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Microneedle-Mediated Gas Delivery: A Synergistic Approach for Enhanced Transdermal Delivery and Combined Therapy

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ABSTRACT

With advantages like avoiding the first-pass effect, painless administration, and simplicity of usage, microneedles (MNs) are a cutting-edge transdermal drug delivery technique. However, there are issues with classic MNs, such as sluggish tip detachment and low efficiency. In order to increase medication penetration and separation rates, this review focuses on current developments in MN-mediated gas delivery. In order to maximize delivery efficiency, it looks at the benefits and limitations of MNs as well as advancements in gas-assisted MNs. The analysis of the therapeutic roles of different gases (H_2, O_2, NO, H_2S, CO, CO_2) and their combined effects with MNs offers important insights for future applications in combination therapy for the treatment of different diseases.

Keywords: Microneedles, Transdermal Patch, Drug Delivery, Gas Therapy, Drug Penetration

INTRODUCTION

Transdermal drug delivery systems (TDDS) offer numerous advantages over traditional administration routes, such as the avoidance of hepatic first-pass metabolism, reduced invasiveness, and simplified application. Despite these benefits, the efficacy of TDDS is fundamentally limited by the skin's outermost layer, the stratum corneum, which acts as a highly effective barrier to drug penetration. To circumvent this limitation, various physical and chemical enhancement techniques have been explored, including iontophoresis, ultrasound, and the use of chemical enhancers. [1]

Among the physical enhancement methods, Microneedles (MNs) have emerged as a highly promising technology. MNs are arrays of microscopic needles that penetrate the stratum corneum to create transient microchannels, thereby significantly enhancing drug permeation while remaining minimally invasive and pain-free. [2] MNs have demonstrated potential across a wide range of medical conditions, including neurological diseases, cardiovascular diseases, and endocrine disorders. [3, 4]

However, the widespread clinical adoption of MNs is hindered by two primary challenges. (a). Slow Separation Rate: Hydrophilic polymer-based MNs often exhibit a slow dissolution rate *in vivo* compared to *in vitro* conditions, leading to insufficient separation of the drug-loaded tip from the base substrate. This necessitates prolonged application times, which diminishes patient compliance. [5] (b). Limited Transdermal Efficiency: Drug delivery from MNs typically relies on passive diffusion, which restricts deep penetration, making them less effective for treating deep-seated lesions or conditions with thickened skin, such as hypertrophic scars and psoriasis. [6]

To address these limitations, researchers have turned to gas therapies utilizing bioactive gaseous molecules (e.g., NO, O_2, H_2, H_2S, CO_2). [7] The integration of MN delivery with gas therapies offers a synergistic approach, leveraging the enhanced delivery efficiency of MNs with the therapeutic benefits and dynamic augmentation provided by gas generation. This combination is explored as a novel strategy for accelerating delivery kinetics and enabling potent combined therapies.

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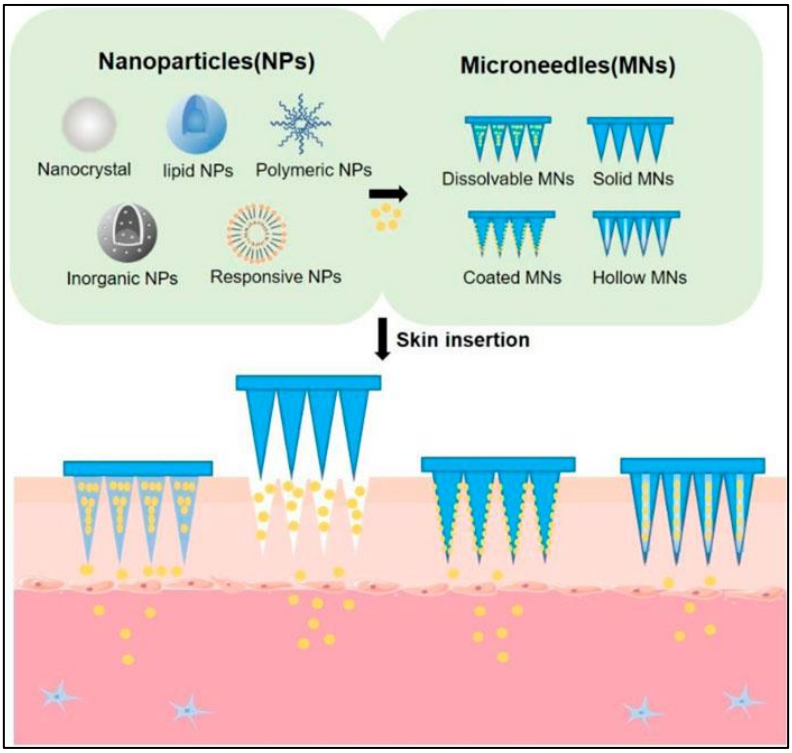

Figure 1: Schematic representations of conventional microneedles (MNs)

MICRONEEDLE-MEDIATED GAS DELIVERY FOR ENHANCED DRUG DELIVERY

The incorporation of gas-producing substances within MN patches serves a dual purpose: to accelerate the physical separation of the MN tip and to enhance the subsequent drug penetration into the deeper skin layers.

Rapid Separation of MN Tips

The prolonged application time required for the dissolution and separation of polymeric microneedle tips from the backing substrate is a major drawback. To enhance patient comfort and compliance, particularly in paediatric applications, researchers have developed actively separable MNs systems that utilize gas generation to facilitate rapid detachment. [8]

A key strategy involves embedding effervescent agents that react with interstitial skin fluid to produce gas bubbles. These bubbles physically push the drug-loaded tip away from the substrate, ensuring the tip remains embedded in the skin while the backing patch can be quickly removed.

(i) Carbon Dioxide Generation

Yang et al. [9] designed an actively separable MN patch for growth hormone delivery by integrating the effervescent agent sodium bicarbonate ($NaHCO_3$) into a separating poly(acrylic acid) (PAA) layer. Upon contact with skin fluid, the PAA generates protons that react with $NaHCO_3$ to produce CO_2. This reaction achieved an ultra-rapid separation of the MN tip from the base within approximately 11.41 ± 0.43 seconds *in vitro*. *Ex vivo* experiments on isolated pig skin demonstrated a separation efficiency exceeding 95%, a significant improvement over the 32% efficiency observed in the absence of $NaHCO_3$. Similarly, Li et al. [10] developed an effervescent backing using $NaHCO_3$ and citric acid for sustained levonorgestrel release, achieving rapid separation in 10.7 seconds.

(ii) Hydrogen Generation

Ning et al. [5] developed a Dual-Layer Dressing Microneedle System (DDMNS) where the backing substrate was loaded with magnesium (Mg) microparticles. The moist environment facilitated by the upper dressing enhanced the reaction between Mg particles and hydrogen ions in an inflammatory environment, generating H_2 gas. This mechanism achieved a separation rate of 87.5% within 5 minutes in model wound tissues, demonstrating effective drug penetration.

Enhanced Drug Penetration

Beyond separation, the gas generated *in situ* acts as a built-in engine to enhance drug diffusion. The formation of gas bubbles and the resulting micro-vortices within the microchannels significantly increase the mass transfer rate of the drug into the deeper skin layers. [11] Effervescent components, typically a combination of organic acids and basic carbonate salts, are commonly used to produce CO_2 upon hydration.

(i) CO_2-Driven Diffusion

Zhang et al. [8] developed gas-driven MNs using polyvinyl pyrrolidone (PVP K30), polyvinyl alcohol (PVA), potassium carbonate (K_2CO_3), and citric acid. The cumulative transdermal drug delivery rate achieved by these gas-driven MNs was 1.19 times greater than that of passive MNs. You et al. [12] developed an ultra-rapid-action MN patch (URA-MN) using $NaHCO_3$ and citric acid, where the rapid CO_2 production created a porous structure that accelerated drug release within minutes. Frozen sections confirmed that the drug loaded in URA-MN diffused rapidly within 5 minutes.

(ii) Targeting Acidic Microenvironments

Gas generation utilizing $NaHCO_3$ can also be exploited to target the acidic microenvironments characteristic of tumors or inflammation.[13] Tao et al. [14] developed a bubble pump MN system where $NaHCO_3$ was integrated within nanoparticles. The generated CO_2 notably improved drug penetration *in vitro*, demonstrating a strategy to couple enhanced delivery with environmental responsiveness.

THERAPEUTIC GASES AND MN-MEDIATED COMBINED THERAPY

The integration of MNs with therapeutic gases allows for a localized, controlled delivery of these bioactive molecules, overcoming the limitations of systemic administration (e.g., inhalation) such as poor control and potential toxicity.[15] These gases possess intrinsic therapeutic properties, enabling a combined therapy approach where the drug and the gas work synergistically.

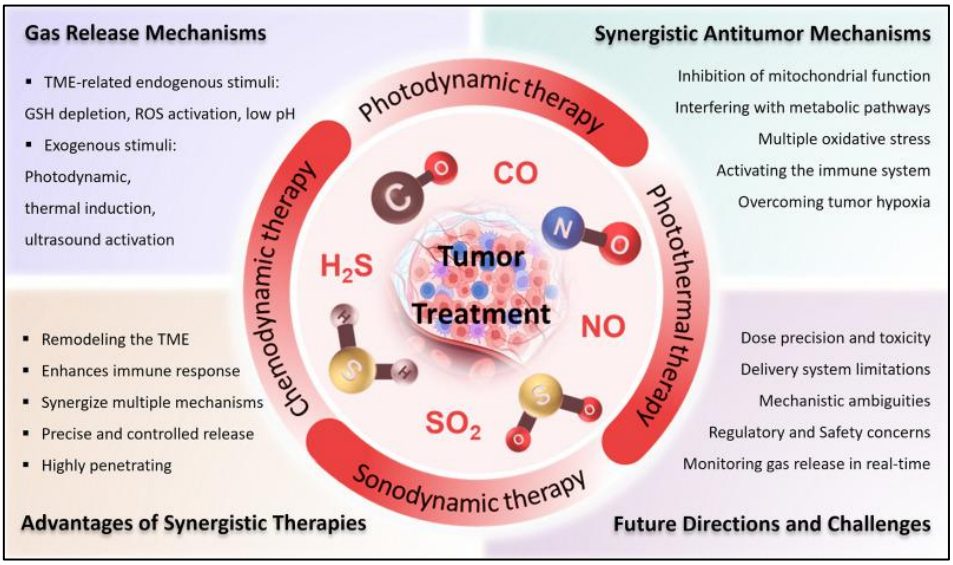

Figure 2: An Outlook of Gas Therapy in Tumour Treatment

Hydrogen Therapy

Hydrogen gas is a potent, selective antioxidant that can neutralize harmful reactive oxygen species (ROS), making it an effective anti-inflammatory and cytoprotective agent.[16] Psoriasis is a chronic inflammatory skin disease characterized by excessive keratinocyte proliferation. Zheng et al. [17] developed a novel MN system for psoriasis treatment that utilized a genetically engineered bacterium, *Enterobacter aerogenes* (*E. aerogenes*), embedded in a bilayer MN. Upon insertion, the bacteria were activated to generate H_2 gas *in situ*. The H_2 gas exhibited a dual function: it enhanced the penetration depth of the co-loaded drug (calcipotriol) and provided therapeutic anti-inflammatory effects, effectively inhibiting keratinocyte proliferation and reducing psoriatic lesions in a mouse model. This innovative approach offers precise control over drug delivery depth and duration.

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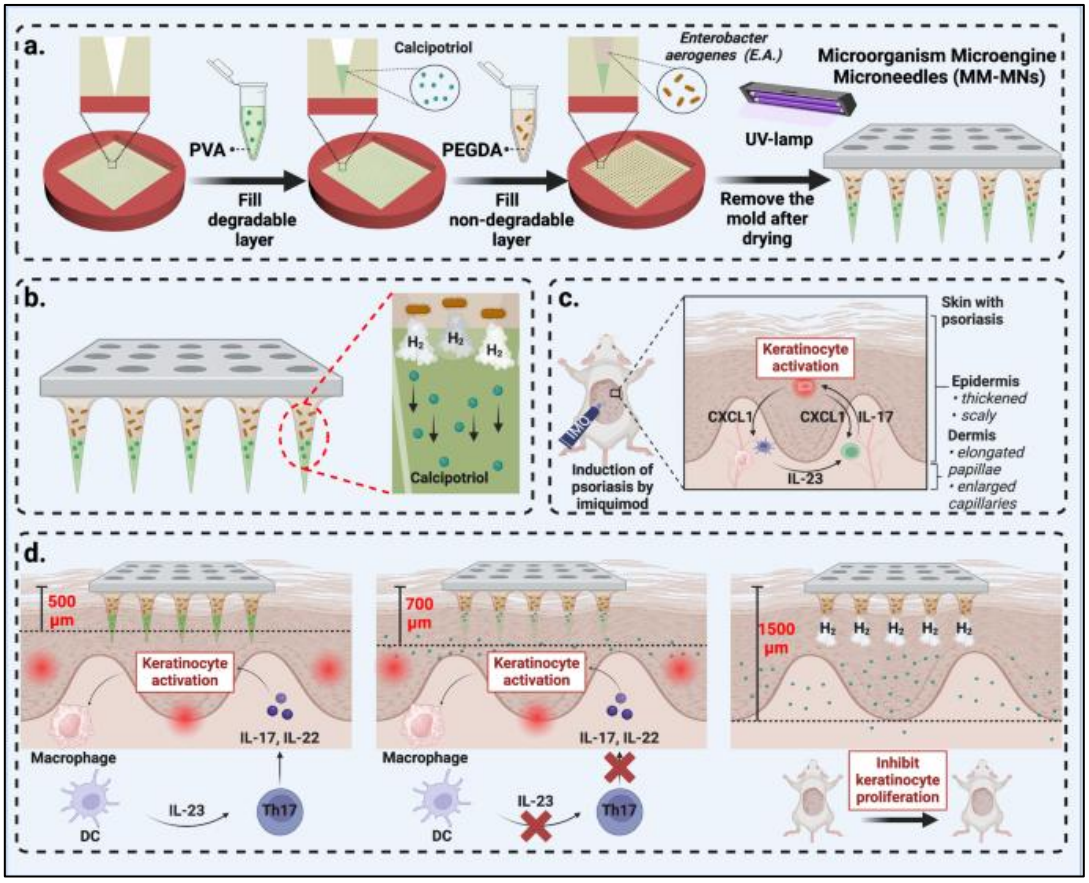

Figure 3: Micro-organism based Microneedle in psoriasis treatment

Oxygen Therapy

Hypoxia, or oxygen deficiency, is a common pathological feature in conditions like diabetic wounds and solid tumours. MN-mediated O_2 delivery can locally re-oxygenate tissues, promoting healing or enhancing the efficacy of other therapies. Chronic diabetic wounds are often characterized by severe hypoxia, which impairs cellular function and delays healing. MNs loaded with O_2-generating precursors, such as calcium peroxide (CaO_2) or manganese dioxide (MnO_2), have been developed. [18, 19] Upon contact with the wound fluid, these precursors decompose to release O_2, which alleviates local hypoxia, promotes angiogenesis, and accelerates wound closure. For instance, a dissolving MN system loaded with MnO_2 and dopamine-enhanced CaO_2 demonstrated significant improvements in wound healing rates in diabetic rat models.[19]

In solid tumours, hypoxia is a major cause of resistance to radiotherapy and photodynamic therapy (PDT). O_2-generating MNs can locally increase tumour oxygenation, thereby sensitizing cancer cells to treatment and significantly improving therapeutic outcomes.[20]

Nitric Oxide Therapy

Nitric oxide is a critical signalling molecule involved in numerous physiological processes, including vasodilation, anti-inflammatory responses, and antimicrobial activity. [21] NO releasing MNs have been developed to leverage its potent biological effects. In cancer therapy, NO can induce apoptosis and inhibit tumour growth. For wound healing, NO's vasodilatory properties improve blood flow to the site, while its antimicrobial action helps prevent infection. A study by He et al. [22] developed a NO-releasing MN patch that demonstrated enhanced wound closure and reduced bacterial load in infected wounds.

Hydrogen Sulfide and Carbon Monoxide Therapy

H_2S and CO are recognized as gasotransmitters, alongside NO, and play crucial roles in cytoprotection, anti-inflammation, and regulating cellular metabolism. [23] The combination of H_2S and CO with chemotherapy or immunotherapy delivered via MNs shows great promise for cancer treatment. H_2S can modulate the tumour microenvironment (TME) and enhance the efficacy of

photodynamic therapy (PDT) [24]. CO is known for its anti-apoptotic and anti-inflammatory effects, and when released locally, it can inhibit tumour growth with minimal systemic toxicity. [25] The synergistic application of these gases with other therapeutic agents is a major focus of current research.

Table 1: List of few studies related to Microneedle-Mediated Gas Delivery

MN System	Gas Generated	Primary Function	Results	Ref.
$NaHCO_3$/PAA MN	CO_2	Rapid Separation	Separation time: 11.41 ± 0.43s; Separation efficiency: >95%	[9]
Mg-Loaded DDMNS	H_2	Rapid Separation	Separation rate: 87.5% within 5 min	[5]
K_2CO_3/Citric Acid MN	CO_2	Enhanced Penetration	Drug delivery rate: 1.19 \times passive MNs	[12]
E. aerogenes MN	H_2	Combined Therapy (Psoriasis)	Enhanced drug penetration and anti-inflammatory effect	[17]

FUTURE PERSPECTIVES AND CHALLENGES

The field of MN-mediated gas delivery is rapidly evolving, with significant potential for clinical translation. Future research directions are likely to focus on several key areas:

Precise Control and Monitoring

Developing MN systems that allow for on-demand, precise control over the rate and duration of gas release is crucial. Integrating smart materials and responsive elements that react to specific biomarkers (e.g., pH, enzyme concentration) within the skin will enable highly personalized and effective dosing. Furthermore, the development of non-invasive methods to monitor gas release *in vivo* in real-time remains a significant challenge.

Novel Gasotransmitters and Combinations

Exploring the therapeutic potential of other gaseous molecules and optimizing synergistic combinations of multiple gases or gas-drug-physical therapy (e.g., photothermal) combinations will unlock new treatment paradigms, particularly for complex diseases like cancer and chronic inflammation.

Scalability and Manufacturing

Translating laboratory-scale MN fabrication into cost-effective, large-scale manufacturing processes is essential for commercial viability. Ensuring the long-term stability and shelf-life of gas-generating components within the MN patch also presents a practical challenge.

Clinical Trials and Regulatory Pathway

While preclinical data are highly encouraging, rigorous clinical trials are necessary to validate the safety and efficacy of gas-assisted MN systems in human subjects. Establishing a clear regulatory pathway for these novel combination products will be vital for their eventual market approval.

CONCLUSION

Microneedle-mediated gas delivery represents a powerful paradigm shift in transdermal drug administration. By ingeniously harnessing the dynamic properties of gas generation, this technology successfully addresses the critical limitations of conventional MNs, achieving ultra-rapid separation and significantly enhanced drug penetration. More importantly, the localized and controlled delivery of therapeutic gases—such as H_2, O_2, NO, H_2S, CO, CO_2—enables highly effective combined therapies for challenging conditions like cancer, psoriasis, and diabetic wounds. As research continues to refine the control mechanisms and explore new gas combinations, MN-mediated gas delivery is poised to become a cornerstone technology in the next generation of personalized and highly efficient therapeutic interventions.

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