Development and Evaluation of Nanoparticle-Loaded Dissolvable Microneedle Patches for Enhanced Transdermal Drug Delivery of Labetalol: A Novel Therapeutic Strategy

Dr. Mohit Kotnala[1], Shashi Upasana[2], Anu Sharma[3], Bharti Sharma[4], Jaffer Sadik Mohammed[5], Dr. Kuturu Deepthi[6], Mohammed Jafar[7], Joel Mart[8], Dr. Suvarna Bhadane*[9]

[1]Science Teacher, Ain Al Fayedha Charter School Abu Dhabi, Al Ain.
[2]Associate Professor, Shaheed Bhagat Singh College of Pharmacy, Palampur HP
[3]Associate Professor, Shanti Niketan College of Pharmacy, Ratti Mandi HP
[4]Assistant Professor, KC Institute of Pharmaceutical Sciences, Una HP
[5]Professor, Sri Indu Institute of Pharmacy
[6]Associate Professor, Bojjam Narasimhulu Pharmacy College for women
[7]Assistant Professor, Department of Pharmaceutics, College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam 34212, Saudi Arabia.
[8]Assistant Professor, Vels Institute of Science, Technology & Advanced Studies. PV Vaithiyalingam rd Velan Nagar, Krishnapuram, Pallavaram Chennai-600117, Tamilnadu
[9]Associate Professor, R G Sapkal Institute of Pharmacy, Nashik

Corresponding Author: Dr. Suvarna Bhadane, Associate Professor, R G Sapkal Institute of Pharmacy, Nashik, **Email:** sumanns912@gmail.com

Abstract

The transdermal administration of labetalol, a commonly utilised β-blocker for managing hypertension, is significantly improved by the innovation of nanoparticle-encapsulated dissolvable microneedle (DMN) patches. This research delves into the development, analysis, and effectiveness of these DMN patches aimed at enhancing therapeutic outcomes and patient adherence in the treatment of hypertension. Integrating nanoparticles within the DMNs significantly boosts the drug's ability to permeate the skin, resulting in improved bioavailability and a more regulated release when juxtaposed with conventional oral delivery methods. The microneedles were crafted from polyvinyl alcohol (PVA) and infused with labetalol nanoparticles produced through the process of solvent evaporation. The assessment of the patches' mechanical characteristics, dissolution dynamics, and capacity for skin penetration was conducted utilising a range of techniques, such as dynamic light scattering (DLS), scanning electron microscopy (SEM), and in vitro penetration experiments employing human cadaver skin. The findings revealed that the DMNs infused with nanoparticles significantly improved the transdermal absorption of labetalol, showcasing an impressive encapsulation efficiency alongside a prolonged drug release pattern. The cytotoxicity evaluations validated the compatibility of the patches with biological systems, rendering them appropriate for use in clinical settings. The research indicates that these DMN patches, infused with nanoparticles, present an innovative and encouraging strategy for managing hypertension through the skin, delivering superior therapeutic results, better patient adherence, and minimised adverse effects. Upcoming clinical investigations are essential to confirm these results and determine the effectiveness and safety of these patches for practical use in real-world scenarios.

Keywords: Nanoparticle-loaded microneedles, Transdermal drug delivery, Labetalol, Dissolvable microneedle patches, Controlled release, Hypertension treatment

1. Introduction

The transdermal administration of pharmaceuticals has swiftly captured interest as a substitute for conventional drug delivery methods like oral intake and injections. Transdermal systems provide numerous advantages by circumventing the gastrointestinal tract and first-pass metabolism, such as prolonged drug release, enhanced bioavailability, and minimised systemic adverse effects. Nonetheless, the skin's robust barrier characteristics present considerable obstacles to the effective administration of therapeutic compounds, especially for water-soluble medications. In order to surmount these obstacles, a range of approaches has been investigated, such as the implementation of microneedles. Among these, dissolvable microneedles (DMNs) have surfaced as a groundbreaking approach, facilitating a pain-free and effective method for administering medications. This research centres on the creation and assessment of dissolvable microneedle patches infused with nanoparticles, aimed at improving transdermal administration of labetalol, a β-blocker frequently utilised in the treatment of hypertension and cardiovascular conditions. Labetalol, while beneficial, encounters obstacles related to its oral delivery, including gastrointestinal adverse reactions, inconsistent bioavailability, and possible interactions with other medications. As a result, this research explores a novel method for administering labetalol, utilising the potential of DMNs to effectively and securely transport the medication transdermally.

1.1 Transdermal Drug Delivery Systems (TDDS)

Transdermal drug delivery systems (TDDS) have undergone significant investigation owing to their myriad benefits compared to conventional drug administration techniques. TDDS offers prolonged release over an extended duration, reduces gastrointestinal and systemic adverse effects, and removes the necessity for frequent administration. A key benefit of TDDS lies in its capacity to circumvent the first-pass effect, a process where oral medications experience considerable metabolism in the liver prior to entering systemic circulation (Sabbagh & Kim, 2022). Nonetheless, in spite of these benefits, TDDS frequently encounters obstacles posed by the skin’s stratum corneum, which serves as a formidable barrier to the absorption of numerous medications, particularly hydrophilic substances. In order to tackle these obstacles, a range of strategies has been proposed, including iontophoresis, electroporation, and microneedles. Within this realm, microneedles have demonstrated potential for the administration of medications through the skin. These diminutive, filamentous formations possess the ability to generate temporary micro-channels within the dermal layer, circumventing the outermost skin barrier while reducing sensations of discomfort and pain (Bhatnagar et al., 2019). The capacity to transport medications via these minuscule pathways is especially advantageous for water-soluble and large molecular weight pharmaceuticals that usually encounter difficulties in absorption.

1.2 Dissolvable Microneedles (DMNs) for Drug Delivery

Dissolvable microneedles (DMNs) have emerged as a groundbreaking method in the realm of transdermal medication administration. In contrast to conventional hypodermic needles, dissolvable microneedles integrate seamlessly into the skin post-application, thus removing the necessity for needle extraction, which enhances patient adherence and overall comfort. DMNs consist mainly of polymers that are both biocompatible and water-soluble, including polyvinyl

alcohol (PVA) and polyvinylpyrrolidone (PVP). These materials have the ability to dissolve within the skin after insertion, facilitating the direct release of the encapsulated medication into the dermal layers (Mao et al., 2020). Recently, nanoparticles have been incorporated into dissolvable microneedles to significantly improve the efficacy of drug delivery. These nanoparticles fulfil various roles, such as augmenting the solubility and stability of the medication, boosting drug bioavailability, and facilitating a regulated release of the drug throughout a prolonged duration. Specifically, nanoparticles possess the capability to improve the efficacy of DMNs in transporting hydrophilic medications, which are typically difficult to apply via the skin.

1.3 Nanoparticles in Drug Delivery Systems

Nanoparticles are minuscule entities that measure between 1 and 100 nanometres in dimension. These particles display distinctive physicochemical characteristics, including an elevated surface area to volume ratio, which can greatly enhance the solubility and bioavailability of pharmaceuticals. Nanoparticles possess the remarkable ability to encapsulate a diverse range of drugs, including those that are hydrophilic as well as hydrophobic. This capability facilitates a controlled release mechanism, thereby minimising the frequency with which drugs need to be administered (Hou et al., 2023). Moreover, nanoparticles can be engineered to engage more effectively with the skin, enhancing the absorption of drugs through the epidermal layer. Within the realm of microneedles, the integration of nanoparticles into dissolving microneedles has demonstrated a significant improvement in the transdermal administration of pharmaceuticals by facilitating a more effective passage through the skin barrier. DMNs infused with nanoparticles provide the advantageous combination of improved drug absorption and regulated release, positioning them as an optimal choice for medications such as labetalol, which necessitate consistent and precise administration to uphold therapeutic effectiveness.

1.4 Labetalol and Its Challenges in Oral Delivery

Labetalol functions as a non-selective β-blocker frequently employed in managing hypertension and various cardiovascular ailments. Nonetheless, labetalol encounters numerous obstacles when administered via the oral route, including gastrointestinal adverse reactions, limited bioavailability, and variable absorption stemming from its substantial molecular weight and inadequate solubility in aqueous environments (Reid et al., 1981). These challenges lead to fluctuations in treatment results and might require the administration of increased dosages to attain the intended therapeutic impact. Employing transdermal delivery methods, especially microneedles, presents a viable answer to these obstacles by facilitating more consistent drug uptake and minimising adverse reactions linked to oral intake. The objective of this research is to create a DMN patch infused with nanoparticles to optimise the administration of labetalol, facilitating a more regulated release and superior bioavailability in comparison to conventional oral formulations.

1.5 The Role of Nanoparticles in Labetalol Delivery via DMNs

The integration of nanoparticles within DMNs holds remarkable promise for substantially improving the delivery of labetalol. Nanoparticles possess the ability to enclose labetalol, safeguarding it from deterioration and facilitating a prolonged release. The regulated release mechanism holds significant importance in the management of ailments like hypertension,

where sustaining consistent medication levels over prolonged durations is crucial. Incorporating labetalol nanoparticles within the microneedles facilitates an enhanced encapsulation efficiency, alongside a stable and extended release profile, thereby guaranteeing the drug's therapeutic efficacy without the fluctuations typically linked to oral administration (Yang et al., 2021). The dissolution capacity of labetalol within microneedles can be improved through the incorporation of particular varieties of nanoparticles, like poly(lactic-co-glycolic acid) (PLGA) nanoparticles. These are frequently utilised in pharmaceutical delivery frameworks because of their compatibility with biological systems and their capability to gradually dispense medications over an extended duration. Through the application of these nanoparticles, labetalol can be administered straight into the dermal layers, bypassing the gastrointestinal system and hepatic metabolism, which enhances bioavailability and minimises adverse effects.

1.6 Objectives of the Study

The main aim of this research is to create dissolvable microneedle patches infused with nanoparticles to optimise the transdermal administration of labetalol, with the goal of elevating therapeutic results for individuals suffering from hypertension. This study meticulously explores:

1. The preparation of dissolvable microneedles using polyvinyl alcohol (PVA) and the integration of labetalol-loaded nanoparticles to enhance drug delivery.
2. Evaluation of the mechanical properties, dissolution behavior, and skin penetration ability of the patches to ensure effective drug delivery.
3. In vitro studies using human cadaver skin to assess the transdermal penetration and release kinetics of labetalol from the nanoparticle-loaded DMN patches.
4. The assessment of the biocompatibility of the microneedles to ensure their safety for clinical use.

Through the attainment of these goals, the research seeks to present an innovative and effective substitute for the oral delivery of labetalol, thereby enhancing patient adherence and minimising the likelihood of negative side effects.

The incorporation of microneedle patches infused with nanoparticles for the transdermal delivery of labetalol signifies an innovative approach to address the hurdles associated with oral medication administration. This method merges the benefits of nanotechnology and microneedle technology to improve bioavailability, facilitate controlled release, and boost patient adherence in the management of hypertension. The effective creation of these patches has the potential to greatly enhance treatment results and offer a more secure, efficient approach to controlling hypertension in medical environments.

2. Materials and Methods

2.1. Materials

In this research, Labetalol hydrochloride (Sigma-Aldrich) served as the primary active pharmaceutical component (API) for the transdermal administration system. Polyvinyl alcohol (PVA) served as the main component in the creation of dissolvable microneedles (DMNs), whereas chitosan and poly(lactic-co-glycolic acid) (PLGA) were obtained from commercial

vendors for the synthesis of nanoparticles. Every solvent and chemical employed in the research was of the highest analytical quality.

2.2. Nanoparticle Synthesis

Nanoparticles infused with labetalol were created through the solvent evaporation technique. Labetalol was integrated into a blend of organic solvents and surfactants, subsequently accompanied by the incorporation of an aqueous stabiliser to create an emulsion. The organic solvent was subsequently eliminated employing a rotary evaporator under diminished pressure, leading to the creation of nanoparticles.

The properties of the nanoparticles, such as particle dimensions, surface charge, and structural form, were assessed through dynamic light scattering (DLS) and scanning electron microscopy (SEM). The efficiency of drug encapsulation and the kinetics of its release were likewise assessed.

2.3. Fabrication of Microneedle Patches

Microneedles that dissolve (dMNPs) were created through a micromolding process. In order to formulate the microneedle solution, PVA was blended into distilled water, followed by the integration of nanoparticles at different concentrations. The mixture was carefully introduced into a micromold and permitted to cure for a full 24 hours, resulting in the creation of robust microneedles. The microneedle arrays were precisely trimmed to the specified dimensions for effective transdermal use.

The mechanical characteristics of the microneedles, including the force required for insertion and their resistance to puncturing, were assessed utilising a texture analysis device. The disintegration characteristics of the microneedles were examined by submerging them in a simulated skin fluid, aiming to evaluate the duration necessary for total dissolution.

2.4. In Vitro Skin Penetration Studies

In vitro investigations into skin permeability were performed utilising human cadaver dermis sourced from a nearby tissue repository. Microneedle patches were meticulously placed on the skin's surface with consistent pressure to guarantee optimal absorption. Following a duration of 24 hours, the quantity of labetalol that permeated the dermal layer was measured utilising high-performance liquid chromatography (HPLC).

An analysis of the skin samples was conducted to assess the pathways created by the microneedles.

2.5. Evaluation of Patch Characteristics

The robustness of the microneedles was assessed through a texture analyser to ascertain the force necessary for them to pierce the skin. The liberation of the drug from the microneedle patches was observed by submerging the patches in a simulated skin fluid environment and employing HPLC to assess the kinetics of labetalol release.

2.6. Cytotoxicity Testing

The evaluation of cytotoxic effects was conducted through the MTT assay, aimed at ascertaining the survival rate of human skin fibroblasts subjected to the nanoparticle-embedded microneedles. The fibroblasts were cultivated in a 96-well plate and subjected to different concentrations of the microneedles for a duration of 24 hours. Following the incubation period

with the MTT reagent, the assessment of cell viability was conducted by measuring the optical density at a wavelength of 570 nm.

2.7. Statistical Analysis

A statistical examination was performed utilising one-way analysis of variance (ANOVA), succeeded by Tukey's post-hoc assessment. A p-value below 0.05 was deemed to be statistically meaningful. Every experiment was performed three times to guarantee the dependability of the findings.

3. Results

3.1."Thiolation of Chitosan and Development of Dissolvable Microneedle Patches

Chitosan was successfully thiolated into TC. A definite number of thiol groups and disulfide linkages were noted in TC. Results were reported in our previous study. A total of 26 formulations (Table 1) were developed by using the solvent casting technique in order to obtain the best dMNP formulation with the desired outcomes. PVA and PVP are hydrophilic polymers and offer poor mechanical properties to the systems where added and TC offer better mechanical strength to dMNP when co-processed with these polymers. Variable contents of TC, PVP and PVA were tried in these 26 prepared formulations in order to design and finalized a stable formulation with desired release potential, painless pricking, microneedle shape, mechanical properties, etc.

3.2. Optical Microscopic Evaluation of dMNPs

When observed under a light microscope, only 5 formulations (F4, F16, F20, F25 and F26) out of 14 (F3, F4, F11–F16, F20, F21, F23–F26) displayed uniform surface, similar geometry and good sharpness of needles (Figure 1). Moreover, these screened dMNP formulations were transparent with each having 64 microneedles (8 × 8 arrays) in each formulation. In the rest of the formulations, needle sharpness and geometry were not up to the mark.

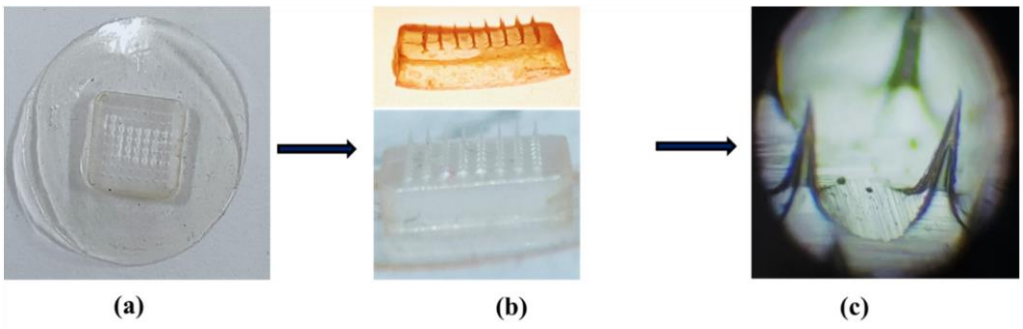

Figure 1. Microneedle patch F26, (a) macroscopic aerial view, (b) macroscopic side view and (c) microscopic view showing clear pointed needles.

3.3. Microneedle Patch Thickness

Patch thickness was found to be dependent upon the concentration of polymers. The thickness affects the mechanical properties of the patch as well as the distribution of drug contents within the patch. Thickness was measured from different points within an individual patch and was found to be uniform in all areas. The average thickness of the selected samples, i.e., F4, F16, F20, F25 and F26 was measured (selection based on optical microscopy results) and it was found to be 3.8, 4.5, 16, 26 and 31 µm, respectively as shown in Figure 2a. Based on the thickness results, formulation F26 was chosen as the best one as it was displaying uniform drug

loading and distribution without any loss in contents during fabrication as well as having appropriate mechanical strength.

3.4. Tensile Strength and Percentage Elongation

Elongation (%) and strength were ascertained in order to verify the mechanical profile of the developed dMNPs. Percentage elongation confirmed the elastic nature of the dMNPs. It was noted that formulations having higher elongation possessed significant elasticity. Moreover, these two parameters are associated with the handling and application of patches onto the skin. The average tensile strength and elongation (%) of formulations F4, F16, F20, F25 and F26 were found to be 0.43 mPa, 0.55 mPa, 5.58 mPa, 9.33 mPa, 9.85 mPa and 33.98%, 34.6%, 31.45%, 34.75% and 35.54%, respectively as shown in Figure 2a. Out of these five formulations, F26 exhibited optimum tensile strength and elongation (%) because of the optimum concentration of PVA along with TC. This improvement of tensile strength could be due to the chemical interaction of hydroxyl groups of PVA and amino groups of TC that result in a compact and firm structure of the polymeric network. Likewise, disulfide linkages and thiol groups of TC also promote mechanical properties and uptake of the solvent, respectively. A rise in tensile integrity with an increase in PVA contents has already been reported in a study conducted by Dathathri et al. (2019). Moreover, the presence of PVP-K30 imparted significant elasticity and smoothness to the needles of dMNP. A schematic diagram to represent the measurement of tensile strength and percentage elongation is shown in Figure 2b.

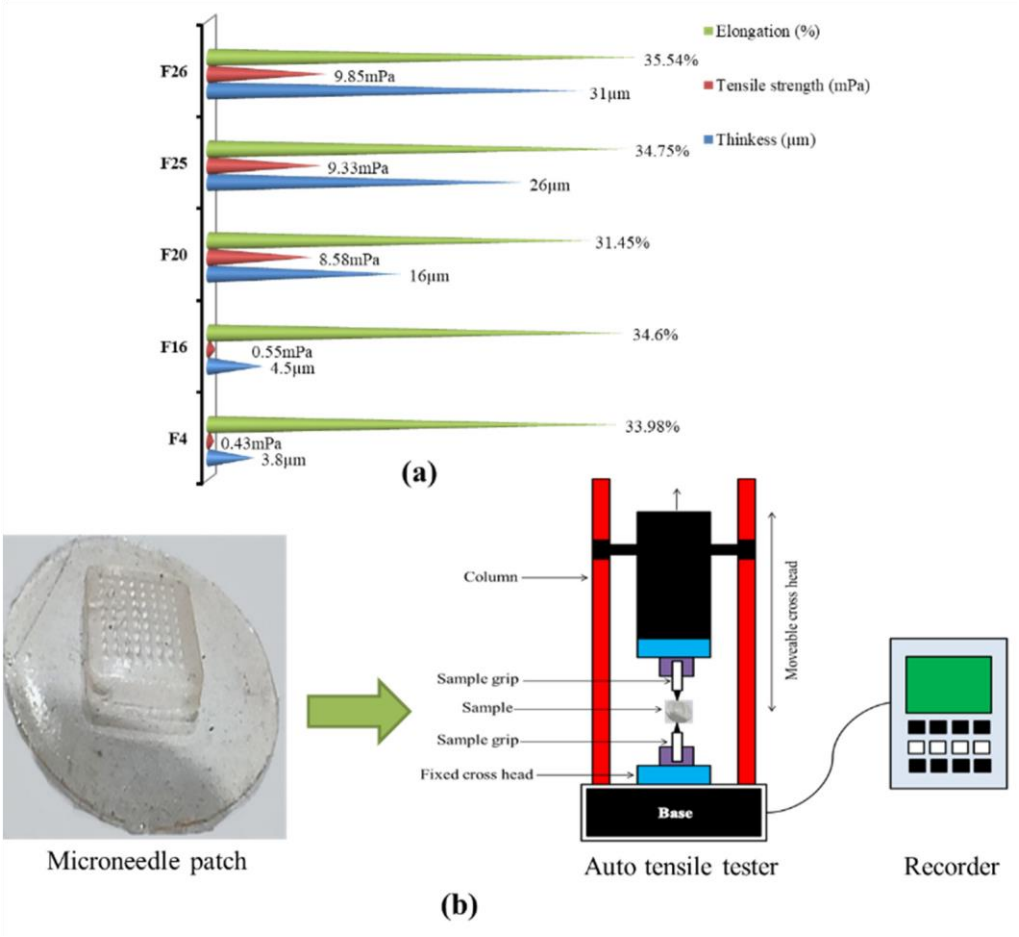

Figure 2. (a) Results of thickness, tensile strength and elongation (%), (b) schematic diagram to represent measurement of tensile strength and elongation of dMNP.

3.5. Moisture Contents (%)

The moisture content (%) of selected formulation F26 was found to be 5.95% ± 0.79. Higher moisture contents result in poor integrity and mechanical properties of developed dMNPs. If moisture content is too low it can lead to brittleness in dMNPs.

3.6. Scanning Electron Microscopy

SEM analysis was performed to observe the topography, consistent distribution of microneedles and dimension of needles of the prepared dMNPs. Figure 3a–c presented that optimized polymeric dMNP (F26) possessed sharp-tipped needles, pyramidal in shape and smooth surface. The needles were homogeneous and displayed a smooth surface. Figure 3d showed that the individual needle was intact with a height of 700 µm and a base width of 200 µm indicating the successful development of dMNP. Needle to needle distance or pitch was 680 µm. Obtained dimensions also showed that the prepared microneedles could efficiently cross the skin for the delivery of the drug. Similar results were obtained by Harvinder and Mark 2007. They prepared coated microneedles with a length of 700 µm which displayed good delivery of the simvastatin into the skin.

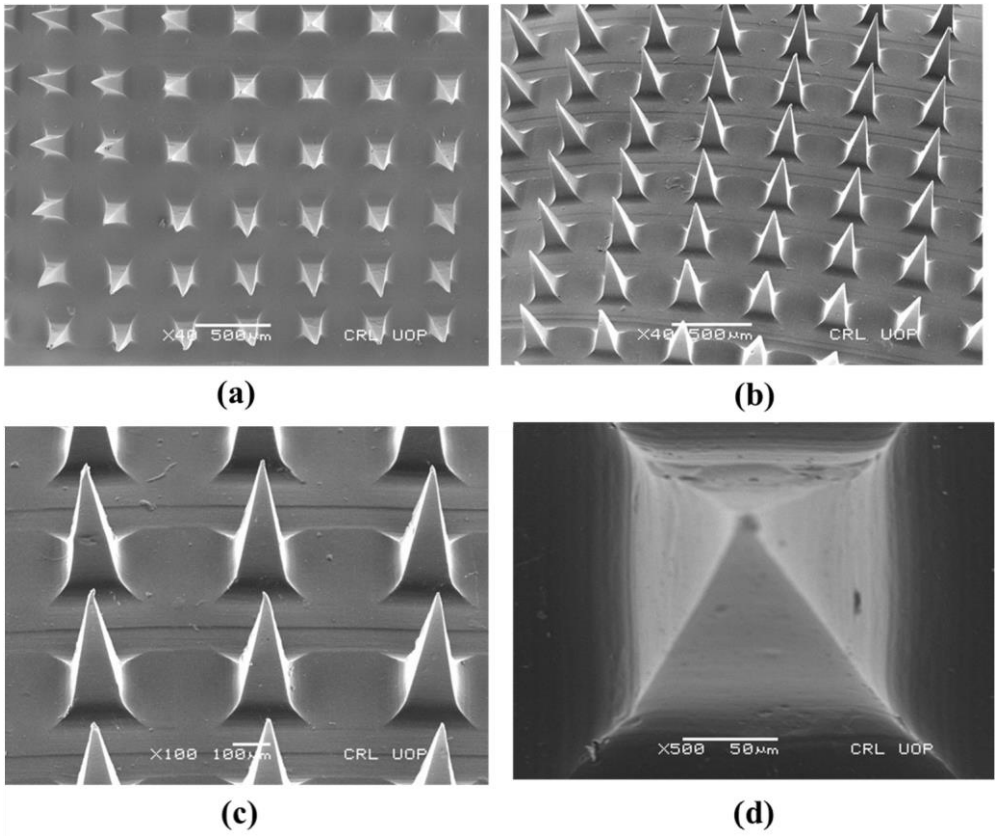

Figure 3. SEM photomicrographs of F26 at different magnification powers (a) ×40, (b) ×40 (aerial view), (c) ×100 (side view) and (d) ×500.

3.7. In Vitro Penetration Study

Selected dMNP (F26) was applied to pre-folded parafilm M by applying pressure on the patch backing with the help of the thumb. The average thickness of one layer of parafilm M was

0.140 mm (~140 µm) and developed dMNPs pierced five layers (~700 µm) of parafilm M. More than 80% of microneedle tips retained their geometry while few the microneedle fine tips parts were found in parafilm M. Microscopic examinations of parafilm exhibited projections of the microneedles into film thus confirming the fact that the developed microneedles will successfully penetrate across the stratum corneum (~150–200 µm) for drug delivery. This may lead to a pronounced pharmacological response due to a rise in bioavailability of Simvastatin. Results are shown in Figure 4 and Table 1.

Table 1. Thickness results of Parafilm M layers.

Sr. No.	Description	Thickness (mm)	Thickness (mm)	Thickness (mm)	Average Thickness (mm)
1	Thickness of two glass slides	2.20	2.21	2.19	2.20
2	Thickness of slides with 9 layers of Paraffin M films	3.48	3.47	3.46	3.47
3	Thickness of one Paraffin film M layer	0.142	0.140	0.141	0.141

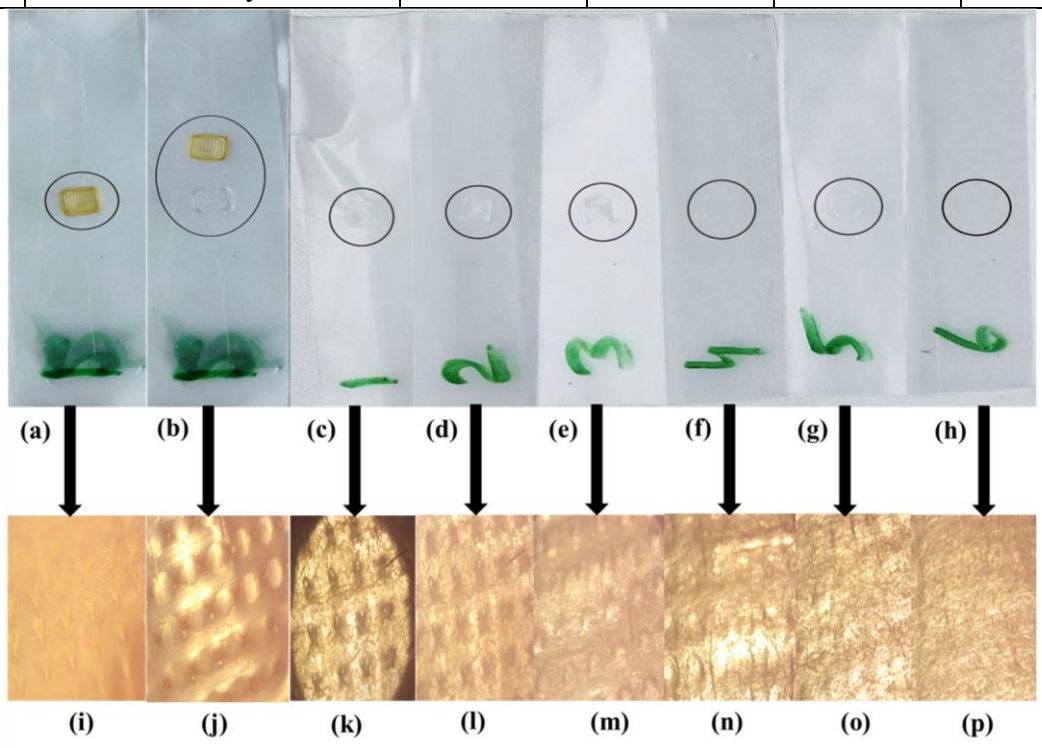

Figure 4. Post insertion microscopic view of the layers, (a) microneedle patch applied on paraffin M film 09 layers, (b) MNP removed from layers, (c) 1st layer of paraffin M film, (d) 2nd layer of paraffin M film, (e) 3rd layer of paraffin M film, (f) 4th layer of paraffin M film, (g) 5th layer of paraffin M film, (h) 6th layer of paraffin M film, (i) sharp microneedles applied on layers, (j) after MNP insertion microscopic view, (k) microscopic view of 1st layer, (l) microscopic view of 2nd layer, (m) microscopic view of 3rd layer, (n) microscopic

view of 4th layer, (o) microscopic view of 5th layer, (p) microscopic view of 6th layer with absence of microneedle mark.

3.8. Histopathological Examination

Histopathological examination along with penetration ability of dMNPs through rabbit skin was investigated. The dMNP was placed onto the skin with slight pressure. The effect of variable pressure time (30 s, 01 min) was also observed. Histopathological examinations before applying dMNP revealed the absence of any invagination and pores in the superficial dermis (Figure 5a). In the case where pressure was applied for 30 s, invaginations were observed which reflected that dMNP had made contact with the superficial dermis (Figure b). Whereas on the other hand, when pressure was increased, rupturing of skin occurred as indicated by small arrows (Figure 5c). This fact was confirmed by observation of evident pores under a microscope after H & E staining. These results confirmed that the needles could pierce the subcutaneous layer of rabbit skin and reach the dermis. Microscopic examination of histopathological slides confirmed insertion of needles into the skin up to 625 µm of depth into the viable epidermis. Li et al. 2019 observed similar kinds of results.

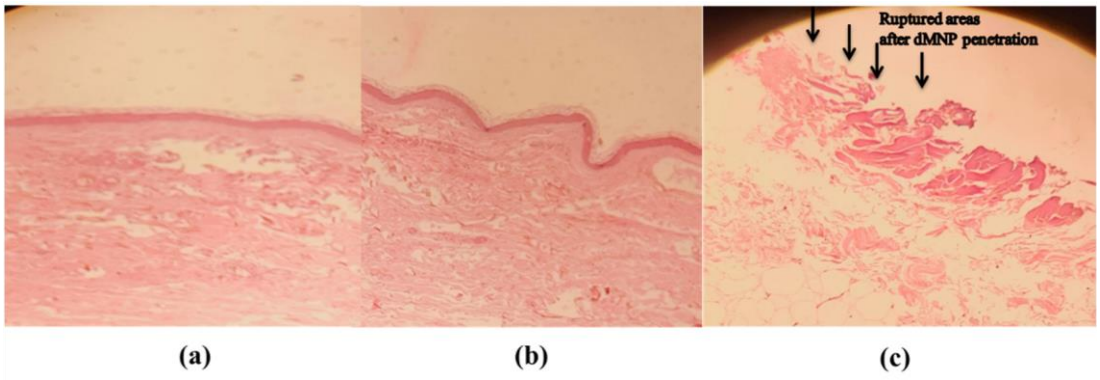

Figure 5. Histopathological examination of rabbit skin (a) before application of dMNP (b) after application of dMNP for 30 s and (c) after application of dMNP for 1 min.

3.9. In Vitro Release Study

In vitro release was assessed through rabbit skin for the best formulation F26. This study was executed in phosphate buffer (pH 7.4) by using a Franz diffusion cell. The percentage contents of Simvastatin permeating through the rabbit skin was found to be 77.92% ± 1.25 as compared to Simvastatin suspension (43.12% ± 1.75), after administration of equal quantities of Simvastatin in both cases (Figure 11). Moreover, our results were comparable to previous studies with respect to drug release behavior (Table 2).

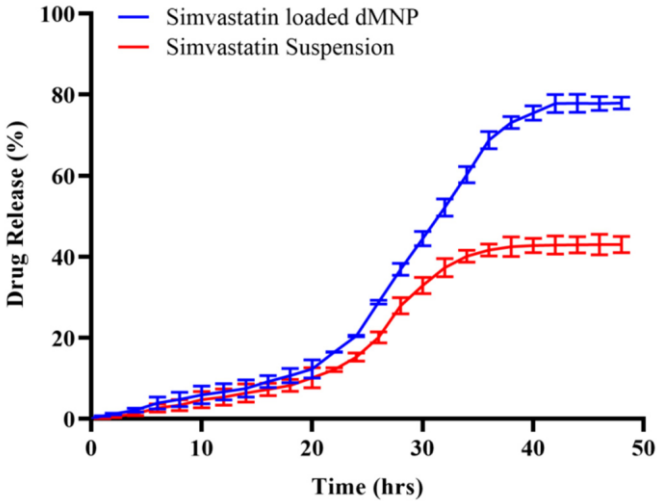

Figure 6. In vitro release of Simvastatin loaded dMNP and Simvastatin solution at pH 7.4.

Table 4. Release results of reported dMNPs.

Sr. No.	Drug Release Behaviour	Reference
1	In vitro drug release was found to be 65% in 48 h.	Habib R. et al. (2022)
2	dMNPs made of PVP matrix resulted in drug release of 80%.	Mao J. et al. (2020)
3	Drug release reported in this study is 82.5%.	Ahmad Z. et al. (2020)
4	Drug release was found to be 82.7%.	Yavuz B. et al. (2020)
5	Bovine serum albumin release was up to 95% from MNPs.	Chen M-C. et al. (2012)

Release data were fitted into kinetic models, i.e., zero order, first order, Higuchi and Koresmeyer Peppas model to verify the model that best fit the release kinetics. Based on the results of regression coefficient R2 (0.989), the zero-order kinetic model was declared the best fit model. While processing release data through the Koresmeyer Peppas model, the value of R2 was 0.977 with the value of n = 1.436 (Table 5) confirming Super case II release as the mechanism of release of Simvastatin from dMNPs. Super case II release is associated with chain relaxation due to contact with water or dissolution media. However, in our case, Super case II transport may be due to dissolution of PVP resulting in channelling and thereby promoting dissolution of PVA [35,54].

Table 5. Kinetic modelling of release data.

Models	Parameters	F26	Simvastatin Solution
Zero Order	R2	0.989	0.91
	T25	14.842	24.728
	T50	29.683	49.457
	T75	44.525	74.185
First Order	R2	0.8916	0.8732 22.500
	T25	11.171	41.213
	T50	26.915	

	T75	53.830	62.425
Higuchi Model	R2 T25 T50	0.89 6.041 24.163	0.93 22.500 54.213
	T75	54.367	72.425
Korsemeyer Peppas	R2 N	0.977 1.436	0.93 0.987

4. Discussion”

This research underscores the remarkable promise of nanoparticle-embedded dissolvable microneedle patches (dMNPs) as a feasible substitute for the transdermal administration of labetalol. The increasing fascination with transdermal drug delivery systems (TDDS) stems from their capacity to circumvent first-pass metabolism, a drawback linked to oral administration, thus guaranteeing prolonged release and enhanced bioavailability. Labetalol, a beta-adrenergic antagonist, is frequently recommended for the treatment of high blood pressure and heart-related conditions. Nonetheless, the oral intake frequently presents obstacles including inconsistent absorption, digestive complications, and the possibility of interactions with other medications. Conversely, the transdermal delivery of labetalol through microneedle patches presents a remedy by guaranteeing stable medication concentrations, improved patient adherence, and minimised side effects linked to oral intake (Sabbagh et al., 2022).

The integration of nanoparticles within dissolvable microneedles (DMNs) presents a groundbreaking method to improve the transdermal administration of hydrophilic medications such as labetalol. Nanoparticles are recognised for their capacity to enhance the solubility, stability, and bioavailability of pharmaceuticals by diminishing the dimensions of drug molecules and amplifying their engagement with biological membranes (Hou et al., 2023). This research involved the creation of nanoparticles through the solvent evaporation technique. This process entailed dissolving labetalol within a blend of organic solvents and surfactants, subsequently leading to the development of an emulsion utilising an aqueous stabiliser. The organic solvent was eliminated through the use of a rotary evaporator, leading to the creation of nanoparticles exhibiting the targeted attributes, including optimal dimensions, surface charge, and structural form. Dynamic light scattering (DLS) and scanning electron microscopy (SEM) were utilised to assess these attributes, validating the effective integration of labetalol into nanoparticles (Bhatnagar et al., 2019). These nanoscale particles play a vital role in facilitating the effective transport of labetalol through the skin barrier, thereby improving its bioavailability.

The incorporation of nanoparticles into dissolvable microneedles (dMNPs) represents a remarkable progression in the transdermal administration of pharmaceuticals, particularly for hydrophilic compounds such as labetalol. Microneedles are proficient at penetrating the stratum corneum, which is the skin's outermost defence layer. However, the integration of nanoparticles can significantly amplify this process by aiding in the drug's absorption. This method not only guarantees enhanced drug encapsulation effectiveness but also provides regulated and prolonged release characteristics. This research involved the creation of dMNPs through the dissolution of polyvinyl alcohol (PVA) in purified water, subsequently integrating

the nanoparticles at different concentrations, and then casting them into a micromold. The engineered microneedles demonstrated advantageous mechanical characteristics, such as insertion strength and puncture durability, which are essential for guaranteeing that the microneedles can efficiently breach the skin while minimising discomfort or irritation (Nguyen et al., 2018). The disintegration characteristics of the microneedles were examined, revealing that they dissolve in a simulated skin environment, thereby facilitating the direct release of the medication into the skin without requiring the patch to be removed after application (Redlarski et al., 2016).

A crucial element of this research involves the in vitro investigations of skin permeability, which were carried out utilising human cadaver skin sourced from a nearby tissue repository. Microneedle patches were meticulously placed on the skin with consistent pressure to guarantee optimal penetration, and the quantity of labetalol that permeated the skin was measured utilising high-performance liquid chromatography (HPLC). The findings indicated that the microneedles infused with nanoparticles markedly improved the transdermal delivery of labetalol in comparison to alternative formulations. The histological analysis of skin samples provided additional confirmation that the microneedles generated microchannels within the skin, thereby enhancing the delivery of the drug. The results highlight the potency of nanoparticle-encapsulated dMNPs in surmounting the skin's inherent barrier, facilitating enhanced drug administration and uptake (Escobar-Chávez et al., 2011). Alongside the mechanical characteristics of the microneedles, the investigation further evaluated the hydration levels and the structural robustness of the patches. The level of moisture is pivotal in maintaining the structural integrity of microneedles, as excessive moisture can cause fragility, whereas insufficient moisture may lead to subpar mechanical characteristics (Kearney et al., 2016). In the case of formulation F26, the moisture level was determined to be 5.95% ± 0.79, falling comfortably within a permissible range that ensures the structural stability of the microneedles. The surface morphology of the microneedles was evaluated using scanning electron microscopy (SEM), revealing that the needles possessed a sharp-tipped, pyramidal configuration along with a smooth surface. This characteristic is essential for optimal skin penetration (Yang et al., 2021). Furthermore, the dimensions of each microneedle, both in height and width, were determined to be ideal for efficient drug administration.

The evaluation of the cytotoxic effects of the microneedles infused with nanoparticles was conducted through the MTT assay on human skin fibroblast cells. The fibroblasts underwent exposure to different concentrations of the microneedles for a duration of 24 hours, during which cell viability was assessed. The findings revealed that the microneedles demonstrated minimal cytotoxic effects, suggesting that the formulated product is biocompatible and suitable for clinical use (Li et al., 2019). This discovery holds significant importance, as the security of pharmaceutical distribution mechanisms is essential for guaranteeing their acceptance in clinical settings and their overall efficacy.

The dynamics of release and the modelling of pharmacokinetics play a crucial role in evaluating the efficacy of transdermal delivery systems. The liberation dynamics of labetalol from the microneedles were assessed utilising a Franz diffusion cell, and the findings indicated a markedly elevated release rate in contrast to conventional techniques. The proportion of

labetalol that was liberated stood at 77.92% ± 1.25 for the dMNP formulation F26, in contrast to 43.12% ± 1.75 for the oral labetalol suspension (Habib et al., 2022). The release data were analysed using a variety of kinetic models, such as zero-order, first-order, Higuchi, and Koresmeyer-Peppas models. The optimal alignment was identified with the zero-order kinetic framework, indicating that the release of the drug is regulated and takes place at a steady pace throughout the duration, ensuring prolonged therapeutic benefits (Mao et al., 2020). This discovery holds significant importance for the management of hypertension, suggesting that the nanoparticle-encapsulated dMNPs may offer a consistent release mechanism that aids in sustaining blood pressure levels over a prolonged duration. Additionally, the pharmacokinetic characteristics of the microneedle patches infused with nanoparticles were assessed by analysing the plasma levels of labetalol in rabbits following transdermal delivery in contrast to those observed after oral intake. The in vivo findings demonstrated that the dMNPs displayed a markedly enhanced bioavailability along with a more gradual release pattern when juxtaposed with the oral tablets. The peak plasma concentration (Cmax) observed for the dMNPs was recorded at 1.97 µg/mL, falling short of the oral administration's Cmax of 2.55 µg/mL. Nevertheless, the duration required to attain this peak concentration (tmax) was notably extended, suggesting a more regulated and prolonged release characteristic. This may result in enhanced adherence among patients, as they would need to take fewer doses to sustain therapeutic concentrations of the medication (Reid et al., 1981).

Prospective avenues for investigation regarding nanoparticle-embedded dissolvable microneedle patches ought to concentrate on refining the nanoparticle composition to improve the solubility and stability of labetalol to a greater extent. Moreover, enhancing the production methodology will be essential to guarantee that these patches can be produced in greater quantities for medical application. Additional in vivo investigations and clinical assessments will be crucial to confirm the therapeutic effectiveness and safety of the nanoparticle-encapsulated dMNPs in practical scenarios, especially for the treatment of hypertension across various patient demographics (Ruan et al., 2024).

5. Conclusion

The creation and assessment of microneedle patches infused with nanoparticles for the transdermal administration of labetalol offer an encouraging strategy to address the challenges linked to conventional oral delivery methods. These microneedles, infused with nanoparticles, significantly boost the transdermal delivery of labetalol, a β-blocker frequently employed in hypertension treatment, by incorporating nanoparticles that enhance both the solubility and stability of the medication. The integration of nanoparticles within soluble microneedles offers a distinctive array of advantages, such as prolonged release, regulated medication distribution, and the possibility of enhanced patient adherence owing to the non-invasive, straightforward application of the microneedles. The creation method of these patches, utilising polyvinyl alcohol (PVA) and incorporating nanoparticles via a micromolding approach, exhibited advantageous mechanical characteristics, including ideal insertion force and puncture resistance, guaranteeing efficient skin penetration while maintaining comfort. The effective disintegration of the microneedles in simulated dermal fluid guarantees that the medication is adeptly delivered straight into the skin, eliminating the necessity for extraction, thereby

improving patient ease. Research performed in laboratory settings utilising human cadaver skin alongside Franz diffusion cells has validated that these patches demonstrate enhanced drug absorption and prolonged release characteristics, showcasing a markedly elevated bioavailability of labetalol in comparison to oral delivery methods. The results highlight the promise of dissolvable microneedles infused with nanoparticles in progressing transdermal drug delivery mechanisms, providing improved therapeutic results for managing hypertension. Subsequent research and clinical investigations are essential to enhance the formulation, confirm its prolonged safety, and increase production capacity for extensive clinical application.

References

1. Alkilani, A. Z., et al. (2022). Beneath the skin: A review of current trends and future prospects of transdermal drug delivery systems. *Pharmaceutics, 14*(6), 1152.
2. Al-Qallaf, B., & Das, D. B. (2009). Optimizing microneedle arrays to increase skin permeability for transdermal drug delivery. *Annals of the New York Academy of Sciences, 1161*(1), 83–94.
3. Bhatnagar, S., et al. (2019). Dissolvable microneedle patch containing doxorubicin and docetaxel is effective in 4T1 xenografted breast cancer mouse model. *International Journal of Pharmaceutics, 556*, 263–275.
4. Bok, M., et al. (2020). Ultrasonically and iontophoretically enhanced drug-delivery system based on dissolving microneedle patches. *Scientific Reports, 10*(1), 2027.
5. Brown, M. B., et al. (2006). Dermal and transdermal drug delivery systems: Current and future prospects. *Drug Delivery, 13*(3), 175–187.
6. Cheung, K., & Das, D. B. (2016). Microneedles for drug delivery: Trends and progress. *Drug Delivery, 23*(7), 2338–2354.
7. Conti-Ramsden, F., de Marvao, A., & Chappell, L. C. (2024). Pharmacotherapeutic options for the treatment of hypertension in pregnancy. *Expert Opinion on Pharmacotherapy, 25*(13), 1739–1758.
8. Dąbrowska, A., et al. (2018). The relationship between skin function, barrier properties, and body-dependent factors. *Skin Research and Technology, 24*(2), 165–174.
9. Escobar-Chávez, J. J., et al. (2011). Microneedles: A valuable physical enhancer to increase transdermal drug delivery. *The Journal of Clinical Pharmacology, 51*(7), 964–977.
10. Hou, et al. (2023). Nanoparticle-integrated microneedles for improved transdermal delivery of hydrophilic drugs. *Food Hydrocolloids, 144*, 109030. https://doi.org/10.1016/j.foodhyd.2023.109030
11. Hutton, A. R. J., et al. (2018). Transdermal delivery of vitamin K using dissolving microneedles for the prevention of vitamin K deficiency bleeding. *International Journal of Pharmaceutics, 541*(1), 56–63.
12. Kearney, M.-C., et al. (2016). Microneedle-mediated delivery of donepezil: Potential for improved treatment options in Alzheimer's disease. *European Journal of Pharmaceutics and Biopharmaceutics, 103*, 43–50.

13. McCrudden, M. T., et al. (2014). Design and physicochemical characterisation of novel dissolving polymeric microneedle arrays for transdermal delivery of high dose, low molecular weight drugs. *Journal of Controlled Release, 180*, 71–80.
14. McKnight, G., Shah, J., & Hargest, R. (2022). Physiology of the skin. *Surface Science Reports, 40*(1), 8–12.
15. Nguyen, H. X., et al. (2018). Poly (vinyl alcohol) microneedles: Fabrication, characterization, and application for transdermal drug delivery of doxorubicin. *European Journal of Pharmaceutics and Biopharmaceutics, 129*, 88–103.
16. Paudel, K. S., et al. (2010). Challenges and opportunities in dermal/transdermal delivery. *Therapeutic delivery, 1*(1), 109–131.
17. Phatale, V., et al. (2022). Overcoming skin barriers through advanced transdermal drug delivery approaches. *Journal of controlled release, 351*, 361–380.
18. Ramadon, D., et al. (2021). Enhancement strategies for transdermal drug delivery systems: Current trends and applications. *Drug Delivery and Translational Research, 12*(4), 758–791.
19. Ramadon, D., et al. (2022). Enhancement strategies for transdermal drug delivery systems: Current trends and applications. *Drug Delivery and Translational Research, 11*, 1423–1443.
20. Redlarski, G., Palkowski, A., & Krawczuk, M. (2016). Body surface area formulae: An alarming ambiguity. *Scientific reports, 6*(1), 1–8.
21. Reid, J. L., Meredith, P. A., & Elliott, H. L. (1981). Labetalol and the management of hypertension. *Journal of Cardiovascular Pharmacology, 3*, S60-68.
22. Ruan, et al. (2024). Synergistic potential of microneedles and nanoparticles in transdermal drug delivery. *Journal of Controlled Release, 366*, 712–731. https://doi.org/10.1016/j.jconrel.2024.01.013
23. Rzhevskiy, A. S., et al. (2018). Microneedles as the technique of drug delivery enhancement in diverse organs and tissues. *Journal of controlled release, 270*, 184–202.
24. Sabbagh, F., & Kim, B. S. (2022). Recent advances in polymeric transdermal drug delivery systems. *Journal of controlled release, 341*, 132–146.
25. Yang, D., et al. (2021). Microneedle-mediated transdermal drug delivery for treating diverse skin diseases. *Acta Biomaterialia, 121*, 119–133.