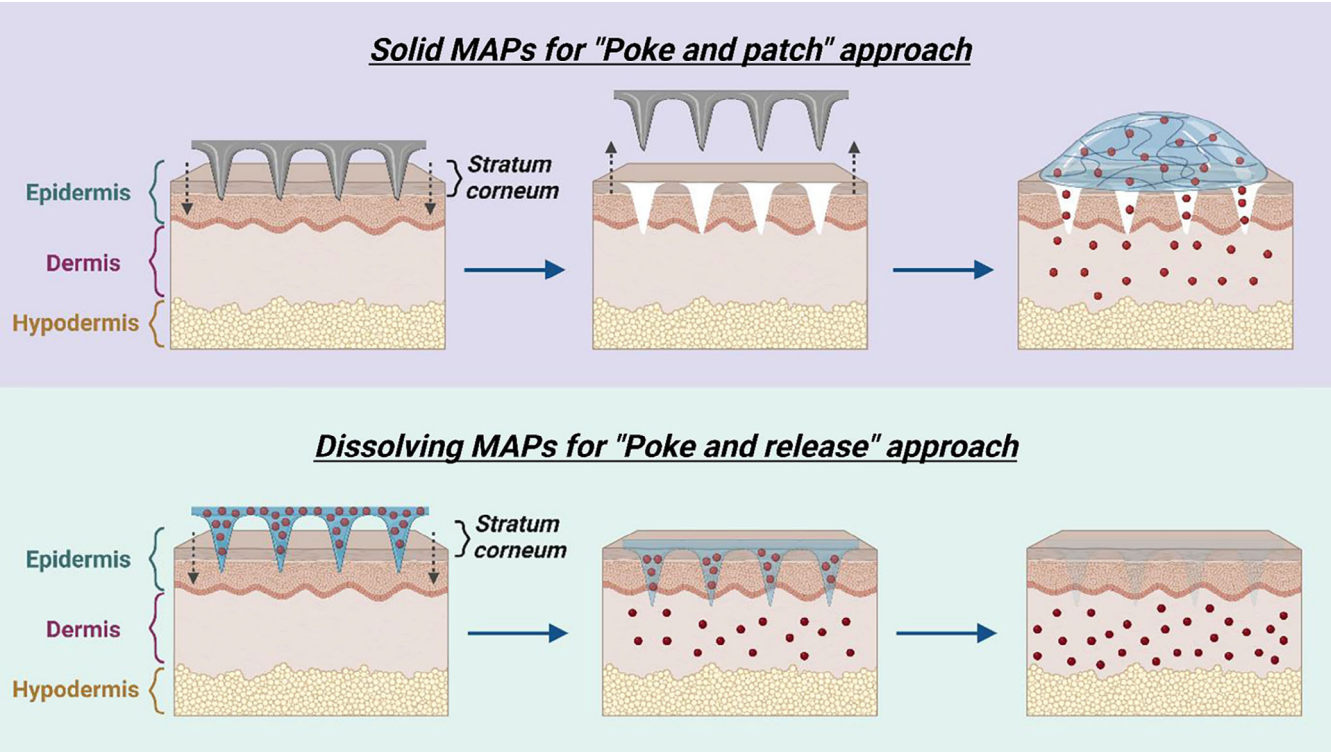

FIGURE 2 Schematic illustration of "poke and patch" and "poke and release" approaches with solid and dissolving microneedle arrays patches (MAPs) respectively. The "Poke and patch" delivery has two phases, the first one is the insertion of the microneedles into the skin, creating micro-conducts in the *stratum corneum* for the drug to reach deeper layers of the epidermis. After that, the drug is applied onto the skin and diffuses through the channels depending on the pore size and drug concentration. The "Poke and release model" involves bulk dissolving microneedles made of biodegradable polymers, where the drug is entrapped. The microneedles are inserted and dissolved within the skin, delivering the drug or nanoparticles in a controlled manner.

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Their main advantages are that they usually present good mechanical properties. However, fractures, corrosion and poor biocompatibility of some metals are their main drawbacks. For its part, the "poke and release" approach is carried out using dissolving MAPs prepared via solvent-casting or micro-molding and made of different water-soluble and biodegradable materials, like poly(vinyl pyrrolidone) (PVP), karaya gum, hyaluronic acid (HA), poly(methyl vinyl ether-alt-maleic acid) (PMVE-MA), poly(vinyl alcohol) (PVA), carboxymethyl cellulose (CMC), chitosan and glycerol different sugars, etc., which include the drug or NPs of interest. After their insertion into the skin, they release the drug or NPs while they are getting dissolved by the interstitial skin fluids (Ali, Namjoshi, Benson, Kumeria, & Mohammed, 2022; Lee et al., 2019) (Figure 2).

Both MAPs types significantly enhance the transport of drugs through the skin, since the barrier function is disrupted. The "poke and patch" approach presents a two-step administration: first, the MAPs are inserted to pierce the epidermis and then removed; second, the dosage form is applied. The simplicity of the idea makes it highly attractive, but the sequential administration process reduces the comfortability for the patients, thus reducing treatment compliance. The other main limitation is that the micropores remain open only for a limited time, prematurely stopping the delivery of the active ingredient. This closure is still a controversial point under in vivo conditions, but it has been reported that the barrier properties recovery takes place within 2 h if occlusive conditions—patches or tapes—are not applied (Gupta et al., 2011; Kalluri & Banga, 2011). However, the early micropores closure offers some benefits such as a decreased risk of infection and irritancy (Haridass et al., 2019).

Dissolving MAPs partially solve these issues. They reduce the drug administration process to one step (Sartawi et al., 2022), as they can pierce the skin and are kept inserted until complete degradation, maintaining the microchannels open and avoiding sharp wastes (Lee et al., 2008). However, they are made of hydrophilic polymers which can only incorporate hydrophilic drugs. The incorporation of macro-suspended drugs can produce air bubbles during the manufacturing process that decrease the mechanical strength and insertion properties or spoil the MAPs' structure (Hutton et al., 2018).

Therefore, how can NPs improve MAPs performance and vice versa? The NPs@MAPs integrate the advantages of both TDDS, and their general synergistic actions are:

1. They obviously help to increase the absorption through the skin of low permeable drugs (BCS class III and IV).
2. MAPs can carry the NPs across the SC allowing their deposition into the deeper epidermal layers, creating three-dimensional NPs reservoirs inside the skin, impossible to achieve otherwise.
3. Poorly-water soluble drugs (BCS class II and IV) can be incorporated in dissolving MAPs via NPs-loading.
4. Water soluble drugs can also be encapsulated in different NPs spaces leading to multi-loaded or "all-in-one" systems.
5. NPs can contribute to an extra control of drug release from MAPs that is especially useful for drugs with a higher permeability through the skin (BCS class I and II), which present a narrow therapeutic range that requires an exceptional release control.

3 | NPs@MAPs COMBINATIONS AND THEIR APPLICATIONS IN DRUG DELIVERY: RECENT AND REPRESENTATIVE INSIGHTS

3.1 | Microparticles: The biggest particles in drug delivery

Microparticles (MPs) are used as a drug delivery strategy for carrying drugs through the skin tissues in topical approaches. Even though MPs are larger than nanoparticles, they can also be useful restricting drug diffusion to other tissues.

Peng et al. developed MPs@MAPs for fungal infections management, using amphotericin B (AmB)-loaded dissolving MAPs made of PVA/PVP (Peng et al., 2021). AmB is a potent fungicide, but its oral application leads to several side-effects (Gigliotti et al., 1987). Besides, AmB presents a high molecular weight (924 Da) and poor aqueous solubility. PVP provides a matrix that helps the reduction of the AmB particle, protects them to aggregate and helps minimize particle size, as AmB-MPs can be adsorbed by the polymer (AL-Quadeib et al., 2015). Therefore, MAPs-assisted AmB administration seems a promising strategy. To analyze the AmB-MPs@MAPs activity, in vitro and in vivo tests in mice were performed to study their dermatokinetic, pharmacokinetic and biodistribution parameters, compared with intravenous (IV) injection of a commercial AmB-formulation as a reference (Fungizone). To test drug diffusion through

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skin, mice were divided into two groups and treated with IV injection and AmB-MPs@MAPs, respectively. The maximum skin drug concentration was achieved 24 h after administration (10.16 ± 8.27 μg/g) and declined to 0.97 ± 0.12 μg/g on day 4. When mice were treated with AmB-MPs@MAPs, the skin drug concentration at 1 h was 1792.22 ± 1336.82 μg/g, reaching its maximum after 4 h (4165.58 ± 1311.00 μg/g). The skin drug levels decreased, but were still higher than the IV group treated with the highest dose at day 7 (219.07 ± 102.81 μg/g). In addition, AmB was detected 2.0 ± 0.5 cm away from the MAPs application site. In vivo biodistribution studies showed AmB levels in the kidneys 4 h after administration, which then decreased to undetectable levels at day 2. In the liver, the maximal concentration was achieved at day 2 and then became undetectable between days 4 and 7.

Permana et al. also designed a MPs-based novel strategy for antibacterial biofilm treatment, including Ag NPs incorporated in PVA/PVP-based MAPs (Ag NPs-MPs@MAPs) (Permana, Anjani, et al., 2021; Permana, Paredes, et al., 2021). According to the Antimicrobial Surveillance Program, a wide range of bacteria can create biofilms around wounds. Among them, the most common are *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Pfaller et al., 1998). The main challenge for the treatment of biofilm infected tissues is that antibiotics are generally ineffective and lead to the generation of resistant bacteria. Ag NPs are a good alternative for bacterial wound healing, although their main disadvantage is the migration of the nanoparticles to other non-infected tissues that can induce toxicity (Beer et al., 2012). To improve their safety and efficacy, Permana et al. incorporated them into chitosan-MPs (Ag NPs-MPs), to reduce NPs migration to non-target tissues. The evaluation of their safety and activity was assessed in an ex vivo model, and the antimicrobial activity was demonstrated in a biofilm assay using rat skin. The bacterial wound was reduced to 50% when Ag NPs cream was used. When Ag-NPs were loaded in MPs and incorporated in a cream, the biofilm was reduced in 60%. Finally, Ag NPs@MAPs achieved a 75% of bacterial bioburden reduction, while Ag NPs-MPs@MAPs reached a 100% reduction of the *S. aureus* and *P. Aeruginosa* biofilm, thus demonstrating the synergistic effect when combining all these strategies.

3.2 | Micelles: Encapsulating non-water solvable drugs

The anatomy of micelles (MCs) is composed by a hydrophobic core coated by a hydrophilic corona that protects the core and provides stability for the MCs in water solutions. They are mainly used for hydrophobic molecule transport. Polymeric MCs present some advantages over biological MCs: nanosized scale, higher thermodynamic stability, and the possibility to modify the core to incorporate complex molecules (Shuai et al., 2004). We analyze several studies that used nano-MCs combined with MAPs technology for the treatment of different diseases, both locally and systemically.

Wei et al. developed PVP/PVA-based MAPs loaded with pH-responsive MCs, charged with aggregation-induced emission luminogens (AIEgen) for photothermal melanoma therapy (Wei et al., 2020) (Figure 3). Melanoma is commonly treated by tumor excision, but in certain situations this strategy is unviable, especially when the tumor is extended or located in the face or a sensitive part of the body. In these cases, immunotherapy is preferred. This study focuses on the use of photothermal therapy (PPT), which aims tumor destruction using photosensitisers or photothermal agents that transform the light energy into heat under certain radiation conditions, burning the cancer cells (Kobayashi & Choyke, 2019). NIR950 (AIEgen) was selected as photosensitizer because of its photostability and emission yields. AIEgens are commonly administered intravenously, but achieving the appropriate dose in the target is a very slow process. In this study, a MAPs for topical NIR950 delivery using polymeric MCs were designed, since they increase NIR950 solubility and minimize systemic distribution, accumulating faster around superficial melanoma cells. NIR-MCs were also pH-sensitive, so they release the drug only under acidic environments, such as the tumor microenvironment. NIR950-MCs@MAPs were tested in an in vivo study in B16 tumor bearing C57 mice, randomly divided into four groups: (1) untreated group; (2) IV injection of NIR950-MCs followed by 808 nm laser irradiation 24 h after administration; (3) intertumoral injection of NIR950-MCs and followed by irradiation with 808 nm laser irradiation 0.5 h later; (4) NIR950-MCs@MAPs followed by with 808 nm laser irradiation 0.5 h after. The tumors disappeared in animals treated with NIR950-MCs@MAPs after 2 weeks. Animals from group 3 presented neglectable tumor reduction. Finally, animals treated with an IV injection of NIR950-MCs (group 2) showed an antitumoral effect on the first 8 days but then tumor regrowth again. These findings pointed out the superior efficacy of the MCs@MAPs combined treatment.

Chen et al. designed dissolving MAPs made by HA and PVA polymers assembled with cancer cell death-inducer IR780 and autophagy inhibitor chloroquine (CQ) co-encapsulated into MCs, for antitumoral therapy (Chen et al., 2021). The strategy used in this study is based into autophagy inhibition, which enhances the photosensitiser agent P780 activity, diminishes the self-protection of the tumor cells and augments the antitumoral immune system

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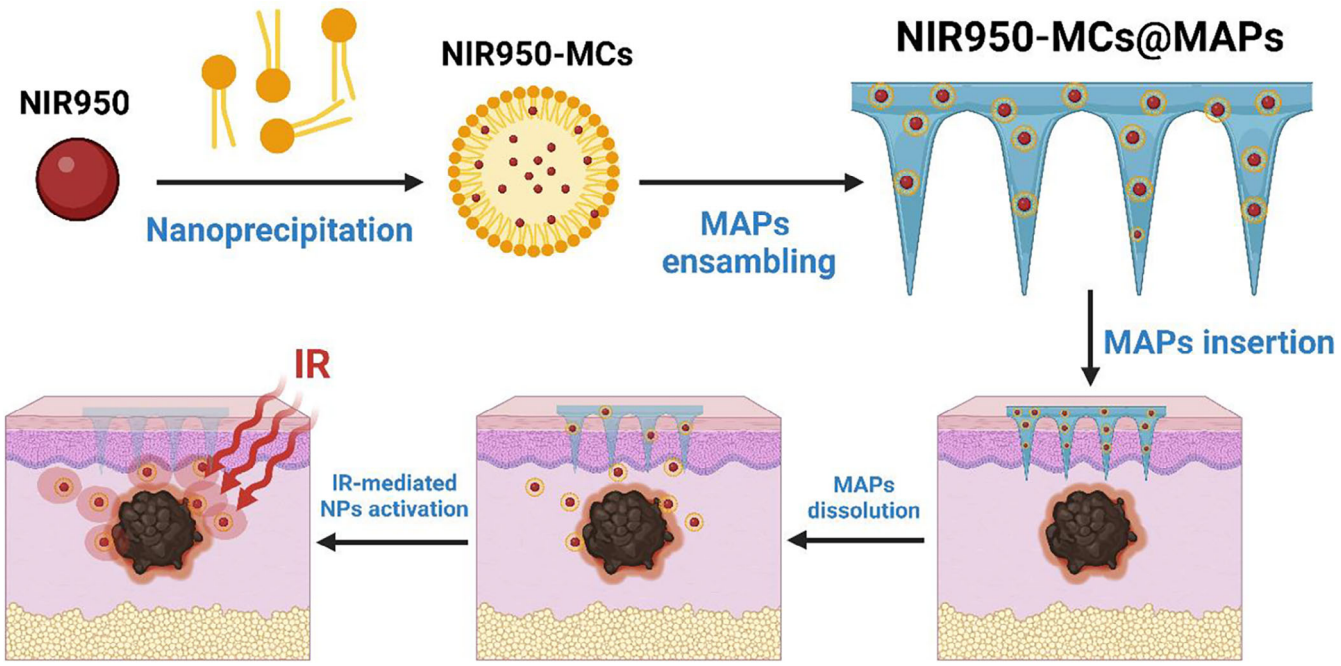

FIGURE 3 Schematic diagram of the NIR950-micelles@MAPs strategy based on Wei et al. work (Wei et al., 2020). NIR950-loaded polymeric micelles are prepared by nanoprecipitation. Then, the micelles were charged into dissolving microneedles by a two-step molding technique, obtaining NIR950-MCs@MAPs. The NIR950-MCs@MAPs dissolution releases the NIR950-MCs to the skin and reach the melanoma tissue. Later, NIR950-MCs are irradiated with IR radiation which induces the PPT activity of the NIR950, and causes the destruction of the cancer cells. MAPs, microneedle array patches; MCs, micelle; NIR, infra-red; PPT, photothermal.

response (Kimmelman & White, 2017). This work combines the PPT with autophagy inhibition therapies. The MAPs performance was tested in vivo in melanoma-bearing mice. The animals were divided in five groups: (1) no treatment (control); (2) CQ-MCs@MAPs; (3) P780-MCs@MAPs; (4) P780/CQ-MCs@MAPs, and (5) combined application of both P780/CQ-MCs@MAPs and CQ-MCs@MAPs. The results showed that CQ (treatment 2) hardly suppressed the tumor growth. Group 3 showed better results suppressing the tumor volume, suggesting a synergy between phototherapy and autophagy. Group 5 showed a significant reduction of the tumor volume. In the group 5, 50% of the mice survived after 40 days, confirming again the optimized delivery of the therapeutic agent using MCs@MAPs over other strategies.

Jung et al. presented a chemo-immune therapy for metastatic tumor and melanoma, based on a dissolving MAPs approach fabricated with a PVA/PVP/PEG three-block co-polymer matrix. The designed MAPs combining co-encapsulated nano-MCs with paclitaxel (PTX), an anticancer drug, and resquimod (R848), an immunomodulator (Jung et al., 2022). This combination can enhance cancer death cell death and promote the tumor antigen activity at the same time. PTX, although widely used for several cancer treatments (lung, ovarian, breast, etc.), has severe adverse effects, such as hematological toxicity, neuropathy, and hypersensitivity reactions, many of which are due to excipients used to improve PTX solubility. R848 also presents a low water solubility and systemic cytotoxicity (Liebmann et al., 1993; Rodell et al., 2018). The use of nano-MCs assisted by MAPs to deliver these drugs can reduce their systemic toxicity, and their immunological effects, while improving their solubility. The antitumor PTX/R848@MAPs efficacy was studied in vivo in a mice melanoma xenograft model (B16F10). Mice were treated with: (1) blank MAPs patches (control group); (2) PTX-MCs@MAPs; (3) 2R848-MCs@MAPs; and (4) PTX/R848-MCs@MAPs. PTX/R848-MCs@MAPs showed the best antitumoral results, even though the dose was lower. In group 3, 80% of the mice survived after six patch administration, and in 50% of them the tumor disappeared on day 23. In groups 1 and 2, mice showed non-significant improvements on survivance rates and a lower reduction on the tumor size. Furthermore, metastasis induction was tested injecting the surviving mice with tumor cells and harvesting the lungs 4 weeks later. No metastatic nodules or tumor were observed.

Other studies for the treatment of other diseases have been conducted. Jing et al. developed karaya gum-fabricated MAPs for psoriasis and inflammatory skin diseases (Jing et al., 2021). They designed a dissolvable MAPs to deliver Shikonin (SKN)-loaded MCs through the skin. The "smart" polymeric micelles described in this study can deliver the

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drug under specific physiological conditions, depending on the pH, thanks to the presence of histidine fragments, that release the drug in acidic conditions, such as the inflammatory skin tissues. Even though SKN is widely used for anti-inflammatory skin diseases, topic administration of SKN is not viable because of its poor stability, low water solubility and skin permeability (Xu et al., 2014). SKN-MCs@MAPs were studied in a psoriasis-like rat model. Rats administered with pH-sensitive SKN-MCs@MAPs presented better psoriasis symptoms alleviation results, measured as psoriasis area severity index (PASI), than those treated with SKN-NPs injection, free SKN-MAPs and non-pH-responsive SKN-MCs@MAPs. However, PASI results were lower for the positive control of dexamethasone.

Tripathy et al. developed MAPs made of PVA to address polycystic kidney diseases (PKD) systemically (Tripathy et al., 2020). Dialysis and transplants are the only two treatments for long-term survivance to PKD, since pharmacological treatments are only short-term administration of kidney-targeted drugs. Tripathy et al. developed kidney targeting-nanoMCs functionalised with folate, due to the high expression of folate in kidney cells. Kidney-targeted NPs (KNPs) were loaded into MAPs for transdermal administration, since avoiding the oral routes can significantly increase the bioavailability of these drugs. Finally, KNPs@MAPs were tested in vivo when labeled with Rhodamine B (RhodB) showing promising results. Healthy CBL/6 J mice were administered with RhodB-KNPs@MAPs and with RhodB-non targeted NPs@MAPs. Later ex vivo analysis demonstrated that RhodB levels on the kidney where 2.2-fold higher at 24 h after administration, and 48 h after administration the RhodB levels were 7.7-fold higher. The results proved the efficacy of the KNPs for transdermal drug delivery although more research needs to be conducted on this topic.

3.3 | Nanocrystals: A trendy way to dissolve poor-water soluble drugs

Multiple hydrophobic drugs have been delivered in nanocrystals (NCs) form to enhance the absorption rates in multiples routes, mainly orally, but also transdermal or transmucosal. NCs is the term used for drug formulations in crystalline state as submicron particles size (from 150 to 500 nm) (Xiang et al., 2022). Their two main advantages are the homogeneous particle size in suspension and the good absorption rates, due to the total-active surface (100% drug loading) (McGuckin et al., 2022).

Permana et al. designed an Abendazole (ABZ) nanocrystal-loaded dissolving MAPs (ABZ-NCs@MAPs) fabricated with PVA and PVP for the treatment of cystic echinococcosis (CE) (Permana, Anjani, et al., 2021; Permana, Paredes, et al., 2021). ABZ is a poor soluble drug with low oral bioavailability rate. Doses usually need to be high and/or prolonged in time (3–6 months) (Atayi et al., 2018). ABZ-NCs@MAPs is an alternative to oral administration, combining easy transdermal delivery by microneedle puncture and the increased solubility thanks to the NCs. Ex vivo and in vivo analysis were performed to study ABZ-NCs@MAPs efficacy. Permeability through porcine-skin was studied in a Franz-cell model to compare ABZ-NCs@MAPs and ABZ-NCs@needle-free patch. This set-up consists of a two compartment set-up, separated by a skin membrane. The formulation under study is placed in the donor compartment and the receptor compartment is filled with an appropriate medium, which simulates the systemic compartment. Samples are taken from the receptor at predetermined time points and analyzed. The cumulative amounts are plotted versus time to observe drug access through the skin and calculate permeation parameters (Ng et al., 2010). As expected, dissolving MAPs showed better ABZ permeability ($\mu g/cm^3$): 211.06 $\pm$ 47.19, 554.52 $\pm$ 121.13 and 107.91 $\pm$ 19.92 at deps of 0.9, 1.3 and 1.5 mm respectively. Needle-free ABZ-NCs@MAPs only delivered ABZ till 1.1 mm. In vivo studies were conducted in mice and the ABZ blood levels were monitored during 48 h. The bioavailability was calculated according to the Area Under the Curve (AUC) values, and the ABZ availability when administered orally ABZ-NCs was similar to ABZ-NCs@MAPs (531.16 $\pm$ 136.11%, and 476.35 $\pm$ 87.11% respectively). In conclusion, the NCs-MAPs combination achieved a similar ABZ bioavailability but bypassing the hepatic first pass effect.

Permana et al. designed a MAPs-based treatment for *Candida albicans* (Permana et al., 2020), a common yeast that can lead to a systemic and fatal infection if not adequately treated (Ray & Wuepper, 1976). Itraconazole (ITZ) is the generally used antifungal drug for management of these infections, but its oral administration is related to several side-effects, such as cholestatic and hepatocellular damage (Boogaerts & Maertens, 2001). To overcome these problems, the authors suggested the topical route, so that ITZ is in direct contact with the infected tissue. This approach is limited by the lipophilia (solubility in water: 1 ng/ml) and poor bioavailability of the drug (Berben et al., 2017). The MAPs were fabricated with a mixture of PVA/PVP and glycerol. The efficacy of ITX-NCs@MAPs and the dermatokinetic performance was tested ex vivo in porcine skin. ITZ-NCs@MAPs released higher amounts of ITZ into the deeper skin layers,

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compared with needle-free patch and a conventional cream. The ex vivo antifungal activity was tested in a fungal infection model on porcine skin. The ITZ-NCs@MAPs patch killed 100% of the fungal burden after 12 h, while the same patch without needles and the conventional cream killed only 48% and 82% of the fungal burden, respectively. These results proved that the combined approach of MAPs and ITZ-NCs provided better antifungal response than other topical strategies.

Wei et al. designed a PVP/HA-based dissolving MAPs combined with methotrexate (MTX) nanocrystals (MTX-NCs@MAPs) for the treatment of rheumatoid arthritis (RA) (Wei et al., 2022) (Figure 4). MTX is not soluble in water and has several side-effects that limits its curative effects (Pivovarov & Zipursky, 2019). NCs can improve non-soluble drugs availability, and combined with MAPs, can be administered transdermally to overcome the main problems from the oral distribution. The efficacy of this system was studied in vivo on an arthritis-induced rat model. Rats were divided in the following groups: (1) no treatment (control group); (2) healthy control group; (3) MTX-NCs@MAPs treatment; (4) MTX-NCs applied in cream; and (5) oral MTX treatment. All groups were treated with 200 μg of MTX (except for group 1 and 2). The rats were administered with their respective treatment every 3 days for 2 months. RA control showed the highest paw swelling rate 27 days after induction, which then decreased slowly. Paw swelling group 4 (cream) reached the highest inflammation rate at day 27, which slowly decreased afterwards. Group 5 showed a constant paw swelling for 33 days and then it decreased slowly. Finally, Group 3 (MTX-NCs@MAPs) significantly reduced the paw swelling on day 21, and levels were lower than the control, proving that MTX-NCs loaded dissolving MAPs improve the relief of RA symptoms compared with the control treatments in vivo.

Nagra et al. developed self-dissolving MAPs for local and systemic acyclovir (AC) delivery, trying to overcome frequent dosing due to low bioavailability (Nagra et al., 2022). They applied topically a lyophilized wafer on ex vivo micropored skin (5 min) using hydroxypropyl methyl cellulose (HPMC) or HPMC/PVP MAPs. Specifically, HPMC produced sharper tips than the HPMC/PVP combination. MAPs pre-treatment provided around 7 and 11-fold higher AC skin concentrations. In vivo testing showed a maximal concentration (C_{max}) of 2.58 μg/ml in rabbit plasma after 24 h. Insertion depth of MAPs in an artificial skin model showed a depth insertion of 237 μm, enough to bypass the SC. MAPs were dissolved after 5 min, and Franz-diffusion cell asays showed that HPMC-based MAPs pre-treated skin allowed a higher cumulative drug release and drug flux. In vivo studies demonstrated that AC accesed the dermis and that the use of lyophilised wafer on pre-treated skin improved the absorption rate (4.5-16-fold higher skin concentration) compared with commercial formulations. The AC plasma levels in albino rabbits after a single wafer administration was maintained above the desired concentration for longer periods.

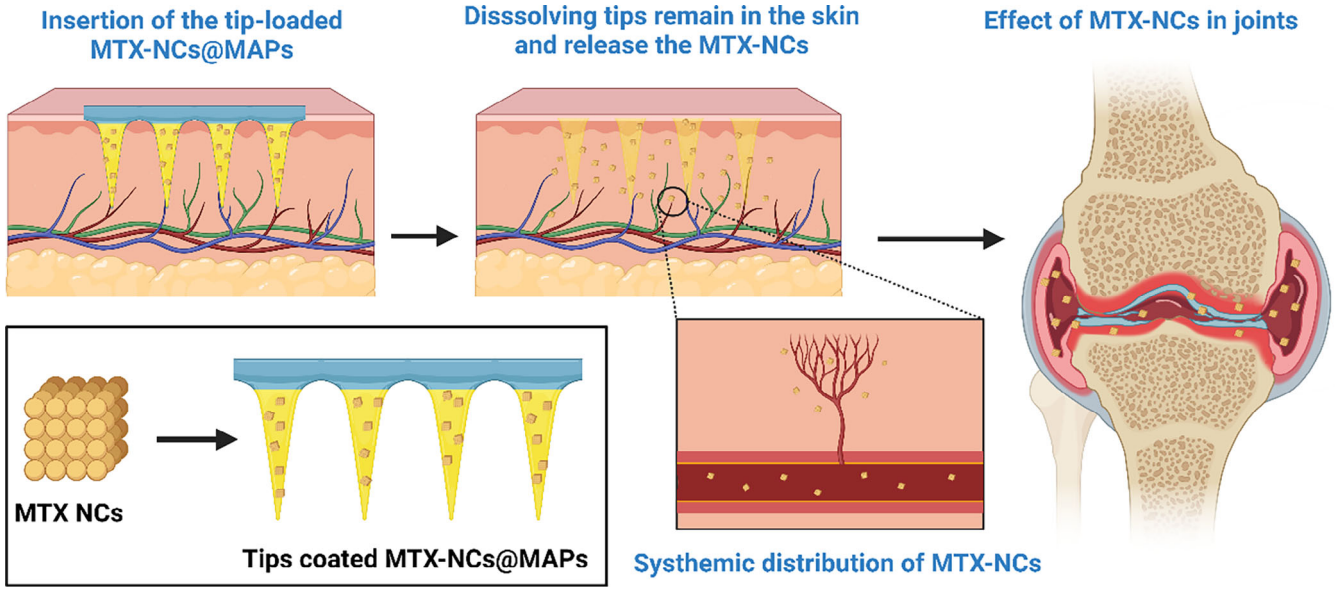

FIGURE 4 Schematic diagram of the transdermal drug delivery strategy of the MTX-NCs@MAPs based on Wei et al. work (Wei et al., 2022). First, MTX-NCs are prepared, and then introduced into the tips of the MAPs. Then, the MTX-NCs@MAPs are inserted into the skin, leading to the tips dissolution and posterior release of the MTX-NCs. The MTX-NCs diffuse towards the skin layers until reaching the capillary, and then, they reach the systemic distribution. MAPs, microneedle array patches; MTX, methotrexate; NCs, nanocrystals.

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3.4 | Nanoemulsions and nanosuspensions: Classical strategies to formulate lipophilic drugs

Nanoemulsions (NEs) and nanosuspensions (NSs) can encapsulate both hydrophilic and hydrophobic drugs. They are suspension droplets of 500 nm to 1 μm. NEs are a water-in-oil/oil-in-water dispersion of particles, stabilized by a surfactant, while NSs are drug-particles, non-solubilized in the matrix, but stabilized by small amounts of surfactant (Fernández-Campos et al., 2013).

Vora et al. developed NSs@MAPs including cholecalciferol (CL) as a hydrophobic drug model CL-NSs@MAPs (Vora et al., 2018). They designed a PVA/PVP polymeric matrix where CL was incorporated as a NSs. The ex vivo permeability in porcine skin was compared with a needle-free patch in a Franz-cell diffusion set-up. CL-NSs@MAPs efficiently delivered CL-NSs (418.2 ± 89.3 μg) through the skin, while a needle-free patch delivered a significant less CL amount (only 73.2 ± 26.5 μg). This experience paved the way for more studies combining NSs@MAPs. A similar study was performed by Abdelghany et al. (Abdelghany et al., 2019), using curcumin (CU) a hydrophobic drug with anti-inflammatory and tumor inhibition properties. Ex vivo permeation studies using neonatal porcine skin compared CU-NSs@MAPs to CU-NSs administration, proving once again the synergies between NSs and MAPs combinations.

Non-invasive and easy self-administration are crucial requirements for on-demand contraceptives, thus MAPs seem an efficient administration strategy for contraceptive drugs delivery. Altuntas et al. designed a soluble PVA/PVP-based MAPs for Nestorone® (NES) nanosuspension-like delivery for "on demand" contraception (Altuntas et al., 2022). NES is a non-androgenic contraceptive that prevents the ovulation at low doses (Kumar et al., 2000). NES-NSs was used to incorporate the drug inside the MAPs matrix and homogenize the dispersion. In vivo experiments were conducted in rats treated with the NES-NSs@MAPs for 24 h. Rats were randomly divided into four groups: (1) control; (2) subcutaneous injection; (3) NES-NSs@MAPs; and (4) NES-@MAPs. The maximum concentration by NES-NSs@MAPs was achieved 1 h after administration (36.26 ± 14.06 ng/ml). Then, drug plasma levels above 3.4 ng/ml were maintained for 2 days and remained around 1 ng/ml until day 6, when they became undetectable. In comparison with the subcutaneous injection of NES-NSs, the relative bioavailability of the patch was 11.5%. Regarding NES@MAPs device, the maximum concentration was lower (25 ± 5.72 ng/ml), and the relative bioavailability compared with the SC injection was 7.8%, showing that NSs improved drug delivery compared with the same formulation without NSs.

Nasiri et al. developed a dissolving MAPs to overcome the limitations in AmB skin delivery (Nasiri et al., 2022). They created a strategy for AmB molecule delivery using a NEs loaded in PVA/PVP dissolving MAPs. NE was prepared with Capmul-C8 EP/EF as an oil phase, not only because of the drug affinity but also for its inherent antifungal activity. AmB-NEs@MAPs permeability was studied in neonatal porcine skin, showing a higher skin permeability (26.60 ± 8.23 μg), compared with the equivalent needle-free patch (5.00 ± 6.15 μg).

Diclofenac (DCF) is one of the most powerful and commercially distributed non-steroidal anti-inflammatory drugs, but its use is related to gastrointestinal, cardiovascular, and renal toxicity (Altman et al., 2015). Pireddu et al. proposed NSs@MAPs strategy as an alternative for the DCF administration to avoid these side-effects (Pireddu et al., 2020). The DCF-NSs@MAPs were tested in new-born pig skin. As expected, MAPs-assisted strategy led to an increased DCF permeability through the skin ex vivo. However, penetration of DCF was measured in different layers of the skin and the drug was notably accumulated in the SC (around 15%), suggesting the need of further investigations to optimize the DFC-NSs formulation for a better transdermal drug delivery.

Wu et al. developed MAPs for intravitreal delivery of triamcinolone acetonide (TA) as an alternative for the intravitreal injection (ITV) (Wu et al., 2022) (Figure 5), which is the most effective currently available therapy for retinal diseases and other eye-related illness. However, ITV is very invasive, and can lead to infection, painful administration, and other complications, such as retinal detachment, endophthalmitis or vitreous hemorrhage (Moshfeghi et al., 2003; Rodríguez Ramírez et al., 2014). TA was used as a lipophilic model drug for NSs delivery since it is very commonly used as anti-inflammatory drug to treat retinal diseases. The PVA/PVP-based TA-NSs@MAPs were designed as a contact lens, so they could be easily self-applied, and the drug was delivered directly to the target site. Permeability assays were performed in ex vivo porcine sclera with these TA-NSs@MAPs and TA@MAPs, both applied during 5 min and then removed. The results showed that TA-NSs@MAPs delivered the 37.09 ± 3.71% of the drug, while the TA@MAPs only delivered 22.77 ± 2.58% of the drug, proving that NSs enhances the ocular delivery. Ex vivo distribution studies performed with IR spectroscopy demonstrated that TA-NSs@MAPs can deliver the drug to deeper ocular structures.

Other study aimed to deliver AmB intracorneally to treat ocular fungal infections using dissolving MAP devices (Albadr et al., 2022). The AmB-NSs@MAPs were made of a PVP polymeric matrix combined with PVA and HA, since PVP enhances corneal permeability of the drug. The antifungal activity of the AmB-NSs@MAPs was proved with two

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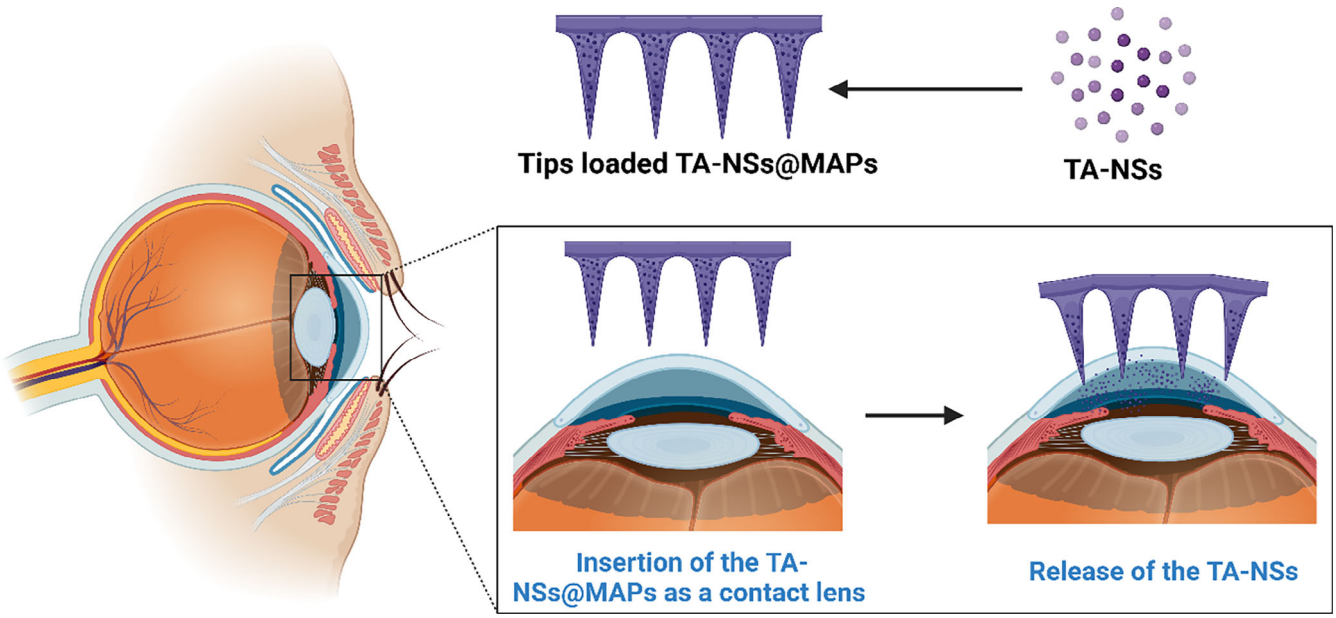

FIGURE 5 Schematic diagram of the intravitreal drug delivery strategy of the TA-NSs@MAPs based on Wu et al. work (Wu et al., 2022). Triamcinolone-NSs was optimized by water dispersion and posterior precipitation with the polymer, and then incorporated into MAPs to form a bilayer structure robust enough to pierce the sclera. The administration TA-NSs@MAPs in the eye imitates the contact lens insertion. Later, the drug is dissolved into the sclera tissue promoting the penetration of lipophilic molecules with higher concentration of the TA. MAPs, microneedle array patches; NSs, nanosuspension; TA, triamcinolone acetonide.

common species in ocular infections: *Candida albicans* and *Aspergillus niger*. MAPs exhibited a rapid post-insertion dissolution (2 min) and a better fungal inhibition ability compared with the AmB-free-suspension formulation. The in vitro intraocular permeability was analyzed by 3D imaging using porcine corneal tissue. AmB-NSs@MAPs delivered the drug through the cornea (0.4 mm depth) while no evidence of drug penetration was found with the AmB solution.

3.5 | Nanoparticles: Nano-sized entities for assisted drug delivery

3.5.1 | Metal-based nanoparticles

Dong et al. aimed to design MAPs to treat superficial skin tumors, especially in those cases where surgery is not possible, using doxorubicine (DOX) (Dong et al., 2018). DOX-loaded Gold nanocages (AuNCs) were incorporated in HA-based MAPs devices (DOX-AuNCs@MAPs) to combine photothermal and chemotherapeutic activities. Au NCs outstand for their chemical stability, ease of synthesis, biocompatibility, but mostly because of its photothermal behavior. Among other Au-based nanoparticles, AuNCs have a high extinction coefficient, and therefore, they can induce high photothermal effects at low concentrations (Au et al., 2010). The photothermal effect and the antitumoral efficacy of the DOX-AuNCs@MAPs were studied in an in vivo model of subcutaneous melanoma in C57 mice. The photothermal activity showed an increase in temperature from the normal temperature of the tumor (33.6°C) to 39.4°C, after NIR irradiation and, 55°C with NIR and DOX-AuNCs@MAPs application. To perform the experiments, rats were divided into seven groups: (1) control; (2) NIR radiation treatment; (3) blank MAPs; (4) DOX@MAPs application for 5 min in the tumor site; (5) AuNCs@MAPs combined with NIR radiation (mice were first treated with the MAPs and then exposed to the NIR laser); (6) intertumoral injection of DOX and AuNCs solution and posterior exposure to NIR; and (7) group treated with DOX-AuNCs@MAPs and latter NIR irradiation. The results showed that, even though NIR irradiation itself and Au NCs had notable antitumoral activity, the tumor weights were significantly reduced when the treatment combined DOX and PPT therapies. The greatest tumor reduction was achieved by DOX and Au NCs injection and DOX-AuNCs@MAPs followed by NIR that reduced the tumor weight to 0.27 ± 0.12 g and 0.30 ± 0.18 g respectively, in comparison with the control group that only reduced the tumor weight to 1.73 ± 0.98 g.

Cárcamo-Martínez et al. designed a gold nanorods (GnRs)-loaded MAPs (GnRs@MAPs) as a proof of concept, with the aim to improve the effectiveness and safety of GnRs medical applications (Cárcamo-Martínez et al., 2020).

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GnRs were selected because of their photothermical properties, since they can absorb NIR radiation and turn it into heat, which can be used for treating several diseases ranging from bacteria/fungal skin infection to skin cancers. However, the use of GnRs is limited due to the high toxicity and tissue accumulation rates. To overcome these challenges and improve the GnRs potential, Carcamo-Martínez et al. designed this GnRs-coated solid MAPs (GnRs@MAPs) for skin hyperthermia treatment. The MAPs were fabricated with a mixture of PEG and Gantrez hydrogel. The heating capacity of the GnRs@MAPs was studied in ex vivo 3 mm-thickness neonatal porcine skin upon NIR irradiation and compared between coated-single needles and coated-MAPs of: (1) 4 mm length and (2) 2 mm length. Even though, insertion was deeper for the single-needle prototypes, the heating performance was higher for the GnRs@MAPs, increasing in 15.1°C the skin temperature, compared with the single-needle devices, which only reached a temperature between 6.77 and 10.1°C. In addition, after MAPs removal, no GnRs or polymeric residue were left, showing that the MAPs in combination with metallic NPs is a safe, minimally invasive, and efficient strategy.

3.5.2 | Polymer-based nanoparticles

Sometimes, the use of nanocarriers does not only aim to achieve a suitable vehicle for non-permeable drugs or to protect them to increase their bioavailability. In other cases, nanocarriers focus on providing a controlled release, sustained in time. Some studies have proved the efficacy of polymeric nanocarriers, such as PLGA for transdermal delivery and targeted intradermal administration on highly non-soluble drugs like CL (Vora et al., 2017).

Lin et al. developed PLGA NPs of rapamycin (RAPA) and Keratin NPs of epigallocatechin gallate (EG) loaded into PVP dissolving MAPs for stimulating hair growth, (Lin et al., 2022). RAPA was selected to promote hair growth and was encapsulated into keratin polymer. RAPA/EG-NPs@MAPs were in vivo tested in C57BL/6J mice at telogen phase using different RAPA and EG doses incorporated in the MAPs and compared with a classical topical administration of the drugs. MAPs for the co-delivery of RAPA and EG NPs generated the best therapeutic effect on hair regeneration, since faster hair growth rate was observed for RAPA-NPs@MAPs devices, but a higher hair follicle density was observed with EG-NPs@MAPs, suggesting a synergistic activity. In addition, activity of hair follicles and their entrance into a new hair cycle were confirmed in the skin area treated with MAPs by an increased expression levels of β-catenin (hair follicle regulatory protein) and p-AKT (a marker of hair follicle cells for proliferation and anti-aging).

One of the main advantages of the transdermal vaccination is the accessibility of a large population of immune cells that can amplify the immune response. In general, NPs-based vaccines improve the immune responses against antigens, due to their resemblance to pathogens, and their prolonged and controlled release profiles of immunizing agents (Matsuo et al., 2013). Mönkäre et al. developed an HA-based dissolving MAPs device for intradermal vaccine delivery. For this purpose OVA and poly(I:C) were encapsulated in PLGA NPs, and loaded into OVA/poly(I:C)-NPs@MAPs (Mönkäre et al., 2018). These MAPs delivered 31.0 ± 14.3 μg of NPs into mice skin in an in vivo model, which corresponds to 0.99 ± 0.46 μg of OVA, and 0.93 ± 0.43 μg of poly(I:C) (around 24% of the doses). They found that, when 100% of the OVA dose was encapsulated in NPs, hollow MAPs mediated delivery resulted in statistically stronger IgG1 responses than OVA/poly(I:C)-NPs@MAPs at all time points. However, when 50% of the OVA dose was in soluble form and the other 50% loaded in NPs, hollow MAPs-mediated delivery produced higher OVA specific IgG1 and IgG2a responses compared with OVA/poly(I:C)-NPs@MAPs, although without statistical difference.

Pu et al. designed and developed HA-based dissolving MAPs for transdermal delivery of DOX formulated in poly-(N-isopropylacrylamide-co-acrylic acid) (PNA) and polydopamine (PDA) NPs as a novel treatment for skin tumors (Pu et al., 2022). Specifically, the structure of this NPs consisted in a DOX-loaded PNA nanogel core with photothermal properties, and a DOX-loaded PDA outer layer that provides dual temperature-/pH-responsive features. DOX-PNA/PDA NPs were effectively carried under SC using these dissolving MAPs and released in a controlled manner by NIR irradiation in an in vitro gelatine gel surrogate skin model. Once released, these DOX-PNA/PDA NPs can be phagocytized by B16F10 cells and release the contained drugs in the acidic microenvironment of tumors.

3.5.3 | Lipid-based nanoparticles

Solid-lipid nanoparticles (SLNs) and nanostructured lipid carriers (NSLCs) have been introduced as carriers for low permeable drugs, both hydrophilic and hydrophobic, as a strategy to increase the molecule permeability through biological membranes. An example of NSLCs@MAPs association is the study done by Guo et al., who achieved a sustained skin

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delivery of Acontium sinomontanum (AS) alkaloids as an alternative for arthritis treatment (Guo et al., 2022). In vitro permeability studies through pre-treated rat skin using solid MAPs (AS-NSLCs@MAPs) ("poke and patch" approach) showed an enhanced but controlled transdermal drug delivery of two alkaloids—lappaconitine (LA) and ranaconitine (RAN), compared with a free-drug mixture. In vivo studies confirmed that AS-NSLCs@MAPs improved drug bioavailability and stabilized drug blood levels. The hypodermic injection of 1 ml As-NPs exceed the narrow therapeutic range and led to a high mortality. Therefore, AS-NPs dose was reduced to 0.3 ml to avoid fatal toxicity and the C_{max} was obtained at 0.5 h post-injections, being 97.26 ± 29.18 and 18.91 ± 2.70 ng/ml, respectively for LA and RAN. AS-NSLCs@MAPs allowed the administration of 1 ml obtaining the maximum drug peaks after 6 h (47.00 ± 16.84 ng/ml for LA and 8.45 ± 4.86 ng/ml for LAN), while AS-NSLCs topical administration without solid MAPs pre-treatment only reached concentrations of 7.00 ± 2.81 and 2.14 ± 1.01 ng/ml for LAN and RAN, respectively. Pharmacological in vivo performance was assessed for anti-inflammatory and analgesic effects, concluding that AS-NSLCs@MAPs provided the best inhibition, as shown by reduced paw swelling, oedema, synovial inflammatory cell infiltration and hyperplasia, compared with the subcutaneous injection group. In addition, AS-NSLCs@MAPs contributed to reduce the cardiotoxic side-effects, such as ventricular tachycardia, atrioventricular block, and other serious arrhythmias that are generally produced by AS-NSLCs subcutaneous injection, caused by a rapid alkaloid absorption, which were not observed in this case.

Other promising results were obtained by Lee et al., who aimed to obtain controlled dermal delivery of Nile red (NR) as a model lipophilic molecule using NSLCs@MAPs (Lee et al., 2014). PLGA-MAPs have successfully been developed with NR (Donnelly et al., 2009), however, PLGA-MAPs have the disadvantage of delaying the skin barrier functions recovery. On the contrary, NR-NSLCs were prepared using the high-pressure homogenization technique and embedded in hyaluronic acid (HA) dissolving MAPs for a rapid dissolution and skin recovery (NR-NSLCs@MAPs). In an in vitro release study, NR-NSLCs showed a controlled release and, although the release reached a plateau at around 36 h, over 75% of the NR was released within 24 h. In contrast, a micellar solution (5% Tween 80) released NR rapidly in comparison to NR-NSLCs dispersion and reached a plateau only after 9 h, which indicated that 96% of the NR was released. In addition, NR-NSLCs@MAPs successfully delivered around 45% of NR dose in the skin, in which 40% was localized in the external skin layers (from 0 to 200 μm depth), and 5% reached the dermal layers. These findings were confirmed by CLSM analysis showing strong fluorescence intensity at different epidermal layers depths.

Prabhu et al. tried to improve curcumin (CU) bioavailability by using PVA-based MAPs containing drug-loaded solid lipid nanoparticles (SLNs). CU-SLNs were developed preparing six different formulations (Prabhu et al., 2022), being the CU-SLNs@MAPs the one that showed the highest release (74.24% of the total CU loaded after 12 h) in an in vitro drug release study. Drug delivery through ex vivo skin showed 69.31% deposition of drug after 12 h, and histological studies revealed that the MAPs were adequate for a safe transdermal systemic delivery. CU-SLNs@MAPs were tested in a rodent model of Parkinson of motor coordination and balance ability, showing a significant neuroprotective effect.

SLNs have also been used with lymph node targeting purposes (Permana et al., 2019). Permana et al. tried to overcome the oral filariasis therapy limitations, especially the incapability to kill adult macrofilaria. They encapsulated DOX, diethylcarbamazine (DEC) and ABZ in lipid-based nanoparticles of <100 nm and administered them intradermally using PVA/PVP-based dissolving MAPs. Drug-loaded SLNs@MAPs showed good properties in terms of appearance and insertion, and drug doses were retained in a porcine skin model after 24 h were adequate, according to the authors. Specifically maximal in vitro concentrations in epidermis and dermis were respectively: 192.44 ± 22.12 μg/cm^3 and 526.56 ± 59.05 μg/cm^3 for DOX; 179.015 ± 18.32 μg/cm^3 and 270.80 ± 31.04 μg/cm^3 for DEC; 137.16 ± 14.37 μg/cm^3 and 461.97 ± 37.72 μg/cm^3 for ABZ. In vivo studies showed a 4 and 7-fold increase in concentration compared with oral, thus the drug arrived at systemic circulation in a higher proportion, but also to the lymph nodes, where filaria is also found in infected patients.

Among the lipid-based nanostructures, cubosomes (CUBs) present a unique composition, of lipotropic bicontinuous cubic phases and a stabilizing copolymer block. CUBs are bigger than lipid vesicles generally, and therefore, they can encapsulate big payloads of large hydrophilic molecules and proteins inside the aqueous structure, and lipophilic drugs within the lipidic membranes (Barriga et al., 2019). Ramalheiro et al. developed rapamycin (RAPA)-loaded MAPs for treating psoriasis (Ramalheiro et al., 2020). The RAPA-CUBs@MAPs was fabricated with a PVA/PVP mixture. NK cell growth inhibition was studied in vitro, and cell proliferation was similar when compared with free RAPA solution and RAPA-CUBs treatments (85.2 ± 3.5% and 82.9 ± 2.5%, respectively). However, RAPA-CUBs showed a continuous release over 14 days, guaranteeing a sustained release of drug with no initial burst. RAPA-CUBs@MAPs promoted

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in vitro drug penetration in an agarose skin-mimicking model and achieved CUBs depth deposition of 310 μm, indicating particle diffusion around the pores generated by the MAPs after their dissolution.

Lipid vesicles (LVs) or liposomes (LPs) are formed by lipid bilayers around a hydrophilic core, being able to encapsulate both lipophilic—within the lipid bilayer—and lipophobic—in the aqueous core—drugs. Among the different NPs, LVs stand out by their biocompatibility and versatility, as they allow modifications with surfactants (transfersomes) or ethanol (ethosomes) to improve their skin delivery ability.

Rajput et al. prepared levonorgestrel (LVN) liposome (LPs) loaded into PVA-based MAPS (LVN-LPs@MAPs) for contraception purposes (Rajput et al., 2022). In an in vivo study with rats, LVN@MAPs reached therapeutic concentrations in 10 days, whereas LVN-LPs@MAPs needed 2 days less to reach the same levels (200 μg/ml) and maintained a LVN concentration above the human therapeutic level for more than 1 month, showing that they are useful as long-acting contraceptives.

Yu et al. combined the use of immunoliposomes and MAPs to design an effective COVID vaccine (Yu et al., 2022). The immunoliposomes (CD11c/OVA-LPs@MAPs) encapsulated in their core the OVA and CD11c antibodies were attached to the particle's surface. Transcutaneous immunization decreases the adverse immune response, but most importantly, MAPs can target the Langerhans cells located in the skin structure, improving the efficiency of antigen presentation and activating the immune response. The HA/PVA-based MAPs successfully penetrated the SC, since insertion tests in mice skin produced microchannels with 50 μm diameter and 100 μm depth after the application of MAPs for 2 min, using a force of 10 N. Transdermal drug delivery studies demonstrated that permeation of OVA through the skin was significantly higher when OVA was encapsulated and administrated with a MAPs-assisted strategy. In addition, the antibody was found at a depth of 200 μm location when observed by fluorescence, confirming that immunoliposomes can be effectively delivered into the epidermis and dermis. The transfer pathway and immunization were also studied in vivo, obtaining a successful delivery as a result, since the immunoliposomes reached the lymph and spleen, triggering both cellular and humoral immunity.

With lymphatic targeting purposes, Yang et al. designed doxycycline (DOX) transferosomes (Ts) to overcome the formulation issues of this drug, and then, embedded them in a hyaluronic acid matrix to produce dissolving MAPs (Yang et al., 2019). The DOX-Ts@MAPs were effectively inserted into rat skin and released DOX into the dermis via self-dissolution, thus promoting a higher bioavailability and breaking the limit of transdermal cargo transit.

Commercial solid MAPs (Dermaroller® device) were used in the work by Ahad et al. (Ahad et al., 2017). They combined the solid MAPs with eprosartan mesylate (EM)-Ts loaded into Carbopol gels. The in vitro skin permeation study showed that transfersomes significantly contribute to control the drug permeability, since a transdermal flux of 33.41 $\pm$ 0.44 μg/cm^2/h was obtained when EM dispersion was combined with Dermaroller use, which was significantly higher than the flux obtained for EM-Ts@MAPs (26.79 $\pm$ 1.66 μg/cm^2/h). The gels showed a good management of hypertension in hypertensive rat models, since the in vivo angiotensin II type-1 blocking efficacy of prepared transfersomal gel was also supported by the decrease of protein-specific expressions on smooth vascular muscles of aorta.

Another study that used Dermaroller-assisted transdermal delivery, was the Ahmed et al. study. In this case of doxorubicin (DOX) and celecoxib (CEL) co-loaded liposomes (DOX/CEL@LPs) were developed to treat skin disorders (Ahmed et al., 2019). DOX/CEL@LPs were included in a Carbopol gel in order to avoid an initial burst release and achieve a sustained release pattern. Skin penetration of DOX/CEL-LPs was tested in female BALB/c mice, obtaining a DOX/CEL penetration 2-fold higher when in skin was pre-treated using the Dermaroller. The in vivo anticancer effect was studied, showing a significant higher inhibition of the tumor growth and a massive increase in drug accumulation in B15 melanoma cells using DOX/CEL-LPs@MAPs strategy.

3.5.4 | Lipid-coated nanoparticles

For transdermal immunization purposes, Tu et al. developed a lipid-coated mesoporous silica nanoparticles (Lc-MSs) loaded with OVA (OVA-MSs@MAPs) (Tu et al., 2017) (Figure 6). Mesoporous silica NPs have a large surface area and porous cavities that can efficiently load drug molecules or proteins, and the addition of the lipid bilayer coating can increase their colloidal stability and improve drug targeting delivery (Porta et al., 2013). Uptake of OVA loaded in LC-MSs by Bone Marrow-Derived Dendritic Cells was higher than that of free OVA, suggesting effective targeting of OVA-Lc-MSs to antigen-presenting cells. To coat the negative charged Lc-MSs on the silicon MAPs, the microneedles were chemically modified by using pyridine groups to obtain a pH-sensitive surface (positively charged at pH 5.8). OVA-Lc-MSs delivery from the OVA-Lc-MSs@MAPs surface into the skin was evaluated in an ex vivo skin model. The

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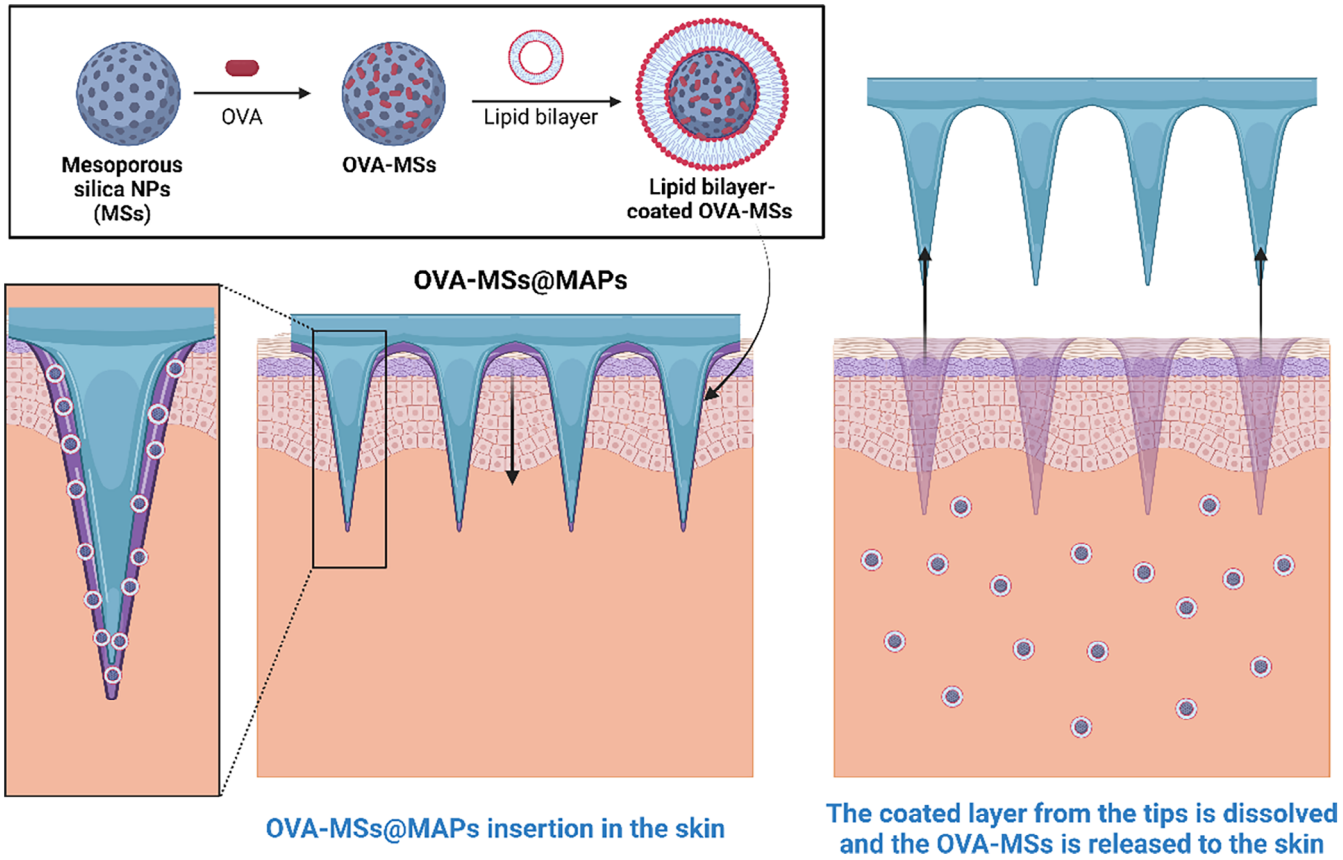

FIGURE 6 Schematic diagram of the transdermal drug delivery strategy of the OVA-MSs@MAPs based on Tu et al. work (Tu et al., 2017). Mesoporous silica nanoparticles are prepared and then coated with OVA by electrostatic interactions. A negative charged lipid bilayer was assembled to enhance the colloidal stability of the OVA-loaded particles. The OVA-MSs@MAPs are inserted into the skin and liberated progressively. The coated layer from the tip is dissolved and the drug is administrated to the human skin. MAPs, microneedle array patches; MSs, mesoporous silica nanoparticles; OVA, ovoalbumin.

intradermal delivery was studied by SEM showing that less particles were observed on surface of microneedles after the penetration and withdrawal from human. In addition, localization of fluorescently marked OVA was observed inside the skin by CLSM, proving that MAPs effectively penetrated the skin and successfully delivered their cargo.

Transdermal insulin (IN) delivery was explored combining commercially available solid MAPs skin pre-treatment and chitosan-based NPs by Zhang et al. (Zhang, 2020). This study addresses the two main challenges of the insulin administration nowadays: first, the low permeability of insulin through the skin and, second, the need of periodic injections that results in a rapid decrease of blood glucose levels, which can lead to hypoglycemic states. IN-NPs were protected with an amphiphilic linoleic acid coating (IN-Lc-NPs) and derivatised with an arginine chain, which has been extensively studied as a cell penetrating peptide that mediates the cell binding and transepithelial transport. In vitro IN permeation through rat skin increased 4.2-fold when IN-Lc-NPs administration was combined with solid MAPs (IN-Lc-NPs@MAPs) in comparison to passive diffusion (10.24 ± 1.06 mg/cm2/h and 2.77 ± 0.64 mg/cm2/h, respectively). To assess the in vivo efficacy a streptozotocin-induced type 2 diabetic model was used, and animals were randomly assigned to the following treatment groups (45 mg/kg): (1) free-IN administered transcutaneously; (2) IN injection (IV); (3) IN-Lc-NPs@MAPs; and (4) free-IN@MAPs. Free-IN was administered without MAPs-assisted pre-treatment did not show any hypoglycemic effect, confirming the inefficiency of passive IN delivery via the transdermal route. The subcutaneous injection of IN resulted in a rapid decrease in blood glucose levels, however, hyperglycemic state was recovered only after 1.5 h. The hypoglycemic effect of free-IN@MAPs was similar to the intravenous injection group, indicating that the nano-microneedle could increase the skin permeability to deliver physiologically and therapeutic amounts of IN. However, it was IN-Lc-NPs@MAPs treatment the one that maintained the long-term hypoglycemic effect (6 h) as a consequence of the controlled release of IN-NPs.

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Cisplatin (CISPt) is one of the most widely used agent for chemotherapies and plays an essential role in DNA-modifying routes for tumor growth blocking, by apoptosis-induction of the cancer cells. It is currently administered intravenously, but its systemic application can lead to important side-effects, such as nephrotoxicity, neurotoxicity, nausea and vomiting, haemolytic anemia, ototoxicity and electrolyte disturbance (Florea & Büsselberg, 2011). Besides, the traditional subcutaneous injections could promote skin necrosis and tumor spreading. To overcome these challenges and increase the treatment safety, Lan et al. designed CISPt DOPA-nanoparticles (CISPt-NPs), which were outer coated with other phospholipids (DOTAP, PEG and cholesterol) for increasing CISP uptake and eventually enhance the anticancer effect (CISPt-Lc-NPs) (Lan et al., 2018). The CISPt-Lc-NPs were incorporated in cellulose-based dissolving microneedles (CISPt-Lc-NPs@MAPs). The effectiveness of the CISPt-Lc-NPs@MAPs was tested on a xenograft head/neck-tumor in an in vivo mice model. Mice were randomly divided in groups as follow: (1) control; (2) CISP IV injection; (3) subcutaneous injection with CISPt-Lc-NPs; (4) subcutaneous injection of CISP in the tumor location; (5) CISPt-NPs@MAPs (nanoparticles without lipid coating); and (6) CISPt-Lc-NPs@MAPs. The CISPt-Lc-NPs subcutaneous injection reduced the tumor volume more than the CISPt IV injection showing that CISPt encapsulation increases drug efficacy, since Lc-NPs were internalized by the cancer cells and then escaped from the endosomal system. Furthermore, the CISPt-Lc-NPs@MAPs increased cytotoxicity and apoptosis in cancer cells with an apoptotic index of 58.6%, resulting in a significantly reduced tumor volume and weight compared with the other treatments. In addition, they also had a marked reduction of systemic toxicity since serum platinum, pulmonary toxicity, hepatotoxicity, and nephrotoxicity were not detected, proving their safety.

Lan et al. also developed a co-loaded CISPt and anti-PD-1 (a blocker of programmed cell death protein (PD-1) NPs. PD-1 combined with programmed cell death ligand-1 (PD-L1) critically accounts for tumor immune evasion (Lan et al., 2020). This CISPt/anti-PD-1-Lc-NPs were effectively delivered including them in PVP-based dissolving MAPs. CISPt/anti-PD-1-Lc-NPs) boosted the immune response and produced an extra effect on tumor regression, due to the synergistic anticancer mechanisms: blockage of PD-1 in T-cells by aPD-1, and an increase in direct cytotoxicity of CISPt in tumor cells observed in the previous work.

4 | SUMMARY AND PROSPECTS OF NPs@MAPs

NPs technology is a TDDS often used in biomedical research nowadays. However, its application in topical and transdermal strategies is extremely limited because of the great skin barrier opposition. Therefore, their association with an auxiliar TDDS seems highly convenient to fulfill the demands from the healthcare professionals to become a real alternative to current medicines. NPs@MAPs strengthens the potential of these nano- and micro-technologies that clears a path for having a feasible clinical translation in the medium- and longer-term future. MAPs contribute to pierce the SC wall that prevents the entrance of NPs into the skin structure and allows, in a minimally invasive way, local and systemic therapies (Waghule et al., 2019). Besides, both can also be used for diagnosis and sampling purposes beyond the treatment of conditions (Agasti et al., 2010; Amarnani & Shende, 2021; Samant et al., 2020), and other fields such as cosmetology and anaesthesiology have already explored the use of both tools for their purposes.

Biomedical engineering focuses not only on the design of new drugs, but the attempt to give a second life to drugs that have failed in the past, mainly due to high systemic toxicity, and the development of personalized therapies (Aguado et al., 2018), that are the other big challenges and objectives in the field. NPs are one of the tools where trust is put on for achieving these goals. Tumor-derived membrane NPs have demonstrated their effectiveness in eliciting strong immune responses against different cancer types (Mizrahy et al., 2017; Xu et al., 2022), making the design of tailored medicines for each patient possible. In the particular case of the skin, these NPs-based treatments or preventive vaccines have been proved with positive outcomes against melanoma (Sainz et al., 2018; Silva et al., 2015), however, they were administered systemically or intratumorally (Mizrak et al., 2013). Their combined use with MAPs would improve the compliance by patients (Rodgers et al., 2019) and accordingly to the potential immune cell targeting, there are clearly new open chances for facing cancer therapy and vaccination (Aikins et al., 2020; Cordeiro et al., 2021). In fact, NPs@MAPs have been proposed as an exceptional tool for COVID-19 vaccination purposes, due to the combination of NPs features that protect the mRNA cargo (Kapnick, 2022; Kim et al., 2020; Korkmaz et al., 2021; Kuwentrai et al., 2021; Yu et al., 2022), and the self-application would make mass vaccination much easier. However, this idea generates several questions and limitations that must be solved. For instance, the technical aspects that surrounds the device application by patients. Although MAPs should be reliably inserted into the skin structure by patients, it could require a minimal training or the use of application devices that would increase the cost of the final product to

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guarantee the consistency between users and ensure optimal results (Rodgers et al., 2018). Nevertheless, the avoidance of sharp and biohazard wastes could compensate some of the inherent inconveniences and make worth the exploration of their use. The mass production of NPs@MAPs systems is the point that probably will determine their arrival to the market, but it will require an intense collaboration of the current developers—the academia—with the industry and healthcare providers, to develop scaling-up and manufacturing processes that achieve the stated systems properties, stability and safety profiles (Guillot et al., 2020). Actually, their safety, when used for the treatment of chronic diseases and associated comorbidities, is another gap to answer.

Although MAPs are usually prepared with biocompatible polymers—mainly PVA, PVP, Hyaluronic acid, Chitosan, CMC, Gantez S-97, etc.—(Weimer et al., 2021), there is a lack of studies addressing the effects of polymer deposition and dermatological testing or the impact in the health of end costumers of sugars used to cryopreserve the NPs, stabilizers or mechanical strength modulators (Rodgers et al., 2018; Zhang et al., 2021). The other remaining aspects that clinical translation may require are the need of pharmacopeial tests, good manufacturing procedures, sterile production, long-term stability, packaging and storage conditions which warrant the desired standards for any pharmaceutical product (Ali et al., 2022; Lutton et al., 2015; Roberts et al., 2021; Ruan et al., 2021).

Finally, it should be noted that despite NPs@MAPs is a novel field, it has a space for innovation based on the use of smart delivery systems. For example, Zou et al. successfully developed a molecular motor-based system for controlled release of L-DOPA and absorption through the skin for the Parkinson's disease treatment (Zhou et al., 2022) (Figure 7). The transdermal administration route seems especially convenient for this drug because the oral delivery is considerably difficult, due to the Parkinson symptoms, the multiple side-effects and the need of a strict coordination with the symptom manifestation. This nano-motor release system was based on the photo-response of cis-trans isomerization

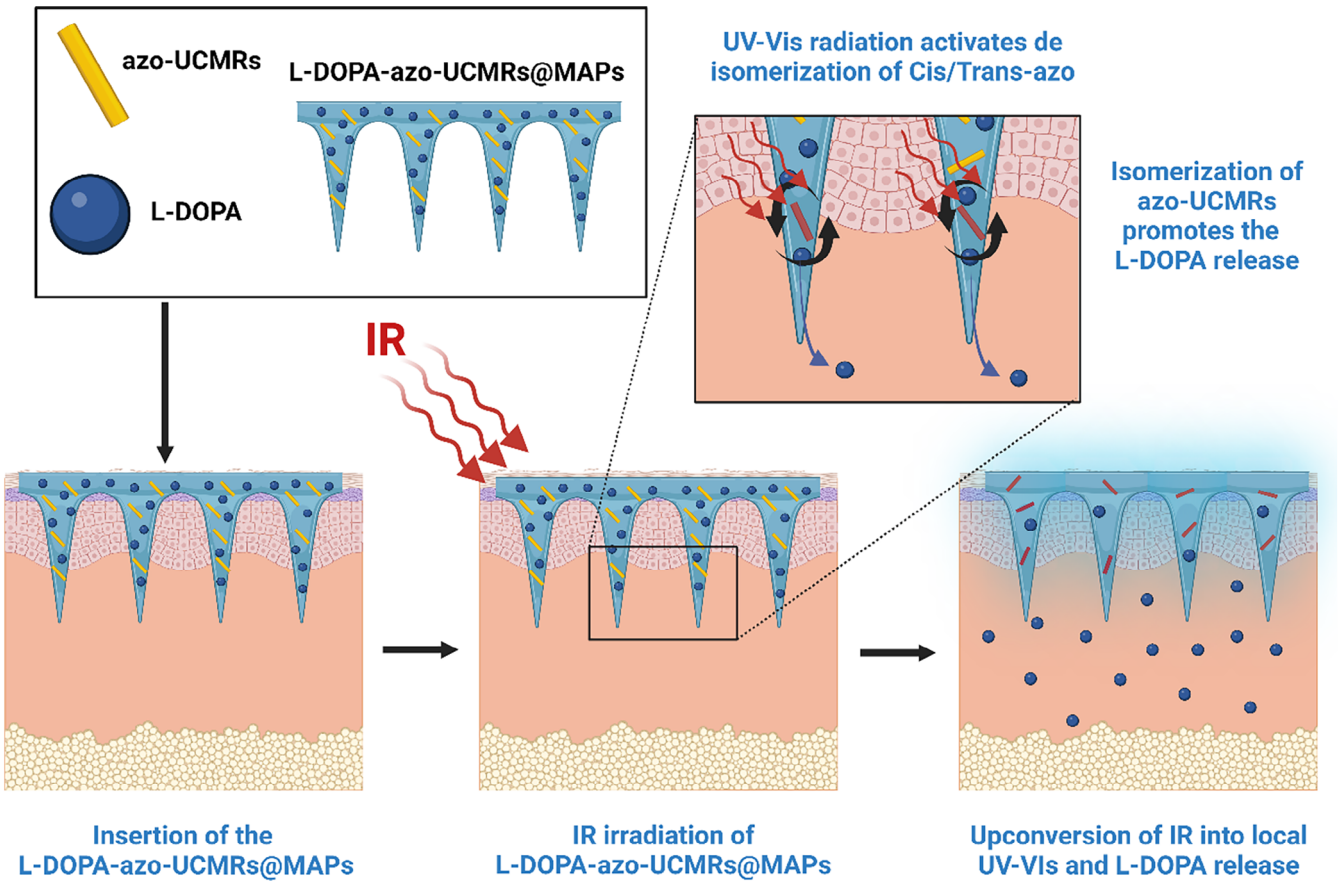

FIGURE 7 Schematic diagram of the transdermal drug delivery strategy of the L-DOPA-UCMRs@MAPs based on Zhou et al. work (Zhou et al., 2022). The L-DOPA-UCMRs@MAPs was designed to release drugs with spatial and temporal precision, triggered by NIR light. The MAPs are loaded with mesoporous silica upconvertion-nanorods (UCMRs). L-DOPA is stored in the (UCMRs). The NIR activates the isomeric upconversion of the azo compounds, which change from cis to iso conformation. This fact induces a rotatory movement that release the L-DOPA. IR, Infra-red; MAPs, microneedle array patches; MCs, micelle; NPs, nanoparticles.

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of azobenzene. Specifically, mesoporous silica upconversion-microrods (UCMRs) were loaded into the MAPs (L-DOPA-UCMRs@MAPs). The delivery mechanism lies in the activation of the reversible azo isomerization on the MS surface when the L-DOPA-UCMRs@MAPs are irradiated with NIR and upconversing agents transforms the IR light into UV–vis light to avoid skin cells damage. The continuous rotation of the azo molecules triggered by UV–vis light, activates the instant release of L-DOPA. The system was challenged in an in vivo model where Parkinson-induced rats showed symptoms reduction in behavioral tests after application of a major NIR rate to L-DOPA-UCMRs@MAPs, compared with free L-DOPA doses and L-DOPA-UCMRs@MAPs without NIR irradiation, proving the efficacy of these nano-motor based release.

Another example of smart delivery are the Glucose-sensitive patches developed by Tong et al. (Tong et al., 2018). PVP-PVA MAPs were prepared with insulin-loaded polymeric vesicles made of glucose and H_2O_2-sensitive polymers, poly (phenylboronic acid) and poly (phenyl boronic acid pinacol ester), respectively. Vesicles were additionally coated with glucose oxidase, which produces an extra amount of hydrogen peroxide from glucose that accelerates the cargo release by the poly (phenyl boronic acid pinacol ester) bond breakage. These Glucose-sensitive NPs@MAPs were shown as an interesting alternative to subcutaneous injections in a type-2 diabetic rat model, since they decreased their glucose levels from 500 to 110 mg/dl in 4 h that gradually increased until the baseline levels after 8 h, achieving normoglycemic levels (<200 mg/dl) for 4 h. In comparison, subcutaneous injection produced a baseline glucose levels dropdown to 80 mg/dl in only 2 h with a faster restoring of basal levels after only 5 h, leading to only 2.5 h of normoglycemic state. The use of stimuli-responsive MAPs has also been explored (Ullah et al., 2021). Duong et al. based their smart system in the use of a pH-sensitive MAPs that were getting dissolved only at physiological pH to improve the results of a DNA vaccine (Duong et al., 2018). DNA polyplexes, an adjuvant and heparin were included in a triblock pH-sensitive copolymer and oligo-(sulfamethazine)-b-poly (ethyleneglycol)-b-poly-(beta-aminoester urethane). The molecular basis of the system relies in the cationic ternary amine structure and anionic sulfonamide groups of the copolymer, which provides a positive charge at pH 4.03, allowing the interaction with heparin. At physiological pH, this charge switches to negative, triggering the patch structure disassembling and releasing its cargo. In an in vitro transfection study, the cellular uptake was confirmed using the macrophages RAW 264.7 cell line, and the system was able to elicit a specific immune response against the antigen-encoding DNA in an in vivo model.

5 | CONCLUSION

Nowadays, the NPs@MAPs is a growing field with a broad number of research articles published recently. In this review we aimed to survey representative articles in which the potential and range of biomedical applications of NPs@MAPs are highlighted. They work in a synergistic manner as MAPs open the pathway and allow NPs deposition in the deeper skin layers, which also exert a control in drug release. They can be used to achieve local and systemic effects, but vaccination and tailored therapies are fields where both NPs and MAPs have great potential due to their inherent characteristics. However, MAPs technology has not been translated towards a clinical experience yet—only several MAPs-based systems are now in clinical trials—(Jeong et al., 2020; Kang et al., 2021). This can be attributed to different causes that decrease the industrial interest, such as potential issues in scalability, the bench-to-bedside transfer process, or the lack of regulatory standards. The future of the NPs@MAPs will greatly depend on the collaborative framework that must be established between basic research, the industry, the healthcare providers and the regulatory organisms to overcome the troubles and limitations mentioned above to make clinical translation on NPs@MAPs a reality.

AUTHOR CONTRIBUTIONS

Antonio José Guillot: Conceptualization (lead); data curation (lead); investigation (lead); writing – review and editing (lead). **Miquel Martínez-Navarrete:** Investigation (supporting); methodology (supporting); validation (supporting); writing – original draft (supporting). **Valeria Zinchuk-Mironova:** Data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); writing – original draft (supporting). **Ana Melero:** Conceptualization (supporting); formal analysis (supporting); funding acquisition (lead); methodology (lead); project administration (lead); supervision (lead); validation (supporting); writing – review and editing (lead).

ACKNOWLEDGMENT

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FUNDING INFORMATION

This publication is part of the grant PID2020-114530GA-I00 funded by MCIN/AEI/10.13039/501100011033. A.J.G. acknowledges the financial support from "Atracció de Talent" grant (ref: UV-INV-PREDOC-18F2-743816) funded by the University of Valencia, and "Margarita Salas" grant (ref: MS21-126) funded by the Spanish Ministry of Universities and European Union (Next generation-EU).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

"Data sharing is not applicable to this article as no new data were created or analyzed in this study."

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How to cite this article: Guillot, A. J., Martínez-Navarrete, M., Zinchuk-Mironova, V., & Melero, A. (2023). Microneedle-assisted transdermal delivery of nanoparticles: Recent insights and prospects. *WIREs Nanomedicine and Nanobiotechnology*, e1884. https://doi.org/10.1002/wnan.1884

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