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Pluronic F127 表面穩定化 MOF 奈米粒結合可溶性微
針以提升經皮治療系統應用潛力

Pluronic F127 Surface-Stabilized MOF Nanoparticles
Integrated into Dissolving Microneedles for Improved
Transdermal Drug Delivery Systems

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MASTER'S THESIS ACCEPTANCE CERTIFICATE
NATIONAL TAIWAN UNIVERSITY

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Microneedles for Improved Transdermal Drug Delivery System

本論文係 黃芷欣 (R13524131) 在國立臺灣大學 化學工程學系 完成之
碩士學位論文，於民國 115 年 06 月 22 日承下列考試委員審查通過及口試及
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致謝



在開始進入這本碩士學位論文前，我想借此機會感謝出現在這兩年光陰的人。首先，我最想要感謝的是我的父親和母親。我的父母是我身後最堅強的依靠，就像一顆可遮蔭又可避雨大樹，是他們給予無限支持和底氣讓我可以持續綻放光芒。接下來，我想要感謝我的指導老師——吳嘉文教授，是教授給予無限的寬容和試錯，讓我可以實驗中大膽地去嘗試各種挑戰。除了實驗上，教授每次針對報告上的指導都讓我深切地知道不只要會做實驗，還要讓人明白和理解其內容，更不能把自己認為的理所當然當成是絕對。兩年的光陰裏也讓我在臺大認識了不少人。實驗室的學長姐和學弟妹絕對是在實驗上幫助和討論最多的人，沒有他們我的論文無法完成。實驗室的生活也多虧和他們一起的笑聲和怨聲，讓我的碩士生涯又變得更精彩一點了。我也想感謝臺大化工游佳欣教授、臺大獸醫蔡沛學教授、清大醫環李亦淇教授實驗室的同學們。如果沒有他們的幫助，我的實驗不可能可以這麼順利的完成。最後，我也想感謝一直在我身邊的朋友們，不管你們身在哪裏，非常感謝你們每次感受到我很困難時或是我的一句“在嗎？”，都可以立即送上一句關心。我想兩年的光陰裏學習到的不只是知識，更多的是待人處事。我在致謝的最後也想要感謝自己，在無數次的放棄和掙扎中，最後成功堅持下來了，辛苦了。未來茫茫，但是當我回過頭時，我想我還是很感謝這兩年光陰的一切。在此也想要引用愛因斯坦的一句名言：

If we knew what it was we were doing, it would not be called research, would it?

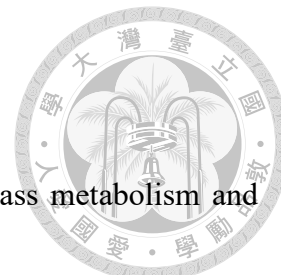
摘要



經皮治療系統能有效避免肝臟的首過效應並提升患者的方便性，具有極大的優勢。然而，皮膚角質層的屏障作用大幅限制了其實際應用。為了克服此瓶頸，本研究應用以 Pluronic F127 表面穩定處理的 MIL-100(Fe) 奈米粒子，嵌入聚乙烯吡咯烷酮與羧甲基纖維素 (PVP/CMC) 的混合高分子基質中，開發出一款複合性溶解型微針貼片。實驗結果顯示，Pluronic F127 的表面修飾成功抑制了奈米粒子的聚集現象，並顯著提升其分散穩定性。XRD、FTIR、XPS、BET 及 TGA 等分析進一步證實了 Pluronic F127 表面修飾的成功。在微針製備上，含有 10 wt% PVP 與 5 wt% CMC 的高分子基質搭配針長 1000 μm 的微針幾何形狀設計，可提供微針貼片足夠的機械強度與良好的加工適性。體外豬皮測試證實該微針能有效於皮膚建立微通道。同時，體外釋放試驗也顯示微針基質能迅速溶解，並在 30 分鐘內達到約 96% 的累積藥物釋放率。總結而言，本研究成功驗證了將 Pluronic F127 包覆之 MIL-100(Fe) 結合至溶解型微針中的可行性，為奈米粒子輔助經皮治療平台提供一項具發展潛力的設計方向。

關鍵字：經皮治療系統，溶解型微針，PVP/CMC，MIL-100(Fe)，Pluronic F127，表面修飾

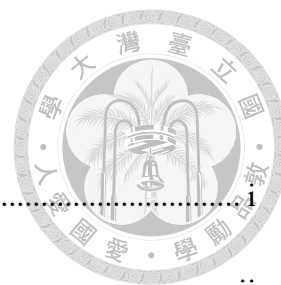
Abstract



Transdermal drug delivery systems can bypass hepatic first-pass metabolism and improve patient compliance, but their applications remain limited by the stratum corneum barrier. To overcome this challenge, this study developed a composite dissolving microneedle patch by incorporating Pluronic F127-stabilized MIL-100(Fe) nanoparticles into a polyvinylpyrrolidone/carboxymethylcellulose (PVP/CMC) matrix. Pluronic F127 surface modification effectively reduced nanoparticle aggregation and enhanced dispersion stability, and this successful surface modification was supported by XRD, FTIR, XPS, BET, and TGA analyses. Microneedles prepared from 10 wt% PVP + 5 wt% CMC with a 1000 μm microneedle geometry exhibited sufficient mechanical strength and suitable processability. *Ex vivo* porcine skin tests confirmed effective microchannel formation, and *in vitro* assays revealed that the cumulative release of the model payload reached approximately 96% within 30 min. In summary, this study validates the integration of PF127-MIL-100(Fe) nanoparticles into dissolving microneedles as a promising strategy for nanoparticle-mediated transdermal drug delivery.

Keywords: transdermal drug delivery, dissolving microneedle, PVP/CMC, MIL-100(Fe), Pluronic F127, surface modification

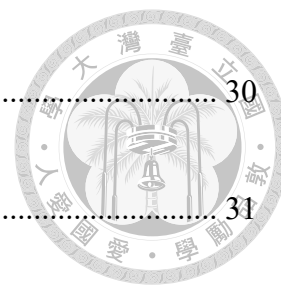
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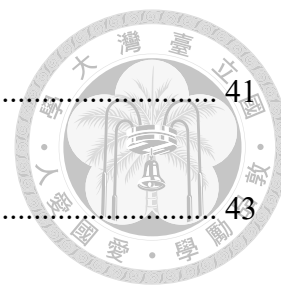
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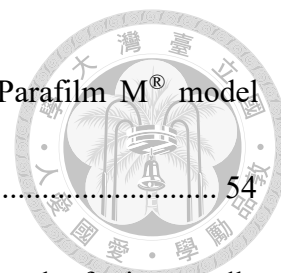


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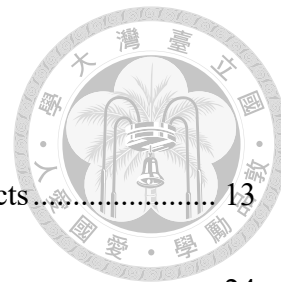


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1. Introduction

1.1. Transdermal drug delivery systems

Drug Delivery Systems (DDSs) have been developed to deliver therapeutic agents to target sites through various administration routes, including oral, transdermal, inhalation, mucosal, and intravenous routes.[1] In recent years, transdermal drug delivery systems (TDDSs), which are designed to transport therapeutic agents across the skin surface, have provided an attractive alternative compared with other administration routes.[2] TDDSs are less affected by gastrointestinal absorption and hepatic first-pass metabolism, while their noninvasive nature enables self-administration.[3] Compared to the traditional injections, TDDSs can reduce pain sensation and hazardous sharps waste because their application does not require needles and specialized skilled personnel.[4] Therefore, the TDDSs represent a potential strategy to improve patient compliance and enhance therapeutic effectiveness. However, a key challenge for TDDS products is skin permeability, as the drug molecules are required to diffuse through multiple layers of the skin.[5] Human skin is composed of multiple layers including epidermis, dermis, and subcutaneous tissue. The outermost skin layer, the stratum corneum (10-20 μm), consists of a dense lipid-rich structure that serves as the primary barrier to drug delivery, especially for high-molecular-weight drugs and nanoparticle carriers. [6, 7] As shown in Figure 1.1,

topical creams are mainly distributed on the skin surface, with only 10-20% of the total loaded drug reported to permeate through the skin. Hypodermic needles can deliver 90-100% of the loaded drug, but their deep penetration into the dermis, where pain receptors are located, often cause pain and lead to poor patient compliance.[8] Therefore, TDDSs have been developed as an alternative approach to deliver drugs across the skin barrier.

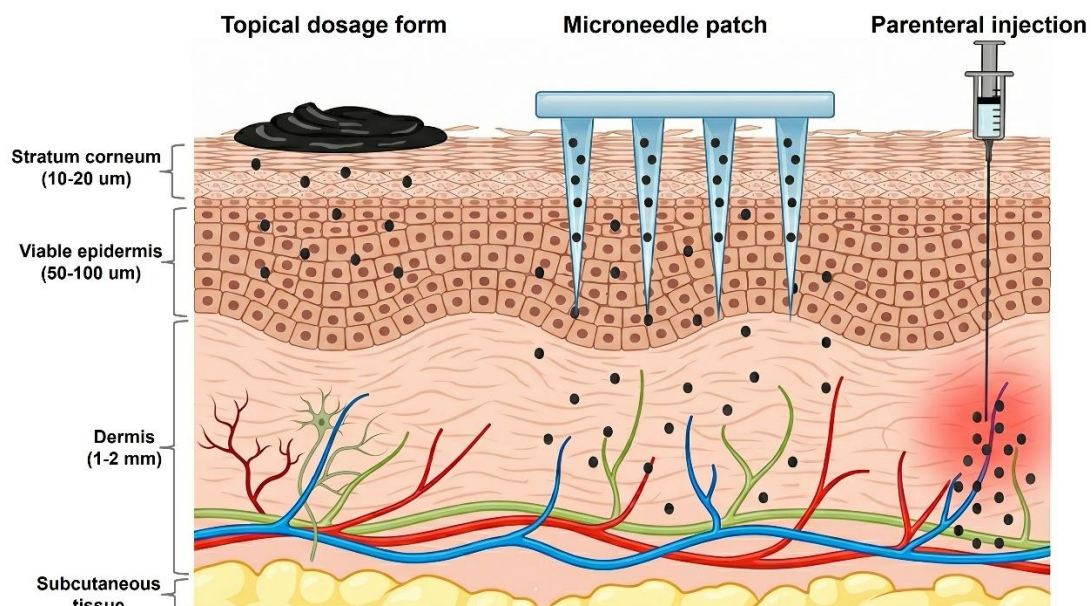


Figure 1.1 Transdermal drug delivery systems and skin barriers. [9]

1.2. Microneedle drug delivery systems



Conventional TDDSs, such as electrical methods and chemical enhancers, can improve skin permeability to some extent but remain limited for the delivery of large molecules.[8, 10] In contrast, microneedle technology provides a physical approach to bypass the stratum corneum and form temporary channels in the outer skin layer, thereby improving drug delivery efficacy. These properties have promoted the development of microneedles to overcome the limited permeability of conventional TDDSs. As micron-scale devices, microneedles also enable the delivery of therapeutic compounds that are normally unsuitable for conventional transdermal routes, especially macromolecules. At the same time, microneedles are designed to be long enough to penetrate the stratum corneum while remaining short enough to reduce contact with deeper nerve endings, making the treatment nearly painless.[11] As a result, patients may be more likely to use microneedle-based systems because they are minimally invasive and nearly painless.[12]

Microneedle drug delivery systems are commonly classified into five types based on their structure and delivery mechanisms, including solid, hollow, coated, hydrogel-forming, and dissolving microneedles.[13] Each type has specific advantages and limitations in drug delivery applications. Solid microneedles offer excellent mechanical strength, but their two-step procedure is inconvenient and generates dangerous sharp waste. Hollow microneedles are hindered by the necessity of external syringes and

frequent clogging issues, while coated microneedles struggle with coating peeling and formulation migration, severely reducing dosing accuracy. Furthermore, hydrogel-forming microneedle variants rely on fluid absorption, presenting the unintended risk of extracting biological fluids.[14] To address these limitations, dissolving microneedles have emerged as a highly promising solution.

Dissolving microneedles made from biocompatible and water-soluble materials have attracted particular attention because their fabrication is relatively low-cost and can be performed under mild processing conditions.[15] Dissolving microneedles deliver drugs through a “poke-and-release” mechanism, in which they first create microchannels in the skin and then dissolve to release the encapsulated drug into these channels.[12] As dissolving microneedles fully dissolve during application, they reduce the needle disposal concerns and risk of secondary infections caused by needle reuse. In addition, the use of dissolving microneedles is based on a one-step application process which is convenient for patients.[16] Dissolving microneedles have emerged as promising drug delivery platforms because they offer several advantages, including improving drug efficacy and safety, as well as ease of self-application.

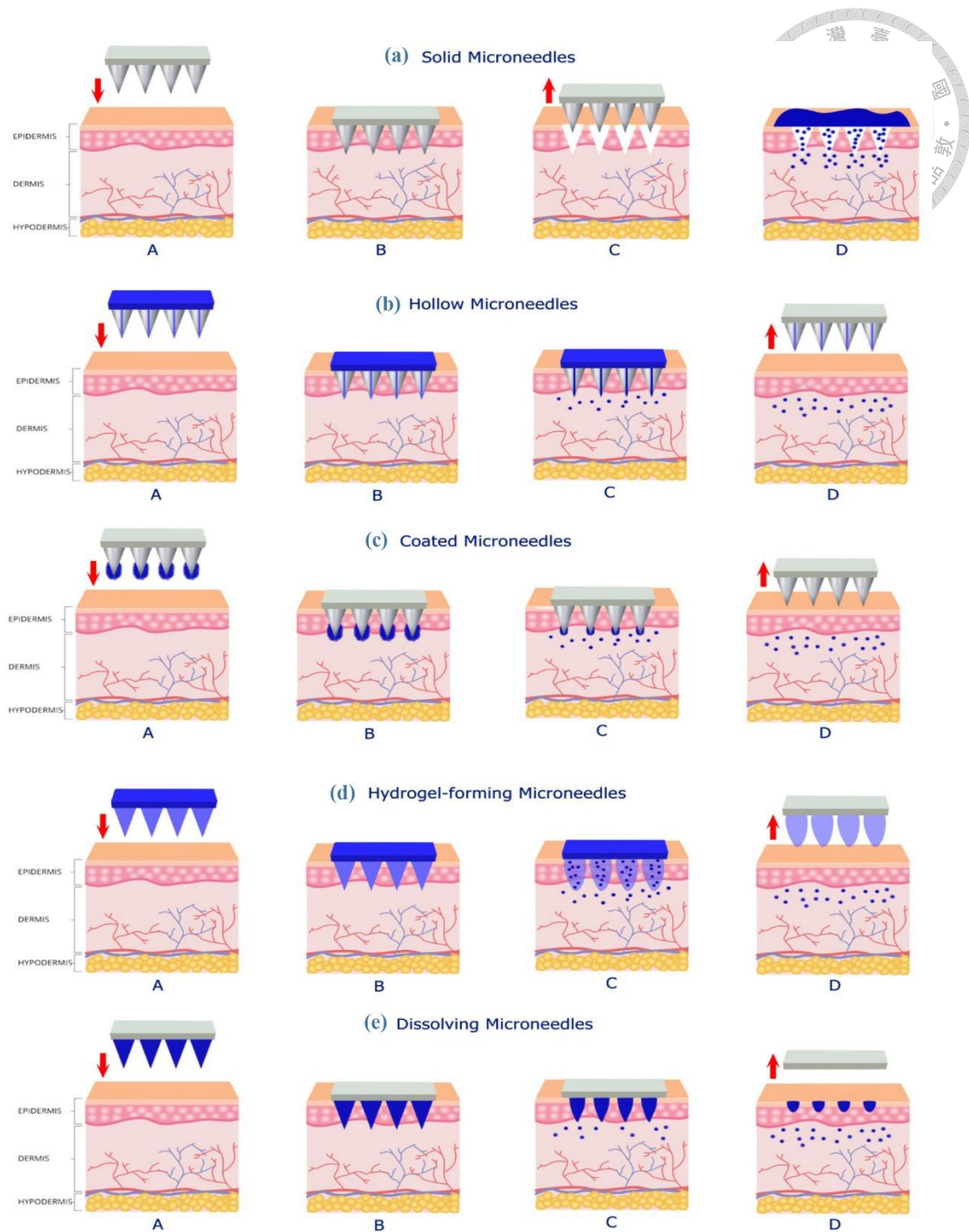


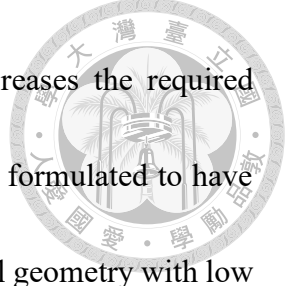
Figure 1.2 Graphical representation of different microneedle types: (a) solid, (b) hollow, (c) coated, (d) hydrogel-forming, and (e) dissolving microneedles.[11]

1.3. Microneedle material and geometry



Material selection is essential for dissolving microneedles because the material properties strongly affect mechanical strength and consequently influence skin penetration behavior.[17] Polyvinylpyrrolidone (PVP) and carboxymethylcellulose (CMC) are FDA-approved biocompatible polymers that have been widely applied in dissolving microneedle fabrication for transdermal drug delivery.[18-20] Although PVP is commonly used as a microneedle matrix, PVP-only microneedles are fragile and prone to bend or break.[21] Chen *et al.* demonstrated that PVP can be blended with other polymers to improve mechanical properties.[22] In particular, the combination of PVP and CMC has been shown in previous studies to positively affect mechanical strength.[23, 24] This improvement is primarily attributed to the abundant hydroxyl groups in CMC, which can form hydrogen bonds with PVP and generate physical crosslinking within the matrix, thus further enhancing the mechanical strength of microneedles.[25] Therefore, a PVP/CMC blend was selected as the matrix of dissolving microneedles to achieve satisfactory mechanical properties.

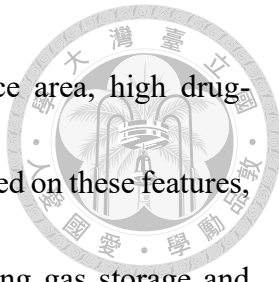
The mechanical properties and skin penetration behavior of microneedles are determined not only by material composition, but also by microneedle geometry, including shape, base diameter, length and interspacing.[17, 26] Park *et al.* showed through mechanical testing that a wider needle base diameter increases the force required



to cause microneedle failure, whereas a longer needle length decreases the required force.[27] Lee *et al.* also showed that dissolving microneedles were formulated to have sufficient mechanical strength to insert into skin by using a pyramidal geometry with low aspect ratio, defined as the needle length divided by the base diameter.[28] Visscher *et al.* recommended an optimal geometry with a length of 600 to 1000 μm , an aspect ratio between 2 and 4, and a spacing of no less than 300 μm . [29] Consequently, these established geometric guidelines serve as the design foundation for fabricating microneedle arrays that enable sufficient skin insertion.

1.4. Metal-organic frameworks (MOFs)

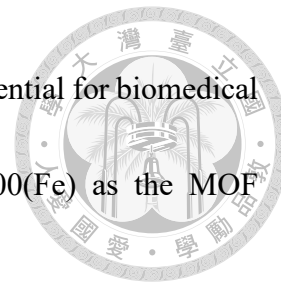
Beyond optimizing polymer composition and microneedle geometry, the integration of functional nanocarriers has recently gained attention as a strategy to improve the versatility and delivery performance of microneedle systems. Among the nanocarriers, MOFs are promising candidates for microneedle integration because their porous structures and large surface areas can provide potential advantages for payload incorporation within the limited loading volume of microneedles.[30] MOFs, which are crystalline materials assembled from metal nodes and organic ligands, have been extensively developed over the past two decades.[31] MOFs offer several advantages,



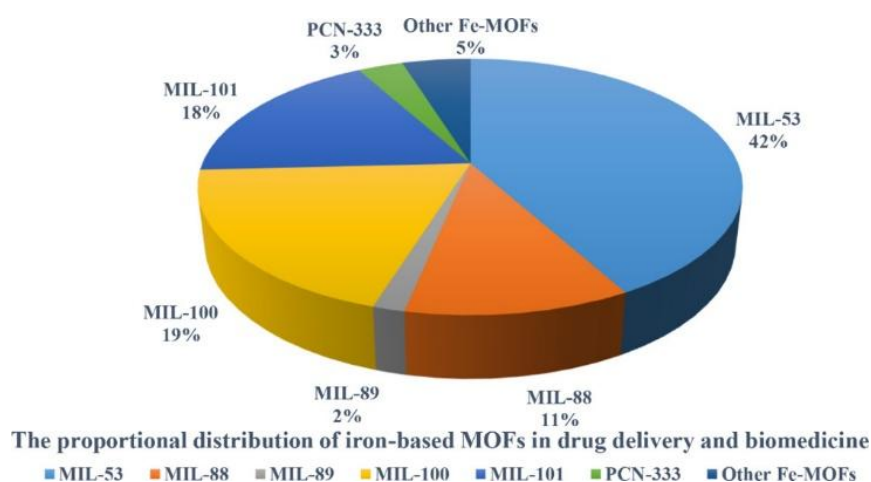
including tunable pore sizes, high selectivity, large specific surface area, high drug-loading capacity, good biocompatibility, and modifiable surfaces. Based on these features, MOFs have been widely explored for diverse applications, including gas storage and separation, catalysis, and energy conversion and storage. In biomedical applications, MOFs have also been investigated as functional alternatives to traditional nanomaterials.[32] However, without an assisted delivery platform, MOF nanoparticles often have limited ability to penetrate the superficial skin layers and may remain near the surface of the wound, thereby reducing their therapeutic effectiveness. Therefore, MOF-integrated microneedle systems provide a promising platform for overcoming the skin barrier and improving localized drug delivery. Previous studies have also shown that MOFs can be directly encapsulated into microneedles for biomedical applications, such as wound healing.[33]

Among the MOFs, MIL-100(Fe), which is composed of iron clusters connected by organic linkers, has attracted biomedical interest because of its relatively low toxicity. In addition, iron is an essential trace element present in the human body at approximately 4 g.[31, 34] Horcajada *et al.* further supported the biocompatibility of MIL-100(Fe) by showing that empty MIL-100 nanoparticles did not exhibit detectable toxicity in the tested cell lines at concentrations up to 10 mM.[35] As shown in Figure 1.3a, MIL-100(Fe) represents 19% of reported therapeutic applications among iron-based MOFs and ranks

as the second most frequently used material, indicating its strong potential for biomedical applications.[36] These findings support the selection of MIL-100(Fe) as the MOF component to integrate with microneedle systems.



(a)



(b)

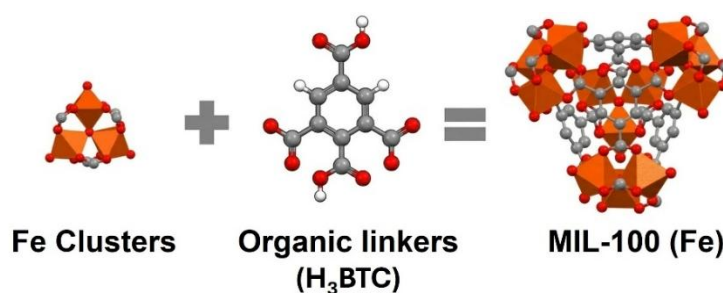


Figure 1.3 (a) Distribution of iron-based MOFs in biomedical applications [36] and

(b) schematic structure of MIL-100(Fe).[37]

1.5. Limitations of MOF nanoparticles



A common drawback in the processing and application of MOF nanoparticles is their tendency to aggregate. For MIL-100(Fe) nanoparticles, this aggregation arises from a low zeta potential, which fails to provide sufficient electrostatic repulsion between particles.[38] Furthermore, Bellido *et al.* reported that in standard physiological salt solutions, electrolytes such as NaCl and CaCl₂ can screen electrostatic repulsion forces, leading to irreversible aggregation of MIL-100(Fe) nanoparticles.[39] After exposure to biological fluids rich in proteins and salts, the nanoparticles may continue to aggregate and form micron-sized clusters. The formation of large aggregates may raise safety concerns, including vascular thrombosis, blood vessel occlusion, embolism, and blood platelet aggregation, leading to higher toxicity.[40, 41] At the same time, MIL-100(Fe) nanoparticles are prone to rapid reticuloendothelial system (RES) clearance in complex biological fluids because of fast opsonization. This process involves protein adsorption onto the outer surface of MIL-100(Fe), which promotes macrophage recognition and reduces *in vivo* circulation half-life, as demonstrated by Baati *et al.*[42-45] Therefore, aggregation and rapid clearance of MIL-100(Fe) nanoparticles need to be overcome as they severely limit bioavailability and reduce their *in vivo* persistence.

1.6. Surface modification

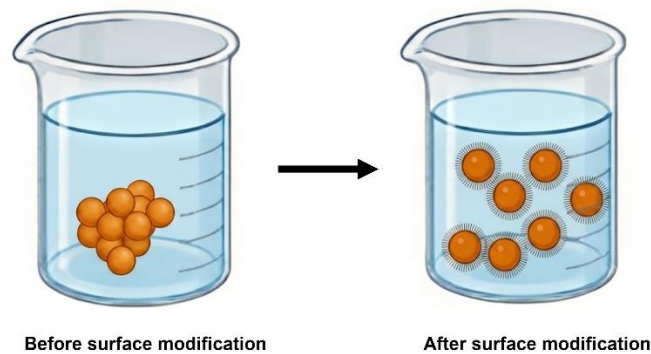


One effective way to maintain the surface stability of MOFs in biological settings for drug delivery applications is to modify their outer surface. Previous studies have shown that the surface modification of MOFs not only enhances their chemical and colloidal stability in physiological environments but also improves the bioactivity and enables *in vivo* delivery.[46, 47] Furthermore, surface modification can provide MOF nanoparticles with stealth-like properties, preventing nonspecific protein adsorption onto their surfaces and reducing clearance by the RES.[43, 48] Among various modifications, Pluronic F127 is a nonionic amphiphilic copolymer widely used in DDSs and composed of poly-ethylene oxide (PEO) and poly-propylene oxide (PPO) in an ABA triblock arrangement (PEO–PPO–PEO).[49, 50] The outer PEO chain of Pluronic F127 can confer antifouling properties to prevent nanoparticle aggregation. This stabilizing effect was reported by Barjasteh *et al.*, who observed improved colloidal stability of MIL-100(Fe) after PEO coating.[51] In addition, Li *et al.* reported that PEO can effectively inhibit protein adsorption and RES recognition, thereby prolonging the blood circulation of nanoparticles.[52] Pluronic F127 coating not only improves dispersion of MIL-100(Fe) but also provides stealth-like behavior that may reduce clearance by the body's innate immune system. Based on these considerations, the integration of Pluronic F127-stabilized MIL-100(Fe) nanoparticles into dissolving microneedles may provide a

feasible strategy for improving nanoparticle stability while enabling localized transdermal delivery.



(a)



(b)

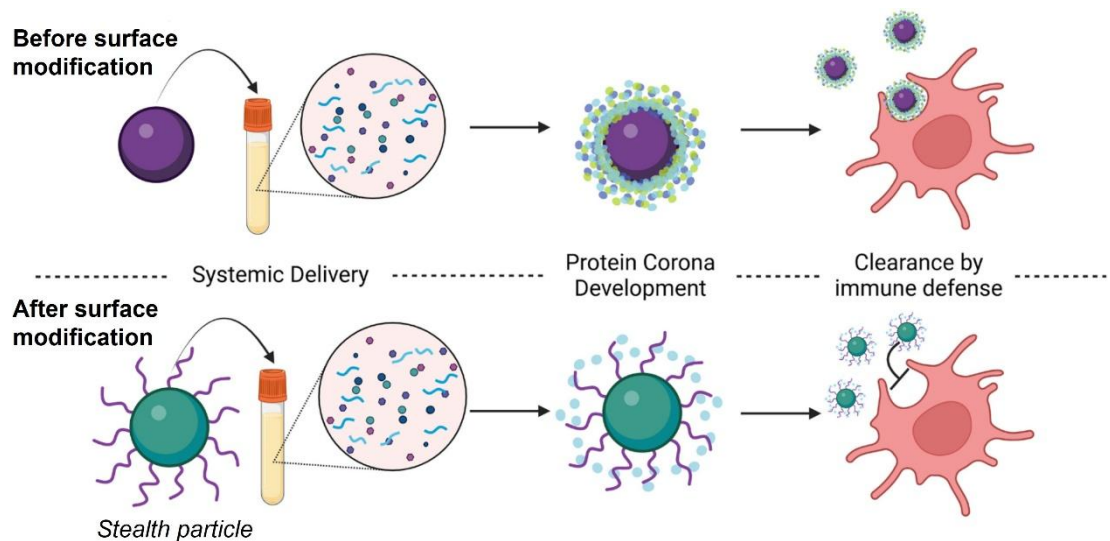


Figure 1.4 Schematic representation of the effects of nanoparticle surface modification: (a) improving colloidal dispersion by preventing aggregation, and (b) providing stealth properties to minimize protein corona formation and immune clearance.

2. Literature Review



2.1. Marketed and clinical-stage dissolving microneedles

Table 2.1 Marketed and clinical-stage dissolving microneedle products

Product	Manufacturer	Drug and Purpose	Reference
MicroHyal	CosMED, Japan	Triple-helical collagen, hyaluronic acid, skin aging treatment	[53]
Acropass	Raphas Co., Ltd, South Korea	Hyaluronic acid, Epidermal Growth Factor (EGF) moisturizing, anti-aging	[54]
I'm Fill	Karatica Co., Ltd, South Korea	Hyaluronic acid, acetylhexapeptide-8 moisturizing, anti-aging	[54]
Needle Patch	Nissha Co., Ltd, Japan	Hyaluronic acid skin care	[54]
Micro Patch	Junmok International Co., Ltd., South Korea	Hyaluronic acid, lactose moisturizing, anti-aging	[54]
Royal skin hyaluronic acid micro patch	Micron Biomedical, USA	Poly(lactic-co-glycolic) acid (PLGA), influenza and contraceptive drug delivery	[55]

2.1.1. Hyaluronic acid (HA) microneedles



Hyaluronic acid (HA) is the most commonly used matrix material for commercial dissolving microneedles as it is a water-soluble polymer, naturally present in skin tissue, and offers excellent biocompatibility. HA-based microneedles offer a relatively painless delivery method that eliminates biohazardous sharps waste and prevents intentional reuse of needles. HA-based microneedles have gained substantial momentum in the cosmetic field for anti-aging and skin moisturizing, with commercialized products such as Acropass and I'm Fill Needle Patch already available on the market, as listed in Table 2.1. Another prominent example of HA-based microneedles is the MicroHyal[®] patch developed by CosMED Pharmaceutical Co., Ltd., Japan, a dissolving microneedle platform evaluated for transcutaneous drug delivery. This HA-based microneedle patch has been used to induce prolonged antigen deposition within the tissue and produce stronger immune responses compared to traditional injections. However, the mechanical strength of the microneedles can be significantly weakened by high environmental humidity and loading with therapeutic agents like all-trans retinoic acid (ATRA) or ovalbumin. Therefore, further improvements to their baseline mechanical strength remain a critical focus to ensure reliable skin insertion without structural failure.[53]

2.1.2. Poly(lactic-co-glycolic) acid (PLGA) microneedles



For commercial development of biodegradable systems, Micron Biomedical, one of the prominent microneedle companies, has exclusively licensed a microneedle technology developed by Li *et al.* This technology administers a long-acting contraceptive for more than 30 days by using poly(lactic-co-glycolic) acid (PLGA), a hydrophobic and slowly biodegradable polymer, as microneedle material with a 40% loading of levonorgestrel (LNG), a well-established contraceptive hormone. In rat models, the microneedles successfully maintained the contraceptive hormone above the human therapeutic threshold for over a month. Furthermore, multi-continental qualitative research has revealed that the convenience and discreteness of microneedle arrays make them a highly preferred platform for administering long-acting contraceptives among female users.[55] Based on this positive clinical potential, Micron has planned a clinical development program that includes three Phase 1 and three Phase 2 trials.

2.2. Previous studies on PVP-CMC based microneedles

Dissolving microneedles are commonly fabricated from water-soluble materials, such as polyvinyl alcohol (PVA), PVP, chondroitin sulfate, dextran, CMC, and HA, which can dissolve completely after insertion and reduce biohazardous sharps waste after use.[12] These polymers have various levels of biodegradability, biocompatibility, and

mechanical properties, but single-polymer matrices may not balance all required properties at the optimum level.[56] Therefore, polymer blends are increasingly used to optimize microneedle performance.



2.2.1. Blends of natural and synthetic polymers

Several researchers have investigated combinations of natural and synthetic polymers for biomedical applications. Natural polymers, such as collagen, chitosan, cellulose, silk and elastin usually offer excellent biocompatibility and biodegradability, making them primary choices for biomedical applications. Although natural polymers are highly biocompatible, their mechanical performance can be limited. In contrast, synthetic polymers generally provide better mechanical properties, which can offset this limitation.[57] Blending two or more polymers enables the integration of natural-polymer biocompatibility with the mechanical and physicochemical properties of synthetic polymers.[56] In addition, the blending of biodegradable polymers offers a practical route to reduce the overall cost and time required for developing new polymer systems, while allowing the adjustment of material properties and degradation rates.[58] This time-saving approach offers a simple way to combine the advantages of different polymers and is highly beneficial for TDDSs.[59]



2.2.2. Physical crosslinking of PVP-CMC

The most common interactions in polymer blends include hydrogen bonding, ionic interactions, dipole-dipole interactions, π -electron interactions and charge-transfer complexes.[57] Hydrogels formed through such reversible intermolecular interactions are called physically crosslinked hydrogels. This type of hydrogel also offers superior biocompatibility by eliminating the need for chemical crosslinking agents, thereby avoiding the cytotoxicity risks associated with unreacted chemical residues.[60]

A representative physically crosslinked hydrogel is the PVP/CMC blend, which combines PVP as a synthetic polymer with CMC as a natural polymer to improve microneedle performance. Hydrogen-bonding interactions between PVP and CMC have been widely reported in previous studies. Abdelghany *et al.* discussed that the interaction mechanisms between PVP and CMC involve dual bonding pathways. The primary hydrogen-bonding interactions occur between the acceptor carbonyl oxygen (C=O) in the pyrrolidone ring of PVP and the donor hydroxyl (–OH) groups on the anhydroglucose units of CMC. Additionally, potential ionic interactions can form between the carboxylate groups (–COONa) of CMC and the partially positive polarized hydrogen atoms on the pyrrolidone ring of PVP.[61] Lü *et al.* also showed the presence of the intermolecular hydrogen bonding interactions between PVP and CMC through peak shifts in Fourier transform infrared (FTIR) spectra.[62] In agreement with these results, Roy *et al.* also

mentioned that the mechanical strength of the PVP/CMC hydrogels is significantly reinforced by the generation of additional intermolecular hydrogen bonds.[24] Therefore, the physical interactions between PVP and CMC can support their use as a matrix to improve the mechanical strength of microneedles.

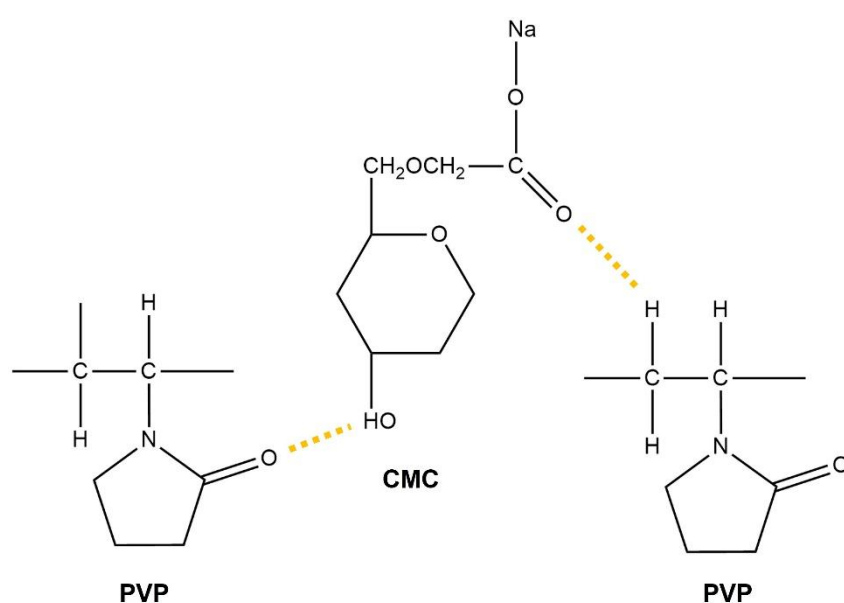


Figure 2.1 Chemical structure illustrating the intermolecular interactions and physical crosslinking network within the PVP/CMC polymer blend.

2.2.3. Previous studies on PVP/CMC-based microneedles



2.2.3.1 Preparation and properties of PVP/CMC soluble microneedles

Qiang *et al.* investigated the material optimization of soluble microneedles by evaluating different mass percentages of PVP and sodium carboxymethyl cellulose (CMC-Na). Using a centrifugal mold casting method, they showed that a formulation of 10 wt% PVP/2 wt% CMC-Na produced the best-performing microneedles. At this specific ratio, the microneedles formed a regular, smooth conical shape and possessed superior mechanical strength for effective skin penetration. Additionally, this optimal blend yielded the highest thermal decomposition temperature (379.8°C) and melting temperature (91°C) among the tested ratios, including 30 wt% PVP/3 wt% CMC-Na and 20 wt% PVP/3 wt% CMC-Na.[45]

2.2.3.2 Dissolvable PVP/CMC microneedle arrays for cutaneous leishmaniasis treatment

Zare *et al.* developed a dissolvable microneedle patch using a mixture of PVP (10% w/v) and CMC (1% w/v) to deliver Amphotericin B (AMB) (0.5% w/v), a common effective drug with poor skin permeability for cutaneous leishmaniasis (CL). This study demonstrated that PVP/CMC-based pyramidal microneedles have the mechanical strength to pierce the skin, where they rapidly dissolve to deliver AMB into the lower

skin layers. The patches were non-toxic to cells and exhibited potent *in vitro* leishmanicidal activity, causing up to 86% death of Leishmania parasites.[63]



2.3. MOF-integrated microneedles

As mentioned in section 1.4, MOFs have gained attention in biomedical research because of their tunable structures and functional properties. Recently, MOF nanoparticles have been integrated with microneedle systems to protect them from premature degradation and enable direct transdermal delivery. MOF-integrated microneedles have been explored in several biomedical fields, including infected wound treatment, cosmetic delivery, and cancer therapy. For infected wound healing treatment, some MOF-integrated microneedles have been designed to release antibacterial metal ions such as Zn^{2+} , Cu^{2+} , and Ag^+ . These released ions may contribute to the antibacterial activity of the corresponding MOFs through multiple mechanisms, including reactive oxygen species (ROS) generate, bacterial cell wall disruption, lipid peroxidation, enzyme deactivation, and inhibition of protein-SH groups.[64]

Among MOF-integrated microneedle systems, MIL-100(Fe)-based microneedles have also been employed to develop cosmetic transdermal patches. For example, caffeine was successfully encapsulated within MIL-100(Fe) and the resulting MOFs were integrated into polyvinyl alcohol (PVA)- and gelatin-based patches. Skin permeation tests

have shown that these MIL-100(Fe) patches are highly effective at regulating the sustained, transdermal release of caffeine over a 24 to 48-hour period.[65]



In addition, Luo *et al.* developed MIL-100(Fe)-based microneedles that are engineered to deliver the chemotherapeutic drug doxorubicin (DOX) and the photosensitizer zinc phthalocyanine (ZnPc) for effective chemophototherapy of hypoxic superficial tumors. In this system, the MIL-100(Fe) serves as both a protective carrier and a catalyst for decomposing intracellular hydrogen peroxide to generate oxygen in the tumor microenvironment by Fenton-like reaction. The loaded MIL-100(Fe) nanoparticles were further coated with Pluronic F127 to maintain colloidal stability and prevent aggregation. By adopting a dissolving microneedle technique, the nanoplatform was delivered directly into superficial tumors rather than relying on systemic circulation. As a result, this study demonstrated increased apoptotic rates and reduced cancer cell proliferation *in vivo*. [66]

3. Objective



This study aims to establish an integrated transdermal drug delivery platform by incorporating surface-stabilized MOF nanoparticles into a dissolving polymer microneedle patch. The research focuses on two main components, which are the microneedle platform and the surface modification of MOF nanoparticles. First, a dissolving microneedle matrix based on a blend of PVP and CMC is formulated, aiming to improve mechanical strength compared to pure PVP or CMC microneedles. This blend is optimized by evaluating polymer composition, mechanical properties, and insertion ability. At the same time, different needle geometries are compared using mechanical strength testing and a Parafilm M[®] skin model to identify the optimal design for effective skin penetration. Subsequently, MIL-100(Fe) nanoparticles are synthesized and their surfaces are modified with Pluronic F127 to improve colloidal stability and introduce stealth-like surface characteristics that may reduce clearance by the RES. These modified MIL-100(Fe) nanoparticles are thoroughly characterized to confirm the successful surface modification. The overall performance of the optimized MOF-integrated microneedle system is then demonstrated by conducting *ex vivo* porcine skin insertion tests and *in vitro* release experiments using Rhodamine 6G as a model payload to confirm successful penetration of the stratum corneum.

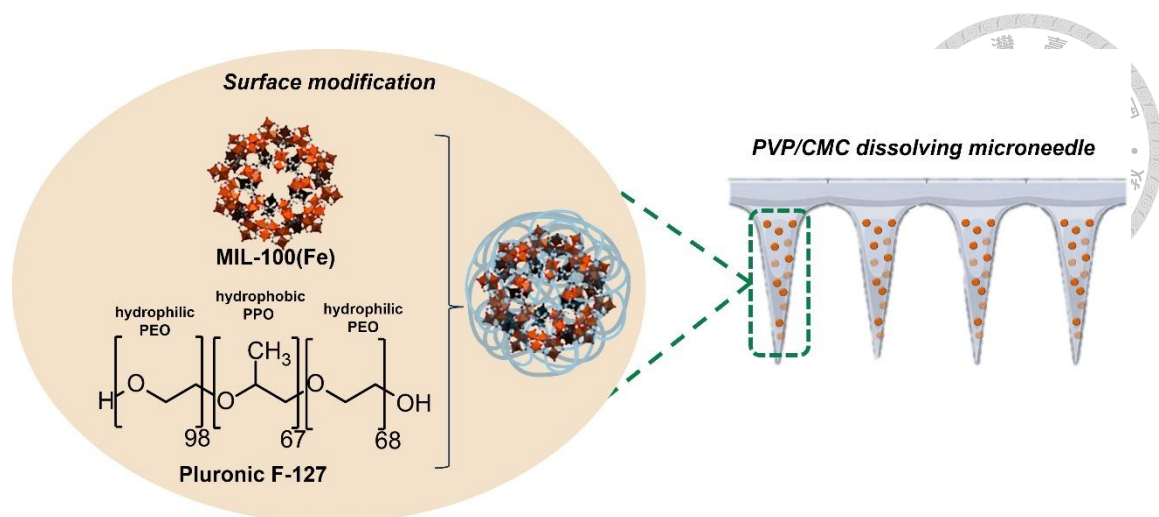


Figure 3.1 Schematic overview of the research objective.

4. Experimental



4.1. Materials

Table 4.1 Materials

Chemical	Formula	Information
Iron (III) chloride hexahydrate	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	Sigma Aldrich
Benzene-1,3,5-tricarboxylic acid	$\text{C}_9\text{H}_6\text{O}_6$	Sigma Aldrich
Pluronic® F-127	$(\text{C}_3\text{H}_6\text{O} \cdot \text{C}_2\text{H}_4\text{O})_n$	Sigma Aldrich
Polydimethylsiloxane (PDMS)	$(\text{C}_2\text{H}_6\text{OSi})_n$	Dow Corning
Sodium carboxymethyl cellulose (CMC)	$\text{C}_8\text{H}_{15}\text{NaO}_8$	MW=90000 Da, Sigma Aldrich
Polyvinylpyrrolidone (PVP)	$(\text{C}_6\text{H}_9\text{NO})_n$	MW=360000 Da, Sigma Aldrich
Rhodamine 6G	$\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_3\text{Cl}$	~95%, Sigma Aldrich
Phosphate-buffered saline (PBS)	N/A	10X

Porcine skin N/A N/A

Parafilm M[®] N/A Bemis

Company Inc.,

Soignies, Belgium



4.2. Equipment

Table 4.2 List of equipment

Equipment	Manufacturer
X-ray diffractometer (XRD)	Rigaku MiniFlex
Dynamic light scattering (DLS)	Malvern, Zetasizer Nano ZS
Brunauer-Emmett-Teller (BET)	Belsorp-max II
Fourier-transform infrared spectroscopy (FTIR)	Perkin Elmer Spectrum 100
X-ray photoelectron spectroscopy (XPS)	Thermo Scientific, Nexsa G2
Centrifuge	Himac. CT18R
Sonicator	Delta
Hotplate	Thermal Scientific
Microwave reactor	Biotage [®] Initiator ⁺



Ultrasonic sonicator	Qsoinca Q700
Ball milling	Ants Scientific Instruments, AM410
Thermogravimetric analysis (TGA)	TA Instruments, SDT 650
Texture Analyzer	Stable Microsystem Ltd, Surrey, UK, TA.XTplusC
Scanning Electron Microscopy (SEM)	Hitachi, S-4800
Stereo microscope	Olympus SZ61
Optical microscope (OM)	Olympus IX73
Fluorescent microscopy	Olympus IX71
Microplate reader	BioTek Cytation 7 Cell Imaging Multi- Mode Reader

4.3. Synthesis of MIL-100(Fe)

The synthesis of MIL-100(Fe) was carried out using a microwave-assisted hydrothermal method.[47] Briefly, 2 mmol of iron(III) chloride hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) was dissolved in 20 mL of deionized water (DI water) in a Biotage microwave reaction vial. After the iron salt was fully dissolved, 1.3 mmol of trimesic acid (H_3BTC) was added to the solution. The mixture was then placed in the Biotage microwave reactor and pre-stirred for 5 min. The solution was subsequently heated to 130°C and maintained at this temperature for 2 min. After the reaction was completed, the resulting orange solution was cooled in an ice bath and then the precipitate was collected by centrifugation (11,000 rpm, 15 min). After washing twice with DI water, the final orange precipitate was resuspended in 20 mL of DI water for further use. Ball milling was conducted using 0.4 mm ZrO_2 balls at a sample-to-ball ratio of 1:2 for 30 cycles (1 min milling, 30 s rest) to obtain finer particle sizes.



Figure 4.1 Schematic illustration of the microwave-assisted synthesis and ball-milling process of MIL-100(Fe).

4.4. Synthesis of PF127-MIL-100(Fe)

The MIL-100(Fe) solution (10 mL, 1 mg/mL) was sonicated for 5 min before use.

Meanwhile, 10 mg of Pluronic F127 was dissolved in 20 mL of DI water under continuous stirring to obtain a homogeneous solution. Subsequently, the sonicated MIL-100(Fe) solution was added to the Pluronic F127 solution. The mixed solution was magnetically stirred at room temperature for at least 12 h. The product was collected by centrifugation (10,000 rpm, 8 min) and washed twice with water. Finally, the obtained precipitate was redispersed in 10 mL of DI water for future use.

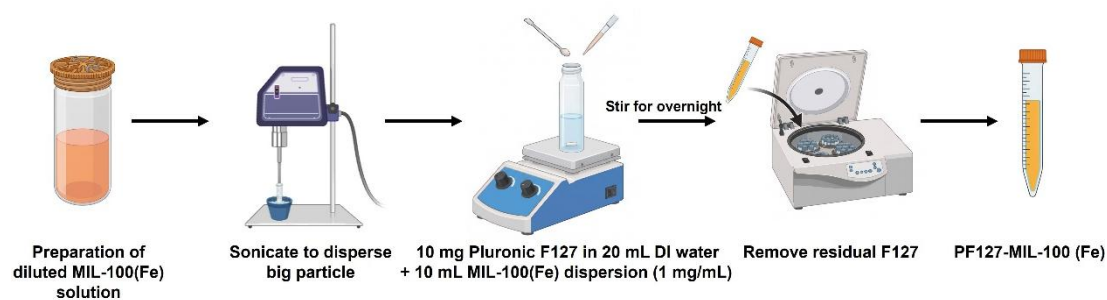


Figure 4.2 Schematic illustration of the preparation process of PF127-MIL-100(Fe).



4.5. Material characterization

4.5.1. X-ray diffraction (XRD)

The crystalline structures of the synthesized materials were characterized by powder XRD using a Rigaku MiniFlex with Cu K α radiation ($\lambda = 1.5418 \text{ \AA}$). The specific measurement parameters are summarized in Table 4.3.

Table 4.3 XRD measurement parameters

Parameters	Value
X-ray source	Cu K α
Wavelength (λ)	1.5418 $\text{\AA}$
Voltage	30 kV
Current	15 mA
Angle range	3° - 20°
Time per step	0.01 s
Scanning rate	5°/min



4.5.2. Fourier-transform infrared spectroscopy (FTIR)

FTIR analysis was performed to identify the characteristic functional groups of the synthesized materials. The analysis was conducted using a Perkin Elmer Spectrum 100. The samples were individually ground with spectroscopic-grade potassium bromide (KBr) in a 1:100 ratio. The blended powder was then pressed into a transparent disk using a Specac hydraulic press under a 15-ton load for at least 2 min. The spectra were recorded over the wavenumber range of 4000-450 cm^{-1} at a resolution of 4 cm^{-1} .

4.5.3. X-ray photoelectron spectroscopy (XPS)

The surface elemental states were investigated by XPS. The measurements were performed using a Thermo Scientific Nexsa G2 with a monochromatic Al $K\alpha$ radiation source. The XPS data were internally calibrated by referencing the binding energy of C 1s at 284.8 eV.

4.5.4. Specific surface area and pore size distribution

N_2 adsorption-desorption isotherms were obtained using a Belsorp-max II analyzer from Microtrac Retsch GmbH (Haan, Germany). The specific surface areas of the samples were calculated using the multiple-point Brunauer-Emmett-Teller (BET) method

in the relative pressure range of $P/P_0 = 0.05-0.30$. The pore size distribution was determined from the adsorption isotherms using the Barrett-Joyner-Halenda (BJH) theory.



4.5.5. Thermogravimetric analysis (TGA)

TGA was performed using a TA Instruments SDT 650 system to evaluate the thermal stability of the samples. The samples were heated from 30 to 650°C at a rate of 10°C /min under a constant flow of nitrogen.

4.5.6. Colloidal stability

4.5.6.1 Polydispersity index (PdI)

The PdI values of the synthesized materials were measured using a Malvern Zetasizer Nano ZS to evaluate their colloidal stability. Before measurement, the samples were dispersed in DI water by sonication. The PdI values were recorded over a period of 4 hours under identical measurement conditions using the same cell.



4.5.6.2 Visual observations

The long-term dispersion stability of the synthesized materials was further examined through visual observation. The aqueous suspensions were placed on a laboratory bench at room temperature, and photographs were taken using a smartphone camera on days 0, 1, 3, 7, and 14.

4.6. Microneedle patches

4.6.1. PDMS mold

A master microneedle mold was fabricated using a 3D-printing technique by Maker Wisdom Corp. (Kaohsiung City, Taiwan). The 3D-printed master mold featured pyramidal microneedles with three sets of parameters, as detailed in Table 4.4 and Figure 4.3. An inverse microneedle mold was fabricated from polydimethylsiloxane (PDMS), which was prepared by mixing silicone elastomer and silicone curing agent at a 10:1 ratio. The PDMS mixture was degassed in a vacuum desiccator to remove air bubbles and then poured over the 3D-printed master mold positioned at the center of a resin container. After the second round of degassing, the PDMS mold was cured in a 50°C oven for 4 days and then peeled gently from the 3D-printed master mold.

Table 4.4 Geometric parameters of the 3D-printed microneedle master molds.

	Group 1	Group 2	Group 3
a) Length (μm)	650	850	1000
b) Tip-to-tip distance (μm)	500	600	700
c) Base (μm)	250	300	300
d) Array (length X width)	25 x 15	21 x 12	18 x 11

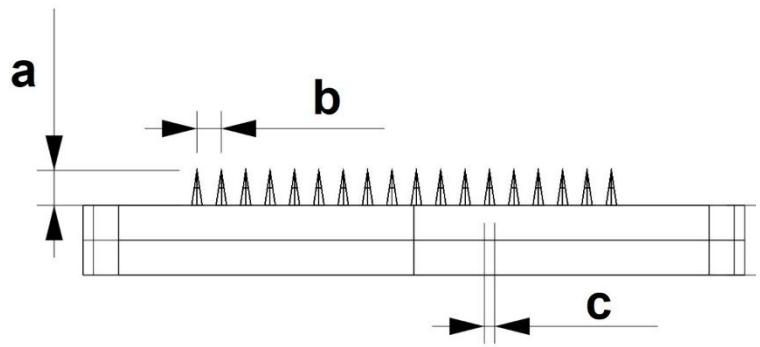


Figure 4.3 Design parameters of the microneedle master mold.

4.6.2. Fabrication of microneedle patches

Microneedle patches were fabricated through a two-step casting process, as illustrated in Figure 4.4. The needle tip polymer solution was prepared by dissolving 10 wt% PVP and 5 wt% CMC in DI water. After 500 μ L of the solution was cast onto the PDMS mold, the mold was placed under vacuum for 3 min to fill the mold cavities. The PDMS mold was then placed in a prepared centrifuge tube and centrifuged at 4000 rpm for 5 min to ensure complete filling of the mold cavities and removal of entrapped air bubbles. The excess solution was removed after centrifugation, and the PDMS mold was left to dry overnight in a hood at room temperature.

The PDMS mold was filled with the backing layer polymer solution, which consisted of 2 wt% PVP and 10 wt% CMC, followed by centrifugation at 4000 rpm for 15 min in the prepared centrifuge tube. After centrifugation, the mold was cleaned by removing the surrounding excess solution and dried in the hood at room temperature for 3 days. Finally, the microneedle patch was carefully detached from the mold and stored in a dry environment until further use.



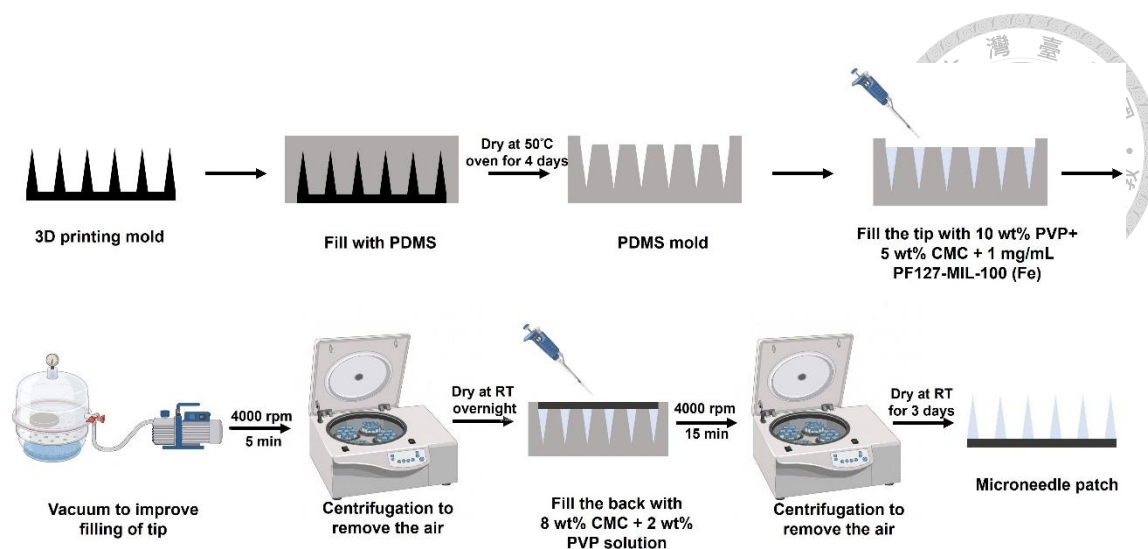


Figure 4.4 Schematic illustration of the two-step casting process for dissolving microneedle patch fabrication.

4.6.3. Microneedle morphology

The morphology, shape, and dimensions of microneedle patches were characterized by stereo microscope and SEM. Before SEM observation, the microneedle patches were cut into small pieces and coated with palladium (Pd) using a sputter coater.

4.6.4. Mechanical strength

The mechanical strength of microneedle patches was measured using the TA.XTplusC Texture Analyzer (Stable Microsystem Ltd, Surrey, UK). The microneedle patches were placed on the lower glass plate with the needle tips facing upward, as shown in Figure 4.5. The upper glass plate was moved vertically toward the microneedles at a

speed of 0.6 mm/min. When the upper glass plate contacted the needle tips, the compression force and displacement were recorded. The upper glass plate was moved downward from the microneedle tips toward the backing layer until reached preset displacements corresponding to the designed microneedle lengths of 650, 850, and 1000 μm .

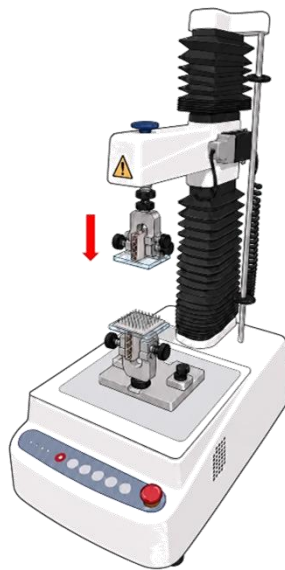


Figure 4.5 Schematic of the Texture Analyzer mechanical strength test setup.

4.6.5. Evaluation of the insertion capability

The insertion capacity of microneedle patches was evaluated using a skin-mimicking model composed of Parafilm M[®] (Bemis Company Inc., Soignies, Belgium).[67] Parafilm M[®] sheets with a thickness of 127 μm were cut into 3 cm x 3 cm squares and stacked into an eight-layer model to mimic the human skin thickness. The microneedle patch was then fixed to the upper glass plate with the needles facing downward and

pressed into the Parafilm M[®] sheets at a constant force of 20 N for 60 s using the Texture Analyzer, as shown in Figure 4.6. The applied force corresponds approximately to a typical human thumb force. After insertion, the microneedle patch was carefully removed, and the Parafilm M[®] model was separated into individual layers for further observation. Each Parafilm M[®] layer was examined under stereo microscope to count the number of puncture holes. The insertion efficiency was then calculated according to Equation 4.1:

$$\% \text{ insertion efficiency} = \frac{\text{Number of puncture holes}}{\text{Number of needles on each patch}} \times 100\% \quad (4.1)$$

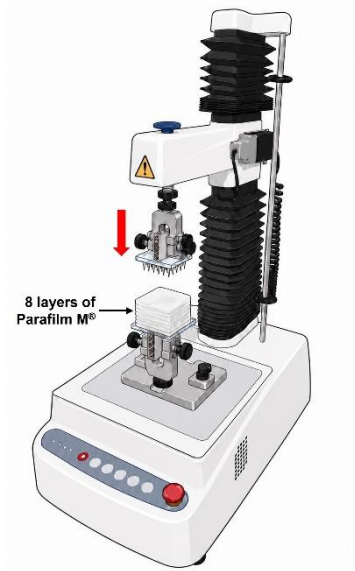


Figure 4.6 Schematic of the microneedle insertion capability test using stacked Parafilm M[®].

4.6.6. *Ex vivo* penetration test

Porcine skin samples were prepared by removing subcutaneous tissue and hair, trimming them to a thickness of 1 mm, and sectioning them into 3×3 cm pieces. After the skin was cleaned with water and dried, Rhodamine 6G-loaded microneedle arrays were first fixed to the upper glass plate and then applied to the porcine skin using the Texture Analyzer under a 20 N constant load for 5 min, as shown in Figure 4.7. Insertion sites were subsequently observed using OM and fluorescent microscopy. For further observation of the microchannels, the skin area penetrated by the microneedles was collected and fixed in 10% paraformaldehyde for 24 h. The fixed skin was then embedded in wax, sectioned, and stained with hematoxylin and eosin (H&E). The microchannels formed by microneedle insertion were evaluated from the stained tissue sections using optical microscopy.[68]

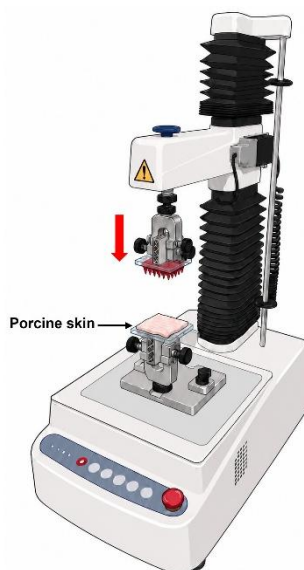


Figure 4.7 Schematic of the *ex vivo* porcine skin penetration test

4.6.7. *In vitro* drug release test

In vitro drug release profiles were evaluated by incubating the microneedle patches in 6-well plates containing 2 mL of PBS release medium. At specific time intervals (0, 5, 10, 20 and 30 min), 1 mL of the sample solution was collected and replaced with an equal volume of fresh PBS to maintain the total volume. The released rhodamine 6G concentration was determined using a microplate reader (BioTek Cytation 7 Cell Imaging Multi-Mode Reader) with excitation and emission wavelengths of 530 and 550 nm, respectively.



5. Results and Discussion



5.1. Characterization of MIL-100(Fe) and PF127-MIL-100(Fe)

5.1.1. Crystalline structures (XRD)

XRD was employed to characterize the crystalline structures of both MIL-100(Fe) and PF127-MIL-100(Fe). As shown in Figure 5.1, the synthesized MIL-100(Fe) exhibited characteristic diffraction peaks at 2θ values of 3.51° , 4.16° , 6.41° , 10.35° and 11.11° , corresponding to the (220), (311), (333), (822), and (911) crystal planes, respectively. These peaks closely matched the simulated pattern of MIL-100(Fe).[37] Furthermore, the diffraction pattern of PF127-MIL-100(Fe) remained nearly identical to that of bare MIL-100(Fe) and no obvious peak shifts were observed. This result indicated that the surface modification with Pluronic F127 had no adverse effect on the crystalline structure of MIL-100(Fe).

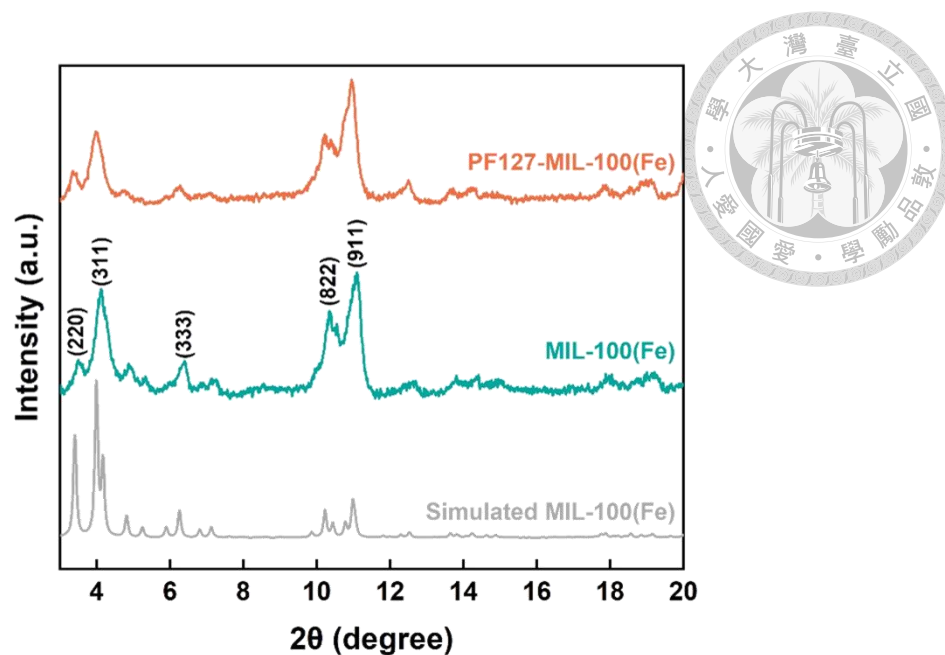


Figure 5.1 XRD patterns of simulated MIL-100(Fe), synthesized bare MIL-100(Fe), and PF127-MIL-100(Fe) nanoparticles.

5.1.2. FTIR analysis

FTIR analysis was utilized to confirm the presence of Pluronic F127 on the as-synthesized MIL-100(Fe). As shown in Figure 5.2, MIL-100(Fe) displayed characteristic peaks at 1448 and 1374 cm^{-1} , which were assigned to the symmetric and asymmetric vibrations of the COO^- group, along with a peak at 1628 cm^{-1} corresponding to the C=O stretching vibrations of the carboxylate groups, confirming the presence of the organic linkers. The peak observed at 615 cm^{-1} corresponds to the Fe-O stretching vibrations, demonstrating the presence of iron in the framework of MIL-100(Fe). Moreover, the peak at 3239 cm^{-1} was due to the O-H stretching vibration in MIL-100(Fe) and adsorbed moisture from the environment. [69] For pure Pluronic F127, a characteristic absorption

peak was observed at 2885 cm^{-1} , corresponding to C–H stretching vibrations. Additional peaks appeared at 1282 cm^{-1} for C–O–C stretching vibrations, 1100 cm^{-1} for symmetric C–C–O stretching vibrations, and 964 cm^{-1} for asymmetric C–C–O stretching vibrations.[70, 71] The appearance of these specific bands in the PF127-MIL-100(Fe) spectrum supported the successful surface modification of MIL-100(Fe) with Pluronic F127.

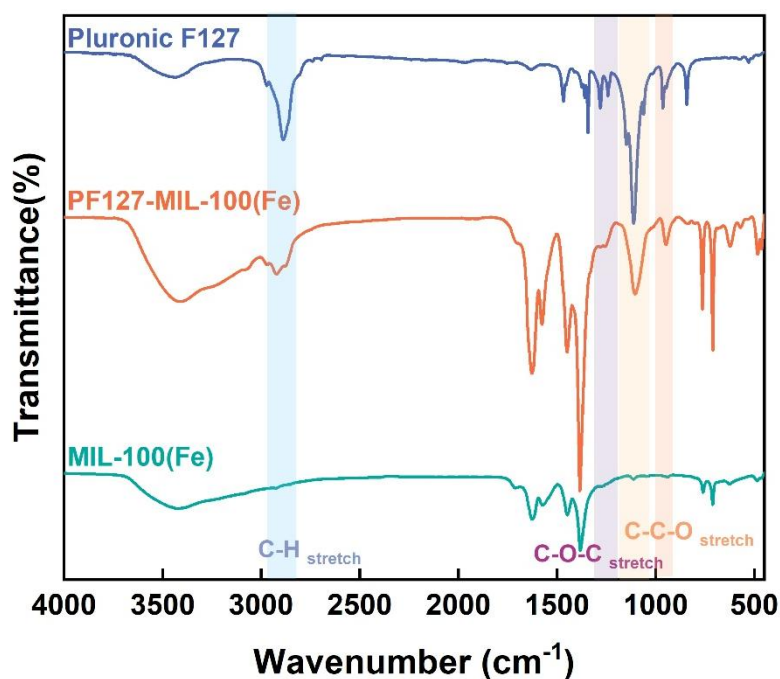


Figure 5.2 FTIR spectra of pure Pluronic F127, bare MIL-100(Fe), and PF127-MIL-100(Fe) nanoparticles.

5.1.3. Surface elemental analysis (XPS)



MIL-100(Fe) and PF127-MIL-100(Fe) were subjected to XPS analysis to further investigate the surface elemental compositions (Table 5.1) and thereby confirm the successful polymer modification. As summarized in Table 5.1, after coating with Pluronic F127, the relative atomic percentage of oxygen increases, whereas that of iron slightly decreases. This result suggests that the Pluronic F127 shell partially covered the MIL-100(Fe) surface, thereby attenuating photoelectron emission from Fe sites and reducing the Fe signal. The C 1s spectrum (Figure 5.3) reveals three constituent peaks at 284.8 eV (C–C), 286.6 eV (C–O) and 288.7 eV (C=O).[72] As shown in Table 5.2, the relative area of the C–O peak markedly increases from 3.29% in the bare MIL-100(Fe) to 22.72% in the PF127-MIL-100(Fe). This enhancement is attributed to the abundant ether (C–O–C) groups present in the Pluronic F127 chains. In agreement with the FTIR analysis, the increased C–O peak provides strong evidence for successful surface modification of MIL-100(Fe).[73]

Table 5.1 Surface elemental compositions of bare MIL-100(Fe) and PF127-MIL-100(Fe) determined by XPS analysis.

	C	O	Fe
	(atomic %)	(atomic %)	(atomic %)
MIL-100 (Fe)	63.80	30.88	5.32
PF127-MIL-100(Fe)	62.53	33.14	4.33

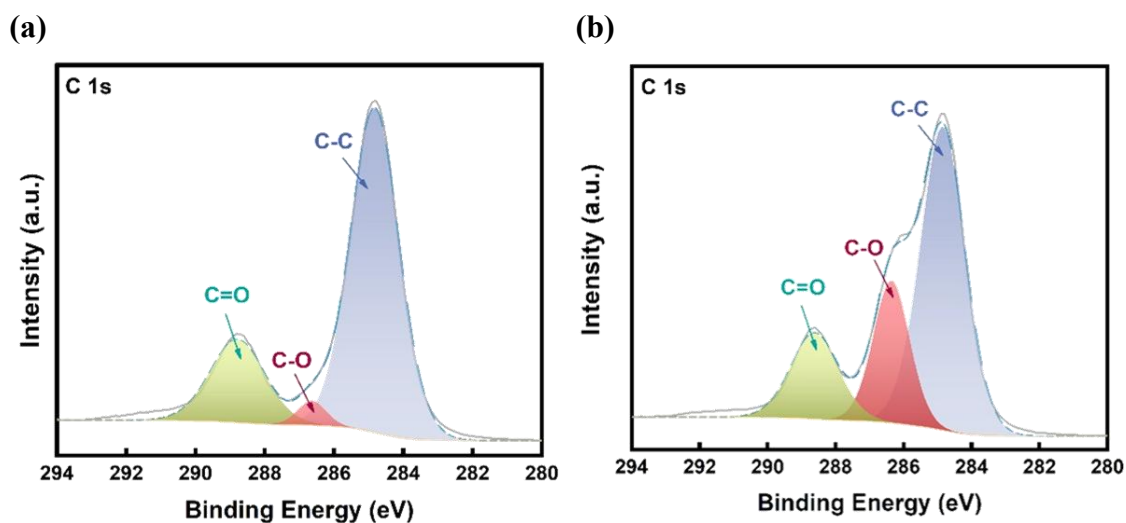
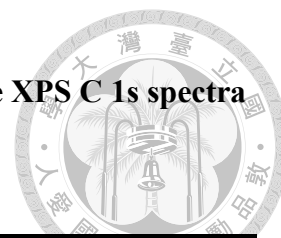


Figure 5.3 XPS C 1s spectra of (a) bare MIL-100(Fe) and (b) PF127-MIL-100(Fe).

Table 5.2 Relative C–O peak area percentages obtained from the XPS C 1s spectra of bare MIL-100(Fe) and PF127-MIL-100(Fe).

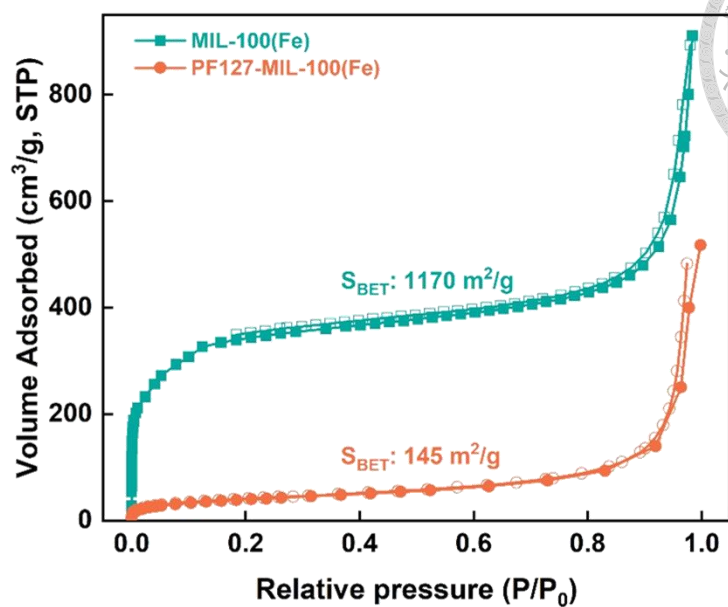


	C–O (286.6 eV) [%]
MIL-100 (Fe)	3.29
PF127-MIL-100(Fe)	22.72

5.1.4. Specific surface area and pore size distribution

The porosity parameters of the nanoparticles before and after polymer coating were obtained from N₂ adsorption/desorption experiments. The N₂ adsorption/desorption isotherm of bare MIL-100(Fe) (Figure 5.4a) exhibits features of both type I and IV nitrogen sorption isotherms, confirming the presence of micro- and mesoporous structures within its framework.[74] The BET specific surface area of bare MIL-100(Fe) was calculated to be 1170 m²/g, which decreased to 145 m²/g after Pluronic F127 coating. Additionally, the pore size distribution profile of PF127-MIL-100(Fe) (Figure 5.4b) became nearly flat, demonstrating that its micro- and mesopore volumes were greatly reduced compared to bare MIL-100(Fe). These results suggest that the Pluronic F127 polymer shell has successfully covered the external surface of the MIL-100(Fe), partially blocking the pore windows and preventing N₂ molecules from accessing the internal framework.

(a)



(b)

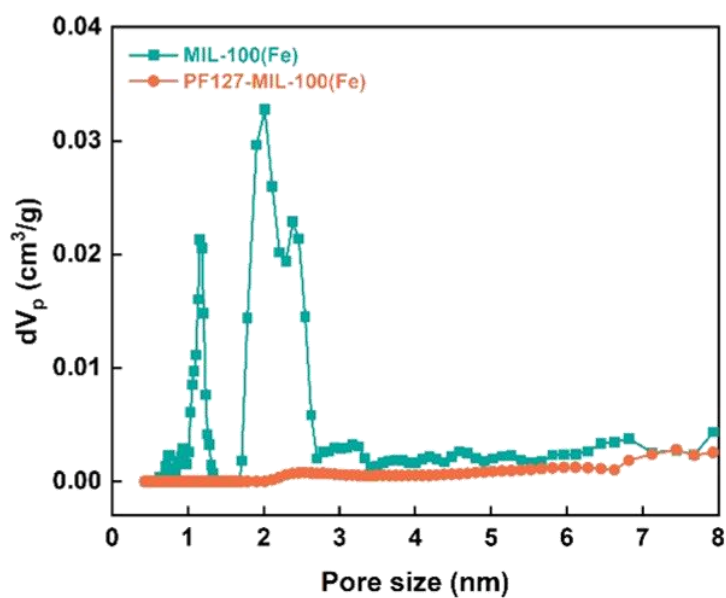


Figure 5.4 (a) N₂ adsorption-desorption isotherms and (b) corresponding pore size distribution curves of bare MIL-100(Fe) and PF127-MIL-100(Fe).

5.1.5. Thermal stability (TGA)



TGA was utilized to estimate the amount of Pluronic F127 coated on the nanoparticle surface. As shown in Figure 5.5, both materials initially exhibit a slight weight loss below 200°C due to the removal of adsorbed moisture. Subsequently, the bare MIL-100(Fe) showed gradual weight loss between 250 and 350°C, which was attributed to the initial thermal decomposition of its organic linkers and led to the structural collapse of the framework. The continuous degradation of the bare MIL-100(Fe) occurred around 400°C, corresponding to framework decomposition and conversion of iron clusters into iron oxides.[37, 75] In contrast, PF127-MIL-100(Fe) exhibits an earlier onset of significant weight loss starting around 250°C. This behavior reflects the thermal breakdown of the Pluronic F127 polymer shell prior to the collapse of the inner MIL-100(Fe) core, since the pure Pluronic F127 generally decomposes in the range of 220-580°C.[76] Interestingly, the final major decomposition stage shifted from 400°C to 440°C for PF127-MIL-100(Fe). This result suggests that the Pluronic F127 coating may act as a thermal barrier, delaying the complete breakdown of the MIL-100(Fe) core. By comparing the final residual masses of the two samples at 600°C, the weight fraction of Pluronic F127 coated on the MIL-100(Fe) nanoparticles was calculated to be 17.04%.

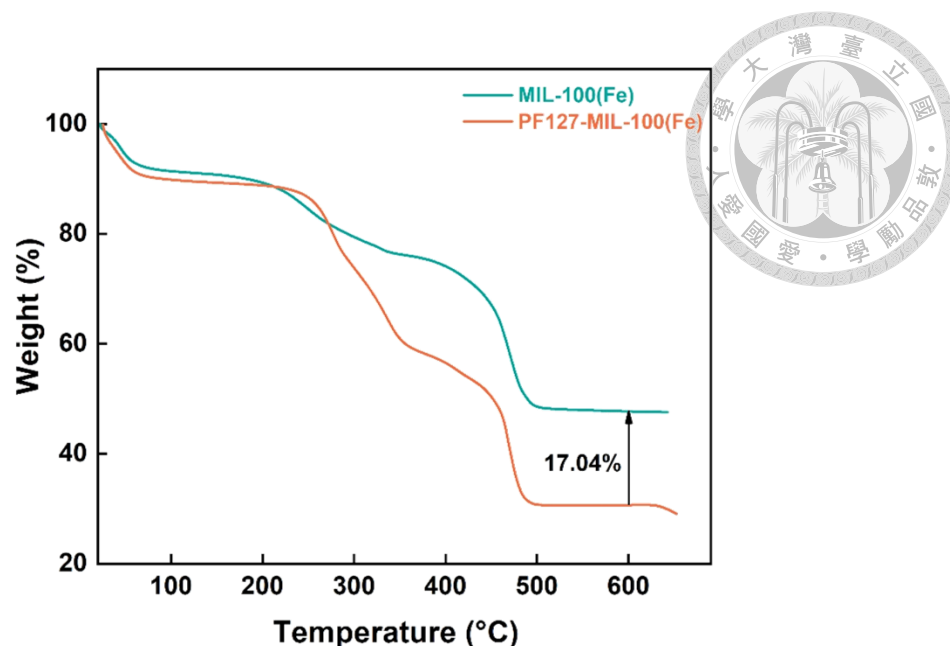


Figure 5.5 Thermogravimetric analysis (TGA) curves of bare MIL-100(Fe) and PF127-MIL-100(Fe) under a nitrogen atmosphere.

5.1.6. Colloidal stability of nanoparticles

The colloidal stability of the suspensions was investigated during the first 4 hours by continuous PdI measurements. The bare MIL-100(Fe) suspension exhibited highly unstable PdI values with large fluctuations, whereas PF127-MIL-100(Fe) remained highly stable in the range of 0.2-0.3 (Figure 5.6). The apparent decreasing trend and large standard deviations in the PdI values of bare MIL-100(Fe) occurred because the particles rapidly aggregated and precipitated to the bottom of the cuvette, thereby falling out of the DLS optical measurement path. Corroborating these PdI results, macroscopic visual observations (Table 5.3) showed that bare MIL-100(Fe) completely precipitated within

one day. Conversely, the PF127-MIL-100(Fe) remained stably suspended for at least 14 days due to the steric hindrance provided by the Pluronic F127.[77] Based on its improved suspension stability, PF127-MIL-100(Fe) was selected for incorporation into dissolving microneedle patches.

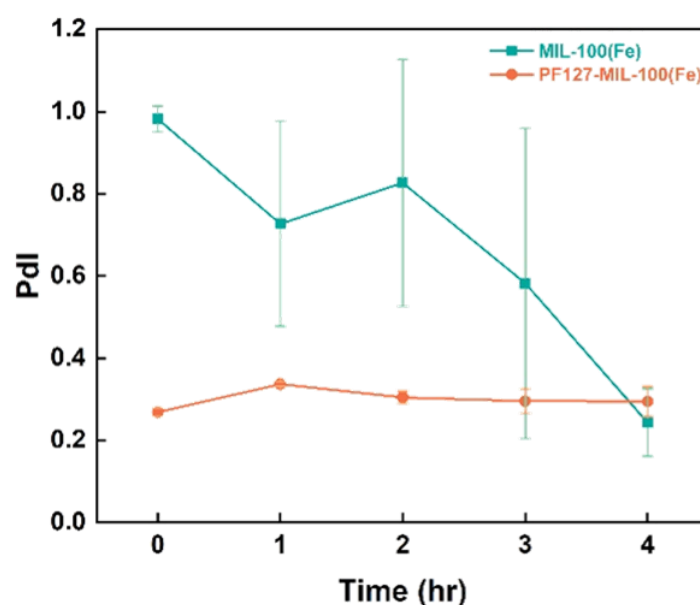


Figure 5.6 Time-dependent variations in the polydispersity index (PDI) of bare MIL-100(Fe) and PF127-MIL-100(Fe) suspensions over a 4-hour period.

Table 5.3 Visual observation of the colloidal stability of bare MIL-100(Fe) and PF127-MIL-100(Fe) aqueous suspensions monitored over 14 days.

	Day 0	Day 1	Day 3	Day 7	Day 14
MIL-100(Fe)					
PF127-MIL-100(Fe)					

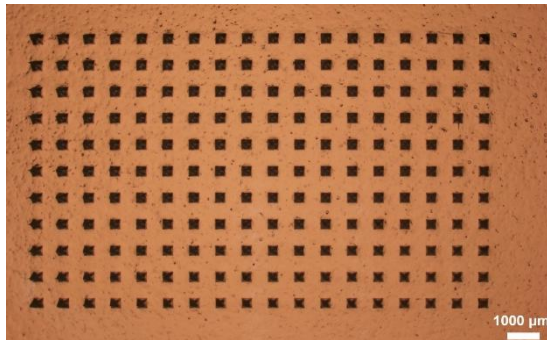
5.2. Characterization of microneedle patches



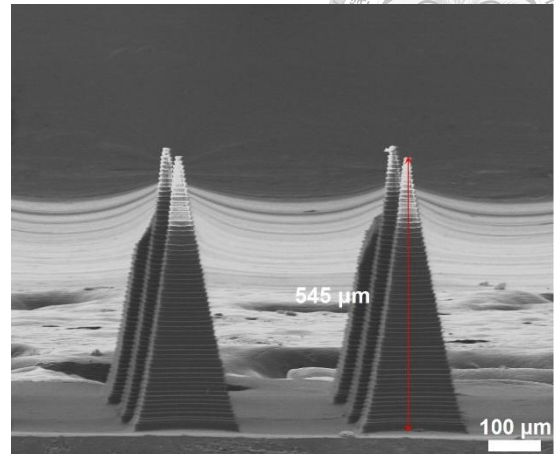
5.2.1. Morphology of microneedle patches

The morphology of the fabricated microneedle patches was characterized using stereo microscope and SEM. The microneedle patches consisted of pyramid-shaped needles fabricated from 650 μm , 850 μm and 1000 μm PDMS molds. As shown in Figure 5.7, the final lengths of fabricated microneedles were measured at 545 μm , 719 μm and 836 μm , corresponding to the 650 μm , 850 μm and 1000 μm molds, respectively. The reduction in length was primarily driven by solvent evaporation during the drying process of the polymer casting solution.[63] Nevertheless, all microneedle patches maintained approximately 84% of their original PDMS mold depths. These geometric profiles indicated that the fabricated microneedle lengths are sufficient to penetrate the human stratum corneum (10-20 μm), while remaining short enough to minimize stimulation of the deeper nerve endings associated with pain.[7, 11] Furthermore, the SEM micrographs revealed sharp, well-defined needle tips without any structural defects, supporting their capability for effective skin piercing.

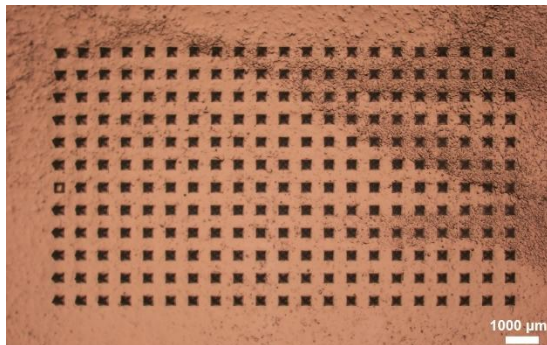
(a)



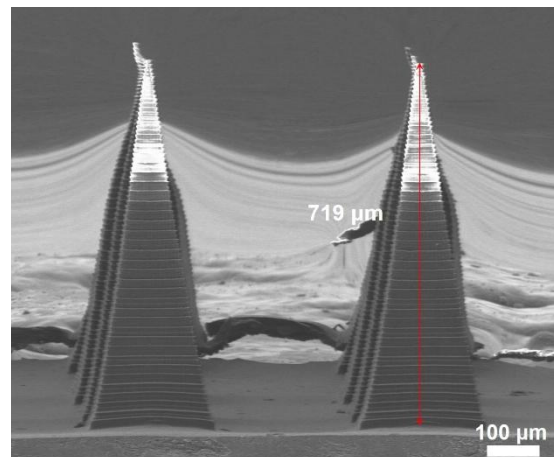
(b)



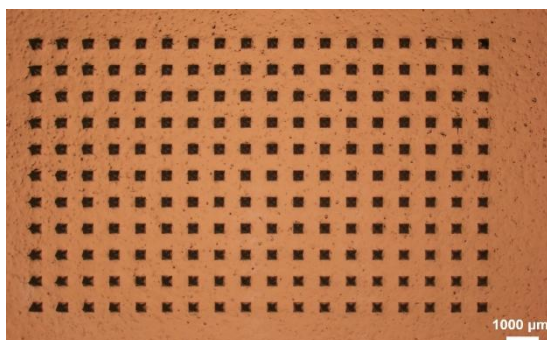
(c)



(d)



(e)



(f)

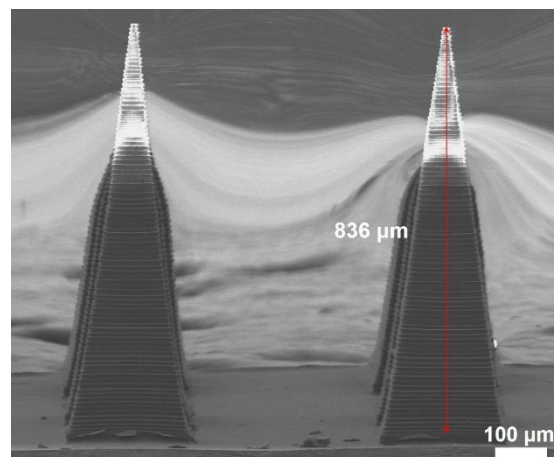


Figure 5.7 OM and SEM images of microneedle patches fabricated from PDMS

molds with different heights: (a, b) 650 μm , (c, d) 850 μm , and (e, f) 1000 μm .

5.2.2. Mechanical strength and penetration efficiency



Mechanical strength is a critical property of microneedles, as it ensures their capacity to penetrate the skin without tip fracture during application. Additionally, preliminary insertion tests of microneedle patches were carried out on a Parafilm M[®] model, providing a quick, easy-to-handle, and reliable simulation of their penetration performance.[78]

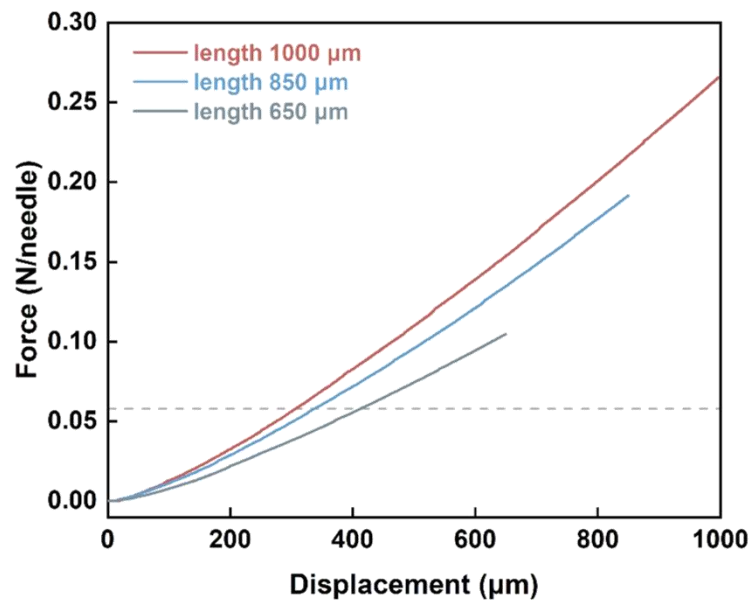
5.2.2.1 Effect of microneedle geometries

The corresponding force–displacement curves for the microneedle geometries with lengths of 650, 850 and 1000 μm are shown in Figure 5.8a. All microneedle patches exceeded the minimum force (0.058 N/needle) required to puncture human skin.[27] Among the tested geometries, the 1000 μm microneedle geometry exhibited the highest mechanical resistance under compression. The continuous and gradual increase in the force per needle shown in the plot indicated that the needles did not break but instead deformed under the applied load, which is characteristic of polymeric microneedles with a pyramidal geometry.[20] The Parafilm M[®] insertion test provided further comparative evidence (Figure 5.8b). Although all patches achieved over 97% insertion efficiency across the first two layers, only the patch fabricated using the 1000 μm microneedle geometry penetrated the third layer, with an insertion efficiency of 9%. Based on its

highest mechanical strength and insertion performance, the 1000 μm microneedle geometry was selected as the optimal geometry for subsequent formulation optimization.



(a)



(b)

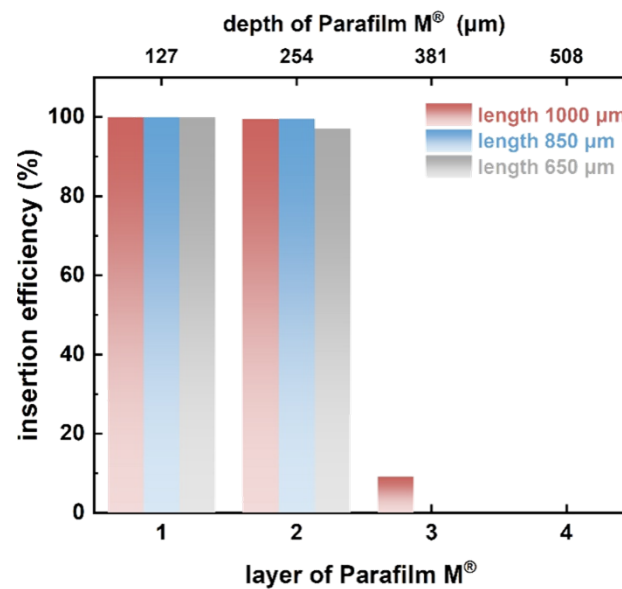


Figure 5.8 Mechanical characterization of microneedle patches with different geometry groups defined by needle lengths of 650, 850, and 1000 μm : (a) force-displacement curves and (b) insertion efficiency into Parafilm M[®] model layers.

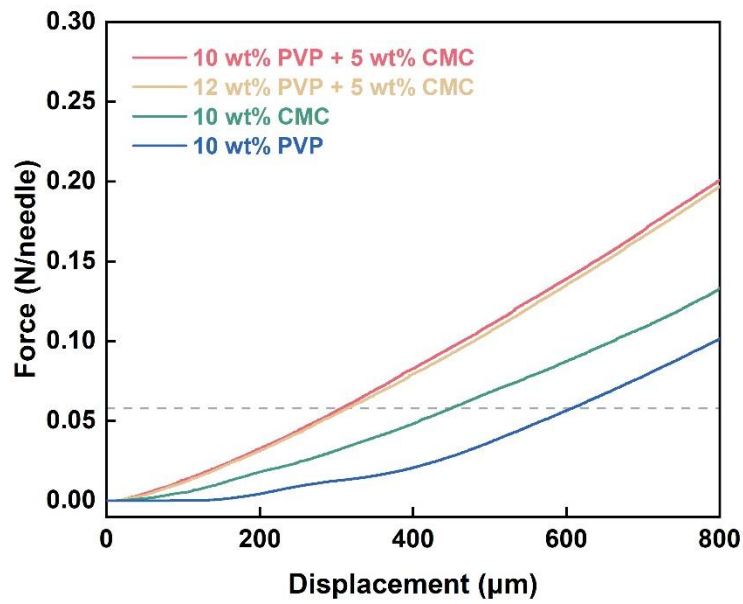
5.2.2.2 Optimization of the polymer matrix composition



As shown in Figure 5.9a, the mechanical strength of microneedle patches composed of a PVP/CMC binary blend is significantly higher than that of pure PVP or CMC alone.

This improvement suggested that the PVP/CMC binary blend promoted intermolecular interactions, including hydrogen bonding and chain entanglement, thereby enhancing mechanical properties through physical crosslinking. However, increasing the PVP content to 12 wt% provided negligible mechanical improvement. Furthermore, raising either the PVP or CMC concentration caused severe viscosity issues that hindered the proper filling of PDMS mold cavities during fabrication. Thus, a ratio of 10 wt% PVP + 5 wt% CMC was selected as the optimal formulation. As shown in Figure 5.9b, the PF127-MIL-100(Fe)-loaded microneedle patch exhibited a slight reduction in overall mechanical strength compared to the unloaded microneedle patch. The slight decrease in strength has also been reported in previous MOF-integrated microneedle studies. This effect may be attributed to the rigid MOF nanoparticles acting as stress concentration sites in the polymeric microneedle matrix, which can slightly disrupt the polymer network to reduce ductility and increase brittleness.[30, 79, 80] Nevertheless, the PF127-MIL-100(Fe)-integrated microneedle patch still exceeded the minimum force required for human skin insertion, supporting its use in subsequent penetration experiments.

(a)



(b)

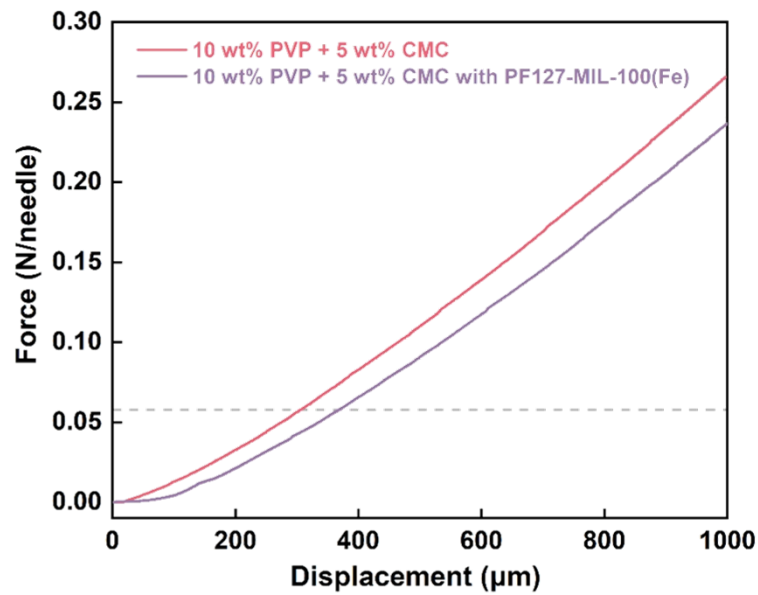


Figure 5.9 Force-displacement curves evaluating the mechanical strength of microneedle patches: (a) patches with different PVP/CMC ratios, and (b) the optimized 10 wt% PVP + 5 wt% CMC matrix with and without PF127-MIL-100(Fe) loading.

5.2.3. *Ex vivo* skin penetration test



The 1000 μm microneedles, fabricated from the optimized 10 wt% PVP + 5 wt% CMC formulation, containing PF127-MIL-100(Fe) and loaded with red Rhodamine 6G, were applied to porcine skin under a constant force of 20 N/patch to verify the insertion capability.[67] After a 5 min insertion period, the microneedle tips dissolved upon contact with the skin's interstitial fluid, allowing the loaded Rhodamine 6G to be deposited at the insertion sites. As shown in Figure 5.10a, the surface of the treated skin displayed a clear grid of red spots, indicating successful microneedle insertion and localized dye deposition into the porcine skin. Furthermore, fluorescence microscopic imaging (Figure 5.10b) showed the localized release of Rhodamine 6G, indicating that the dye had started diffusing into the tissue microchannels after a 5 min insertion period. Histological analysis was also performed to evaluate the actual penetration depth of the microneedle array in skin tissue. The H&E-stained section of porcine skin (Figure 5.10c) showed the microneedles successfully penetrated the stratum corneum and reached a penetration depth of approximately 220 μm . The measured insertion depth was lower than the designed 1000 μm needle length, mainly because of the viscoelastic properties of the natural skin.[68]

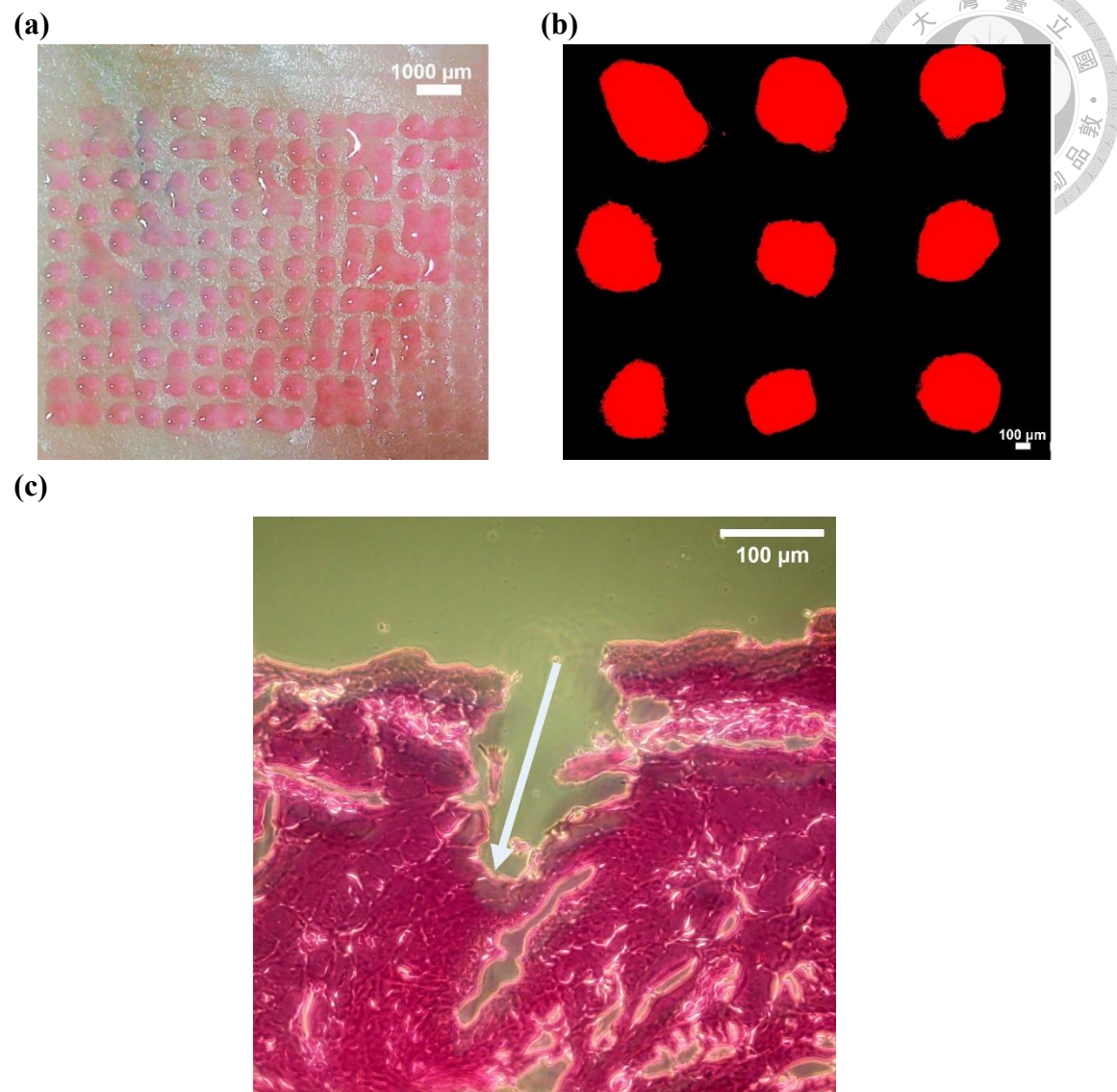


Figure 5.10 *Ex vivo* porcine skin penetration test: (a) optical micrograph of the punctured porcine skin surface. (b) fluorescence microscopy image showing the diffusion of Rhodamine 6G within the microchannels. (c) H&E-stained section of porcine skin after microneedle insertion.

5.2.4. *In vitro* drug release profile

The *in vitro* drug release profile of the composite microneedle patch is shown in Figure 5.11. The 10 wt% PVP + 5 wt% CMC microneedle patch containing PF127-MIL-100(Fe) released approximately 96% of Rhodamine 6G within 30 min. According to the literature, dissolving microneedles made of pure PVP typically exhibited rapid matrix degradation, with complete dissolution occurring between 10 and 180 s.[81, 82] Therefore, the release profile indicated that the inclusion of CMC prolonged the release duration, consistent with the previous study showing that CMC can modulate the dissolution behavior of microneedles.[63] Additionally, this prolonged release might be attributed to the hydrogen bonding between PVP and CMC, which creates a physically crosslinked polymer network that restricts rapid water penetration.[83]

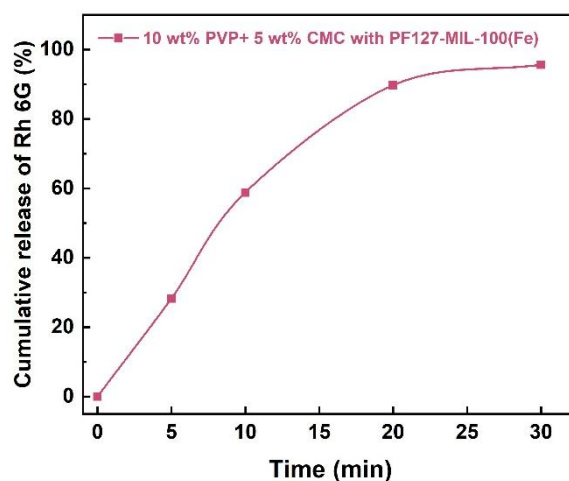


Figure 5.11 *In vitro* cumulative release profile of Rhodamine 6G from the 10 wt% PVP + 5 wt% CMC microneedle patch containing PF127-MIL-100(Fe) within 30 min.

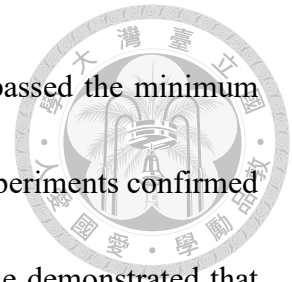
6. Conclusions



This research successfully developed a transdermal delivery platform by integrating Pluronic F127-modified MIL-100(Fe) nanoparticles with physically crosslinked PVP-CMC dissolving microneedles. XRD patterns confirmed the preservation of the original MIL-100(Fe) crystalline framework following polymer modification. The surface modification of MIL-100(Fe) with Pluronic F127 was supported by the appearance of characteristic Pluronic F127 bands in FTIR spectra and the significantly increased C-O peak contribution in XPS C 1s analysis. Furthermore, the substantial decrease in specific surface area after modification indicated that the polymer shell covered the MIL-100(Fe) surface and partially restricted pore access. TGA further verified this coating, yielding an estimated PF127 mass fraction of 17.04 wt%. Colloidal stability tests highlighted the effectiveness of the surface modification. Bare MIL-100(Fe) rapidly precipitated within a day, whereas PF127-MIL-100(Fe) remained stably suspended for over 14 days due to effective steric hindrance.

Regarding the formulation of the microneedle arrays, the 1000 μm design exhibited optimal skin penetration among the tested geometries. When formulated with 10 wt% PVP and 5 wt% CMC, the optimal matrix exhibited enhanced mechanical strength compared with single-polymer formulations, attributed to the physical crosslinking within the polymer blend. Although the incorporation of PF127-MIL-100(Fe) nanoparticles

slightly reduced mechanical strength, the loaded microneedles surpassed the minimum force required for skin insertion. Subsequent *ex vivo* porcine skin experiments confirmed successful microchannel formation, while the *in vitro* release profile demonstrated that approximately 96% of Rhodamine 6G was released within 30 min. In conclusion, this study demonstrates the potential of combining PF127-MIL-100(Fe) nanoparticles with PVP/CMC dissolving microneedles as a promising transdermal delivery platform.



7. Future works



Several aspects should be further investigated to strengthen the biomedical relevance of this platform. First, future studies should replace the model dye with therapeutic agents and evaluate drug-loading efficiency, release behavior, and biological activity after microneedle delivery. Second, the biological safety of the system should be examined through cell viability assays, hemocompatibility tests, skin irritation studies, and histological analysis after microneedle insertion. Third, the stabilizing effect of Pluronic F127 should be further validated in physiological media, including PBS, serum-containing solutions, and protein-rich environments, to determine whether the coating can reduce aggregation and nonspecific protein adsorption. Fourth, the release behavior may be tuned by adjusting the PVP/CMC ratio, nanoparticle loading amount, or backing layer composition. Finally, practical factors such as storage humidity, long-term stability, patch uniformity, and scalable fabrication should be optimized before moving toward *in vivo* animal studies and translational development.

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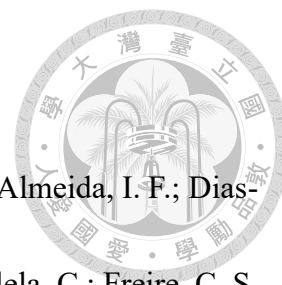
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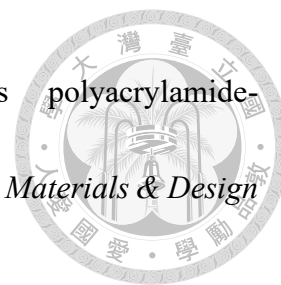
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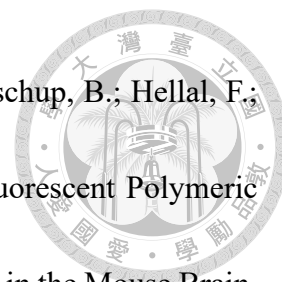
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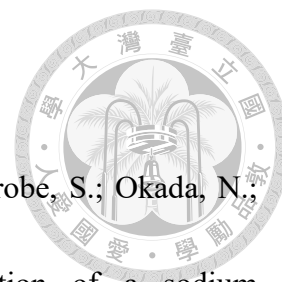
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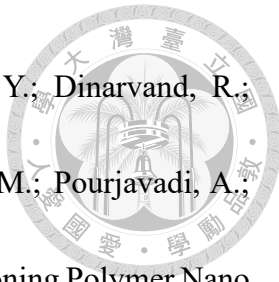
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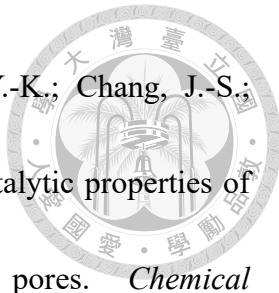
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